

COMPREHENSIVE ORGANIC FUNCTIONAL GROUP TRANSFORMATIONS II

Editors-in-Chief
Alan B. Katritzky, Richard L.K. Taylor

Volume

1

Carbon with No Attached Heteroatoms

Volume Editor
Ianine Cowie





ÔUT ÚÜÒÐÒÐÙÒÀÁÜÕÖÐÔÁ
 ÔMPÔNÔÐÔÖÖÜUWÁ
 VÜÖÐÙØÜT ÖVÔÐÙÁÖ



9X]hcf!]b! 7\]YZ`
 5"F ""? Uhf]m_ni` I b]j Yfg]hmcZ: `cf]XUž`
 ; U]bYgj]`Yž! G5
 F">"? "HUmcfž`8YdUfha YbhicZ7\Ya]ghfnž`
 I b]j Yfg]hmcZMcf_ž! ?

J c`i a Yg`d+!`+!J c`i a Y`GYh
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8YgV]dh]cb`
 7ca dFY\Ybg]j Y`Cf[Ub]W: i bV]cbU` ; fci d`HfUbgžcfa Uh]cbg`=f7C: ; H!
 =k`j`dfcj]XY`hY`Z]fghdc]bhicZYbhfmihc`hY`j]hYfUhi fY`žcf`U`gVYb]ghg`
]bhYfghYX`]b`VX`Ya]W`HfUbgžcfa Uh]cbg`DfYgYbh]b[`hY`j Ughgi V`YVh`cZ
 cf[Ub]Wgnb`hYg]g]b`hYfa g`cZ`hY`]bhfcXi V]cb`UbX`]bhYfVb] Yfg]cb`cZ
 U`_bck b`ž bV]cbU`[fci dgž`7C: ; H!=k`j`dfcj]XY`U`i b]ei Y`
]bžcfa Uh]cb`gci fV`XcW`a Ybh]b[`U`a Yh`cXg`cZYZZVYb]midYfžcfa]b[`U`dUfh]W`Uf`HfUbgžcfa Uh]cb`Cf[Ub]gYX`Vmi`hY`ž bV]cbU`[fci d`
 žcfa YXž`7C: ; H!=k`j`Vb]g]ghicZ%(`gdYV]U`]ghfYj]Yk gž`k f]hYb`Vmi
 `YUX]b[`gVYb]ghg`k`c`k`j`Yj U`i UhY`UbX`gi a`a Uf]gY`hY`a Yh`cXg`
 Uj`Uj`UV`Y`žcf`YUV`ž bV]cbU`[fci d`HfUbgžcfa Uh]cb`

J c`i a Yg`

J c`i a Y`%` 7UfVcb`k]h`Bc`5HhUWYX`<YhYfcUha`g`

J c`i a Y`&` 7UfVcb`k]h`CbY`<YhYfcUha`5HhUWYX`VmiU`G]b[`Y`
 6cbX`

J c`i a Y`"`. 7UfVcb`k]h`CbY`<YhYfcUha`5HhUWYX`VmiU`A i`h]d`Y`
 6cbX`

J c`i a Y`(. 7UfVcb`k]h`Hk`c`<YhYfcUha`gž`9UW`5HhUWYX`VmiU`
 G]b[`Y`6cbX`

J c`i a Y`). 7UfVcb`k]h`Hk`c`5HhUWYX`<YhYfcUha`g`k]h`Uh`
 @YUghCbY`7UfVcb`!hc!<YhYfcUha`A i`h]d`Y`@]b_`

J c`i a Y`*. 7UfVcb`k]h`H`fYY`cf` : ci f`5HhUWYX`<YhYfcUha`g`

J c`i a Y`+. 5i`h`cf`=bXYI`UbX`7i`a`i`Uh]j`Y`Gi`V`YVh`=bXYI`

Editors-in-Chief

Professor Alan R. Katritzky, FRS

University of Florida, Gainesville, FL, USA

Professor Richard J. K. Taylor

University of York, York, UK

Editors-in-Chief



Alan Katritzky, educated at Oxford, held faculty positions at Cambridge and East Anglia before migrating in 1980 to the University of Florida, where he is Kenan Professor and Director of the Center for Heterocyclic Compounds. He has trained some 800 graduate students and postdocs, and lectured and consulted worldwide. He led the team which produced *Comprehensive Heterocyclic Chemistry* and its sequel *CHECII*, has edited *Advances in Heterocyclic Chemistry*, Vols. 1 through 86 and conceived the plan for *Comprehensive Organic Functional Group Transformations*. He founded Arkat-USA, a nonprofit organization which publishes *Archive for Organic Chemistry* (ARKIVOC) electronic journal completely free to authors and readers at (www.arkat-usa.org). Honors include 11 honorary doctorates from eight countries and membership or foreign membership of the National Academies of Britain, Catalonia, India, Poland, Russia, and Slovenia.



Richard Taylor is currently Professor of Organic Chemistry at the University of York, where his research focuses on the development of novel synthetic methodology and the synthesis of natural products and related compounds of biological/medicinal interest. The methodology is concentrated primarily on organometallic, organosulfur, and oxidation processes, and the targets include amino acids, carbohydrates, prostaglandins, and polyene and polyoxygenated natural products, particularly with activity as antibiotics and anti-cancer agents.

Richard Taylor is a graduate and postgraduate of the University of Sheffield. After his studies at Sheffield, he carried out postdoctoral research at Syntex, California (Dr. I. T. Harrison) and University College London (Professor F. Sondheimer). His first academic appointment was at the Open University in Milton Keynes. This post gave Professor Taylor the opportunity to contribute to Open University textbooks, radio programs and television productions on

various aspects of organic chemistry. Professor Taylor then moved to UEA, Norwich, where he established his independent research program, before taking up his present position in York in 1993.

Richard Taylor has just finished his term as President of the Organic Division of the Royal Society of Chemistry and was awarded the 1999 RSC Tilden Lectureship and the 1999 RSC Heterocyclic Prize. He is currently the UK Regional Editor of the international journal *Tetrahedron*.

Volume Editors

EDITOR OF VOLUME 1



Janine Cossy did her undergraduate and graduate studies at the University of Reims. After a postdoctoral stay with Barry Trost, for two years (1980–1982) at the University of Wisconsin, she returned to Reims, where she became a Director of Research of the CNRS in 1990. In the same year she moved to Paris to become Professor of Organic Chemistry at the ESPCI (Ecole Supérieure de Physique et de Chimie Industrielles de la Ville de Paris). She is interested in synthetic methodologies (radicals, organometallics, photochemistry, thermal reactions, ring expansions, enantioselectivity, synthesis of heterocycles, synthesis of solid support) and in their applications to the synthesis of natural products and biologically active molecules.

EDITOR OF VOLUME 2



Chris Ramsden was born in Manchester, UK in 1946. He is a graduate of Sheffield University and received his Ph.D. (W. D. Ollis) in 1970 and D.Sc. in 1990. After postdoctoral work at the University of Texas (M. J. S. Dewar)(1971–1973) and University of East Anglia (A. R. Katritzky)(1973–1976), he worked in the pharmaceutical industry. He moved to Keele University as Professor of Organic Chemistry in 1992. His research interests are heterocycles and three-center bonds and applications of their chemistry to biological problems.

EDITOR OF VOLUME 3



Keith Jones was born in Manchester. He studied at Cambridge University for his B.A. in Natural Sciences (1976) and stayed to carry out research with Professor Sir Alan Battersby obtaining his Ph.D. in 1979. In 1979, he moved to a lectureship at King's College London. In 1984, he caught up with his postdoctoral research by spending a year working with Professor Gilbert Stork at Columbia University, New York. After returning to King's College, he became a reader in 1995. In 1998, he moved to a chair in organic and medicinal chemistry at Kingston University. His research interests cover natural product synthesis, heterocyclic chemistry and the use of radicals in synthesis. He has been a visiting professor at Neuchatel and Barcelona Universities as well as the Australian National University.

EDITOR OF VOLUME 4



Professor Gary Molander was born in Cedar Rapids, Iowa. He received his B.S. degree at Iowa State University and subsequently entered the graduate chemistry program at Purdue University in 1975, obtaining his Ph.D. degree in 1979 under the direction of Professor Herbert C. Brown. He joined Professor Barry Trost's group at the University of Wisconsin, Madison 1980 as a postdoctoral research associate, and in 1981 he accepted an appointment at the University of Colorado, Boulder, as an Assistant Professor of chemistry, where he rose through the academic ranks. In 1999 he joined the faculty at the University of Pennsylvania, and in 2001 was appointed Allan Day Professor of Chemistry. Professor Molander's research interests focus on the development of new synthetic methods for organic synthesis and natural product synthesis. A major focus of his research has been the application of organolanthanide reagents and catalysts to selective organic synthesis.

EDITOR OF VOLUME 5



Ray Jones started his chemistry career as an undergraduate and then completing a Ph.D. at Cambridge University under the supervision of Professor Sir Alan Battersby, in the area of alkaloid biosynthesis. After a year as an ICI Postdoctoral Fellow in the laboratories of Professor Albert Eschenmoser at the ETH Zurich, he was appointed as Lecturer in Organic Chemistry at University of Nottingham in 1974. He progressed to Senior Lecturer at Nottingham and then took up the Chair of Organic Chemistry at the Open University in 1995, before moving to the Chair of Organic and Biological Chemistry at Loughborough University in 2000.

His research interests span heterocyclic and natural product chemistry, with over 100 publications. Example topics include the acyltetramic acids and pyridones, Mammecoumarins, spermine and spermidine alkaloids, imidazolines as templates for (asymmetric) synthesis, dipolar cycloadditions, and unusual amino acids and peptide mimetics.

EDITOR OF VOLUME 6



Eric F. V. Scriven is a native of Wales, UK. After working at BISRA and ESSO Ltd, he attended the University of Salford and graduated in 1965. He obtained his M.Sc. from the University of Guelph, and his Ph.D. from the University of East Anglia (with Professor A. R. Katritzky) in 1969. After postdoctoral years at the University of Alabama and University College London, he was appointed Lecturer in organic chemistry at the University of Salford. There, his research interests centered on the reactivity of azides and nitrenes. While at Salford, he spent two semesters on secondment at the University of Benin in Nigeria. He joined Reilly Industries Inc. in 1979 and was director of Research from 1991 to 2003. He is currently at the University of Florida. He edited *Azides & Nitrenes* (1984), and he and Professor H. Suschitzky were founding editors of *Progress in Heterocyclic Chemistry*, which has been published annually since 1989 by the International Society of Heterocyclic Chemistry. He also collaborated with Professors

A. R. Katritzky and C. W. Rees as Editors-in-Chief of *Comprehensive Heterocyclic Chemistry II* (1997). His current research interests are in novel nitration reactions, ionic liquids, and applications of polymers in organic synthesis.

Preface

Comprehensive Organic Functional Group Transformations (COFGT 1995) presented the vast subject of organic synthesis in terms of the introduction and interconversion of functional groups, according to a rigorous system, designed to cover all known and as yet unknown functional groups.

Comprehensive Organic Functional Group Transformations II (COFGT-II), designed for specialist and nonspecialist chemists, active in academic, industrial, and government laboratories, now updates the developments of functional group transformations since the publication of the COFGT 1995. COFGT-II is structured in precisely the same manner as the original COFGT work, allowing truly comprehensive coverage of all organic functional group transformations.

COFGT-II, in combination with COFGT 1995, provides an essential reference source for the all-important topic of methodologies for the interconversion of functional groups in organic compounds, and provides an efficient first point of entry into the key literature and background material for those planning any research involving the synthesis of new organic compounds. With the increase in our understanding of the way in which the chemical structure of compounds determines all physical, chemical, biological, and technological properties, targeted synthesis becomes ever more important. The making of compounds is germane not only to organic chemistry but also to future developments in all biological, medical, and materials sciences.

The availability of the work in electronic format through ScienceDirect will greatly enhance its utility.

The Editors-in-Chief would like to extend their warm thanks to the Volume Editors, the chapter authors, and the Elsevier staff for operating in such an efficient and professional manner.

A. R. Katritzky
R. J. K. Taylor

Introduction to Volume 1

Since 1995, there has been great activity in organic synthesis, particularly concerning the formation of carbon–hydrogen and carbon–carbon bonds. This volume deals with synthetic reactions which result in the alteration of bonding at carbon atoms which are left with no attached heteroatoms. All the major structural influences are treated in this volume, such as the effects of configuration, remote substituents, ring stereochemistry, strain, kinetic or thermodynamic factors, solvation, etc.

This volume is divided into three parts. Part I deals with the formation of tetracoordinated carbon by reduction of heteroatomic bonds and by addition to carbon–carbon bonds. In Part II, the formation of tricoordinated carbons such as $=CH$, $C=CC$, $C=C$ bonds are covered, i.e., involving substitution, addition, elimination, condensation, pericyclic processes, and rearrangements. In this part, tricoordinate anions, cations, and radicals are also discussed. In Part III, allenes, cumulenes, alkynes as well as ions, radicals carbenes, and other monocoordinated systems are examined.

The philosophy of this volume has been to rationalize the enormous amount of information within a logical framework and in a critical fashion. This volume is designed to provide a fast entry to the literature for synthetic organic chemists, and could also stimulate new research areas.

Janine Cossy
Paris, France
August 2004

Explanation of the reference system

Throughout this work, references are designated by a number-lettering coding of which the first four numbers denote the year of publication, the next one to three letters denote the journal, and the final numbers denote the page. This code appears in the text each time a reference is quoted. This system has been used successfully in previous publications and enables the reader to go directly to the literature reference cited, without first having to consult the bibliography at the end of each chapter.

The following additional notes apply:

1. A list of journal codes in alphabetical order, together with the journals to which they refer is given immediately following these notes. Journal names are abbreviated throughout using the CASSI "Chemical Abstracts Service Source Index" system.
2. The references cited in each chapter are given at the end of the individual chapters.
3. The list of references is arranged in order of (a) year, (b) journal in alphabetical order of journal code, (c) part letter or number if relevant, (d) volume number if relevant, and (e) page number.
4. In the reference list the code is followed by (a) the complete literature citation in the conventional manner and (b) the number(s) of the page(s) on which the reference appears, whether in the text or in tables, schemes, etc.
5. For non-twentieth-century references, the year is given in full in the code.
6. For journals which are published in separate parts, the part letter or number is given (when necessary) in parentheses immediately after the journal code letters.
7. Journal volume numbers are not included in the code numbers unless more than one volume was published in the year in question, in which case the volume number is included in parentheses immediately after the journal code letters.
8. Patents are assigned appropriate three-letter codes.
9. Frequently cited books are assigned codes.
10. Less common journals and books are given the code "MI" for miscellaneous with the whole code for books prefixed by the letter "B-".
11. Where journals have changed names, the same code is used throughout, e.g., CB refers to both *Chem. Ber.* and to *Ber. Dtsch. Chem. Ges.*

JOURNAL ABBREVIATIONS

AAC	<i>Antimicrob. Agents Chemother.</i>	CLY	<i>Chem. Listy</i>
ABC	<i>Agric. Biol. Chem.</i>	CM	<i>Chem. Mater.</i>
AC	<i>Appl. Catal.</i>	CMC	<i>Comp. Med. Chem.</i>
ACA	<i>Aldrichim. Acta</i>	COC	<i>Comp. Org. Chem.</i>
AC(P)	<i>Ann. Chim. (Paris)</i>	COFGT	<i>Comp. Org. Func. Group Transformations</i>
AC(R)	<i>Ann. Chim. (Rome)</i>	COMCI	<i>Comp. Organomet. Chem., 1st edn.</i>
ACH	<i>Acta Chim. Acad. Sci. Hung.</i>	CONAP	<i>Comp. Natural Products Chem.</i>
ACR	<i>Acc. Chem. Res.</i>	COS	<i>Comp. Org. Synth.</i>
ACS	<i>Acta Chem. Scand.</i>	CP	<i>Can. Pat.</i>
ACS(A)	<i>Acta Chem. Scand., Ser. A</i>	CPB	<i>Chem. Pharm. Bull.</i>
ACS(B)	<i>Acta Chem. Scand., Ser. B</i>	CPH	<i>Chem. Phys.</i>
AF	<i>Arzneim.-Forsch.</i>	CPL	<i>Chem. Phys. Lett.</i>
AFC	<i>Adv. Fluorine Chem.</i>	CR	<i>C.R. Hebd. Seances Acad. Sci.</i>
AG	<i>Angew. Chem.</i>	CR(A)	<i>C.R. Hebd. Seances Acad. Sci., Ser. A</i>
AG(E)	<i>Angew. Chem., Int. Ed. Engl.</i>	CR(B)	<i>C.R. Hebd. Seances Acad. Sci., Ser. B</i>
AHC	<i>Adv. Heterocycl. Chem.</i>	CR(C)	<i>C.R. Hebd. Seances Acad. Sci., Ser. C.</i>
AHCS	<i>Adv. Heterocycl. Chem. Supplement</i>	CRAC	<i>Crit. Rev. Anal. Chem.</i>
AI	<i>Anal. Instrum.</i>	CRV	<i>Chem. Rev.</i>
AJC	<i>Aust. J. Chem.</i>	CS	<i>Chem. Scr.</i>
AK	<i>Ark. Kemi</i>	CSC	<i>Cryst. Struct. Commun.</i>
AKZ	<i>Arm. Khim. Zh.</i>	CSR	<i>Chem. Soc. Rev.</i>
AM	<i>Adv. Mater. (Weinheim, Ger.)</i>	CT	<i>Chem. Tech.</i>
AMLS	<i>Adv. Mol. Spectrosc.</i>	CUOC	<i>Curr. Org. Chem.</i>
AMS	<i>Adv. Mass Spectrom.</i>	CZ	<i>Chem.-Ztg.</i>
ANC	<i>Anal. Chem.</i>	CZP	<i>Czech. Pat.</i>
ANL	<i>Acad. Naz. Lincei</i>	DIS	<i>Diss. Abstr.</i>
ANY	<i>Ann. N. Y. Acad. Sci.</i>	DIS(B)	<i>Diss. Abstr. Int. B</i>
AOC	<i>Adv. Organomet. Chem.</i>	DOK	<i>Dokl. Akad. Nauk SSSR</i>
AP	<i>Arch. Pharm. (Weinheim, Ger.)</i>	DOKC	<i>Dokl. Chem. (Engl. Transl.)</i>
APO	<i>Adv. Phys. Org. Chem.</i>	DP	<i>Dyes Pigm.</i>
APOC	<i>Appl. Organomet. Chem.</i>	E	<i>Experientia</i>
APS	<i>Adv. Polym. Sci.</i>	EC	<i>Educ. Chem.</i>
AQ	<i>An. Quim.</i>	EF	<i>Energy Fuels</i>
AR	<i>Annu. Rep. Prog. Chem.</i>	EGP	<i>Ger. (East) Pat.</i>
AR(A)	<i>Annu. Rep. Prog. Chem., Sect. A</i>	EJI	<i>Eur. J. Inorg. Chem.</i>
AR(B)	<i>Annu. Rep. Prog. Chem., Sect. B</i>	EJM	<i>Eur. J. Med. Chem.</i>
ARP	<i>Annu. Rev. Phys. Chem.</i>	EJO	<i>Eur. J. Org. Chem.</i>
ASI	<i>Acta Chim. Sin. Engl. Ed.</i>	EUP	<i>Eur. Pat.</i>
ASIN	<i>Acta Chim. Sin.</i>	FCF	<i>Fortschr. Chem. Forsch.</i>
AX	<i>Acta Crystallogr.</i>	FCR	<i>Fluorine Chem. Rev.</i>
AX(A)	<i>Acta Crystallogr., Part A</i>	FES	<i>Farmaco Ed. Sci.</i>
AX(B)	<i>Acta Crystallogr., Part B</i>	FOR	<i>Fortschr. Chem. Org. Naturst.</i>
B	<i>Biochemistry</i>	FRP	<i>Fr. Pat.</i>
BAP	<i>Bull. Acad. Pol. Sci., Ser. Sci. Chim.</i>	G	<i>Gazz. Chim. Ital.</i>
BAU	<i>Bull. Acad. Sci. USSR, Div. Chem. Sci.</i>	GAK	<i>Gunmi Asbest Kunstst.</i>
BBA	<i>Biochim. Biophys. Acta</i>	GC	<i>Green Chem.</i>
BBR	<i>Biochem. Biophys. Res. Commun.</i>	GEP	<i>Ger. Pat.</i>
BCJ	<i>Bull. Chem. Soc. Jpn.</i>	GSM	<i>Gen. Synth. Methods</i>
BEP	<i>Belg. Pat.</i>	H	<i>Heterocycles</i>
BJ	<i>Biochem. J.</i>	HAC	<i>Heteroatom Chem.</i>
BJP	<i>Br. J. Pharmacol.</i>	HC	<i>Chem. Heterocycl. Compd. [Weissberger-Taylor series]</i>
BMC	<i>Biorg. Med. Chem.</i>	HCA	<i>Helv. Chim. Acta</i>
BMCL	<i>Biorg. Med. Chem. Lett.</i>	HCO	<i>Heterocycl. Commun.</i>
BOC	<i>Bioorg. Chem.</i>	HOU	<i>Methoden Org. Chem. (Houben-Weyl)</i>
BP	<i>Biochem. Biopharmacol.</i>	HP	<i>Hydrocarbon Process</i>
BPJ	<i>Br. Polym. J.</i>	IC	<i>Inorg. Chem.</i>
BRP	<i>Br. Pat.</i>	ICA	<i>Inorg. Chim. Acta</i>
BSB	<i>Bull. Soc. Chim. Belg.</i>	IEC	<i>Ind. Eng. Chem. Res.</i>
BSF	<i>Bull. Soc. Chim. Fr.</i>	IJ	<i>Isr. J. Chem.</i>
BSF(2)	<i>Bull. Soc. Chim. Fr., Part 2</i>	IJC	<i>Indian J. Chem.</i>
BSM	<i>Best Synthetic Methods</i>	IJC(A)	<i>Indian J. Chem., Sect. A</i>
C	<i>Chimia</i>	IJC(B)	<i>Indian J. Chem., Sect. B</i>
CA	<i>Chem. Abstr.</i>	IJM	<i>Int. J. Mass Spectrom. Ion Phys.</i>
CAN	<i>Cancer</i>	IJQ	<i>Int. J. Quantum Chem.</i>
CAR	<i>Carbohydr. Res.</i>	IJS	<i>Int. J. Sulfur Chem.</i>
CAT	<i>Chim. Acta Turc.</i>	IJS(A)	<i>Int. J. Sulfur Chem., Part A</i>
CB	<i>Chem. Ber.</i>	IJS(B)	<i>Int. J. Sulfur Chem., Part B</i>
CBR	<i>Chem. Br.</i>	IS	<i>Inorg. Synth.</i>
CC	<i>J. Chem. Soc., Chem. Commun.</i>	IZV	<i>Izv. Akad. Nauk SSSR, Ser. Khim.</i>
CCA	<i>Croat. Chem. Acta</i>	JA	<i>J. Am. Chem. Soc.</i>
CCC	<i>Collect. Czech. Chem. Commun.</i>	JAN	<i>J. Antibiot.</i>
CCHT	<i>Comb. Chem. High T. Scr.</i>	JAP	<i>Jpn. Pat.</i>
CCR	<i>Coord. Chem. Rev.</i>	JAP(K)	<i>Jpn. Kokai</i>
CE	<i>Chem. Express</i>	JBC	<i>J. Biol. Chem.</i>
CEJ	<i>Chem. -Eur. J.</i>	JC	<i>J. Chromatogr.</i>
CEN	<i>Chem. Eng. News</i>	JCA	<i>J. Catal.</i>
CHE	<i>Chem. Heterocycl. Compd. (Engl. Transl.)</i>	JCC	<i>J. Coord. Chem.</i>
CHECI	<i>Comp. Heterocycl. Chem., 1st edn.</i>	JCO	<i>J. Comb. Chem.</i>
CHECII	<i>Comp. Heterocycl. Chem., 2nd edn.</i>	JCE	<i>J. Chem. Ed.</i>
CHIR	<i>Chirality</i>	JCED	<i>J. Chem. Eng. Data</i>
CI(L)	<i>Chem. Ind. (London)</i>	JCI	<i>J. Chem. Inf. Comput. Sci.</i>
CI(M)	<i>Chem. Ind. (Milan)</i>	JCP	<i>J. Chem. Phys.</i>
CJC	<i>Can. J. Chem.</i>	JCPB	<i>J. Chim. Phys. Physico-Chim. Biol.</i>
CJS	<i>Canadian J. Spectrosc.</i>	JCR(M)	<i>J. Chem. Res. (M)</i>
CL	<i>Chem. Lett.</i>	JCR(S)	<i>J. Chem. Res. (S)</i>

JCS	<i>J. Chem. Soc.</i>	PB	<i>Polym. Bull.</i>
JCS(A)	<i>J. Chem. Soc. (A)</i>	PC	<i>Personal Communication</i>
JCS(B)	<i>J. Chem. Soc. (B)</i>	PCS	<i>Proc. Chem. Soc.</i>
JCS(C)	<i>J. Chem. Soc. (C)</i>	PH	'Photochemistry of Heterocyclic Compounds', O. Buchardt, Ed.; Wiley, New York, 1976
JCS(D)	<i>J. Chem. Soc., Dalton Trans.</i>	PHA	<i>Pharmazi</i>
JCS(F1)	<i>J. Chem. Soc., Faraday Trans. 1</i>	PHC	<i>Prog. Heterocycl. Chem.</i>
JCS(F2)	<i>J. Chem. Soc., Faraday Trans. 2</i>	PIA	<i>Proc. Indian Acad. Sci.</i>
JCS(P1)	<i>J. Chem. Soc., Perkin Trans. 1</i>	PIA(A)	<i>Proc. Indian Acad. Sci., Sect. A</i>
JCS(P2)	<i>J. Chem. Soc., Perkin Trans. 2</i>	PJC	<i>Pol. J. Chem.</i>
JCS(S2)	<i>J. Chem. Soc., (Suppl. 2)</i>	PJS	<i>Pak. J. Sci. Ind. Res.</i>
JEC	<i>J. Electroanal. Chem. Interfacial Electrochem.</i>	PMH	<i>Phys. Methods Heterocycl. Chem.</i>
JEM	<i>J. Energ. Mater.</i>	PNA	<i>Proc. Natl. Acad. Sci. USA</i>
JES	<i>J. Electron Spectrosc.</i>	POL	<i>Polyhedron</i>
JFA	<i>J. Sci. Food Agri.</i>	PP	<i>Polym. Prepr.</i>
JFC	<i>J. Fluorine Chem.</i>	PRS	<i>Proceed. Roy. Soc.</i>
JGU	<i>J. Gen. Chem. USSR (Engl. Transl.)</i>	PS	<i>Phosphorus Sulfur (formerly); Phosphorus Sulfur Silicon (currently)</i>
JHC	<i>J. Heterocycl. Chem.</i>	QR	<i>Q. Rev., Chem. Soc.</i>
JIC	<i>J. Indian Chem. Soc.</i>	QRS	<i>Quart. Rep. Sulfur Chem.</i>
JINC	<i>J. Inorg. Nucl. Chem.</i>	QSAR	<i>Quant. Struct. Act. Relat.</i>
JLC	<i>J. Liq. Chromatogr.</i>	RC	<i>Rubber Chem. Technol.</i>
JMAC	<i>J. Mater. Chem.</i>	RCB	<i>Russian Chemical Bull.</i>
JMAS	<i>J. Mater. Sci.</i>	RCC	<i>Rodd's Chemistry of Carbon Compounds</i>
JMC	<i>J. Med. Chem.</i>	RCM	<i>Rapid Commun. Mass Spectrom.</i>
JMOC	<i>J. Mol. Catal.</i>	RCP	<i>Rec. Chem. Prog.</i>
JMR	<i>J. Magn. Reson.</i>	RCR	<i>Russ. Chem. Rev. (Engl. Transl.)</i>
JMS	<i>J. Mol. Sci.</i>	RHA	<i>Rev. Heteroatom. Chem.</i>
JNP	<i>J. Nat. Prod.</i>	RJ	<i>Rubber J.</i>
JOC	<i>J. Org. Chem.</i>	RJGC	<i>Russ. J. Gen. Chem. (Engl. Transl.)</i>
JOM	<i>J. Organomet. Chem.</i>	RJOC	<i>Russ. J. Org. Chem. (Engl. Transl.)</i>
JOU	<i>J. Org. Chem. USSR (Engl. Transl.)</i>	RP	<i>Rev. Polarogr.</i>
JPC	<i>J. Phys. Chem.</i>	RRC	<i>Rev. Roum. Chim.</i>
JPJ	<i>J. Pharm. Soc. Jpn.</i>	RS	<i>Ric. Sci.</i>
JPO	<i>J. Phys. Org. Chem.</i>	RTC	<i>Recl. Trav. Chim. Pays-Bas</i>
JPP	<i>J. Pharm. Pharmacol.</i>	RZC	<i>Rocz. Chem.</i>
JPR	<i>J. Prakt. Chem.</i>	S	<i>Synthesis</i>
JPS	<i>J. Pharm. Sci.</i>	SA	<i>Spectrochim. Acta</i>
JPS(A)	<i>J. Polym. Sci., Polym. Chem., Part A</i>	SA(A)	<i>Spectrochim. Acta, Part A</i>
JPU	<i>J. Phys. Chem. USSR (Engl. Transl.)</i>	SAP	<i>S. Afr. Pat.</i>
JSC	<i>J. Serbochem. Soc.</i>	SC	<i>Synth. Commun.</i>
JSP	<i>J. Mol. Spectrosc.</i>	SCI	<i>Science</i>
JST	<i>J. Mol. Struct.</i>	SH	<i>W. L. F. Armarego, 'Stereochemistry of Heterocyclic Compounds', Wiley, New York, 1977, parts 1 and 2.</i>
K	<i>Kristallografiya</i>	SL	<i>Synlett</i>
KFZ	<i>Khim. Farm. Zh.</i>	SM	<i>Synth. Met.</i>
KGS	<i>Khim. Geterotsikl. Soedin.</i>	SR	<i>Sulfur Reports</i>
KO	<i>Kirk-Othmer Encyc.</i>	SRC	<i>Supplements to Rodd's Chemistry of Carbon Compounds</i>
KPS	<i>Khim. Prir. Soedin.</i>	SRI	<i>Synth. React. Inorg. Metal-Org. Chem.</i>
L	<i>Langmuir</i>	SS	<i>Sch. Sci. Rev.</i>
LA	<i>Liebigs Ann. Chem.</i>	SSR	<i>Second Supplements to Rodd's Chemistry of Carbon Compounds</i>
LC	<i>Liq. Cryst.</i>	SST	<i>Org. Compd. Sulphur, Selenium, Tellurium [R. Soc. Chem. series]</i>
LS	<i>Life. Sci.</i>	SUL	<i>Sulfur Letters</i>
M	<i>Monatsh. Chem.</i>	SZP	<i>Swiss Pat.</i>
MC	<i>Mendeleev Communications</i>	T	<i>Tetrahedron</i>
MCLC	<i>Mol. Cryst. Liq. Cryst.</i>	T(S)	<i>Tetrahedron, Suppl.</i>
MI	<i>Miscellaneous [journal or B-yyyyMI for book]</i>	TA	<i>Tetrahedron Asymmetry</i>
MIP	<i>Miscellaneous Pat.</i>	TAL	<i>Talanta</i>
MM	<i>Macromolecules</i>	TCA	<i>Theor. Chim. Acta</i>
MP	<i>Mol. Phys.</i>	TCC	<i>Top. Curr. Chem.</i>
MRC	<i>Magn. Reson. Chem.</i>	TCM	<i>Tetrahedron, Comp. Method</i>
MS	<i>Q. N. Porter and J. Baldas, 'Mass Spectrometry of Heterocyclic Compounds', Wiley, New York, 1971</i>	TFS	<i>Trans. Faraday Soc.</i>
N	<i>Naturwissenschaften</i>	TH	<i>Thesis</i>
NAT	<i>Nature</i>	TL	<i>Tetrahedron Lett.</i>
NEP	<i>Neth. Pat.</i>	TS	<i>Top. Stereochem.</i>
NJC	<i>Nouv. J. Chim.</i>	UK	<i>Usp. Khim.</i>
NJC	<i>New J. Chem.</i>	UKZ	<i>Ukr. Khim. Zh. (Russ. Ed.)</i>
NKK	<i>Nippon Kagaku Kaishi (J. Chem. Soc. Jpn.)</i>	UP	<i>Unpublished Results</i>
NKZ	<i>Nippon Kagaku Zasshi</i>	URP	<i>USSR Pat.</i>
NMR	<i>T. J. Batterham, 'NMR Spectra of Simple Heterocycles', Wiley, New York, 1973</i>	USP	<i>U.S. Pat.</i>
NN	<i>Nucleosides & Nucleotides</i>	WOP	<i>PCT Int. Appl. WO (World Intellectual Property Organization Pat. Appl.)</i>
NZJ	<i>N. Z. J. Sci. Technol.</i>	YGK	<i>Yuki Gosei Kagaku Kyokaishi</i>
OBC	<i>Organic and Biomolecular Chemistry</i>	YZ	<i>Yakugaku Zasshi</i>
OCS	<i>Organomet. Synth.</i>	ZAAC	<i>Z. Anorg. Allg. Chem.</i>
OL	<i>Org. Lett.</i>	ZAK	<i>Zh. Anal. Khim.</i>
OM	<i>Organometallics</i>	ZC	<i>Z. Chem.</i>
OMR	<i>Org. Magn. Reson.</i>	ZN	<i>Z. Naturforsch.</i>
OMS	<i>Org. Mass Spectrom.</i>	ZN(A)	<i>Z. Naturforsch., Teil A</i>
OPP	<i>Org. Prep. Proced. Int.</i>	ZN(B)	<i>Z. Naturforsch., Teil B</i>
OPRD	<i>Org. Process Res. Dev.</i>	ZOB	<i>Zh. Obshch. Khim.</i>
OR	<i>Org. React.</i>	ZOR	<i>Zh. Org. Khim.</i>
OS	<i>Org. Synth.</i>	ZPC	<i>Hoppe-Seyler's Z. Physiol. Chem.</i>
OSC	<i>Org. Synth., Coll. Vol.</i>	ZPK	<i>Zh. Prikl. Khim.</i>
P	<i>Phytochemistry</i>		
PA	<i>Polym. Age</i>		
PAC	<i>Pure Appl. Chem.</i>		
PAS	<i>Pol. Acad. Sci.</i>		

List of Abbreviations

TECHNIQUES/CONDITIONS

18-C-6	18-crown-6
))))	ultrasonic (sonochemistry)
Δ	heat, reflux
AAS	atomic absorption spectroscopy
AES	atomic emission spectroscopy
AFM	atomic force microscopy
approx.	approximately
aq.	aqueous
b.p.	boiling point
CD	circular dichroism
CIDNP	chemically induced dynamic nuclear polarization
CNDO	complete neglect of differential overlap
conc.	concentrated
CT	charge transfer
ee	enantiomeric excess
equiv.	equivalent(s)
ESR	electron spin resonance
EXAFS	extended X-ray absorption fine structure
FVP	flash vacuum pyrolysis
g	gaseous
GC	gas chromatography
GLC	gas-liquid chromatography
h	Planck's constant
h	hour
HOMO	highest occupied molecular orbital
HPLC	high-performance liquid chromatography
$h\nu$	light (photochemistry)
ICR	ion cyclotron resonance
INDO	incomplete neglect of differential overlap
IR	infrared
l	liquid
LCAO	linear combination of atomic orbitals
LUMO	lowest unoccupied molecular orbital
MCD	magnetic circular dichroism
MD	molecular dynamics
min	minute(s)
MM	molecular mechanics
MO	molecular orbital
MOCVD	metal organic chemical vapor deposition
m.p.	melting point
MS	mass spectrometry

MW	molecular weight
NMR	nuclear magnetic resonance
NQR	nuclear quadrupole resonance
ORD	optical rotatory dispersion
PE	photoelectron
ppm	parts per million
rt	room temperature
s	solid
SCF	self-consistent field
SET	single electron transfer
S _N 1	first-order nucleophilic substitution
S _N 2	second-order nucleophilic substitution
S _N i	internal nucleophilic substitution
STM	scanning tunneling microscopy
TLC	thin-layer chromatography
UV	ultraviolet
vol.	volume
wt.	weight

REAGENTS, SOLVENTS, ETC.

Ac	acetyl CH ₃ CO-
acac	acetylacetonato
acam	acetamide
AcO	acetate
AcOH	acetic acid
AIBN	2,2'-azobisisobutyronitrile
Ans	ansyl
Ar	aryl
ATP	adenosine 5'-triphosphate
9-BBN	9-borabicyclo[3.3.1]nonyl
9-BBN-H	9-borabicyclo[3.3.1]nonane
BEHP	bis (2-ethylhexyl) phthalate
BHT	2,6-di- <i>t</i> -butyl-4-methylphenol (butyrated hydroxytoluene)
binap	2,2'-bis(diphenylphosphino)-1,1'-binaphthyl
bipy	2,2'-bipyridyl
Bn	benzyl C ₆ H ₅ CH ₂ - (NB avoid confusion with Bz)
<i>t</i> -BOC	<i>t</i> -butoxycarbonyl
bpy	2,2'-bipyridyl
BSA	<i>N,O</i> -bis(trimethylsilyl)acetamide
BSTFA	<i>N,O</i> -bis(trimethylsilyl)trifluoroacetamide
Bt	benzotriazole
BTAF	benzyltrimethylammonium fluoride
Bz	benzoyl C ₆ H ₅ CO- (NB avoid confusion with Bn)
Bzac	benzoylacetone
CAN	ceric ammonium nitrate
Cbz	carbobenzoxyl
chalcogens	oxygen, sulfur, selenium, tellurium
CH ₂ Cl ₂	dichloromethane
COD	1,5-cyclooctadiene
COT	cyclooctatetraene
Cp	cyclopentadienyl
Cp*	pentamethylcyclopentadienyl
18-crown-6	1,4,7,10,13,16-hexaoxacyclooctadecane
CSA	camphorsulfonic acid
CSI	chlorosulfonyl isocyanate
CTAB	cetyl trimethyl ammonium bromide
DABCO	1,4-diazabicyclo[2.2.2]octane

DBA	dibenzylideneacetone
DBN	1,5-diazabicyclo[4.3.0]non-5-ene
DBU	1,5-diazabicyclo[5.4.0]undec-5-ene
DCC	dicyclohexylcarbodiimide
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DEAC	diethylaluminum chloride
DEAD	diethyl azodicarboxylate
DET	diethyl tartrate (+ or -)
DHP	dihydropyran
DIBAL-H	diisobutylaluminum hydride
diglyme	diethylene glycol dimethyl ether
dimsyl Na	sodium methylsulfinylmethide
DIOP	2,3- <i>O</i> -isopropylidene-2,3-dihydroxy-1,4-bis(diphenylphosphino)butane
DIPT	diisopropyl tartrate (+ or -)
DMA	dimethylacetamide
DMAC	dimethylaluminum chloride
DMAD	dimethyl acetylenedicarboxylate
DMAP	4-dimethylaminopyridine
DME	dimethoxyethane
DMF	dimethylformamide
DMI	<i>N,N'</i> -dimethylimidazolidinone
DMN	diaminomaleonitrile
DMSO	dimethyl sulfoxide
DMTSP	dimethyl(methylthio)sulfonium fluoroborate
DPPB	1,2-bis(diphenylphosphino)butane
DPPE	1,2-bis(diphenylphosphino)ethane
DPPF	1,1'-bis(diphenylphosphino)ferrocene
DPPP	1,2-bis(diphenylphosphino)propane
E ⁺	electrophile
EADC	ethylaluminum dichloride
EDG	electron-donating group
EDTA	ethylenediaminetetraacetate
EEDQ	<i>N</i> -ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline
Et	ethyl
Et ₂ O	diethyl ether
EtOH	ethanol
EtOAc	ethyl acetate
EWG	electron-withdrawing group
HMPA	hexamethyl phosphoramide
HMPT	hexamethylphosphoric triamide
IpcBH ₂	isopinocampheylborane
Ipc ₂ BH	diisopinocampheylborane
KAPA	potassium 3-aminopropylamide
K-selectride	potassium tri- <i>s</i> -butylborohydride
LAH	lithium aluminum hydride
LDA	lithium diisopropylamide
LICA	lithium isopropyl cyclohexylamide
LITMP	lithium tetramethyl piperidide
L-selectride	lithium tri- <i>s</i> -butyl borohydride
LTA	lead tetraacetate
MAO	monoamine oxidase
MCPBA	3-chloroperoxybenzoic acid
MCT	mercury cadmium telluride
Me	methyl
MEM	methoxyethoxymethyl
MEM-Cl	methoxyethoxymethyl chloride
MeOH	methanol
MMA	methyl methacrylate
MMC	methylmagnesium carbonate
MOM	methoxymethyl

Ms	methanesulfonyl (mesylate)
MSA	methanesulfonic acid
MsCl	methanesulfonyl chloride
MVK	methyl vinyl ketone
NBS	<i>N</i> -bromosuccinimide
NCS	<i>N</i> -chlorosuccinimide
NMO	<i>N</i> -methylmorpholine <i>N</i> -oxide
NMP	<i>N</i> -methyl-2-pyrrolidone
Nu [−]	nucleophile
PPA	polyphosphoric acid
PCC	pyridinium chlorochromate
PDC	pyridinium dichromate
Ph	phenyl
phen	1,10-phenanthroline
Phth	phthaloyl
PPE	polyphosphate ester
PPO	2,5-diphenyloxazole
PPTS	pyridinium <i>p</i> -toluenesulfonate
Pr	propyl
Pyr	pyridine
Red-Al	sodium bis(methoxyethoxy)aluminum dihydride
SDS	sodium dodecyl sulfate
SEM	trimethylsilylethoxymethyl
Sia ₂ BH	disiamylborane
SM	starting material
TAS	tris(diethylamino)sulfonium
TBAF	tetra- <i>n</i> -butylammonium fluoride
TBDMS	<i>t</i> -butyldimethylsilyl
TBDMS-Cl	<i>t</i> -butyldimethylsilyl chloride
TBDPS	<i>t</i> -butyldiphenylsilyl
TBHP	<i>t</i> -butyl hydroperoxide
TCE	2,2,2-trichloroethanol
TCNE	tetracyanoethylene
TEA	tetraethylammonium
TES	triethylsilyl
Tf	triflyl (trifluoromethanesulfonyl)
TFA	trifluoroacetyl
TFAA	trifluoroacetic anhydride
THF	tetrahydrofuran
THP	tetrahydropyranyl
TIPBSCl	2,4,6-triisopropylbenzenesulfonyl chloride
TIPSCl	triisopropylsilyl chloride
TMEDA	tetramethylethylenediamine [1,2-bis(dimethylamino)ethane]
TMS	trimethylsilyl
TMSCl	trimethylsilyl chloride
TMSCN	trimethylsilyl cyanide
Tol	tolyl C ₆ H ₄ (CH ₃)–
TosMIC	tosylmethyl isocyanide
TPP	meso-tetraphenylporphyrin
Tr	trityl (triphenylmethyl)
Tris	tris(hydroxymethyl)aminomethane
Ts	4-toluenesulfonyl (tosyl)
TTFA	thallium trifluoroacetate
TTMSS	tris(trimethylsilyl)silane
TTN	thallium(III) nitrate
X	halogen or leaving group

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1.01

One or More CH Bond(s) Formed by Substitution: Reduction of C—Halogen and C—Chalcogen Bonds

A. G. SUTHERLAND

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1.01.1 REDUCTION OF C—HALOGEN BONDS TO CH

1.01.1.1 General Methods

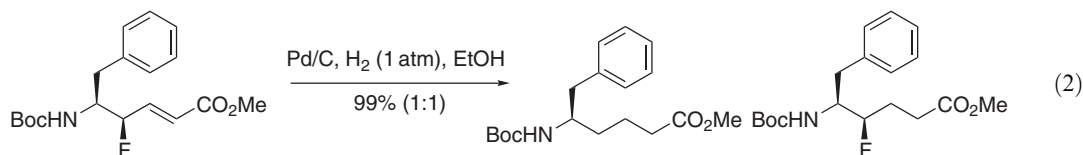
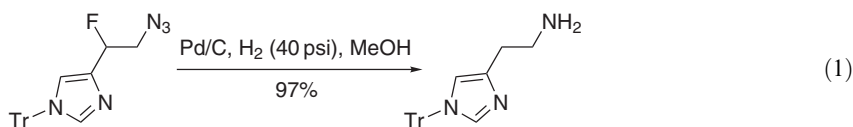
There are four common general methods for the reduction of alkyl halides to the corresponding alkanes: radical reduction (typically employing a tin or silicon hydride reagent); catalytic hydrogenation with transition metal catalysis; low-valent metal reduction and metal hydride reduction (by an ionic mechanism such as with lithium aluminum hydride).

The radical reduction methods came to the fore in the 1980s and 1990s and continue to be dominant, with the caveat that these cannot be used for fluoroalkanes. It is interesting to note that although more environmentally friendly alternatives to tin hydrides continue to be mooted most chemists tend not to be swayed and opt for the reliability and selectivity of these reagents!

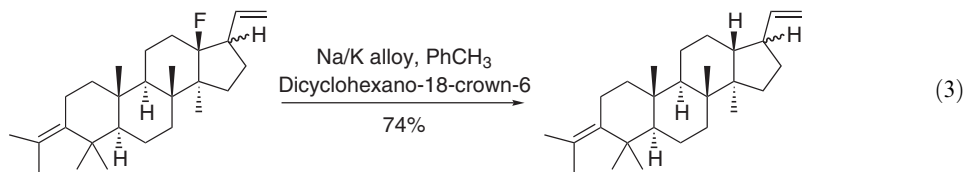
Hydrogenation remains a distant second in popularity with the sometime need for high pressures and catalyst poisoning issues tending to weigh against their selection. Low-valent metal reductions and metal hydride reductions often suffer from chemoselectivity problems but when such factors are less relevant these can often be the method of choice.

1.01.1.2 Reduction of Fluoroalkanes

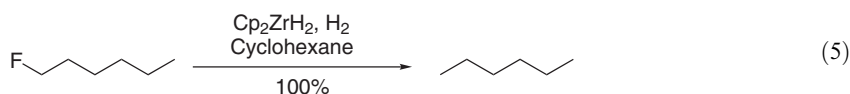
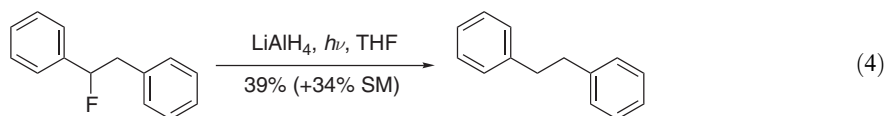
As fluoroalkanes are inert to radical reagents, the most common method for their reduction is by hydrogenolysis over a transition metal catalyst, although often relatively forcing conditions are required. Thus, while the reduction of an azido fluoride by hydrogen over palladium-on-carbon (Equation (1)) is reported to proceed in high yields at relatively high pressure, only the azide is reduced under 1 atm <2001JOC4687>. Allylic fluorides are relatively reactive and can be reduced to the corresponding alkane although generally alkyl fluoride products are also found (Equation (2)) <1999T13819>. These reactions can be sensitive to steric effects as illustrated in the given example where the epimeric fluoride was resistant to reduction.



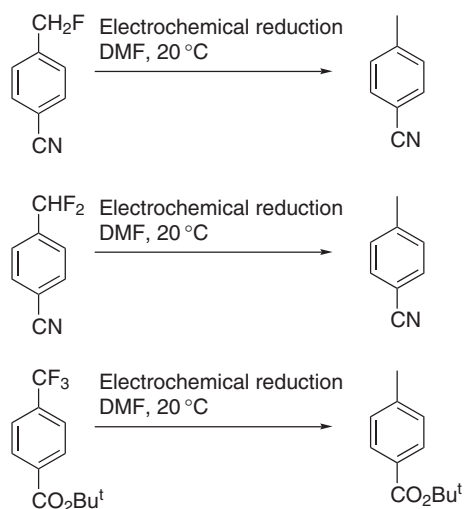
Low-valent metal-mediated reductions are also of utility. Sodium–potassium alloy, in the presence of a crown ether, was used to remove a fluorine from a steroidal skeleton, the subsequent protonation of the intermediate organometallic species being stereoselective <1999JOC9587> (Equation (3)).



While fluoroalkanes are largely inert to reduction by either reagents such as lithium–aluminum hydride or photochemical means, it has been reported that the combination of these two conditions has a synergistic effect and, although competing elimination reactions are not entirely avoided, reasonably clean conversions to the alkane are observed <1995TL7921> (Equation (4)). Zirconium hydrides have been reported to effect quantitative reductions of simple primary, secondary, and tertiary fluoroalkanes under increasingly forcing conditions <2000JA8559> (Equation (5)) although little information on the chemoselectivity of this methodology is yet available.

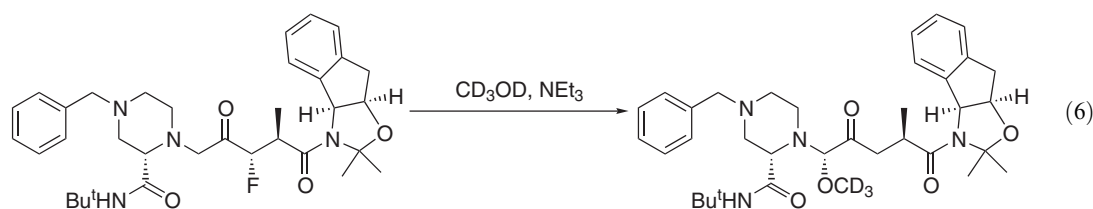


A detailed study suggests that there is considerable scope for the use of electrochemical reduction, at least for benzylic fluorides. Although no specific isolated yields are discussed, the reaction appears to proceed cleanly for mono-, di-, and trifluorides while other potentially sensitive groups such as nitriles or *t*-butylesters are untouched <1997JA9527> (Scheme 1).



Scheme 1

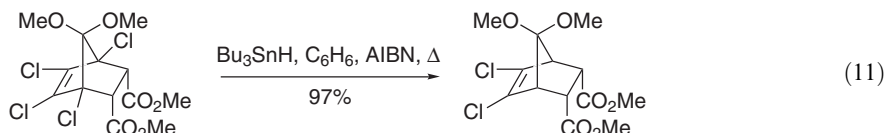
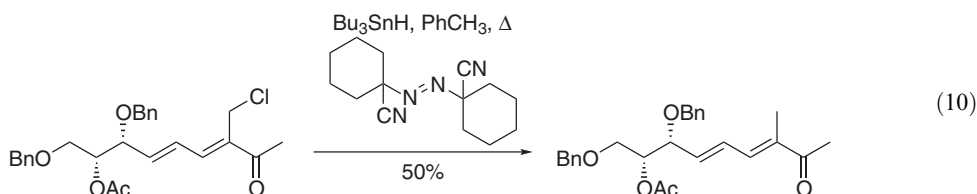
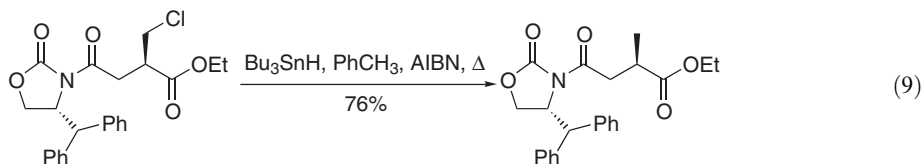
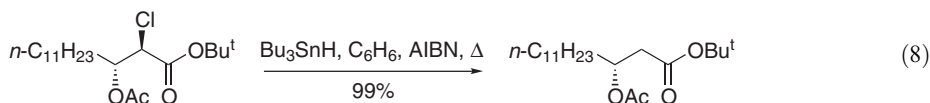
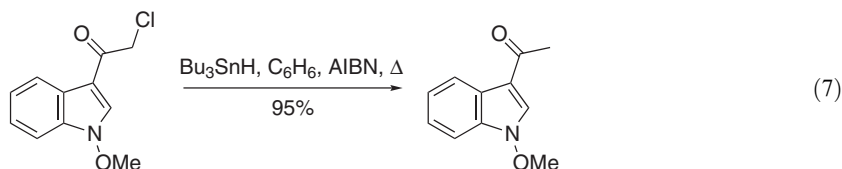
A rather unusual rearrangement, which involves a formal fluoride reduction (with a concomitant oxidation at a nearby carbon), has been reported where α -amino- α' -fluoroketones are converted to α -amino- α' -alkoxyketones <2001OL425> (Equation (6)). A body of evidence was amassed that suggests that this reaction proceeds via a hydroxyvinyliminium ion intermediate and the authors did not seek to investigate this transformation on a preparative scale.



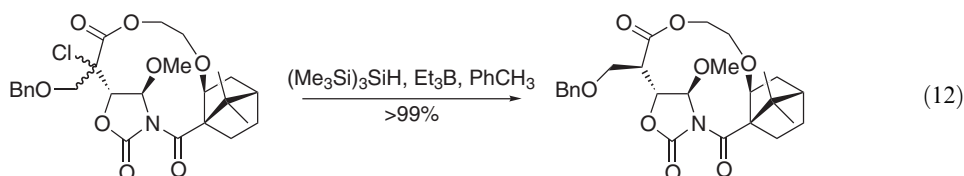
1.01.1.3 Reduction of Chloroalkanes

A wide range of methods are available for the reduction of chloroalkanes but it is worth noting at this point that, particularly in the case of primary systems, many investigators take the option of using the simple Finkelstein procedure to convert the chloroalkane to the corresponding iodoalkane which can then be reduced more easily <1999CPB1380, 2002JOC3861>.

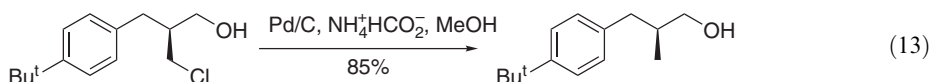
Radical reduction methods, predominantly using tin hydrides and an appropriate radical chain initiator (although photochemical activation is still occasionally seen <2001JCS(P1)891>), offer excellent chemoselectivity. Thus, chloroalkanes are cleanly reduced in the presence of *N*-methoxyindoles <1999H1949> (Equation (7)), β -acetoxyesters <1995TA961> (Equation (8)), *N*-acylcarbamates <2002JOC1738> (Equation (9)), enones, benzylethers <2002T3535> (Equation (10)), and vinyl chlorides <1999TL9289> (Equation (11)) *inter alia*. Methodology that is catalytic in tin reagents (and stoichiometric in polymethylhydrosiloxane) has also been suggested, although incomplete reactions do seem to be an issue in the reduction of chloroalkanes <1999JOC342>.

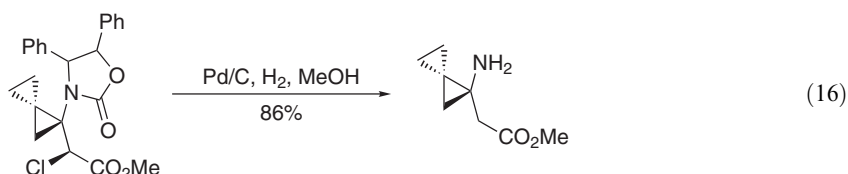
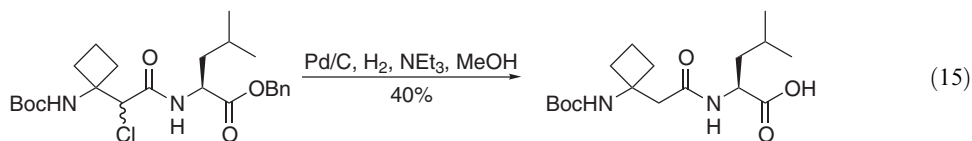
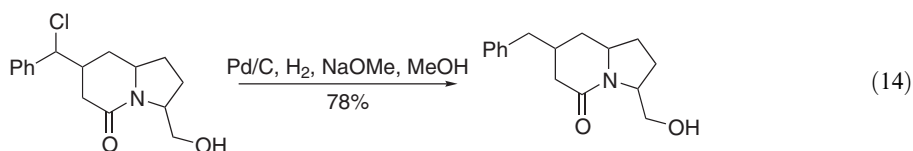


Silicon hydrides are an attractive alternative to tin hydride reagents in these reactions and can offer selectivity advantages as well as circumventing toxicity issues. Thus tris(trimethylsilyl)silane gives a diastereoselective reduction of a complex macrocycle where tributyltin hydride gave poor selectivity [<1998TL7131>](#) (Equation (12)).

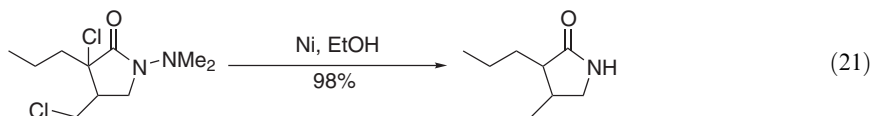
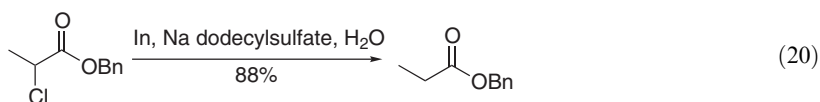
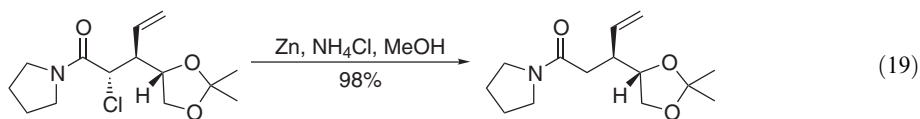
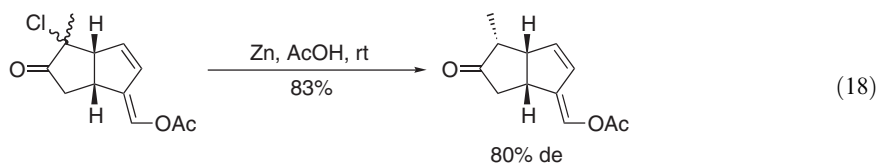
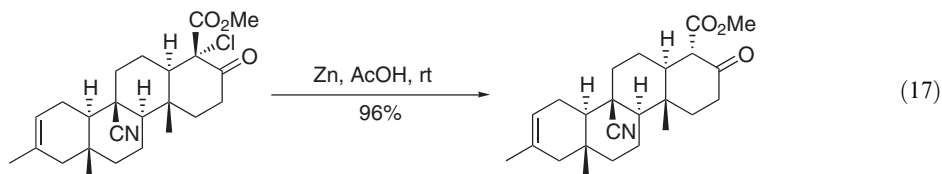


Hydrogenation over palladium on carbon, typically in the presence of a base, remains a useful and quite general method for chloroalkane reduction. Primary [<1995S1427>](#) (Equation (13)), secondary (Equations (14)–(16)), and tertiary systems [<1998JOC8155>](#) are all reduced cleanly and it is notable that strained ring systems neighboring the chloro moiety, which might be sensitive to radical reduction conditions, are unaffected [<1998JOC2469, 1999EJO3105>](#) (Equations (15) and (16)). It is notable, however, that benzylic esters are also reduced under these conditions although this was by design in the given instances.

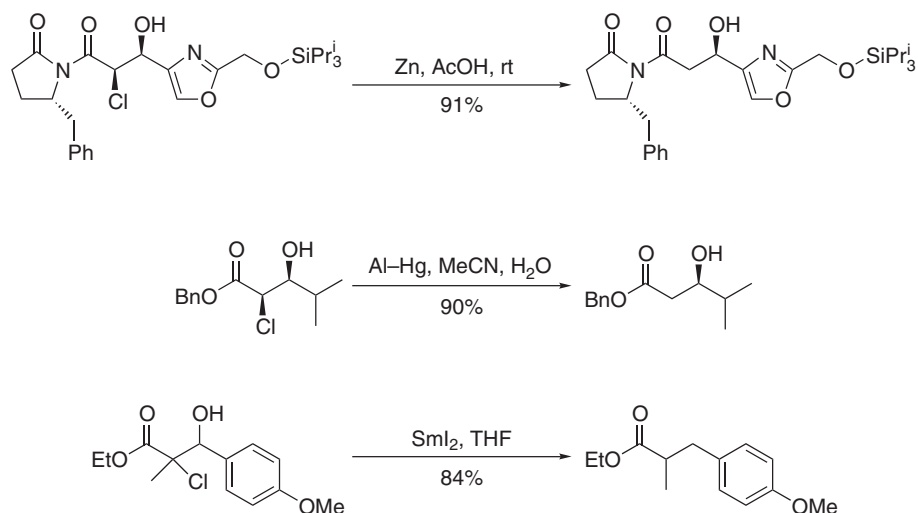




Low-valent metal methods remain very popular for the reduction of α -chlorocarbonyl compounds. The “classic” combination of zinc in acetic acid remains justifiably popular through its excellent chemoselectivity [<1998JOC7213, 1999JOC659>](#) (Equations (17) and (18)), and the replacement of this solvent system with methanol and use of ammonium chloride has been shown to allow clean reductions in the presence of acid-sensitive functional groups [<1996JOC3677>](#) (Equation (19)). Other metals have also been used where indium in water shows promise [<2000JCS\(P1\)4462>](#) (Equation (20)) while Raney nickel is effective in scenarios where multiple functional group reductions are required [<2000JOC6249>](#) (Equation (21)).

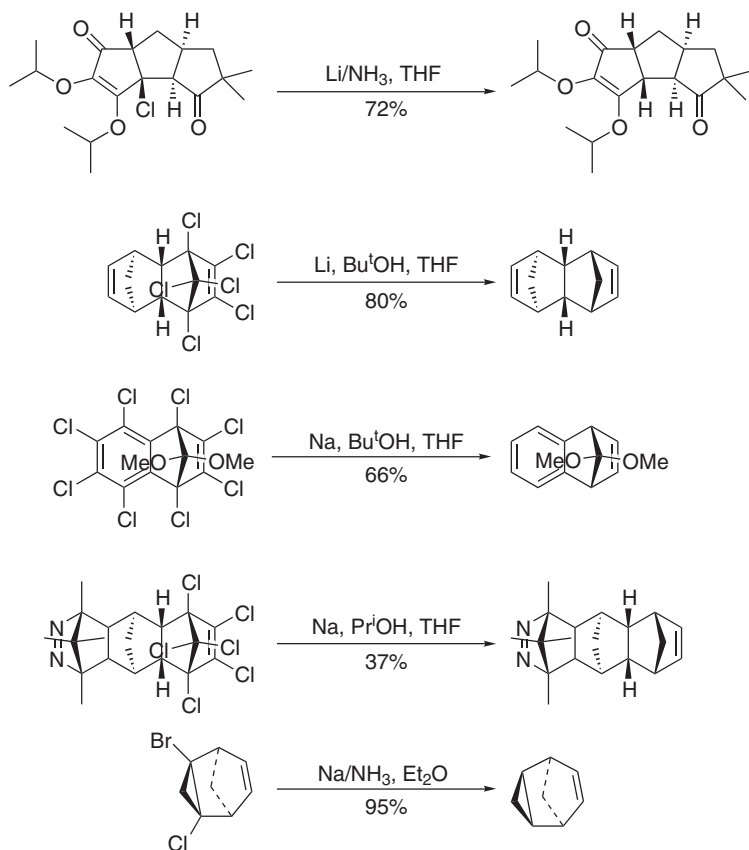


The dechlorination of α -chloro- β -hydroxy esters presents a range of chemoselectivity issues including eliminations and oxirane formation but in fact either zinc/acetic acid [<2000JA10033>](#) or aluminum amalgam in aqueous acetonitrile [<2000CC545>](#) selectively reduce the chloro moiety, whereas samarium iodide in THF removes both the chloro- and hydroxy-functionalities [<2001CEJ4266>](#) (Scheme 2).



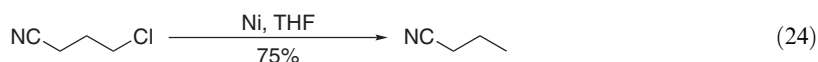
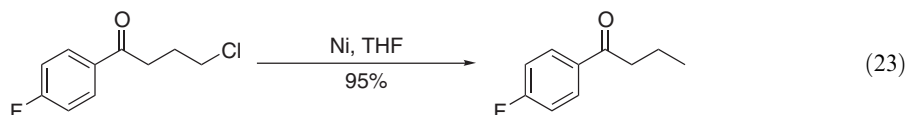
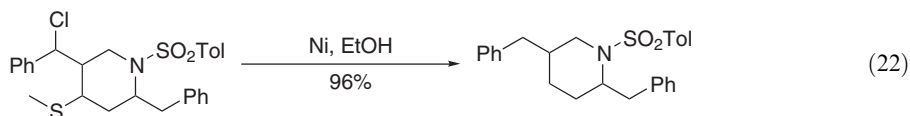
Scheme 2

Low-valent metal methods can, of course, be applied to the reductions of other classes of chloroalkanes—although the mechanism is more typically an electron-transfer process rather than the radical anion chemistry seen with α -chlorocarbonyl compounds—and the use of lithium [<2002JA9199, 1995SC2091>](#) or sodium [<1995T7777, 1995LA351, 1997JOC3355>](#) in the reduction of polycyclic, often polychlorinated, systems is particularly effective (Scheme 3). As is

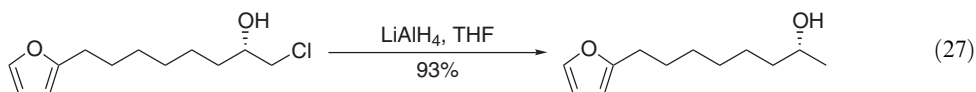
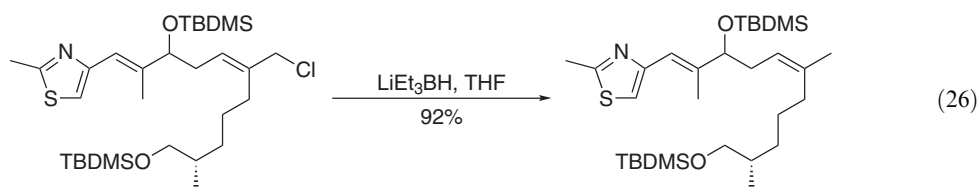
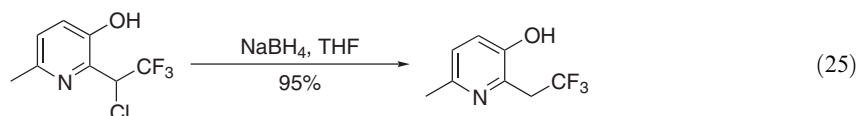


Scheme 3

already seen (Equation (21)), Raney nickel is also an attractive option here—although sulfides are, unsurprisingly, reduced concomitantly <1998TL147> (Equation (22)), significant selectivity over a range of other functional groups has been demonstrated <2001SL485> (Equations (23) and (24)). The recent discovery that the combination of samarium bromide and HMPA also provides clean chloroalkane reductions also merits further investigation <2001OL2321>.

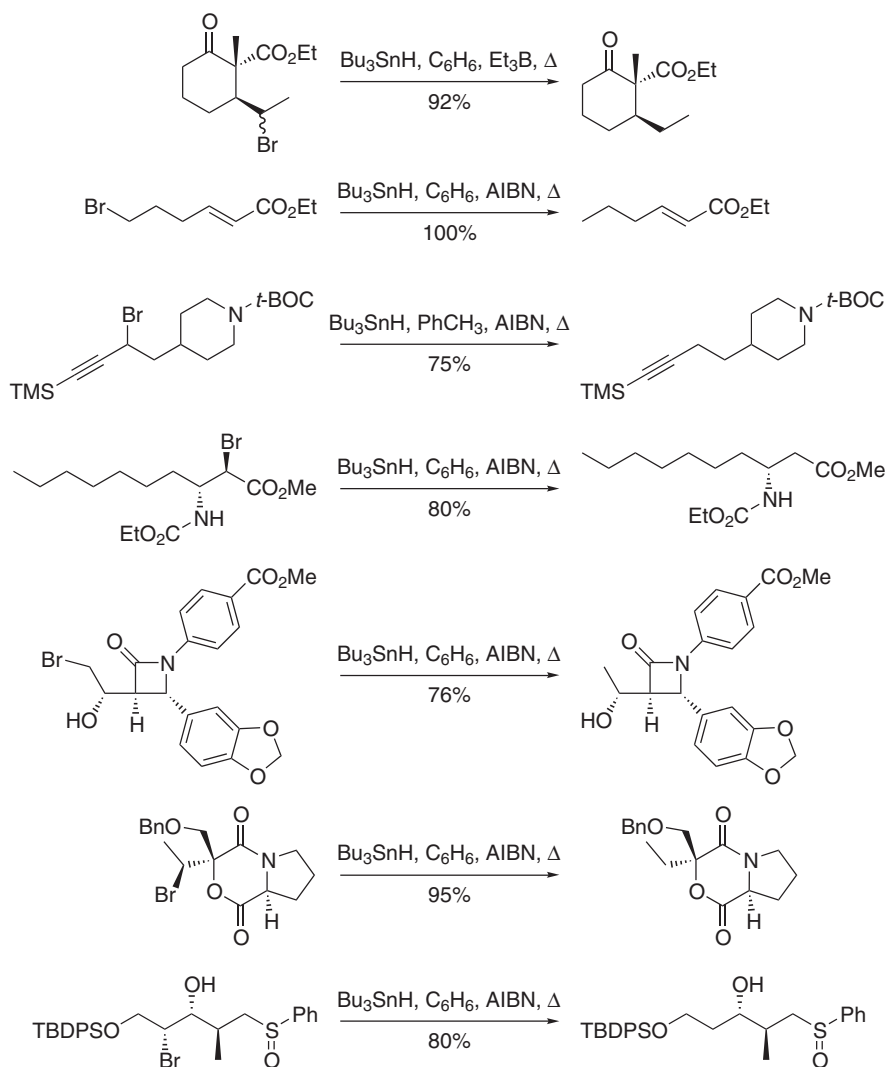


Ionic metal hydride chemistry sees some use here, although less so than with the more reactive bromo- and iodoalkanes, and tends to be used to reduce more reactive systems. Thus, sodium borohydride has been shown to reduce a range of phenolic benzylic chlorides via quinomethane intermediates <2002SL431> (Equation (25)), whereas lithium triethylborohydride has seen utility in the conversion of primary allylic chloroalkanes <1999CC519, 2001OL2221> (Equation (26)). Lithium aluminum hydride has also been employed in the reduction of primary chloroalkane systems <1998JOC7505> (Equation (27)).



1.01.1.4 Reduction of Bromoalkanes

The reduction of bromoalkanes is dominated by radical reduction methods, in particular, using tin hydrides. The popularity is justified as this methodology tends to be chemoselective and high yielding. Examples include reduction in the presence of ketones <2001JA8612>, enoates <1997TL6521>, alkynes <2001H747>, β -carbamoylestere <1997TA903>, β -lactams <2001JCR(S)166>, benzyloxy moieties <2000TA3985>, and sulfoxides <2002JOC5838> (Scheme 4).



Scheme 4

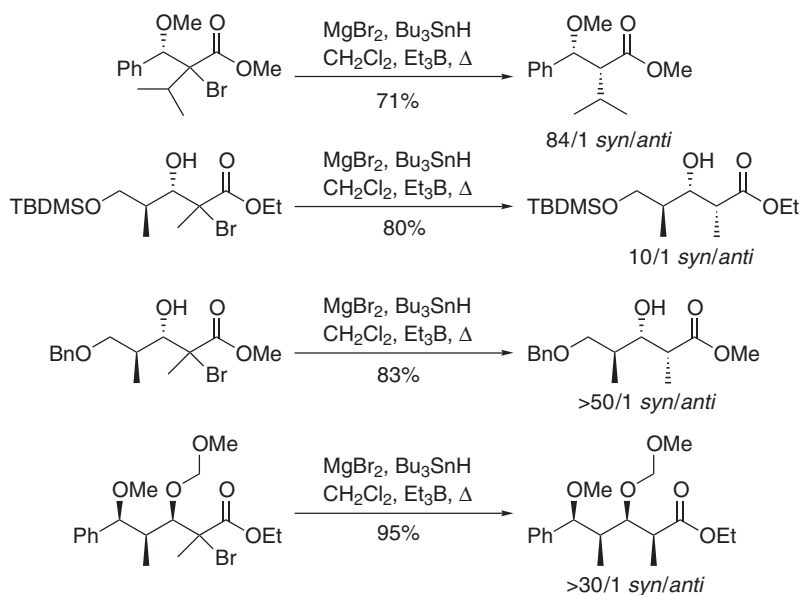
While these radical reductions are typically initiated by the use of AIBN (or analogs thereof) or by the triethylborane/oxygen combination, other initiators have also been advocated, including trialkylaluminums [<1995SL1045>](#), diethylzinc/air [<1998TL6335>](#), and indium [<1998TL1929, 2001TL4661>](#) and cupric chlorides [<1999TL2133>](#). However, these methods do not yet seem to have been adopted widely, at least in this application.

Given the toxicity and purification issues that are associated with trialkyltin hydrides, a number of researchers have sought alternatives. While Enholm and co-workers report methodology which is catalytic in a polymer-bound trialkyltin hydride [<1999OL1275>](#), silicon hydrides appear the main alternative of choice. While tris(trimethylsilyl)silane is a clear favorite here [<1998TL2385, 1999JA5155>](#), phenyl silane [<1997SC1023>](#) and poly(phenyl silane) [<1997JOM475>](#) have also been advocated. Phosphinic acid has also been reported to be an efficient radical-reducing reagent [<1996TL5367>](#) and now that conditions have been reported that allow the transformation of less water-soluble substrates [<2001BCSJ225>](#), perhaps this methodology will become increasingly popular.

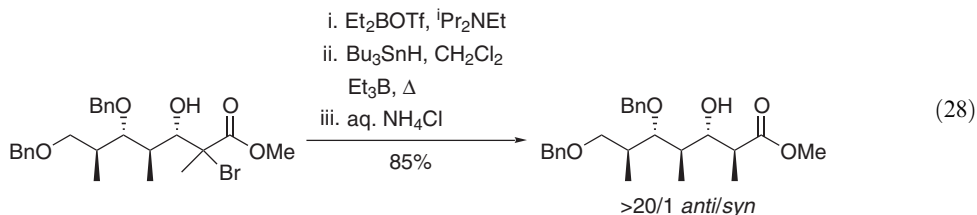
An alternative approach, which completely avoids the use of tin hydrides, etc., is to generate the radical by photochemical means in the presence of triethylamine. This does provide clean reduction chemistry [<2001T5173>](#); however, over the review period this methodology has typically seen more use in carbon-carbon bond-forming processes.

There has been considerable study into the stereoselective radical reduction of α -bromo- α -alkyl- β -oxygen esters as a means of entry to the synthesis of polypropionate natural products and analogs. Performing the reduction using tributyltin hydride in the presence of magnesium

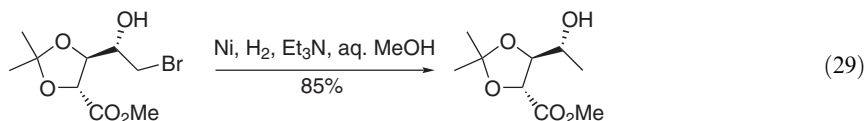
bromide has been demonstrated to give excellent *syn*-stereoselectivity with high tolerance for different functionality along the carbon backbone <1998JOC6554, 2001JA8496, 2002TL5377, 2002TL6373> (Scheme 5). Furthermore, it has also been discovered that conversion of a β -hydroxy functionality into a boronate ester prior to reduction, without the presence of magnesium bromide, affords very high *anti*-selectivity <2002TL7067> (Equation (28)).



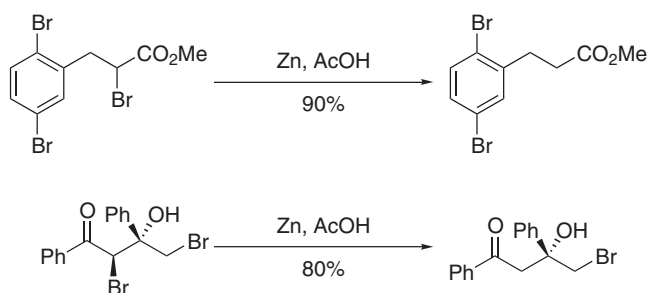
Scheme 5



There have been surprisingly few examples of the reduction of bromoalkanes by hydrogenation in the review period. The use of Raney nickel as a catalyst in this process proved effective in the reduction of a dioxolane derivative <1997TL13883> (Equation (29)) while the merits of triethylsilane <2000JCR(S)432> and of decaborane <2001SC2251> as hydrogen sources in palladium-catalyzed reductions have also been espoused.



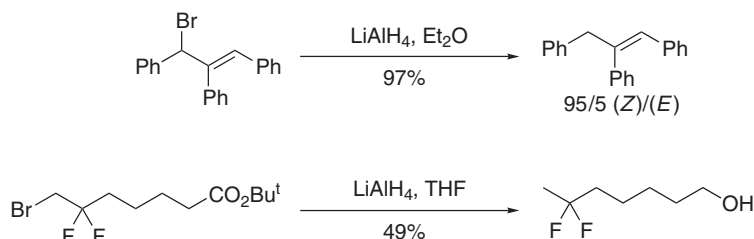
In a parallel with the chloroalkanes, low-valent metal reduction methods are popular in the conversion of α -bromocarbonyl compounds. Notably, the “classical” conditions of zinc powder in acetic acid offer excellent selectivity, the generation and quenching of a radical anion being sufficiently facile that aryl and even primary alkyl bromides are unaffected <1997S1085, 2000S1259> (Scheme 6). In the reduction of β -hydroxy- α -bromoesters aluminum amalgam has been mooted for the reduction of only the halogen <2000CC545, 2000JOC6752> while samarium iodide offers removal of both the bromo- and hydroxy-functionalities <2001CEJ4266>. The closely related reductions of α -bromoimines have been demonstrated to proceed cleanly using tin chloride <2000SL1283, 2001JOC53>.



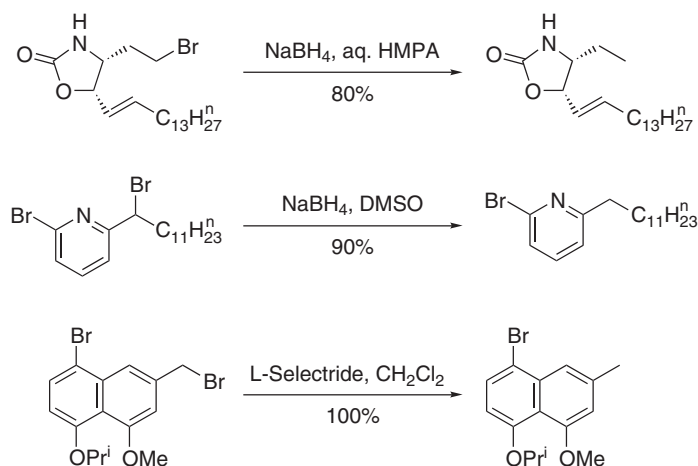
Scheme 6

There are occasional reports of the use of low-valent metal methods for the reduction of bromoalkanes other than those contiguous with a carbonyl group where the use of sodium in ammonia <1997JOC3355> (Scheme 3) and of Raney nickel <1998BCJ1939, 2001SL485> have met with success.

Ionic metal hydride chemistry is employed relatively sparingly for this transformation but is nonetheless often very useful, particularly in the reduction of primary or benzylic systems. Where over-reduction is either not an issue or a concern, lithium aluminum hydride <2000EJO257, 2001JMC1099> can be employed (Scheme 7). Where chemoselectivity is more important, sodium borohydride <1997BMCL573, 2000JOC7634> and L-Selectride can be very effective <1999TL3037> (Scheme 8).



Scheme 7

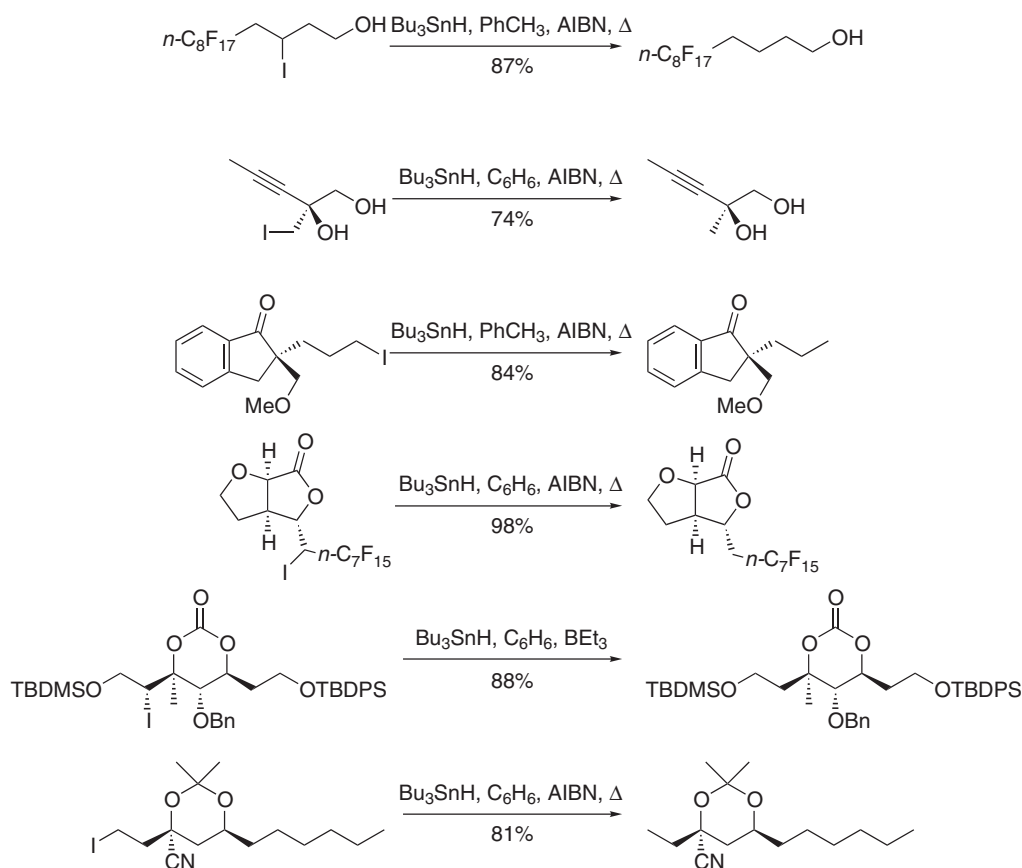


Scheme 8

1.01.1.5 Reduction of Iodoalkanes

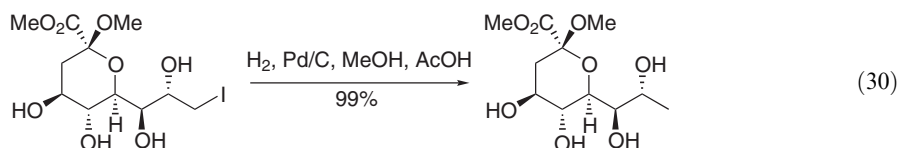
Radical reduction methods, largely through the use of tributyltin hydride, dominate the reduction of iodoalkanes to a greater extent than even the chloro- and bromoalkanes. While alternative reductants, such as polymer-supported trialkyltin hydrides (used catalytically with sodium

borohydride as co-reductant) <1999OL1275>, poly(phenyl silane) <1997JOM475>, phenyl silane <1997SC1023>, and even phosphinic acid <2001BCSJ225> have their advocates, few chemists seem to be willing to diverge from the time-tested methodology. This is not unreasonable given the steady flow of examples of highly selective reductions in the presence of a range of other functional groups which might also be reduced by other methods, including polyfluoroalkanes <2000EJI1975>, alkynes <1997JOC4349>, ketones <1999CPB1380>, lactones <1997SL387>, benzyl- and silyl-protected alcohols <2000SL1733>, and nitriles <1997T16489> (Scheme 9). Diastereoselective reductions of tertiary iodoalkanes using this methodology have also been reported and are often very successful <2000JA12458, 2001OL1391>.

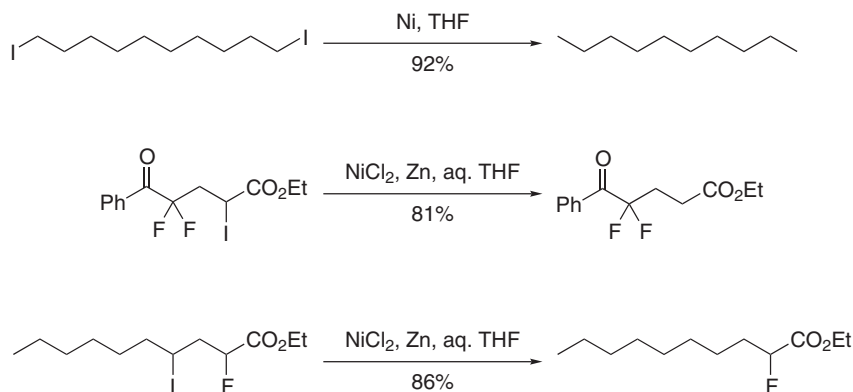


Scheme 9

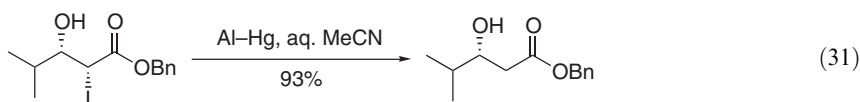
Reduction by catalytic hydrogenation, typically over palladium, is still occasionally seen <1996LA693, 1996OM1508, 2001MI227> (Equation (30)). Yields are often high and, given the selectivity that this technique offers, it is surprising that it is not employed more frequently.



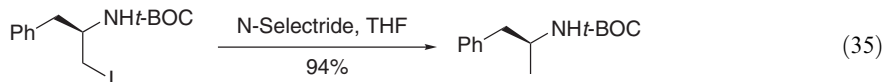
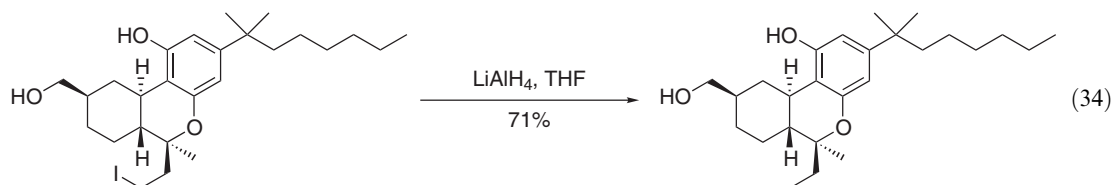
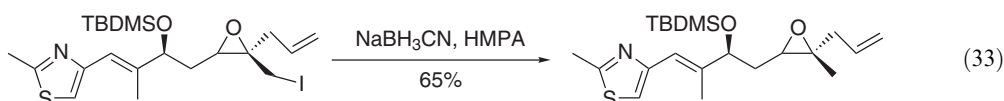
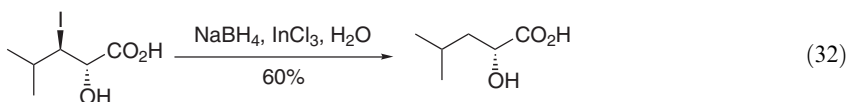
Low-valent metal reduction methodology is similarly underutilized. Raney nickel reduces a wide variety of iodoalkanes <2001SL485> while the combination of zinc and nickel chloride is also very effective, e.g., reducing the iodo moiety in the presence of α -fluoroesters <1995JOC6798, 1996JCS(P1)1741> (Scheme 10). Similarly aluminum amalgam can be used to good effect in the reduction of α -iodoesters <2000CC545> (Equation (31)).



Scheme 10



The above pattern is repeated in the case of ionic metal-hydride-mediated reductions where the few examples indicate that this is a perfectly viable technique for this transformation. Thus, selective reductions of a range of iodoalkanes in the presence of other, potentially reactive, functionality using sodium borohydride/indium chloride [<2001JOC4463>](#) (Equation (32)), sodium cyanoborohydride [<2002AG\(E\)1381>](#) (Equation (33)), lithium aluminum hydride [<1998JMC3596>](#) (Equation (34)), and N-Selectride [<2000JOC5037>](#) are displayed (Equation (35)).



1.01.1.6 Reduction of Hypervalent Haloalkanes

No further advances have occurred in this area since the publication of chapter 1.01.1.6 in COFGT (1995) [<1995COFGT\(1\)1>](#).

1.01.2 REDUCTION OF C—OXYGEN BONDS TO CH

1.01.2.1 General Methods

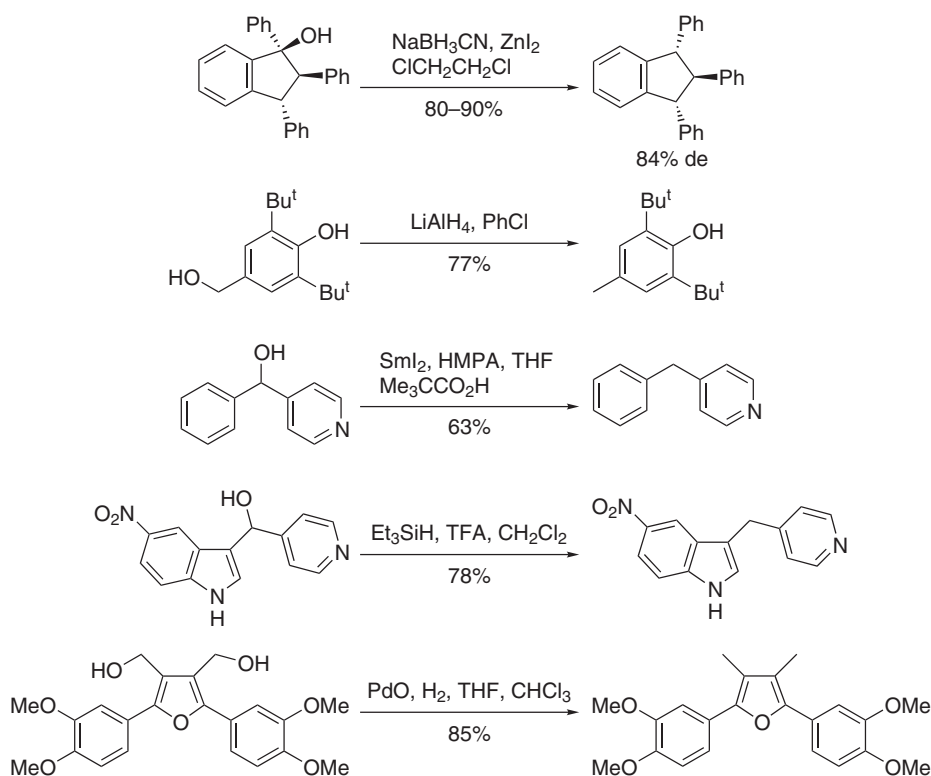
The diverse chemical nature of the carbon—oxygen bond mitigates against there being an all-encompassing method for the reduction of all the different classes. Indeed some of the reduction

chemistry is orthogonal in nature—such as the radical methods used to convert thionoethers compared to the metal hydride reduction of sulfonates. Some generalities can be observed; thus, almost any benzylic oxygenation can be removed by hydrogenation over palladium or platinum given sufficiently forcing conditions. Meanwhile, Gevorgyan's recent discovery (and minor adaptation by others) of the reduction chemistry of silanes in the presence of catalytic amounts of *tris*(pentafluoro)borane—which offers the conversion of many aldehydes, carboxylic acids, acid chlorides, carboxylic esters, alcohols, and ethers to the alkane oxidation state—begins to threaten the validity of the opening sentence of this paragraph!

1.01.2.2 Reduction of C—OX Bonds

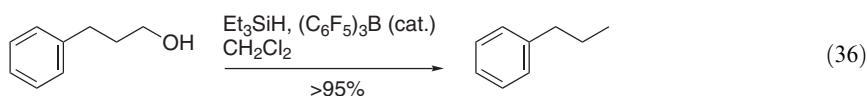
1.01.2.2.1 Reduction of C—OH bonds

The direct reduction of an alcohol to the corresponding alkane remains relatively uncommon—typically the alcohol is first converted to a more labile group. The exception to this is the reduction of benzylic alcohols which—depending to some extent on how electron rich the arene is—have been reduced by a wide range of reagents and catalysts including sodium cyanoborohydride/zinc iodide <1995TL3299>, lithium aluminum hydride <1998TL8125>, samarium iodide <1999TL8823>, triethylsilane/trifluoroacetic acid <2001TL7333>, and hydrogenation over palladium oxide <1997SC2087> (Scheme 11).



Scheme 11

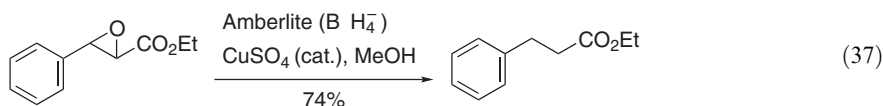
Gevorgyan and co-workers <2000JOC6179> have reported that the use of triethylsilane in the presence of a catalytic amount of *tris*(pentafluorophenyl)borane reduces primary alcohols in high yield—benzhydryl and trityl systems are also converted (Equation (36)). While this methodology has yet to be widely adopted and the chemoselectivity of the process has yet to be fully delineated, there does seem to be considerable potential here.



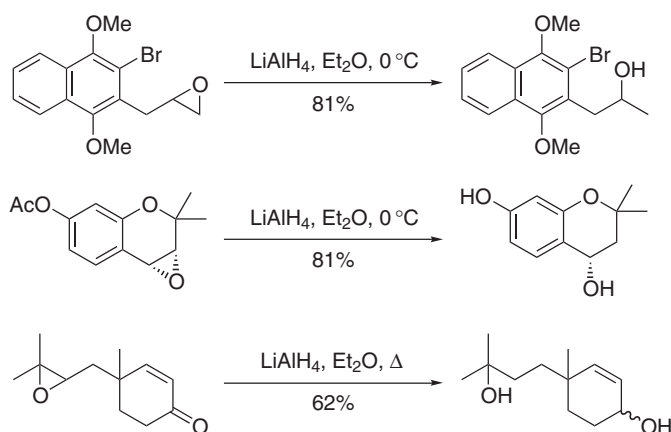
1.01.2.2.2 Reduction of C—O—C bonds

(i) Reduction of oxiranes

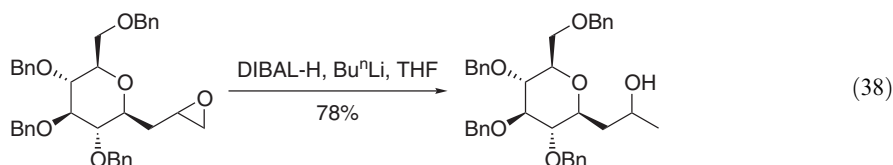
The complete deoxygenation of benzylic oxiranes using polymer-supported borohydride in the presence of copper sulfate has been reported [\[1997BCJ1101\]](#) (Equation (37)). It is interesting to note that nonbenzylic epoxides are essentially unreactive under the same conditions, perhaps suggesting a deceptively complex mechanism.

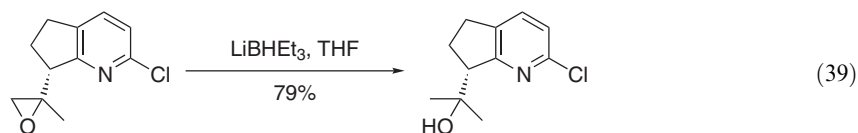


The reagent of choice for the reduction of oxiranes at the less sterically hindered position remains lithium aluminum hydride, which offers good regioselectivity and high yields in the reduction of terminal [\[2002T183\]](#), 2,3-disubstituted systems [\[2001TL4001, 2002JOC2435\]](#) (at least in examples where there is a reasonable steric difference in the substituents [\[1998EJO1675\]](#)) and 2,2,3-trisubstituted systems [\[1999JOC8965\]](#) (Scheme 12). This holds true even when the more hindered position is benzylic [\[1997T6337, 2002JOC2435\]](#), allylic [\[1996TA1683\]](#), or propargylic [\[2002JOC2435\]](#). Where chemoselectivity is an issue, reagents such as DIBAL-H [\[1998JA10326\]](#) (Equation (38)) and lithium triethylborohydride [\[1996T3905\]](#) (Equation (39)) have a widely demonstrated utility, while sodium borohydride [\[2001CC1040\]](#) and hydrogenation over ethylenediamine-doped palladium on carbon [\[1999CC1041\]](#) have also been used with success.

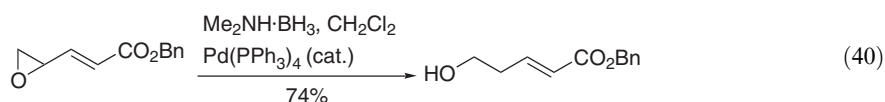


Scheme 12

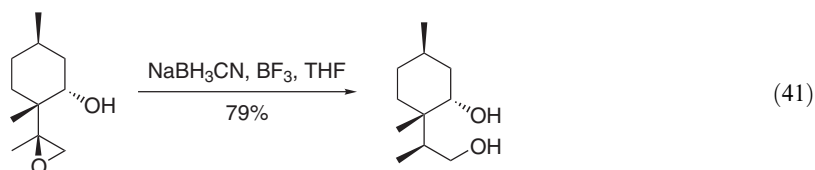




Oxiranes bearing aryl or vinyl substituents can be reduced at the benzylic positions <2001BMCL2597, 2002JA14544> and allylic positions <1998CL109, 2000TL3335> (Equation (40)), respectively, by a variety of reducing agents (hydrogen, formate, borane *inter alia*) under palladium(0) catalysis, regardless of steric influences. DIBAL-H has also been utilized for the reduction of an aryl oxirane at the benzylic position <1998JOC6914>.

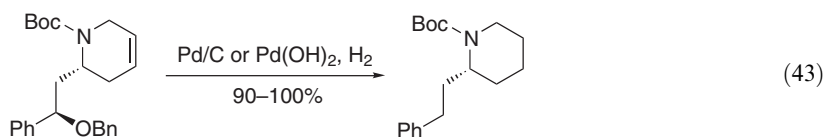
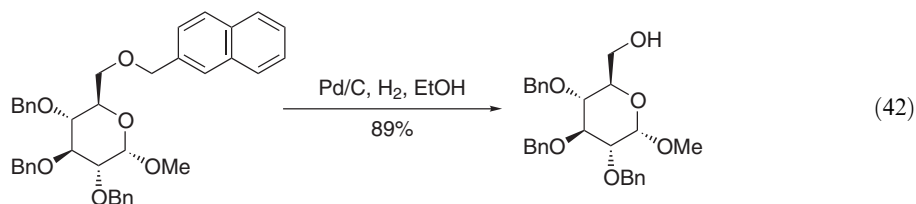


Steric factors can also be subverted when an alcohol functionality is close to the oxirane (typically in a glycidol-like system). Here reduction is then directed to the proximal oxirane carbon <2001JCS(P1)2356, 2001TL9065, 2002SL239> (Equation (41)).

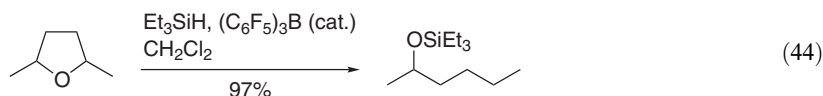


(ii) Reduction of other ethers

Hydrogenation over palladium remains the method of choice for the reduction of benzylic ethers. While the reduction of simple benzyl ethers of complex molecules to give toluene (and a complex alcohol) is not considered in detail, it is worth noting that Spencer and co-workers <1998JOC4172> have reported that 2-methylnaphthyl ethers can be reduced in the presence of benzyl ethers, allowing easy differentiation of these otherwise relatively inert protecting groups (Equation (42)). Examples where complexity is retained in the reduced aryl alkane continue to appear <1995JOC1727, 2000SL1461> (Equation (43)). Electron-rich benzylic ethers have also been reduced by sodium in liquid ammonia <2000JHC751> and sodium cyanoborohydride/chlorotrimethylsilane <1998TL7059>, while aryloxetanes have been reduced with lithium aluminum hydride <1996TL4363>. Among other ethers the recent report that prenyl ethers are reductively cleaved by zirconium chloride/sodium borohydride in the presence of a range of other similar systems (including benzyl ethers and prenyl esters) merits further study <2003TL2525>, while examples of the reduction of α -alkoxyketones by samarium iodide continue to be reported <1995JOC1110, 2000T351>.



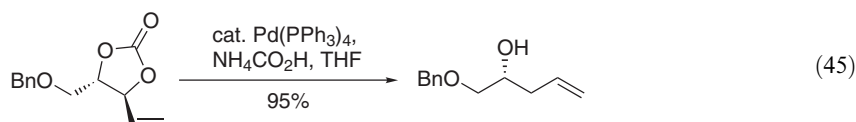
The use of triethylsilane in the presence of catalytic amounts of tri(pentafluorophenyl)borane shows promise in the reduction of alkyl ethers <2000JOC6179>. A wide range of primary and secondary ethers are reduced, the only caveat is that a number of other functional groups (e.g., aldehydes and primary alcohols) are also reduced under these conditions (Equation (44)).



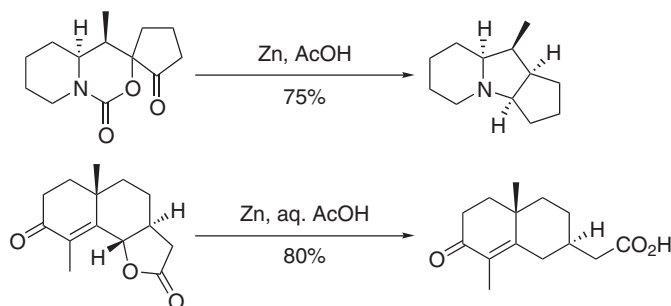
(iii) *Reduction of oxycarbonyls*

As was the case with benzylic ethers, the bulk of the examples in the literature of reductions of benzylic esters involve hydrogenation over palladium(0) and give trivial products such as toluene (and a more complex carboxylic acid) <1998JOC2469, 1999EJO3105> (Equations (15) and (16)). Again there are examples where more complex arylalkanes are generated by this type of methodology <2001T4817>, but these are relatively rare.

The situation is broadly similar with allylic systems where, at least from the perspective of this chapter, the reaction product is propene—together with a more complex carboxylic acid. Again there are examples of more complex reduced products where a series of selective reductions of allylic carbonates merits attention <1995SC203> (Equation (45)). Similar reductions via allyl-titanium species have also been advocated <1998TL7513>.



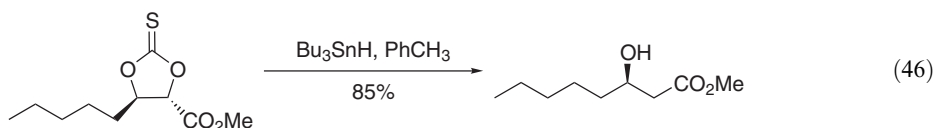
Zinc in acetic acid effects a clean reductive cleavage of α -oxycarbonyl ketones <1995TL2971> (and γ -oxycarbonyl enoates <1995TL8469>). Occasionally further reduction chemistry is then seen under these conditions—in the cited example, after decarboxylation of the carboxyamine, an intramolecular reductive amination takes place (Scheme 13).



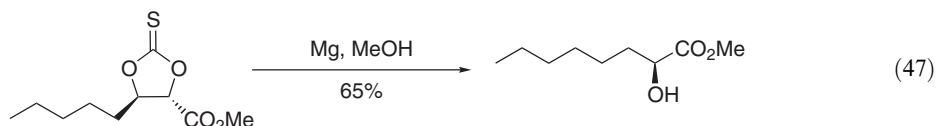
Scheme 13

(iv) *Reduction of thionoethers*

The net reduction of alcohols by first converting them to a thionoether derivative (typically a thiocarbonate or xanthate) then utilizing radical reduction methods remains an important method. The selectivity that can be afforded by these techniques is illustrated by the regioselective reduction of a cyclic thiocarbonate <1997SC3887> (Equation (46)). Interestingly, the avoidance of the use of stoichiometric amounts of the ubiquitous tributyltin hydride seems to have received more attention here than in the case of haloalkanes. Examples include polymethyl hydrosilane <1997JA6949> or trimethoxysilane <2000TL3377> in the presence of catalytic amounts of tributyltin hydride, phosphinic silane <2000TL247>, dibutylphosphine oxide <1998SL39>, and diphenylphosphine oxide <2000S1917>.



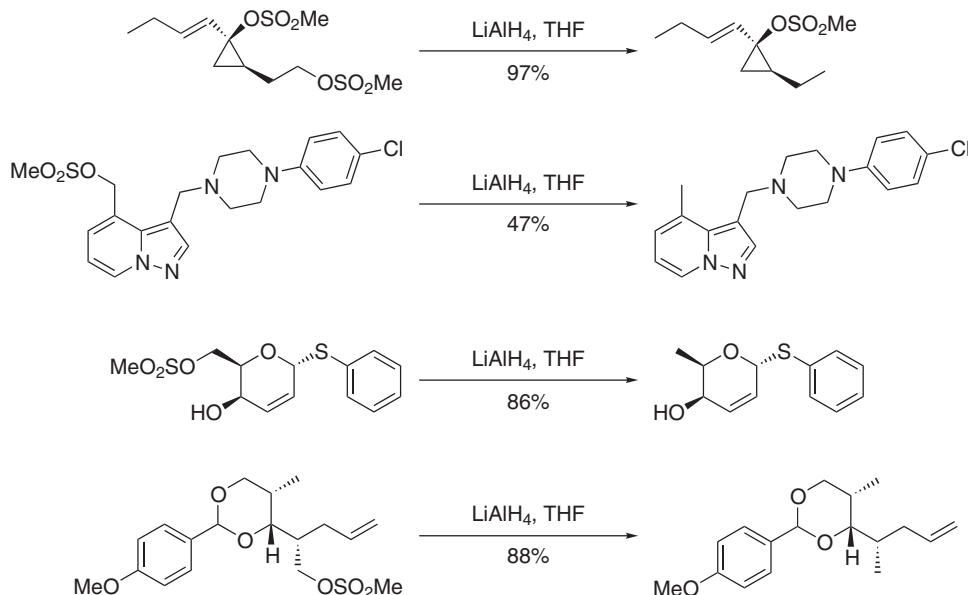
Cyclic thiocarbonates can also be reduced using magnesium in methanol—this has the advantage of showing opposite regioselectivity to the radical method above <1999SC2875> (Equation (47)).



1.01.2.2.3 Reduction of C—O—heteroatom bonds

The strategy of converting alcohols (particularly primary systems) to sulfonates prior to reduction offers useful complementarity to the thionoether methodology above as orthogonal reducing chemistry is employed. The most frequently employed reagents for sulfonate reduction are lithium aluminum hydride followed by lithium triethyl borohydride <2001JOC4870, 2002JOC5124, 2002TA339>, although sodium borohydride <2002BMC2583> and low-valent metal methods are occasionally seen <1998TL6341, 1999T14479, 2000JCS(P1)1919>.

Primary sulfonates are sufficiently reactive that rather good chemoselectivity is observed even when reducing these systems with lithium aluminum hydride. Thus, primary sulfonates can be reduced selectively in the presence of secondary <2002BMCL715> and tertiary <2002EJO2160> sulfonates as well as a range of other potentially sensitive functional groups <2002BMCL633, 2001AG(E)1128, 2002AG(E)1404> (Scheme 14).



Scheme 14

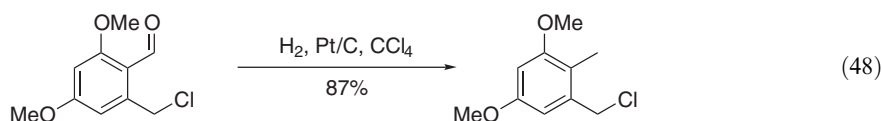
There are occasional reports of the reduction of other C—O—heteroatom systems; thus, a wide range of phosphoramidites have been reduced by lithium naphthalenide <1998TL367> while the combination of chlorotrimethylsilane and sodium iodide in acetonitrile has been utilized to reduce some benzylic silylethers <2000SC2873>.

1.01.2.3 Reduction of C=O Bonds to CH₂

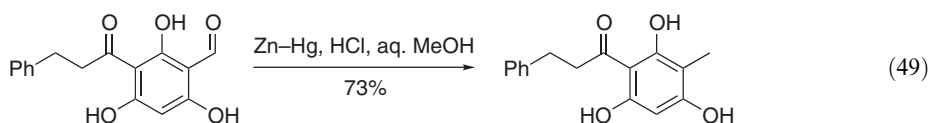
1.01.2.3.1 Reduction of aldehydes

While the Wolff–Kishner procedure still sees some use for the reduction of aldehydes <2002JOC4821> and has been examined in fluorosolvents <2002T4071>, other methods have tended to predominate of late. The caveat here is that the bulk of these syntheses reported in the review period generally involves electron-rich benzaldehydes which are more prone to reduction by these alternatives.

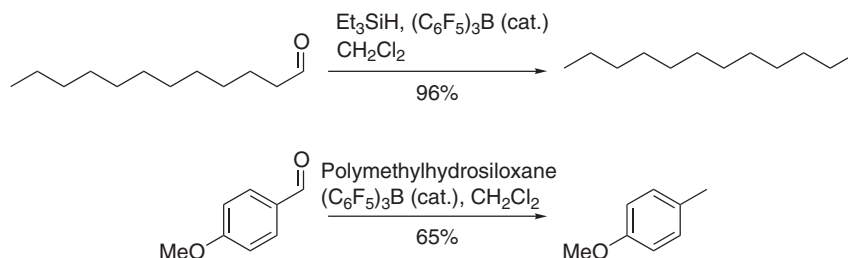
Hydrogenation over palladium remains a popular approach to the reduction of benzaldehydes <1996JMC46, 1997JCS(P1)1421>. The reduction of a benzaldehyde to the corresponding methyl group in the presence of a benzylic chloride illustrates the advantages that can be obtained using platinum catalysis <1995JOC5717> (Equation (48)).



Low-valent metal methods akin to the Clemmensen procedure are also useful for the reduction of electron-rich benzaldehydes and both zinc <1996JMC4181> and Raney nickel <1998JCS(P1)2939> have been utilized. The report of zinc-amalgam-mediated reduction of an aldehyde in the presence of a ketone is notable <1995P491> (Equation (49)).



The combination of a silane and either a protic acid (such as trifluoroacetic acid <2001JA11381>) or a Lewis acid shows considerable promise in this area as, in particular when *tris*(pentafluorophenyl)borane is employed as catalyst, a wide range of aldehydes, including aliphatic systems can be reduced. Initial work using triethylsilane reduced aliphatic systems but was found to arrest at the silyl ether oxidation state with benzaldehydes <2001JOC1672>. However, the recent modification of this procedure using polymethyl hydrosiloxane as the reducing agent extended the scope to include aromatic systems <2002JOC9080> (Scheme 15).

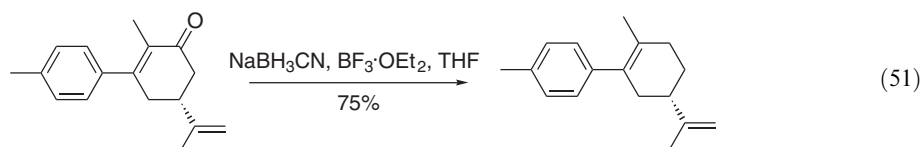
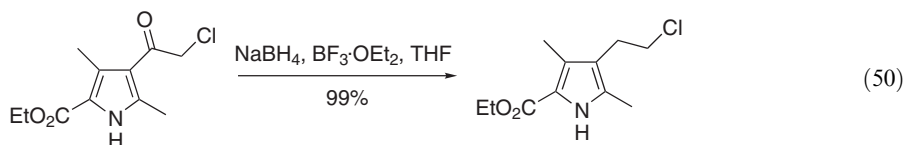


Scheme 15

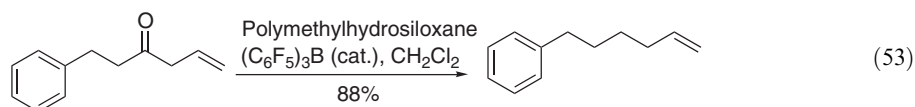
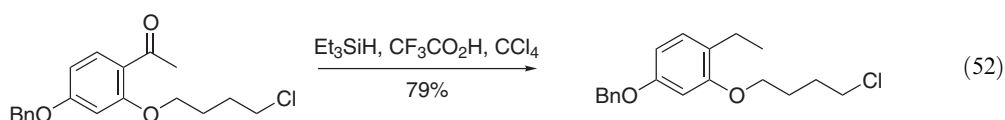
1.01.2.3.2 Reduction of ketones

In a parallel with aldehydes, the more traditional reductions such as the Wolf-Kischner <1999T7441, 2001EJO1663, 2002BMCL533> and Clemmensen procedures <1995T12923> seem to be seeing less use than emerging methods, despite the high yields that can also be obtained from these methodologies. Similarly, while the reduction of benzylic ketones by hydrogenation over palladium is often an efficient procedure <1996JMC3951, 2001JMC3424>, it again sees limited use. An isolated report of the reduction of aliphatic ketones by hydrogenation over platinum on Montmorillonite K-10 merits both attention here and further study <2000SL631>.

The most popular reagent for this transformation of late is the combination of a formal hydride source—typically a borohydride or silane—with an acid. Among the borohydride-mediated reductions the combination of either sodium borohydride <2000OPP481> (Equation (50)) or sodium cyanoborohydride <1995TL2347> (Equation (51)) with boron trifluoride appears particularly effective although both hydrochloric acid <1998TL7059> and chlorotrimethylsilane <2001SL1391> have also been used with success.

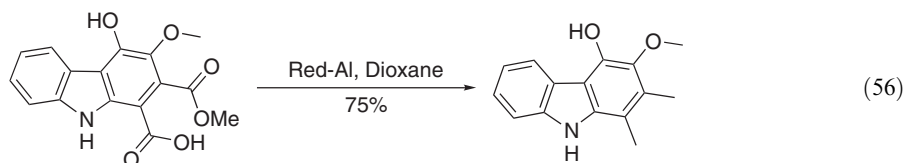
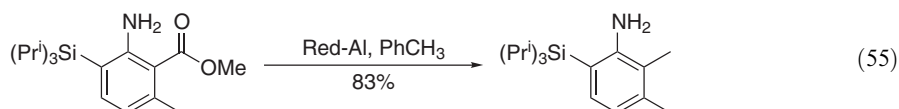
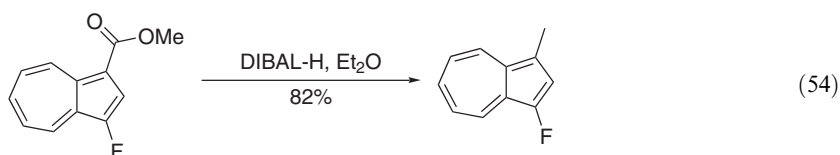


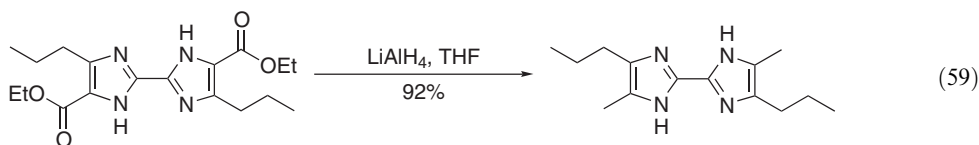
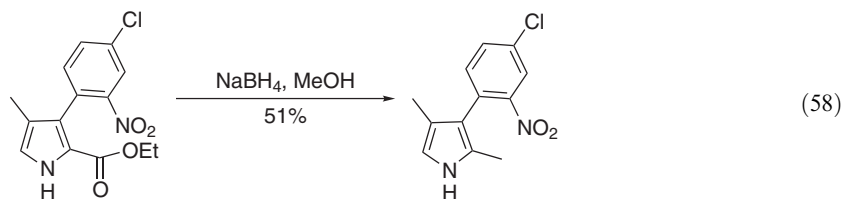
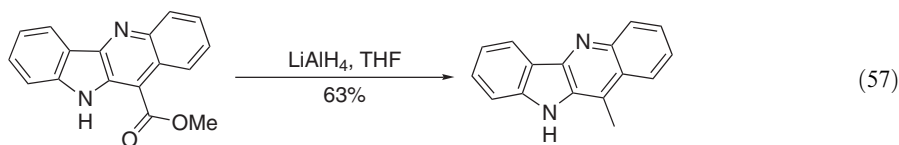
The use of triethyl silane in combination with trifluoroacetic acid provides efficient reductions of electron-rich aryl ketones [<1995JMC4411, 2000BCJ747>](#) (Equation (52)). Lewis acids (e.g., titanium tetrachloride and trimethylsilyltrifluorosulfonate [<2001T5353>](#)) are also employed in tandem with silanes where the use of only catalytic amounts of tris(pentafluoro)borane together with polymethyl hydrosiloxane reduces a wide range of aromatic and aliphatic ketones in high yields [<2002JOC9080>](#) (Equation (53)).



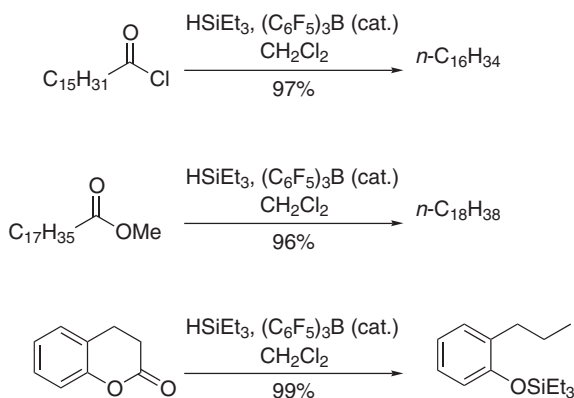
1.01.2.4 Reduction of C(=O)X to CH₃

A number of electron-rich arylcarboxylic esters such as azulenes [<1996BCJ1645>](#) (Equation (54)), anilines [<2002EJO2094>](#) (Equation (55)), (aza)carbazoles [<1996T3029, 1999JNP976>](#) (Equations (56)–(57)), pyrroles [<1997JHC13>](#) (Equation (58)), and imidazoles [<2001CEJ721>](#) (Equation (59)) have been reduced to the corresponding aryl methyl system by metal hydride reagents. Typically—although not exclusively—aluminum hydrides are employed and the reactions are often high yielding.





Gevorgyan and co-workers report a remarkable new method where, apparently for the first time, aliphatic acid chlorides, carboxylic acids, and esters are fully reduced to the corresponding alkane. The reduction is effected by triethylsilane in the presence of only catalytic amounts of tris(pentafluorophenyl)borane [<2001JOC1672>](#) (Scheme 16). Although the reduction of arylcarboxylic ester substrates stops at the aryl methyl silyl ether, the methodology is clearly a breakthrough for the reduction of the aliphatic systems.

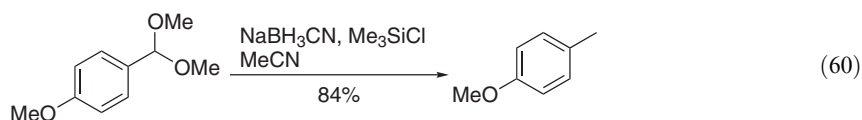


Scheme 16

No examples of the reduction of thioesters, acid bromides, or acid iodides were reported since the publication of COFGT (1995).

1.01.2.5 Reduction of C(OX)_n Systems

Examples of the reduction of acetals and orthoesters to the corresponding alkanes have historically been somewhat rare, perhaps due to the many methods for the reduction of aldehydes and ketones in the former case and indeed there has only been one example in this class of reaction in the review period i.e., since the publication of COFGT (1995). Thus, treatment of the dimethyl acetal of *p*-anisaldehyde with sodium cyanoborohydride and chlorotrimethyl silane gives the corresponding toluene in good yield [<1998TL7059>](#) (Equation (60)). The reduction of less electron-rich systems halted at the benzyl methyl ether.



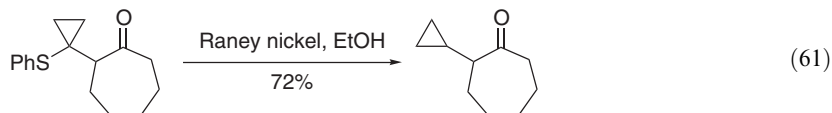
1.01.3 REDUCTION OF C—SULFUR, C—SELENIUM, AND C—TELLURIUM BONDS TO CH

1.01.3.1 General Methods

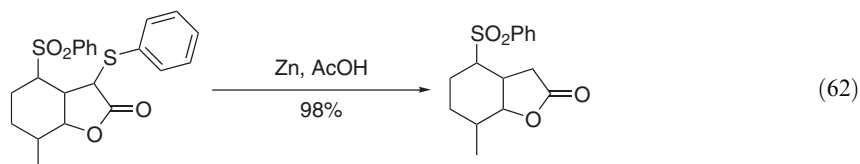
Sulfur-containing compounds are almost universally reduced by Raney nickel and this chemistry is sufficiently selective that it is unlikely ever to be threatened as the method of choice. Although this reagent can also be used to reduce organoselenium compounds, there is a dramatic shift to the use of tin hydride radical chemistry for these transformations, a trend which carries into the reduction of tellurides.

1.01.3.2 Reduction of C—SX Bonds

Raney nickel remains the stock reagent for the reduction of sulfides <1997TL6759> (Equation (61)). Chemoselectivity can be an issue here; for example, benzylic chloroalkanes are concomitantly reduced <1998TL147> (Equation (22)), but there are many examples such as benzylic alcohols and ethers where functional groups that might prove reactive under forcing conditions are unaffected <1995TL6755, 1996JA13103, 1997T12883>. Raney nickel reduction of sulfides has also been mooted in the cleavage of alkyl groups from arylthiol-modified polyethylene glycol supports as an alternative to other “traceless” cleavage methodologies <1997T6645>.

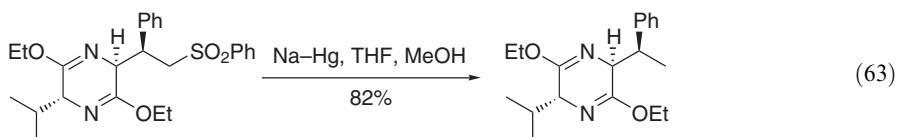


Other reduction methods see occasional use: radical reduction has been utilized to cleave benzylic sulfides <1996T13867>, while low-valent metal methods can also be very effective <1995JA5757, 1995TL7243> (Equation (62)).



Sulfoxides are also typically reduced by Raney nickel <2000TA3079>, although it has been suggested that nickel boride is superior for this transformation <2000SL1725>.

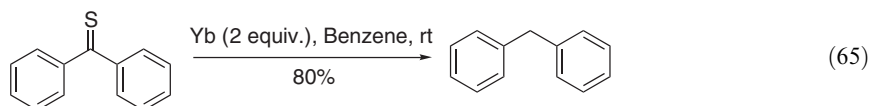
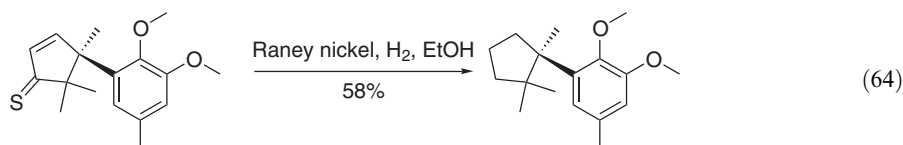
Sulfones are commonly reduced by low-valent metal methods, although a tin hydride radical procedure met with success in the reduction of an α -sulfonyl ketone <1995SL973>. While both magnesium <1995TL5691> and samarium <2000SC2559> in the presence of a catalytic amount of mercuric chloride have been used with success, the classical choice of sodium amalgam is generally preferred <1995JOC4978> (Equation (63)) and has even been applied as a method of cleaving compounds from polymeric supports <1997TL977>.



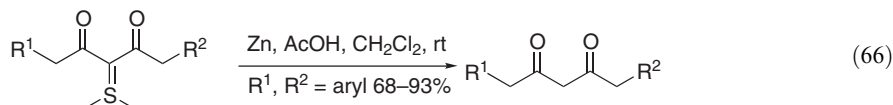
S-Alkyl xanthates, in common with the *O*-alkyl thionoethers above, are readily reduced by radical means. While tin hydride chemistry is efficient for this transformation <2000CC535, 2001CC1304>, dilauroyl peroxide has also been used with success <1996TL5877> (see Chapter 1.05).

1.01.3.3 Reduction of C=S to CH₂

In contrast to the received wisdom that Raney nickel is of little utility in the reduction of thioketones <1995COFGT(1)1>, the complete reduction of an α,β -unsaturated system to the corresponding alkane in reasonable yield has been reported using this reagent <1999JA2762> (Equation (64)). Ytterbium metal has also been mooted for thioketone reductions. Although a range of reactions is possible depending on the solvent, temperature, and ratio of metal to substrate, the authors identified conditions which were very selective for the reduction of diaryl thioketones <1996JOC372> (Equation (65)).

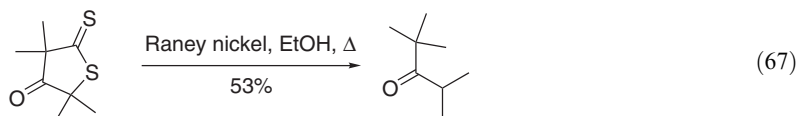


The reduction of dimethylsulfonium ylides to the corresponding alkanes by zinc in acetic acid in often excellent yields has been described <1996JOC8604> (Equation (66)). The conditions are sufficiently mild that a nascent 1,3-diketone functionality is not reduced.



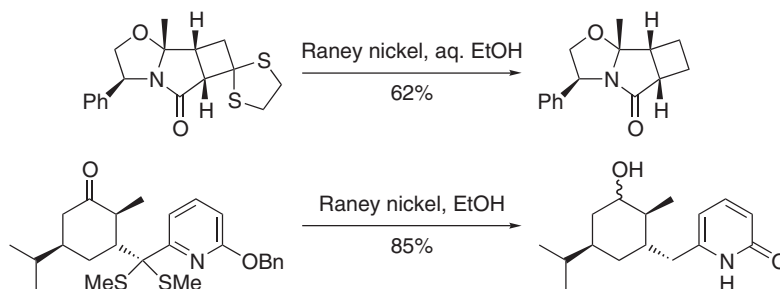
1.01.3.4 Reduction of C(=S)X to CH₃

Huisgen and co-workers <1997LA1517> have reported the successful reduction of a thiolactone using Raney nickel (Equation (67)). Although only a modest yield was reported, this must at least, in part, be due to the volatile product being isolated by distillation on a very small scale, so the method should not be dismissed for other synthetic applications.



1.01.3.5 Reduction of C(SX)_n Systems

As was observed in the case of sulfides, Raney nickel is a largely universal choice for the reduction of thioacetals to alkanes, although nickel boride <1996TA2181> and sodium in *i*-propanol <1998TL9609> have been utilized for this application. Raney nickel has sufficient versatility that it can be employed to perform selective reductions of relatively sensitive molecules <1995JOC4359> or, if desired, can be used under more forcing conditions to reduce other groups at the same time <1995T1337> (Scheme 17).

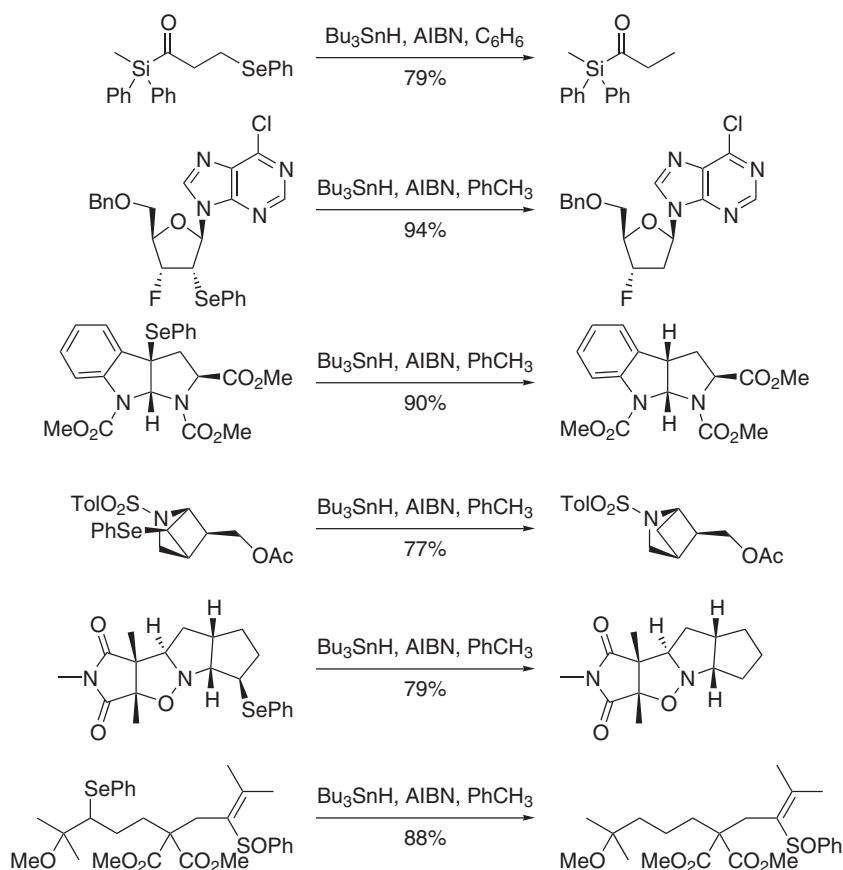


Scheme 17

1.01.3.6 Reduction of C—Se Systems

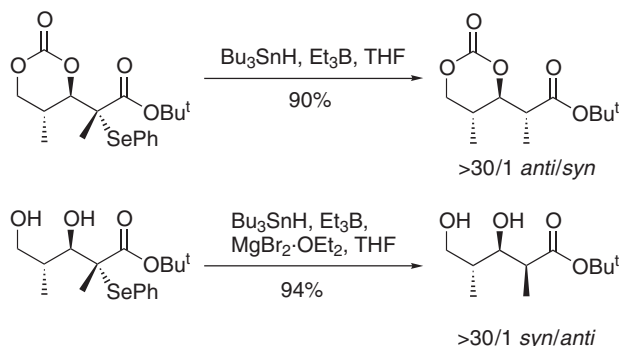
The much greater propensity of the carbon—selenium bond, relative to the carbon—sulfur bond, to undergo homolytic cleavage results in a dramatic, though not absolute, shift away from the use of Raney nickel to radical reduction chemistry.

As was seen above, most of the radical reductions are performed with tributyltin hydride and triphenyltin hydride—while alternatives such as tris(trimethylsilyl)silane [<1995TL6781>](#), tetraphenyldisilane [<1999JCS\(P1\)2891>](#), silyl-1,4-hexadienes [<2000AG\(E\)3080>](#), and even acid soluble tin hydrides [<1995JOC2607>](#) have all been advocated, they see little general use. The case for the classical tin hydride approach is again easily made—selectivity over a wide range of other functionality is excellent and the yields of these processes are frequently high [<1997JOC9089, 1999JOC1375, 1999JOC7218, 2001JOC4187, 2001T7035, 2002EJO1776>](#) (Scheme 18).



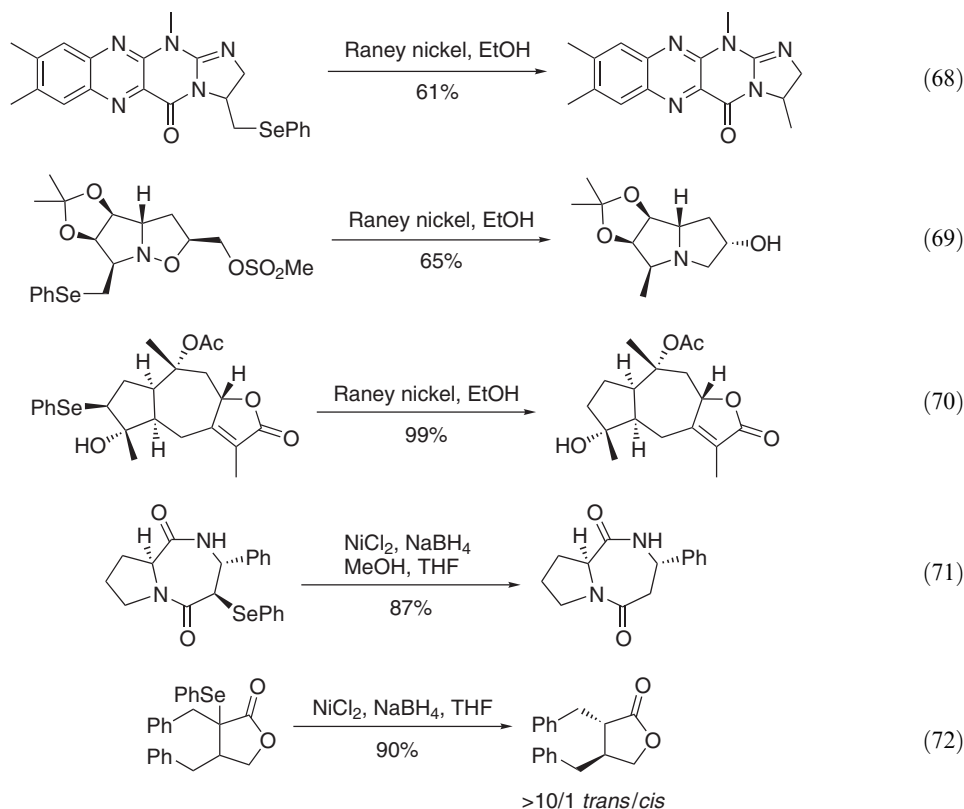
Scheme 18

These reductions, at least in the case of α -selenoesters, can be performed with high diastereoselectivity. It is striking that subtle variation in nearby functionality and reaction additives give opposite selectivity <2001JOC5427, 2002OL1019> (Scheme 19).



Scheme 19

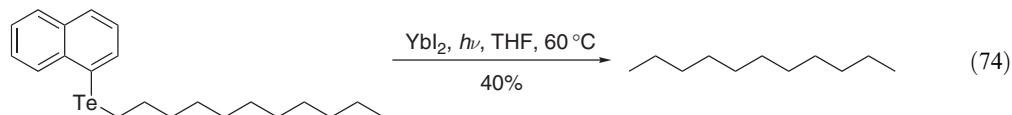
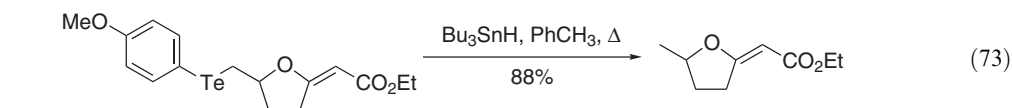
The bulk of the remaining reductions of selenides is split relatively evenly between the use of Raney nickel <1996JHC169, 1997SL123, 2000JOC6703> (Equations (68)–(70)) and of the combination of nickel chloride and sodium borohydride <1998JCS(P1)969, 1999T12387> (Equations (71)–(72)). The yields for these reactions are typically comparable to the radical processes above with potential over reduction either not being an issue or being advantageously exploited (Equation (69)).



1.01.3.7 Reduction of C–Te Systems

New examples of telluride reductions are unsurprisingly somewhat sparse. Tin-hydride-mediated radical reduction <1999SL567> seems to remain the method of choice (Equation (73)), although the use of ytterbium diiodide in combination with near-UV light has also been advocated

<1997TL9017> (Equation (74))—it remains to be seen how popular the latter reagent system will become for this application.



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1.02

One or More C—H Bond(s) Formed by Substitution: Reduction of Carbon—Nitrogen, —Phosphorus, —Arsenic, —Antimony, —Bismuth, —Carbon, —Boron, and —Metal Bonds

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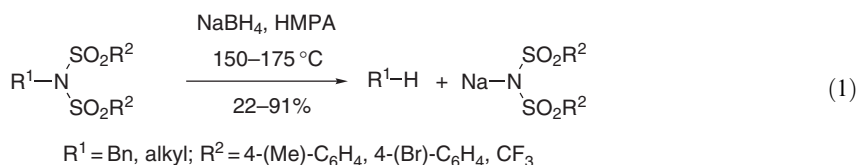
1.02.1 REDUCTION OF C—N BONDS TO C—H BONDS

1.02.1.1 Reduction of C—N Single Bonds

Reductive deaminations have been the subject of many reviews [<B-1982MI931, B-1956MI001, 1995COFGT\(1\)27>](#). The following sections are categorized according to the type of nitrogen moiety lost during deamination.

1.02.1.1.1 Reductive cleavage of sulfonimides

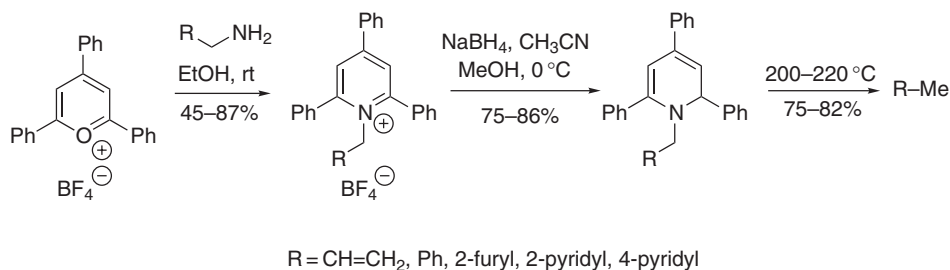
Sodium borohydride in polar aprotic solvents (HMPA, DMSO) is used for the reductive displacement of disulfonimides ([Equation \(1\)](#)) [<1978JOC2259>](#). The incorporation of two electron-withdrawing sulfonyl groups on nitrogen stabilizes the sulfonimide anion and allows the reaction to proceed efficiently. The synthesis of disulfonimides from primary amines [<1974JOC3525, 1998TL1799>](#) is easy but the preparation of sulfonimides from hindered amines remains problematic, restricting the scope of this deamination.



1.02.1.1.2 Deamination using pyridinium salts as intermediates

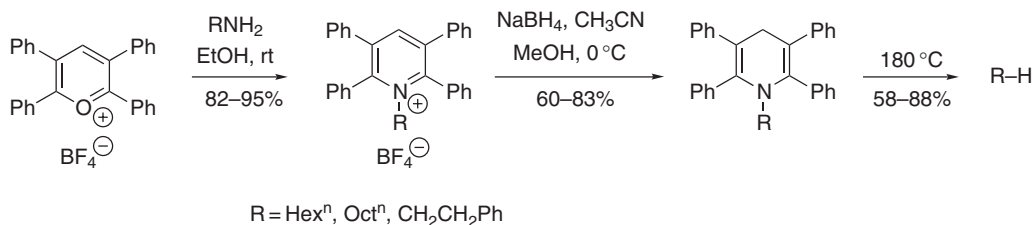
This method of reduction has been thoroughly investigated <1980T679>. Highly substituted pyrylium salts are used for a two-step conversion of the amino group into numerous other functionalities. The first step involves the reaction between the pyrylium salt and the amine to produce an *N*-substituted pyridinium salt. This pyridinium salt is then reacted with a nucleophile and, in the case of reduction, the nucleophile is a hydride donor. Depending on the amine the substituted pyrylium salt required to perform the deamination will be different.

With allylic, benzylic, or heteroarylmethyl amines <1979JCS(P1)442>, *N*-substituted 2,4,6-triphenylpyridinium salts are synthesized. They are reduced with sodium borohydride in good yields to the 1,2-dihydro derivatives, and the corresponding dihydropyridines decompose around 200 °C to give 2,4,6-triphenylpyridines and hydrocarbons in good yields (Scheme 1).



Scheme 1

2,3,5,6-Tetraphenylpyrylium cations are transformed to the corresponding pyridinium salts using nonactivated primary alkylamines <1980JCS(P1)2554>. Steric hindrance directs the attack of sodium borohydride leading to 1,4-dihydropyridines, which decompose at 180 °C to produce the corresponding alkane (Scheme 2). NMR studies have suggested that a radical mechanism may be involved in this type of reaction.



Scheme 2

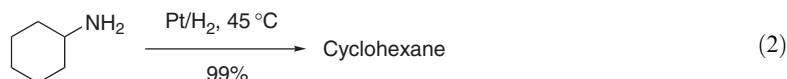
The method described above can be applied to anilines, but the temperature required for decomposition is higher (300 °C) and the reaction suffers from low reproducibility <1980T679>.

1.02.1.1.3 Direct reduction of amines or ammonium salts

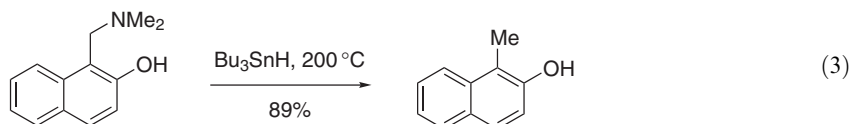
Methods for the direct reduction of amines or ammonium salts exist. Such transformations involving catalytic hydrogenation, metal reductions, and various hydrides are well known and have been extensively reviewed <B-1956MI001, 1966JCE398, B-1985MI005>. In addition, electrolytic reductions have also been reviewed.

Catalytic hydrogenation using palladium on carbon (Pd/C) and formic acid has been reported to reduce allylic amines <1980JOC4926>. Essentially the corresponding alkenes are formed but rearrangement or over-reduction are common side reactions. However, hydrogenolysis using palladium on carbon is a well-known method to reduce Mannich bases derived from benzaldehyde derivatives to the corresponding methyl derivatives <1973S703>. The selective cleavage of benzylic amines to the corresponding hydrocarbons has also been reported using low-valent titanium reagent in modest yields (46–67%) <1996SC1051>.

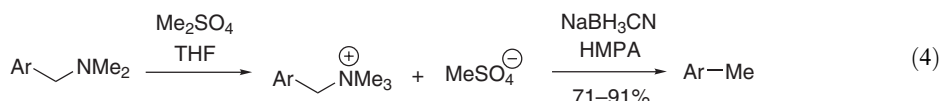
Reduction of a range of aliphatic amines to the corresponding hydrocarbons and ammonia using a platinum catalyst at high temperature has been investigated (Equation (2)) <1984JOC2875>. The reaction system also reduces nitrogen heterocycles to cycloalkanes and ammonia.



Tributyltin hydride was also employed to reduce a series of arylmethyl and heteroarylmethyl amines (Equation (3)) <1988SC1207> but temperatures of 200 °C were required to effect the reactions. The method can also be used to reduce *N*-oxides and amine salts.

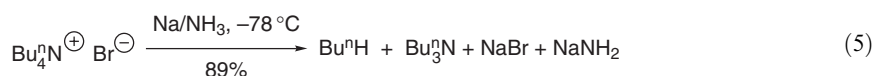


Sodium cyanoborohydride has been successfully used in the high-yield reduction of quaternary ammonium salts (Equation (4)) <1978CC1089>. The reduction tolerates a large range of functionalities (halogen, ester, nitrile, and nitro groups), and the authors claimed this method to be superior to the sodium borohydride–dimethyl sulfoxide system.

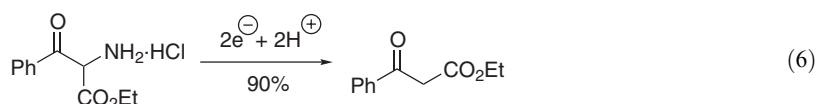


Early methods for reducing amines to the corresponding alkanes commonly required zinc in refluxing acetic acid <1958JA1654>, Raney-nickel hydrogenolysis <1953JA1128>, sodium methoxide at 180 °C <1951JA2718>, and tin chloride <1983SC677>. In these methods harsh conditions are used, and since more selective methods for functional group manipulation have been developed, the tendency to apply these methods has decreased.

Cleavage of tetraalkylammonium halides with sodium in liquid ammonia has been carried out on a large number of substrates and results in hydrocarbons in good yields in almost every case (Equation (5)) <1959JA4850>. This is a mild way of reducing amines, as long as the molecule tolerates the conditions of dissolving metal reductions.



Reduction of α -amino esters to the corresponding β -keto esters has been carried out under electrolytic conditions (Equation (6)) <1973JOC2731>.

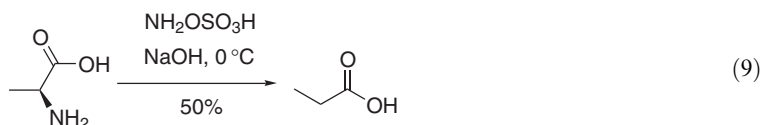
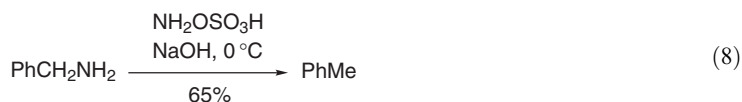


1.02.1.1.4 Deamination using diazenes as intermediates

Amine reductions, which result in the formation of a nitrogen molecule, are in most cases believed to proceed via a diimide intermediate <1963JA1108>. For example, primary amines react with difluoroamine to yield hydrocarbon, albeit in modest yields (Equation (7)). This conversion and its mechanism have been previously reviewed <1963JA97, 1964JA2233>.



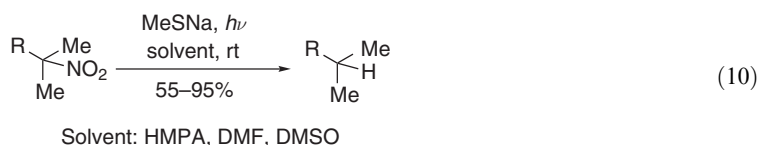
A direct and selective method for the deamination of primary amines with hydroxylamine-*O*-sulfonic acid has been reported (Equations (8) and (9)) but the scope of the reaction is rather limited <1964JA1152, 1978JA341>.



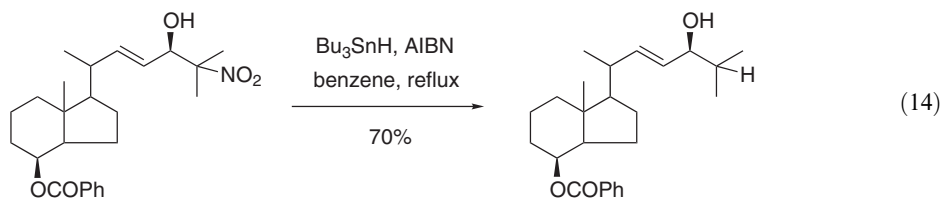
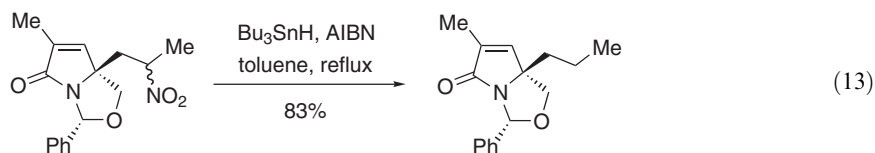
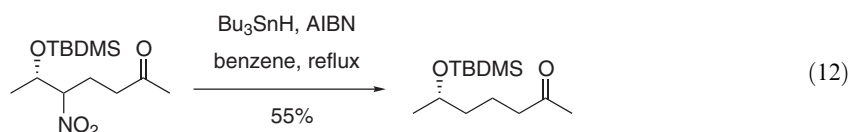
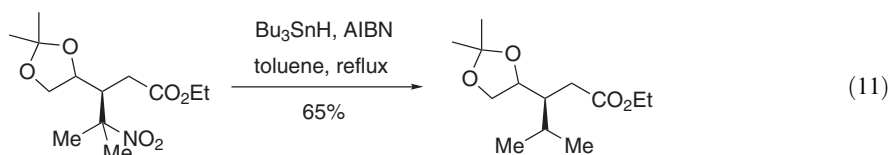
1.02.1.1.5 Reductive cleavage of nitro groups

In the last decades, the nitro group has found wide applications in organic synthesis, and as a consequence it appears that a clean removal of such a useful group is of interest. The synthetic utility of such a transformation has been reviewed [<1986S693>](#).

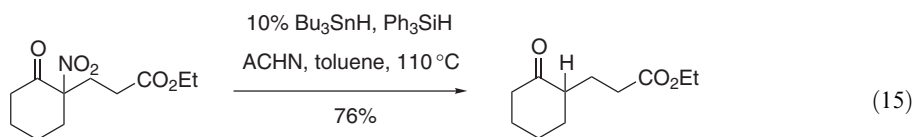
Kornblum, in 1979, reported a general method for the replacement of a nitro group by a hydrogen atom [<1979JA647>](#). A large range of tertiary nitro groups was removed using sodium thiolate in a nonprotic polar solvent upon exposure to fluorescent light (Equation (10)). The solvent of choice is HMPA but can be replaced by DMF or DMSO if nucleophilic attacks of the thiolate compete with the desired process.



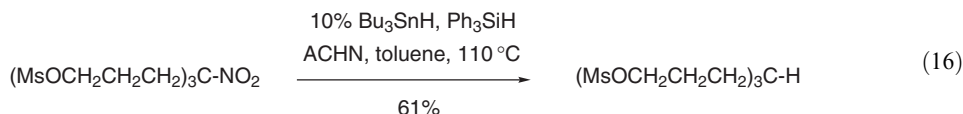
Tributyltin hydride was reported independently by two groups to be an efficient reagent for the reduction of nitro groups [<1981JA1557, 1981TL1705>](#). Countless applications witness the importance of such a transformation. Selected examples are shown in Equations (11)–(14) [<1997JOC4002, 1996T6139, 2000H1011, 1997TA2579>](#).



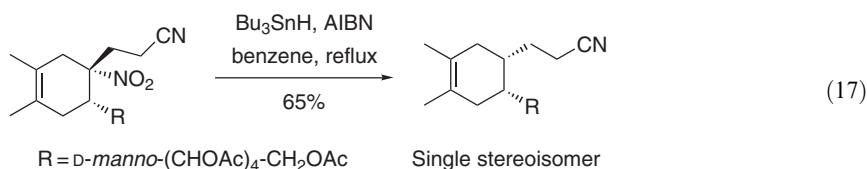
Recently, Fu [<1998JOC5296>](#) reported an improved procedure using a catalytic amount of tributyltin hydride and triphenylsilane as the stoichiometric reducing agent. The reaction is extremely versatile and tolerates a broad range of functionalities as shown in Equations (15) and (16).



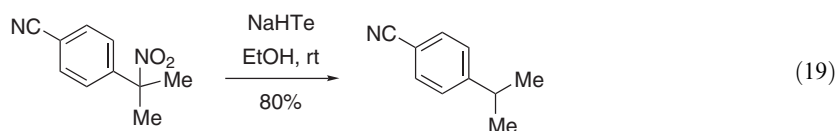
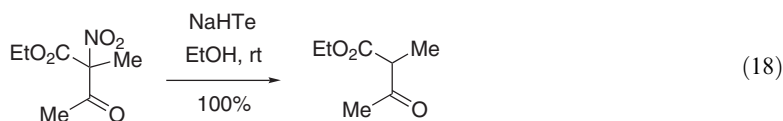
ACHN: 1,1'-azobis(cyclohexanecarbonitrile)



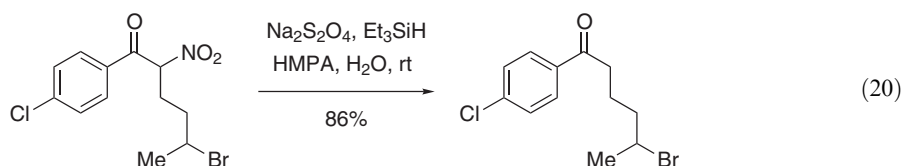
Reduction of the nitro group can be highly stereoselective if the substrate allows an important facial differentiation during the quenching of the intermediate radical (Equation (17)) <2001TA1673, 2003S1419>.



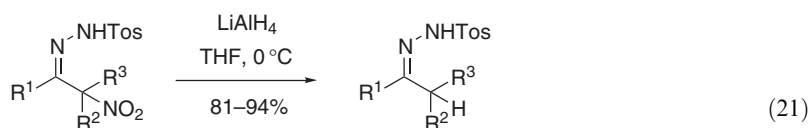
Other hydrides such as sodium hydrogen telluride have been used to remove the tertiary nitro group in high yields under very mild conditions (Equations (18) and (19)) <1985BCJ1067>. The authors claimed that this reaction overcomes drawbacks associated with other methods (high temperature, purification).



A general procedure for the reductive denitration of α -nitro ketones using sodium dithionite and triethylsilane has been reported <1989TL4819> (Equation (20)).

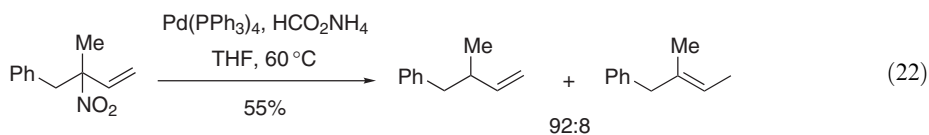


Lithium aluminum hydride (LAH) has also been used as a reductant of the nitro group (Equation (21)) <1983S137>. It is interesting to note that although LAH can reduce tosylhydrazones in refluxing THF (see Section 1.02.1.2.1), this reagent is chemoselective at 0 °C and tosylhydrazones are not reduced at this temperature.

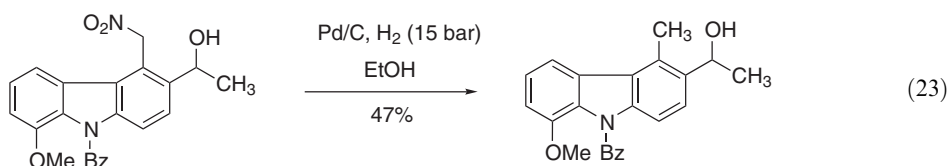


R¹ = alkyl, R² = alkyl, R³ = H, Me

Removal of an allylic nitro group using radical conditions generally leads to the migration of the double bond. However, a palladium-catalyzed hydride transfer has been shown to be highly regioselective as shown in Equation (22) <1986JOC3734>.



An isolated example of selective removal of a benzylic nitro group using hydrogenolysis conditions (Pd/C, H₂) has been reported (Equation (23)) <1996T6373>.

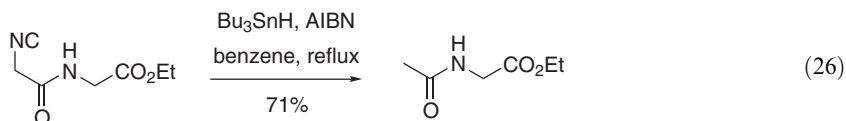
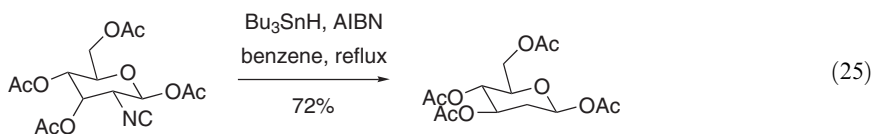
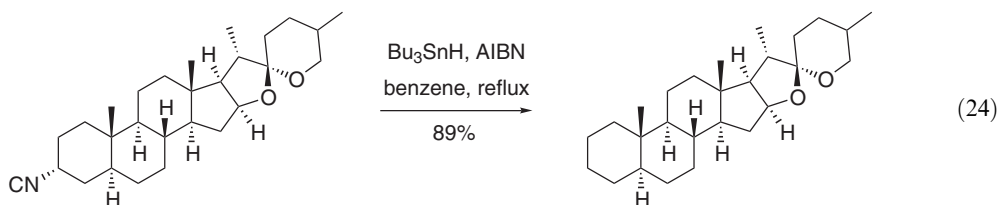


Other methods for the reduction of nitro groups to the corresponding alkanes involve 1-benzyl-1,4-dihydronicotinamide <1983JA4017>, potassium hydroxide in ethylene glycol <1979TL1243>, or triethylsilane with a Lewis acid (SnCl₄ or AlCl₃) <1987TL2277>.

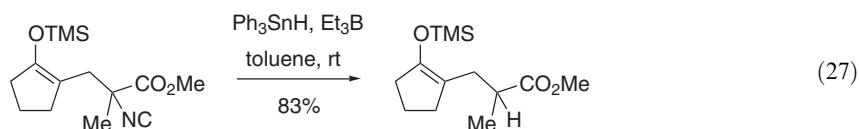
1.02.1.1.6 Reductive cleavage of isonitrile groups

Because isonitriles can behave as an activating group for the selective introduction of electrophilic species, its mild reductive cleavage to a C—H bond has become a challenging area of research in the last decades.

The main procedure uses tributyltin hydride as the reductant. This radical-induced deamination of isonitriles was first reported in 1968 <1968JA4182> and has been thoroughly reviewed <1987S665>. Further developments were achieved by Barton using AIBN as the radical initiator (Equations (24)–(26)) <1979TL2291, 1980S68>.

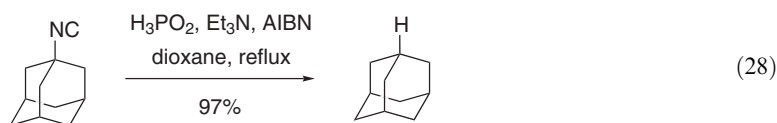


Triethylborane as initiator and triphenyltin hydride as hydride donor have been reported as a good system for such transformations (Equation (27)) <1989TL1257>.

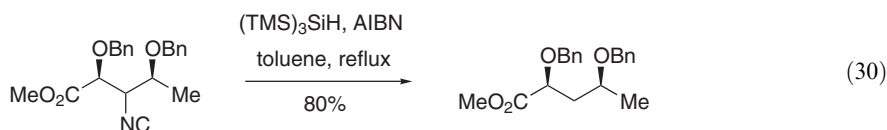
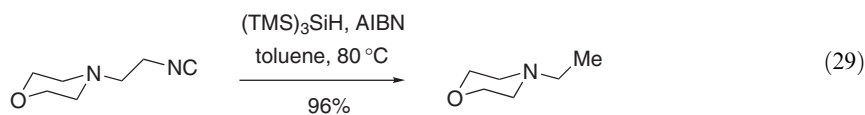


The use of a recyclable polymer-supported tin hydride has been proposed to overcome the toxicity generally associated with tin reagents <1991JOC5971>.

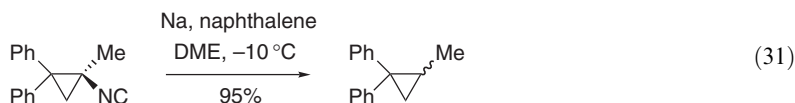
Barton <1993JOC6838> introduced hypophosphorous acid and dimethylphosphite as alternative hydride donors (Equation (28)). This method has been applied in a recent synthesis of sorgolactone <1996TL3491>.



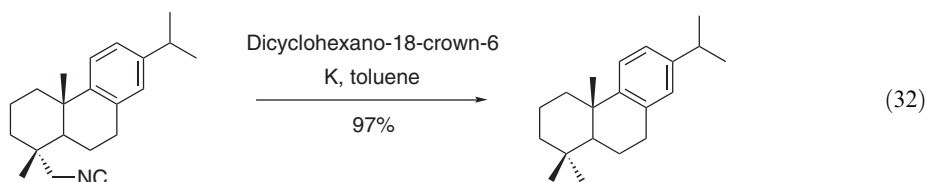
Tris(trimethylsilyl)silane has been used as a more acceptable reducing agent than triorganotin compounds from toxicological and ecological perspectives (Equation (29)) <1991JOC678>. Such a system has been reported to be effective for the deamination of a more elaborate structure (Equation (30)), whereas tributyltin hydride and other hydride donors failed to give good yields <1993JOC1646>.



Another method for the reduction of isonitriles to the corresponding hydrocarbons utilizes a dissolving metal reduction. Several isonitriles have been reduced by sodium or lithium in liquid ammonia <1961CB1157, 1966HCA1145, 1974T1341>. For sensitive substrates prone to rearrangement, a milder procedure using sodium naphthalenide has been reported (Equation (31)) <1978JOC2396>.

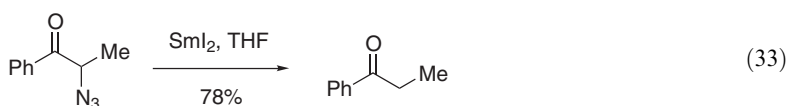


Finally, the use of excess potassium and crown ether in toluene has been used to selectively reduce a wide range of simple alkyl isonitriles in excellent yields (90–96%) (Equation (32)) <1989TL845>.



1.02.1.1.7 Reductive cleavage of azido groups

The reduction of an azide derivative to the corresponding hydrocarbon has been neglected in the literature. Isolated examples have been reported: when 2-azido-1-phenyl-propan-1-one reacted with samarium(II) iodide (Equation (33)), the reduced compound was selectively obtained instead of the desired 2,4-diphenylpyrrole <2002TL1863>.



Some other research suggests that such deazidation of an alkyl azide by stannyl radicals can be feasible <1999JOC7836>. As a primary amine can be readily transformed into an azide, the

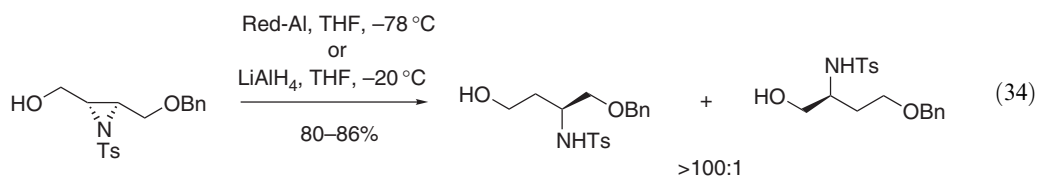
development of a selective method for the reductive cleavage of alkyl azides would become a useful deamination strategy.

1.02.1.1.8 Reductive ring cleavage of aziridines

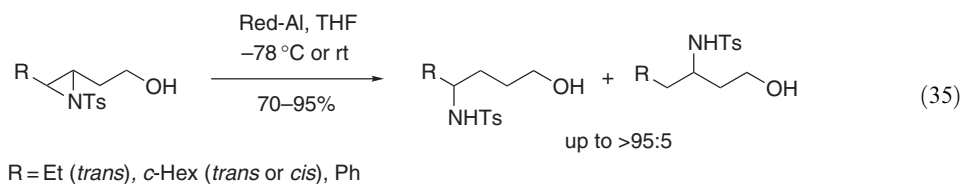
Due to the strained nature of aziridines, ring-opening reactions are a dominant feature of this class of compounds. The regioselective reductive opening of aziridines has been widely investigated since the 1990s using hydride reagents, hydrogenolysis conditions, or single-electron transfer agents.

(i) Use of hydride reagents

Some reports deal with the opening of aziridines with a hydride source such as LAH, diisobutylaluminum hydride, or Red-Al <1987TL1211, 1992T6069, 1994AG(E)599>. The regiocontrol of the reaction relies on the neighboring group assistance of a hydroxyl group (Equation (34)). When hydride reagents such as LAH or Red-Al are used, a complete regioselective ring opening is observed while the use of diisobutylaluminum hydride gave less coherent results and incomplete conversion.

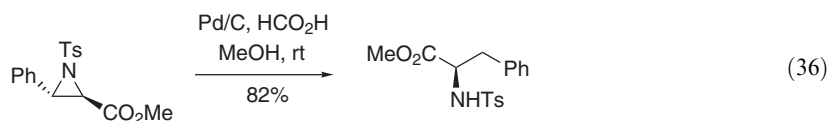


Even aziridines derived from homoallylic alcohols have shown a good regioselectivity during their reductive ring opening (Equation (35)) <1997T16139>. A cyclic six-membered transition state was invoked to explain such selectivity. When R = Ph, the reagent of choice is Red-Al. When LAH is used, the electronic effect of a phenyl group can interfere to afford mainly the undesired 1,3-amino alcohol.

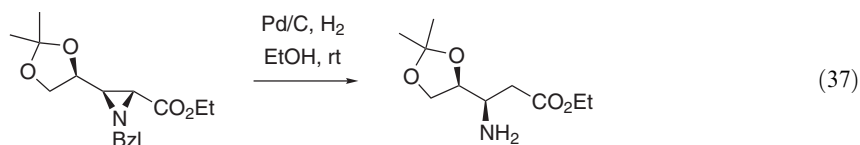


(ii) Use of palladium-mediated hydrogenolysis

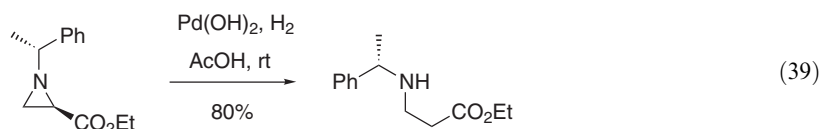
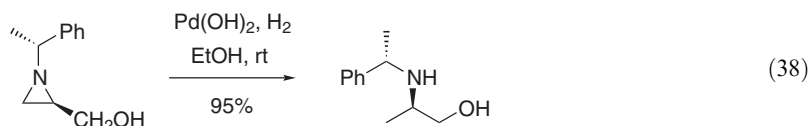
Evans <1993JA5328, 1994JOC3243, 1996TL5473> has reported that the regiospecific reductive ring opening of a tosyl aziridine ester can be achieved by transfer hydrogenation (Equation (36)).



Prolonged hydrogenolysis of aziridino esters yields the corresponding β -amino ester via a selective C(2)—N bond cleavage (Equation (37)) <1994TL7613>.

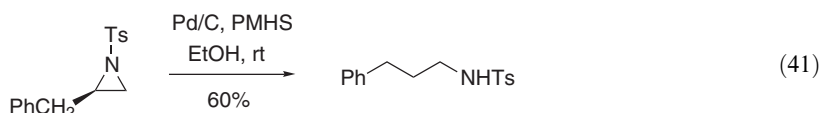
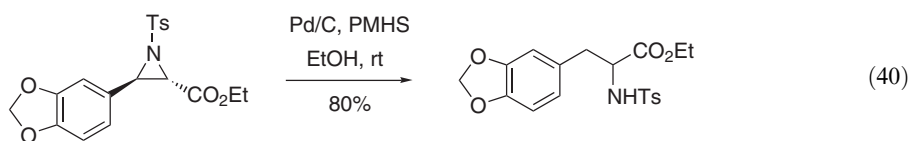


This methodology has been extended with Pearlman's catalyst to the reductive ring opening of an *N*-alkyl chiral aziridino alcohol (Equation (38)) <1995TL8431, 2001T8267>. Interestingly, exclusive C(3)—N bond cleavage occurred leading to the formation of the β -amino alcohol in excellent yield (Equation (39)). The corresponding aziridino esters were converted into the β -amino esters in 80% yield when submitted to hydrogenolysis in acetic acid.

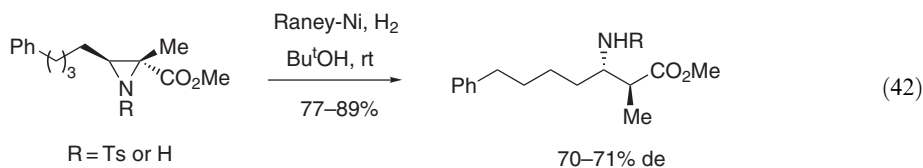


This reaction seems to be sensitive to the nitrogen-protecting group since the authors reported that the cleavage of the C—N bond failed when protecting groups other than methylbenzylamine are present (tosyl, benzyl, or trityl).

The benzylic character of the C—N bond is obviously at the origin of the observed selectivity in the reductive opening of aziridines. A similar approach has been employed using polymethylhydroxysiloxane (PMHS) as a soluble hydrogen source (Equations (40) and (41)) <1999TL9325>. The benzylic-substituted aziridine shown in Equation (41) reacted similarly when a phenyl substituent is present, but in lower yield.

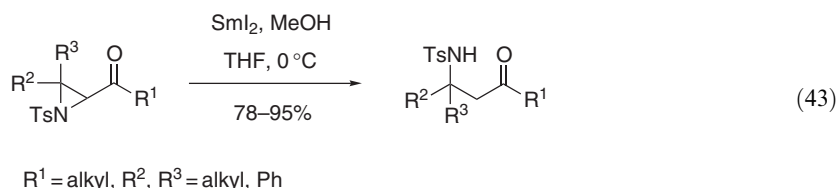


The use of Raney-nickel has been reported to be effective for the stereoselective reductive opening of trisubstituted aziridines (Equation (42)) <2002T7135>. Interestingly, retention/inversion of configuration was observed and the reaction was solvent dependent. The best selectivity was observed when *t*-butanol was used as the solvent (71% de).

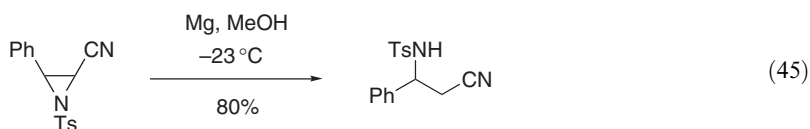
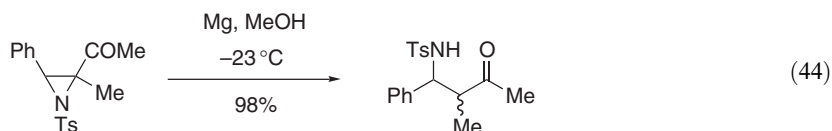


(iii) Use of single electron-transfer reagents

Samarium(II) iodide is known to effect the reductive cleavage of α -heterosubstituted carbonyl substrates such as epoxy- or cyclopropyl ketones. Recently, this reagent has been applied to aziridino ketones and satisfactory yields of the corresponding β -amino ketones were obtained (Equation (43)) <1995JOC6660, 1997T8887>. Similar behavior for aziridine esters and aziridine amides has been reported (*N,N*-dimethylethanolamine was used as proton source to prevent regioselectivity problems). Amino protecting group tolerance has also been demonstrated for a wide range of protection and even unprotected aziridines have been successfully reduced.



More recently, the same transformation was realized using magnesium in methanol as a synthetically useful and economic single-electron-transfer reagent (Equations (44) and (45)) <1998JOC10006>.

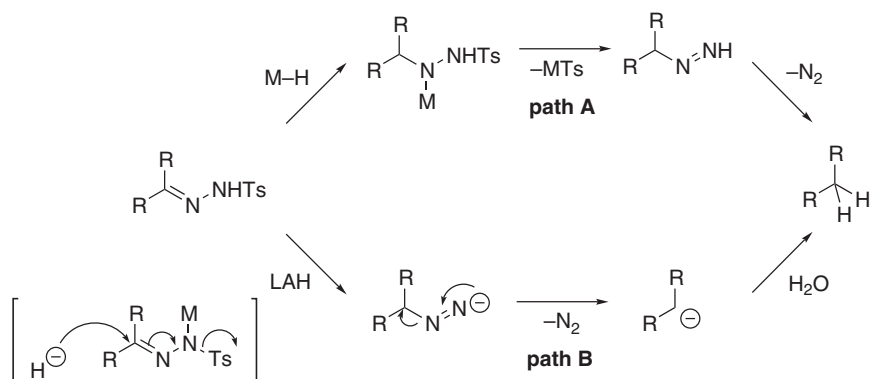


1.02.1.2 Reduction of C—N Double Bonds to Methylene and Methyl Groups

This section considers the reduction of systems (C=N)X to methylene or methyl groups, where X is carbon or nitrogen. Four distinct groups of substrates can be considered for the reduction of double bonds: (a) tosylhydrazones derived from an aldehyde or a ketone, (b) hydrazones of general formula C=N—NR¹R² where R¹ or R² are not arylsulfonyl groups, (c) imino compounds of general formula C=NR¹R², and (d) diazo compounds.

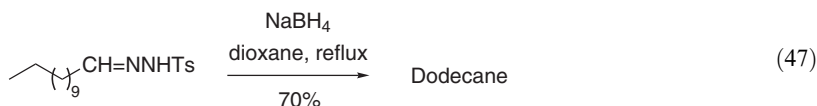
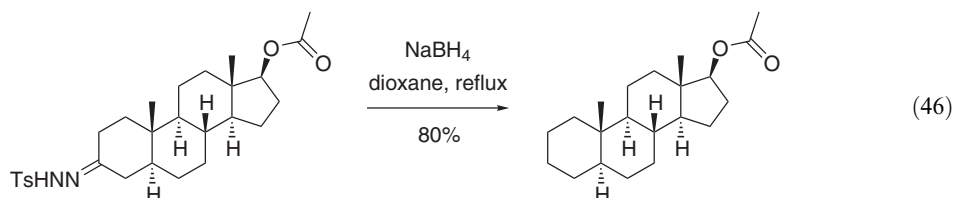
1.02.1.2.1 Reduction of tosylhydrazones

The conversion of tosylhydrazones into methylene groups has been investigated in a very detailed fashion. Alkyl tosylhydrazides can undergo thermal decomposition, with or without basic catalysis, through an alkyl diimide intermediate <1963JA1108>. Since alkyl tosylhydrazones are easily obtained from the corresponding ketones or aldehydes, it has been proposed that a clean reduction of the C—N double bond would lead to the corresponding tosylhydrazides, and then the decomposition of the latter should lead to the formation of a methylene group. In the absence of a strong base, diimide represents the key intermediate rather than the diimide anion involved in the Wolff–Kishner reaction (Scheme 3, path A). Reduction with LAH probably follows a different pathway due to its highly basic character and the diimide anion should then be considered as the key intermediate (Scheme 3, path B).

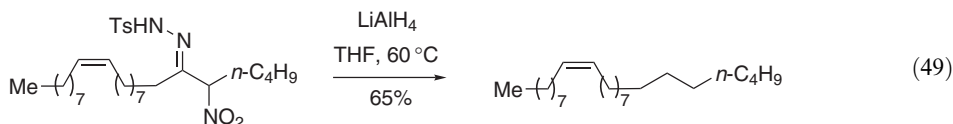
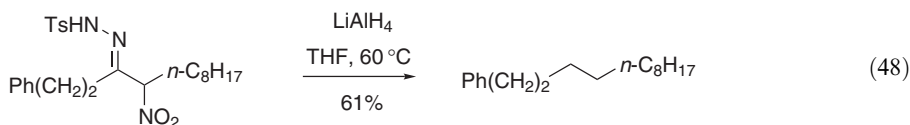


Scheme 3

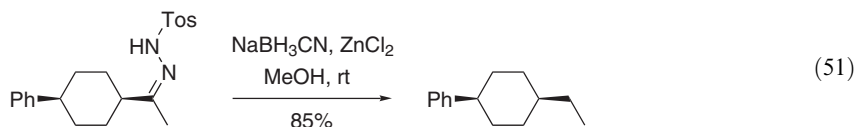
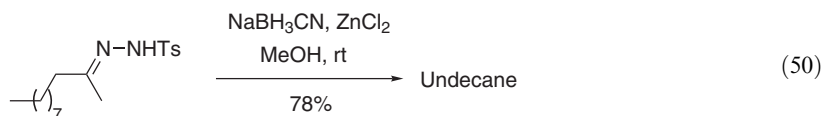
A whole series of tosylhydrazones—derived from both ketones and aldehydes (Equations (46) and (47))—was reduced with sodium borohydride <1966T487>.



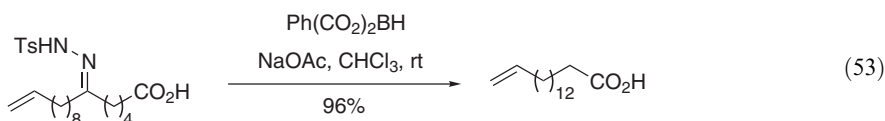
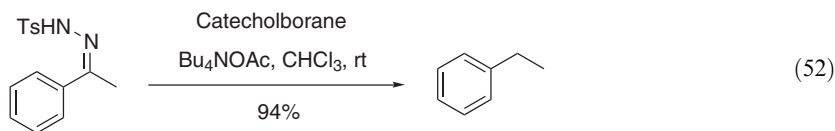
The reduction of tosylhydrazones can also be achieved with LAH and this reducing agent has been used successfully in some natural product syntheses. A particular example is the tandem denitration/deoxygenation of α -nitroketones, which have been used for the synthesis of *cis*-9-tricosene, the sex pheromone of the domestic housefly (Equations (48) and (49)) <1990JOC5159>.



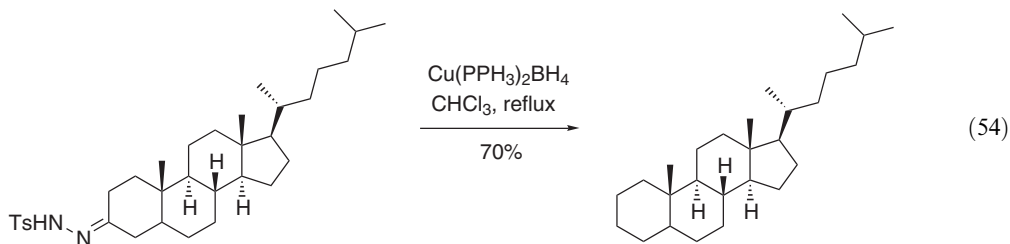
Other reducing agents have been used to effect this transformation. One of them is a combination of sodium cyanoborohydride and zinc chloride (2:1), which has been utilized in the reduction of various tosylhydrazones (Equation (50)) <1985JOC1927>. The same method was used to produce disubstituted cyclohexanes with the aim of synthesizing aliphatic liquid crystals (Equation (51)) <1988CB1039>.



A modification of the Wolff–Kishner reaction involving catecholborane as a mild reducing agent for tosylhydrazones has been reported (Equation (52)) <1975JOC1834, 1979SC275>, and bis(benzyloxy)borane has also been employed with some success (Equation (53)) <1981JOC1217>.

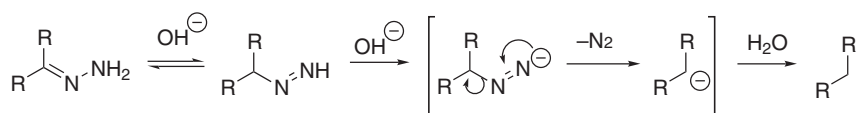


A modified copper borohydride, bis(triphenylphosphine)copper(I) tetrahydroborate, has been reported to reduce efficiently a wide range of tosylhydrazones derived from ketones. Interestingly, a modest conversion has been obtained with tosylhydrazones derived from aldehydes (Equation (54)) [1980TL4031](#).



1.02.1.2.2 Reduction of $C=N-NR^1R^2$ systems where R^1 or R^2 is alkyl, acyl, aryl, or hydrogen

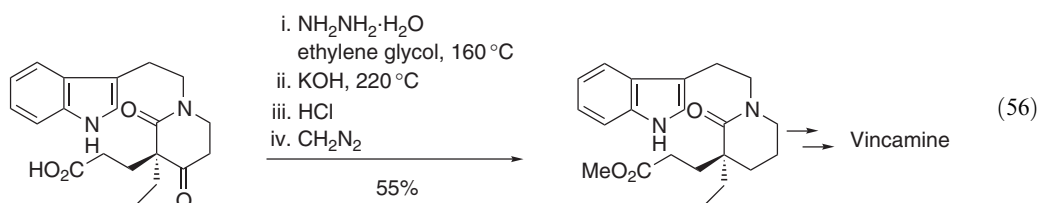
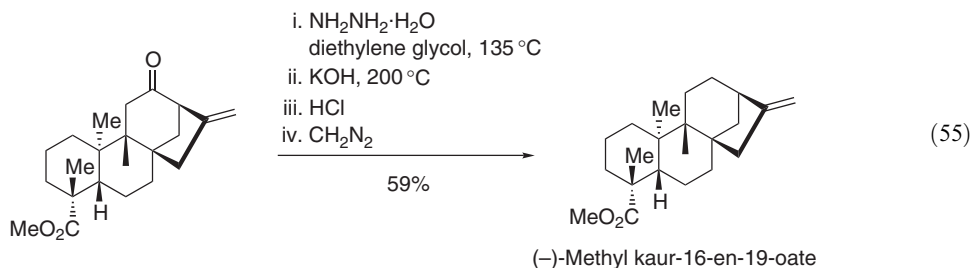
This second type of reduction of C=N double bonds is dominated by the Wolff–Kishner reaction (Scheme 4). A ketone is transformed to the hydrazone and treated *in situ* with a strong base to form an alkane and evolution of nitrogen is observed. The reaction was originally discovered in 1912 and has been comprehensively reviewed <1948OR(4)378, 1968AG(E)120>. Experimental evidence for an sp^3 -hybridized carbanion intermediate has been reported <1992TL903>.



Scheme 4

The original reaction conditions have almost entirely been replaced by the Huang–Minlon modification <1946JA2487> in which the reaction is carried out in diethylene glycol at reflux. The method is not suitable for α,β -unsaturated aldehydes or ketones (pyrazoline formation). For sterically hindered ketones, a vigorous treatment with anhydrous hydrazine is required, which is known as the Barton modification of the Wolff–Kishner reaction <1955JC2056>.

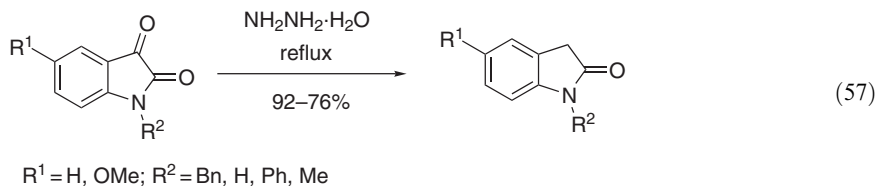
This reaction is very useful and has been used in a great number of syntheses [<2001S364, 1999JCS\(P1\)1265, 1993T2613>](#) such as (-)-methyl kaur-16-en-19-oate ([Equation \(55\)](#)) [<2000JOC4565>](#) and in the synthesis of (+)-vincamine ([Equation \(56\)](#)) [<1997JOC3890>](#). In this latter example, and after extensive experimentations, the authors claimed that the best way to reduce the ketone is the Wolff-Kishner reaction.



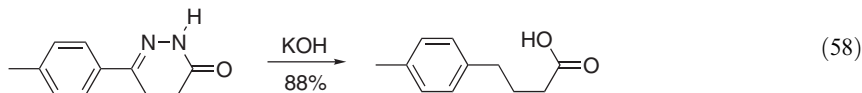
In some cases, double-bond isomerization has been reported, but the use of additives such as silver(I) carbonate completely suppresses such side reactions <1986TL4111>.

Microwave irradiation has been recommended to effect the reduction of a range of acetophenone and benzophenone derivatives in the presence of potassium hydroxide <1999SL1573>. The reaction proceeds efficiently in excellent yields (75–97%) at atmospheric pressure within minutes and in the absence of solvent. It is worth noting that under such conditions, methoxy, chloro, and carbomethoxy groups are not affected.

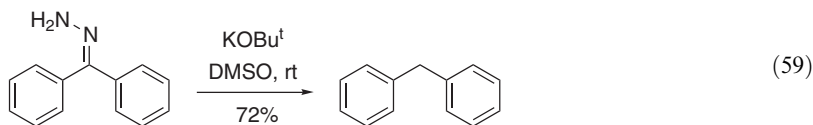
In some specific cases, it has been shown that α -keto-carbonyl compounds can be reduced under milder conditions <1983JOC3866> or even without base <1994SC2835>. For the development of a new synthesis of 2-oxindoles <1994SC2835>, an intramolecular deprotonation of the intermediate hydrazone was invoked. Interestingly, very short reaction times are reported for this transformation (15–30 min) (Equation (57)).



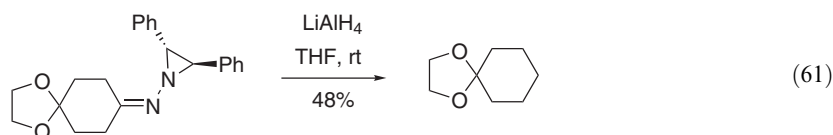
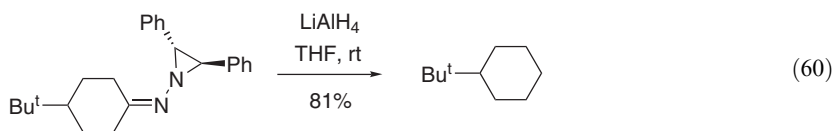
Several hydrazones derived from heterocyclic aldehydes (pyrrole, furan, and thiophene) have been transformed to the corresponding methyl analogs by initial conversion into the semicarbazone followed by reduction using a strong base <1951JA4033, 1956JOC918, 1976T829>. Another cyclic semicarbazone, which has been reduced to the corresponding alkane, is displayed in Equation (58) <1959CB916>.



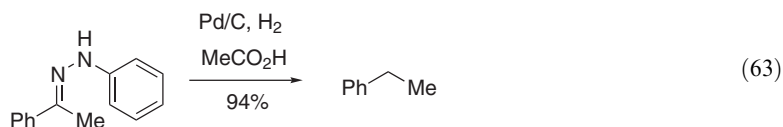
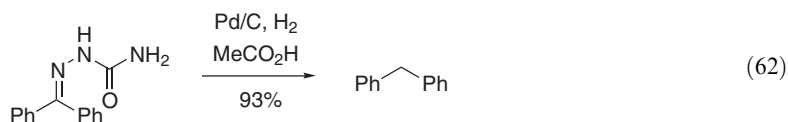
A further modification of the Wolff–Kishner reaction, named the Cram modification, involves the slow addition of hydrazones to a solution of potassium *t*-butoxide in anhydrous dimethyl sulfoxide at room temperature (Equation (59)) <1962JA1734> and the reduction of carbonyl hydrazones in refluxing toluene with potassium *t*-butoxide is called the Henbest modification of the Wolff–Kishner reaction <1963JCS1855>.



An alternative method is the reduction of hydrazones derived from *N*-aminoaziridine with LiAlH_4 (Equations (60) and (61)). Unlike most other hydrazone reductions, this reaction proceeds at room temperature under mild conditions, thus furnishing a mild pathway to the methylene group <1991TL1691>. Several substrates have been examined and the reaction gives similar yields to those reported when tosylhydrazones are employed.



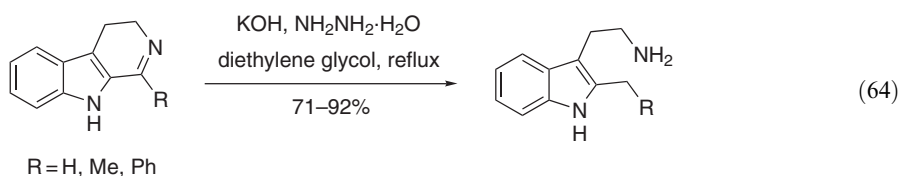
Another efficient method is the hydrogenation of benzylic hydrazones in the presence of palladium on carbon (Pd/C) (Equations (62) and (63)) <1971JOC737>.



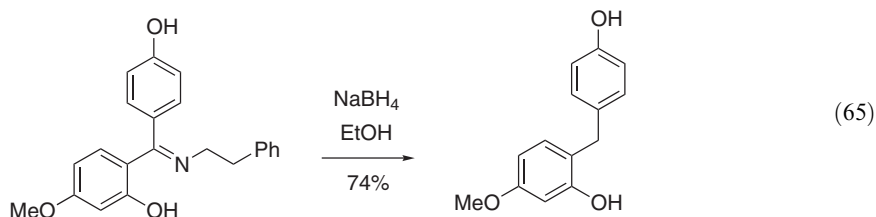
This method has also been used to reduce arylhydrazones derived from aldehydes to the corresponding methyl compound [<1958CB2383>](#).

1.02.1.2.3 Reduction of *N*-alkylimine type systems

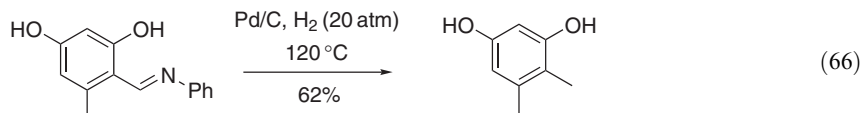
Several methods for the deamination of *N*-alkylimines have been reported. The first one is an extension of the Wolff–Kishner reduction mentioned in [Section 1.02.1.2.2 \(Equation \(64\)\) <1966JCS\(C\)425>](#).



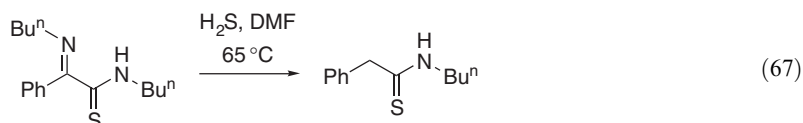
Sodium borohydride in ethanol has also been used in the reduction of 2-hydroxydiarylimines to the corresponding diarylmethanes ([Equation \(65\)\) <1985IJC\(B\)59>](#).



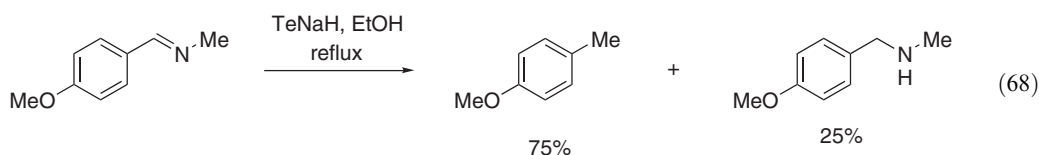
Methyl-substituted resorcinols can be prepared by hydrogenation of arylimines in the presence of a palladium catalyst ([Equation \(66\)\)](#). However, the conditions employed are rather drastic [<1943HCA800>](#).



One isolated case has been reported where an imine was reduced to the corresponding methylene compound by hydrogen sulfide in dimethylformamide at 20–65 °C ([Equation \(67\)\) <1969M724>](#).



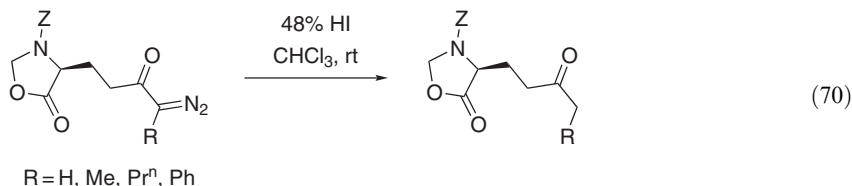
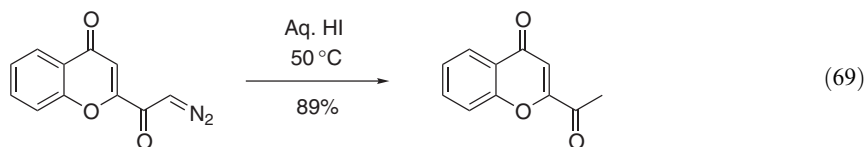
The methylimine of anisaldehyde was reduced to 1-methoxy-4-methylbenzene using sodium telluride, but competitive reduction to the amine also occurred ([Equation \(68\)\) <1988TL2571>](#).



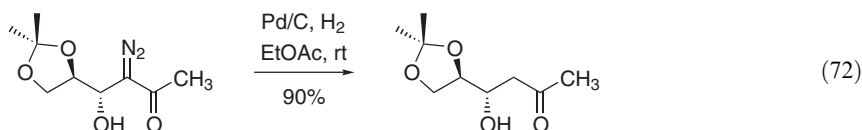
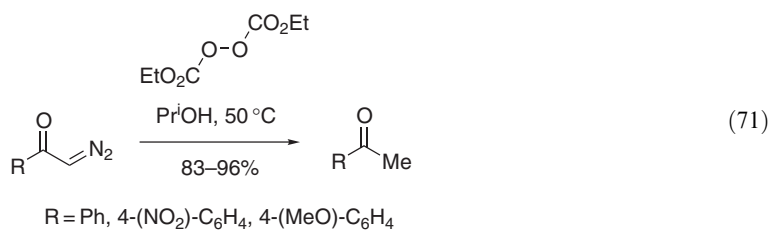
1.02.1.2.4 Reduction of diazo compounds

The reduction of the diazo group to the corresponding methylene group has been the subject of scattered studies. The first reduction of ethyl diazoacetate with zinc in acetic acid was described by Curtius in 1883, and in 1912 Wolff observed an indirect reduction of diazoacetophenone when subjected to basic conditions [\[1943JA1516\]](#).

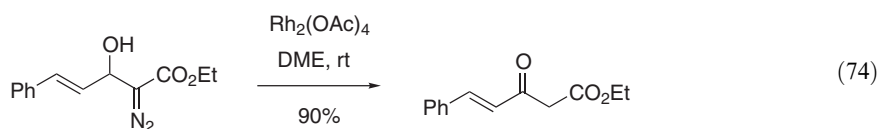
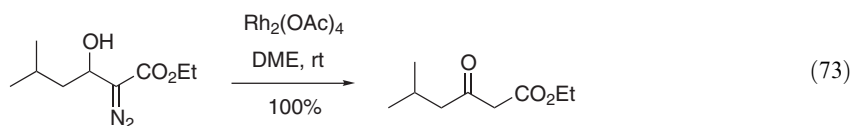
In 1943, Wolfrom found that treatment of a diazomethyl ketone derivative of galactose with aqueous hydrogen iodide led to the corresponding methyl ketone [\[1943JA1516\]](#). Presumably, the initially formed iodomethyl ketone is reduced to the saturated ketone under the reaction conditions. This reaction is illustrated in [Equation \(69\)](#) [\[1999TA4745\]](#) and [Equation \(70\)](#) [\[1986JOC2405\]](#).



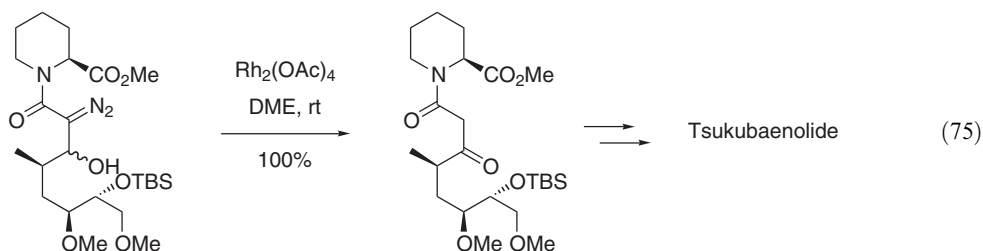
The reduction of diazoacetates has been reported using a catalytic amount of diethyl peroxycarbonate in isopropanol ([Equation \(71\)](#)) [\[1966TL3579\]](#), or under hydrogenolysis conditions in an autoclave at room temperature [\[1985JCS\(P1\)493\]](#). Recently, these conditions have been reported for the reduction of a diazoketone in order to correlate its absolute configuration with a known β -hydroxy ketone ([Equation \(72\)](#)) [\[1998T6867\]](#).



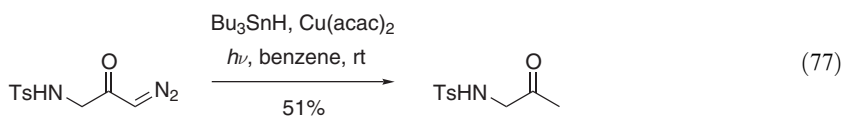
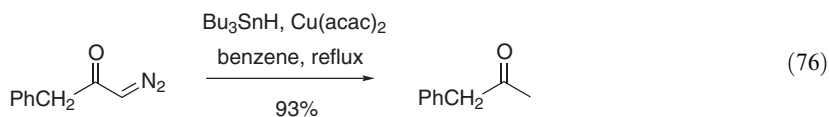
A better reducing system (in terms of yields) involving rhodium(II) acetate as the catalyst has been reported [\[1979CC959\]](#). This reagent is particularly useful for the synthesis of β -keto esters since it also catalyzes the oxidation of a neighboring hydroxyl group ([Equations \(73\)](#) and [\(74\)](#)). The conditions are milder than the usual conditions employed for such a transformation (heating in the presence of hydrogen chloride or vacuum pyrolysis) [\[1978JOC3983\]](#).



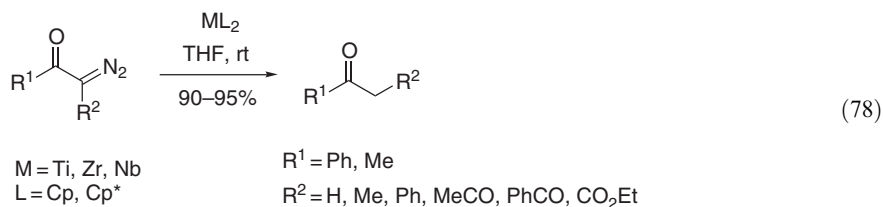
This reaction has found widespread applications in the synthesis of β -diketones <1981JCS(P1)2566, 1992T8007>, particularly in the efficient synthesis of a precursor of tsukubaenolide (Equation (75)) <1988TL4481>.



Tributyltin hydride in the presence of copper(II) acetylacetonate has also been used to reduce efficiently α -diazoketones to the corresponding ketones (Equations (76) and (77)) <2000T7457>.



Other reagents such as activated titanium, zirconium, or niobium metallocenes have been shown to be effective catalysts for the reduction of α -diazoketones (Equation (78)) <1990SL465>.



1.02.1.3 Reduction of C—N Triple Bonds to the Methyl Group

The direct substitution of a nitrile by a methyl group can be accomplished under different conditions (e.g., an α -amino nitrile treated with a methyl Grignard reagent). This transformation related to a C—C bond formation will not be discussed here.

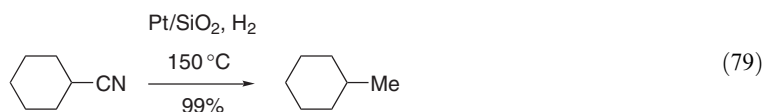
Indeed, there are few conditions allowing the direct reduction of a nitrile to a methyl group. The first one is a metal-mediated hydrogenolysis of aromatic nitriles and the second method is a sequence including the partial reduction of a nitrile to an aldehyde followed by a Wolff–Kishner reaction.

1.02.1.3.1 Reduction of nitriles using hydrogenolysis conditions

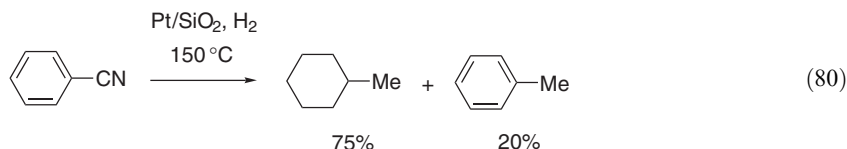
The direct reduction of a nitrile to the corresponding hydrocarbon is only observed with arylcyanides under prolonged hydrogenation.

In one of the first examples, 4-aminobenzonitrile was heated under hydrogen at 330 °C in the presence of nickel oxide on a copper/silica support, to produce 4-aminotoluene <1959BCJ861>. Using the same catalyst, the reduction of cinnamonnitrile afforded propenylbenzene chemoselectively.

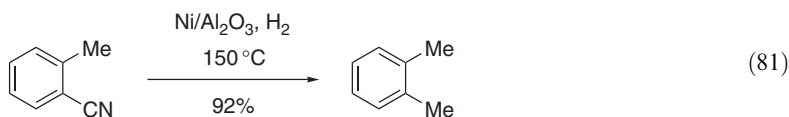
Some years later, several nitriles were reduced over a platinum/silica catalyst (Equation (79)) <1984JOC2875>. This method is the most powerful method for the N—C bond cleavage since it also reduces alkynitriles to hydrocarbons while minimizing direct defunctionalization through C—C bond cleavage (see Section 1.02.3.1).



Although the yields for this method were excellent in most cases, there are two major drawbacks: (i) it requires a special flow apparatus, which for a one-off experiment would be prohibitive and (ii) the catalyst requires a high percentage of platinum, thus making the method costly. Sometimes, chemoselectivity is lost as illustrated by the reduction of benzonitrile that affords mainly methylcyclohexane (Equation (80)). Another flow method was devised to reduce 1-cyano-adamantane with aluminum oxide as support <1979AG(E)939>.



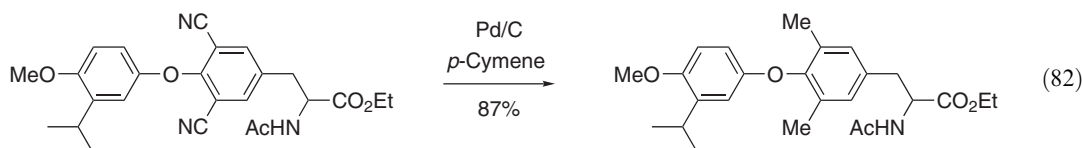
The reduction of several nitriles using Raney-nickel has been also achieved (Equation (81)) <1980S802>. A dramatic decrease of chemoselectivity was observed when alkynitriles were tested: C—C bond cleavage became the main pathway (as mentioned in Section 1.02.3.1.) except for 1-adamantanecarbonitrile.



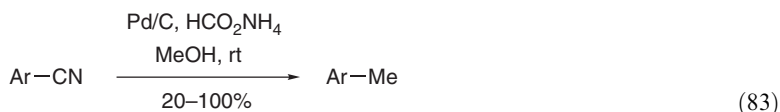
Similarly, various 2-cyanotriazines have been successfully reduced to the 2-methyltriazines using Raney-nickel in acetic anhydride under 1 atm of hydrogen <1962JA3744>. When 3-cyano-2-(methylthioindole) was subjected to Raney-nickel in ethanol under reflux, it has been reported that desulfurization accompanied the reduction of the nitrile group (65–89% yield) <1987S846>.

Various cyanopyridines have been inadvertently reduced to the corresponding methylpyridine using zirconium oxide in 2-propanol. The method requires high temperature (300 °C) and the yields are modest (30–50%) <1990CL311>.

Pioneering investigations examined the use of palladium with cyclic terpenes that functioned both as solvent and hydrogen donor <1966CB227>. It was observed that aromatic nitriles were readily reduced to the corresponding methyl compounds. Applications to multifunctional systems have been reported (Equation (82)) <1974JMC434>.



Ammonium formate has been employed as the source of hydrogen, using Pd/C as the catalyst <1982S1036>. This represents a very useful reaction for the reduction of aromatic nitrile groups to methyl groups (Equation (83)). Alkynitriles were not reduced under these conditions.

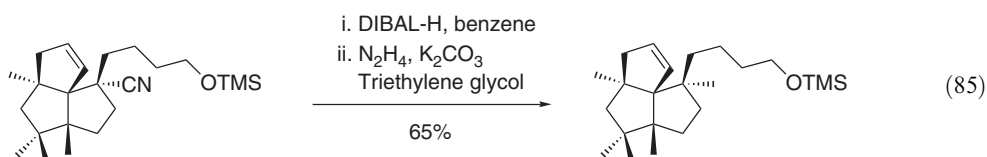
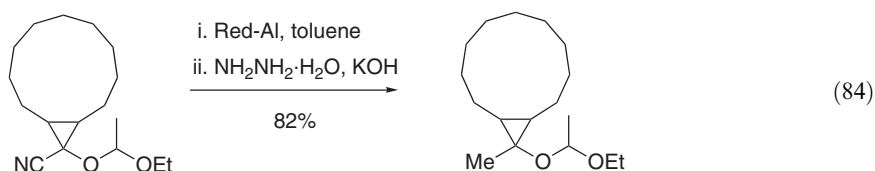


Ar = 4-(MeO)-C₆H₄, 4-(OH)-C₆H₄, 3-(OH)-C₆H₄, 1-naphthyl
2-naphthyl, 1-(4-(MeO)-naphthyl), 5-indolyl

1.02.1.3.2 Reduction of nitriles to methyl groups using hydride reagents

The direct reduction of an alkylnitrile to the corresponding hydrocarbon with a hydride reagent has not been reported as of early 2000. However, it is possible to achieve such a transformation through a two-step sequence. The first step is the partial reduction of the nitrile with an appropriate hydride reagent into an aldehyde, and the second step is a Wolff–Kishner reduction of the aldehyde.

Such a process has been reported rarely but two selected examples are shown in Equation (84) <1986T2429> and Equation (85) <1988JOC477>.



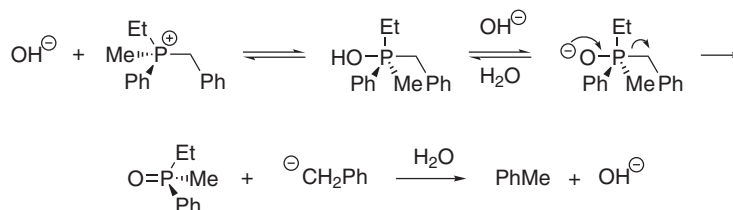
1.02.2 REDUCTION OF CARBON—PHOSPHORUS, —ANTIMONY, AND —BISMUTH BONDS TO CARBON—HYDROGEN BONDS

1.02.2.1 Reduction of Carbon—Phosphorus Bonds

The reduction of C—P bonds to one or two C—H bonds can be achieved under basic or acidic conditions, or by using hydride reagents.

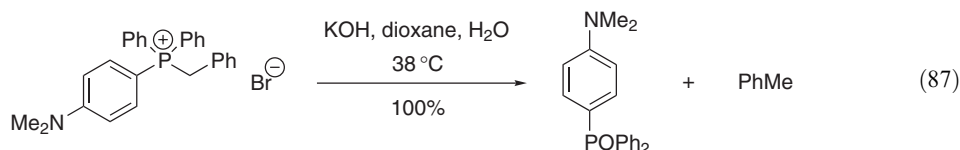
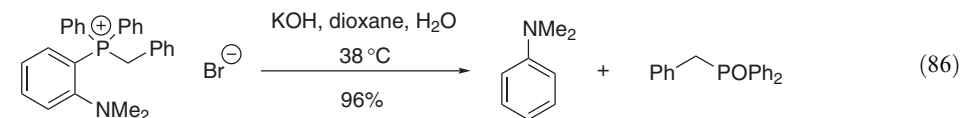
1.02.2.1.1 Cleavage of C—P bonds under basic conditions

The alkaline cleavage of quaternary phosphonium salts is a well-documented reaction, which represents one of the most important methods for preparing phosphine oxides. Hydrocarbons are the other products of this reaction. The generally agreed mechanism is indicated in Scheme 5 based on numerous investigations <B-1973MI003, 1978CJC1933, 1978JA7312, 1983JCS(P2)1923, 1986TL1209>. The order of displacement of groups attached to the phosphonium salt is allyl, benzyl > phenyl > methyl > 2-phenylethyl > ethyl, higher alkyls <1991COS(8)858>.

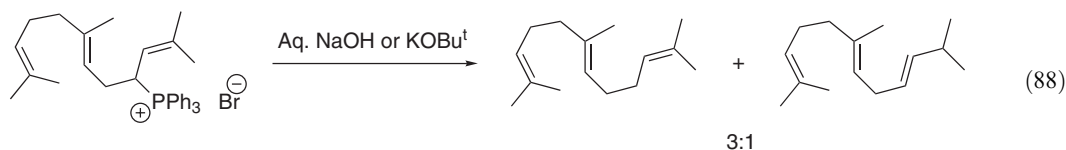


Scheme 5

Interesting effects on the rate and the regioselectivity of the alkaline cleavage of quaternary phosphonium salts are observed when *o*- or *p*-methoxy- or *o*- or *p*-dimethylamino-phenyl groups are present in the molecule. For example, benzyl[2-(*N,N*-dimethylamino)phenyl]diphenylphosphonium bromide undergoes alkaline cleavage in dioxane/water (1/1) to give *N,N*-dimethylaniline (96.5%), benzene (3.5%), and benzyldiphenylphosphine oxide (96%) 10^3 times more rapidly at 38 °C than benzyl[4-(*N,N*-dimethylamino)phenyl]diphenylphosphonium bromide, which gives only toluene as the hydrocarbon product (Equations (86) and (87)) <1987JOC4829>.



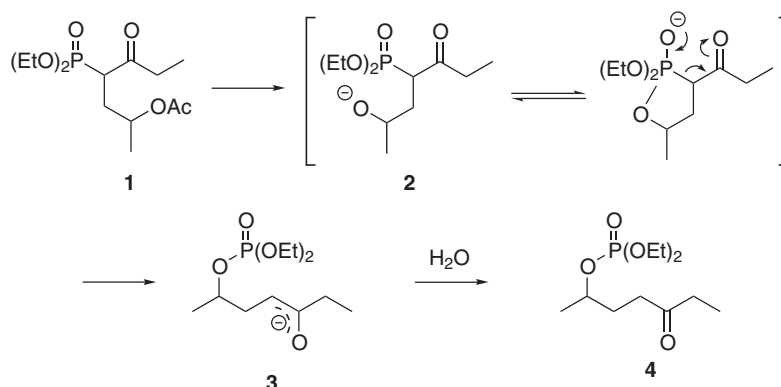
The cleavage of an allylphosphonium bromide with hydroxide or *t*-butoxide resulted in a 3:1 mixture of two triene isomers (Equation (88)) <1970JA2139>. A significant competition between allyl and phenyl group as the leaving group is described.



Alkaline hydrolysis of phosphorus ylides is a general method for the reductive cleavage of the C—P bond. Protonation of ylides affords a phosphonium hydroxide, which can react with hydroxide and then decomposes into hydrocarbon and phosphine oxide. Among the four ligands of the ylide, the ligand that is the most electronegative or the best stabilized as an anion is the best leaving group (Equation (89)) <1991COS(8)858>.



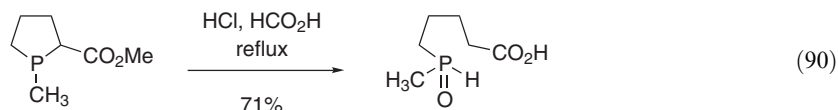
The hydrolysis of acetate **1** under basic conditions (KOH or NH₄OH or KCN/alcoholic solution) led to the quantitative formation of the phosphate **4**. The sequence of reactions which explain the formation of **4** involves: (a) hydrolysis of acetate **1** by hydroxide, (b) intramolecular attack of alkoxide **2** onto the phosphonate, (c) fragmentation and formation of phosphate **3**, and (d) protonation (Scheme 6) <1997T2199, 1988JCS(P1)2971, 1985TL5713>.



Scheme 6

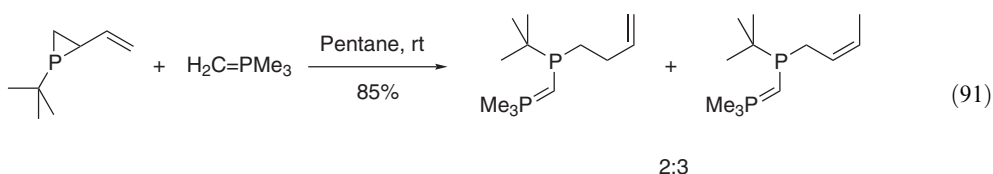
1.02.2.1.2 Cleavage of C—P bonds under acidic conditions

The C—P bond of simple phosphines is known to withstand the conditions of common organic reactions. However, it was found that the C—P bond β to a carbonyl group is sensitive to cleavage when treated in acidic conditions (Equation (90)) <1974JOC3423>. The mechanism of the cleavage of these β -carbonylphosphines presumably involves the attack of water on the protonated phosphine.



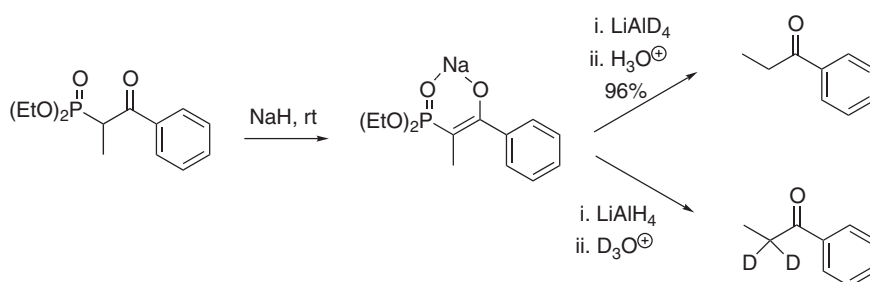
1.02.2.1.3 Cleavage of C—P bonds under neutral conditions

The reaction of a methylenetriethylphosphorane with 1-*t*-butyl-2-vinylphosphirane produces two phosphino-substituted phosphorus ylides in a ratio of 2:3 resulting from a ring-opening and a proton transfer (Equation (91)) <1984T3273>.



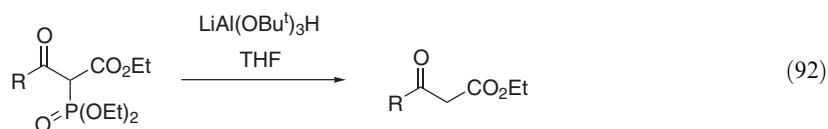
1.02.2.1.4 Cleavage of C—P bonds with hydride

LAH has been employed for the cleavage of the C—P bond <1957JA3567>. Dephosphonylation of β -ketophosphonates using LAH has recently been accomplished to afford the corresponding ketones (Scheme 7) <1996JOC2199>. During the cleavage of the C—P bond the hydride does not attack the carbon linked to the phosphorus atom, as shown by the deuterium labeling but it seems that an intermediate with a dianion character might be involved.



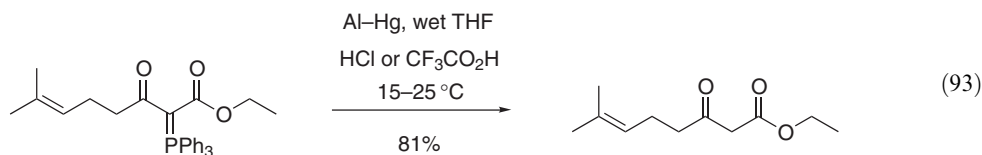
Scheme 7

Lithium tri-*t*-butoxyaluminumhydride ($\text{LiAl}(\text{O}^t\text{Bu})_3\text{H}$) selectively cleaves the C—P bond in the presence of keto or ester functional groups (Equation (92)). It is worth noting that reduction of the same type of compounds with sodium borohydride leads to the corresponding β -hydroxyphosphonates and does not cleave the C—P bond <1972JCS(P1)2582>.

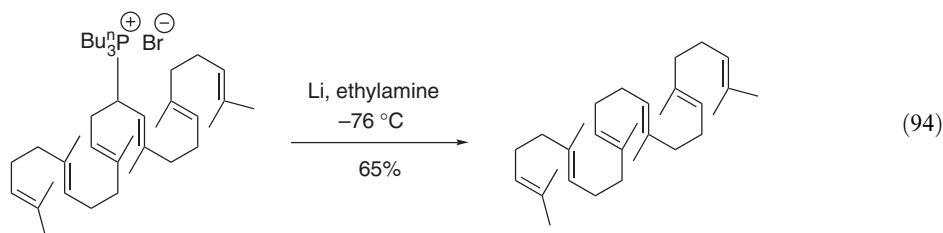


1.02.2.1.5 Miscellaneous methods

Acylhydrides have been reduced successfully by aluminum amalgam with excellent yields <1964JA1639, 1982JOC4963>. The reductions were conducted typically with an excess of aluminum amalgam with a periodical addition of either trifluoroacetic acid or hydrochloric acid (Equation (93)).



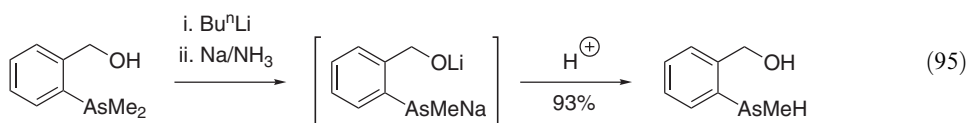
1,5-Dienes can be prepared by reduction of substituted allylphosphonium salts by using lithium–ethylamine (Equation (94)) <1970JA2139>. Tri-*n*-butylphosphonium salts were used instead of triphenylphosphonium salts in order to avoid other competitive side reactions.



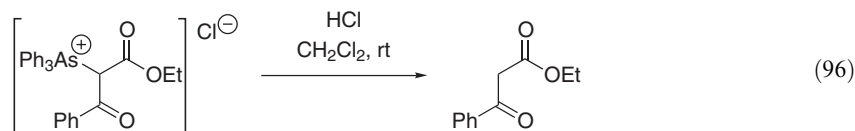
Zinc in the presence of acid has also been utilized for the reduction of phosphoranes <1955JA3230, B1979MI102-01>. Photolysis has also been employed for the cleavage of C—P bonds. Thus, under photolysis *p*-nitrophenylmethylphosphonic acid undergoes C—P bond scission in alkaline ethanol to produce *p*-nitrotoluene, orthophosphate, and ethyl phosphate <1986BCJ1505, 986CC1516>.

1.02.2.2 Reduction of C—As Bonds

When compared with phosphorus, the reduction of C—As bonds to C—H bonds has been severely neglected. There are few examples of this type of reaction in the literature. An alkyl substituent on the arsenic atom can be removed by addition of sodium in ammonia <1988JA4346>. The example given in Equation (95) was carried out in an attempt to produce optically active arsenic-containing macrocycles.

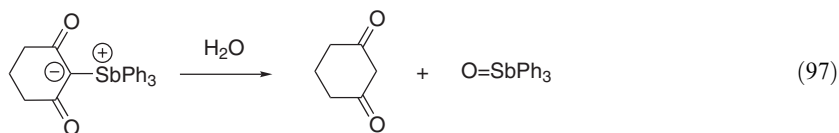


A further example of the cleavage of a C—As bond is where an arsonium chloride derivative is treated with hydrogen chloride to form β -keto esters (Equation (96)) <1986MI261>.

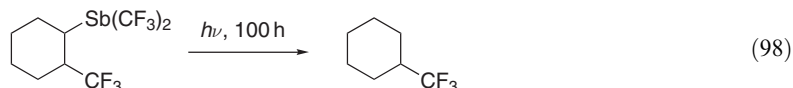


1.02.2.3 Reduction of C—Sb Bonds

Stilbonium ylides having α -electron-withdrawing groups have been prepared under mild conditions by reaction between triphenylantimony and an appropriate diazo compound in the presence of homogeneous copper catalyst <1986T3887>. These stilbonium ylides are stable in a dry atmosphere but slowly decompose to give triphenylantimony oxide and the corresponding methylene compound in protic solvents (Equation (97)) <1986T3887>.

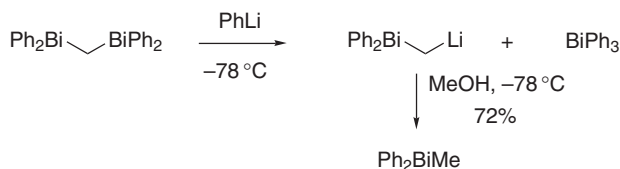


Antimony compounds containing the $\text{Sb}(\text{CF}_3)_2$ group can lose this moiety on photolysis over 100 h <1988ZAAC(560)141>. As shown in Equation (98), trifluoromethylcyclohexane is formed resulting from the simple replacement of $\text{Sb}(\text{CF}_3)_2$ by hydrogen.



1.02.2.4 Reduction of C—Bi Bonds

Only one example of a C—Bi bond cleavage to give the corresponding hydrocarbon has been described. Bis(diphenylbismutino)methane was synthesized in 1985 <1985CB1039>. It is possible to remove one of the diphenylbismuth groups using phenyllithium. This leads to an anion which produces the methyl diphenyl bismuthine after addition of methanol (Scheme 8).



Scheme 8

1.02.3 REDUCTIVE CLEAVAGE OF C—C BONDS TO C—H BONDS

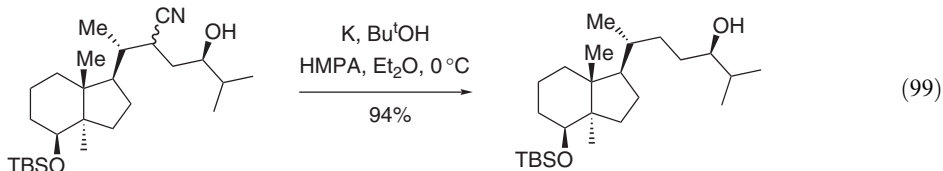
There are four types of reaction devoted to the reductive cleavage of a C—C bond to a C—H bond: (a) the reductive cleavage of a nitrile, (b) the direct cleavage of an alkyl C—C bond to give two distinct hydrocarbons, (c) the decarboxylation of aliphatic carboxylic acids and derivatives, and (d) the decarboxylation of carboxylic acids with electron-withdrawing groups at the α -position.

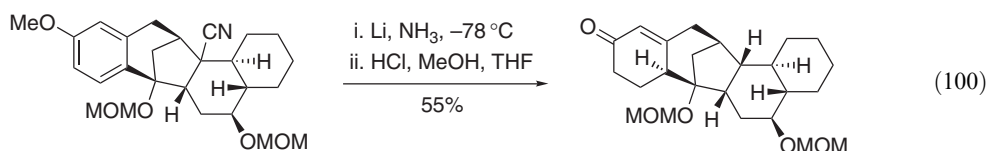
1.02.3.1 Reductive Decyanation

There are two main methods for the cleavage of a nitrile to give the corresponding C—H bond, namely dissolving metals and radical conditions, which are accompanied by various miscellaneous methods.

1.02.3.1.1 Use of dissolving metals

The reduction of nitriles occurs with dissolved alkali metals in HMPA with *t*-butanol as the proton source <1973BSF1174, 1975TL3851> or with sodium or lithium in ammonia <1967JA6794, 1975JOC1162>. Such conditions have found wide synthetic applications as illustrated by the decyanation of an intermediate used in the synthesis of dihydroxyvitamin D₃ (Equation (99)) <1997T4703> as well as an intermediate used in the synthesis of a galbulimima alkaloid <2003JA2400> (Equation (100)).

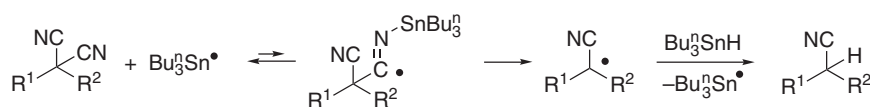




A crown ether in combination with potassium in toluene has been reported to be an efficient system for the reductive decyanation of alkylnitriles and disubstituted malononitriles (76–96% yields) [<1985TL6103>](#). However, excess potassium and crown ether are required for this reaction.

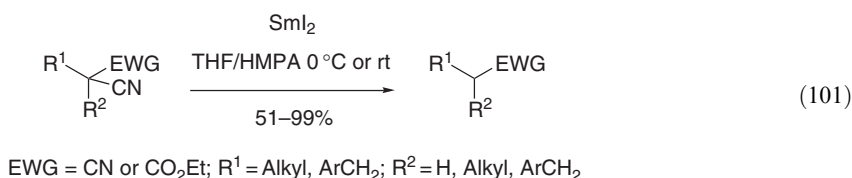
1.02.3.1.2 Use of radical conditions

The discovery by accident of the reductive decyanation of malononitriles promoted by tributyltin hydride has been reported [<1990JA9401, 1991SL107>](#), but the scope of the reaction is restricted to malononitriles. A mechanism was proposed where the tin radical adds first to the nitrogen atom prior to fragmentation ([Scheme 9](#)).



Scheme 9

After this report, a milder method using SmI_2 has been described [<1995TL7661>](#) ([Equation \(101\)](#)) and applied to the decyanation of malononitriles and α -cyano esters.



1.02.3.1.3 Miscellaneous methods for reductive decyanation

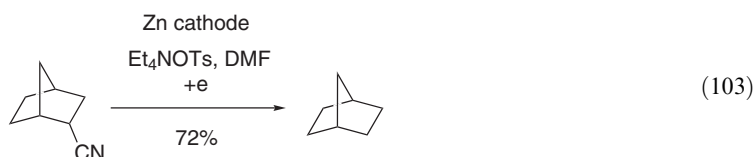
More drastic conditions such as alkali fusion (KOH , 150°C , 55–95% yields) have been reported to reduce C—C bonds to C—H bonds [<1980SC939>](#). Although the method is absolutely cost effective, the substrates that can stand these drastic conditions are limited to unfunctionalized benzylic nitriles.

Potassium on alumina has been successfully evaluated as a reagent for the reductive cleavage of alkylnitriles but the tedious preparation of the reagent restricts its utility ([Equation \(102\)](#)) [<1980JOC3227>](#).

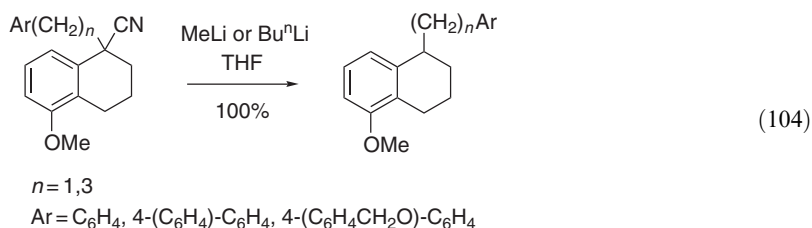


$\text{R} = \text{Functionalized primary, secondary, tertiary alkanes}$

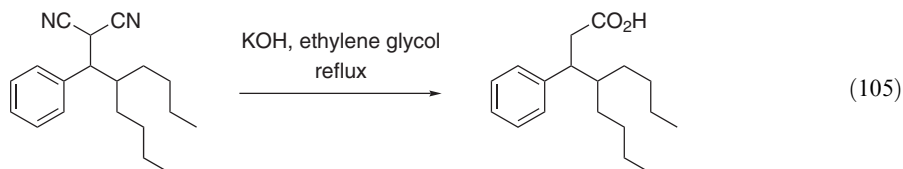
More recently, a method involving electroreductive decyanation of alkylnitriles has been devised and has led to efficient syntheses of the corresponding hydrocarbons ([Equation \(103\)](#)) [<1992T8253>](#).



While nitriles can react with alkyllithium reagents to form ketones, decyanation of tertiary nitriles has been observed in some cases in quantitative yields (Equation (104)) <1990JOC1479>. A strong solvent effect is observed: in diethyl ether, the addition of methyl lithium affords mainly the corresponding methyl ketones. The authors invoked a four-membered transition state accompanied by an internal hydride capture. Similar behavior has been noticed previously with a Grignard reagent <1952JA5793>.



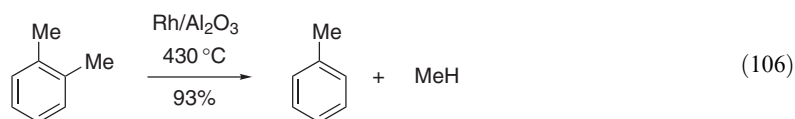
Finally, malononitriles are prone to decarboxylation and are easily transformed into the corresponding carboxylic acid when they are treated with potassium hydroxide in refluxing ethylene glycol (Equation (105)) <2000AG(E)758>.



1.02.3.2 Cleavage of C—C Bonds Where Both Products are Hydrocarbons

1.02.3.2.1 Dealkylation of alkylbenzenes

In general, reaction conditions are drastic and the molecules involved are simple. The dealkylation of xylene using alumina-supported rhodium is extremely efficient, giving toluene in 93% yield (Equation (106)) <1971MI1567>.

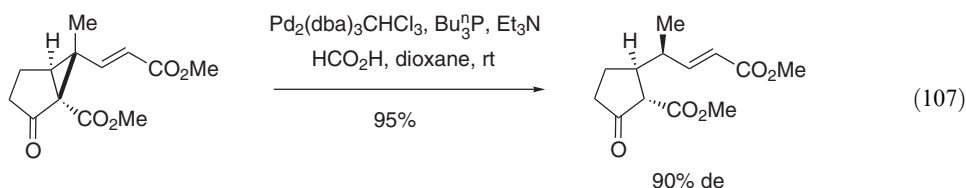


Under rather drastic reaction conditions, toluene was converted into benzene (95%) using a cobalt/molybdenum/alumina catalyst in the presence of sodium hydroxide at 560–600 °C <1958IEC1677>. A similar catalytic system, nickel/aluminum oxide, has been studied and various isomers of picoline, cresol, and xylene were demethylated when heated around 400 °C <1965MI39>.

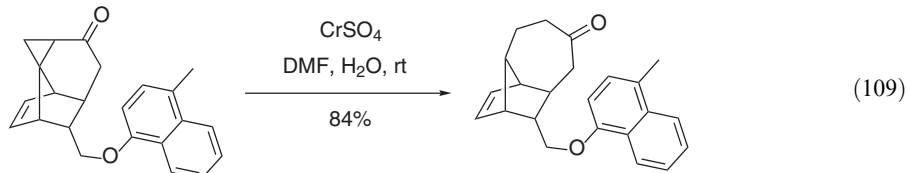
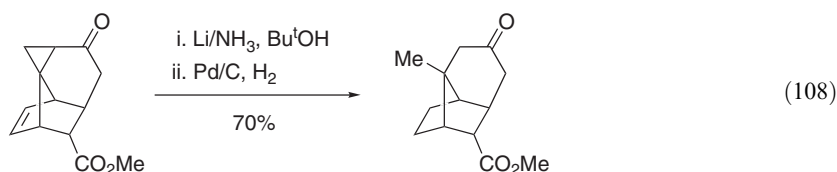
1.02.3.2.2 Reductive cleavage of cyclopropylketones

Cyclopropanes are important synthetic intermediates due to their exceptional reactivity related to the strained nature of such cyclic hydrocarbons. A variety of methods exist for the reductive cleavage of cyclopropane conjugated to a ketone and the earlier approaches have been reviewed <1979AG(E)809>.

The palladium-catalyzed reductive cleavage of cyclopropylketones afforded the compound, which results from preferential cleavage of the least substituted bond <1983TL681>. Such a strategy has been used in a synthesis of clavukerin (Equation (107)) <1994TL1905>.

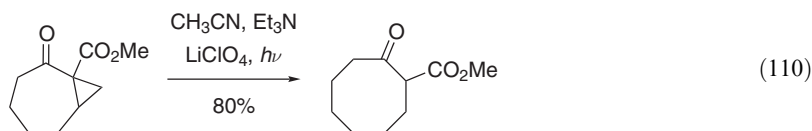


Lithium in liquid ammonia results in the cleavage of the bond that overlaps most efficiently with the π -orbital of the carbonyl group and chromium(II)-induced cleavage is subject to subtle stereoelectronic effects. Such conditions have been used to effect selective cleavage of bridged-ring cyclopropyl ketones (Equations (108) and (109)) <1983TL681>.



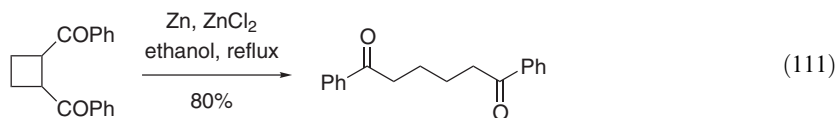
Prolonged treatment of such cyclopropyl ketones with excess zinc and zinc chloride has been found to be another important system for their reductive ring opening <1986JCS(P1)1445, 1975TL2489>.

In cyclopropylketones, samarium(II) iodide has been reported to promote reductive ring opening of the cyclopropane under mild conditions in modest yields (39–49%) <1991TL6211>. Photochemical electron transfer has also been reported to efficiently induce such ring opening. The reaction proceeds cleanly for a wide range of substrates (Equation (110)) <1995T11751>.

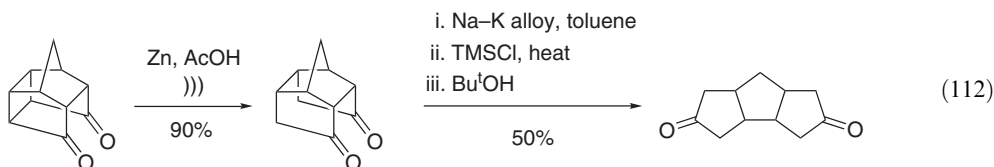


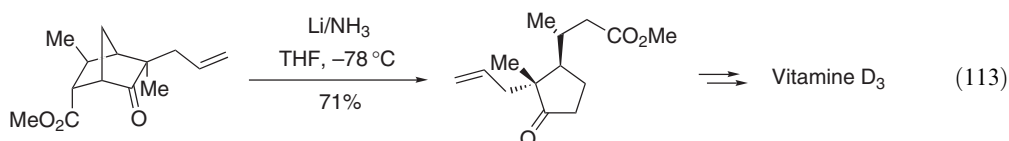
1.02.3.2.3 Reductive cleavage of other constrained cycloalkanes

1,2-Dibenzoyl cyclobutanes have been reported to undergo facile ring cleavage when treated with zinc and zinc chloride in a protic solvent (Equation (111)) <1975TL2489>.



Similarly, strained cyclobutanes and cyclopentanes involved in a norbornyl system can be reductively cleaved by using zinc in acetic acid or dissolving metals. This interesting reactivity has been exploited in a synthetic approach to triquinanes (Equation (112)) <1985JOC5537> and in a synthesis of vitamin D₃ ring synthons (Equation (113)) <1990TL4899>.





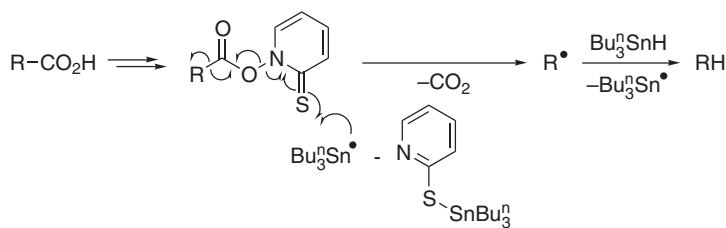
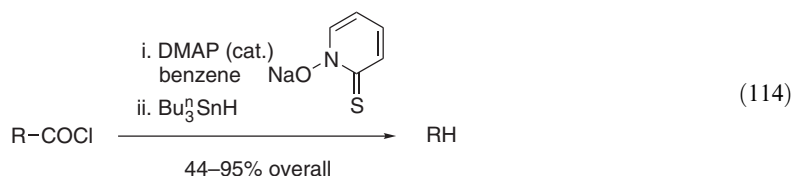
1.02.3.3 Reductive Decarboxylation of Aliphatic Carboxylic Acids, Esters, and Aldehydes

Unactivated aliphatic carboxylic acids generally undergo decarboxylation at a temperature greater than 300 °C. Many procedures have been developed to render this interesting reaction more synthetically useful and to extend it to other carbonylated functionalities.

1.02.3.3.1 Decarboxylation of aliphatic carboxylic acids and esters

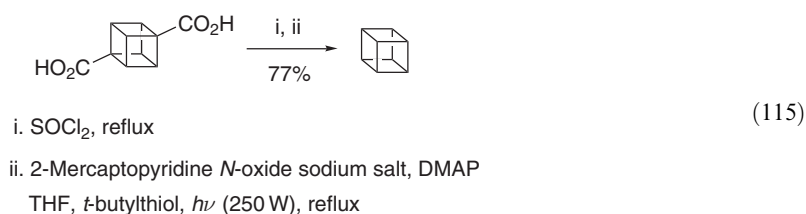
(i) Barton reductive decarboxylation of carboxylic acids

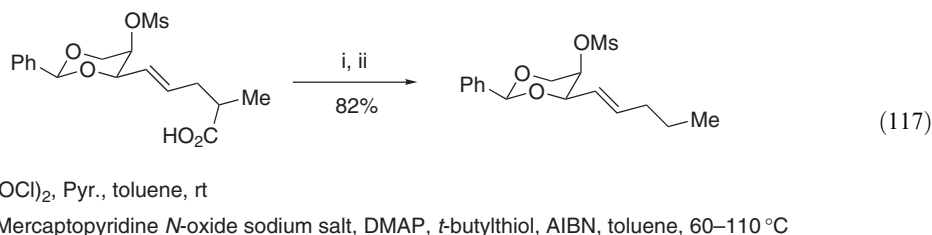
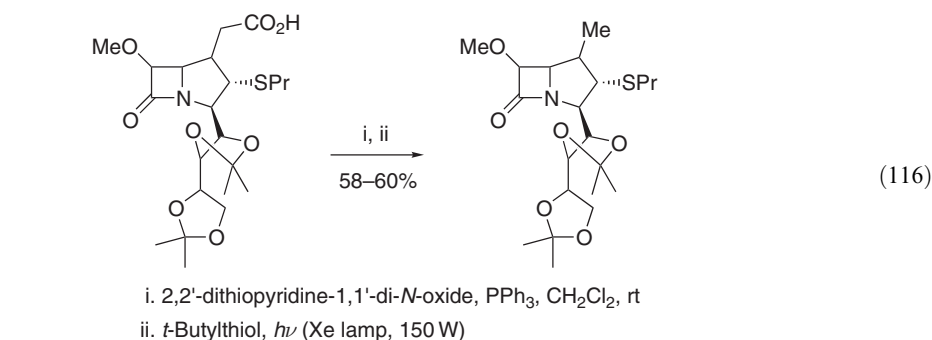
The Barton decarboxylation is a well-established reaction for the radical decarboxylation of carboxylic acids to the corresponding nor-hydrocarbons under mild conditions (Equation (114)) <1983CC939, 1985T3901, 1992T2529>. In this radical process tributyltin hydride or *t*-butylthiol as hydride donor can be used. The mechanism is described in Scheme 10.



Scheme 10

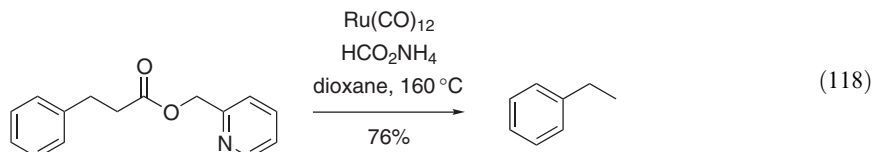
Such conditions have been utilized for a clean preparation of cubane (Equation (115)) <1995S501>, for a synthesis of complex 1-methylcarbapenem antibiotic precursor (Equation (116)) <1994TA2137> and for a synthesis of sphingosines (Equation (117)) <1995S868>.





(ii) *Metal-mediated reductive decarboxylation of unactivated acids and esters*

Photochemical decarboxylation of thallium(III) or lead(III) carboxylates has been reported, but invariably a mixture of alkanes and alkenes was obtained [<1968JOC75>](#). More recently, Ru₃(CO)₁₂ has been found to be a more general catalyst (5 mol.%) for the decarboxylation of a broad range of 2-pyridylmethyl esters in good yields and especially aliphatic esters (76–78%) ([Equation \(118\)](#)) [<2001JA4849>](#). A wide variety of functional groups is tolerated, thus making this reagent versatile.



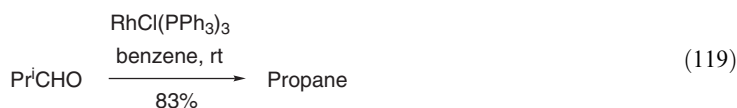
1.02.3.3.2 Reductive decarbonylation of aldehydes and acyl halides

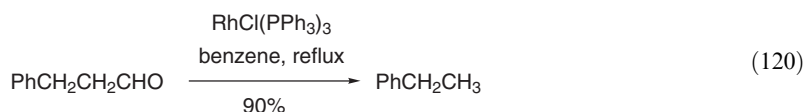
(i) *Metal-mediated decarbonylation of aldehydes*

Decarbonylation of aldehydes to produce the corresponding hydrocarbon is a synthetically useful reaction that can be achieved at high temperature by a free-radical chain reaction initiated by peroxides [<1963JA4010>](#). Alternatively, photochemical conditions can be employed [<1970JA4906, 1995JA10391>](#). However, the transition metal-catalyzed processes dominate the recent developments in this area.

A palladium/polystyrene catalyst has been shown to be an effective catalyst for the decarbonylation of docetanal to undecane (77%), but the reaction requires extended reaction time (60 h) in refluxing toluene [<1983JOC4179>](#).

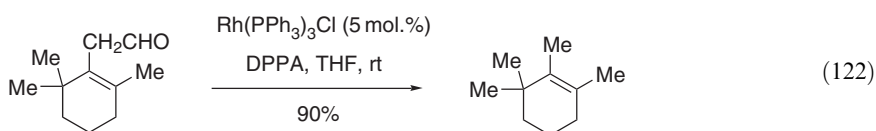
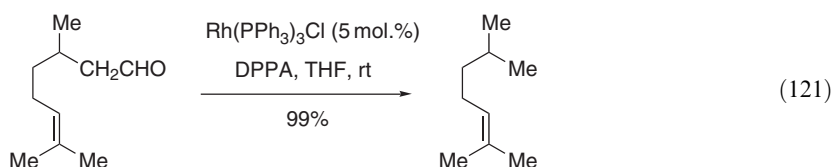
Wilkinson's catalyst RhCl(PPh₃)₃, was demonstrated to be an effective catalyst for the decarbonylation of aliphatic aldehydes to the corresponding nor-hydrocarbons ([Equations \(119\) and \(120\)](#)) [<1965TL3969, 1968JA99>](#). However, the reaction is catalytic in rhodium only at high temperature and thermal decomposition of the substrate can compete with the desired process.





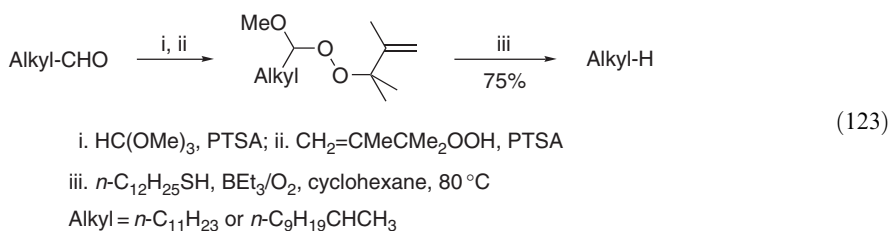
The impossibility to regenerate the active species $\text{RhCl(PPh}_3)_2$ at lower temperature made it an expensive process and led to the development of many other catalysts such as $[\text{Rh(dppe)}_2]\text{Cl}$ or $[\text{Rh(dppp)}_2]\text{Cl}$ with improved catalytic activity at reasonable temperatures <1978JA7083>. Other rhodium-based catalysts have been reported <1992JA2520>. A ruthenium–porphyrin complex and an iron analog have been described as alternatives to the costly rhodium catalysts but these catalysts involve radical mechanisms and thus suffer from substrate rearrangement and low reproducibility <1980CC939>.

The decarbonylation of aldehydes was recently achieved at room temperature in THF with a catalytic amount of Wilkinson's catalyst (Equations (121) and (122)) <1992JOC5075>. The process involves stoichiometric amount of diphenylphosphoryl azide (DPPA, a readily available, nonexplosive azide used in peptide synthesis) to regenerate active rhodium species by carbon monoxide abstraction from inactive $\text{RhCl(PPh}_3)_2(\text{CO})$.



(ii) Free-radical decarbonylation

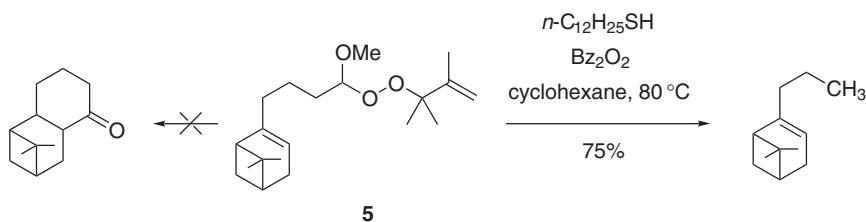
Direct free-radical decarbonylation of aldehydes was first developed by Berman <1963JA4010>, but the conditions employed (high temperature, UV irradiation) limit the reaction to aldehydes that decarbonylate faster than they react by alternative pathways. Specific photodecarbonylation of β,γ -unsaturated aldehydes has also been reported <1970JA4906>. Milder conditions involve the decomposition of peroxides derived from aldehydes (Equation (123)) <1999CC139, 2000JOC3961>.



This process is particularly recommended when standard free-radical conditions led to side reactions. As shown in Scheme 11, homolytic cleavage of the peroxide **5** affords deformylated compound in 75% yield, while direct free-radical conditions used with the starting aldehyde are known to afford a cyclized ketone.

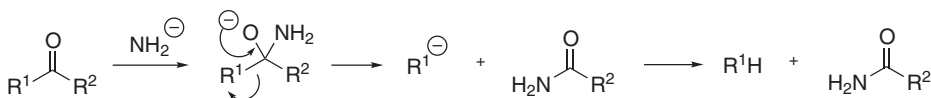
1.02.3.3.3 Reductive cleavage of nonenolizable ketones

The base-induced C—C bond cleavage of nonenolizable ketones to give a carboxylic acid derivative and a hydrocarbon is known as the Haller–Bauer reaction (Scheme 12). The direction of cleavage is determined by the carbanion-stabilizing abilities of R^1 and R^2 . The initial reaction conditions involve sodium amide in boiling benzene or toluene, but other bases such as



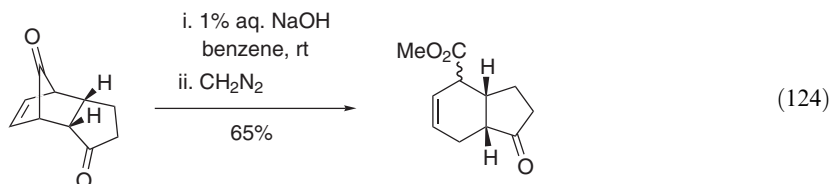
Scheme 11

hydroxides can be equally efficiently employed (sodium hydroxide, sodium methoxide, potassium *t*-butoxide). The steric course of this reaction and recent synthetic applications have been reviewed <1990OPP169, 2000T1399>.



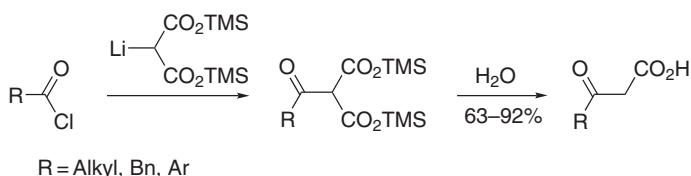
Scheme 12

The synthetic utility of this transformation was illustrated in the synthesis of pumiliotoxin C where norbornenone was selectively cleaved to produce a key intermediate (Equation (124)) <1995JOC279>. Optimized conditions have been reported to prevent the isomerization of double bonds. Other applications are related to the controlled ring opening of bicyclo[2.2.2]octenones <2001TL1287>.



1.02.3.4 Reductive Decarboxylation of Activated Carboxylic Acids and Esters

The presence of an electron-withdrawing group at the α -position of an acid or an ester dramatically enhances the ability for decarboxylation as shown by the Van der Baan method for the homologation of carboxylic acids (Scheme 13) <1979S787, 1999JA7425>.

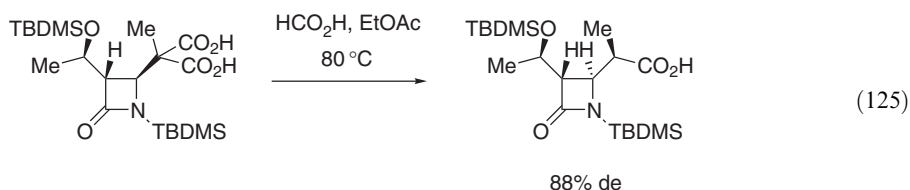


Scheme 13

1.02.3.4.1 Thermal decarboxylation of disubstituted malonic acids

Refluxing disubstituted malonic acids in aprotic solvent is a convenient procedure to achieve decarboxylation. Simple reflux in dioxane <1999SL1371> or toluene <2001TL6015> generally provides high yields of the corresponding carboxylic acid. Microwave heating was found to effect rapid decarboxylation of malonic acids in water (190°C , 800 W, 15 min, 80–98%) <2000SC2099>.

Similarly, heating malonic acid derivatives in acetic acid <1995SC521, 2000JMC4868> led to high yields of the corresponding acids. These conditions have found broad utility in organic synthesis. It is worth noting that unusual stereoselective decarboxylation has been reported as a key reaction in an industrial synthesis of carbapenem antibiotic (Equation (125)) <1995JOC8367>.



From extensive computational studies, the authors concluded that the selectivity observed was derived from a kinetically controlled protonation of the intermediate ketene acetal.

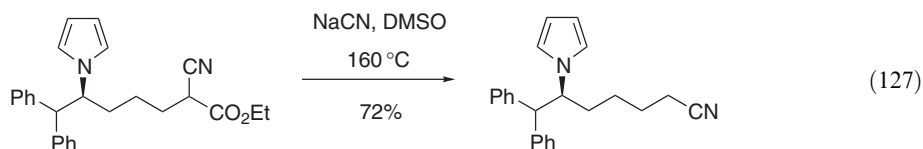
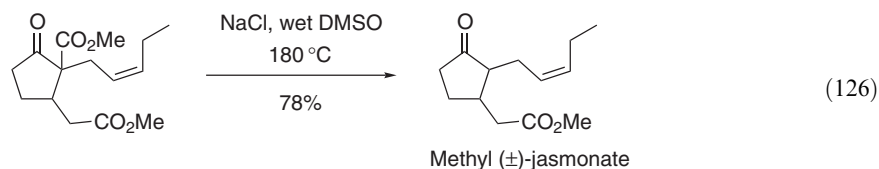
1.02.3.4.2 Nucleophile-mediated decarboxylation of malono esters

The decarboxylation of an activated ester (malonates, β -keto esters, α -cyano esters, α -sulfonyl esters) usually involves heating of the substrate in a dipolar aprotic solvent at high temperature in the presence of nucleophiles such as water, halides, cyanides, acetates, *t*-butoxides, thiocyanates, amines, or thiolates. Reports in the literature describe countless examples of such useful transformations.

(i) Use of cyanide or halide nucleophiles

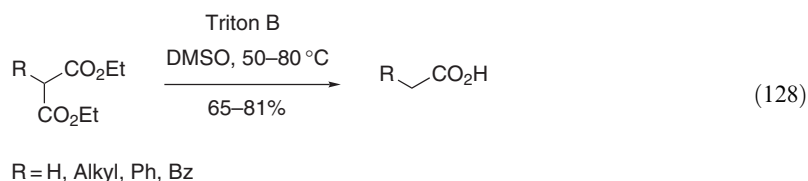
The use of nucleophiles such as cyanides or halides in hot dimethyl sulfoxide to decarboxylate an activated ester is named the Krapcho reaction. This well-known reaction has been widely exploited. The scope and limitations have been reported by Krapcho <1978JOC138> and a review covering the range of synthetic applications of this useful reaction has been published <1982S805, 1982S893>.

Recent applications are illustrated by a successful decarboxylation leading to a synthesis of methyl (\pm)-jasmonate (Equation (126)) <1992SC1283> and an efficient preparation of an intermediate involved in a synthesis of a chiral bicyclic amidine (Equation (127)) <1995TL4279>.

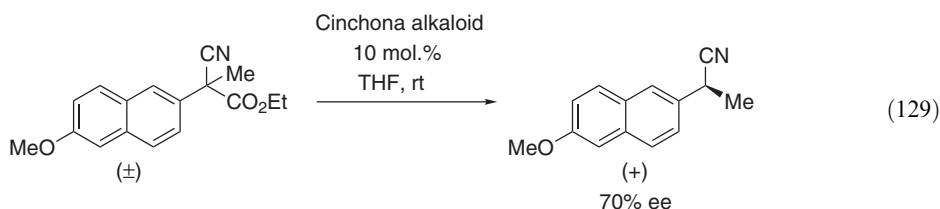


(ii) Use of other nucleophiles

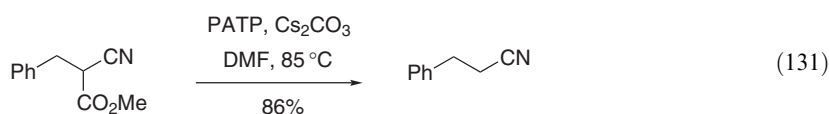
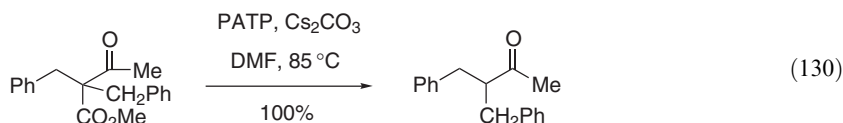
Other weak nucleophiles catalyze the decarboxylation reaction of activated esters such as *N*-methylmorpholine <1997BMCL2299>, 1,5-diazabicyclo[4.3.0]non-5-ene (DBN), or diazabicyclooctane (DABCO) <1976JOC208>. Recently, the use of Triton B has been described to be an efficient reagent for the mild decarboxylation of malonates (Equation (128)) <1998SC4179>.



Naproxen has been prepared enantioselectively using a cinchona-alkaloid-mediated enantioselective decarboxylation as the key step (Equation (129)) <2000EJO2119, 2002EJO2405>.

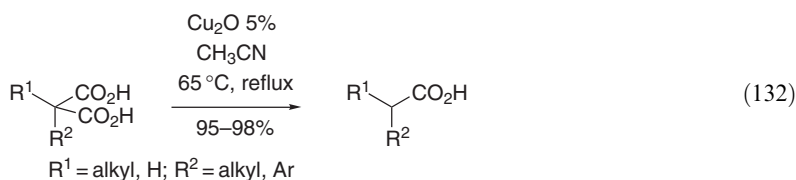


The use of *p*-aminothiophenolate (PATP) and catalytic quantities of caesium carbonate in DMF has been described to afford better yields than Krapcho procedure for the decarboxylation of activated methyl esters. The reported process uses shorter reaction time and lower temperatures relative to the original Krapcho conditions (Equations (130) and (131)) <1986JOC3165>.



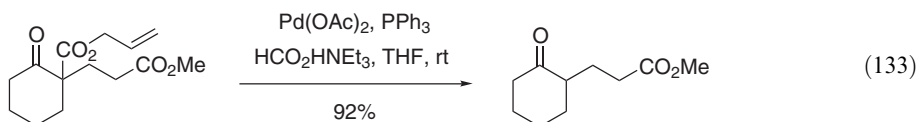
1.02.3.4.3 Metal-mediated decarboxylation of activated acids and esters

Quinoline/copper is a classical system for the decarboxylation of α,β -unsaturated acids and malonic acids and have found some recent applications <1995JMC923>. An optimized copper catalyst has been reported to afford a mild and quantitative process for the selective decarboxylation of malonic acids. The low temperatures employed improve the yields (Equation (132)) <1984T3229, 1986S1029>. Some transfer of chirality (ee up to 31%) has been observed when such conditions have been used in the presence of cinchona alkaloid <1987TL539>.

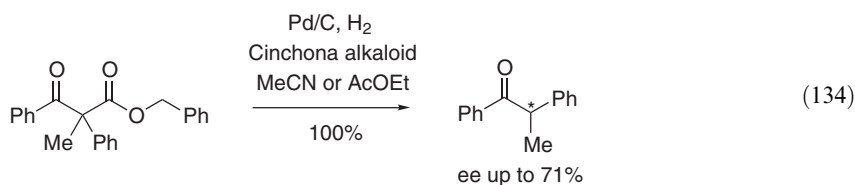


Recently, a tungsten-based complex <1993JA4675> was found to be an effective catalyst for the decarboxylation of cyanoacetic acid under mild conditions but shows little improvement against the former copper catalyst.

Palladium-catalyzed deprotection–decarboxylation is a mild and nearly neutral method for the decarboxylation of activated allyl esters as illustrated by Equation (133) <1985JOC3416>.

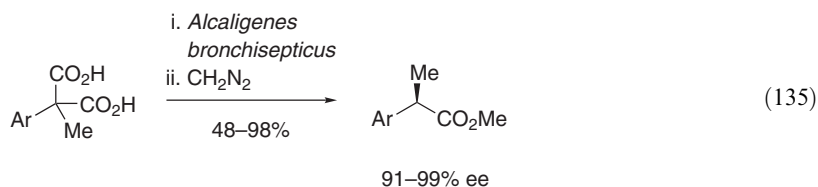


Decarboxylation followed by asymmetric protonation of the intermediate enol has been observed when subjecting an α -keto ester to hydrogenolysis conditions in the presence of a Cinchona alkaloid (Equation (134)) <2001CC533>.



1.02.3.4.4 Miscellaneous methods

Decarboxylation is a well-known metabolic process for activated carboxylic acid derivatives such as amino acids. Interestingly, this reaction has been successfully applied to the enantioselective decarboxylation of malonates (Equation (135)) <1990JA4077>. This procedure is a useful new entry for the preparation of chiral-substituted benzylic esters.



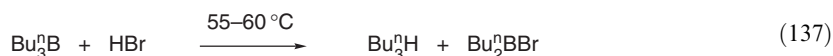
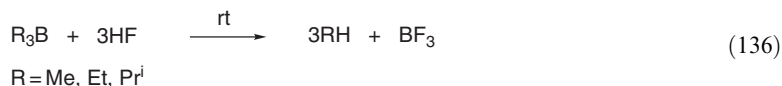
1.02.4 REDUCTION OF CARBON—BORON, —SILICON, AND —GERMANIUM BONDS TO CARBON—HYDROGEN BONDS

1.02.4.1 Reduction of Carbon—Boron Bonds to Hydrocarbons

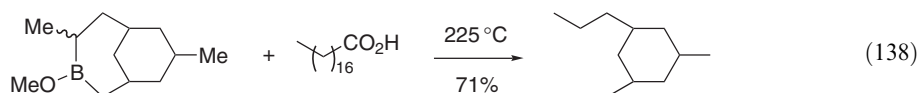
The cleavage of C—B bonds can be effected under various conditions, namely acidic, neutral, or basic conditions.

1.02.4.1.1 Cleavage of carbon—boron bonds under acidic conditions

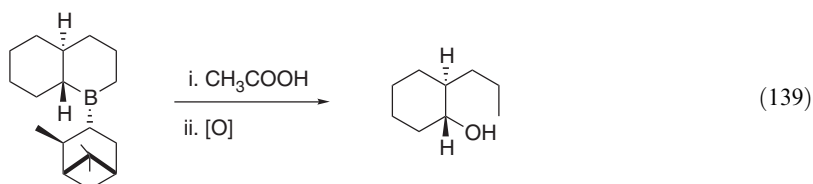
The use of acids in C—B bond cleavage was systematically studied in 1986 <1986T5497>. Trialkylboranes are inert toward water or strong mineral acids with the exception of anhydrous hydrogen fluoride (Equation (136)). For example, hydrogen bromide reacts slowly and incompletely (Equation (137)).



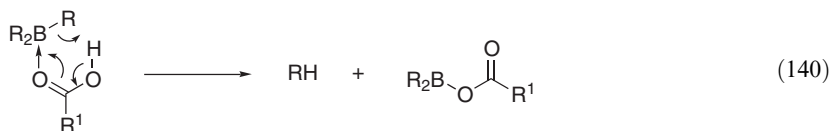
Organoboranes react readily with carboxylic acids to liberate the corresponding alkanes (Equation (138)) <1986T5497, 1984JOM(260)17, 1984JOM(270)9>. The steric requirements of the alkyl groups attached to boron play an important role in the rates of protonolysis. The first alkyl group of a trialkylborane is protonolyzed easily, followed by increased difficulty in the removal of the second and third alkyl groups.



This property has been successfully used in the preparation of a secondary alcohol through the selective protonolysis of a primary C—B bond with acetic acid, followed by an oxidation step (Equation (139)) <1998JOC8276>.

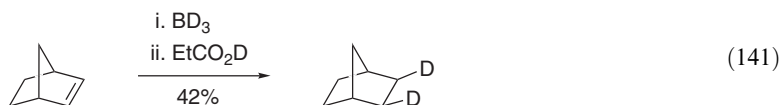


Protonolysis of the organoboranes with carboxylic acids involves coordination of the carbonyl oxygen atom to the boron atom, followed by an easy intramolecular proton transfer (Equation (140)) <1986T5497>.

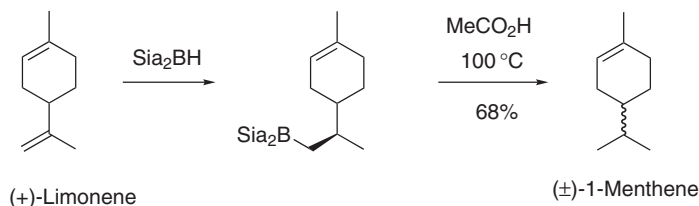


Replacement of an alkyl group by an acyloxy group renders the boron atom less electrophilic, and explains why the acyloxyboron intermediates become progressively less reactive toward acidolysis <1986T5497>.

The stereochemistry of the protonolysis was established via deuterioboration of norbornene and deuterolysis of the product. Protonolysis occurs with retention of configuration at the carbon atom originally attached to boron (Equation (141)) <1986T5497>.



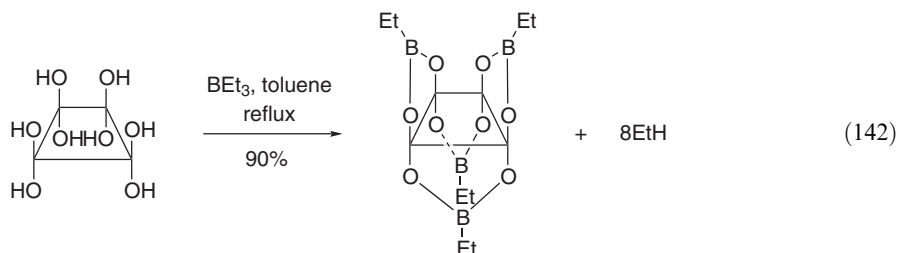
The protonolysis reaction tolerates functionalities such as halides or ether groups in the alkylboranes <1986T5497>. However, systems that are intrinsically labile to either acid or heat may be problematic. For example, enantiomerically pure *d*-limonene produces the racemic 1-menthene under hydroboration–protonolysis (Scheme 14) <1986T5497>.



Scheme 14

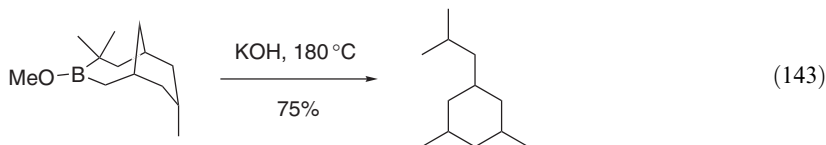
1.02.4.1.2 Cleavage of carbon–boron bonds under neutral conditions

Several organoboranes have been cleaved by alcohols. An interesting example of this process is the use of the cyclic polyol octahydroxycyclobutane <1983CB1336>. When a suspension of the cyclic polyol in mesitylene reacted with triethylborane (activated with diethylboryl pivalate), 8 equiv. of ethane were released and the product was formed (Equation (142)).



1.02.4.1.3 Cleavage of carbon–boron bonds with base

Cleavage of organoboranes can also be achieved with potassium hydroxide. An example is given below (Equation (143)) <1982JOM(226)115>.

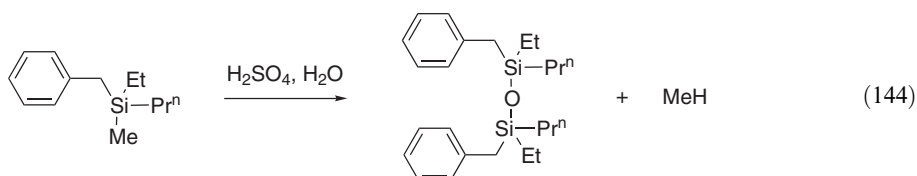


1.02.4.2 Reduction of Carbon—Silicon Bonds

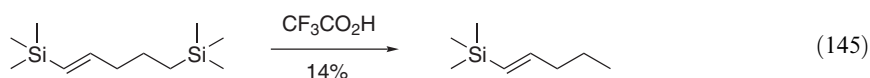
There are a plethora of methods for the cleavage of C—Si bonds to give C—H bonds, ranging from the use of acid or base to thermolysis.

1.02.4.2.1 Cleavage by acid

Acids have been used on several occasions for desilylation. Cleavage of an alkyl silicon bond using concentrated sulfuric acid was first reported in 1910 [<1980JPR503>](#) and has since been used with functionalized organosilicon compounds ([Equation \(144\)](#)).



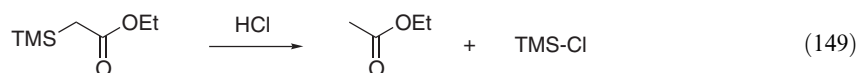
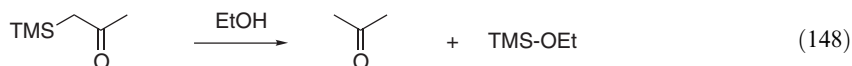
Trifluoroacetic acid has also been used to cleave C—Si bonds. Trifluoroacetic acid selectively cleaves specifically the alkyl silicon bond in preference to the vinylsilicon bond, but the yield is very poor ([Equation \(145\)](#)) [<1981ZOB420>](#).



The cleavage of the C—Si bond by electrophilic reagents such as Lewis acids is well established in organosilicon chemistry ([Equation \(146\)](#)) [<1983ZOB806>](#). In some cases a Lewis acid is used in conjunction with hydrogen halides ([Equation \(147\)](#)) [<1980JPR503>](#).



Simple α -trimethylsilylketones can be desilylated in ethanol to give the corresponding ketone ([Equation \(148\)](#)) [<1970MI355>](#). Hydrogen chloride was required for the cleavage of α -trimethylsilyl esters ([Equation \(149\)](#)).

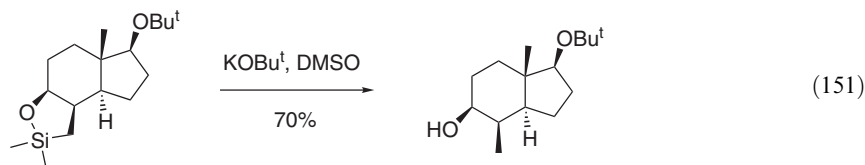


1.02.4.2.2 Cleavage by base

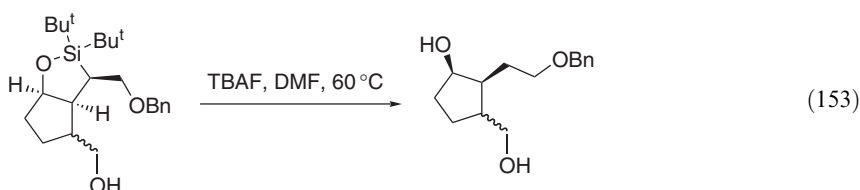
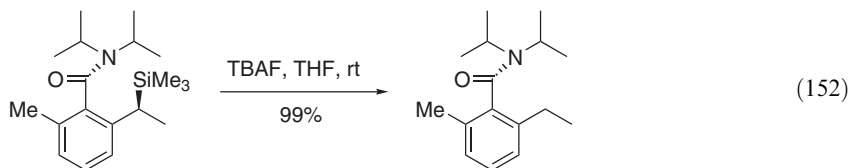
There have been several reports that show the cleavage of a C—Si bond to give a C—H bond using a base. One of the earliest of these reports showed that tetramethylsilane could be cleaved by potassium *t*-butoxide in dimethyl sulfoxide ([Equation 150](#)) [<1967JOC4126>](#).



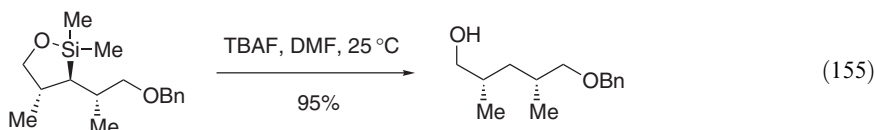
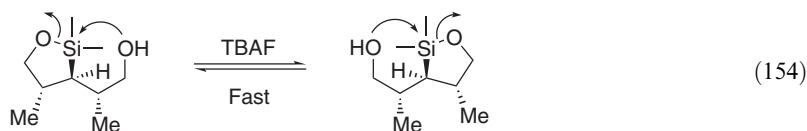
Unactivated hydroxysilanes can undergo protodesilylation when treated with potassium *t*-butoxide in aqueous DMSO. Water was used as the proton source to favor formation of the protodesilylation product. Under these conditions, no racemization is observed ([Equation \(151\)](#)) [<1986JA6826, 1982JA6809>](#).



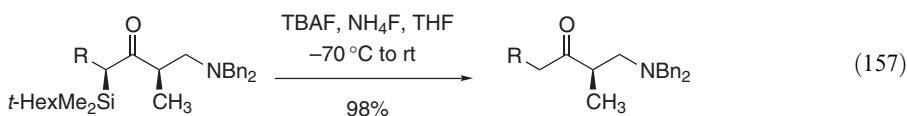
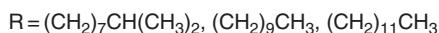
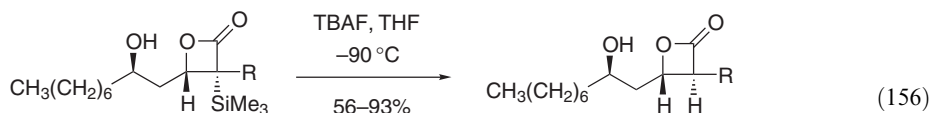
Fluoride-induced hydrodesilylations presumably involve carbanion or radical intermediates and have been widely used (Equations (152) and (153)) <2000JOC7033, 1999JOC2776, 2001JOC4841, 1992JA7578, 1999EJO1939, 1995CRV1253>.



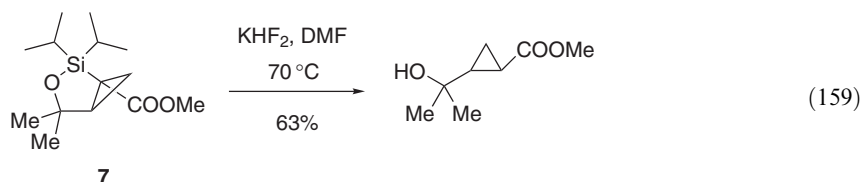
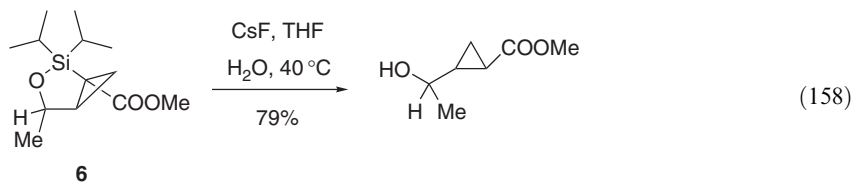
Protodesilylation is sensitive to subtle structural variations. When a neighboring hydroxyl group is not protected, no reaction takes place even when the mixture is stirred at 25 °C. This may be attributed to a facile equilibrium between the two corresponding siloxanes, which on average could be viewed as a hypervalent siloxane complex (Equation (154)). When the alcohol is protected, TBAF-mediated protodesilylation occurs readily (Equation (155)) <1992JOC1643>.



The desilylation of α -silylcarbonyl compounds can be achieved at room temperature by treatment with tetrabutylammonium fluoride in THF, since the intermediate carbanion is stabilized as an enolate (Equation (156)) <1998JCS(P1)1373, 1995JOC7334>. However, sometimes this desilylation is accompanied by racemization, due to the formation of basic $\text{Bu}_4\text{N}^+\text{OH}^-$. This problem was solved by the addition of solid ammonium fluoride used as a buffer and by carrying out the reaction at low temperature to control the rate of formation of the base (Equation (157)) <1996AG(E)981, 1997AG(E)2362, 2000SL644>.

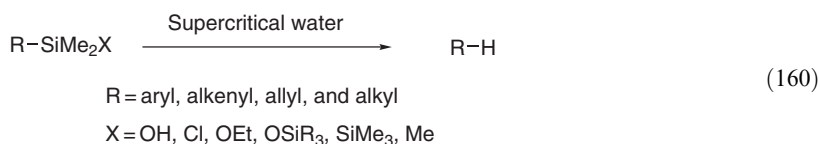


Desilylation of **6** could be achieved with caesium fluoride in wet THF (Equation (158)), but potassium hydrogen fluoride in DMF was required for **7** (Equation (159)). Other methods, such as KF/18-crown-6 or tetrabutylammonium fluoride in THF, were unsuccessful <1999EJO1939>.

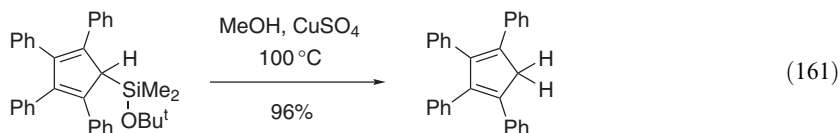


1.02.4.2.3 Desilylation by miscellaneous methods

Supercritical water (scH₂O), the critical temperature and pressure of which are 374 °C and 22.1 MPa, respectively, has recently been used to cleave the C—Si bond of a wide range of organo-silicon compounds (Equation (160)) <2003JA6058>.

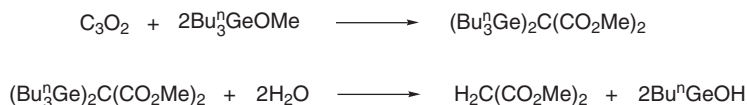


When a benzene solution of cyclopentadienyl *t*-butoxydimethylsilane was heated in a sealed tube at 100 °C in the presence of a catalytic amount of anhydrous cupric sulfate, the corresponding cyclopentadiene was obtained in 96% yield (Equation (161)) <1985OM584>.



1.02.4.3 Cleavage of Carbon—Germanium Bonds to Carbon—Hydrogen Bonds

Some work has been carried out to investigate the addition of alkoxides to carbon suboxide <1988G577>. When germanium alkoxides are exposed to carbon suboxide, a germanium malonate is formed. The C—Ge bond is cleaved by addition of water to form dimethyl malonate and BuⁿGeOH (Scheme 15).



Scheme 15

1.02.5 REDUCTION OF CARBON—METAL BONDS TO CARBON—HYDROGEN BONDS

The reduction of C—Hg bonds is the most common process. The reduction of other carbon—metal bonds (where the metal is an alkali or alkali earth metal) to a C—H bond usually involves the reaction with a proton donor, such as water or acid.

1.02.5.1 Reduction of C—Hg Bonds

The reduction of C—Hg bond consists mainly in protonolysis and metal hydride reductive demercuration. In addition, a few miscellaneous reactions will be discussed.

1.02.5.1.1 Protonolysis

The protonolysis of organomercurials has been studied extensively. The organomercurials are easy to prepare in high purity and easy to handle. These properties make them ideal candidates for mechanistic studies on the protonolysis of carbon—metal σ bonds, and several reviews <1968PAC79, 1978T2827> and an article <1984JA3703> have been written on this topic.

As one could expect there are several mechanisms for the protonolysis reaction. The protonolysis reaction of an alkyl mercury halide with hydrochloric acid proceeds through a four-center transition state according to Scheme 16 <1968PAC79>.



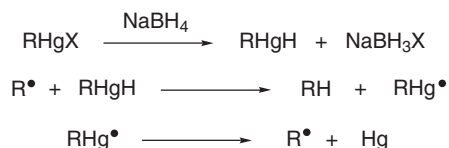
Scheme 16

The intramolecular nucleophilic participation of the chloride conjugate base is arguable. There is evidence, based on studies of protonolysis of unsymmetrical alkyl mercurials, which suggests a three-center transition state <1969JCS(B)1071>. Whatever the transition state, further reaction occurs by front side attack on the carbon center, forming a transition state containing a pentacoordinate carbon atom <1984JA3703>. There are some reports on unimolecular $\text{S}_{\text{E}}1$ reactions <1968PAC79, 1969JCS(B)1071>.

The C—Hg bonds are generally stable to water and alcohols, and thus the protonolysis of these bonds requires stronger acids such as hydrochloric acid or sulfuric acid. Carboxylic acids are much less effective. In general the acid cleavage of dialkylmercurials is much easier than that of alkylmercuric salts. Alkyl—mercury bonds are cleaved less readily than aryl—mercury bonds <B-1980MI004>.

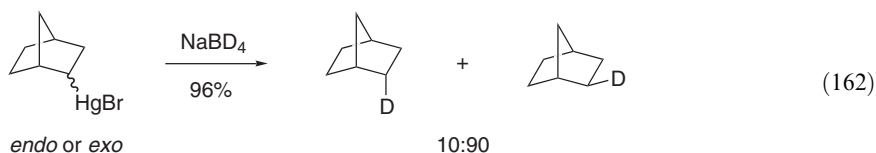
1.02.5.1.2 Metal hydride demercuration

Sodium borohydride has been widely used to reduce organomercurials to produce the corresponding hydrocarbons. The mechanism involving the reduction of the organomercurials with sodium borohydride is believed to be a free radical process as shown in Scheme 17 <1976JA5973, 1984TL5239, B-1985MI006, 1991COS(8)850>.

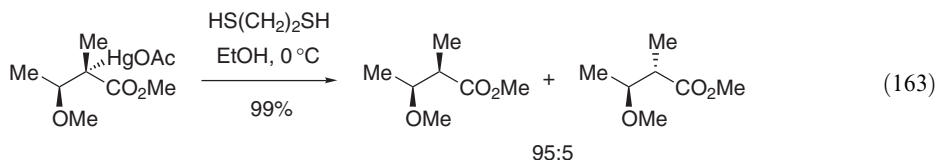


Scheme 17

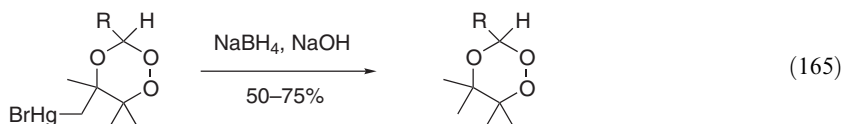
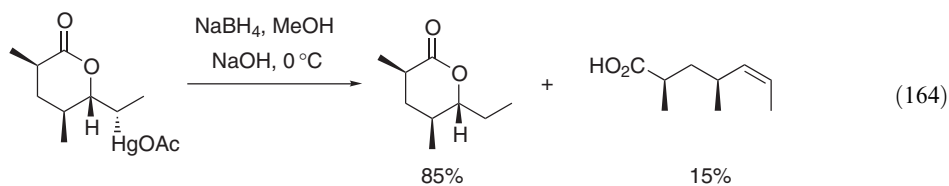
Reduction of *exo*- and *endo*-norbornylmercury(II) bromide with sodium borodeuteride provides *exo*-[2-D]norbornane as the major product (Equation (162)) <1970JA6611>. Other examples of this phenomenon can be found in the literature <1981JOC563>.



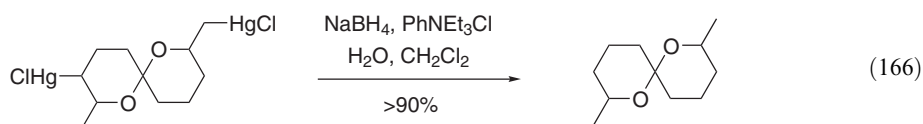
The diastereoselectivity in metal hydride demercuration of α -mercury(II) carbonyl compounds depends on the nature of the solvent, the amount of hydride used, the mode of addition, the nature of the hydride source, and the ligand on mercury (Equation (163)) <1986JOC2024>.



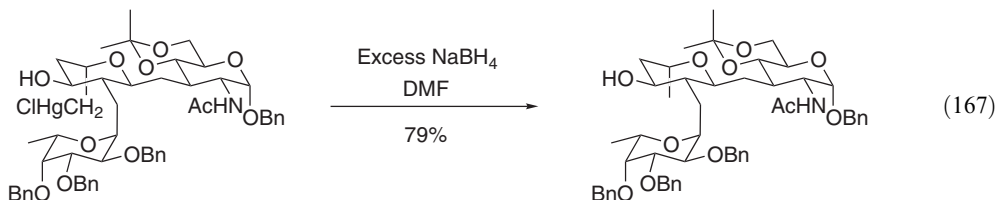
A frequent problem associated with the reductive demercuration of organomercurial compounds is deoxymercuration, which would result in the isolation of alkenes. This is often minimized by using alkaline borohydride (Equation (164)) <1984T2317, 1966JA993, 1983TL4923, 1997T2835, 2001T9915>. Alkaline borohydride in the demercuration of peroxymercurials has also been accomplished (Equation (165)) <1992CC428, 1992CC926, 1992T3835, 1993T2729>.



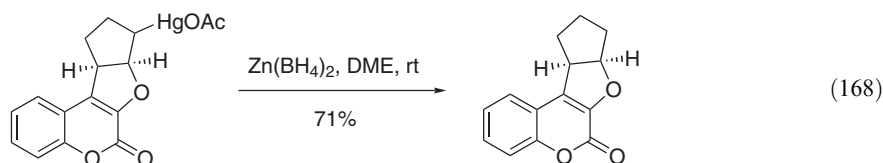
Phase-transfer reagents are sometimes used to avoid deoxymercuration and other side reactions (Equation (166)) <1986CC855, 1979S891, 1984JOC2838>.



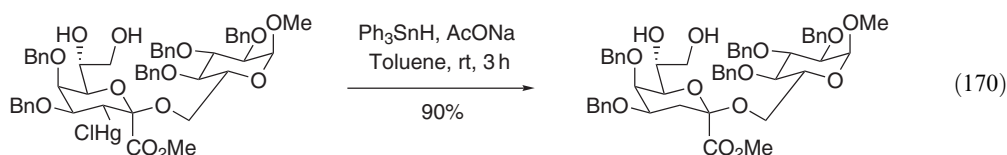
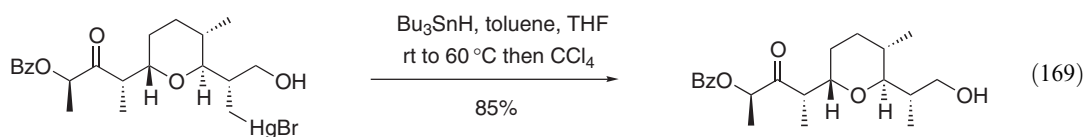
Reductive demercurations using an excess of sodium borohydride in DMF without sodium hydroxide have been reported to give good results (Equation (167)) <1997JOC5267>. However, it seems that it is not a general method for the reduction of C—Hg bonds.



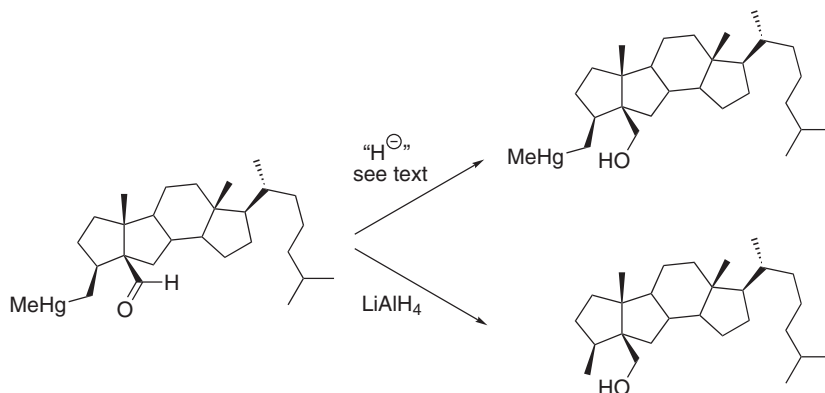
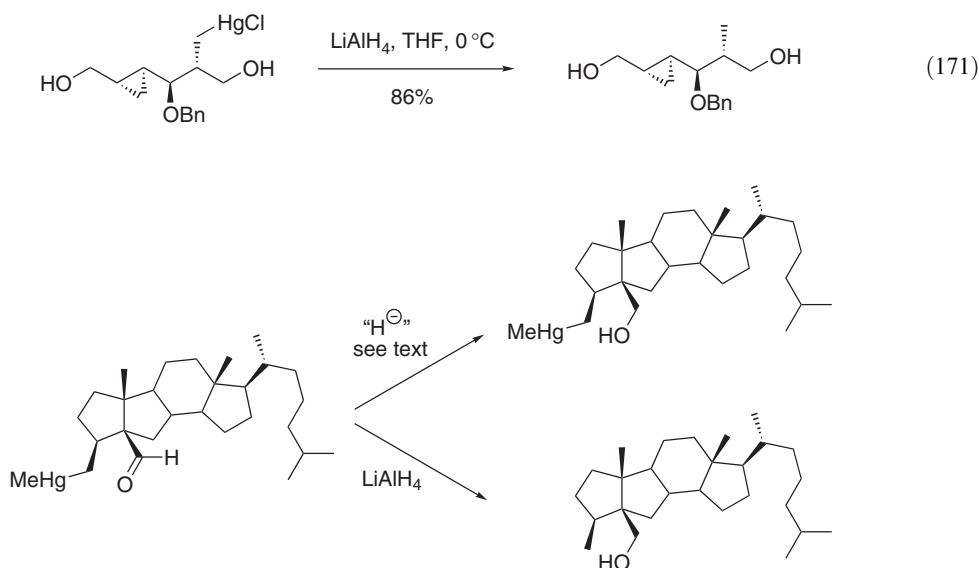
Zinc borohydride has been successfully used for reductive demercuration to give desired product as a milder reducing agent compared to alkaline borohydride, which resulted in the isolation of the starting alkenes used prior to mercury addition (Equation (168)) <1992SC3013>.



A number of demercurations also use tributyltin hydride (Equation (169)) <2002AG(E)2144, 2001TA597, 2001OL2567, 1996JOC2109, 1984T2317, 1983JA6882>, or triphenyltin hydride <1984JA8313, 1996CAR69>, but complete removal of tin residues can be difficult. As with sodium borohydride, there is also a problem with competitive deoxymercuration when tin hydrides are used <1984T2317>. The presence of sodium acetate prevents this problem if triphenyltin hydride is employed (Equation (170)) <1984JA8313, 1996CAR69>.



LAH has been used as the reducing agent in demercuration (Equation (171)) <1999JOC101, 1983JA6882, 1986JA2094, 1997JOC4653>. Methylmercurio derivatives R—HgMe are stable toward a number of hydrides (NaBH₄, LiAl(OBu^t)₃H, L-selectride, or superhydride) and the halomercurio functionality can be regenerated by treatment with HgCl₂ or HgBr₂. Alternatively, LAH gave the fully reduced product (Scheme 18) <1999JOC101>.



Scheme 18

The reduction of organomercury(II) halides with LAH has been investigated and the findings suggest an electron-transfer mechanism involving attack of the alkyl radical on the metal hydride (Scheme 19) <1983TL1411>.



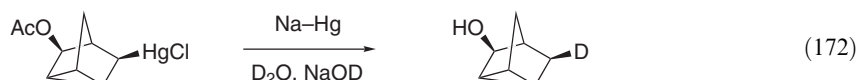
Scheme 19

1.02.5.1.3 Miscellaneous methods

Although sodium borohydride is most often employed for the reduction of C—Hg bonds, there has been a significant increase in the use of other reducing reagents such as thiols and sodium amalgam (*vide infra*). Reduction with hydrogen sulfide <1984JCS(P1)1689>, sodium dithionite <1979JOC228>, metals <1980JA337, 1992CC1086>, Wilkinson's catalyst <1980JA337>, and electrochemical reductions have also been reported <1985JOC673>.

Organomercurials react with thiols by a free-radical substitution mechanism <1983JA1398>. A limitation in the use of certain thiol reagents is, as for most reagents used for demercuration, competitive deoxymercuration.

The sodium amalgam cleavage of alkylmercurials involves an ionic mechanism <1972JOC4341>. The reaction is also stereospecific with retention of configuration at the carbon center. No rearrangement was observed in the rearrangement-prone nortricycyl–norbornenyl system (Equation (172)) <1981JOC563>.



The latest addition to the numerous reagents for reduction of mercurials is *N*-benzyl-1,4-dihydronicotinamide (BNAH), which is proposed to reduce C—Hg bonds via an electron-transfer chain substitution mechanism <1981TL4495>.

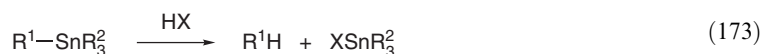
1.02.5.2 Cleavage of Other Metals from Carbon to Give a C—H Bond

1.02.5.2.1 Protonolysis

There are many carbon—metal bonds, which can be reduced on addition of a proton donor to the reaction. The C—Al bond can be readily cleaved on addition of HX (where X is a hydroxyl or alkoxyl group, etc.) to give the corresponding hydrocarbon <B-1972MI002>.

In general, all organometallic compounds of type RM (where R is lithium, sodium, or potassium) and of type RMgX (where X is halogen) will undergo protonolysis readily, if not violently, when they come into contact with a proton donor <B-80MI004>.

The C—Sn bond is very susceptible to protonolysis. Water and aliphatic alcohols are generally inert, but phenols, mercaptans, and carboxylic acids readily cleave the C—Sn bond to give a C—H bond (Equation (173)) <B-80MI004>.



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1962JA3744
1963JA97
1963JA1108
1963JA4010
1963JCS1855
1964JA1152
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1965MI39
- 1965TL3969
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1966JCS(C)425
1966T487
1966TL3579
1967JA6794
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1968AG(E)120
1968JA99
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1968JOC75
1968PAC79
1969JCS(B)1071
1969M724
1970JA2139
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1970JA6611
1970MI355
1971JOC737
1971MI1567
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1972JOC4341
B-1972MI002
1973BSF1174
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- 1973S703
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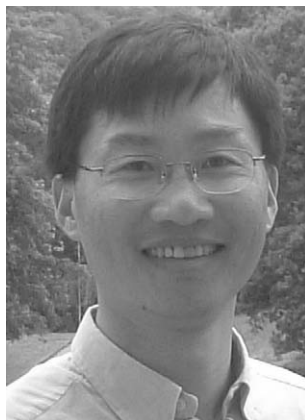
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1.03

Two or More CH Bond(s) Formed by Addition to CC Multiple Bonds

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1.03.1 REDUCTION OF ALKENES

1.03.1.1 General Methods for Alkene Reduction

Since the very first report of ethene reduction in 1874 [<1874CB352>](#) and the first extensive developments of the reaction between hydrogen and organic compounds by Sabatier and his group [<1897CR1358>](#), heterogeneous catalytic hydrogenation continues to be one of the most useful techniques for the addition of hydrogen to C—C multiple bonds and to the aromatic nucleus. As a clean, scalable process, this reaction has major applications both on the laboratory and industrial scale and has been regularly reviewed [<1985CRV129, 1995HOU\(E21d\)4239, B-1998MI001, 2001AC\(221\)93, B-2001MI001, 2003MI103>](#). The performance of catalysts used in such a reaction can be influenced by numerous parameters, sometimes difficult to control in a reproducible manner. The characteristic of the metal is usually dominant: in the hydrogenation of propene, the catalytic activities of the metals decrease in the following sequence: Rh > Ir > Ru > Pt > Pd > Ni > Fe > Co > Os [<B-1996MI001>](#). Among them, Pd, Pt, Rh, Ru, Ni, and Cu are often used. The structure and morphology of metal particles exert an influence on the macroscopic catalytic behavior, which can also be tuned by a second metal. The type of support (usually charcoal, alumina, silica as well as CaCO₃, BaSO₄, or SrCO₃ to a lesser extent [<1996T4495>](#)), the particle size, the pore structure, and acid–base properties are also important parameters for catalyst activity. Theoretical and practical aspects of the hydrogenation process from an industrial point of view have been reviewed [<B-1994MI001>](#). The mechanism of the

reaction is complicated. The initial Horiuti–Polanyi proposal <1934TFS1164> has been investigated in detail when techniques of molecular surface science became available <2001AC(222)3>. Ethene hydrogenation has been studied on single-crystal Pt surfaces (Figure 1).

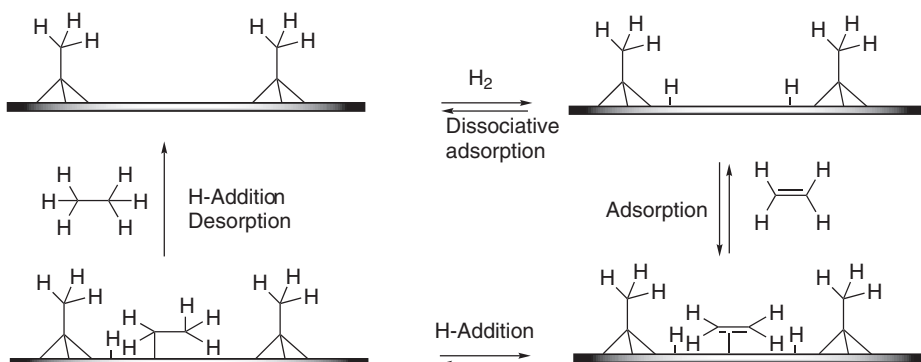
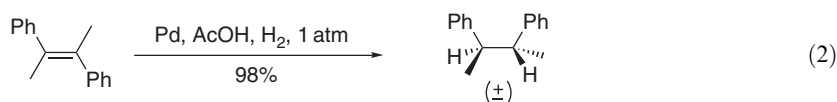
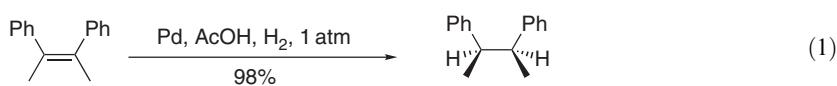


Figure 1 Mechanism of ethene heterogeneous hydrogenation.

Ethene is adsorbed in the form of unreactive ethylidyne at room temperature. This does not prevent the reversible dissociative adsorption of hydrogen, but strong adsorption of additional ethene in a π -bonded fashion occurs only after the diffusion of an ethylidyne species and opening of a vacant site <2002JA10982>. Sequential hydrogen transfers from adjacent sites give a mono-absorbed ethyl and ethane, which is then desorbed from the metal. Recent studies on Ni surfaces indicate that unbonded energetic bulk H atoms might also be reactive species in this process <2001ACR737>. The major side reaction that can occur during heterogeneous hydrogenations is isomerization and double bond migration. This of course goes unnoticed unless the isomer shows an appreciably different reactivity or hydrogenation results in stereochemical scrambling. Two mechanisms have been proposed for the double bond migration. First, the “associative” pathway is based on the reversibility of the first H addition step in the Horiuti–Polanyi proposal (Figure 1). This can happen only if two vacant sites are able to accept the leaving hydride and the alkene near the σ -bonded intermediate. Second, the “dissociative” pathway, proposed by Farkas and co-workers <1934MI630>, involves an allylic intermediate. This mechanism requires at least three vacant coordination sites to bind the alkene and the hydrido group <1991COS(8)417>. Since the surface of a metal might provide several coordinating sites, both mechanisms may operate. A decreasing order of activity in the double bond migration is $\text{Pd} > \text{Ni} \gg \text{Rh} \gg \text{Ru} = \text{Os} > \text{Ir} = \text{Pt}$ <1991COS(8)417>. In a comparative study, an associative pathway has been proposed for Pt-, Ir-, and Rh-catalyzed isomerizations, whereas a π -allyl species is involved in Pd-catalyzed migrations <1984JOC1845>. Besides the choice of the metal, several parameters can be optimized to favor the addition of hydrogen over isomerization. Since, for both pathways, double bond migration requires a vacant site to accept a hydride, decreasing the number of vacant sites by increasing the hydrogen availability (pressure, solubility, etc.) or by adsorption of bases (tertiary amines, phosphines, or CO groups) can prevent this isomerization. The use of benzene as a solvent with Pt and Rh catalysts is known to lower the isomerization rate <1991COS(8)417>, which has also been correlated with the polarity of the substrate to be hydrogenated <1997JOC(118)255>. The addition of two hydrogen atoms on a C=C double bond occurs in a *syn*-manner. Thus, hydrogenation of (*Z*)-2,3-diphenyl-2-butene leads to the *meso*-isomer (98%) of 2,3-diphenylbutane (Equation (1)), whereas the (*E*)-isomer leads to a racemic mixture of 2,3-diphenylbutane (Equation (2)) <1991COS(8)417>.



Apparent *anti*-addition might be obtained in some cases, and is the result of a *syn*-hydrogenation of an isomerized intermediate <1973CL855>. The stereochemistry of hydrogenation of alkenes generally involves a *cis*-addition of hydrogen to the least hindered face of the olefin. A model of the mode of adsorption on active sites provides a good estimation of the outcome of hydrogenation of 4-alkyl methylenecyclohexanes, leading to the predominant formation of 1,4-*cis*-disubstituted cyclohexanes (Figure 2) <1997MI419>.

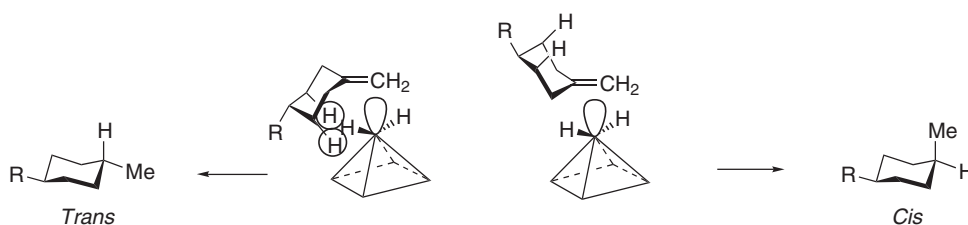


Figure 2 Stereoselectivity in the hydrogenation of 4-alkylmethylenecyclohexanes.

The preferred direction of adsorption can also be influenced by the presence of substituents other than alkyl groups. π -Electrons of phenyl groups can promote attractive interactions with the surface, and the location of hydroxyl groups near the double bond can strongly influence the facial selectivity of hydrogen addition. The relative importance of this phenomenon, called haptophilicity <1973JA6379>, is sometimes difficult to predict, and might vary with the nature of the catalyst <1997MI419>. A comparative hydrogenation (5% Pd/C catalyst) study performed on alkenes incapable of isomerizing led to the following order of haptophilicity for the groups studied (Equation (3) and Table 1): $R = \text{CH}_2\text{NH}_2 > \text{CH}_2\text{NMe}_2 > \text{CH}_2\text{OH} > \text{CHNOH} > \text{CH}_2\text{OMe} > \text{CHO} > \text{CONH}_2 = \text{CH}_2\text{NHCOMe} > \text{COOK} > \text{COMe} > \text{CN} > \text{CONHOH} > \text{COOH} > \text{COOMe} > \text{COONa} > \text{COOLi}$ <2002JOC2813>.

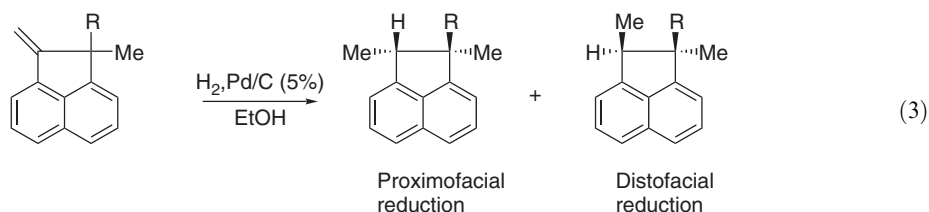


Table 1 Percent proximofacial product <2002JOC2813>

<i>R</i>	Proximofacial product (%)	<i>R</i>	Proximofacial product (%)
CH ₂ NH ₂	87	COOK	30
CH ₂ NMe ₂	62	COMe	22
CH ₂ OH	48	CN	20
CHNHOH	45	CONHOH	18
CH ₂ OMe	44	COOH	17
CHO	42	COOMe	16
CONH ₂	33	COONa	10
CH ₂ NHAc	33	COOLi	7

This phenomenon is sometimes markedly influenced by the solvent, with an increase of haptophilic effectiveness accompanied by a lowering of the dielectric constant. The use of chiral modifiers for enantioselective transformations has been reviewed <2003MI45>. Only modest (when compared to the classical standards of homogeneous catalysis) enantioselectivities could be obtained on selected substrates.

Although heterogeneous catalysts offer an excellent method for the reduction of alkenes, especially for large-scale transformations, the development of homogeneous catalysis, based on soluble reducing species, was in recent years very spectacular and led to important results in the field of asymmetric transformations, as recognized by the 2001 Nobel prize to W. S. Knowles and

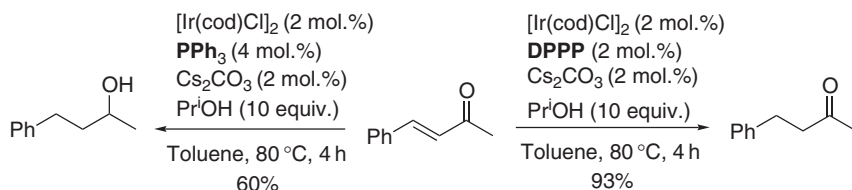
R. Noyori for enantioselective hydrogenation (with K. B. Sharpless for enantioselective oxidation) <2002AG(E)1998>. The attractiveness of homogeneous hydrogenation relies on a versatile hydrogen activation by numerous transition metals <B-1994MI002>, and the tuning of the complexes reactivity by the electronic and steric properties of the ligands, and, with cationic species, the counter-anion. Despite their lower activities, heterogeneous catalysts are more selective, not susceptible to poisoning, and also enable enantioselective hydrogenations. They also cause fewer rearrangements and less isotope exchanges and are therefore suitable for deuteration, although in some cases a mixture of partially deuterated products can be obtained with the Wilkinson catalyst $\text{RhCl}(\text{PPh}_3)_3$ <1965CC131> in chlorinated or alcoholic solvents <1970CC495, 1970CC497, 1970CC571>. The Wilkinson catalyst and, to a lesser extent, Crabtree's catalyst $[\text{Ir}(\text{cod})(\text{py})(\text{PCy}_3)]\text{PF}_6$ <1979ACR331> are most widely used for olefins lacking coordinating functionalities. Most of the other functional groups are tolerated by the Wilkinson catalyst with the exception of aldehydes, which lead to decarbonylation. This side reaction can be avoided by increasing the catalyst loading and hydrogen concentration <1966TL1605>. The rates of hydrogenation generally depend on steric effects, with the following order of reactivity: terminal alkenes > *cis*-alkenes > *trans*-alkenes <1991COS(8)443>. When applicable, functional groups such as hydroxyl, ester, and amide can direct the stereochemistry of hydrogenation <1993CRV1307>. This directing effect, however, is not necessary since significant stereocontrol can also arise from the intrinsic conformational preferences of the reactant <1998CC277>.

Although the real catalytic species is often short-lived and present at a very low level, the initial or intermediate complexes can be isolated or characterized by spectroscopic methods, leading to a good understanding of the catalytic cycle. Most of the mechanistic investigations have been performed with the Wilkinson catalyst and have been reviewed <2000CRV439>. Even if proposed classical mechanisms for Rh and Ru are taught in textbooks, such a reaction involving widely different metals, ligands, and substrates cannot be described by a single mechanism, as recently highlighted <2001AG(E)4611>. Low-valent Ru, Rh, and Ir complexes stabilized by tertiary phosphorus ligands are the most versatile catalysts for homogeneous hydrogenation, although hydrogenation of octene has been reported with nickel phosphane complexes <1998CC2689>, and Ti-based <1993JA12569> and Zr-based catalysts <1999JA4916> gave good results in the enantio- and diastereoselective reduction of olefins. Despite an impressively large number of chiral ligands recorded for this reaction <2003MI103>, this field is still very active with the recent revival of chiral monodentate phosphorus ligands <2001AG(E)1197, 2003MI308>, or the discovery of secondary phosphines <2002AG(E)612> and carbenes <2002AG(E)1290, 2001OM1255>, as valuable stabilizing ligands in such a reductive system. The use of homogeneous catalysis for the enantioselective reduction of olefins has been regularly reviewed <2003MI45, B-1999MI001>.

Although several industrial applications are well established already for the preparation of enantiomerically enriched chiral fine chemicals, at production, pilot, or bench stage <2001AC(221)119>, new reaction conditions have been investigated, mainly with the aim of addressing the immobilization or the recycling problem of the catalyst, and to get cleaner processes. The general strategy is to have the substrate and the catalyst in two different phases. For instance, hydrogenations have been carried out in biphasic aqueous medium <2002ACR738, 2002MI221, 2002MI239>, using mainly rhodium or ruthenium complexes, generally associated with water-soluble ligands. In some cases, it has been shown that colloidal rhodium, stabilized by oxidized phosphines, was the real catalytic species <B-1998MI002>. The substrate can be hydrogenated in solution or in dispersion. Addition of a surfactant, leading to a micellar system, can significantly enhance both activity and, with chiral catalysts, enantioselectivity in the hydrogenation reaction, provided its concentration is above the critical micellar concentration <1999CCR(185-186)585>. The influence of pH in such systems has been investigated <2002MI312>. Water-soluble catalysts can also be dissolved in a film of water supported on a high surface-area hydrophilic solid. This concept of supported aqueous phase catalyst (SAPC) <1989NAT(339)454> has been extended to its asymmetric version <1994NAT(370)449>. Although water is a "simple" solvent for chemical reactions, its reactivity can interfere with hydrogenation processes. Furthermore, the solubility of hydrogen is low in such a medium. The complete miscibility between hydrogen and supercritical fluids such as scCO_2 is particularly attractive for hydrogenation reactions, which are sometimes limited by the rate of diffusion of H_2 from the gas to the liquid phase. Furthermore, the pressure/solvation tuning enables the recovery of homogeneous catalyst by preferential precipitation. The use of these reaction conditions has been investigated both with homogeneous <1999CRV475> and heterogeneous <1999CRV453> catalysts. Addition of co-solvents or counter-anion modifications

<1995JA8277> can improve the solubility of the charged complexes involved in the catalytic cycle. The addition of water, leading to microemulsions, enables the solubilization of Pd nanoparticles, which catalyze the hydrogenation of hydrophilic as well as hydrophobic alkenes <2002JA4540>. It must be noted that scCO_2 is not inert and might interfere with hydrogenation processes by insertion into the metal-hydride bond, or by reduction to CO on the surface of heterogeneous catalysts. Hydrogenation can be conducted using fluoruous biphasic catalysis <1998ACR641, 1999CEJ1677>. The low miscibility of the cold fluoruous phase with organic solvents allows the recycling of the fluorocarbon soluble catalysts for several catalytic runs. A suitable design of fluoroponytailed ligands <2002T3911> and weakly coordinating counteranions <2003MI625> enables catalytic activities of ionic rhodium complexes close to that of Wilkinson catalyst, with low rhodium or phosphane leaching <2003MI603>. Catalytic hydrogenation of various alkenes has been performed in ionic liquids <2002MI495>. The good solubility of hydrogen in such a reaction medium contributes to the overall good catalytic activity, although the reaction is not truly homogeneous. The use of imidazolium ionic liquids for the formation and stabilization of iridium nanoparticles has been reported. These nanoclusters proved to be as active as Crabtree's catalyst in the hydrogenation of 1-decene, and could be recycled several times without significant decrease of activity <2002JA4228>. The recycling of the catalyst has been obtained by different immobilization techniques. Ligands can be functionalized and grafted to various supports such as polymers (soluble and insoluble) <2002CRV3345, 2002CRV3217, 2002CRV3275, 2001T4637>, dendrimers <2001ACR181, 2002CRV3717>, or inorganic oxide supports <2003MI584>, included in the soluble or insoluble support at the polymerization <2003TL2703> or co-polymerization step <1999JA7407>. The use of chiral-nonracemic ligands enables asymmetric reduction under heterogeneous conditions <2003HCA1753>. Bimetallic nanoparticles anchored within silica nanopores (nanocatalysts) have shown good performances in the hydrogenation of various substrates <2003ACR20>. Homogeneous catalysts can also be entrapped in sol-gel matrices <2002CRV3543> or in polymers <2003MI202> and recycled by ultrafiltration processes.

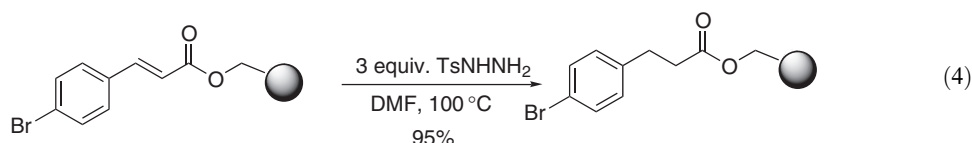
The reduction of alkenes using catalytic transfer hydrogenation can be a practical way at the laboratory level, since this method uses solids or liquids as hydrogen donors, and does not require special equipments such as hydrogenators. Furthermore, they can lead to more selective reductions than with the use of molecular hydrogen. Both homogeneous and heterogeneous catalysts can be used in conjunction with a wide range of donors <1985CRV129>. The most common donors are ammonium or trialkylammonium formates, formic acid, cyclohexene, cyclohexadiene, indoline, tetralin, pyrrolidine, hydrazine, and triethyl silane <B-1996MI001>. An ion-exchange resin-supported formate has been described as a recyclable hydrogen donor source <2001TL5963>. Among the heterogeneous catalysts, the most commonly used is palladium <B-2002MI001>, and platinum, rhodium, and Raney nickel to a lesser extent, whereas homogeneous catalysts based on Pd, Pt, Ru, Ir, Fe, and Ni have been reported. Although hydrogen donors are usually simple hydrogen precursors by an oxidative process, generally obtained by heating, other mechanisms, involving different rates of the individual steps within the catalytic cycle, might take place with homogeneous catalysts and hydride donors such as formate derivatives <2002JCS(D)752> and alcohols. In the latter case, the choice of suitable ligands for Ir-catalyzed transfer hydrogenation of α,β -unsaturated ketones enables a chemoselective alkene reduction, whereas over-reduction to aliphatic alcohols occurs with PPh_3 <2001JOC4710> and allylic alcohols are obtained with diamines or amino alcohols (Scheme 1) <1997ACR97>.



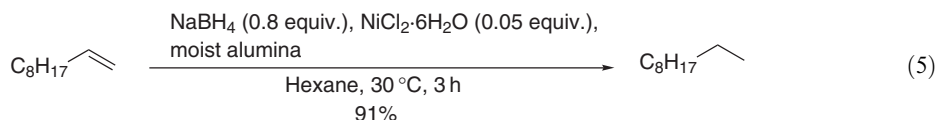
Scheme 1

In some cases, the use of transfer hydrogenation might cause some chemoselectivity problems, since hydrogen donors are known to be particularly useful in benzylic bond hydrogenolysis <B-1999MI003>.

Not only catalytic methods, but also several stoichiometric methods are valuable for the reduction of alkenes. Among them, the reduction by diimide (sometimes called diimine or diazene) appears to be the most versatile <B-1996MI001, 1991COS(8)471>. This reactive species can be generated from hydrazine with oxygen or hydrogen peroxide in the presence of a small quantity of Cu(II) salt and/or a carboxylic acid in a wide range of solvents, or by the acid-catalyzed hydrolysis of the commercially available dipotassium or disodium salt of azodiformate <1965JOC3985>. It can also be obtained by thermal decomposition of anthracene-9,10-diimine <1962JA685> or various aromatic sulfonylhydrazides. The reaction with diimide is a concerted addition, proceeding through a six-membered transition state, and results in complete stereospecific *syn*-addition. The main side reaction observed during diimide reduction is the formation of nitrogen gas by the disproportionation of the reducing agent. A large excess of diimide precursor is, therefore, generally required for the completion of the reaction, which has to be faster than the disproportionation. The relative rate of reduction of various alkenes has been established <1991COS(8)471>. For nonfunctional alkenes, reactivity decreases with alkyl substitution, increases with bond angle bending strain, and *trans*-double bonds are generally more reactive than *cis*-double bonds. Substitution with an electron-withdrawing group enhances the alkene reactivity <1962AG215> as well as the conjugation with another unsaturated bond <1975JOC3599>. This reactivity pattern enables very interesting chemoselective reductions of double bonds in the presence of sensitive functions such as peroxides <1987JMC1505>, or more generally in polyfunctionalized systems <2002JA9825>. Furthermore, as a soluble reducing agent, diimide is particularly well suited for the reduction of solid-supported alkenes (Equation (4)) <1998TL6785>.



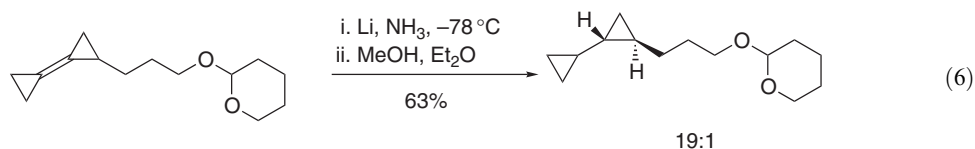
Metal hydrides are useful reducing agents, but they generally do not reduce simple alkenes <B-1997MI>. Addition of transition metal salts into the reaction medium enables the reduction of alkenes, via the formation of transition metal hydrides as hydrometallation species. In a comparative study, the ability of alkenes to be reduced by LiAlH_4 in the presence of first-row transition metal salts has been found to follow the order: $\text{Co(II)} > \text{Ni(II)} > \text{Fe(II)} > \text{Fe(III)} > \text{Ti(III)} > \text{Cr(III)} > \text{V(III)} > \text{Mn(II)} > \text{Cu(I)} > \text{Zn(II)}$. The addition of the transition metal hydride is in this case supposed to be due to the *d* orbital overlap between the metal and the double bond, explaining why d^{10} Cu(I) and Zn(II) and d^5 Mn(II) are less active in the series <1978JOC2567>. Partial or polydeuteration is generally observed with deuterated metals, indicating that several steps in the reduction are reversible. Transition metal salts and LiAlH_4 are usually mixed in equimolar quantities, except with CoCl_2 , NiCl_2 and TiCl_3 , which are used in substoichiometric amounts. Catalysis is slower for di- and trisubstituted alkenes. Sodium hydride <1976CL581> as well as NaBH_4 <1979JOC1014> can also serve as the hydride source in such systems. Aliphatic and aromatic alkenes have been reported to be reduced by NaBH_4 in the presence of a catalytic amount of nickel chloride and moist alumina <2000TL6795>. The reaction is believed to involve the formation of a nickel boride, and to take place at the alumina surface (Equation (5)).



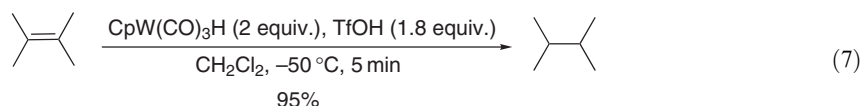
A two-stage reduction can also be performed by hydrometallation, followed by protonolysis of the transient C—metal bond. With boranes, the final alkylborane can be hydrolyzed with retention of configuration under acidic conditions <B-1997MI>. Hydrozirconation of alkenes with *i*-BuZrCp₂Cl can be accelerated by a catalytic amount of various Lewis acids, leading to alkanes after acidic treatment <1999EJO969>.

Numerous metal hydrides have been described in the conjugate reduction of unsaturated double bonds (see Section 1.03.1.5). A comprehensive comparative study on the elaboration of the *trans*-hydrindane portion in steroids or related natural products by reduction has been reported <1998T12071>. This field is growing with the development of new reagents <2001JOC8692> and catalysts for asymmetric conjugate reductions <1999JA9473>.

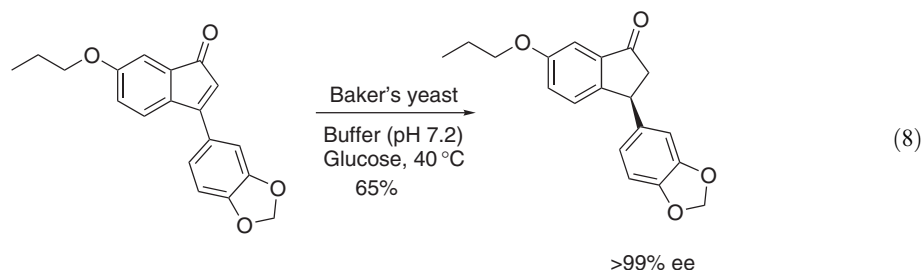
Although the reduction of alkenes to alkanes has been reported to proceed stereoselectively with sodium in HMPA in the presence of Bu^tOH <1970JOC3565>, the use of dissolving metals in such reactions has been mainly limited to the reduction of α,β -unsaturated ketones <1996JA8765>. The reduction of bis-cyclopropylated alkenes with lithium in ammonia has been reported to proceed in a stereoselective manner (Equation (6)) <2000EJO2979>.



The use of strong acidic media enables the reduction of hindered double bonds in the presence of hydrides. Ionic hydrogenation has been described at low temperature in dichloromethane using triflic acid and several transition metal carbonyl hydrides or triethyl silane (Equation (7)) <1994JA8602>. In some cases, the secondary carbenium ion formed by protonation can undergo alkyl migration or hydride shift. The intermediacy of both olefin cation radicals and carbocations in ionic hydrogenation with borane–dimethyl sulfide complex has been discussed <1996JOC5246>.



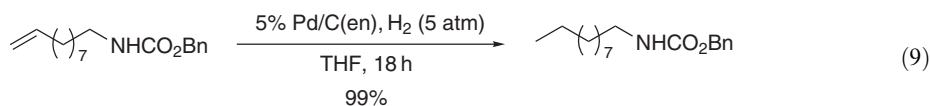
Enzymes can also catalyze hydrogenations. Although the biohydrogenation of double bonds represents a relatively small area within the field of biotransformations, interesting selectivity can be obtained in such reductions <1995HOU(E21d)4364>. If isolated and purified enzymes are used, a coenzyme must be added and recycled. With whole cells as catalysts, all the cofactors are present and readily regenerated <1999OL1839> (Equation (8)).



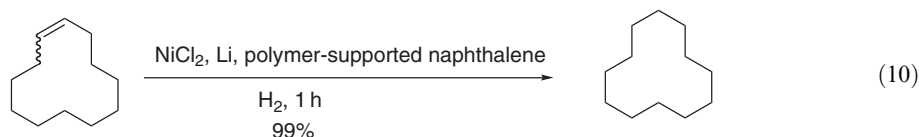
Besides carbohydrates, hydrogen gas or a cathode can serve as electron donors. Investigations into the stereoselective reduction of nitro olefins have been reported, showing that nonredox reactions can explain the stereochemical outcome of the reduction <2000PNA10733>. Since most of the reductions occur by hydride transfer from reduced NADH or NADPH coenzymes, several biomimetic hydride donors have been prepared and used in the reduction of alkenes <1998SL1144>.

1.03.1.2 Reduction of Alkyl-substituted Alkenes

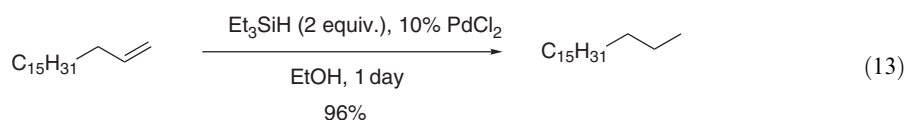
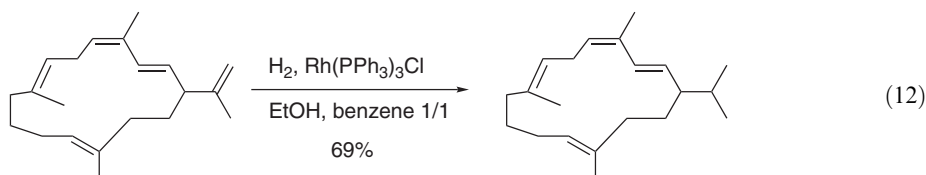
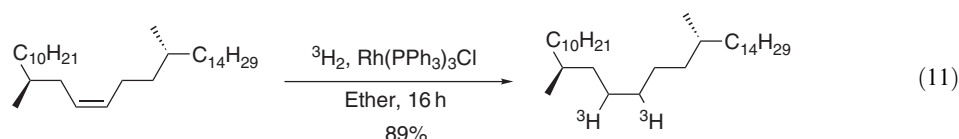
Isolated double bonds are best reduced by catalytic hydrogenation. Heterogeneous catalysis is generally the method of choice, either with hydrogen or hydrogen donors, although the reduction becomes more difficult as the number of alkyl substituents increases. Some selectivity can be observed with substrates bearing several double bonds <2001TA29, 2001AG(E)1211>. A combination of 5% Pd/C–ethylenediamine [5% Pd/C(en)] in THF or dioxane as solvent enables the selective reduction of double bonds in the presence of sensitive *N*-benzyloxycarbonyl protective groups (Equation (9)) <2000T8433>. Hydrogenolysis-free hydrogenation has also been reported with Pd-black powder as a catalyst in benzene or toluene <2001SL1590>.



The catalytic mixture NiCl_2 –Li–naphthalene has been proposed as an alternative to Raney nickel in alkene reductions, with similar activity and better handling conditions [<2001MI188>](#). The use of polymer-supported naphthalene enables its easy recovery by filtration and reusability [<2003MI275>](#) (Equation (10)). Oct-1-ene can be reduced by transfer hydrogenation using NiBr_2 in alkaline isopropanol [<2000CC1647>](#).



The reduction of simple alkenes with homogeneous catalysts can also proceed efficiently. A selective tritiation of a linear alkene, without scrambling along the chain, can be achieved with the Wilkinson catalyst (Equation (11)) [<2000T5493>](#). The same catalyst enables the chemoselective reduction of a terminal double bond in the presence of several unsaturations (Equation (12)) [<1996JCS\(P1\)57>](#). The use of borohydride exchange resin–nickel boride has been described as a catalyst for the hydrogenation of monosubstituted alkenes [<1996S597>](#). Triethyl silane in ethanol in the presence of PdCl_2 can lead to the reduction of 1-alkenes in excellent yields (Equation (13)) [<2003TL4579>](#).



Unlike some transition metal-catalyzed reductions, organolanthanide-catalyzed processes are usually not directed by polar groups, but appear purely steric in their selectivity patterns. They are therefore attractive for the stereoselective reduction of nonfunctional alkyl-substituted alkenes [<1996JOM\(524\)275, 2002CRV2161>](#). Intramolecular complexation of the electrophilic center with a π -system or a heteroatom might be responsible for the lower reactivity (Equation (14), Table 2).

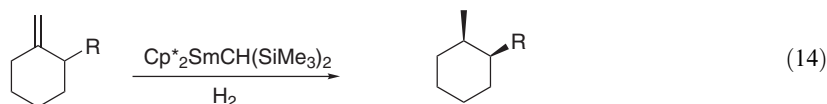


Table 2 Stereoselective reduction of methylenecyclohexanes [<1996JOM\(524\)275>](#)

<i>R</i>	Mol.% cat./reaction temp (°C)	Yield (%)	<i>cis:trans</i>
Me	3/–20	77	93:3
Bu ⁱ	3/–20	90	95:5
Bu ^t	5/rt	95	100:0
Bn	3/–20	95	93:7
Ph	5/50	96	100:0
(CH ₂) ₃ NMe ₂	3/50	76	91:9
OMe	5/70	0	

The enantioselective reduction of alkyl-substituted alkenes still remains a challenge. The lack of a coordinating group on the substrate is a problem for strategies involving transition metal catalysis. Furthermore, a reproducible, simple, and general method for enantiomeric excess determination of alkanes is still necessary <B-1999MI002>.

1.03.1.3 Reduction of Alkenyl-, Aryl-, Heteroaryl-, and Alkynyl-substituted Alkenes

Partial reduction of conjugated dienes or polyenes is a complex reaction. Besides over-reduction, heterogeneous hydrogenation of butadiene can lead to three different alkenes <2001JMOC(173)185>. The product distribution of this reduction catalyzed by evaporated films of the majority of the elements in groups 3–11 on the periodic table has been investigated <2002AC(229)251>. According to this study, the butadiene hydrogenation can be interpreted by processes involving σ - and $\pi\sigma$ -adsorbed half hydrogenated states (Figure 3) with all transition metals except Pd, for which the *trans*:*cis* ratio of but-2-ene is up to 20, which can be interpreted as the result of an *anti*:*syn* preference of butadiene in the gas phase and a 1,4-addition via noninterconvertible π -allylic intermediates (Figure 4). Correlation of but-1-ene yield with the Pauling electronegativity scale indicates that an electronic effect governs the extent of overall 1,2-addition for all metals.

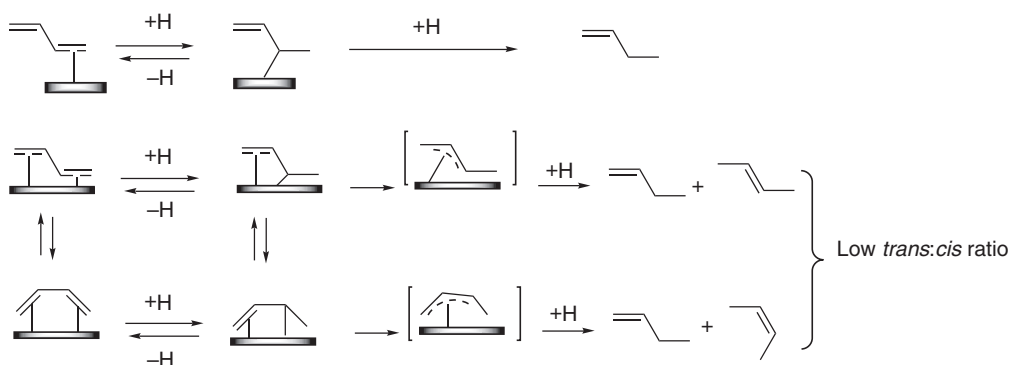


Figure 3 Hydrogenation of butadiene leading to a low *trans*:*cis* ratio.

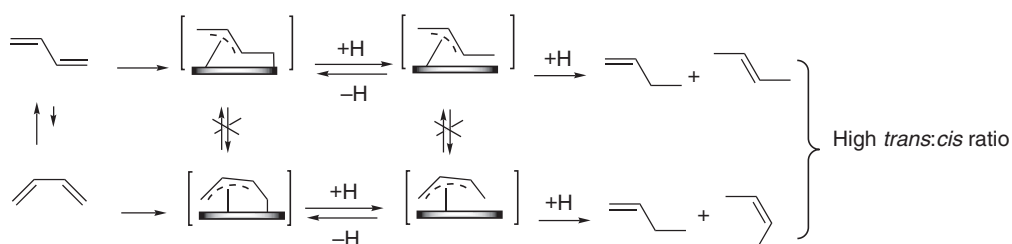
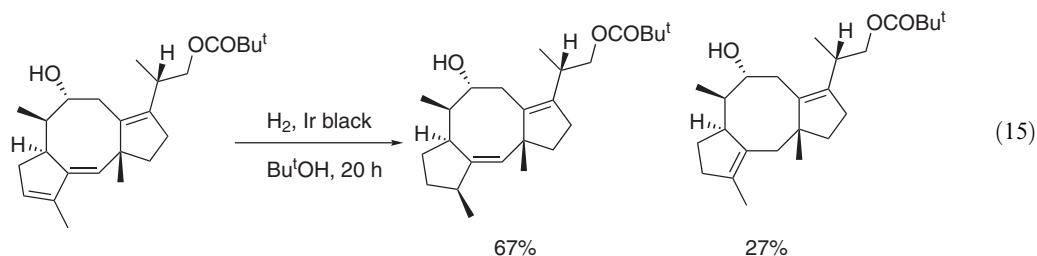
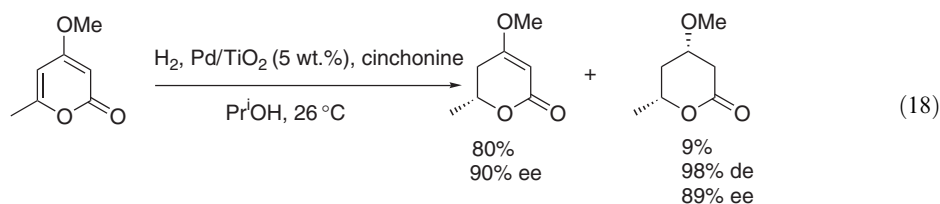
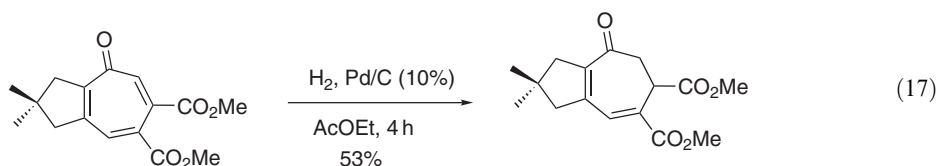
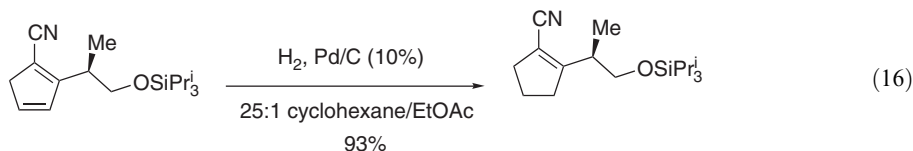


Figure 4 Hydrogenation of butadiene leading to a high *trans*:*cis* ratio.

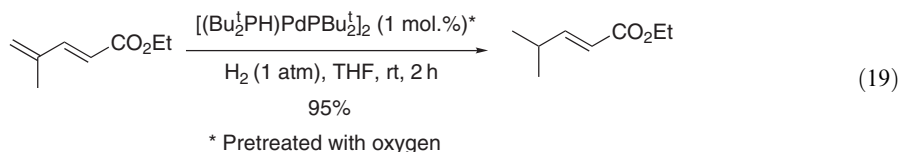
Unless there is an important difference between the two double bonds in terms of substitution patterns and/or electron density, selectivity of heterogeneous reduction is generally difficult to achieve (Equation (15)) <1991COS(8)523, 1998JCS(P1)2473>.



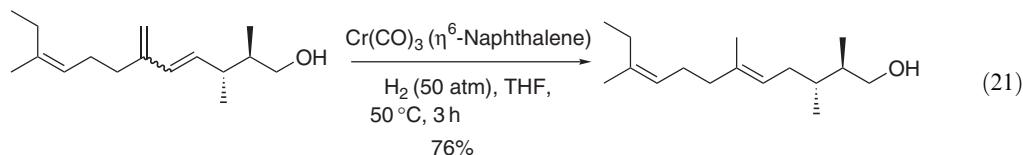
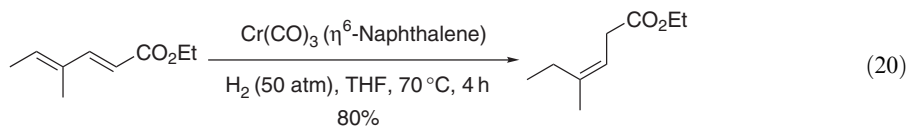
With several conjugated systems, however, selective mono-hydrogenation could be performed on dienes (Equation (16)) <1998TL5675> or polyenes (Equation (17)) <1997T13703>. A good chemoselectivity could be obtained in the hydrogenation of 2-pyrone derivatives with cinchona-modified Pd/TiO₂. Furthermore, enantioselectivity up to 94% could be obtained under high dilution conditions (Equation (18)) <2002NJC6>.

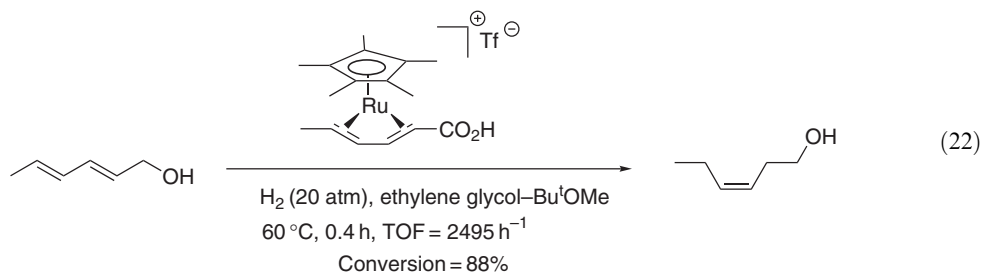


A wide range of homogeneous catalysts can selectively lead to a 1,2-reduction of linear or cyclic dienes <1991COS(8)443>. The less-substituted exocyclic double bonds are generally selectively reduced with the Wilkinson catalyst <1995TL4039>. The binuclear palladium complex [(Bu₂PH)PdPBu₂]₂ pretreated with oxygen can catalyze the 1,2-hydrogenation of simple and functionalized dienes, under mild conditions (Equation (19)) <1995TL5673>. Di- or polynuclear palladium clusters <1998NJC1217> or tungsten complexes <1995CC1599> are also efficient catalysts in the monohydrogenation of dienes. Several complexes, having arenes or cycloheptatriene ligands, are good catalysts for selective 1,4-hydrogen addition (Equation (20)) <2000JCS(P1)2211>. Thus, (η⁶-naphthalene)chromium tricarbonyl enables the reduction of a mixture of (*Z*)- and (*E*)-isomers to (*E*)-alkenes in the presence of a nonconjugated double bond (Equation (21)) <2000JCS(P1)2211>. A less toxic Cp*Ru complex (Equation (22)) has been proposed as an effective catalyst for the hydrogenation of sorbic alcohol into *cis*-hex-3-en-1-ol (leaf alcohol, commercial fragrance) <2000CC217>.

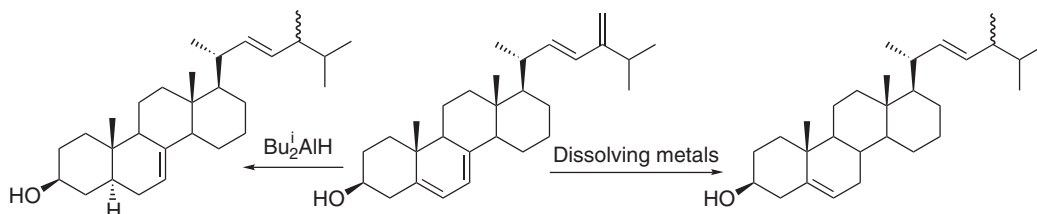
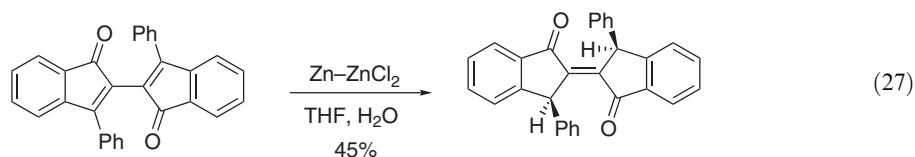
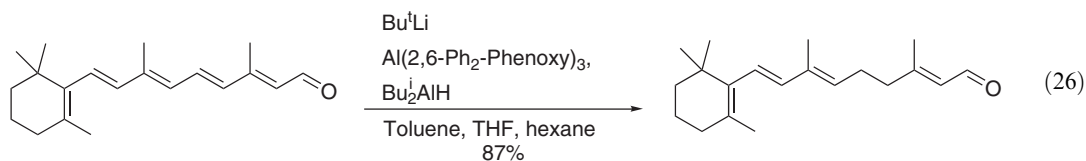
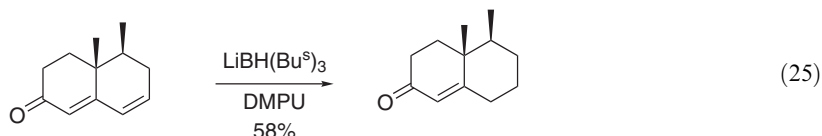
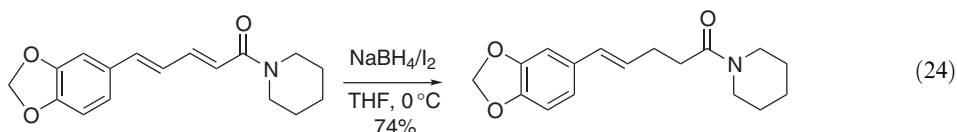
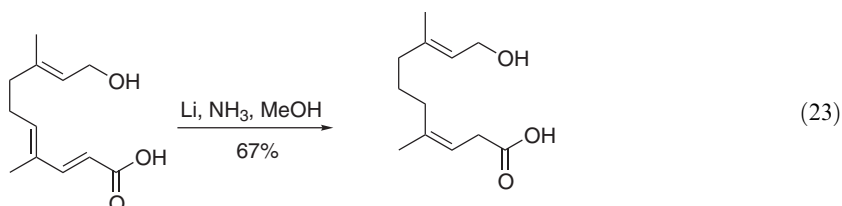


* Pretreated with oxygen



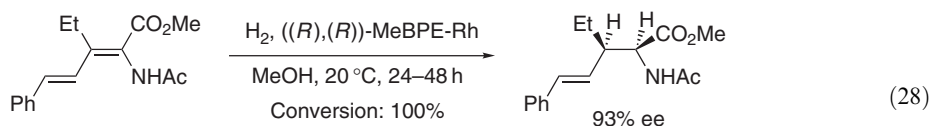


Diene systems can be reduced under the general conditions of the Birch reduction (Equation (23)), leading to the corresponding (*E*)-alkene exclusively <1996JOC6454>. In selected cases, stoichiometric reducing agents may also provide a way to control the reduction of polyene systems (Equation (24)–(27), Scheme 2) <1998TL677, 1997TL7463, 1996JOC2928, 1995TL8359>.

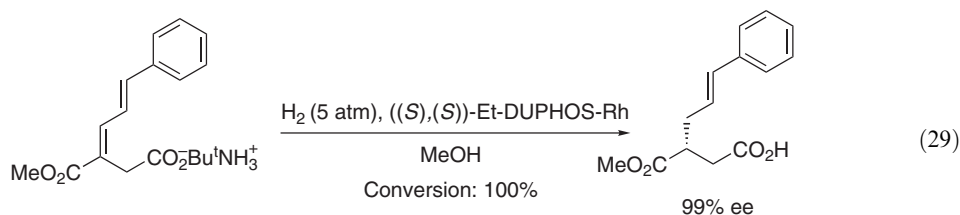


Scheme 2

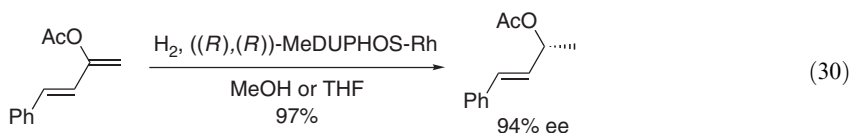
The enantioselective reduction of dienes has been reported [<1998JA657>](#). Chelation through the *N*-acetyl group ensures a high regioselectivity, even with tetra-substituted double bonds [<1999TL3093>](#). Stopping the reaction before over-reduction is critical for obtaining products of high enantiomeric purity (Equation (28)). Diene esters (Equation (29)) [<1998AG\(E\)1931>](#) or enol esters (Equation (30)) [<1998TL5505>](#) are reduced in a similar way, as well as pyrones with ruthenium catalysts [<1999JOC5768>](#).



((R),(R))-MeBPE: 1,2-Bis((2(R),5(R))-2,5-dimethylphospholano)ethane



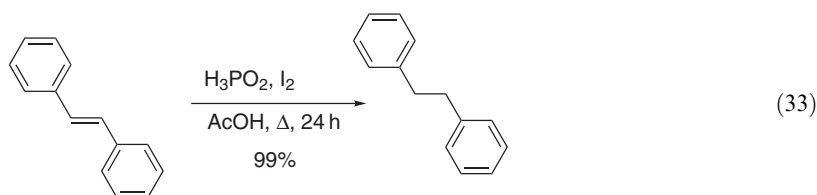
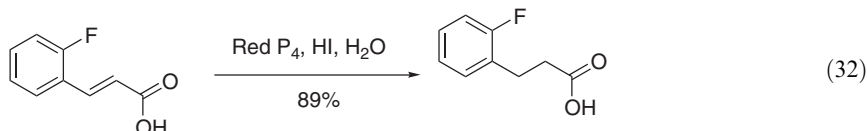
((S),(S))-Et-DUPHOS: 1,2-Bis((2S,5S)-2,5-diethyl-phospholano)benzene

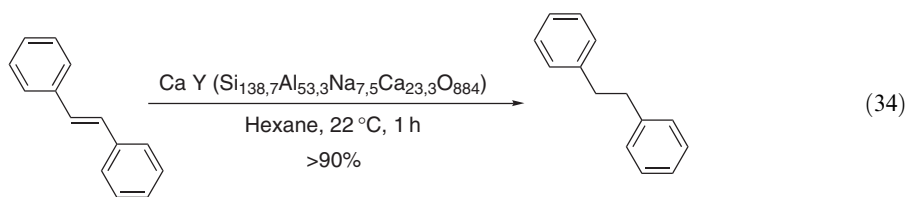


The selective reduction of alkynyl-substituted double bonds is generally problematic using standard hydrogenation conditions. A regio- and stereoselective ionic hydrogenation of enamino-1-yne has been reported [<1999JA10012>](#). An acyliminium reactive species is probably involved in this selective reduction (Equation (31)).

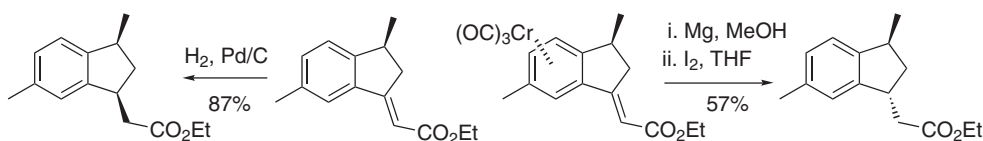


There are many examples of the reduction of aryl-substituted double bonds. In addition to heterogeneous catalysis [<1991COS\(8\)417>](#), hydrides [<1996SC763>](#), dissolving metals [<1995BSB563>](#), and ionic hydrogenations [<1995H925, 2000BMCL2701>](#) have been reported to proceed efficiently. The use of hydrosilanes in the presence of a copper salt enables the selective reduction of aromatic-substituted double bonds, without reducing alkyl-substituted alkenes [<2000SL479>](#). Red phosphorus, in the presence of hydrogen iodide, is able to reduce cinnamic acid derivatives (Equation (32)) [<1998JOC432>](#). Diarylalkenes are easily reduced under acidic conditions, by hypophosphorus acid-iodine in acetic acid (Equation (33)) [<2002T4411>](#) or by zeolites (Equation (34)) [<1997CC127>](#).

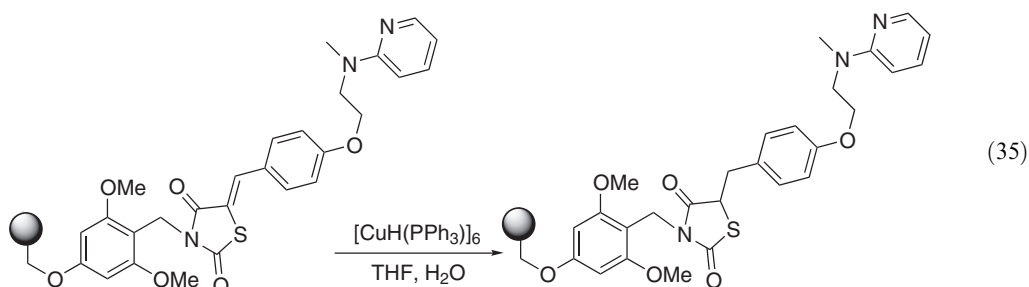




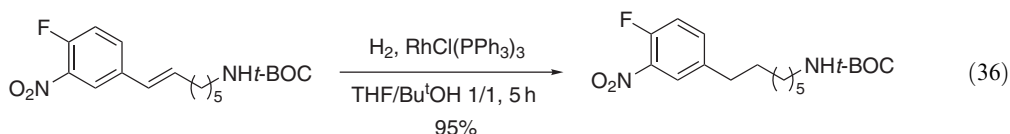
1,3-*cis*- or *trans*-Dialkyl indanes can be obtained from the same precursor by selective reduction of the free or complexed alkene (Scheme 3) <1997JOC3365>. The reduction of solid-supported alkenes has been performed using Stryker's reagent (Equation (35)) <1999JOC1723> or ionic hydrogenation <2001JA2428>. Ionic hydrogenation has also been proposed as a good method to remove residual vinyl groups of a cross-linked polystyrene matrix arising from the co-polymerization of divinylbenzene and styrene monomers <1997JOC8987>.



Scheme 3



Homogeneous catalytic hydrogenation has been used for the reduction of aryl- or heteroaryl-substituted alkenes. The use of a 1:1 mixture of THF:Bu^tOH as a solvent enables the selective reduction of double bonds in the presence of a highly reducible aromatic nitro group (Equation (36)) <2002JOC3163>.

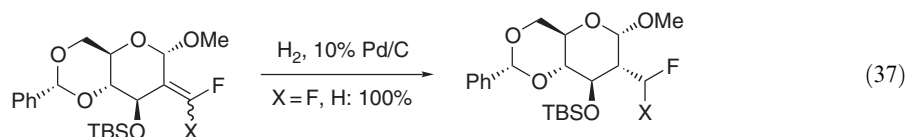


The enantioselective hydrogenation of aromatic-substituted double bonds has made impressive progress <2003MI33>. Enantioselectivities greater than 95% have been achieved with cationic zirconocene catalysts <1999JA4916>, cationic iridium complexes with *P,N*- <1998AG(E)2897, 2001AG(E)4445, 2001CEJ5391>, or *N*-carbene <2001JA8878, 2003JA113> ligands. The use of Pd-based <1997JOM(531)159>, Ti-based <1995OM4865>, lanthanide-based <1994JA10241, 1997OM4486>, or Ru-based catalysts <2000TL9471> has been reported for the reduction of “nonfunctionalized” double bonds, albeit with lower efficiency.

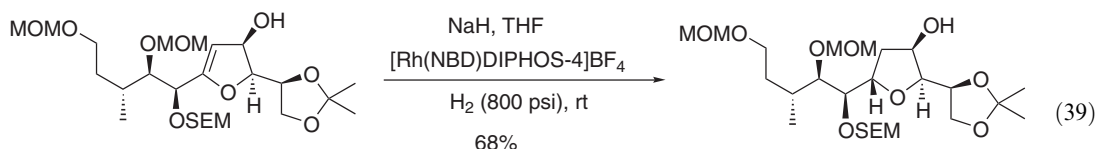
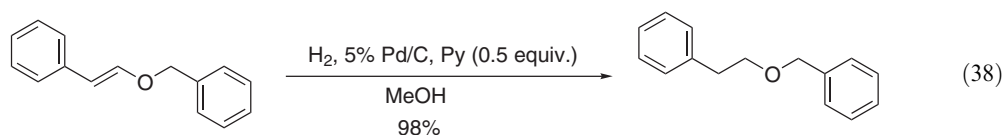
1.03.1.4 Reduction of Heteroalkyl-substituted Alkenes

Although the hydrogenolysis of the C—heteroatom bond is a known side reaction during catalytic hydrogenations, heteroalkyl-substituted alkenes can be reduced by different methods. Introduction of fluorine-containing methyl groups at the C2 position of glucose has been attained by a

diastereoselective reduction of fluoroalkenes (Equation (37)) <1997SL669>. Although hydrogenation of vinylic fluorides or chlorides has been mainly described over palladium on carbon <1998TL4009, 2000JMC4893, 2000JFC(102)43, 2000T4253>, homogeneous conditions are also efficient in such reductions <1996TL2007>.

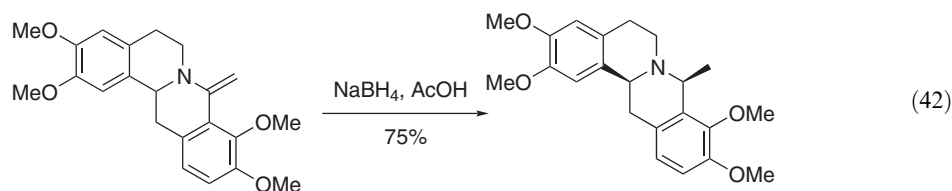
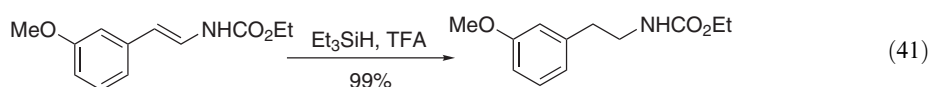
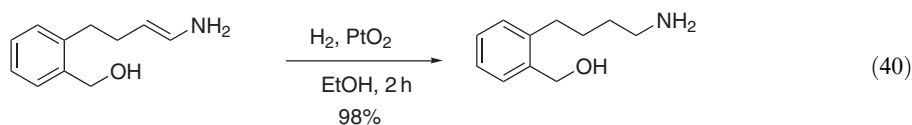


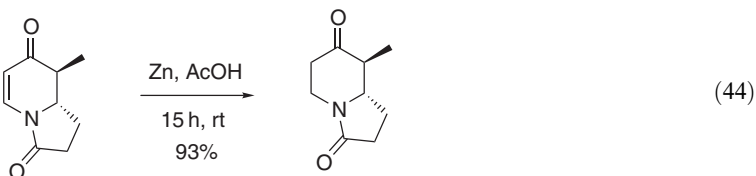
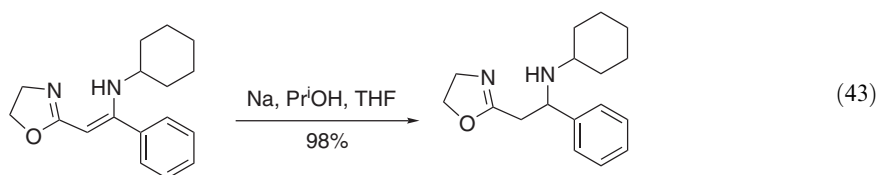
Enol ethers are reduced by hydrogen in the presence of various catalysts <1991COS(8)443>. The presence of ammonia, pyridine, or ammonium acetate has been reported to inhibit hydrogenolysis side reactions (Equation (38)) <1995TL3465>. Dihydrofuryl rings have been hydrogenated over Pd/C in excellent yield <1995S1517>. The use of homogeneous catalysis enables alkoxide-directed stereoselective reductions (Equation (39)) <2002OL937>.



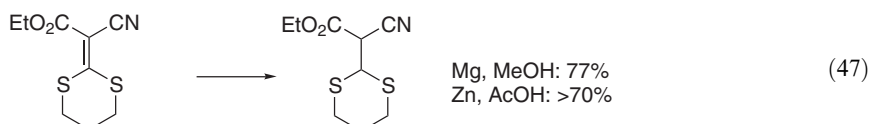
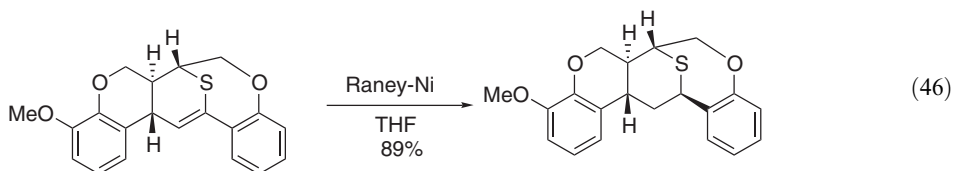
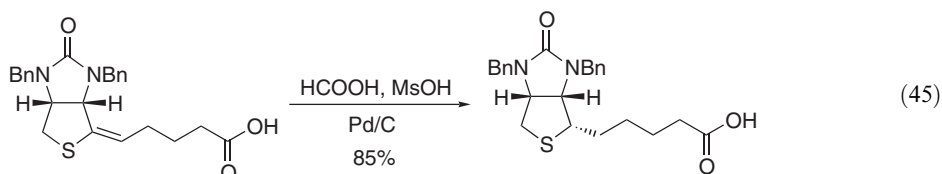
NBD: norbornadiene
DIPHOS-4: 1,4-bis(diphenylphosphino)butane

Enamines can be reduced to the corresponding amines by different methods. Catalytic hydrogenation of terminal enamines has been reported (Equation (40)) <1999EJO1459>. The use of acidic conditions enables their reduction via the corresponding iminium ion, with Et_3SiH (Equation (41)) <2001TL8263>, $(\text{Bu}^t)_2\text{MeSiH}$ <1995TL7949>, or borohydrides (Equation (42)) <2000JOC7495>. These reductions can be performed in the presence of terminal double bonds <1999SL1799>. Furthermore, the stereochemical issue of the ionic hydrogenation can complement the heterogeneous hydrogenation approach <1995TL4869>. The use of Birch conditions has been reported for the reduction of conjugated enamino-oxazolines (Equation (43)) <2001T703>. *N*-Acyl-2,3-dihydropyridones have been reduced into the corresponding piperidones with zinc and acetic acid (Equation (44)), whereas over-reduction to alcohols could not be prevented using catalytic hydrogenation over palladium on carbon <2001JOC2181>.

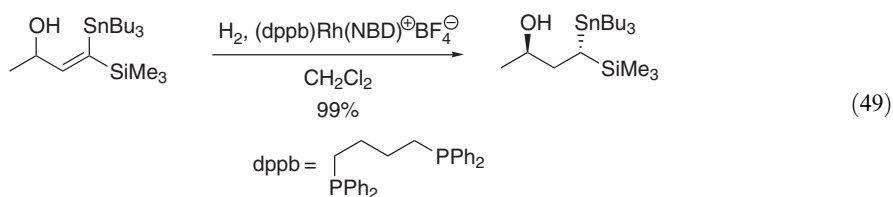
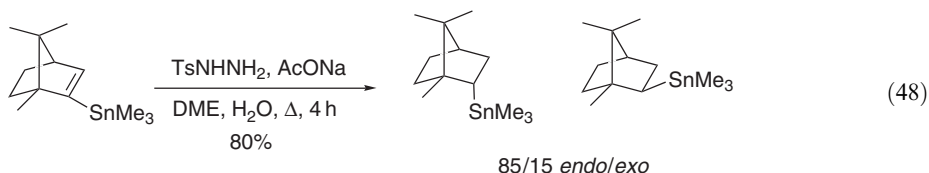




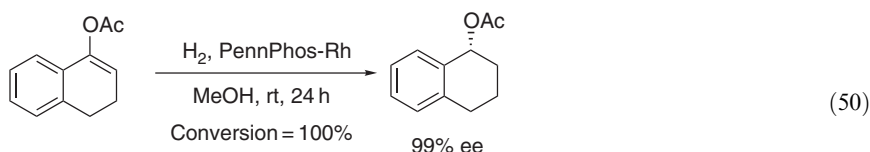
Although sulfur is known to be an excellent poison for heterogeneous catalysts, the reduction of vinylic sulfides has been reported on Pd/C under hydrogen transfer conditions (Equation (45)) <2000S2004> or with Raney nickel (Equation (46)) <1996SL72>. Borohydrides can also be useful in several cases <2000T4531>. Two general methods permitting the reduction of ketene dithioacetals to give the corresponding dithianes have been developed (Equation (47)). The use of magnesium in methanol proved to be less reliable than the reduction with zinc and acetic acid <1997T17151>.



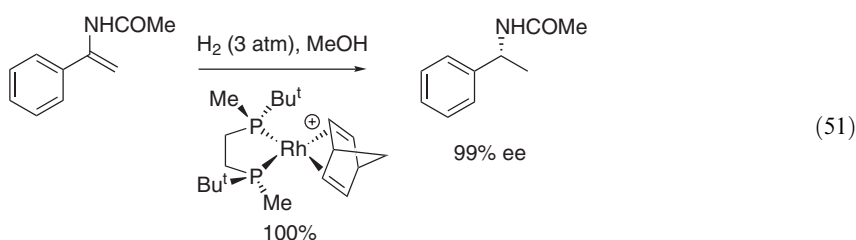
The diimide reduction of vinylic tin compounds is a convenient entry to organostannanes (Equation (48)). The preferred formation of the *endo*-compound has been explained by steric interactions between an *exo*-2-bulky tin and the 7-*syn*-methyl group in the transition structure for an *endo*-reduction <2002JCS(P1)1286>. A diastereoselective synthesis of γ -alkoxy stannanes and silanes has been developed, based on the hydroxyl-directed hydrogenation of their vinylic precursors (Equation (49)). Interestingly, this method enables the diastereoselective synthesis of heterobimetallic compounds <1994JOC6208>.



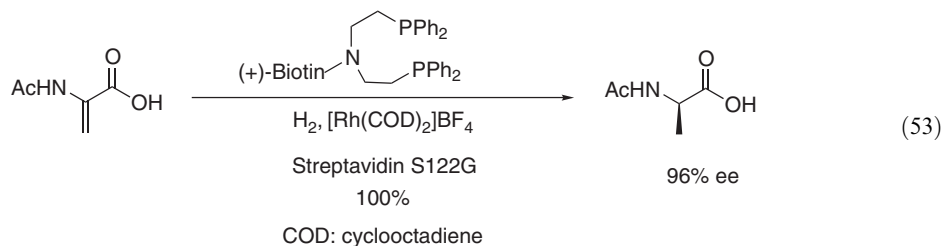
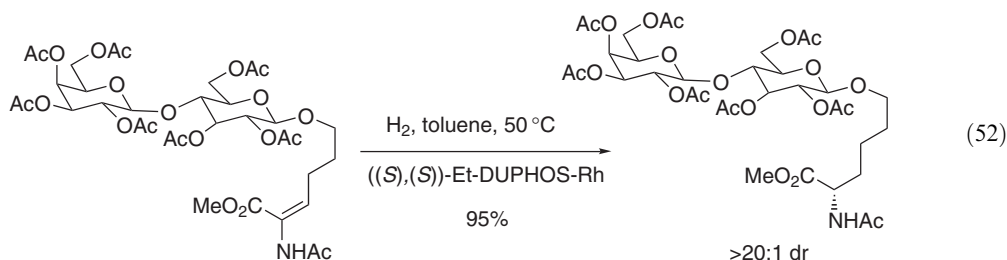
Enantioselective reductions of various heteroatom-substituted alkenes have been developed <2003MI103>. Enol acetates (especially cyclic ones) have been hydrogenated with ee up to 99% <1999AG(E)516>, but the catalytic activity has still to be improved (Equation (50)). The reduction of acyclic (Equation (51)) <1999OL1679, 2001JA5268, 2002AG(E)847> or to a lesser extent exocyclic enamides <2001MI331> also proceeds with excellent enantioselectivities, and provides an interesting alternative to the difficult problem of the enantioselective reduction of imines. Not only diphosphines, but also monodentate phosphoramidites <2002AG(E)2348> are efficient ligands in these enantioselective reductions.



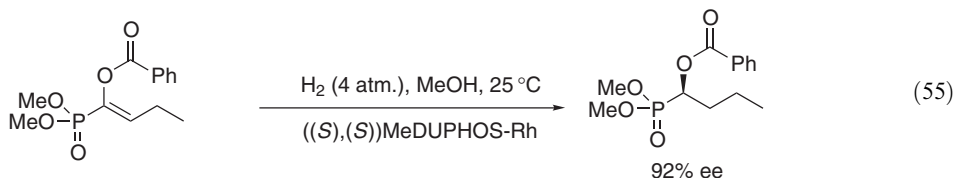
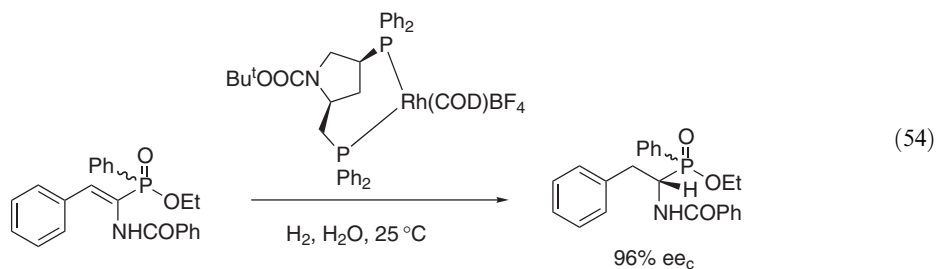
PennPhos : *P,P'*-1,2-phenylenebis(*endo*-2,5-dialkyl-7-phosphabicyclo[2.2.1]heptane)



Enantioselective reduction of dehydroamino acid derivatives is now a classical entry to enantiopure amino acids and has been reviewed regularly <B-1999MI001, 2003MI103>. Interestingly, these methods can be used to control the diastereoselectivity of the reduction in more complex molecules (Equation (52)) <2000JPR736, 2001TL3159>. A new conceptual approach has been reported in this field: the enantioselective reduction of dehydroamino acid can be performed by an achiral biotinylated complex of rhodium using streptavidin as the host protein <2003JA9030>. Tuning of the “chiral pocket” could be accomplished by site-directed mutagenesis, leading to ee improvement (Equation (53)).

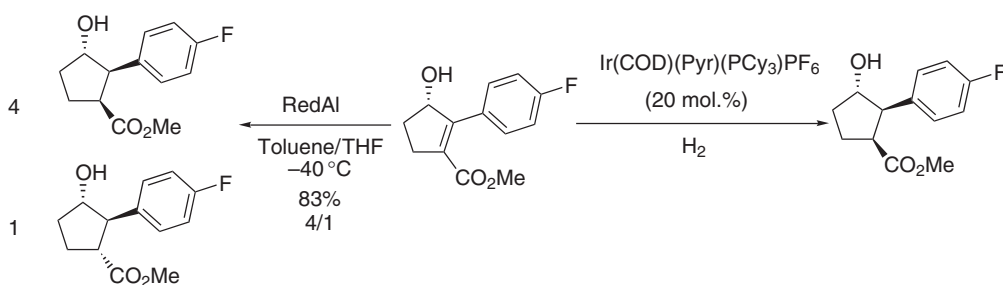


Not only dehydroamino acids but also dehydroamino-phosphonic <1996SC777> or phosphinic <1998AG(E)2851> acids can be hydrogenated in an enantioselective manner (Equation (54)). A similar approach to the enantioselective synthesis of α -hydroxy- or amino phosphonates has been reported (Equation (55)) <1999OL387>. The reduction of alkenylboronic acids and esters with enantioselectivities up to 80% has been described <2002JOM(642)145>.

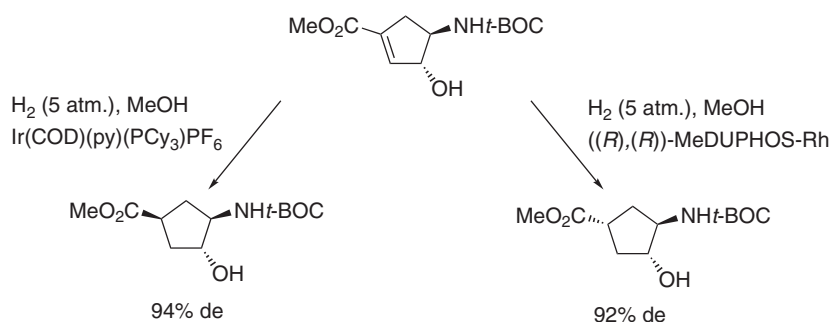


1.03.1.5 Reduction of Remotely Substituted Alkenes

Remote groups can exert a dramatic influence on the reduction of alkenes. Allylic substituents are readily prone to hydrogenolysis reactions when using Pd- and, to a lesser extent, Pt- or Rh-catalyzed hydrogenations [<1991COS\(8\)417>](#). The presence of a remote functional group is not always a problem for selective hydrogenations, and in some cases can be very helpful to achieve stereo- and regioselective reductions [<1993CRV1307, 1995HOU\(E21d\)4317>](#). Hydroxyl-directed reduction of cyclopentenones has been investigated with several catalysts. Whilst hydrogenation with catalysts Rh(COD)(dppb)PF_6 and $\text{Rh(C}_7\text{H}_8\text{)(dppb)PF}_6$ was generally not selective, the use of Crabtree's catalyst or iridium-carbene complexes gave excellent stereoselectivity [<2002JOC5996>](#), but with low catalytic activity. Finally, the use of RedAl provided a cheaper alternative for the reduction with the desired 1,2-*anti* stereochemistry (Scheme 4). A general study of the hydrogenation of cyclopentenonic esters bearing two different directing groups in a *trans*-relationship has shown that a judicious choice of catalyst allows selective reduction to either one or the other face of the double bond (Scheme 5) [<2001TL1347>](#).

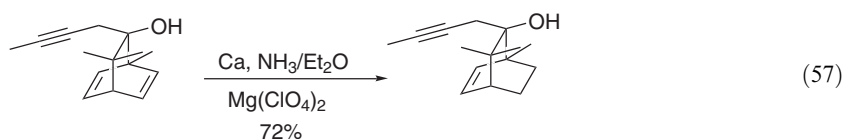
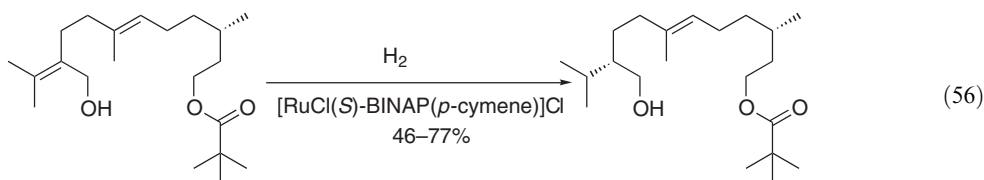


Scheme 4

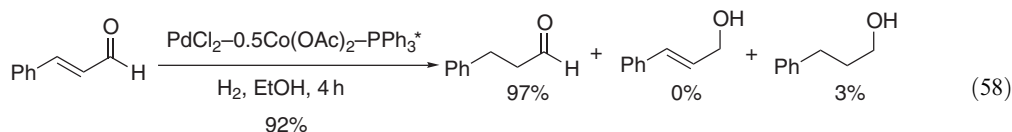


Scheme 5

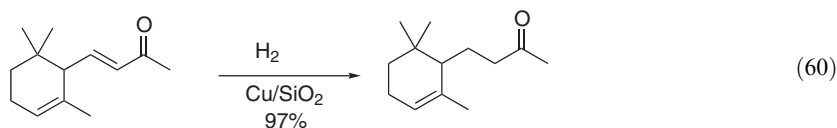
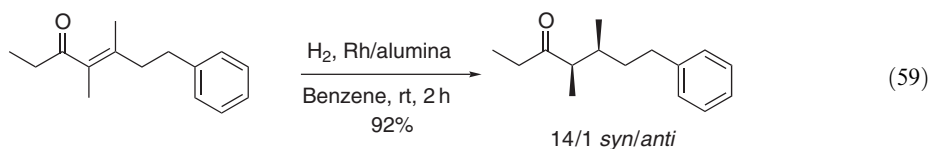
Regioselective reductions are also observed with allylic alcohols, enabling the diastereoselective hydrogenation of the most-substituted double bond (Equation (56)) <2000OL2737>. Chemo- and regioselective reduction has also been reported using calcium in ammonia as a reducing agent in the presence of magnesium perchlorate (Equation (57)). Homoconjugation of the diene and hydroxyl-directed reprotonation of the transient radical-anion probably explains this result <1995TL7607>.



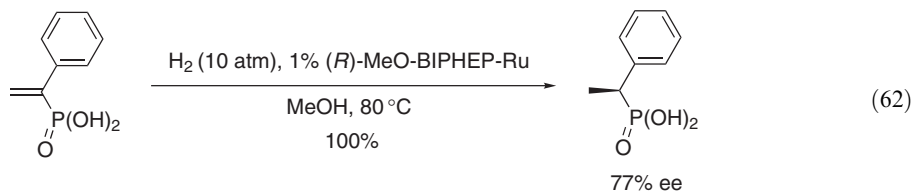
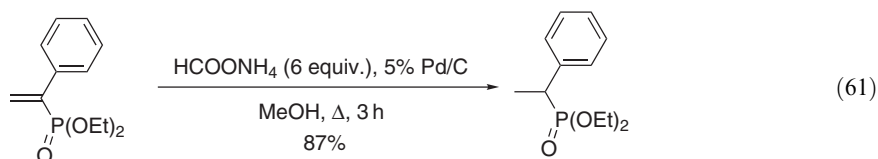
A particularly useful alkene reduction is the selective reduction of the C—C double bond of α,β -unsaturated carbonyl and related compounds. Since reduction of the carbonyl group is rare during hydrogenation over palladium, the heterogeneous catalytic system is probably the most suitable for this kind of reduction <B-2002MI002> and can be very chemoselective <2001S2003>. The chemoselective conjugate reduction of α,β -unsaturated carbonyl compounds can be achieved with a Pd/C-pyridine combination as a catalyst in the presence of a benzylic protective group <1997TL399>. The selective reduction of cinnamaldehyde can however be problematic. The use of bimetallic palladium-based catalysts has been reported to selectively hydrogenate this compound to dihydrocinnamaldehyde, without any carbonyl reduction and less than 3% over-reduction (Equation (58)) <2000AC(192)247>. Different catalysts have been tested in the stereoselective hydrogenation of tetrasubstituted enones <1997SL117>. Best results were obtained using Rh/alumina, whereas Pd/C, PtO₂, Pt/Al₂O₃, Pt/C, [RhCl(COD)]₂, RhCl(PPh₃)₃, and [Rh(COD) (dppp)]BF₄ gave lower selectivity, Ru/C and OsCl₃ were ineffective and cationic [RhCl(COD)]₂-AgBF₄ promoted (*E*)/(*Z*) isomerization (Equation (59)). The chemoselective reduction of unsaturated ketones has been reported using hydrogenation over Cu/SiO₂ (Equation (60)) <1996TL3529>.



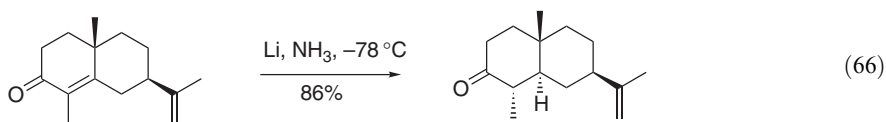
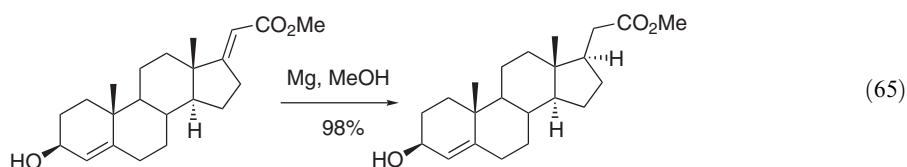
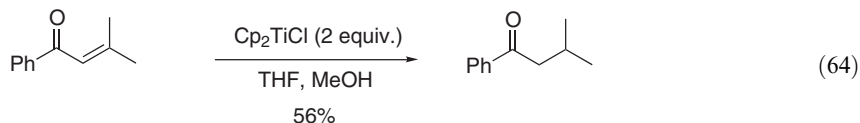
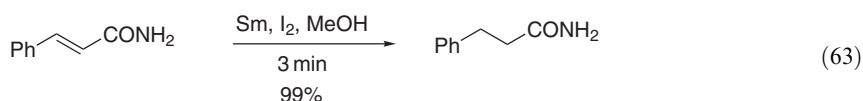
* First reduced by NaBH₄



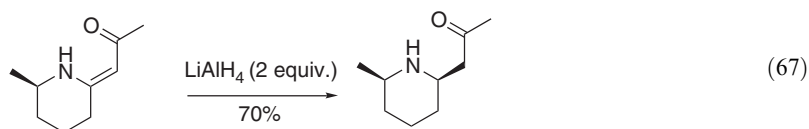
Several examples of hydrogenation of α,β -unsaturated phosphonates have been reported. Most of the reductions were performed on Pd/C using hydrogen <1995S539> or hydrogen donors <2001TA319> (Equation (61)). The enhanced diastereoselectivity of phosphorus-substituted olefins in heterogeneous hydrogenations has been studied <1997TL8627>. Enantioselective reduction of vinylphosphonic acids and esters has also been described <1998TL3473> (Equation (62)).

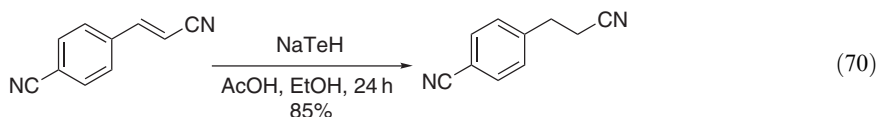
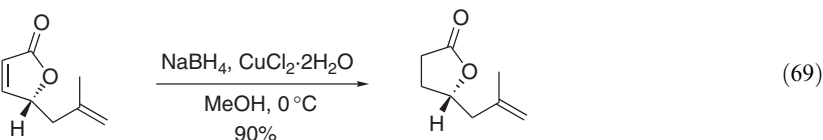
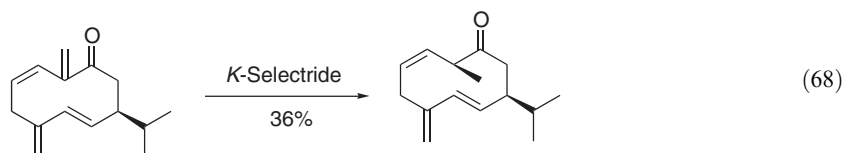


The reduction of various α,β -unsaturated carboxylic acid derivatives (ester, amide, nitrile, and carboxylic acid) can be conducted with metallic samarium and iodine in alcohol [<1995SL443>](#) (Equation (63)). It provides an alternative to the well-known SmI_2 -mediated reductions [<1980JA2693, 1997TL2121>](#). The low-valent titanium complex Cp_2TiCl selectively reduces selected α,β -unsaturated ketones via a postulated single-electron transfer mechanism [<2002TL2013>](#) (Equation (64)). A chemoselective reduction of α,β -unsaturated esters has been reported with Mg in methanol (Equation (65)). Interestingly, the reaction did not occur when absolute ethanol was used under similar conditions [<1996S455>](#). Selectivity can also be achieved using lithium in ammonia (Equation (66)) [<2001SI305>](#). The use of iodotrichlorosilane, generated *in situ* from SiCl_4 and NaI, has also been reported for the reduction of α,β -unsaturated ketones and nitriles [<1996TL2297>](#).

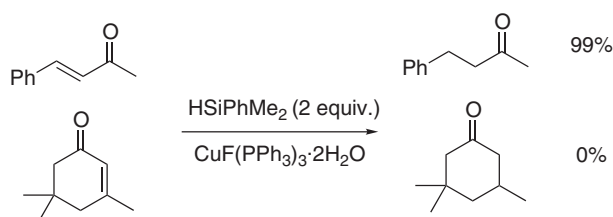


α,β -Conjugated double bonds are readily reduced by various hydrides, including LiAlH_4 [<1997TL3471, 2001TL4609>](#) (Equation (67)), *K*-selectride (Equation (68)) [<1997T7209>](#), sodium borohydride in the presence of nickel [<2000TL4363>](#), copper [<1998TL4971>](#) (Equation (69)) or indium [<2002TL7405>](#) salts, and the combination of $\text{Co}(\text{acac})_2$ -DIBAL-H [<1999SL96>](#). Aluminum tris(2,6-diphenylphenoxide) (ATPH) acts as a receptor binding carbonyls and inhibits the troublesome 1,2-reduction [<1996JOC2928>](#) (Equation (26)). The reduction of α,β -unsaturated nitriles can be conducted with NaTeH (Equation (70)) [<1996T8611>](#).



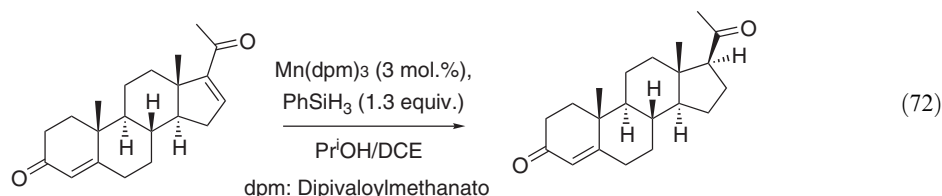
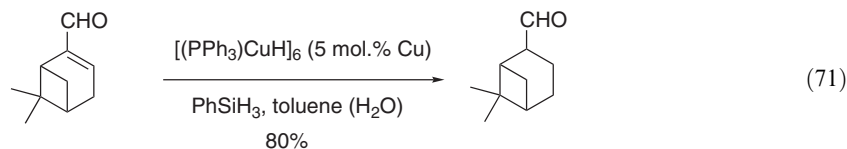


Copper hydride is an efficient reducing agent. It can be generated from several hydrosilanes <1997CC2159> by transmetalations, and can selectively reduce unsaturated ketones whereas congested enones are recovered unchanged (Scheme 6). The use of CuCN/DIBAL-H/BuLi as a source of copper hydride has also been reported in the chemoselective reduction of tetrasubstituted conjugated double bonds <2001JOC944>.

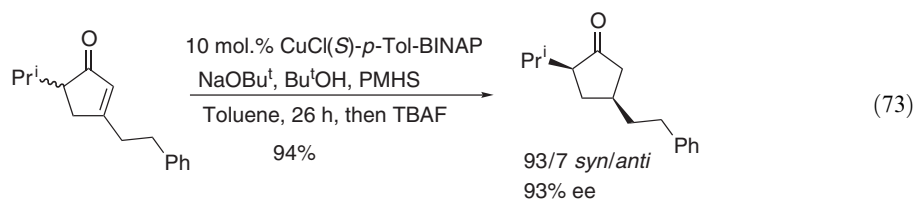


Scheme 6

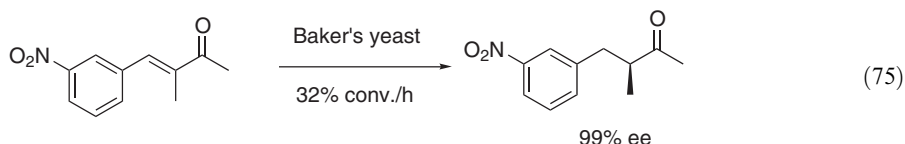
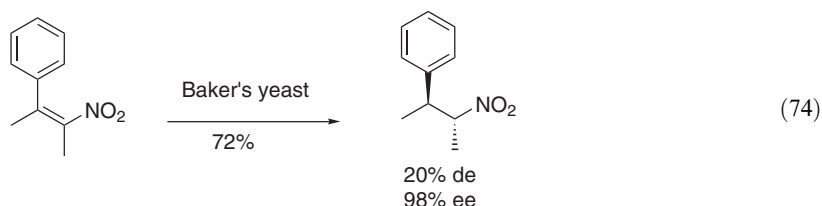
The use of less than 5 mol.% (based on copper for 1/6 [(PPh₃)CuH]₆) of Stryker's reagent allows the catalytic conjugate reduction of α,β -unsaturated ketones and aldehydes with Bu₃SnH or PhSiH₃ as hydride donors (Equation (71)), the lifetime of the catalytic [(PPh₃)CuH]₆/PhSiH₃ combination being greater <1998TL4627>. Mn(dpm)₃ has also been reported as an effective catalyst with PrⁱOH as a proton source (Equation (72)) <2000TL9731>.



Enantioselective reduction of α,β -conjugated double bonds can be achieved by several ways. Besides homogeneous asymmetric reduction <2003MI103>, impressive progress has been made in the field of catalyzed asymmetric conjugate reduction of esters <1998SI1655, 1999JA9473> and cyclic ketones <2000JA6797>. An elegant kinetic dynamic resolution of 3,5-dialkylcyclopentenones has been reported based on this reaction (Equation (73)) <2002JA2892>. The use of polymethylhydrosilane (PMHS) as a polymeric hydride donor greatly enhances the utility of this catalytic process.



The enantioselective reduction of tetrasubstituted nitroalkenes <2001TA309> can be performed with Baker's yeast (Equation (74)). With unsaturated ketones, isolated enzyme enables the reduction with similar enantioselectivity as with the whole cell (Equation (75)) <1998TL5225>.



1.03.2 REDUCTION OF ARENES AND HETEROARENES

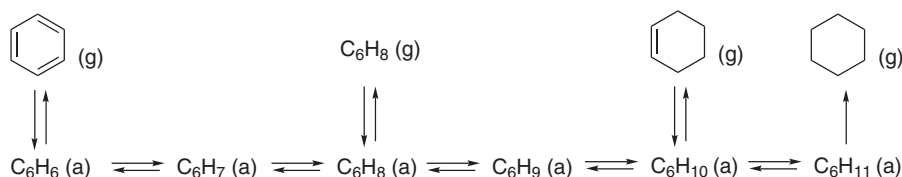
1.03.2.1 Types of Reactions

The reduction of arenes and heteroarenes can be accomplished by a variety of methods. It is generally more difficult than that of alkenes, dienes, or alkynes, since the resonance energy has to be overcome <B-1996MI001>. Heterogeneous hydrogenation using a number of different metals as catalysts has been reviewed <1991COS(8)417, 1996AC(137)203>. Such reductions are of great importance in several industrial processes. More recently, homogeneous hydrogenation of arenes has been reported <1991COS(8)443, 2003MI103>. Dissolving metal reductions have found considerable applications in synthesis, and recent progress has been made in their use for the asymmetric synthesis of saturated heterocycles <1996TA317, 1996PAC553>. The reduction of electron-deficient heteroarenes by hydrides is also one of the methods to prepare partially saturated compounds, as are electrochemical methods. The following sections will consider each of these methods separately.

1.03.2.2 Heterogeneous Hydrogenation

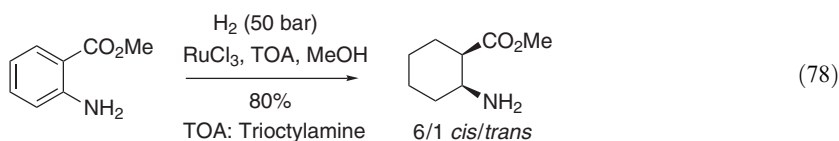
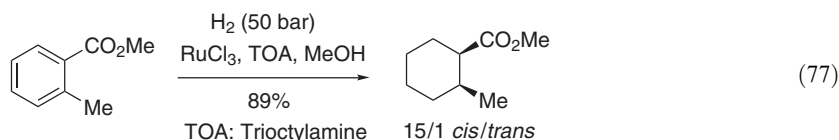
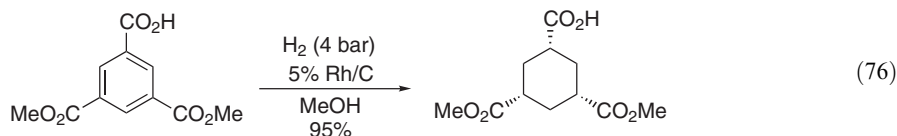
Even though benzene hydrogenation was reported at the beginning of the twentieth century using finely divided nickel as the catalyst <1901CR210>, the hydrogenation of monocyclic arenes is still an active area of research <2003JMOC(191)187>. Industrial applications, such as cyclohexane synthesis, partial arene hydrogenation to cyclohexenes, aromatic saturation of distillates, polystyrene, or lignin hydrogenations, are important transformations that stimulate discovery of new processes. Monocyclic arene hydrogenation is usually performed using heterogeneous catalysts with metal activities decreasing in the order $Rh > Ru > Pt > Ni > Pd > Co$ <B-1996MI002>, and metal sulfides, generally less active but also less sensitive to poisoning by sulfur compounds, and therefore used in petroleum refining <1996AC(137)203>. An efficient Zr-based catalyst has been reported for arene hydrogenation <1998JA13533>, and partial reduction of benzene has been described by lanthanide precipitates <2001CL450>. The use of soluble transition-metal nanoclusters for the reduction of monocyclic aromatic compounds is a growing research area, and has been reviewed <2003JMOC(191)187>. Polyphasic reduction conditions have been described, as well as the use of ionic liquids <2003MI216> as a reaction medium. The

ease of hydrogenation parallels the loss of resonance energy. Thus, reduction of phenanthrene and anthracene will be easier than that of naphthalene, and easier than that of benzene <B-1996MI001>. The mechanism of benzene saturation can be presented as a series of hydrogen transfers from the catalyst to the adsorbed reactive intermediates <1991COS(8)417> (Scheme 7). While diene intermediates are usually not observed, the partial reduction to cyclohexene is possible, even on an industrial scale <1990MI25>. When using a catalyst composed of a rhodium complex grafted on silica-supported dispersed palladium nanoparticles, an improvement of the arene hydrogenation speed has been observed <2003AG(E)2636>. A synergistic effect has been proposed, with the cyclohexadiene intermediate being more rapidly reduced at rhodium while cyclohexene predominantly hydrogenated at palladium.



Scheme 7

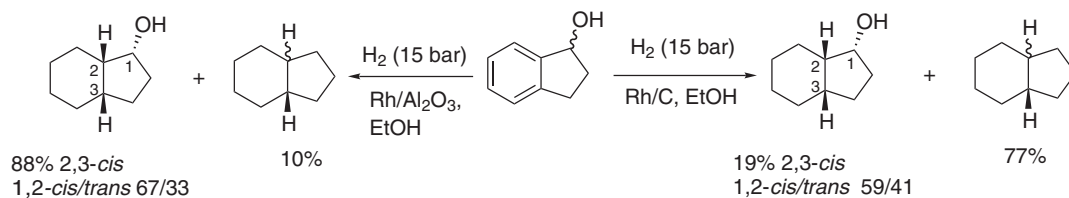
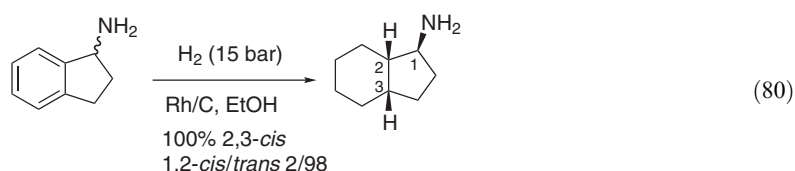
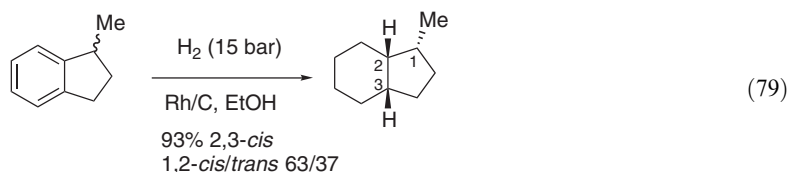
Although *cis*-isomers are the principal products of hydrogenation of substituted benzenes (Equation (76)) <1997T12497>, a competition between the addition of the six hydrogen atoms and the desorption of intermediates can exist, leading to the formation of *trans*-isomers through partially desorbed saturated species. Fine tuning of the catalyst, as well as experimental conditions (temperature, pressure) <1979JCA370> can change the isomer ratio, which is also dependent on the nature of the substituents (Equation (77) and (78)) <1995TL885>.



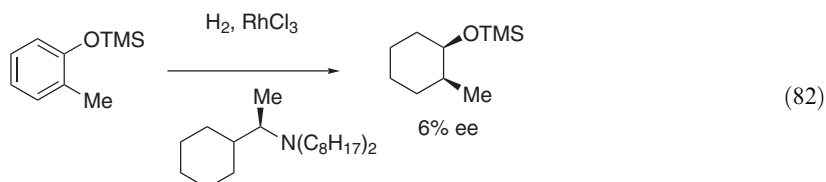
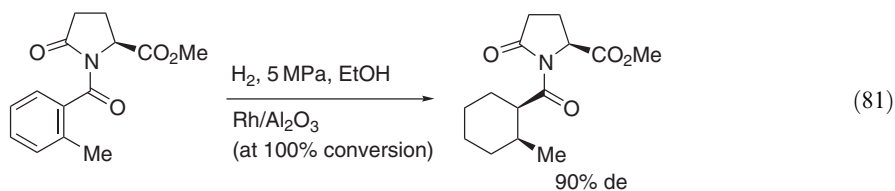
Hydrogenation of various xylene isomers using stabilized rhodium suspension has been described (Table 3). The *cis/trans* ratio varied with the isomer <2003MI222>. Haptophilicity can play an important role in the diastereoselective reduction of arenes. The functional-group directed hydrogenation of a series of monosubstituted indanes and tetralins has been studied <1999JOC8862>. The methyl group (Equation (79)) led only to a small preference for the *cis,cis*-isomer, whereas the amino group (Equation (80)) strongly interacted with the catalyst, leading to almost exclusively the *cis,trans*-saturated compound. Hydrogenation of 1-indanol revealed a mild haptophilic effect of the hydroxyl group, and a substantial amount of hydrogenolysis was observed. This side reaction could be minimized by changing the catalyst support (Scheme 8).

Table 3 Reduction of xylenes with a stabilized aqueous rhodium suspension
<2003MI222>

Isomer	Product	Ratio (cis/trans)
<i>o</i> -Xylene	1,2-Dimethylcyclohexane	97:3
<i>m</i> -Xylene	1,3-Dimethylcyclohexane	90:10
<i>p</i> -Xylene	1,4-Dimethylcyclohexane	70:30
<i>o</i> -Methylanisole	1-Methoxy-2-methylcyclohexane	98:2
<i>p</i> -Methylanisole	1-Methoxy-4-methylcyclohexane	84:6

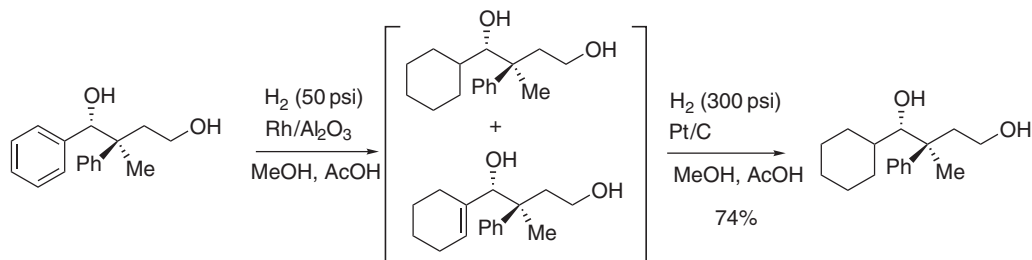
**Scheme 8**

The stereoselective hydrogenation of disubstituted phenyl rings over heterogeneous catalysts has attracted some attention in recent years. Until now, the use of a covalently bonded chiral auxiliary gave the best selectivities (Equation (81)) <2000TA1809, 2000CEJ949>, while the use of chiral adjuvant in colloidal systems has been described to give poor enantioselectivity (Equation (82)) <1994JMOC107>, but might provide an interesting entry for enantioselective reductions of arenes in the future.

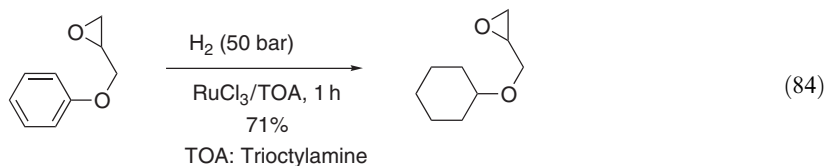
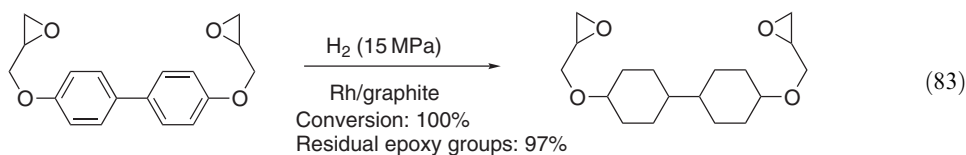


Since benzene hydrogenation requires generally strong reducing conditions, hydrogenolysis is a classical side reaction in such a process. The amount of benzylic hydrogenolysis is generally important with palladium, whereas the use of Ru or Rh, enabling the reduction under milder conditions, can lead to chemoselective hydrogenations. A two-stage procedure has been described

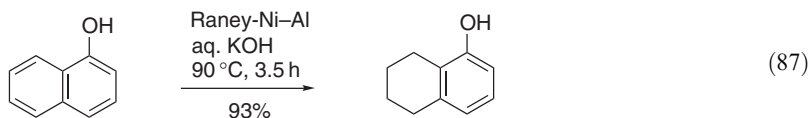
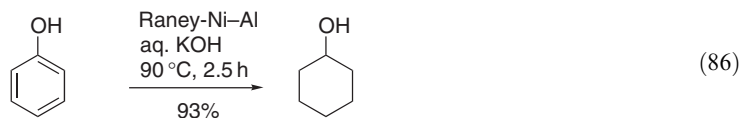
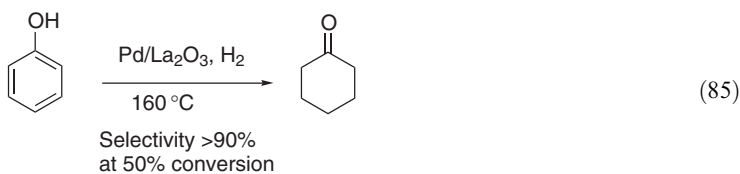
for the chemoselective hydrogenation of a benzylic alcohol in the presence of another phenyl ring (Scheme 9) <2002OL1951>. Among the various catalysts tested, Rh supported on graphite with a high surface area proved to be the most potent catalyst for the selective hydrogenation of bisphenol diglycidyl ether (Equation (83)). Surface properties of the catalyst are one of the crucial factors in controlling the selectivity <2002CL1116>. A similar selectivity has also been obtained with colloidal ruthenium (Equation (84)) <1995TL885>.

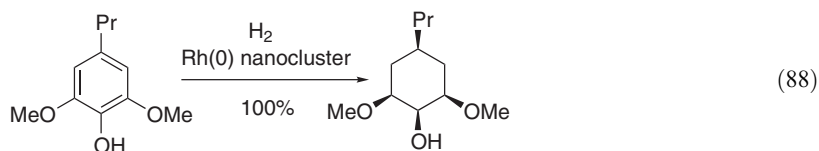


Scheme 9

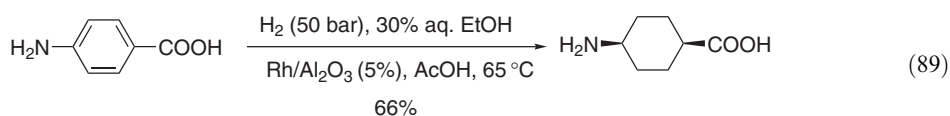


The reduction of phenolic systems can lead to hydrogenated compounds, cyclohexanone, or cyclohexanol derivatives. The production of cyclohexanone is of great industrial interest, and can be achieved with Pd catalysts. In a comparative study on the influence of different supports and Pd precursors in the selective hydrogenation of phenol to cyclohexanone, monometallic catalysts prepared from PdCl₂ showed the following activity and selectivity order: Pd/La₂O₃ > Pd/CeO₂ > Pd/Al₂O₃ (Equation (85)) <2002AC(235)21>. Addition of calcium strongly improved the catalytic performance of the Pd/Al₂O₃ catalyst, but no significant improvement could be observed with other supports. Formation of the cyclohexanol product is favored using rhodium or ruthenium catalysts. Raney Ni–Al alloy enables the efficient saturation of phenol in dilute aqueous alkaline solution without any solvent (Equation (86)). Naphthol is reduced as well, leading to the corresponding tetrahydro-naphthalene (Equation (87)) <2000TL5865>. The reduction of polysubstituted phenols can occur stereoselectively with nanocluster catalysts (Equation (88)) <1997CJC1234>.



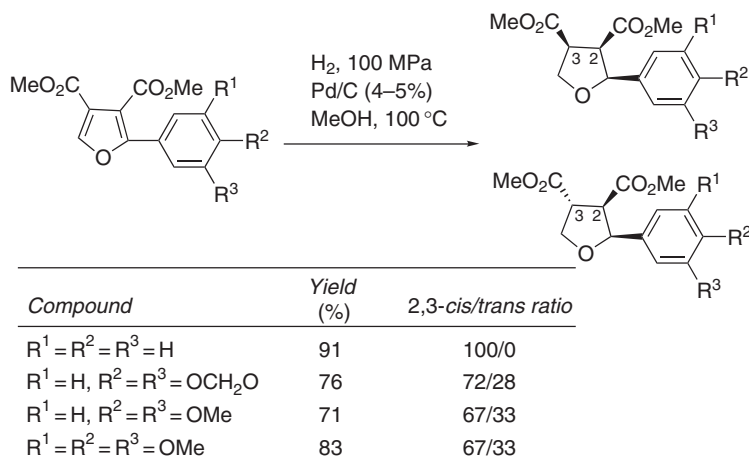


Aniline reduction can be performed over Rh or Ru catalysts. A stereoselective hydrogenation of 4-aminobenzoic acid has been reported with Rh/Al₂O₃ as catalyst [<1996JFC35>](#). The reaction temperature (65 °C) was critical since no reduction was observed at lower or higher temperatures (± 10 °C) ([Equation \(89\)](#)).

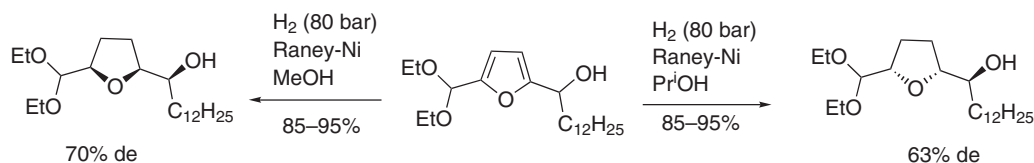


Reduction of heteroaromatic systems can be performed under heterogeneous conditions. In some cases, the presence of a cyclic heteroatom (N, S) can lead to the formation of strongly coordinating species on hydrogenation, and catalyst inhibition. The addition of acid is often helpful to prevent poisoning by protonation. Unlike π -deficient heterocycles, such as pyridine and related compounds, π -excessive heterocycles such as pyrroles, furans, and analogs are more difficult to reduce [<1991COS\(8\)603>](#). In several cases, heterocycles can be more difficult to reduce than a phenyl ring, enabling chemoselective hydrogenations [<1996BMCL1753>](#).

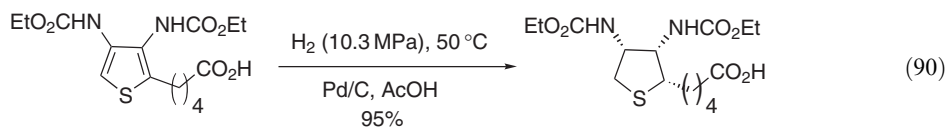
Furan can be hydrogenated over various catalysts [<B-1996MI001>](#), including Ru or Rh catalysts. Although Pd is generally not very convenient for arene hydrogenation, it is the catalyst of choice for furan reductions. A chemo- and stereoselective reduction of aryl-substituted furans has been described [<2000S2069>](#). The 3,4-*cis/trans* ratio variation with the substitution of the phenyl ring suggests that the reduction did not occur via a 1,4-addition mechanism ([Scheme 10](#)). Reduction of 2,5-disubstituted tetrahydrofurans has been investigated [<1996S349>](#). While Pd/C and Rh/Al₂O₃ proceeded with low selectivity, a diastereoselectivity up to 70% could be obtained using Raney nickel. The change of PrⁱOH to MeOH as a solvent led to a reversal of stereoselectivity ([Scheme 11](#)). Catalytic hydrogenation of thiophene is problematic since noble metal catalysts are poisoned and Raney nickel causes desulfurization. The reduction of polysubstituted thiophene over Pd has been described in a biotin synthesis ([Equation \(90\)](#)) [<1977JOC135>](#).



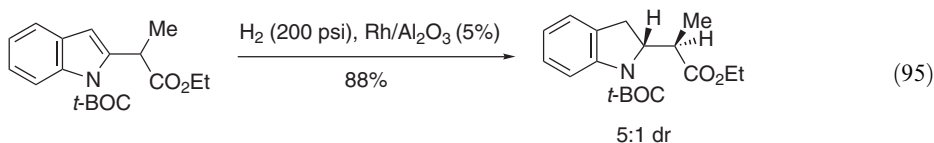
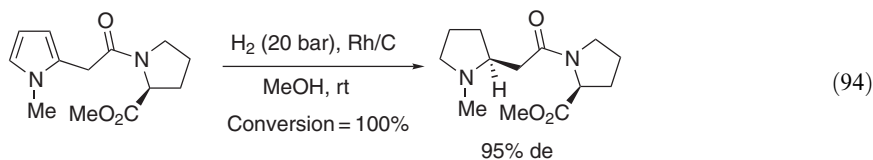
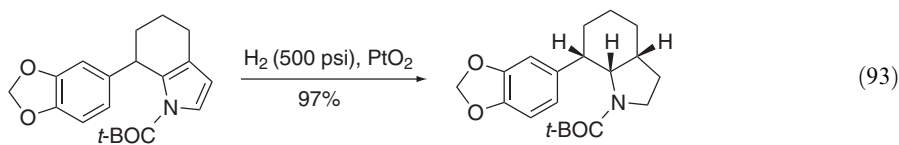
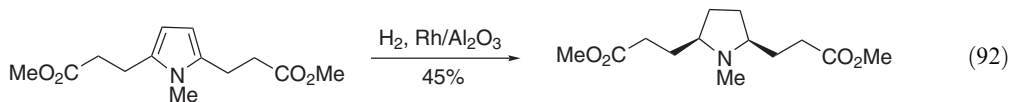
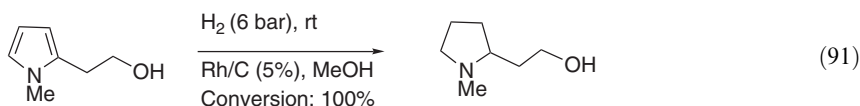
Scheme 10



Scheme 11

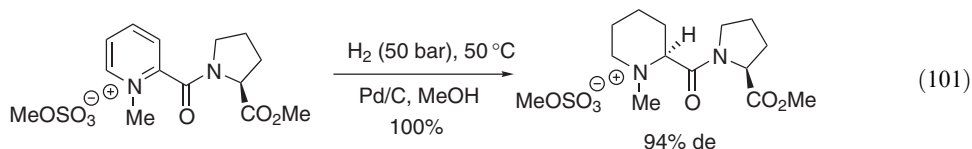
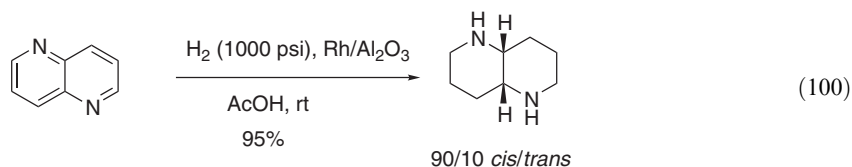
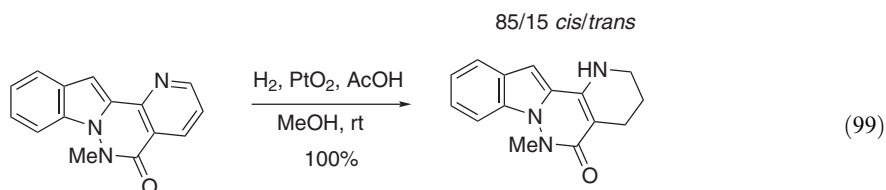
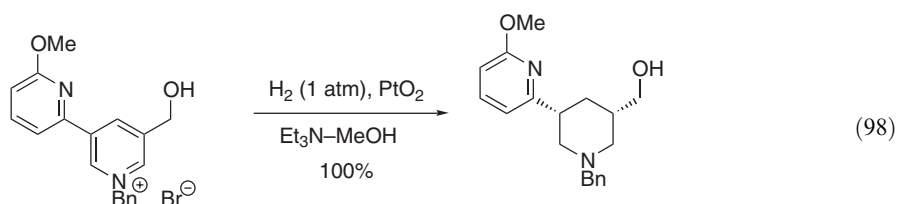
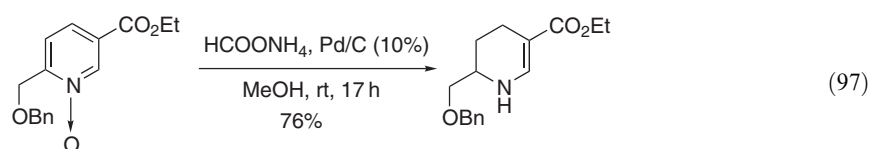
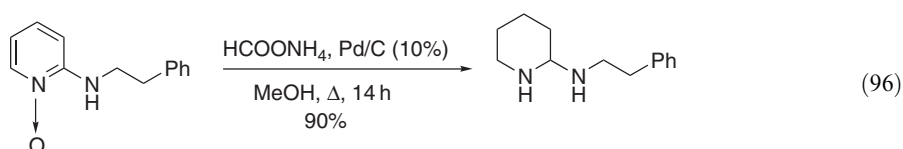


Pyrrole and its derivatives are known to be strong catalyst poisons, and their hydrogenation generally requires protonation or the use of electron-withdrawing *N*-protective groups. Raney Ni, Pt, Ru, and Rh catalysts have been used in the saturation of pyrrole ring, in the presence of acids. The reduction of 1-methyl-2-pyrroleethanol has been investigated in detail [\[1996AC\(143\)309, 1996AC\(147\)407\]](#). With this substrate, best results were obtained with Rh/C, in a nonacidic medium (Equation (91)). Ruthenium on carbon had also high activity at 80 °C. A similar trend has been reported with the hydrogenation of *N*-methyl pyrrole [\[1997AC\(152\)143\]](#), whereas hydrogenation of pyrrole required acidic conditions. 2,5-Disubstituted pyrroles can be reduced in a stereoselective manner (Equation (92)) [\[1996TL131\]](#), as well as 2,3-derivatives (Equation (93)). In the latter case, the pendant aromatic ring was not hydrogenated [\[1995TL6185\]](#). The use of a chiral auxiliary has been reported in the diastereoselective hydrogenation of 2-acetyl pyrrole derivatives (Equation (94)) [\[2001AC\(210\)165\]](#). Although indoles are readily hydrogenated, it is generally difficult to control the site and degree of reduction [\[1991COS\(8\)603\]](#). A partial hydrogenation of *N*-*t*-BOC-indole-propanoate has been reported to occur over Rh/Al₂O₃ (Equation (95)) [\[1995TL8693\]](#).



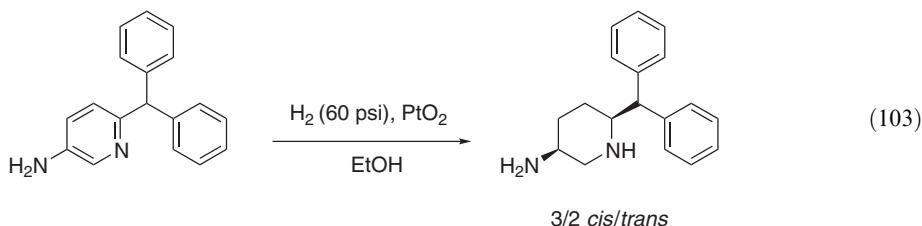
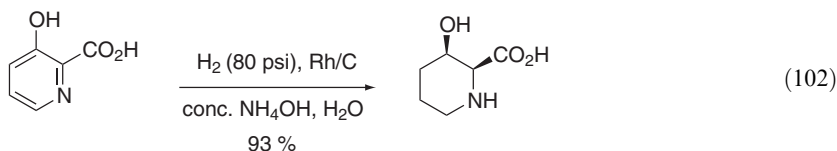
Catalytic hydrogenation of pyridine is a classical method for the synthesis of piperidines. Complete reduction generally occurs, as partially hydrogenated intermediates are reactive under the conditions employed. Rh, Pd, and Ru catalysts can be used, generally under acidic conditions, and Ni requires higher pressure and temperature [\[1991COS\(8\)579\]](#). When performed under

acidic conditions, hydrogenation of pyridines can suffer from a lack of chemoselectivity <1996TL459>. A mild procedure for the reduction of pyridine *N*-oxides over Pd has been reported (Equation (96)) <2001JOC5264>. Several reducible functions are unaffected with this method. Partial hydrogenation can be achieved using this procedure (Equation (97)) <2003JMC2216>. Only 10% of debenzoylation was observed, whereas the hydrogenation of the corresponding pyridine over PtO₂ under acidic conditions led to nearly 50% of C2 reduction (hydrogenolysis). Selective reduction of pyridinium salts can also be achieved under mild conditions (Equation (98)) <2000OL4201>. Hydrogenation of the unactivated alcohol prior to the formation of the benzylpyridinium salt affords product only of hydrogenolysis. The chemoselective reduction of pyridine in the presence of an indolic nucleus has been described <1996TL3071>. Pyridine rings included in polycyclic systems can be partially (Equation (99)) <1995T1941> or fully hydrogenated (Equation (100)) <2000OL875>. In the latter case, the *cis*-perhydronaphththyridine was obtained as the major isomer. Diastereoselective reductions of pyridines bearing a chiral auxiliary have been reported (Equation (101)) <2000AC(201)107>. A two-step, enantioselective reduction of ethyl nicotinate has been described using modified catalysts, albeit with limited success (ee ~20% at 10% conversion) <1999JMC253>.



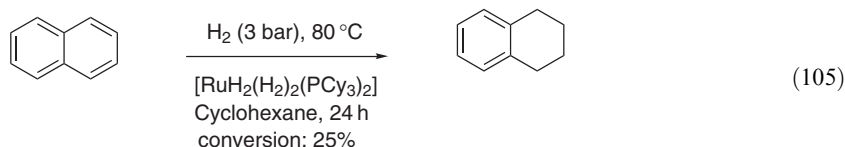
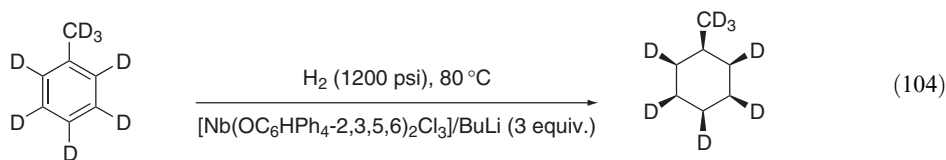
Although hydrogenation of 3-hydroxy- or aminopyridines can result in hydrogenolysis, some examples of such reductions have been reported (Equations (102) and (103)) <2000TL8413, 2001BMCL2337>. Hydrogenation of pyrazine-carboxylic acid can be conducted over Pd/C catalyst <1999BMCL1121>. The reduction of quinoline under mild conditions has been

investigated using Pd, Rh, or Ru/Al₂O₃ catalysts. 1,2,3,4-Tetrahydroquinoline was the main product obtained with Pd and Rh catalysts, while Ru proved to be inactive. Perhydrogenation could not be achieved with increasing temperature or pressure, or in the presence of Brønsted acid or base, whereas the addition of Hünig's base enabled the partial formation of decahydroquinoline <2002JMOC(179)287>.

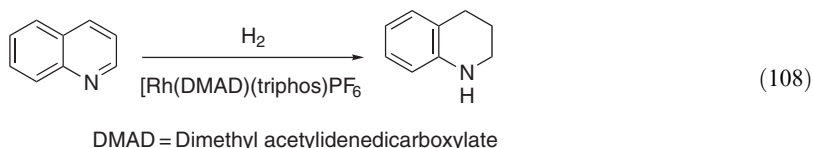
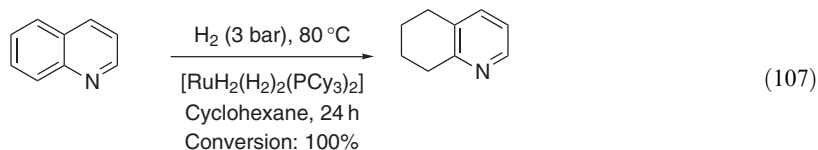
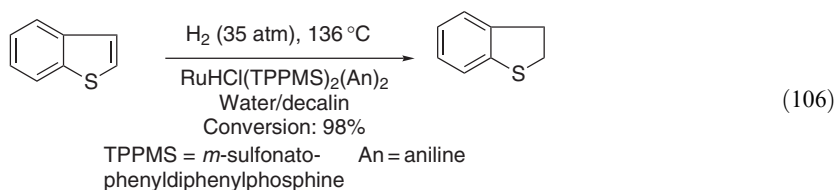


1.03.2.3 Homogeneous Hydrogenation of Arenes

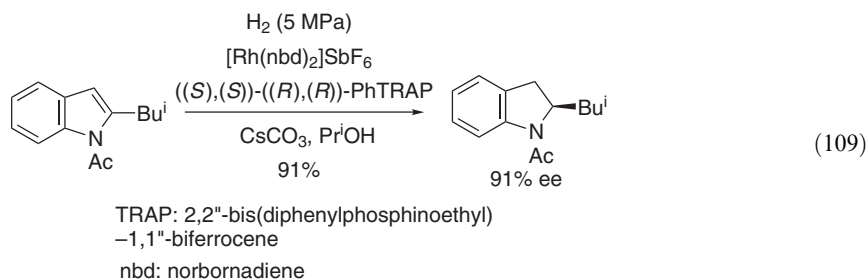
The hydrogenation of monocyclic arenes with homogeneous transition metal catalysts is not a simple task <1991COS(8)443>. Furthermore, several claimed “homogeneous” arene hydrogenation catalysts can in fact be “heterogeneous” nanoclusters described in Section 1.03.1.1 <1998JA5653>. The fact that the lack of catalytic activity in benzene hydrogenation has been sometimes proposed, erroneously, as a test for the homogeneous character of a catalyst illustrates this problem. However, several systems have been developed and have been proven to be homogeneous. Among them, allylcobalt catalysts <1979ACR324> with phosphine or phosphite ligands or Ziegler-type catalysts <1963JOC1947> have been known for sometime. A new generation of homogeneous arene hydrogenation catalysts has been described <1997CC1331>. These Nb or Ta hydrido aryloxide complexes catalyze the reduction of a large variety of aromatic hydrocarbons, including benzene. The hydrogenation of [2-H₈]-toluene affords the all-*cis* isotopomer (Equation (104)). Polycyclic aromatic hydrocarbons are much more easily reduced using homogeneous catalysts. Hydrogenation of naphthalene and anthracene is catalyzed by Ru catalysts (Equation (105)) <2001JMOC(174)69>. Interestingly, a decrease of conversion has been noted with increase of pressure, suggesting that a dissociation of dihydrogen is needed for substrate coordination. Benzene was also reduced under these conditions, but inhibition by addition of Hg(0) suggests the formation of colloids in this case.



Removal of heteroatoms from fossil fuels under hydro-treating conditions is an important industrial process. The partial or total saturation of benzo[b]thiophene (Equation (106)), quinoline, acridine, or indole has been investigated using Rh <2001HCA2895, 2002OM1430> or Ru catalysts <2002JMOC(189)211, 2003OM1630>. The regioselectivity of quinoline reduction can vary with the catalyst (Equation (107) and (108)).

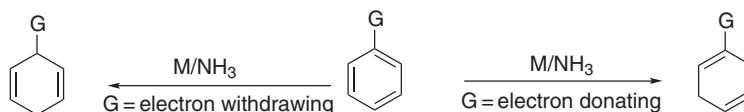


Several enantioselective hydrogenations of heteroaromatic compounds have been reported [<1998OM3308, 2000M1335, 2003MI103>](#). The partial asymmetric reduction of *N*-acyl indoles occurs in good enantioselectivity (Equation (109)) [<2000JA7614>](#).



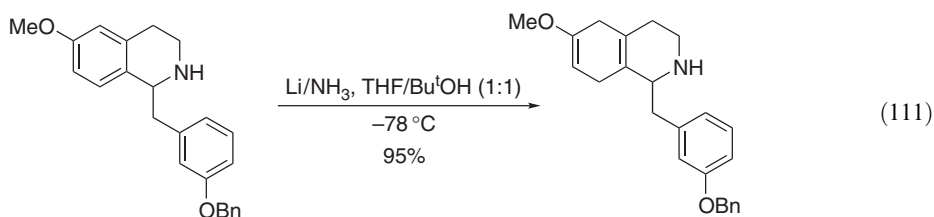
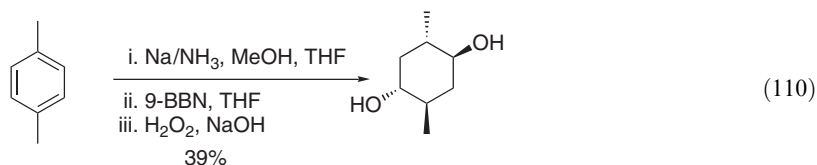
1.03.2.4 Dissolving Metal Reductions

The reduction of aromatic compounds by dissolving metals is an extremely useful transformation. Because of the much higher electron affinity of arene substrates over the products, the formation of partially reduced compounds is generally favored under such reducing conditions. Although the first example of the partial reduction of an arene with sodium in ammonia was reported by Wooster and Godfrey [<1937JA596>](#), this reaction has been extensively developed by Birch and is now known as the Birch reaction [<1991COS\(8\)489>](#). Since the reduction involves two electron transfers and two protonation steps, the exact pathway followed will depend on the substitution pattern of the aromatic ring, the choice of the metal, and the proton source. Thus, the mechanism involving radicals, radical-anions, and anions might be more subtle than the simple general reaction pattern summarized in Scheme 12. Furthermore, iron impurities contained in ammonia have been shown to be a major cause for the lack of reproducible results in several reductions.

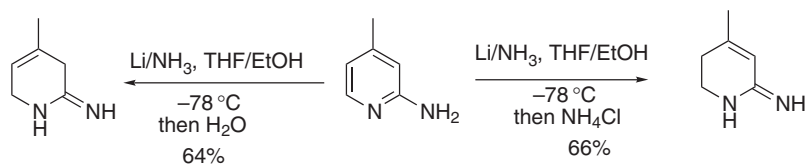
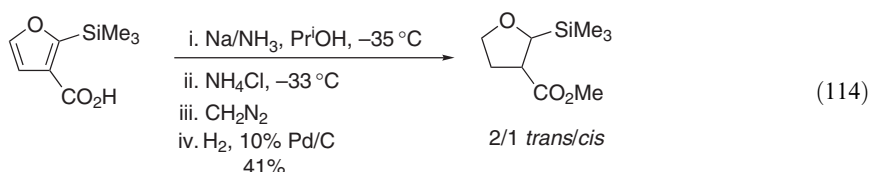
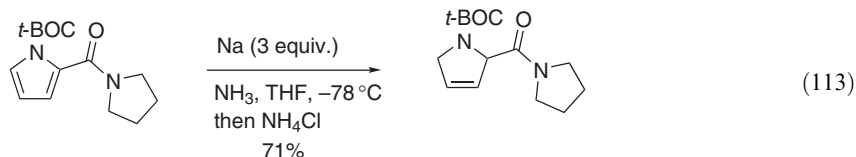
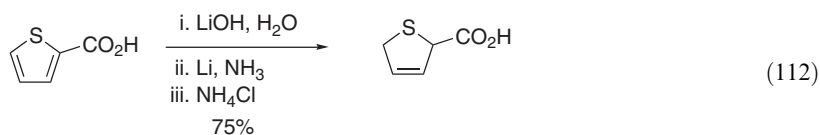


Scheme 12

The Birch reduction is of great synthetic interest, either for the reduction of simple arenes (Equation (110)) [<2003TA71>](#) or for the selective reduction of polyfunctional compounds [<2002TL2913>](#). Chemoselective aromatic reduction can be achieved by tuning their substitution pattern (Equation (111)) [<2002BMCL1981>](#).

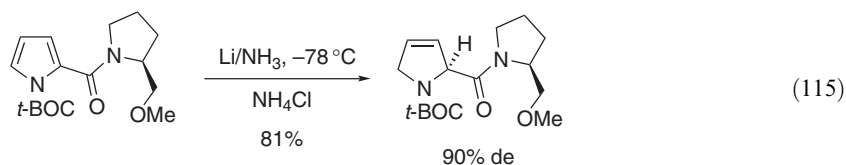


Although only simple reductions will be described in this section, quenching the reaction with an electrophile can lead to a reductive alkylation process, which has seen important developments in recent years, mainly by the groups of Schultz [<1999CC1263>](#) and Donohoe [<2003OBC3749>](#). Several heterocycles can be reduced using Birch conditions. Thiophene-2-carboxylic acid (Equation (112)) [<1997T6019>](#), electron-deficient pyrroles (Equation (113)) [<1998JCS\(P1\)667>](#), pyridines [<2001JCS\(P1\)1435>](#), silylfuroic acids (Equation (114)) [<1996TL9119>](#), or aminopyridines (Scheme 13) [<2003BMCL689>](#) have been reduced using dissolving metal conditions. In the latter case, the proton source had a strong influence on the outcome of the reduction.

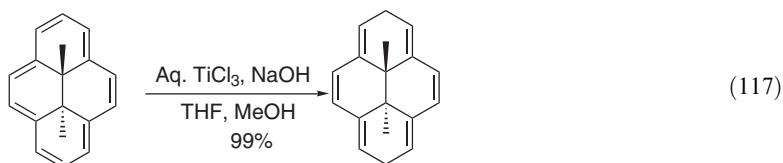
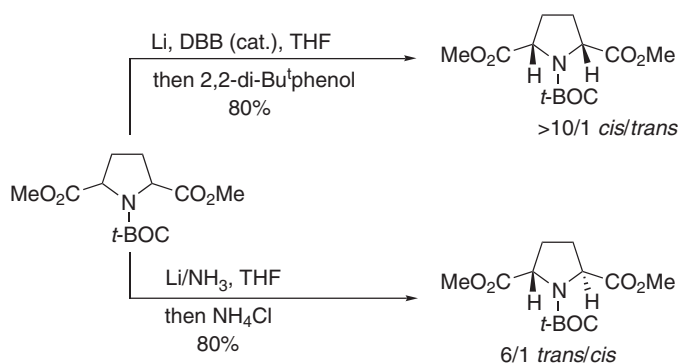
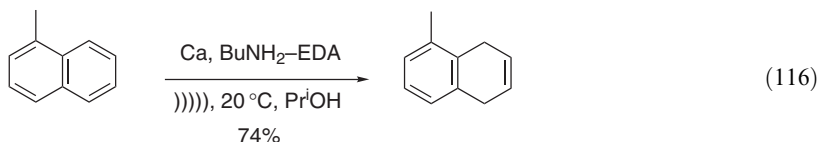


Scheme 13

The asymmetric protonation of an enolate resulting from Birch reduction has been studied. The better selectivity observed with protonation than with other electrophiles has been discussed on the basis of quantum chemical calculations (Equation (115)) [<1999T12309>](#).

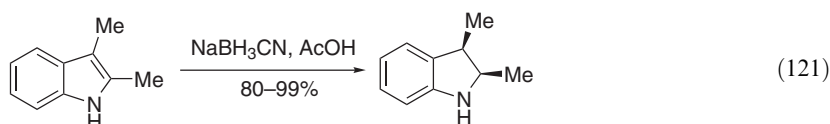
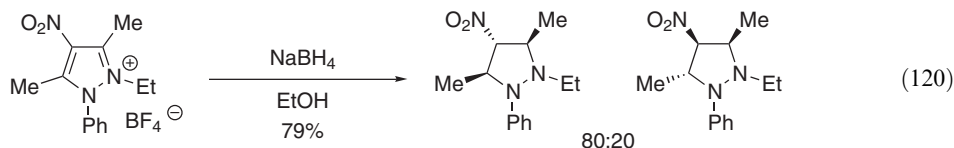
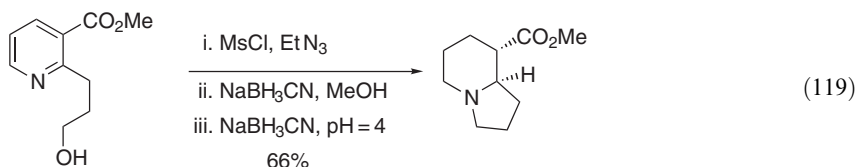
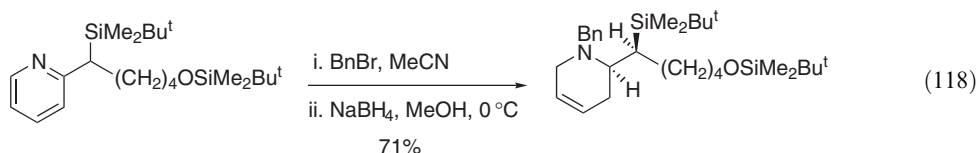


Reaction conditions other than the standard Birch protocol (group I and II metals in liquid ammonia) have been reported for the reduction of arenes. The most popular alternative is the Benkeser reduction, using low-molecular weight aliphatic amines as a solvent <1991COS(8)489, 1984TL2089>. The use of ultrasonic irradiation can improve the reduction of aromatics with calcium (Equation (116)) <2000MI53>. Ammonia-free reduction is possible using lithium di-*t*-butylbiphenyl (LiDBB) as a source of electrons and bis(methoxyethyl)amine (BMEA) as a protonating agent <2002JOC5015>. Interestingly, the stereochemical outcome of the Birch reduction of disubstituted electron-deficient pyrroles can be reversed using this new process and a bulky acid (Scheme 14) <2003OL999>. The use of titanium trichloride in water has been reported for the reduction of nonbenzenoid annulenes (Equation (117)) <2003TL1271>.



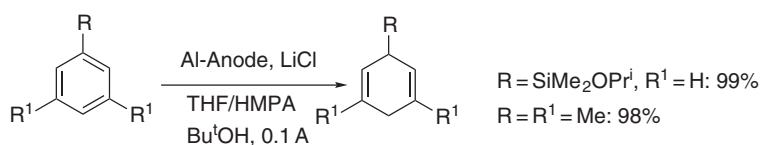
1.03.2.5 Hydride Reductions

Aromatic C—C double bonds are generally not reduced by metallic hydrides, but the reduction of nitrogen heteroaromatic compounds is a classical entry for the synthesis of partially saturated heterocycles <B-1997MI>. With pyridines, the presence of electron-withdrawing substituents will enable the controlled reduction with borohydrides to dihydro- or tetrahydropyridines <1991COS(8)579>. Tetrahydropyridines can generally be obtained via their corresponding pyridinium salts. Activation can be performed by intermolecular alkylation (Equation (118)) <1996TA2775, 1998T5959> or in an intramolecular manner (Equation (119)) <2001JCS(P1)654>. A similar activation has been reported for the reduction of pyrrolidinium salts (Equation (120)) <1996T9193>. Although pyrrole is inert to hydride-reducing reagents, indoles are reduced by several borohydride species <1991COS(8)603>. The stereoselective reduction of several substituted indoles with NaBH₃CN has been reported to yield the corresponding indolines in a completely stereoselective manner (Equation (121)) <1998BMCL745>.



1.03.2.6 Electrochemical Reductions

Electrochemistry can be a valuable tool for the selective reduction of arenes, and has been widely explored by industry. Since the classical Birch reduction proceeds by successive electron transfers and protonations, it is not surprising that electrochemistry can be a useful alternative to this method, although synthetic organic chemists might be reluctant to use it. The electrochemistry of solvated electrons and its use in hydrogenation of aromatics has been reviewed [\[1995RTC259\]](#). The generation of solvated electrons and Birch reduction of 3-methylanisole in liquid ammonia has been studied [\[2001JEC\(507\)144\]](#). The use of power ultrasound, leading to faster mass transport and electrode depassivation, allows the process to be conducted with high overall rate. Several substituted cyclohexadienes have been prepared by the electrochemical reduction of the corresponding arene precursors (Scheme 15) [\[2002EJO4037\]](#).



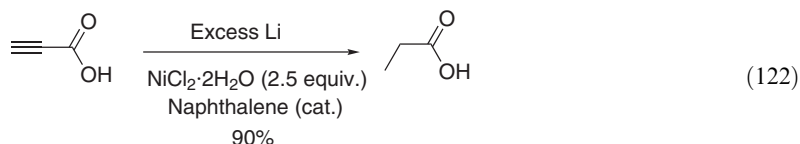
Scheme 15

In some cases, large-scale preparative reductions can be achieved with the use of a tubular flow cell. Electrocatalytic hydrogenation of arenes can be an alternative route to partially hydrogenated derivatives [\[2000MI4279\]](#). The stereochemical outcome of the reduction of *m*-xylene has been reported to be dependent on the potential on which the hydrogenation has been carried out [\[2000MI4291\]](#).

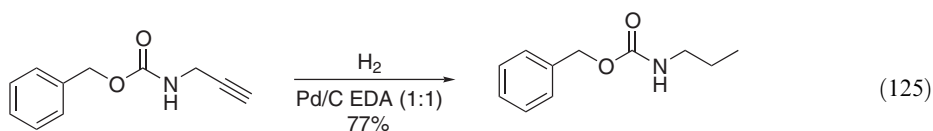
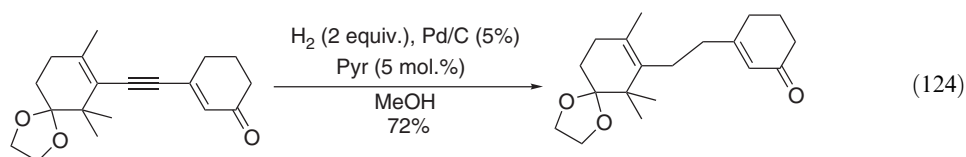
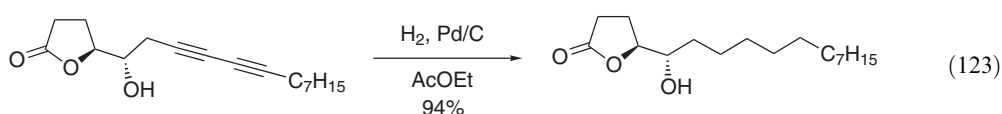
1.03.3 REDUCTION OF ALKYNES AND ALLENES

The reduction of triple bonds to alkanes is a typical side reaction observed during partial hydrogenation of alkynes. Although this reaction is generally less interesting than the semihydrogenation, it could be useful to introduce an alkyl group in combinatorial chemistry, using a

two-step sp - sp^2 coupling/full reduction sequence. Saturation of triple bonds can be accomplished by hydrogenation, using heterogeneous <1991COS(8)417, 2002EJO2288, 1996SL1041> or homogeneous <1991COS(8)443, 1995JOC7170> catalysts. Hydrogen transfer conditions can be used in such transformations <1996JMC2971>. The reduction of functional alkynes has been reported with the Li-NiCl₂-naphthalene combination (Equation (122)) <1997TL149>.

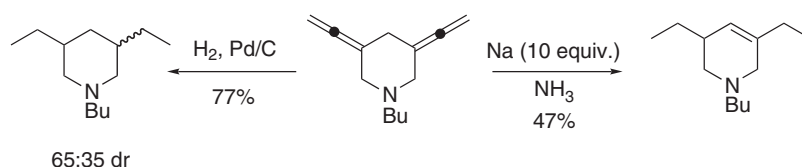


Conjugated diynes can be reduced under various conditions (Equation (123)) <1995TL8087, 2000CL1416>. The selective reduction of conjugated enynes has been reported (Equation (124)) <1995TL5891, 2000SL1205>, as well as the chemoselective hydrogenation of a triple bond in the presence of a hydrogenolysis-sensitive protective group (Equation (125)) <1998JOC7990>.

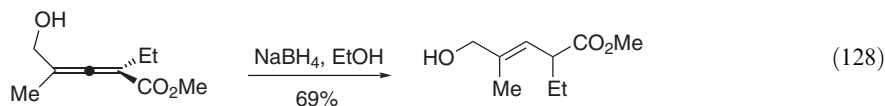
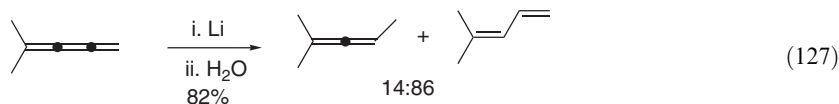
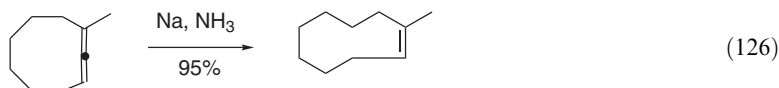


EDA = ethylenediamine

Acyclic allenes can be hydrogenated with high selectivity to monoenes over palladium catalysts <1991COS(8)417>. Terminal allenes are generally reduced at the terminal double bond. Sodium/ammonia reduction of 1-methyl-1,2-cyclononadiene provides mainly *cis*-1-methylcyclononene in excellent yield (Equation (126)) <1975S194>. A similar approach can be used for the preparation of 1,6-cycloundecadiene <1972S612>. The reductive metallation of butatrienes has been investigated (Equation (127)) <1996T6149>. Experimental procedures had to be carefully optimized to get reproducible results. The reduction of 3,5-divinylidenepiperidine has been conducted under several conditions (Scheme 16) <2001JOM94>, leading to partial or full reduction. The π -facial selectivities of nucleophilic addition to allenecarboxylate derivatives has been investigated <1995SL711, 2000JCS(P1)3188>. Interestingly, the borohydride reduction can lead to (*E*)-alkene in a diastereoselective manner via an internal delivery of hydride (Equation (128)).



Scheme 16



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 1901CR210
 1934TFS1164
 1934M1630
 1937JA596
 1962AG215
 1962JA685
 1963JOC1947
 1965CC131
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 1966TL1605
 1970CC495
 1970CC497
 1970CC571
 1970JOC3565
 1972S612
 1973CL855
 1973JA6379
 1975JOC3599
 1975S194
 1976CL581
 1977JOC135
 1978JOC2567
 1979ACR324
 1979ACR331
 1979JCA370
 1979JOC1014
 1980JA2693
 1984JOC1845
 1984TL2089
 1985CRV129
 1987JMC1505
 1989NAT(339)454
 1990MI25
 1991COS(8)417
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Biographical sketch

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1.04

One or More CC Bond(s) Formed by Substitution: Substitution of Halogen

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1.04.1 INTRODUCTION AND SCOPE

Carbon—carbon bond formation involving substitution of halogen by a carbon center represents undeniably the most common and important transformation in organic synthesis. In most cases, the selective introduction of an alkyl, allyl, benzyl, or propargyl chain in place of hydrogen atom at the carbon center of elaborated substrates has been achieved by generation of related organometallics and subsequent quenching with haloalkanes. In the context of this chapter, mainly based on the functionalization of tetrahedral carbons, discussions will be limited to $C(sp^3)-C(sp^3)$ bond formation. Coverage of structural studies and practical procedures will be kept to a minimum.

A great deal of effort has been devoted to the preparation of mono- and dicarbanions and their reaction with alkylating agents. In this area, a large number of metallation methods have been disclosed in the literature and, among these, proton abstraction is by far the main strategy employed for the functionalization of activated position adjacent to benzyl, allyl, heteroatoms, or electron-withdrawing groups, which can stabilize the intermediate carbanion. Alternative methods such as halogen- or selenium-exchange, tin–metal transmetallation, reductive cleavage, and carbometallation have also been developed.

Tremendous progress has also been achieved in asymmetric synthesis for stereoselective C—C bond formation including asymmetric alkylation of organometallic compounds generated by metallation of prochiral methylene groups. Several methods based on asymmetric deprotonation by chiral bases or on auxiliary controlled alkyl introduction have been reported and found to be particularly efficient, offering a high degree of control in the C—C bond formation. The enormous interest to catalytic asymmetric C—C bond formation and the recent progress in asymmetric enolate chemistry have been the focus of many studies in synthetic organic chemistry. Selected examples will be discussed herein. Furthermore, applications of these metallation–substitution sequences in natural product and solid-phase synthesis are beyond the scope of this chapter.

1.04.2 CARBANIONS WITH NO STABILIZING GROUP

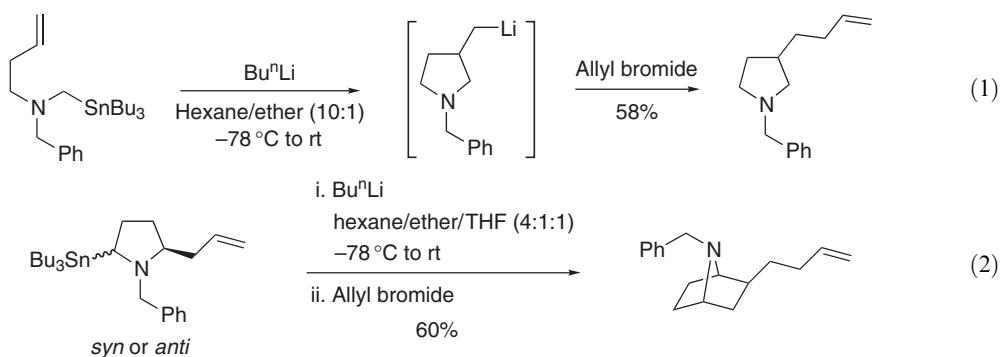
1.04.2.1 Group I Metals (Li, K)

The use of organolithium reagents has steadily increased since the early 1990s and have become of significant interest in organic synthesis. For a long time, their high reactivity and basicity were considered as major drawbacks for chemoselective transformations. However, some of the observed side-reactions, such as Wurtz coupling, metal–halogen exchange, electron-transfer process, α -metallation, and α - or β -elimination have been widely exploited for synthetic purposes. Synthesis of diastereomerically and enantiomerically enriched alkyllithiums has also been intensively studied.

A lot of attention has been turned to sequential asymmetric deprotonation followed by substitution of alkyl halides. Since 1995, several investigations and synthetic applications have been developed in this area and various aspects will be covered throughout this work <1997AG(E)2282, 2002AG(E)716>.

1.04.2.1.1 Alkylation of alkyllithiums generated by intramolecular carbolithiation of alkenes

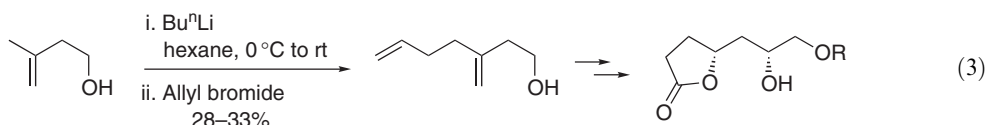
Anionic cyclization of organolithiums onto alkenes has found widespread applications in synthesis to the preparation of nonaromatic heterocycles. Intramolecular carbolithiation of a terminal alkene by an α -amino-stabilized carbanion leads to a novel nonstabilized alkyllithium, which can be trapped by alkyl halides. During the process, two C—C bonds have been created from an acyclic precursor. Coldham and co-workers have been interested in the synthesis of elaborated amino-containing heterocycles from α -amino organolithiums. The metallic species, generated by tin—lithium exchange from the corresponding stannane, proved to cyclize easily onto the unactivated terminal alkene. The 3-lithiomethylpyrrolidine intermediate gave the desired 2-substituted product by addition of allyl bromide (Equation (1)) <1996JA5322>. Furthermore, the 2-functionalized 7-azabicyclo[2.2.1]heptane system was elaborated from the 5-allyl-2-tri-*n*-butylstannyl-*N*-benzylpyrrolidine following a similar reaction sequence. Both *trans*- and *cis*-organostannanes undergo a stereoselective cyclization leading to the common and unique 2-*exo* isomer (Equation (2)) <1999TL1819>.

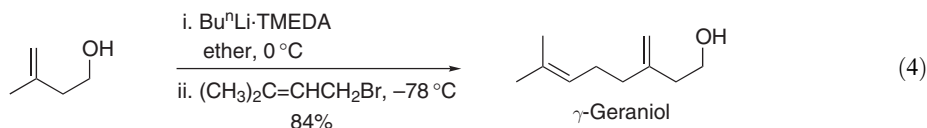


1.04.2.1.2 Alkylation of allyllithium and allylpotassium species

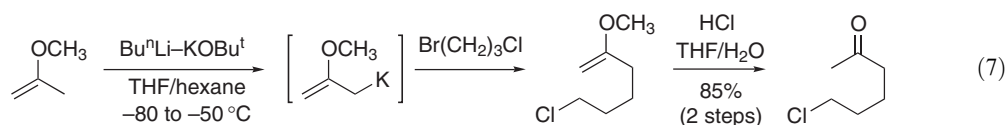
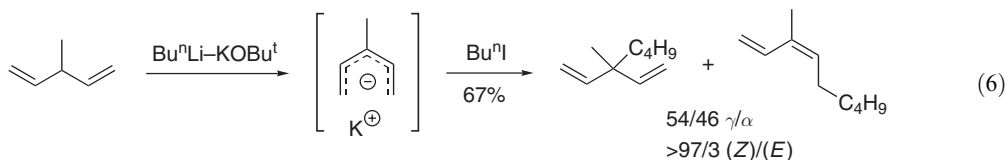
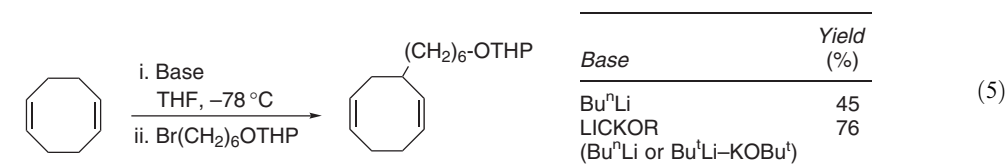
(i) Metallation through hydrogen abstraction by lithiated or potassium bases

Deprotonation of a simple alkyl chain in the allylic position usually requires the use of strong bases. Metallation of 3-methyl-3-buten-1-ol followed by alkylation of its dianion with allylic halides was introduced in 1974 <1974TL2215> and more recently applied by Brückner to the synthesis of a butyrolactone precursor. The protocol involved the deprotonation of 3-methyl-3-buten-1-ol with Bu^nLi in the presence of TMEDA or using KH. Subsequent alkylation gave moderate-to-poor results (Equation (3)) <1998EJO1023>. Later, Chong reexamined the metallation conditions and tried to generalize this methodology to other alkylating agents, in order to apply it to the synthesis of natural products such as γ -geraniol <2001JOC8248>. Different experiments revealed that the solvent has a significant effect on the metallation/alkylation yield. Indeed, the best results have been reached for sequences achieved in diethyl ether with TMEDA (Equation (4)).

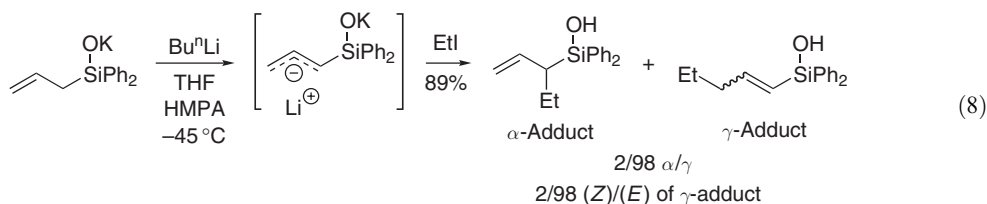




Ganesan and co-workers studied the alkylation of 1,5-cyclooctadienyllithium by $\text{Br}(\text{CH}_2)_6\text{OTHP}$ under various conditions. Lithium–potassium alkoxide reagents (LICKOR) metallation of 1,5-cyclooctadiene followed by reaction with alkyl halides gave the 3-substituted 1,5-cyclooctadienes in high yields compared to a simple Bu^nLi deprotonation with or without TMEDA as co-solvent (Equation (5)) <2002JOC6250>. The poor yield observed in this case confirms Winkler and Sridar's results <1986JA1708>. Schlosser showed that 3-methyl-2,4-pentadienylpotassium, obtained by deprotonation with LICKOR superbase, was easily alkylated by 1-iodobutane at the α - and γ -position without any selectivity by opposition to other electrophiles such as TMSX , CO_2 , or $\text{B}(\text{OMe})_3$. The configuration of the trisubstituted double bond formed was proved to be (Z) (Equation (6)) <2001S1830>. A synthetic equivalent of acetone enolate was easily generated by metallation of methyl isopropenyl ether with LICKOR base. The organolithium intermediate can be trapped by various alkylating agents at low temperature. Above -30°C , the metallated methyl isopropenyl ether decomposes rapidly to form allene. Acid hydrolysis of the enol ether adducts led to the expected methyl ketones (Equation (7)) <1997CB45>.

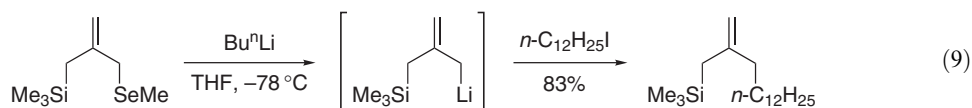


Oshima and co-workers <1997TL5189> reported the regioselective γ -alkylation of a 1-silylallyl-lithium directed by an anionic oxygen present on the silicon atom (Equation (8)).



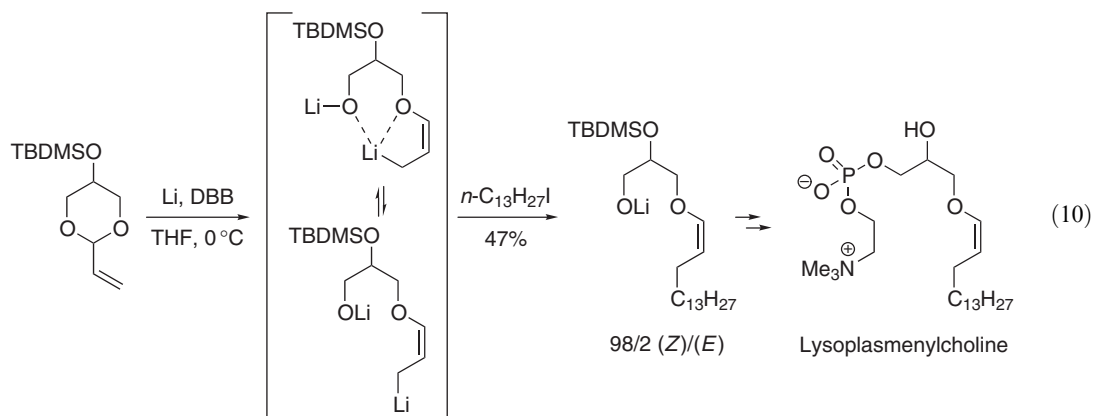
(ii) Selenium–lithium exchange

During his studies on the reactivity of 1,1-bis(metallomethyl)ethenes, Livinghouse has been interested in the generation of [2-((trimethylsilyl)methyl)prop-2-enyl]lithium and its synthetic utilization as a versatile 1,3-bis(nucleophile). The lithiated propenyl silane can be prepared through lithium–selenium exchange according to Krief's methodology. Treatment of the corresponding allyl selenide with Bu^nLi affords the lithio compound, which can be alkylated by 1-iodododecane providing the 2-substituted allyl silane in excellent yield (Equation (9)) <1997JOC4842>.



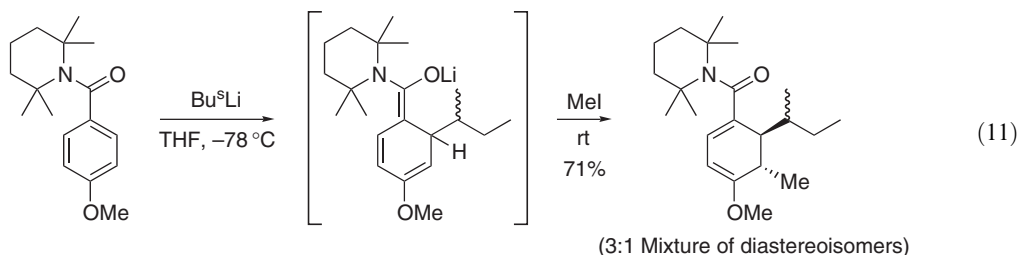
(iii) Reduction of acetals

Barbier-type reductive alkylation of vinyl dioxanes and vinyl dioxolanes with alkyl halides in lithium 4,4-di-*t*-butylbiphenyl (LiDBB) solution has been developed by Thompson and co-workers. [<2002JOC6503>](#) and applied to the synthesis of phospholipids such as plasmenylcholines, used for the delivery of low-molecular-weight drugs, proteins, and genes. LiDBB induces the reductive acetal ring opening, and the reaction of the resulting allyllithium species with haloalkanes leads to the (*Z*)-enol ethers in moderate yields ([Equation \(10\)](#)).



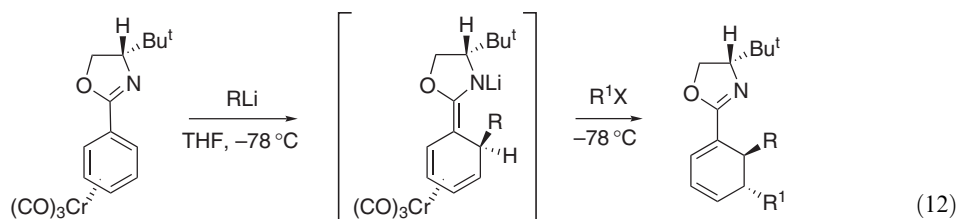
(iv) Carbolithiation of aromatic rings

Recently, Clayden and co-workers reported the intermolecular addition of organolithium compounds to hindered aromatic amides instead of their usual *ortho*-lithiation, without resorting to the arene-chromiumtricarbonyl chemistry. Regioselective nucleophilic attack of various organolithium compounds to *N*-benzoylamides of 2,2,6,6-tetramethylpiperidine gives the corresponding dearomatized enolates, which can be alkylated by a range of alkyl and benzyl halides. Highly substituted cyclohexadienes are obtained in moderate-to-good yields giving the *trans*-adducts as a single diastereoisomer ([Equation \(11\)](#)) [<2002CC2138, 2002EJO3558>](#).

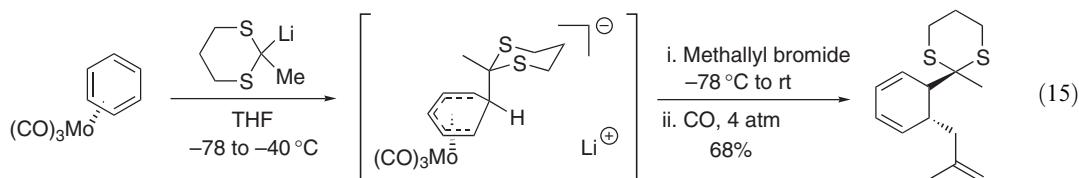
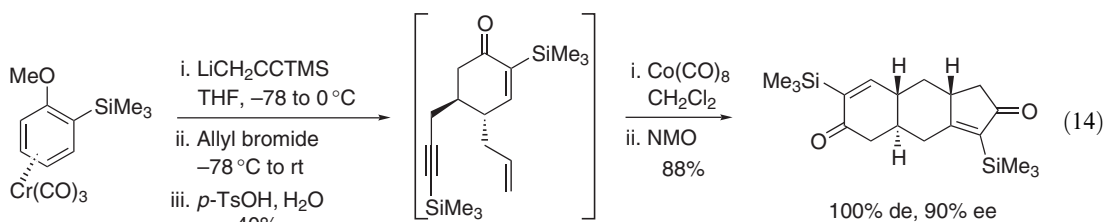
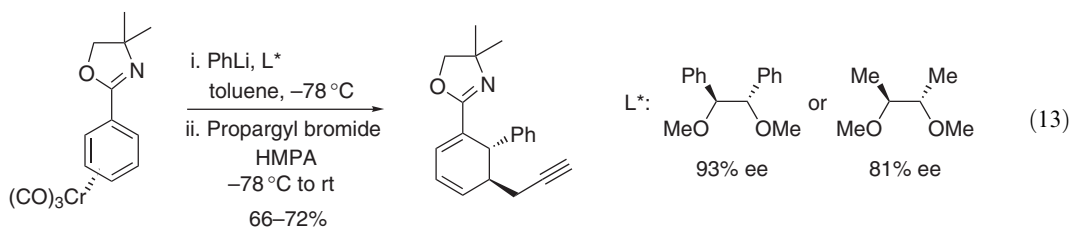


Kündig and co-workers [<1992AG\(E\)1071, 2001S2040>](#) developed two interesting approaches for the synthesis of enantiomerically enriched *trans*-disubstituted cyclohexadiene compounds from aromatic rings. Both routes are based on either regio- and diastereoselective addition of organolithium reagents to chiral nonracemic phenyloxazolinechromium tricarbonyl complexes ([Equation \(12\)](#)) or asymmetric addition of lithiated *C*-nucleophiles in the presence of a chiral ligand ([Equation \(13\)](#)) [<1996JOC2258>](#) followed by quenching with allyl or propargyl bromide. High diastereomeric (>98% de) and enantiomeric excesses (up to 93%) were reached for methyl-, vinyl- and phenyllithium additions. An elegant application to the synthesis of bicyclo[3.3.0]octan-3-ones,

via an intramolecular Pauson–Khand cyclization of 1,6-enynes, is depicted in Equation (14) <1997JA4773>. Finally, sequential addition of 2-lithio-1,3-dithiane and allyl bromide to π -benzene–molybdenum complex was recently reported in the literature (Equation (15)) <2002AG(E)4577>.

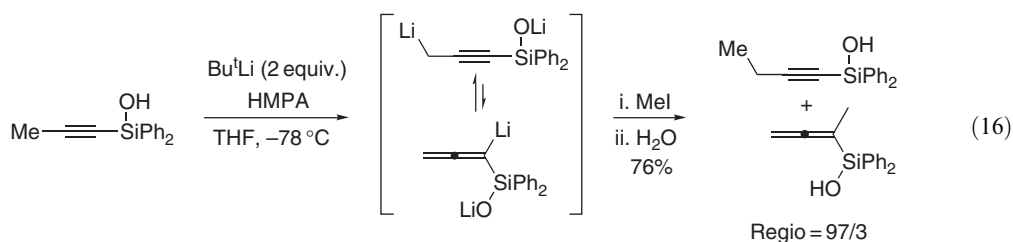


RLi	R^1X	Yield (%)	dr (anti/syn)
MeLi	Allyl bromide	58	>98/2
–	Propargyl bromide	79	>98/2
–	Mel	58	>98/2
PhLi	Allyl bromide	54	92/8



1.04.2.1.3 Reactivity of propargyllithiums

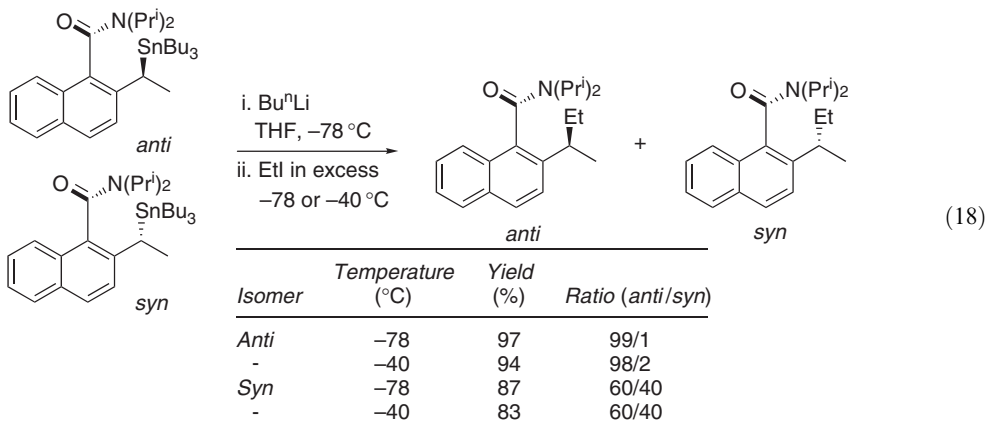
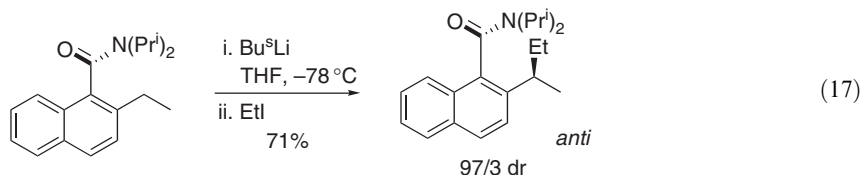
Alkylation of propargyl organolithiums can occur either in the propargylic or in the allenic position, but usually after equilibration a mixture of both forms is observed. To solve this problem of regioselectivity, other metals such Al, B, Zn, or Sn were tested with success leading to the acetylenic adducts. Later, Oshima and co-workers <1998SL1096> reported the effect on the regioselectivity of an anionic oxygen presents on the silicon atom. Treatment of the dilithiated 1-alkynylsilanol with methyl iodide afforded the alkylated compound in the propargylic position (regio, 97:3). The reaction proceeds in a regioselective manner contrary to 1-alkynyldiphenylmethylsilane. In this case, a 89:11 ratio in favor of alkyne derivatives was observed (Equation (16)).



1.04.2.1.4 Alkylation of benzyllithiums

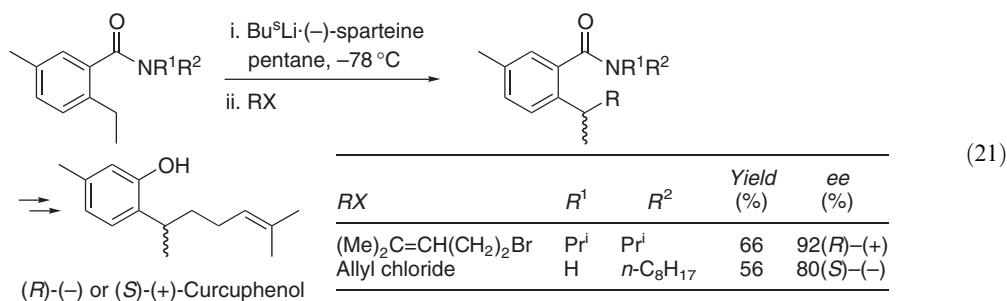
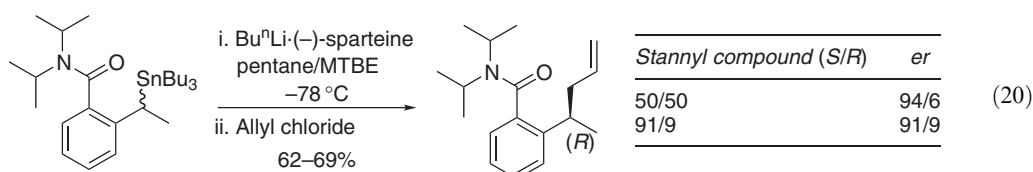
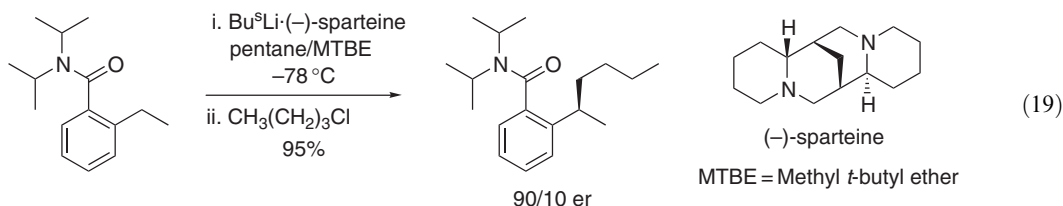
(i) Metallation by lateral hydrogen abstraction with lithiated bases or via tin–lithium transmetallation

Benzylic organolithium compounds have a high tendency to undergo a rapid configurational inversion compared to those bearing α -heteroatoms. However, intramolecular lithium chelation with the carbonyl group of amides or with heteroatoms can efficiently stabilize the intermediate metallic species at low temperature, and no inversion is observed. For example, Clayden and co-workers [<2001JA12449>](#) have reported the atroposelective lateral lithiation of aromatic amides followed by an electrophilic quenching. The sequence involved deprotonation by Bu^sLi of naphthamides in the benzylic position (Equation (17)) [<1997TL2561>](#) or tin–lithium exchange at -78°C (Equation (18)) [<1997TL2565>](#) followed by alkylation with ethyl iodide. The organolithium intermediate proved to be configurationally stable and led preferentially to the *anti*-product. The same diastereomeric ratios have been reported for the transmetallation at -78 and -40°C on the *anti*-stannane, but NMR studies on the *syn*-isomer showed no stereospecificity in both organolithium formation and its subsequent alkylation explaining the inversion of selectivity leading to the *anti*-product.

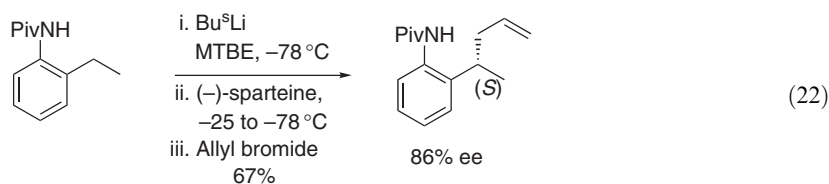


Asymmetric lateral lithiation of benzamides promoted by $\text{Bu}^s\text{Li}/(-)$ -sparteine proton abstraction (Equation (19)) or by $\text{Bu}^n\text{Li}/(-)$ -sparteine tin–lithium exchange (Equation (20)) was reported by Beak and co-workers. Alkylation of the benzyllithium intermediate with alkyl halides takes place in high yield and provides the related adducts with high enantiomeric ratios specially if chlorides are used instead of bromides or iodides. A dynamic kinetic resolution, where a rapid equilibration between both diastereomeric lithiated benzamide/ $(-)$ -sparteine complexes occurs and where one diastereomeric organolithium/ $(-)$ -sparteine complex is more reactive with

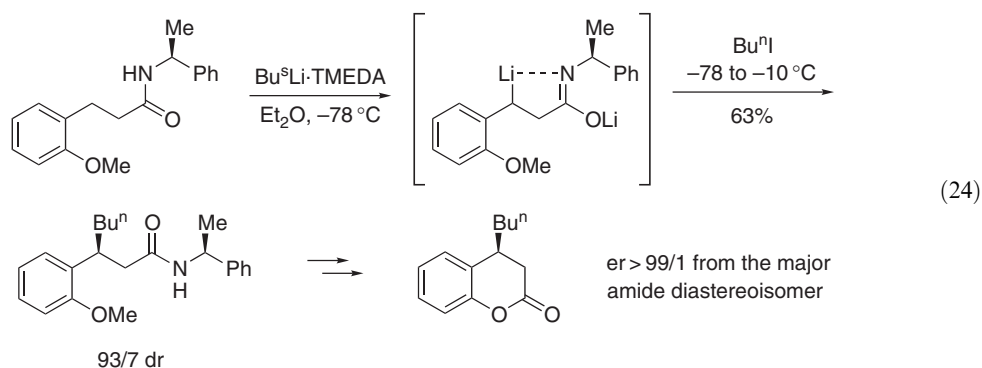
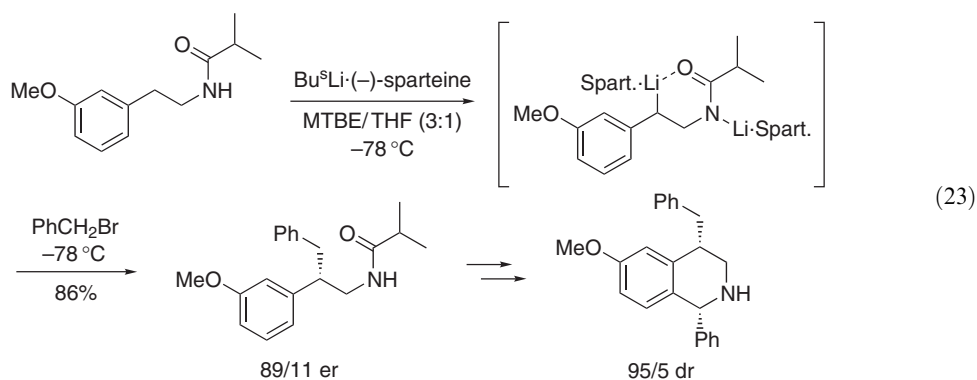
the haloalkane than the other one, is operating. The asymmetric induction is controlled by the complex/electrophile interaction in the transition state [<1997JA8209>](#). (*R,R*)-1,5-Diaza-*cis*-decalin used as ligand conferred modest-to-poor selectivity and the opposite configuration was produced [<2000OL875>](#). An application to the formal synthesis of both enantiomers of curcuphenol from a 2-ethyl-*m*-toluamide derivative was published by Kimachi. High and opposite enantioselectivities were observed for the tertiary and secondary amide metallation–alkylation sequences ([Equation \(21\)](#)) [<2001JOC2700>](#).



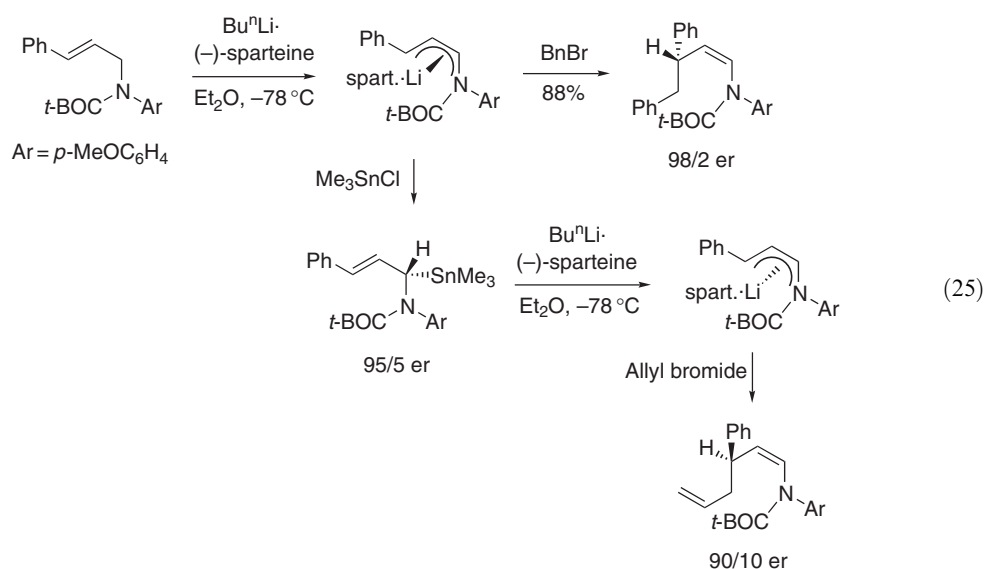
Lateral lithiation of *N*-pivaloyl-*o*-ethylaniline in the presence of (–)-sparteine forms a configurationally stable diastereomeric complex at low temperature, which equilibrates at –25 °C to the thermodynamically favored diastereomer and reacts with alkyl halides at –78 °C ([Equation \(22\)](#)). Here, the substitution involves a dynamic thermodynamic resolution (for a review on this topic, see Beak and co-workers [<2000ACR715>](#)). This implies that a warm–cool protocol is required for inducing high enantioselectivities. The asymmetric induction is again controlled by the intermediate organolithium/chiral ligand complex in the transition state [<1996JA1575, 1997JA8209>](#).



Reactivity of β -lithiated- β -phenylcarbamides in the presence of (–)-sparteine was also investigated. As shown previously, the enantioselectivity is induced in the post-deprotonation step through a dynamic thermodynamic resolution and a possible contribution of dynamic kinetic resolution [<1996JA11391, 2002JOC6797>](#). When α -methylbenzylamine is used as chiral auxiliary, the β -lithiation–substitution sequence involves complete diastereocontrol [<1998JOC2>](#). Applications to dihydrocoumarin and 1,2,3,4-tetrahydroisoquinoline derivatives are shown ([Equations \(23\) and \(24\)](#)) [<1998JOC2, 2002JOC6797>](#).

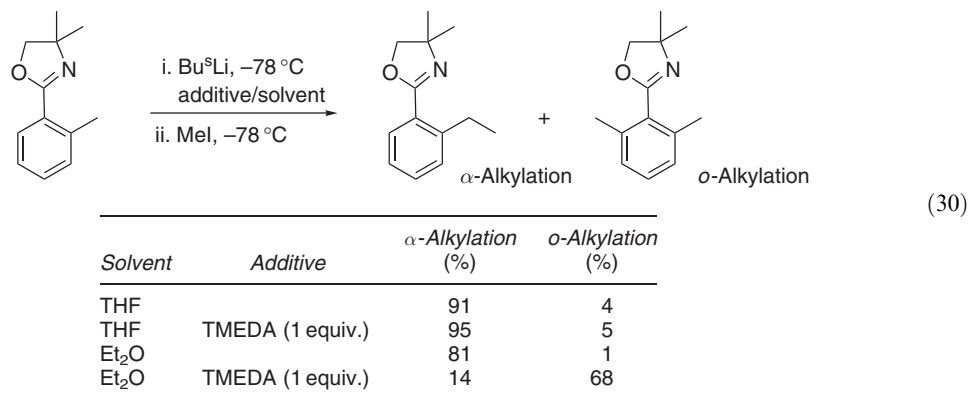


Beak extended his studies to the asymmetric alkylation of lithiated cinnamylamines in the benzylic position. The η^3 -allyllithium/(-)-sparteine complex intermediate, generated by metallation with $\text{Bu}^n\text{Li}/(-)\text{-sparteine}$ and characterized by X-ray [<1998AG\(E\)2522>](#), can be trapped by various alkyl halides leading to the desired enantiomerically enriched substituted products ([Equation \(25\)](#)). The substitution proceeds through an *anti*- S_{E} reaction. Stannylation of the intermediate followed by lithium–tin exchange in the presence of (-)-sparteine and methylation led to the opposite enantiomer [<1996JA12218, 1998AG\(E\)2522>](#).

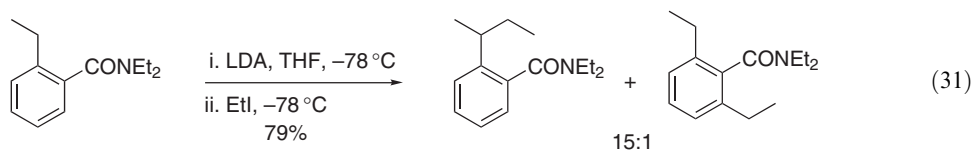


(iv) Competition between *ortho*- versus benzylic lithiation

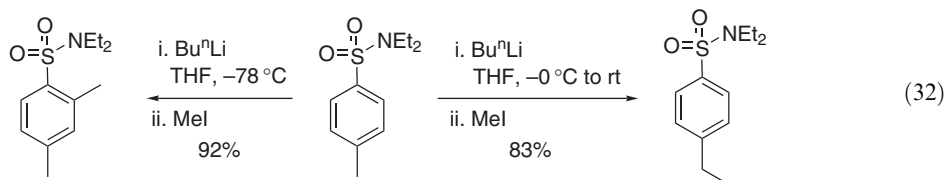
Benzene derivatives substituted by a directing functional group can be easily metallated at the *ortho*-position. With methylated substrates, deprotonation also takes place in the benzylic position due to the intrinsic high acidity of the related protons. This chemistry has been reviewed in 1995 by Clark and Jahangir <1995OR1>. More recently, Iwao showed that the lateral lithiation of 4,4-dimethyl-2-(*o*-tolyl)oxazolines proceeds in THF or Et₂O at -78°C by treatment with Bu^sLi, whereas in the presence of TMEDA in Et₂O the *ortho*-alkylation is favored. The resulting organolithium is quenched with methyl iodide (Equation (30)) <2002TL9069>.



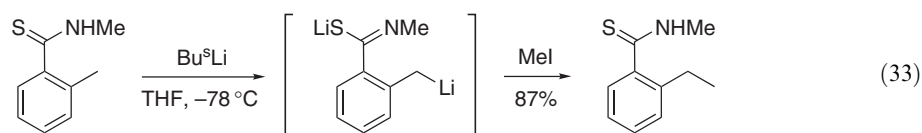
Hlasta and co-workers <1996TL1335> have reported the selective directed *ortho*- versus benzylic metallation of substituted *N,N*-diethylbenzamides followed by electrophilic substitution. Ratios of α - to *ortho*-lithiation products were shown to be dependent upon the anion formation under kinetic conditions, the nature of the alkyl halide and the side-chain (Equation (31)).



Studies on the metallation of secondary and tertiary *p*-tolylsulfonamides were carried out by Snieckus and co-workers <2001JOC3662>. Kinetic and thermodynamic controlled deprotonation lead to *ortho*- and benzylic metallation products, respectively. Consequently, the reaction of secondary and tertiary *p*-tolylsulfonamide with BuⁿLi gives either the *ortho*-anion at low temperature (-78°C) or the benzylic position is metallated under thermodynamic conditions using BuⁿLi or the Lochmann–Schlosser superbase (BuⁿLi/Bu^tOK) at room temperature. Methylation of each anions gave the alkylated compounds in high yields (Equation (32)).

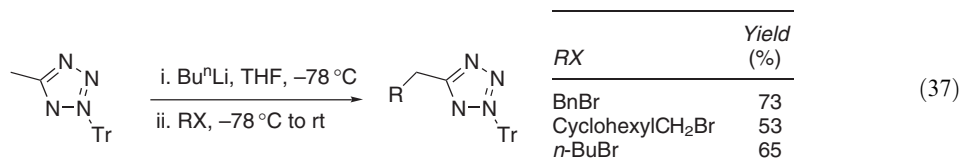
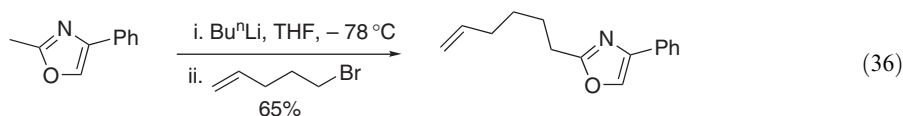
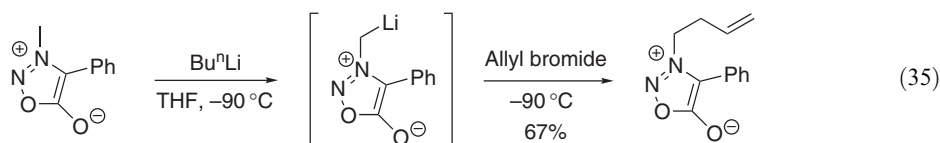
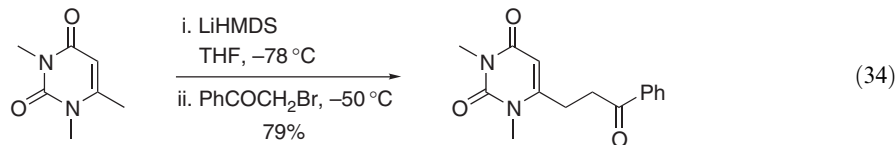


Deprotonation of thiobenzamides and thionaphthamides with Bu^sLi readily forms a yellow monoanion. Addition of a second equivalent of base results in lateral metallation. In the presence of methyl iodide, the dianion was alkylated at sulfur atom and benzylic carbon center, then the corresponding thioimido ester was isolated in high yield (Equation (33)). No *ortho*-metallation product was detected <2002EJO2573>.



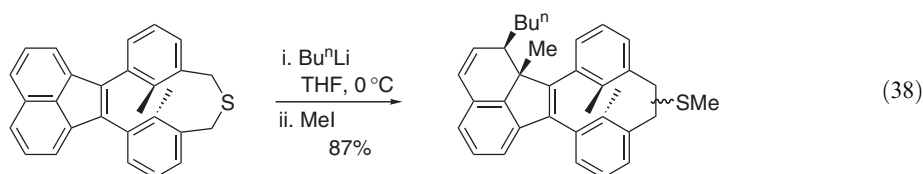
(v) Lateral lithiation of heterocycles

Several groups have also been interested in benzylic metallation of heterocycles. Regioselective lithiation of the CH activated benzylic position of 6-methyluracil (Equation (34)) <1996H1687>, 3-methyl-4-phenylsydnone (Equation (35)) <1998SL667>, 2-methyloxazole (Equation (36)) <1991JOC3058>, or 5-methyl-tetrazole (Equation (37)) <1996TL3655> with alkyl lithium bases results in the corresponding lithio heterocycle, which can be trapped by benzyl, allyl, or alkyl halides.

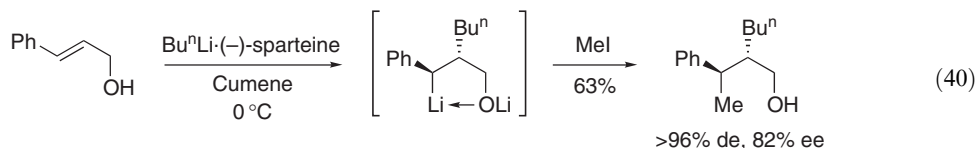
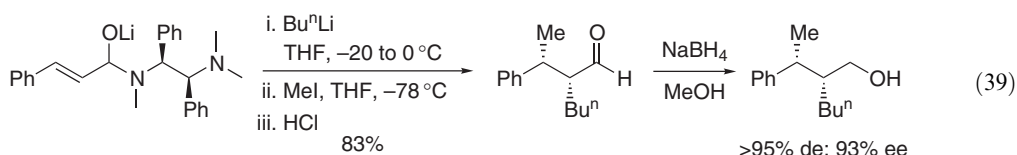


(vi) Carbolithiation of styrene systems

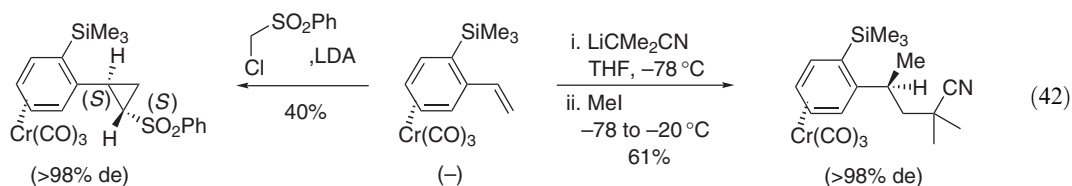
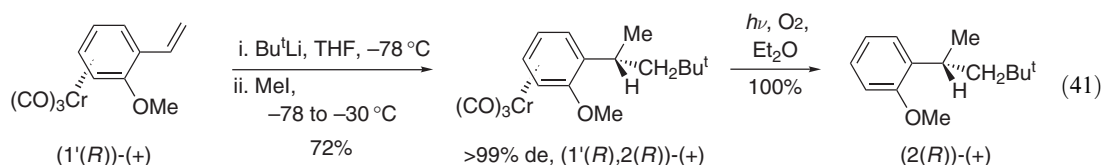
Carbometallation of alkenes, and particularly styrene systems, has progressed since the 1990s and numerous reviews have been published dealing with this topic <B-1998MI271, 1999JCS(P1)535, 2001T5899>. Carbolithiation of unactivated olefins involves two C—C bond formation in a one-pot procedure by addition of an alkyl lithium to the double bond. The new organometallic generated can be trapped by an electrophilic carbon. For example, Lai and Chen published the stereoselective attack of cyclophane derivatives by BuⁿLi. Electrophilic quenching of the aromatic indenide anion gave the ring-contracted adduct in good yield and with a high level of diastereoselectivity (Equation (38)) <2003TL23>.



Regio- and stereoselective carbolithiation of cinnamaldehyde can be used for the preparation of enantiomerically enriched α,β -substituted aldehydes. This approach, designed by Normant, involves the addition of organolithiums to lithium aminoalkoxide derivatives of cinnamaldehyde, and subsequent substitution of methyl iodide by the intermediate anion. Enantiomeric excesses up to 93% have been measured (Equation (39)) <2001TL1883>. Finally, asymmetric carbolithiation of (*E*)-cinnamyl alcohol by BuⁿLi in the presence of (–)-sparteine leads to a red solution of benzyl organolithium which can be trapped directly by methyl iodide. Formation of both contiguous stereogenic centers has been controlled with a diastereoselectivity up to 96% and good level of enantioselection (82% ee) (Equation (40)) <1995JA8853>.

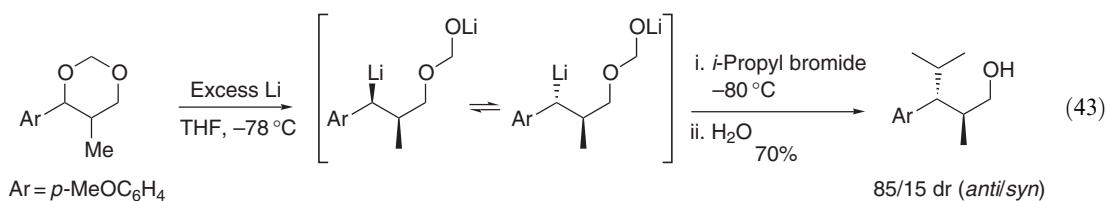


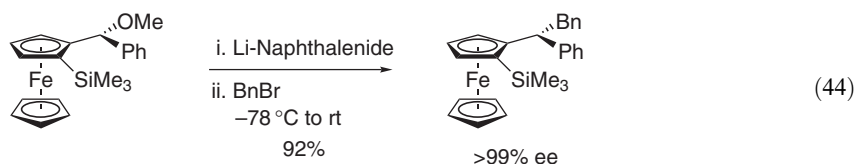
Stereoselective addition of Bu^tLi or lithium anion of isobutyronitrile to *ortho*-substituted tricarbonyl(styrene)chromium(0) derivatives was developed by Davies (Equation (41)) <1995SL69> and Gibson (Equation (42)) <1996JCS(P1)1007>, respectively. Arene-chromium-tricarbonyl complexes proved to stabilize the benzylic carbanion and then favor the carbometallation process. In addition, substituents present in the *ortho*-position showed their influence on the stereoselectivity of the process. Application to the stereoselective synthesis of cyclopropanes, prepared from α -chloro organometallics, was also presented and is depicted in Equation (42) <1996JCS(P1)1007>.



(vii) Reduction of dioxanes or ethers

An alternative to the previous carbometallation of cinnamyl alcohol strategy was proposed by Azzena. Reductive lithiation of diastereoisomeric mixtures of 4-aryl-5-methyl-1,3-dioxanes gave the corresponding γ -oxy-substituted benzyllithium intermediates with epimerization at the benzylic center. A rapid interconversion led to diastereoisomeric organolithiums stabilized by intramolecular chelation. Electrophilic substitution of alkyl and benzyl halides furnished 2-methyl-3-substituted-3-phenyl-propan-1-ol adducts in satisfactory to high diastereoselectivities (Equation (43)) <2002TL5137>. Knochel and co-workers <1999AG(E)1457> reported the reductive lithiation of a ferrocenyl ether by treatment with lithium naphthalenide. The intermediate α -ferrocenyllithium reagent reacts stereoselectively with benzyl bromide with complete retention of configuration to give new chiral ferrocenyl derivatives (Equation (44)).

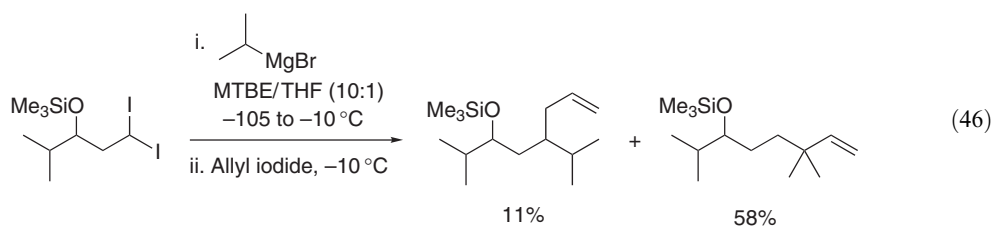
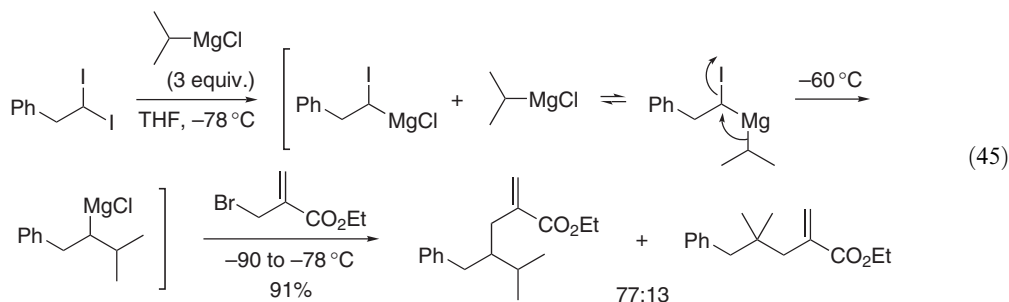




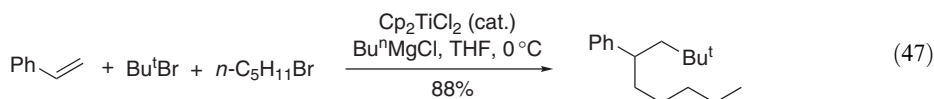
1.04.2.2 Group II Metals (Mg, Ba)

1.04.2.2.1 Alkylation of organomagnesiums

Since the historical discovery of Grignard in 1900, organomagnesium reagents have been widely used for organic transformations. Numerous published reports dealing with the preparation and the reactivity of these species prove that they are extensively utilized in synthesis. More recently, Hoffmann has investigated the formation of Grignard reagents by carbenoid-homologation and carbenoid-CH insertion reactions. A diiodoalkane treated with 3 equiv. of isopropylmagnesium chloride first undergoes magnesium–iodine exchange giving the α -iodoalkylmagnesium compound. The second equivalent of isopropylmagnesium generates the expected Grignard reagent and a variable amount of rearranged Grignard compound, which depends on the nature of the solvent (THF or Bu^tOMe). Therefore, the organomagnesium intermediate can be trapped by α -bromomethylacrylate (Equation (45)) as well as allyl iodide (Equation (46)) without any magnesium–iodine exchange detected <2000AG(E)1462>.



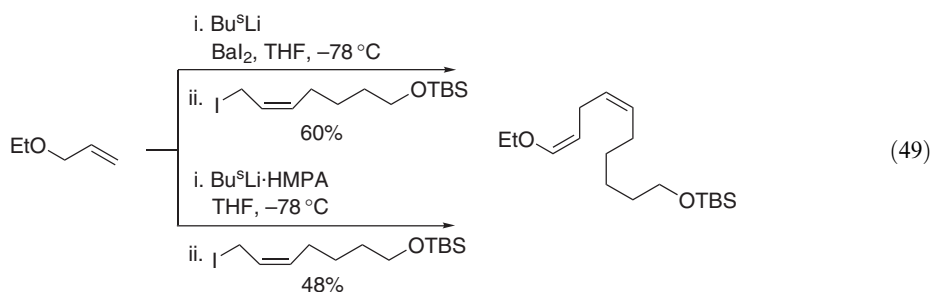
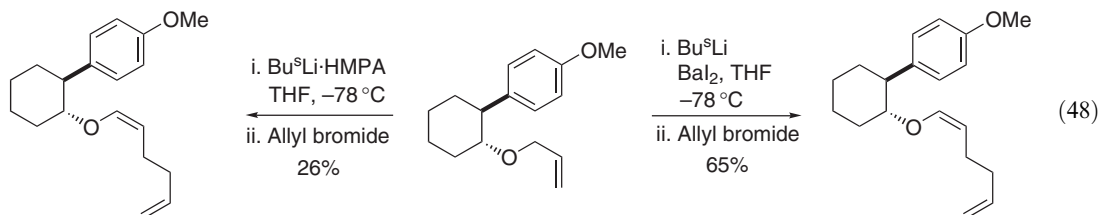
Titanocene-catalyzed double alkylation of styrene with alkyl halides in the presence of BuⁿMgCl was developed by Kambe and co-workers <1998JA11822>. The reaction involves formation of a benzyl titanium intermediate through a radical pathway, and transmetalation with BuⁿMgCl. The resulting Grignard reagent can react with the second equivalent of haloalkane (Equation (47)).



1.04.2.2.2 Alkylation of organobariums

An efficient preparation of chiral-substituted (Z)-enol ethers involving isomerization of allylic ethers and alkylation was developed by Langlois and co-workers <2000TL337>. Lithiation of allylic ethers with Bu^sLi followed by substitution of allyl halides gave poor yields of the corresponding

enol ethers. However, a prior transmetalation of the lithium homoenolate intermediates with BaI_2 and electrophilic quenching afforded the γ -alkylated products in good yields (Equations (48) and (49)).



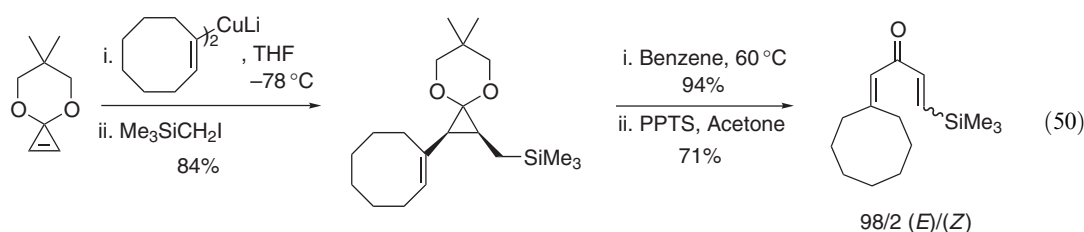
1.04.2.3 Organocopper Derivatives and Copper(I)-catalyzed Couplings

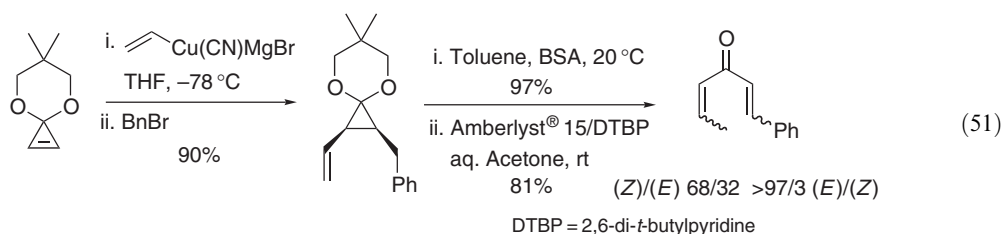
Organocopper chemistry represents a highly versatile tool for the transformation of organic molecules. Highly efficient synthetic methods were developed and used for natural product synthesis as well as preparation of fine chemicals. Conjugate addition, carbometallation of alkynes and alkenes, $\text{S}_{\text{N}}2'$ allylic alkylations, and Sonogashira coupling reactions have been extensively investigated. A majority of organocopper reagents employed in these transformations has been prepared from simple organomagnesium and organolithium reagents. More recently, particular attention has been devoted to the synthesis of highly functionalized organocopper reagents from less reactive organometallics such as zinc, samarium, or zirconium reagents. Transmetalation with stoichiometric or catalytic amounts of copper(I) salts proved to enhance their reactivity toward alkyl halides. In the presence of chiral ligands, asymmetric transformations can be performed with high enantiomeric excesses.

1.04.2.3.1 Transmetalation of organolithium derivatives—reactivity of organocuprates

(i) Carbocupration of alkenes

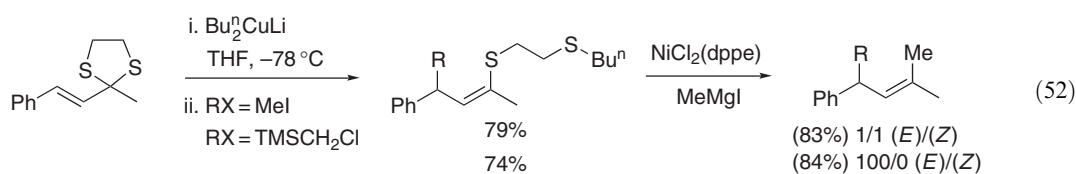
In the 1990s, Nakamura and co-workers [\[1996H565\]](#) published several reports on the carbometallation of cyclopropene derivatives. Studies based on stereoselective carbocupration followed by retentive electrophilic quenching of the cyclopropyl copper intermediates leads to the *cis*-1,2-disubstituted cyclopropanone acetals. For example, addition of a vinyl cuprate to a cyclopropenone acetal and alkylation of the resulting organocopper give the *cis*-disubstituted cyclopropane, which can be converted into a cross-conjugated dienyl ketone. The transformation involves 1,5-hydrogen migration reaction under thermal conditions and hydrolysis (Equations (50) and (51)).





(ii) Alkylation of allyl organocoppers

Luth and co-workers [<2001SL977>](#) have shown that reaction of allylic dithioacetals with dibutylcuprates results in nucleophilic attack at the sulfur atom with umpolung of the C—S bond. The π -allylcopper intermediate can be alkylated regioselectively at the α -position with various alkyl halides leading to a mixture of (*E*)- and (*Z*)-vinyl sulfides. Nickel-catalyzed cross-coupling of the previous vinyl sulfides with MeMgI affords the trisubstituted alkenyl adducts in good yields ([Equation \(52\)](#)).

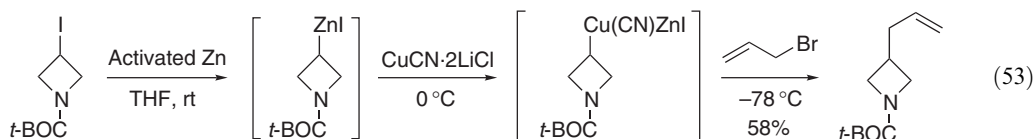


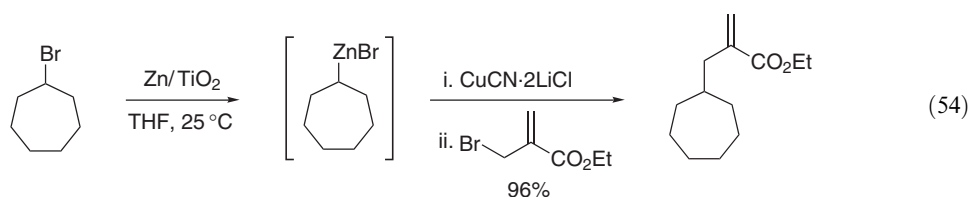
1.04.2.3.2 Transmetalation of organozincs

Organozinc derivatives have been used in many synthetic transformations due to their high functional group tolerance. However, this moderate reactivity can be a serious drawback for further functionalizations. To enhance this, transmetalation with copper(I) salts has become a valuable tool to allow substitution reactions with alkyl halides. Many routes have been reported for the elaboration of organozinc reagents and their subsequent alkylation but only selected examples are presented below.

(i) Zinc insertion into carbon–halogen bonds

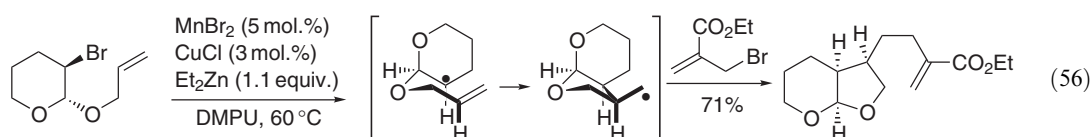
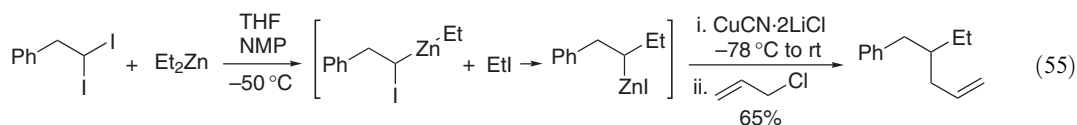
One protocol, first reported by Gaudemar and co-workers [<1998SL379>](#), involves the insertion of zinc into C—I bond of alkyl iodides. This process was improved by Knochel using 1,2-dibromoethane and chlorotrimethylsilane to activate the metal. For example, treatment of 3-iodo-*N*-BOC-azetidines and 4-iodo-*N*-BOC-piperidines by activated zinc furnished the corresponding organozinc intermediate which can be allylated by allyl bromide after transmetalation with CuCN·2LiCl ([Equation \(53\)](#)). More stable alkyl halides such as alkyl bromides need more highly activated zinc. Various methods of activation such as reduction of zinc chloride by lithium naphthalene (Rieke zinc) or by potassium–graphite have been already reported. But more recently, another protocol developed by Knochel, based on reduction of zinc chloride by sodium dispersed on titanium(IV) oxide, allowed efficient synthesis of secondary alkyl and benzylic zinc bromides without formation of Wurtz-coupling side products. After transmetalation with CuCN·2LiCl, the corresponding zinc–copper reagents react with different electrophiles giving the expected functionalized compounds ([Equation \(54\)](#)) [<1995S69>](#).





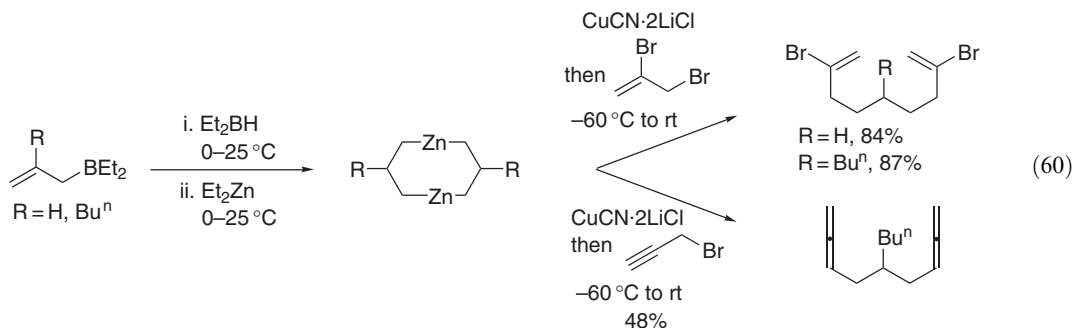
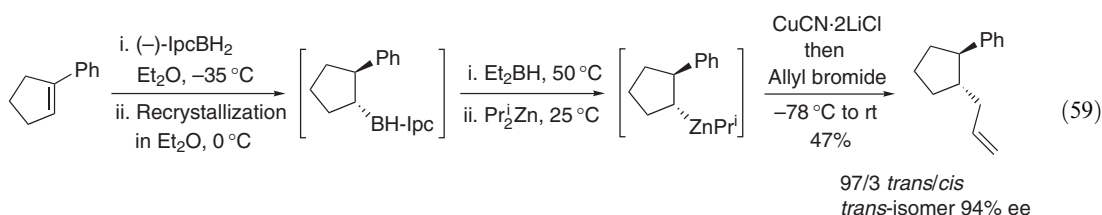
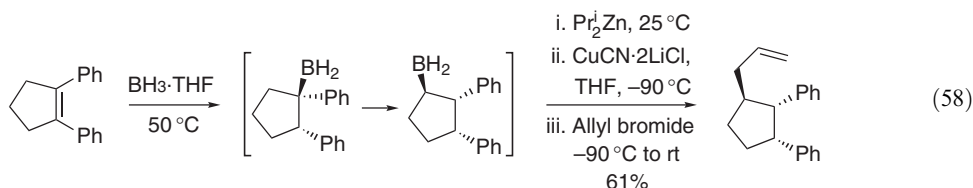
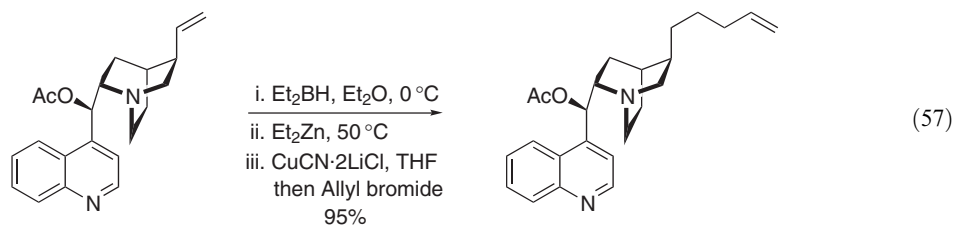
(ii) Zinc halide exchange promoted by dialkylzincs

Functionalized diorganozincs can be easily prepared by the I—Zn exchange reaction. Several methods have been published [<1993CR2117>](#) and for instance, simple dialkylzincs such as diethylzinc in the presence of *N*-methylpyrrolidinone (NMP) [<1996TL4495>](#) or LiBr were shown to be good reagents for Zn—I exchange reaction. Indeed, Marek and co-workers [<2001SL818>](#) reported the preparation of secondary organozinc iodides by treatment of *gem*-diiodoalkanes with both dialkylzinc and NMP (or LiBr). Between -50°C to rt, the resulting carbenoid readily undergoes an intermolecular nucleophilic rearrangement into a secondary organozinc species. After transmetalation with $\text{CuCN}\cdot 2\text{LiCl}$, the organocopper derivative can react with various electrophiles ([Equation \(55\)](#)). A catalytic amount of mixed metals MnBr_2 (5 mol. %)/ CuCl (3 mol. %) in the presence of diethylzinc and DMPU can induce the stereoselective radical cyclization of unsaturated alkyl bromides to alkenes. The cyclized organozinc species are easily allylated by reaction with ethyl (α -bromomethyl)acrylate in 71–73% yields ([Equation \(56\)](#)) [<1996TL5865>](#).



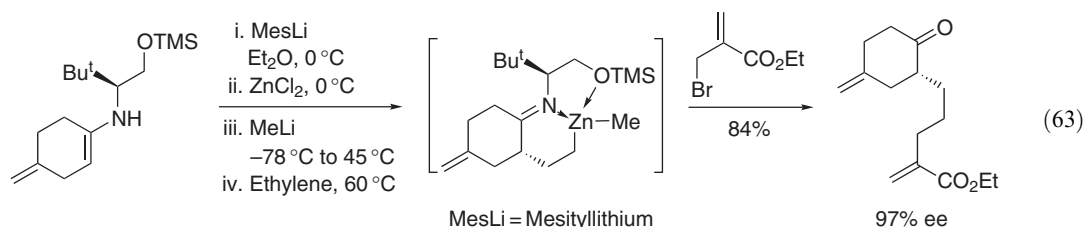
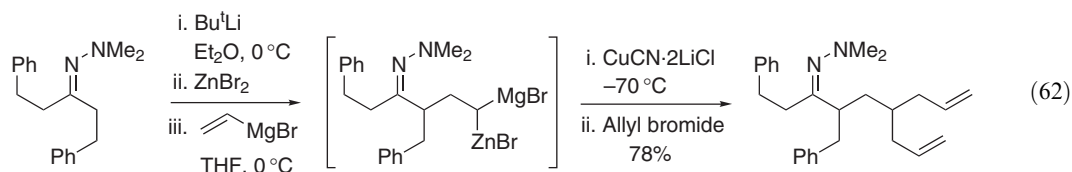
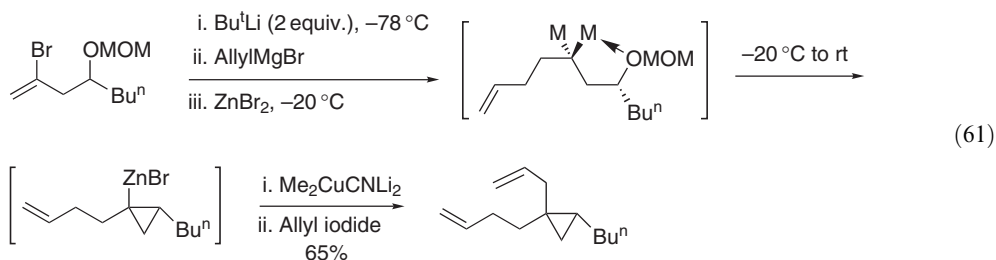
(iii) Boron–zinc transmetalation

Investigations on B—Zn exchange were first reported in 1960 for the preparation of diethyl zinc from dimethylzinc and triethylborane. This interesting property was widely developed by Oppolzer for the enantioselective synthesis of allylic alcohols and, more recently, it was used by Knochel in the preparation of functionalized dialkylzincs from the corresponding alkenes. Organoboranes, obtained by hydroboration of olefins with diethylborane, undergo clean and efficient B—Zn transmetalation with neat diethylzinc. Alkylation of the resulting diorganozinc was achieved by transmetalation with $\text{CuCN}\cdot 2\text{LiCl}$ and substitution of various alkyl halides ([Equation \(57\)](#)) [<1996JOC8229>](#). It has to be mentioned that hydroboration of tetrasubstituted olefins with $\text{BH}_3\cdot\text{THF}$ provides tertiary alkylboranes, which undergo stereoselective *syn*-1,2-migration ([Equation \(58\)](#)) [<1998AG\(E\)2460>](#). Hydroboration of trisubstituted cyclic and acyclic olefins by monoisopinocampheylborane affords enantiomerically enriched organoboranes. They can be functionalized without any racemization after sequential diethylborane–diisopropylzinc– $\text{CuCN}\cdot 2\text{LiCl}$ transmetalations and electrophilic trapping ([Equation \(59\)](#)) [<1998SL1438>](#). An example of allylation and allenylation of 1,3-dizinc derivatives was also reported ([Equation \(60\)](#)) [<1996AG\(E\)218>](#).

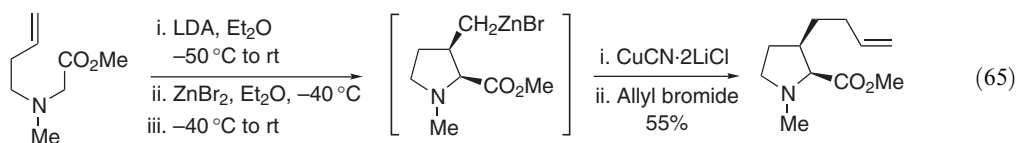
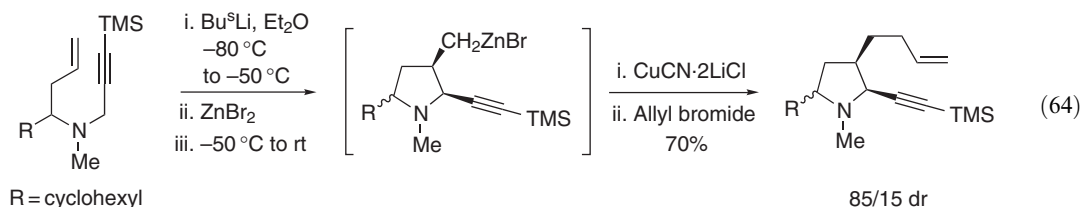


(iv) Carbozincation of alkenes

Intermolecular carbozincation of alkenes can be illustrated by the important contribution of Marek and Normant in this field. Some of their studies have been devoted to the stereoselective formation and the reactivity of sp^3 -*gem*-bimetallic reagents, easily obtained by addition of allylzinc to substituted vinyl metals. An application to the preparation of stereodefined substituted cyclopropanes was reported. The sequence involved cyclization of the 1,1-dimetallic species bearing a methoxymethyl ether in the γ -position and alkylation of the resulting organozinc after transmetalation to the corresponding organocopper. High diastereoselectivities have been observed (Equation (61)) <1995JOC2488>. Nakamura and co-workers <1997JAC5457> reported the addition of zincated hydrazone to a vinyl Grignard. The *gem*-dimetallic intermediate, generated *in situ*, can be selectively quenched with various electrophiles considering the important difference of reactivity between Grignard and organozinc reagents (Equation (62)). In a recent paper, they described the stereoselective addition of nonracemic chiral zinc enamides, derived from (*S*)-valinol and (*S*)-*t*-leucinol, to ethylene. Copper(I)-catalyzed electrophilic trapping of the γ -zincioimine intermediate led to the enantiomerically enriched α -substituted ketone (Equation (63)) <2003JA6362>.

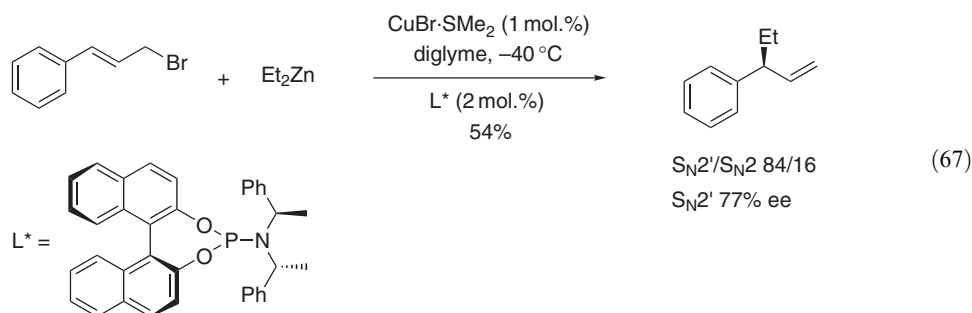
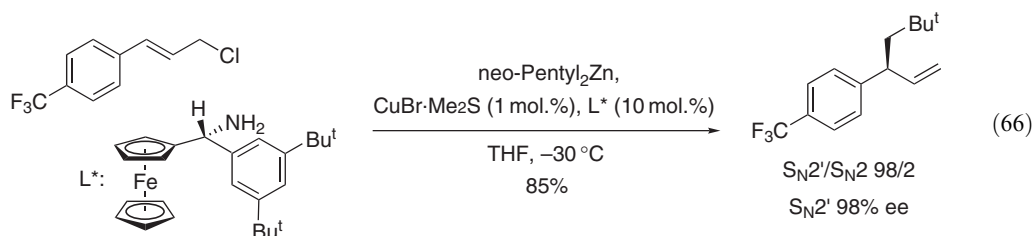


Intramolecular carbometallation of alkenes has also been studied. For instance, Marek and Normant have shown that allenyl zinc bromides (Equation (64)) and zinc-enolates (Equation (65)) undergo diastereoselective and/or enantioselective carbocyclizations onto terminal alkenes. In the presence of CuCN·2LiCl, the resulting primary alkylzinc intermediate can be functionalized with allyl bromide. A chair-like transition state was proposed to explain the stereochemistry of the adduct. This approach provides a straightforward and valuable method for the preparation of polysubstituted pyrrolidines <1997TL89, 1998JOC2442>.



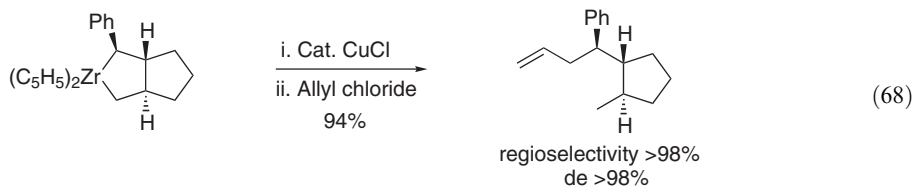
(v) *Asymmetric allylation of organozinc reagents*

Reactivity of organocopper reagents with allylic halides is now well documented. Several investigations have been concentrated on the regio- and stereoselectivity of the process. An S_N2' mechanism leading to γ -alkylated products is highly favored. More recently, a copper(I)-catalyzed allylation reaction of dialkylzincs has received a great deal of interest and some applications to asymmetric synthesis have been published by Knochel [<2000TL9233>](#) and Feringa [<2001OL1169>](#), respectively. Regio- and enantioselective S_N2' allylic alkylation of cinnamyl halides with primary organozinc reagents takes place in the presence of catalytic amount of $CuBr \cdot Me_2S$ and with either ferrocenyl amines (Equation (66)) or phosphoramidites (Equation (67)) as chiral ligand. Enantiomeric excesses up to 98% and 77% have been reached, respectively.



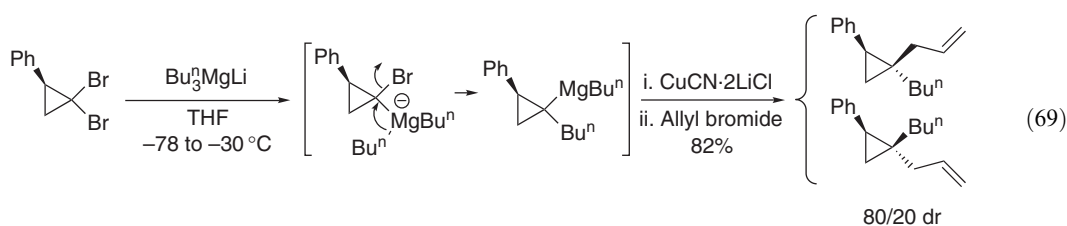
1.04.2.3.3 Transmetallation of organozirconiums

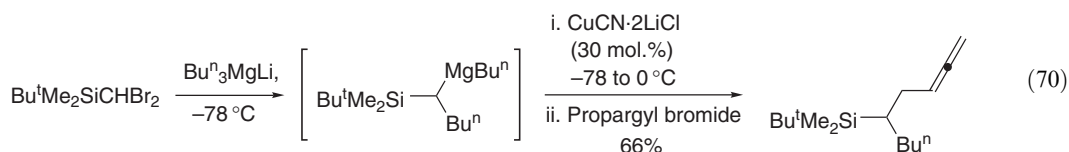
Takahashi and co-workers [\[1997CC1599\]](#) showed that allylation of unsymmetrical bicyclic zirconacyclopentanes can be promoted by copper(I) chloride in the presence of allyl chloride ([Equation \(68\)](#)). The process occurs in the benzylic position with high regio- and diastereoselectivities, and also with total retention of configuration.



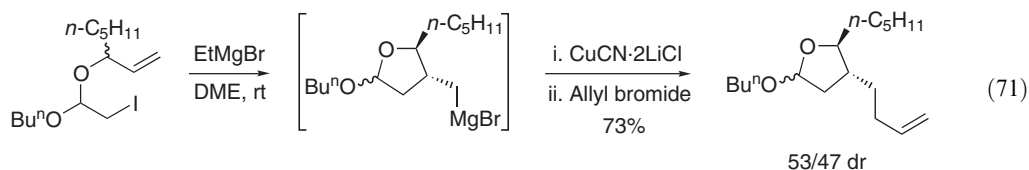
1.04.2.3.4 Transmetallation of organomagnesiums

In his studies on the reactivity of *gem*-dihalocyclopropanes, Oshima has also examined the double alkylation of *gem*-dibromocyclopropane compounds with tributylmagnesium and various electrophiles. Upon treatment with $\text{Bu}_3^{\text{n}}\text{MgLi}$, *gem*-dibromocyclopropanes first undergo bromide-magnesium exchange to give magnesate intermediates which rearrange by 1,2-migration (or intramolecular nucleophilic substitution) of an alkyl group. The resulting monoalkylated cyclopropylmagnesium species can be transmetallated by copper(I) salts and trapped by allyl bromide [\[2002T1581\]](#). In [Equation \(69\)](#), the product was isolated in 82% yield and with a 80:20 dr [\[2002MI1730\]](#). A similar protocol was carried out in the preparation and the alkylation of α -silylalkylmagnesium species generated from dibromomethylsilane ([Equation \(70\)](#)) [\[2001AG\(E\)2085\]](#).

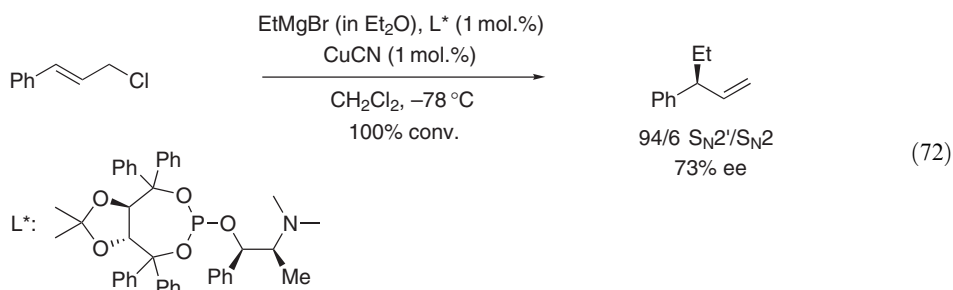




EtMgBr-mediated radical cyclization of allyl β -iodoacetals and subsequent copper(I)-catalyzed allylation of the tetrahydrofuranyl methylmagnesium intermediate have been performed in DME in good yields (Equation (71)) <2000OL651>.



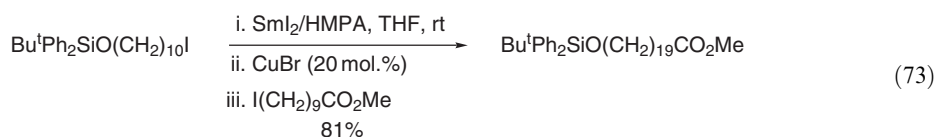
Alexakis and co-workers have also reported an example of copper(I)-catalyzed selective $\text{S}_{\text{N}}2'$ allylic substitution of cinnamyl chlorides by Grignard reagents. High regio- and moderate enantioselectivities (up to 73% ee) were observed in the presence of a chiral phosphorus ligand derived from TADDOL (Equation (72)) <2001SL927>.



Polyfunctional alkenyl-, aryl-, and heteroarylmagnesium reagents can be easily prepared from related alkenyl and aryl halides through iodine or bromide–magnesium exchange with trialkylmagneses at low temperature. Subsequent alkylation proceeds with retention of configuration of the olefin. Several examples of reaction with heteroaryl halides <2000JOC4618, 2000T1349, 1998SL1359>, aryl and alkenyl halides <2002T4787, 2002AG(E)1610, 2001JOC4333, 2000AG(E)2481, 2000MI767, 2000JOC4618> are depicted in the literature. An application to solid-phase synthesis was also proposed <1998AG(E)1701>.

1.04.2.3.5 Transmetalation of organosamariums

Considering the lack of reactivity of alkylsamariums toward alkyl halides, Berkowitz and Wu have developed a new protocol of alkylation with copper salts as catalyst taking advantage of Curran and Wipf research on conjugate addition. Reduction of alkyl iodides and bromides by SmI_2/HMPA led to alkylsamarium intermediates which can be transmetalated by a catalytic amount of CuBr or Li_2CuCl_4 , and therefore can undergo cross-coupling reactions with alkyl iodides (Equation (73)) <1997TL3171>.



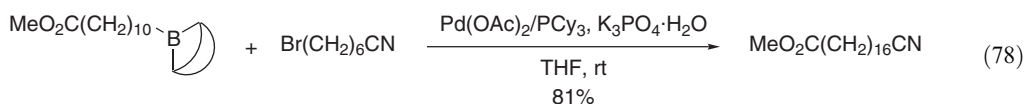
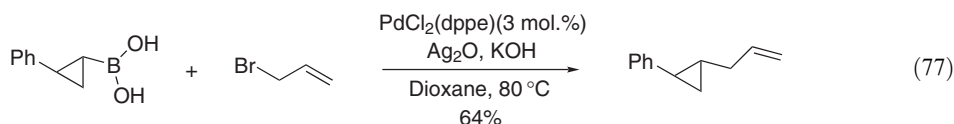
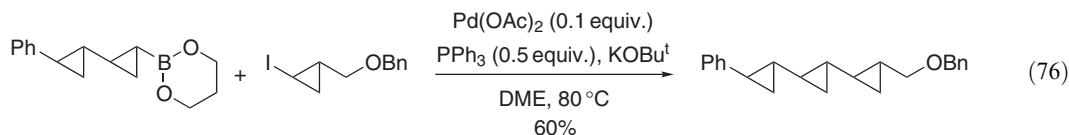
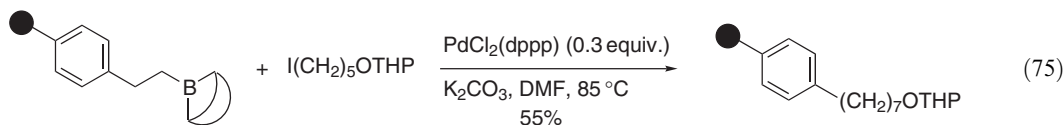
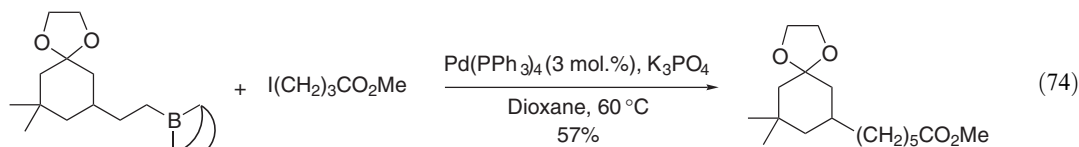
1.04.2.4 Pd(0)- and Ni(0)-Catalyzed C(sp³)-C(sp³) Cross-couplings

Since the early 1980s, transition metal-catalyzed cross-coupling reactions have become an important tool for modern organic transformations <B-1995MIT, B-1997MI, B-1999MI833>. They proved to be extremely efficient in the formation of C(sp²)-C(sp²) and C(sp²)-C(sp) bonds between poorly reactive organometallics (such as borane, Grignard, organozinc, or stannane reagents) and aryl or alkenyl halides. However, only few reports on C(sp³)-C(sp³) bond formation have been published. This was first explained by a slow oxidative addition of the alkyl halide to the transition metal (such as Pd(0) or Ni(0)) and a possible β -elimination of the organometallic intermediate before the transmetalation and the reductive elimination steps. Some of the most important studies on this topic are summarized here.

1.04.2.4.1 Pd(0)-Catalyzed couplings

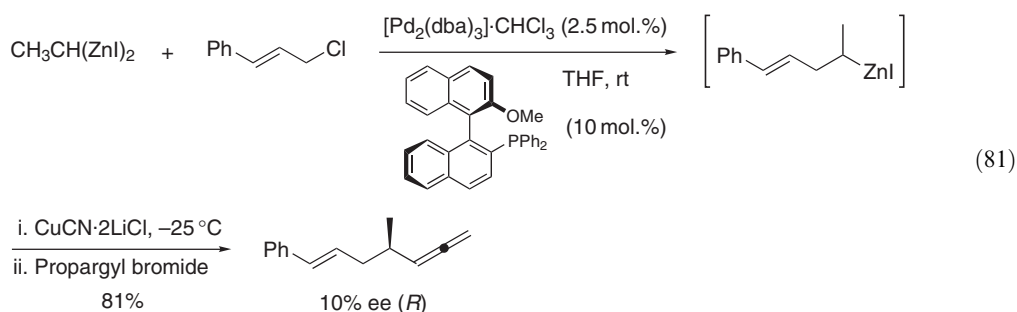
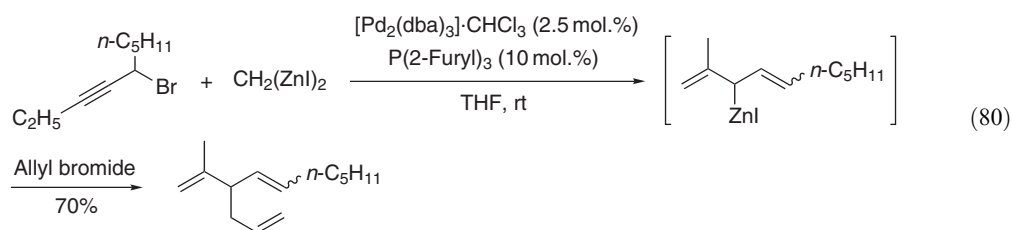
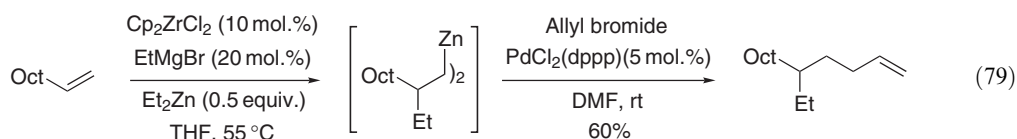
(i) Suzuki-coupling process

The first report on Suzuki cross-coupling reactions between two C(sp³) centers appeared in 1992. Suzuki and co-workers found that Pd(0)-catalyzed cross-coupling reactions of alkylboranes and primary alkyl iodides proceed in good yields (up to 71%) (Equation (74)). But under these conditions (Pd(PPh₃)₄, 60 °C), no reaction with simple alkyl bromides was observed <1992CL691>. An application of this protocol to solid-phase synthesis has been achieved by Mioskowski (Equation (75)) <1999TL4335>. In the course of his studies on synthesis of polycyclopropane natural products such as (-)-FR-900848 or (-)-U-106305, Charette has been interested in cross-coupling reactions between iodocyclopropanes, on which no β -hydrogen is present, and cyclopropylboronate esters (Equation (76)) or boronic acids <1997TL2809>. Deng and co-workers <2000JOC4444> demonstrated that the presence of silver oxide can influence Pd(0)-couplings between cyclopropylboronic acids and allyl bromide (Equation (77)). In 2001, Fu and co-workers reported major advances in C(sp³)-C(sp³) Suzuki reactions of alkyl bromides and alkyl chlorides, possessing β -hydrogen atoms, with 9-BBN-alkyl compounds. The use of Pd(OAc)₂/PCy₃ catalyst system, in the presence of K₃PO₄·H₂O, proved to be extremely efficient even at room temperature (Equation (78)) <2001JA10099, 2002AG(E)1945>.



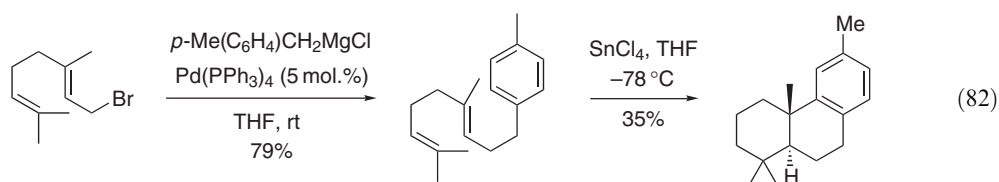
(ii) Negishi-coupling type reactions

In order to circumvent the lack of reactivity of organozinc derivatives toward alkyl halides, Negishi and co-workers developed a new methodology involving Pd(0)-mediated cross-coupling reactions. Dialkylzincs can be alkylated with allyl, benzyl, and propargyl halides in the presence of a Pd(0) catalyst (Equation (79)) <2000OM2417>. Utimoto and co-workers reported different examples of $[\text{Pd}_2(\text{dba})_3]/\text{tris}(2\text{-furanyl})\text{phosphine}$ -catalyzed coupling reactions of *gem*-bis(iodozincio) alkanes with allyl chlorides or propargyl bromides. The organozinc intermediate can be functionalized under the same palladium catalysis conditions or after transmetalation with copper cyanide by reaction with allyl or propargyl bromide (Equation (80)) <1997AG(E)2804>. Similar studies employing chiral phosphines as ligands did not show detrimental effect on the yield but an extremely poor induction (up to 10% ee) was observed (Equation (81)) <2000SL987>.



(iii) Coupling of Grignard reagents

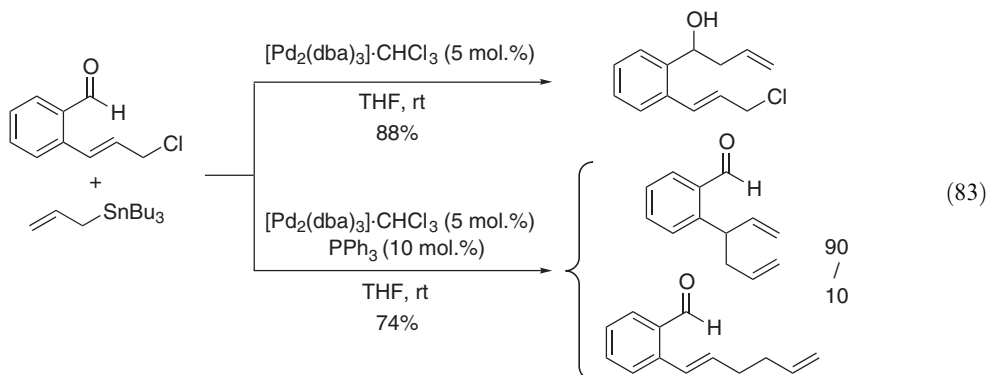
A recent extension of this reaction to organomagnesium compounds was proposed by Demuth and co-workers. They developed a regioselective α -alkylation process of allylic bromides and chlorides with various benzylic Grignard reagents using a catalytic amount of palladium catalyst. α -Benzylated allylic derivatives are obtained rapidly in high yield at room temperature. These compounds can be easily converted into abietane-type terpenoids and also into natural or unnatural tetracyclic polyprenoids in two steps (Equation (82)) <2002JOC1167>.



(iv) Stille coupling

In the early 1980s, Stille pioneered the use of palladium(0) in cross-coupling reactions between tetraalkyltin reagents and allyl or benzyl halides <1986AG(E)508>. The Pd(0)-catalyzed reaction of allylic chlorides and allyltributyltin has received a particular attention. The process involves

formation of a bis(η^3 -allyl)palladium intermediate by oxidative addition and transmetalation with allyltributyltin. The triphenylphosphine coordinates the palladium complex which undergoes a reductive elimination and liberates the 1,5-hexadiene as coupling adduct (Equation (83)). Without phosphine ligand, the allyl chloride remains unchanged. In this case, the allyltributyltin may react with other functions such as aldehydes present on the substrate, to furnish the homoallylic alcohol <2001AG(E)3208>.

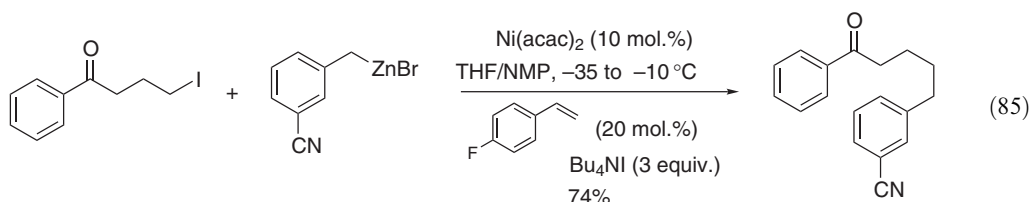
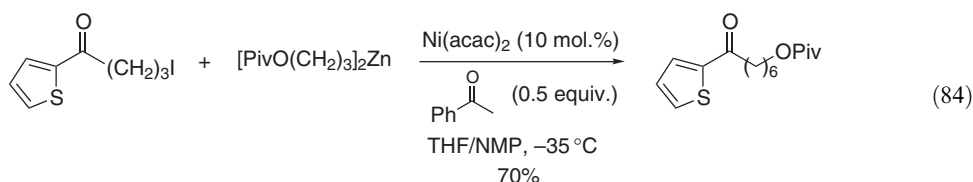


(v) Coupling of aluminum reagents

An example of Pd(0)-catalyzed methylation of benzyl bromide by [3-(dimethylamino)propyl-C,*N*]dimethylaluminum was examined by Blum and co-workers <1997JOC8681>. The reaction operates quantitatively under mild conditions.

1.04.2.4.2 Ni(0)-Catalyzed couplings

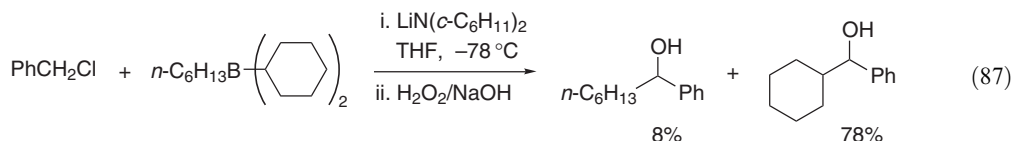
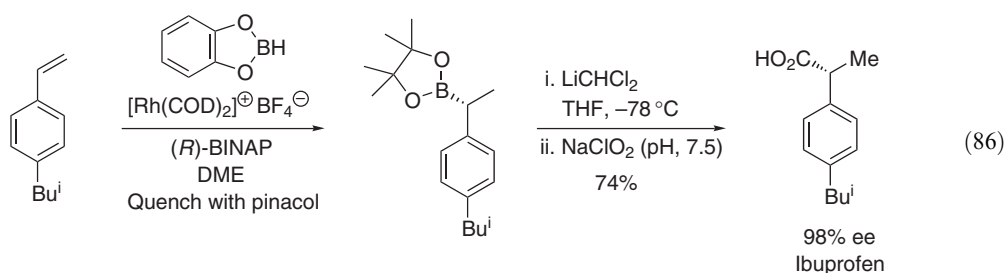
Knochel and co-workers discovered that dialkylzincs undergo efficient cross-coupling reactions with functionalized or unfunctionalized primary alkyl bromides and iodides <1995AG(E)2723, 1998AG(E)2387> in the presence of Ni(acac)₂ as catalyst and additives such as LiI or NMP, 4-fluorostyrene as promotor, acetophenone as co-catalyst which enhances the rate of the reaction and suppresses the I–Zn exchange side-reactions (Equation (84)). With benzylzinc bromide, the use of 3 equiv. of tetrabutylammonium iodide proved to accelerate the coupling process (Equation (85)) <1999OL1323>.



1.04.2.5 Miscellaneous Species with No Stabilizing Group

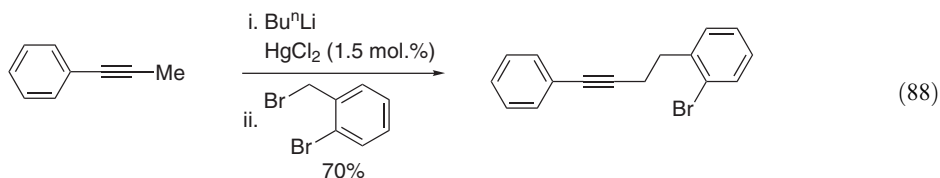
(i) Alkylation of organoboron derivatives

The ability of organoboranes to form ate-complexes has been greatly exploited in organic synthesis particularly for C—C formation. 1,2-Metallate Matesson rearrangement has received great interest for homologation of trialkylboranes and alkylboronate esters. For instance, Crudden and co-workers combined rhodium(I)-catalyzed asymmetric hydroboration and homologation of pinacol boronate intermediates with chloro- or dichloromethyl lithium. After oxidative treatment, enantiomerically enriched alcohols or carboxylic acids were isolated. Ibuprofen could be synthesized in 74% yield and with a 93% ee from the corresponding vinyl arene (Equation (86)) <1999JOC9704>. Kabalka found that simple trialkylboranes also react with (α -chloroaryl)methyl anions. The ate-complex intermediate can readily rearrange to afford the alkylarylcannabinol after oxidative treatment (Equation (87)) <1997OM709>.



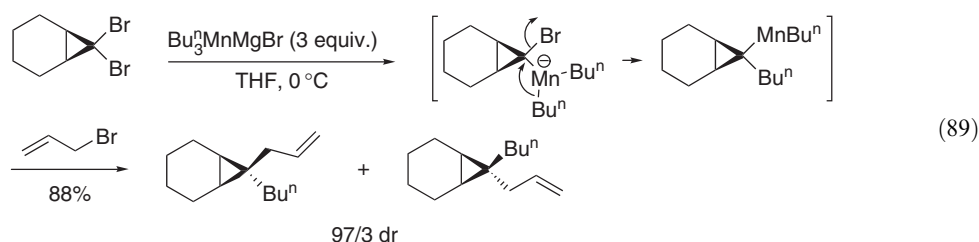
(ii) Alkylation of organomercury reagents

The crucial role of mercury(II) salts in the benzylation of 1-aryl-1-propynes has been demonstrated by the lack of reactivity of lithiopropargylic anions with benzyl bromides. By using HgCl_2 , satisfactory yields of 1,4-diaryl-1-butyne are obtained with both benzyl bromides and benzyl chlorides as electrophiles (Equation (88)) <1998JOC3497>.



(iii) Alkylation of organomanganese compounds

α -Alkylcyclopropylmanganese reagents, obtained by treatment of *gem*-dibromocyclopropanes with trialkylmanganates, react efficiently and stereoselectively with methyl iodide and allyl bromide and give rise to the *gem*-dialkylated cyclopropanes. The reaction of the dibromide with Bu_3MnMgBr affords the cyclopropylmanganate intermediate, obtained via bromide–manganese exchange, which undergoes 1,2-metallate rearrangement with inversion of configuration (Equation (89)) <2000T2131>.



1.04.3 CARBANIONS WITH ONE STABILIZING GROUP

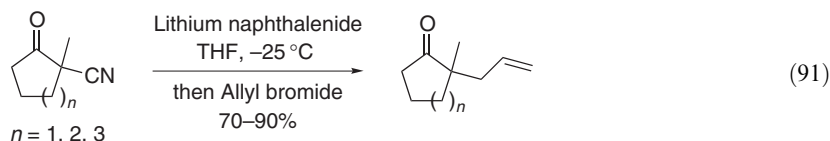
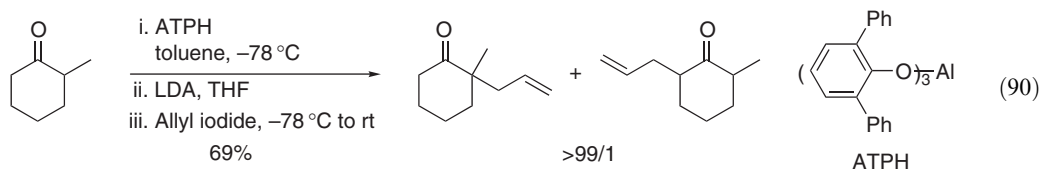
1.04.3.1 Enolates and Related Carbanions

One of the most straightforward methods used for the formation of C—C bonds is the alkylation of enolates and related carbanions with organic halides. Several methodologies taking advantage of the versatility of such species have been developed to carry out chemo-, regio-, and stereo-selective transformations. Recent advances in this area are disclosed in this part.

1.04.3.1.1 Alkylation of enolates

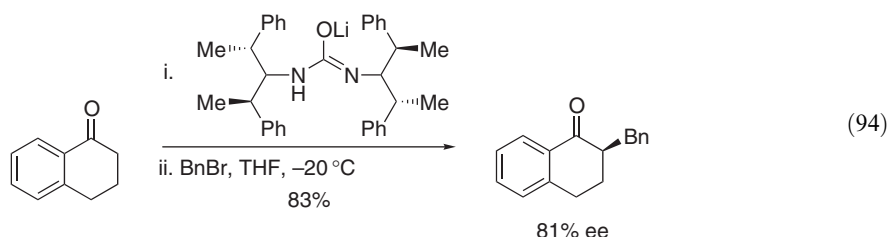
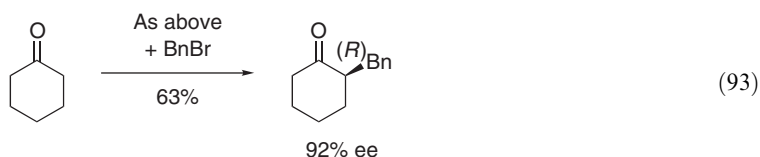
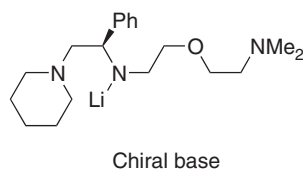
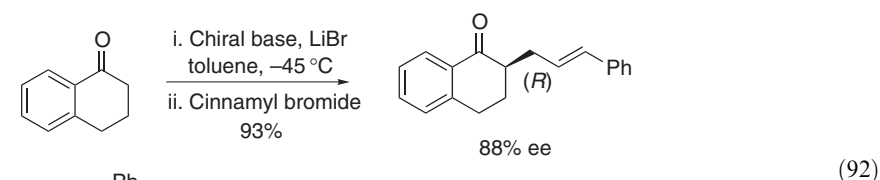
(i) Lithium ketone enolates

Lithium enolates have largely demonstrated their omnipresence in organic synthesis playing a central role in C—C bond formation. As carbon nucleophiles, they react with various carbon electrophiles including haloalkanes to give α -substituted carbonyl compounds. The main method used for enolate formation is the direct deprotonation of ketones with strong and non-nucleophilic bases under either kinetic or thermodynamic conditions. Regio- and stereoselectivity in the enolate formation and its subsequent alkylation depend on a variety of parameters already discussed in COFGT (1995). Metallation of unsymmetrical ketones at low temperature with hindered amide bases (such as LDA, LiHMDS, etc.) provides less substituted kinetic enolates whereas at higher temperatures under $\text{Bu}^t\text{OK}/\text{Bu}^t\text{OH}$ conditions, thermodynamic enolates are alkylated at the more substituted carbon with moderate selectivities (for more recent investigations, see <1996JOC2232>). To enhance this regioselectivity in favor of α,α -dialkylated compounds, Yamamoto and co-workers proposed the use of hindered oxophilic Lewis acids to generate exclusively the more substituted enolate by deprotonation under kinetic conditions. With aluminum tris(2,6-diphenylphenoxide) (ATPH), the precomplexation of the unsymmetrical ketone proceeds from the less hindered side. Selective lithiation by LDA at -78°C followed by electrophilic trapping with allyl and propargyl halides afforded the α,α -disubstituted ketones with impressive regiocontrol (Equation (90)) <1997JA611>. Another method based on reductive alkylation of α -alkylated α -cyanoketones with lithium naphthalenide was reported by Liu and co-workers <1998TL4183> and gave also excellent results (Equation (91)).



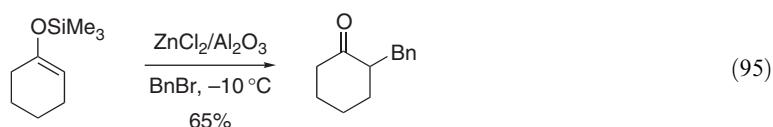
Chiral base-mediated asymmetric alkylation of cyclohexanone and 1-tetralone has been widely investigated by Koga and co-workers. Treatment of the prochiral cyclic ketones with an equimolar amount of phenylglycine-derived lithiated tetradentate chiral base and lithium bromide salt gives

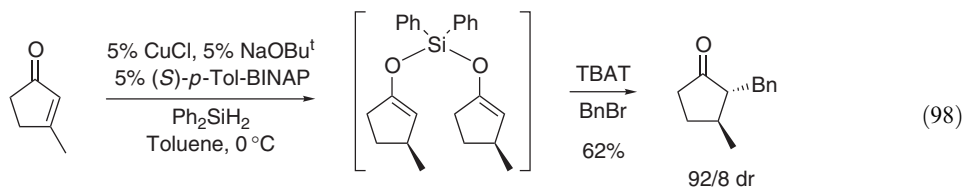
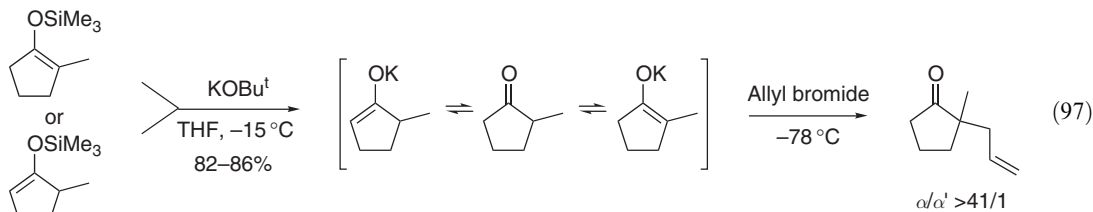
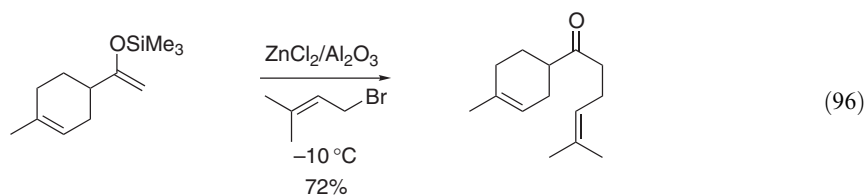
the corresponding enolates, which react with a range of haloalkanes to furnish the enantioenriched α -alkylated carbonyl compounds in up to 98% ee (Equations (92) and (93)) <1998T2449>. The incorporation of additives such as 1,1,4,7,10,10-hexamethyltriethylenetetramine provides a substantial rate acceleration <1999TL8129> and the presence of LiBr is essential for the selectivity. At the same time, Knochel reported the preparation of a new chiral pseudo- C_2 -symmetric urea and its use in enantioselective deprotonation. The monoanion, generated by deprotonation with Bu^nLi , acted as a chiral base and promoted the enolization of α -tetralone. The transient lithium enolate was benzylated in 83% yield and with 81% ee (Equation (94)) <1998AG(E)3014>.



(ii) Reactivity of silyl enol ethers

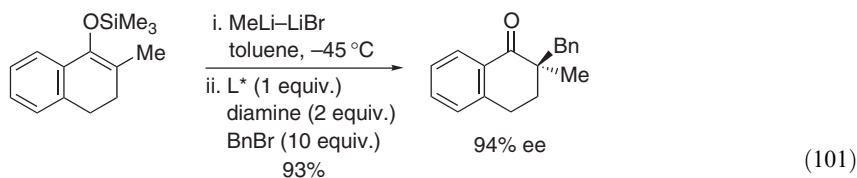
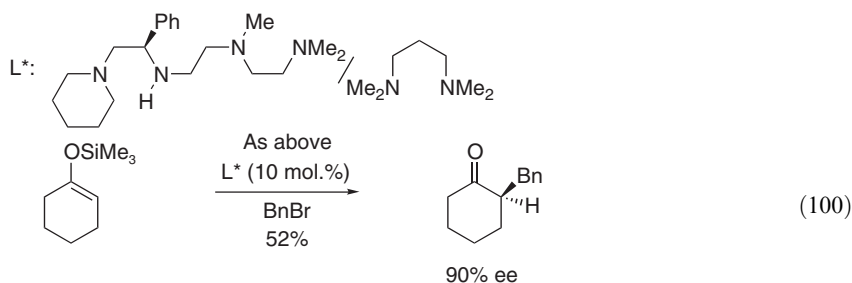
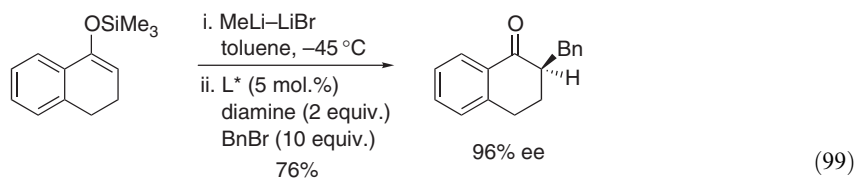
Upon treatment with methyllithium, benzyltrimethylammonium fluoride or silver(I) catalysis, direct alkylation of silyl enol ethers with organohalides occurs in modest yields. However, more efficient procedures have been published since the early 1990s. For instance, Kad and co-workers <1999SC3439> reported an interesting acceleration of the α -alkylation of silyl enol ethers with allylic, benzylic, and tertiary alkyl halides by using ZnCl_2 impregnated on acidic alumina as catalyst (Equations (95) and (96)). In general, silyl enol ethers react regioselectively from the less substituted α -side, whereas Duhamel's group showed that potassium enolate of unsymmetrical ketones, generated by reaction of KO^tBu with related silyl enol ethers, undergo alkylation at the more substituted carbon whatever the regioisomer used (Equation (97)) <1998SL413>. A recent report from Buchwald and co-workers described an elegant approach to enantiomerically enriched *trans*-2,3-disubstituted cyclopentanones which involves asymmetric copper-catalyzed Michael reduction of β -substituted cyclopentenones with Ph_2SiH_2 and subsequent alkylation of the resulting silyl enol ethers, promoted by the presence of fluoride anions (Equation (98)) <2001OL1129> (see also <2000T2779>).





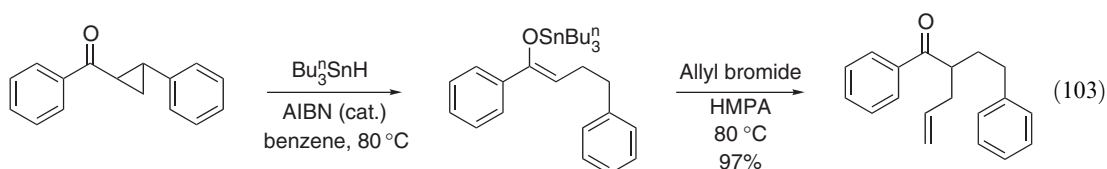
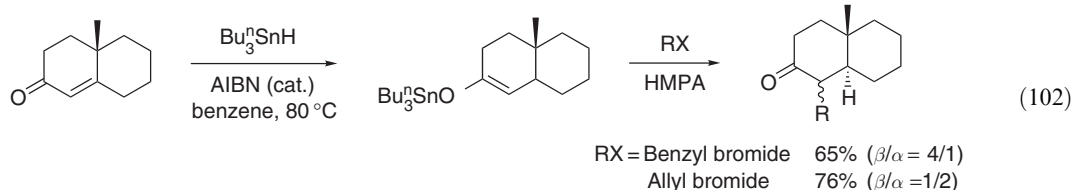
TBAT: Triphenyldifluorosilicate

Enantioselective alkylation of silyl enol ethers mediated by MeLi·LiBr and a chiral ligand present in catalytic (Equations (99) and (100)) <1994JA8829, 1999TL2803> or equimolar amount (Equation (101)) <1998T2449> was reported by Koga. The reaction proceeds through initial Li–Si exchange with methyllithium and subsequent alkylation of the lithium enolate/ligand complex. It was mentioned that the incorporation of a second achiral bidentate ligand activates the intermediate and provides an acceleration of the process. A variety of tetradentate amine ligands were tested that led to enantioselectivities up to 96%, 97%, and 90% starting from silyl enol ethers of tetralone, α -substituted tetralone, and cyclohexanone, respectively (Equations (99)–(101)).



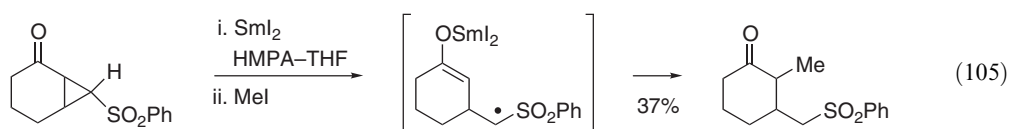
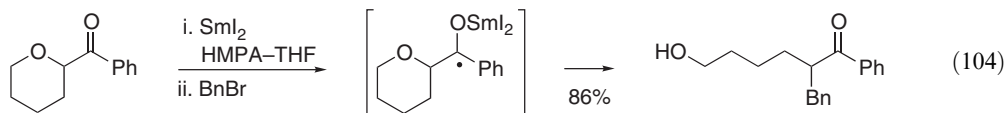
(iii) Alkylation of *Sn*(IV) enolates

Sn(IV) enolates are known to be stable intermediates which are less reactive than lithium or copper enolates. However, they may undergo selective monoalkylations with organic halides in the presence of a coordinating co-solvent such as HMPA. Usually prepared by transmetalation of more reactive enolates (Li, Cu) or transesterification of enol acetates <1994OPP87>, tin(IV) enolates can also be obtained by reduction of α,β -unsaturated ketones (Equation (102)) <1996JOC5384> and tandem ring-opening reduction of cyclopropyl ketones (Equation (103)) <1997JOC5248, 2001JOC5249> by tin hydride, involving *O*-stannyl ketyl radical intermediates. After addition of 5 equiv. of HMPA prior to haloalkanes, the enolate alkylation proceeds in good yields.



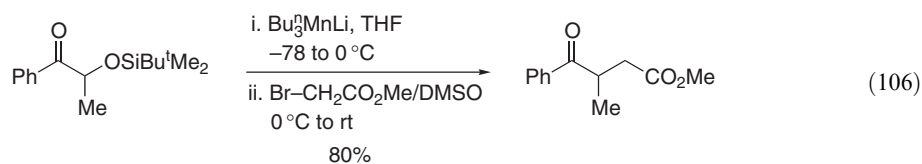
(iv) Alkylation of samarium(III) enolates

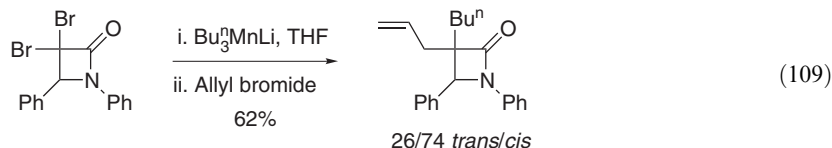
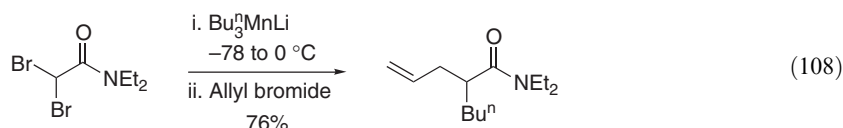
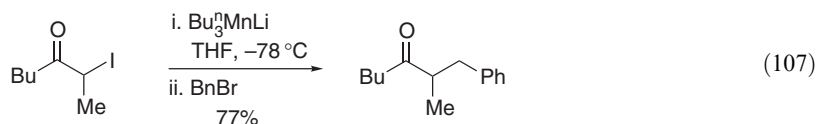
Samarium(III) enolates, prepared from an α -keto-tetrahydropyran (Equation (104)) <1995JOC1110> or cyclopropyl ketone (Equation (105)) <1999TL1019> via tandem SmI_2 -generated ketyl/ring-opening, showed that they can also react efficiently with organic halides, leading to related α -alkylated ketones.



(v) Alkylation of manganese(II) enolates

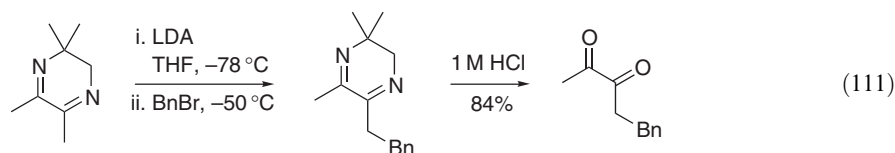
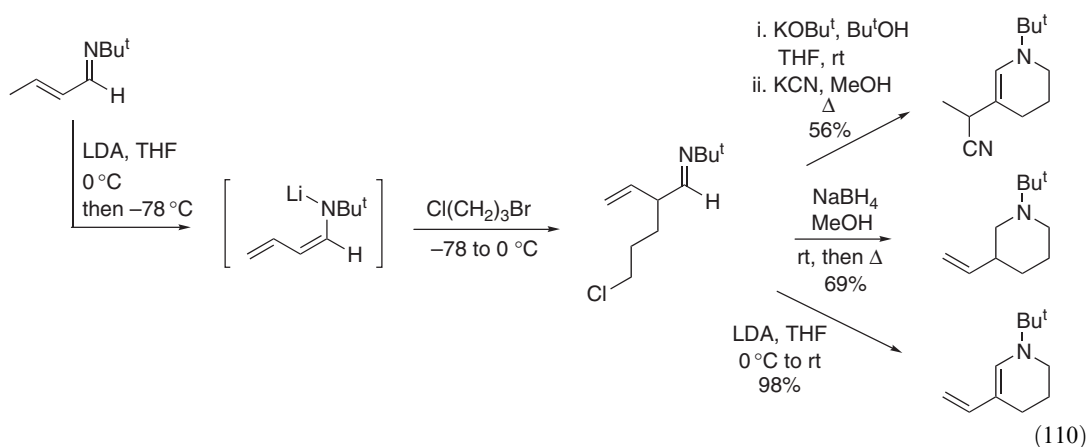
Manganese(II) enolates are readily available from carbonyl compounds by proton abstraction with LiHMDS and Ph(R)NMnCl as described by Reetz <1993TL7395> and Cahiez <1994TL3065>, by transmetalation of lithium enolates <1994TL3069> or by reduction of acetoxy and silyloxy groups or halogens adjacent to a carbonyl moiety with organomanganese(II)-ate complexes. This approach was recently developed by Hosomi and co-workers. They showed that reaction of α -silyloxy ketones (Equation (106)) and α -iodo ketones (Equation (107)) with Bu_3MnLi affords the related manganese enolates, which can be selectively alkylated by organic halides <1997JA5459>. The use of *t*-butyl dibromoacetate and *N,N*-diethyldibromoacetamide (Equation (108)) or dibromo β -lactams (Equation (109)) instead of α -silyloxy and α -iodo ketones gives the butylated manganese enolates, which result from bromide–manganese exchange by Bu_3MnLi and subsequent 1,2-butyl migration (see Section 1.04.2.5) <1998JOC910>.





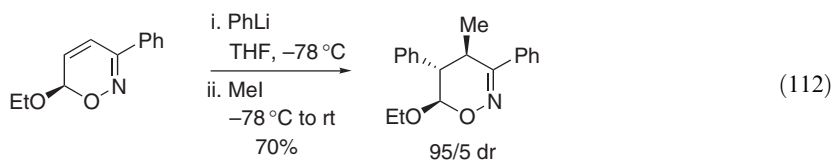
(vi) α -Alkylation of imines

In general, anions from α,β -unsaturated imines are exclusively alkylated at the α -position by a variety of alkyl halides. This predominant formation of α -products was illustrated by De Kimpe with studies on the reactivity of 1-azapentadienyl anions. Deprotonation of *N*-(2-buten-1-ylidene)-alkylamines with LDA generates conjugated 1-azaenolates which react with 1-bromo-3-chloropropane adjacent to the imine and cyclize to 3-vinylpiperidines under $\text{NaBH}_4/\text{MeOH}$ reductive conditions or to 5-vinyl tetrahydropyridines by treatment with LDA. These cyclic enamines are suitable dienes for Diels–Alder reactions. KO^tBu isomerization of the α -alkylated β,γ -unsaturated imines to conjugated analog followed by Michael addition of cyanide anion and subsequent ring closure leads to 5-substituted tetrahydropyridines in moderate yields (Equation (110)) <1998T2563>. Monoalkylation of unsymmetrical dihydropyrazines was reported by Sayre and co-workers for the functionalization of symmetrical α -diones. The selective lithiation of the corresponding 1,2-diimides with LDA at -78°C occurs at the less hindered methyl group, and then the monoanion intermediate is alkylated with a variety of alkyl halides in 34% to 84% yields. The monoalkylated α -diones are liberated under acidic hydrolysis (Equation (111)) <1998TL1877>.

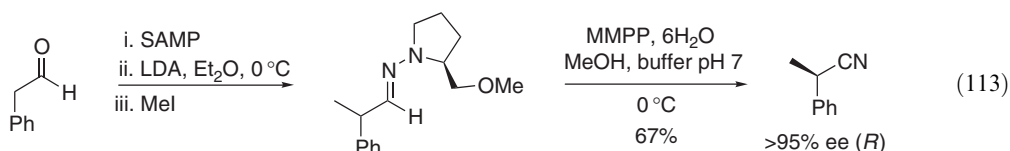


(vii) α -Alkylation of oxime derivatives

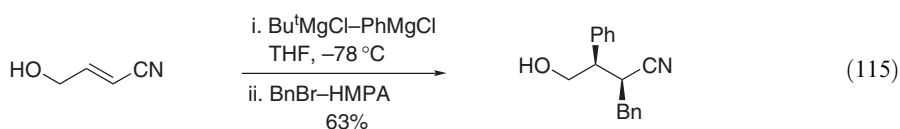
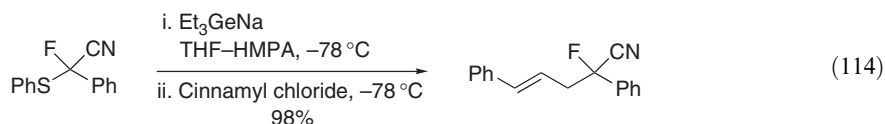
Stereoselective conjugate addition of organolithiums to standard 6*H*-1,2-oxazines generates the 4-lithiated 1,2-oxazines as Michael adducts, which can be trapped selectively by methyl iodide and allyl bromide. The *trans*-diastereoisomer was isolated as the only product in good yields (Equation (112)) <2002SL1412>.

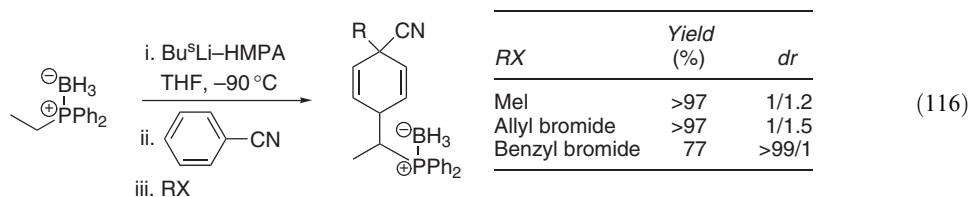
(viii) α -Alkylation of hydrazones

Chiral hydrazones are important precursors for asymmetric synthesis. Most of the investigations published in this area, particularly on chiral (*S*)-(-)-1-amino-2-methoxymethylpyrrolidine (SAMP) and (*R*)-(+)-1-amino-2-methoxymethylpyrrolidine (RAMP) hydrazones, have been performed by Enders and co-workers. In 1995, they reported the preparation of chiral nonracemic α -substituted nitriles by asymmetric alkylation of SAMP and (*S*)-(-)-1-amino-2-methoxydimethylpyrrolidine (SADP) hydrazones and subsequent oxidative cleavage with magnesium monoperoxyphthalate (MMPP). The optically active nitriles were isolated with high enantiomeric excesses (>95% ee) (Equation (113)) <1995T10699>. Alkylation of α -silylhydrazones has been successively examined by Enders <1996LA189> and Richards <1998TL3617>. Sequential enolization of α -silyl RAMP and SAMP hydrazones followed by methyl iodide trapping occurred from the less substituted side under kinetic conditions (LDA or Bu^tLi, -78°C) and adjacent to the silyl group after equilibration at 0°C (or with BuⁿLi at -78°C). α -Silyl dimethylhydrazones tend to react much more from the less substituted side leading to a better ratio at -78°C . Finally, the regioselectivity depends on a variety of parameters such as the nature of the base, the hydrazone moiety and the temperature.

(ix) α -Alkylation of nitriles

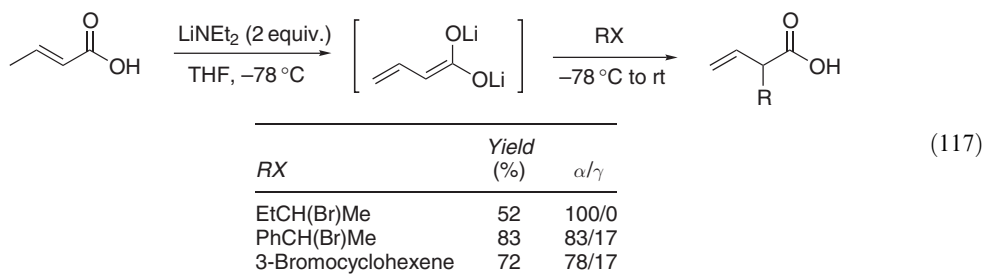
A large number of nitrile-containing natural products have been isolated in recent years. Therefore, developments of new synthetic methods for their elaboration and precisely for the functionalization of adjacent centers to nitriles, are still required. In response, Yokoyama reported the introduction of allyl and prop-2-ynyl groups to cyanofluoromethylene units. Cleavage of the S—C bond of 2-fluoro-2-phenylthio-2-phenylacetonitrile with an organogermanium-ate complex (Et₃GeNa) gave the intermediate anion that can be captured by allyl and propargyl chlorides (Equation (114)) <1998CC1093>. Fleming showed that 1,4-addition of Grignard reagents to γ -hydroxy α,β -unsaturated nitriles is highly favored by chelation control of the hydroxy moiety. The alkyl group should be delivered intramolecularly and the nitrile-stabilized transient anion alkylated with benzyl bromide (Equation (115)) <2000OL1477>. Finally, benzonitrile undergoes regioselective *para*-addition of lithiated alkyl(diphenyl) phosphine boranes, thus resulting in dearomatized lithium adducts which are readily trapped α - to the cyano group with MeI, allylBr, and BnBr to form functionalized 1,3-cyclohexadienes (Equation (116)) <2002TL9611>.





(x) α -Alkylation of carboxylic acids

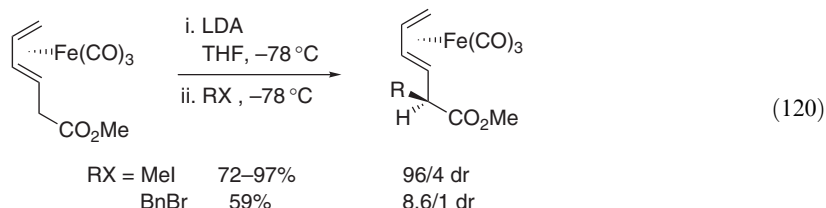
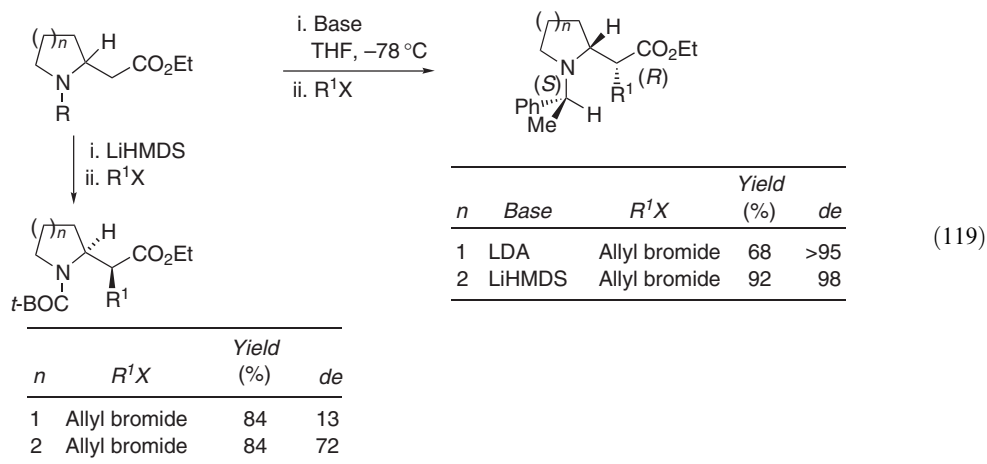
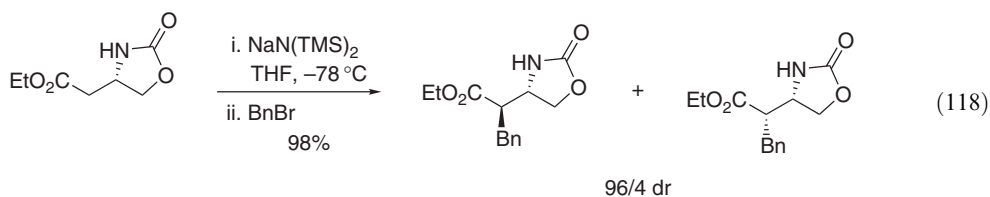
Metallation of carboxylic acids can be performed successfully with lithium amide bases to provide lithium dienolates, which can be regio- and stereoselectively alkylated at the α -carbon center [<B-1991MI99, B-1994MI88>](#). In the 1990s, much attention has been turned to the reactivity of α,β -unsaturated analogs, widely investigated by Parra and Mestres. On treatment with lithium diethylamide, unsaturated carboxylic acids afford the corresponding π -extended dienediolates. Alkylation with alkyl, benzyl, or allyl halides were successively reported [<1994T5109, 1998T4357, 1998T15305, 2000S1160, 2001SL156>](#). The attack occurs preferentially at the α -site but usually leads to a mixture of both regioisomers. This lack of selectivity depends on the reactivity of the dienediolate with the electrophile, partially controlled by addition of lithium chelating compounds which may influence the aggregation state ([Equation \(117\)](#)).



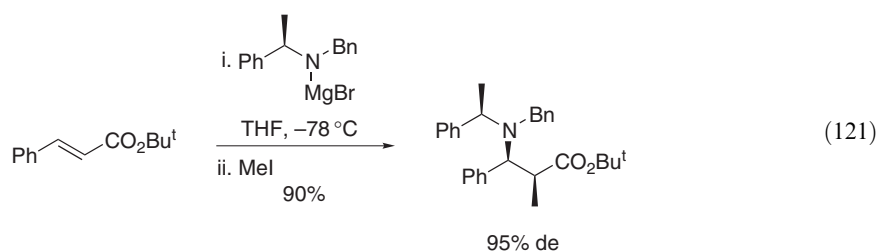
(xi) α -Alkylation of esters and lactones

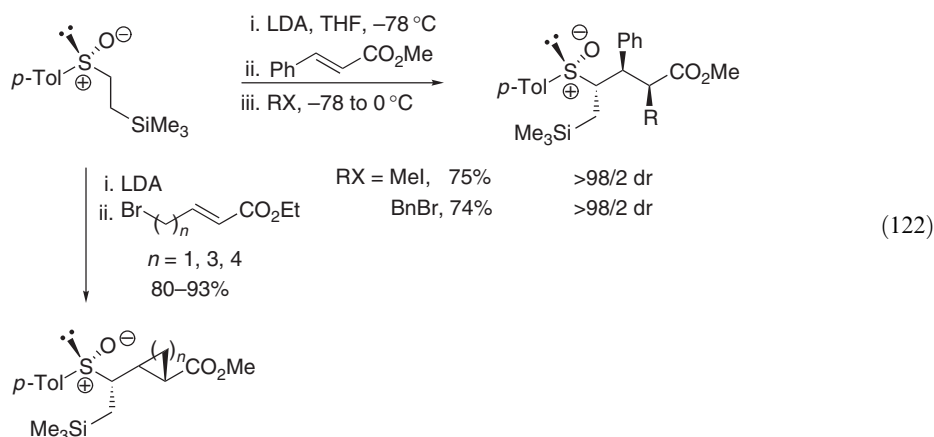
Ester enolates are important intermediates for synthetic transformations. Their reactivity has been widely investigated in recent years and applied in numerous total syntheses. This broad application cannot be summarized in a few lines, but nevertheless selected examples will be provided herein.

(a) *Diastereoselective alkylations.* Particular attention has been devoted to the control of the diastereoselectivity in alkylation processes and this still remains a challenge for organic chemists. Investigations on 1,2-asymmetric induction in acyclic series have been reported on esters substituted in the β -position by stereodefined groups containing heteroatoms. Ha and co-workers showed that the enolate dianion of (*S*)-4-carboethoxymethyl-2-oxazolidinone, generated by proton abstraction with LiHMDS or NaHMDS at -78°C , undergoes diastereoselective alkylation with alkyl iodides, and allyl and benzyl bromides ([Equation \(118\)](#)). The nature of the counter-cation of the base and the presence of HMPA improve the selectivity in favor of the *anti*-product formation. This result was rationalized by a stereoelectronic effect of the nitrogen atom [<1996TL5723>](#). Chiral heterocyclic β -amino esters are versatile synthons for the synthesis of azabicyclic pyrrolizidine and quinolizidine alkaloids. For their elaboration, direct allylation of lithium enolates derived from chiral nonracemic pyrrolidyl and piperidyl acetates was developed by Knight and co-workers. But low-to-moderate diastereomeric excesses were observed [<1990TA147, 1991JCS\(P1\)1615>](#). More recently, Lhommet showed that alkylation of chiral cyclic β -amino esters, prepared from (*S*)-methylbenzylamine, occurs with complete diastereocontrol ([Equation \(119\)](#)) [<1997TL8507, 1999TL9019>](#). The bulky (tricarbonyliron) group also provides a remarkable stereocontrol. An approach reported by Donaldson and co-workers deals with $\text{Fe}(\text{CO})_3$ -stereodirected alkylation of lithiated methyl (3,5-hexadienoate) $\text{Fe}(\text{CO})_3$ complex adjacent to the ester functionality. An excellent level of diastereoselectivity is reached (up to 96:4 dr) when methyl iodide is used as electrophile ([Equation \(120\)](#)) [<1997T4185>](#).

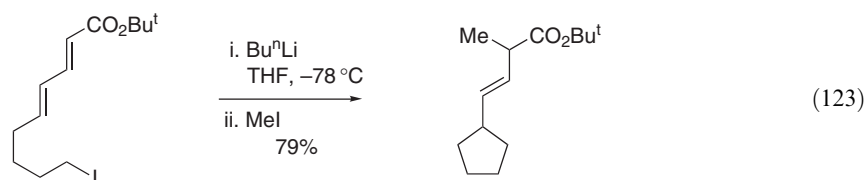


(b) *Intermolecular conjugate additions.* Owing to their high reactivity toward nucleophilic attacks, α,β -unsaturated esters are among the most studied substrates for Michael additions. To illustrate this reactivity, two examples have been selected. In 1994, Davies and co-workers examined the sequential conjugate addition of the chiral Hauser base to the *t*-butyl cinnamate and treatment of the lithium enolate with methyl iodide. The *syn*-adduct was isolated as major product with a diastereomeric excess of 95% (Equation (121)) <1994TA35>. In another example, Toru and co-workers showed that enantioenriched β -silyl- α -sulfinyl carbanions also add to α,β -unsaturated esters with excellent 1,2-asymmetric induction (*dr* > 98:2). Thus, the intermediate enolate reacts with various alkyl halides and leads to the *syn,anti,syn*-trisubstituted adducts as a single diastereoisomer (*dr* > 98:2) (Equation (122)) <1997SL449>. When ω -halo- α,β -unsaturated esters are used, the transient enolate undergoes intramolecular alkylation with total diastereocontrol giving the corresponding cyclopropane, cyclopentane or cyclohexane carboxylates (Equation (122)) <2000JOC1758>.

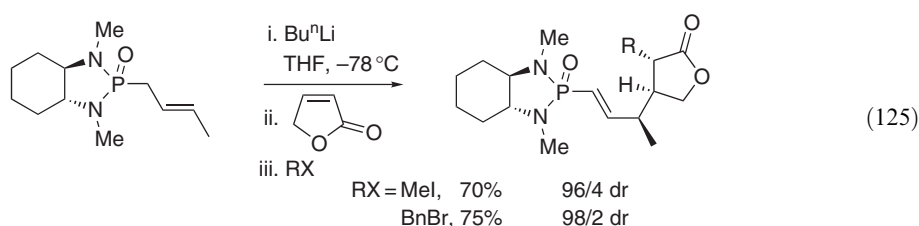
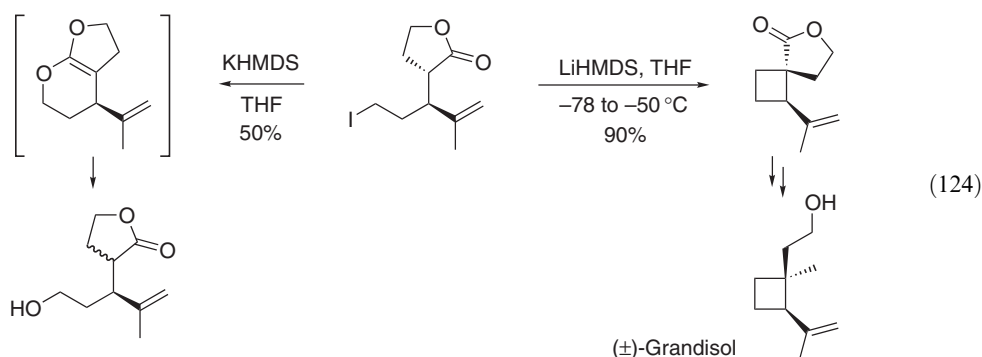




(c) *Intramolecular conjugate additions.* Starting from ω -iodo unsaturated esters or activated ω -iododienes, Cooke, Jr., and co-workers showed that intramolecular 1,4-addition of primary organolithiums, initiated by a rapid lithium–iodide exchange with Bu^nLi , followed by methylation of the intermediate enolates proceeds in good yields (Equation (123)) <1997SL535>.

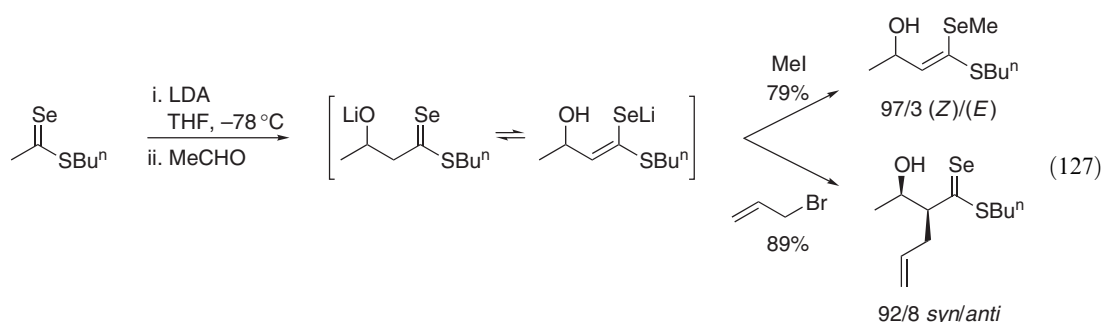
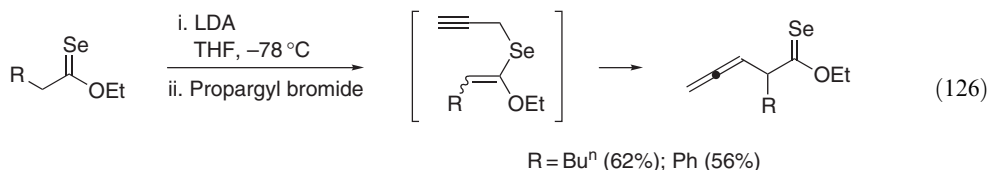


(d) *Alkylation of lactone enolates.* An example of regio divergence in *C*- versus *O*-alkylation of lactone enolates has been reported by Kim and co-workers. ω -Iodo lactones, deprotonated either by LiHMDS or KHMDS, readily underwent *C*- and *O*-intramolecular alkylation, respectively. Thus, the *C*-alkylated compound or spiro lactone has been converted into (\pm)-grandisol in a stereospecific manner (Equation (124)) <1994TL9211>. Alternatively, lactone enolates can be generated by 1,4-addition of organolithium reagents to related α,β -unsaturated carbonyl compounds. As shown by Hanessian, the lithiated chiral allylic phosphonamide reacts regioselectively with various α,β -unsaturated lactones (and lactams) to give α -Michael adducts with high diastereomeric excess. Electrophilic quenching of the intermediate lithium enolate occurs with an excellent diastereoselectivity (Equation (125)) <2000JOC5623>.

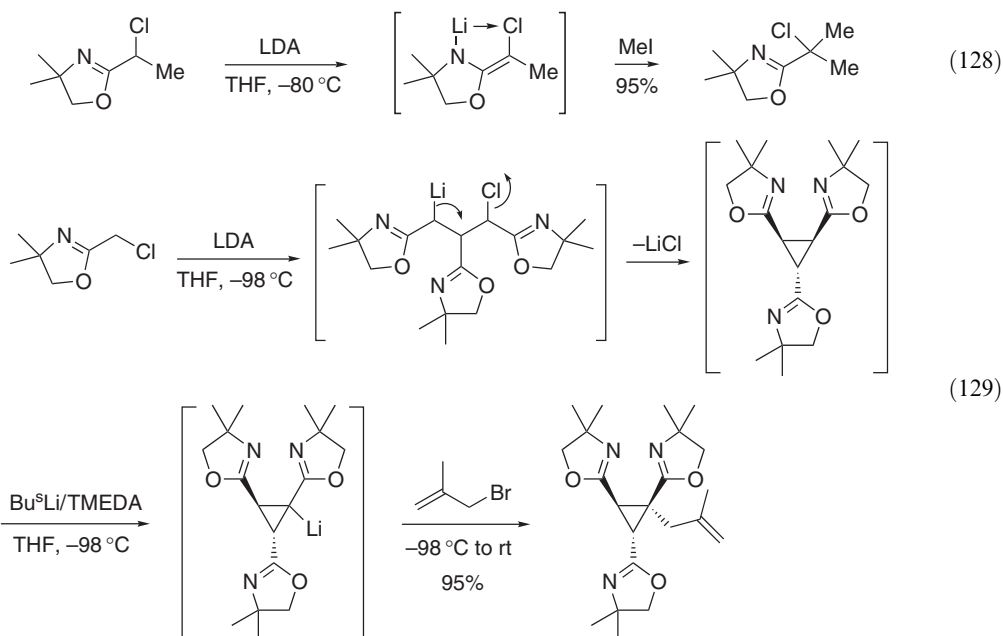


(xii) α -Alkylation of selenolates, dithioesters and selenothioesters

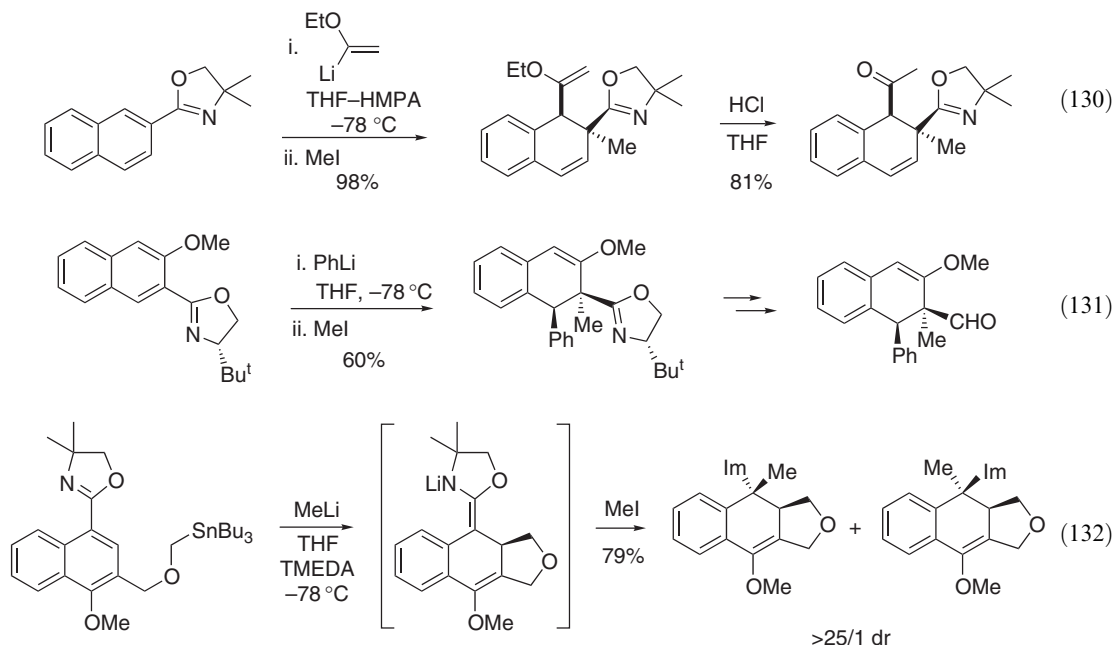
In 1995, Kato and co-workers reported that alkylation of lithium 1-alkoxyeneselenolates, prepared by direct deprotonation of selenoesters with LDA at -78°C , with propargyl bromide involves sequential propargyl selenide formation and its subsequent [3,3]-rearrangement to liberate allenic selenoesters in good-to-moderate yields (Equation (126)) <1995TL2807>. Under similar conditions, lithiated β -hydroxy selenothioic esters also undergo exclusive *Se*-alkylation, a regioselectivity already observed in the sulfur series with dithioic esters <1995TL6225>. Electrophilic quenching with allyl bromide leads to vinyl allyl selenides as excellent precursors for seleno-Claisen rearrangement. The α -allylated product was isolated in fair yield (Equation (127)) <1999JOC2130>.

(xiii) α -Alkylation of oxazolines

As Florio and co-workers recently found, 2-(1-chloroethyl)-4,4-dimethyl-2-oxazoline is easily deprotonated with LDA at -80°C . The transient chlorocarbenoid, stabilized by an intramolecular chelation between chlorine and lithium atoms, can substitute methyl iodide in 95% yield (Equation (128)) <2001S2299>. Otherwise, the lithiated 2-chloro-methyl-2-oxazoline tends to “trimerize” into *trans*-1,2,3-tris(oxazoliny)cyclopropane which can be alkylated by sequential lithiation with Bu^sLi/TMEDA followed by electrophilic trapping (Equation (129)) <2002JOC759>.

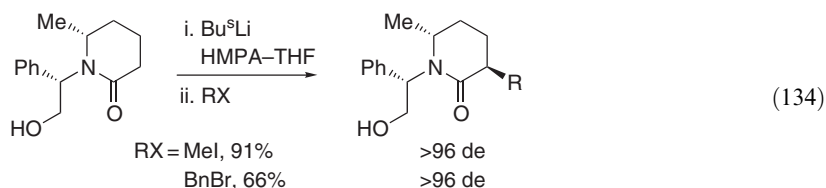
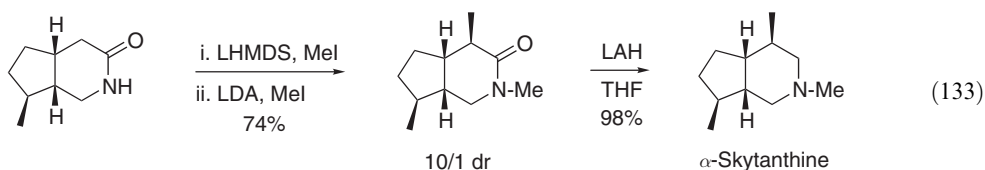


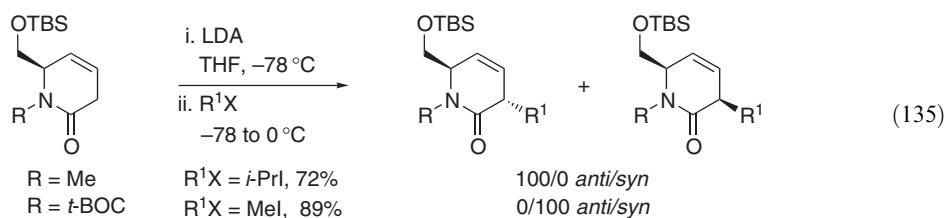
Naphthyl oxazoline compounds were shown to be excellent Michael acceptors for intermolecular addition of Grignard reagents and alkyllithiums such as α -ethoxyvinyl lithium, a useful acyl anion equivalent (Equation (130)) <1998TL5301>. In the presence of alkyl halides, oxazoline lithium enolates undergo electrophilic quenching adjacent to the oxazoline moiety <1994T2297, 2000JOC3018>. More recently, asymmetric addition to 3-methoxynaphthalen-2-yl oxazolines has been reported (Equation (131)) <2000JOC3018>. Independently, Meyers and Clayden applied this methodology to the preparation of natural products including aphanorphine <1995JOC1265> and podophyllotoxin core <2002OL787>. In the last case, Clayden's approach involves the dearomatizing anionic cyclization of oxa-analogs of γ -lithiopropynaphthalenes as key step followed by alkylation of the resulting anion α to the oxazoline (Equation (132)).



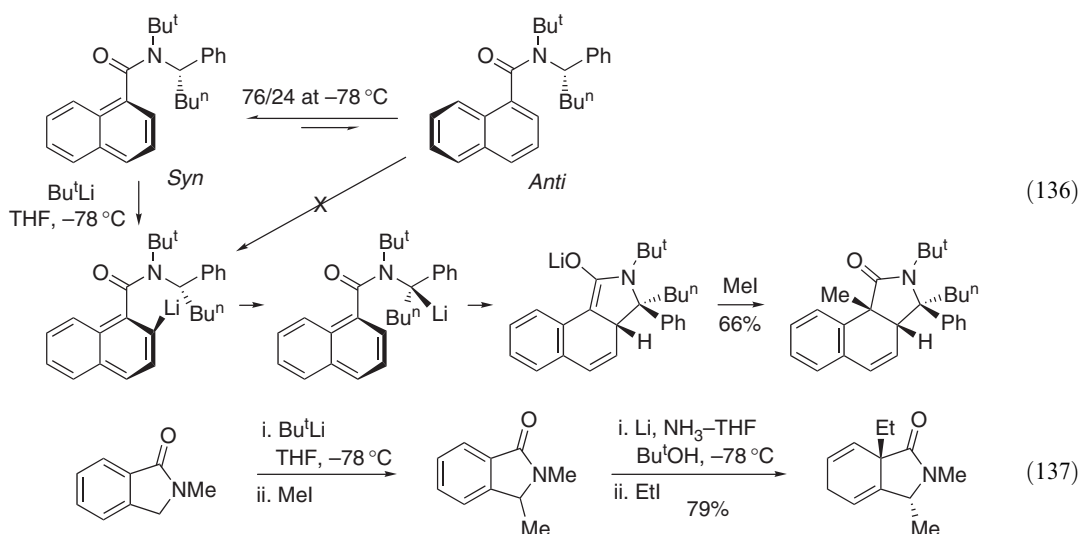
(xiv) α -Alkylation of amides and lactams

Amide enolates are synthetically very useful intermediates, particularly in the synthesis of natural products. For their generation, several methods have been reported including metallation by proton abstraction or Birch reduction of adjacent aromatic rings. For example, Ernst and Helmchen studied the enolization of a bicyclic γ -lactam using LDA at -78°C and the stereo-selective alkylation with methyl iodide leading to the related α -branched lactam with a 10:1 diastereoselectivity, a synthetic intermediate which allowed the preparation of α -skytanthine (Equation (133)) <2002S1953>. Similarly, it is possible to alkylate a series of substituted pyridinones (Equation (134)) <1995TL1035> and dihydropiperidones (Equation (135)) <2003TL757> with high diastereoselectivity.





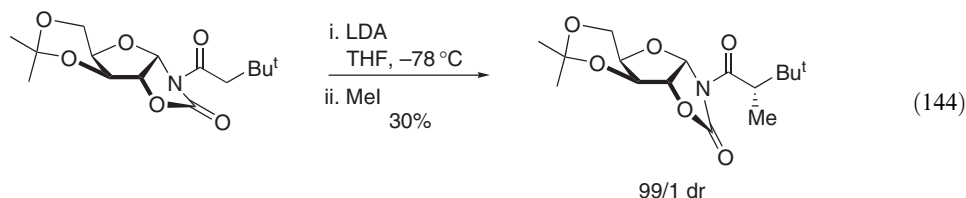
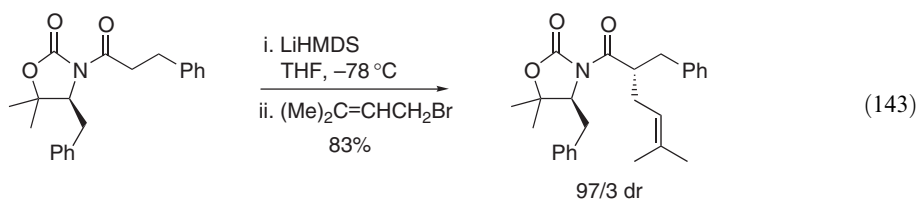
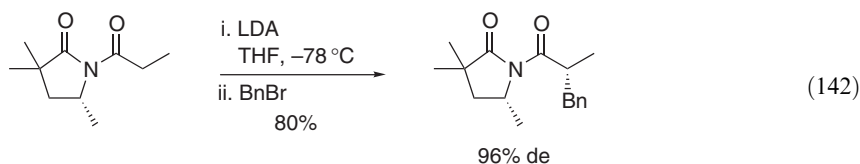
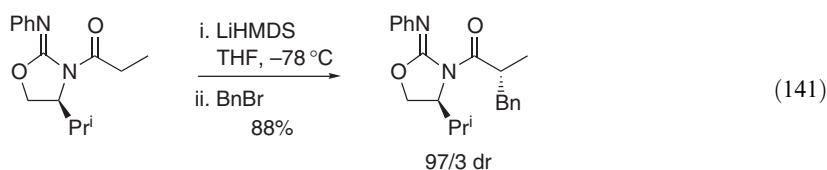
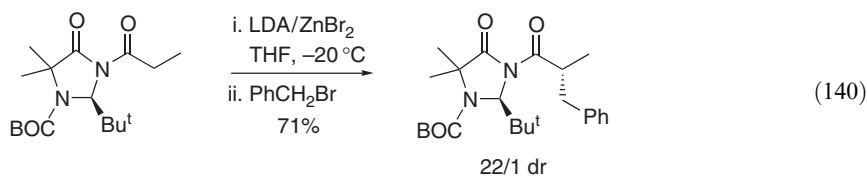
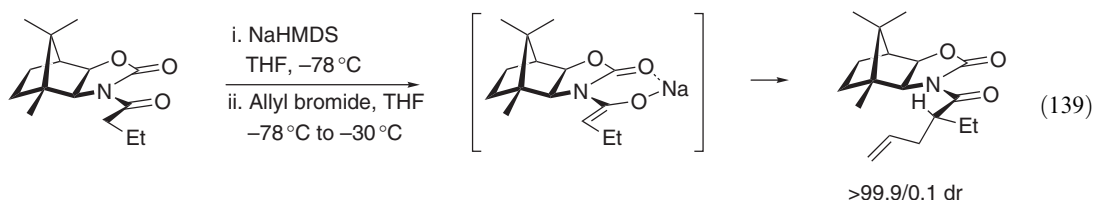
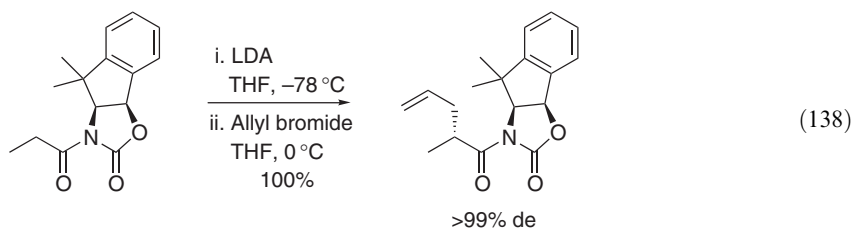
Clayden reported an interesting example of Bu^tLi -mediated stereospecific and retentive cyclization of *N*-substituted tertiary 1-naphthamides bearing a chiral α -butyl benzyl group, followed by methylation of the intermediate enolate. The highly substituted pyrrolidinone was isolated in enantiomerically pure form. The excellent stereospecificity may be explained by a selective ortholithiation of one of the two atropisomers which are in equilibrium at -78°C , followed by aryllithium translocation to a chiral α -amino carbanion, which readily cyclizes to a unique diastereoisomeric adduct with retention of configuration (Equation (136)) <1999TL8327>. Another approach to pyrrolidinones was described by Guo and Schultz. *N*-Methylphthalimide can be first alkylated in the benzylic position, as reported in Section 1.04.3.4, and then the related adducts undergo sequential diastereoselective Birch reduction–alkylation to give 3-substituted-2-methyl-2,3-dihydroisindol-1-ones in good yields (Equation (137)) <2001JOC2154>.



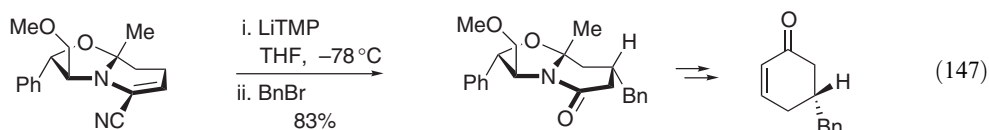
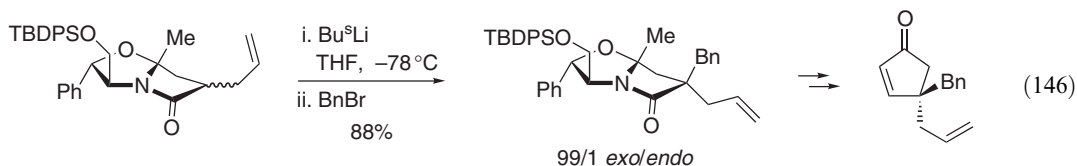
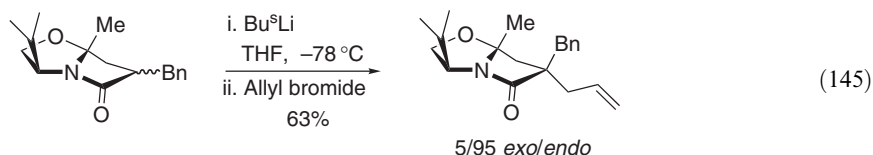
1.04.3.1.2 Asymmetric alkylation of amide enolates

(i) Introduction of chirality from chiral auxiliaries

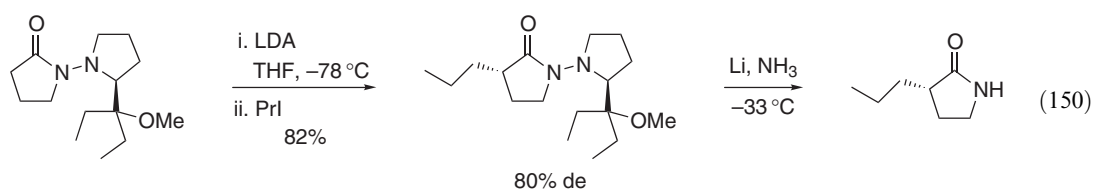
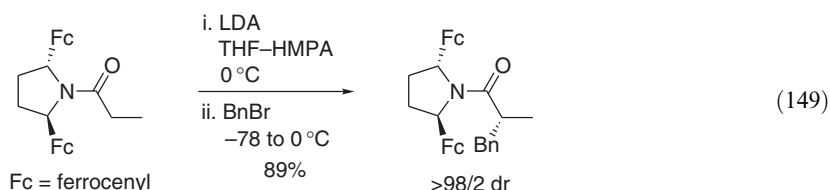
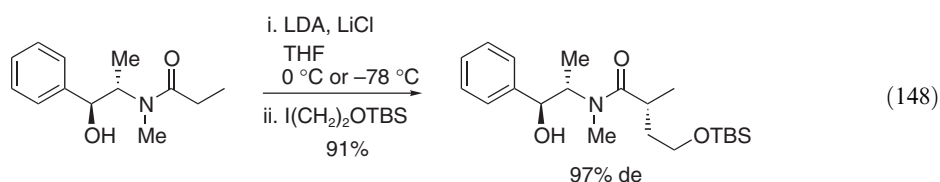
The use of chiral auxiliaries proved to be very efficient for the preparation of enantiopure materials. When the auxiliary is attached to an achiral carbonyl function, asymmetric enolate alkylation of the acyl moiety can be realized with an excellent facial discrimination <B-1995MI, 2000T917>. Originally reported by the Evans group, studies with enantioenriched 4-branched-2-oxazolidinones, derived from α -amino acids, have attracted a great deal of attention and now represent the most popular auxiliaries used for sequential enolization-asymmetric trapping with alkyl halides <1982AA23>. Analogous chiral templates derived from amino indanol (Equation (138)) <1996TA2939>, *exo,exo*-amino borneol (Equation (139)) <1994CC1861> or protected imidazolidinones (Equation (140)) <1995HCA1185, 1996AG(E)2708, 1996TL4565, 1998EJO1337>, phenylimino-oxazolidine auxiliaries (Equation (141)) <2002TA9> and “Quat” (Equation (142)) <1994TL2373, 1995TA671, 1998SL963, 2002TA647> or “SuperQuat” (Equation (143)) <2000TA3475> have been synthesized and tested in alkylation processes. In most cases, high levels of stereocontrol have been reached and the corresponding acids liberated by selective cleavage of the N–CO bond under mild conditions without any racemization. Excellent diastereoselectivity has been also obtained with bicyclic carbohydrate oxazolidinones derived from D-xylose (Equation (144)) <1996TA637>.

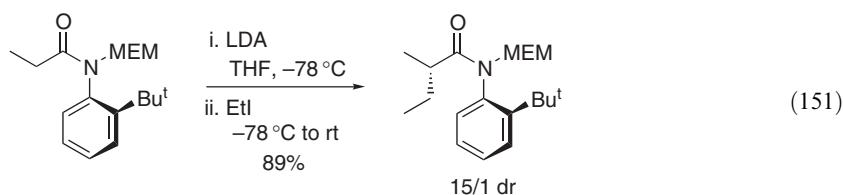


Chiral bicyclic lactams, developed by Meyers, are important examples of oxazoline type chiral inducers often used for the stereoselective formation of quaternary carbon centers by dialkylation of related amide enolates or cyanoenamine anions with organic halides [<1991T9503>](#). *Endo*-versus *exo*-attack depends on the nature and the relative position of the substituents present on the oxazoline ring. Good-to-excellent levels of stereoselectivity are observed in the formation of α,α -dialkylated adducts. After reduction or alkyl lithium addition and subsequent hydrolysis, 4,4-disubstituted cyclopentenones ([Equations \(145\) and \(146\)](#)) as well as 4,4-dialkylcyclohexenones ([Equation \(147\)](#)) are isolated in good yields [<1996JOC5712, 1997CC1, 1997JA4565, 1998JA7429, 1998JOC1619, 1997T8795>](#).



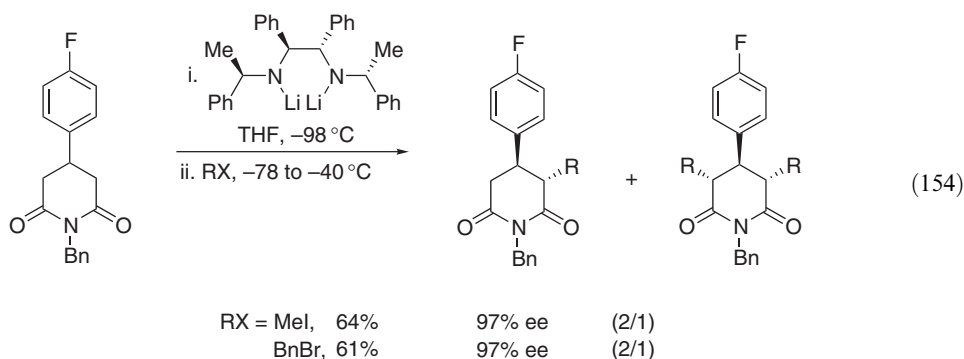
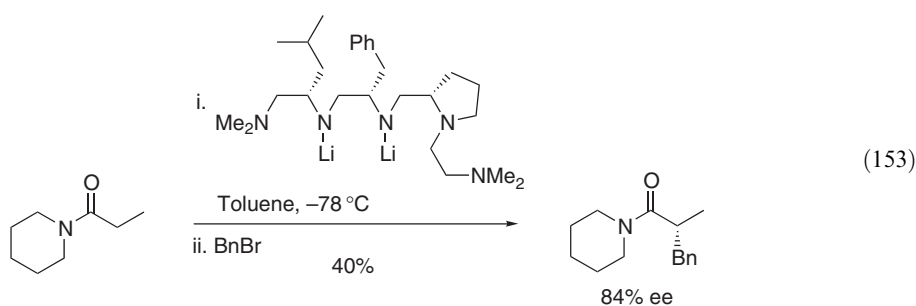
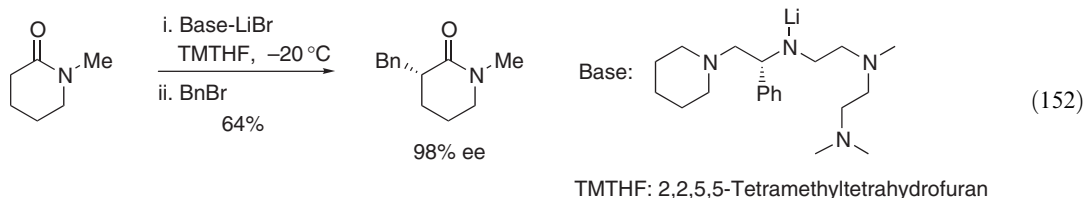
Larchevêque [<1978TL3961, 1979JOM5>](#), and later Myers used the inexpensive and readily available D-(+)-pseudoephedrine as chiral inductor for selective C—C bond formation. In the presence of lithium chloride, *N*-acyl derivatives undergo enolate alkylation with very high diastereofacial selectivities (94% to >99% de) ([Equation \(148\)](#)) [<1994JA9361, 1997JA6496>](#). A new C_2 -symmetrical ferrocenyl amine, reported by Schwink and Knochel, has been effective in the stereoselective alkylation of amide enolates with alkyl halides. Crystalline α -substituted ferrocenylamides are formed in 65–89% yields as a single diastereomer ($dr \geq 98/2$). Then, the auxiliary was easily removed by hydrolysis with 2M HCl in dioxane:H₂O at reflux ([Equation \(149\)](#)) [<1997TL3711>](#). The enantioenriched hydrazines introduced to synthesis by Enders for the asymmetric alkylation of hydrazones can also be used as chiral auxiliaries for the α -alkylation of chiral *N*-(dialkylamino)lactams. Reductive *N*—*N* bond cleavage by lithium in liquid ammonia led to 2-substituted lactams in moderate with high enantiomeric excesses (71–99% ee) ([Equation \(150\)](#)) [<1996S941>](#). Finally, an example of asymmetric alkylation controlled by a chiral auxiliary with an axis of chirality instead of stereogenic centers was reported by Simpkins. Atropisomeric amides, available from *o*-*t*-butyl aniline, were deprotonated with LDA at -78°C to generate the corresponding lithium enolates, which were treated by alkyl halides to produce the α -alkylated adducts with diastereomeric ratios up to 25:1 ([Equation \(151\)](#)) [<1996TL7607>](#).





(ii) *Introduction of chirality from chiral lithium amides*

The use of chiral lithium amide bases in deprotonation steps has largely contributed to the development of new methods for asymmetric α -alkylation of carbonyl compounds such as amides and lactams <1998JCS(P1)1439>. On this subject, Kobayashi and Koga have reported an interesting chiral base-mediated enantioselective alkylation of lactams and lactones, which proceeds through sequential proton abstraction by a nonracemic tetradentate lithium amide in the presence of LiBr and subsequent alkylation of the intermediate enolate (Equation (152)) <1998TL9723>. Recently, a chiral pentamine ligand has been developed for α -benzylation of acyclic amides (Equation (153)) <1999OL345>. Finally, an example of asymmetric desymmetrization of *meso*-imides by enantioselective deprotonation with a chiral *bis*-lithium amide has also been studied. Simpkins showed that monalkylation of 4-aryl substituted glutarimides with methyl iodide, allyl bromide, and benzyl bromide can be realized up to 97% ee (Equation (154)) <2002SL2074>.



1.04.3.2 Oxygen-stabilized Carbanions

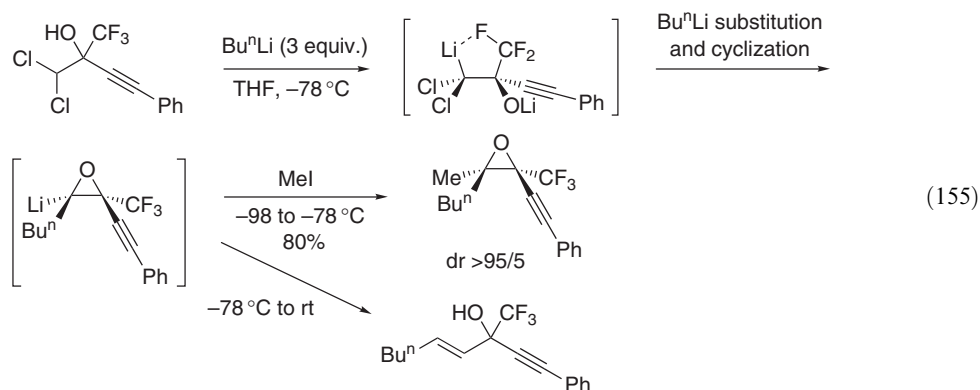
Despite the high electronegativity of the oxygen atom, generation of α -oxygenated carbanions by direct deprotonation of simple alkyl ethers at low temperature is far from being straightforward. However, the presence of other activating groups such as trifluoromethyl, allyl, propargyl, and

benzyl substituents should favor the metallation and may also stabilize the organometallic reagent generated. Alternative methods for metallation, based either on metal insertion, tin–metal exchange, carbometallation of alkenes or reduction of sulfides, sulfoxides as well as selenides have been developed. Selected examples are reported below.

1.04.3.2.1 Alkylation of nonstabilized α -oxycarbanions

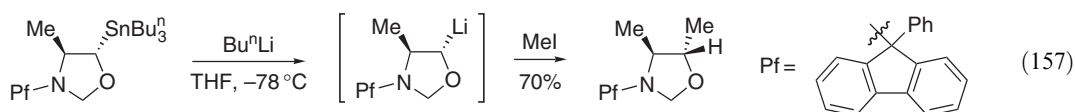
(i) Metallation by proton abstraction

Shimizu and co-workers reported the stereoselective preparation and the alkylation of lithiated epoxides derived from 2-alkynyl-3,3-dichloro-1,1,1-trifluoro-2-propanol. First, the *gem*-dichloromethyl group can be metallated at -98°C giving a β -alkoxycarbenoid which undergoes successive inter- and intramolecular substitutions of chlorine atoms by RLi and -OLi, respectively. A lithium–fluorine chelation and a substitution of chlorine by RLi from the -OLi side may explain the high level of diastereoselectivity observed. Then, the trifluoromethylithiooxirane can be quenched by allyl bromide or different alkyl iodides. Above -78°C , the carbenoid rearranges into allylic alcohols through sequential α -elimination and C–H bond insertion of the carbene (Equation (155)) <2001JA6947>. Uneyama and co-workers showed that the presence of a trifluoromethyl group on a simple oxirane promotes α -lithiation with Bu^nLi at -102°C . The enantiomerically enriched precursor was alkylated by methyl iodide in good yield and with a total retention of configuration. No trace of by-product coming from β -elimination reactions was detected (Equation (156)) <2002OL173>. For more information, the chemistry of oxiranyl anions has been successively reviewed by Satoh <1996CR3303> and Hodgson <2002S1625>.



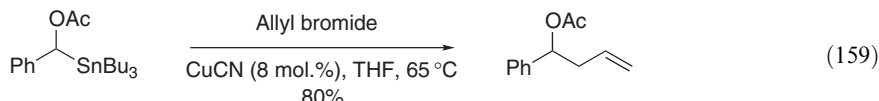
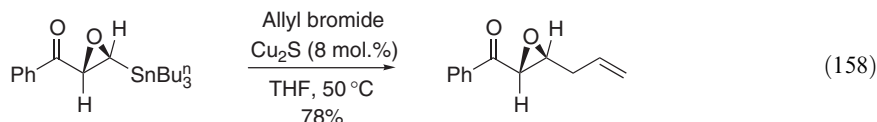
(ii) Metallation by tin–lithium exchange

Stereoselective alkylation of lithiated oxazolines has been examined by Sardina and co-workers. In the presence of Bu^nLi at -78°C , the stannyl precursor may undergo a lithium–tin exchange reaction that generates the α -alkoxy β -aminoalkylcarbanion, which can be trapped by methyl iodide in 70% yield (Equation (157)). The sequence proceeds without loss of configuration and β -elimination side reaction <2001JA2095>.



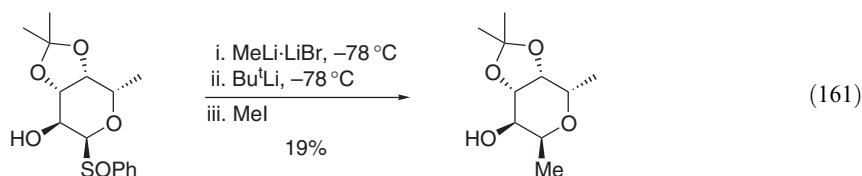
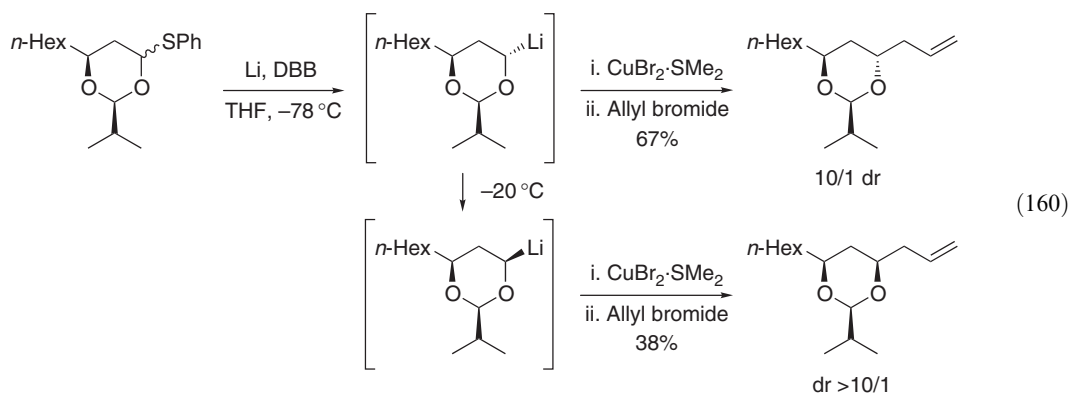
(iii) Copper(I)-catalyzed cross-coupling reactions

Falck and co-workers have shown that α -stannyl epoxides (Equation (158)) <1997SL481> and α -(acyloxy)alkylstannanes (Equation (159)) <1995JA5973, 1996JOC6492> can be coupled with allyl bromide in the presence of a catalytic amount of copper(I) salt (Cu_2S or CuCN). The reaction is totally stereoselective. Only one diastereomer of the substituted oxirane is formed in good yield.



(iv) Metallation by reduction of sulfide or by lithium–sulfoxide exchange

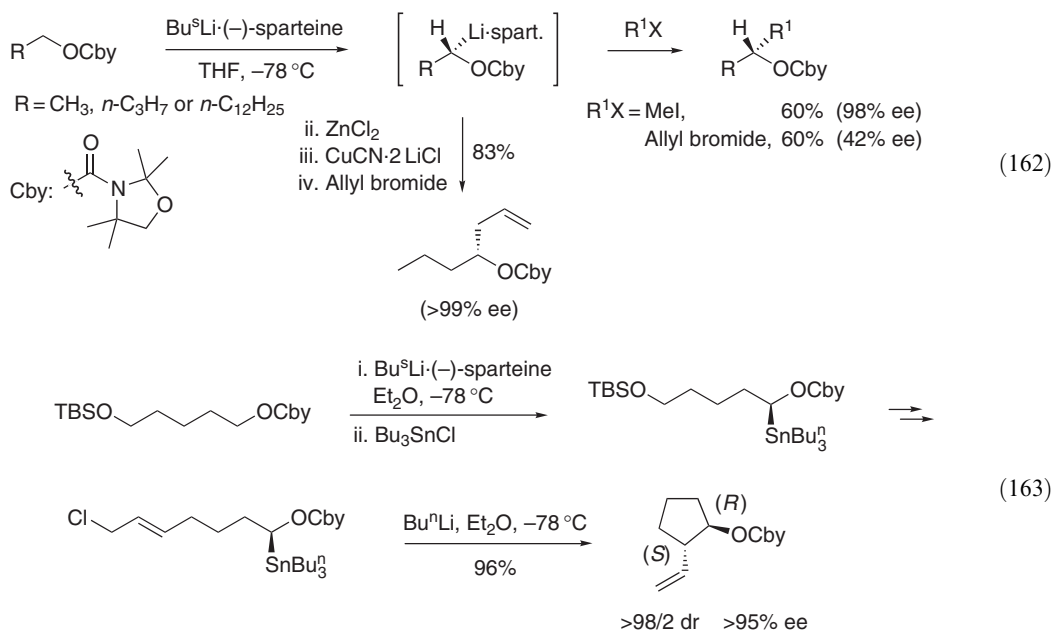
α -Alkoxy sulfides and α -alkoxy sulfoxides were also shown to be excellent precursors of α -alkoxy-lithium reagents. Reductive lithiation of 4-(phenylthio)-1,3-dioxanes by lithium di-*t*-butylbiphenylide (LiDBB) at -78°C represents a valuable method to generate anomeric carbanions with a high stereoselectivity. The alkyllithium generated takes up preferentially an axial position and may equilibrate above -20°C to the equatorial configuration (for unhindered substrates). After transmetalation with $\text{CuCN}\cdot 2\text{LiCl}$, electrophilic trapping with various electrophiles such as allyl bromide affords the desired functionalized products with retention of configuration (Equation (160)) <1999JOC6849>. Phenylsulfinyl–lithium exchange may be an alternative to the previous approach. Fernández-Mayoralas and co-workers have illustrated this reactivity by synthetic studies on glycosides derived from α -L-fucopyranose. Treatment of fucopyranosyl phenyl sulfoxide with Bu^tLi then $\text{MeLi}\cdot\text{LiBr}$ in THF at -78°C followed by methyl iodide quenching also proceeds with retention of configuration but in low yield (Equation (161)) <2001JOC1768>.



(v) Alkylation of dipole-stabilized anions

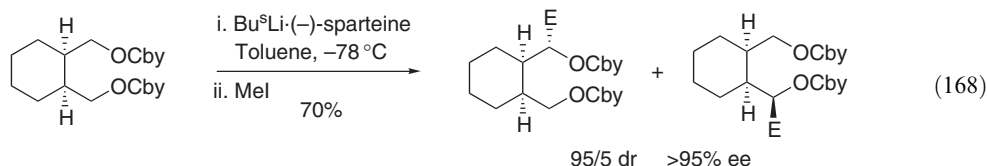
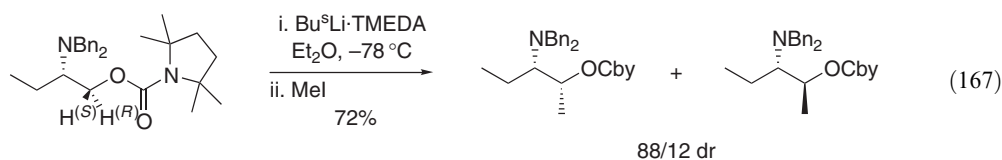
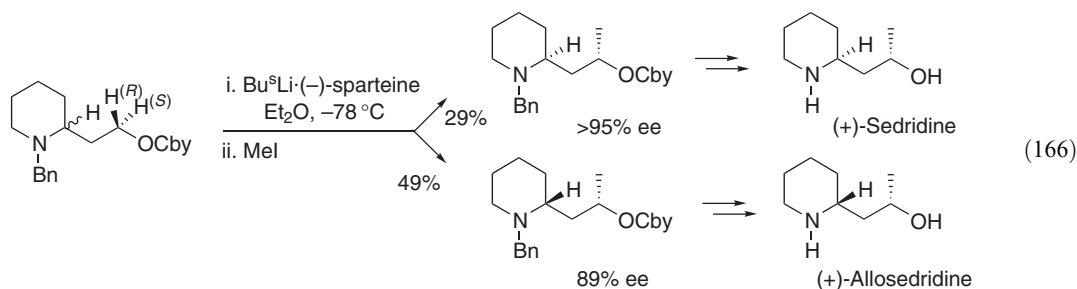
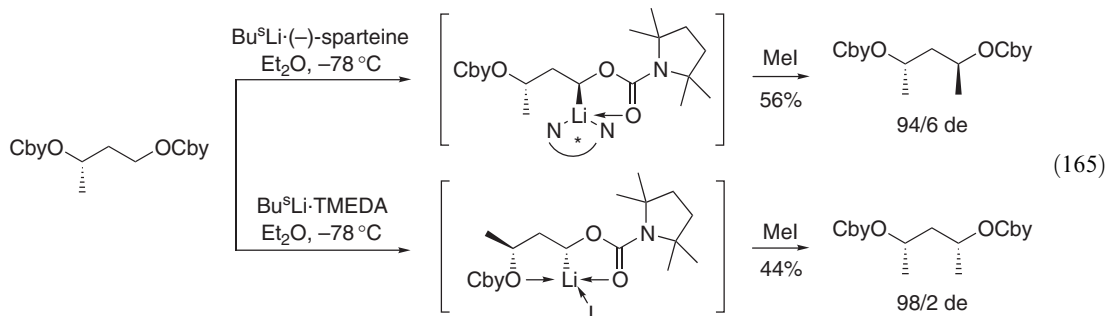
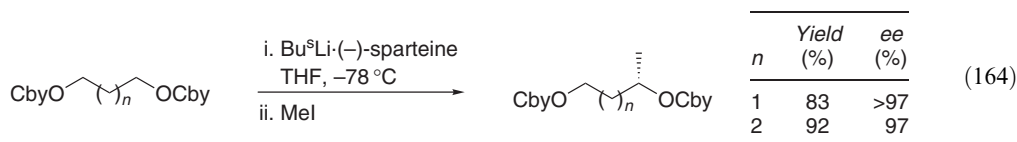
α -Lithiation of alcohols protected as esters or carbamates is highly favored first by the complexation of the organolithium base to the carbonyl group which directs the metallation and also by a dipole-stabilization of the organometallic intermediate. Intensive studies on stereoselective

deprotonation induced by an alkyllithium base/(–)-sparteine complex and subsequent alkylations have been reported by Hoppe and co-workers for the preparation of substituted nonracemic secondary alcohols. To explain the asymmetric induction, they suggested the formation of an aggregate between Bu^sLi , (–)-sparteine and the carbamate prior to the deprotonation step. The organolithium/(–)-sparteine complex generated is configurationally stable and can substitute stereospecifically various electrophiles. Mechanistic studies based on kinetic isotopic effects, NMR experiments and semi-empirical calculations have been reviewed by Hoppe and Hense <1997AG(E)2282>. The first application of this methodology concerned the enantioselective deprotonation of a carbon atom adjacent to a carbamate which derived from a primary alcohol. The latter gives, upon treatment with $\text{Bu}^s\text{Li}/(–)\text{-sparteine}$ in THF at -78°C , the α -oxygenated organolithium complex (measurements of D/H kinetic isotopic effect revealed a preference for the *pro-S*-proton abstraction) which can be trapped by different electrophiles such as methyl iodide <1990AG(E)1422, 1992S1216, 1997AG(E)2282>. High enantiomeric excesses up to 98% have been reached but a partial racemization involving single-electron transfer may explain the low ee observed with allyl bromide. However, transmetallation successively with ZnCl_2 and $\text{CuCN}\cdot 2\text{LiCl}$ liberates the mixed Cu–Zn, which can be allylated with an overall retention of configuration. Several allyl bromides have been tested by Taylor and co-workers (Equation (162)) <2002OL119>. Intramolecular $\text{S}_{\text{N}}2'$ substitution of allyl chloride by enantiomerically enriched α -oxy-organolithiums, generated *in situ* by Sn–Li exchange, furnishes disubstituted cyclopentanols as a single diastereomer (dr > 98/2) and enantiomer (>95% ee) (Equation (163)) <2002OL2193>.

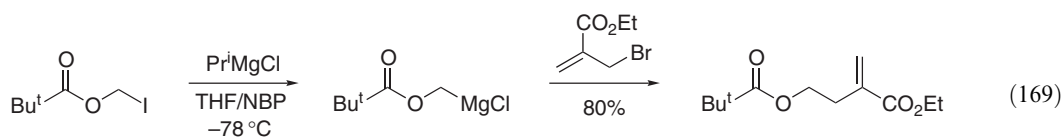


A second carbamoyloxy group at the γ - or δ -position may interfere with the aggregate organization, for instance by displacement of the (–)-sparteine ligand, and consequently should influence the asymmetric induction. The enantioselective deprotonation of 1,3- as well as 1,4-dicarbamates and subsequent alkylations with methyl iodide still gave the enantioenriched adducts up to 97% ee. This result shows that the extra carbamoyloxy group does not modify the selectivity (Equation (164)) <1992TL5327>. Moreover, the presence of a stereogenic center in the γ -position promotes a diastereoselective lithiation by the $\text{Bu}^s\text{Li}/\text{TMEDA}$ complex whereas deprotonation carried out in the presence of (–)-sparteine affords the opposite diastereoisomer. With TMEDA, the selectivity is controlled by a double chelation of the carbamoyloxy groups (Equation (165)) <1992TL5327>. A very similar explanation was suggested for the excellent diastereomeric ratio observed with the acetonide of (S)-3,4-dihydroxybutyl dicarbamate without additional diamine <1995SL978>. Stereoselective lithiation of 2- and 3-aminoalkyl carbamates by Bu^sLi with or without diamine has been also investigated. Only selected examples will be presented here. A strong preference for the abstraction of the *pro-(S)* hydrogen was observed with 3-(piperidine-2-yl)ethyl carbamate. Starting from the racemic compound, a mixture of two diastereoisomers was obtained and converted into (+)-sedridine and (+)-allosedridine (Equation (166)) <1997AG(E)2282>. In addition, removal of *pro-(R)* hydrogen is much favored with

(*R*)-2-aminoalkyl carbamates. Without additive, a kinetic deprotonation was suggested to explain this selectivity. In the presence of (–)-sparteine, the substrate remains unchanged because of a mismatched-pair situation (Equation (167)) <1997AG(E)2282>. Hoppe's methodology was then applied to the desymmetrization of *meso*-dicarbamates by differentiation between the two enantiotopic branches and a preferential abstraction of *pro*-(*S*) protons for each pair of diastereotopic methylene protons (Equation (168)) <1999MI1905>.



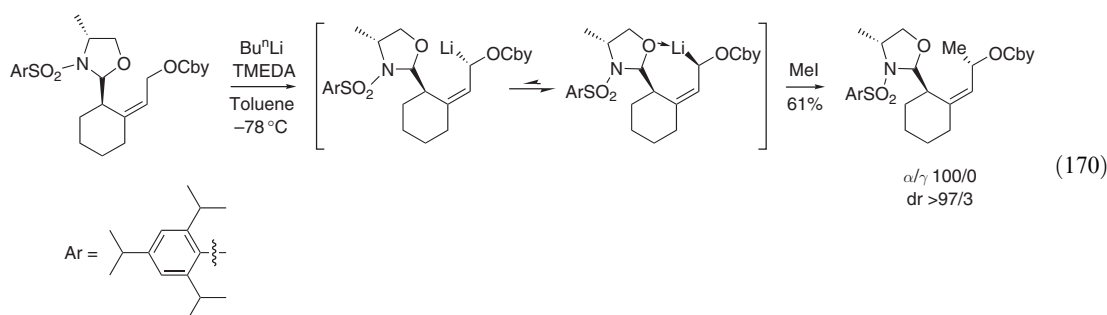
Allylation of magnesium carbenoids bearing an ester function was reported by Knochel <1999SL1820>. Iodomethyl pivalate treated with Pr^iMgCl in THF/*N*-butyl pyrrolidinone (NBP) at -78°C undergoes an iodine–magnesium exchange and leads to the corresponding magnesium carbenoid, which can be trapped by ethyl (2-bromomethyl)acrylate. The allylated compound was isolated in 80% yield (Equation (169)).



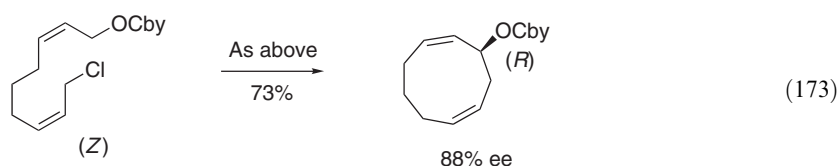
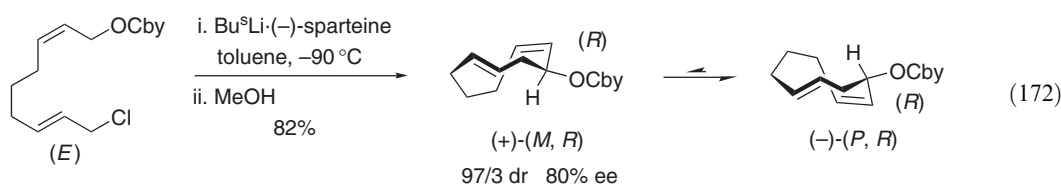
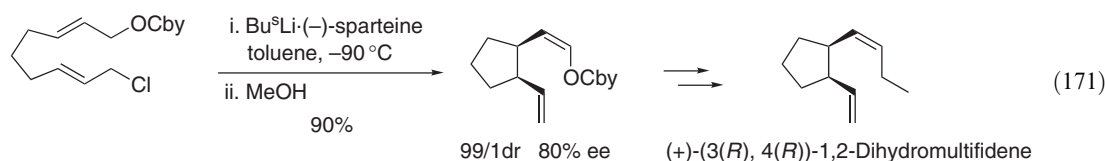
NBP: *N*-butyl pyrrolidinone

1.04.3.2.2 α -Alkylation of 1-oxy-substituted allyllithiums

All the reports recently published on this topic were focused on the reactivity of enantioenriched lithiated 2-alkenyl carbamates [<1997AG\(E\)2282, 2002AG\(E\)716>](#). Asymmetric deprotonation with allyllithium bases can be induced by a chiral ligand such as (–)-sparteine or by a chiral auxiliary already present on the substrate. The organolithium intermediate shows a limited configurational stability even at low temperature. One epimer can be enriched by dynamic kinetic resolution, caused by the preferential crystallization of one epimeric lithium complex or by a rapid electrophilic trapping. δ -(3-Arenesulfonyl-1,3-oxazolidine)-substituted allyl carbamates were deprotonated with $\text{Bu}^n\text{Li}/\text{TMEDA}$ complex at -78°C and treated with methyl iodide to give exclusively α -adducts as a single diastereoisomer. This result may be explained by a complete epimerization of the allyllithium to the most thermodynamically favored intermediate where the lithium chelates the chiral auxiliary. Therefore, a substitution with inversion of configuration may justify the stereochemistry observed ([Equation \(170\)](#)) [<2000SL950>](#).



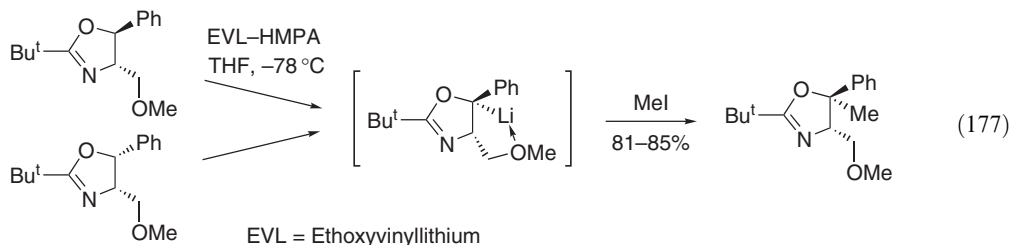
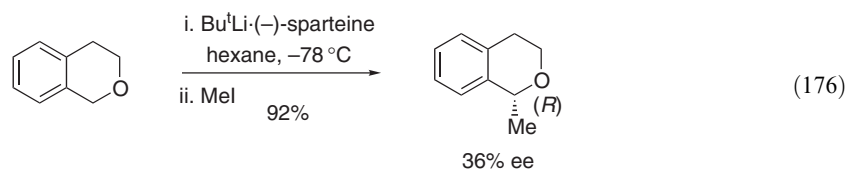
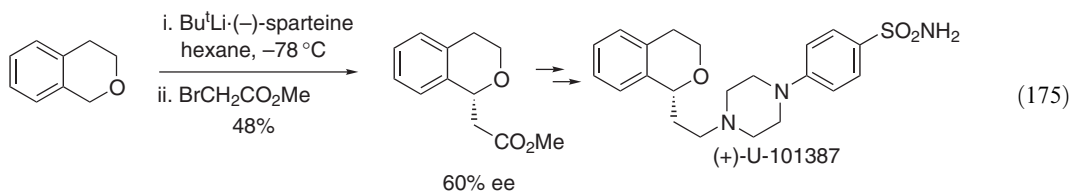
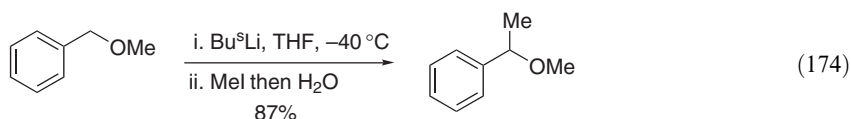
This chemistry was then applied to intramolecular processes. The only examples reported in this field concern the cyclization of lithiated 9-chloro-2,7-nonadienyl carbamates. A (2(*E*),7(*E*)) arrangement of double bonds gave the expected disubstituted cyclopentane as opposed to a (2(*Z*),7(*Z*)) or (2(*Z*),7(*E*)) disposition which led to nine-membered carbocycles. Enantioselective deprotonation of 9-chloro-2,7-nonadienyl carbamates with $\text{Bu}^s\text{Li}/(-)\text{-sparteine}$ proceeds with a preference for the *pro*-(*S*) proton. The (2(*Z*),7(*Z*))-isomer cyclized to give a 1,2-dialkenyl-substituted cyclopentane with a regioselective γ,γ' -bond formation. An *anti*- $\text{S}_{\text{N}}'-\text{S}_{\text{E}}'$ mechanism has been proposed to explain the diastereoselectivity and the reaction was used for the synthesis of (+)-(3(*R*),4(*R*))-1,2-dihydromultifidene ([Equation \(171\)](#)) [<1999AG\(E\)546, 2001JOC2842>](#). In addition, the (2(*Z*),7(*Z*))- and (2(*Z*),7(*E*))-isomers undergo intramolecular α,α' -coupling of both allyl moieties with inversion of configuration. This method provides a straightforward route to enantiomerically enriched functionalized 1,5-cyclononadienes ([Equations \(172\) and \(173\)](#)) [<2000AG\(E\)2105, 2000OL2415>](#).



1.04.3.2.3 α -Alkylation of 1-oxy-substituted benzyllithiums

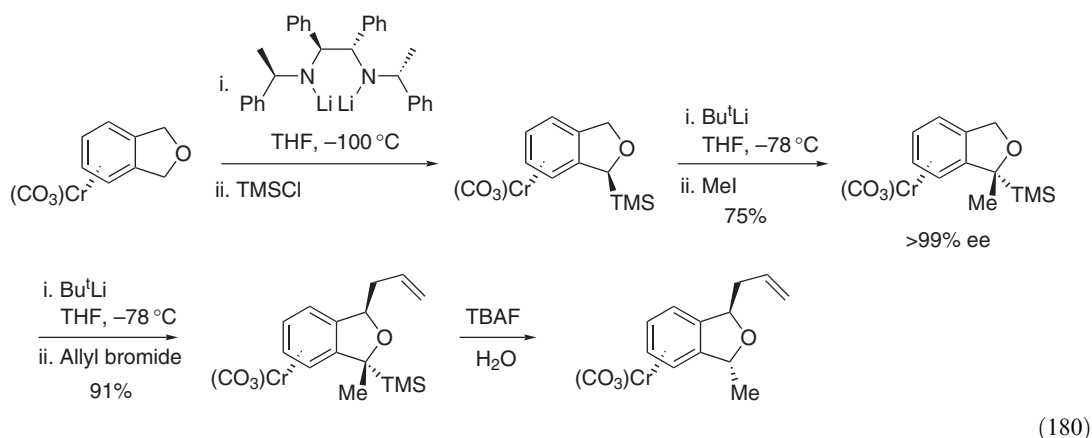
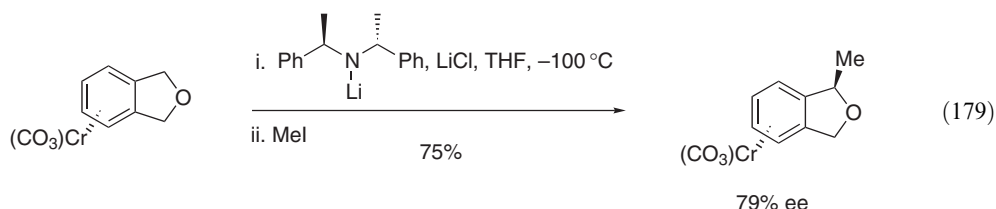
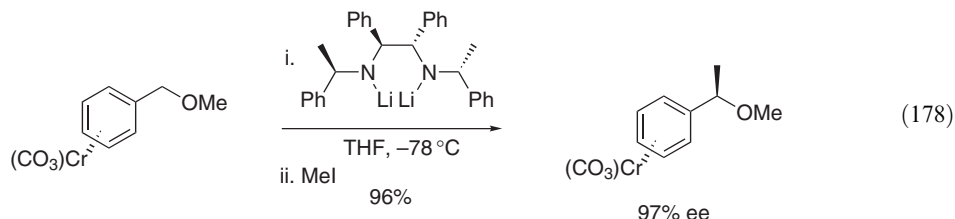
(i) Lithiation by proton abstraction

Lithiation of arylmethyl alkyl ethers has received a particular attention. One protocol, first reported by Yeh, involved a deprotonation of benzyl methyl ether with Bu^nLi /TMEDA in hexane followed by substitution of Bu^nBr <1981JCS(P1)1652>. Several experiments carried out in THF underline the relative instability of these metallic species. Indeed, due to their carbenoid properties, α -lithiated alkyl benzyl ethers may undergo β -elimination or 1,2-Wittig rearrangement. Azzena and co-workers found that benzyl methyl ether and isopropyl benzyl ether can be deprotonated either with Bu^nLi or Bu^sLi in THF at -40 or -80°C , respectively. Then, the resulting carbanion is sufficiently stable to react with alkyl iodides and alkyl bromides in good yields (Equation (174)) <1998T12389>. An example of the enantioselective alkylation of isochroman and phthalan was published by Nakai and co-workers. Asymmetric lithiation with $\text{Bu}^t\text{Li}/(-)$ -sparteine complex at -78°C gave the chiral lithiated species which undergoes an $\text{S}_{\text{E}}2$ substitution of different alkyl halides. Poor-to-moderate enantiomeric excesses have been measured. The origin of this enantioselectivity is the result of a dynamic thermodynamic resolution mechanism where the epimerization is slower than the substitution. However, the reactivity of the electrophile influences the enantiomeric excess and may explain the difference between methyl bromoacetate (Equation (175)) and benzyl bromide as well as other halides (Equation (176)) <2000TL6121>. Shimano and Meyers have shown that metallation of *trans*- and *cis*-oxazolines, prepared from *t*-butyl cyanide and ((*S,S*)-2-amino-3-phenylpropane-1,3-diol, with α -ethoxyvinyl lithium-HMPA complex (EVL-HMPA) results in the formation of α -alkoxybenzyllithium exclusively. The latter was quenched with methyl iodide with retention of configuration (Equation (177)) <1997TL5415>.



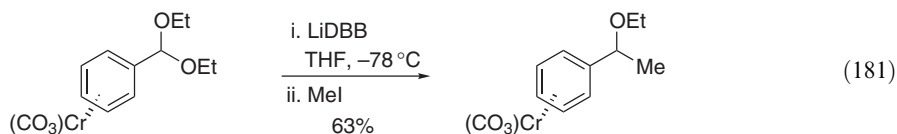
(Alkyl benzyl ether)tricarbonylchromium(0) complexes have been reported to undergo facile deprotonation at the benzylic position <1986JCS(P1)1581>. Sequential chiral lithium diamide-mediated enantioselective lithiation-electrophilic quenching was examined by Gibson and co-workers <2000CC989>. Methylation of methyl and benzyl benzyl ethers proceeds in 89% and 96% yields with high enantiomeric excesses (97% and >99%), respectively (Equation (178)) <1996CC839>. A similar experiment carried out on the tricarbonyl(η^6 -arene)chromium complex of

phthalan furnished the α -methylated product in 75% yield and 79% ee (Equation (179)) <1996SL317>. An enantioselective benzylic deprotonation/silylation sequence generated the nonracemic silylated intermediate, which was alkylated regioselectively α to the TMS group and diastereoselectively on the *endo*-face. Then, a second substituent was selectively introduced at the benzylic position leading to the *trans*-1,3-dialkylated dihydroisobenzofuran (Equation (180)) <2002AG(E)2525>. Synthesis of achiral *cis*-configured compounds has been already reported by Davies <1989JOM81>.



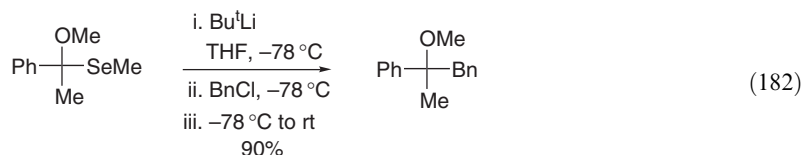
(ii) Lithiation by reductive cleavage

Siwek and Green have shown that (arene)tricarbonylchromium diethyl acetal in the presence of LiDBB at -78°C undergoes reductive cleavage of the benzylic C—O bond. Reaction of the benzyllithium intermediate with methyl iodide afforded the functionalized chromium tricarbonyl-benzyl ether in 63% yield (Equation (181)) <1996SL560>.



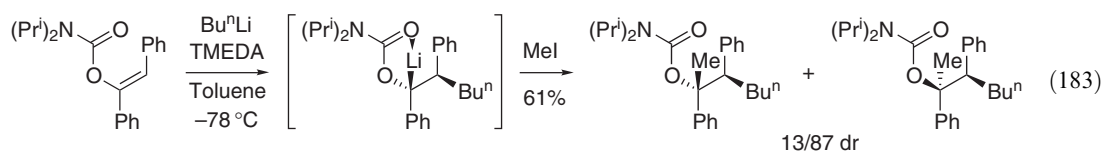
(iii) Lithium–selenium exchange

Krief and Bousbaa reported the preparation of α -methoxy-benzyllithiums from α -methoxyalkyl selenides through a Li—Se exchange reaction. The C—Se bond cleavage, promoted by addition of Bu^tLi in THF at -78°C , provides the α -methoxy-organolithium which reacts efficiently with various alkyl halides including benzyl chloride, allyl bromide, *n*-pentyl and *s*-butyl bromide (Equation (182)) <1997TL6289>.



(iv) *Lithiation by intermolecular carbolithiation*

Intermolecular *syn*-addition of alkylolithiums to 1-aryl-1-alkenyl *N,N*-diisopropylcarbamates forms secondary α -carbamoyloxy benzylolithiums stabilized by chelation. This intermediate can be trapped by various electrophiles. To illustrate this reactivity, Hoppe and co-workers reported the carbolithiation of (*Z*)-stilbene carbamate with BuⁿLi/TMEDA complex followed by reaction with methyl iodide, occurring with inversion of configuration. The expected adduct was isolated in 61% yield. However, the organolithium/diamine complex acts as a base and deprotonates the (*E*)-diastereomer instead of adding to the double bond <2002SL381>. The vinyl carbenoid generated undergoes β -elimination and liberates the diphenylethyne (Equation (183)).



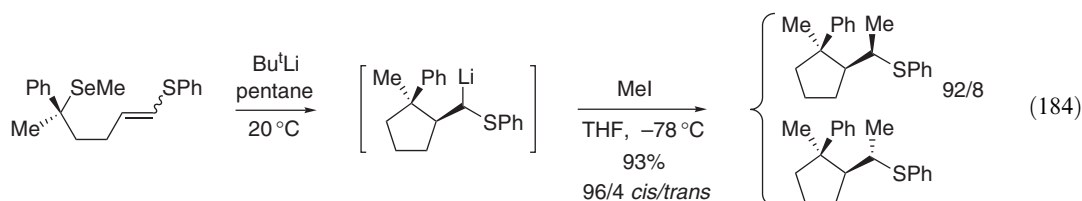
1.04.3.3 Sulfur-stabilized Carbanions

The chemistry of organosulfur compounds as synthetic intermediates is now well established in organic synthesis. These compounds have been used in numerous important organic transformations and among these, great attention has been devoted to α -metallation of sulfur-containing functional groups, which can stabilize the adjacent carbanion by taking advantage of the polarizability of the sulfur atom. The transient metallated species showed a good reactivity toward a wide range of electrophiles, particularly alkyl halides.

1.04.3.3.1 Alkylation of nonstabilized α -thiocarbanions

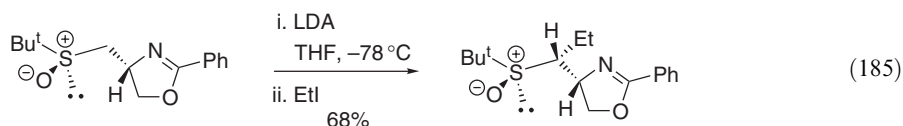
(i) *Alkylation of α -lithio sulfides—carbolithiation of vinyl sulfides*

Krief and co-workers reported the carbocyclization of benzylolithium intermediates across the activated double bond of a vinyl sulfide. The 6-methylseleno-6-phenyl-1-phenylthio-1-heptene is cleanly metallated with Bu^tLi at room temperature by C—Se bond cleavage. Readily, the resulting benzyl-lithium derivative undergoes a stereoselective cyclization and gives the *cis*-1,2-dialkyl-1-phenyl cyclopentane intermediate. The α -thioalkyllithium moiety can be alkylated with methyl iodide leading preferently to the *cis*- β -adduct. A higher selectivity is obtained when the alkylation is carried out after transmetallation with copper(I) salts (Equation (184)) <1995TL7917>.

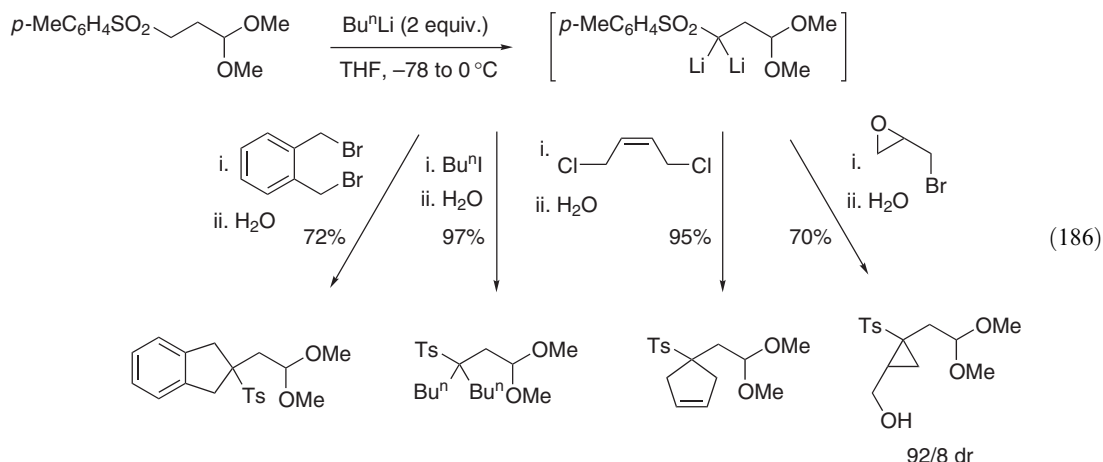


(ii) Alkylation of α -lithio sulfoxides

α -Sulfinyl carbanions exhibit an interesting configurational stability that can be rationalized by a planar chelate structure. The stereochemistry of the alkylation is dependent on the choice of the electrophile: electrophiles that chelate the lithium atom are delivered *syn* to the S—O bond and the others in an *anti*-fashion <2002AG(E)716>. Stammeler and co-workers described the selective lithiation of 4-(*t*-butylsulfinylmethyl)-2-phenyl-2-oxazoline at the carbon center adjacent to the sulfinyl group, directed by the oxazoline and the sulfinyl moieties. Electrophilic trapping with alkyl halides occurs in good yield and with high diastereoselectivity depending on the steric hindrance of the alkylating reagent (Equation (185)) <1997LA1013>.

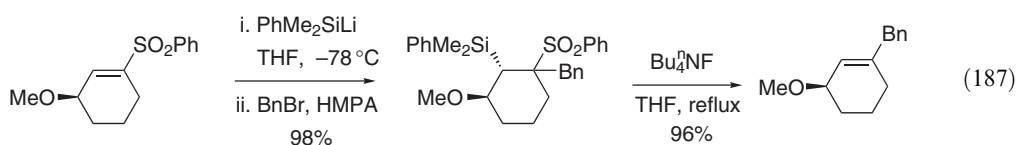
(iii) Alkylation of α -lithio sulfones—generation and reactivity of α,α -dilithio sulfones

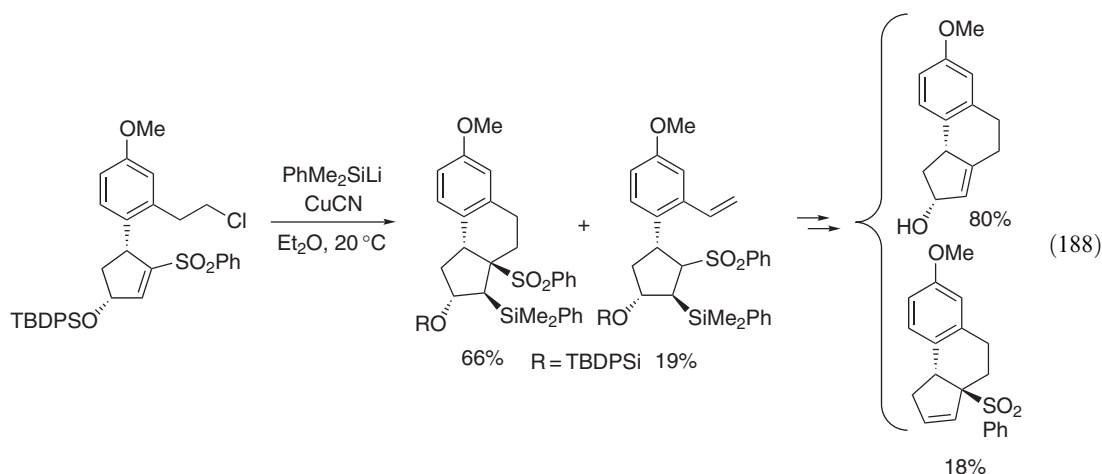
The synthesis of *gem*-dilithio sulfones by direct proton abstraction with a lithiated base has been reported by Bonete and Nájera. The dianion is successfully generated by treatment with 2 equiv. of Bu^nLi in THF between -78°C and 0°C . The latter reacts with mono- and dialkyl halides to give the dialkylated products in high yields (Equation (186)) <1996T4111>.



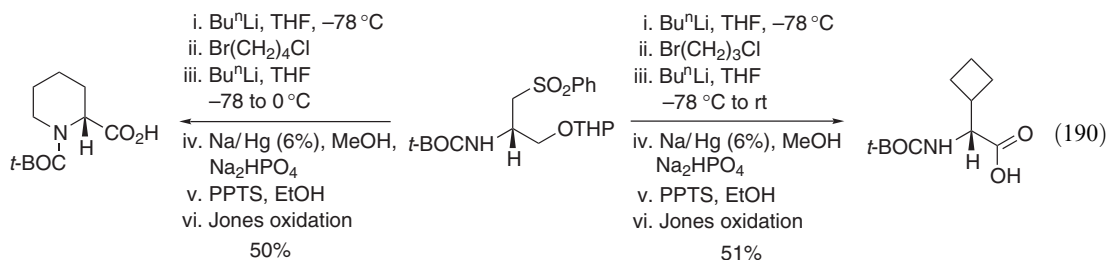
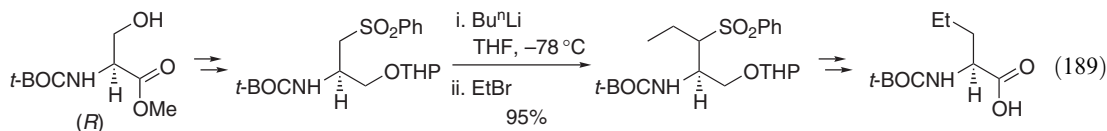
(iv) Conjugate addition to vinyl sulfones

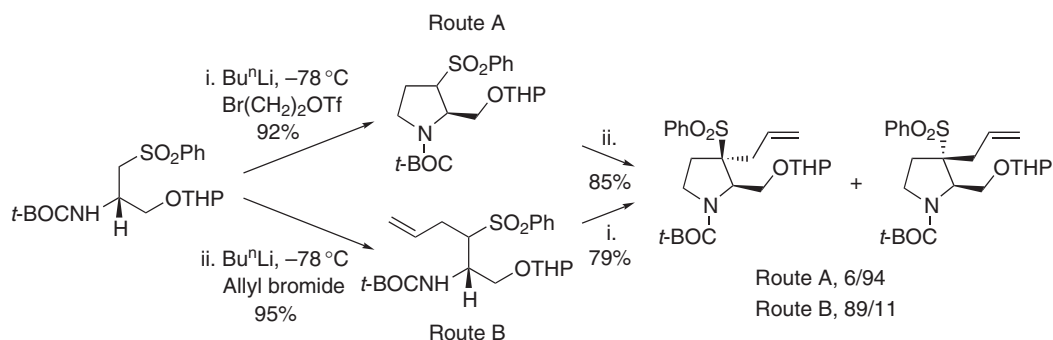
Alkenyl sulfones are renowned to be excellent acceptors for conjugate addition reactions. For instance, Fuchs and co-workers achieved the addition of phenyldimethylsilyllithium or the related cyanocuprates to vinyl sulfones. The Michael addition is followed by an intermolecular electrophilic trapping of the α -sulfonyl anion either with allyl or benzyl halides. In this case, the α -alkylated β -silyl sulfone when treated with fluoride anion undergoes a 1,2-elimination of fluorosilane and phenylsulfinate providing the trisubstituted olefin (Equation (187)). An example of intramolecular alkylation with an organic chloride was also presented, giving a tricyclic sulfone derivative in 66% yield (Equation (188)) <1995TL4013>.



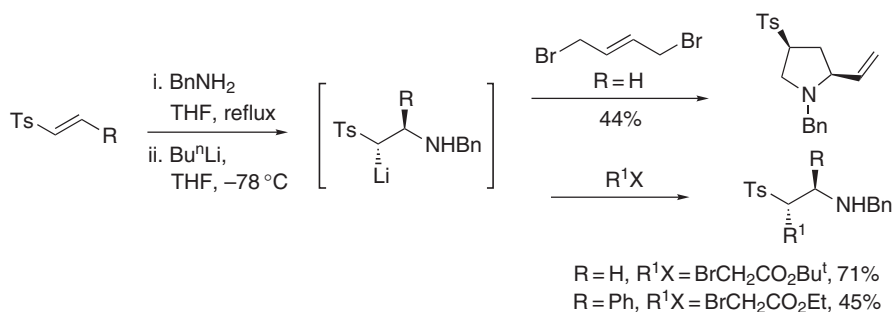


In pioneering research, Eisch and Galle have reported a few examples of lithiation of β -aminoalkyl sulfones followed by substitution of methyl iodide [<1980JOC4534>](#). Sasaki and co-workers have taken advantage of this transformation to devise a new methodology for the synthesis of enantiomerically enriched nonproteinogenic α -amino acids from L-serine. The THP derivative of (2(*R*))-2-BOC-amino-3-phenylsulfonyl-1-propanol is available in five steps from *N*-BOC-L-serine methyl ester. Alkylation of this β -aminoalkyl sulfone involved monolithiation of the methylene group adjacent to the sulfonyl moiety with Bu^nLi and reaction with various electrophiles [<1987TL6069>](#). The α -lithio β -aminoalkyl intermediate can also act as a 1,3-dinucleophile, which is able to perform two successive substitutions with a dielectrophile such as 1,*n*-dihalides ($2 \leq n \leq 5$). α,α -Dialkylated compounds may also be prepared from *gem*-dilithio- β -aminoalkyl derivatives. Further applications to different types of cyclic α -amino acids, cycloalkylglycines, and *N*-heterocyclic α -amino acids synthesis have been published [<1994TL237, 1997JOC765>](#). Simple addition of nitrogen nucleophiles across the double bond of vinyl sulfones generates β -amino sulfones, readily alkylated at the α -position ([Equations \(189\)–\(191\)](#)). Nájera and co-workers have reported the 1,4-addition of benzylamine to *p*-tolyl vinyl sulfone and β -tosyl styrene ([Equation \(192\)](#)). Functionalization α to the sulfone was performed under usual conditions. This methodology has been applied to the preparation of nitrogen-containing heterocycles and, for example, to the synthesis of benzoazepine as precursor of capsazepine ([Equation \(193\)](#)) [<1997T4791>](#). An extension of these studies to the enantioselective synthesis of acyclic α -substituted β -amino sulfones has been investigated by Enders and co-workers. Yb(OTf)₃-Catalyzed conjugate addition of SAMP to (*E*)-alkenyl sulfones generates the corresponding Michael adducts with introduction of a stereogenic center at the γ -carbon. A moderate diastereoselectivity (de: 30–61%) was observed. After separation of the diastereomers and removal of the chiral auxiliary by reductive cleavage, the major diastereomer yields the (*R*)- β -aminoalkyl sulfone with a high enantiomeric excess ($\geq 96\%$ ee) [<1999AG\(E\)195>](#). Monolithiation with LDA/TMEDA generates the α -sulfonyl carbanion which can react with a range of electrophiles. The ((*R*),(*R*))-product was isolated in good-to-high diastereomeric excesses (dr: 64–97%) and without any racemization ([Equation \(194\)](#)) [<1999SL741>](#).

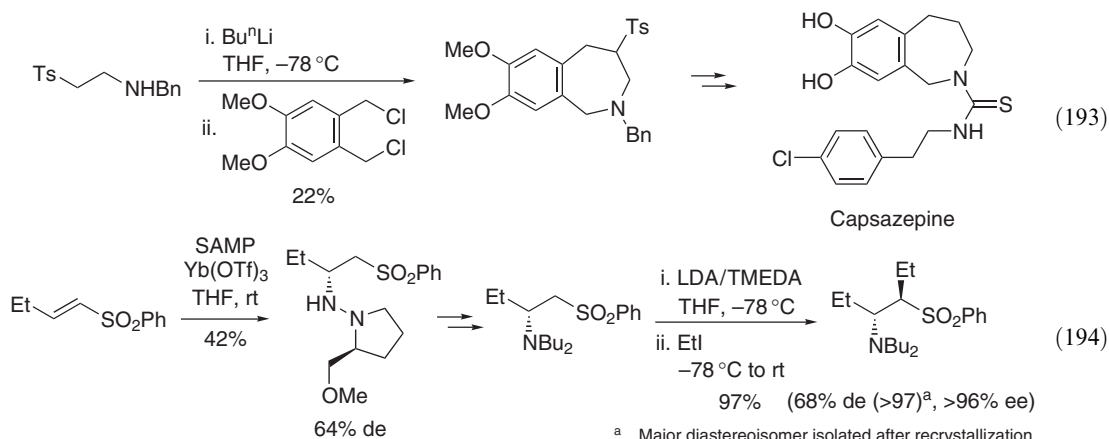




(191)



(192)

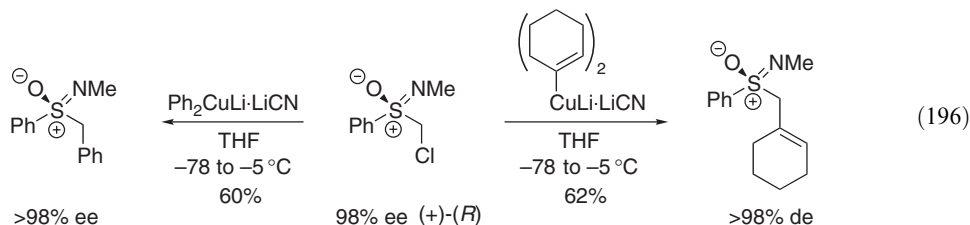
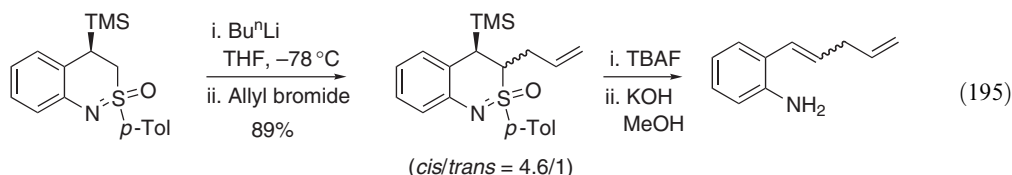


(193)

(194)

(v) α -Alkylation of sulfoximines

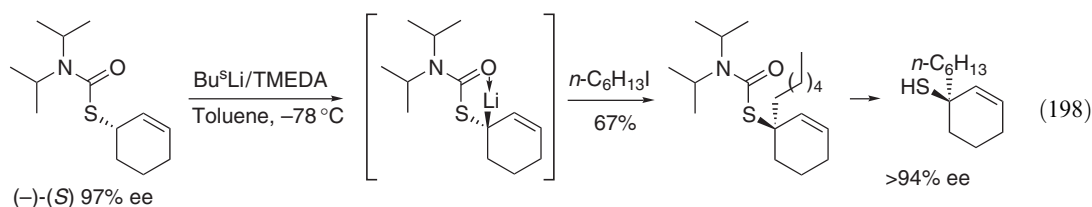
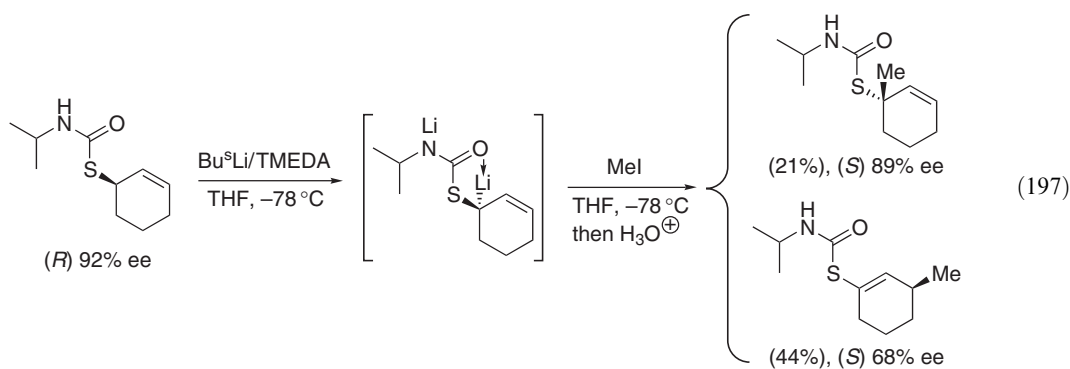
The functionalization of sulfoximine derivatives at the adjacent position has been realized either by metallation with Bu^nLi and treatment with different alkyl halides or by substitution of related α -chlorosulfoximines with alkyl metals. Therefore, the reactive center can behave as a nucleophile or an electrophile. Both aspects are illustrated by the following studies. Harmata and co-workers reported the sequential α -deprotonation of a β -silylated benzothiazine and its subsequent alkylation. When methyl iodide and MEMCl are used as electrophiles, excellent stereocontrol is observed in favor of the *cis*-isomer (25:1 and 37:1 mixture of diastereomers, respectively) (Equation (195)) <1998T9995> but moderate selectivities are obtained with other organohalides. Upon treatment with TBAF and after basic hydrolysis, these alkylated β -silylbenzothiazines can be converted into 2-alkenylanilines. Boßhammer and Gais have shown that alkenyl- and arylcuprates can substitute chiral nonracemic (+)-(*R*)-*S*-(chloromethyl)-*N*-methyl-*S*-phenylsulfoximine and give rise to enantiomerically enriched allylic and benzylic sulfoximines (Equation (196)) <1998SL99>.



1.04.3.3.2 α -Alkylation of 1-thiosubstituted allyllithiums and related compounds

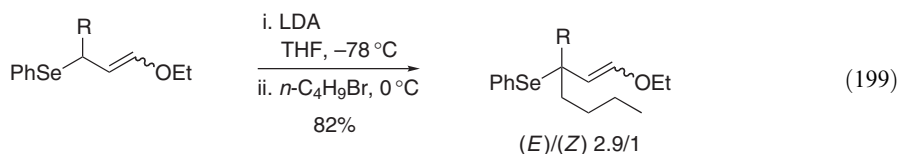
(i) Alkylation of *S*-allylthiocarbamates

Despite all the studies on the configurational stability of chiral α -heteroalkyllithium derivatives, only a few of them concern the behavior of α -thioallyllithiums. In a seminal work, Hoppe and co-workers have shown that the configurational stability of enantioenriched α -thioallyllithiums deriving from *S*-allylthiocarbamates is highly dependent on the solvent and the temperature. The organodilithiated species, obtained by deprotonation of (*R*),*S*-(2-cyclohexenyl)*N*-isopropylthiocarbamate, readily racemizes in toluene and Et₂O at -78°C , in contrast to THF, where the organolithium is configurationally stable. Indeed, under these conditions, the ion-pair separation is strongly disfavored. The main disadvantage of this reaction is the poor regioselectivity observed in the alkylation step caused by the competing α - versus γ -substitution of methyl iodide which occurs with inversion of configuration (Equation (197)) <1999OL2081>. Similar studies carried out on *N,N*-diisopropyl monothiocarbamates provide α -alkylated products with complete control of the regioselectivity and a total inversion of configuration. Upon treatment with LAH/ZnCl₂, highly enantioenriched tertiary cyclohexylthiols were isolated in good yield and without modification of the optical purity (Equation (198)) <2002OL4217>.



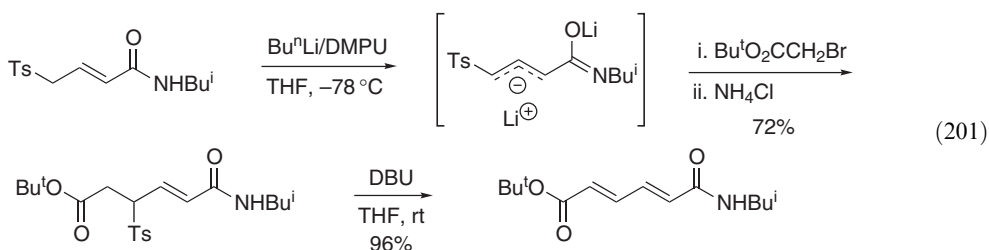
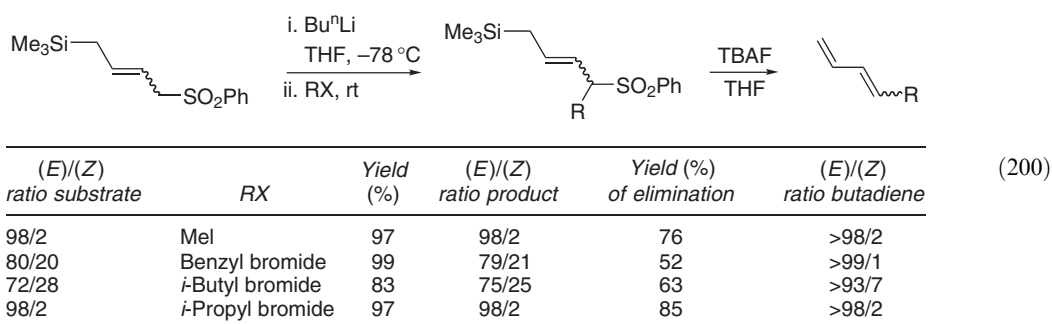
(ii) Alkylation of allylseleniums

In 1999, Nishida and Sonada reported the deprotonation of 1-alkoxy-3-phenylseleno-1-alkenes with LDA followed by a regioselective alkylation with organohalides. Stabilization of the lithium anion intermediate by the phenylselenyl group may explain the exclusive α -attack. Furthermore, the presence of (*Z*)-enol ethers in the reaction mixture may result in a rapid isomerization of the allyllithium and a stabilization by chelation of the alkoxy moiety by the metal (Equation (199)) <1999SL611>.



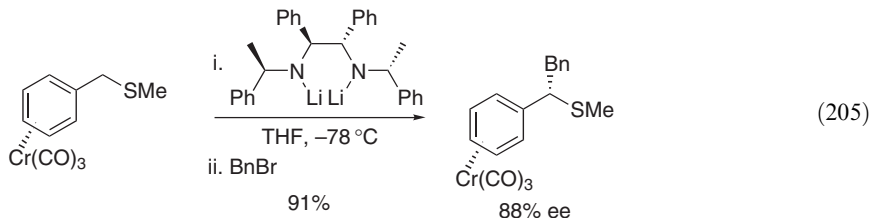
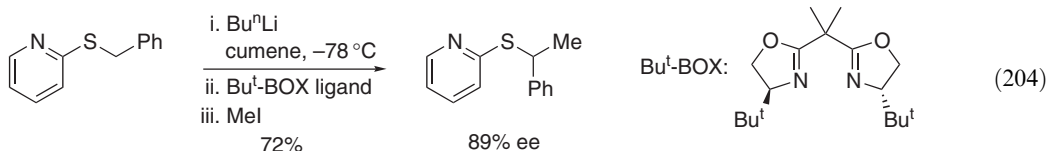
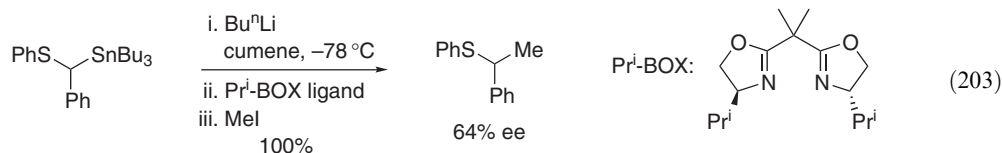
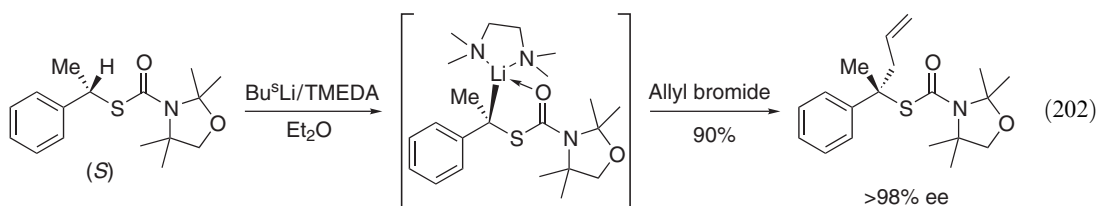
(iii) Alkylation of allyl sulfones

Allyl sulfonyl anions obtained by lithiation of allylic sulfones undergo alkylation exclusively at the α -position <1999CR665>. For example, Shechter and co-workers have reported that (*E*)- and (*Z*)-silylsulfonylbutenes can easily be metallated by Bu^nLi at -78°C in THF. The lithiated intermediate reacts efficiently with different alkyl halides and leads preferentially to the formation of α -products in high yield with almost complete retention of configuration of the double bond. A second alkylation can be carried out under similar condition. These compounds are considered as valuable synthetic equivalents of the 1-(1,3-butadienyl) anion and the 1-(1,3-butadienyl) dianion. Indeed, the alkylated silylsulfonylbutenes when treated with fluoride liberate the corresponding substituted conjugated dienes (Equation (200)) <1998JOC4181, 1998JOC4193>. As reported by Caturla and Nájera, the dianion of (*E*)-*N*-isobutyl-4-tosyl-2-butenamide undergoes exclusive γ -alkylation upon addition of benzyl bromide or *t*-butyl bromoacetate. The regiospecific and stereoselective attack affords to γ -substituted (*E*)-*N*-isobutyl-4-tosyl-2-butenamides in high yields. Under basic conditions, the elimination of the tosyl group allowed the stereoselective synthesis of (2(*E*),4(*E*))-dienamides (Equation (201)) <1996TL4787>. In other studies, Caturla and Nájera showed that the reaction of methyl (*E*)-4-tosyl-2-butenate with sodium hydride (2 equiv.) and various mono- or dihalides produces a mixture of γ,γ - and α,α - or α,γ - and γ,γ -dialkylated products <1996T15243>.



1.04.3.3 α -Alkylation of 1-thiosubstituted benzylolithiums

As reported by Hoppe and co-workers, the enantioenriched tertiary α -thio benzylolithium derivative, obtained by deprotonation of (*S*)-*S*-1-phenylethyl thiocarbamate with $\text{Bu}^s\text{Li}/\text{TMEDA}$, exhibits a remarkable configurational stability at -70°C , whereas at 0°C , decomposition competes with racemization. The substitution of ethyl and hexyl iodide as well as allyl and benzyl bromide is presumed to proceed with inversion of configuration ($>98\%$ ee) (Equation (202)) <1997AG(E)2784, 2001MI423>. In contrast, the secondary α -lithio benzyl phenyl sulfide is configurationally labile at low temperature. In a recent example, Toru and co-workers reported the asymmetric alkylation of the lithiated benzyl phenyl sulfide, formed by Sn-Li exchange, with alkyl halides in cumene at -78°C and in the presence of a bis(oxazoline) ligand (Equation (203)). The influence of the nature of the electrophile on the enantioselectivity values suggests that a dynamic kinetic resolution is operating here. The related α -lithio benzyl 2-pyridyl sulfide intermediate also undergoes electrophilic substitution with a higher enantiomeric excess. The reaction proceeds through a dynamic resolution under thermodynamic conditions (Equation (204)) <2000JA11340>. In 1997, Gibson and co-workers reported the asymmetric alkylation of tricarbonylchromium(0) complexes of benzene sulfide. Deprotonation with a chiral lithium diamide base generates the enantioenriched α -sulfenyl carbanion which can be quenched with various alkyl halides. By increasing the steric bulk of the sulfide substituent, the enantiomeric excess drops dramatically. However, reaction with methyl, ethyl, or benzyl sulfide complexes provides the tertiary thioethers in high yields and in excellent enantiomeric purities (Equation (205)) <1997JCS(P1)2161>. The substitution proceeds with inversion of configuration, compared to the analogous alkoxy systems (Equation (178)).



1.04.3.4 Nitrogen-stabilized Carbanions

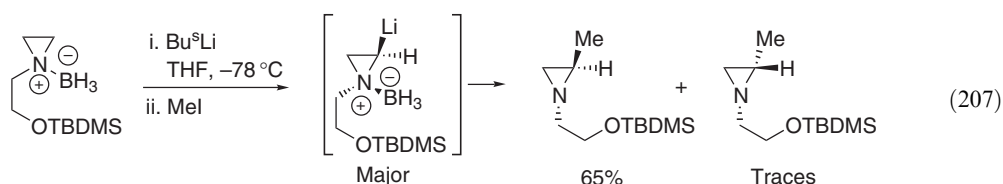
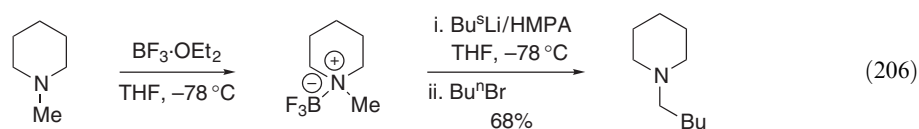
Recent methodologies developed for the functionalization of nitrogen-containing derivatives, particularly at the adjacent position to the amino group are of considerable interest for the synthesis of natural compounds including alkaloids and amino acids. Among these, alkylation of α -amino carbanions is the most common and attractive route to the formation of C—C bonds at the α -position of an amino group even if the use of allyl and benzyl halides can initiate

single-electron transfer (SET) processes. In contrast to organosulfur derivatives, generation and stabilization of α -amino carbanions are governed only by the inductive effect of the nitrogen atom. In order to favor their formation, various strategies have been developed based on either activation of the hydrogens present on the amino-substituted carbon atom or carbamate-directed metallation. Functionalization of allylic- and benzylic-stabilized α -amino carbanions as well as reactivity of related chiral α -carbanions have been also investigated and are disclosed here. Since the early 1990s, several of these topics have been reviewed by Beak <1996ACR552>, Katritzky <1998T2647, 1999CR665>, Hoppe <1997AG(E)2282>, and Basu <2002AG(E)716>.

1.04.3.4.1 Alkylation of nonstabilized α -amino carbanions

(i) Lithiation by deprotonation of borane-complexed amines

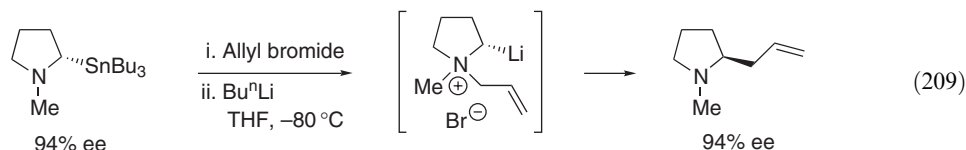
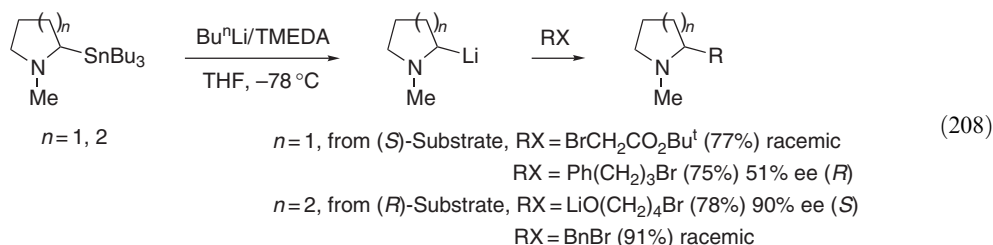
Borane complexation of tertiary amines revealed an extremely useful tool for activation of methylenes adjacent to amino groups toward lithiation by proton abstraction. Seminal studies reported by Kessar and co-workers showed that deprotonation of boron trifluoride-complexed *N*-methylpiperidine can easily be carried out with Bu^sLi at low temperature <1991CC568>. Alkyl substituents have been successfully introduced at the α -position in the presence of HMPA (Equation (206)). However, the corresponding α -stannylamine gave, after Sn-Li exchange, better results in alkylation and also benzylation products. The critical effect of CsF on the latter reaction has been strongly pointed out <2001SL517>. Another example of activation of tertiary amines by borane complex formation was reported by Vedejs on simple aziridines (Equation (207)) <1997JA6941>. All these results have been reported in pertinent reviews published in 1997 by Kessar and Singh <1997CR721> and in 1998 by Katritzky and Qi <1998T2647>. General information on the chemistry of amine-boranes are available in another review by Carboni and Monnier <1999T1197>.



(ii) Lithiation by Li-Sn(IV) exchange

In most cases, nonstabilized 2-lithio-*N*-methylpiperidines and -pyrrolidines were obtained by transmetallation of the corresponding organostannanes with Bu^nLi following Peterson's methodology <1971JA4027, 1974JOM209>. The related nonracemic secondary organolithiums are configurationally stable at -78°C and their reaction with unactivated alkyl halides occurs with inversion of configuration through a $\text{S}_{\text{E}}2_{\text{inv}}$ mechanism. The partial racemization observed with pyrrolidine derivatives may be explained by a competing retentive substitution ($\text{S}_{\text{E}}2_{\text{ret}}$) <1995JOC5763>. In addition, activated alkyl halides such as benzyl bromide and *t*-butyl bromoacetate yield racemic products arising from a radical mechanism involving SET <2000JA3344>. For 2-tributylstannyl-*N*-methylpiperidines, the presence of a *t*-butyl group at the C4 position locks the conformation and the axial alkylolithium, generated by transmetallation, reacts in moderate-to-poor yields with organohalides. The reaction provides dimers and disproportion by-products according to a SET process (Equation (208)). When the stannyl group is in the equatorial position, transmetallation fails completely <2000OL1561>. Gawley reported the allylation of 2-lithio-*N*-methylpyrrolidines through a [2,3]-ylide rearrangement. Allylation of the

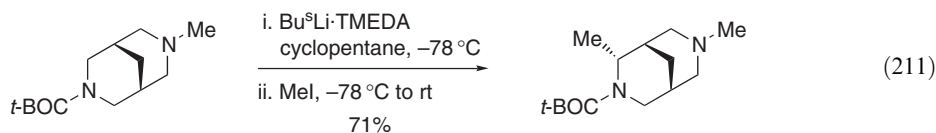
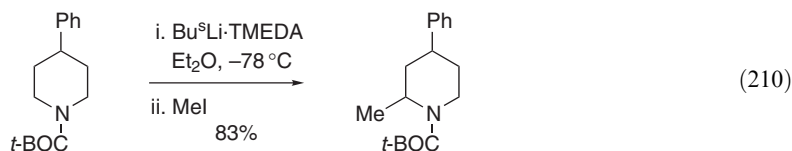
stannyl precursor by allyl bromide affords the *N*-methyl-*N*-allylstannylpyrrolidinium bromide which undergo a sigmatropic rearrangement after transmetalation with Bu^nLi . The transformation occurs with inversion of configuration (Equation (209)) <1995JA11817>.



1.04.3.4.2 Alkylation of stabilized α -amino carbanions

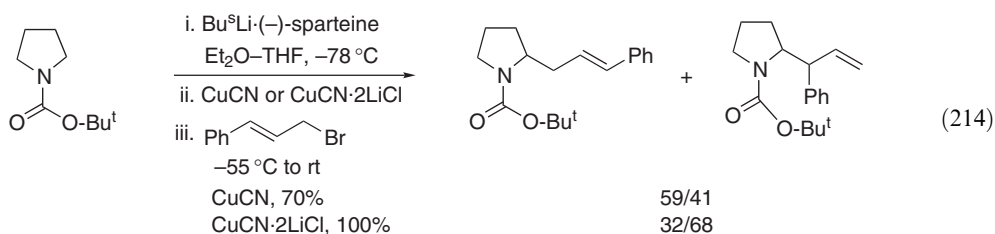
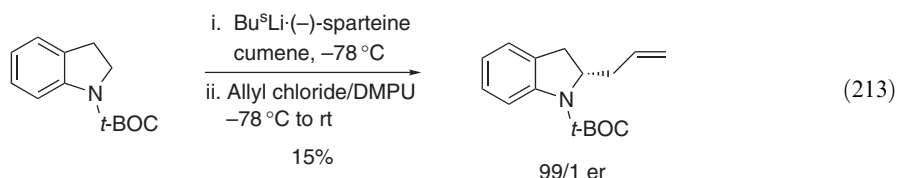
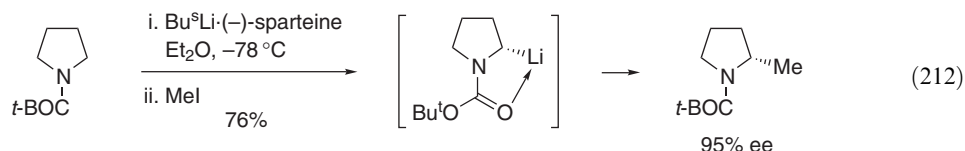
(i) Dipole-stabilized anions

Lithiation of α -amino methylenes is usually facilitated by the formation of amide, formamidine, and nitroso groups on the nitrogen atom of the substrate. The protecting group activates the protons α to the nitrogen atom, increasing their kinetic acidity, directs the metallation and stabilizes the resulting organolithium to render it configurationally stable. Pioneering research on lithiation of 2,2-diethylbutanamides and *N*-BOC-protected piperidines have been reported by Beak and co-workers. They showed that α -deprotonation can easily be promoted by Bu^sLi /TMEDA at low temperature so as to generate the racemic dipole-stabilized organolithium intermediate which can be quenched with various alkyl halides (RI and allyl bromide) (Equation (210)) <1984JA1010, 1989TL1197>. A few years later, Harrison and O'Brien published the diastereoselective sequential lithiation/substitution of *N*-BOC bispiperidines under similar conditions. A range of sparteine analogs has been synthesized (Equation (211)) <2000TL6161>.



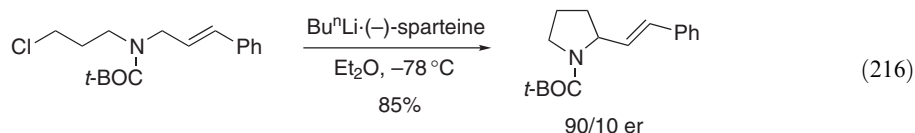
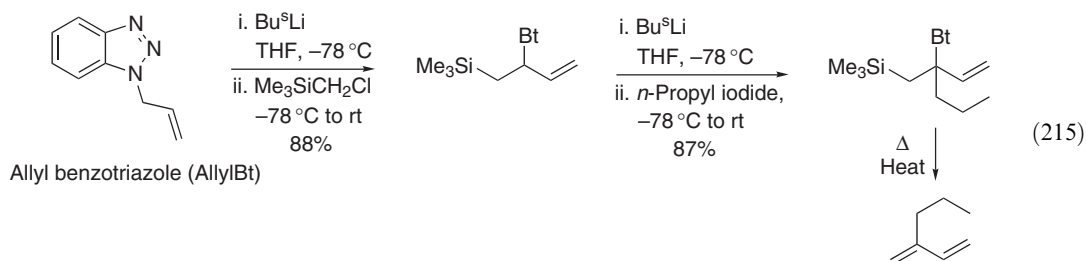
In 1991, Beak and co-workers reported the enantioselective deprotonation of *N*-BOC protected pyrrolidine with Bu^sLi and a chiral ligand. In the presence of (–)-sparteine, the *pro*-(*S*) proton is removed more rapidly than the *pro*-(*R*) proton (Equation (212)) <1991JA9708>. The related *N*-BOC indoline was functionalized at the C2-position using an identical protocol. The asymmetric lithiation with Bu^sLi /(–)-sparteine in cumene and subsequent reaction with allyl bromide affords the regioselective 2-substituted *N*-BOC indolines in low yields with moderate enantiomeric ratios. The addition of *N,N'*-dimethylpropyleneurea (DMPU) to the reaction mixture increased dramatically the selectivity to 99:1 er (Equation (213)) <1997JOC7679>. Dieter and co-workers were interested in the reactivity of α -aminoalkylcuprates toward competitive $\text{S}_{\text{N}}2/\text{S}_{\text{N}}2'$ nucleophilic substitution of allylic halides. Cinnamyl and crotyl bromides undergo allylic substitutions by organocuprates, prepared from *N*-BOC protected pyrrolidine, with poor regioselectivities

whatever the reaction conditions used. However, reaction of acyclic dimethylaminomethyl cuprates gives the S_N2' substitution adducts with excellent selectivities up to 4:96 S_N2/S_N2' (Equation (214)) <1997SL1114>.



1.04.3.4.3 α -Alkylation of 1-aminosubstituted allyllithiums

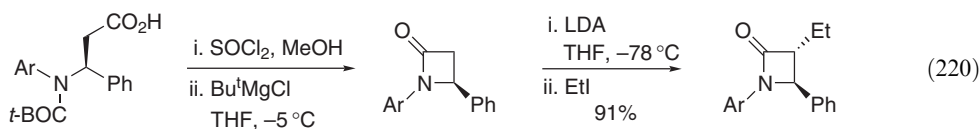
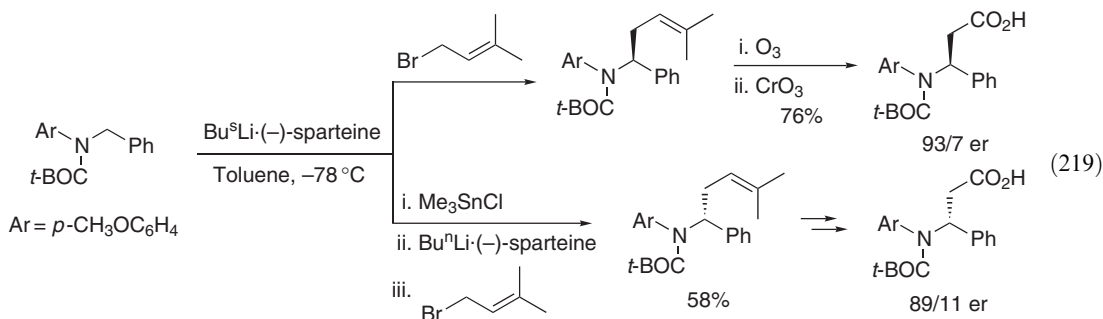
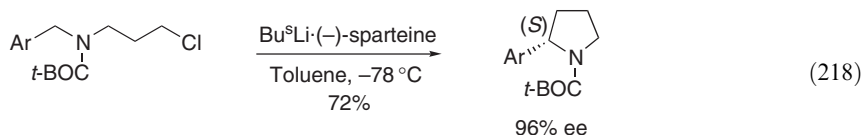
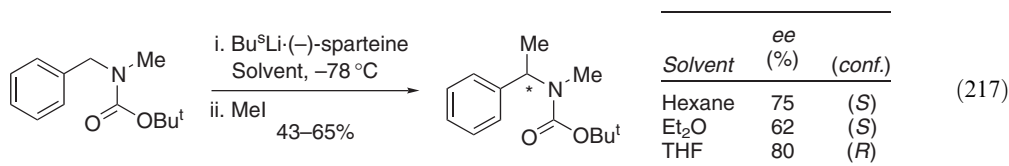
Functionalization of aminoallyl derivatives by sequential lithiation–substitution did not receive much attention since the early 1990s. In 1999, Katritzky and co-workers reported the use of *N*-allylbenzotriazole for the synthesis of 2-alkyl-substituted 1,3-butadienes. The η^3 -allyllithium intermediate obtained by treatment of 1-allyl-1*H*-benzotriazole with Bu^sLi at low temperatures undergoes α -attack upon alkylation with chloromethyltrimethylsilane. A second lithiation followed by an electrophilic substitution of organohalides affords the α,α -dialkylated *N*-allylbenzotriazole. At higher temperatures, the latter gives 2-alkyl-substituted 1,3-butadienes by elimination of silicon and benzotriazole groups (Equation (215)) <1999JOC1888>. In contrast, sequential asymmetric lithiation–substitution initiated by Bu^nLi ·(-)-sparteine with cinnamylamines <1996JA12218> and cyclohexylallyl amines <2001JA4919> leads predominantly to γ -products, whereas lithiated *N*-BOC-2-*N*-(3-halopropyl)- and *N*-BOC-2-*N*-(3-halobutyl)-allyl amines undergo intramolecular substitution α to the nitrogen atom (Equation (216)) <1999JOC1160>. More details about these transformations reported by Beak and co-workers are presented in Section 1.04.2.1.



1.04.3.4.4 α -Alkylation of 1-aminosubstituted benzyllithiums

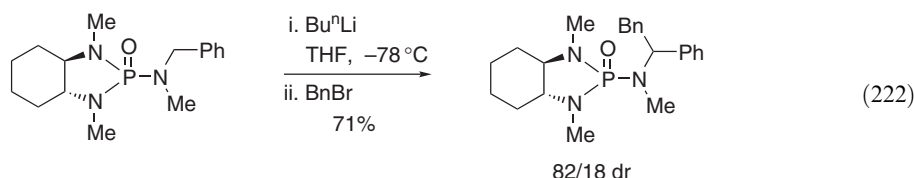
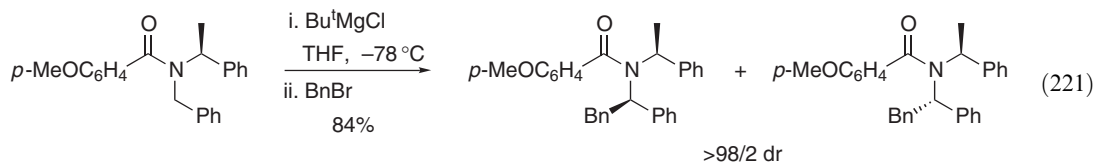
(i) Metallation through hydrogen abstraction by lithiated bases

Schlosser and Limat first studied the asymmetric deprotonation of *N*-BOC-*N*-methylbenzylamine with Bu^sLi/(–)-sparteine followed by alkylation with methyl iodide. The resulting benzyl lithium/sparteine complex immediately racemizes and one of both diastereomeric complexes reacts preferentially. They noted the precipitation of a single diastereoisomer in THF. The enantiomeric ratio and the absolute configuration were proved highly dependent on the metallation time and the nature of the solvent (THF/hexane), respectively (Equation (217)) <1995JA12342>. Extension of this procedure to enantioselective synthesis of (*S*)-2-aryl-BOC-pyrrolidines from *N*-BOC-*N*-(3-chloropropyl)-benzylamine has been investigated by Beak and co-workers. The benzyllithium compound, generated by selective *pro*-(*S*) proton abstraction with Bu^sLi or BuⁿLi/(–)-sparteine in toluene, undergoes rapid intramolecular alkylation without racemization (Equation (218)) <1996JA715>. At the same time, they showed that the enantioenriched dipole-stabilized lithium carbanion/(–)-sparteine complex of *N*-BOC-*N*-(*p*-methoxyphenyl)-benzylamine is configurationally stable at –78 °C and the substitution of isoprenyl bromide proceeds with retention of configuration <1997JA11561>. The related epimer was obtained by invertive stannylation of the organolithium and a retentive transmetalation–alkylation sequence with a high enantiomeric ratio (Equation (219)) <1997JOC1574>. An application of this methodology to lactam ring preparation and its alkylation at the C-3 position has been provided (Equation (220)) <1999JOC1705>.

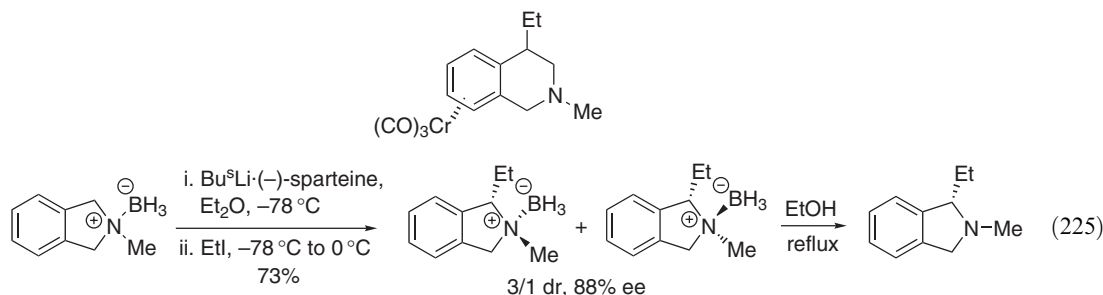
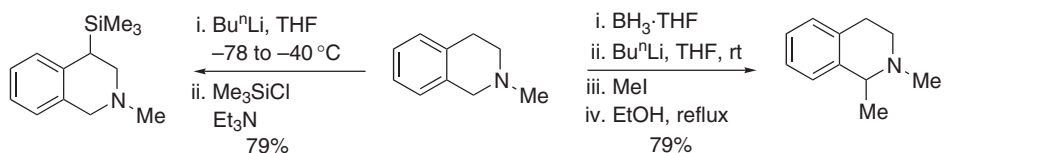
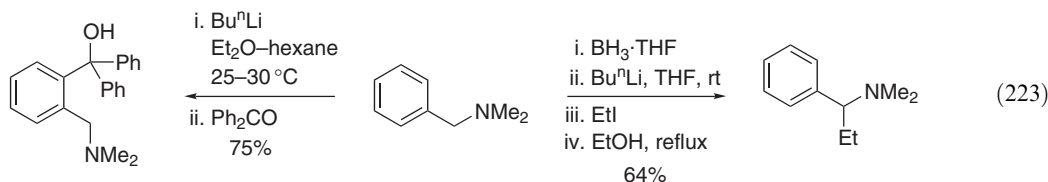


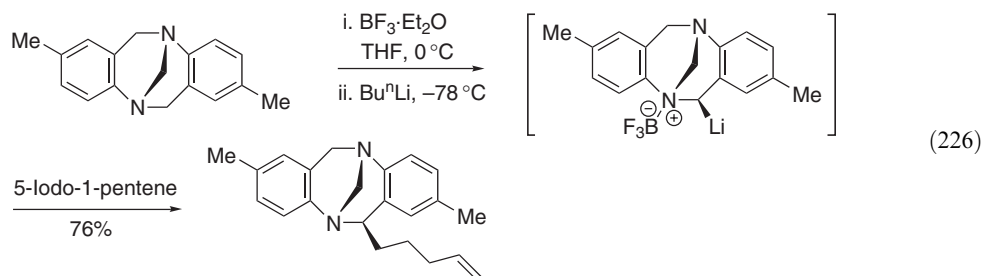
In 1995, Clayden reported a straightforward and highly diastereoselective route to *meso*-bis-(α -methylbenzyl)amide through α -lithiation of amide derivatives of *N*-benzyl- α -methylbenzylamine with Bu^tLi in THF at –78 °C, then methylation with methyl iodide <1999TL8323>. Extensions of this methodology to other alkyl halides gave the unsymmetrical benzylamide adducts in good yields and with high stereoselectivities. Based on this approach, *N*-carbamate derivatives react selectively with methyl iodide whereas allyl and benzyl bromides returned the alkylated product as a 50:50 mixture. This result suggests that a radical mechanism initiated by a SET may operate. However, thermodynamic (rapid equilibration for amides) and kinetic (kinetic deprotonation—slow equilibration for carbamates) factors determine the formation of a single diastereoisomer of organolithium in each case (Equation (221)) <2002TL1955>. Müller, Spingler, and Zehnder have been interested in

diastereoselective alkylation of chiral bicyclic phosphoric triamides derived from *N*-methyl benzylamine. Thus, deprotonation in the benzylic position allows the formation of the stable chiral α -lithiophosphoric triamide, which can react with different alkyl halides (benzyl bromide, methyl iodide, *iso*-propyl iodide, and allyl bromide). The best yields and diastereomeric ratios were obtained with 2 equiv. of electrophile at -78°C in THF (Equation (222)) <1997SL1059>.

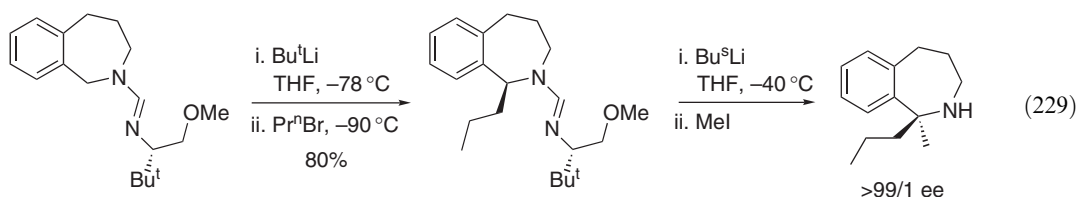
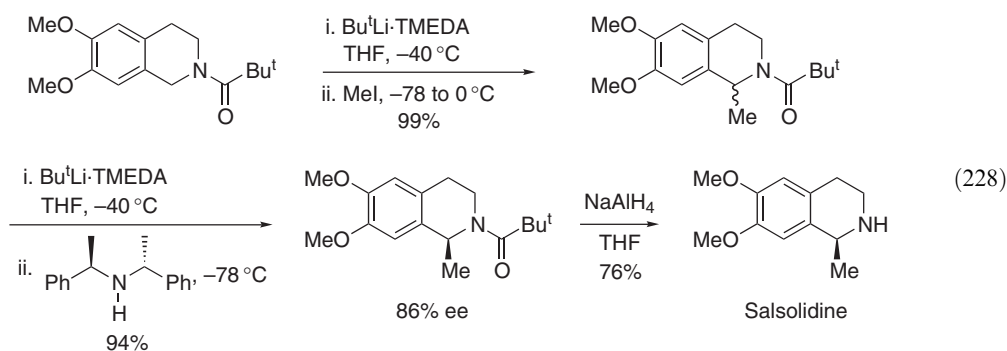
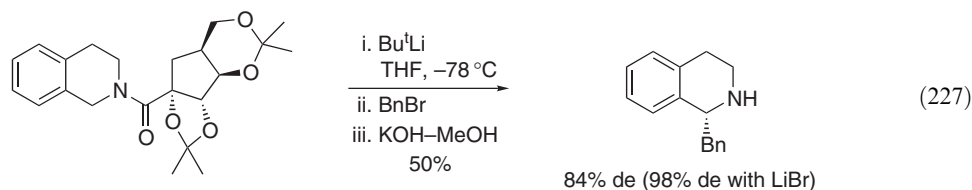


Simpkins and co-workers showed that lithiation of borane-complexed benzylamine and tetrahydroisoquinoline followed by substitution of alkyl halides occurs regioselectively at the amino-substituted benzylic carbon atom <1995TL8697>. However, as reported in the literature <1997CR721>, reaction of free and tricarbonylchromium-complexed amines with Bu^nLi and electrophiles leads to either *ortho*-substituted <1963JA2467, 1967JOC1479> or C4-alkylated products <1982JA7609, 1986JCS(P1)2257, 1991CC568> (Equations (223) and (224)). In 1998, they reported that the *N*-methylisoindoline-borane complex undergoes diastereoselective alkylation in the benzylic position *syn* to the borane group. Asymmetric lithiation with $\text{Bu}^s\text{Li}/(-)$ -sparteine gives rise the enantioenriched isoindoline-borane complex in up to 88% ee (Equation (225)) <1998SL189>. The borane-complexation methodology has been also used to functionalize Tröger's base. In practice, the boron trifluoride-amine complex renders the adjacent hydrogens more labile and favors lithiation with Bu^nLi . Thus, the resulting organometallic can react with a selection of alkyl, allyl, and benzyl halides diastereoselectively in quite good yields (Equation (226)) <1996TL6267>.

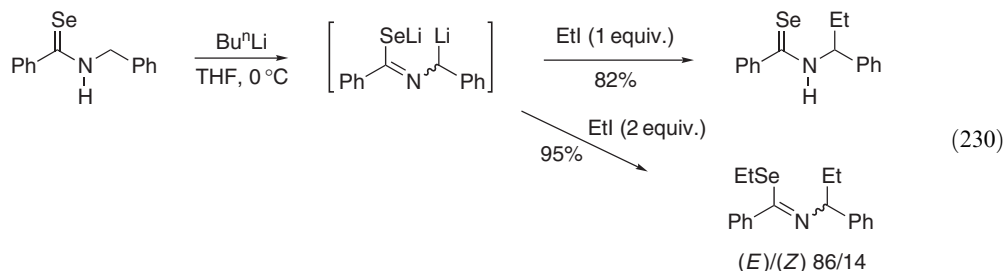




The nitrogen atom of tetrahydroisoquinolines when converted into an amide group should activate the methylenes adjacent to the nitrogen atom by increasing the acidity of the related protons. Due to the coordinating ability of the oxygen atom, the amide functional group can stabilize the benzylic organolithium, generated by deprotonation with Bu^nLi , which reacts with different organohalides [\[1983T1963\]](#). The use of chiral amides, derived from gulonic acid, favors the formation of diastereomeric organolithium intermediates, which are in equilibrium. Investigations revealed that the diastereoselectivity is determined during the post-deprotonation step. Thus, methylation and benzylation lead to the corresponding substituted compounds in good yields and with excellent diastereoselectivities in contrast to the allylation step. Functionalization of tetrahydro- β -carboline has been also discussed ([Equation \(227\)](#)) [\[2001JOC8744\]](#). Enantioselective protonation of the lithiated 1-methyltetrahydroisoquinoline by a chiral amine gave the adduct in up to 86% ee. This methodology was applied to the synthesis of the natural product salsolidine ([Equation \(228\)](#)) [\[2000SL1640\]](#). As with chiral amides, formamides derived from enantioenriched amino alcohols are able to provide asymmetric alkylations in the benzylic position. A couple of diastereoselective lithiation–substitution sequences of 2-benzazepine formamides occur with high diastereoselectivities (up to >99:1 dr) leading to the 1,1-disubstituted-2-benzazepine products ([Equation \(229\)](#)) [\[1996H475\]](#).

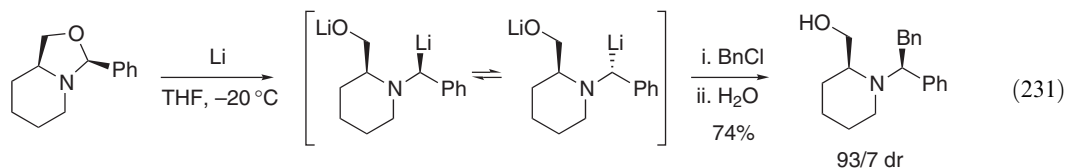


In 2002, Murai and co-workers reported studies on the functionalization of *N*-benzyl selenobenzamide. Its treatment with 2 equiv. of Bu^nLi gave the dianion, which reacts with alkyl and allyl halides selectively in the benzylic position. An excess of ethyl iodide gave the *Se*-ethyl thioimide in high yield (Equation (230)) <2002OL1407>.



(ii) Lithiation by reductive cleavage

α -Amino-substituted benzyllithiums may also be obtained from oxazolidines by reductive cleavage of the benzylic C—N bond <2001TL129>. The reaction involves formation of configurationally labile benzylic radicals, which lead to racemic organolithium intermediates. Thus, the latter undergo diastereoselective substitutions with various alkyl halides. *syn*-Amino alcohols are isolated in moderate yields (Equation (231)).

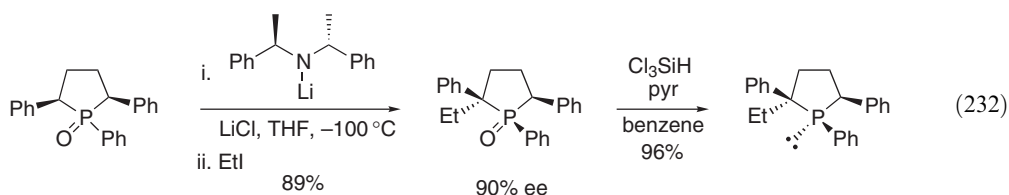


1.04.3.5 Phosphorus-stabilized Carbanions

α -Metallated alkylphosphorus compounds are useful intermediates, which have been extensively studied because of their synthetic utility as Wittig or Horner–Wittig precursors of alkenes. Investigations have revealed the ability of functional groups containing a phosphorus atom, such as phosphonates and phospholane oxides, to stabilize adjacent carbanions. These phosphorus anionic intermediates could be trapped by various carbon electrophiles including haloalkanes.

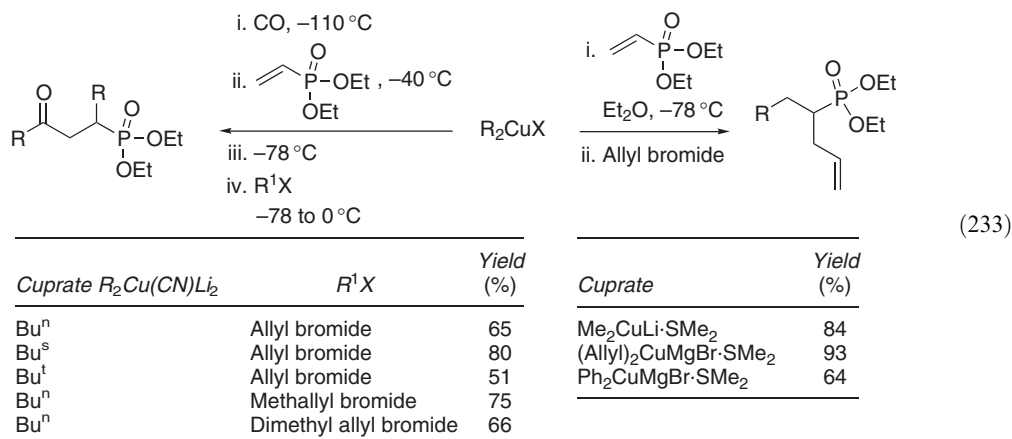
1.04.3.5.1 Alkylation of phospholane oxides in the α -position

The increasing use of chiral lithium bases in asymmetric deprotonation involving discrimination of two enantiotopic hydrogens has prompted Simpkins' group to develop enantioselective α -lithiation of 1,2,5-triphenylphospholane oxide. The chiral lithiated intermediate can be efficiently trapped by a range of alkyl halides and yields the triphenyl-substituted phospholane oxides with good levels of enantioselectivity. Reduction to phospholanes was realized by treatment of the oxides with a mixture of Cl_3SiH and pyridine (Equation (232)) <1998JOC912>.

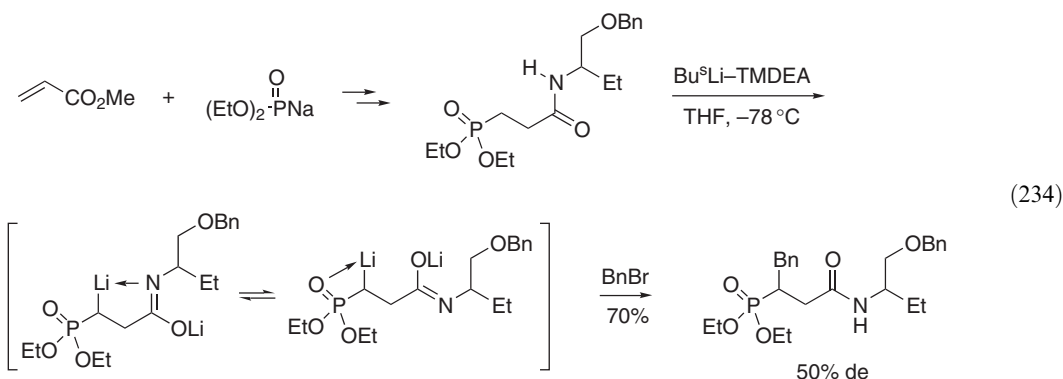


1.04.3.5.2 Alkylation of phosphonates in the α -position

The conjugate addition of organometallics to alkenylphosphonates, compared to α,β -unsaturated carbonyl compounds, has been briefly examined. As first reported by Russo and co-workers <1984CC5>, nucleophiles such as simple cuprates can promote 1,4-addition to diethyl vinyl phosphonate. Kabalka extended the reaction to acyl cuprates, generated by addition of dialkyl cuprates to carbon monoxide <1999OM1811>. In each case, the resulting phosphonate-stabilized anionic intermediate was trapped by allyl bromide liberating the α -allylated alkyl- and oxoalkyl-phosphonate, respectively (Equation (233)) <1996S34, 1999OM1811>.

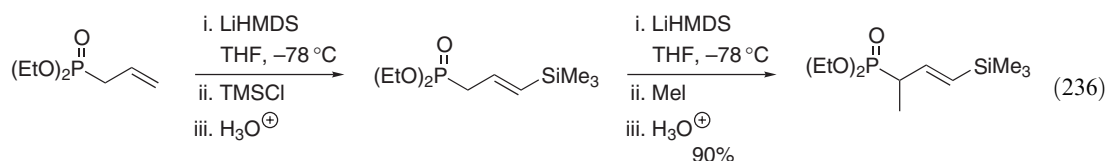
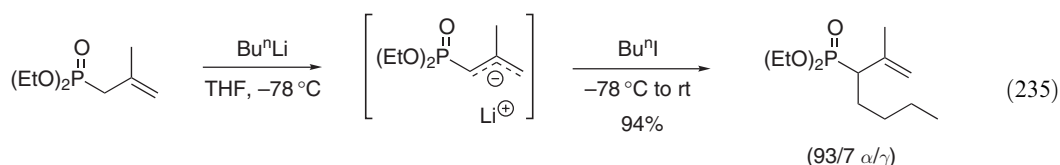


In addition, conjugate addition of diethyl phosphite to ethyl acrylate gave, after further transformations, β -amidophosphonates. 1,5-Inductive alkylation adjacent to the phosphonate group was readily obtained by lithiation with Bu^sLi/TMEDA followed by electrophilic quenching with methyl iodide and benzyl bromide. However, only poor diastereoselectivities have been reached (up to 50%). This result may be explained by the presence of two intermediates in equilibrium where the lithium chelates either the phosphonate oxygen atom or the nitrogen of the amide group (Equation (234)) <2001EJO3031>.



1.04.3.5.3 Alkylation of allylphosphonates

The chemistry of P-stabilized allyl anions is well developed in synthesis for the preparation of molecules containing olefin and polyene residues. The presence of the allyl moiety should render hydrogens α to the phosphonate functional group more acidic. Indeed, allylphosphonate anions variously substituted can be generated by deprotonation with BuⁿLi and reacted with halides to give preferentially the α -products (Equation (235)) <1998SC3601, 2000SC789>. In addition, metallation of 3-trimethylsilylallylphosphonate with LiHMDS followed by substitution forms exclusively α -alkylated adducts in excellent yields (Equation (236)) <2001TL2345>.

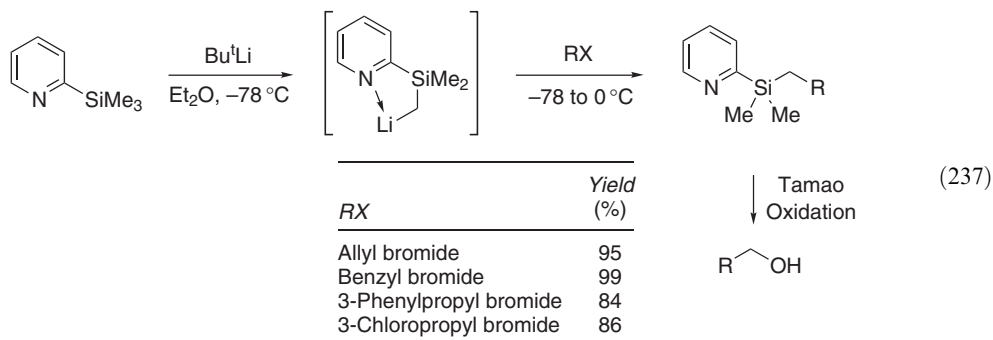


1.04.3.6 Silicon-stabilized Carbanions

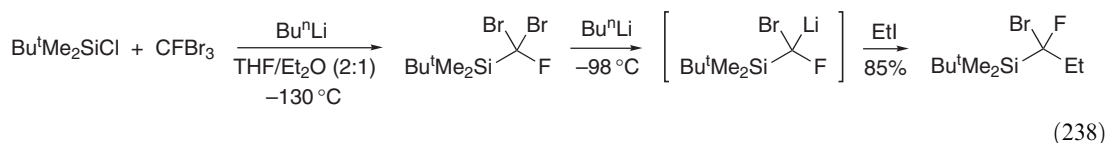
The use of α -silyl carbanions in organic synthesis is dominated by the seminal research of Peterson reported in 1968 <1968JOC780>. Formation of carbanions adjacent to a silyl group is highly favored due to their stabilization by overlap between the appropriate carbon–metal bond orbital (or the $2p$ orbital on carbon) and the empty $3d$ orbital on silicon or the C–Si σ^* orbital. Several methods of formation of α -silyl organometallic compounds and their subsequent alkylations will be described in this section.

1.04.3.6.1 α -Alkylation of alkyl silanes

The ease of metallation and the stabilization of the resulting organometallic is usually increased by the presence of neighboring heteroatoms and electron-withdrawing groups. However, Yoshida showed that the presence of a simple pyridyl group can assist the generation of α -silyl carbanions by deprotonation with Bu^tLi or LDA and stabilize the lithiated intermediate by intramolecular coordination <1999TL5533>. Thus, the related (2-pyridyldimethylsilyl)methyl lithium undergoes alkylation with various alkyl bromides. Tamao oxidation of the silicon adducts leads to primary alcohols quantitatively (Equation (237)) <1999TL5537, 2001JOC3970>.

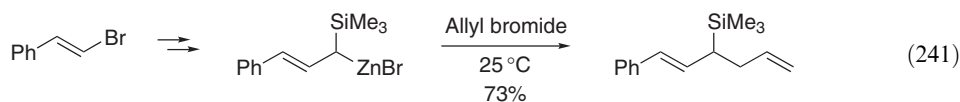
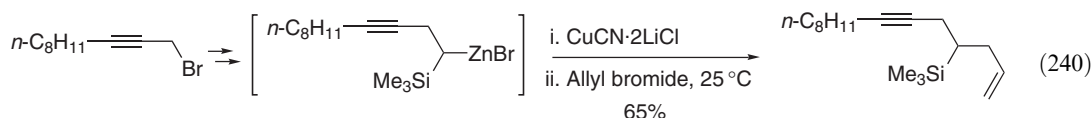
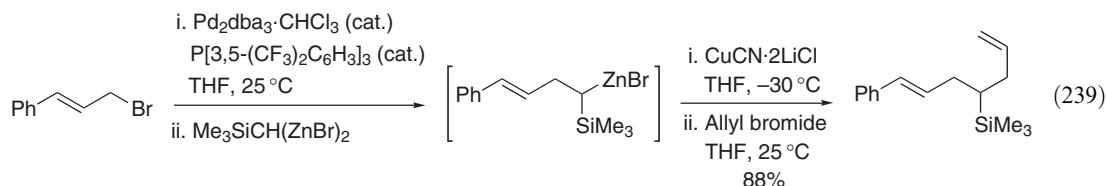


In 1997, Shimizu and co-workers found that lithiation of dibromofluoromethyl(*t*-butyl)dimethylsilane by metal–bromide exchange occurs at -78°C with Bu^nLi to produce the silicon-containing lithium carbenoid which can be alkylated with organic bromides in good yields (Equation (238)) <1997TL4591>.



The cross-coupling reaction of silyl-substituted dizincmethanes, prepared from zinc insertion into the corresponding dibromide, with (*E*)-cinnamyl bromide and under palladium catalysis, affords the homoallylzinc species which is transmetalated by $\text{CuCN} \cdot 2\text{LiCl}$ at -30°C . The former

Cu—Zn derivative can be alkylated with allyl or propargyl bromide in fair yields (Equation (239)). Similarly, propargyl bromide as well as bromostyrene were coupled with the geminal dizinc compound and the resulting monoalkylated species were functionalized after treatment with (Equation (240)) or without copper salts (Equation (241)) <1998SL1315>.



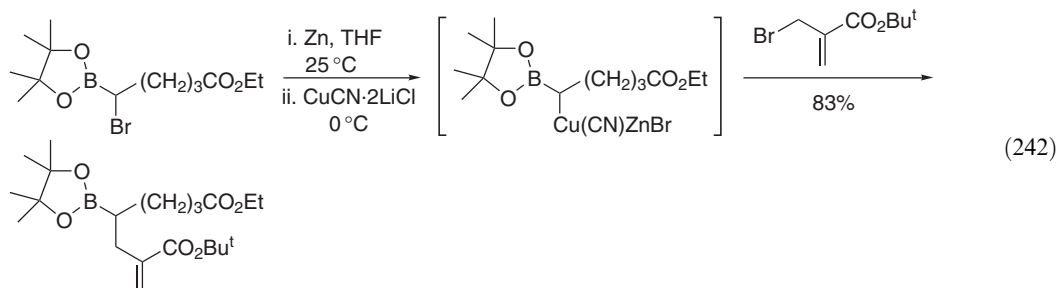
1.04.3.7 Boron-stabilized Carbanions

Since H. C. Brown's outstanding achievements in boron chemistry over the last century, organo-boranes still remain omnipresent in organic synthesis. Many areas have witnessed a growth in the preparation of new boron-containing compounds and their use in modern synthetic transformations, by taking advantage of the electron deficiency caused by the vacant *p*-orbital on the boron atom. In particular, a negative charge in the α -position can be stabilized by overlap of the filled *p*-orbital on carbon with the vacant *p*-orbital on boron. A rich chemistry has been developed around this property including alkylation of carbanions adjacent to boryl substituents.

1.04.3.7.1 Reactivity of 1,1-borio-zincioalkane reagents

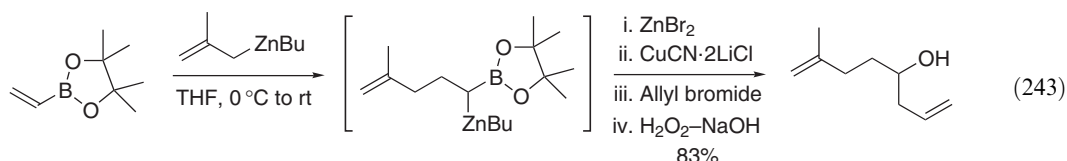
(i) Synthesis via zinc insertion

As reported by Knochel in 1990, [α -(alkylenedioxy)-boryl]alkyl]zinc halides are readily accessible by insertion of zinc dust into α -haloboronic esters. Transmetalation with the copper salt CuCN·2LiCl gave a new mixed organo-*gem*-dimetallic species which can substitute different allyl bromides in good yields (Equation (242)) <1990JA7431>.



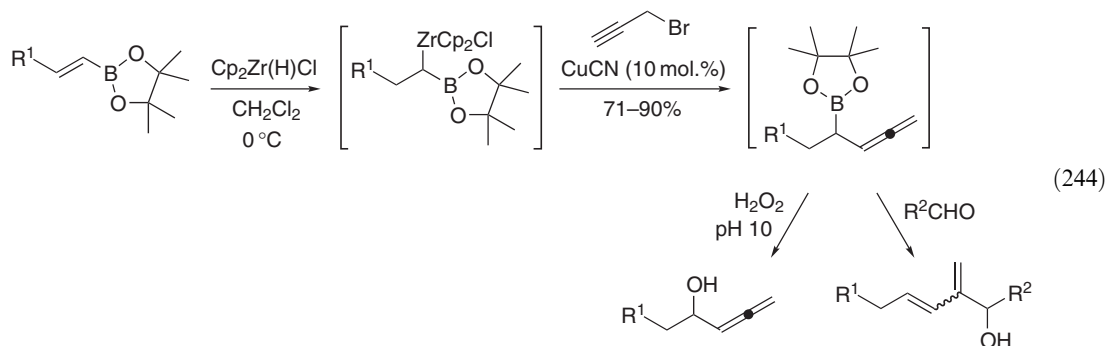
(ii) Synthesis via allylzincation reaction

A different method involves regioselective addition of allylzinc reagents to alkenylboronates and liberates the boron and zinc 1,1-dimetallic species via a carbometallation process. The mono-allylation of such intermediates was realized first by a selective transmetalation of the organozinc moiety with copper(I) cyanide and its subsequent functionalization with allyl bromide (Equation (243)) <2001OL3137>.



1.04.3.7.2 Reactivity of 1,1-borio-zirconioalkane reagents

Zheng and Srebnik reported that hydrozirconation of alkenylboronic esters by Schwartz's reagent ($\text{Cp}_2\text{Zr}(\text{Cl})\text{H}$) gave the geminate borazirconocene alkanes. The new dimetallic species can react selectively with propargyl bromide in the presence of a catalytic amount of copper(I) cyanide to provide the corresponding α -allenic boronic esters in good yields. These products can be either oxidized into alcohols or added to a variety of aldehydes (Equation (244)) <1995JOC486>.

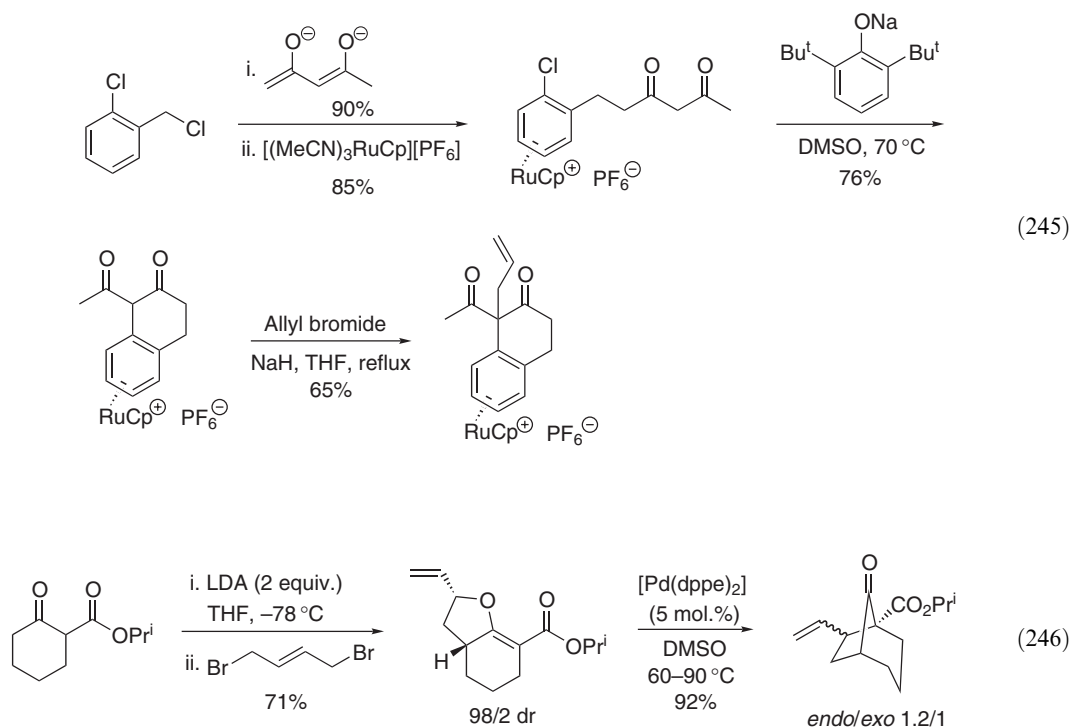


1.04.4 CARBANIONS WITH TWO AND THREE STABILIZING GROUPS

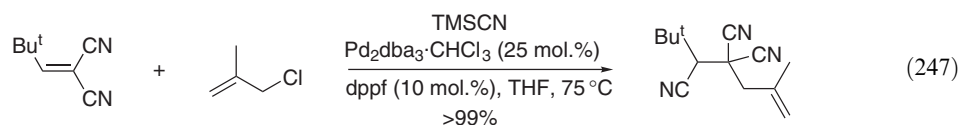
In the light of previous studies, the presence of two or three functional units instead of one branched on methylene groups should increase the acidity, labilize the hydrogens toward base attacks, and strongly stabilize the organometallics generated. This area has been widely explored since the early 1990s but only selected examples of alkylation will be reported in this section.

1.04.4.1 C- versus O-Alkylation of β -Dicarbonyls and Related Compounds

It is known from many years that the dianions of β -keto esters and β -dicarbonyls are first alkylated at the α' -position, which is considered to be the more nucleophilic site. A second alkylation of the enolate, readily available by deprotonation with weak bases such as NaH or K_2CO_3 , occurs this time at the α -position via nucleophilic substitution of organic halides. Numerous examples of dianion functionalization have been reported in the literature. For instance, Pigge and Fang recently developed a new synthetic approach to substituted 2-tetralones. Selective alkylation of the dianion of acetylacetone with 2-chlorobenzylchloride leads to the α' -substituted β -dicarbonyl adduct. Complexation of the arene ring with the $[(\text{CH}_3\text{CN})_3\text{RuCp}][\text{PF}_6]$ complex and its subsequent nucleophilic aromatic substitution ($\text{S}_{\text{N}}\text{Ar}$) with the β -dicarbonyl enolate affords the Ru-coordinated 1-acetyl-2-tetralone. The monoanion, generated by deprotonation with NaH, can then undergo C-alkylation with allyl bromide and O-alkylation with methyl chloroformate (Equation (245)) <2001TL17>. Recent reports deal with successive intramolecular C- and O-dialkylations of dilithiated 1,3-dicarbonyl compounds by 1-bromo-2-chloroethane or 1,4-dibromo-2-butene. These reactions probably proceed through regio- and diastereoselective domino $\text{S}_{\text{N}}/\text{S}_{\text{N}}$ and $\text{S}_{\text{N}}/\text{S}_{\text{N}}'$ processes, respectively. The methodology was then used in the synthesis of 2-alkylidenetetrahydrofuran derivatives from the respective 1,3-dicarbonyl dianions (Equation (246)) <2001JOC6057, 2002MI917> and also from the dimethyl acetone-1,3-dicarboxylate dianions <1996SL339>.

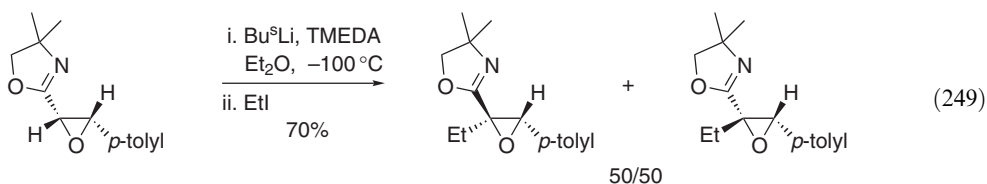
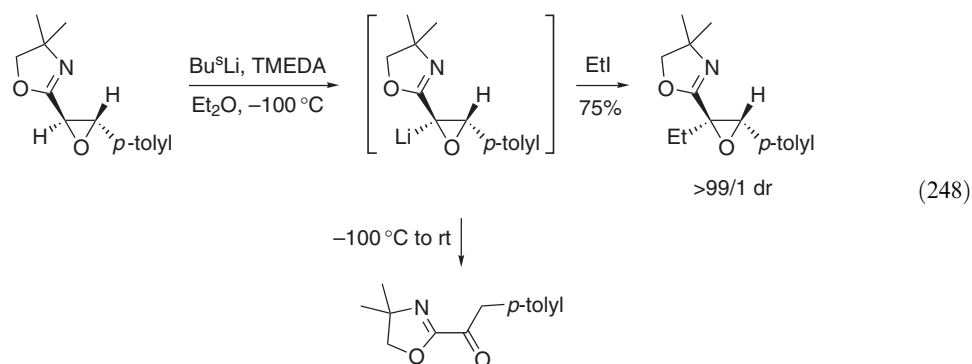


Pd(0)-Catalyzed allylation of β -dicarbonyl monoanions with allylic halides has been extensively investigated and applied in synthesis, leading to a variety of synthetically useful products [<B-1995MIT, B-1997MI, B-1999MI833>](#). Recently, Yamamoto and co-workers showed that treatment of alkylidene malonitrile with allylic chlorides and trimethylsilyl cyanide in the presence of $\text{Pd}_2\text{dba}_3\cdot\text{CHCl}_3/2\text{dppf}$ catalyst affords different cyanoallylation products in fair yields. The combination of allyl chloride, trimethylsilyl cyanide, and palladium in a catalytic amount presumably generates a π -allylpalladium cyanide complex which readily reacts with the activated alkene. The cyanide ligand acts as a nucleophile and adds in a 1,4-fashion. Thus, the resulting π -allylpalladium intermediate undergoes reductive coupling and liberates the allylated adducts (Equation (247)) [<2000TL2911>](#).



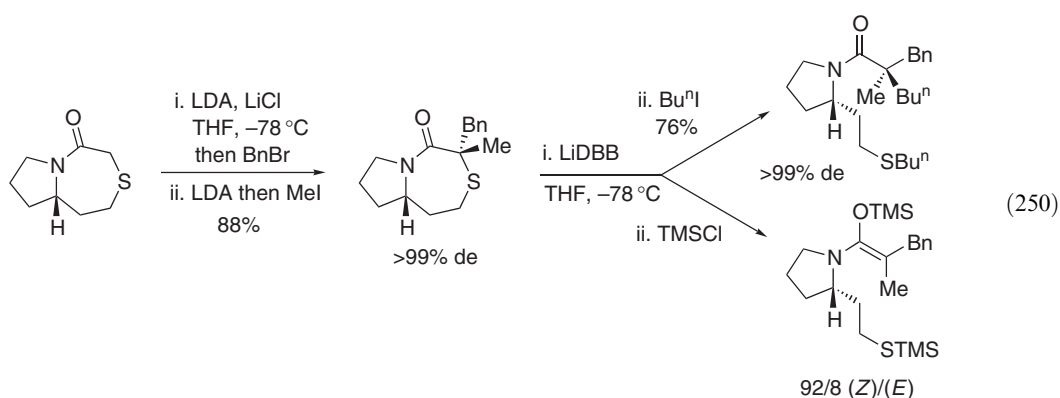
1.04.4.2 Alkylation of Oxazoline, O-Stabilized Carbanions

In a series of papers, Florio and co-workers reported the direct lithiation of mono- and disubstituted oxazolinylloxiranes with $\text{Bu}^t\text{Li}/\text{TMEDA}$ at -100°C and their subsequent alkylation with alkyl and allyl halides [<1999EJO409>](#). The presence of the oxazolinyl moiety stabilizes the lithiated intermediate at -100°C ; however, upon warming to room temperature, the transient lithiooxirane rearranges to α -ketone-2-oxazoline (Equation (248)) [<2000TL8835>](#). An interesting stereochemical problem was observed with oxazolinyl *p*-tolylloxiranes. *trans*-Oxiranyllithium was found to be configurationally stable and the reaction with electrophiles occurs with retention of configuration whereas the *cis*-isomer exhibits a lack of stability leading to a mixture of diastereoisomers of alkylated adducts (Equation (249)) [<2001JOC3049>](#).

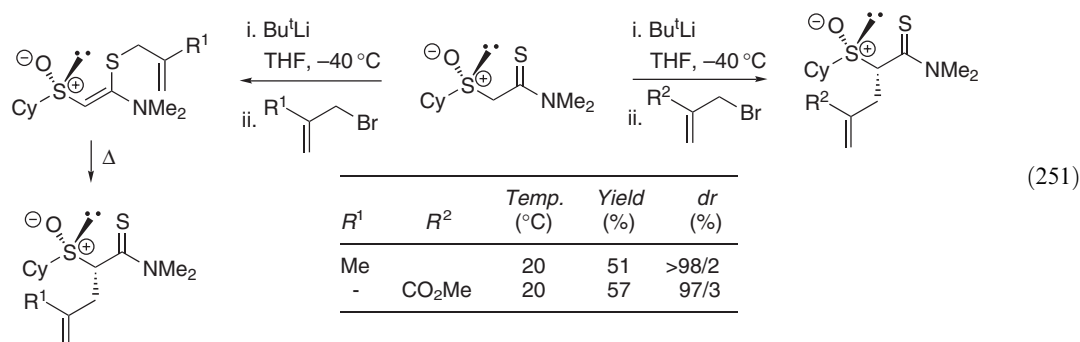


1.04.4.3 Alkylation of Enolate, *S*-Stabilized Carbanions

Very recently, Manthorpe and Gleason reported the stereoselective double alkylation of bicyclic thiolglycolate lactams relying on sequential deprotonation with LDA at -78°C and alkylation with a range of organic halides. From these adducts, they developed a novel approach for the stereoselective formation of (*E*)- and (*Z*)-disubstituted amide enolates [<2001JA2091>](#) and the preparation of enantioenriched quaternary carbon centers [<2002AG\(E\)2338>](#), that involves the reduction of the C—S bond of α,α -dialkylated lactams with lithium di-(*t*-butyl)-biphenyl (LiDBB) followed by *O*- or *C*-electrophilic trapping with TMS chloride or *n*-alkyl iodides, respectively (Equation (250)).

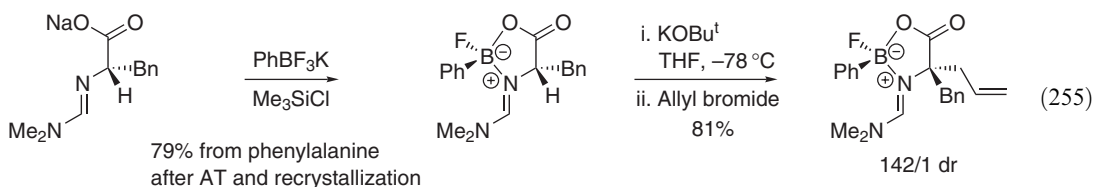
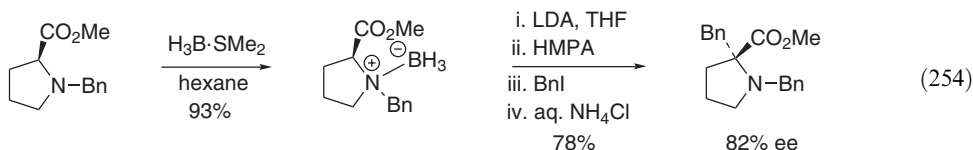
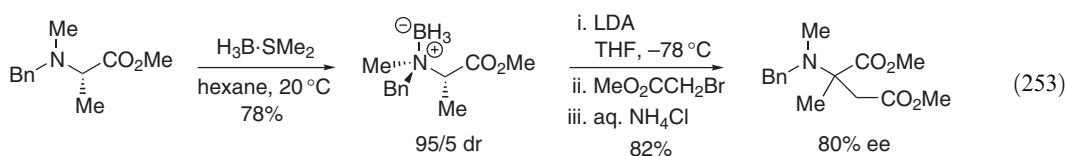
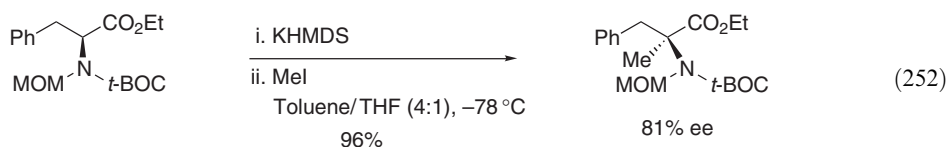


Metzner and co-workers also reported the *C*-alkylation of the enantioenriched (*R*)-2-cyclohexylsulfinyl-*N,N*-dimethylethanethioamide enolate by allyl halides activated by electron-withdrawing groups (CO_2R , CN , SO_2R) [<2002JOC6852>](#), whereas simple allyl, methallyl, crotyl, and cinnamyl bromides undergo *S*-allylation followed by a thio-Claisen rearrangement leading to the corresponding α -substituted α -sulfinyl acetamides [<2001JOC7841>](#). The *C*-allylation process involves Michael addition–halide elimination or $\text{S}_{\text{N}}2'$ mechanism. The excellent 1,2-stereo-induction observed may be explained by an electronic control (Equation (251)) [<2002JOC6852>](#).

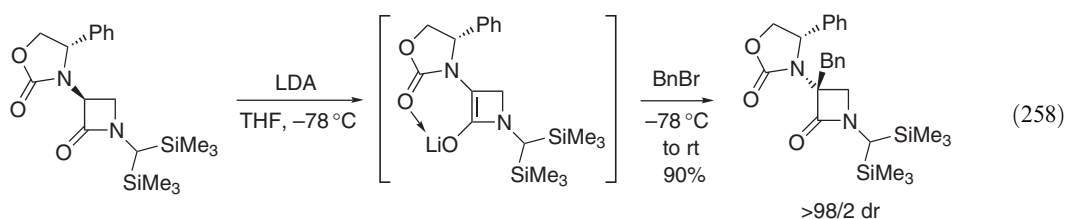
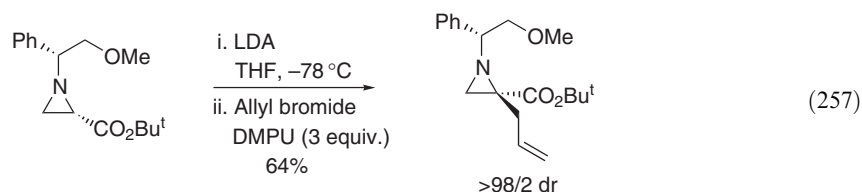
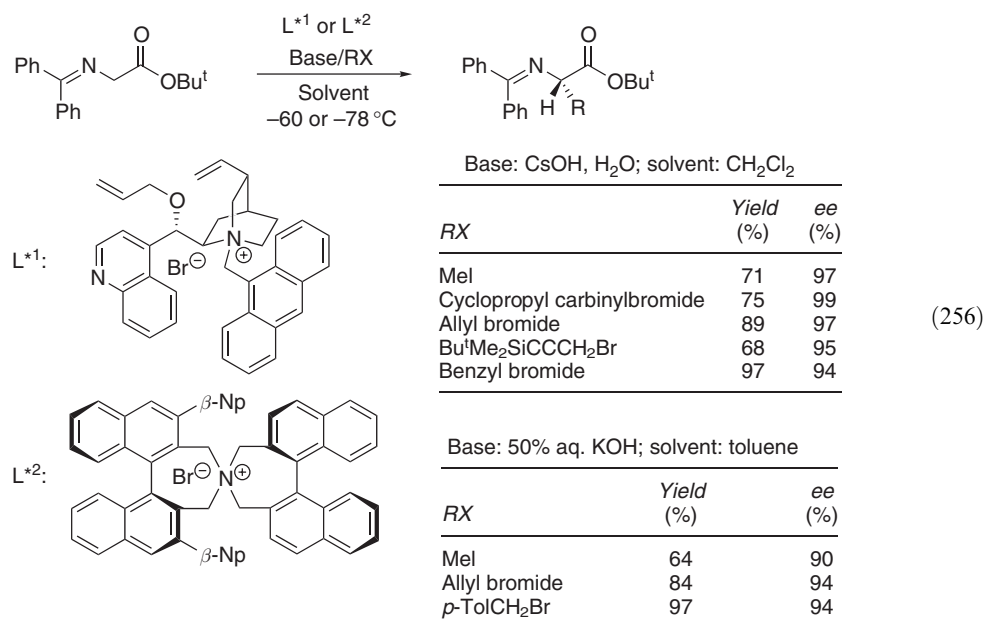


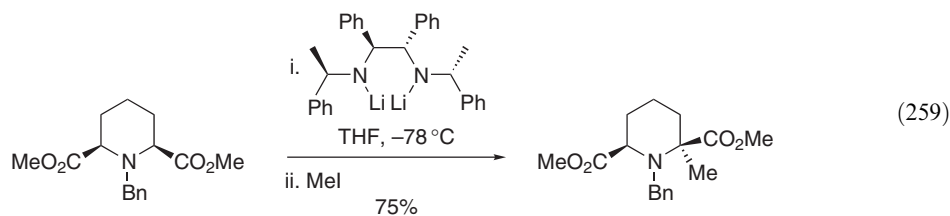
1.04.4.4 Alkylation of Enolate, *N*-Stabilized Carbanions

A phenomenon of memory of chirality was observed by Kawabata and co-workers during the α -alkylation of phenylalanine derivatives [<1998MI373>](#). The authors implied that the asymmetry due to a stereogenic center present in the substrate may be preserved in the aggregate structure of the enolate intermediate in the form of dynamic axial chirality. Enantiomeric excesses were shown to be highly solvent- and electrophile-dependent ([Equation \(252\)](#)) [<1994JA10809, 2000OL3883, 2003T965>](#). An original strategy based on Seebach's concept of self-regeneration of stereogenic centers (SRS principle) [<1996AG\(E\)2708>](#) using preformed chiral amine-borane complexes was published by Mioskowski, Le Gall, and co-workers and was applied in the asymmetric alkylation of alanine ([Equation \(253\)](#)) [<1996AG\(E\)430>](#) and proline derivatives ([Equation \(254\)](#)) [<1996JOC7244>](#). Thus, deprotonation of a unique amine-borane diastereoisomer, obtained by treatment of α -amino acid derivatives with $\text{BH}_3\cdot\text{SMe}_2$ in hexane, with LDA or KHMDS gave the resulting enolate which can be selectively quenched by a variety of primary haloalkanes. Another example of asymmetric memory maintained by a stereogenic boron atom has been reported by Vedejs for the enolate alkylation of oxazaborolidinones. Substrates are prepared from the corresponding α -amidino carboxylate derivatives as unique diastereomers by crystallization-induced asymmetric transformation (AT). The alkylation proceeds under Bu^tOK metallation conditions without loss of configuration at the boron center and with good-to-high diastereoselectivities ([Equation \(255\)](#)) [<1999JA2460>](#).



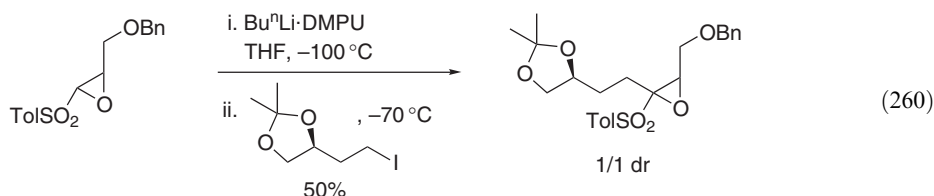
The enantioselective alkylation of prochiral *t*-butyl glycinate-benzophenone Schiff bases under mild phase-transfer conditions has been recently developed by Corey for the preparation of variously substituted chiral nonracemic amino acids. The asymmetry was introduced by using enantioenriched ammonium salts as phase-transfer catalysts. Experiments carried out with *O*-(9)-allyl-*N*-(9-anthracenylmethyl)-cinchonidinium bromide <1997JA12414> or Maruoka's *C*₂-symmetric chiral spiro-ammonium salt <1999JA6519> gave excellent enantiomeric excesses (Equation (256)). Copper(salen) complex is capable of catalyzing the asymmetric alkylation of alanine enolates under mild conditions <2003TL2045>. Seebach and co-workers <1987HCA1676> had initially investigated lithiation and functionalization of aziridine esters and thioester analogs; for aziridine esters derived from *D*-serine it was recently reported by the research group of Husson. The carboxylate anion of the (2(*S*))-*t*-butyl ester, generated by deprotonation with LDA in THF, is chemically and configurationally stable at -78°C due to the presence of a chelating methoxy group. Thus, the lithioenolate was alkylated with retention of configuration. In contrast, the (2(*R*))-compound gives only self-condensation adducts. However, a chelating solvent such as DME, can stabilize the lithioenolate intermediate and reduce the amount of self-condensation (Equation (257)) <2000TL651, 2001EJO2589>. Recently, Palomo used oxazolidinone auxiliaries for diastereoselective α -alkylation of 3-oxazolidinyl azetidin-2-one giving α -substituted α -amino β -lactams as the key intermediates required in the preparation of lactam peptide fragments (Equation (258)) <1999AG(E)3056, 2000T5563>. Within the context of his studies on asymmetric enolization reactions, Simpkins recently achieved the desymmetrization of a *meso*-piperidine diester via a diastereo- and enantioselective lithiation–substitution sequence mediated by a chiral *bis*-lithium amide base. Substituted piperidines were isolated in good yields (Equation (259)) <1999SL1292>.





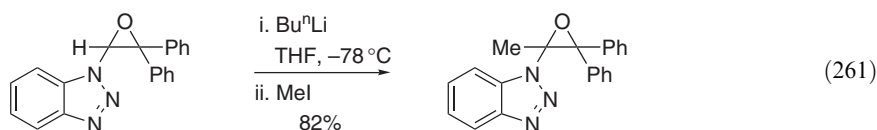
1.04.4.5 Alkylation of *O,S*-Stabilized Carbanions

Seminal studies on α -lithiation of phenylsulfonyl epoxides were carried out by Jackson in 1991, who confirmed the configurational stability of the related oxiranyl anions <1991JCS(P1)897, 1992JCS(P1)2863>. A general procedure for their alkylation was also described and then applied by Mori and co-workers. Deprotonation with Bu^nLi at -100°C in THF/DMPU followed by reaction with elaborated alkyl iodides liberates the substituted epoxides in moderate yields (Equation (260)) <1996TL2605>.



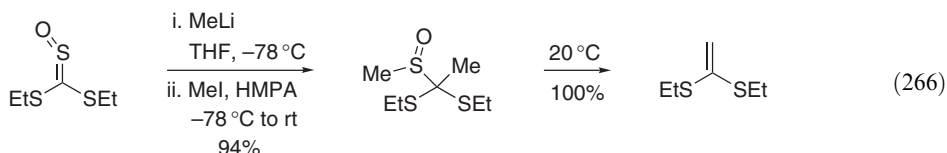
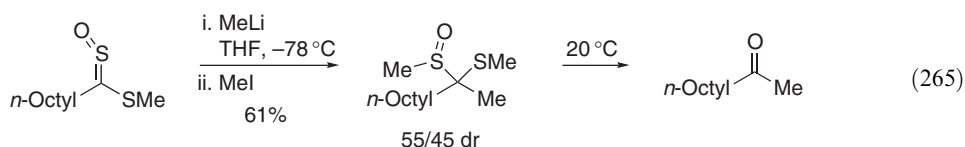
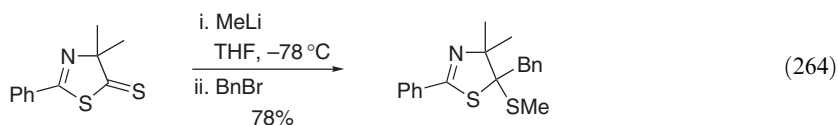
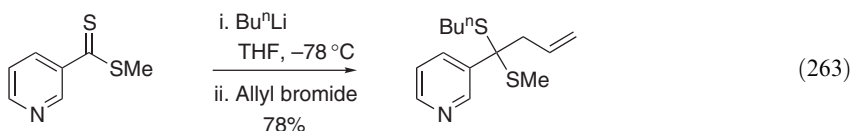
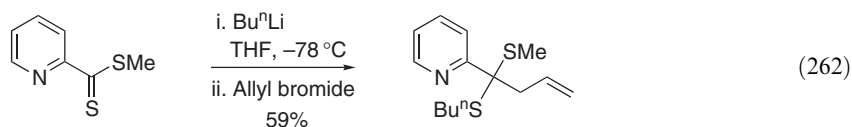
1.04.4.6 Alkylation of *O,N*-Stabilized Carbanions

As reported by Katritzky, a similar lithiation of benzotriazolyloxiranes with Bu^nLi at low temperature (-78°C) gives benzotriazolyl-stabilized oxiranyllithiums, which react with primary haloalkanes (Equation (261)) <2003JOC407>.



1.04.4.7 Alkylation of *S,S*- or *Se,Se*-Stabilized Carbanions

Thiophilic addition of organolithiums and Grignard reagents to dithioesters has focused the attention of several research groups over the past few years. These various studies are now part of a review published by Metzner in 1992 <1992S1185>. Compared with carbonyl groups, the small difference of electronegativity between sulfur and carbon atoms as well as the high polarizability of sulfur were found to sometimes reverse the reactivity of thiocarbonyls toward nucleophilic addition of organometallics. Thus, the transient dithioacetal-stabilized anion, considered as an equivalent of acyl anion, can be trapped by organic halides. To illustrate this reactivity, Quéguiner and Metzner reported the sequential alkyl- and aryllithium addition to 2- and 3-pyridyl dithioesters followed by the electrophilic quenching of the resulting carbanions (Equations (262) and (263)) <1998H(48)2019>, while Shi and Heimgartner achieved this transformation on 4,4-dimethyl-1,3-thiazole-5(4*H*)-thiones (Equation (264)) <1996HCA371>. According to research by Zwanenburg <1978T1585, 1982RTC1>, and more recently Metzner <1993TL6741, 1996TL4507, 1998H(48)2019>, aliphatic and heteroaromatic sulfines behave like dithioesters toward organolithiums leading to substituted dithioacetal oxides which are cleaved spontaneously to related ketones at room temperature in moderate yields (Equation (265)). An example of addition-alkylation of trithiocarbonate oxides is depicted in Equation (266) <1997T1323>.

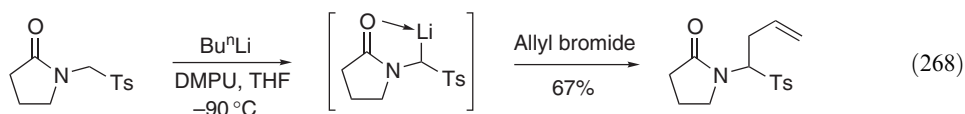


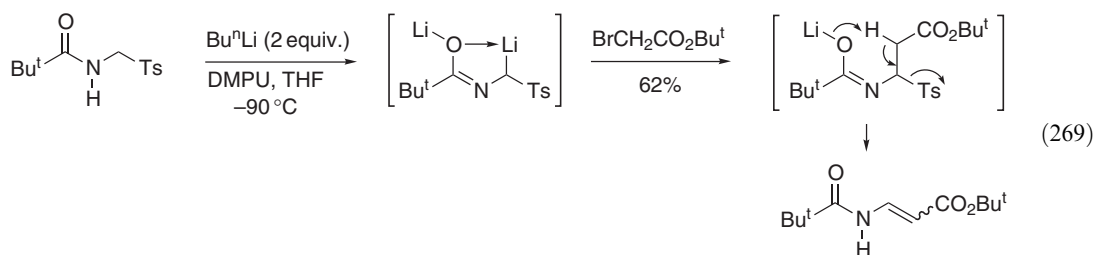
By analogy with dithianes, metallation of 1,3-diselenanes has been investigated by Krief and Defrère. Treatment of diselenanes with strong bases such as LDA leads to the formation of 2-lithio 1,3-diselenanes, whereas alkylolithiums act as nucleophiles and tend to cleave one of the C—Se bonds instead of the C—H bond by proton abstraction [\[1996TL8011\]](#). Methylation of the generated metallic species with methyl iodide proceeds in good yield [\[1996TL2667\]](#). On conformationally rigid systems including 4,6-dimethyl-1,3-diselenanes, deprotonation with metal amides (LDA or KDA) or organolithiums affords the related organometallics exclusively in the equatorial position, which undergo subsequent alkylation with retention of configuration (Equation (267)).



1.04.4.8 Alkylation of *N,S*-Stabilized Carbanions

Yus, Nájera and co-workers reported that *N*-(tosylmethyl)amides can be α -lithiated with BuⁿLi/DMPU at -90°C . The monanion reacted with activated halides and gave the α -substituted amido sulfones (Equation (268)) whereas the unstable dianion underwent sequential alkylation and intramolecular elimination of the sulfinyl group affording *N*-acylenamines (Equation (269)) [\[1997SL491\]](#).

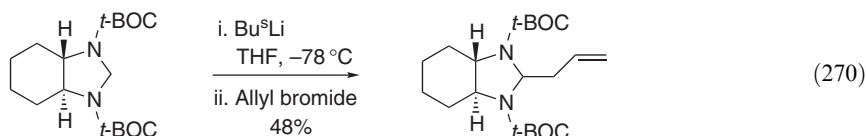




1.04.4.9 Alkylation of *N,N*-Stabilized Carbanions

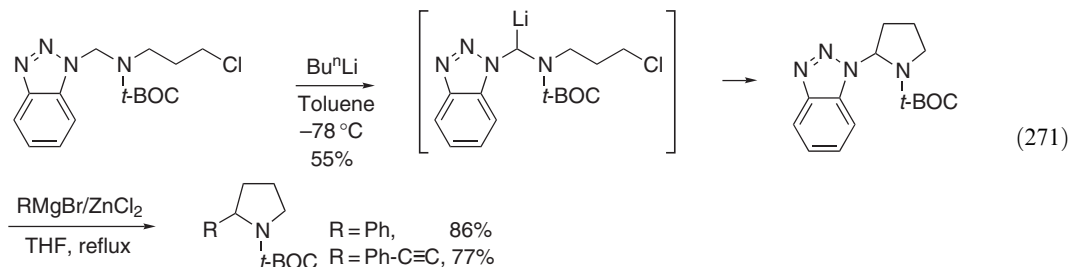
1.04.4.9.1 By intermolecular substitution

Synthetic equivalents of acyl anions are well represented by the chemistry developed on lithiated dithianes and mixed ketals [<1989T7643>](#). More recently, Coldham's group showed that the direct lithiation of imidazolidine with Bu^sLi occurs at the C-2 position between the two nitrogen atoms giving the corresponding anion, which may be also considered as a potential equivalent of an acyl anion. This transient lithiated species reacts as a nucleophile with alkyl halides and yields the C-2 alkylated imidazolidines. Thus, the carbonyl group can be liberated by hydrolysis of the imidazolidine ring by action of TFA ([Equation \(270\)](#)) [<1996SL1109, 1998T14255>](#).



1.04.4.9.2 By intramolecular substitution

In this area, an example reported by Katritzky and co-workers concerns the preparation of 2-substituted *N*-BOC pyrrolidines by intramolecular substitution of primary chloride present on the side chain of *N*-BOC-*N*-(benzotriazol-1-ylmethyl)-3-chloropropylamine, by the α -lithiated intermediate. The regioselective proton abstraction, achieved at the C-2 position with Bu^nLi in toluene at -78°C , leads to the related carbanion-stabilized by *N*-BOC and benzotriazole moieties. Thus, alkylation at the C-2 position can be realized via nucleophilic displacement of the benzotriazolyl group by organozinc reagents ([Equation \(271\)](#)) [<2000TL9691>](#).



ACKNOWLEDGMENTS

The authors thank the Centre National de la Recherche Scientifique (CNRS) and the Ministère de l'Éducation Nationale for the financial support.

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Biographical sketch



Maurice Santelli was born in Marseille in 1939. He received his Ph.D. in chemistry working with Professor M. Bertrand (homo-allenylic participation, nonclassical ion). He had a postdoctoral position at the University of Cambridge (UK) in 1973 (Professor R. A. Raphael). After an appointment at the University of Oran (Algeria) (1975–1977), he is presently Professor of Chemistry at the University of Aix-Marseille III. His main research areas are physical organic chemistry, electrophilic activation, palladium-chemistry with new ligands, and the synthesis of bioactive products (polyunsaturated fatty acids, Prelog-Djerassi lactone, non-natural steroids).



Cyril Ollivier was born in Neuilly, France, in 1971. He received his Diplôme d'Etudes Approfondies in Organic Chemistry from Pierre et Marie Curie University (Paris) under the guidance of Professor Jean-François Normant and Dr. Fabrice Chemla in 1995, working on the reactivity of carbenoids in 1,2-metallate rearrangement. After one year of national service at the ENSTA (Paris) as scientist associate in the laboratory of Dr. Laurent El Kaim, he joined Professor Philippe Renaud's group at the University of Fribourg in 1996 for a Ph.D. program in collaboration with the laboratory of Prof. Max Malacria, Pierre et Marie Curie University (Paris). He worked on the utilization of organoboranes as source of radicals, on the developments of novel radical hydroxylation and azidation processes, and gained his doctorate in cotutelle in 2000. He was awarded a Swiss National Foundation Fellowship to pursue research studies at the University of Texas at Austin (Austin, TX) in Professor Philip Magnus' group where he was involved in the total synthesis of guanacastepene. In 2002, he joined the CNRS at Aix-Marseille III University where is working with Prof. Maurice Santelli. His research focuses on the synthesis of steroids, particularly vitamin D analogs.

1.05

One or More CC Bond(s) Formed by Substitution: Substitution of Chalcogen

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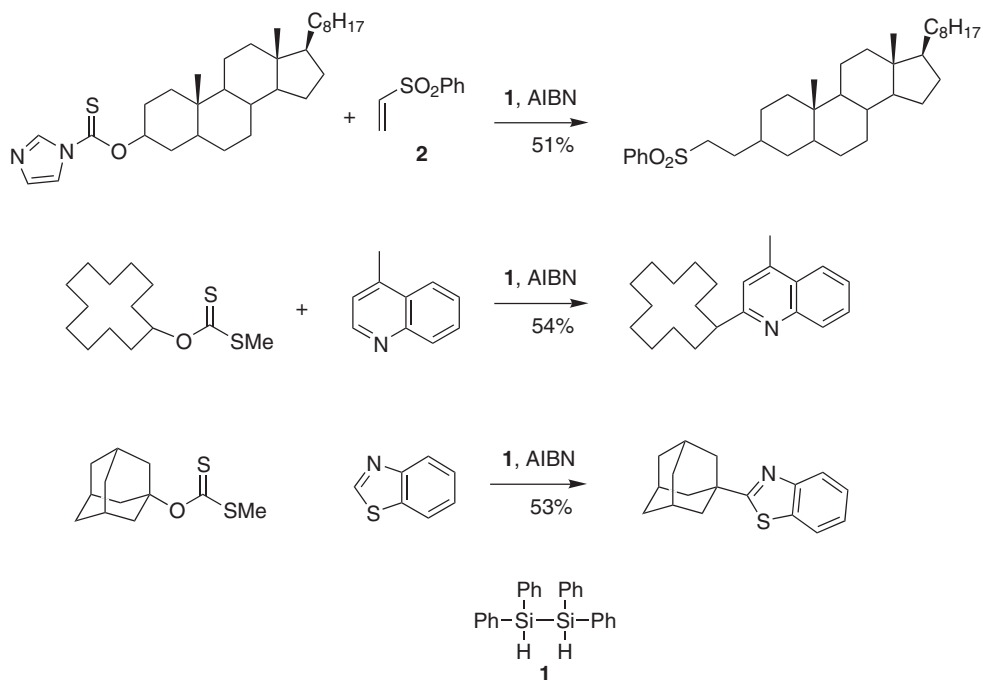
1.05.1 SUBSTITUTION OF OXYGEN FUNCTIONS

1.05.1.1 Radical Reactions

Radical reactions have become an important tool in organic synthesis. Numerous reviews and books have recently been published (e.g., <[B2001MI001](#), [B2001MI002](#)>). Aspects of stereoselectivity have also been reviewed <[B1996MI003](#)>.

1.05.1.1.1 Intermolecular reactions

Various examples of radical formation from thiocarbonyl derivatives such as xanthates or thiocarbonates and their subsequent addition to olefins have been mentioned in the corresponding chapter 1.05 <1995COFGT(1)171>. For recent reviews on radical reactions with xanthates, see <1997AG(E)672, B2001MI004>. Further examples involving cleavage of the C—S bond, which is frequently applied in organic synthesis, are discussed in Section 1.05.2.1. In the Barton–McCombie reaction, which leads to deoxygenation, radical intermediates are generated with tin reagents and a radical chain initiator (e.g., AIBN). These intermediates readily add to sterically unhindered alkenes such as acrylate derivatives. There are several problems related to the use of tin derivatives such as toxicity, difficulties in the work-up, and their complete removal from the products. Other reagents such as tetraphenyldisilane **1** have been tested (Scheme 1) <2000JOC2816>. Methylxanthate and imidazole thiocarbonyl groups were successfully used as leaving groups. The procedure was applied to the addition of alkyl radicals to phenylvinyl sulfone **2** and nitrogen-containing heterocycles.

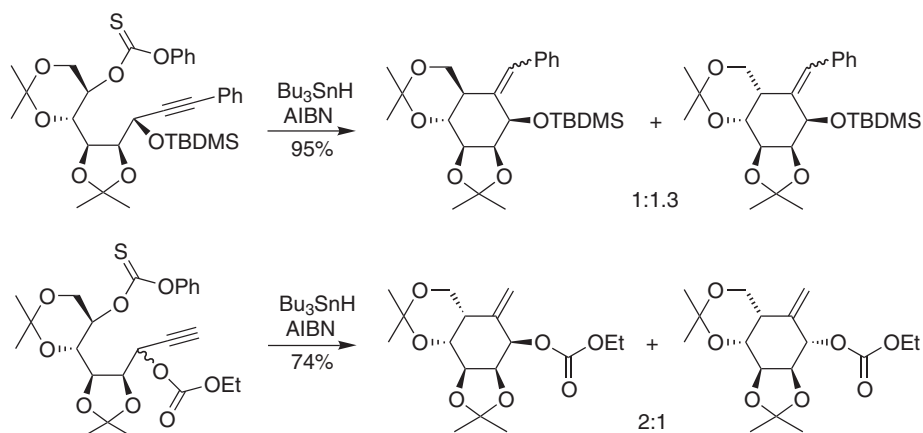


Scheme 1

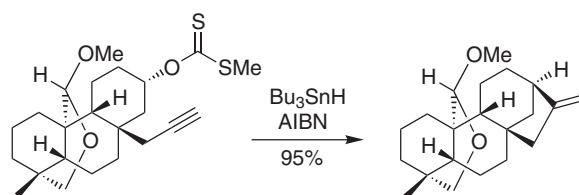
1.05.1.1.2 Intramolecular reactions

As already shown in COFGT (1995), intramolecular radical reactions are more frequently studied than intermolecular reactions and they have recently been reviewed <1996OR301>. The intramolecular cyclization of thiocarbonates was successfully applied to the synthesis of carbasugar structures starting from pyranose derivatives (Scheme 2) <1999CC175, 2002TL5559>. These examples indicate that the methodology is compatible with a large variety of functional groups and can be applied to the synthesis of natural products and constrained oligocyclic systems (Scheme 3). In the latter case, the methylxanthate function was used as a leaving group <1997JA9929>.

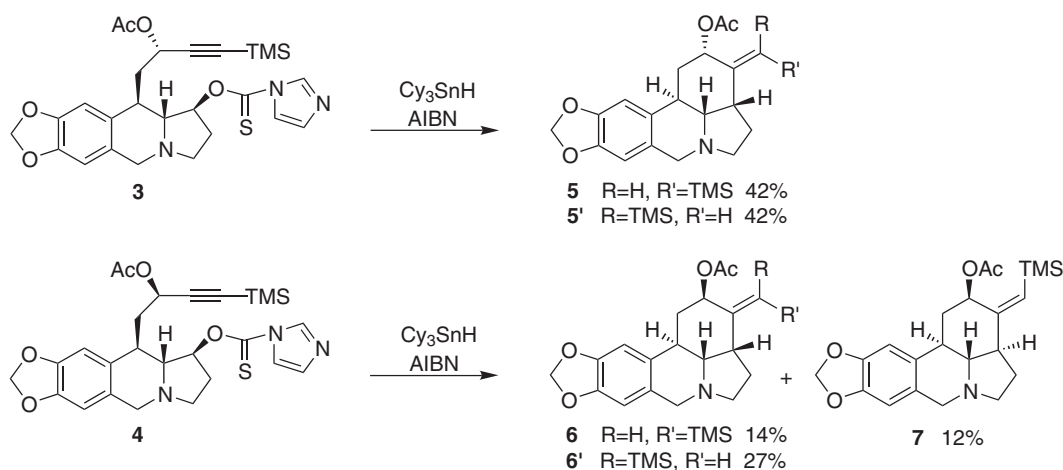
In intermolecular reactions, the imidazole thiocarbonyl function was successfully used as a leaving group. The reaction was applied to the synthesis of complex structures such as lycorine derivatives (Scheme 4) <2002H2279>. It should be mentioned that the cyclization proceeded according to an *exo*-cyclic process leading to a mixture of regioisomers and that the stereogenic centers influence the stereoselectivity of the reaction. The epimer **3** stereospecifically yielded the cyclization products **5** and **5'**, whereas the stereoisomer **4** yielded **6** and **6'**, in addition to the diastereomeric lycorine derivative **7**.



Scheme 2



Scheme 3



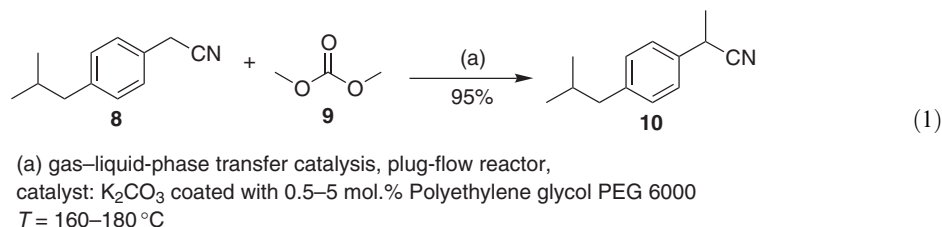
Scheme 4

1.05.1.2 Displacement of Alcohol Derivatives

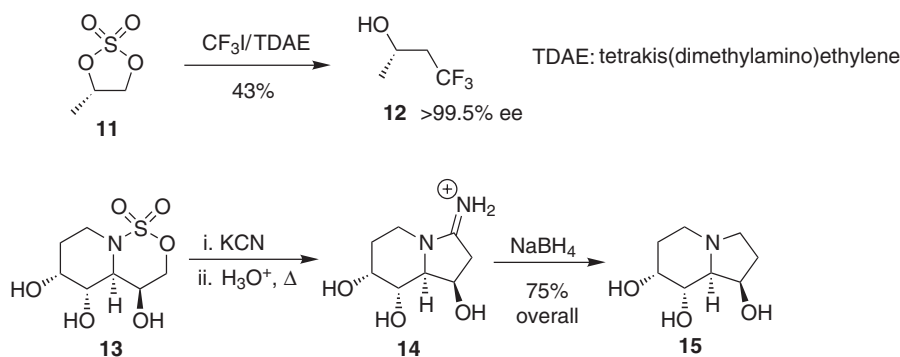
Under various conditions, the hydroxy group or many of its derivatives are good leaving groups and C—C bonds can be formed via nucleophilic substitution by using C-nucleophiles. Recently, a large variety of methods have been developed in the field of organometallic chemistry [<2000CRV2739, B1998MI009>](#). In this context, cross-coupling reactions have been particularly studied [<B1998MI005>](#). Halogen atoms are frequently used as leaving groups along with oxygen derivatives such as esters and the triflates. In the following sections, cross-coupling reactions are preferentially discussed. For further reviews and books, see [<1995CRV2457, B1998MI009, B2002MI010, 2002S2473, 2002SL1939, 2003AG\(E\)1604>](#). For reviews on asymmetric catalysis, see [<B1999MI016>](#).

1.05.1.2.1 Alkyl alcohol derivatives

The well-known dimethylcarbonate **9** was recently used for C-methylation under particular optimized eco-friendly reaction conditions. This methylation reagent is nontoxic and biodegradable which make it a “green reagent” <2002ACR706>. The monomethylation of the phenylacetonitrile derivative **8** leading to the ibuprofen precursor, compound **10** was achieved using special reaction conditions or phase transfer catalysis (Equation (1)). For various other examples, see <2002JOC1071>.

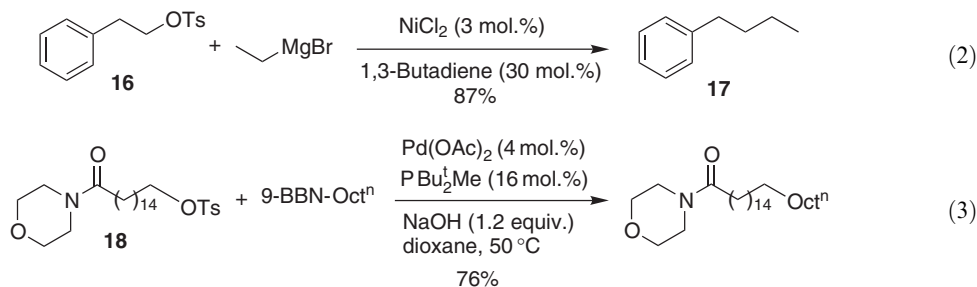


Cyclic sulfate derivatives have been used to synthesize complex natural products or products possessing interesting biological activity <2000T7051>. For instance, the fluorinated chiral butanol **12** was obtained by opening the optically active cyclic sulfonate **11** which was attacked by the trifluoromethyl anion (Scheme 5) <2002OL4671>. This anion was generated by reduction of trifluoromethyl iodide with tetrakis(dimethylamino)ethylene (TDAE). In the case of **13**, the oxathiazinane ring was opened by the attack of the cyanide anion and the obtained bicyclic iminium derivative **14** was transformed to the indolizidine derivative **15** <2003JA2028>.

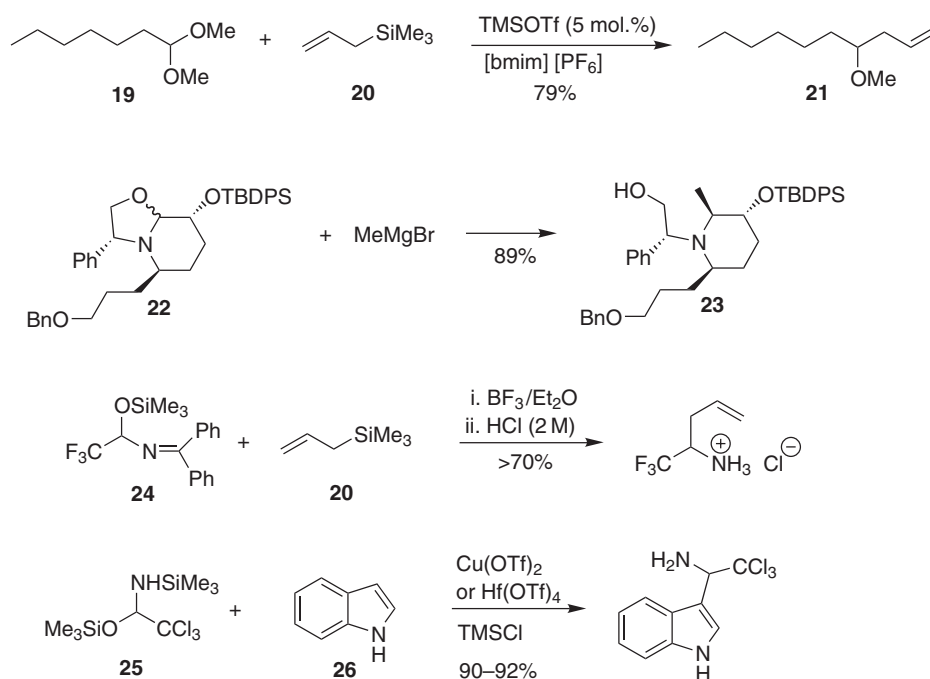


Scheme 5

For a long time, cross-coupling reactions of Grignard reagents with alkyl halides, triflates, or tosylates had not been very efficient, since slow oxidative addition of the substrates and β -elimination from the alkyl metal intermediates easily occur <2003AG(E)384>. Recently, however, efficient reaction conditions have been developed to carry out these cross-coupling reactions (Equation (2)). In a nickel-catalyzed reaction, 1-phenylbutane **17** was obtained in high yields from the cross-coupling of 2-phenylethyl tosylate **16** with ethylmagnesium bromide <2002JA4222>. The high efficiency of the reaction is due to the use of 1,3-butadiene instead of phosphine ligands. Recently, a flexible method for the coupling of various alkyl tosylates such as **18** with alkyl 9-borabicyclononane derivatives (Suzuki cross-coupling) has been developed (Equation (3)) <2002AG(E)3910>. The reaction tolerates a variety of other functional groups such as esters, amides, nitriles, ketones, or free alcohols.



In the case of acetals or amins, C—C bonds can be formed by replacement of oxygen-containing groups. Recent examples are depicted in Scheme 6. Acetal **19** was transformed into **21** when heated with allyltrimethyl silane **20** <2003OL55>. For a similar reaction with chiral induction, see <2003OL2367>. In these reactions silicon-containing Lewis acids such as TMSOTf are used. For a review on C—C bond-forming reactions mediated by such Lewis acids, see <2003CRV733>. It is worth noting that the reactions were carried out in ionic liquids such as butylmethylimidazolium hexafluorophosphate ([bmim][PF₆]). Reactions carried out in such media are eco-friendly and can be easily performed <2000AG(E)3772>. The stereospecific reaction of oxazolidine **22** with methylmagnesium bromide yielded the piperidine derivative **23** <2003EJO2062>. Trifluoromethyl derivatives are also obtained by the addition of nucleophiles such as allyltrimethyl silane **20** to the amins derivative **24** <2002JOC997>. A similar reaction was used for the addition of heterocyclic aromatic compounds such as **26** to the trichloroacetaldehyde-derived amins **25**. The reaction was also performed with isocyclic aromatic compounds. The procedure was particularly efficient when Cu(OTf)₂ or more frequently Hf(OTf)₄ were used as Lewis acid catalysts <2003JOC483>.

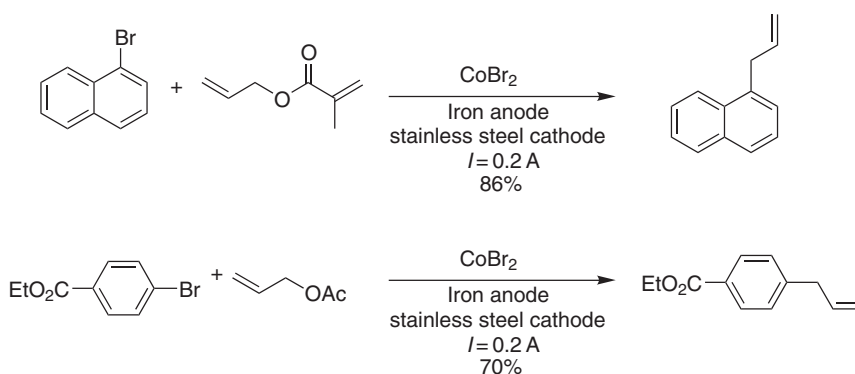


Scheme 6

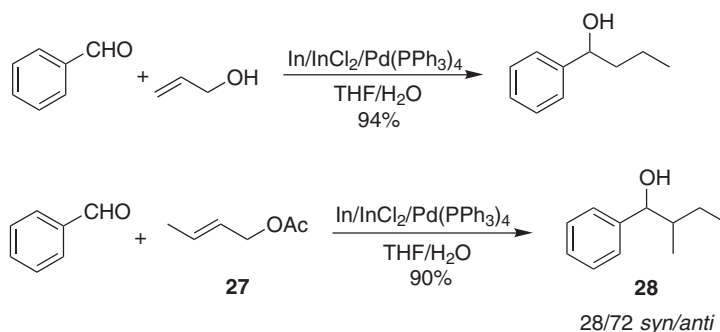
1.05.1.2.2 Allylic alcohol derivatives

The allylation of aromatic compounds was achieved using a cross-coupling of allyl esters with aryl halides (Scheme 7) <2003JOC1142>. The reaction tolerates a variety of functional groups on the aromatic ring and this reaction can also be carried out with heterocyclic aromatic compounds. The reaction is catalyzed by CoBr₂ which is regenerated by a sacrificial iron anode. This efficient electrochemical process competes with more classical reaction conditions when zinc or manganese in the presence of FeBr₂ are used as reducing agents <2003OL1043, 2003JOC2195>. Recently, a Cu(OTf)₂ catalyzed addition of alkyl or aryl substituents to cinamyl alcohol derivatives using trialkyl- or triaryliminium compounds has been published <2003JOC2518>.

Indium-mediated addition of allyl groups to carbonyl compounds, mainly to aromatic aldehydes, can be carried out in the presence of water. These reactions have recently been reviewed <2003S633, 2003S765, 1999T11149, B1998MI007>. Allylic alcohols can also be used, and in this case the reaction is catalyzed by palladium (Scheme 8) <2003S775>. When butenyl acetate **27** was used, only the branched product **28** was isolated. In this case, an electrochemical method, using only FeBr₂, was also developed to perform the addition of allylic alcohol derivatives to aliphatic and aromatic aldehydes and ketones with yields greater than 90% <2003JOC3121>.

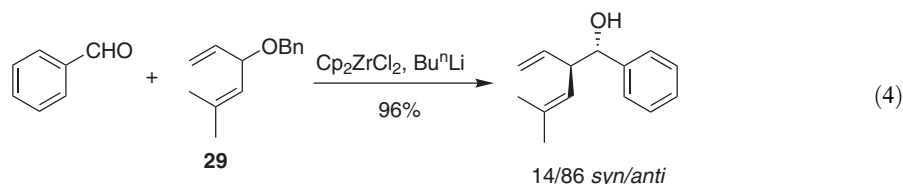


Scheme 7

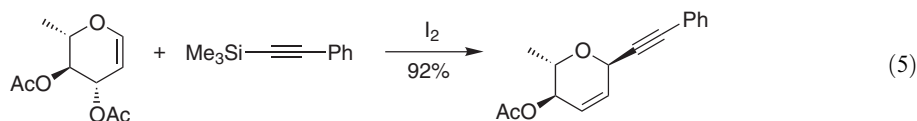


Scheme 8

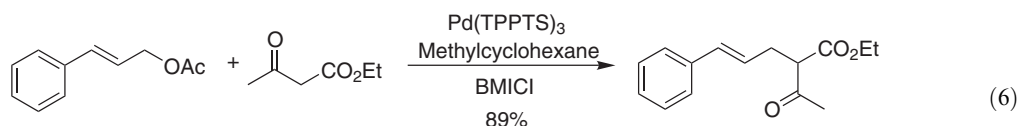
The addition of pentadiene derivatives such as **29** to aromatic aldehydes mediated by zirconocene dichloride was achieved (Equation (4)) <2001TL1677>. The reaction was also carried out with aliphatic aldehydes. The addition was regio- and stereoselective. For similar transformations, see <1995T4507>.



In carbohydrate chemistry, the iodine-catalyzed addition of silylacetylene derivatives was applied to the stereoselective synthesis of C-glycosides using an S_N2' reaction (Equation (5)) <2003S247>. The reaction was also carried out with methoxy or allyloxy functions as leaving groups.

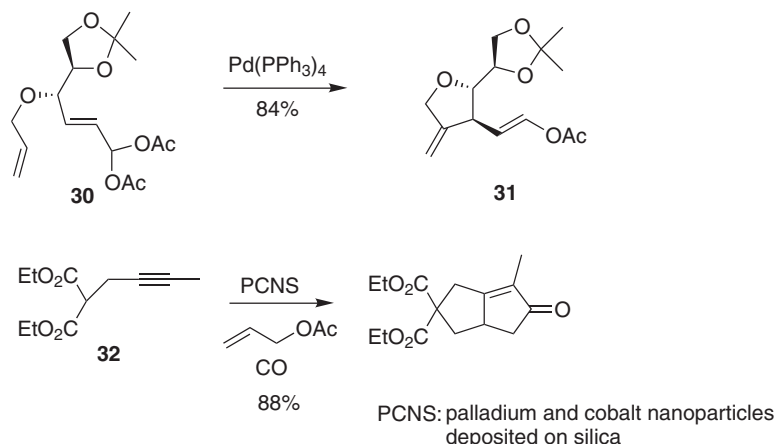


The palladium-catalyzed addition of C-nucleophiles such as malonates or acetoacetate to allyl acetates (Trost–Tsuji reaction) has been intensively studied by many research groups <B2002MI006>. Recently, this reaction has been carried out in ionic liquids which enormously facilitates the procedure (Equation (6)) <1999JMOC121>. The reaction was performed in the ionic liquid 1-butyl-3-methylimidazolium chloride (BMICl) using palladium chloride as catalyst precursor. Under these conditions, the reaction is faster, the catalyst is more stable, and no cinnamyl alcohol is isolated as a by-product. The reaction was also performed on solid support with various substrates <1998CC793>. For a review of palladium-catalyzed reactions on solid phase, see <2003T885>.



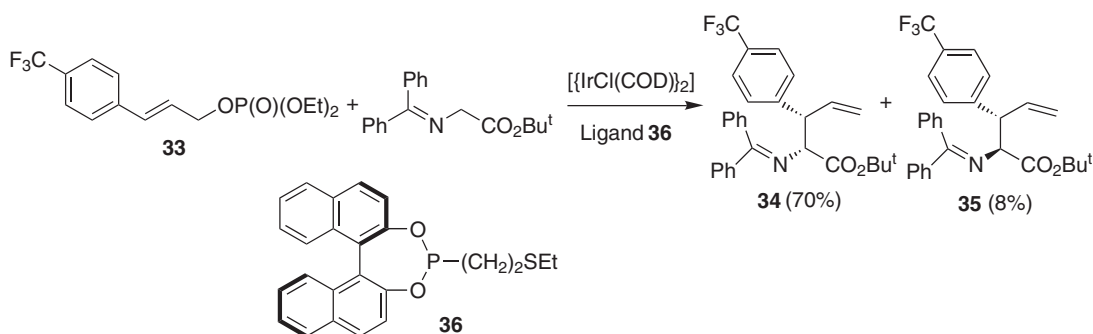
TPPTS: triphenylphosphinetrisulfonate, sodium salt

Intramolecular metalla-ene reactions can be catalyzed by Pd(0) to produce cyclic products. When substrate **30** is treated with Pd(PPh₃)₄, one acetyl group of the acetal function acts as a leaving group and compound **31** is isolated in good yield (Scheme 9) <1999T3467>. For another interesting stereoselective cyclization of this type, see <2003TL653>. For a review on palladium-catalyzed allylic substitutions, see <B1998MI014, B1998MI015>. A bifunctional heterogeneous catalyst was developed for the sequential allylic alkylation Pauson–Khand reaction <2002OL4361>. This reaction sequence is catalyzed by palladium and cobalt nanoparticles deposited on silica (PCNS). The palladium nanoparticles catalyze the addition of allyl acetate to **32** and the cobalt nanoparticles catalyze the Pauson–Khand reaction when carbon monoxide is present. In the absence of CO, the Pauson–Khand reaction does not take place.



Scheme 9

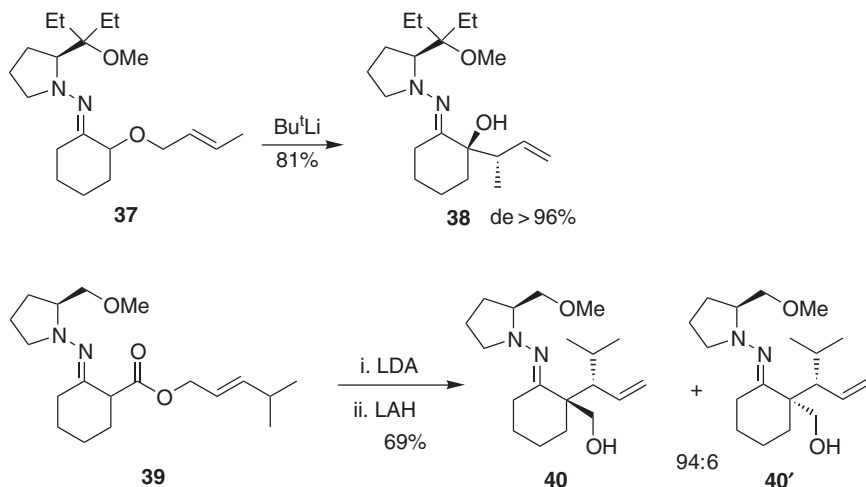
Recently, in the context of these reactions, much attention has been paid to chiral induction and asymmetric catalysis <1996ACS189> in order to apply them to the total synthesis of natural products and/or biologically active compounds <2003AG(E)2580> (see also Section 1.05.1.2.4). In Scheme 10, an iridium-catalyzed reaction effects the transformation of the allylphosphonate derivative **33** to **34** and **35** <2003AG(E)2054>. The reaction is regiospecific and highly diastereoselective and the enantioselectivity of both diastereomers **34** and **35** exceeds 90%. The high ee values result from the chiral induction of the binaphthol-derived ligand **36**. An



Scheme 10

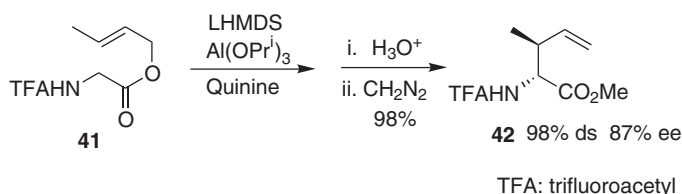
iridium-catalyzed reaction with malonate and allyl acetate derivatives was also performed using binaphthylphosphate ligands similar to **36** <2003EJO1097>. For a review on iridium-catalyzed reactions, see <2002SL1954>.

Various sigmatropic rearrangements involving allylic alcohol derivatives have been carried out and one of the main topics in these reactions concerns the stereoselectivity. For reviews on these reactions, see <1996TA1847, 1999CSR43>. In Scheme 11, examples of stoichiometric chiral induction are depicted. Compound **37** is stereospecifically transformed via a [2,3]-Wittig rearrangement and only the *anti* isomer **38** is obtained <1996S1438>. For examples in the acyclic series, see <1996T1503>, and for a review of this reaction, see <2003SL1088>. Substrates such as **39** have been transformed with high diastereoselectivity, via a [3,3]-sigmatropic Carroll rearrangement, into **40** and **40'** <1995AG(E)2278>. For further examples, see <1996LA1095>.



Scheme 11

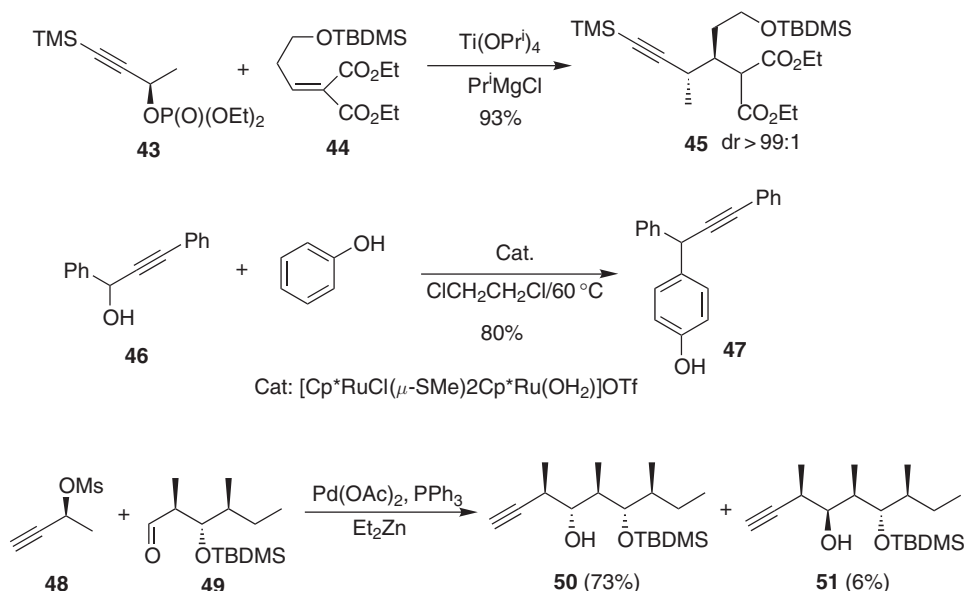
Chiral induction can also be performed via asymmetric catalysis. For instance, the glycine derivative **41** was transformed into the chiral α -amino acid derivative **42** with high diastereoselectivity and enantioselectivity (Scheme 12) <2002CEJ1850>. For this transformation, quinine was shown to be the best asymmetric catalyst. For an application to the asymmetric synthesis of natural products using a similar reaction, see <1995JA193>.



Scheme 12

1.05.1.2.3 Propargylic alcohol derivatives

In Scheme 13, some recent examples of metal-catalyzed nucleophilic substitution with propargylic alcohol derivatives are presented. The titanium-mediated coupling reaction between the propargyl derivative **43** and the malonate derivative **44** yielded **45** in high yields <2003TL2113>. Only one diastereomer was isolated. Using a binuclear ruthenium complex as catalyst, the propargylic alcohol **46** can add to phenol to produce **47** which was isolated in high yield <2003AG(E)1495>. The reaction was also extended to heterocyclic aromatic compounds such as furans, pyrroles, or thiophenes, and to bicyclic aromatic compounds such as naphthalene and azulene. For a review on ruthenium-catalyzed C—C bond formation, see <2001CRV2067>. The reaction is similar to the Nicholas reaction in which the triple bond is protected by a binuclear

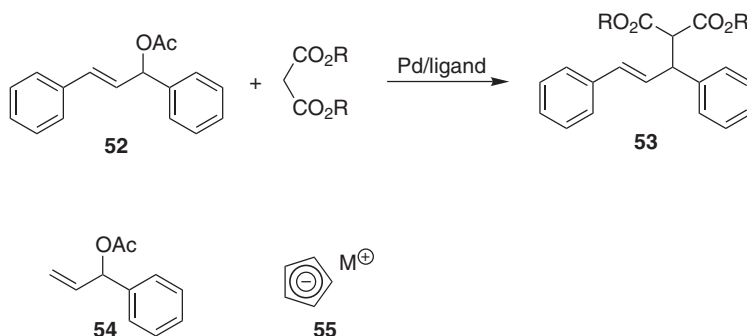


Scheme 13

cobalt complex. For a review on this reaction, see <2002T4133>. A palladium-catalyzed coupling reaction between the propargylic mesylate **48** and the aldehyde **49** is also highly diastereoselective, and the *anti,anti,anti*-polypropionate derivative **50** is obtained as the major product <2001JOC7825>. Only minor amounts of the epimer **51** were isolated. The configuration of the stereogenic center of the secondary alcohol formed in **50** is induced by the chiral center of the propargylic mesylate **48**. The configuration of the chiral center in the α -position of the aldehyde **49** plays a minor role. For a review of palladium-catalyzed reactions of propargylic compounds, see <1995AG(E)2589>.

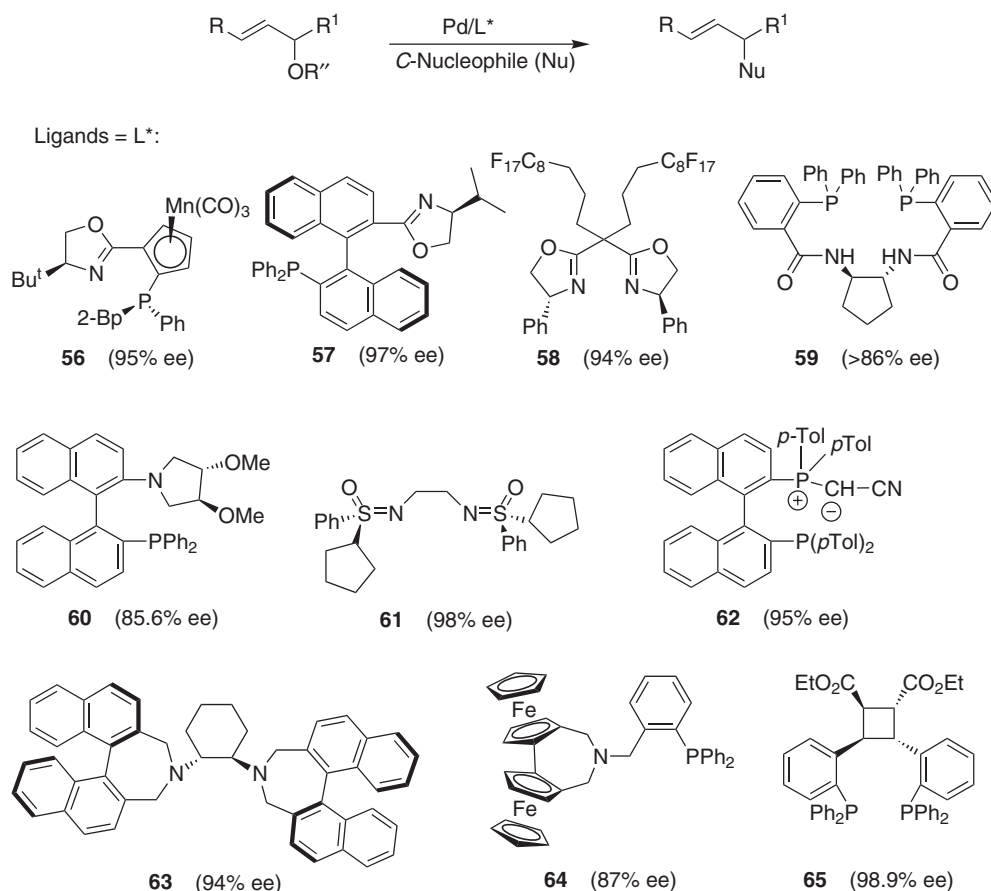
1.05.1.2.4 Benzylic alcohol derivatives

Palladium-catalyzed addition of malonate to **52** (Trost–Tsuji reaction, cf. Section 1.05.1.2.2, Equation (6)) has been very frequently reported (Scheme 14). Other electrophiles of this type such as **54** <2003OL1713> or allyl alcohol derivatives and various C-nucleophiles, mainly stabilized by adjacent carbonyl functions, can be used <B1995MI007, B2002MI006>. In some cases, a rhodium catalyst was used. Stabilized carbanions such as the cyclopentadienyl anion **55** <2003TA511> have also been added. However, the transformation of **52** into **53** is frequently used to test different reaction conditions. Recently, the reaction was studied in aqueous media <2003ASC357> (for a review on this topic, see <1999JOM305>) and ionic liquids <2003OL31>.



Scheme 14

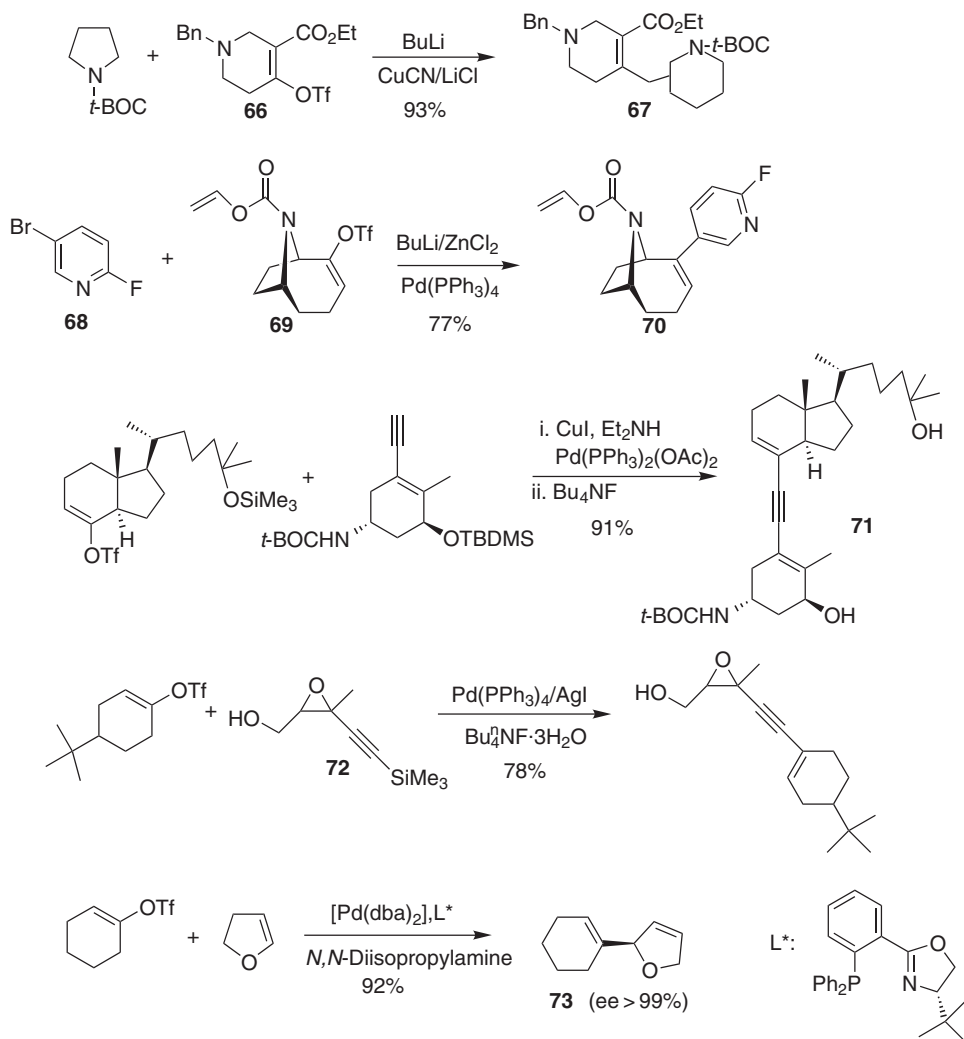
Many investigations were performed on chiral induction by using different optically active ligands <1995HCA265>. For reviews, see <1996CRV395, 1996ACS189, 1996SL705, B1999MI016, 1999JOM203>. Several studies have considered the design of suitable ligands. For a review on this topic, see <2000ACR336>. Some recently investigated ligands are depicted in Scheme 15: **56** <2002CC1270>, **57** <2003OL1713> (in a rhodium-catalyzed reaction), **58** <2003TL1449>, **59** <2001AG(E)4289>, **60** <2002TL159>, **61** <2001SL1878>, **62** <2003TA537>, **63** <2003JOC3258>, **64** <2002JOC2206>, **65** <2003OL1349>.



Scheme 15

1.05.1.2.5 Vinyl alcohol derivatives

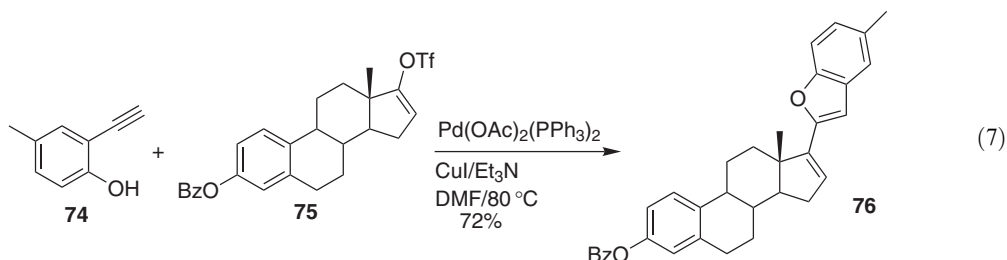
Vinyl triflates are now frequently used in cross-couplings. For a review, see <B1998MI013>. Since several functional groups are tolerated, the method can be applied to the synthesis of complex heterocyclic compounds such as **67** (Scheme 16) <2003JOC969>. Compound **67** was obtained from the coupling reaction between the vinyl triflate **66** and an organocopper reagent prepared from *N*-BOC-pyrrolidine. In this case, no further activation (e.g., by palladium) is necessary due to the presence of the α,β -unsaturated ester function in **66**. Frequently, these reactions are mediated by palladium, as in the synthesis of compound **70** <2003JOC2475>. In this case, an organozinc reagent prepared from **68** was coupled with the vinyl triflate **69**. For cross-couplings with palladium in heterocyclic chemistry, see <B2000MI008>. After deprotonation, acetylides can also be coupled with vinyl triflates as in the preparation of **71**. Most frequently, such reactions need additional copper catalysis and a secondary amine as base <2003JOC1154>. For similar examples, see <1997JOC1582>. Recently, a process using silver co-catalysis was developed <1998JOM173>. Under these reaction conditions, silylacetylene derivatives such as **72** could be coupled, and in this case fluoride is used to activate the reaction instead of an amine base <2001TL8641>. Furthermore, the use of silver instead of copper prevents a competitive ring opening of the epoxide. For further



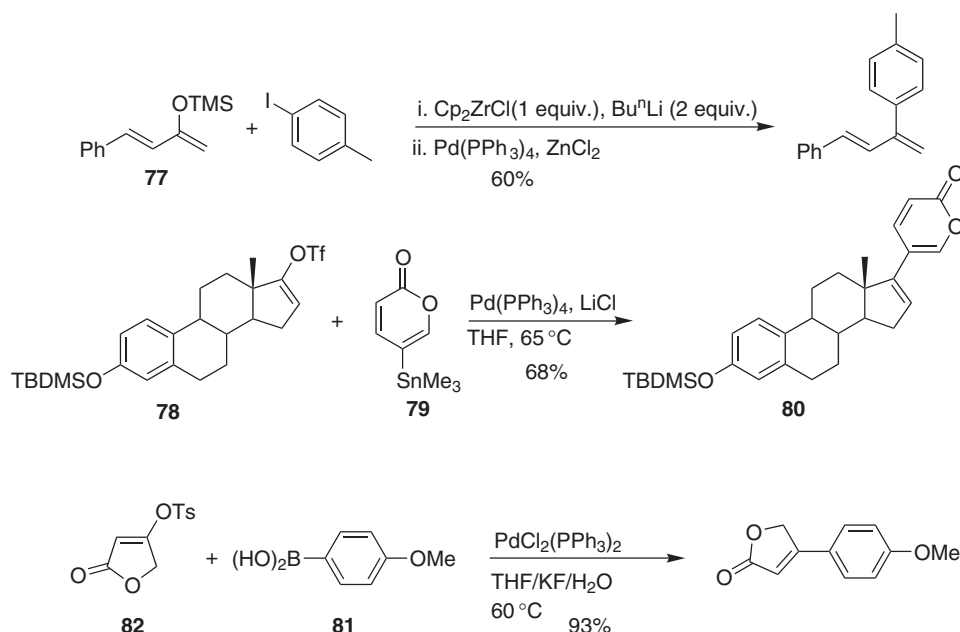
Scheme 16

discussion of the reaction conditions, see [<2001EJO4391>](#). The reaction was also successfully performed under asymmetric catalysis [<1996AG\(E\)200>](#). By adding a chiral ligand, **73** was isolated as an enantiopure compound.

When triflate **75** was added to the *o*-alkynylphenol derivative **74**, a consecutive cyclization took place, and the benzofuran derivative **76** was obtained (Equation (7)) [<1996JOC9280>](#). For a review on similar reactions, see [<1999JOM42>](#).



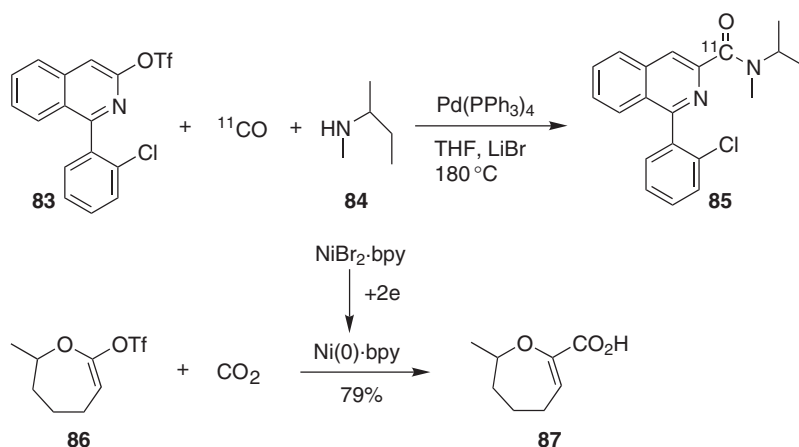
Silyl enol ether **77** (Scheme 17) was transformed into a vinylzirconium intermediate which undergoes a palladium- and zinc-catalyzed cross-coupling reaction with aryl halides [<2001SL123>](#). The steroid derivative **78** was coupled with the vinyltin compound **79** to yield **80** (Stille reaction) [<1996JOC6693>](#). Under the same conditions, the vinyltin compound **79** was



Scheme 17

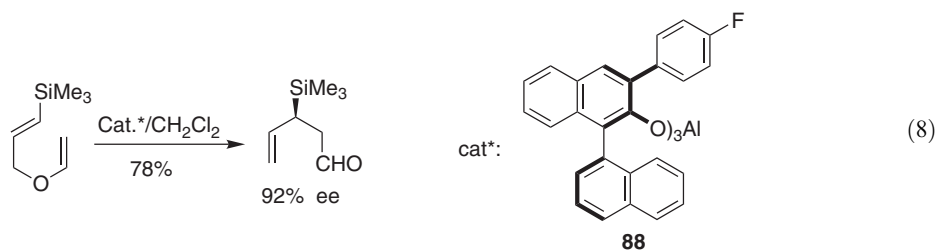
replaced by the corresponding vinyl borate [<2001TL9081>](#). Arylboronic acid **81** was coupled with the vinyl tosylate **82**. The reaction can also be performed with heterocyclic and bicyclic arylboronic acids [<2003JOC670>](#).

In a palladium-catalyzed reaction, in the presence of CO and the secondary amine **84**, triflate **83** was transformed into the amide **85** (Pk11195) which is a ligand for the ω_3 receptor and by using ^{11}C , the reaction was applied to the synthesis of isotopically labeled **85** (Scheme 18) [<2002JCS\(P1\)2699>](#). The reaction was also applied to the total synthesis of phomoidrides [<2003JOC1693>](#). For reviews on such carbonylation reactions, see [<B1998MI012, 1996AG1050>](#). In a nickel-catalyzed electrochemical reaction, the vinyl triflate **86** was transformed to the carboxylic acid **87** in the presence of CO_2 [<2002SL140>](#).



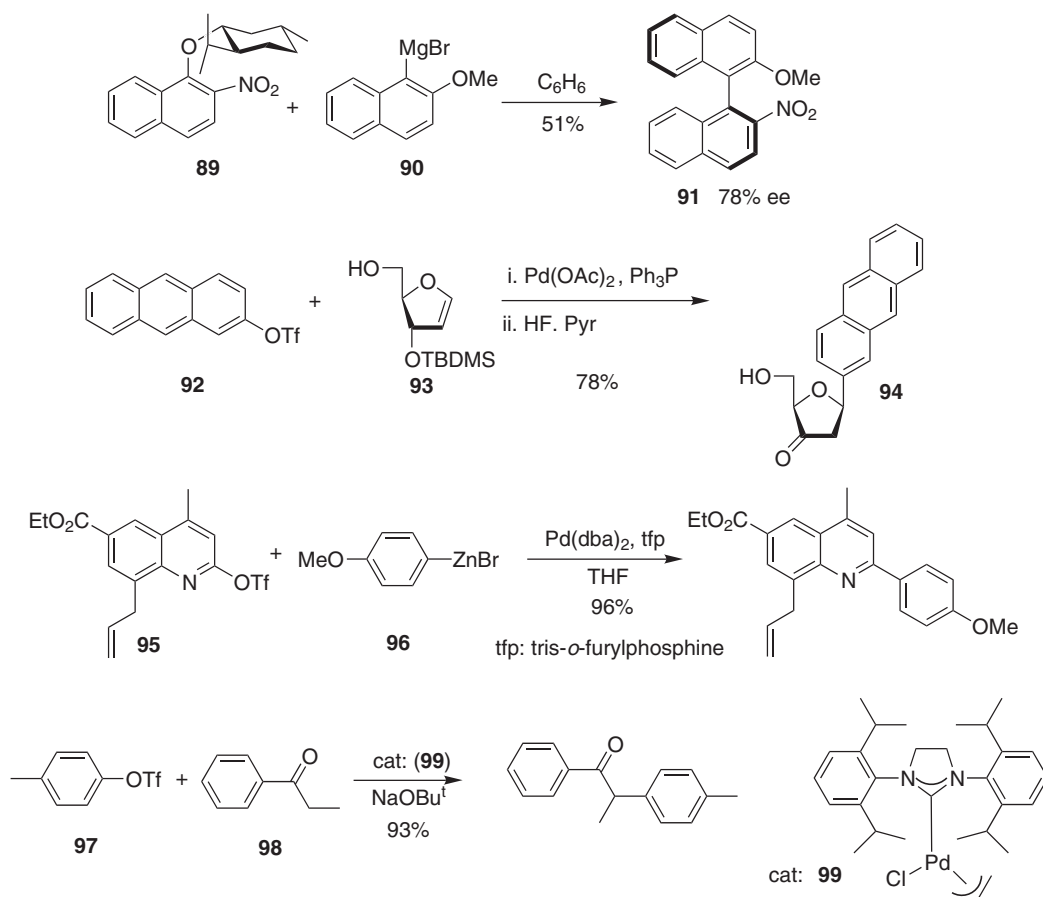
Scheme 18

The Claisen rearrangement was carried out with allyl vinyl ether. Particular catalysts have been developed to induce chirality in this reaction. Sterically hindered trinaphthoxy-aluminum derivatives such as **88** were particularly efficient (e.g., see Equation (8)) [<1995JA1165>](#).



1.05.1.2.6 Aryl alcohol derivatives

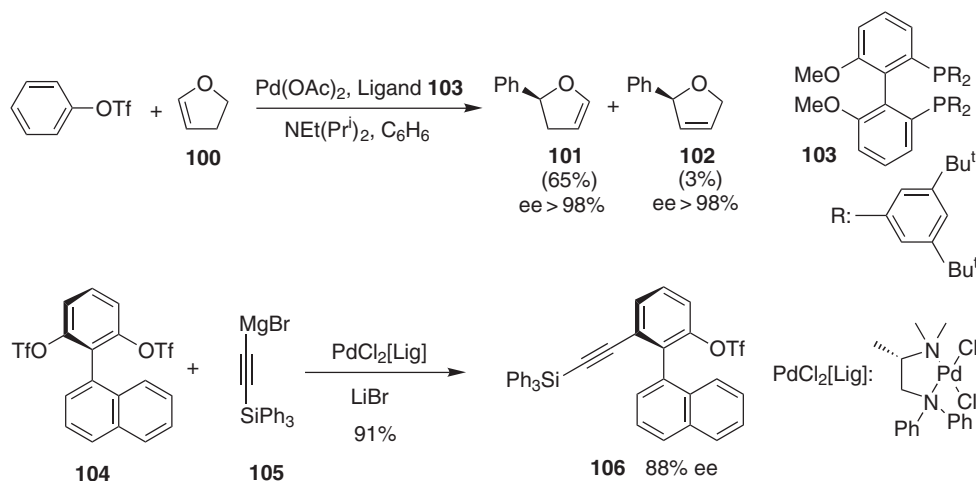
Nucleophilic displacement of an oxygenated leaving group on aromatic compounds can be carried out with C-nucleophiles. The nucleophilic substitution of the menthyloxy group in **89** by the Grignard reagent **90** leads to the binaphthyl derivative **91** in relatively high enantiomeric excess (Scheme 19) <2002T233>. In this field, many reactions were performed under palladium or nickel catalysis. The anthracene triflate **92** was coupled with the furanose-derived enol ether **93** to yield the isonucleoside **94** <2003TL1215>. Aryl tosylates were also transformed under similar reaction conditions. For another example, see <1999JA1473>. A palladium-mediated aryl–aryl coupling was carried out between quinolinylnyl triflates **95** and phenylzinc bromide **96** <2003S233>. Once again the reaction tolerates many functional groups. For an extensive review on aryl–aryl coupling reactions, see <2002CRV1359>. Using nickel catalysts, cross-coupling and homocoupling reactions can be performed with aryl mesylates, tosylates, or triflates <1995JOC176,



Scheme 19

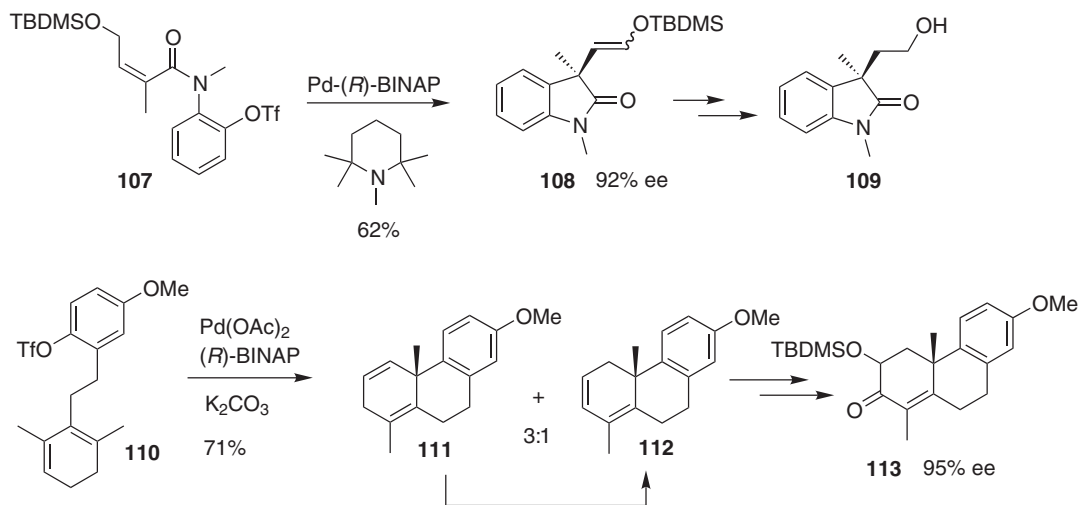
1995JOC6895, 1997JOC261>. A particularly efficient air-stable and well-defined palladium carbene catalyst **99**, which belongs to a new generation of catalysts, was used for the coupling of **97** and **98** <2002OL4053>. Chirality was also induced via asymmetric catalysis.

Phenyl triflate was added to 2,3-dihydrofuran **100** using $\text{Pd}(\text{OAc})_2$ as a catalyst and biphenyl-bisphosphine **103** as a chiral ligand (Scheme 20) <1997JA6315>. Both regioisomers **101** and **102** were obtained in high enantiomeric purity. The axial prochiral ditriflate **104** underwent asymmetric monosubstitution with the Grignard reagent **105**. Various reaction conditions have been tested in order to minimize the formation of the achiral disubstituted product and to enhance the enantiomeric excess of **106** <1996TL3161>.



Scheme 20

Intramolecular cross-coupling reactions have been performed using asymmetric catalysis. For a recent review on such reactions, see <2003CRV2945>. Using the BINAP ligand for chiral induction, the aryl tosylate **107** cyclized to yield the indole derivative **108** (Scheme 21) <1997AG(E)518>. Further transformations lead to **109** with high enantiomeric excess. In a similar way, **110** was transformed into the two regioisomeric benzocyclohexadienes **111** and **112** <1995TA2453>. The tricyclic compound **111** could be isomerized to **112** and the latter product was transformed into **113** which was isolated with high optical purity. For an investigation which focused on ligand optimization of a similar reaction, see <2003OL595>.



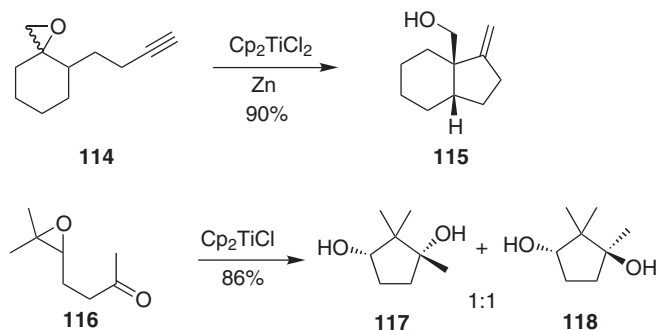
Scheme 21

1.05.1.3 Opening of Epoxides

Epoxides are versatile synthons in organic synthesis and ring-opening reactions are widely used. The corresponding chapter in COFGT (1995) extensively reviews different electrophilic and nucleophilic opening reactions. Recently, radical and transition metal-catalyzed transformations have been developed. Some of these methods are presented here.

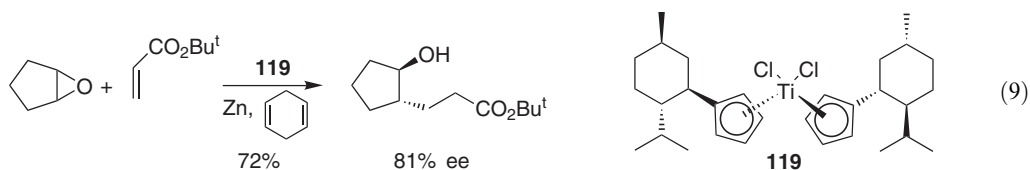
1.05.1.3.1 Simple and vinylogous epoxides

For a review on radical reactions with epoxides, see <2001T1>. In a titanium-mediated cyclization, epoxide **114** possessing an alkynyl side chain was transformed stereospecifically into **115** (Scheme 22) <2001S2500>. Cp_2TiCl_2 was used in catalytic amounts in the presence of zinc powder as reductant. The reaction was also successfully performed with substrates with an olefinic substituent. Tetrahydrofuran or pyrrolidine derivatives were obtained when the unsaturated side chain contained an ether function or sulfonamide, respectively. For a review on such reactions, see <2000CRV2771>. Under similar conditions, ω -epoxyketones and aldehydes can cyclize to produce functionalized five- or six-membered rings. For example, the cyclopentanediol derivatives **117** and **118** were isolated from the reaction of epoxyketone **116** <1999OL607>. For another example, see <2002JOC8243>.

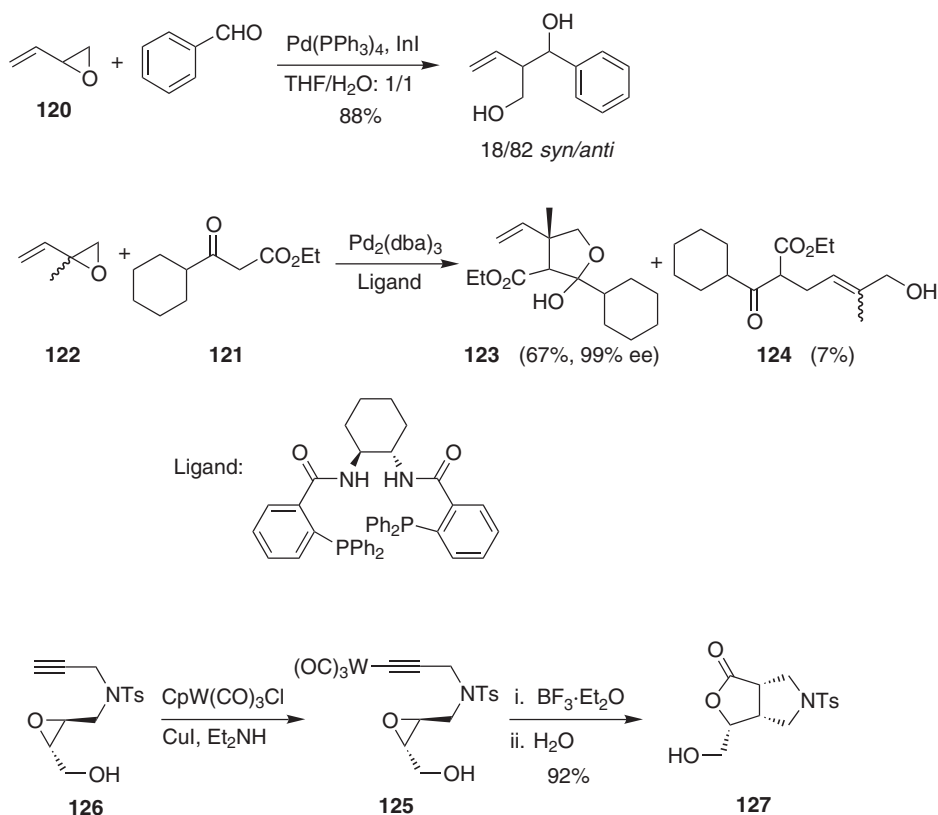


Scheme 22

Titanium-mediated ring opening of epoxides can generate radicals which add intermolecularly to activated alkenes. This reaction was performed in an enantioselective way using chiral titanium catalyst **119** (Equation (9)) <2003CEJ531>.

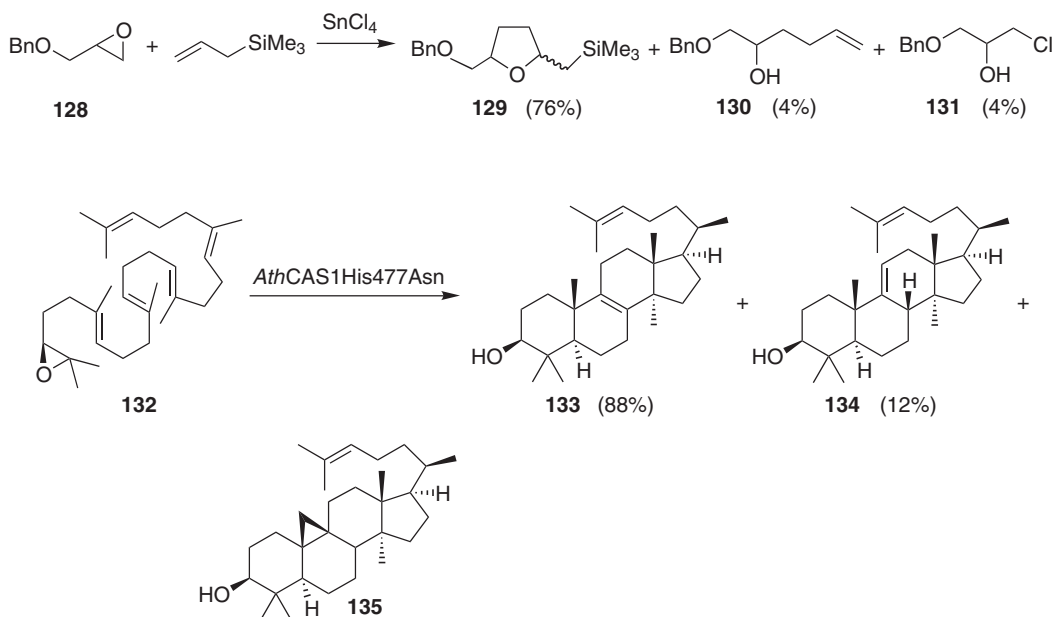


The palladium-mediated ring opening of vinyloxyepoxides **120** in the presence of InI and benzaldehyde led to the exclusive formation of the 1,3-diol when the reaction was performed in water or in a mixture of THF and water (Scheme 23) <2001JOC7919>. For similar examples, see <2003S751>. The addition of the C-nucleophile **121** to the epoxide **122** was carried out under asymmetric catalysis <2001JA12907>. The main product **123** resulted from a 1,2-addition of **121** to **122** followed by the formation of the lactol. This reaction occurred with high enantioselectivity. The formation of the minor product **124** resulted from the 1,4-addition of **121** to **122**. For an application of this reaction to the asymmetric synthesis of natural products, see <2003OL1563>. The alkyne tungsten complex **125**, synthesized from **126**, reacts in an intramolecular way with the epoxide <2003JOC1872>. A large variety of γ -lactones such as **127** have been obtained by this reaction. For a review on these reactions, see <2000CRV3127>.



Scheme 23

A formal Lewis acid-catalyzed [3+2]-cycloaddition of epoxyalcohol derivative **128** was performed with allyl silanes such as trimethylallyl silane (Scheme 24) <1999TL5877>. Under optimized reaction conditions, the tetrahydrofuran **129** was isolated as the major product. However, the formation of the side products **130** and **131** indicated that formation of both the C—O

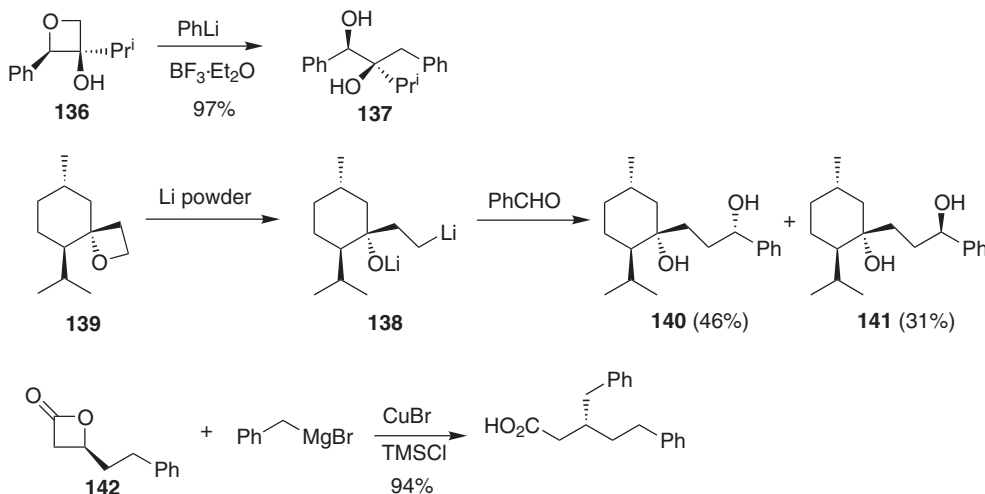


Scheme 24

σ -bond and the C—C σ -bond did not occur at the same time. A Johnson-type cyclization occurred when oxidosqualene **132** was treated with an enzyme and four C—C σ -bonds were created in a cascade process <2002OL4459> (see also <2000AG(E)4090>). In this latter case, the reaction was performed with the mutant of a cycloartenol synthase *AthCAS1His477Asn* which was obtained by directed evolution. This enzyme only catalyzes the formation of lanosterol **133** and to a minor degree the formation of parkeol **134** while the formation of cycloartenol **135** is not observed. For a review on enzyme mechanisms for polycyclic triterpene formation, see <2000AG(E)2812>.

1.05.1.3.2 Oxetanes and β -lactones

Oxetanes are less reactive than epoxides; however, some ring-opening reactions can be performed. For reviews on chemical reactions with oxetanes, see <1997LA1627, 2000SL1699>. Several alkyl- and aryllithium compounds were added to the oxetane **136** (Scheme 25), and diols **137** were isolated in good yields <1998EJO2161>. For similar reactions, see <1999EJI2187>. For an addition of alkyl- or aryllithium compounds under asymmetric catalysis, see <1997T10699>. The dilithiated intermediate **138** was obtained when the oxetane **139** was treated with lithium powder and trapped with electrophiles such as benzaldehyde to yield two diastereomeric diols **140** and **141** <1997TA2633>. The structurally related β -lactones are more reactive. The copper-catalyzed nucleophilic addition of Grignard reagent to lactone **142** occurred stereoselectively with inversion of configuration <2002JOC4680>.

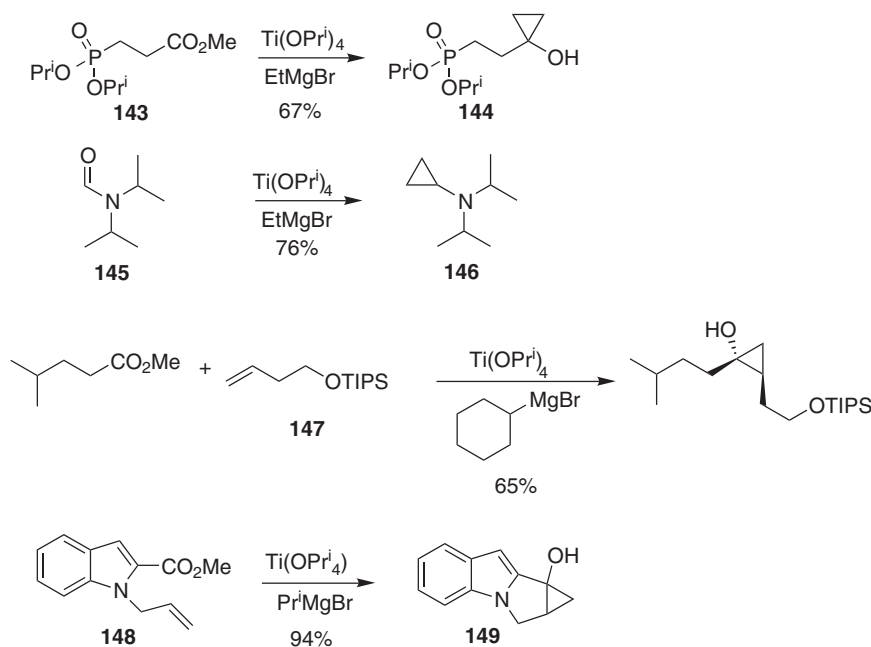


Scheme 25

1.05.1.4 Cyclopropanation of Carbonyl and Carboxyl Compounds

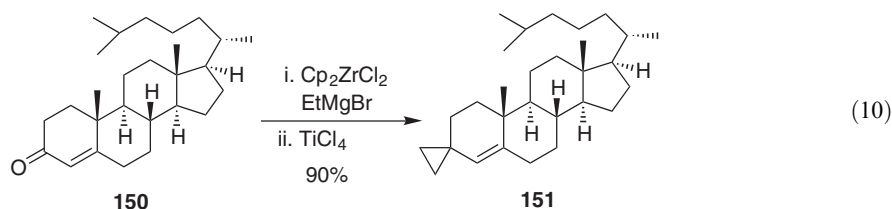
Recently, several methods have been developed for the synthesis of cyclopropanes starting from carbonyl or carboxyl compounds. For a review on these reactions see <2000CRV2789>.

Titanium-mediated reaction of Grignard reagents such as ethylmagnesium bromide with ester **143** leads to cyclopropanol **144** (Kulinkovich reaction, Scheme 26) <1999SL1999>. The same reactions could be carried out with amides. In this case, cyclopropyl amine **146** was readily available from the corresponding formamide **145** <1996AG(E)413>. When less reactive Grignard reagents such as cyclohexylmagnesium bromide are used, esters can react with more reactive terminal olefins such as **147** to produce trisubstituted cyclopropanols <1996JA4198>. The same reaction was also carried out with amides <2002CEJ3789>. Due to this reactivity, intramolecular reactions can be carried out and the ester **148** was transformed to the tetracyclic indole derivative **149** <1997JA6984>. As in the case of the intermolecular version, the same reaction can also be carried out with amides <1997JOC1584>.



Scheme 26

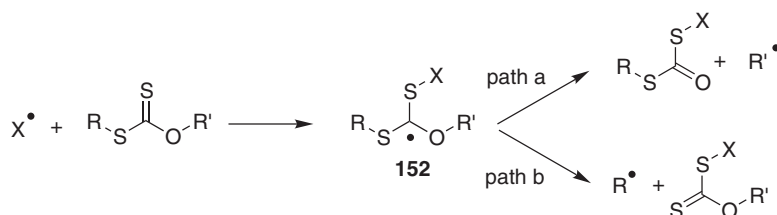
Cyclopropanations have also been carried out in a zirconium-mediated way. A large variety of ketones, aldehydes, especially α,β -unsaturated ketones such as **150**, can be transformed into cyclopropane derivatives such as **151** (Equation (10)) <2000EJO3713>. The method was particularly efficient when the work-up was performed with Lewis acids such as TiCl_4 or $\text{BF}_3 \cdot \text{OEt}_2$. For various reviews on such reactions as well as on other applications of titanium and zirconium in organic synthesis, see <B2002MI011>.



1.05.2 SUBSTITUTION OF SULFUR FUNCTIONS

1.05.2.1 Radical Reactions

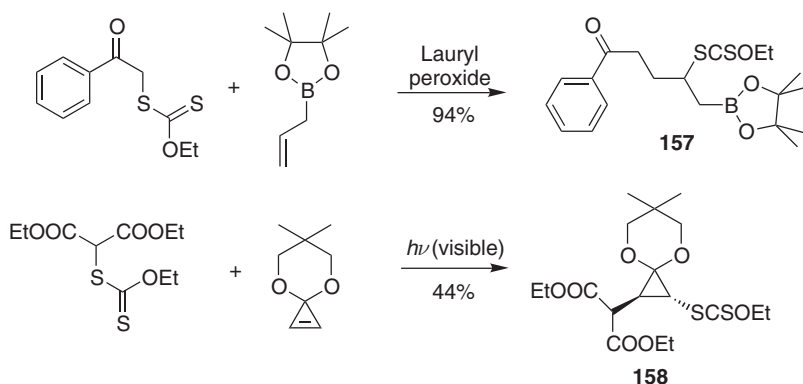
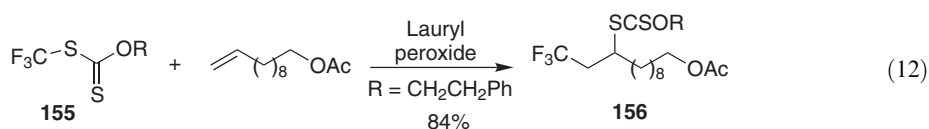
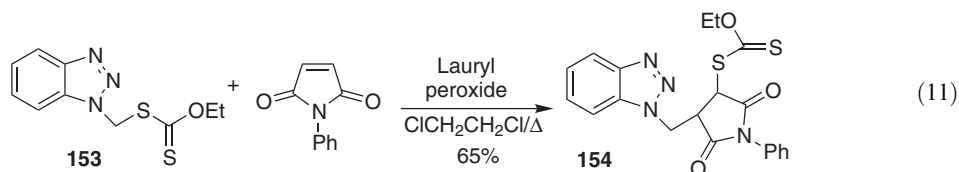
As mentioned in Section 1.05.1.1, radical reactions became particularly interesting in organic synthesis <B2001MI001, B2001MI002>. Recently xanthates were applied to the synthesis of many different structures. In this context a principal mechanistic question emerged as the addition of radicals to the thiocarbonyl function leads to the radical species **152** (Scheme 27). The radical



Scheme 27

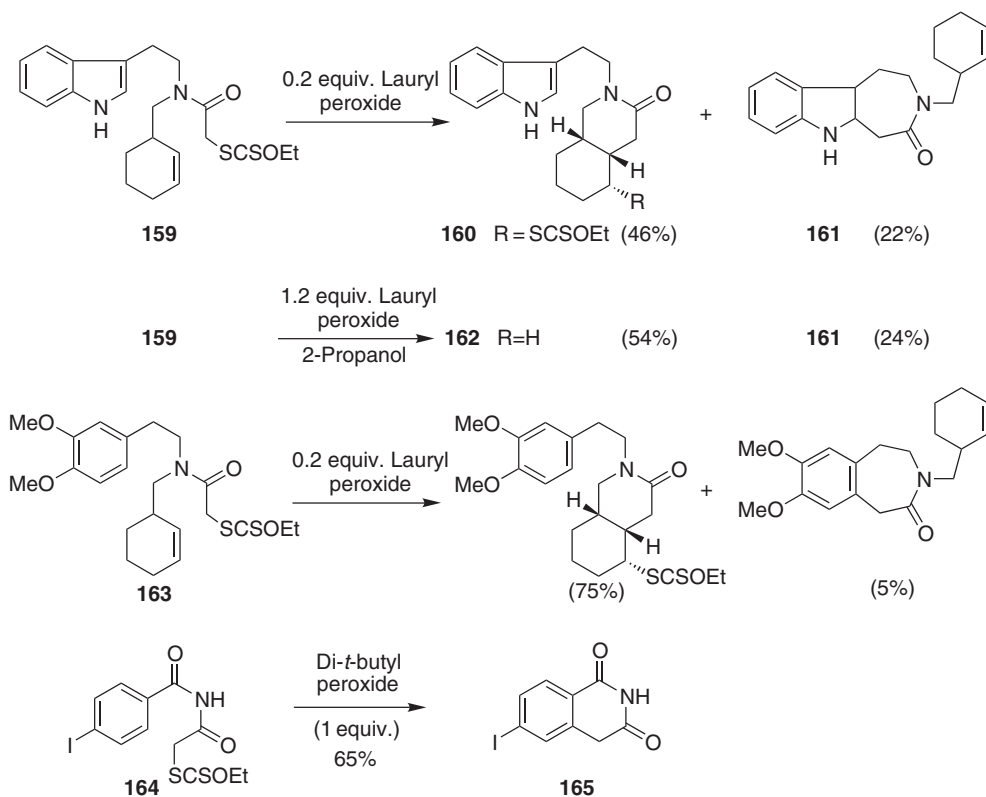
152 can fragment either by C—O bond cleavage via path “a” or by C—S bond cleavage via path “b.” The resulting carbon-centered radicals R^{\bullet} or R'^{\bullet} can react with unsaturated molecules in order to generate C—C bonds. The conditions for path “a” or path “b” have been discussed in a review <1997AG(E)673> and some examples of reactions via path “a” are discussed in Section 1.05.1.1 (Scheme 1). Many reactions involving path “b” have been recently published.

Xanthates have been added to a variety of olefins. The method tolerates many functional groups, even those that might react under radical conditions. The benzotriazole derivative **154** was obtained in good yields when **153** was heated in the presence of *N*-phenylmaleimide and when lauryl peroxide was used as a radical initiator (Equation (11)) <2001H301>. For similar examples with tetrazole or triazole derivatives, see <1998TL19, 2001CC2618, 2002OL4345>. Fluoroalkylation of olefins leading to products such as **156** was carried out in the same way (Equation (12)) <2001OL1069>. In this case, the trifluoromethylxanthate **155** was used. High yields were also obtained for the synthesis of boronates **157** (Scheme 28) <2001CC2618>. The radical reaction could also be initiated by light instead of peroxides as shown for the preparation of **158** <2000TL2979>. In these reactions the xanthate function is present in the final products which can be interesting for further transformation. However, for many applications it is helpful when this substituent is removed in the same operation. This can be achieved when the reaction is carried out with an excess of tin hydride reagent. Recently, a procedure to avoid tin hydrides was developed using isopropanol as reductant (see also Scheme 29) <1996TL5877>.



Scheme 28

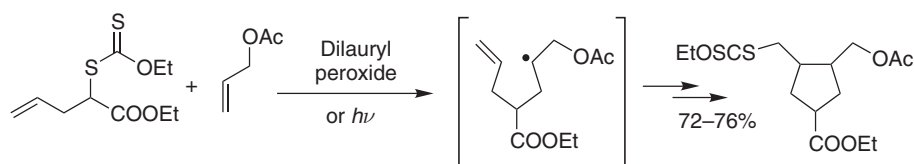
The intramolecular version of the reaction was successfully applied to the synthesis of nitrogen-containing heterocycles. An example is shown in Scheme 29 <2001OL3125>. When the lauryl peroxide was used in substoichiometric amounts, product **160** was obtained from **159**, resulting from an intramolecular radical addition with the olefinic double bond and a xanthate transfer. Furthermore, product **161**, resulting from a radical addition to the indole system, was isolated. In the presence of isopropanol and an excess of peroxide, the desulfurized product **162** was obtained together with **161**. The reaction was more selective when the catechol derivative **163** was



Scheme 29

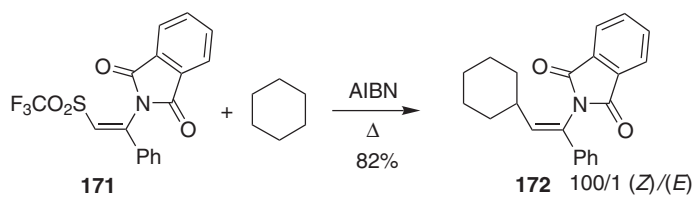
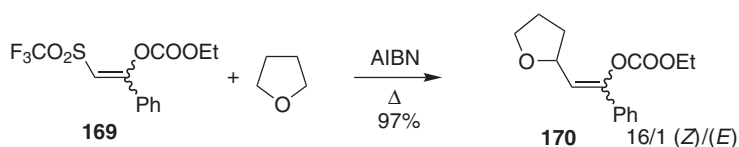
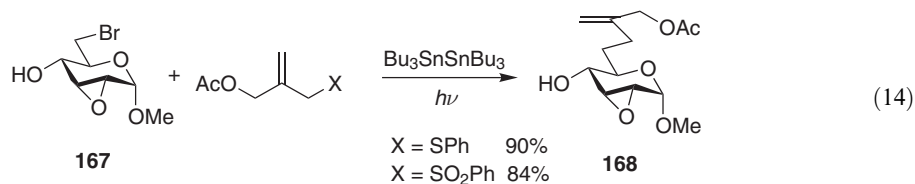
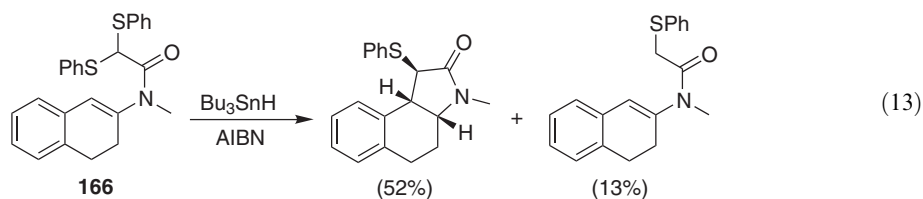
transformed. Even if a radical attack at a benzene moiety is less favored, the absence of a competing olefinic double bond as in **164** led to the cyclized product **165** (Scheme 29) <2002CC2306>.

Using photochemical or peroxide activation, an intermolecular tandem addition–cyclization process could be carried out (Scheme 30) <1998SL1435>. Such transformations were also performed in two steps <1997TL1759, 2000AG(E)731, 2002OL4345>.



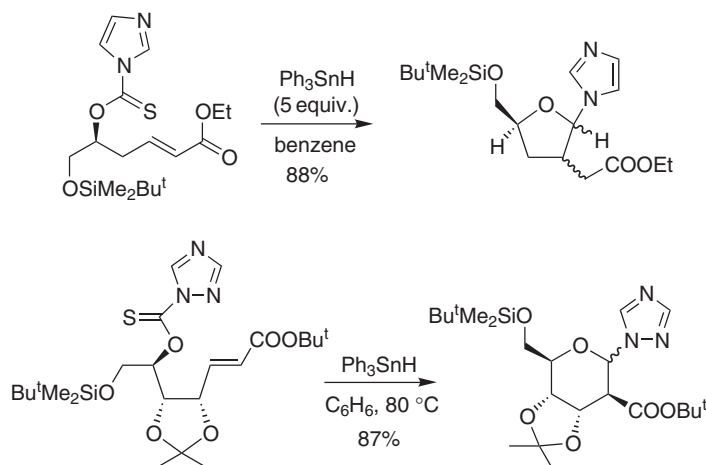
Scheme 30

Various other sulfur-bearing groups have been used in radical reactions. The thioacetal **166** cyclized when heated with $\text{Bu}_3\text{SnH/AIBN}$ (Equation (13)) <1998JCS(P1)1763>. Only a small amount of side product was isolated. The aryl sulfide group, as well as the corresponding sulfone, has been used as leaving groups in intermolecular reactions of glucosyl derivatives such as **167** (Equation (14)) <1996JOC7463>. The radical generated from **167** attacks the olefin at the less sterically hindered position, and after a β -elimination of a PhS or a PhSO_2 radical **168** was isolated in high yields. For an intramolecular reaction of this type, see <2003SL1058>. β -Elimination of sulfone groups at vinyl positions can also occur after radical addition as shown in the transformation of **169** to **170** and in the transformation of **171** to **172** (Scheme 31) <1997JA4123>. For similar reactions, see <1999AG(E)1943>.



Scheme 31

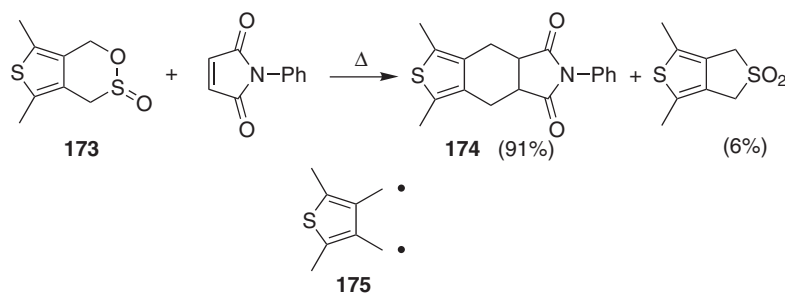
As shown in [Section 1.05.1.1](#), thiocarbonylimidazole derivatives are suitable precursors for radical intermediates which can add to olefinic double bonds. In some intramolecular reactions and when the hydrogen donor (tin derivatives) is used in large excess (5 equiv.), a C—C bond is generated and the thiocarbonyl sulfur group is eliminated ([Scheme 32](#) <2003JA1492>).



Scheme 32

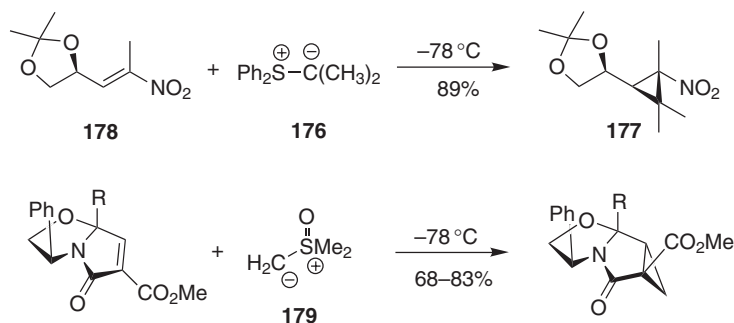
1.05.2.2 Ring Constructions

Sulfur compounds such as thienosultine **173** are frequently used for the synthesis of six-membered rings such as **174** (Scheme 33) <2002JOC9267>. In these cases, biradical intermediates such as **175** are formed and trapped by alkenes or alkynes. For similar examples, see <1995T129>. In the case of benzenoid analogs, the biradical intermediates possess a higher singlet character and therefore the character of a quinodimethane <1997ACR238>. For a review on *o*-quinodimethanes, see <1999CRV3199>.

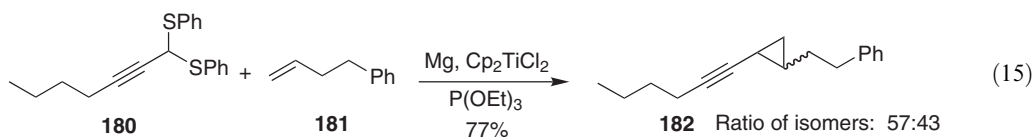


Scheme 33

Sulfur reagents have been used for the synthesis of cyclopropane derivatives. Most frequently, sulfur ylides such as **176** derived from sulfonium salts are used (Scheme 34) <1996TL6307>. Only one diastereoisomer **177** was isolated from the reaction of **176** with α,β -unsaturated nitro compound **178**. Similarly, sulfoxonium ylides such as **179** were used for asymmetric cyclopropanation <1995CC141>. For a review on asymmetric ylide reactions, see <1997CRV2341>. In a titanium-mediated reaction the thioacetal **180** was used to transform the terminal olefin **181** into cyclopropane **182** (Equation (15)) <2002TL5641>. For further examples, see <1997JOC3678>.



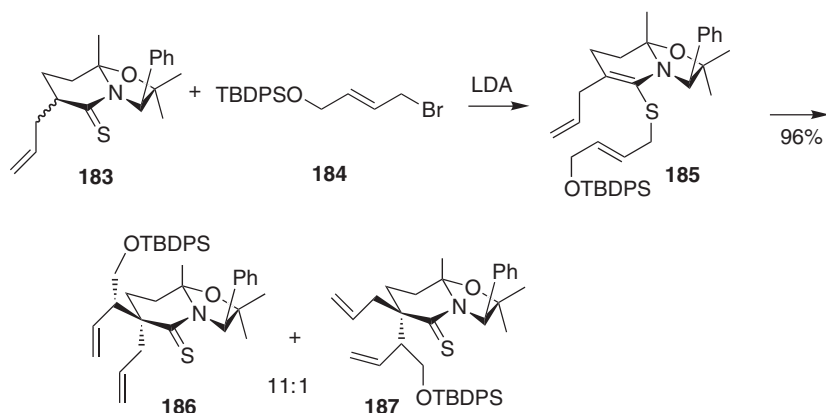
Scheme 34



1.05.2.3 Sulfur Leaving Groups

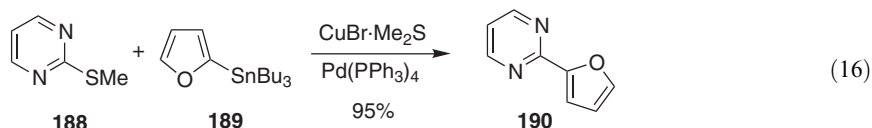
1.05.2.3.1 Sulfides as leaving groups

The thio-Claisen rearrangement has been successfully performed with allyl vinyl sulfides (Scheme 35) <1999JOC3585>. When **183** was treated under basic reaction conditions in the presence of allyl halides such as **184**, the allyl vinyl thioether **185** was formed as an intermediate



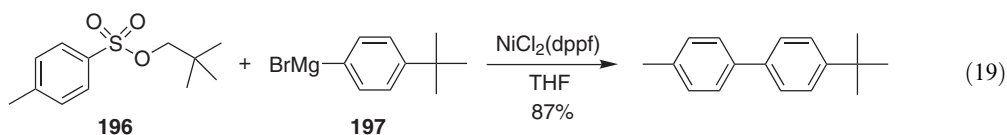
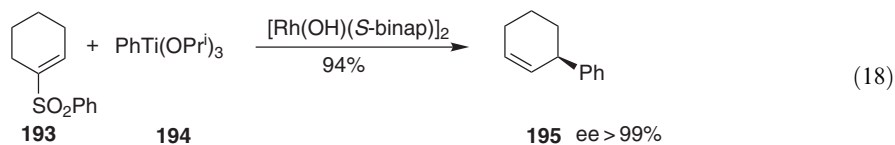
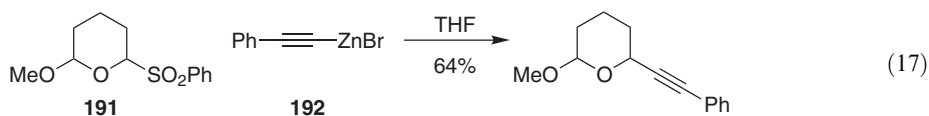
Scheme 35

which immediately rearranged to give the major product **186**. A further isomer was also isolated in small quantities. It was characterized as the *exo*-isomer **187** and not as a diastereomer resulting from a different stereochemical position of the (CH₂OTBDPS) group. For investigations on metal catalysis for this reaction, see <2000TL1363>. In a copper- and palladium-mediated cross-coupling reaction, the heteroaryl thioether **188** reacted with stannyl aromatic compound **189** or with the corresponding vinyl derivatives leading in high yield to the bis-aryl product **190** (Equation (16)) <2003OL803>. For further examples of this reaction, see <2003OL801>.



1.05.2.3.2 Sulfones and sulfonates as leaving groups

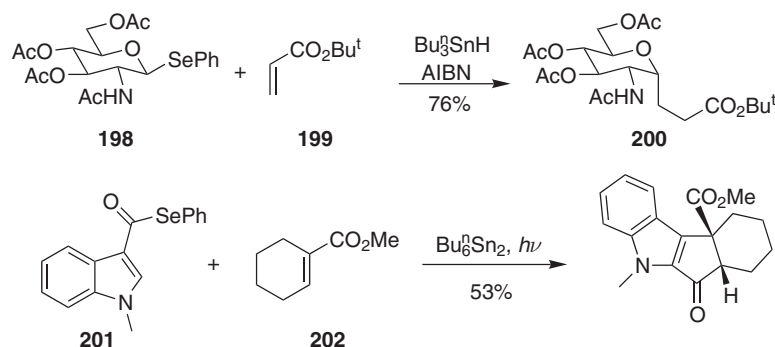
Alkynyl-zinc reagents have been added to functionalized compounds. When **191** was treated with phenylacetylenyl zinc bromide **192**, a displacement of a sulfone group occurred (Equation (17)) <2003JOC4392>. In an asymmetric rhodium-catalyzed reaction with the phenyltitanium reagents **194**, the vinyl sulfone **193** was transformed into the corresponding allylaryl coupling product **195** (Equation (18)) <2003JA2872>. Aryl sulfonates have frequently been used as leaving groups in nucleophilic substitution or in cross-couplings (see, for instance, Equation (3)). Recently, in a nickel-catalyzed reaction, the neopentyl aryl sulfonates **196** were coupled with the arylmagnesium bromide **197** (Equation (19)) <2003JOC3017>. Due to steric hindrance, the C—S bond was cleaved and not the C—O bond of the neopentyl substituent.



1.05.3 SUBSTITUTION OF SELENIUM AND TELLURIUM

1.05.3.1 Radical Reactions of Selenides

In the field of radical reactions, numerous applications of selenides have recently been described. The glycosyl radical which was generated from the corresponding selenium derivative **198** has been added to activated alkenes such as the acrylate **199** (Scheme 36) <2002OL4623>. Only the α -isomer **200** was obtained. A radical intermolecular addition–cyclization has been carried out with the selenoester **201** and a variety of electron-deficient alkenes such as **202** <2001JOC7547>.



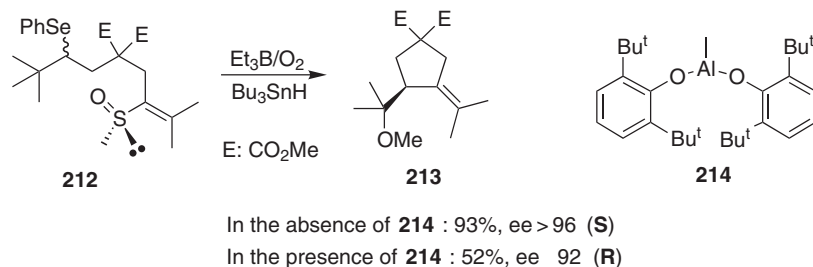
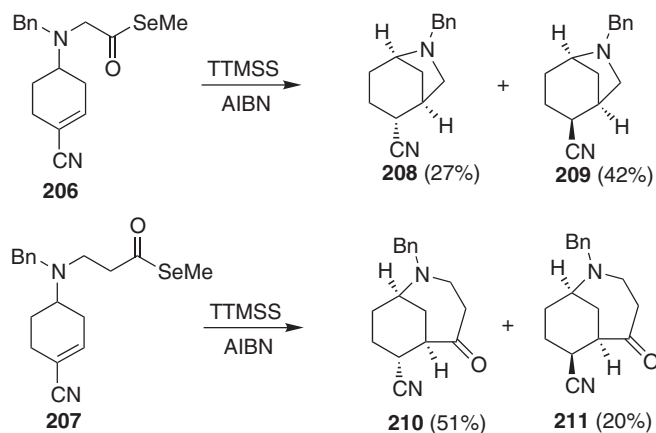
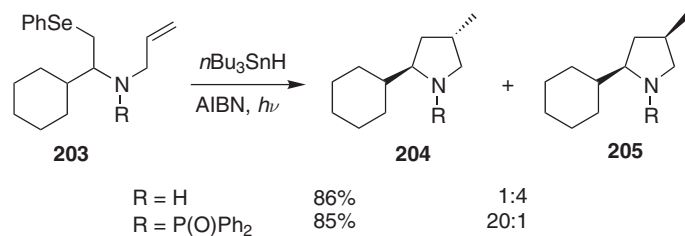
Scheme 36

Many intramolecular radical reactions with selenium derivatives have been performed. In the case of the cyclization of the allylamine derivative **203**, the ratio of the *cis/trans* isomers **204** and **205** depends significantly on the nitrogen atom substituents (Scheme 37) <2000OL1589>. Two different kinds of products could be isolated from the reaction of the selenoesters **206** and **207** <2002JOC2323>. For compound **206**, a decarbonylation takes place before the cyclization leading to **208** and **209**. This reaction was not observed in the transformation of **207** since **210** and **211** were isolated. For a review on reactions of radicals with carbon monoxide and on decarbonylation of acyl radicals, see <1996AG(E)1050>. Product **213** was obtained in high enantioselectivity from the cyclization of the seleno derivative **212** possessing a vinyl sulfoxide which induced chirality and after cyclization, this auxiliary is eliminated as a sulfinyl radical <1998AG(E)2116>. It is particularly interesting to note that in the absence of any Lewis acid the *S*-enantiomer is formed while in the presence of the sterically hindered Lewis acid such as **214** the *R*-enantiomer is obtained.

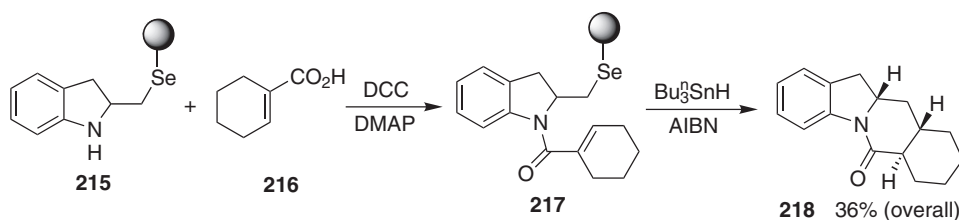
This reaction was also applied to combinatorial chemistry and, especially on solid phase, to synthesize indoline derivatives (Scheme 38) <2003BMC465>. The indoline fragment **215** was linked via a selenoether function to the polymer. Various α,β -unsaturated acids such as **216** were added to the amino function of **215**. In a radical reaction, the σ -bond between selenium and the methylene group of the indolamide moiety **217** was cleaved and the resulting carbon radical attacked the double bond of the α,β -unsaturated amide moiety. The radical cleavage of the C–Se bond induced the radical cyclization as the key step of the synthesis and the separation of the product from the resin. Similar reactions were carried out with *N*-allylindole derivatives.

1.05.3.2 Reactions with Tellurium Compounds

For a review on organic reactions with tellurium compounds, see <1997S373>. *exo*-Cyclization was observed when the tellurium compound **219** was treated with $\text{Bu}_3\text{SnSnBu}_3$ (Equation (20)) <1995CC2515>. In this case, the TeAr group was transferred onto the terminal carbon of the cyclopentylmethyl radical. In a copper-mediated 1,4-addition, the vinyl telluride **220** reacted with the α,β -unsaturated ketone **221** (Equation (21)) <1996JOC4975>. Only traces of 3-methylcyclohexanone **222** were detected. Copper-mediated addition of vinyl tellurides to epoxides can also be



Scheme 37



Scheme 38

performed and a copper-mediated substitution at a vicinal position of the α,β -unsaturated ketone **223** was carried out (Equation (22)) <1995SL180>. A copper- and palladium-catalyzed coupling between the organotellurium dichloride **224** was carried out with the alkyne **225** (Equation (23)) <2003TL1779>. An interesting chemoselectivity was observed with the seleno-telluro derivative **226**, and in this case only the tellurium function reacts (Equation (24)) <2003SL579>. Palladium-catalyzed cross-coupling reactions were also performed with alkyl tellurofuran derivatives <2001TL8927, 2003TL1387>.

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Biographical sketch

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1.06

One or More CC Bond(s) Formed by Substitution: Substitution of Carbon–Nitrogen, –Phosphorus, –Arsenic, –Antimony, –Boron, –Silicon, –Germanium, and –Metal Functions

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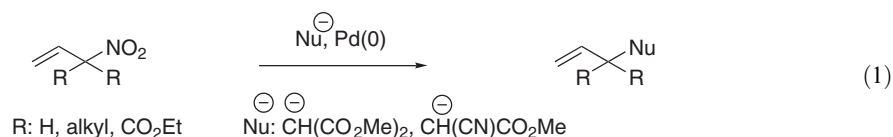
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1.06.1 SUBSTITUTION OF NITROGEN FUNCTIONS

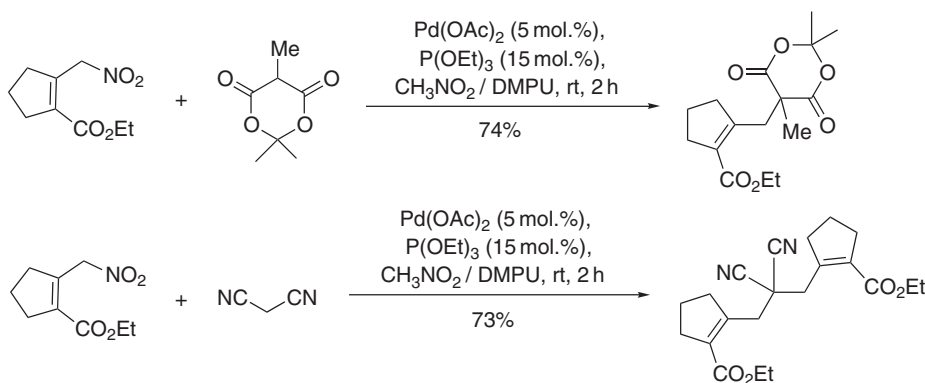
1.06.1.1 Nitro Compounds

Aliphatic nitro compounds are useful synthetic intermediates which may be transformed into various other functions <B-1996MI106-2>. The substitution reaction of nitro group into tertiary nitroalkanes by soft nucleophiles leads to the formation of a new carbon–carbon bond. Attempts to achieve this substitution with hard nucleophiles such as lithium–dialkyl cuprates resulted in the formation of alcohols as major products <1998MI537>.

The palladium-catalyzed substitution of primary, secondary, and tertiary allylic nitro compounds was developed as an equivalent to the known Tsuji–Trost reaction (Equation (1)).



In a recent study connected with carbapenem synthesis, allylic substitution reactions of ethyl 2-nitromethyl 1-cyclopentenecarboxylate with various soft nucleophiles (including carbon nucleophiles) were studied <1999OL1783>. Although the reaction with Meldrums' acid gave cleanly the substitution product, reaction with the malonitrile led to double substitution (Scheme 1).



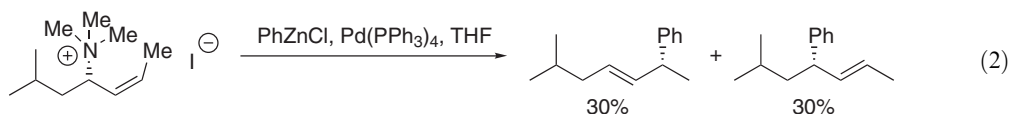
Scheme 1

Electrophilic substitution of arenes by tertiary allylic, benzylic, or tertiary nitroalkenes proceeds under Lewis acid catalysis, generally with tin tetrachloride. This reaction proceeds through an $\text{S}_{\text{N}}1$ mechanism with a carbocation intermediate. In an analogous reaction, allylation of tertiary-benzylic nitroalkanes occurs by treatment with allyltrimethylsilane and tin tetrachloride.

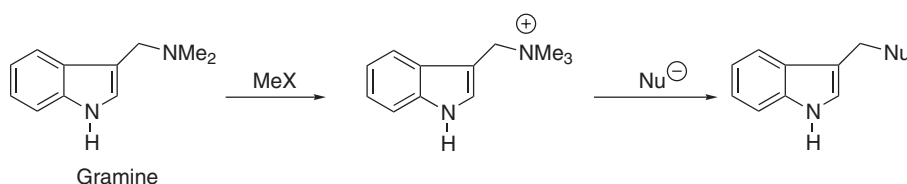
1.06.1.2 Quaternary Ammonium Salts

Nucleophilic substitution of quaternary ammonium salts is rather a common reaction in synthesis, and has been especially applied to allylic and benzylic substrates. With allylic compounds, nucleophilic substitution may be catalyzed by palladium complexes, as a variant of the Tsuji–Trost reaction. Thus, treatment of various chiral allylic ammonium salts with soft and hard nucleophiles was studied <1995TA389>. With soft nucleophiles, the reaction proved to be

solvent-dependent, the best results being obtained in acetonitrile. Although the reaction with phenylzinc chloride was not regioselective, complete stereoselectivity was observed (Equation (2)).

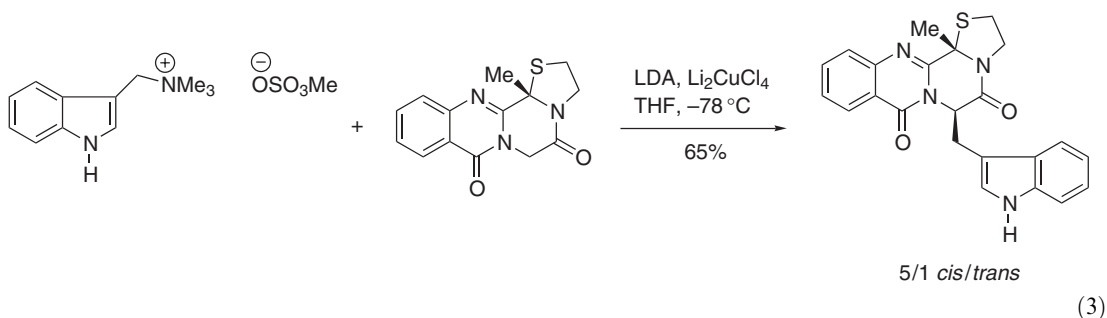


Nucleophilic substitution of benzylic quaternary ammonium salts is a useful reaction, especially when difficulties occur in the preparation of the corresponding benzylic halides. A typical reaction is the Kametani gramine alkylation, which allows the introduction of 3-indolylmethyl moiety (Scheme 2).



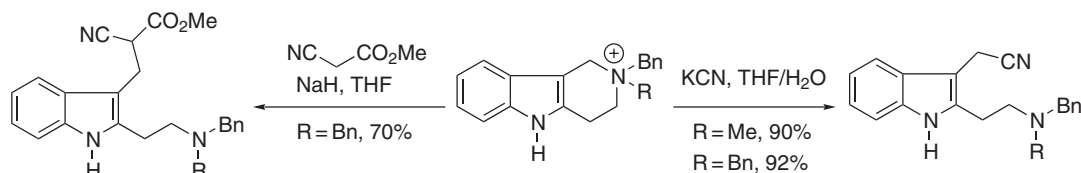
Scheme 2

This reaction was recently applied to the synthesis of helical peptidomimetics <1994BMCL2825> and the preparation of a highly substituted thiazolidine derivative <2001JOC839> (Equation (3)). In the latter case, the alkylation with gramine methyl sulfate was stereoselective. Asymmetric alkylation of a chiral glycine equivalent with a quaternary guanine salt has been developed as a stereoselective entry to tryptophan analogs <1999SL453>.



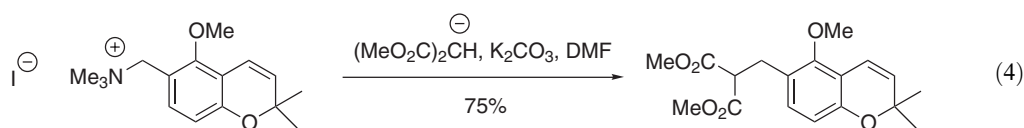
(3)

Another application of gramine alkylation is the ring opening of a cyclic quaternary ammonium salt with a cyanide ion or cyanoacetic acid <1995TL3511> in the synthesis of macrocyclic indole derivatives (Scheme 3).

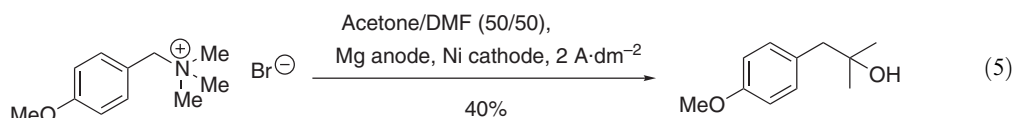


Scheme 3

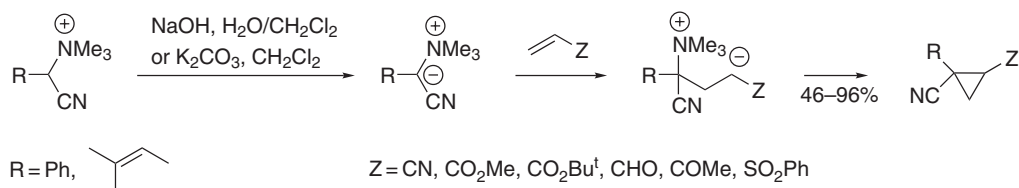
Other benzylic substitutions with quaternary ammonium salts were used to prepare a naturally occurring 2,2-dimethyl-2H-1-benzopyran derivative <2001T5335> (Equation (4)), for the introduction of carborane to pyrroles <2001TL7759>, and for the synthesis of fused oligoporphyrins <2000JA11295>.



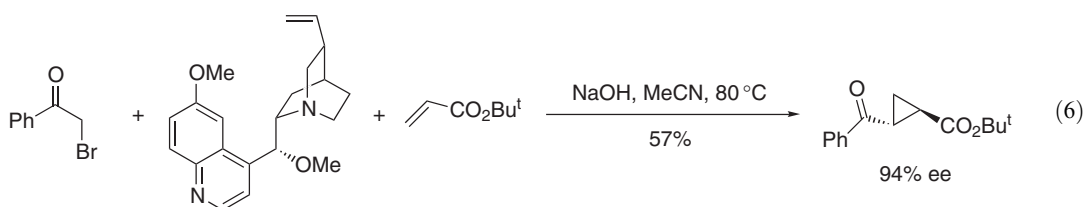
Electroreductive coupling of benzylic compounds, including benzylic quaternary ammonium salts, with anhydrides or carbonyl compounds provides access to benzylic ketones or alcohols (Equation (5)) <1996NJC375>. The influence of nitrogen substituents and of the anion was studied, showing that iodides gave the best yields, with a phenyl substituent on nitrogen being beneficial. The reaction was also applied to the coupling of heterocyclic compounds.



Ammonium ylides, which are obtained by treatment of ammonium salts substituted in the α -position with electron-withdrawing groups, react with Michael acceptors to give cyclopropanes or with carbonyl compounds to give epoxides. Thus, generation of ammonium ylides from cyanomethyl trimethylammonium iodide and reaction with electron-deficient alkenes gave the corresponding cyclopropanes in good yields as a mixture of stereoisomers <1999SL1085> (Scheme 4). In a more recent study, ammonium ylides were generated *in situ* from α -chlorinated carbonyl compounds and a tertiary amine such as 1,4-diazabicyclo[2.2.2]octane (DABCO). Upon treatment with a base and reaction with various Michael acceptors, cyclopropanes were obtained in good yields and with excellent stereoselectivity <2003AG(E)828>. The use of a chiral ammonium salt derived from cinchonine gave cyclopropanes in ee's up to 94% (Equation (6)).



Scheme 4

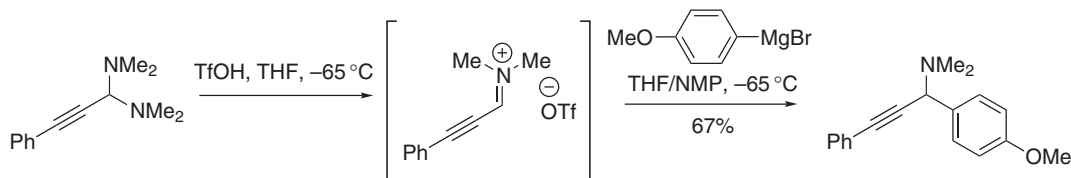


The preparation of cyclopropanes from ammonium ylides linked on a solid support was attempted <1997TL7951>. Wang resin-bound pyridinium ylides were generated by treatment with a tertiary amine and reacted with electron-deficient alkenes to give the corresponding cyclopropyl derivatives, which were isolated after resin cleavage.

1.06.1.3 Tertiary Amines

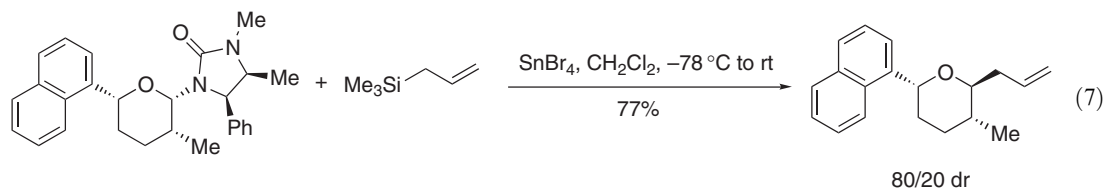
Mannich reactions of enolates with iminium ions derived from *N,N,N',N'*-tetramethyldiaminomethane are the most common examples of substitution of a tertiary amine. Activation with a strong electrophile such as trifluoromethanesulfonic anhydride leads to an iminium ion, which can react with nucleophiles. In a recent study, α,β -unsaturated amins after activation were treated with various Grignard reagents to give polyfunctional allylic or propargylic amines <2002S2143> and no conjugate addition was observed in these reactions (Scheme 5). In an

analogous reaction, 1,1-bis(dimethylamino)-2,2,2-trifluoroethane was treated with a variety of carbon nucleophiles, e.g., alkynes, alkenes, or trimethylsilyl cyanide, to give trifluoromethylated alkynyl or alkenylamines in good yields <2000JOC2134>.

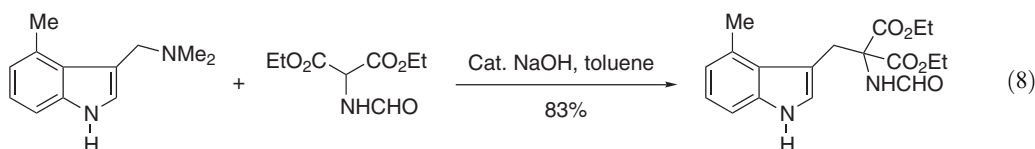


Scheme 5

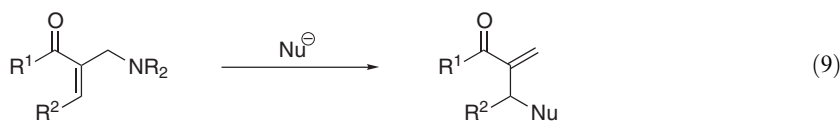
Substitution of nitrogen functions at the anomeric position of pyranoses has been recently described. Reaction of a cyclic urea with allyltrimethylsilane was achieved in the presence of Lewis acid to give the C-glycosidic product <2003SL791>. The best yield and selectivity were obtained using tin tetrabromide (Equation (7)).



Substitution reactions of tertiary amines with hard or soft nucleophiles occurs easily with allylic or benzylic amines. The gramine alkylation may be performed using gramine base instead of a quaternary ammonium salt. In a recent example, treatment of 4-substituted gramine with formamidomalonic acid ester in the presence of sodium hydroxide led to the formation of new tryptophan derivatives <1995TL1425> (Equation (8)).



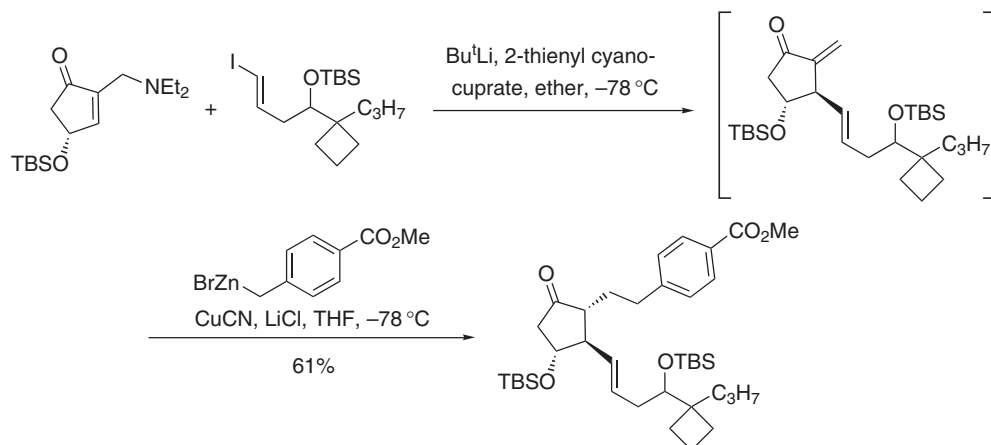
3-Alkyl-2-*exo*-methylene ketones may be prepared by substitution of α,β -unsaturated 2-alkylaminomethyl ketones with carbon nucleophiles (Equation (9)). The advantages of using the dialkylamino function as the leaving group are the easier preparation and greater stability of the starting 3-dialkylaminoketone. In a project related to the synthesis of prostaglandin analogs, reaction of a vinyl organolithium with a chiral 2-diethylaminomethyl cyclopentenone gave the *exo*-methylene derivative with excellent stereoselectivity. Further conjugate addition to the *exo*-methylene ketone provided new PGE₂ analogs <2002BMC1093> (Scheme 6).



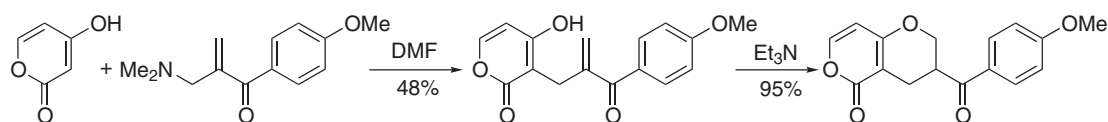
The same substitution reaction was employed for the coupling of pyrones with aryl ketones <2000H2421> (Scheme 7). When the reaction was performed in the presence of a base, intramolecular conjugate addition of the hydroxyl group occurred.

Transition metal-catalyzed allylic substitution of allylic tertiary amines with hard and soft nucleophiles has been recently studied. Since amines are not as good leaving groups as the corresponding acetates or carbonates, highly reactive catalysts are necessary. Coupling of allyl diethyl amine with soft nucleophiles such as malonates or acetoacetates proceeded in the presence of the Ni(dppb)₂ [dppb: 1,4-bis(diphenylphosphino)butane], which proved to be more efficient

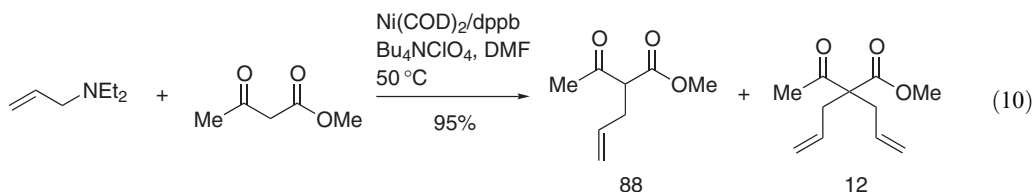
than the corresponding palladium complex, although reaction with acetyl acetone showed severe decrease of catalytic activity <1997CC1393> (Equation (10)) and double allylation was also observed.



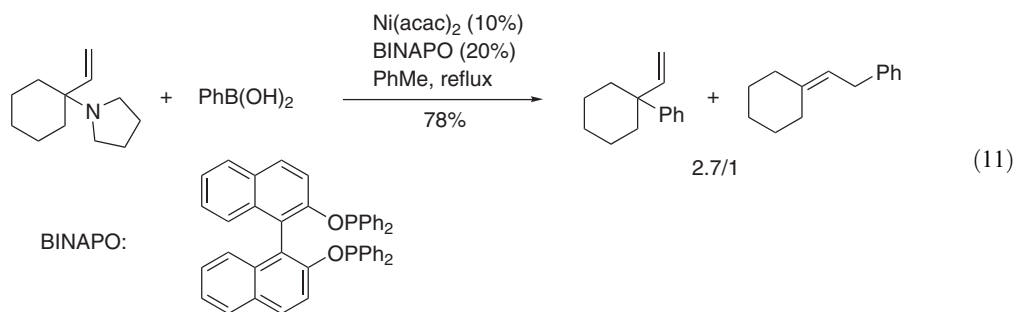
Scheme 6



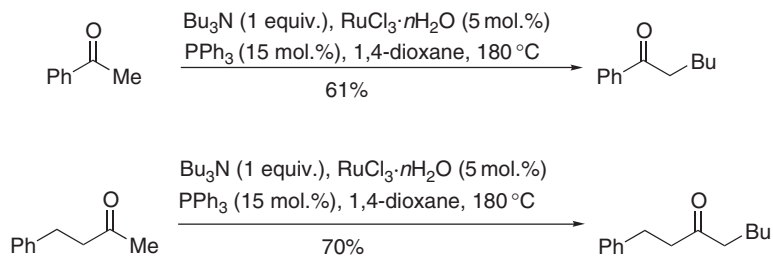
Scheme 7



Nickel complexes were also used for the coupling of tertiary allylic amines with hard nucleophiles such as boronic acids <1995JCS(P1)2083> (Equation (11)). The regioselectivity was however low, best results being obtained using the BINAPO ligand (BINAPO: 1,1'-bis-diphenylphosphinyloxy-2,2'-binaphthalene). The mechanism of this allylation involves coordination of boronic acid to the metal, followed by intramolecular alkyl or aryl group transfer. This study showed that amine oxides were also good leaving groups for the substitution reaction.



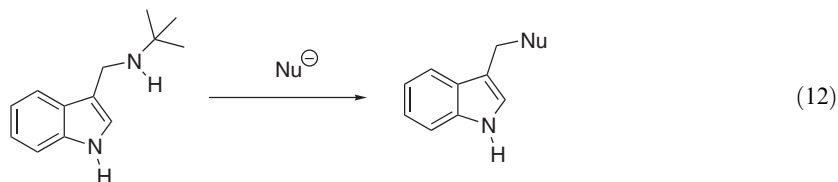
The first direct alkylation of enolates and related compounds with trialkylamines was recently disclosed: in the presence of a ruthenium catalyst, enolizable ketones were alkylated with various trialkylamines in moderate-to-good yields, without any polyalkylation <2001AG(E)958> (Scheme 8). The reaction is highly regioselective as alkylation is occurring only at the less hindered position. Imines were also efficient for alkyl group transfer.



Scheme 8

1.06.1.4 Secondary Amines

The classical gramine alkylation of indole derivatives may also be accomplished using bulky secondary amines instead of tertiary amines or quaternary ammonium salts (Equation (12)). Substitution reaction with soft nucleophiles is achieved under basic conditions at a lower temperature than for the tertiary amine. Despite its mild conditions, this reaction has encountered little application in synthesis.

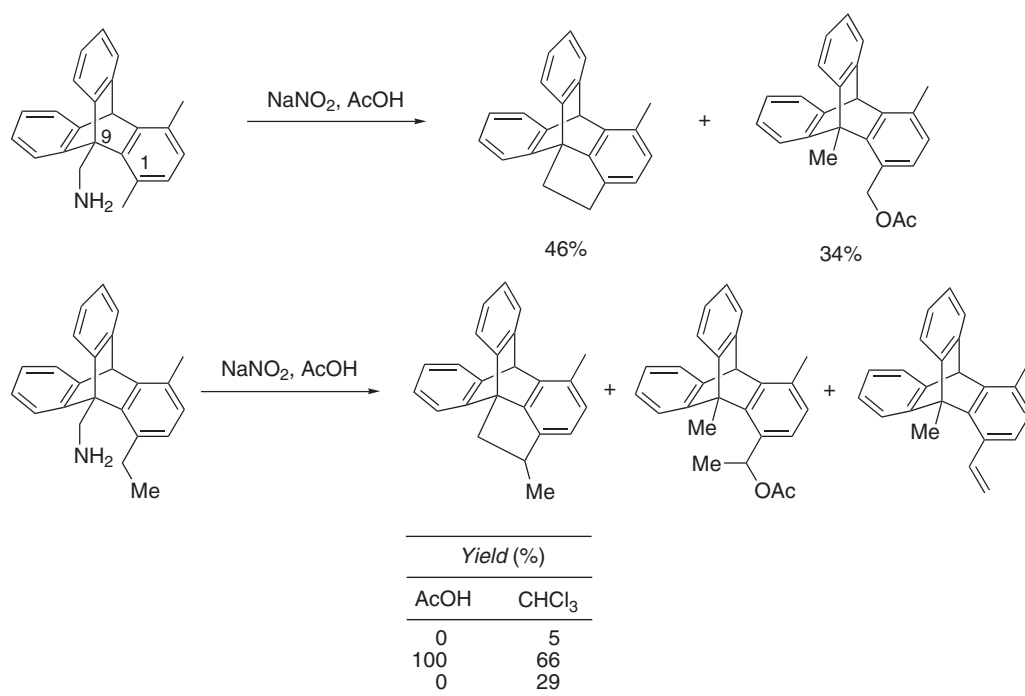


1.06.1.5 Diazotization of Primary Amines

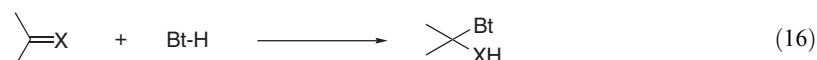
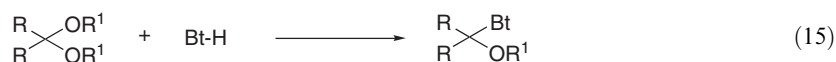
Diazotization of primary amines with nitrous acid gives diazonium salts, which react with various nucleophiles with subsequent loss of nitrogen. Diazonium salts obtained from primary aliphatic amines generally lose nitrogen to give carbocations which often rearrange. The diazotization reaction of 9-aminomethyl-1-methyltryptycene has been shown to give predominantly a new cyclic hydrocarbon derivative through insertion in the neighboring methyl group at C1; intermolecular nucleophile trapping occurred only at the methyl at C1 position, proving the existence of an internal hydride transfer. Further studies have been undertaken, showing the strong solvent dependence on product distribution: protic solvents such as acetic acid favor formation of a carbocation at C1 (Scheme 9). When an ethyl substituent is present at C1, products derived from an elimination followed by a nucleophilic attack are predominant, because of the greater stability of the secondary carbocation <2000CL454>.

1.06.1.6 Functionalized Benzotriazoles

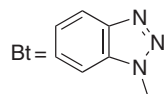
The chemistry of functionalized 1-substituted benzotriazoles has been extensively studied in recent years and comprehensively reviewed <1998CRV409, 2000PAC1597>. The benzotriazole group may be considered as a stable, easy to handle, and recoverable pseudo-halogen group. Introduction of the benzotriazole function may be accomplished either by halide displacement, alkoxy group displacement in acetals or ketals, by addition to carbon-heteroatom multiple bonds, or through multiple-component synthesis (Equations (13)–(17)).



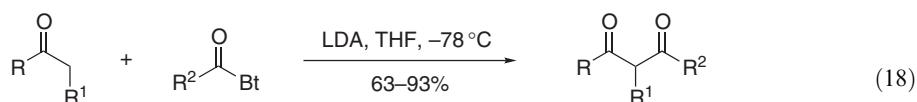
Scheme 9



R = H, alkyl, aryl; R¹ = Me, Et, X = O, N, S

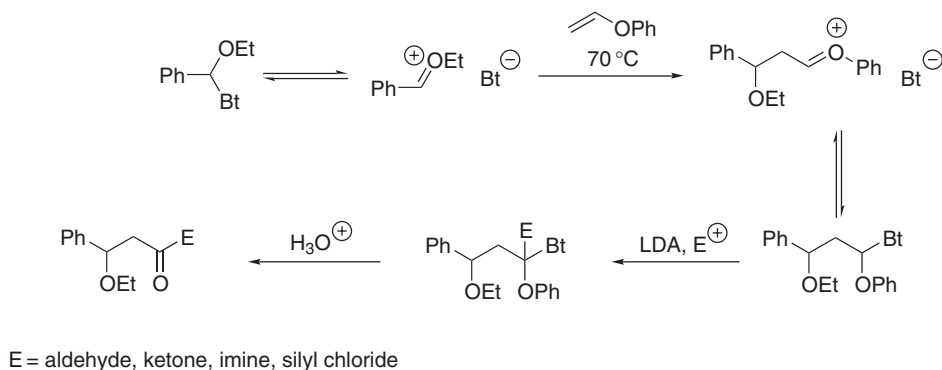


Functionalized benzotriazoles may be used in a vast array of synthetic transformations, including carbon–carbon bond formation. Recently, it was discovered that 1-acylbenzotriazoles were good C-acylating reagents for ketone enolates, allowing the easy formation of β -dicarbonyl compounds [<2000JOC3679>](#) (Equation (18)). Acyl transfer was accomplished by treating the ketone enolate (obtained by treatment of the ketone with lithium diisopropylamide (LDA) with the acylbenzotriazole reagent; the reaction was selective as only C-acylation products were obtained.



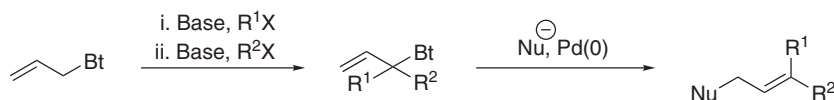
R, R¹ = alkyl, aryl; R² = Me, Ph, *t*-amyl

Reaction of 1-benzotriazolyl alkyl ethers (obtained from acetals or ketals) with phenyl vinyl ether provides another access to carbon–carbon bond formation [<1998JOC1473>](#). The newly formed 1-benzotriazolyl ether may react after deprotonation with a variety of electrophiles, to give, after hydrolysis, polyfunctionalized ketones (Scheme 10).

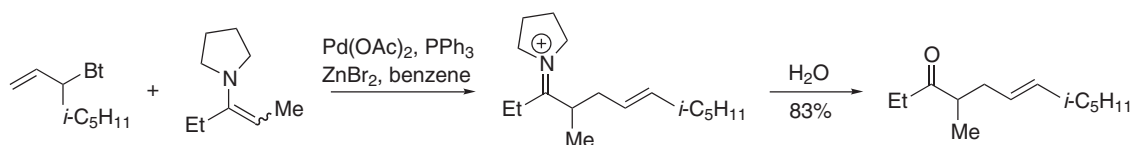


Scheme 10

Transition metal-catalyzed nucleophilic substitution of *N*-allylbenzotriazoles is a potentially advantageous reaction since allylbenzotriazoles are easily prepared and transformed into π -allyl palladium complexes. In contrast with allylic amines, the use of more reactive nickel complexes is not required and the nucleophilic substitution is highly regioselective (Scheme 11). This methodology has been applied to a new synthesis of γ,δ -unsaturated ketones by reaction of allylbenzotriazoles with enamines <1999JOC7625> (Scheme 12). Reaction was performed using a $\text{Pd}(0)$ complex with zinc bromide as additive. The ketones were obtained in a highly stereoselective fashion, the (*E*)-isomer being predominant.

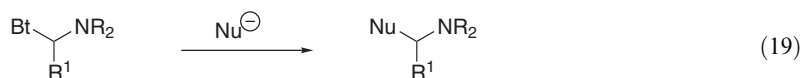


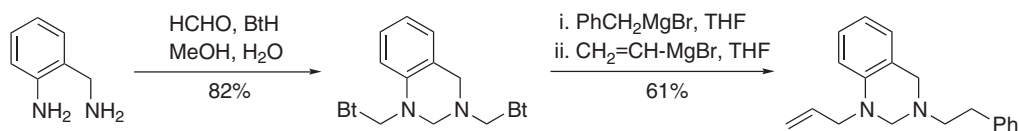
Scheme 11



Scheme 12

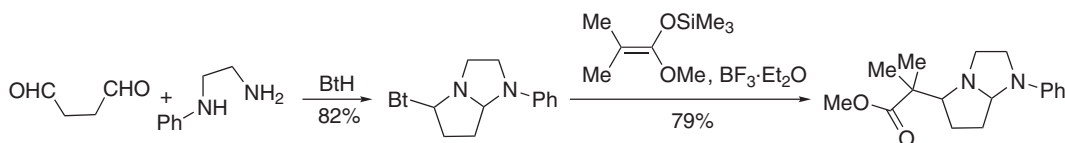
One of the most important substitution reactions of benzotriazoles is the nucleophilic displacement of $\text{Bt}-\text{C}-\text{N}$ type compounds with soft or hard nucleophiles (Equation (19)). The reaction tolerates a wide variety of substituents on nitrogen, since amines, amides, or imines are suitable substrates for the substitution reaction. Alkyl or aryl groups are introduced with Grignard reagents, or better, organozinc compounds, whereas other nucleophiles such as cyanide, enolates, or nitroalkanes are introduced via $\text{S}_{\text{N}}2$ -type substitutions. Examples and applications may be found in the review <1998CR409>. A recent representative example describes the synthesis of hexahydropyrimidines and tetrahydroquinazolines <2002JOC3115> (Scheme 13). The heterocyclic ring is prepared by a three-component synthesis with benzotriazole, formaldehyde, and a 1,3-diamine. Treatment with Grignard reagents allows the introduction of alkyl substituents on nitrogen atoms.





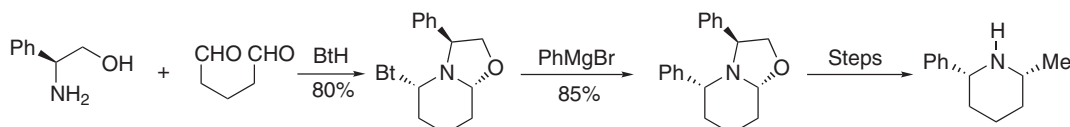
Scheme 13

In an analogous strategy, condensation of a bis-aldehyde such as succinaldehyde with a diamine and benzotriazole gives the hexahydro-1*H*-pyrrolo[1,2-*a*]imidazole ring system, which can be further substituted by benzotriazole displacement [<2000JOC3683>](#) (Scheme 14). Reaction with Grignard reagents allows the introduction of alkyl or aryl groups, whereas Lewis acid-mediated condensation with silyl enol ethers gives ketones.



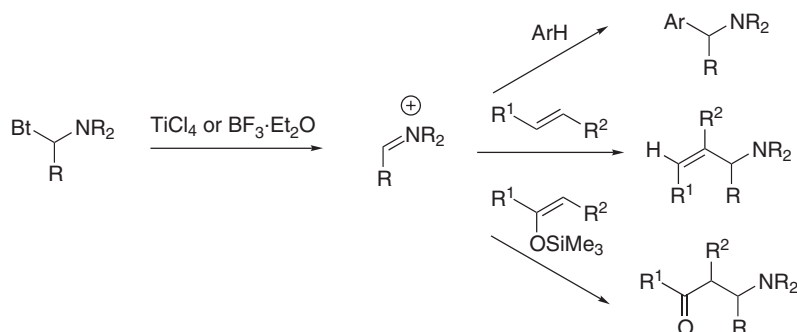
Scheme 14

Asymmetric synthesis of 2,6-disubstituted piperidines using benzotriazole substitution was recently accomplished as a modification of the classical method with chiral aminonitriles [<1998JOC6699>](#). Treatment of benzotriazole with glutaraldehyde and phenyl glycinol gave in one step the chiral aminoalkyl benzotriazole (Scheme 15). Substitution with phenyl magnesium bromide, followed by oxazolidine ring opening, gave, after hydrogenolysis of the chiral auxiliary, the *cis*-disubstituted piperidine in an enantiomerically pure form.

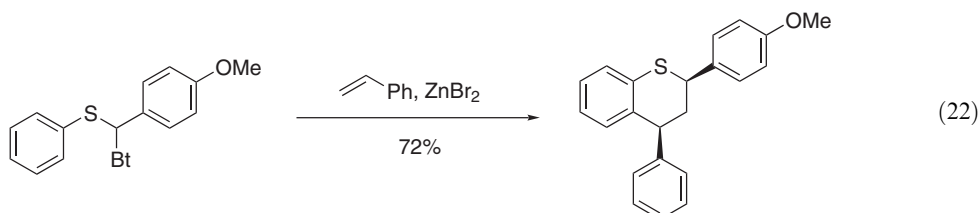
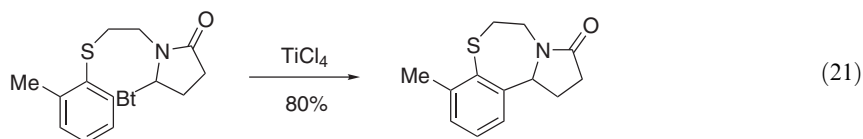
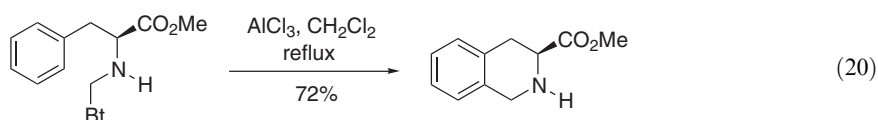


Scheme 15

Treatment of aminoalkyl benzotriazoles with a Lewis acid gives a planar iminium cation, which may react with carbon nucleophiles such as alkenes, arenes, or silyl enol ethers [<2000JOC3683>](#) (Scheme 16). These properties were applied to the synthesis of various heterocyclic systems such as tetrahydroquinolines [<2001TA2427>](#) (Equation (20)), indolo-isoquinolines [<2001JOC148>](#), 1,4-benzothiazepines (Equation (21)), or 1,4-benzoxazepines [<2001JOC5590>](#). Addition of the iminium cation to alkenes followed by intramolecular substitution onto an aromatic ring results in an annulation reaction [<2001JOC5595>](#) (Equation (22)).

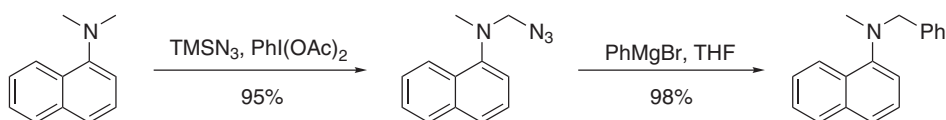


Scheme 16



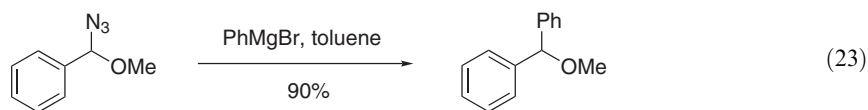
1.06.1.7 Azides

Substitution of alkyl azides with carbon nucleophiles is rather an uncommon reaction; however, it was recently discovered that α -azidoethers or α -azidoamines react with Grignard reagents to give ethers or amines in good yields. Thus, azidation of an aryl dialkylamine gave an α -azidoamine, which reacted with phenylmagnesium bromide [<1998S547>](#) (Scheme 17).

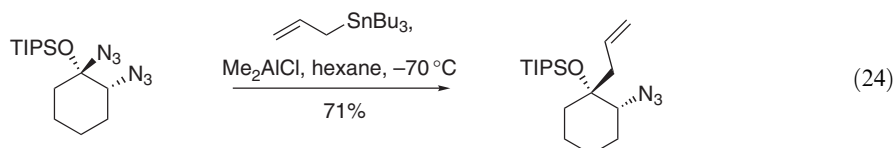


Scheme 17

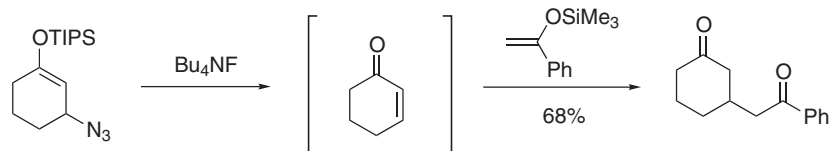
In contrast, the corresponding α -azidoethers are less reactive toward substitution, and reaction with Grignard compounds occurs only if toluene is used as solvent ([Equation \(23\)](#)). Under these conditions, good yields of ethers are obtained [<2002JCS\(P1\)509>](#).



1,2-Bis-azido-1-triisopropylsilyl ethers are prepared by bis-azidation of triisopropylsilyl enol ethers and undergo substitution of the azido function at the C1 position only ([Equation \(24\)](#)). The overall sequence is highly stereoselective, giving *cis*-1,2 azidoethers [<1995CC263>](#).



β -Azidosilyl enol ethers, prepared by the azidation of silyl enol ethers, undergo substitution of the azido function by carbon nucleophiles, after treatment with tetrabutylammonium fluoride [<1998JA12486>](#). The reactive intermediate is believed to be an α,β -unsaturated ketone, which undergoes a conjugate addition ([Scheme 18](#)). Since intermediates need not to be isolated, the overall process can be regarded as a β -alkylation of ketones.

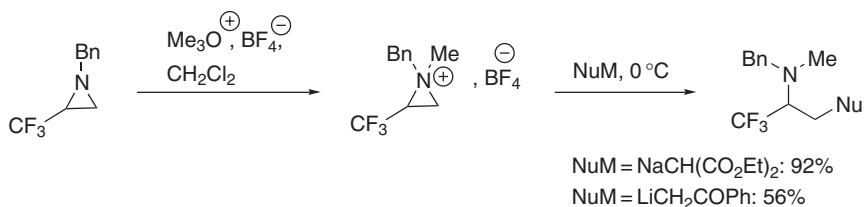


Scheme 18

1.06.1.8 Ring Opening of Aziridines

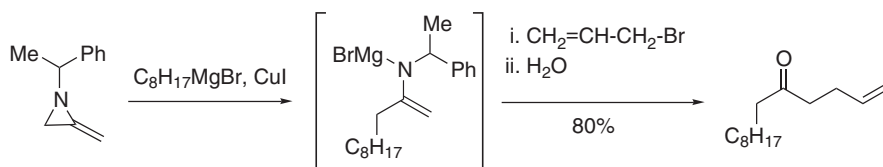
The synthesis and reactivity of aziridines have been the object of intense studies in recent years. Carbon–carbon bond formation with aziridines as substrates has attracted much attention, with the concomitant development of modern aziridination methods. As a consequence, many recent reviews concerning the reactivity of aziridines toward carbon nucleophiles are available [<1994AG\(E\)599, 2000S1347, 2002CSR247>](#).

Reactivity of aziridines toward ring opening strongly depends on the nature of the nitrogen substituent, simple *N*-alkyl aziridines being poorly reactive. Activation may be provided by protonation, quaternarization with alkylating reagents or treatment with a Lewis acid. *N*-Benzyl-trifluoromethyl aziridine was thus opened with various nucleophiles, including carbon nucleophiles, after treatment with trimethyloxonium tetrafluoroborate (Scheme 19). The intermediate aziridinium ion was characterized by ^{19}F NMR spectroscopy. The regioselectivity was in favor of an attack at the less hindered position [<1999JOC7323>](#).



Scheme 19

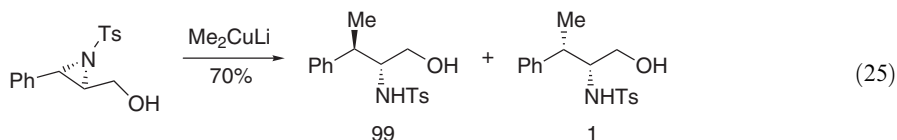
In a multicomponent synthesis of unsymmetrical ketones, *N*-benzyl-2-methylene aziridines were used as building blocks for alkyl group transfer. These highly reactive substrates were treated first with a Grignard reagent in the presence of copper iodide to give a metallo-enamine in a highly regioselective fashion. This metallo-enamine could be further alkylated with electrophiles to give the corresponding ketone after aqueous treatment [<2002JOC935>](#). This multicomponent ketone synthesis tolerates a wide variety of nucleophiles and electrophiles; substitution on the exocyclic double bond in the starting 2-methylene aziridine is also allowed (Scheme 20).



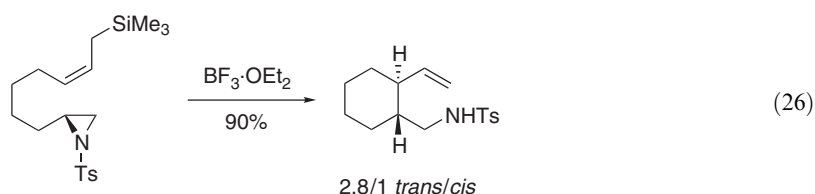
Scheme 20

Substitution of a nitrogen atom by an electron-withdrawing group strongly increases the reactivity of the aziridine ring toward nucleophiles. *N*-Sulfonyl groups are widely used because of their stability, ease of introduction, crystallinity, and absence of a competing reaction with nucleophiles, the only drawback being the harsh conditions required for the deprotection. *N*-Tosylaziridines react with a great variety of carbon nucleophiles, including organolithium derivatives [<1995TA2033>](#) or heteroatom-substituted allyl anions [<1999JCS\(P1\)1927>](#), the best reagents for this operation being organo-copper reagents: an *N*-tosyl protected 2-aziridine methanol was reacted with Gilman reagent to give the aminoalcohol in nearly quantitative yield [<1999JOC3237>](#).

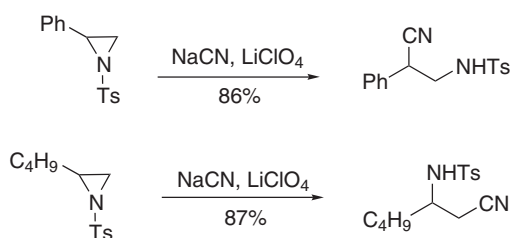
The regio- and stereoselectivity of ring opening of various *N*-tosyl-3-phenyl-2-aziridinemethanols with methyl transfer reagents was studied [<1995T8279>](#). Ring opening of the *trans*-isomer showed complete regioselectivity in favor of an attack at the C3 position; cuprate reagents cleanly gave inversion of configuration, whereas trimethylaluminum gave a mixture of inversion and retention, depending on the protecting group at the hydroxyl function. Ring opening of the *cis*-isomer is less selective ([Equation \(25\)](#)).



Intramolecular reaction of *N*-tosylaziridine with allyl silanes was developed as an efficient approach to cyclic systems with an amine function [<1999JOC3237, 2002T7109>](#). Reaction was performed in the presence of a Lewis acid to give selectively a γ -aminoalkene in high regio- and stereoselectivity ([Equation \(26\)](#)). This strategy was applied to the synthesis of various alkaloid ring systems.

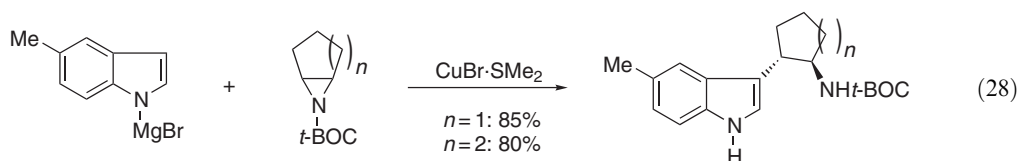
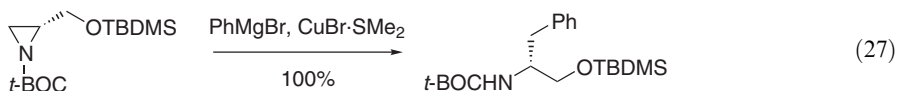


Reaction of unfunctionalized *N*-tosylaziridines with a cyanide ion is achieved using lithium perchlorate as catalyst [<2002S2383>](#) ([Scheme 21](#)). Regioselectivity is in the favor of an attack at the less hindered position, unless a phenyl group substitutes the aziridine ring.

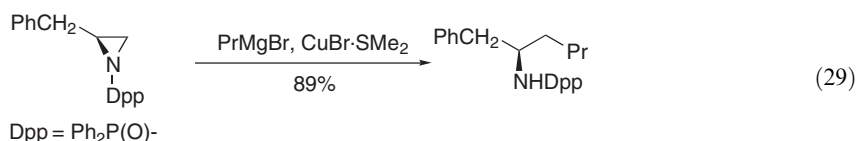


Scheme 21

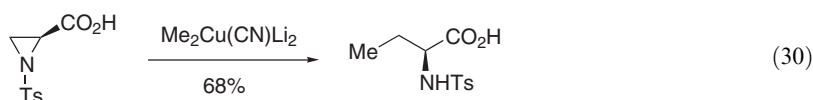
Besides the tosyl group, the *t*-butoxycarbonyl (*t*-BOC) protecting group was also used for *N*-protection of aziridines. Ring-opening reactions of *N*-BOC aziridines are accomplished using Grignard reagents in the presence of copper bromide–dimethyl sulfide complex; this method was applied to the synthesis of chiral aminoalcohols as precursors of D-amino acids, starting from protected aziridine-2-methanol [<1998TL9389>](#) ([Equation \(27\)](#)). Reactions occurred in high yield and with complete regioselectivity. The same reaction conditions were used for the ring opening of BOC-aziridines with the indole nucleus [<1996TL683, 1997T8237>](#). This reaction was applied to the synthesis of new serotonin analogs ([Equation \(28\)](#)).



The diphenylphosphinyl (Dpp) group was recently introduced as an easily removable protecting group for aziridines <1998T2181>. However, reactions of carbon nucleophiles with *N*-Dpp aziridines suffered from a competitive attack at phosphorus. Once again, the combination of Grignard reagents and copper bromide–dimethyl sulfide complex allowed selective ring opening in good yields (Equation (29)).

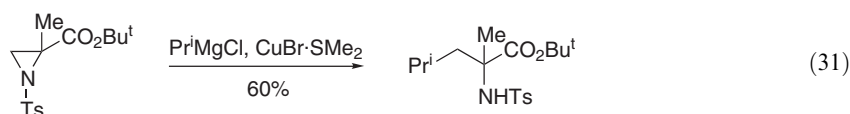


Aziridine 2-carboxylates are important building blocks since their ring-opening reactions lead to α -amino acids. Initial studies showed lack of regioselectivity in the ring-opening reactions and competitive attack on the carboxylic ester function. The problem was circumvented by the use of a free carboxylic acid as substrate and *N*-tosyl protection <1995TL151>. Under these conditions, reactions with higher-order cuprates gave, regioselectively, the *N*-tosyl amino acids, with complete attack at the C3 position (Equation (30)).

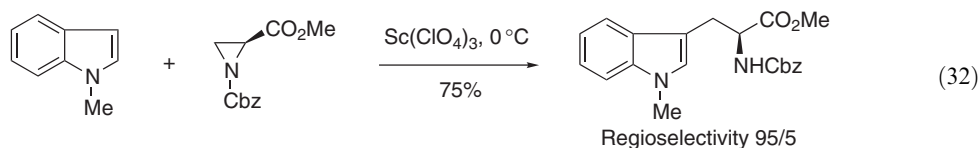


The same conditions were applied for the ring opening of 3-substituted aziridine 2-carboxylic acids, albeit in modest yield and regioselectivity, only lithium trimethylsilyl acetylide giving satisfactory yields and good regioselectivity. These conditions were also unsuitable for the introduction of soft nucleophiles or a cyanide ion.

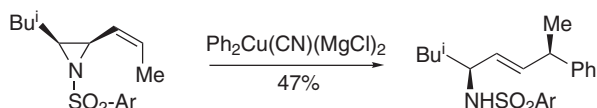
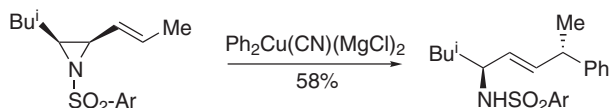
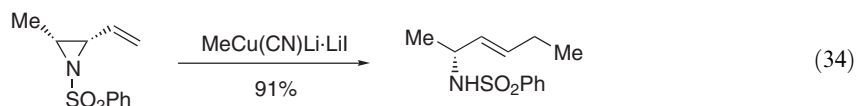
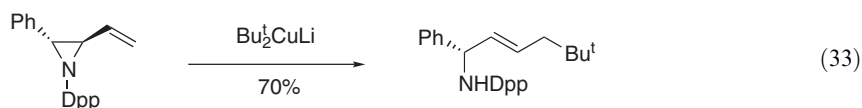
The introduction of a substituent on the C2 position of aziridine carboxylates increases reactivity and selectivity in favor of an attack at the C3 position <1996T13035>. Reaction with Grignard compounds in the presence of copper bromide–dimethyl sulfide may be achieved with the *t*-butyl ester without a competing reaction (Equation (31)). The corresponding alcohols were also used as substrates to give amino alcohols; yields were slightly better than with the aziridine esters.



Ring-opening reaction of *N*-Cbz aziridine 2-carboxylates with indole nucleus in the presence of a Lewis acid allows the formation of tryptophan analogs. Since initial conditions with zinc triflate required high temperatures even for low conversions and yields, other Lewis acids have been investigated. The use of scandium triflate strongly accelerated the reaction and allowed the use of *N*-benzyloxycarbonyl-protected aziridines <1998SL754>. A more recent report recommended scandium perchlorate as a superior Lewis acid for the ring opening of aziridine 2-carboxylates with respect to regioselectivity and scaling up <2002S1658> (Equation (32)). The reaction could be performed at low temperature, and allows the preparation of various tryptophan analogs.

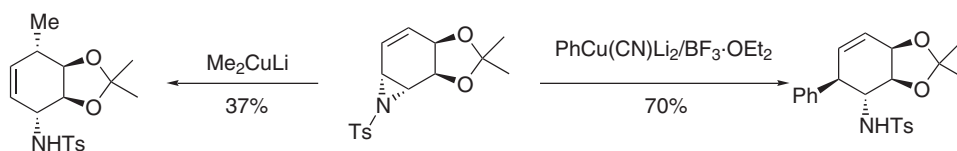


2-Alkenylaziridines react with organocopper reagent to give allylic amines through an $\text{S}_{\text{N}}2'$ mechanism. 2,3-*trans*-*N*-Diphenylphosphoryl vinylaziridines are readily opened with low-order cuprate reagents to give predominantly (*E*)-allylic amines <1996SL847> (Equation (33)). The use of Grignard reagent resulted in lower regioselectivity. Soft nucleophiles like malonate anions could also be used with the help of a palladium catalyst. A more recent study reported higher yields and stereoselectivities with *N*-sulfonyl vinylaziridines using higher-order cuprate reagents (Equation (34), Scheme 22). This study also revealed the importance of aziridine configuration as 2,3-*cis*-aziridines gave better regio- and stereoselectivities than the 2,3-*trans*-aziridines <1998JOC7053>.



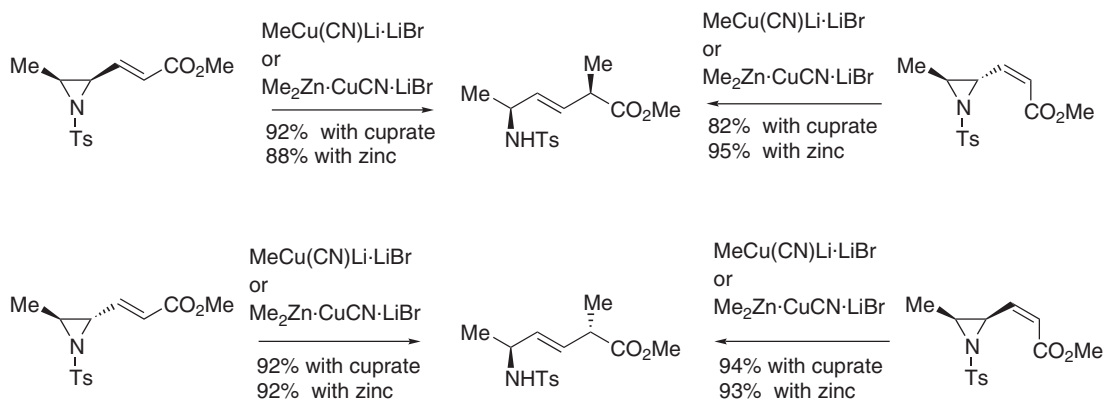
Scheme 22

Investigation in the ring-opening reaction of hindered bicyclic aziridines revealed strong dependence on the nature of the nucleophile <1996JA10752> (Scheme 23). Although Grignard reagents or low-order cuprates gave predominantly *syn*-1,4-addition, high-order cuprates gave divergent results: lithium dimethyl cuprate gave a *syn*-1,4-addition, whereas aromatic cuprates gave an *anti*-1,2-addition.



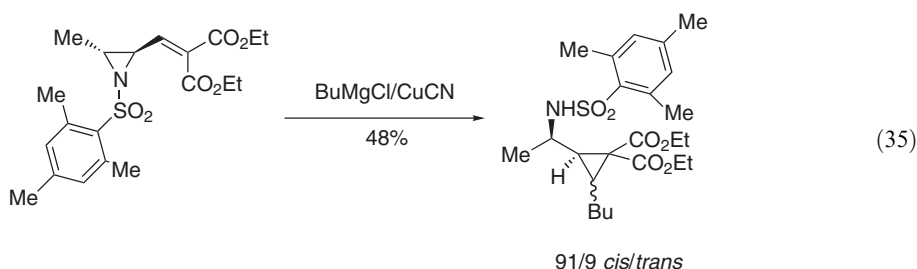
Scheme 23

2-Vinylaziridines with an ester function on the double bond are precursors to (*E*)-alkene dipeptide isosteres through a reaction with organometallic reagents <1994JOC4875>. A recent study recommended the use of low-order cuprates or dialkylzinc reagents in the presence of copper cyanide <1995JCS(P1)1359> (Scheme 24). Under these conditions, *N*-tosylaziridines are opened in high yields and stereoselectivities through an *anti*-S_N2' mechanism.

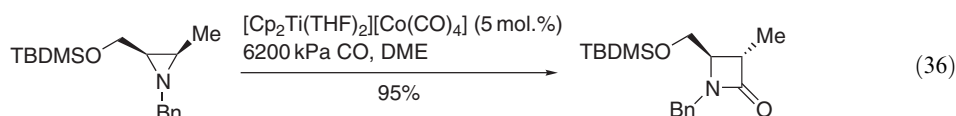


Scheme 24

When two ester functions are appended to the double bond of 2-vinylaziridines, reaction with organometallic reagents results in the cyclopropane formation through an intramolecular Michael addition [<1996T12253>](#). The best results were obtained using Grignard reagents in the presence of copper cyanide (Equation (35)); increasing steric bulk on nitrogen gave a better *cis/trans* ratio.

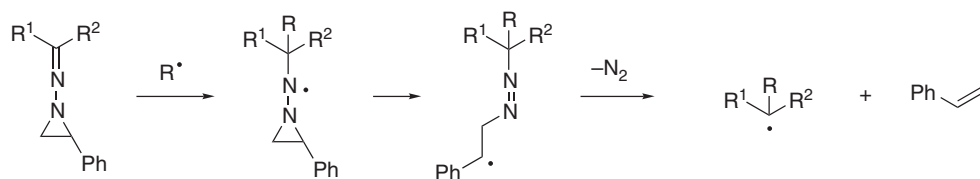


Aziridines may be used as precursors to azetidinones (β -lactams) by carbon monoxide insertion (Equation (36)). Treatment of *N*-tosylaziridines with a cobalt catalyst and carbon monoxide under pressure resulted in azetidinone formation, with insertion at the less hindered carbon [<2002AG\(E\)2781>](#). The reaction occurred with inversion of configuration.

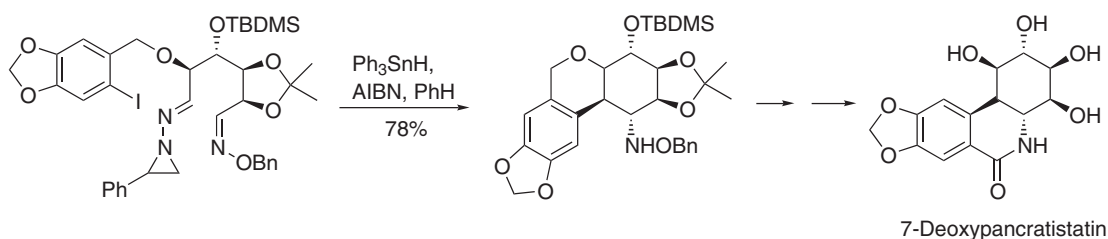


1.06.1.9 Radical-mediated Processes

Carbon–carbon bond formation via radical-mediated cleavage of carbon–nitrogen bonds is rather uncommon. This kind of process may occur with a radical initiator such as aza-bis-isobutyronitrile, which can recombine with carbon radicals. *N*-Aziridinylimines have been designed as good precursors for tandem radical cyclizations: addition of a carbon-centered radical to this imine results in the formation of a nitrogen-centered radical, which decomposes through aziridine-opening, followed by loss of styrene and nitrogen (Scheme 25). A new carbon radical is therefore generated, which can react with various acceptors. This tandem radical cyclization strategy has been recently applied to the syntheses of zizaene [<1997SL947>](#), cedrene [<1998TL7713>](#), and 7-deoxypancratistatin [<1998JOC9164>](#) (Scheme 26).



Scheme 25



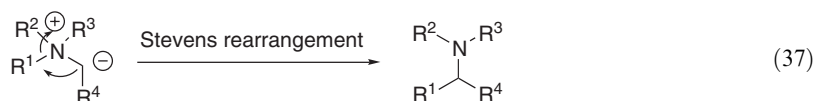
Scheme 26

1.06.1.10 Rearrangements

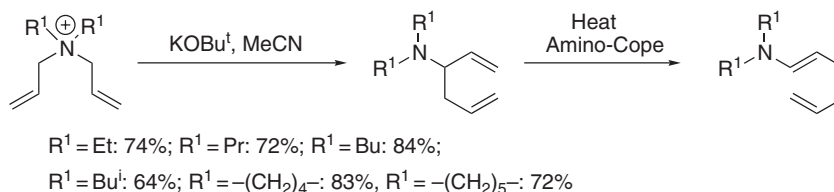
Many rearrangements of nitrogen-containing compounds involve the formation of a carbon–carbon bond with a cleavage of the carbon–nitrogen bond.

1.06.1.10.1 The Stevens rearrangement

The Stevens rearrangement of ammonium ylides is a classical reaction, which has often been used in natural product synthesis. Stereospecific [1,2]-shift from nitrogen to carbon allows the formation of tertiary amines in good yields (Equation (37)). Ammonium ylides may be prepared via two routes: deprotonation of quaternary ammonium salts or addition of carbenes to tertiary amines.

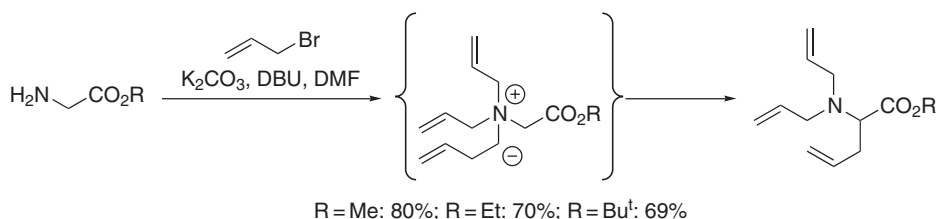


The generation of ammonium ylides from quaternary ammonium salts is facilitated by the presence of a substituent which increases proton acidity, such as unsaturation or an electron-withdrawing group. Thus, quaternary diallylammonium salts easily undergo Stevens rearrangement when treated with potassium *t*-butoxide <1997SL725> (Scheme 27) to give a tertiary amine, which may lead to enamines via an Amino-Cope rearrangement.

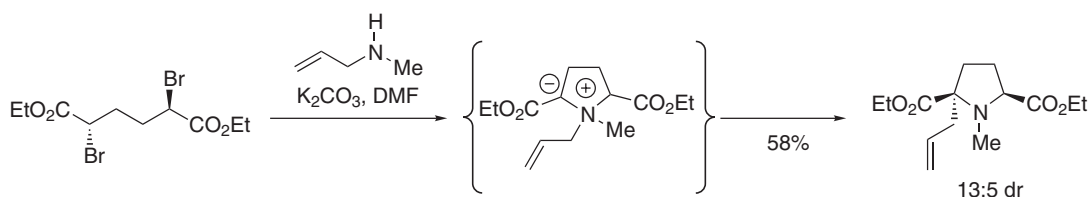


Scheme 27

Allyl transfer from nitrogen to carbon was also used in an approach to the synthesis of allylated amino acids <2000SL236>. Glycine ester, when treated with an excess of allyl bromide with 1,5-diazabicyclo[5.4.0]undec-5-ene (DBU), gave the intermediate triallylammonium ylide, which underwent rearrangement to give *N,N*-diallylallylglycine esters in good yields (Scheme 28). Nitrogen deprotection gave allylglycine ester. Yields were lower when quaternary amino acids were formed from alanine or phenylalanine. When enantiomerically pure *N*-benzylproline ester was submitted to the same conditions, optically active α -allylproline was obtained, thus suggesting an enantioselective allylation of nitrogen atom followed by a stereospecific rearrangement. In a related strategy, a C_2 symmetrical *N*-allyl-*N*-methylpyrrolidine bis-ester was prepared *in situ* and treated under basic conditions to give the corresponding 2-allylpyrrolidine with modest stereoselectivity in favor of the *cis*-product <2002TL899> (Scheme 29).

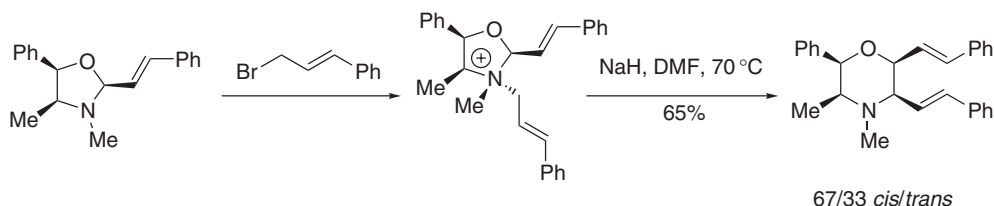


Scheme 28



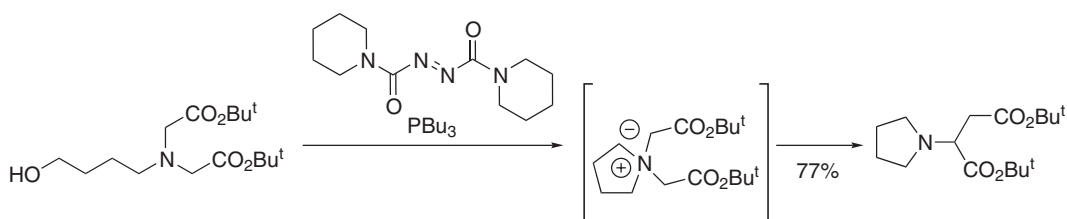
Scheme 29

A new synthesis of chiral morpholines has been described, using *N*-allylation of ephedrine-derived 2-allyloxazolidines, followed by sodium hydride-mediated Stevens rearrangement [<2000SL893>](#) (Scheme 30). Migration of the carbon–nitrogen bond in the oxazolidine ring gave a mixture of diastereoisomeric morpholines with modest selectivity.



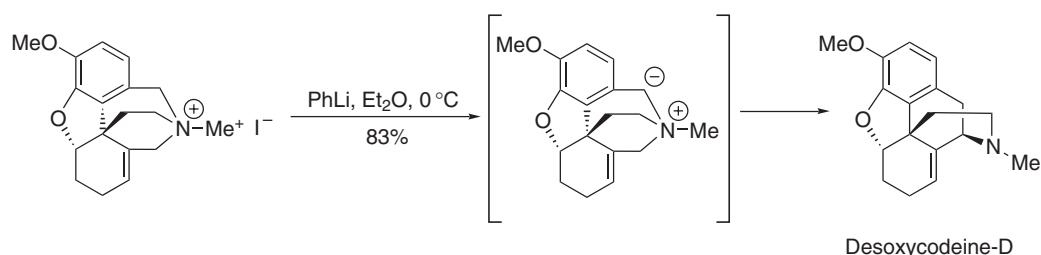
Scheme 30

An unexpected intramolecular nitrogen alkylation followed by a Stevens rearrangement was observed when a tertiary γ -hydroxyamine was treated under Mitsunobu conditions [<1996TL8133>](#) (Scheme 31). Careful optimization of the reaction conditions leads to an appreciable yield of a tertiary pyrrolidine. The hydrazodicarboxylate obtained through the Mitsunobu procedure is believed to act as a base for the rearrangement.



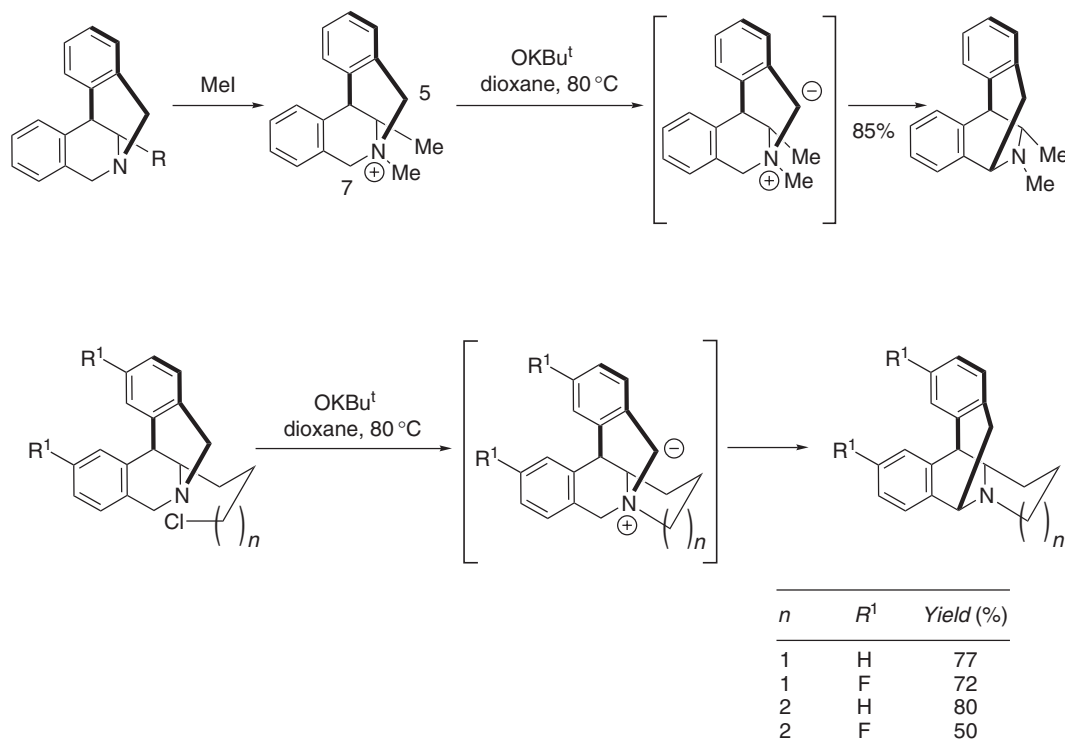
Scheme 31

Benzylic quaternary ammonium salts are also good substrates for the Stevens rearrangement. The final step for the total synthesis of the morphine analog desoxycodine-D involves deprotonation at the benzylic position of octahydroisoquinoline ammonium salt [<2000TL915>](#). Stevens rearrangement occurred at low temperature to give the benzomorphane skeleton (Scheme 32).



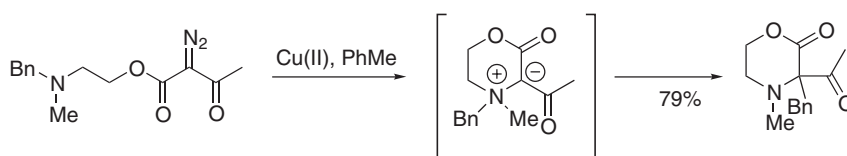
Scheme 32

The same strategy was applied to the preparation of isopavine alkaloids from azocine ions <2001AG(E)3810>. Diastereoselective [1,2]-rearrangement occurred after deprotonation of azocinium ions with potassium *t*-butoxide (Scheme 33). The stereoselectivity of the rearrangement was explained by a favored reaction pathway involving deprotonation at the C5 position, whereas the formation of the ylide at the concurrent C7 position yields an iminium ion which is destabilized by allylic strain. This highly stereoselective rearrangement gave a family of isopavine analogs which were tested as morphinomimetics <2003JMC34>.



Scheme 33

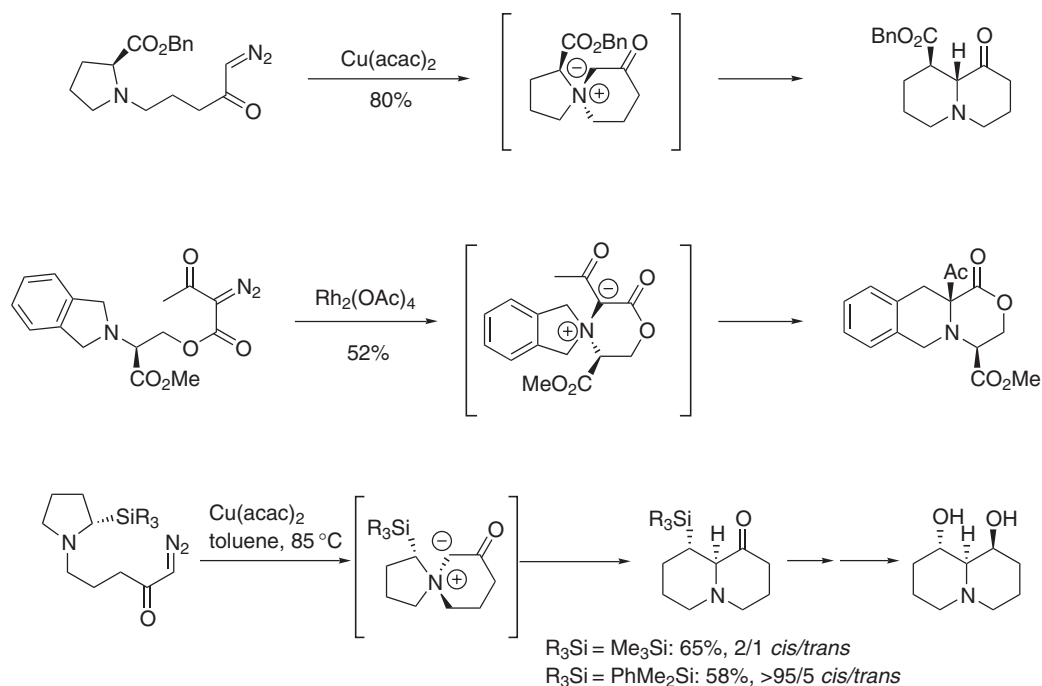
Stabilized ammonium ylides may also be prepared by addition of a carbene to a tertiary amine, the carbene being generally generated *in situ* by rhodium or copper-mediated decomposition of a diazoester. In recent years, the intramolecular version of this reaction, leading to cyclic ammonium ylides, has been thoroughly investigated. Thus, morpholine-2-ones were prepared from 2-(*N,N*-dialkylamino)ethyl diazoacetates by heating in presence of copper <1994JOC6051>. The intermediate cyclic ammonium ylide undergoes alkyl group transfer from nitrogen to a neighboring carbon atom (Scheme 34). The overall process shows good generality, apart from highly hindered substrates which fail to rearrange.



Scheme 34

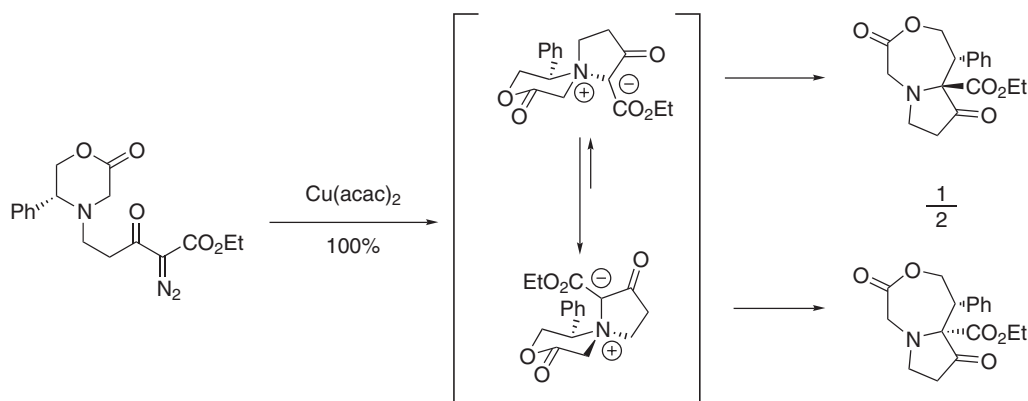
Intramolecular reactions of carbenoids with cyclic tertiary amines give spirocyclic ammonium ylide intermediates which undergo Stevens rearrangement to yield bicyclic products. This rearrangement has been widely used in alkaloid synthesis, via diazo decomposition of proline <1994JA8420> and serine <1995SL237> derivatives (Scheme 35). Diastereoselection was

controlled by the ester substituent that directs the carbenoid attack on the nitrogen atom. A trialkylsilyl substituent on the nitrogen ring has also been used for directing the Stevens rearrangement of a 2-silylpyrrolidine [<2002OL2813>](#) (Scheme 35). The silyl substituent efficiently controls diastereoselective ammonium ylide formation and may be used as a masked hydroxyl group, thus allowing entry to hydroxylated pyrrolidines. Stereoselectivity in the Stevens rearrangement depends on the nature of alkyl groups on silicon, the bulkier phenyldimethylsilyl group allowing isolation of a single diastereomer. It was also observed that partial racemization occurred during the ammonium ylide formation, indicating a possible proton transfer α to the silicon atom.



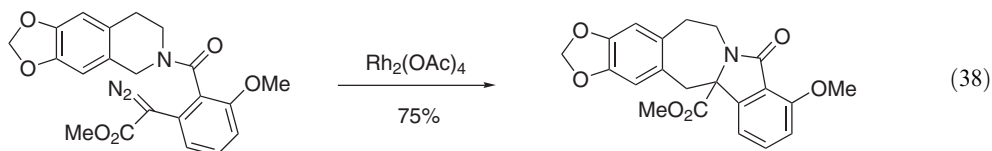
Scheme 35

Phenylglycinol-derived morpholine-2-ones, after nitrogen alkylation with a diazoester, undergo ammonium ylide formation followed by Stevens rearrangement in quantitative yield [<2000TA3449>](#) (Scheme 36). Stereocontrol in the formation of the ammonium ylide was less efficient with a six-membered ring than with a five-membered ring, giving a 2/1 mixture of diastereoisomers. These compounds were easily separated since the minor *trans*-isomer was insoluble in the reaction solvent.

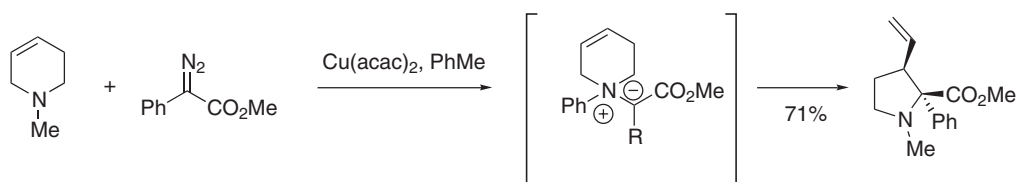


Scheme 36

The isoindolobenzazepine ring system, a 5,7-fused nitrogen heterocycle, may be found in rhoeadine and papaverrubine alkaloids. A rapid entry to this ring system employs the intramolecular ammonium ylide formation–Stevens rearrangement sequence between a benzylic diazoester and a tetrahydroisoquinoline [<2001JOC2414>](#) (Equation (38)). The carbenoid formation is assured by the use of rhodium acetate.



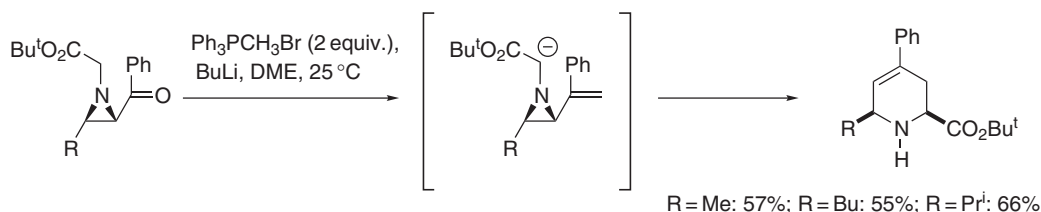
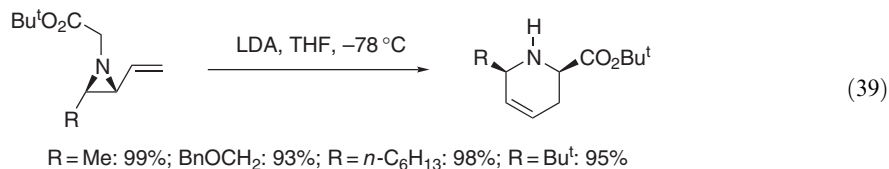
Finally, [2,3]-sigmatropic rearrangements of unsaturated ammonium ylides have also been studied. A recent example describes the preparation of 3-vinylproline derivatives through of addition ethyl diazoacetate to *N*-methyltetrahydropyridine [<2003JOC4083>](#). The rearrangement gave stereoselectively the *cis*-product, and by using substituted diazoesters, quaternary proline derivatives were obtained (Scheme 37). The best catalyst for carbenoid addition to the tetrahydropyridine was copper(II) acetylacetonate.



Scheme 37

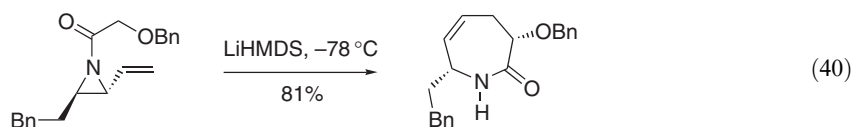
1.06.1.10.2 Rearrangements of aziridines

The aziridine ring system has been involved in many rearrangement processes, leading to nitrogen-containing heterocycles. In recent years, ring expansion of aziridines to piperidines via an aza-Wittig rearrangement has been thoroughly investigated [<1994JA9781, 1996JOC8148>](#). Enantiomerically pure *trans*-2-vinylaziridines with an acidic proton α to the nitrogen atom undergo rapid and stereoselective [2,3]-rearrangement to give tetrahydropyridines in high yields and stereoselectivity (Equation (39)). *cis*-Substituted aziridines rearrange with low stereoselectivity. Substitution on the C1 position of the double bond leads to 4-substituted 4-tetrahydropyridines with high selectivity [<1995TL3557>](#), and one stereoisomer has also been obtained (Scheme 38). The vinylaziridine is prepared *in situ* by olefination of 2-acylaziridines, thus allowing a one-pot procedure.

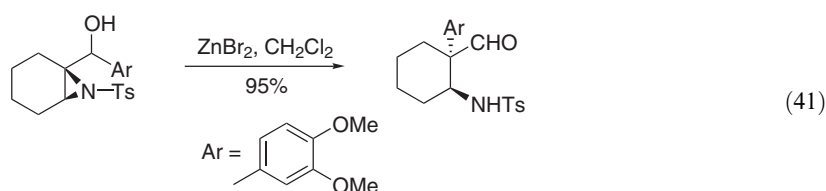


Scheme 38

A [3,3]-rearrangement of a vinylaziridine leading to a seven-membered ring lactam has also been described [<1997JA8385>](#) (Equation (40)). Once again, a single stereoisomer was obtained from a *trans*-disubstituted aziridine.

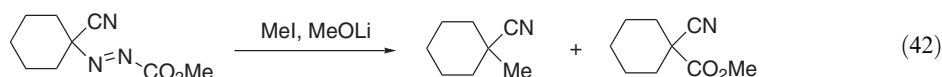


Like 2,3-epoxyalcohols, secondary 2,3-aziridinoalcohols may undergo Lewis acid-mediated rearrangement with aziridine ring opening and migration of an alkyl or aryl group. This reaction has recently been applied to a cyclic aziridino alcohol, leading to a β -aminoaldehyde with a quaternary carbon center [<2003OL2319>](#) (Equation (41)). Zinc bromide-mediated rearrangement occurred with high stereoselectivity, affording precursors to the crinane family of alkaloids.



1.06.1.11 Electrophilic Substitutions

Substitution of nitrogen functions with formation of a carbon–carbon bond generally involves reactions with carbon nucleophiles, and electrophilic substitutions are extremely rare. Unsymmetrical tertiary azocarboxylates may lose nitrogen upon treatment with an electrophile and a base to give a mixture of alkylated and acylated products (Equation (42)). This reaction does not seem to have been used in synthesis.



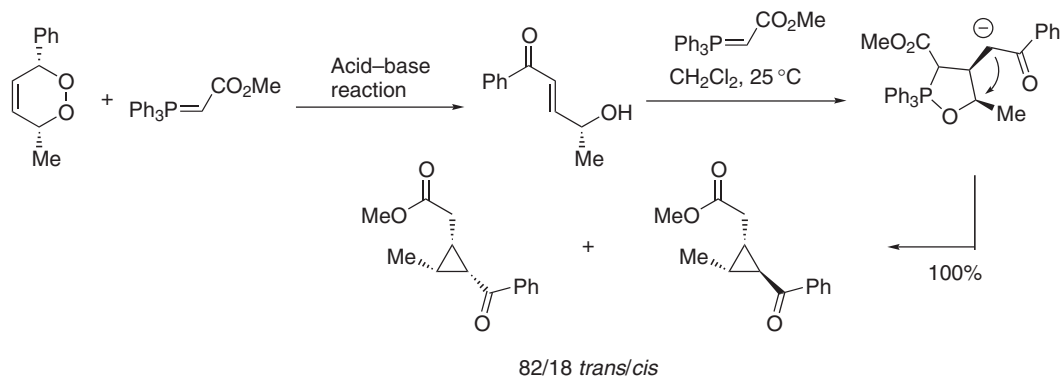
1.06.2 SUBSTITUTION OF PHOSPHORUS, ARSENIC, AND ANTIMONY FUNCTIONS

1.06.2.1 Substitution of Phosphorus Functions

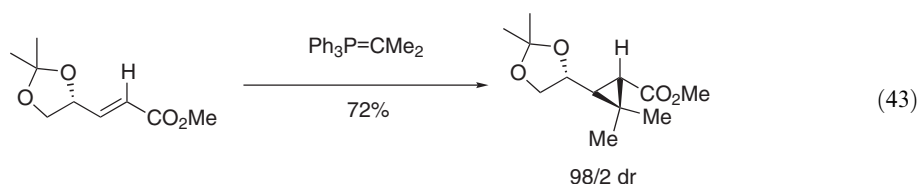
The formation of sp^3 carbon–carbon bonds by substitution of alkylphosphorus compounds generally involves cyclopropanation reactions between phosphorus ylides and activated alkenes. Although this reaction was described well for nonstabilized ylides, their stabilized analogs show little reactivity. Recent research work has introduced the use of 1,2-dioxines as cyclopropane precursors through reactions with stabilized phosphorus ylides [<1998CC333>](#). Reaction of 1,2-dioxines with a first equivalent of phosphorane, which acts as a weak base, results first in oxygen–oxygen bond cleavage and then rearrangement to give a γ -hydroxy α,β -unsaturated ketone. Conjugate addition of a second equivalent of the phosphorane and recyclization give cyclopropyl ketones in good yields and stereoselectivity, in the favor of a *trans*-1,2-disubstituted cyclopropane (Scheme 39). The scope and mechanism of this synthetic transformation have been further investigated, showing good substrate generality [<2000JOC5531, 2001JOC7955>](#). Alkylphosphonates are also efficient for this reaction [<2002JOC3142>](#).

Recent studies on the cyclopropanation reaction with nonstabilized phosphorus ylides have focused on the stereoselective synthesis using chiral substrates or auxiliaries. A general review dealing with asymmetric cyclopropanation reactions has been published [<2003CRV977>](#).

Isopropylidene mannitol-derived α,β -unsaturated esters react with unstabilized phosphorus ylides to give the corresponding chiral cyclopropanes. Although reaction with isopropylidene triphenylphosphorane gave complete stereocontrol <1998TL1437> (Equation (43)), one with methylene triphenylphosphorane gave low diastereoselectivity <1997TL7599>. In general, yields and selectivities are lower with phosphonium ylides than with sulfonium ylides.

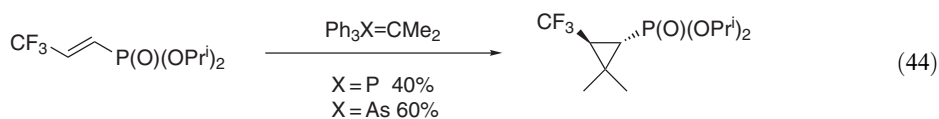


Scheme 39



1.06.2.2 Substitution of Arsenic Functions

As for phosphorus, substitution of arsenic functions involves cyclopropanation reactions with ylides. Arsonium ylides are generally more reactive than the phosphonium equivalents. For the synthesis of trifluoromethylcyclopropyl phosphonates, reactions of an α,β -unsaturated phosphonate with phosphonium and arsonium ylides were studied <1996JCR(S)328> (Equation (44)). As expected, yields were better using arsonium ylides.

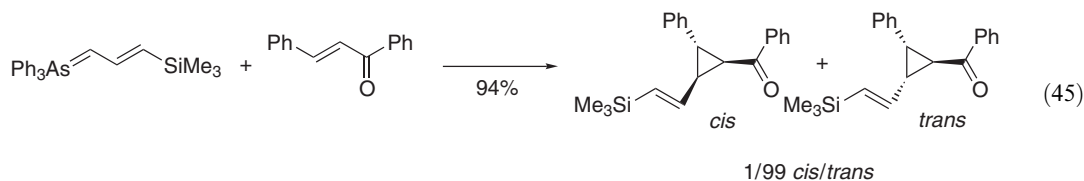


In contrast with stabilized phosphonium ylides, stabilized arsonium ylides react with acceptors such as methyl acrylate to give cyclopropanes. Higher homologs of alkoxy carbonylidenetriphenylarsonane have been synthesized in good yields via a new reaction sequence involving alkylation of triphenylarsine with alkyl 2-trifluoroalkanoates and deprotonation with potassium fluoride on alumina <1994T13765> (Scheme 40). Reaction with methyl acrylate gives the corresponding cyclopropanes in good yields and in high stereoselectivity.

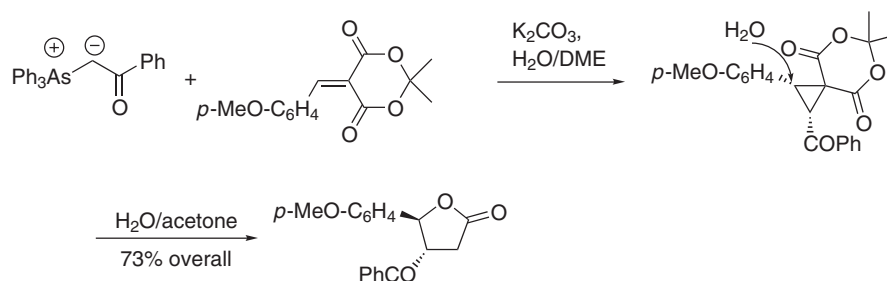


Scheme 40

Reactions of semistabilized arsonium ylides such as vinyltriphenyl arsonium ylides with α,β -unsaturated aromatic ketones give selectively *trans*-2,3-disubstituted cyclopropyl ketones <1997JOC954> (Equation (45)). This study investigated the role of base, solvent, and temperature and their effect on stereoselectivity. The best conditions for ylide formation were potassium *t*-butoxide with lithium bromide, except for styryl-substituted arsonium salts, which were deprotonated with sodium hexamethyldisilazide.

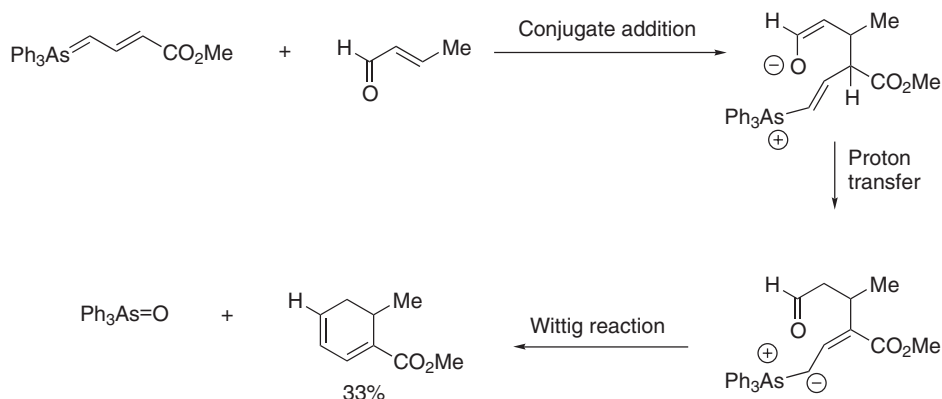


Reaction of stabilized arsonium ylides with 2-arylidene Meldrum's acid derivatives gives unstable cyclopropane products which are readily opened with water to give γ -butyrolactones. The stability of the cyclopropane intermediate depends on the electronic effects of the aryl ring: electron-donating groups strongly destabilize the cyclopropane ring, which is readily opened at room temperature, whereas electron-withdrawing group-substituted arylcyclopropanes are opened in wet refluxing acetone (Scheme 41). This reaction sequence has been used to synthesize 4,5-disubstituted γ -butyrolactones with complete stereocontrol, starting from benzoylmethyl triphenylarsonium bromide <2000SC3793>, or from methoxycarbonylmethyl triphenylarsonium bromide <2002SC1953>.



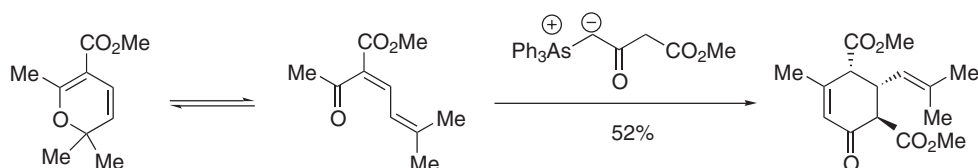
Scheme 41

Recently, new annulation techniques have been described, involving the reaction of stabilized arsonium ylides with conjugated carbonyl compounds; when the ylide itself is conjugated, these reactions do not give cyclopropane ring as expected, but cyclohexene rings through conjugate addition and recyclization via a Wittig reaction (Scheme 42). Thus, crotonate arsonium ylides react with conjugated carbonyl compounds to give a 1,3-cyclohexadiene carboxylate through an initial 1,4-attack <1997SL126>. Hindered aldehydes or ketones give trienes via a normal Wittig reaction (1,2-attack).



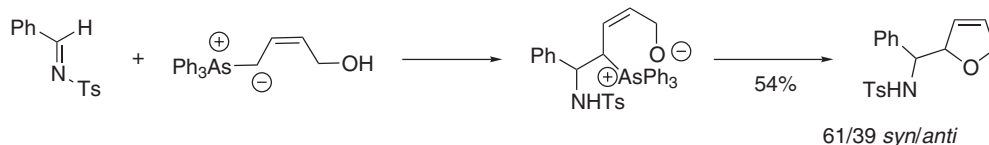
Scheme 42

2*H*-Pyrans-5-carboxylates may undergo electrocyclic ring opening to give dienic ketoesters, which are substrates for conjugate addition. Although the addition of nonconjugated 1,2-arsonium ylides gives rise to vinylcyclopropanes <1996TL9349>, reaction of 1,4-arsonium ylides such as 3-(methoxycarbonyl-2-oxopropyl)triphenylarsonium bromide gives cyclohexenone dicarboxylates through the annulation reaction <1997T2241> (Scheme 43). Arsonium salt deprotonation was accomplished using potassium *t*-butoxide. The reaction products could be used as precursors for highly functionalized aromatic compounds.



Scheme 43

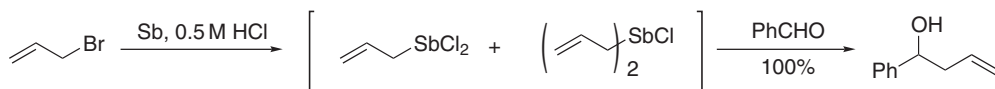
In an attempt to synthesize vinylaziridines by reaction of a conjugated hydroxyl group-containing arsonium ylide (obtained by deprotonation with potassium hydroxide) with an aromatic aldimine, cyclization to a five-membered ring was observed instead of aziridine formation <2000T2967> (Scheme 44). Formation of the dihydrofuran ring occurred with modest stereoselectivity.



Scheme 44

1.06.2.3 Substitution of Antimony Functions

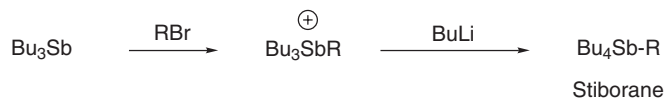
The organic chemistry of antimony compounds (together with bismuth) has been reviewed <B-1994MI761>. Despite the high reactivity of organoantimony derivatives, few applications in carbon–carbon bond formations have been described. Allylation reactions of aldehydes with allyldichlorostibines have been developed using Barbier-type conditions: treatment of allyl chloride with an aldehyde in the presence of antimony(III) chloride cleanly gave the allylated product; the reactive intermediate is likely to be an allyldichlorostibine derivative <1998JOC59>. The stability of antimony in the presence of aqueous solvents allowed the allylation of aliphatic and aromatic aldehydes in water by mixing allyl chloride, antimony powder, and an aldehyde in dilute hydrochloric acid solution <2001CJC1536> (Scheme 45). The presence of an acid was necessary to activate the metal powder. Investigations into the nature of the reactive intermediate showed a mixture of allyldichlorostibine and diallylchlorostibine to be the allylating species.



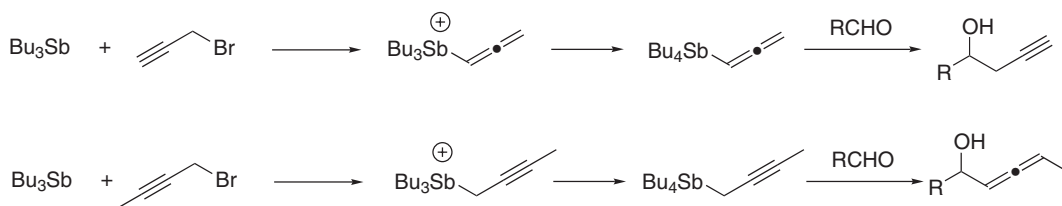
Scheme 45

Pentaorganostiboranes are prepared by alkylation of trialkylstibines (R₃Sb) to give tetraalkylstibonium salts (R₄Sb⁺). Treatment of this salt with an organometallic compound (e.g., butyllithium) gives the corresponding pentaalkylstiborane (Scheme 46). The reactivity of these compounds toward carbonyl compounds has been studied. Recent work describes the preparation of acetylenic and allenic stiboranes <1994JOM(471)77>. Reaction of propargyl bromide with tributylstibine gave

an allenylstiborane, whereas the reaction of 1-bromo-2-butyne gave an acetylenic stiborane (Scheme 47). Both compounds reacted with aldehydes to give homopropargylic alcohols and allenic alcohols, respectively. The regioselectivity was high for both reactions.



Scheme 46



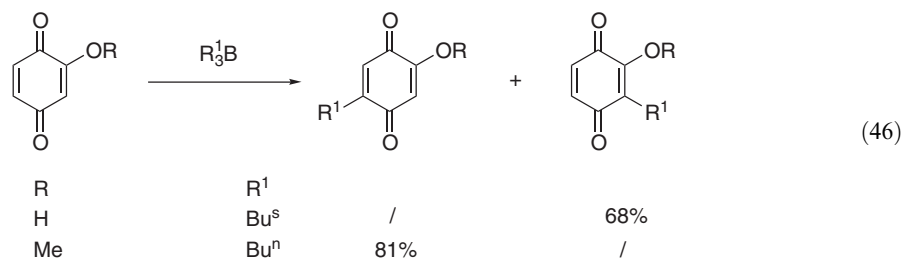
Scheme 47

1.06.3 SUBSTITUTION OF BORON, SILICON, AND GERMANIUM FUNCTIONS

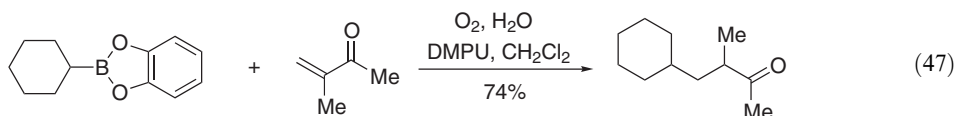
1.06.3.1 Substitution of Boron Functions

1.06.3.1.1 Conjugate addition to α,β -unsaturated ketones and aldehydes

The conjugate addition of triorganoboranes to α,β -unsaturated carbonyl compounds to give β -alkyl ketones or aldehydes is a well-described reaction. Investigation into the reaction mechanism has highlighted the radical character of the reaction, with the prior formation of a carbonyl-organoborane complex <2000TL1195>. Oxygen is generally used as a radical initiator. Photo-induced reaction of tetramethylammonium trialkylphenylborates has also been described <1995TL5483>. This reaction has been recently applied to the regioselective alkylation of substituted quinones <1999TL4473> (Equation (46)). The regioselectivity depends on the nature of the substituent, a hydroxyl group directing the attack on the vicinal position, whereas a methoxy group favored 1,4-attack. It should be pointed out that reactive trialkylboranes such as trimethylborane gave no selectivity.

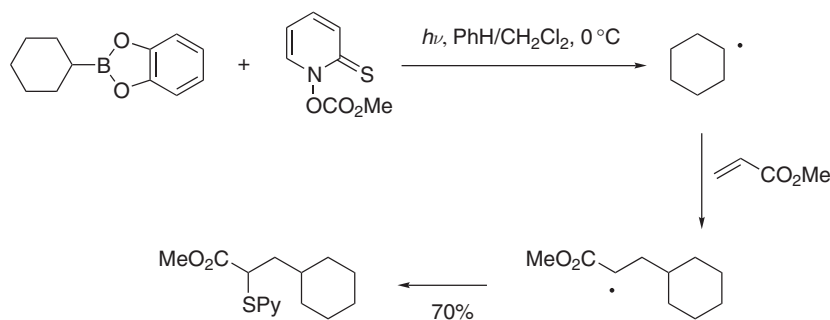


The major drawback in the conjugate addition of trialkylboranes to α,β -unsaturated carbonyl derivatives is that only one of the three alkyl groups is transferred, thus restricting the methods to readily available alkylborane reagents. Recently, the use of *B*-alkylcatecholborane as a convenient source of alkyl radicals has been recommended <1999CEJ1468>. These compounds are conveniently prepared by hydroboration of alkenes with catecholborane and are converted to radicals in the presence of oxygen (Equation (47)). Addition to α,β -unsaturated aldehydes or ketones gives good yields of the alkylated products.



1.06.3.1.2 Conjugate addition to α,β -unsaturated carboxylic acid derivatives

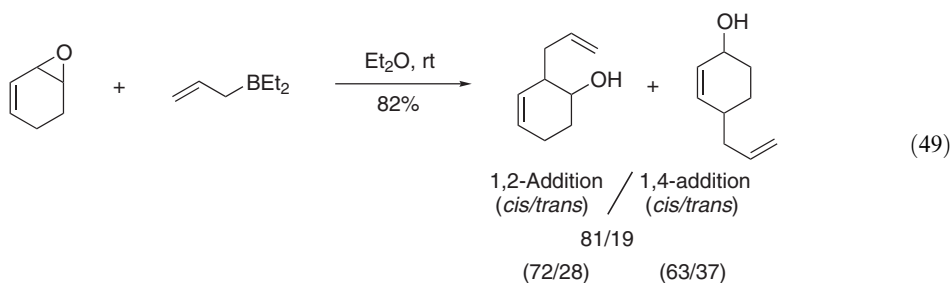
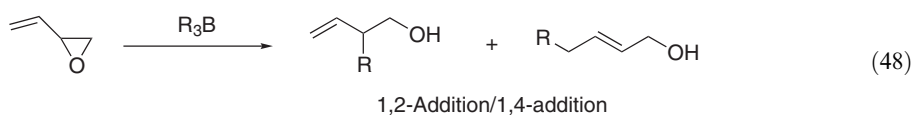
The radical-mediated cleavage of *B*-alkylcatecholboranes and subsequent addition to radical acceptors such as α,β -unsaturated esters, nitriles, sulfones, or phosphonates has recently been reported independently by two groups [<2000AG\(E\)925, 2000CC1017>](#). Irradiation of various secondary *B*-alkyl catecholboranes in the presence of methylcarbonyloxy(pyridine-2-thione), gave an alkyl radical that added to the activated double bond ([Scheme 48](#)). Radical chain reaction is stopped by addition of the thiopyridyl radical. Excellent diastereoselectivity was observed with α -substituted cyclic secondary alkylboranes, the radical reaction occurring with retention of configuration.

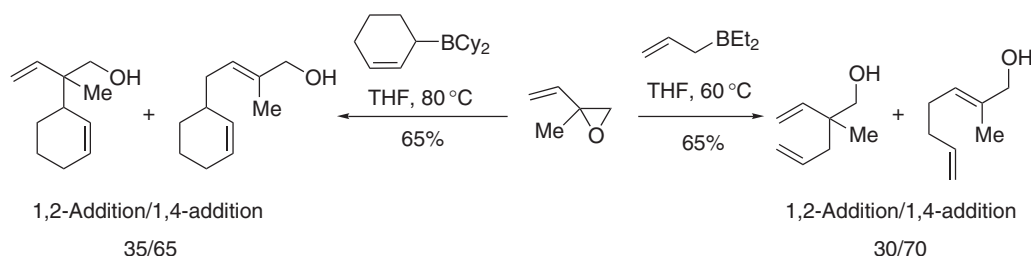


Scheme 48

1.06.3.1.3 Conjugate addition to vinyl- and alkynylepoxides

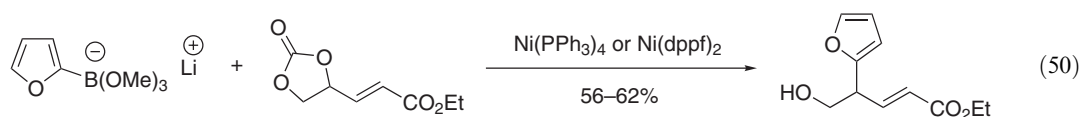
Addition of organoboranes to vinylepoxides may result in a 1,2-addition to give homoallylic alcohols or in a 1,4-addition to give allylic alcohols ([Equation \(48\)](#)). Reaction of cyclic and acyclic vinylepoxides with allylic borane reagents has shown preference for a *cis*-1,2-addition for cyclic substrates ([Equation \(49\)](#)) and 1,4-addition for acyclic substrates ([Scheme 49](#)) [<2000OL3897>](#); the stereochemistry of addition is opposite to other allyl metal reagents. With epoxycyclopentenes, a fragmentation reaction leading to trienols was observed.



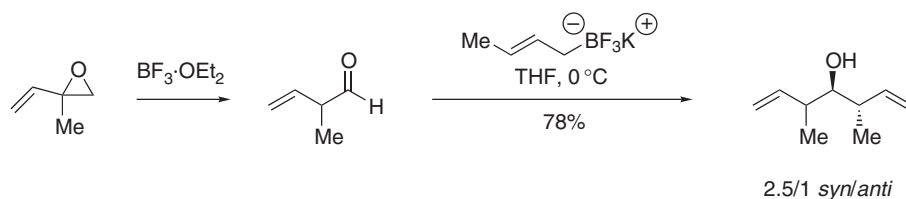


Scheme 49

Allylic carbonates possess a reactivity close to vinyl epoxides, and their reactions with organoborates in the presence of nickel catalysts give alkylated products in good yields and high regioselectivity <1995JCS(P1)2073> (Equation (50)). The presence of an alkene or ester function directs attack of the organoborate to give the conjugated product.



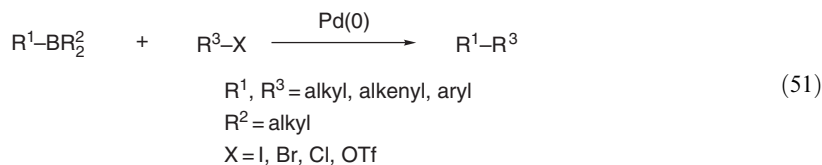
A nonconjugated addition of allyl- and crotylfluoroborates to vinyl epoxides has been described. In the presence of a Lewis acid, vinylic oxiranes rearrange to α,β -unsaturated aldehydes which undergo classical allyl- or crotylboration <2000AG(E)4079> (Scheme 50). Crotylation using crotylfluoroborates occurs with excellent diastereoselectivity depending on the configuration of the boron nucleophile.



Scheme 50

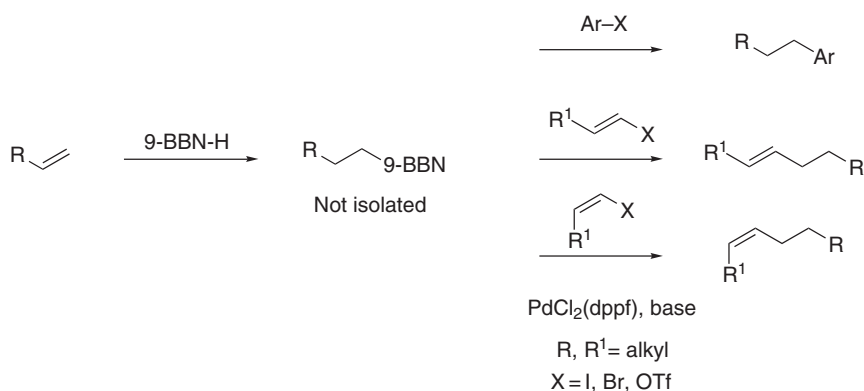
1.06.3.1.4 Aromatic and alkenic substitution

Transition metal-catalyzed cross-coupling reactions of alkyl, alkenyl, alkynyl, and aryl groups have gained enormous importance in modern synthesis. Amongst all the reactions, the Suzuki–Miyaura reaction, which involves palladium-catalyzed cross-coupling of organoboron reagents with alkenyl or aryl halides (or triflates), has found many applications, due to its mild reaction conditions, functional group tolerance, and easier purification. Furthermore, the reaction may be carried out in the presence of water. As a consequence, many recent reviews on this topic are available <1995CRV2457, B-1998MI49, 1999JOM(576)147, 2002JOM(653)83, 2002T9633>. The extension of this reaction to *B*-alkyl substrates has brought further interest to this cross-coupling reaction, with alkyl transfer to alkenyl, aryl, or even alkyl groups (Equation (51)). A recent review on the *B*-alkyl Suzuki–Miyaura reaction describes the conditions, scope, and applications of this reaction in the synthesis of natural products <2001AG(E)4545>.



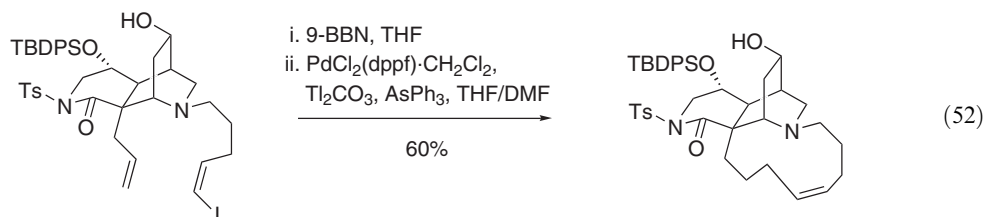
(i) With organoboron reagents

Organoboron reagents are the most often used substrates for the Suzuki–Miyaura reaction. These compounds are generally prepared *in situ* from terminal alkenes; the alkylboron reagent is not isolated but immediately engaged in the cross-coupling reaction with the aryl or alkenyl halide (or triflate). 9-Borabicyclononane (9-BBN) is by far the most often used borane reagent. Alternatively, treatment of a primary alkyl iodide with *t*-butyllithium and condensation to 9-methoxy-BBN affords boronate complexes which are immediately used in the coupling reaction. Cross-coupling is accomplished in the presence of palladium(tetrakis)triphenylphosphine, or better, palladium dichloride bis(diphenylphosphino)ferrocene (dppf), in the presence of a phosphine or arsine ligand (Scheme 51). An inorganic base is added to the reaction medium, usually caesium carbonate; in the case of low reactivity, thallium salts (Caution: thallium salts are toxic) may be added in order to increase the reactivity.

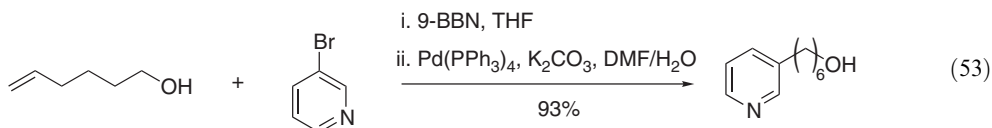


Scheme 51

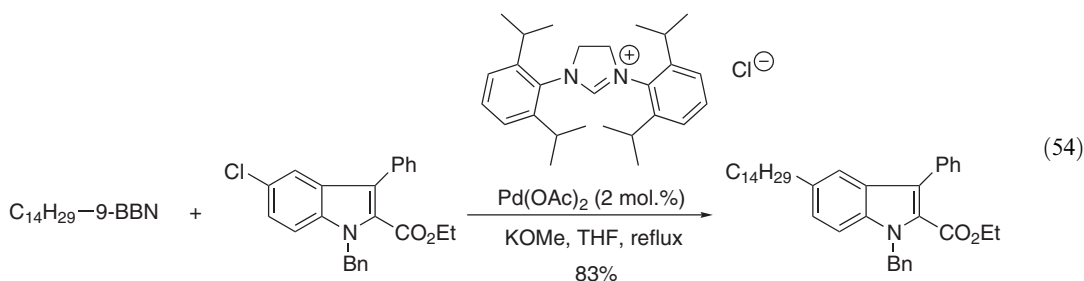
Inter- or intramolecular cross-coupling reactions of alkylboron reagents with alkenyl halides, triflates, or phosphates have widely been used in natural product synthesis. The recent examples in the syntheses of gambierol <2002JA14983>, ciguatoxin <2002OL2771>, sphingofungins <2001JA12191>, phomactin A <2003JA1712>, and epothilone analogs <2002JOC7730> illustrate the high efficiency and functional group tolerance in the synthesis of highly complex molecules. An example of a *B*-alkyl Suzuki reaction as the key step in an approach to xestocyclamine <2002AG(E)1581> is shown in Equation (52).



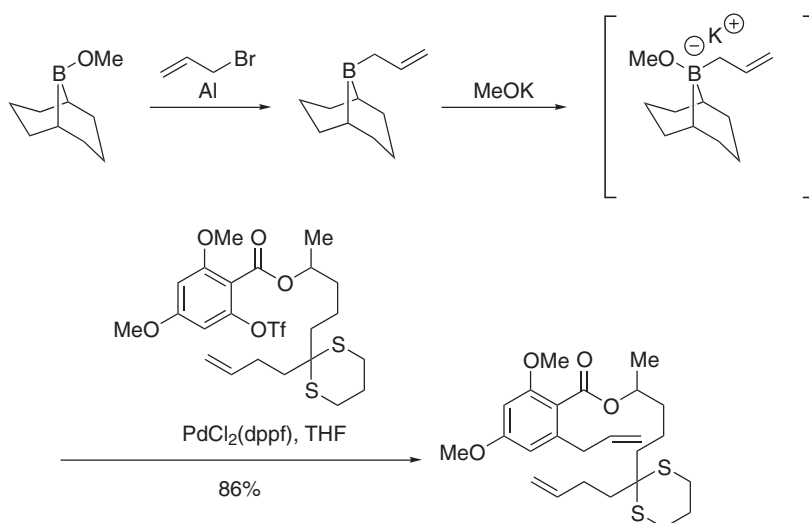
Coupling of alkylboron reagents with aryl bromides or triflates is achieved under similar conditions; the combination of PdCl₂(dppf) and aqueous sodium hydroxide in DMF gives the best results; base-sensitive substrates are generally reacted in the presence of sodium carbonate or phosphate in DMF. Some recent examples include the allylation of an electron-deficient arene <1998SL161>, alkylation of an azulene derivative <2001OL1081>, or the introduction of a hydroxyl-containing alkyl chain onto 3-bromopyridine <2001T3125> (Equation (53)).



Since aryl bromides or triflates are expensive, more reactive catalytic systems were designed for the coupling of aryl chlorides. Recently, a general protocol for the coupling of organoboron reagents, including alkylboron reagents, with aryl chlorides has been developed, using an imidazolium salt as ligand [<2001SL290>](#) (Equation (54)). A highly hindered biphenylic phosphine ligand has also been reported to be effective for the same coupling reaction [<1999JA9550>](#).

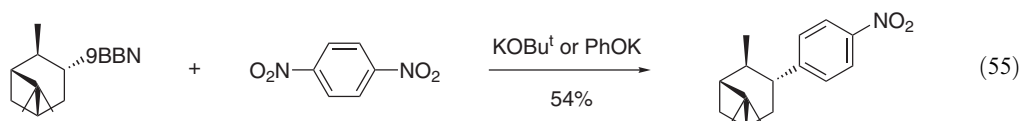


The Suzuki–Miyaura reaction of allylboron reagents has been reported to be rather difficult, giving low yields of coupled products, probably because of the instability of the organoboron reagent. A recent study describes the preparation of *B*-allyl-9-BBN, which is activated by formation of the borate complex [<1998SL161>](#). This ate complex undergoes cross-coupling reactions with aryl halides or triflates in good yields (Scheme 52).



Scheme 52

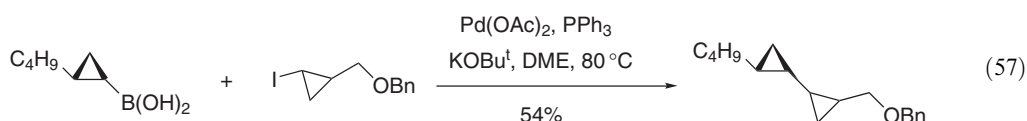
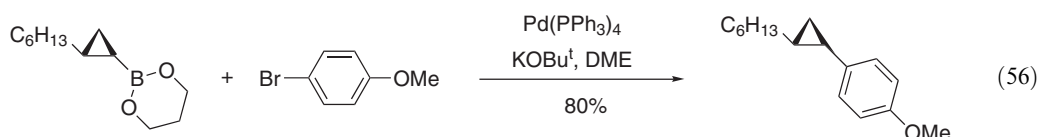
The synthesis of *p*-nitroaryl alkyl derivatives has been described, involving the mono-substitution of *p*-dinitrobenzene with trialkylborane reagents [<2003JOC4388>](#). The reaction is performed in the presence of a base and gives the alkylated product via a radical anion intermediate (Equation (55)). The use of alkyl-9-BBN reagents allows selective alkyl group transfer.



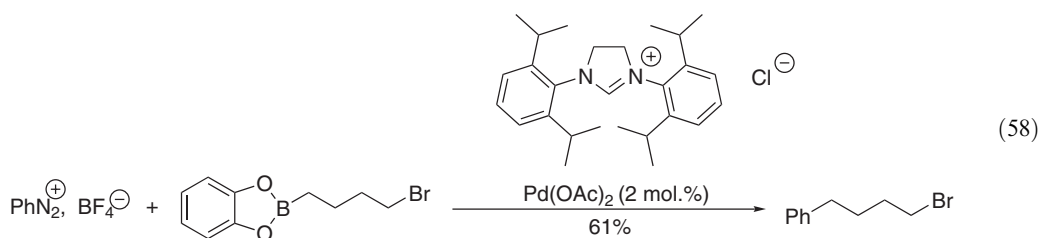
(ii) With boronic acids and boronic esters

Boronic acids have the advantage over alkylboron reagents of being isolable, more water tolerant, and that they give only inorganic by-products. Therefore, many attempts have been made to carry out the Suzuki–Miyaura reaction with alkyl boronic acids or their boronate esters.

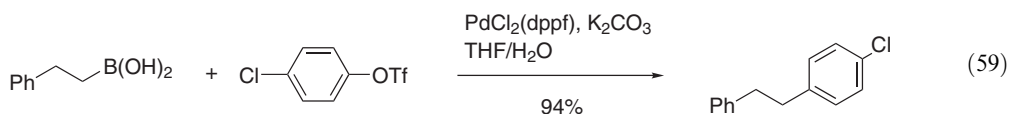
Cyclopropyl boronic acids, because of the sp^2 character of the cyclopropane ring, enjoy good reactivity in the cross-coupling reactions. They are easily prepared by cyclopropanation of vinylboronates and may be stored. Cyclopropylboronic esters and acids may be easily coupled with a variety of reagents including aryl bromides <1996JCS(P1)266, 1996SL893> and triflates <2000S1095>, heteroaryl bromides <1999SC2477>, vinyl halides <1998SL198, 2000TL3951> and triflates <2000TL9083>, allyl bromides (with added silver salts) <2000JOC4444>, or acyl chlorides <2000OL1649, 2000JOC5034>. An example of such a coupling is shown in Equation (56). When optically active cyclopropyl boronic acids (obtained by asymmetric cyclopropanation) were used, complete retention of configuration occurred <1998AG(E)2845>; a bis-cyclopropane derivative could be synthesized by coupling with a iodocyclopropane <1997TL2809> (Equation (57)).



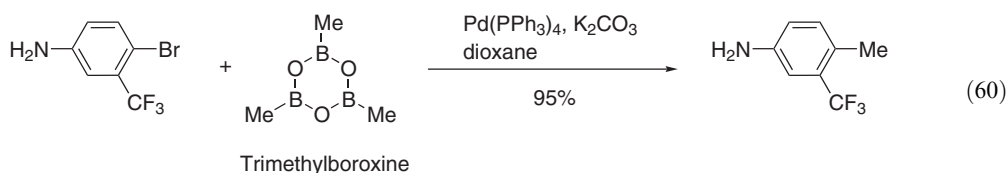
Coupling of alkylboronic acids or esters with alkenyl or aryl halides suffers from a lack of reactivity, and low yields of coupled products are obtained unless additives such as silver oxide are used <2001TL7213, 2001JOC2459>. Therefore, various catalytic systems have been designed in order to improve yields and turnovers. Thus, a palladium-imidazolium carbene catalytic system allows low-temperature coupling of boronic acids and boronates with aryldiazonium salts <2001OL3761> (Equation (58)).



Finally, a general method for the cross-coupling of primary alkylboronic acids with aryl bromides and triflates and heteroaryl chlorides has been described, using $\text{PdCl}_2(\text{dppf})$ in the presence of potassium carbonate <2002T1465>. Good yields of coupled products are obtained under mild conditions, the best results being obtained with electron-deficient arenes (Equation (59)).

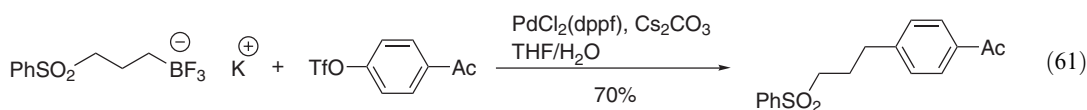


One particular problem in the cross-coupling reaction of boronic acids is the transfer of a methyl group, which generally shows poor reactivity. Various systems have been designed for efficient methylation of alkenes or arenes via the Suzuki–Miyaura reaction: the use of $\text{Pd}(\text{PPh}_3)_4$ as a catalyst has allowed polymethylation of porphyrins under harsh conditions <1996JOC3590>, whereas imidazolopyridines were monomethylated under the same conditions <2000JOC6572>. A general method for the methylation of aryl halides employs trimethylboroxine (the anhydride of methylboronic acid) and $\text{Pd}(\text{PPh}_3)_4$ as the catalyst, in the presence of potassium carbonate <2000TL6237> (Equation (60)). Even aryl chlorides give appreciable yields.



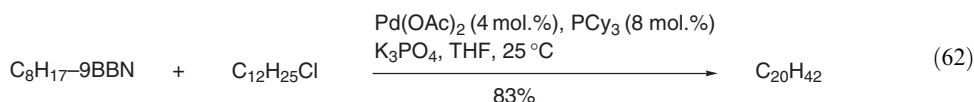
(iii) With alkylfluoroborates

Organotrifluoroborates are easily prepared by treatment of various boron derivatives (boronic acids and esters, dihaloboranes) with excess of potassium hydrogen fluoride. These reagents are air stable, easy to handle, and may be stored for long periods. The coupling reactions of alkyltrifluoroborates have been recently studied [\[2001OL393, 2003JOC5534\]](#), and showed excellent results in the palladium-catalyzed reaction with aryl bromides and triflates. The reaction tolerates many functional groups on both coupling partners. A selected example in the alkyl-aryl coupling is shown in [Equation \(61\)](#).

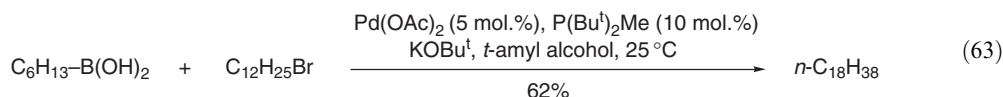


1.06.3.1.5 Aliphatic substitution

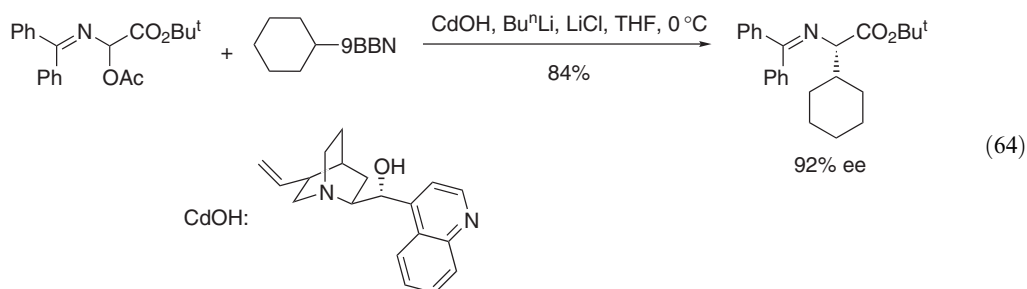
Cross-coupling reaction of alkylboron reagents with alkyl halides is hampered by slow reaction rates and competitive β -elimination of the intermediate alkyl-palladium complex. Nevertheless, alkyl-alkyl cross-coupling (including carbonylative cross-coupling) with alkyl iodides can be undertaken using $\text{Pd}(\text{PPh}_3)_4$ as the catalyst in moderate-to-good yields. A spectacular improvement was brought about by the use of bulky ligands which accelerate reductive elimination: thus, palladium acetate in the presence of tricyclohexylphosphine and potassium phosphate allows room-temperature coupling of various alkyl bromides [\[2001JA10099\]](#) with alkyl-9-BBN derivatives in good yields and with high substrate generality. Further improvements allowed the coupling of alkyl chlorides [\[2002AG\(E\)1945\]](#) ([Equation \(62\)](#)) and alkyl tosylates with di-*t*-butylmethylphosphine [\[2002AG\(E\)3910\]](#).



The latter catalyst is also efficient for the coupling of boronic acids with alkyl bromides at room temperature [\[2002JA13662\]](#) ([Equation \(63\)](#)). Unhindered alkylboronic acids may be used as substrates for this reaction.

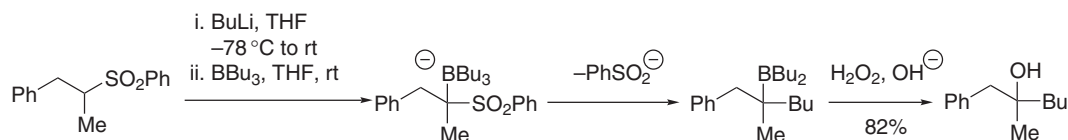


Other aliphatic substitutions with organoboron reagents involve intramolecular alkyl group transfer from a boron ate complex to a carbon-bearing leaving group. The deprotonation of an α -acetoxy α -iminoester followed by treatment with a trialkylborane gives an ate complex that undergoes alkyl transfer with subsequent departure of the acetoxy group. An enantioselective version of this reaction has been developed, using a cinchona alkaloid as a chiral protonating group [\[2002JA9348\]](#), thus allowing the preparation of chiral amino acids ([Equation \(64\)](#)).

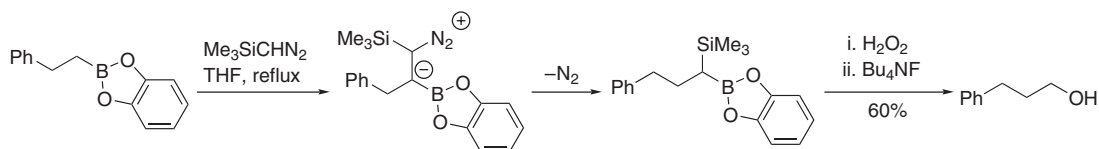


Treatment of the anion of a sulfone with a trialkylborane gives an ate complex that transfers one alkyl group from boron to carbon, the sulfone playing the role of the leaving group [<2003TL4451>](#) (Scheme 53). This allows rapid assembly of tertiary alcohols from sulfones.

In a similar strategy, one carbon homologation of alkylcatecholboronates has been realized with trimethylsilyl diazomethane [<2000OL1455>](#) (Scheme 54). Alkyl transfer with subsequent loss of nitrogen gives α -silylboronates which can be converted into alcohols.

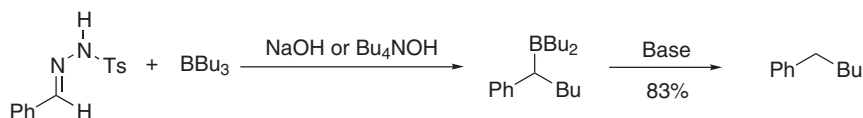


Scheme 53



Scheme 54

Trialkylborane derivatives react with the arenesulfonylhydrazones of aryl aldehydes to give alkylated products [<1997JOC3688>](#) (Scheme 55). The reaction is performed under basic conditions and tolerates a wide variety of functional groups. Hydrazones derived from heteroaryl aldehydes are also good substrates for the reaction.



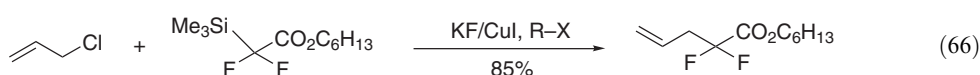
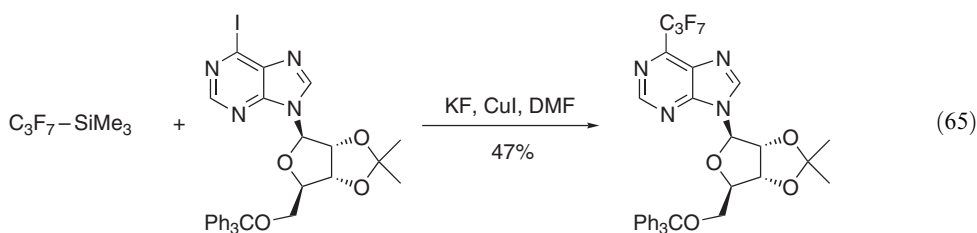
Scheme 55

1.06.3.2 Substitution of Silicon Functions

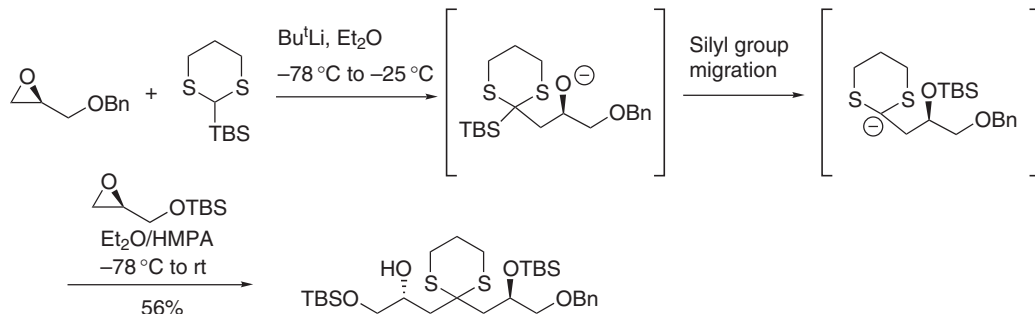
1.06.3.2.1 Alkylation

Substitution of carbon–silicon bonds with carbon–carbon bond formation generally involves desilylation followed by reaction with an electrophile. Desilylation may be accomplished with a fluoride source such as tetrabutylammonium fluoride (TBAF) or caesium fluoride. Fused salts obtained from caesium fluoride and caesium hydroxide have been recommended as efficient reagents for carbon–silicon bond cleavage [<1999TL2065>](#).

Simple alkylation of carbanions obtained from alkyl silanes are not very common and often involves perfluorinated silanes. Trifluoromethylation of primary tosylates was achieved with trifluoromethyl trimethylsilane in the presence of fluoride anion [<2001SL379>](#). The same conditions were used for the nucleophilic substitution of an iodopurine with the heptafluoropropyl anion derived from the corresponding silane [<1999CCC229>](#) (Equation (65)). Alkyl α -trimethylsilyl- α,α -difluoroacetate also reacts with various electrophiles in the presence of fluoride ion to give homologated difluoroesters [<1999JOC6717>](#) (Equation (66)).

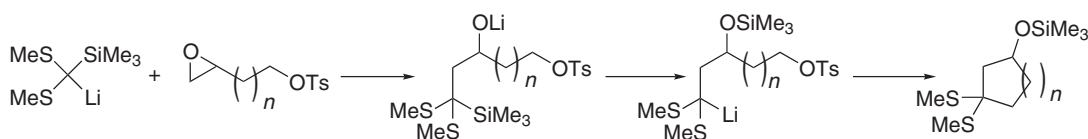


Condensation of the anion of 2-trialkylsilyl-1,3-dithiane with epoxides gives an alkoxide that undergoes a silyl group transfer from carbon to oxygen (Brook rearrangement) to give a new nucleophilic species. Under carefully controlled conditions, reaction with a different terminal epoxide gives rise to unsymmetrical 1,5-diols [<1997JA6925>](#) (Scheme 56). This methodology has been applied to the synthesis of spongistatin [<1997TL8671, 1997TL8675, 2002OL783>](#), bryostatin [<2000OL2189>](#), and carbasugars [<1999SL1322>](#).

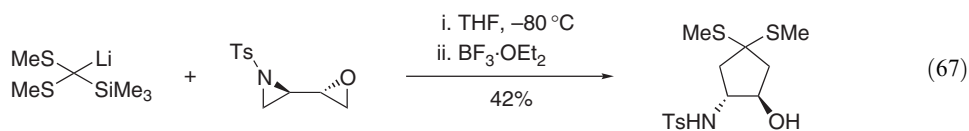


Scheme 56

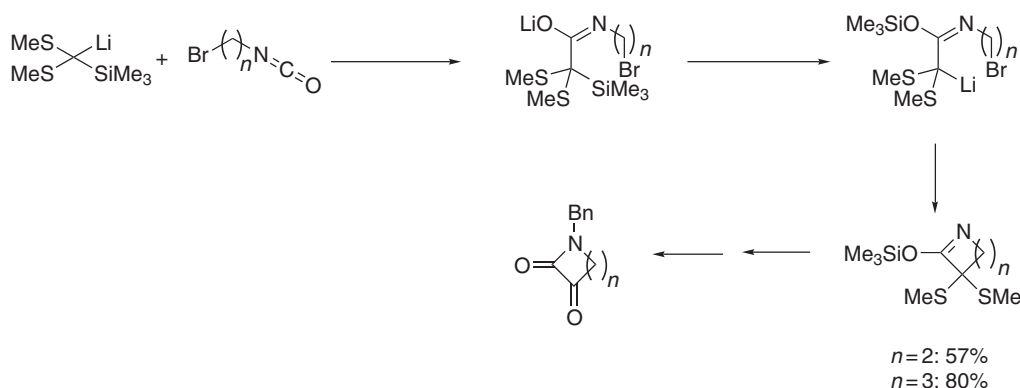
Functionalized carbocycles may be prepared by a cascade reaction involving the condensation of 2-lithio-2-trialkylsilyl thioacetals with epoxides bearing a leaving group within the side chain [<1998T11481>](#), with subsequent silyl group migration and internal nucleophilic attack (Scheme 57). Symmetrical bis-epoxides were also used as substrates for this reaction [<1999TL2921>](#), and an aminohydroxylated cyclopentane was obtained by condensation with 1,2-epimino-3,4-epoxy butane [<2001S577>](#) (Equation (67)). Since chiral epoxides are readily available compounds, this strategy provides access to chiral hydroxylated cycloalkanes.



Scheme 57

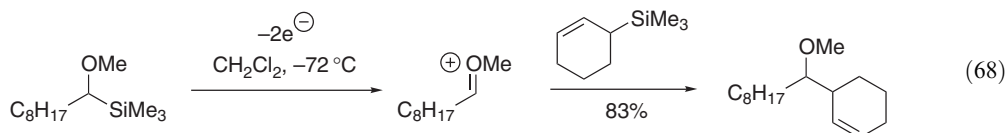


Other bis-electrophiles such as brominated alkyl isocyanates may be used in the same cascade reaction to provide functionalized lactams [<2000SL92>](#) (Scheme 58). Silyl group transfer occurs from carbon to a lactam enolate oxygen atom.

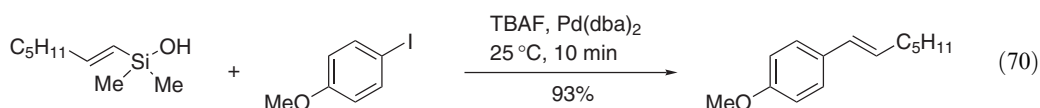
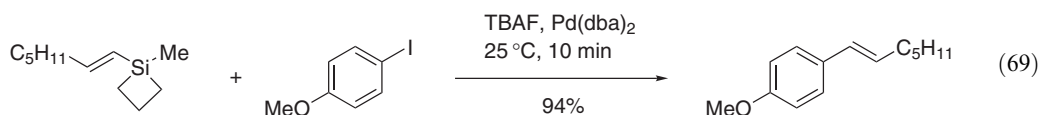


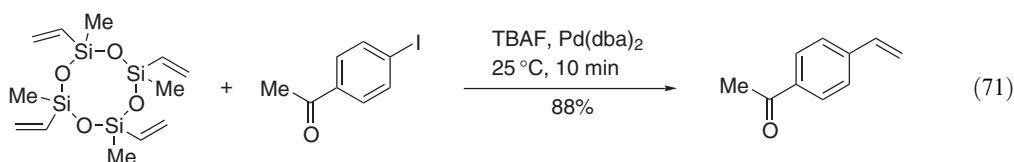
Scheme 58

Besides electrophilic alkylation, nucleophilic substitution of α -silyl ethers with allylic silanes or silyl enol ethers has been developed [<2000JA10244>](#). Electrooxidation of α -silyl ethers gives alkoxy-carbenium ions (oxonium cations), which react with nucleophiles to give ethers in good yields (Equation (68)). This electrochemical method allows preparation of high concentrations of alkoxy-carbenium ions.



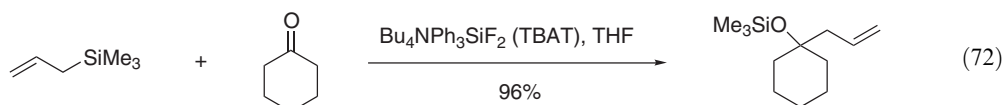
Transition metal-catalyzed cross-coupling reactions of organosilane derivatives have recently emerged as alternatives to the classical organotin or organoboron cross-coupling reactions [<2002ACR835>](#). The principal advantages in organosilane derivatives are their high reactivity, low toxicity and molecular weight, and substrate diversity: strained organosilane reagents such as alkenylsilacyclobutanes [<1999JA5821>](#) (Equation (69)), alkenylsilanols [<2000OL565>](#) (Equation (70)), or alkenylsiloxanes [<2001JOM\(624\)372>](#) (Equation (71)) are coupled with aryl iodides in the presence of fluoride ion and a palladium catalyst. Tandem hydrosilylation–cross-coupling reactions of alkynes have also been developed as an entry into stereodefined trisubstituted alkenes [<2003JOC5153>](#). All these cross-coupling reactions have been described using aryl or alkenyl substrates and have not been applied so far to the coupling of alkyl silane derivatives.



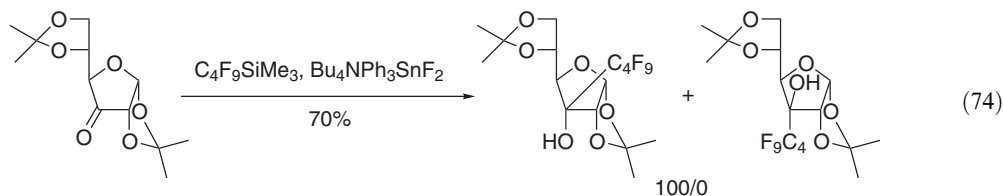
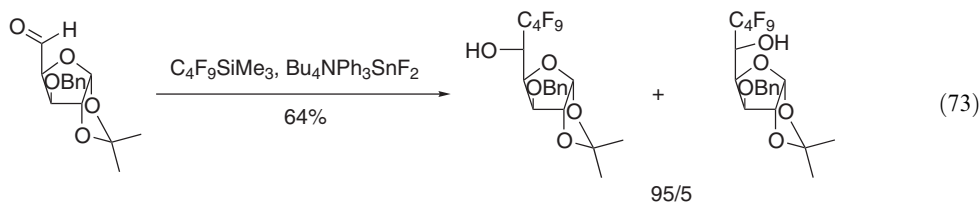


1.06.3.2.2 Hydroxylation/aldol reactions

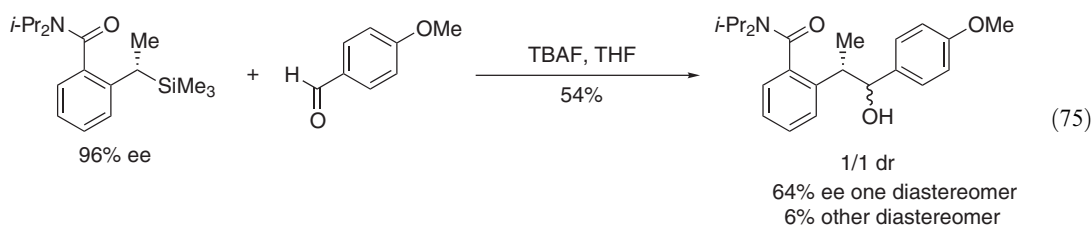
Aldol reaction of alkyl silanes involves cleavage of the carbon–silicon bond in the presence of fluoride salts, and condensation of the resulting carbanion with carbonyl compounds. Generally, stabilized carbanions such as benzyl, allyl, or acetyl are used for the reaction. Tetrabutylammonium triphenyldifluorosilicate (TBAT) has been used as an efficient fluoride source in anhydrous conditions for the condensation of alkyltrimethylsilanes onto aldehydes, ketones, and even aldimines [<1996JOC6901>](#) (Equation (72)). Alkylation of the organosilicon derivatives with primary bromides or iodides (but not sulfonates) is also efficient.



Nucleophilic alkylation of carbonyl compounds with perfluoroalkylsilanes is the method of choice for the preparation of fluorinated carbohydrate derivatives [<1998TA213>](#), both in terms of yields and stereoselectivity. Addition of various fluoroalkylsilanes on carbohydrate-derived aldehydes (Equation (73)) or ketones (Equation (74)) occurs in the presence of tetrabutylammonium triphenyldifluorostannate to give the corresponding secondary or tertiary fluorinated alcohols. Fluorinated organometallic reagents such as Grignard compounds gave lower yields and lower stereoselectivities in the addition to ketones.

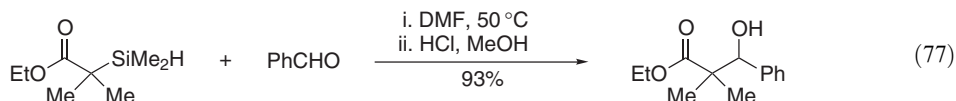
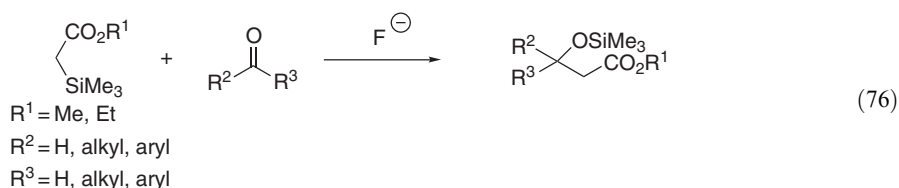


Desilylation of a chiral benzyl silane with TBAF and condensation with aldehydes gives secondary alcohols with moderate stereoselectivity [<1997TL5429>](#); yields and selectivities strongly depend on reaction conditions (Equation (75)). A chiral siliconate complex is believed to be the reactive species rather than an atropoisomeric benzylammonium derivative.

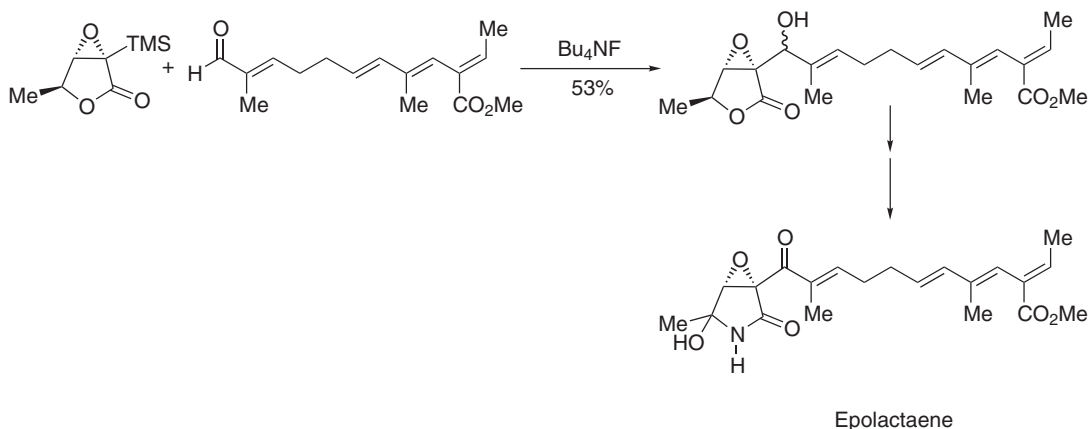


Electrosynthesis of difluorobenzyltrimethylsilane and its condensation with carbonyl compounds in the presence of potassium fluoride has been described <1999S829>. Alternatively, perfluorinated alkyl silanes may be synthesized by samarium diiodide-induced alkylation of perfluoroalkyl iodides <1997JCS(P1)643>.

α -Trimethylsilyl esters are easily condensed with carbonyl compounds through treatment with a fluoride source (Equation (76)). Trimethylsilyl acetate, the simplest of these reagents, is a convenient source of acetate anion, which has been condensed onto aldehydes, ketones, and even lactones <1995T5657>. The reaction generally occurs in the presence of TBAF. Recently, an “uncatalyzed” condensation of dimethylsilyl esters with aldehydes has been described <1998TL2585>. Dimethylsilyl alkanes are more reactive than their trimethylsilyl counterparts and react with carbonyl compounds upon heating in DMF, this solvent being crucial for the reaction (Equation (77)). Branched α -silyl esters cleanly give the aldol products without the self-condensation that often occurs in the presence of fluoride salts. Another nonconventional activation of silylacetic esters for the aldol reaction employs a hindered phosphine as the base <2000TL103>. Tris(2,4,6-trimethoxyphenyl)phosphine efficiently cleaves carbon–silicon and even oxygen–silicon bond to form enolates. In one example, treatment of ethyl trimethylsilylacetate with this phosphine in the presence of benzaldehyde gave 60% of the aldol product when treated at 120 °C in dimethylformamide.

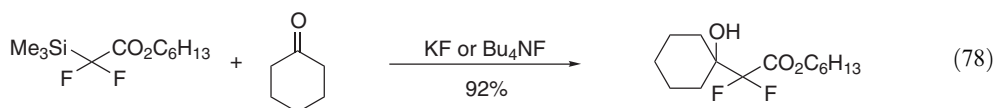


In the total synthesis of epolactaene, the key step coupling reaction between a bridged oxirane and the side chain was accomplished by desilylation of a trimethylsilyl oxirane and condensation of the corresponding anion with an α,β -unsaturated aldehyde <1999TL7371> (Scheme 59). The reaction occurred with retention of configuration at the oxirane ring.



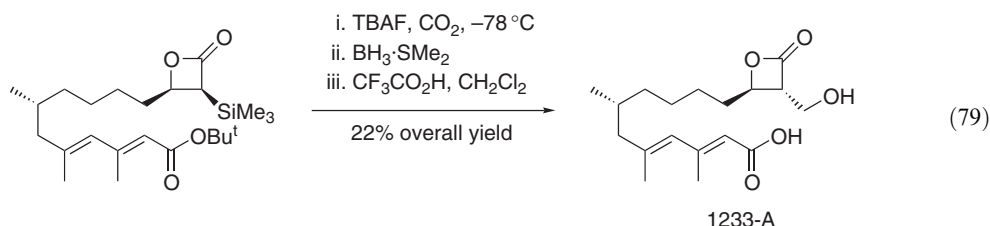
Scheme 59

2,2-Difluoro-2-trimethylsilyl acetate is a convenient reagent for the preparation of 2,2-difluoroesters by treatment with fluoride and condensation with electrophiles. Alkyl 2,2-difluoro-2-trimethylsilyl acetates are prepared by electroreductive silylation of trifluoroacetates <1999JOC6717> or chlorodifluoroacetates <2000TL8763>, and react with carbonyl compounds such as aldehydes, ketones, and ketimines upon treatment with potassium fluoride (Equation (78)). Yields were higher with hexyl ester <1999JOC6717> than with ethyl ester <2000TL8763>.

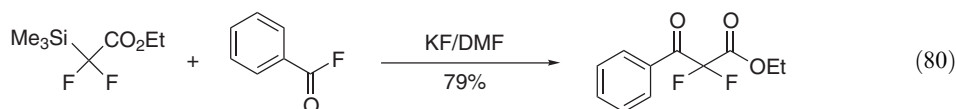


1.06.3.2.3 Acylation

An α -trimethylsilyl- β -lactone, obtained by a [2+2]-cycloaddition between trimethylsilyl ketene and an aldehyde, was desilylated with TBAF and treated with carbon dioxide to give the carboxylic acid in convenient yield [<1998S1655>](#) (Equation (79)), which after reduction led to compound natural product 1233-A. It should be pointed out that all attempts to quench the anion with formaldehyde were unsuccessful.



Ethyl 2,2-difluoro-2-trimethylsilyl acetate may also be used as a difluoroacetate building block for acylation reactions. Treatment of the silylacetate ester with acyl chlorides or fluorides in the presence of potassium fluoride cleanly gives the fluorinated β -ketoesters. A few examples of this reaction have been recently reported [<2000TL8763>](#) and one of them is shown in Equation (80).

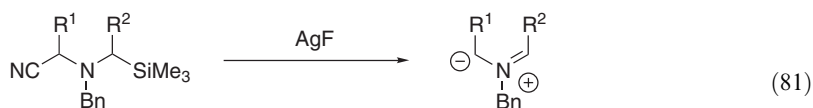


1.06.3.2.4 1,3-Dipole formation

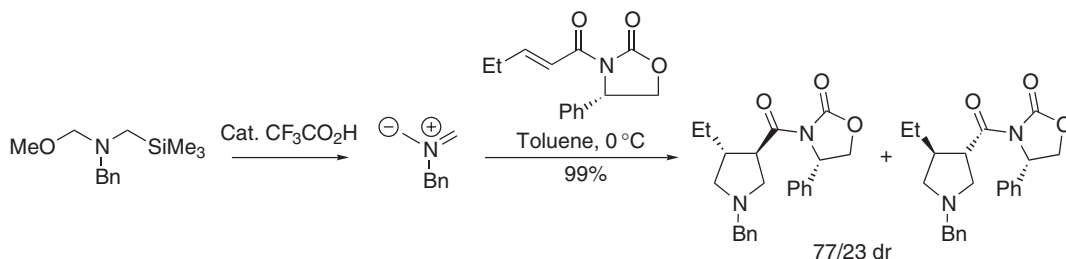
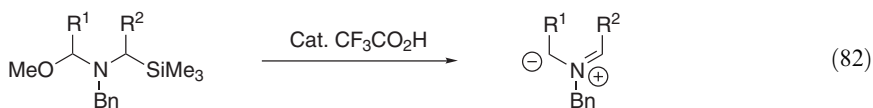
Cleavage of a carbon–silicon bond is an efficient route for the generation of various dipolar systems. The preparation of azomethine ylides, trimethylenemethane, and thiocarbonyl ylides are the main applications of this reaction.

(i) Azomethine ylides

A comprehensive review on the chemistry of azomethine ylides (including those prepared from organosilicon compounds) has been recently published [<B-2002MI106-4>](#). Carbon–silicon bond cleavage of an *N*-trialkylsilylmethylaminonitrile is a common way for the generation of unstabilized azomethine ylides. Desilylation is generally accomplished with silver fluoride (Equation (81)). Another mild method for the generation of azomethine ylides is the acid-catalyzed elimination of trimethylsilylmethanol from an *N*-trimethylsilylmethyl aminoacetal (Equation (82)). The azomethine ylides generated by these routes are generally substituted by a benzyl group on nitrogen. Recent application of these methods involves the generation of the simplest azomethine ylide and its diastereoselective cycloaddition with chiral unsaturated acyl oxazolidinones [<1997TA883>](#) (Scheme 60). Trifluoroacetic acid-catalyzed decomposition of *N*-benzyl-*N*-methoxymethyl-trimethylsilylmethylamine gave *N*-benzyl azomethine ylide, which reacted with the α,β -unsaturated amides in excellent yields and in modest-to-good stereoselectivity. The best results were obtained with a phenylglycinol-derived oxazolidinone by using toluene as solvent. This reaction was applied to the synthesis of enantiomerically pure 3,4-disubstituted pyrrolidines.

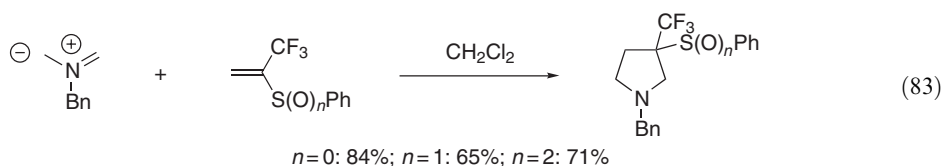


$\text{R}^1, \text{R}^2 = \text{H, alkyl, aryl}$



Scheme 60

The same azomethine ylide, obtained through the same method, was reacted with 2-phenylthio-3,3,3-trifluoropropene and its sulfoxide and sulfone [<1996T4383>](#). The three dipolarophiles reacted with azomethine ylide in good yields to give 3-trifluoromethyl-pyrrolidine derivatives, thus representing an efficient entry into fluorinated heterocycles. Although reaction with the sulfide occurred in refluxing dichloromethane, cycloaddition with the sulfoxide and the sulfone could be performed at room temperature ([Equation \(83\)](#)).

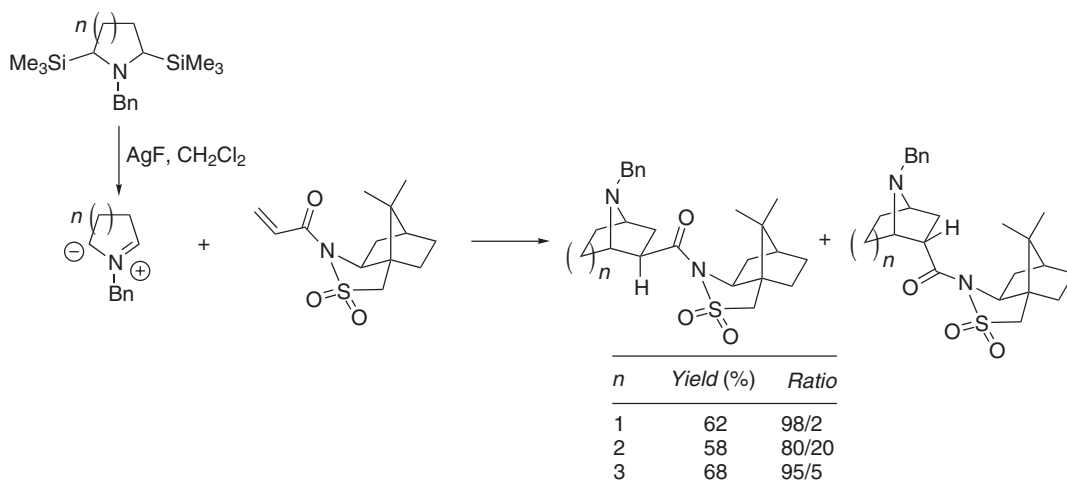


Treatment of 2,5-bis(trimethylsilyl)pyrrolidine with silver fluoride gave the pyrrolidine azomethine ylide, which underwent diastereoselective dipolar cycloaddition with the acrylate of camphorsultam [<1999TL6065>](#) ([Scheme 61](#)). Piperidine and azepane-derived azomethines also gave good yields and stereoselectivity in the cycloaddition.

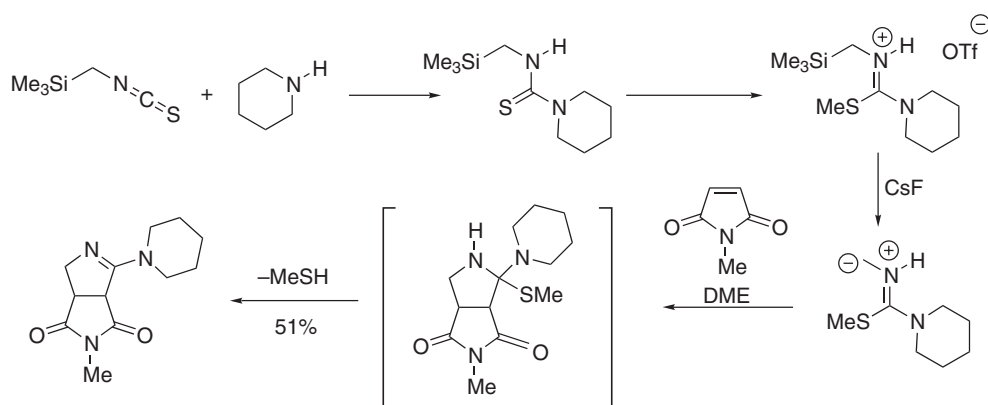
The preparation of *N*-unsubstituted azomethine ylides has been the subject of intense study in the recent years. These nonstabilized dipoles are highly reactive and may be used for the preparation of heterocycles which are otherwise difficult to prepare.

Caesium fluoride-mediated desilylation of *N*-trimethylsilylmethylthiureas has been reported to give new azomethine ylides with a hydrogen on the nitrogen atom [<1997CL945>](#). Initial *S*-alkylation of the silylmethylthiurea, followed by treatment with the fluoride source, give the azomethine ylide, which reacts with *N*-methylmaleimide to give bicyclic amidines after elimination of methanethiol ([Scheme 62](#)). Cycloadditions with fumaronitrile have also been reported.

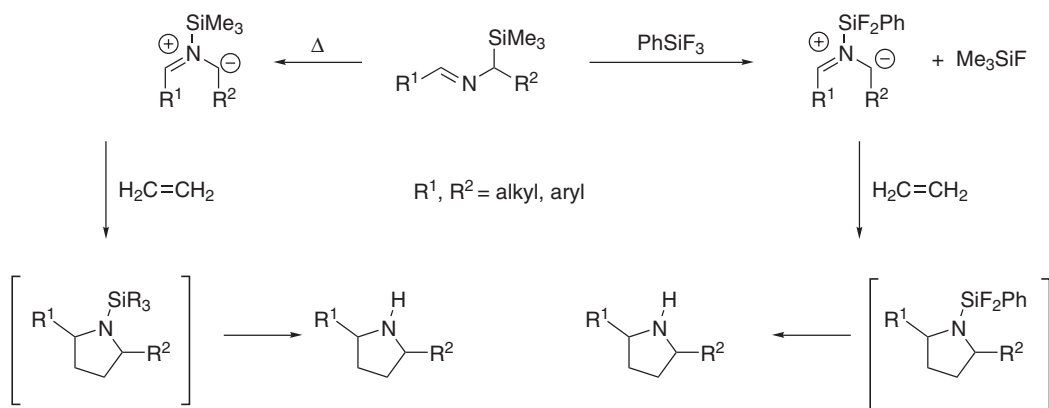
An important method for the generation of *N*-unsubstituted azomethine ylides is the silyl group migration from carbon to nitrogen in α -silylimines. This migration is promoted by heat or fluoride reagents such as phenyltrifluorosilane. The incipient azomethine ylide undergoes cycloaddition to give *N*-unsubstituted pyrrolidines after hydrolysis of the nitrogen-silicon bond ([Scheme 63](#)). This strategy has been recently applied to solid-phase-supported synthesis of pyrrolidines [<2003T197>](#): an aromatic aldehyde, *p*-hydroxybenzaldehyde is linked to the Merrifield resin by the hydroxy group, then condensed onto an α -trimethylsilylamine to give the corresponding imine. Upon treatment with phenyltrifluorosilane in the presence of *N*-phenylmaleimide, cycloaddition occurs to give the polymer-supported bicyclic pyrrolidine, which can be released from the resin by acidic treatment ([Scheme 64](#)). Although the *endo/exo* selectivity was poor, 2,5-*cis*-pyrrolidines were formed predominantly.



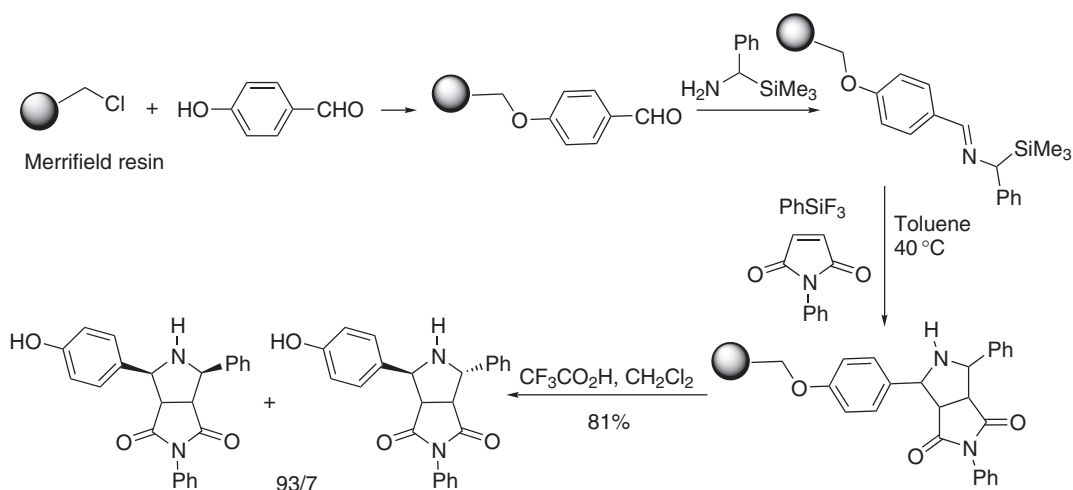
Scheme 61



Scheme 62

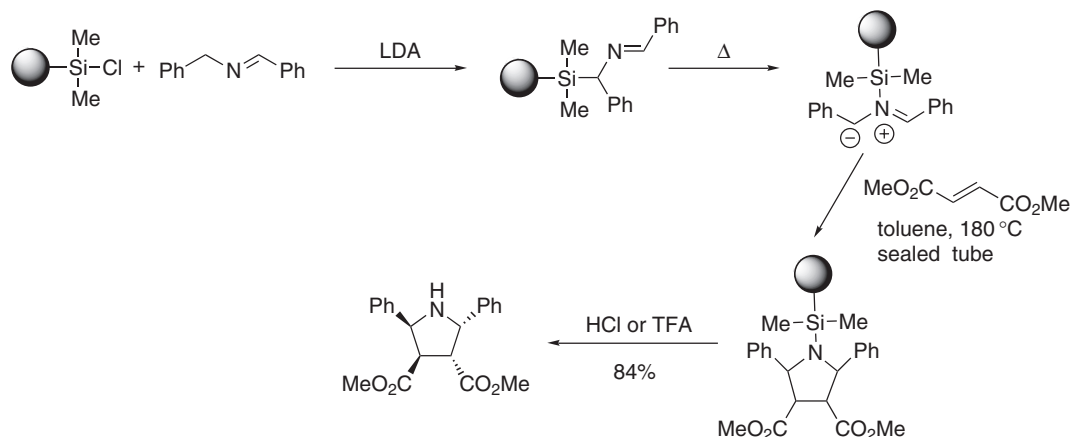


Scheme 63



Scheme 64

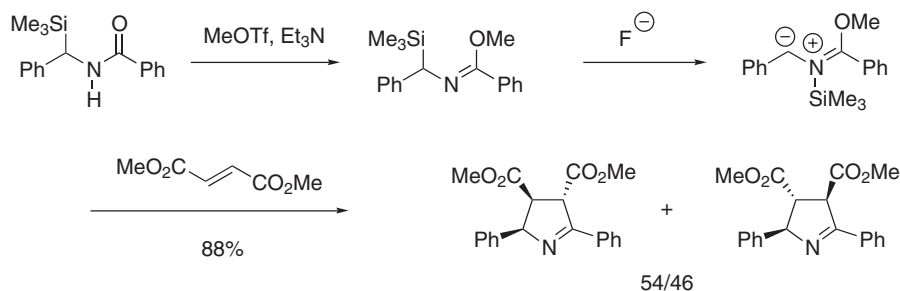
In a recent study, a traceless linker with the silicon atom linked to a resin was used for solid-phase-supported azomethine ylide generation and cycloaddition [<2002OL3505>](#). Resin-bound α -silylimines were heated in toluene to promote silyl group migration from carbon to nitrogen and subsequent cycloaddition of the azomethine ylide (Scheme 65). Molecular diversity was brought by the silylimine and the substituents on the dipolarophile. Resin cleavage was easily accomplished by mild acidic treatment.



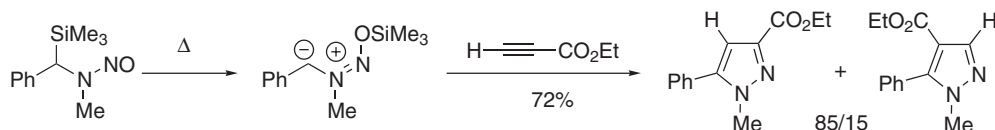
Scheme 65

The properties of silicon migration from carbon to heteroatom have been applied to the generation of various azomethine ylides. Thus, α -silylimidates, obtained through *O*-alkylation of the corresponding amides, are transformed into azomethine ylides when treated with phenyltrifluorosilane [<1999T12969>](#). Cycloaddition with activated alkenes gives, after alcohol elimination, pyrroles in low stereoselectivity, whereas cycloaddition with dimethyl acetylenedicarboxylate gives pyrroles after rearomatization (Scheme 66). A one-pot protocol for the synthesis of pyrroles from α -silylamides by *O*-alkylation and desilylation with caesium fluoride has been developed.

In an analogous reaction, azomethine imines were prepared by silicon group migration of tertiary α -silylnitrosamines [<1999TL8849>](#) (Scheme 67). Cycloadditions of these dipoles with activated alkynes gave pyrazole derivatives. Aromatic α -silylnitrosamines and simple trimethylsilyl nitrosamines were used as precursors to the azomethine imines. Reaction with terminal alkynes led predominantly to 3-substituted pyrazoles. As for azomethine ylides, polymer-supported synthesis and cycloaddition reactions of azomethine imines, with a resin-bound silicon group was developed [<2000TL691>](#).

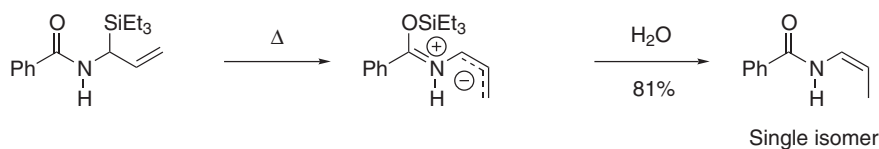


Scheme 66



Scheme 67

Silyl group migration from carbon to oxygen (Brook-type rearrangement) of α -silylallylamides has been used for the stereoselective synthesis of *cis*-enamides. Aliphatic and aromatic α -triethylsilylallylamides were heated in toluene or xylene to give, after hydrolysis of the *O*-silylimidates, the propenylamides in good yields [<2002AG\(E\)512>](#) (Scheme 68). The reaction is remarkable for its stereoselectivity as only *cis*-propenylamides are obtained. Mechanistic investigations have demonstrated the presence of an intermediate azomethine ylide, which is stabilized by allylic resonance, with the favored *cis*-configuration of the allylic anion [<2003JA5111>](#). This highly stereoselective rearrangement has been used for the synthesis of the proteasome inhibitors TMC-95A and TMC-95B [<2002AG\(E\)512>](#).

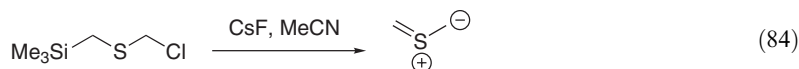


Scheme 68

(ii) Thiocarbonyl ylides

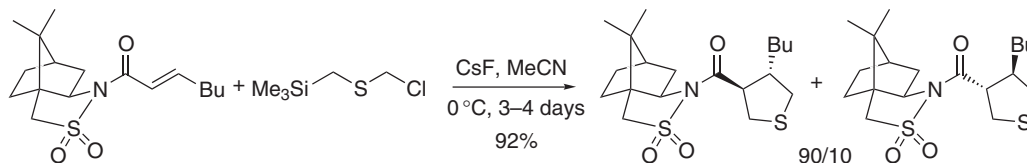
Thiocarbonyl ylides are reactive species which may undergo various reactions, including [3 + 2]-cycloaddition. Applications of these reactions are directed toward the synthesis of sulfur-containing heterocycles. As for azomethine ylides, the chemistry of thiocarbonyl ylides has been recently reviewed [<B-2002MI106-5>](#).

There are many methods for the generation of thiocarbonyl ylides, including those involving the cleavage of a carbon–silicon bond. In analogy with the formation of azomethine ylides, treatment of trimethylsilyl(chloromethyl)sulfide with caesium fluoride leads to the formation of a thiocarbonyl ylide through elimination of chlorotrimethylsilane (Equation (84)).

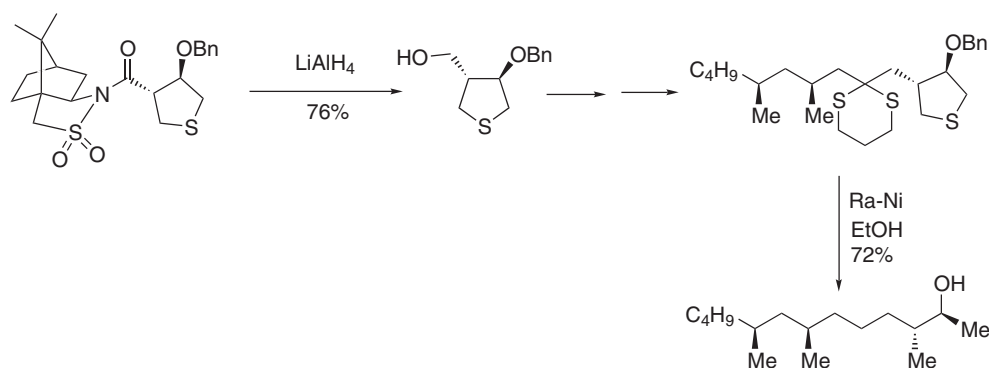


This electron-rich dipole reacts with activated alkenes to give 3,4-disubstituted tetrahydrothiophenes. A diastereoselective version of this cycloaddition with chiral α,β -unsaturated amides, leading to enantiomerically pure tetrahydrothiophenes, has been described, using camphorsultam as the chiral auxiliary [<1999OL1667>](#) (Scheme 69). The best diastereoselectivities were obtained at 0 °C despite long reaction times. Performing the reaction in refluxing acetonitrile resulted in strong increase of reactivity, with slight decrease in selectivity. Enantiomerically pure

3,4-disubstituted tetrahydrothiophenes were obtained after hydrolysis of the chiral auxiliary. These heterocycles are interesting compounds, since sulfur extrusion with Raney nickel gives stereochemically defined 2,3-dimethyl carboxylic acids, which are difficult to prepare otherwise. This strategy has been applied to the synthesis of a fragment of pheromone component of *Macrodiprion Nemoralis* <2000S1863> (Scheme 70).



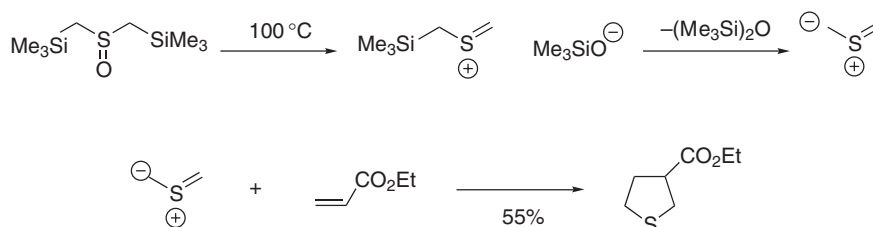
Scheme 69



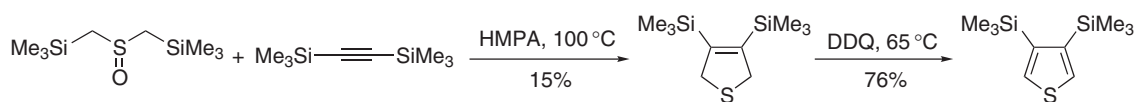
Pheromone of *Macrodiprion Nemoralis*

Scheme 70

A different route to the same thiocarbonyl ylides involves the thermal decomposition of bis-trimethylsilylmethylsulfoxide <1995H249>. Thiocarbonyl ylides are obtained *in situ* under mild conditions, generally heating at 100–110 °C in an aprotic solvent, and without any fluoride source. [3 + 2]-Cycloadditions with various activated alkenes gives the tetrahydrothiophenes in moderate-to-good yields (Scheme 71). This method for thiocarbonyl ylide generation is quite general and has become the method of choice for the synthesis of thiophene-type heterocycles: a recent report described the thermal [3 + 2]-cycloaddition between unsubstituted thiocarbonyl ylide and C[60]-fullerene <1999TL1543>. Cycloaddition of the same thiocarbonyl ylide with bis-trimethylsilylacetylene gives, after rearomatization, 3,4-bis(trimethylsilyl)thiophene <1997JOC1940> (Scheme 72). This latter compound may be used as the starting material for the preparation of various 3,4-disubstituted thiophenes.

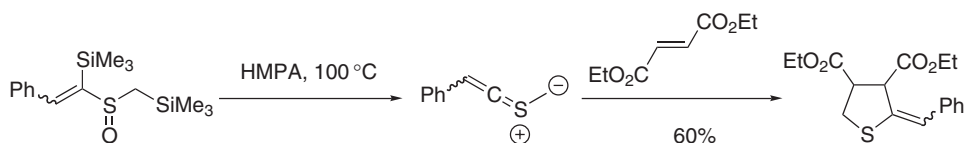


Scheme 71



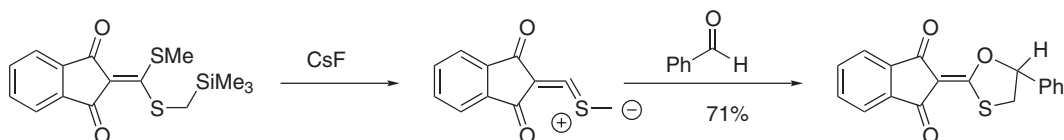
Scheme 72

The thermal elimination of sulfoxides for generation of thiocarbonyl ylides allows the preparation of new dipoles, in which an additional double bond is included. Thus, thermal elimination of α -benzylidene- α -trimethylsilylmethyl trimethylsilylmethyl sulfoxide gives an allenic dipole, which undergoes cycloaddition with activated alkenes to give 2-alkylidene tetrahydrothiophenes <1995H249> (Scheme 73).



Scheme 73

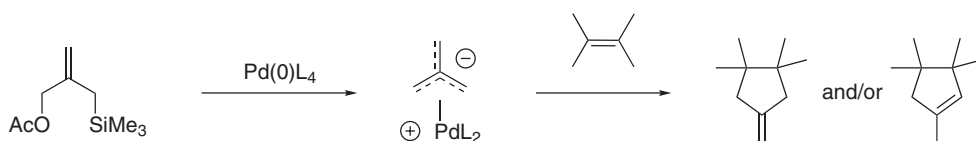
Alkylidenethiocarbonyl ylides may also be prepared by fluoride-mediated desilylation: thus, a 1,3-indanedione-derived ketene dithioacetal was desilylated using caesium fluoride and underwent cycloaddition with carbonyl compounds to give 2-alkylidene monothioacetals <1994TL3555> (Scheme 74). Both electron-withdrawing and electron-donating groups were tolerated on the carbonyl compound, although the former gave better yields in the cycloaddition reaction.



Scheme 74

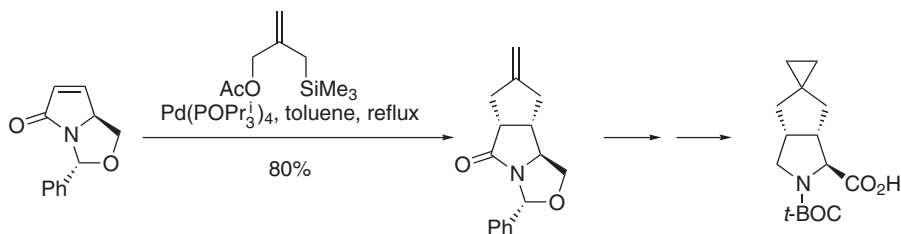
(iii) Trimethylenemethane

As for azomethine ylides, carbon–silicon bond cleavage is a common and efficient way to generate trimethylenemethane species. The acetate ester of 2-trimethylsilylallyl alcohol, when treated with a palladium complex, gives rise to trimethylenemethane, which undergoes [3 + 2]-cycloadditions with various unsaturated systems to give methylenecyclopentane derivatives, as well as the isomeric product with an endocyclic double bond (Scheme 75). Product distribution depends on the nature of palladium ligand, greater amount of methylene cyclopentane being obtained using phosphite ligands. The scope and application of the trimethylenemethane cycloadditions have been extensively reviewed <1996CRV49, B-2002MI106-6>. The concerted character of the [3 + 2]-cycloaddition of palladium trimethylenemethane complex has been recently demonstrated <1999JA9313>.



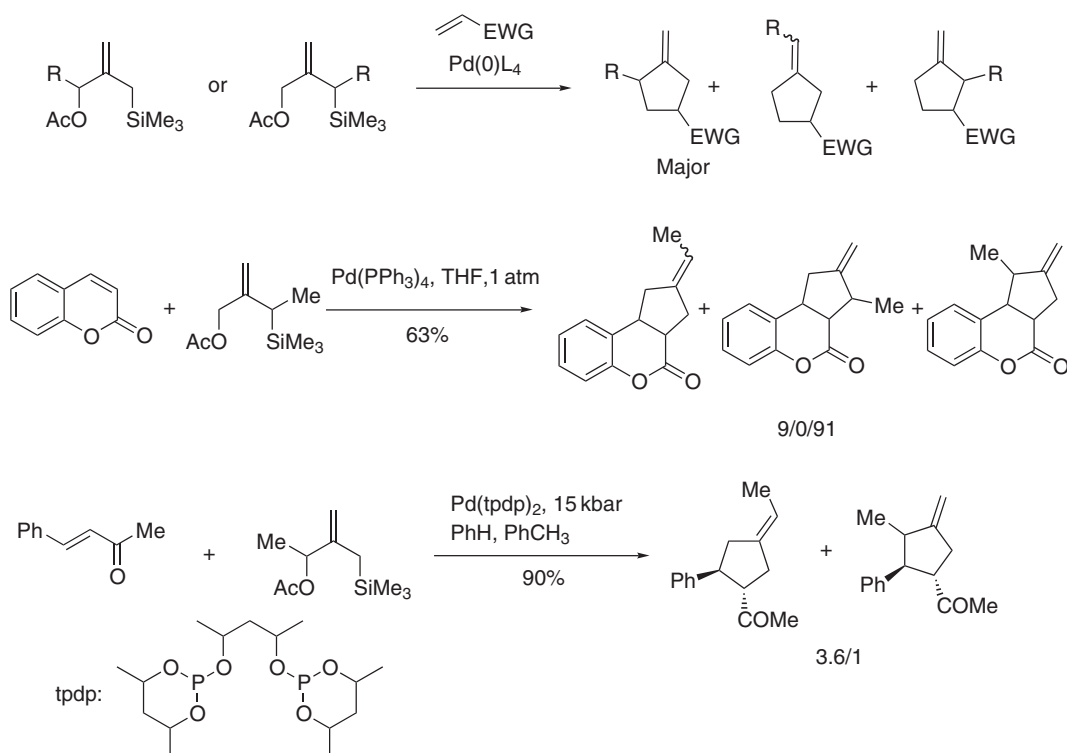
Scheme 75

Unsubstituted trimethylenemethane has been recently used for the preparation of new proline derivatives, via diastereoselective cycloaddition with an enantiomerically pure α,β -unsaturated lactam <2003TL5033> (Scheme 76). Further cyclopropanation of the exocyclic double bond and chiral auxiliary removal afforded a new fused proline surrogate.



Scheme 76

The regioselectivity of [3 + 2]-cycloaddition of substituted trimethylenemethane derivatives with electron-deficient alkenes is the subject of continuous study. Three isomers may be formed during the cycloaddition process, the major isomer being the *exo*-methylene cyclopentane derivative with the substituent β to the electron-withdrawing group. Similar results are obtained from both isomeric precursors, due to probable isomerization of trimethylenemethane–palladium complex before cycloaddition. This isomerization could be suppressed by the use of high pressure, which favors the bimolecular process. Thus, cycloadditions between the methyl-substituted trimethylenemethane complex and electron-deficient alkenes showed complete reversal of regioselectivity, when the reaction was performed at high pressure <1995JA3284> (Scheme 77). Regioselectivity was further increased when a bidentate phosphite ligand was used. Both isomeric precursors did not lead to the same regioisomers, indicating that no complex isomerization occurred before cycloaddition. This reversal of selectivity was observed for cyclic and acyclic systems.

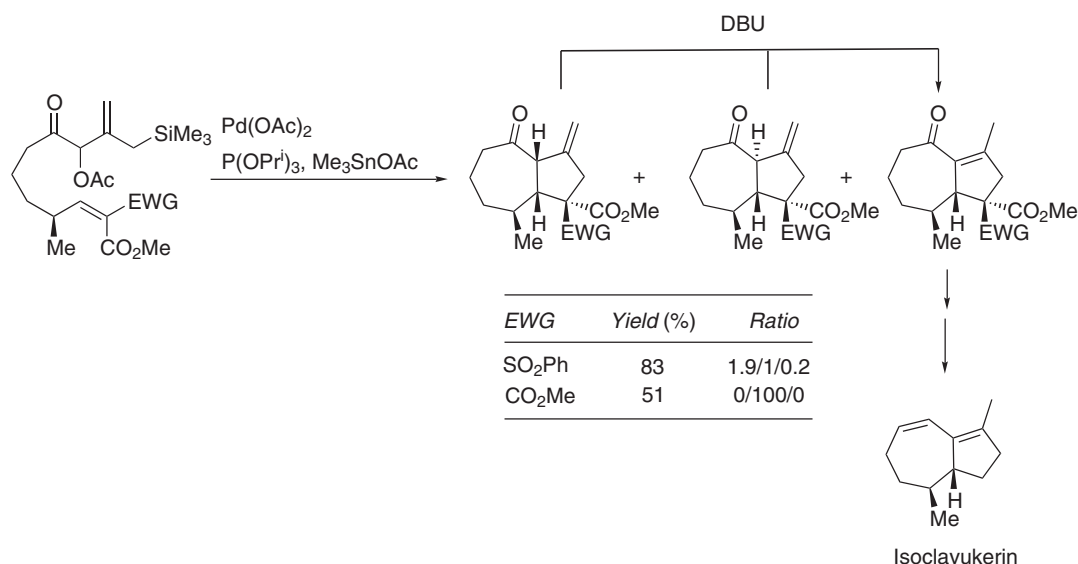


Scheme 77

The cyclopropyl-substituted trimethylenemethane–palladium complex is prepared from 2-(1-trimethylsilyl-1-cyclopropyl) allyl pivaloate and its reaction with dimethyl benzylidene malonate shows reversal of regioselectivity depending on the nature of palladium ligand <1995TL2917>. Although the use of the triisopropylphosphite ligand gave predominantly the methylenecyclopropane derivative, the bidentate ligand tris (2,4-pentanedioxy)diphosphite (tpdp) gave the vinylcyclopropane derivative with excellent stereoselectivity. Reaction with methyl cinnamate or coumarin showed preference for the formation of the vinylcyclopropane isomer, albeit with a lower isomeric ratio.

Compounds in which the trimethylenemethane moiety is included in a cyclopentene ring have recently been studied <2001EJO767>. These undergo [3 + 2]-cycloadditions in the presence of a palladium complex, with the regioselectivity depending on the presence of substituents on the cyclopentene ring. Although the presence of a *gem*-dimethyl substituent induced a regioselective reaction, it was completely opposite to the one generally observed. This particular outcome has been explained by the absence of equilibration of the trimethylenemethane species, due to conformational freezing by the *gem*-dimethyl substituent.

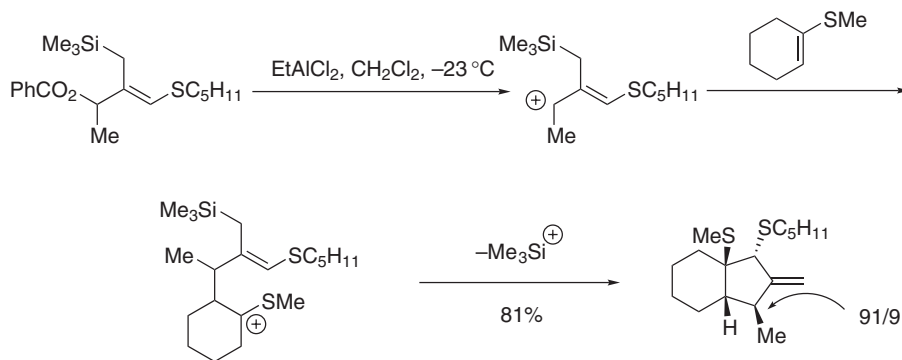
Intramolecular trimethylenemethane cycloadditions represent an efficient strategy for the synthesis of bicyclic ring systems. In the total synthesis of isoclavukerin, intramolecular cycloaddition of an optically active precursor was studied <1996JA10094> (Scheme 78). The efficiency of this cycloaddition depends on the nature of the electron-withdrawing group on the double bond. Although a simple vinyl sulfone failed to react with the trimethylenemethane, an alkene doubly activated with both sulfone and ester groups on the same carbon gave the perhydroazulene ring system, as a mixture of isomers in good yields. Isomerization of the crude product gave the compound with internal double bond as a single isomer. Surprisingly, the alkylidenemalonate precursor (with two ester functions) gave a single cycloadduct, indicating that with the bis-ester, cycloaddition is faster than trimethylenemethane isomerization.



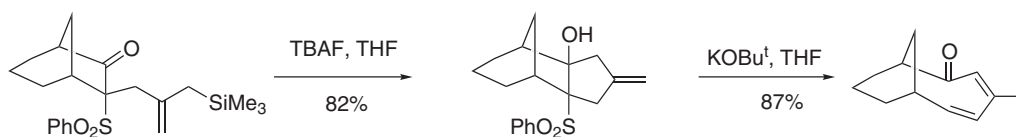
Scheme 78

A formal [3 + 2]-cycloaddition reaction of an allyl silane derivative leads to methylenecyclopentane products via a nonconcerted mechanism, with an anionic or cationic intermediate. Sulfur-substituted methylene cyclopentanes have been prepared by Lewis acid-catalyzed reaction of 2-trimethylsilylallylic acetates or benzoates <1996TL5943> (Scheme 79). In contrast to the concerted [3 + 2]-cycloaddition of trimethylenemethane, electron-rich alkenes such as enol ethers and vinyl sulfides are better partners for the reaction. This method may be therefore regarded as complementary to the [3 + 2]-cycloaddition.

Bridgehead bicyclic systems have been prepared by a formal methylenecyclopentane annulation on bicyclic β -keto sulfones, followed by fragmentation <1999TL2053>. Desilylation of the allyl silane with TBAF gave an allylic anion, which added onto the ketone. Upon basic treatment, fragmentation gave a dienic ketone with a larger ring system. An example is shown in Scheme 80.



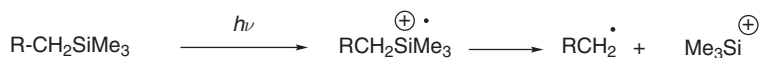
Scheme 79



Scheme 80

1.06.3.2.5 Free-radical-mediated reactions

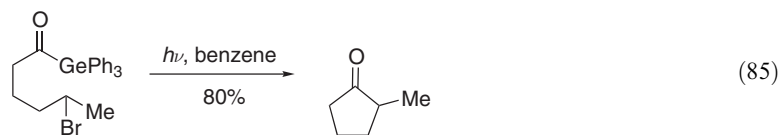
Homolytic cleavage of a carbon–silicon bond is often a difficult process and only precursors to stabilized radicals such as benzyltrimethylsilane or allyltrimethylsilane have been employed. The generation of alkyl radicals from alkyl silanes generally involves irradiation of the substrate to give a cation radical, which fragments to a trimethylsilyl cation and an alkyl radical. The photochemistry of organosilanes has been reviewed [\[1995CRV1527\]](#). The rate of the photodecomposition of benzyltrimethylsilane has been greatly increased by nucleophilic assistance [\[1997JA1876\]](#), a basic solvent such as acetonitrile or dichloromethane or an alcohol coordinating to the silicon and therefore facilitating the generation of benzyl radical ([Scheme 81](#)). These radicals are not trapped with carbon nucleophiles, but dimerized to give 1,2-diphenylethane, in the case of $\text{R}=\text{Ph}$.



Scheme 81

1.06.3.3 Substitution of Germanium Functions

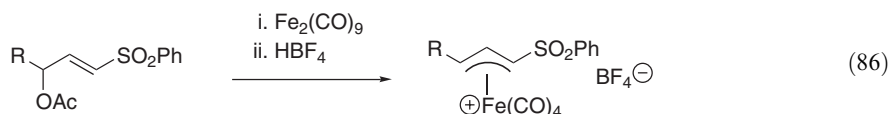
Although alkylgermanium derivatives possess little application in organic synthesis, the chemistry of acyltrialkyl germanium derivatives has shown some interest in terms of acyl radical precursors and radical acceptors. A general method for the synthesis of acyltrialkyl germanes has been described, involving the addition of trialkylgermyllithium to aldehydes, followed by oxidation [\[1994JCS\(P1\)1589\]](#). Intramolecular reactions of alkyl halides (bromides or iodides) with acyltriphenylgermanes lead to the formation of cyclic ketones upon irradiation [\[1997JA4797\]](#) ([Equation \(85\)](#)). In contrast to acyl silanes, no Brook-type rearrangement (migration of germanium group from carbon to oxygen) was observed. Different ring-size cyclic ketones could therefore be synthesized from primary, secondary, or tertiary alkyl halides.



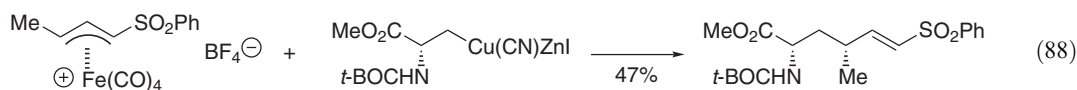
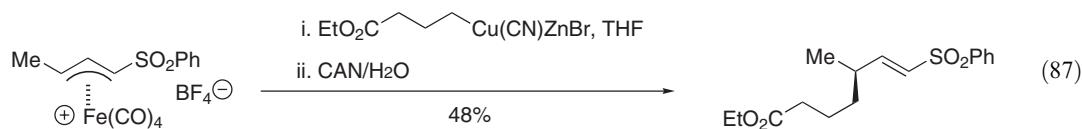
1.06.4 SUBSTITUTION OF METAL FUNCTIONS

Carbon–carbon bond formation by reaction of an alkyl metal reagent with another organometallic species is a very rare reaction. However, various carbon nucleophiles may react with cationic η^3 -allyl metal complexes in a regio- and stereoselective fashion to give allylated products. Since chiral complexes are available, recent studies have focused on the preparation and reactions of these systems.

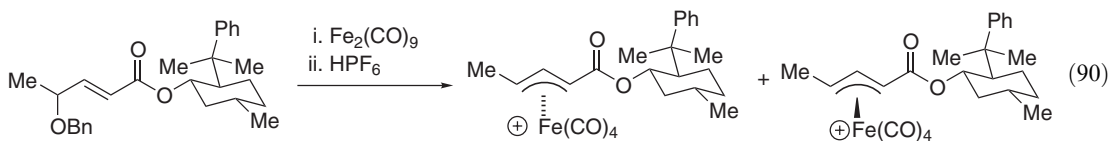
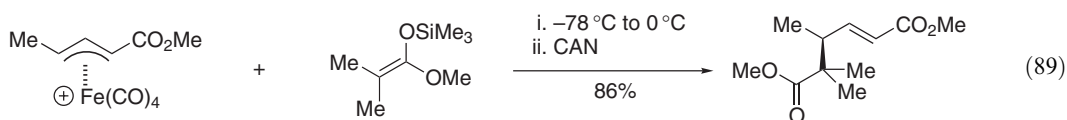
Cationic tetracarbonyl (η^3 -allyl) iron(I) complexes bearing an electron-withdrawing group (ester or sulfone) are prepared from a γ -alkoxy- α,β -unsaturated ester or sulfone by reaction with iron pentacarbonyl followed by acidic treatment (Equation (86)). Detailed preparation of a chiral sulfone cationic iron complex from ethyl (*S*)-lactate has been described <2000OS177, 2000OS189>. This enantiomerically pure complex is obtained with inversion of configuration with respect to the starting leaving group.



Reaction with nucleophiles occurs with high regioselectivity *anti* to the electron-withdrawing group, and with high stereoselectivity, resulting in an overall retention of configuration, giving allylated products after oxidative decomplexation of the resulting η^2 -iron complex. In contrast to π -allyl palladium complexes, hard nucleophiles may be used. Functionalized organozinc reagents have been used on both sulfone <1996SL18> and ester <1997SL789> complexes, although yields were slightly better with the sulfone complex (Equations (87) and (88)). All compounds were obtained as single regio- and diastereomers after decomplexation. Allyl silanes are also excellent reaction partners for the cationic iron complex. The stereoselective allylation of chiral cationic tetracarbonyl (η^3 -allyl) iron(I) complexes has been used as the key step for numerous syntheses of natural products <1997SL421>.

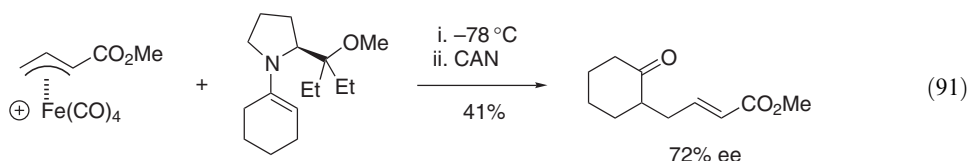


The reaction of silyl enol ethers or silyl ketene acetals provides an efficient and stereoselective entry to 1,6-diester or 1,6-ketoesters <1996JOM(519)147> (Equation (89)). Reaction of the chiral, enantiomerically pure ester complex gave the corresponding adducts essentially as pure regio- and stereoisomers. This study also revealed the importance of a stereochemically defined leaving group for the preparation of the chiral cationic tetracarbonyl (η^3 -allyl) iron(I) complex since diastereomeric γ -benzyloxy esters of 8-phenylmenthol gave a mixture of diastereomeric iron complexes upon complexation and acidic treatment, showing that configuration of C–Fe bond is less controlled by chiral auxiliary than by the configuration of the leaving group (Equation (90)).



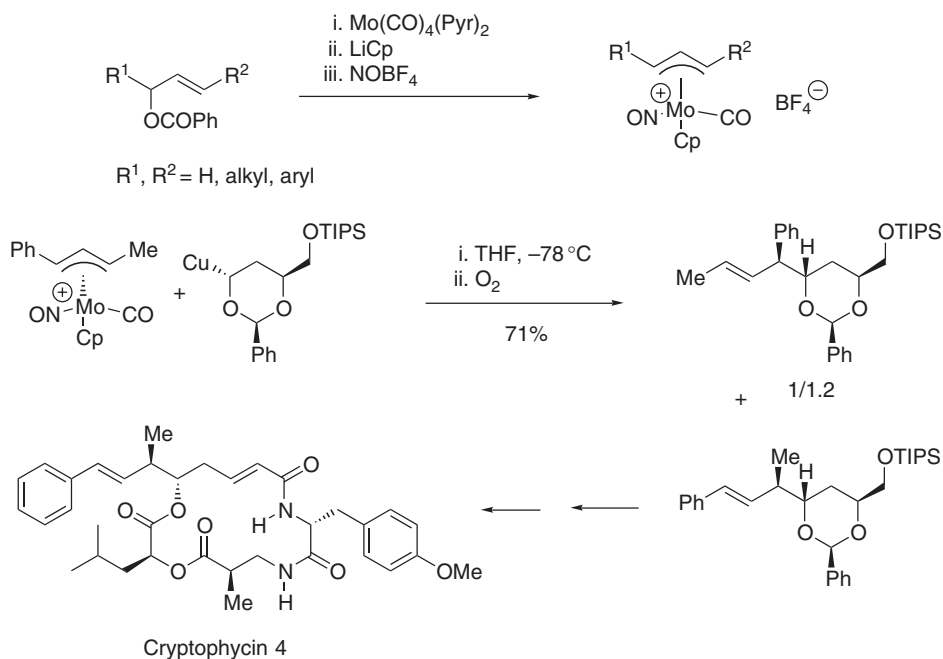
Condensation of the sulfone-containing chiral iron(I) complex with silyl enol ethers leads to 1,6-ketosulfones in a highly regio- and stereoselective fashion. This reaction was applied to a total synthesis of the furanosesquiterpene myoporone [<1997SL421>](#).

In another approach to chiral 1,6-ketoesters, a racemic cationic tetracarbonyl (η^3 -allyl) iron(I) complex was reacted with a variety of chiral nucleophiles, including chiral enamines, metallated imines, or α -silyl ketones [<1996JOM\(514\)227>](#). Reactions occurred with moderate-to-good stereocontrol, showing substrate control is more effective than reagent control. An example of the alkylation of a chiral enamine is shown in [Equation \(91\)](#).

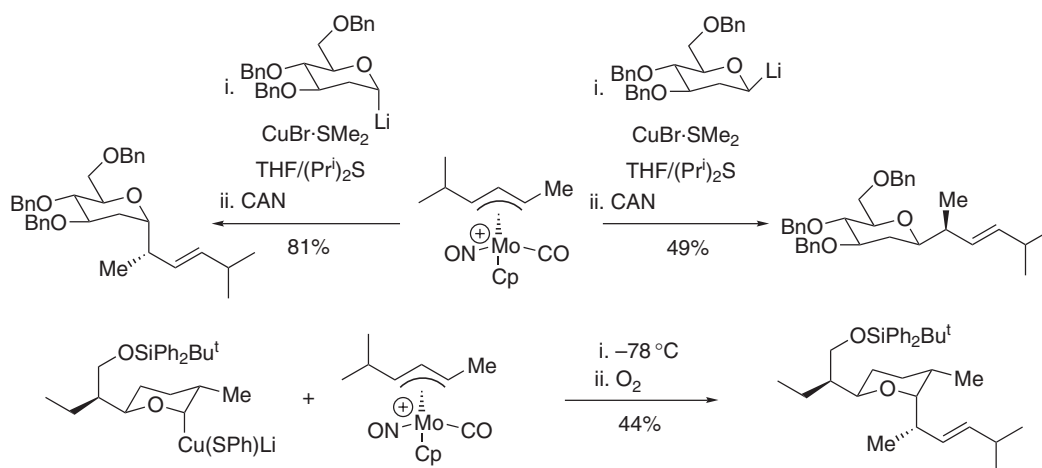


Planar chiral cationic molybdenum complexes are prepared from allylic acetates by treatment with molybdenum carbonyl complexes followed by ligand displacement with cyclopentadienyl anion. The cationic complex is obtained by treatment with nitrosonium tetrafluoroborate. Recently, the use of the $\text{Mo}(\text{CO})_4(\text{Pyr})_2$ complex as a more reactive reagent for preparation of η^3 -allyl molybdenum complexes has been recommended [<2000SL1765>](#). In the same way as for iron complexes, planar chiral molybdenum complexes are prepared from enantiomerically pure allylic esters, benzoates giving the best yields. These highly electrophilic complexes react with carbon nucleophiles with good stereoselectivity, after decomplexation using cerium ammonium nitrate (CAN) or oxygen. In contrast to iron complexes, an electron-withdrawing group on the allylic moiety is not necessary. Stereoselective allylation reactions using chiral cationic molybdenum complexes have been used for the assembly of stereodefined acyclic chains: in a synthesis of cryptophycin 4, reaction between an allylic molybdenum complex and a functionalized organolithium reagent gave an allylated dioxane with high stereocontrol, although regioselectivity was low ([Scheme 82](#)). One of the isomers was used for completion of the cryptophycin 4 synthesis [<2000SL463>](#).

A new approach to stereodefined C-glycosides involves alkylation of a chiral cationic molybdenum complex with glucosyl copper reagents [<1998SL425>](#). Reaction occurs with complete retention of configuration at the anomeric position, and with complete regioselectivity ([Scheme 83](#)). This methodology has been applied to the synthesis of the C1—C9 fragment of the naturally occurring antibacterial compound salinomycin [<1998JCS\(P1\)9>](#).



Scheme 82



Scheme 83

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Biographical sketch

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1.07

One or More CC Bonds Formed by Addition: Addition of Carbon Electrophiles and Nucleophiles to CC Multiple Bonds

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1.07.1 INTRODUCTION

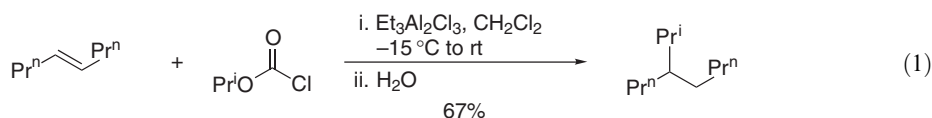
This chapter serves to update the earlier account <1995COFGT(1)293> of several key processes in C—C bond formation which formally involve addition of carbon electrophiles or nucleophiles to C—C multiple bonds. Because it is the formation of tetracoordinate products that is of interest, virtually all the addition processes discussed involve addition to alkenes rather than to alkynes. Since the original chapter was written, the most striking advances are the greatly improved levels of reagent-controlled enantioselectivity that have been realized, particularly in catalytic asymmetric conjugate addition processes.

1.07.2 ADDITION OF CARBON ELECTROPHILES TO C—C MULTIPLE BONDS TO GIVE TETRACOORDINATE PRODUCTS

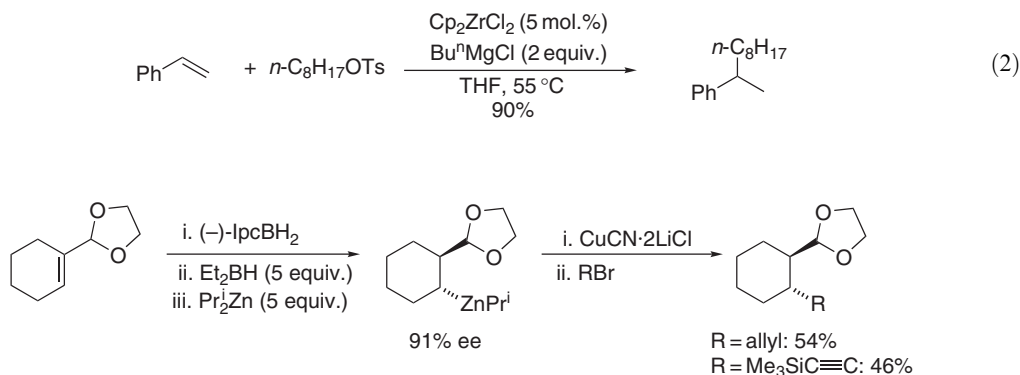
Addition of carbon electrophiles to alkenes plays a role in several synthetically useful reactions in C—C bond formation. Work by Mayr and co-workers in recent years <2003ACR66> has allowed development of a set of quantitative parameters for π -nucleophilicity, allowing prediction of the reactivity of particular electrophile/nucleophile pairs. The initial product of formal electrophilic addition to an alkene is a carbocation; a general discussion of the formation of these species appears in Chapter 1.19. Subsequent reactions of carbocations (e.g., loss of a proton, trapping with nucleophiles) often lead to the formation of functionality that are the subject of later chapters, so only limited coverage is presented here. Hydroformylation is also briefly presented, although it is also discussed later (Chapters 3.01, 3.04, 5.02, and 5.03).

1.07.2.1 Addition of Alkanes and Alkyl Electrophiles to Alkenes

Direct addition of alkanes to alkenes continues to be of industrial importance, but of lesser significance in the laboratory due to issues of chemo- and regioselectivity. The overall alkylation of alkenes is accomplished in a new system reported by Biermann and Metzger <1999AG(E)3675>. These authors exploited the known decarboxylation of chloroformates in the presence of Lewis acids, resulting in the formation of carbocations which can add to alkenes. Thus, reaction of *trans*-4-octene with isopropyl chloroformate mediated by ethylaluminum sesquichloride ($\text{Et}_3\text{Al}_2\text{Cl}_3$) gave a good yield of 4-isopropyloctane (Equation (1)). Interestingly, hydride is transferred from the aluminum more rapidly than ethyl. Addition of a more effective hydride donor such as triethyl silane allowed the method to be extended to cyclohexene and to 1,1-disubstituted alkenes, reducing competing alkene oligomerization. Use of isopentyl or neopentyl chloroformate gave products arising from rearrangement of these alkyl substituents.



A recently described Zr-catalyzed system allows reaction of styrenes with carbon electrophiles (Equation (2)) <1998TL9201, 2000JA5977, 2001OL2097>; intramolecular reactions are possible <2002OL395>. Knochel has demonstrated that hydroboration of enones which are protected as acetals or dithianes, followed by boron–zinc exchange, leads to organozinc reagents, which may be quenched with allylic, alkynyl, or propargyl halides. Overall, the transformation represents addition of the carbon electrophile to the alkene. The boron–zinc exchange proceeds with retention of configuration, allowing preparation of optically active products via asymmetric hydroboration (Scheme 1) <2001AG(E)3022>.



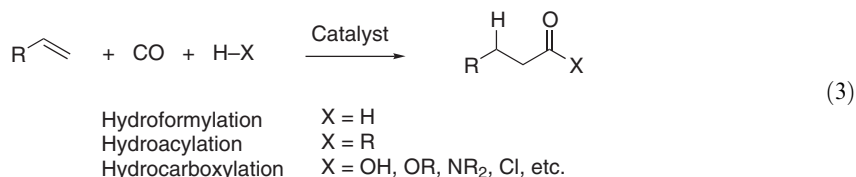
Scheme 1

1.07.2.2 Addition of Alkenes to Alkenes

The most spectacular examples of addition of alkenes to alkenes are polyene cyclizations, which mimic the biosynthetic pathway to steroids. Recent work has focused on control of enantioselectivity [<2002JA3647>](#). A catalytic antibody has also been developed which effects polyene cyclization [<1999AG\(E\)1743>](#).

1.07.2.3 Hydroformylation, Hydroacylation, and Hydrocarboxylation

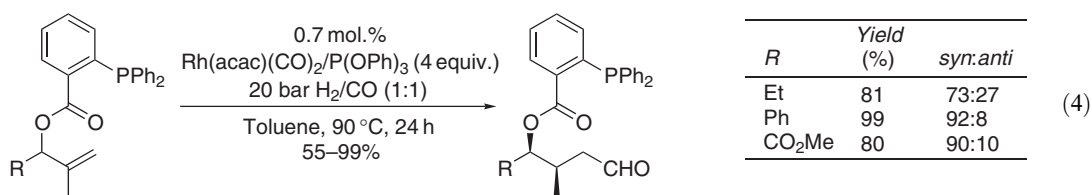
Hydroformylation and hydrocarboxylation (Equation (3)) are extremely important industrial processes. Since these reactions and the related hydroacylations result in preparation of aldehydes, carboxylic acid derivatives, and ketones, respectively, they are also covered in Chapters 3.01, 3.04, 5.02, and 5.03.

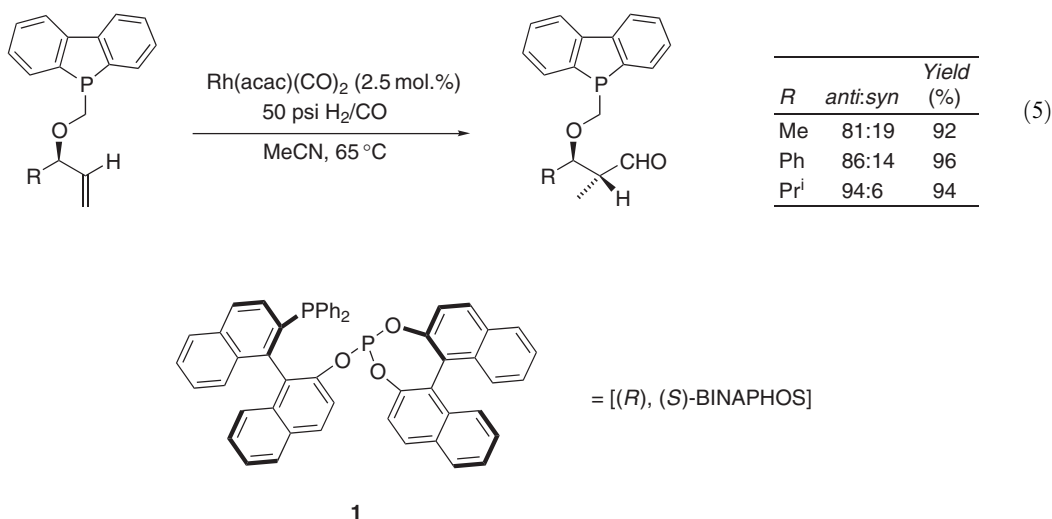


1.07.2.3.1 Hydroformylation

Hydroformylation, the addition of carbon monoxide and hydrogen to an alkene, is generally performed using cobalt or rhodium catalysts, the latter being more reactive. An industrial view of the status and importance of the reaction has appeared [<2002MI1>](#), as well as a comprehensive account of recent work relevant to the use of the reaction in organic synthesis [<2001S1>](#). The hydrogen and aldehyde functionalities are added in a *syn*-fashion, and a wide range of functional groups is tolerated. Generally, greater substitution on the alkene results in slower hydroformylation; reactive Rh-phosphabenzene complexes give promising results here [<2001CEJ3106>](#). For unsymmetrical alkenes, regiochemistry is an issue. 1,1-Disubstituted and trisubstituted alkenes usually display high regioselectivity, with the formyl group becoming attached to the less substituted end of the alkene. Terminal aliphatic alkenes generally lead to linear aldehydes, although specific ligand systems can promote the formation of branched products. Styrenes often afford branched products. Regiocontrolled hydroformylation of 1,2-disubstituted alkenes remains difficult.

Control of diastereoselectivity, i.e., stereocontrol relative to pre-existing stereocenters, has received much attention recently. Breit has developed the concept of “substrate-bound catalyst-directing groups” in which the substrate contains a phosphine binding site for the rhodium catalyst [<2003ACR264>](#). This allows *syn*-selective hydroformylation of methallylic alcohols (Equation (4)). Leighton has explored the directing properties of dibenzophosphol-5-ylmethyl ethers of allylic alcohols, resulting in highly diastereoselective formation of branched aldehydes, the reverse of the usual regiochemical outcome (Equation (5)) [<2001JA11514>](#). Enantioselective hydroformylation has been reviewed [<1995CRV2485, 1995TA1453, 2001S1>](#). The most generally successful system appears to be a BINAPHOS **1** rhodium complex [<1993JA7033>](#).

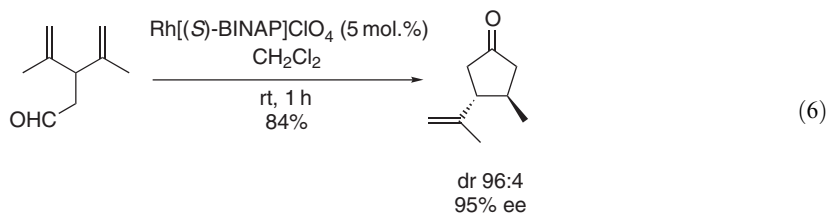




Tandem processes in which the aldehyde product is modified by, for example, olefination, reductive amination, allylboration, or aldol addition have been comprehensively reviewed [\[1999CRV3329, 2001SI\]](#).

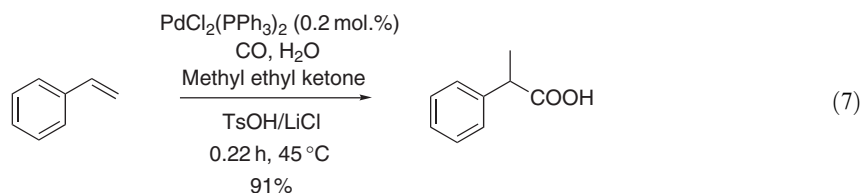
1.07.2.3.2 Hydroacylation

Hydroacylation, the addition of an aldehyde to an alkene, has progressed far less than hydroformylation. A key problem to overcome is the decarbonylation of the intermediate acylmetal hydride formed from the oxidative addition of a transition metal into the aldehyde C—H bond. Strategies adopted have involved incorporating functionality capable of stabilizing this intermediate by chelation, e.g., by *in situ* preparation of picolylimine derivatives (generally limited to nonenolizable aldehydes) [\[2001CC2558, 2002CEJ2423, 2003OL1365\]](#) or by the incorporation of a β -sulfide in the aldehyde [\[2004AG\(E\)340\]](#). Intramolecular hydroacylation has been used for obtaining cyclopentanones ([Equation \(6\)](#)) [\[2000JOC5806\]](#).



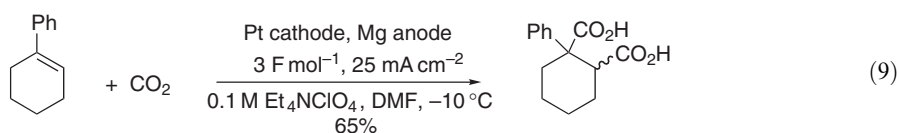
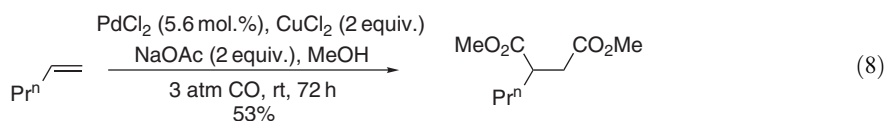
1.07.2.3.3 Hydrocarboxylation

Hydrocarboxylation ([Equation \(3\)](#)) allows access to many different carboxylic acid derivatives via reaction of an alkene with carbon monoxide and a catalyst in a protic solvent, H—X. Palladium-catalyzed hydrocarboxylation of vinyl aromatics is a convenient route to 2-arylpropionic acid derivatives ([Equation \(7\)](#)) [\[1999OL459\]](#); a review of the mechanism of this reaction has appeared [\[2001EJI2719\]](#). Relative to hydroformylation, control of regio- and stereochemistry in this process has received little attention in recent years. An amine-directed hydrocarboxylation leading to the formation of γ - and δ -lactones has been described [\[1998OM2076\]](#). For direct introduction of amido and ester groups to alkenes, as with hydroacylation, substrates capable of chelation to the metal catalyst have been developed to minimize decarbonylation of the intermediate metal hydroacyl [\[2003OL2687, 2002JA750\]](#). Asymmetric hydrocarboxylation of vinylarenes can be achieved by asymmetric hydroboration followed by homologation [\[1999JOC9704\]](#).



1.07.2.3.4 Dicarboxylation

Palladium-catalyzed dicarboxylation, the 1,2-addition of two carboxyl groups to an alkene, has been known for some time (Equation (8)) <1976JA1810>, and proceeds in a *syn*-fashion <1976JA1806>. More recently, the electrochemical dicarboxylation of aryl-substituted alkenes has been described <2001SL418> (Equation (9)); this reaction is not stereospecific.



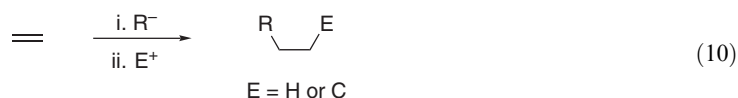
1.07.2.4 Cyclopropanation

Reaction of alkenes with carbenes or metal carbenoids is an extremely common approach for the synthesis of cyclopropanes <2001T8589>. This topic is discussed in Chapter 1.08. Methods for cyclopropane formation which involve initial nucleophilic attack on the alkene are covered elsewhere in this chapter (Section 1.07.3.2.1).

1.07.3 ADDITION OF CARBON NUCLEOPHILES TO C—C MULTIPLE BONDS TO GIVE TETRACOORDINATE PRODUCTS

1.07.3.1 Introduction

This section considers addition of carbon nucleophiles to alkenes to form new C—C single bonds (Equation (10)). This process is clearly most facile for electron-poor alkenes, which have therefore been most widely studied. These reactions are often known as conjugate addition, or, in the case where a carbonyl group activates the alkene, as 1,4-addition. When stabilized nucleophiles are used, the process is sometimes called the Michael reaction. Recent developments in nucleophilic addition to unactivated alkenes are also discussed.



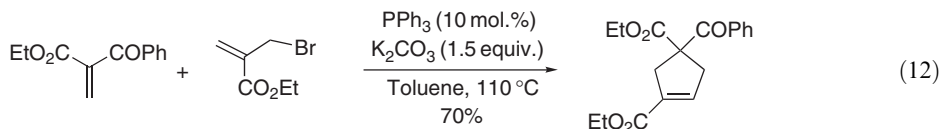
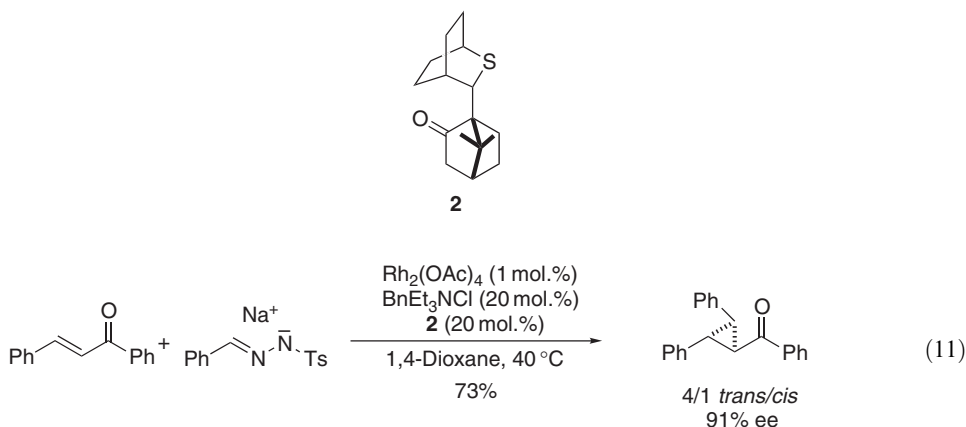
1.07.3.2 Addition to Electron-deficient Alkenes

1.07.3.2.1 Introduction and general aspects

In <1995COFGT(1)293> the principles governing reactivity of electron-poor alkenes and the factors influencing the balance between 1,4- versus 1,2-addition to α,β -unsaturated carbonyl systems were summarized. It also gave an overview of attempts to render the additions

diastereoselective, for example, using chiral auxiliaries. In recent years, attention has focused heavily on reagent-controlled asymmetric synthesis, particularly enantioselective catalysis, and so the dramatic progress in this area will make up a large part of this section. Some excellent reviews have appeared recently <2000T8033, 2001S171, 2003AG(E)1688>, so the emphasis here will be on key reactions and the most recent developments. Reviews on asymmetric addition to specific substrates—namely, nitroalkenes <2002EJO1877> and unsaturated nitriles <2003CRV2035>—have also appeared.

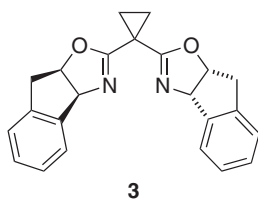
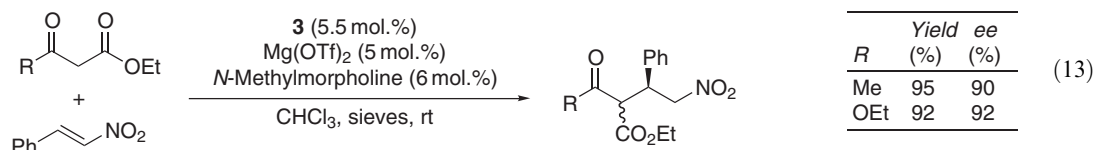
A synthetically valuable aspect of many conjugate addition reactions is the possibility of trapping the initially formed anion with an electrophile. A specific class of reaction is cyclopropanation using telluronium <1996JOC5762, 1997JOC954, 2000JOC6257> or sulfur ylides <1997CRV2341>. Stoichiometric chiral sulfur ylides for asymmetric cyclopropanation have been reported <1998AG(E)1689, 2002JA2432>. Aggarwal and co-workers <1997CC1785, 2000JCS(P1)3267> have developed a catalytic system in which a sulfur ylide is generated by Rh-catalyzed reaction of a sulfide with a diazo compound. A recent advance is the ability to generate the diazo compound *in situ* (Equation (11)) <2001AG(E)1433>. Another interesting catalytic (albeit currently nonasymmetric) method for ylide-mediated C—C bond formation which formally involves conjugate addition and enolate trapping is shown in Equation (12) <2003AG(E)1035>. Here, an allylic phosphorus ylide is generated by reaction of triphenylphosphine with an allylic halide or acetate; conjugate addition and ring closure provides a cyclopentene product and allows regeneration of the phosphine.



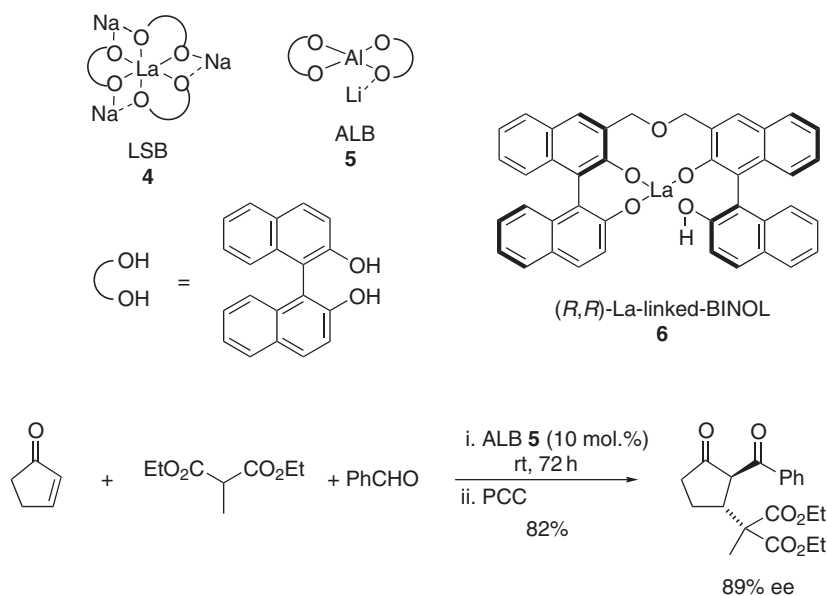
1.07.3.2.2 Addition of stabilized nucleophiles

(i) Addition of 1,3-dicarbonyl compounds and related nucleophiles

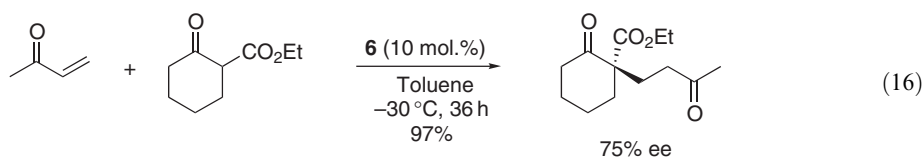
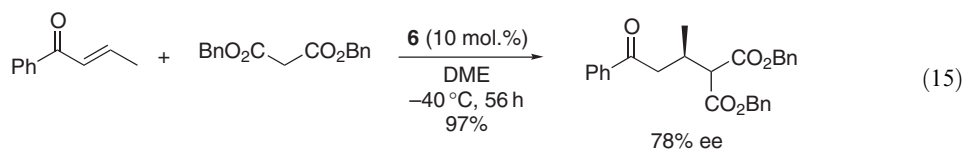
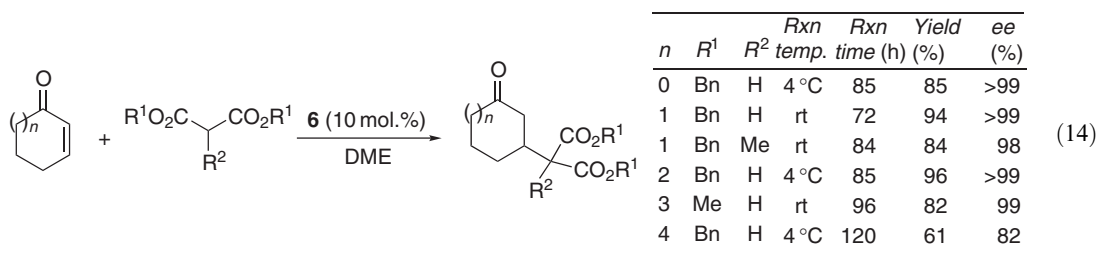
Addition of 1,3-dicarbonyl compounds to electron-poor alkenes is a well-established method for C—C bond formation, and has continued to attract considerable attention. Nitroalkenes are excellent acceptors, and asymmetric Michael addition to these substrates has been reviewed <2002EJO1877>. Ji and co-workers <1999JA10215> reported a catalytic asymmetric variant of this reaction (Equation (13)) utilizing Mg(OTf)₂ to promote enolization in the presence of chiral bisoxazoline ligand **3**.

**3**

Addition of 1,3-dicarbonyls to α,β -unsaturated carbonyl compounds is also of exceptional synthetic value. Traditionally, strongly basic reaction conditions were employed, which often led to several side reactions. Christoffers has summarized the advantages of using transition metal catalysis [<1998EJO1259>](#), which can avoid these problems. Ferric chloride trihydrate is a particularly effective catalyst [<2001SL723, 2003EJO1665>](#). Asymmetric catalysis of the reaction has developed enormously in the last few years. Early results were summarized in recent reviews [<2000T8033, 2001S171, 2003AG\(E\)1688>](#). These include catalysis by rubidium prolinates [<1993AG\(E\)1176>](#); $\text{Ni}(\text{OAc})_2$ in the presence of a chiral diamine [<1998EJO1259, 2000EJO701>](#) or a supported quinine derivative [<1999TL7091>](#); $\text{Co}(\text{OAc})_2$ in the presence of a chiral ligand [<1998CEJ818>](#); and the Rh-catalyzed addition of α -cyano esters to enones and acrolein [<1994T4439, 2002CEJ2968>](#). More recently, asymmetric addition of cyclic 1,3-dicarbonyl compounds to unsaturated α -keto esters catalyzed by chiral Cu(II)-bisoxazoline complexes has been described [<2003JOC5067>](#). Some of the most spectacular results in the Michael addition of 1,3-dicarbonyls have come from Shibasaki and co-workers using metal BINOL complexes. These include the heterobimetallic complex $(\text{Na}_3[\text{La}(\text{BINOL})_3])$ (LSB, **4**) [<1995JA6194, 1996TL5561>](#) and its aluminum counterpart $(\text{Li}[\text{Al}(\text{BINOL})_2])$ (ALB, **5**) [<1996AG\(E\)104, 1996CEJ1368, 1998JOC3666, 1998JOC7547>](#) which possess both Lewis acid and Brønsted base properties, and can therefore activate both components of the Michael addition [<2002CRV2187>](#). The ALB complex **5**, prepared by reaction of LiAlH_4 with 2 equiv. of BINOL, may be used in low loadings (0.3–1 mol.%) at room temperature, but is moisture sensitive. The initially formed Al-enolate can be trapped in an aldol reaction with aldehydes (Scheme 2) [<1996AG\(E\)104>](#), a feature that has been used in the synthesis of prostaglandin derivatives [<1998JOC3666>](#). α -Nitro esters may be used as nucleophiles in place of 1,3-dicarbonyls [<1997TA3403>](#). The sodium-free version of the lanthanum BINOL complex **4** also gives excellent Michael addition enantioselectivities [<1994JA1571>](#). Even better in terms of practicality is the linked-BINOL system **6** [<2000JA6506, 2002CRV2187, 2002MI3>](#). The ether bridge can coordinate to the metal center, resulting in the catalyst being stable, storable, and reusable. Relative to the ALB system **5**, **6** is easier to handle but the reactions require higher catalyst loadings (10 mol.%). Some examples of highly enantioselective Michael addition catalyzed by **6** are shown in Equation (14). Excellent enantioselectivities are obtained for addition to cycloalkenes, including seven- and eight-membered enones (Equation (14)), with slightly lower ee for cyclononene. Addition to acyclic enones was performed at lower reaction temperature and affords good selectivity (Equations (15) and (16)). LSB **4** gives better ee (93% ee) for the reaction in Equation (16), again at low temperature (-50°C). Catalyst **6** has been attached to an insoluble polymer to facilitate recovery [<2000TL8473>](#). Low reactivity with this polymer-supported system was countered by preparation of a more reactive La–Zn-linked-BINOL catalyst.

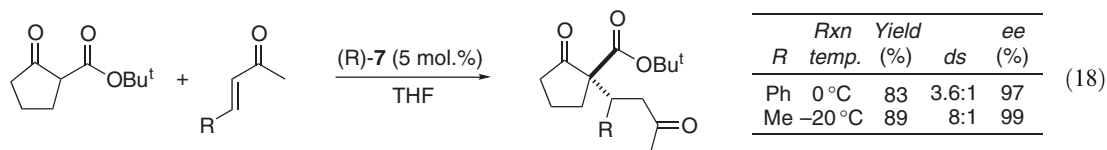
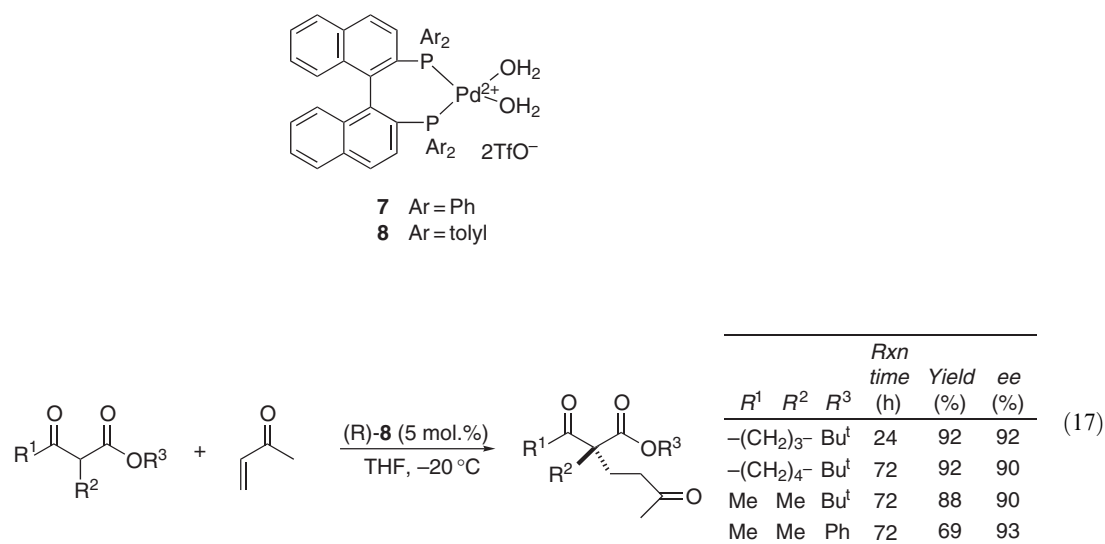


Scheme 2

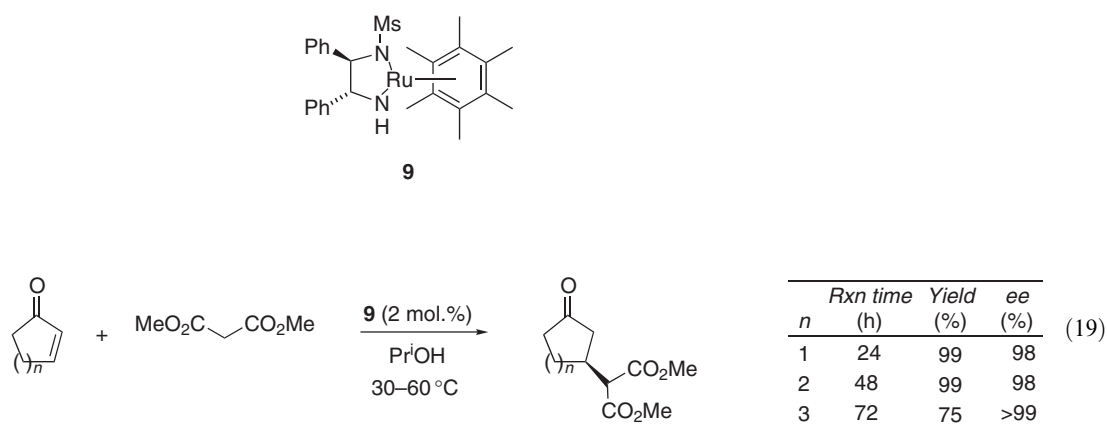


As indicated in [Scheme 2](#) and [Equation \(16\)](#), Shibasaki's catalysts require low reaction temperatures for the formation of quaternary centers. In this regard, very encouraging results have been reported by Sodeoka and co-workers [\[2002JA11240, 2003AG\(E\)1688\]](#), who have described asymmetric Michael addition to enones by chiral palladium enolates, generated directly from 1,3-dicarbonyl compounds in the presence of catalysts **7** and **8**. Cyclic keto esters provide

quaternary stereocenters (Equation (17)). In an impressive example (Equation (18)), the method allows the construction of highly crowded vicinal tertiary and quaternary stereocenters in good diastereoselectivity and excellent enantioselectivity.

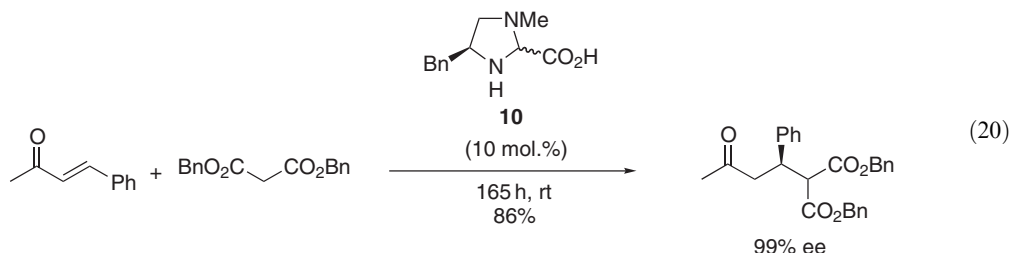


Another highly promising and selective catalyst system involves Ru–amido complexes such as **9** [<2003JA7508>](#), which affords excellent enantioselectivities for the addition of malonates and methyl acetoacetate to cyclic enones (Equation (19)). Mechanistically, it is believed that **9** reacts with the malonate to give a C-bound malonato complex, which then adds to the enone. Linear α,β -unsaturated ketones give unsatisfactory results with this system.



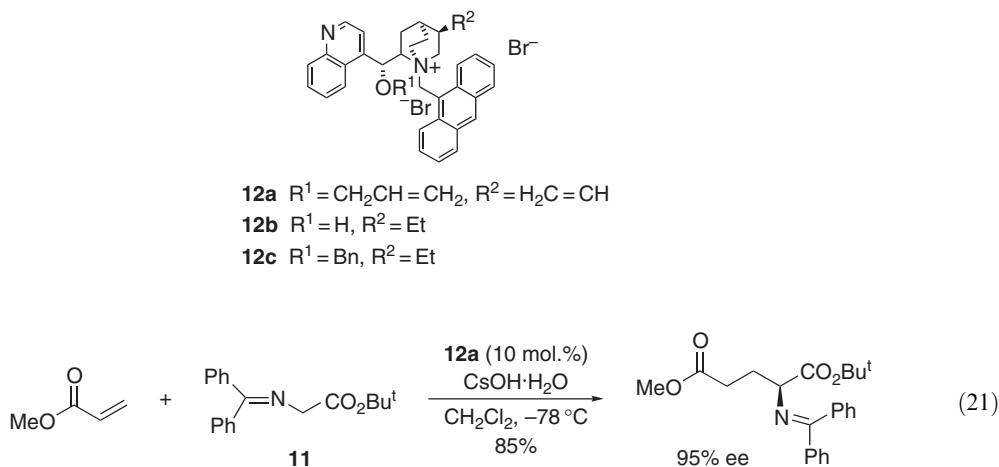
The use of small organic molecules as catalysts in place of metals is attracting intense interest due to operational simplicity and relative ease of product purification. Amine-catalyzed reactions are proving particularly successful, and this concept has been applied to

Michael additions of malonates to acyclic enones (Equation (20)) <2003AG(E)661>. The imidazolidine catalyst **10**, prepared from phenylalanine, reversibly forms a reactive iminium species with the enone substrate. The method works for a range of β -aryl- and heteroaryl-substituted enones; β -alkyl-substituted enones reacted slower and with lower yields, although enantioselectivities were still high. The size of the malonate ester substituent was found to be important, with medium-sized malonates (e.g., ethyl, benzyl) giving best results. When non-symmetrical malonates were used, little diastereoselectivity was observed.

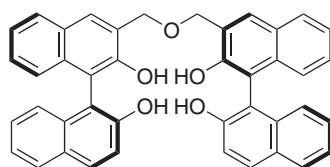
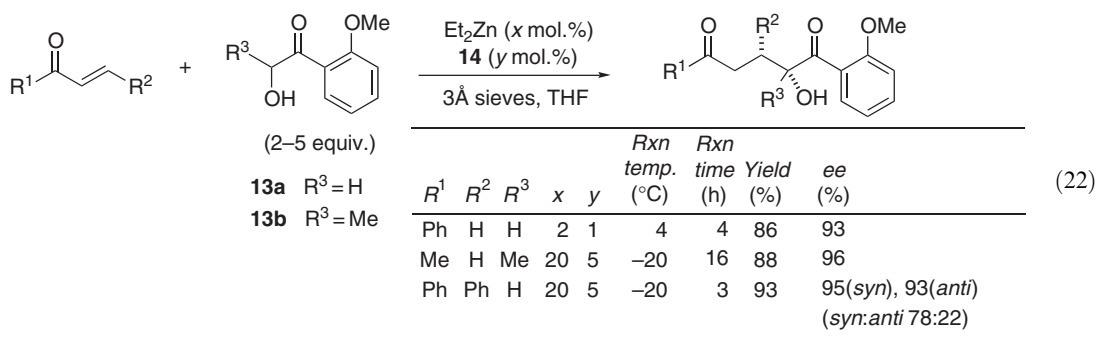


(ii) Addition of other carbonyl compounds

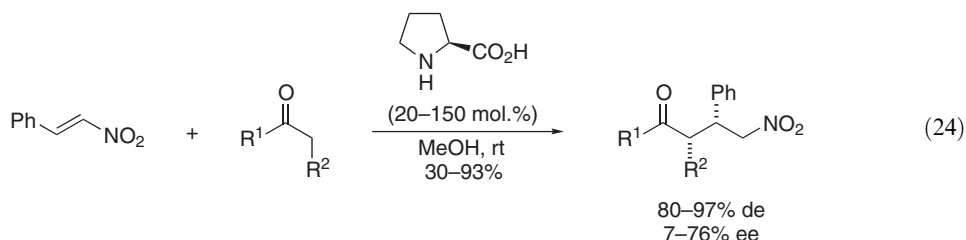
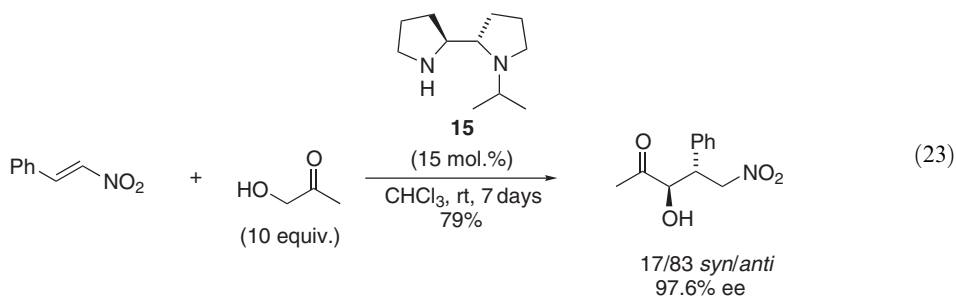
Conjugate addition of the glycine derivative **11** to methyl acrylate, cyclohexenone, ethyl vinyl ketone <1998TL5347>, and acrylonitrile <2000OL1097> catalyzed by the chiral quaternary ammonium salt **12a** proceeds with excellent enantioselectivity (Equation (21)), allowing efficient synthesis of several important amino acid derivatives. Catalysts **12** are believed to form ion pairs with the enolate derived from **11**.



Following on from the results mentioned in Section 1.07.3.2.2.(i) using 1,3-dicarbonyl nucleophiles, Shibasaki and co-workers <2001OL4251, 2003JA2582> have extended their linked-BINOL ligand system to the use of α -hydroxyketones **13** as nucleophiles (Equation (22)). In general, best results are obtained with a 4:1 ratio of Et_2Zn to ligand **14**, with the presence of activated molecular sieves also being important to ensure catalyst turnover. For β -unsubstituted enones, ligand loadings as low as 0.01 mol.% can be employed, but more hindered enones require up to 10 mol.%. Kinetic resolution in the addition of racemic **13b** to methyl vinyl ketone was shown to be possible, leading to the formation of a quaternary center.

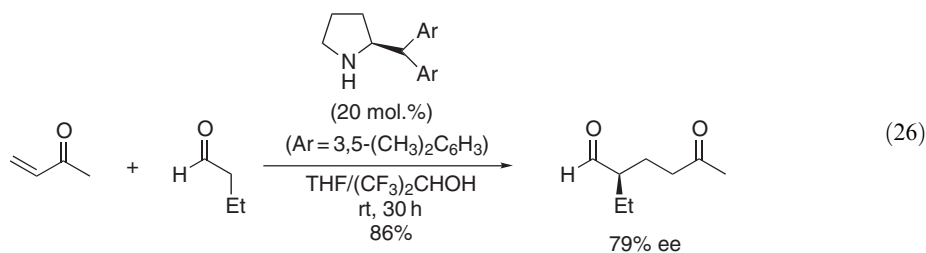
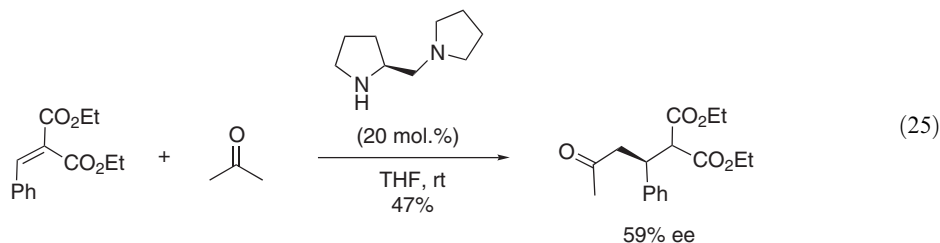
(S,S)-linked BINOL
14

Alexakis and co-workers [<2003OL2559>](#) have demonstrated that hydroxyacetone may be added to aromatic nitroalkenes in the presence of a chiral amine catalyst **15** (Equation (23)). The reaction is unsuccessful for nonaromatic nitroalkenes. The opposite enantiomer of amine catalyst has also been used for the addition of simple aldehydes and ketones to nitrostyrene [<2002OL3611>](#), with moderate enantioselectivities and general preference for the *syn*-product. Asymmetric addition of aldehydes [<2001OL3737>](#) and ketones [<2001JA5260, 2001OL2423, 2001TL4441, 2002SL26>](#) to nitroalkenes [<2002EJO1877>](#) under amine catalysis has also been reported by several other groups; enantioselectivities are observed to be generally moderate to good. The use of readily available proline as a catalyst [<2001JA5260, 2001OL2423, 2002SL26>](#) is particularly attractive; Enders reports best results using small amounts of MeOH as solvent to solubilize the proline (Equation (24)).



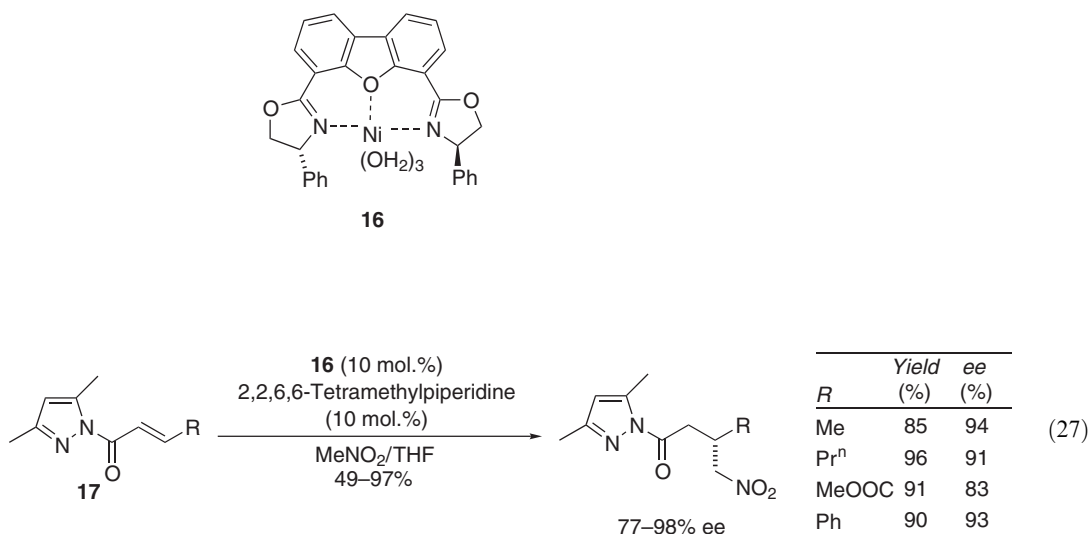
Asymmetric addition of simple aldehydes and ketones to α,β -unsaturated carbonyl compounds has received less attention. Zhang and Corey [<2000OL1097>](#) have described an example of using catalyst **12b** for the addition of acetophenone to an aromatic enone. Barbas has reported

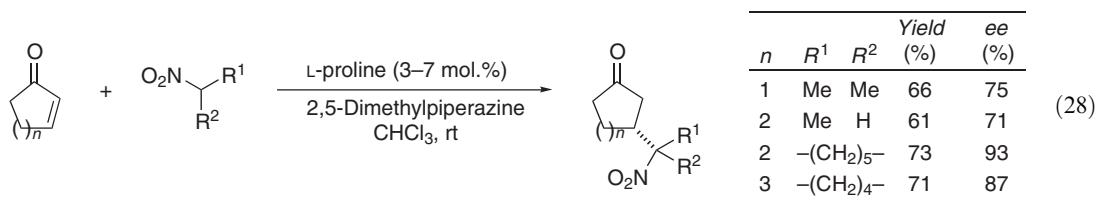
amine-catalyzed addition of acetone, cyclopentanone, and cyclohexanone to alkylidene malonates (Equation (25)), albeit in moderate yields and enantioselectivities <2001TL4441>. Jorgensen <2003JOC4151> has screened several chiral amines as catalysts for the addition of aldehydes to vinyl ketones (Equation (26)). Again, yields and selectivities are currently moderate to good and so further progress in this area is awaited.



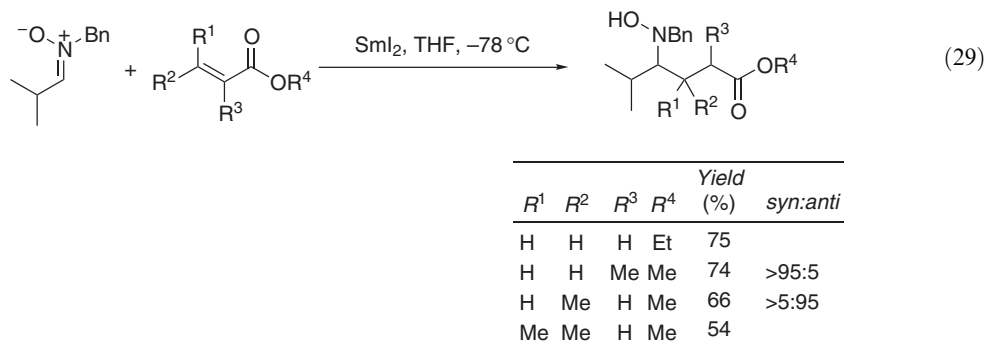
(iii) Addition of nitro compounds and other α -aminocarbanion equivalents

Asymmetric addition of nitromethane to chalcones can be catalyzed by the Shibasaki and co-workers heterobimetallic complexes <1998TL7557> or by the Corey and Zhang cinchoninium salt **12c** <2000OL4257>, amongst other methods <1997TL7259>. Itoh and Kanemasa <2002JA13394> have proposed the term “catalytic double activation method” to describe the simultaneous use of catalytic amounts of a chiral nickel complex **16** to activate the Michael acceptor **17** and an amine base to activate nitromethane (Equation (27)). For addition of nitromethane to cyclic enones, Hanessian and Pham <2000OL2975> have exploited L-proline as a catalyst in the presence of 2,5-dimethylpiperazine as an additive (Equation (28)). Jorgensen and co-workers <2002JOC8331> have investigated the addition of nitromethane to acyclic enones, promoted by the chiral imidazolines such as **10** (Section 1.07.3.2.2.(i)).

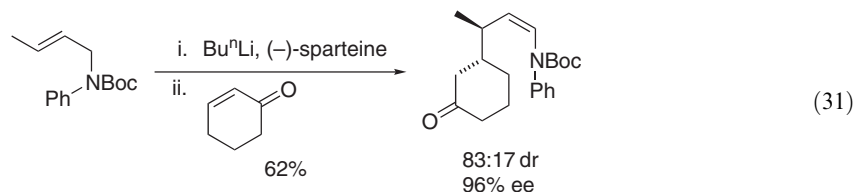
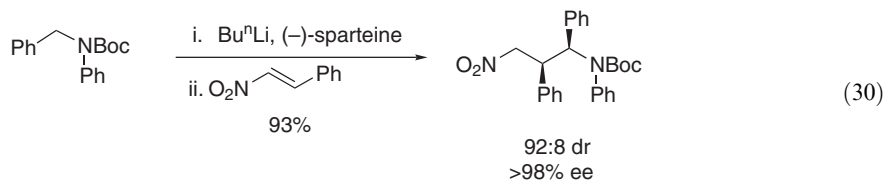




An interesting reductive conjugate addition of nitrones to α,β -unsaturated esters was reported recently <2003AG(E)2265>, which formally effects umpolung of the C=N bond (Equation (29)). The reaction can be rendered diastereoselective by placing chiral substituents on nitrogen <2003AG(E)2265>.



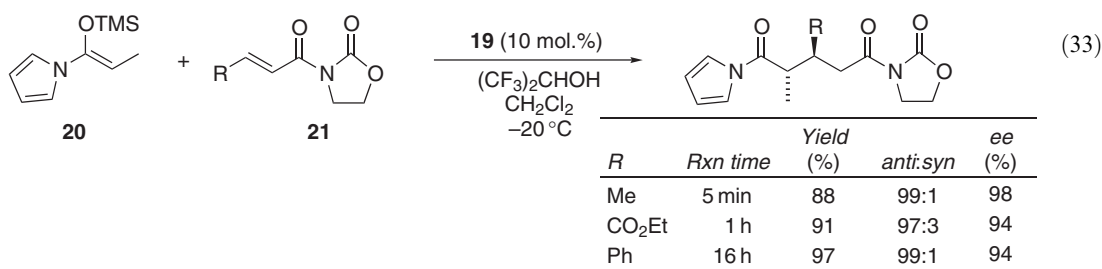
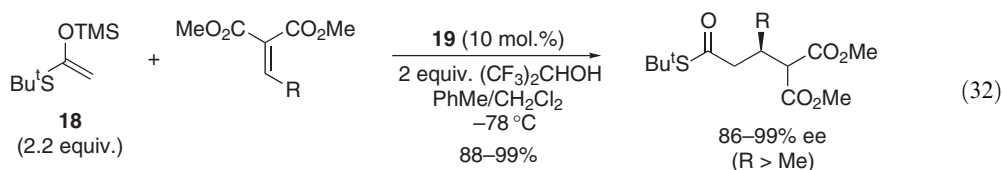
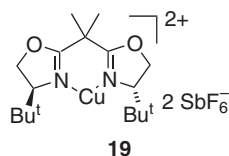
Beak and co-workers <1999JOC2996, 2001OL711, 2002JA11689> have reported that configurationally stable amido-substituted benzylic and allylic organolithiums will undergo asymmetric conjugate addition to nitroalkenes and to unsaturated carbonyl compounds (Equations (30) and (31)).



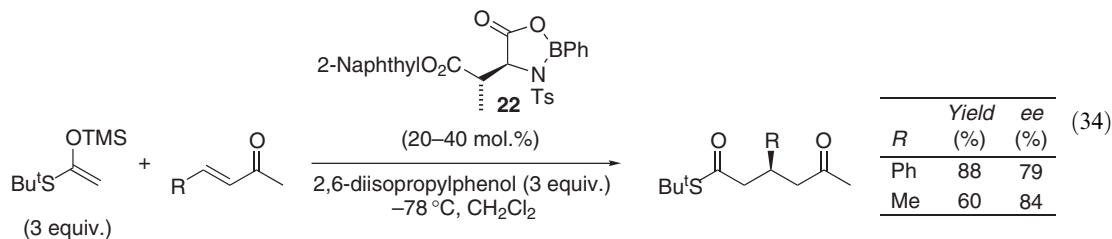
(iv) Addition of silyl enol ethers and silylketene acetals: Mukaiyama–Michael reaction

As outlined in Section 1.07.3.2.2.(ii), direct enantioselective addition of simple aldehydes and ketones requires further exploration if uniformly high enantioselectivities are to be achieved. An alternative approach, known as the Mukaiyama–Michael reaction, involves the use of silyl enol ethers or silylketene acetals as nucleophiles. Early results included high selectivity (90% ee) in the addition of a thioester-derived silylketene acetal to cyclopentenone, catalyzed by a BINOL-derived titanium oxide <1994CL97>, and further studies on the use of chiral titanium complexes in the conjugate addition of silylketene acetals to 2-carboxycyclopentenones <1997T13009>. Good results have been obtained by using substrates capable of bidentate coordination with Cu(II) bisoxazoline catalysts <1996TL8921, 1997T17015, 1999JA1994, 1999OL865, 2001JA4480>. Evans showed that the addition of the thioester-derived silylketene acetal **18** to alkylidene malonates could be rendered catalytic in Cu(II) bisoxazoline complex **19** by addition of 2 equiv. of hexafluoro-2-propanol <1999JA1994>. This additive promotes turnover but also

hydrolysis of **18**, a side reaction that could be minimized by using a toluene/CH₂Cl₂ solvent mixture. Excellent yields and enantioselectivities were obtained for alkylidene malonates bearing substituents larger than methyl (Equation (32)). Evans and co-workers [<1999OL865, 2001JA4480>](#) have also studied the addition of silylketene acetals and enol silanes to oxazolidinone-bearing substrates such as **21** (Equation (33)), again mediated by Cu-complex **19**, in some detail. In general, (*E*)-enol silanes afford *anti*-products, whereas (*Z*)-enol silanes are *syn*-selective. Pyrrole enol silanes such as **20** are particularly reactive. Mechanistic studies suggest that the reaction proceeds via [4+2]-cycloaddition followed by hydrolysis of the resulting dihydropyran intermediate.

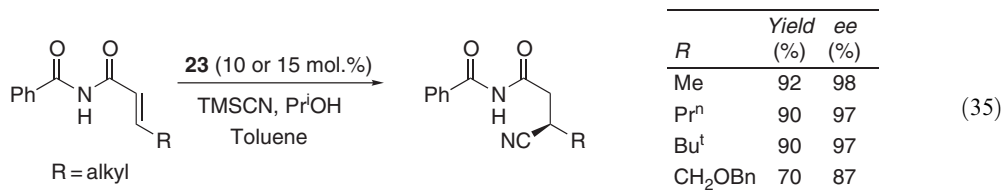
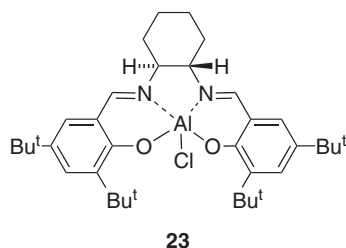


Asymmetric addition of silylketene acetals to simple acyclic enones is promoted by the *allo*-threonine-derived *B*-aryloxazaborolidine **22** in good ee [<2001OL2101>](#) (Equation (34)). The additive 2,6-diisopropylphenol is essential to retard competing racemic reaction pathways promoted by electrophilic silicon species.



(v) Addition of cyanide

Sammis and Jacobsen [<2003JA4442>](#) have described the first catalytic asymmetric conjugate addition of cyanide to α,β -unsaturated imides, catalyzed by the aluminum–salen complex **23** (Equation (35)). The reaction gives excellent enantioselectivities for a range of β -alkyl-substituted imides. The method used to generate the cyanide source proved to be important: no reaction was observed with HCN alone, whereas *in situ* reaction of TMSCN and *i*-PrOH led to good reactivity.



1.07.3.2.3 Addition of unstabilized nucleophiles: alkyl, alkenyl, alkynyl, and aryl anion equivalents

(i) Alkyl addition

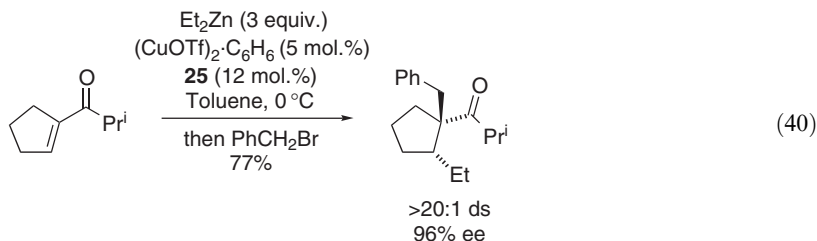
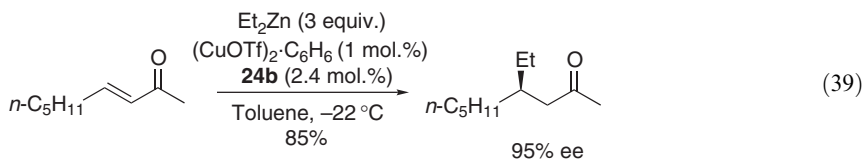
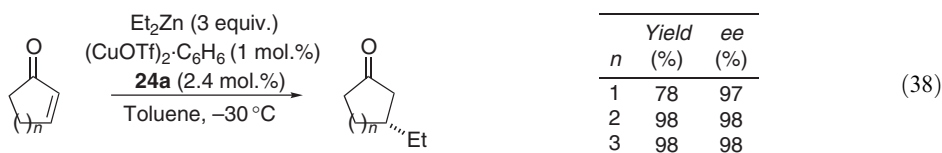
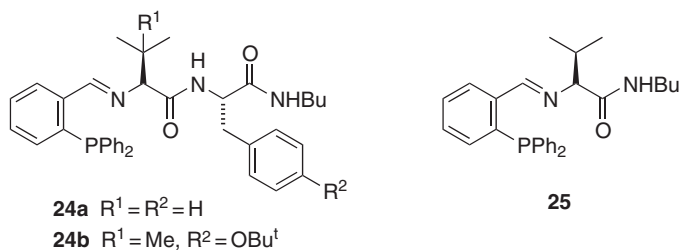
Organocopper-based reagents are the classic choice for C—C bond formation by conjugate addition to electron-poor alkenes, particularly α,β -unsaturated ketones and esters. Several comprehensive reviews have appeared [\[1972OR\(19\)1, 1991COS\(4\)169, 1992OR\(41\)135, 1997AG\(E\)186, 2000AG\(E\)3751, 2000CSR393, B-2002MI002\]](#), including a collection of practical procedures [\[B-1994MI001\]](#). Understanding of the reagents' structural features and the mechanisms of the conjugate addition reaction has progressed considerably in recent years, and the reader is referred to two excellent recent reviews [\[2000AG\(E\)3751, 2000CSR393\]](#). Several different types of organocopper reagents have been employed, differing in the stoichiometry and ratios of copper to lithium; the presence of alkali metal salts and the nature of the solvent can also influence the reactive species. Mono-organocopper species, RCu , prepared according to [Equation \(36\)](#), are less widely used than organocuprates because they are generally less stable and less reactive. Lower-order organocuprates, R_2CuLi , are usually prepared *in situ* by the reaction between 2 equiv. of RLi and copper(I) iodide in ether ([Equation \(37\)](#)). There are many examples of their use in conjugate addition, delivering alkyl, alkenyl, or aryl groups. It is not generally possible to transfer alkynyl groups (see [Section 1.07.3.2.3.\(iii\)](#)).



During conjugate addition of lower-order organocuprates, R_2CuLi , only one of the two R groups is transferred, with the other being lost as RH on work-up. While this is not a problem where simple, commercially available RLi precursors are involved, the process is clearly unsatisfactory for more valuable organolithiums. Much effort has therefore been expended in developing mixed cuprates, $\text{R}_\text{T}\text{R}_\text{D}\text{CuLi}$, where R_T is the transferable ligand and R_D is a nontransferable, “dummy” ligand. Alkynes have been used for this purpose [\[1974JOC400\]](#), as have neopentyl and neophyl ($-\text{CH}_2\text{C}(\text{Me})_2\text{Ph}$) groups [\[1999S312\]](#) as well as cyanocuprates, prepared from 1 equiv. of $\text{R}_\text{T}\text{Li}$ and CuCN . However, the latter species are relatively unreactive and so have not seen widespread use. More effective are the “higher-order cyanocuprate” reagents formed by the addition of 2 equiv. of organolithium to CuCN , in which the 2-thienyl group may be employed as a “dummy” ligand [\[1987S325, 1990SL119, B-1994MI283\]](#). Lipshutz formulated these as $\text{R}_2\text{Cu}(\text{CN})\text{Li}_2$, but the details of their structure have been the subject of considerable debate. Current evidence [\[2000AG\(E\)3751, 2000CSR393\]](#) suggests that the tricoordinated species $[\text{R}_2\text{Cu}(\text{CN})]^{2-}$ is not a stable structure in ethereal solution. Notwithstanding the structural and mechanistic intricacies, the Lipshutz mix can prove more effective than conventional organocuprates.

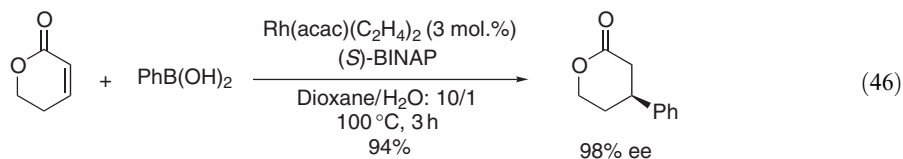
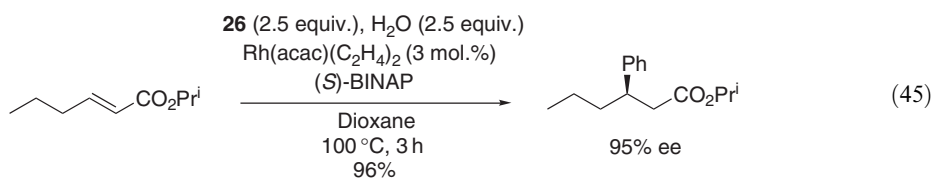
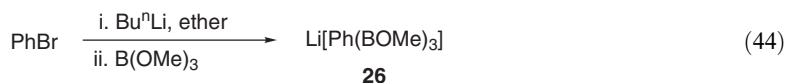
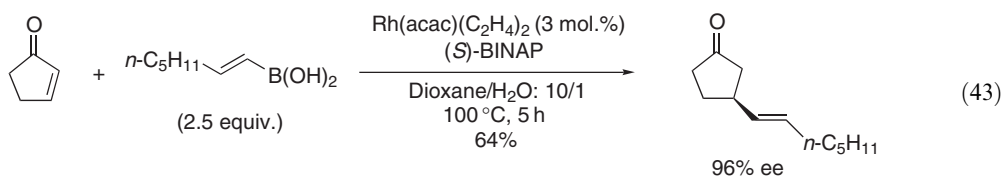
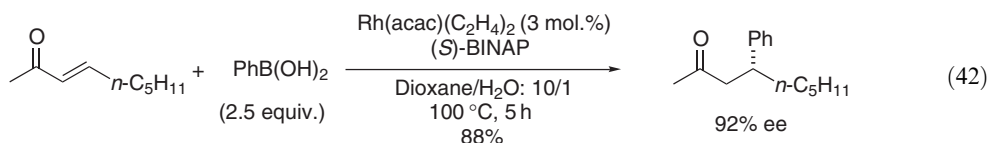
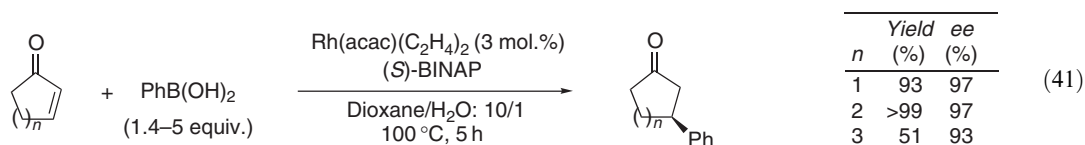
Another approach that can greatly increase organocuprate reactivity as well as improving 1,4- versus 1,2-selectivity is the addition of Lewis acids <1986AG(E)947, 1991COS(4)139> such as boron trifluoride etherate <1982JOC119>. Trimethylsilyl chloride (in THF) is another additive that has proved extremely effective at increasing the rate of conjugate addition processes. For example, lower-order organocuprates by themselves undergo little addition to α,β -unsaturated amides, but this transformation is clearly achieved in high yield in the presence of trimethylsilyl chloride <1986TL1047>. Use of trimethylsilyl chloride together with HMPA has also been recommended, particularly for additions to α,β -unsaturated aldehydes <1986TL4029>. The mechanistic role of the silyl chloride has been the subject of some debate <2000AG(E)3751, 2000CSR393>.

The demand for a catalytic asymmetric method for conjugate addition of alkyl groups has driven attention away from chiral analogs of standard organocuprate reagents to the use of organozinc reagents, catalyzed by salts of Ni, Co, or, most commonly, Cu. An advantage here is the ability to employ functionalized organozinc reagents. Numerous chiral phosphorus-containing ligands have been investigated, progress in the area up to mid-2002 being summarized in some excellent reviews <2000T8033, 2001S171, 2002EJO3221>. Some of the most impressive and general recent results have come from Hoveyda's group, who have developed novel peptide-based phosphine ligands that have widened the scope of the addition process. High enantioselectivities are obtained for cyclic enones (Equation (38)) <2001JA755>, with cyclopentenones being notably successful substrates, since these are problematic for most ligand systems due partly to facile self-aldol reaction of the product enolate. Equation (39) exemplifies the excellent enantioselectivities that may be obtained even for acyclic enones using the modified ligand **24b** <2002JA779>. Trisubstituted cyclic enones (five- or seven-membered rings) also give good results: here, the simpler and readily prepared ligand **25** is optimum <2002JA13362>. The example in Equation (40) demonstrates the powerful possibility of trapping the intermediate zinc enolate with electrophiles. The chemistry has also been applied to unsaturated *N*-acyloxazolidinones <2003AG(E)1276> and cyclic nitroalkenes <2002JA8192>; highly enantioselective addition to acyclic nitroalkenes using chiral phosphoramidite ligands has been reported <2003JA3700>.

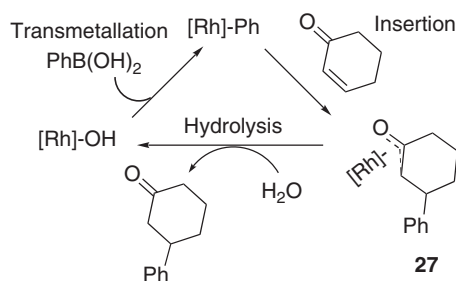


(ii) Aryl and alkenyl addition

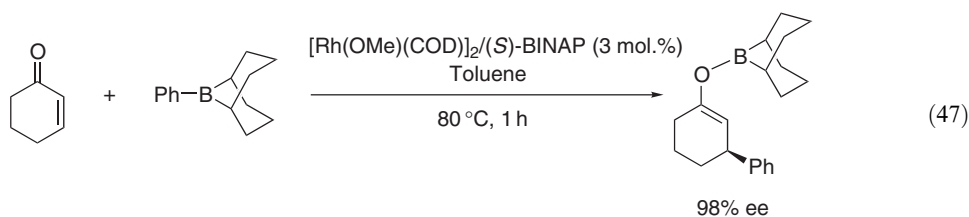
Complementary to the Cu-catalyzed asymmetric addition of dialkylzincs mentioned above, an outstanding process for catalytic asymmetric conjugate addition of aryl and alkenyl groups is the Rh-catalyzed addition of organoboronic acids to electron-deficient alkenes <1997OM4229, 1998JA5579>, which has been reviewed in detail <2001SL879, 2003CRV169, 2003CRV2829>. The reaction affords excellent enantioselectivities for addition of a variety of alkenyl- and arylboronic acids to both cyclic and acyclic α,β -unsaturated ketones (Equations (41)–(43)); an excess of boronic acid is used in some cases due to competing hydrolytic deboronation. Replacing the boronic acids with lithium trimethyl arylborates (e.g., **26**), generated *in situ* by reaction of aryl bromides with butyllithium and trimethoxyborane (Equation (44)), can give improved results for conjugate addition to enones if an equimolar amount of water is present, which presumably displaces one of the methoxy groups on boron. These are the reagents of choice for less reactive substrates such as acyclic enoates (Equation (45)), although cyclic enoates work well with arylboronic acids (Equation (46)). α,β -Unsaturated amides are also less reactive than enones, and the addition of a base (e.g., K_2CO_3) can improve the yields of addition of arylboronic acid <2001JOC8944>. Addition to α,β -unsaturated phosphonates <1999JA11591> and cyclic nitroalkenes <2000JA10716> has also been reported, the latter being noteworthy since substitution α to the electron-withdrawing group is present, usually not possible with this reaction system.



The essential details of the catalytic cycle for the Rh-catalyzed reaction of phenylboronic acid with cyclohexenone [<2002JA5052>](#) are shown in [Scheme 3](#). The use of water as co-solvent in the reactions described so far precludes the trapping of the intermediate oxo- π -allylrhodium **27** with alternative electrophiles. Hayashi and co-workers [<2002JA10984, 2003JOC1901>](#) have developed aprotic conditions that allow this to be achieved ([Equation \(47\)](#)). Trapping by intramolecular aldol reaction can occur even in the presence of water [<2003JA1110>](#).

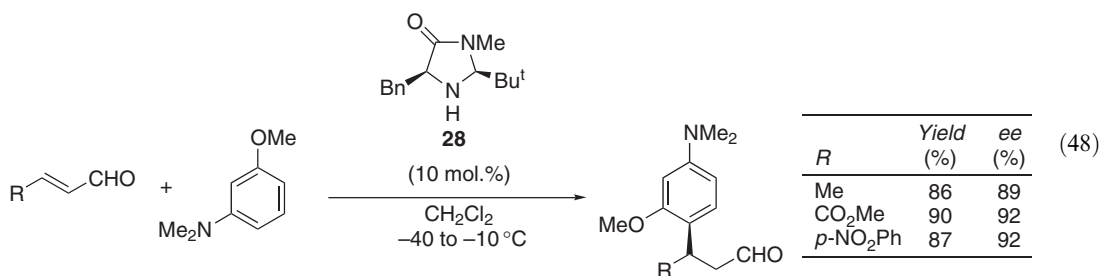


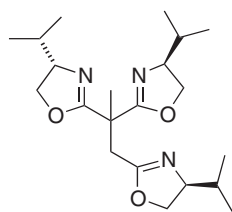
Scheme 3



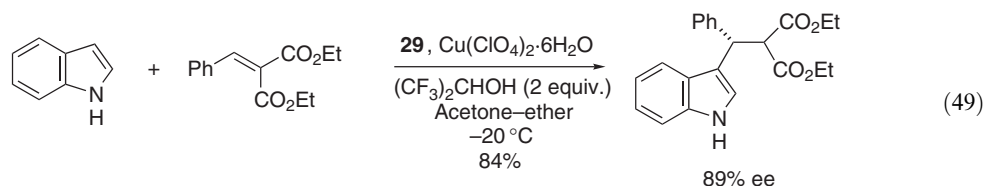
Aryl and vinyl organosiloxanes have also been added asymmetrically to enones under Rh(I)-catalysis [<2003OL97>](#).

Friedel–Crafts-type reactions offer another important approach for the addition of aryl and heteroaryl groups. Paras and MacMillan [<2002JA7894>](#) have extended their organocatalysis work to the 1,4-addition of electron-rich benzenes to α,β -unsaturated aldehydes, promoted by the chiral amine **28**, which forms a reactive iminium ion with the aldehyde. The reaction works well with a wide range of anilines and for a wide range of substituents β to the aldehyde ([Equation \(48\)](#)). Chiral Cu(II)-bisoxazoline complexes catalyze the asymmetric addition of indoles to β,γ -unsaturated α -keto esters [<2001AG\(E\)160, 2003S1117>](#) and to alkylidene malonates [<2001CC347>](#). Higher enantioselectivities have been observed using a trisoxazoline ligand **29** in the presence of hexafluoroisopropanol as an additive ([Equation \(49\)](#)) [<2002JA9030>](#). Asymmetric addition of indoles to α,β -unsaturated acylphosphonates is catalyzed by bis(oxazolinyl)pyridine–scandium(III) triflate complexes [<2003JA10780>](#).



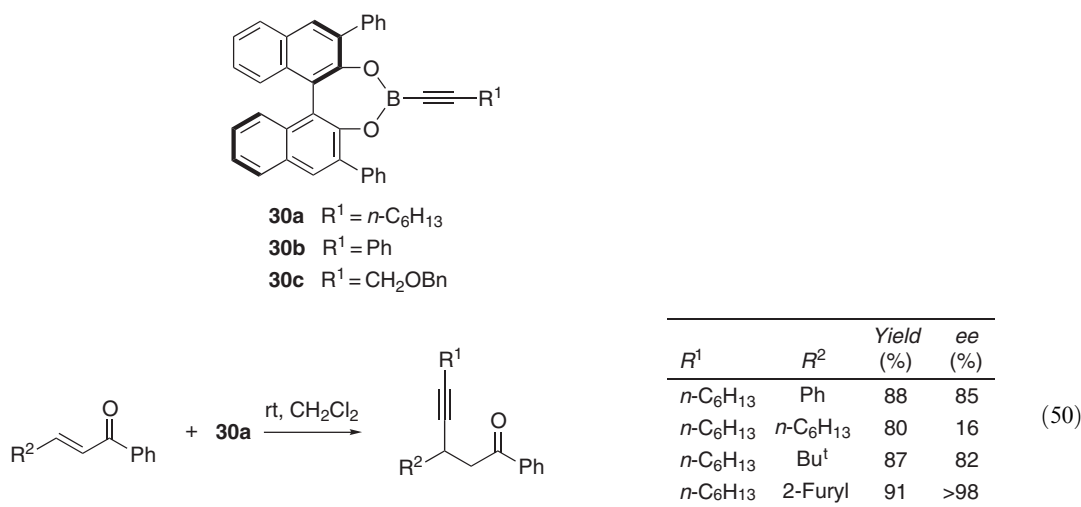


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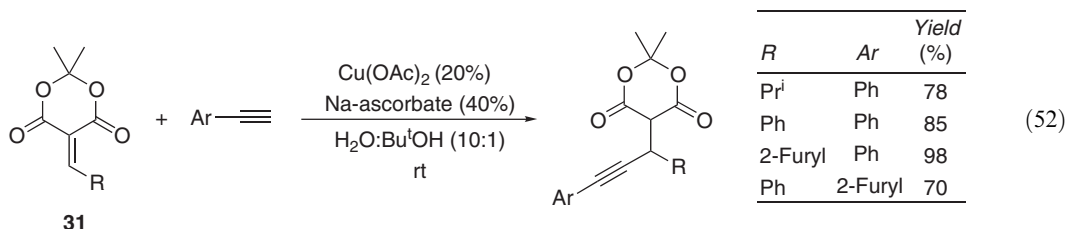
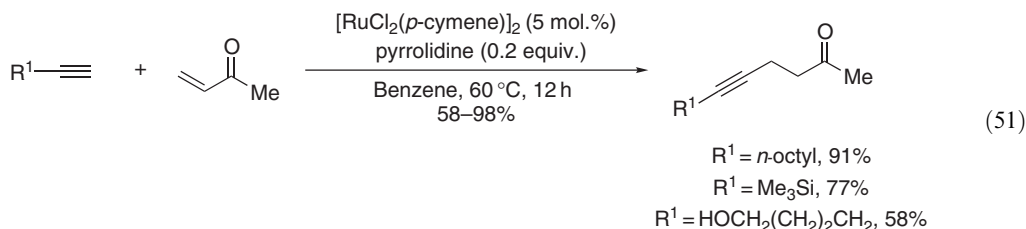
(iii) Alkynyl addition

As mentioned in [Section 1.07.3.2.3\(i\)](#), alkynyl groups are not readily delivered from copper for conjugate addition, explaining the choice of this substituent as a nontransferable, “dummy” group in mixed cuprate reagents. However, conjugate addition of alkynylcoppers has been observed in the presence of trimethylsilyl iodide [<1993JOC7238, 1997JOC182>](#) or TBSOTf [<1995MI783>](#). Other metal alkynylides that have been shown to react with unsaturated carbonyl compounds include those of aluminum [<1971JA7320>](#), which requires the enone to be able to adopt the *s-cis* conformation, precluding the use of cycloalkenones. Addition of alkynylzincs in the presence of TBSOTf [<1990TL7627>](#) appears more general. Alkynylboron reagents have also been employed; again they are limited to enones which can adopt an *s-cis* conformation, but an asymmetric variant has been developed ([Equation \(50\)](#)) [<2000JA1822>](#). Good enantioselectivities were obtained for β -aryl-substituted enones, particularly with electron-rich aryl substituents, or with a bulky β -alkyl group.



An efficient Ru-catalyzed 1,4-addition of terminal alkynes to conjugated enones has been reported ([Equation \(51\)](#)) [<2001OL2089>](#); the reaction is limited to unsubstituted vinyl ketones, but a wide range of functionality is tolerated in the alkyne, including a free hydroxyl. Another interesting conjugate addition, which does not require prior formation of an acetylide anion, is catalytic in copper, and is performed under aqueous conditions, has been described by Knopfel

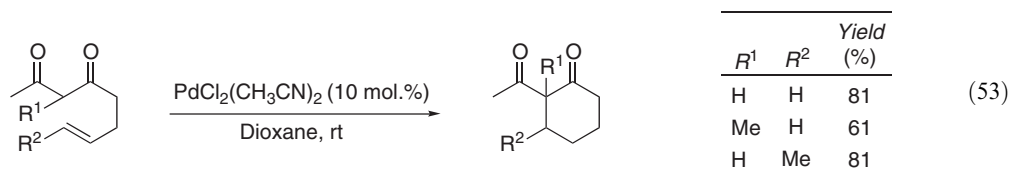
and Carreira (Equation (52)) <2003JA6054>. The chemistry involves addition of aryl- and heteroaryl-substituted terminal alkynes to acceptors **31**, which are readily obtained by condensation of Meldrum's acid with aldehydes. The presence of ascorbate as reductant was postulated to effect *in situ* conversion of Cu(II) to Cu(I), as well as preventing oxidative coupling of the alkyne, although preliminary mechanistic studies suggested that it may play a wider role. The addition products can be readily decarboxylated to afford β -alkynyl acids.



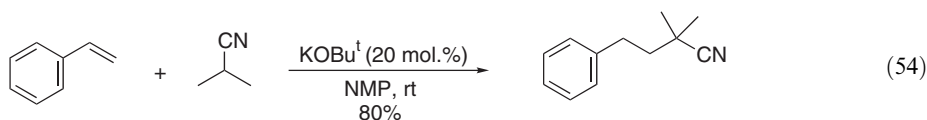
1.07.3.3 Addition to Unactivated Alkenes

1.07.3.3.1 Addition of stabilized nucleophiles

In 1980, Hegedus and co-workers <1980JA4973, 1980JA4980> showed that terminal or disubstituted internal alkenes can be alkylated with stabilized nucleophiles ($pK_a \approx 10\text{--}17$) mediated by stoichiometric palladium(II) chloride. Pei and Widenhoefer <2001JA11290> have discovered that the intramolecular variant can be run using substoichiometric Pd(II) (Equation (53)). The reaction proceeds with *endo*-regioselectivity, leading to a synthesis of cyclohexanones from unsaturated 1,3-diones. Substitution α to the carbonyls or at the alkene terminus is tolerated.

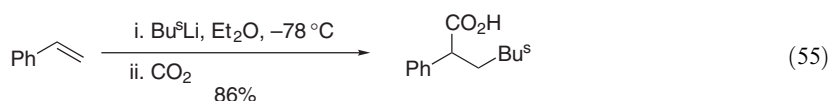


A catalytic amount of potassium *t*-butoxide in NMP or DMSO mediates the addition of ketones, imines, and nitriles to styrenes (Equation (54)) <2000OL3285>. Addition of zinc hydrazones to simple alkenes has been reported <1997AG(E)2491>.



1.07.3.3.2 Addition of unstabilized nucleophiles

Addition of organometallic reagents to unactivated alkenes to form a new C—C bond and a new organometal is known as carbametalation: the process <1991COS(4)865> and asymmetric versions have been reviewed <1999JCS(P1)535, B-1999MI431>. The reaction also constitutes a useful method for the synthesis of carbanions, so Chapter 1.19 should also be consulted. Oligomerization by reaction of the organometal adduct with starting alkene must be avoided. Performing intramolecular cyclizations, which are entropically favored, is a common tactic: in particular, 5-exo cyclizations of organolithiums have been widely employed for the preparation of carbocycles and pyrrolidines <2002CEJ195, B-2002MI003>. Using substrates with neighboring heteroatoms capable of stabilizing the carbanion <2001T5899> is also a widely used strategy. Direct intermolecular addition of organolithium reagents to styrenes <2000JCS(P1)1109> is possible if ether is used as solvent; the resulting benzylic anion can be trapped with electrophiles (Equation (55)), and the reaction can be rendered asymmetric by the addition of sparteine <1997TA665>. Organolithium additions to cinnamyl derivatives <1999CEJ2055, 2000TL6575>, including asymmetric induction <1997TL7523, 1999CEJ2055>, have also been accomplished.



Regioselective zirconium-catalyzed addition of Grignard reagents to terminal alkenes <1985JOM(285)43, 1993JA6614> can be rendered diastereo- <1991JA5079, 1993JOC4237> and enantioselective <1993JA6997, 1995JA7097> but is generally limited to the use of EtMgBr. Zirconium salts also catalyze the addition of organoaluminums to unactivated alkenes <2002PAC151>, and an iron-catalyzed addition of Grignard reagents or organozincs to strained alkenes has appeared <2000JA978>.

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Biographical sketch

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1.08

One or More CC Bond(s) Formed by Addition: Addition of Carbon Radicals and Electrocyclic Additions to CC Multiple Bonds

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1.08.1 ADDITION OF CARBON RADICALS TO CARBON—CARBON MULTIPLE BONDS TO GIVE TETRACOORDINATE PRODUCTS

1.08.1.1 Introduction

Creation of carbon—carbon bonds is crucial to construct organic molecules. In this area, the chemistry of carbon-centered radicals has become an essential component for their capacity to add to carbon—carbon multiple bonds and create carbon—carbon bonds. This review is a complement to the original edition of this book <1995COFGT(1)319> covering the field of addition reactions of carbon-centered radicals to carbon—carbon multiple bonds from 1995 to 2003 and will focus on the reactivity, chemoselectivity, regioselectivity, and stereoselectivity of carbon radical reactions. Reviews cited in COFGT (1995) are still relevant today. Nevertheless readers are also directed to recent books, which cover the important concepts and principles <B-2001MI011, B-2000MI010, B-1999MI009>. Numerous reviews have been published covering all domains in radical chemistry. Among them, particular attention has been devoted to intramolecular cyclizations <1996CRV339, 2001T7237, 1998ACA50, 2002H2413, 2002JCS(P1)2747>. Radical cascade and annulation processes which have known remarkable developments in the construction of more and more complex frameworks have been reviewed <2001AG(E)2224, 2001JCS(P1)3215, 2003S803>. New trends have emerged and gained in popularity. The development of tin substitutes <2002JCS(P2)367, 2002S835, 1998AG(E)3072>, the emergence of new concepts such as the translocation reaction <2001CSR94>, or even the use of polarity reversal catalysis <1999CSR25> show great promise. First examples of radical reactions in aqueous media have also been developed <2002SL674>. Reviews of transition metal-mediated radical reactions have been published <1996CRV307, 2002JOM159>. The use of carbon-centered radical additions for the stereoselective formation of C—C bonds is also under intense investigation <1998AG(E)2563, 2003CSR251>. First successes in enantioselective catalysis are particularly remarkable <1999ACR163, 2003CRV3263>.

This chapter is organized according to the classification of the reaction (e.g., intermolecular, intramolecular, or tandem radical additions) and the type of the method by which it is conducted.

1.08.1.2 Basic Principles

1.08.1.2.1 Synthetic advantages of carbon-centered radical reactions

To avoid repetition of the basic principles readers are referred to COFGT (1995). Carbon-centered radicals are generally prepared under neutral conditions which avoids side reactions associated with ionic conditions. Moreover, they can be used with diverse functionalities unreactive toward them, thus limiting the number of steps in syntheses. In addition, another difference with ionic reactions is that β -eliminations are not so favorable and are limited to Br, SR, and SnR_3 , which can be a limiting factor or an advantage <1995COFGT(1)319>.

1.08.1.2.2 Stability and structure of alkyl and vinyl radicals

As these data are well established, the readers should refer to COFGT (1995) <1995COFGT(1)>.

1.08.1.3 Intermolecular Radical Additions

1.08.1.3.1 Introduction

The addition of carbon-centered radicals to alkenes leads to the formation of a new carbon—carbon σ bond at the expense of a carbon—carbon π -double bond. Theoretical and experimental studies concerning quantification of factors controlling addition reactions to alkenes have been published recently <2001AG(E)1340>. Factors determining the activation energy for reagents in radical additions have also been studied empirically and by calculation <2000RCR153>. The angle of attack of a radical onto an alkene is well defined as being a tetrahedral angle (109°) with the double bond <1995COFGT(1)319>.

1.08.1.3.2 Electronic nature of radicals

Carbon-centered radicals can be classified into three types: nucleophilic radicals such as simple alkyl radicals that react preferentially with electron-poor alkenes, electrophilic radicals attached to two electron-withdrawing groups (e.g., esters or nitriles) that react preferentially with electron-rich alkenes, and ambiphilic radicals which have intermediate energies and can react with all types of alkenes. These considerations are well documented in COFGT (1995) and will not be developed in this chapter.

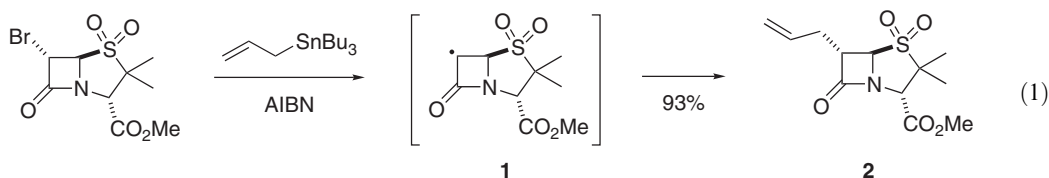
1.08.1.3.3 Stereoselectivity

(i) Introduction

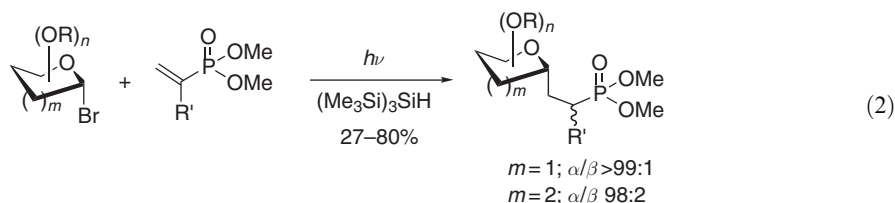
Carbon-centered radicals have long been considered as highly reactive short-lived species poorly suited for stereoselective transformations. In recent years, however, new methods have emerged that allow radical reactions to be conducted under milder conditions (see Section 1.08.1.3.4). This has led to a better understanding of the determining factors for selectivity and, consequently, has spurred renewed activity in the development of stereoselective radical transformations. Today, the radical reactions can be highly diastereo- and enantioselective in the formation of carbon—carbon bonds. Remarkably, the first examples of enantioselective conjugate additions of radical intermediates was only reported in the mid-1990s. Since then, high levels of ee have been achieved. The strategies used to induce stereoselectivity in radical reactions are essentially based on well-established precedents learned from the ionic and pericyclic processes. Compared with the other methods the radical reactions allow the formation of stereogenic quaternary centers with high levels of selectivity and, being conducted under neutral conditions, they avoid acid- or base-induced epimerization or decomposition of sensitive molecules. They are also compatible with many functional groups. For an exhaustive and comprehensive illustration of stereoselective radical processes the reader is referred to the following reviews <B-1996MI005, 1998AG(E)2563, 1999ACR163, 2000T8033, B-2001MI011, 2003CEJ28, 2003CRV3263, 2003CSR251>. Studies involving proton, deuterium, or halogen abstraction by chiral radicals will not come under the remit of this chapter.

(ii) Cyclic radical additions

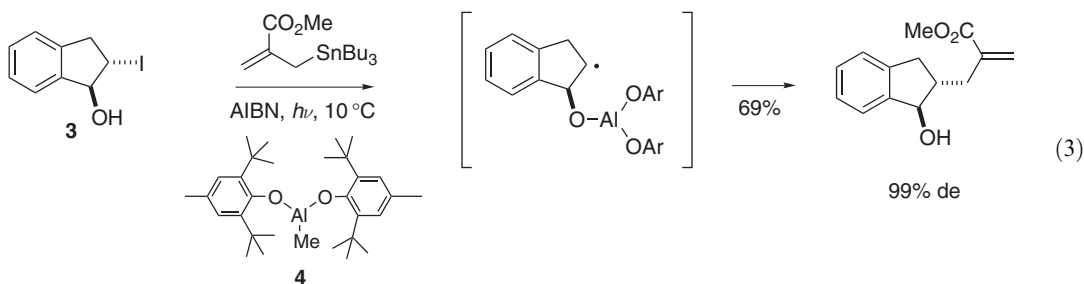
Substituent effects on the stereoselectivities of additions of alkenes to cyclic carbon radicals have been investigated <B-2001MI011>. Steric effects can generally explain the stereoselectivities observed <1992JA4067>. It has been established that β -substituents direct *anti*-addition. For instance, Equation (1) shows the preferential addition of allylstannane to the less hindered face (the face opposite to the sulfone group) of four-membered radical **1** to give the corresponding allylated compounds **2** <1989T941>.



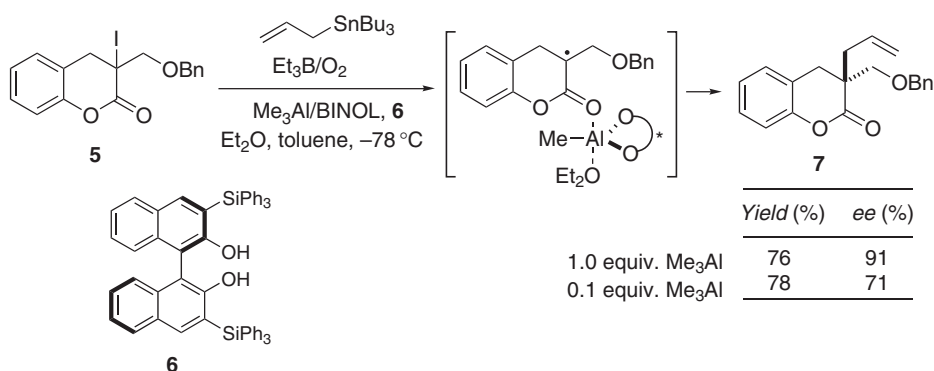
Electronic interactions have been found to influence the stereochemical outcome of reactions involving glycosyl radicals [<1989AG\(E\)969>](#). The stereoselective addition of radicals at the anomeric position of carbohydrates to alkenes proceeds generally with a marked preference for axial pseudoanomeric bond formation [<1999TL7063>](#) (Equation (2)).



The use of additives to enhance diastereoselectivity has also been reported [<1998AG\(E\)2563>](#). For example, alcohol **3** was treated with methyl aluminum bis(di-2,6-*t*-butyl-4-methylphenoxide) (MAD) **4** prior to radical reaction. The bulkiness of the resulting aluminum alkoxide derivative allowed a remarkable steric differentiation of the two faces [<1995HCA1001>](#) (Equation (3)).



Induction of enantioselectivity through chiral Lewis acid complexation has been recently achieved [<2003CRV3263>](#). For instance, allylation of iodolactone **5** using the system Me_3Al /BINOL **6** afforded the corresponding product **7** in up to 91% ee [<1997JA11713>](#). The reaction also proceeds catalytically, albeit with a small decrease in asymmetric induction (Scheme 1).

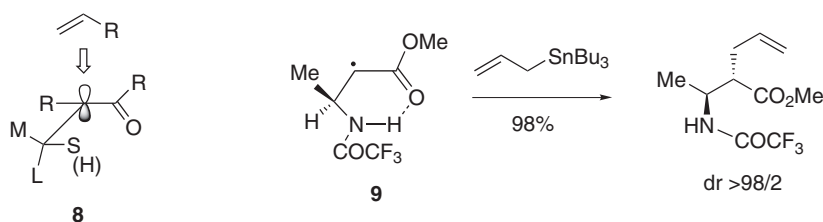


Scheme 1

(iii) Acyclic radical additions

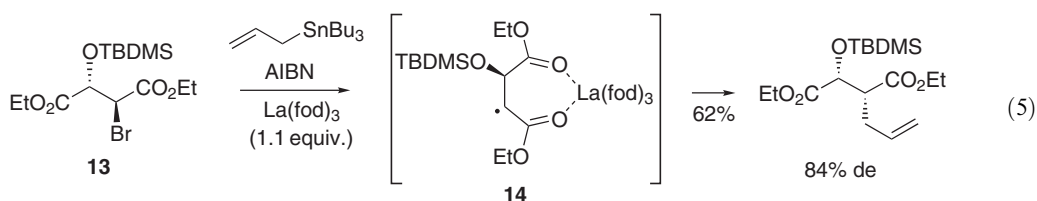
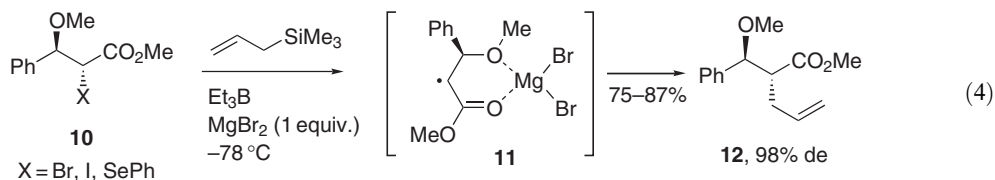
Stereoselectivity based upon conformational control and steric hindrance is more difficult to achieve in acyclic radical additions to alkenes due to free rotation around the carbon–carbon bond.

Particular attention has been given to 1,2-asymmetric induction in reactions of alkenes with carbonyl-substituted radicals possessing a center of chirality in the β -position. Radicals α to a carbonyl group **8** are considered as planar, delocalized in a manner similar to an enolate anion and the observed stereoselectivities can generally be rationalized using the concept of 1,3-allylic strain (Scheme 2) <1999CRV1191>. In this planar radical model, the C—H bond at the chiral center is pointing in the direction of the carbonyl function and attack of the radical is preferred from the face opposite to the large group (L). Addition reactions of alkenes to ester enolate radicals have been particularly well studied and minimization of allylic strain ($A^{1,3}$ and $A^{1,2}$) as well as torsional strain have been found of importance in these reactions. Further studies have shown that electronic effects may also dominate for ester enolate radicals bearing β -alkoxy substituents or other resident groups <1991SL425, 1992JOC4457, 1993T4841, 1998SL213, B-2001MI011>. Intramolecular hydrogen bonding has also been used as a stereocontrolling element in allylation reactions of related systems in nonpolar solvents <1996JA2507, 1996TL6335>. For instance, it was suggested that radical **9** adopts a pseudo-six-membered ring conformation due to hydrogen bonding and the attack of allyltributyltin occurs selectively from the face opposite to the methyl group. The same model was exploited to achieve high stereoselectivity in 1,3-, 1,4-, and 1,5-asymmetric induction <1996JA2507>.

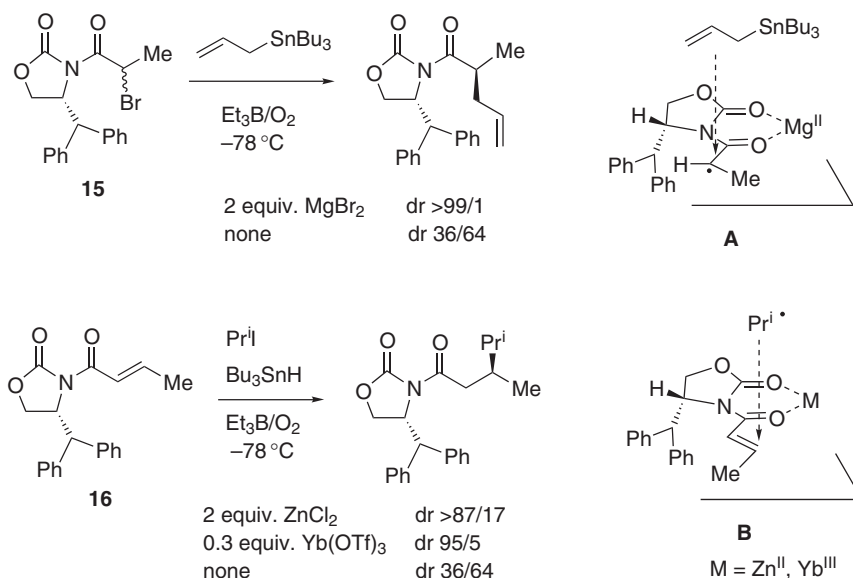


Scheme 2

Lewis acids have been recently investigated as important tools for inducing stereoselectivity through chelation stereocontrol of the substrate conformation <1998AG(E)2563, B-2001MI011>. β -Hydroxy- <1996TL6335> and β -alkoxy- <1995JCS(P1)389, 1996JA12528> ester enolate radicals proved to be interesting models owing to their ready availability in enantiopure form and their utility as starting materials for natural product synthesis. β -Methoxy α -halo (and seleno) esters **10** react with allyltrimethylsilane in the presence of triethylborane as the initiator and magnesium bromide as the Lewis acid to afford the corresponding *anti*-allylation products **12** with high diastereoselectivity <1996JA12528>. Formation of a six-membered ring chelate **11** accounts for the stereochemical outcome of the reaction (Equation (4)). In contrast, allylation of 3-bromo-2-oxy succinate **13** in the presence of lanthanum tris(6,6,7,7,8,8,8-heptafluoro-2,2-dimethyloctane-3,5-dione) [$\text{La}(\text{fod})_3$] leads selectively to the corresponding *syn*-product. It was suggested that the bulkiness of the *t*-butyldimethyl silyl protecting group disfavors ring chelates involving the oxygen of the silyl ether, and the complexation of both ester carbonyl groups to form a seven-membered ring chelate **14** was proposed to explain the observed stereoselectivity (Equation (5)) <1996JCS(P1)389>.



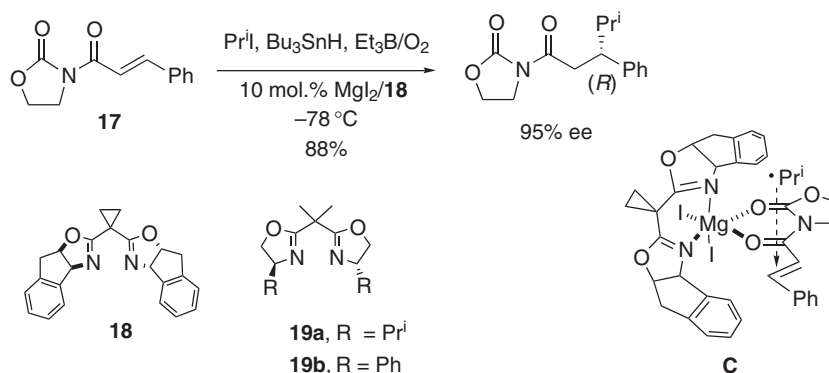
Chiral auxiliaries have been attached to the olefin moiety or at the radical center for asymmetric 1,4- or 1,5-diastereocontrol. Removal of the auxiliary allows the formation of enantioenriched materials. Reactions of amides or imines containing chiral oxazolidinones, C-2 symmetric 2,5-disubstituted pyrrolidines, or Oppolzer's sultam have been particularly studied and good levels of diastereocontrol have been obtained <1991ACS296, B-1996MI005, B-2001MI011>. Recent investigations in this area have focused on the use of the readily available and easily removable oxazolidinone auxiliary in conjunction with Lewis acids <1998AG(E)2563, B-2001MI011>. For instance, high levels of diastereoselectivity have been obtained using oxazolidinones derived from diphenyl alaninol. Allylation of **15** in the presence of 2 equiv. of magnesium bromide was achieved in high yield and in over 99% de. The $\text{Et}_3\text{B}/\text{O}_2$ initiation system offers the opportunity to conduct the reaction at low temperature. The stereoselectivity was explained based on model A (Scheme 3). Complexation of the Lewis acid with the bidentate radical ligand prevents free rotation about the amide bond, the methyl group at the planar radical centre points away from the nitrogen substituent thus avoiding steric interactions implying that the attack of allyltributyltin occurs from the face opposite to the diphenylmethyl group <1996AG(E)190>. It should be noted that high levels of asymmetric 1,3-diastereocontrol have been recently achieved in acyclic radical allylations based on Lewis acid chelation of chiral α -hydroxyketones <2003TL531>. β -Stereoselectivity may also be controlled in radical additions to nonterminal acrylamides of type **16**. Generally, substrates complexed by Lewis acids are also much more reactive toward radical addition than are free substrates which may allow the use of a catalytic amount of the Lewis acid. For instance, the diastereoselective addition of the isopropyl radical to **16** was promoted using substoichiometric amounts of ytterbium triflate. In the proposed model B (Scheme 3), the enoyl system lies preferentially in an *s-cis* conformation as a result of the chelation <1995JA10779, 1997AG(E)274, 2002JOC1738>. The stereochemical outcome of prochiral radical addition to such β -substituted enoyl oxazolidinones has also been studied <2002JA2924>.



Scheme 3

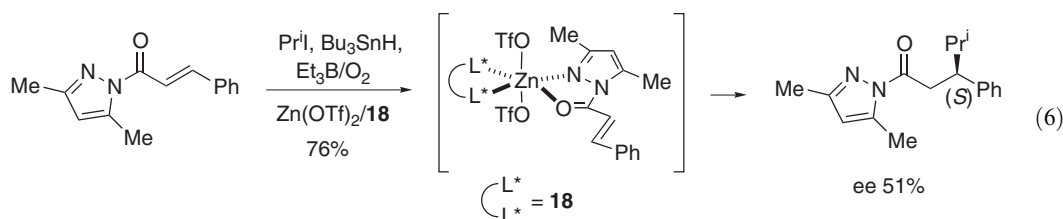
Highly enantioselective radical additions can be achieved using chiral Lewis acids <B-2001MI011, 2003CRV3263>. For instance, isopropyl radical addition to achiral enoyl oxazolidinone template **17** was investigated in the presence of magnesium diiodide and chiral bisoxazoline ligands. 10 mol.% MgI_2 proved sufficient to reach 95% ee and 88% chemical yield in the presence of **18**. Reactions could also be run at room temperature without much loss in selectivity. A model C with *cis*-octahedral geometry around magnesium was proposed to explain the selective formation of the (*R*)-enantiomer (Scheme 4). The ligand confines the substrate into an *s-cis* conformation and shields one of the diastereotopic faces thus forcing the radical to attack preferentially from the opposite direction. Other ligands **19** were less selective. Interestingly, however, **19a**

(R = Prⁱ) led also to the (*R*)-enantiomer, whereas **19b** (R = Ph) afforded the (*S*)-enantiomer. In the latter case a model with a *trans*-octahedral geometry was suggested <1996JA9200, 1997JOC3800>.



Scheme 4

The use of a pyrazole as an achiral template instead of an oxazolidinone also gave an inversion of selectivity in the presence of zinc triflate and ligand **18**. This reversal of enantioselectivity was attributed to the change of the chelate ring size together with a *trans*-octahedral geometry (Equation (6)) <1997TL5955>.



Enantioselective allylation reactions have also been studied with various template models. For instance α -acyl radicals **20** were reacted with allylstannanes or silanes in the presence of zinc and magnesium Lewis acids in combination with bis-oxazoline ligands. Excellent levels of enantioselectivity were obtained. Interestingly, allyl silanes have been found to be superior to allylstannanes in inducing enantioselectivity. This was explained by the fact that allylstannanes are converted into stannyl halides. These may compete with the chiral Lewis acid in catalyzing the reaction thereby producing racemic products <1997JOC6702>. Similar conditions allowed good levels of enantioselectivity to be obtained in reactions of the cyclic *N*-pyridyl γ -lactam radical **21** with allyltrimethylsilane <1999TL6713>. The use of sulfonamide **22** as an acyclic template has been investigated using aluminum, titanium, or magnesium Lewis acids with diamines, diols, and sulfoxides as chiral ligands (Figure 1). The reactions, performed with allyltributyltin, proved remarkably selective despite the presence of two oxygen atoms at the sulfur binding center <2000TL7071>. In fact, the sulfur becomes a new asymmetric center by selective complexation of one of the two enantiotopic oxygen atoms with the chiral Lewis acid. The sulfonyl group is acting here as a chiral relay <2003CEJ28>.

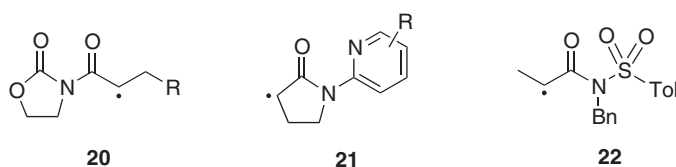
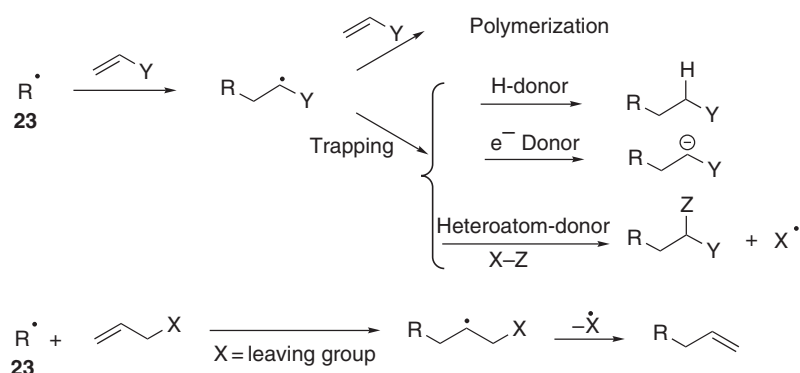


Figure 1

1.08.1.3.4 Methods for conducting radical reactions

(i) Introduction

To conduct successfully addition of carbon-centered radicals to alkenes, some factors must be controlled. The initial radical must add faster to the double bond than any secondary processes such as dimerization or disproportionation which can be avoided by working at a lower concentration of radical (10^{-7} – 10^{-8} M) than that of the alkene. In this case, the chain reaction is only maintained if the rate of hydrogen atom-donation is not too low otherwise alkene polymerization can occur. The evolution of the radical **23** can follow different pathways such as trapping by hydrogen donors, heteroatom donors, electron donors, or intramolecular β -elimination of a suitable leaving group (Scheme 5). The rate of trapping must be faster than polymerization but less than the trapping of the initial radical **23**, otherwise no addition of this radical will occur. Despite these limitations, radical additions know a growing interest in the area of organic synthesis <B-1986MI001, B-2001MI011>.



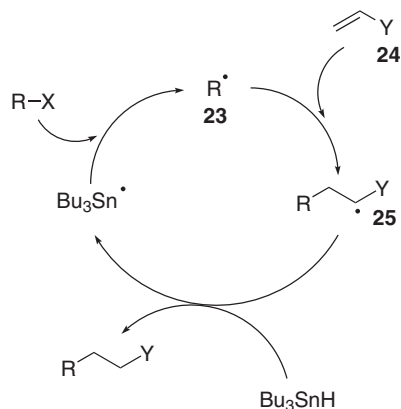
Scheme 5

(ii) Initiation of chain reactions

Initiation of radical chain reactions is usually achieved by photolytic or homolytic fragmentation of a chemical initiator <2002JCS(P2)367>. Peroxides and azo compounds, particularly 2,2-azobis-isobutyronitrile (AIBN), have been widely used for this purpose <B-2001MI011>. However, in recent years, the homolytic substitution reaction between triethylborane and oxygen has become a very popular method to initiate radical reactions <B-2001MI011, 2001CRV3415>. Indeed, the $\text{Et}_3\text{B}/\text{O}_2$ system offers the opportunity to conduct radical reactions under mild conditions at low temperature (-78°C), a great advantage when thermally unstable compounds are involved or when the stereoselectivity has to be controlled. It also allows reactions to be conducted in aqueous media <2002SL674> and, potentially, in ionic liquids <2002BCSJ853>. Water-soluble azo-initiators have also been recently investigated <2001BCSJ1963>.

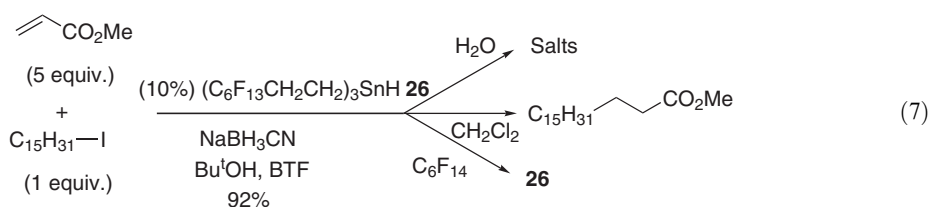
(iii) Chain reactions

(a) *Tin hydrides.* To date, most radical reactions are still conducted using tin hydrides (Bu_3SnH , Me_3SnH , Ph_3SnH) but these suffer from the toxicity of organotin compounds. The difficulties encountered to remove the toxic by-products generated in these reactions limit the applications of radical chemistry in the pharmaceutical industry <1987S665, B-1987MI002, B-1995MI004, B-1997MI006, B-2001MI011>. The mechanism shown in Scheme 6 is well defined. The chain carrier $\text{Bu}_3\text{Sn}^\bullet$ (generated by an initiator, AIBN for example) reacts with an alkyl halide to form an alkyl radical **23**, which adds to the activated alkene **24** to generate a new electrophilic radical **25**. This latter radical abstracts a hydrogen atom from Bu_3SnH to give the addition product and regenerates $\text{Bu}_3\text{Sn}^\bullet$ which can continue the chain reaction.



Scheme 6

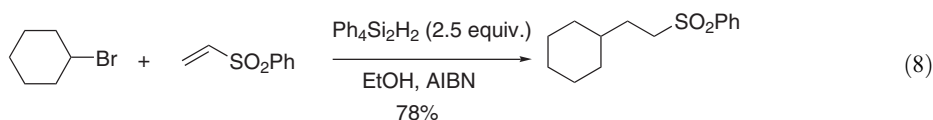
One of the major drawbacks of tin hydrides is the competitive trapping of the carbon radical **23** before addition to the double bond. This can be avoided by using excess alkene or low concentration of the hydride donor. Generally, a slow addition via a syringe pump, or *in situ* generation of a catalytic quantity of Bu_3SnH (resulting from reduction of Bu_3SnCl by NaBH_3CN or NaBH_4) are the best methods to overcome this difficulty <1984AG51, 1986JA303>. Alternatively, if the rate of hydrogen-atom donation is too slow then alkene polymerization can occur. The rate of reaction of a tin radical with an organohalide depends on the nature of halogen groups and, to a lesser extent, on the alkyl or aryl group <1998T2893>. Thus, the weaker carbon-iodide bond involves greater reactivity compared to corresponding bromide or chloride. Other functional groups can undergo similar reactions, the order of reactivity with tin radical <1984JA343, 1986AJC77> being in general as follows: $\text{RI} > \text{RBr} > \text{RSePh} \sim \text{R-OC(=S)SMe} > \text{RCl} > \text{RSPH}$. In recent years, major improvements in organotin radical reactions have resulted from the development of new methodologies using either catalytic quantities of organotin compounds <2002S835, 1998JOC2796>, new work-up procedures facilitating elimination of tin by-products <1999TL6729, 1998TL2123>, or specially designed tin hydrides easily removable from the reaction medium <2002JOC1192>. Furthermore, Curran and co-workers have developed perfluorotin hydride catalysts such as **26**, which are easily removable and re-usable by a simple two phase extraction using a fluorinated and a conventional organic solvent <1998AG(E)1174>. This method has been used for an efficient synthesis of a small library of nine compounds (Equation (7)).



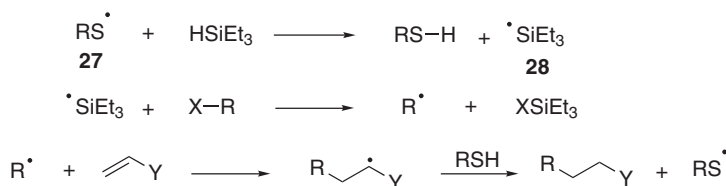
(b) *Germanium hydrides*. Germanium hydrides, although they are not so reactive, can efficiently replace tin hydrides. Hydrogen donor abilities of germanium hydrides have been measured recently <1999OM2395>. Nevertheless, this weaker reactivity can be useful to minimize the amount of reduction versus addition products <1991COS(4)715>. However, germanium derivatives remain expensive and are rarely used in organic synthesis <2002S835>.

(c) *Silicon hydrides*. Despite their lower reactivities, silicon hydrides are extremely useful as substitutes for toxic organotin hydrides <2002S835, 2002JCS(P2)367, 1998AG(E)3072>. However, due to the greater stability of Si-H bond, H-abstraction from trialkylsilanes by C-radicals is in general too slow to maintain chain reactions. Higher temperatures and excesses of silane reagents are necessary. The method is therefore limited to substrates which are not too temperature sensitive. The most popular silicon-hydride is tris(trimethylsilyl)silane $[(\text{TMS})_3\text{SiH}]$ for which hydrogen-atom abstraction is accelerated by the presence of trimethylsilyl groups on the silicon atom <1992ACR188, B-1998MI007, B-2001MI008>. The presence of bulky groups around silicon weakens the Si-H bond, enhancing its reactivity. For instance, the rate of hydrogen-atom

transfer to alkyl halides is only 10 times slower than with Bu_3SnH <1991JOC6399>. All classical radical precursors (halides, selenides, xanthates, etc.) can be used with this reagent. Other silicon hydrides bearing bulky groups have been studied <1995CRV1229>. Among these, 1,1,2,2-tetraaryldisilanes ($\text{Ar}_4\text{Si}_2\text{H}_2$) have been recently developed and used as novel tin-hydride substitutes. These reagents are crystalline, stable to air, and easy to handle. Bromocyclohexane adds to vinyl sulfone with an excellent yield using $\text{Ph}_4\text{Si}_2\text{H}_2$ (Equation (8)) <1998TL1921, 1999T3735>.

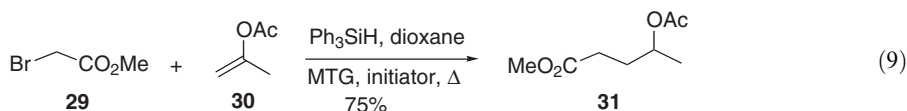


An interesting concept, named “polarity reversal catalysis,” has been developed by Roberts <1999CSR25>. This ingenious method allows the use of less reactive silicon hydrides such as triethyl or triphenylsilane with thiols as catalysts. A thiyl radical **27** generated by a suitable initiator (which too slowly abstracts a halogen atom from alkyl halides to maintain the chain reaction itself) reacts easily with triethylsilane forming silane radical **28** which can react with alkyl halides (Scheme 7). The thiyl radical is regenerated by reaction of the carbon-centered addition radical with thiol thus maintaining the chain reaction.

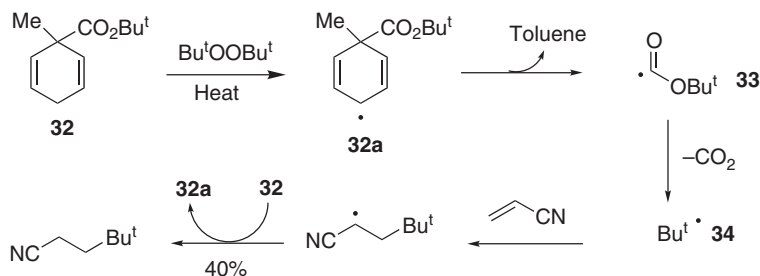


Scheme 7

Addition of bromoacetate **29** to alkene **30** using triphenylsilane and a catalytic amount of methylthioglycolate (MTG) provided the reductive addition compound **31** (Equation (9)) <1999JCS(P1)2061>.



(d) *Carbon hydrides*. Generation of carbon-centered radicals directly from C—H reagents is generally difficult due to the strength of the C—H bond compared, for example, to the Si—H bond. This method has been limited to activated C—H bonds (adjacent to carbonyl groups) or to generate reactive aryl or vinyl radicals <1995COFGT(I)319>. Recently, a new concept presented in Scheme 8 has been developed by Walton <1997JCS(P2)757> based on the properties of modified cyclohexa-1,4-dienes which present a weak methylene C—H bond ($\sim 305 \text{ kJ mol}^{-1}$) where hydrogen-atom abstraction is facilitated. After generation of carbon radical **32a** with $\text{Bu}^t\text{O}^\bullet$, the cyclohexadienyl radical undergoes fragmentation to toluene and alkoxy carbonyl radical **33**. The latter fragments via β -scission to carbon dioxide and the nucleophilic *t*-butyl radical **34** which adds to the double bond of acrylonitrile to form a new radical adduct that in turn reacts with another molecule of cyclohexadiene **32** to maintain the chain reaction (Scheme 8).



Scheme 8

The limitations of this method were generally the formation of by-products (polymers, isobutane, etc.) resulting from competitive side reactions. Recently, in a similar strategy, Studer and Amrein have synthesized other cyclohexadiene derivatives which possess a silyl function **35** (Figure 2). After fragmentation, a silyl radical is formed which can react with alkyl halides (xanthate or phenyl selenide can also be used) to form carbon-centered radicals which can add to alkenes <2000AG(E)3196>. Various silylated cyclohexadienes have been designed and their reactivities evaluated <2003JA5726>.

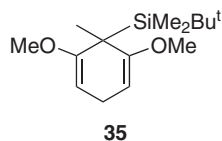
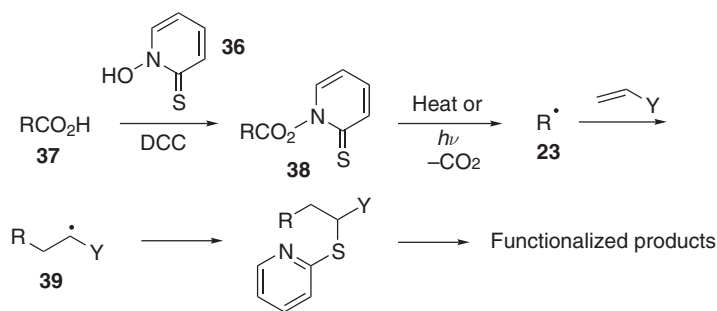


Figure 2

(e) *Mercury hydrides*. Despite their important use in the 1980s <1985AG(E)555>, to date, mercury hydrides seem to have been passed over in favor of less toxic reagents for generating carbon radicals. Their use in synthesis has been reviewed by Barluenga <1988CRV487>.

(f) *The Barton method and xanthates in radical reactions*. Generation of carbon radicals from carboxylic acids, the so-called Barton-ester method, is one of the most famous methodologies developed in radical synthesis <B-1993M1003>. The commercially available *N*-hydroxypyridine-2-thione **36** reacts with carboxylic acid **37** in the presence of dicyclohexylcarbodiimide (DCC) to yield to the thiohydroxamate ester **38**, which upon irradiation or heating undergoes elimination of CO₂ to generate the carbon-centered radical **23**. This radical adds to an activated alkene, and the newly formed radical **39** can then be trapped by the pyridyl sulfide to yield functionalized products as useful precursors for functional groups (Scheme 9) <1992T7083, 2002HAC169>.

Recently, chaetomelic anhydrides were synthesized using this method <1997JCS(P1)2175>, and the first addition of alkyl radicals onto double bonds on solid phase was realized <1999JCO157>. When hindered carboxylic acids were used, lower yields were generally obtained due to the incomplete formation of Barton esters. To overcome this difficulty, a new reagent *S*-(1-oxido-2-pyridinyl)-1,1,3,3-tetramethylthiuronium hexafluorophosphate (HOTT) **40**, which is a stable white crystalline solid, was developed (Figure 3) <1998JOC5732>. It was successfully used, for example, for the synthesis of hydroxyalkyl radicals which can add diastereoselectively to carbon double bonds <2002JOC6195>.



Scheme 9

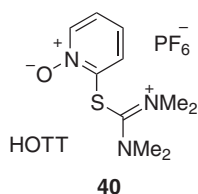
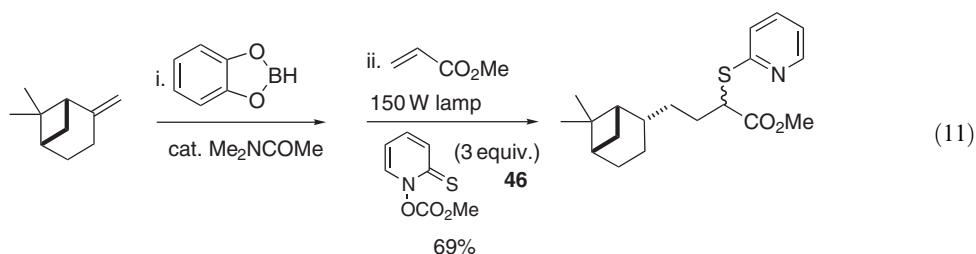
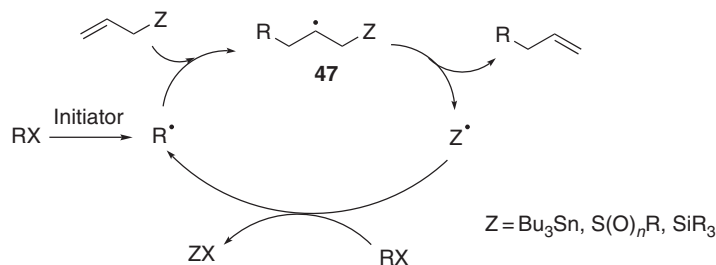


Figure 3

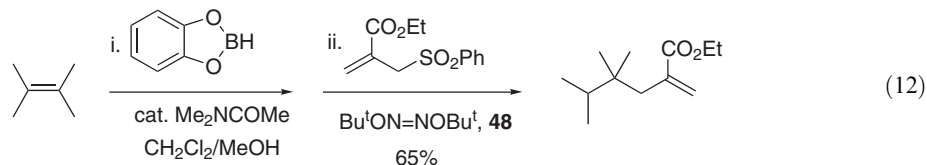


(h) *The fragmentation method.* Fragmentation reactions involve addition of a radical to a neutral alkene, followed by β -scission of the resultant radical to produce an adduct radical which propagates the chain reaction (Scheme 11). Relatively weak bonds such as C—Sn, C—S, or even C—Si are prone to undergo such β -elimination processes. Compared to the above discussed methods for conducting radical chain reactions, the present method tolerates unactivated alkenes and offers several other advantages. The nonreduction of the radical precursor, contrary to the reaction achieved in the presence of metallic hydride donors as in the Giese reaction (see Section 1.08.1.3.4.(iii).(a)), represents a major advantage. The nonreductive nature of the method makes it particularly interesting for the preparation of functionalized compounds. The fragmentation method is a very popular method to effect allylation transfer reactions which have been mainly carried out by using allylstannanes as radical traps <B-2001MI011>, but allylic sulfones <2003AG(E)2658> as well as allyl silanes <1996TL6387> have been recently suggested as “tin-free” alternatives. However, SiR_3 radicals (47, $\text{Z} = \text{SiR}_3$) have been postulated to undergo group transfer prior to fragmentation <1996JA12528, 1997JOC6702>.



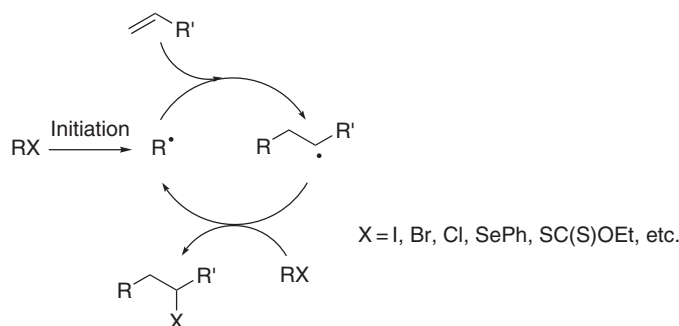
Scheme 11

The fragmentation method has thus been recently applied to the allylation reaction of *B*-alkylcatecholboranes using allyl sulfones as radical traps <2003AG(E)2658>. The process is initiated with di-*t*-butylhyponitrite 48 and propagation of the chain is sustained by reaction of the alkyl borane with the stable phenyl sulfonyl radical issued from fragmentation (Equation (12)).

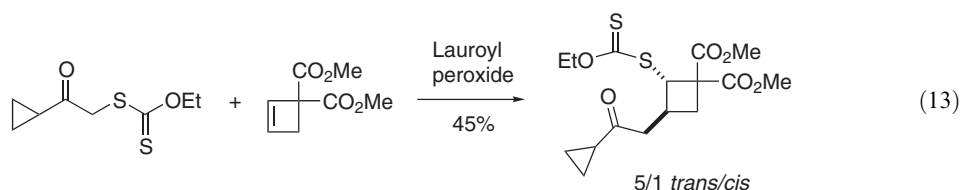


(i) *The atom transfer method.* Homolysis of the C—X bond in organic halides, followed by the transfer of both radical components to an unsaturated system constitutes an attractive, non-reductive way of conducting radical reactions <B-2001MI011>. The method is very interesting from an atom economy point of view since all atoms remain in the reaction product (Scheme 12). Initiation may be obtained by direct photolytic cleavage of the initial C—X bond or by conducting the reaction in the presence of an initiator, usually $(\text{Bu}_3\text{Sn})_2$ <2002JCS(P2)367> but also $\text{Et}_3\text{B}/\text{O}_2$ <2001CRV3415> or dilauroyl peroxide (DLP) <2000S1598> as tin-free substitutes. Halide atom transfer reactions generally involve addition of electrophilic radicals to electron-rich terminal alkenes. By generating an adduct radical less stable than the initial radical, this ensures that the rate of atom transfer is fast enough to avoid

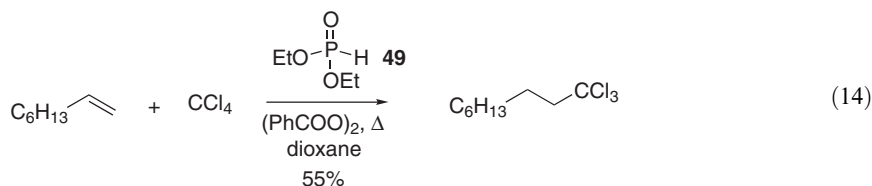
unwanted side reactions such as polymerization. Halomalonates and -malononitriles, as well as α -haloesters, nitriles, or amides are commonly used as organic halides, with the iodo derivatives generally giving better results. Lewis acids have recently been shown to significantly improve intermolecular halide atom-transfer reactions by increasing the electron-withdrawing nature of the functional group α to the halide, which is expected to widen the scope of alkene partners <1999JA5155>. Aside from the popular halide atom transfer reaction, recent developments have also focused on phenyl selenide transfer processes as synthetically useful alternatives which allow, for instance, photochemical additions of the sulfur-stabilized dithiane radical <1996TL2743>. Although the selenium transfer is a relatively slow process compared to the corresponding iodine transfer <1993JOC4691>, the stability and versatility of the incorporated phenylseleno group is of value for subsequent transformations <2000TCC81>. The transfer of xanthates (dithiocarbonates) <1997AG(E)693> is also a synthetically useful transformation, which can be applied to strained cycloalkenes <2000TL2979, 2000TL9815> (Equation (13)).



Scheme 12

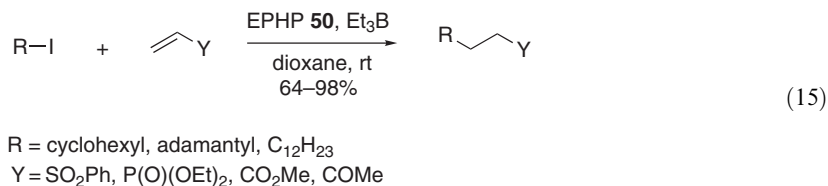


(j) *Phosphorus hydrides*. Replacement of tin hydrides by nontoxic reagents in order to favor green chemistry has been one of the major goals of free-radical chemistry. Phosphorus-based compounds, firstly used by Barton <1993JOC6838, 1992TL5709>, have recently demonstrated their abilities to generate carbon-centered radicals. The strength of the P—H bond in dialkyl phosphine is only around $\sim 310 \text{ kJ mol}^{-1}$ and these reagents can act as effective hydrogen-atom donors <2002JCS(P2)367>. Phosphinyl radicals are not as reactive as the corresponding phenyl silanes but, nevertheless, rate constants for the addition to double bonds are comparable <1998JOC1327, 2002JCS(P2)367>. Rate constants for reactions of the diphenylphosphinoyl radicals with some organohalides have been determined <1996JA7367, 1998JA11773, 1983JA3580>. One of the major difficulties encountered is the propensity of phosphorus radicals to add themselves to double bonds. Nevertheless, it has been shown that CCl_4 can add to alkenes using benzoyl peroxide as initiator, dioxane as solvent, and diethyl phosphite **49** as hydrogen donor <2001SL1719> with large excesses of CCl_4 (4 equiv.) and diethyl phosphite (10 equiv.) (Equation (14)).

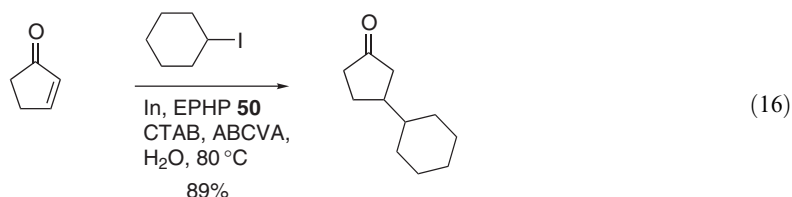


Simultaneously, it was reported that hypophosphorous acid salts, first used by Murphy in radical cyclizations <1999TL2415, 1999JCS(P1)3071>, can be used as reducing reagents in

intermolecular radical addition reactions. The reagent used, *N*-ethylpiperidine hypophosphite (EHP) **50** (3equiv.), is commercially available, and allowed the generation of radicals from primary, secondary, and tertiary halides and their additions to diverse alkenes (1equiv.) (Equation (15)) <2001SL1923>.

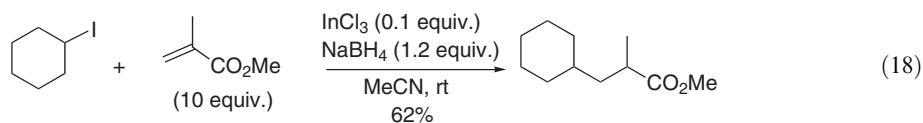
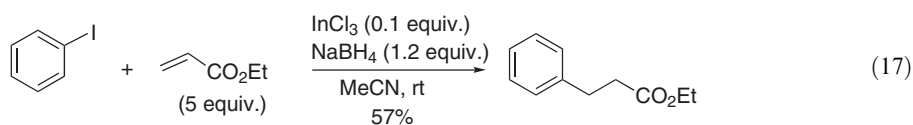


The great advantage of the phosphorus compound is that polar by-products were easily removed by simple flash-chromatography and that no slow addition was required. More recently, it has been demonstrated that this addition can also be conducted with β -substituted alkenes in water by using acetyl trimethylammonium bromide (CTAB) and the water-soluble 4,4'-azobis(4-cyanovaleric acid) (ABCVA) as radical initiator. However, this addition works only in the presence of indium metal (2equiv.), and large quantities of both the alkene (10equiv.) and EHP (7equiv.) were also required <2002SL631>. A Lewis acid (e.g., Yb(OTf)₃) can also be used to replace indium metal (Equation (16)) <2003MI15>.



Xanthates can also be used with diethyl phosphite and a suitable initiator in intermolecular additions of radicals to alkenes <2003OL1645>.

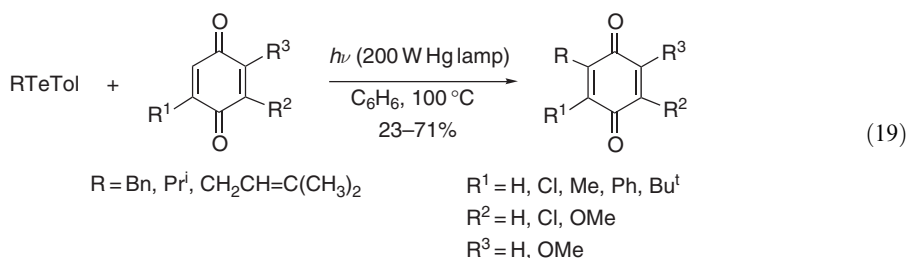
(k) *Indium hydrides*. A promising methodology using a catalytic quantity of indium trichloride and sodium borohydride which allows generation of indium hydride as catalytic active species has been developed. No initiator is needed, and this new method has been applied with success to intermolecular additions of organohalides (aryl or alkyl) to electron-rich or -poor alkenes (Equations (17) and (18)) <2002JA906>.



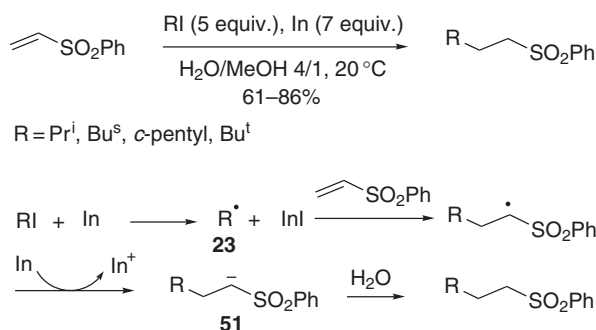
(iv) Nonchain reactions

(a) *Organocobalt group transfer*. In the 1980s, formation of alkyl radicals by photolysis or thermolysis of organocobalt derivatives has been used in numerous addition reactions to alkenes <1995COFGT(1)319, 1988CSR361>. Nevertheless, this methodology is currently not used because it requires stoichiometric organocobalt reagents.

(b) *Organotellurium compounds*. Very recently, carbon-centered radicals have been generated from organotellurium compounds under thermolysis or photolysis <1999TL2339>. This method has been used to add carbon radicals to substituted quinones (Equation (19)) <2002T6805>.

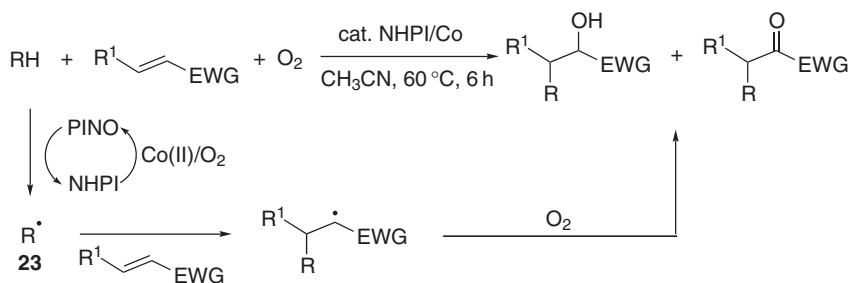


(c) *Indium*. The usefulness of indium metal as a single electron transfer radical initiator in the addition of an iodoalkane to phenyl vinyl sulfone has been demonstrated <2002OL131>. The proposed mechanism involves formation of a first radical **23** which adds to the double bond. A second single electron transfer (SET) leads to the anion **51** which is then trapped by water (Scheme 13).



Scheme 13

(d) *Phthalimide N-oxyl (PINO)*. The generation of alkyl radicals directly from alkanes would be the best method for conducting radical reactions but this is still a challenge in free radical chemistry. From this perspective, a new methodology using *N*-hydroxyphthalimide (NHPI) and a cobalt complex (Co(acac)₃) as catalyst under an oxygen atmosphere has been developed. The reaction involves the generation of an alkyl radical **23** by the NHPI/Co/O₂ system followed by radical addition to an alkene. Subsequent trapping of the addition radical by molecular oxygen results in a formal oxyalkylation of the alkene (Scheme 14) <2001JOC6425, 2001MI397>.

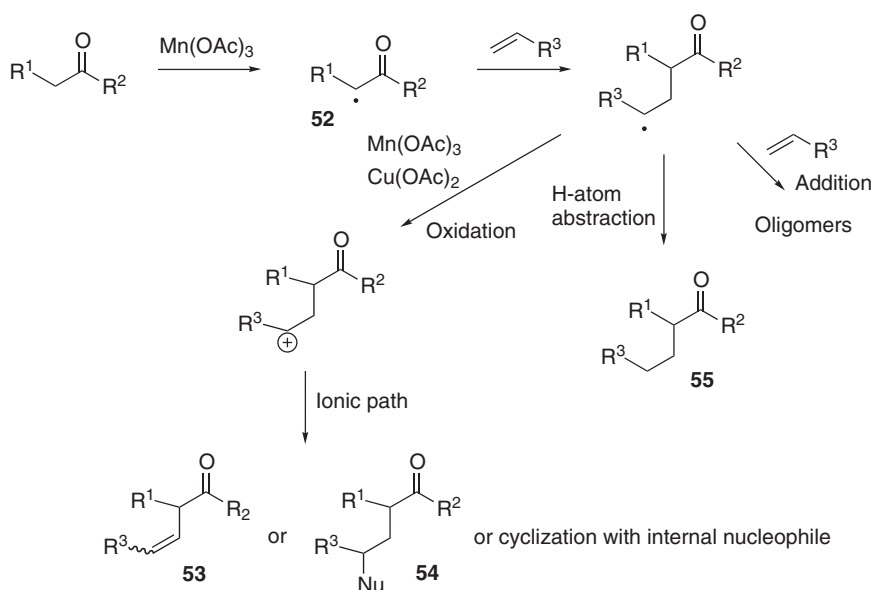


Scheme 14

The same concept has been applied to the addition of α -hydroxy radicals to alkenes, which leads to various lactones by subsequent cyclization <2000CC613>, as well as to the radical addition of 1,3-dioxolanes <2000CC2457>.

(e) *Electron-transfer processes*. Carbon—carbon bond formation can be mediated by transition metals of higher valency via a single-electron transfer step. Metals, such as Mn, Co, Cu, Fe, Ag, Pb, and Ce, have been widely used in organic synthesis <B-2001MI011>. Among them, manganese(III)

has received great attention for its ability to oxidize carbonyl compounds leading to electrophilic radicals that can add to electron-rich double bonds (Scheme 15) <2002JOM159, 1996CRV339, 1998ACA50>.



Scheme 15

However, the newly created radical **52** can react through different competitive pathways leading to complex mixtures of products in some cases. An ionic path leads to the classical products of carbocationic chemistry (products resulting from elimination **53**, or from trapping by an external nucleophile **54** or an internal nucleophile leading to cyclized products), whereas a radical path leads to H-transfer products **55** or oligomers. When the radical intermediate is a tertiary radical, $\text{Mn}(\text{OAc})_3$ is sufficient to oxidize it, whereas $\text{Cu}(\text{OAc})_2$ must be added in the cases of primary or secondary radical <1996CRV339>. Recently, a methodology allowing selective formation of a hydrogen-atom transfer product has been developed. This new approach is based on an *in situ* generation of catalytic amounts of $\text{Mn}(\text{OAc})_3$ resulting from oxidation of $\text{Mn}(\text{OAc})_2$ by KMnO_4 <2002JOMC159>. Due to milder reaction conditions, ceric ammonium nitrate (CAN) was found to be superior in some cases to $\text{Mn}(\text{OAc})_3$ for applications in carbohydrate chemistry <1997JA9377>. Nevertheless, despite their great interest, all these reported procedures suffer from the large quantity of the metal reagent required. To avoid this problem a new procedure that works with catalytic quantities of $\text{Mn}(\text{OAc})_2$ and $\text{Co}(\text{OAc})_2$ as co-oxidant under an oxygen atmosphere in AcOH as solvent has been devised. To date, cyclic and acyclic ketones, malonates, and anhydrides have given excellent results using these catalytic additions to alkenes <2000CC2317, 2002JOC970, 2003JOC5974>. Such additions can also be conducted in ionic liquids <2001CC1350>.

1.08.1.4 Intramolecular Radical Additions

1.08.1.4.1 Introduction

This section is organized similarly to the section dealing with intermolecular additions. The reader is strongly recommended to read the previous section for a more detailed account of the mechanisms and principles involved in carrying out radical reactions and to read the following reviews which cover recent literature on cyclization reactions <1996CRV195, 1998AG(E)2563, 1999T9349, 2001JCS(P1)3215, 2001T7237, 2001AG(E)2224, 2002JCS(P1)2747, 2003S803,

[2003CRV3263](#)>. Radical cyclization reactions are favorable processes compared to intermolecular additions. All requirements have been discussed in COFGT (1995) which should be consulted.

1.08.1.4.2 The 5-hexenyl radical: regioselectivity

To avoid repetition of basic principles concerning cyclization reactions, readers are directed to COFGT (1995). In the 5-hexenyl cyclization type, between the two competing cyclization modes, the 5-*exo-trig* mode is always the major pathway versus the 6-*endo trig* mode (50 times faster). Nevertheless, in most cases, final products are contaminated by products generated by the secondary process. However, when alkenes are substituted by an electron-withdrawing group, products resulting from 6-*endo* cyclization become insignificant. The presence of an alkyl substituent on the alkene, or a heteroatom in the chain strongly affects the course of the cyclization [<1995COFGT\(1\)319>](#). In certain cases, 5-*endo-trig* cyclizations of 5-pentenyl radicals which are recognized as a disfavored process can be realized [<2002S695>](#).

1.08.1.4.3 Stereoselectivity in substituted 5-hexenyl radical cyclizations

The major stereomer in a 5-*exo*-radical cyclization can generally be predicted by using the Beckwith transition state model as discussed in COFGT (1995) [<1995COFGT\(1\)319>](#).

1.08.1.4.4 Allyl, vinyl, and aryl cyclizations

Vinyl radicals and aryl radicals are widely used in organic synthesis as they are more reactive than their alkyl homologs (see COFGT (1995) for a more detailed account of their reactivities [<1995COFGT\(1\)319>](#)) [<2001T7237>](#). However, under tin-mediated cyclization conditions vinyl radicals give a mixture of both 5-*exo*- and 6-*endo*-products which can be a limitation. Generally, this ratio is a function of the tin hydride concentration, high concentrations favoring the 5-*exo*-products. Unfortunately, this high concentration also increases the amounts of acyclic products due to the trapping of the initial vinyl radical. Nevertheless, it has been reported that 5-*exo*-products can be obtained preferentially by adding a catalytic amount of PhSeSePh to the reaction medium [<1996TL3105>](#). Another study involving vinyl radicals has shown that six-membered rings can be obtained selectively from 1-vinyl-5-methyl-5-hexenyl radicals [<2002TL4997>](#).

Allyl radicals, which are less reactive than vinyl radicals have been used in diverse syntheses of complex natural products [<1999TL9379>](#). Aryl radical cyclizations are widely used in synthesis of complex frameworks and readers are directed to previous issue of this volume and to the reviews cited in the introduction.

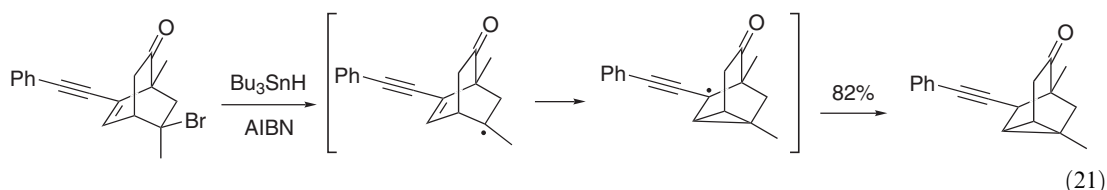
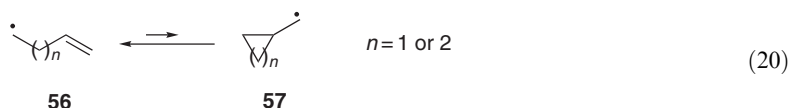
1.08.1.4.5 Formation of six-membered rings

Formation of six-membered rings by *exo*-cyclizations of 6-heptenyl radicals is slower than the radical cyclization of 5-hexenyl radicals. Requirements for the formation of six-membered rings have been developed in COFGT (1995) and are still relevant today [<1995COFGT\(I\)319>](#).

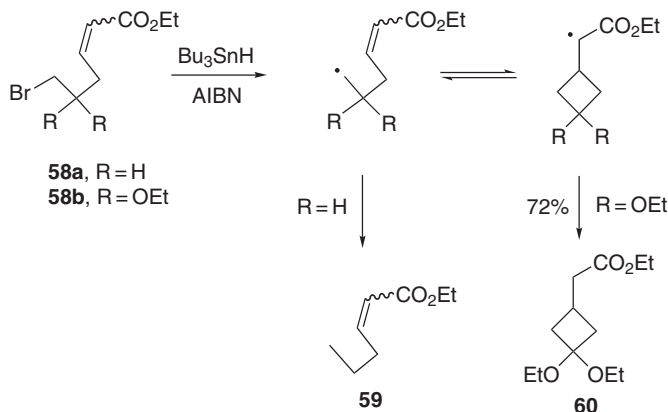
1.08.1.4.6 Formation of other ring sizes

Formation of small rings *via* intramolecular radical addition to alkenes is a highly disfavored process. For instance, 3-*exo*-cyclization of the parent 3-butenyl radical (**56**, $n = 1$) is 10^4 times slower than the reverse ring opening of the resulting cyclopropylmethyl radical (**57**, $n = 1$) (Equation (20)) [<1980JA1734>](#). The equilibrium is thus strongly shifted toward the acyclic intermediate unless the cyclized radical is strongly stabilized by adjacent unsaturation or keto group, or if ring strain in the cyclization precursor induces favorable geometric alignments of the

carbon-centered radical and the alkene. The example depicted in Equation (21) takes advantage of these two features <1997JCS(P1)177>. 3-*Exo*-radical cyclizations have also been shown to be facilitated by intramolecular trapping of the cyclopropylmethyl radical via β -elimination of a phenylthio group <2001CR(C)599>.

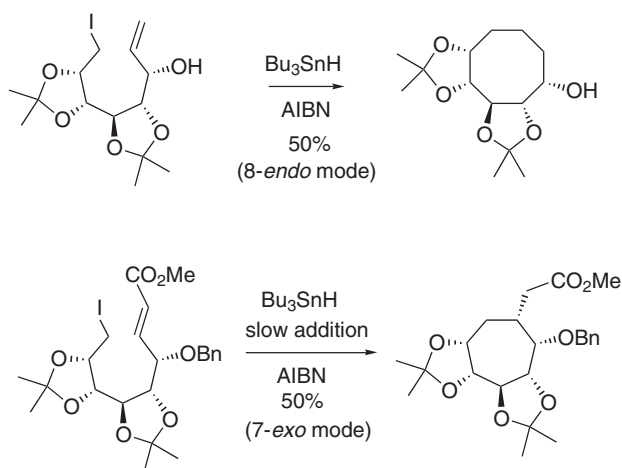


gem-Disubstituent effects have been reported to significantly facilitate 4-*exo*-radical cyclizations <1999TL2661>. For instance, while reaction of ethyl 6-bromo-2-hexenoate (**58a**, R = H) with tributyltin hydride only furnished the reduced product **59**, the analogous *gem*-diethoxy substrate (**58b**, R = OEt) underwent clean cyclization to afford the corresponding cyclobutane derivative **60** (Scheme 16).



Scheme 16

Methods for medium-sized ring elaboration have been recently reviewed <1999T9349, B-2001MI011>. In general, formation of medium-sized rings using radical cyclization methods is a relatively disfavored process and competitive reduction of the intermediate radicals by hydrogen donors may represent a serious problem. These rings have therefore often been obtained via ring expansion of smaller rings or by cyclization of the highly reactive σ -aryl radicals. Another method for obtaining medium-sized rings is to cyclize electrophilic alkyl radicals onto weakly nucleophilic alkenes or vice versa. In these reactions, *endo*-cyclizations are generally favored over *exo*-cyclizations. The 8-*endo*-cyclization of unsaturated α -haloesters has been investigated to access eight-membered lactones <1998JA7469>. Macrocyclic lactones have been obtained via 12-, 15-, 18-, 21-, and 24-*endo*-cyclizations of ω -iodopolyoxaalkyl acrylates <1998JOC6814> and water seems to be a very promising solvent to promote the macrolactonizations <2000JA11041>. As demonstrated in Scheme 17, one common method to control the regioselectivity in favor of the *exo*-mode of cyclization is to substitute the terminal position of the alkene with electron-withdrawing groups to direct radical addition onto the β -position of the α,β -unsaturated system <2002JOC3717>. Metal-mediated radical approaches to medium-sized rings have also been reported and recently reviewed <2000CRV2963>.



Scheme 17

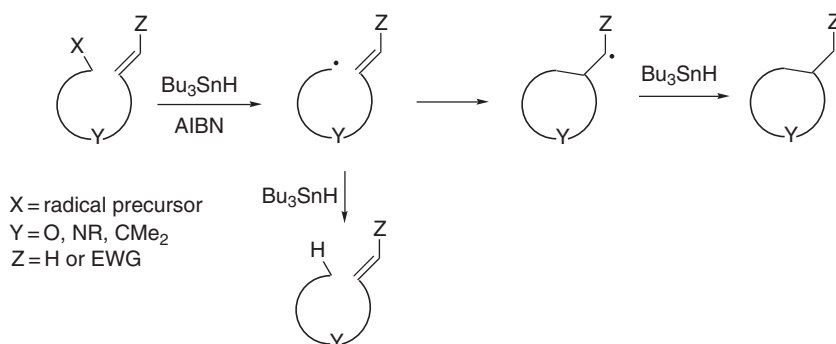
1.08.1.4.7 Methods for facilitating radical cyclization reactions

(i) Introduction

The following sections indicate the different methods available to facilitate radical cyclization reactions. The reader is strongly advised to first read [Section 1.08.1.3.4](#) to become familiar with the factors which affect the success of radical chain reactions.

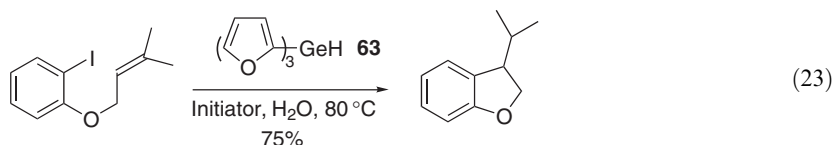
(ii) Radical chain methods

(a) *Tin hydrides and germanium hydrides.* Tin hydrides remain the most commonly employed reagents to facilitate radical cyclizations. An increasing number of syntheses have been developed in recent years leading to various natural and non-natural products [<B-2001MI011, 2001T7237, 2002JCS\(P2\)367, 2002JCS\(P1\)2747, 2002H2413>](#). The mechanism for the chain reaction has already been described in [Section 1.08.1.3.4.\(iii\).\(a\)](#). In fact, carbon-centered radicals are generated in the same way as for intermolecular additions from various precursors, the order of abstraction by $\text{Bu}_3\text{Sn}^\cdot$ being $\text{I} > \text{Br} > \text{SePh} \sim \text{OC(S)Me} > \text{Cl} > \text{SPh}$ [<1991CRV1237>](#). Alkyl, vinyl, or aryl precursors typically react with AIBN and tin hydride and the formed radicals add intramolecularly to a suitable double bond ([Scheme 18](#)).

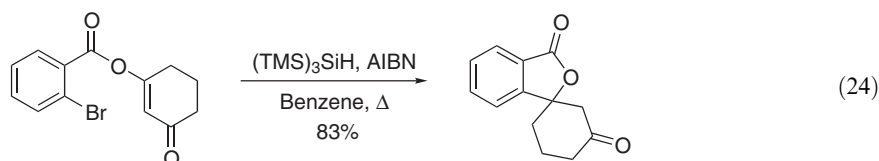


Scheme 18

Trialkylgermanium hydrides have been less widely used in radical reactions. Recently, tri-2-furylgermanium hydride **63** was used as the radical mediator to synthesize various THFs and dihydrobenzofurans. Interestingly, the reaction can be conducted in water using Et_3B or 2,2'-azobis(4-methoxy-2,4-dimethylvaleronitrile), a soluble form of AIBN, as initiator (Equation (23)) <2001BCJ747>. Tris(trimethylsilyl)germanium hydride, another source of radicals, has also been used to realize the intramolecular addition of an aryl radical to pyridine <2003OBC4047>.



(b) *Silicon hydrides.* Development of alternative hydrogen atom donors to overcome difficulties in removing highly toxic organotin reagents or by-products is a growing necessity with regard to potential applications of radical chemistry in the pharmaceutical industry. Silicon hydrides, despite their lower reactivities (see Section 1.08.1.3.4.(iii).(c)), are useful substitutes for organotin hydrides. In the recent literature, two reagents predominate: tris(trimethylsilyl)silane (TTMSS) developed by Chatgililoglu <1995CRV1229> and 1,1,2,2-tetraphenyldisilane (TPDS) developed by Togo <2001CR(C)539>. TTMSS-promoted radical cyclizations have been applied to the synthesis of complex structures such as nitrogen heterocycles <2003T3009>, tri- and tetracyclic isoindolinones <1999TL7591>, as well as spirolactones and lactams (Equation (24)) <1999TL7595, 2000TL2523>. The expeditious formation of a complex aza-structure has also been reported which may be applied to the synthesis of recently isolated polyguanidium alkaloids possessing important bioactivity against HIV <2001TL6637>.



TPDS is a promising, commercially available crystalline reagent, stable to air, which has been successfully used in sugar chemistry to facilitate radical cyclizations. A comparative study has been conducted with tributyltin hydride (Table 1). The use of silane reagents led exclusively to the cyclization product, whereas tin hydride reagents gave mixture of cyclized and reduced products <2000JOC5440>.

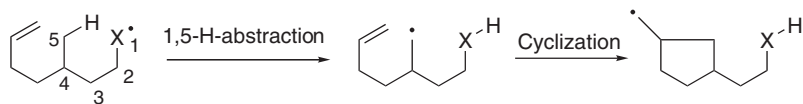
Table 1 Silicon hydride versus tin hydride for the cyclization of glycosyl radicals

$\text{Ph}_4\text{Si}_2\text{H}_2$, Et_3B	84		0
$\text{Ph}_4\text{Si}_2\text{H}_2$, AIBN	78		0
Bu_3SnH , Et_3B	37		44
Bu_3SnH , AIBN	65		32

(c) *Mercury hydrides.* Mercury hydrides can be used to carry out reductive radical cyclizations <1995COFGT(1)319, 1988CRV487>. Limitations are mainly high toxicity and need for stoichiometric quantities of organomercurials. An 8-*endo* cyclization leading to an eight-membered lactone has been realized by addition of Bu^tHgI to an unsaturated acrylate ester and subsequent photolysis of the resulting organomercurial in the presence of PhSSPh , the final radical being trapped by PhSSPh <1996TL2557>.

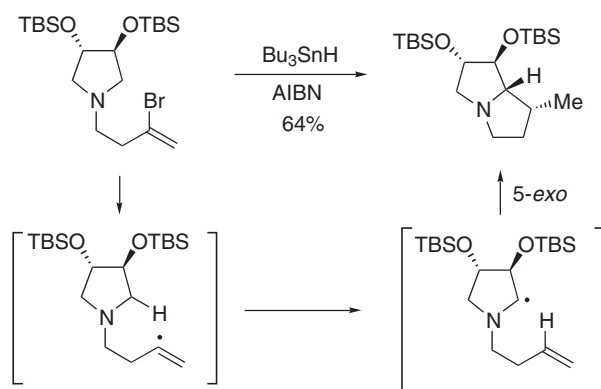
(d) *Hydrogen atom transfer reactions.* In particular cases where radical precursors are difficult to synthesize, or if a position is itself unreactive toward abstraction to give a carbon radical, a methodology involving hydrogen atom transfer can be used. The strategy involves a radical

translocation, i.e., an intramolecular abstraction of an hydrogen atom by a radical center which, in turn, can react with an unsaturation present in the molecule (Scheme 21) <2001CSR94>.



Scheme 21

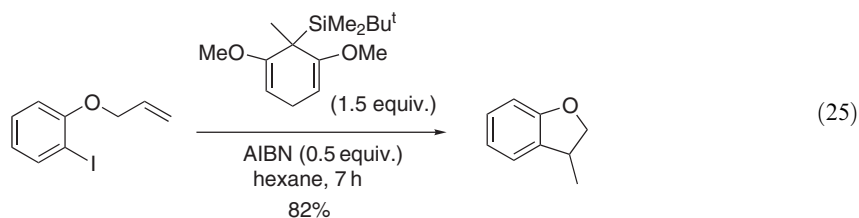
Generally, 1,5-hydrogen atom transfer is a favored process compared with 1,6- or 1,*n*-abstractions. The precursors can be vinyl, aryl, or more rarely alkyl radicals obtained from halides or classical precursors. This methodology has been applied with success to the synthesis of diverse structures such as pyrrolizidines (Scheme 22) <1996TL5825>, spironucleosides <1996JOC1908>, as well as spiro- or fused-cyclic ketones <2000TL9865>.



Scheme 22

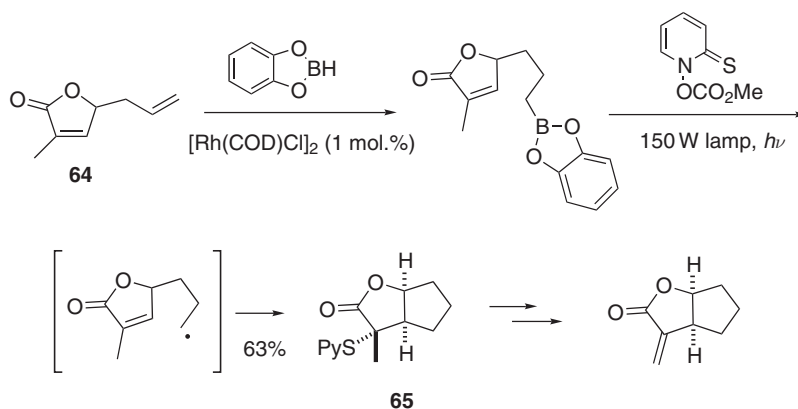
The mitomycins, a family of naturally occurring compounds which possess pronounced antibiotic and antitumor activities, can also be accessed using a similar strategy <2003SL1431>. γ -Lactams have been synthesized using radical translocation to avoid the synthesis of unstable α -haloamino acids as radical precursors <1998TL5339>. In this case, the radical precursor is an aryl halide which after 1,5-hydrogen atom transfer remains on the final cyclized compound as an *N*-protective group. A similar strategy has been used as a new stereoselective entry to the azaspirocyclic nucleus of halichlorine and pinnaic acids <2003OL3017>. Alkynes can also be used as radical acceptors after a first 1,5-hydrogen atom transfer <2002JCS(P1)1438>.

(e) *Carbon hydrides*. Cyclohexadienes presented in Section 1.08.1.3.4.(iii).(d) can be useful precursors of carbon radicals as demonstrated by the respective research of Walton <2000CC2327> and Studer <2003JA5726>. Specially designed silylated cyclohexadienes have been recently used to conduct radical cyclizations avoiding the use of toxic tin hydrides (Equation (25)). These new reagents have been found superior to tin hydrides in some cases.



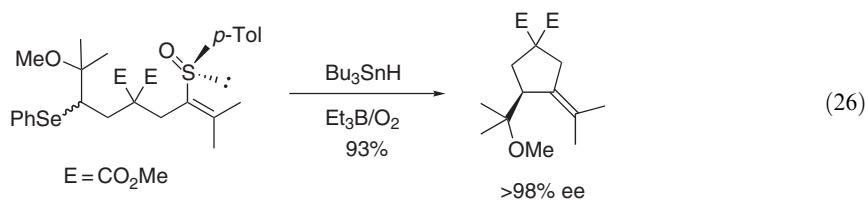
The persistent radical effect has also been used by Studer to obtain cyclized structures using 2,2,6,6-tetra methylpiperidinoxy (TEMPO)-substituted precursors of carbon radicals. A cascade reaction, where two carbon—carbon bonds and a new carbon—heteroatom bond are formed in one operation illustrated the interest of this tin-free methodology <2000AG(E)1108>.

(f) *The borane method.* As already mentioned in Section 1.08.1.3.4.(iii).(g), *B*-alkyl catecholboranes, easily prepared *in situ* by hydroboration of alkenes, are valuable precursors of alkyl radicals which undergo conjugate addition to activated alkenes. This sequential process has recently been applied to the cyclization of dienyl systems where one of the double bonds is substituted by an electron-withdrawing group <1999CEJ1468, 2003SL1485>. For instance, efficient and selective hydroboration of the terminal electron-rich double bond in **64** was performed under rhodium catalysis, and cyclization occurred under irradiation in the presence of Barton carbonate PTOC-OMe as chain-transfer reagent. The overall process furnished α -methyl- α -(*S*-pyridyl)lactone **65**, which may subsequently be transformed into the α -methylenelactone via thermal fragmentation of the corresponding sulfoxide (Scheme 23) <2003SL1485>.

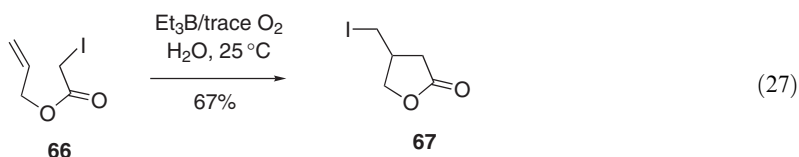


Scheme 23

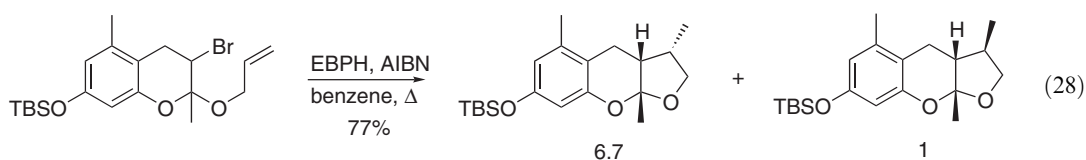
(g) *The fragmentation method.* Fragmentation reactions involve addition of a radical to a neutral alkene, followed by β -scission of the resultant radical to produce an adduct radical which propagates the chain reaction (see Section 1.08.1.3.4.(iii).(h) for details). In contrast with the method based on metallic hydride donors, reduction of the initial radical before cyclization is not a matter of concern. The fragmentation method is therefore well suited for conducting particularly slow radical cyclizations. Allyl- and vinylstannanes have often been used to generate the chain carrier. Vinyl sulfoxides have recently been used as temporary chiral auxiliaries to effect enantioselective alkenylations (Equation (26)) <1998AG(E)2116, 1999JA11395>.



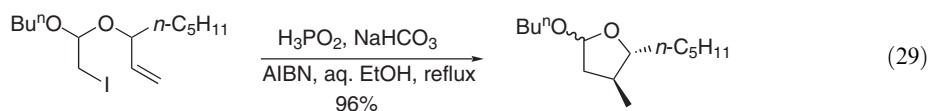
(h) *Atom transfer reactions.* The atom transfer of a C—X group (X = halogens, SePh, SC(=S)OEt) across a double bond (see Section 1.08.1.3.4.(iii).(i)) is a suitable method for performing slow radical cyclization provided there is no fast radical trap like tin hydride in the reaction media, which may reduce the initial radical prior to cyclization. Radical cyclization of allyl iodoacetate **66** in the presence of triethylborane as radical initiator was found to proceed efficiently at room temperature in water to yield γ -lactone **67** (Equation (27)). Interestingly, this reaction did not occur in organic solvents such as hexane or benzene. Calculations suggested that this remarkable solvent effect was due to the large dielectric constant of water which lowers the barrier to rotation from the (*Z*)- to the (*E*)-rotamer that undergoes cyclization. In addition, the high cohesive energy density of water forces a decrease in the volume of the reactants and therefore effects acceleration of the reaction <2000JA11041>. It is noted that the same transformation had been previously reported to occur in benzene in the presence of Bu₃SnSnBu₃ as radical initiator but required higher temperatures (80 °C) and resulted in lower yields (~40%) <1991JOC2746>. Highly enantioselective atom transfer radical cyclization reactions catalyzed by chiral Lewis acids have been recently reported <2001JA8612>.



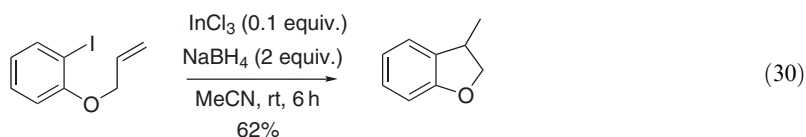
(i) *Phosphorus hydrides.* Many efforts have been made to develop new radical mediators avoiding the use of toxic tin hydrides. Among the newly developed reagents, hypophosphorous acid and its salts have received considerable attention [<2002S835>](#). *N*-Ethylpiperidinium hypophosphite (EHPH) is the most widely used reagent to date. Its low cost and the easy removal of the by-products by simple acid- and base-washes makes it very attractive. EHPH can be used in organic solvents such as benzene and toluene and can lead to bi- or tricyclic structures in the synthesis of various oxygen heterocycles (Equation (28)) [<1999TL2415, 1999JCS\(P1\)3071, 2000TL1833>](#). Synthesis of THFs and more particularly dihydrosesamin have also been realized using the same methodology [<2002T2435>](#).



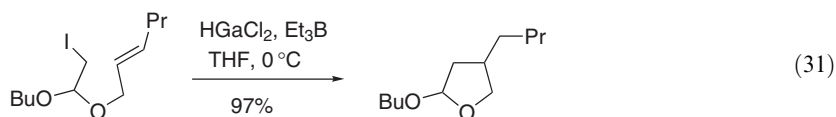
The cyclization can also be conducted in aqueous ethanol with a combination of hypophosphorous acid (H_3PO_2) and an inorganic base such as NaHCO_3 (Equation (29)) [<2000CL104, 2002SL674>](#). Selective deuteration can also be accomplished using D_3PO_2 and D_2O as solvent [<2001BCJ225>](#). Cyclization reactions of hydrophobic substrates can be performed with EHPH in water as the only solvent by using a surfactant (cetyltrimethylammonium bromide) and a water-soluble initiator [<2001OL1157, 2003T77>](#). Diethylphosphine oxide (DEPO), another phosphorus derivative developed recently, gave also interesting results in this area. It allowed cyclizations to be carried out in water with no extra additives but a water-soluble initiator [<2003OL2971>](#).



(j) *Indium hydrides and gallium hydrides.* Indium hydride has been successfully used as a tin hydride alternative to facilitate radical cyclizations (Equation (30)). This new procedure is based on the use of a catalytic amount of indium chloride which is reduced *in situ* by sodium borohydride (2 equiv.) in acetonitrile. The mechanism is similar to the mechanism reported for the tin hydride-promoted reactions. The indium hydride acts as the hydrogen donor in the reduction of the carbon radical [<2002JA906>](#).



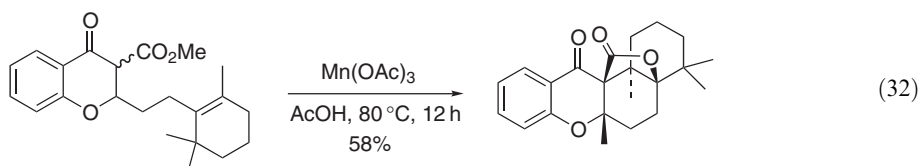
Gallium hydride (HGaCl_2) is another tin substitute used in various radical 5-*exo*-cyclizations. HGaCl_2 is readily prepared *in situ* from commercially available GaCl_3 and sodium bis(2-methoxyethoxy)aluminum hydride (Red-Al, 1 equiv.) in THF. However, in contrast with indium hydride, an initiator (Et_3B) must be added to initiate the reactions (Equation (31)) [<2001OL1853>](#).



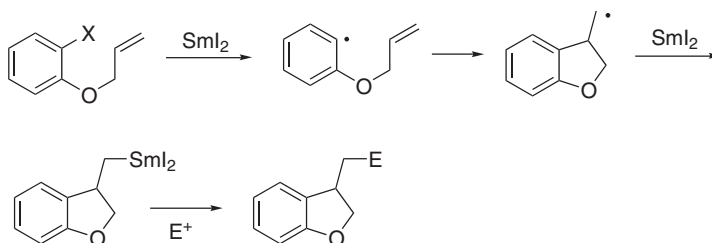
(iii) Nonchain reactions

(a) *Organocobalt group transfer.* Organocobalt reagents have been widely used in radical cyclizations but no major advances have occurred in this area since the publication of COFGT (1995) <1995COFGT(1)319>.

(b) *Manganese-mediated cyclizations.* Oxidative radical cyclizations involving $\text{Mn}(\text{OAc})_3$ continue to grow in popularity since they allow generation of a carbon radical α to carbonyl compounds such as β -ketoesters, β -diketones, or β -diesters <1996CRV339, 1998ACA50, 1997OR427>. As shown previously (see Section 1.08.1.3.4.(iv).(e)), the carbon radical produced from addition or cyclization can react following different pathways. Generally, $\text{Mn}(\text{OAc})_3$ itself is able to oxidize tertiary radicals giving rise to carbocations which can further lose a proton leading to an olefin or react with a suitable internal or external nucleophile. In the case of primary or secondary radicals, $\text{Mn}(\text{OAc})_3$ does not oxidize such intermediates and hydrogen abstraction from the solvent or from an acidic hydrogen generally occurs. A co-oxidant must be added to transform such radicals into carbocations which can react as previously described. In most cases $\text{Cu}(\text{OAc})_2$ is added which is known to oxidize secondary radicals to alkenes 350 times faster than $\text{Mn}(\text{OAc})_3$ <1971JA524, 1972JA2888>. When the elimination product is obtained, the less substituted (*E*)-double bond is primarily formed, which is of interest for synthetic applications. Snider has investigated the effects of alkene geometry on the stereochemistry of radical cyclizations <1998T10641>. This methodology has been applied in numerous syntheses of complex frameworks including macrocyclic lactones <2002TL9031>, spiro lactams <2000JOC7257>, β -lactams (via a 4-*exo-trig* radical cyclization) <2000OL401>, polycyclic systems in a series of naturally occurring phenolic sesquiterpenes (Equation (32)) <2001JCS(P1)206>, and pyrrolidinones <2001JOC3726>. In some cases, $\text{Cu}(\text{OAc})_2$ has been substituted for $\text{Cu}(\text{OTf})_2$ to facilitate the radical cyclization of methylthio-acetamides to access the erythrinane structure <2003JOC312>. Enantioselective versions of the $\text{Mn}(\text{OAc})_3$ -promoted cyclization have been achieved and it has been demonstrated that lanthanide triflate can catalyze such reactions <1999TA4427, 1999JA5579, 2000JA1658, 2000JOC2208>.

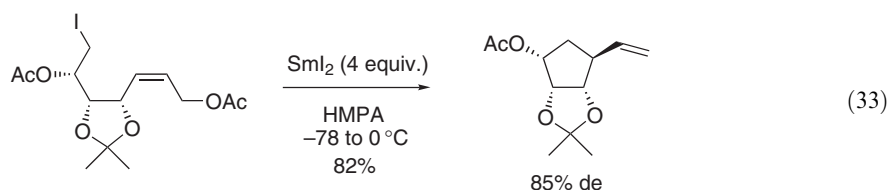


(c) *Samarium-mediated cyclization reactions.* Samarium(II) iodide has become a very popular reagent to generate alkyl, alkenyl, and aryl radicals via the reduction of organic halides. Interestingly, in contrast with the tin hydride and the silicon hydride processes, SmI_2 -promoted cyclizations are followed by reduction of the cyclized radical to the corresponding anion which can be trapped with a number of electrophiles including aldehydes and ketones <1996CRV307, 1998T3321, B-2001MI011>. In this process, fast cyclization rates are required to avoid competitive reduction of the initial radical by SmI_2 . Aryl radicals (mainly generated from aryl iodides) have therefore received a great deal of attention since they are particularly resistant to such reduction and have been found to cyclize in a 5-*exo-trig* mode with rates up to $4 \times 10^9 \text{ s}^{-1}$ (Scheme 24). HMPA is generally used as co-solvent to enhance electron transfer from SmI_2 to the halide but irradiation with light at 560–700 nm has recently been found to be effective <1997JA2745>. Reactions have

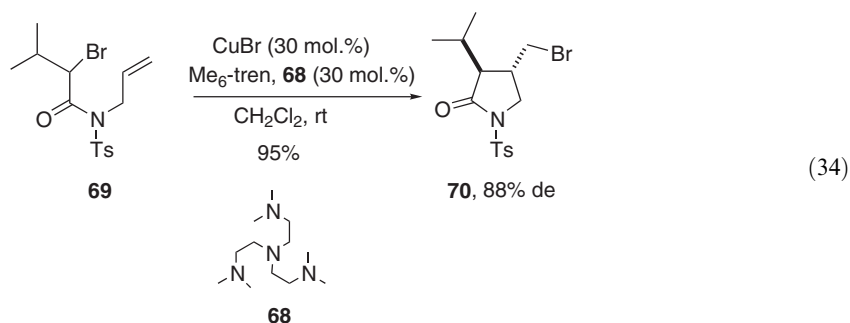


Scheme 24

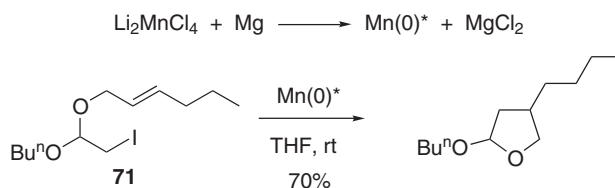
also been developed on polymeric support <1998TL2281>. SmI₂-promoted cyclizations may alternatively terminate in an elimination process as illustrated in Equation (33) <1997TL1153>.



(d) *Other metal-mediated radical cyclization reactions.* Ni, Ru, Fe, and Cu complexes have been used as an alternative to organotin hydrides to conduct intramolecular halogen atom transfer reactions <B-2001MI011>. Initial studies have concerned cyclization reactions of unsaturated polyhaloalkane compounds and will not be described in this chapter. However, highly activated copper complexes generated from copper salts and polydentate amine ligands have recently been found to efficiently catalyze the cyclization of mono-halo substrates <2002CSR1>. Ligands solubilize the copper salt and significantly alter the redox potential of the catalyst system. The tetradentate Me₆-tren ligand **68** is particularly effective and allows cyclization of 2-chloroacetamide **69** at room temperature. In this oxidative cyclization, abstraction of the bromine atom by CuBr generates CuBr₂ and initiates the radical cyclization. The resulting cyclic radical then abstracts a bromine atom from CuBr₂ to produce the γ -lactam **70** and regenerate the catalyst (Equation (34)) <2000JCS(P1)671>.

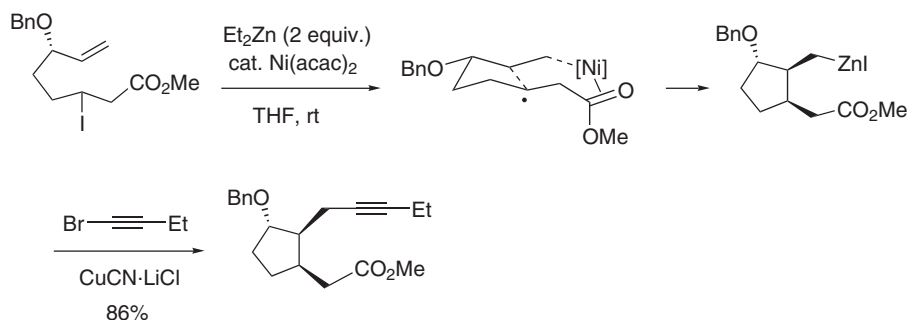


The cyclization of haloalkenes may also be promoted by chromium(II) <1999S1> and manganese(0) <1998SL1075>. For instance, the cyclization of 2-haloethanal acetal **71** was promoted by an active manganese reagent prepared by reduction of Li₂MnCl₄ with magnesium turnings activated by 1,2-dibromoethane (Scheme 25).



Scheme 25

In the presence of organozinc reagents, Ni complexes also catalyze the cyclization of haloalkenes. For an overview of these reactions, see <2000T817, B-2001MI011>. The reaction is initiated by one-electron transfer from the Ni(0) complex onto the alkyl halide. As shown in Scheme 26, an advantage of this method is that the cyclic radical is converted via transmetalation into a stable organozinc halide which can further react to give elaborated compounds <1995AG(E)2723, 1996JOC5743>.

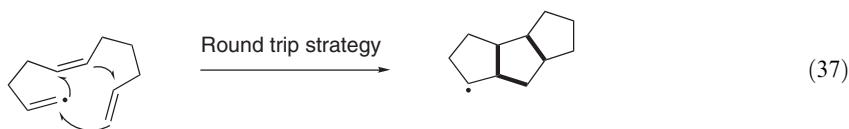
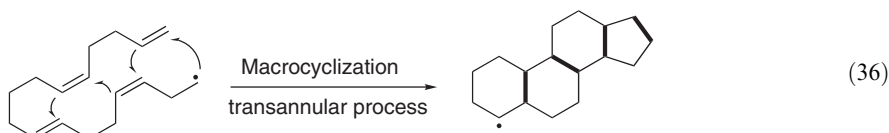
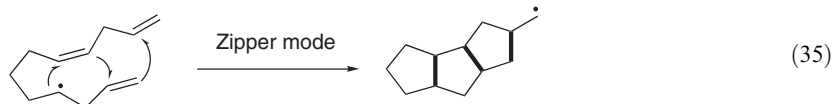


Scheme 26

1.08.1.5 Tandem Processes

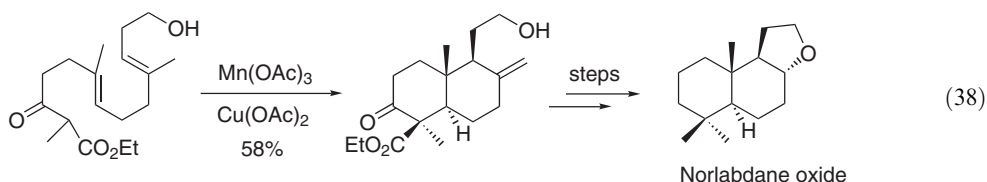
1.08.1.5.1 Intramolecular/intramolecular sequences

Chemical processes that allow the creation of several bonds in a single operation, the so-called cascade, tandem, domino, or sequential reactions, are among the most powerful methodologies in terms of atom economy, cost, and time consumption. In this area, radical strategies have been involved in numerous syntheses of polycyclic structures as reviewed recently [\[2001AG\(E\)2224, 1998S417\]](#). Three general types of cascade reactions starting from linear acyclic precursors have been defined by Curran [\[2000JOC2007\]](#). The first one, the “zipper” strategy, involves an initial radical which starts from the middle of the structure and moves to the end ([Equation \(35\)](#)). The second one, the “macrocyclization-transannular cyclization,” is virtually the reverse of the zipper cyclization, that is to say the initial radical is created at the end of the structure via a macrocyclization and goes to the middle of it ([Equation \(36\)](#)). Finally, the third one which is less common has been called “round trip” strategy. In this case, the radical generated initially goes from one end back to the same end ([Equation \(37\)](#)) [\[1996CRV195\]](#).

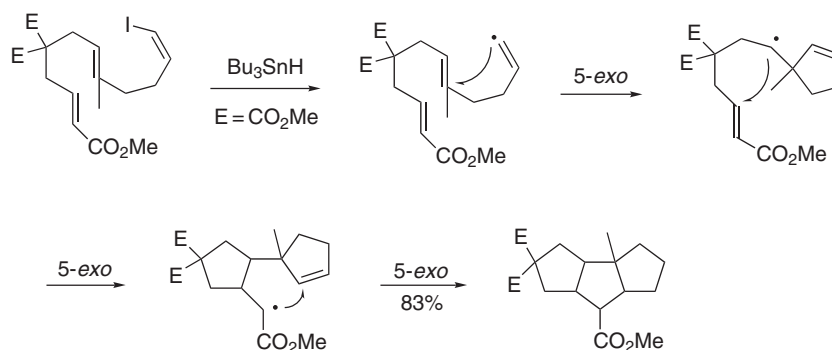


During such reactions the same general rules which govern the regioselectivity and stereoselectivity of normal radical cyclizations can be applied. To avoid a premature termination step, such as reduction with tributyltin hydride, all radical intermediates must add faster to the double bonds than any trapping reactions. Consequently, a low concentration of the hydrogen donor or catalytic methods are required for such processes. Zipper cyclizations are commonly used to prepare easily polycyclic structures. The total synthesis of (+)-paniculin, a tetracyclic compound, has been accomplished using this method [\[1999JA9875\]](#). Pyrrolizidinones have been obtained via a 5-endo/6-endo cyclization sequence [\[1999JCS\(P1\)427\]](#) and an approach to the five-fused rings of pseudocopsinine has been based on a similar method [\[1996T647\]](#). Methods using $\text{Mn}(\text{OAc})_3$ to generate alkyl radicals are also widely used in cascade cyclizations as demonstrated by the synthesis of the tetracyclic diterpene spongiatrol [\[1998JOC1162\]](#) and by the synthesis of norlabdane oxide which is highly valuable in the fragrance industry ([Equation \(38\)](#)) [\[1998JOC4779\]](#). Enantioselective synthesis of the two enantiomers of wilforonide, a bioactive terpene has been realized via a $\text{Mn}(\text{OAc})_3$ -mediated cascade cyclization, by using a chiral ester

derived from (*R*)-pulegone <2001OL1785>. Enantioselective zipper cyclizations using chiral Lewis acids have also been investigated <2002AG(E)3014>.



The macrocyclization-transannular strategy has been used in the synthetic approaches to oestrogen steroids <2001CR(C)571> and taxanes <1998JCS(P1)3181>. A new access to the BCD-ring system of progesterone has been developed <1999TL2363>. Round-trip radical reactions are less common <2000JOC2007>. They have been applied to the synthesis of the triquinane framework via three sequential 5-*exo* cyclizations (Scheme 27) <2001TL2157>. Other tandem processes have been conducted based on atom transfer <2002AG(E)3014, 2002OL1239, 2000T6479> as well as translocation <2002SL1431>.



Scheme 27

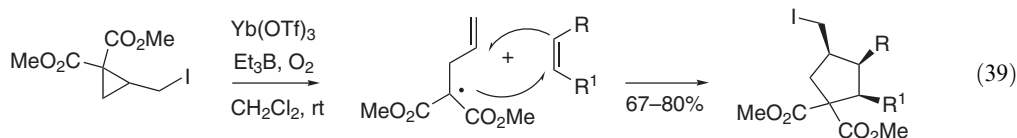
1.08.1.5.2 Intramolecular/intermolecular processes

The concept of a first radical cyclization followed by a second intermolecular addition of the resulting cyclized radical has been used relatively rarely <1991CRV1237, 2002AG(E)3206>. Difficulties encountered mainly arose from a premature intermolecular addition of the initial radical before cyclization. This method has been used for the synthesis of a triquinane skeleton <1994TL7845>.

1.08.1.5.3 Intermolecular/intramolecular additions

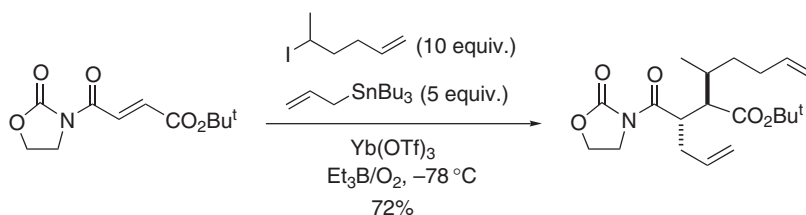
The process of one intermolecular radical addition followed by an intramolecular cyclization is known as annulation. For reviews on radical-mediated annulations reactions, the following reviews have to be read <2003S803, 2001JCS(P1)3215>. One major problem is that the initial and final radicals are often electronically similar so that a further unwanted intermolecular addition can take place <1995COFGT(1)319>. Among all the classical methods developed previously, the fragmentation and atom transfer methods can be employed to terminate the sequence thereby avoiding formation of by-products. Thus, annulation reactions have been realized with diverse atom transfer groups such as xanthate, iodide, and selenide <1998SL1435, 1999EJO477, 1998AG(E)1128>. Based on this concept, an original transformation using a cyclopropane ring-opening methodology for a novel generation of homoallyl radicals has been realized. Such intermediates can add to electron-rich olefins to produce functionalized iodocyclopentanes (Equation (39)) <2001TL2165, 2002JOC922>. Indium has also been used as initiator to produce carbon radicals in such reactions conducted in aqueous media <2003OL3835>. The fragmentation-terminated annulation is another process currently used with the great advantage that the fragmentation of the final intermediate radical is often faster than other competing processes. Trialkylstannanes, phenyl sulfides, and phenyl sulfones are commonly employed as

terminating functional groups <2001OL3679, 2002JA2924, 1997TL4165>. Oxidative radical annulations with $\text{Mn}(\text{OAc})_3$ have also been applied in intermolecular/intramolecular addition reactions <1995SC2337, 1996TL7615>. A tin-free procedure using xanthates as radical precursors and dilauroyl peroxide as the radical initiator has been used in addition/cyclization strategies and applied to the synthesis of natural products <2003OL3717> and nine-membered rings <1999TL9239>.



1.08.1.5.4 Intermolecular/intermolecular additions

Sequential intermolecular/intermolecular additions are scarcely used because of their tendencies to lead to oligomers or polymers. Reactions of this type generally involve conjugate addition of nucleophilic radicals to α,β -unsaturated compounds followed by intermolecular trapping of the resulting radical with allylstannanes as illustrated in Scheme 28 <2003OL2885>. Stereocenters can be created at the α and β carbon atoms in the α,β -unsaturated acceptors, the relative and absolute configuration of which may be controlled using chiral Lewis acid catalysis <1995JA11029, 2003CRV3263>.



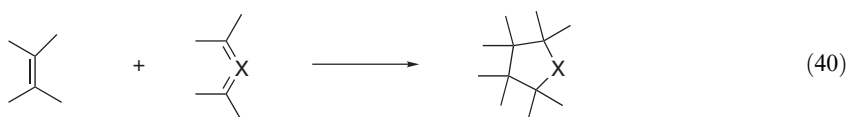
Scheme 28

1.08.2 ELECTROCYCLIC ADDITIONS TO CARBON—CARBON MULTIPLE BONDS TO GIVE TETRACOORDINATE PRODUCTS

1.08.2.1 Introduction

The term “electrocyclic addition” is usually used for reactions which proceed in a concerted manner. As it is often difficult to establish if a cycloaddition reaction is truly concerted, the reactions proceeding via a two step mechanism have been included for short-lived intermediates.

This chapter will focus upon cycloaddition reactions involving $\text{C}=\text{C}$ bonds that have been developed since COFGT (1995) <1995COFGT(1)319>. Most of these reactions are summarized by Equation (40). It should be noted that addition of free carbenes to produce cyclopropanes is not included in this review since the mechanism of “carbene transfer” from these ylides is clearly stepwise. The conventional Diels–Alder reaction which could have been considered for the electrocyclic addition to carbon–carbon multiple bonds is also not discussed here since it will be included most properly in Chapter 1.17.



The reader is strongly recommended to read COFGT (1995) <1995COFGT(1)319>, which covers the general mechanistic aspects and principles of these electrocyclic reactions. Other reviews on this topic have also appeared recently <B-2002MI012, B-2002MI013>.

1.08.2.2 Formation of Three-membered Rings

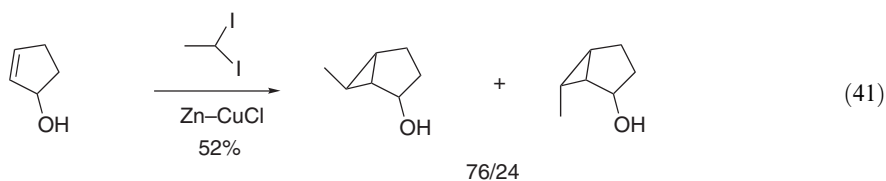
1.08.2.2.1 Addition of free carbenes

Free carbenes are in general too reactive to be useful for the preparation of cyclopropanes. Some competing reactions are generally observed, in particular C—H insertion. For the reasons developed in the introduction, the chemistry of these ylides is not reviewed here. The synthesis of cyclopropanes is more usually achieved by using two classes of reagents, the zinc-based carbenoid reagents and the transition metal-based carbenoid reagents. The cycloaddition chemistry of these derivatives is described below.

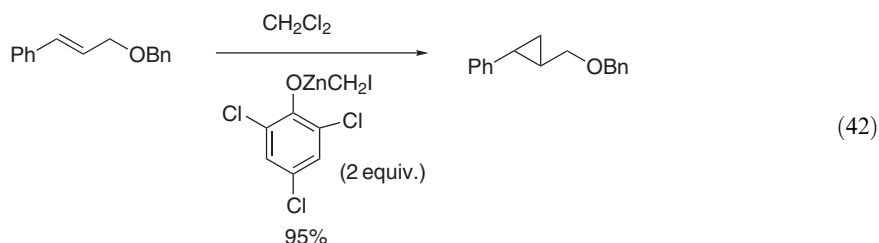
1.08.2.2.2 Addition of metal carbenoids

Among the different methods of cyclopropanation, the Simmons–Smith reaction involving zinc-based carbenoid reagents has been widely studied during the last decade. The most commonly used cyclopropanating agents are generally prepared from diethylzinc and diiodomethane. Alternative methods to prepare these active reagents have been recently introduced [<2001OR11, B-1999MI014>](#).

In this cycloaddition reaction, bond formation proceeds, as if concerted, with retention of stereochemistry and the mechanism of this reaction is therefore referred to as a [2 + 1]-cycloaddition (Equation (41)) [<1982JOC1615>](#).



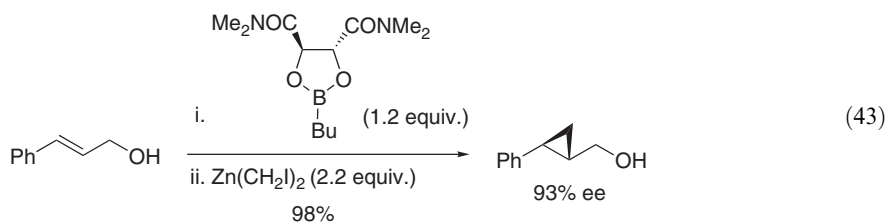
Many publications on the Simmons–Smith reaction have focused on the cyclopropanation of oxygen-containing olefins. In contrast, cyclopropanation of unfunctionalized olefins is much less common, as the absence of a directing group reduces the substrate reactivity toward cyclopropanation. Charette's group reported that some reagents of general structure $\text{ArOZnCH}_2\text{I}$ are very reactive species for the cyclopropanation of unfunctionalized olefins (Equation (42)) [<2000AG\(E\)4539>](#).



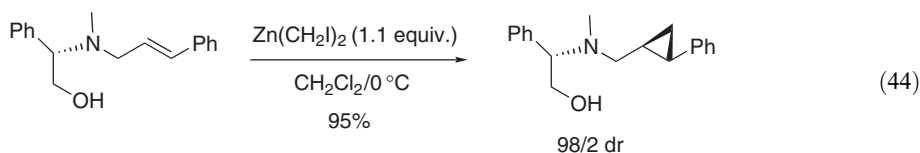
Furthermore, a Simmons–Smith reagent prepared from a 1:1:1 mixture of trifluoroacetic acid, diiodomethane, and diethylzinc can react with alkenes without directing groups especially with stilbene that is often unreactive under classical Simmons–Smith protocols [<1998TL8621>](#).

Recently, many efforts have focused on the development of methods for the preparation of enantio-enriched or enantiomerically pure cyclopropanes using a chiral catalyst or auxiliary [<B-2002MI015>](#). Efficient asymmetric Simmons–Smith reactions have been developed using a variety of chiral auxiliaries such as chiral ketals [<1998CC2479>](#), chiral enol ethers [<1999CL831>](#), chiral vinyl boronic esters [<1996SL893>](#), and chiral allylic ethers [<1999T8845>](#). Most of the asymmetric Simmons–Smith reactions involving chiral catalysts were developed on allylic alcohols. Relatively good enantioselectivities were obtained with a C_2 -symmetric chiral disulfonamide ligand [<1995T12013, 1997JOC584>](#) or TADDOL ($\alpha, \alpha', \alpha', \alpha'$ -tetraaryl-1,3-dioxolane-4,5-dimethanol) and a

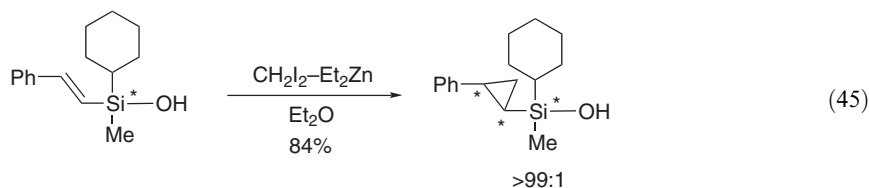
titanium-Lewis acid <1995JA11367>. Charette reported <1998JA11943> a new chiral dioxaborolane ligand derived from tetramethyltartaric acid diamide for the conversion of allylic alcohols, unconjugated and conjugated polyenes, and homoallylic alcohols into the corresponding enantio-merically enriched cyclopropanes (Equation (43)).



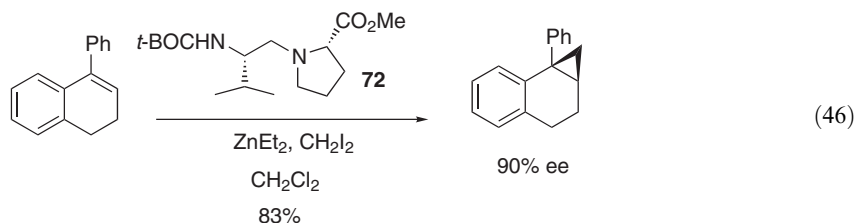
The first diastereoselective Simmons–Smith cyclopropanation of allylic amines was recently achieved by using chelating groups in close proximity to the amine <2003OL4417>. Best results were obtained with allylic amines derived from (1*R*,2*R*)-pseudoephedrine (Equation(44)). The success of the cyclopropanation was attributed to the formation of a chelating complex between the zinc reagent and the chiral amino alcohol group.



A diastereoselective Simmons–Smith cyclopropanation of chiral nonracemic alkenylsilanols was recently reported <2002TA13>. In this reaction, the stereogenicity of the silicon center was successfully transferred to the carbons via the Simmons–Smith cyclopropanation. However, the introduction of a bulky substituent such as a cyclohexyl group on the silicon atom is necessary to improve the diastereoselectivity (Equation (45)).

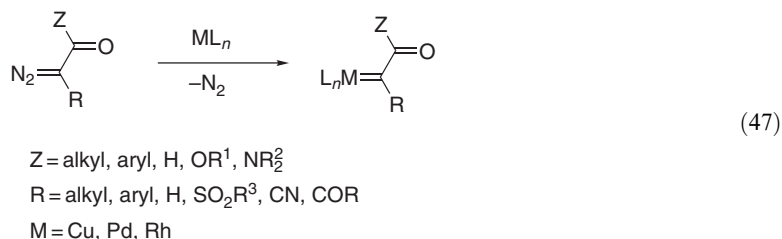


The common feature of the preceding strategies is the involvement of a directing heteroatom in the alkenyl substrate. It was recently shown that the asymmetric Simmons–Smith cyclopropanation of unfunctionalized olefins can be realized by treating the dipeptide **72** with ZnEt₂ and CH₂I₂ <2003JA13632>. For example, when a dihydronaphthalene was used as a substrate, the corresponding cyclopropanation product was obtained in 83% yield and 90% ee (Equation (46)).

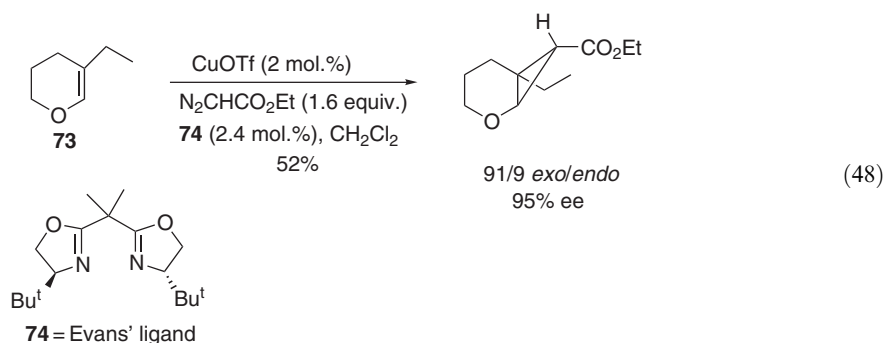


The transition metal-catalyzed reactions of diazo compounds with various alkenes are another route to make cyclopropanes. Metal-stabilized keto carbenoids have been widely used for this

purpose and are efficiently prepared by reaction of diazo esters or diazo ketones with rhodium(II), palladium(II), and copper(I) or (II) salts (Equation (47)).

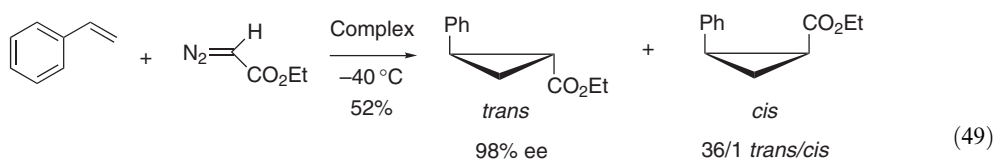


The reaction between metal carbenes derived from α -diazocarbonyl compounds and alkenes assisted by metal complexes has been intensively studied over the last 10 years and is summarized in several reviews <1994AG(E)497, 1998CRV911, 1998T7919, 1995COMCII387, B-1998MI016>. New work in this area includes studies on the diastereocontrol and enantiocontrol during the intermolecular cyclopropanation of unsymmetrical olefins. Since the pioneering work of Nozaki and co-workers' <1968T3655> extensive studies have been conducted for the synthesis of enantiomerically enriched cyclopropanes using chiral copper(I), ruthenium(II), or rhodium(II) catalysts. The most important progress in this area was made with copper complexes incorporating chiral ligands such as C₂-symmetric semicorrin <1986AG(E)1005>, bisoxazolines <1992AG(E)430> or ferrocene Schiff bases <1998SL617, 1998JA10270>. A typical example is the asymmetric cyclopropanation of cyclic enol ethers such as dihydrofuran **73** <1998JOC6007>. An enantioselectivity higher than 95% and an excellent diastereoselectivity have been reported by using ethyl diazoacetate and Evans' bisoxazoline ligand **74** (Equation 48)). This reaction was used as the key step in the asymmetric synthesis of (+)-quebrachamine, an indole alkaloid.



Chiral ligands have also been used to modify rhodium and ruthenium catalysts. In particular, Doyle and co-workers <1997CC211> have compared the enantiocontrol obtained in the intramolecular cyclopropanation of diazoacetates using chiral copper, rhodium, and ruthenium catalysts.

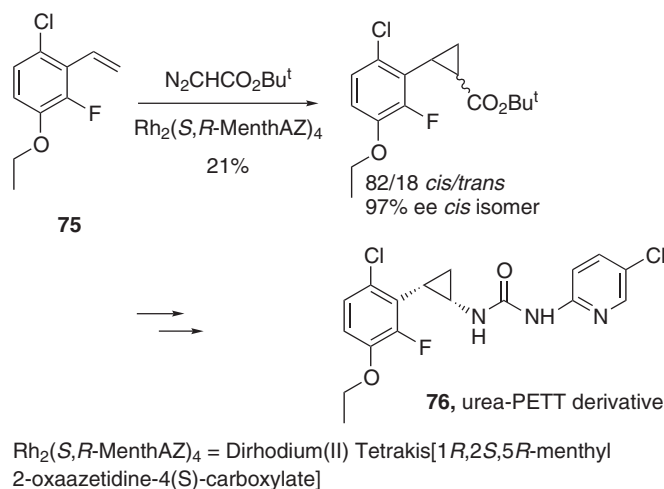
The cyclopropanation of styrene with alkyl diazoacetates is often studied as a model for the diastereoselectivity of this reaction. However, this selectivity is often rather poor and most catalysts lead to *cis/trans* ratio in the range 1/1 to 1/3 <1998T7919>. Recent studies have showed that it is possible to increase significantly the proportion of the *trans*-isomer. Chiral copper, cobalt, and ruthenium catalyst generally showed a marked preference for the *trans*-isomer. Cyclopropanation of styrene with ruthenium-Pybox (2,6-bis (oxazolynil)pyridine) as catalyst results in high enantioselectivity (ee up to 91%). Asymmetric intermolecular cyclopropanations of alkenes with diazoacetates catalyzed by chiral ruthenium porphyrins <1997CC927, 2001JA4119> or cobalt porphyrins <2003JOC8179> were recently studied. In particular, it was shown that cyclopropanation of styrene with ethyl diazoacetate, in the presence of a chiral ruthenium porphyrin [Ru(P*)(CO)(EtOH)], gives the corresponding cyclopropyl esters in up to 98% ee with high *trans/cis* ratios and extremely high catalyst turnovers when the reaction was performed at -40 °C (Equation (49)).



complex: [Ru(P*)(CO)(EtOH)]

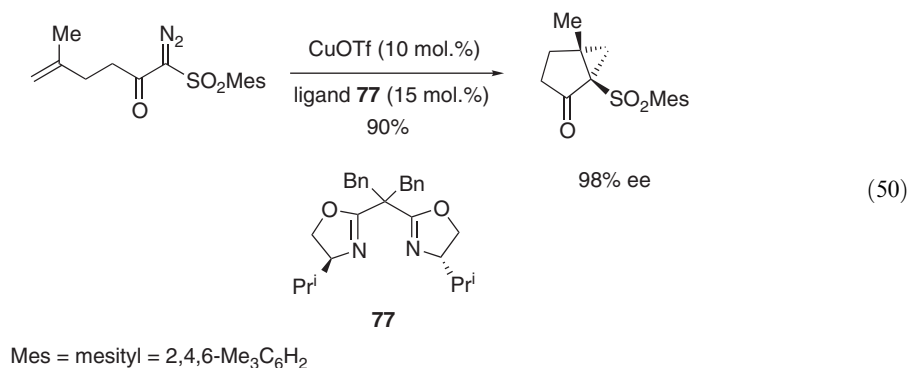
P* = 5,10,15, 20-tetrakis(1*S*,4*R*,5*R*,8*S*)-1,2,3,4,5,6,7,8-octahydro-1,4:5,8-dimethanoanthracene-9-yl]porphyrinato dianion

The preparation of the *cis*-disubstituted cyclopropanes is often challenging and few catalysts are known to favor the formation of the *cis*-isomer. Remarkable high *cis*-selectivity (up to 98/2) and high enantioselectivity (up to 98% ee) was reported for the reaction of styrene with *t*-butyl diazoacetate in the presence of ruthenium-salen [<1999SL1163>](#) or cobalt-salen [<2000T3501, 2000TL3647>](#). Very high values of diastereoselectivity (*cis/trans* 97/3) toward the *cis*-isomer have also been obtained for styrene when using a copper(I) homoscorpionate catalyst [<2002JA978>](#). Doyle and co-workers developed a new azetidine-ligated dirhodium(II) catalyst having a 1-menthyl ester attachment that provided a significant diastereocontrol (up to 82:18) and high enantiocontrol for the preparation of the *cis*-cyclopropane adduct from reaction of the trisubstituted styrene **75** with *t*-butyl diazoacetate ([Scheme 29](#)). The *cis*-cyclopropane isomer was then converted to the urea-PETT derivative **76** (PETT = phenyl-ethylthiazolylthiourea), a new class of potent non-nucleoside HIV-1 reverse transcriptase inhibitors [<2002OL901>](#).

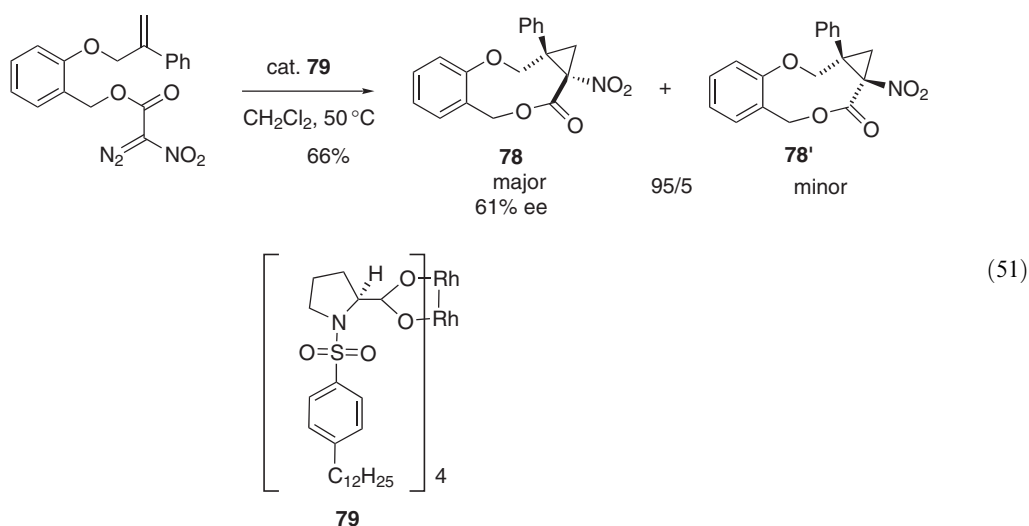


Scheme 29

Intramolecular cyclopropanation reactions of alkenyl diazocarbonyl compounds have been widely used in organic synthesis to prepare polycyclic structures such as bicyclic ketones with a cyclopropane ring fused to cyclopentanes or cyclohexanes. In these cases, the problems of stereochemistry are avoided since the diastereocontrol is fixed [<1991COS\(4\)1031>](#). Recently, attention has been directed to the development of the enantioselective version by means of chiral transition metal catalysts. Only modest enantioselectivities have been found for α -diazo- β -keto esters [<2001HCA1093>](#) while excellent enantioselectivities have been obtained for the catalytic asymmetric intramolecular cyclopropanation of α -diazoketones [<1995SL491, 2001OL3317>](#), and more recently of α -diazo- β -keto sulfones [<2003JA2860>](#) (Equation (50)).



The first intramolecular cyclopropanation of α -nitro α -diazocarbonyls was reported recently <2003JMOC83>. The nine-membered nitro cyclopropyl lactone **78** was obtained in high diastereoselectivity and with enantioselection up to 61% when using the commercial chiral Rh(II) carboxylate **79** (Equation (51)).



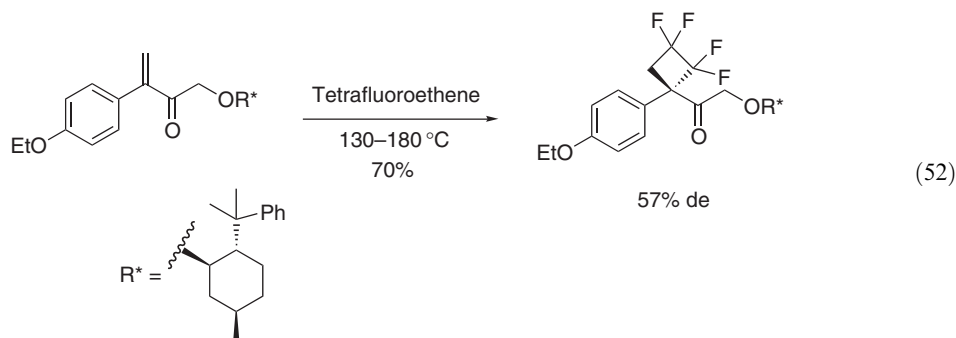
1.08.2.3 Formation of Four-membered Rings

One of the most efficient strategies for the construction of the four-carbon ring system is the [2+2]-cycloaddition of alkenes. The thermal suprafacial [2+2]-cycloaddition of alkenes being forbidden by the Woodward–Hoffmann rules, this cycloaddition has been achieved in three ways: (i) by thermal reactions via biradical intermediates, (ii) photochemically, or (iii) by metal catalysis. This topic has been recently reviewed <2003CRV1449>.

1.08.2.3.1 Thermal [2+2]-additions

The thermal suprafacial [2 π +2 π]-addition of alkenes is forbidden by the Woodward–Hoffmann rules. However, such additions do occur. The review by Baldwin <1991COS(5)63> as well as the introduction to this topic in March <B-1992MI017> are recommended for further reading.

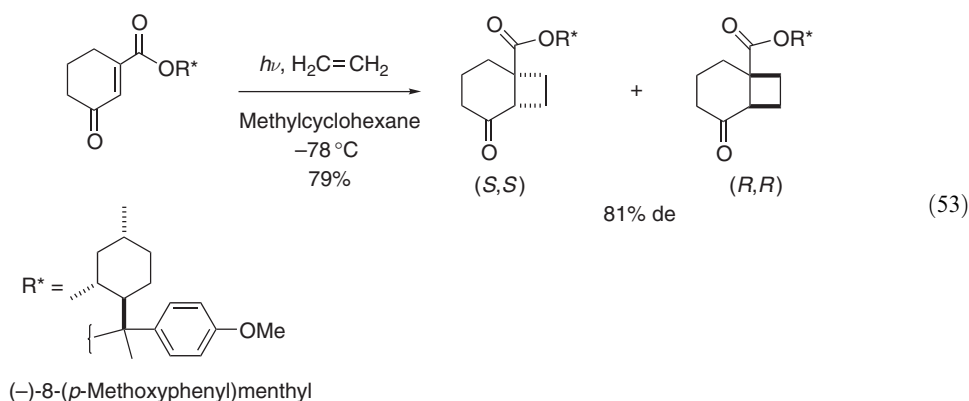
A diastereofacial selectivity is generally observed in thermal [2+2]-additions <1991COS(5)63>. This point is illustrated in Equation (52) by the cycloaddition of tetrafluoroethene to acrylate esters derived from chiral auxiliaries leading to the formation of tetrafluorocyclobutane esters <1997TL4277>. The largest stereoselectivity was found for the case of (–)-(1*R*,2*S*,5*R*)-8-phenylmenthyl ester, the addition of the tetrafluoroethene occurring preferentially on the *si*-face of the chiral-substituted alkene.



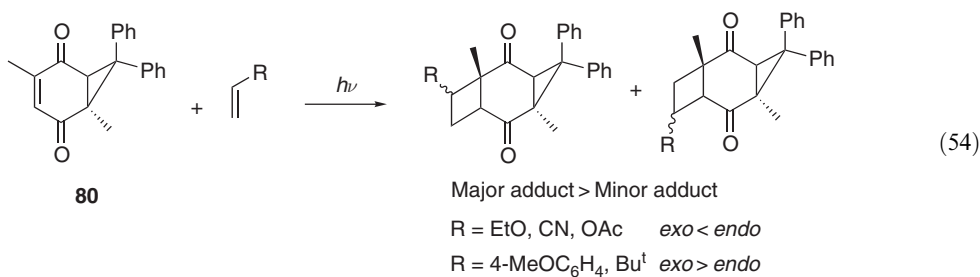
1.08.2.3.2 Photochemical [2+2]-additions

[2+2]-Photocycloaddition of activated alkenes is the most useful route to cyclobutane derivatives and has been the subject of several recent reviews <1995CRV2003, 1996MI135, 1993OR297, 1998S683>.

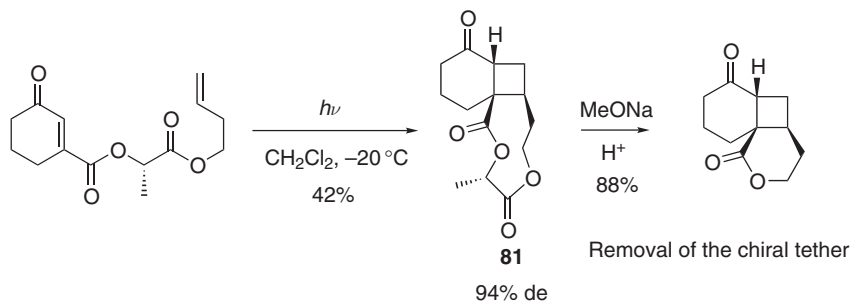
The diastereoselective [2+2]-photocycloaddition of cyclohexenone carboxylates bearing a chiral auxiliary to ethene was recently studied <2003CHIR504>. Best results (de = 81%) were obtained using the (–)-8-[(*p*-methoxy)phenyl]menthyl group (Equation (53)). In order to rationalize the origin of the diastereoselectivity, it was suggested that the *s-trans*-stacked conformer (ST) is the most stable of all the conformers.



The [2+2]-photocycloaddition of alkenes to cyclic enones generally leads to the formation of several regio- and stereoisomers depending on the nature of the substituents of the alkenes and enones <1998S683>. The reaction in Equation (54) illustrates the substituent effects on the stereochemistry in the [2+2]-photocycloaddition of homobenzoquinone **80** with various substituted alkenes. The preferred regioisomer for all the reactions was attributed to the more stable 1,4-biradical intermediate (major addition mode) and the minor isomer was attributed to the less stable biradical (minor addition mode). With respect to the stereoselectivity, the alkenes with relatively small substituents (R = EtO, CN, OAc) preferentially gave the *endo*-adducts while *exo*-selectivity was observed with larger substituents (R = aromatic or *t*-butyl groups) <2002JA8912>.

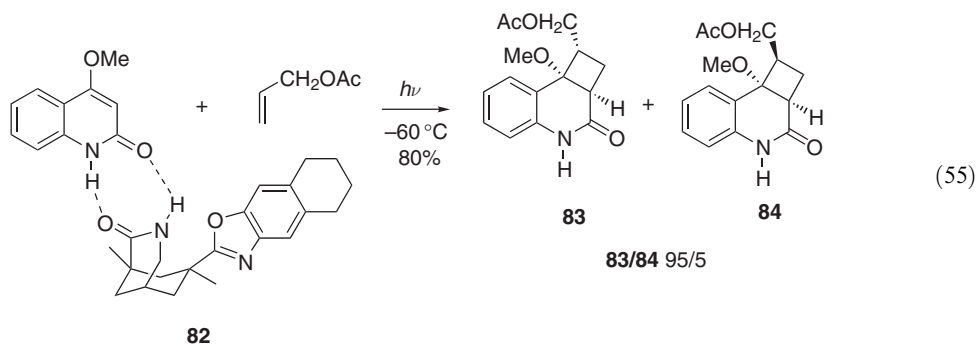


An interesting application of the chiral tether methodology with alkenes having a chiral auxiliary group is illustrated in [Scheme 30](#) [<1997TL1045, 2002JOC1061>](#). One of the major advantages of this method compared to other diastereoselective [2+2]-photocycloadditions using different temporary chiral linkers is the easy removal of the tether group. Compound **81** was obtained with very good π -facial selectivity with a diastereomeric excess up to 94%.



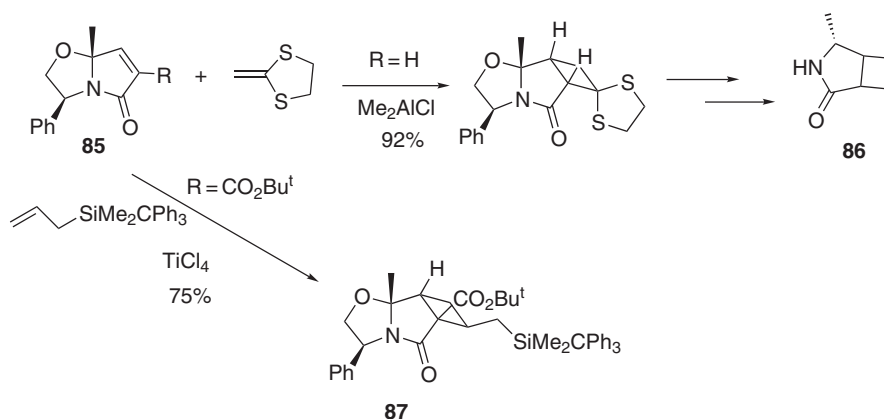
Scheme 30

A new concept based on the use of chiral complexing agents (hosts) binding one substrate and thereby inducing facial discrimination was recently developed. In the presence of the chiral benzoxazole **82** (chiral host), highly enantioselective inter- [<2002JA7982>](#) and intramolecular [<2000AG\(E\)2302>](#) [2+2]-photocycloaddition reactions have been conducted. The chiral information was almost completely transferred from the host to the corresponding substrates **83** and **84**. The differentiation of the enantiotopic faces of the prochiral quinolone was explained by assuming a coordination of this substrate to the lactam via two hydrogen bonds ([Equation \(55\)](#)).

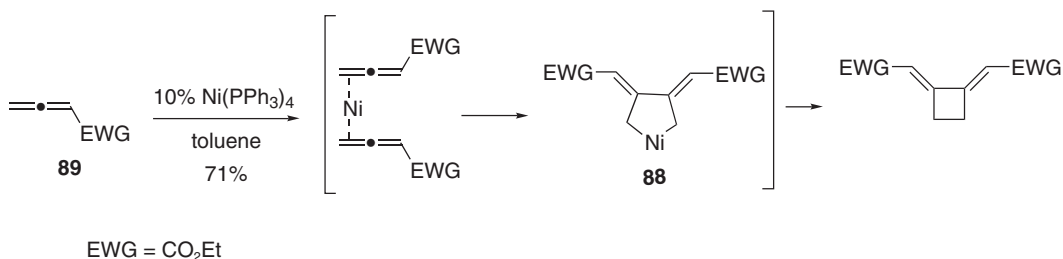


1.08.2.3.3 Metal-catalyzed [2+2]-additions

While photochemically promoted [2+2]-cycloadditions of alkenes have been intensely studied since the 1990s, related metal-catalyzed [2+2]-cycloadditions are less exemplified [<1996CRV49>](#). Some of them are catalyzed by Lewis acids. Methyleneedithiolane was shown to be an excellent cycloaddition partner for the reaction with chiral lactam **85** (R = H) in the presence of dimethylaluminum. The cyclobutane adduct was obtained as a single diastereomer. Removal of the phenylglycinol auxiliary by reductive cleavage gave the cyclobutane-pyrrolidinone **86** in 92% yield and in very high ee values (>99%). This fused pyrrolidinone represents a rigid analog of γ -aminobutyric acid (GABA), which has been shown to act as an inhibitory neurotransmitter in the brain [<1995JOC4359>](#). A novel route to the formation of an enantiomerically pure cyclobutane-fused pyrrolidine **87** was recently developed [<2001T2635>](#) using a similar Lewis-catalyzed (TiCl_4) cycloaddition of a silyl allyl ether with the substituted chiral bicyclic lactam **85** (R = CO_2Bu^t) ([Scheme 31](#)).



The thermal [2+2]-annulation of allenes generally leads to the formation of bis-methylenecyclobutanes as a mixture of regioisomers. It was recently shown [\[2000JA10776\]](#) that the nickel-catalyzed [2+2]-annulation of electron-deficient allenes proceeds efficiently in a highly regioselective manner under very mild conditions to afford the head-to-head bis-methylenecyclobutanes as single isomers ([Equation \(56\)](#)). The high regioselectivity of the reaction was explained by the regioselective formation of the metallacycle **88**, which could be controlled by the electronic and steric effects of the substituent of the electron-deficient allenic substrate **89**.



(56)

1.08.2.4 Formation of Five-membered Rings

1.08.2.4.1 [3+2]-Additions of three-carbon fragments

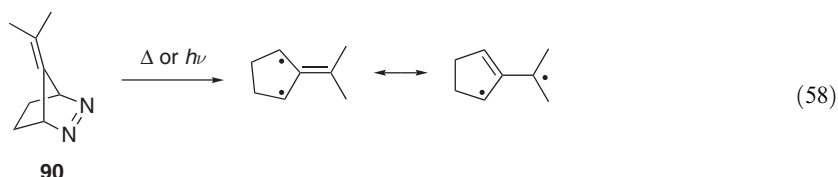
(i) Additions of trimethylenemethane

Trimethylenemethane (TMM) has been the subject of numerous studies [\[1972ACR242, 1978ACR446\]](#). The reader is also directed to the review of Nakamura [\[2002ACR867\]](#). TMM and its derivatives possess four π -electrons which, on addition to alkenes, give cyclopentanes. Free TMM ([Equation \(57\)](#)) is too reactive to be synthetically useful [\[1986AG\(E\)1\]](#) but the successful use of precursors is described below.

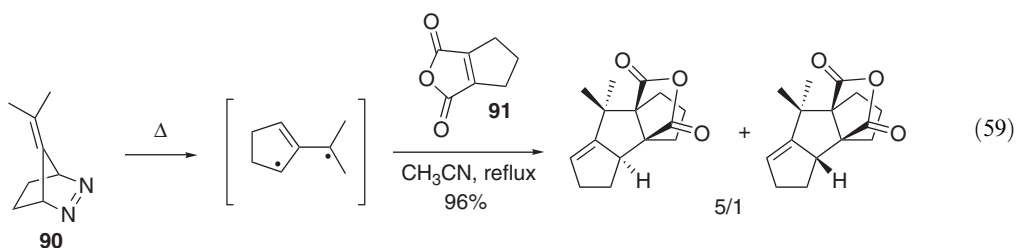


(57)

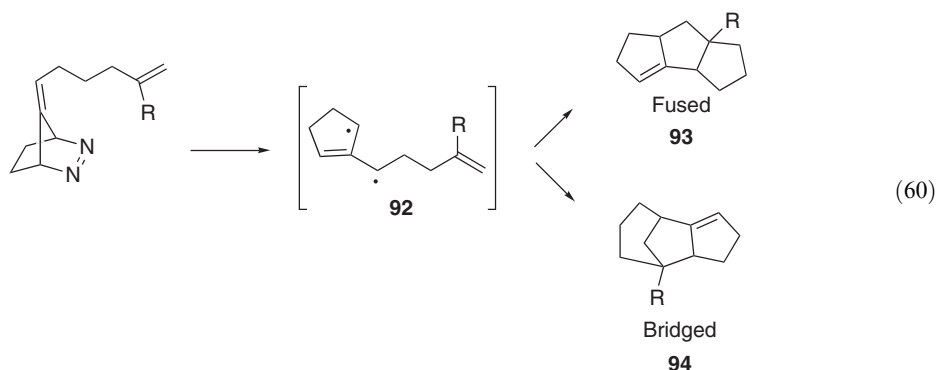
(a) *2-Alkylidenecyclopentane-1,3-diyls*. Diyl species are generated either photochemically or thermally from bicyclic diazenes ([Equation \(58\)](#)). The diyl typically equilibrates before cycloaddition. This very reactive species can be trapped either inter- or intramolecularly by various electron-deficient alkenes and alkynes to produce a great variety of ring systems. The various methods for the preparation of these trimethylenemethane-like diradicals (TMM diyls) and their chemical reactivity have been reviewed [\[1992SL107, 1996CRV93, 1998EJO1\]](#).



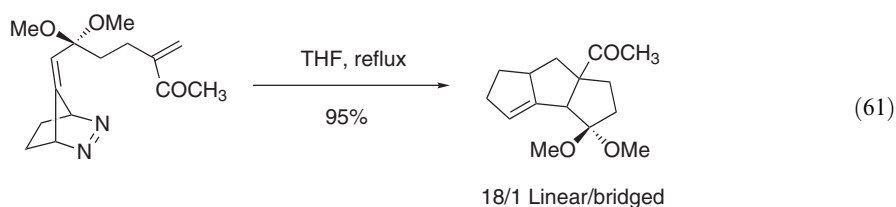
A low regio- and stereoselectivity is generally associated with the intermolecular cycloaddition reaction with unsymmetrical electron-deficient alkenes <1996CRV93>. Little and co-workers investigated <1996JOC1787> the intermolecular trapping of the dimethyl diyl **90** with symmetrical diylophiles such as the bicyclic anhydride **91**. A preferred isomer resulting from the *endo*-transition state was obtained. It was suggested that, in this case, secondary orbital interactions between the diyl and the diylophile could play a role in determining the stereochemical outcome of the diyl trapping cycloaddition (Equation (59)).

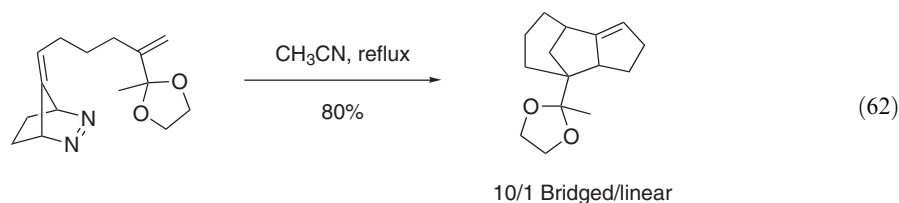


The intramolecular diyl-cycloaddition reaction has been used to prepare complex tricyclic structures. In this case, the intermediate **92** can undergo two different cycloaddition modes to give the linearly fused adduct **93** or the bridged-tricyclic skeleton **94** (Equation (60)).

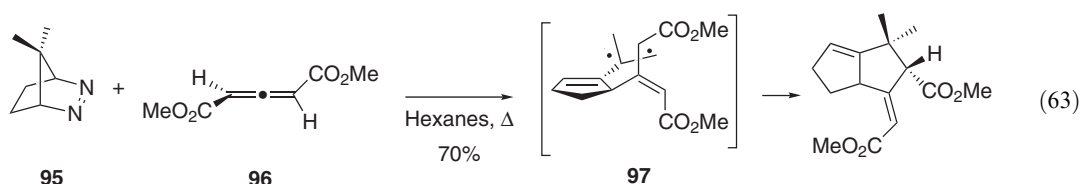


It is possible to selectively form either regioisomers and the two typical examples in Equations (61) and (62) illustrate this point <1997JOC1610>. Bridged-adducts are obtained via a 6-*endo-trig* cyclization when a large substituent is present on the internal carbon of the diylophile (Equation (62)), while a less bulky substituent such as the acetyl group led to the formation of the linear fused tricyclic adduct via a 5-*exo-trig* process (Equation (61)).

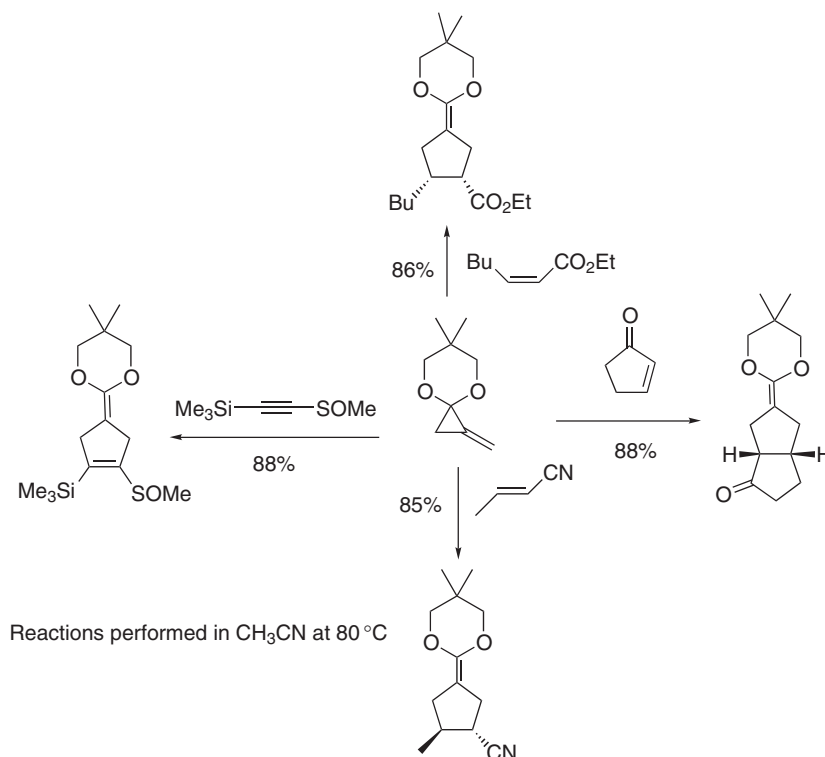




The first example of the intermolecular diyl trapping reaction using allene diyllophiles was reported by Little and co-workers. The cycloaddition of the diazene **95** and symmetrical allene diester **96** led to only one regio- and stereoisomer [<1997TL15>](#). The stereochemical outcome of the reaction was rationalized by suggesting that diradical **97** preferentially adopts a geometry wherein the plane of the five-membered ring and the five-carbon side chain are nearly perpendicular ([Equation \(63\)](#)).

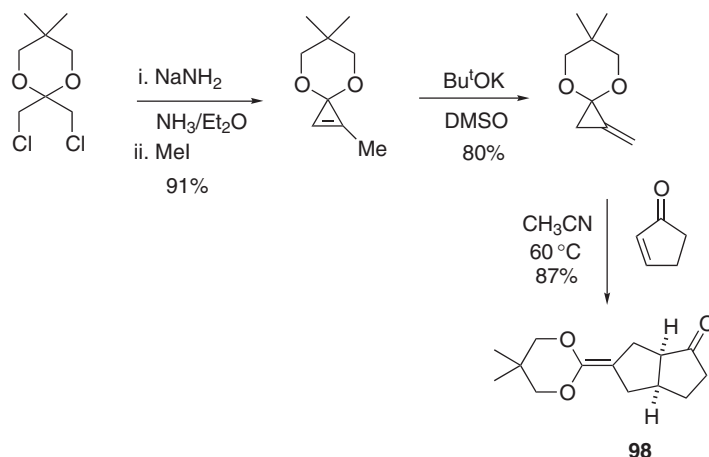


(b) *Trimethylenemethane acetals*. The use of 1,1-dialkoxy-2-methylenecyclopropane (DMCP) as a precursor of trimethylenemethane (TMM) was pioneered by Nakamura [<1989JA7285>](#). This TMM species undergoes [3 + 2]-cycloadditions to a variety of electron-deficient alkenes and alkynes. Generally, the reaction proceeds with retention of the olefin geometry ([Scheme 32](#)). The thermal reaction of these dipolar trimethylenemethane species has been recently reviewed [<2002ACR867>](#).



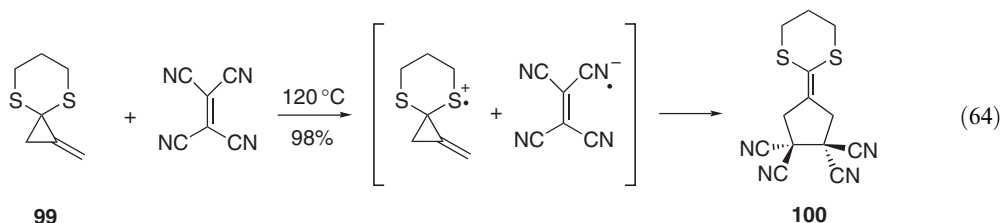
Scheme 32

Further investigations by the same group <1993JA5344> established that the thermal [3 + 2]-cycloadditions of the dipolar TMM with a variety of electron-deficient alkenes take place through an *endo*-transition state (concerted *endo*-cycloaddition). However, a stepwise cycloaddition of this dipolar TMM was observed with highly electron-deficient substrates such as benzyl methyl β -(methoxy)methylenemalonate. The simplicity of the cycloaddition of TMM acetals, which can be prepared in three steps from the commercially available 1,3-dichloro-2-propanone, makes this method of cyclopentane synthesis very attractive <2002OS1>. This was illustrated by a preparative scale synthesis of the bicyclo[3.3.0]octane **98** by this route (Scheme 33).

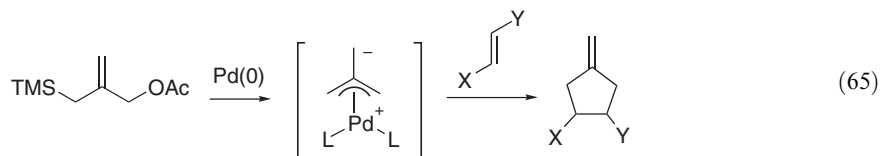


Scheme 33

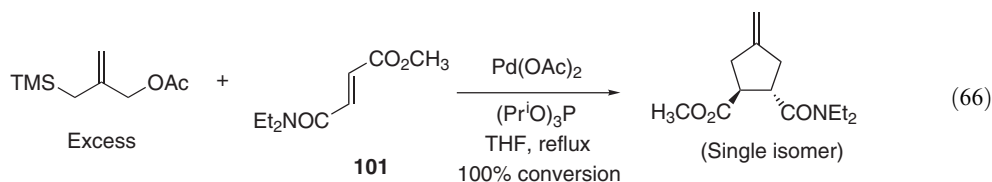
The cyclization of the dialkylthio analog is restricted to highly electron-deficient olefinic substrates. This reaction is supposed to take place via radical ions pairs. For example, the dithiomethylenecyclopropane **99** was shown to react with tetracyanoethylene to give the ketene dithioacetal adduct **100** in 98% yield when the reaction was carried out at 120 °C (Equation (64)) <1999OL7>.



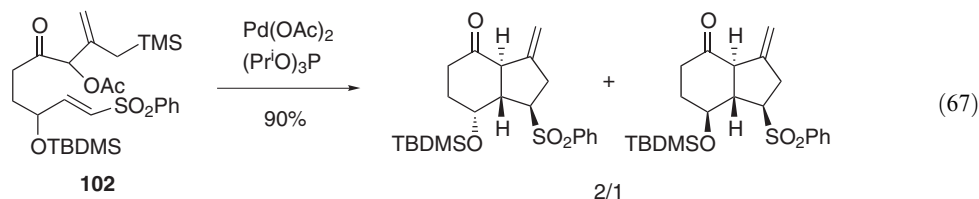
(c) *Transition metal-trimethylenemethane complexes.* Palladium complexes of trimethylenemethane (Pd-TMM complexes), generated by reaction of 3-acetoxy-2-trimethylsilylmethyl-1-propene or substituted derivatives with a Pd(0) catalyst, are known to react with electron-deficient olefins to produce methylenecyclopentanes (Equation (65)). The chemistry of these transition metal trimethylenemethane complexes has been studied in detail by Trost and co-workers and has been the subject of several reviews <1986AG(E)1, 1996CRV49, 1988PAC1615, 1991COS(5)271>.



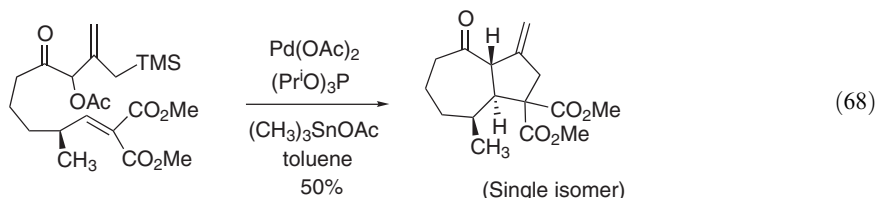
A mixture of *cis*- and *trans*-adducts is generally obtained in the reaction with *cis*-alkenes. This lack of stereospecificity suggests a stepwise process involving a conjugate addition at the first step. However, a concerted mechanism has recently been proposed <1999JA9313> for the palladium trimethylenemethane cycloaddition of the “nearly symmetrical fumarate ester amide” **101**. Carbon kinetic isotope effects were determined at natural abundance for this reaction and the results strongly suggested a concerted process for this cycloaddition (Equation (66)).



Intramolecular cycloadditions involving the palladium complex of trimethylenemethane have been developed [<1991JA7363, 1992JOC686>](#). The cyclization of the linear substrate **102** having a vinyl sulfone was found to be highly regioselective. However, only a 2/1 diastereofacial selectivity was observed during the formation of the perhydroindane ring ([Equation \(67\)](#)).

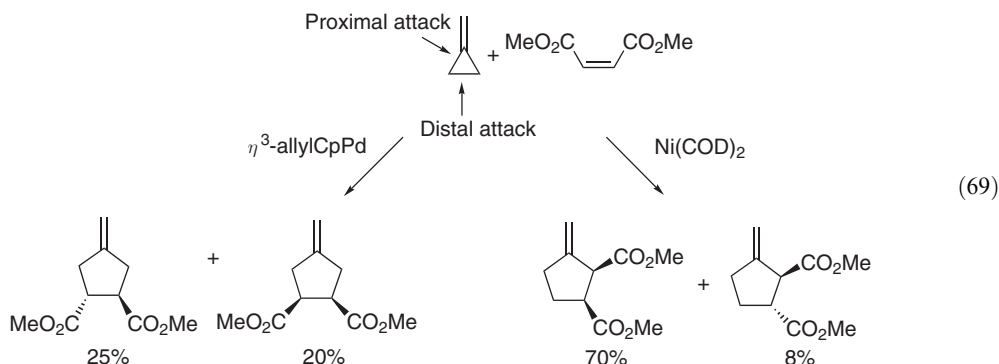


The factors that influence the stereocontrol of trimethylenemethane intramolecular cycloadditions were then studied by the same group [<1996JA10094>](#). The diastereoselectivity of palladium-catalyzed TMM cycloaddition with respect to the stereogenic center adjacent to the acceptor has been shown to be very high with doubly activated acceptors ([Equation \(68\)](#)). Thereby, the *Z*-situated ester group was proposed as a diastereoselective control element. The effect of this *cis*-substituent on the alkene was rationalized by an analysis of the possible cyclization intermediates. A conformer seems to be preferred among the four possible reactive conformers due to the interactions associated with this substituent.

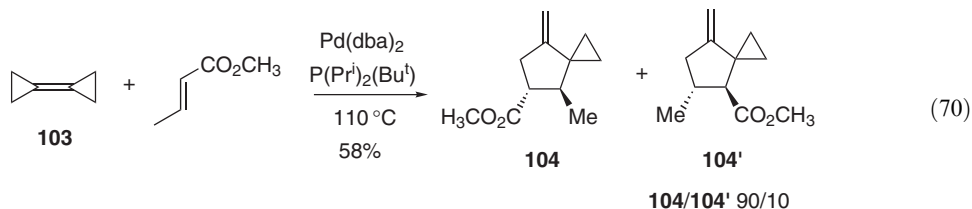


Asymmetric versions of this reaction have been carried out using chiral olefins and good diastereoisomeric excesses were obtained for the cycloaddition of these TMM species to chiral sulfoxides [<1989TL1803>](#), chiral cyclohexenyl sulfones, [<1989JA7487>](#) and chiral allylic ketals [<1993S129>](#).

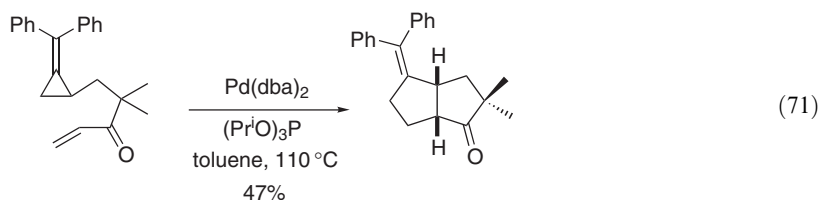
Another synthetic route to methylenecyclopentanes involves the palladium(0)- or nickel(0)-catalyzed additions of methylenecyclopropanes to electron-poor alkenes. This approach was pioneered by both Noyori [<1970JA5780>](#) and Binger [<1987TCC77>](#). Extensive studies by Binger and co-workers revealed that the regiochemical outcome of the [3+2]-cycloaddition of methylenecyclopropane is dependent on the nature of the catalytic system ([Equation \(69\)](#)). Palladium catalysts gave cycloadducts derived from distal ring cleavage, whereas, with “naked” nickel catalysts, the cycloadducts resulted from cleavage of the proximal bond of the cyclopropane. This topic has been reviewed [<1996CRV49, 1995COMCII923>](#).



The palladium-catalyzed [3+2]-cycloaddition of bicyclopropylidene **103** with electron-poor alkenes was recently investigated and it was found that the cycloaddition proceeds with high regioselectivity with respect to the bicyclopropylidene and with high regio- and stereoselectivity with respect to the alkene. For example, reaction of bicyclopropylidene **103** with methyl acrylate produced the 4-methylenespiro[2.4]heptane derivative **104** as a mixture of diastereomers. This compound results from a distal cleavage of one of the three-membered rings of **103** (Equation (70)) <1998EJO113>.



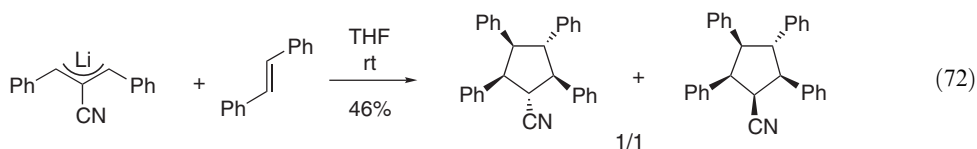
Intramolecular palladium-catalyzed cycloaddition reactions of methylenecyclopropanes containing olefinic (Equation (71)) or acetylenic acceptors have been developed by Motherwell and co-workers. Functionalized bicyclo[3.3.0]octanes were obtained in a regiocontrolled manner via distal cleavage of the cyclopropane ring <1995T3289, 1995T3303>.



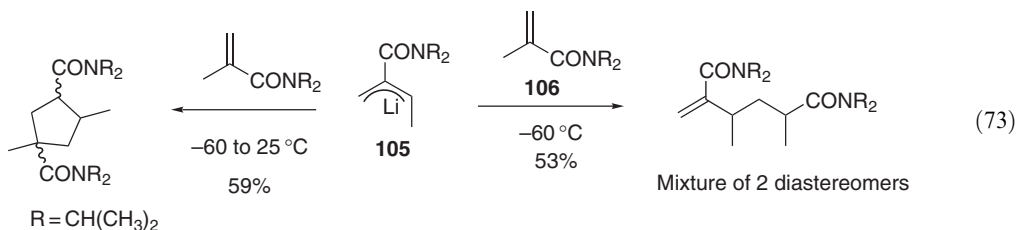
(ii) Additions of allyl anions

Anionic [3+2]-cycloaddition of allyl anions or allyllithium compounds to double or triple bonds is an efficient method for the formation of carbocyclic five-membered rings. This work was pioneered by Kaufmann and co-workers <1970AG(E)380> and was further extended notably by Beak and co-workers <1986JOC4627, 1989JOC1647>. Allyl anions are very electron-rich systems, which react with olefins having aromatic or electron-withdrawing substituents.

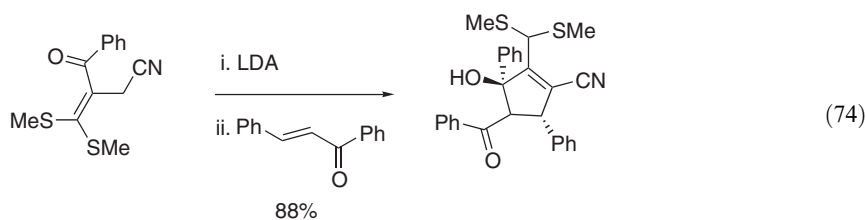
Some allyl anions are known to react stereospecifically without forming any open-chain side products <1986JOC4627>. As an example, the addition of 2-cyano-1,3-diphenylallyllithium to *trans*-stilbene gave only two diastereomers among the 10 possible (Equation (72)).



Subsequent investigations <1998JA3357> have shown that cycloadditions of allyl anions with dipolarophiles may occur in a stepwise or concerted manner. Indeed, it was found that the reaction of 2-carbamoylallyllithium **105** with its parent alkene **106** was strongly dependent on the temperature. The cyclopentane was produced at 65°C while open-chain products were obtained at -60°C (Equation (73)).

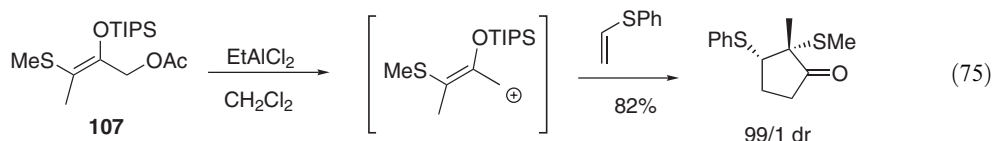


The allyl anion derived from deprotonation of benzoyl(cyanomethyl)ketene dithiacetal with lithium diisopropylamide (LDA) was shown to undergo anionic [3 + 2]-annulation with various activated olefins via tandem-Michael addition-aldol condensation to afford the corresponding cyclopentenones in a highly diastereoselective manner <1994JCS(P1)2439> (Equation (74)).



(iii) Additions of allyl cations

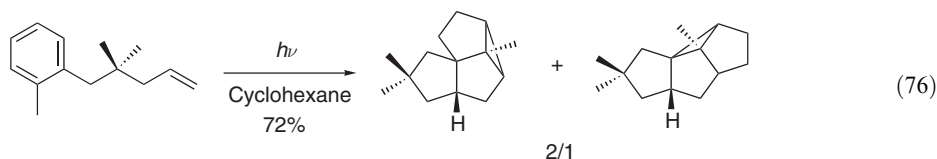
The use of alkoxy and trialkylsilyloxy groups for the preparation of allyl cations has been studied by Hoffmann and co-workers <1988T3899>. There has been little further development in this area. However, a new synthetic method for the preparation of functionalized cyclopentenones was developed by the group of Kuwajima on the basis of a [3 + 2]-cycloaddition reaction of 1-(methylthio)-2-siloxyallyl cationic species with various olefins such as enol ethers, vinyl sulfides, styrenes, and trialkylefins (Equation (75)). The methylthio group on the three-carbon unit was chosen for its important role in stabilization of the 2-oxyallyl cation intermediate as well as in control of the regiochemistry. These allyl cationic species were prepared by reaction of 1-(methylthio)-2-siloxyallyl acetates with a Lewis acid, generally EtAlCl₂ or AlCl₃. The reaction proceeds with almost complete regioselectivity and the sterically more hindered regioisomer was predominantly formed in every case. In particular, a high stereoselectivity was observed in the reaction of **107** with vinyl sulfide <1998JA1724>. Similar methylenecyclopropane annulation could also be effected by using a substrate having a -CH₂TMS group in place of the siloxy group <1996TL5943>. This strategy was used by the same group for the synthesis of (-)-coriolin, a triquinane having important biological activities <1999JOC2648>.



The intramolecular version of the [3 + 2]-cycloaddition reaction of allyl cations has been recently reviewed <1997T6235>.

(iv) Meta-photocyclization of arenes

The inter- as well as the intramolecular version of the *m*-photocycloaddition of arenes to alkenes have been shown to be useful methods for the preparation of complex molecules <1996JOC3576, 1996TL7687> (Equation (76)).

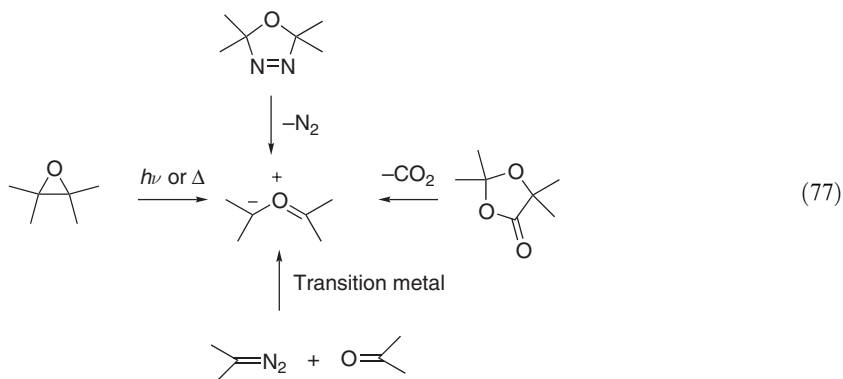


This topic has been reviewed by Cornelisse <1993CRV615> and more recent work in this area has been developed by the same group <1999EJO463>.

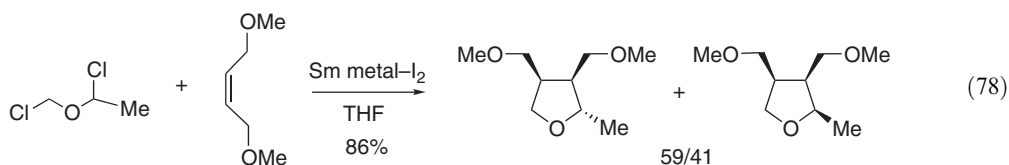
1.08.2.4.2 [3+2]-Additions of CXC fragments

(i) Additions of carbonyl ylides

The earliest approaches to carbonyl ylides involved thermolysis of certain epoxides <1981T3345, 1998JCS(P1)313>, oxadiazolines <2000JCS(P1)2161> or dioxolanones <1991COS(4)1069>, as well as the reaction of a carbene or carbenoid with a carbonyl compound <1989TL4089> (Equation (77)).

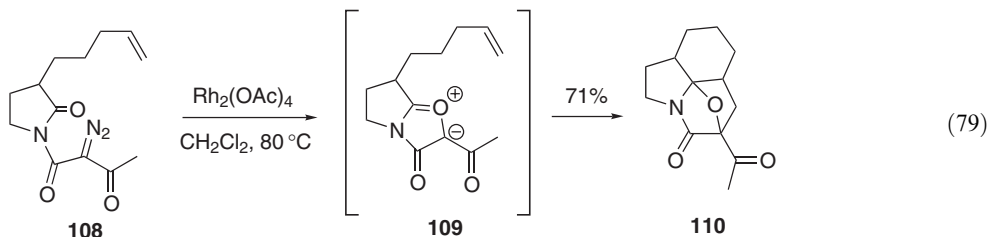


Nonstabilized carbonyl ylides bearing only alkyl substituents or no substituents through a samarium-mediated reaction were recently prepared <1996TL9241, 1996JA3533>. These carbonyl ylides react intermolecularly with alkenes to produce THFs as shown in Equation (78).



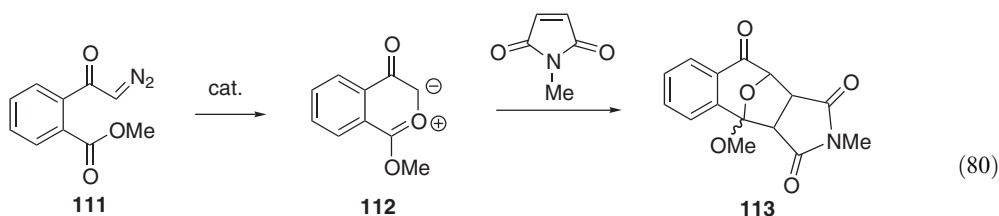
The intramolecular carbenoid-carbonyl group cyclization is one of the most effective methods for generating carbonyl ylides from α -diazoketones. Initially reported by Ibata and co-workers with copper catalysts <1979BCJ3582>, the carbonyl ylide formation with dirhodium(II) carboxylate catalysts was further extensively studied by Padwa and co-workers. This chemistry has been the subject of numerous articles and reviews <1998CRV911, 1996CRV223, B-1998MI018, B-2002MI019, B-2002MI020, 1997TCC121>.

In this method, the rhodium(II) metal-catalyzed decomposition of an α -diazo-ketone produced a stabilized metalcarbenoid, which readily adds onto the oxygen of carbonyl groups such as ketones, aldehydes, esters, amides, or ureas. These carbon ylides can be trapped by various dipolarophiles in both an intra- or an intermolecular fashion. For example, cyclization of the rhodium carbenoid generated from **108** with the carbonyl of the amide provided the carbonyl ylide **109**, which underwent an intramolecular cycloaddition leading to the oxo-bridged tricyclic amide **110** <2000JA8155> (Equation (79)).



A Lewis acid-mediated stereocontrolled 1,3-dipolar cycloaddition of the cyclic ylide **112**, derived from the diazo-decomposition of **111**, with *N*-substituted maleimides was recently reported <1998TL3165>. While the rhodium-catalyzed (5% $\text{Rh}_2(\text{OAc})_4$) reaction gave cycloadducts **113**

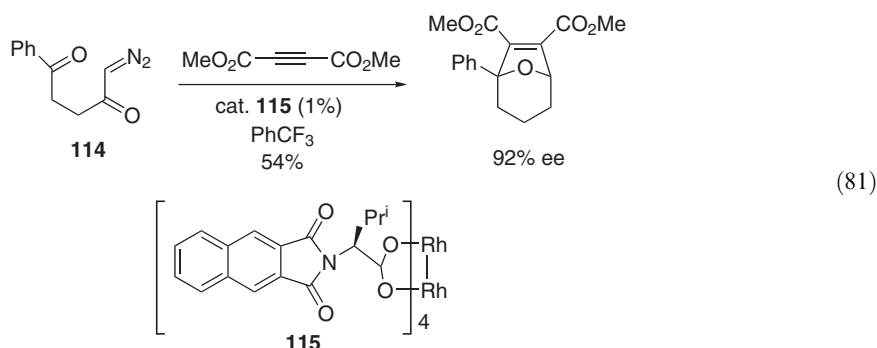
with *exo*-selectivity (*endo*/*exo* = 11/89), the CuCl-Yb(OTf)₃ catalyzed reaction gave cycloadducts in an *endo*-selective manner (*endo*/*exo* = 94/6). The latter selectivity is probably due to an activation of the cycloaddition reaction through a coordination of the Lewis acid to the oxygen dipolarophile (Equation (80)).



Rh₂(OAc)₄ (5%), refluxing benzene, 70% (11/89 *endo*/*exo*)

CuCl (5%) + Yb(OTf)₃ (5%), refluxing benzene, 52% (94/6 *endo*/*exo*)

The first enantioselective intramolecular version of the tandem cyclization-cycloaddition of α -diazo ketones (up to 53% ee) was reported by Hodgson and co-workers in 1997. This has been achieved through the use of dirhodium tetrakis(1,1'-binaphthyl-2,2'-diylphosphonate) catalysts <1997TL6471>. Conceptually related (but intermolecular) asymmetric carbonyl ylide cycloadditions have been reported more recently <2000OL3145, 1999JA1417>. High levels of enantioselectivity (up to 92%) were obtained in the tandem formation of the carbonyl ylide from α -diazo ketone **114** followed by a 1,3-dipolar cycloaddition with dimethyl acetylenedicarboxylate (DMAD) using a chiral rhodium catalyst having *N*-benzene-fused phthaloyl-(*S*)-valine as the ligand (Equation (81)).

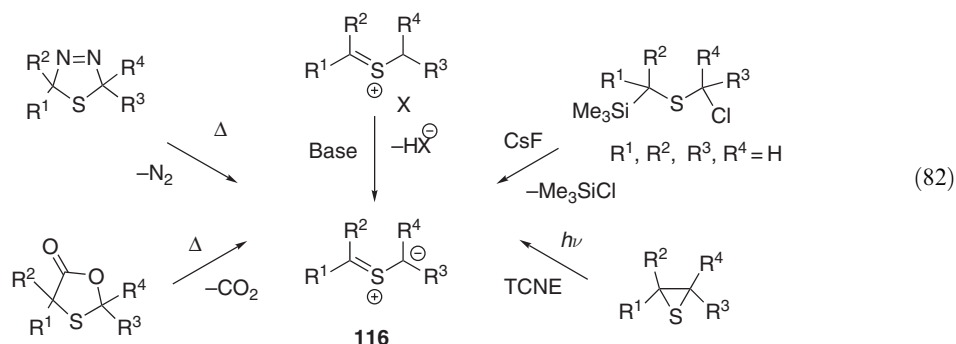


This methodology has recently been used <B-2002MI021, 2001OL1721> to prepare complex polycyclic structures such as polyazacyclic and oxacyclic systems found in many bioactive natural products.

(ii) Additions of thiocarbonyl ylides

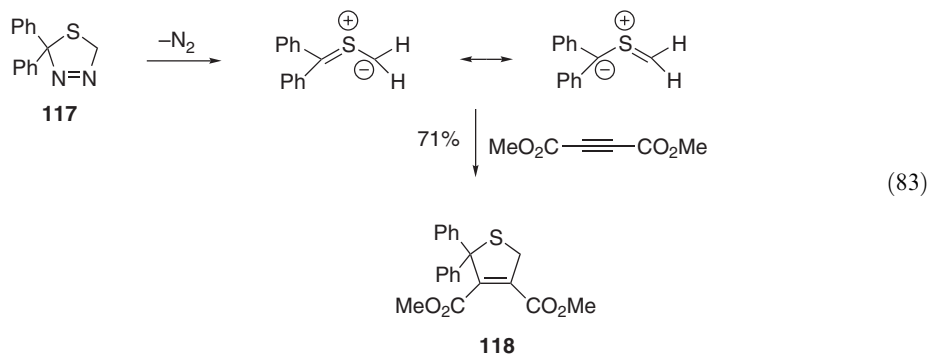
While carbonyl ylides have been the subject of numerous studies, thiocarbonyl halides are less common species. The cycloaddition chemistry of these 1,3-dipoles has been summarized in reviews <B-2002MI022, 2000PJC1503>.

The methods of generation of thiocarbonyl ylides are very similar to those used for the preparation of carbonyl ylides. Hence, thermal elimination of nitrogen from 2,5-dihydro-1,3,4-thiadiazoles <2000EJO1685>, thermolysis of 1,3-oxathiolan-5-ones <1980JA744>, fluoride-catalyzed elimination of silylated thioethers, addition of carbenes and carbenoids to thiocarbonyl groups <1999OL1667, 1994TL3555>, deprotonation of sulfenium salts, <2000PJC1503> as well as photochemical rearrangements of thioethers <1994JA1137> gave access to the dipolar structure **116** (Equation (82)).

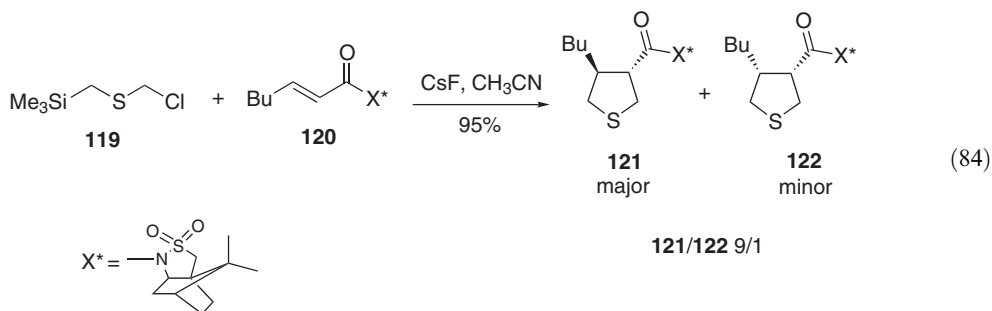


These thiocarbonyl ylides undergo intra- and intermolecular 1,3-dipolar cycloaddition reactions preferably with electron-deficient dipolarophiles to provide five-membered sulphur heterocycles.

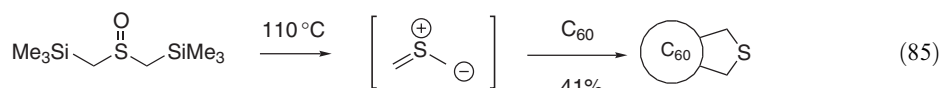
2,5-Dihydrothiophenes may be efficiently prepared by reaction with acetylenic dipolarophiles [<2001HCA981>](#). Elimination of nitrogen from 2,5-dihydro-1,3,4-thiadiazole **117** generated *in situ* the thiobenzophenone (*S*)-methylide which reacts with (DMAD) to afford the 2,5-dihydrothiophene **118** in 71% yield ([Equation \(83\)](#)).



The first auxiliary-induced diastereoselective cycloaddition between thiocarbonyl ylides and dipolarophiles was investigated in 1999 [<1999OL1667, 2000S1863>](#). As shown in [Equation \(84\)](#), the CsF-catalyzed decomposition of chloromethyl dimethylsilylmethyl sulphide **119** produced a thiocarbonyl ylide which reacted with the α,β -unsaturated ((1*S*)-5-)-camphorsultam amide **120** as chiral dipolarophile to give the two diastereomeric *trans*-3,4-disubstituted tetrahydrothiophenes **121** and **122** in high diastereoselectivities (dr 9/1).



The first 1,3-dipolar cycloaddition reaction of [60]fullerene with a thiocarbonyl ylide, generated *in situ* by *sila*-Pummerer rearrangement of bis(trimethylsilylmethyl)sulfoxide, was recently reported [<1999TL1543>](#) ([Equation \(85\)](#)). The tetrahydrothiophene-fused C₆₀ derivative was then obtained and further oxidized to give the corresponding sulfone derivatives, which could be used for further functionalization [<1999TL1543>](#).



(iii) Additions of azomethine ylides

The nitrogen analogs of carbonyl and thiocarbonyl ylides are called azomethine ylides. They are generally not isolable dipoles and thus they have to be prepared *in situ* from a stable precursor. These species have been widely studied and used for a variety of organic syntheses and the reader is directed to recent reviews of Harwood <B-2002MI023>, Kanemasa, <2002SL1371, B-2002MI024> and Pearson <2003SL903, 1998CRV863>. For these reasons, in this review, this chemistry will be briefly summarized and a more detailed discussion focused on recent developments involving nonstabilized ylides by aryl or electron-withdrawing group as well as those concerning the asymmetric version.

The principal routes to stabilized azomethine ylides (those bearing an electron-withdrawing group such as **123**) (Figure 5) are the photolysis or thermolysis of aziridines **124** (Equation (86)), reduction of the oxazolium salts **125** with $\text{Ph}_3\text{SiH}/\text{CsF}$ (Equation (87)), or proton abstraction of imine derivatives of α -amino acids **126** (Equation (88)). The intermolecular reaction of these stabilized azomethine ylides with electron-deficient alkenes produces substituted pyrrolidines (Equation (89)). The regioselectivity of these additions can be predicted since they are generally highest occupied molecular orbital (HOMO) (dipole)-LUMO (lowest occupied molecular orbital) (dipolarophile) controlled. However, the cycloadducts formed in these reactions are usually a mixture of diastereomers.

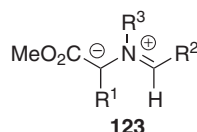
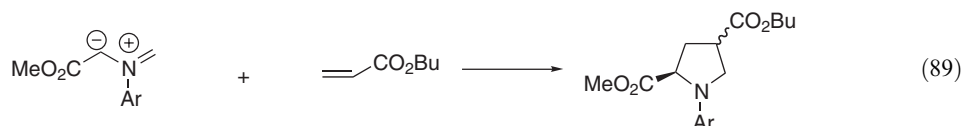
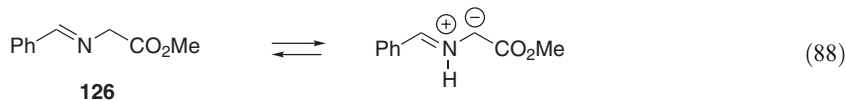
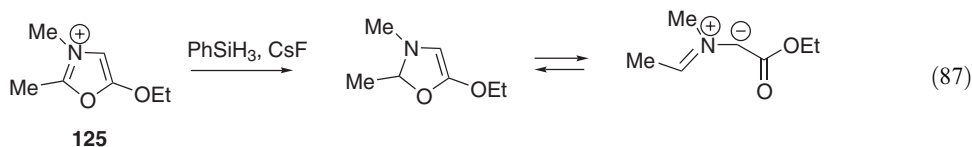
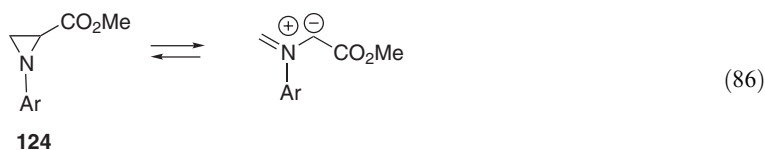
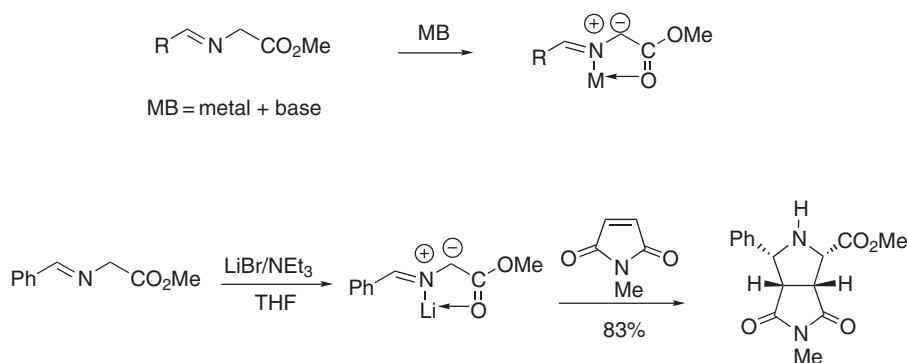


Figure 5



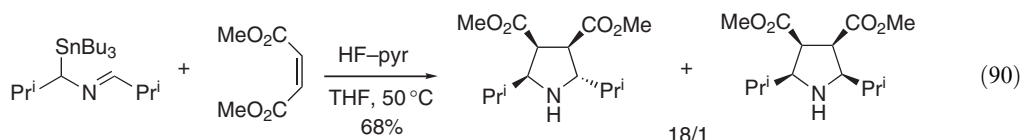
One of the most significant developments in the chemistry of stabilized azomethine ylides was the discovery of *N*-metallated azomethine ylides. They are easily prepared from α -(alkylidene-amino) esters by treatment with lithium bromide and triethylamine <2002SL1371>. These metallazomethine ylides were shown to undergo *endo*-selective 1,3-dipolar cycloadditions with α,β -unsaturated carbonyl acceptors. For example, only an *endo*-cycloadduct was obtained in 83% yield during the reaction of an *N*-lithiated ylide with *N*-methylmaleimide (Scheme 34).



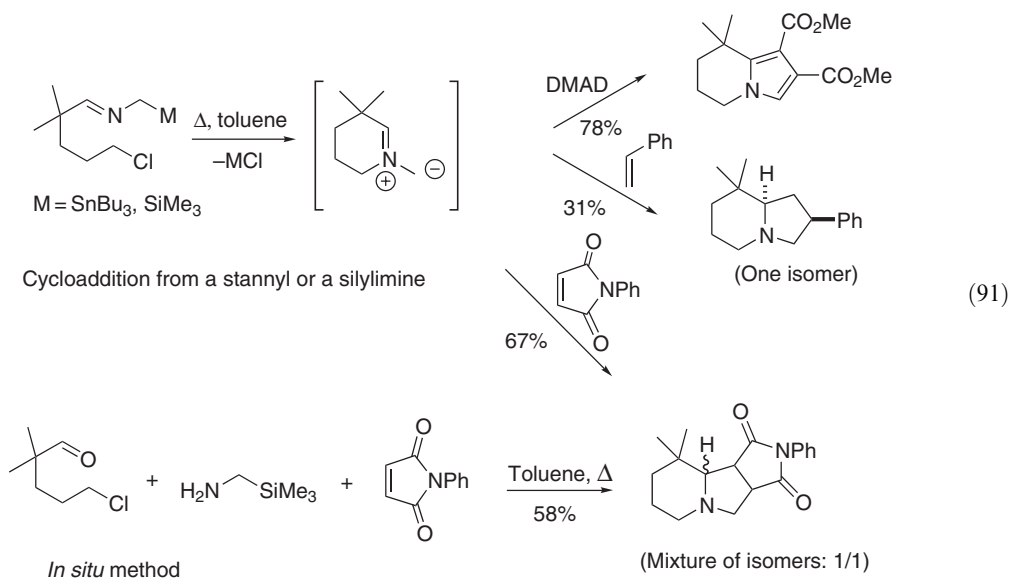
Scheme 34

All of the reactions outlined so far involved stabilized azomethines ylides. As pointed out by Pearson in his review [<2003SL903>](#), nonstabilized azomethines ylides are less accessible and are generally prepared by using various fluorine-mediated desilylation strategies.

Nonstabilized 1-alkyl and 1,3-dialkyl *N*-unsubstituted azomethine ylides were more recently generated by protodesilylation of (2-azaallyl)stannanes or (2-azaallyl)silanes with protic acids. Cycloadditions of these ylides with electron-deficient alkenes gave 2-alkyl- or 2,5-dialkylpyrrolidines. High stereoselectivity was observed with azomethine ylides derived from (2-azaallyl)stannanes [<1999TL4467>](#) (Equation (90)).



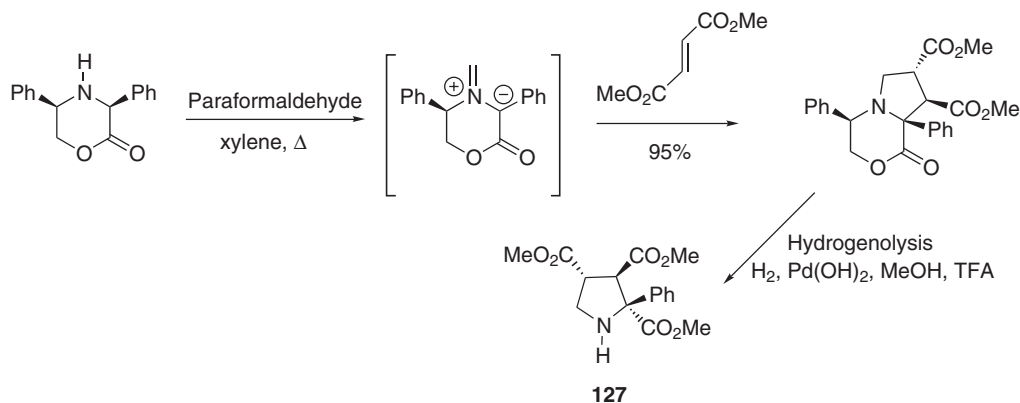
Nonstabilized azomethine ylides have been prepared by an intra- or intermolecular *N*-alkylation of (2-azaallyl)stannanes or (2-azaallyl)silanes [<1997TL5441>](#). These ylides underwent cycloaddition with various dipolarophiles leading to indolizidines or monocyclic pyrrolidines. The formation and the cycloaddition of these (2-azaallyl)stannanes or (2-azaallyl)silanes may be accomplished in a one pot operation by mixing the carbonyl compound, the α -amino stannane or α -amino silane and the dipolarophile in refluxing toluene. (Equation (91)).



Extensive studies on the asymmetric 1,3-dipolar cycloaddition reactions of azomethine ylides have been developed over the past few years using either a chiral azomethine ylide, a chiral dipole,

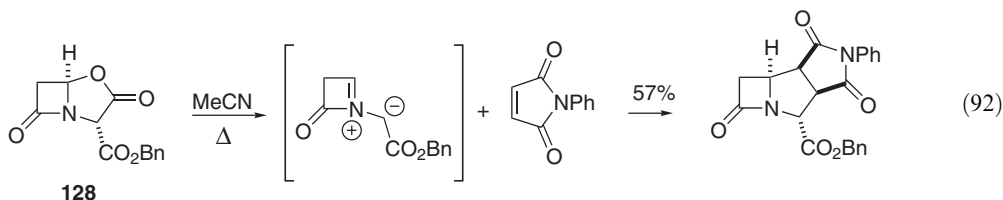
or a chiral catalyst. Among these three approaches, the most popular has been the use of chiral dipolarophiles.

Since the first asymmetric 1,3-dipolar cycloaddition reaction of a chiral azomethine ylide reported in 1985 <1985TL3529>, several new asymmetric reactions using a chiral auxiliary attached to the ylide have been successfully applied <1998CRV863>. In a series of papers, Harwood and co-workers studied the asymmetric 1,3-dipolar cycloaddition, reaction of the chiral azomethine ylide generated *in situ* by condensation of the (5*S*)-phenyl-morpholin-2-one with paraformaldehyde <1995TA2465>. This 1,3-dipole was trapped with various electron-deficient alkenes such as dimethyl fumarate to produce a single cycloadduct, which can be subsequently hydrogenolyzed to furnish the substrate **127** (Scheme 35).



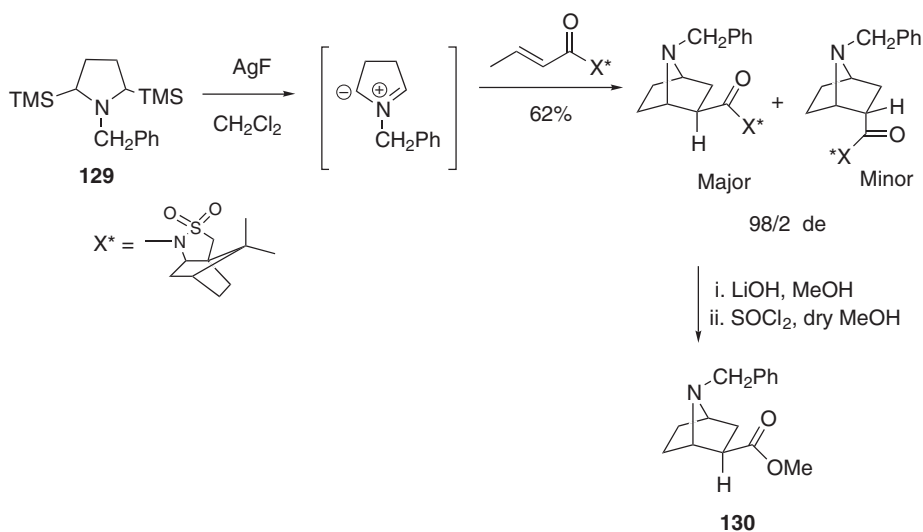
Scheme 35

Simple oxazolidin-5-ones are known to undergo thermal decarboxylation (1,3-dipolar cyclo-reversion) to give nonstabilized azomethine ylides <1988JCS(P1)2703>. This study was extended to the β -lactam-based oxazolidinone **128** <1997JA2309>. A thermolytic decarboxylation generated the oxazolidine-based ylide, which was trapped *in situ* by the dipolarophile. These reactions proceeded regiospecifically and led to *endo*-selective cycloadducts in moderate yields (Equation (92)).

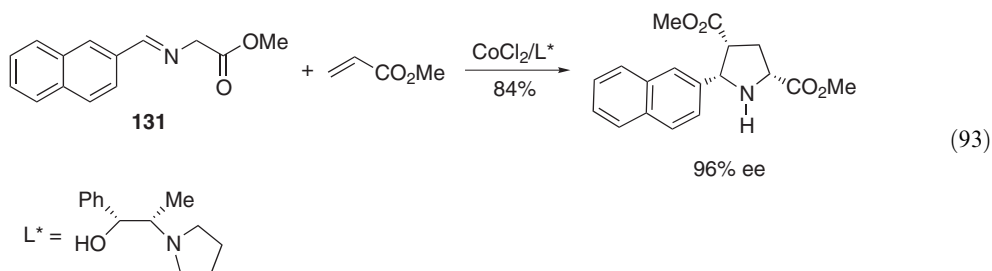


1,3-Dipolar cycloaddition reactions of azomethine ylides with chiral alkenes, in which a chiral auxiliary directs the stereochemical outcome of the reaction, have been developed <1995T273, 1995TL2511, 1995TA2475, 1997TA883, 1999T8129>. As an example <1999TL6065>, the asymmetric [3 + 2]-cycloaddition of the cyclic nonstabilized azomethine ylide **129** (generated *in situ* by a sequential double desilylation using AgF as one electron oxidant) with a chiral dipolarophile such as Oppolzer's acryloyl camphor sultam led to the formation of the azabicyclo[*m*.2.1]alkane **130** in enantiomerically pure form after cleavage of the auxiliary from the cycloadduct (Scheme 36).

A new development in the asymmetric version of the cycloaddition of azomethine ylides with dipolarophiles concerned the use of a chiral metal complex catalyst (*N*-metallated azomethine ylides). A typical example is shown in Equation (93). In this example, a cobalt salt in combination with a chiral ligand was used for the cycloaddition of **131** with methyl acrylate. The pyrrolidine product was isolated in 84% yield with an ee value of 96%.

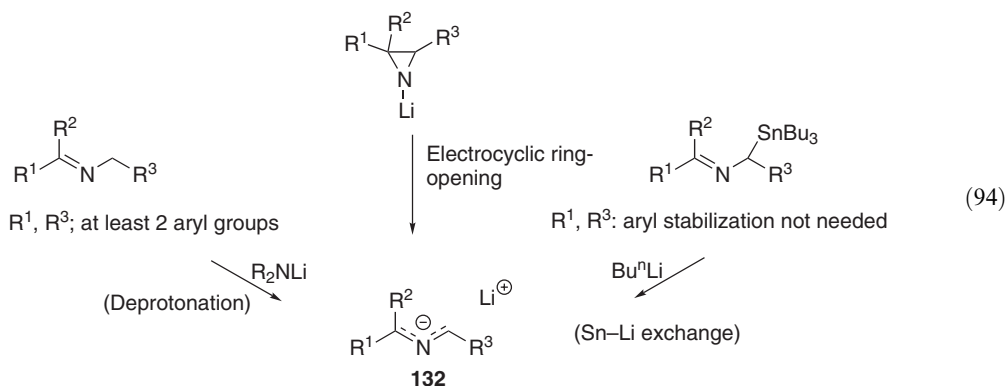


Scheme 36



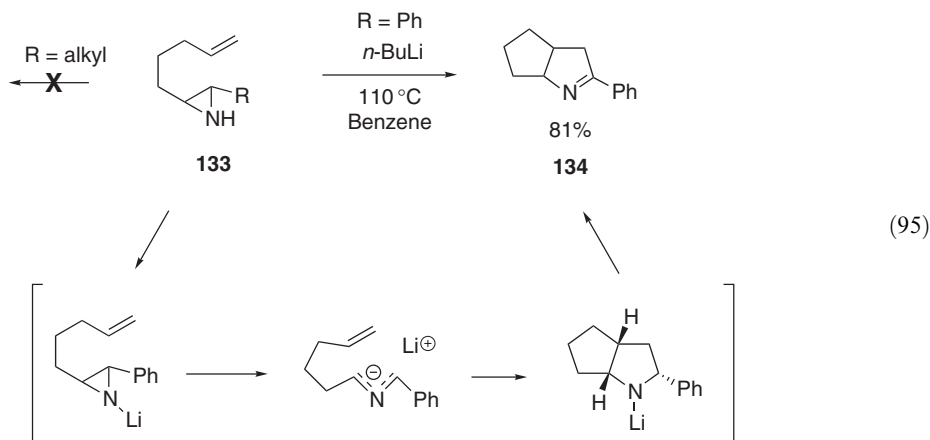
(iv) Additions of azaallyl anions

2-Azaallyl anions **132** are the nitrogen analogs of allyl anions (see Section 1.08.2.4.1). The traditional methods pioneered by Kauffmann <1977CB638> for the generation of these semi-stabilized active reagents (those bearing aryl groups) were the lithiation of an imine bearing two or more aryl rings <1974AG(E)627> and the electrocyclic ring opening of an *N*-lithiated diarylaziridine. The chemistry of azaallylanions has been recently reviewed <2003SL903> (Equation (94)).

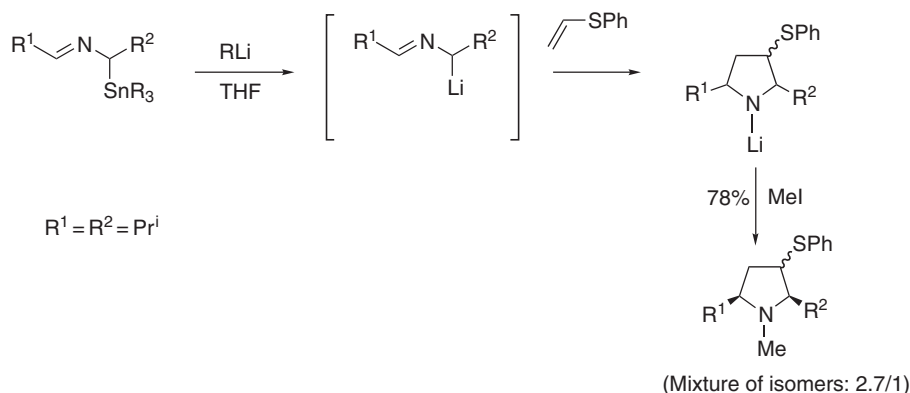


Intramolecular versions of these two strategies involving stabilized anions have been developed <1986JA2769, 1972AG(E)291>. Pearson and co-workers recently reinvestigated the intramolecular cycloaddition via electrocyclic ring-opening of a *N*-lithioaziridine. It was shown that

this method can be extended to semistabilized anions bearing one phenyl group as shown in Equation (95). The thermal conrotatory ring-opening of the mono-aryl-substituted aziridine **133** occurs at 110 °C in benzene to produce the pyrroline **134**. At this high temperature, a lithium hydride elimination from the initially formed *N*-lithiopyrrolidine was observed. However, this method cannot be used to make nonstabilized anions since no cycloadduct was observed for the reaction of aziridines bearing an alkyl group <2002MI91>.

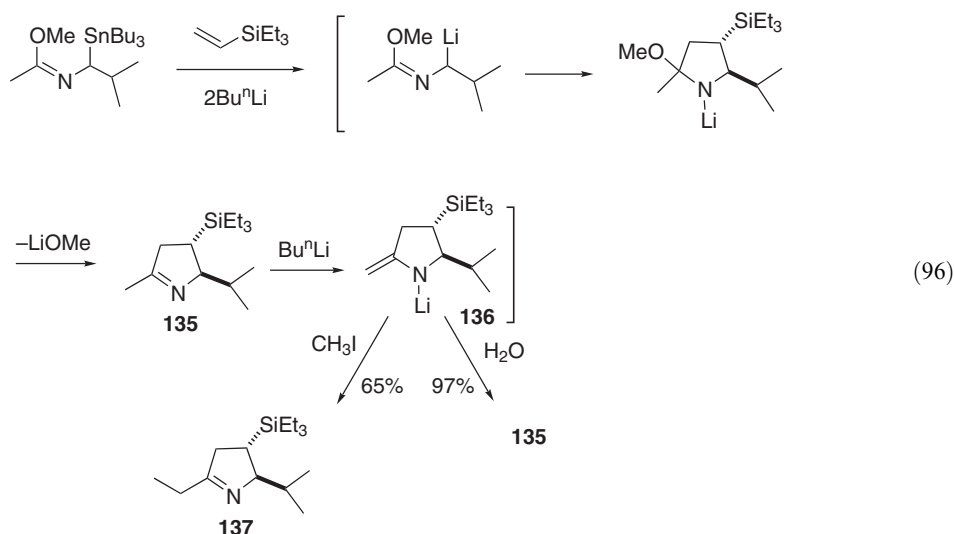


The major new development in this area is the generation of nonstabilized 2-azaallyllithiums (e.g., those bearing only hydrogen or alkyl group) using a tin–lithium exchange method <1992JOC6354, 1999JOC688, 2001JA6724>. These species were shown to undergo intermolecular addition with alkenes bearing aryl groups, vinyl sulfides, vinyl selenides, and vinyl silanes to produce pyrrolidine products in generally good yields after quenching with an electrophile. A typical example is given in Scheme 37.

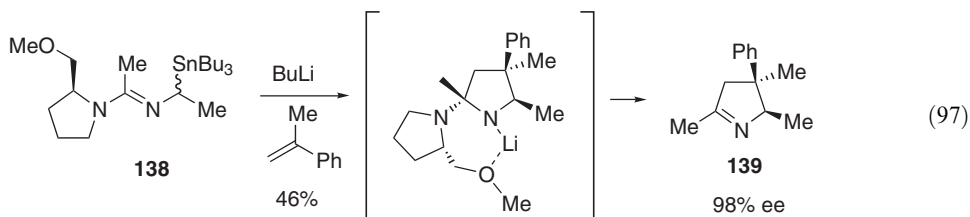


Scheme 37

Recently, it has been reported that 2-azaallyllithiums bearing heteroatoms such as nitrogen, oxygen, and sulfur may be engaged in cycloaddition reactions with alkenes. These nonstabilized heteroatom-substituted 2-azaallylanions are generated by tin–lithium exchange on stannyl imidates, thioimidates, and amidines. These reactions allowed access to 1-pyrrolines after loss of the heteroatom group after the cycloaddition (Equation (96)) <1994TL2641>. Under the basic reaction conditions, **135** is deprotonated to give the metalloenamine **136**. This may be quenched with water to regenerate **135** or may be alkylated to give a different 1-pyrroline such as **137**. The cyclic version of the heteroatom-substituted 2-azaallyllithiums was developed by the same group <1998JOC9812>.



The first enantioselective addition of 2-azaallyl anions was recently achieved by using the heteroatom as an attachment point for a chiral auxiliary [<2001TL7361>](#). As shown in [Equation \(97\)](#), the chiral nonracemic amidine **138** in the presence of α -methyl styrene and butyllithium gave the pyrroline **139** isolated in 46% yield with a 98% ee.



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Biographical sketch

Geneviève Balme was born in Saint Symphorien s/s Coise, a small town situated in the hills about 30 km west of Lyon. After a first academic position as a primary school teacher (2 years in France, 3 years in Island of Reunion), she studied chemistry at the University of Lyon and received her PhD degrees in the same University (Doctorat de 3^{ième} cycle-1979: supervisors Professor Jacques Goré and Dr. Max Malacria; Doctorat d'état-1983: supervisor Professor Jacques Goré). In 1994, she was promoted to Directeur de Recherche at the Centre National de la Recherche Scientifique. Her main research interests focus on the development of new synthetic methods using transition metal complexes such as palladium-catalyzed sequential reactions, multicomponent reactions, and their applications to the synthesis of natural products and biologically active compounds.



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1.09

One or More CH and/or CC Bond(s) Formed by Rearrangement

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1.09.1 TYPES OF REACTION

This chapter addresses the formation of saturated carbon atoms with no attached heteroatoms by rearrangement reactions. It is divided into three sections according to mechanistic aspects: the first one is devoted to the recent advances in nonsigmatropic rearrangements, involving the cases where the migrating group is either an ionic species or not. The second and third sections are devoted to sigmatropic rearrangements and electrocyclic reactions, respectively. In each subsection, a particular effort is made to emphasize the use of the discussed rearrangements in multistep syntheses and its ability of being the key step of a retrosynthetic process.

This section discusses the main electrophilic and nucleophilic rearrangements. As outlined in the corresponding chapter of the COFGT (1995) <1995COFGT(1)377>, electrophilic rearrangements are essentially concerned with rearrangements of substituents able to support an additional pair of electrons (namely aryl groups) and are therefore scarcely used, while mostly prohibiting

the formation of asymmetric centers. The scarce examples of chirality transfer in related rearrangements are mainly found in recent advances in the carbenoid-mediated Fritsch–Buttenberg–Wiechell rearrangement (Section 1.09.1.1.3) using alkyl migrating groups, and the chirality transfer is, in this case, the result of the presence of an adjacent asymmetric center.

Alternatively, nucleophilic rearrangements have been widely used on polycyclic structures with a good stereochemical control of the stereogenic centers formed in the course of the reaction. Indeed, in nucleophilic rearrangements, interaction between the migrating group and the developing cation clearly occurs in most of the cases without complete ionization at the migration terminus, thus allowing a quasi-concerted process to occur. In these cases, inversion of the configuration at the migration terminus is observed, while the necessary colinearity of the forming C—C and the breaking C—C (or C—X) bonds allows the complete retention of configuration at the migrating carbon atom (if this center is chiral).

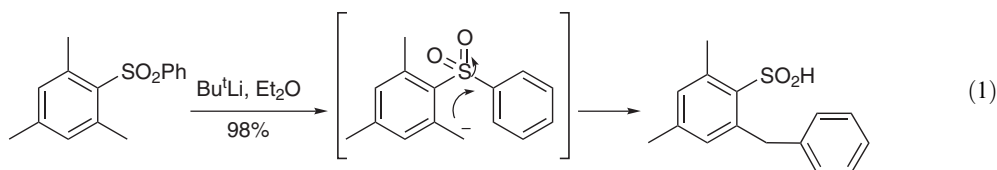
1.09.1.1 Substituent Migrates as a Cation

1.09.1.1.1 1,2-Electrophilic migration

The 1,2-electrophilic migration of a substituent, mainly devoted to the migration of aryl groups, has found no significant advances since the publication of chapter 1.09.1.1.1 in <1995COFGT(1)377>.

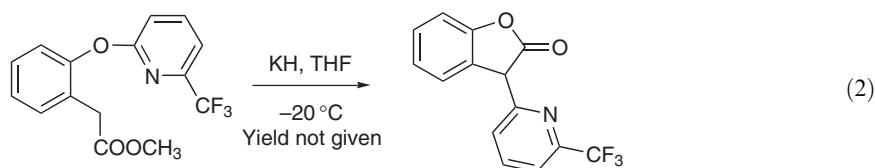
1.09.1.1.2 Truce–Smiles rearrangement

The originally reported Truce–Smiles rearrangement involving the formation of a C—C bond between a benzylic carbon and an aromatic ring migrating from a neighboring sulfonyl group allows the formation of *o*-benzylarenesulfinic acids from the corresponding *o*-methyl aryl sulfone (Equation (1)).



It has been clearly demonstrated that this rearrangement proceeded through an ipso mechanism with attack of the benzylic carbanion on the aromatic ring at the carbon atom bonded to the sulfur.

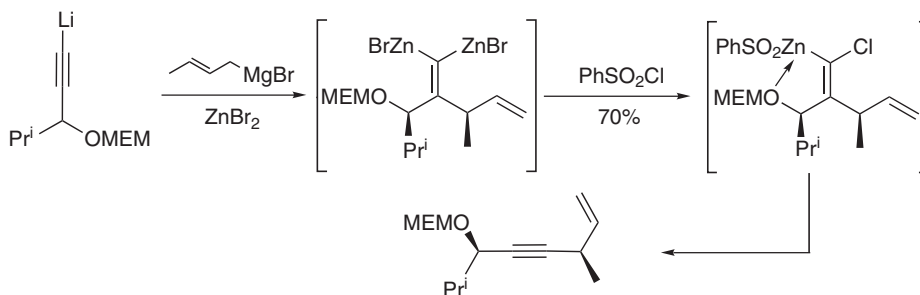
This rearrangement has been poorly used in synthetic research but an interesting report has been made of a Truce–Smiles-type rearrangement in a study devoted to the synthesis of strobilurine analogs. It shows the possible migration of an ester enolate on a pyridine ring, leading to a substituted benzofuranone (Equation (2)) <2000TL4541>.



1.09.1.1.3 Fritsch–Buttenberg–Wiechell rearrangement

The Fritsch–Buttenberg–Wiechell rearrangement, which was reported for the first time at the end of the nineteenth century, has been for a long time a useful route for the synthesis of alkynes. This rearrangement has been widely reviewed <1997AG(E)1164, 1998S271, 1996T8143> and used to perform the synthesis of a variety of polyynes via alkyne migration in carbene/carbenoid intermediates <2000JA10736, 2001TL8575>. This rearrangement is not discussed in this chapter, since it produces sp^2 or sp carbon atoms. However, an interesting modification of this rearrangement

has been proposed in the aliphatic series <2000OL419>, which allows a novel chirality transfer to occur in the 1,2-migration of a secondary aliphatic carbon <1999TL1899> (Scheme 1).

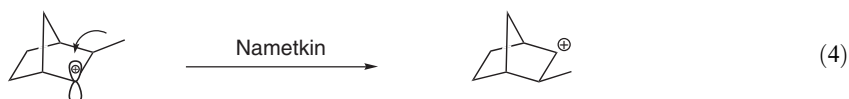


Scheme 1

1.09.1.2 Substituent Migrates as an Anion

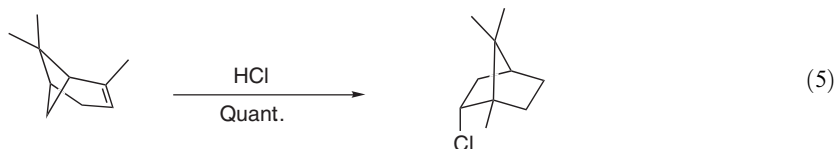
1.09.1.2.1 Wagner–Meerwein rearrangement

Since their discovery at the end of the nineteenth century, the Wagner–Meerwein rearrangement (Equation (3)) and the related Nametkin rearrangement (Equation (4)) have attracted a lot of research mainly in terpenoid systems.

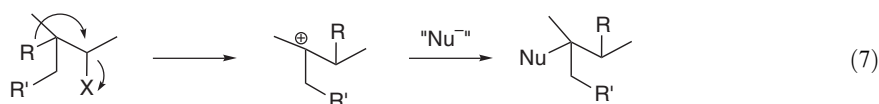


The nucleophilic Wagner–Meerwein rearrangement involves the 1,2-migration of a carbon atom in polycyclic structures. It produces therefore interesting polycyclic structures, with rearranged backbones, often difficult to access through conventional chemical methodologies. Moreover, since the stereochemical requirements for the 1,2-migration are well known (best antiperiplanarity of the leaving and the migrating groups), the product of the rearrangement can be in some cases predicted and the rearrangement used in a retrosynthetic analysis. Some studies have been devoted to the density functional theory (DFT) study of this type of rearrangement <1999JOC60>. The most widely accepted mechanism for these reactions involves a two-electron, three-center bond termed a classical or nonclassical carbonium ion. The balance between Wagner–Meerwein and Nametkin rearrangement products depends on the geometry of the starting material and the stability of the final product but can also be controlled in some cases by the experimental procedure <1998T4607, 1998JOC2262>.

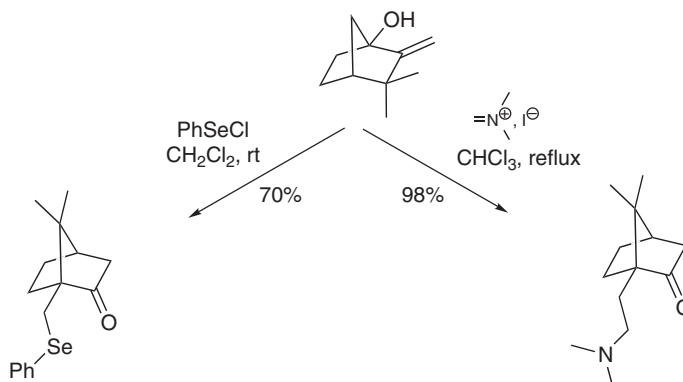
Even if the initially described Wagner–Meerwein rearrangement (Equation (5)) involves the formation of the initial cation through addition of HCl on a double bond ending with the trapping of the resulting cation by a chlorine atom, some new features in this reaction involve either the design of other leaving groups, different reagents for the formation of the initial carbocation, or the use of different nucleophilic species for the trapping of the final carbocation.



Most of the research in the Wagner–Meerwein area has involved a noncatalytic methodology, and may differ in the choice of the leaving group X and in the trapping of the resulting carbocation, which can either undergo deprotonation (Equation (6)) or be trapped intra- or intermolecularly by an appropriate nucleophile (Equation (7)). In the case where R' is a hydroxy group, a ketone is of course exclusively generated through deprotonation.



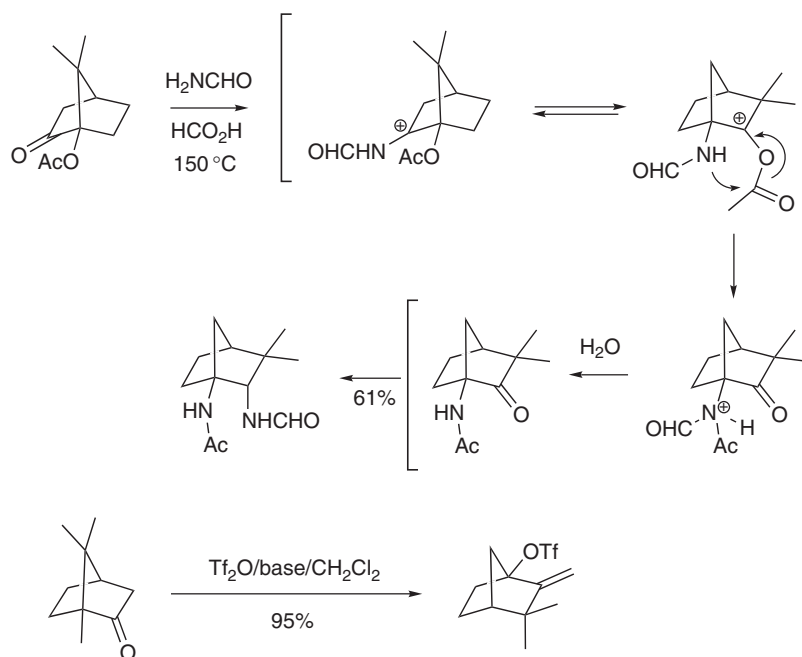
The leaving group X can be either a halogen <2001JCS(P1)1511>, or derived from an oxygenated function. In this latter case, X can be either a hydroxy group <1997TL2235, 2001TA189>, an ether <1997TL2159>, a sulfonic ester <2001EJO1279, 1996TL1035, 2003JOC6935>, or an epoxide <1998T1615, 2001TA2091, 1996JAF1840, 2000TA4437, 2001TA3325>. When the leaving group is a halogen, a bromine atom is possibly introduced in the same step through nucleophilic addition on a double bond (NBS) <2000TA4437, 2001TL6539, 2000TA3059>; in this case, the bromonium intermediate can undergo a Wagner–Meerwein rearrangement and the bromine atom is incorporated in the resulting product; this type of methodology is compatible with the use of other nucleophiles such as sulfides, selenides <2001TL5017>, or Eschenmoser's salt <2002TA17, 2002TL1183> (Scheme 2).



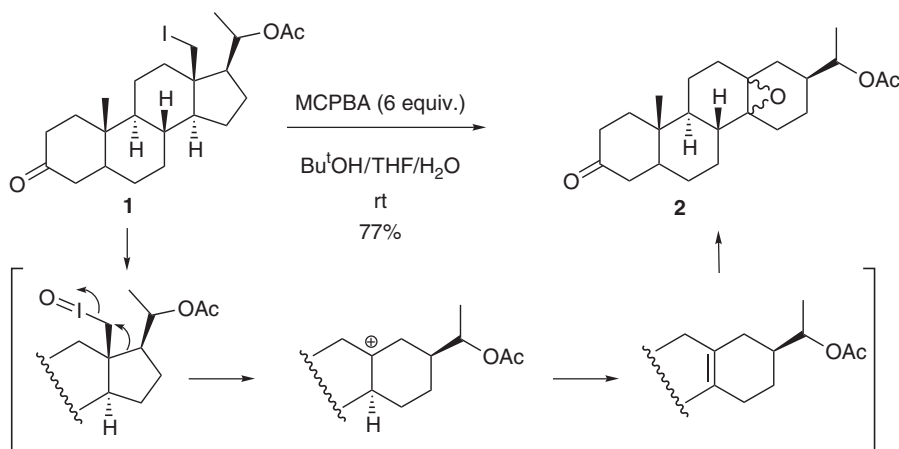
Scheme 2

Interestingly, the initial carbocation can also be generated directly from a carbonyl group through treatment either by TiF_2O in the presence of an organic base <2000TA3059>, in the presence of TiCl_4 <1999AG(E)2583>, or under the Leuckart reaction conditions <1996TL8177, 1999H611>; this methodology has the advantage that the carbocation is generated at a carbon atom bearing either an oxygen or a nitrogen atom. As the hetero atom is conserved in the product of the reaction, this Wagner–Meerwein rearrangement results in the formation of tertiary alcohols and amines <2001EJO2805> of controlled configurations, which would have been difficult to access using other methodologies (Scheme 3).

However, the experimental conditions have to be adapted to each particular case and no generalization can be made. An interesting set of conditions has been proposed in the case where the leaving group is an iodide using hypervalent iodine chemistry <2001JCS(P1)1511>. Indeed, iodopregnane derivative **1** undergoes spontaneous Wagner–Meerwein-like rearrangement upon treatment with MCPBA through an iodosyl intermediate as a masked carbocation, affording epoxide **2** through deprotonation and further nonstereoselective oxidation of the resulting double bond (Scheme 4).

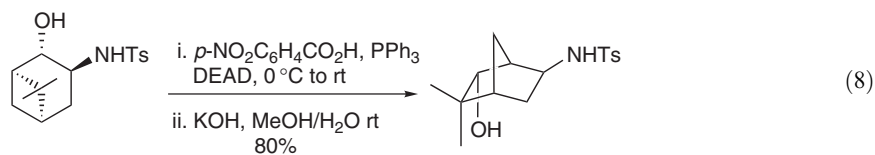


Scheme 3

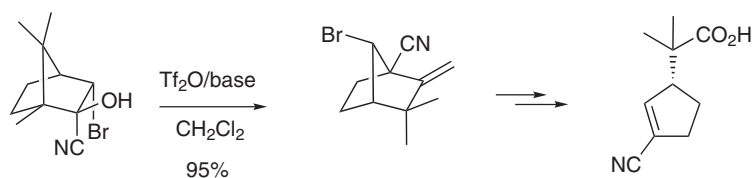


Scheme 4

The formation of the initial cation can also be made from a free hydroxy group under Mitsunobu conditions: in this case trapping of the resulting carbocation is effected by the benzoic acid used, which avoids the deprotonation (Equation (8)) <1997TL2235>. Furthermore, the crucial formation of the initial carbocation can be effected even if there are several carbocation precursors in the molecule provided that their reactivity can be managed. An example of this possibility is given in Scheme 5 <2001TA189>.

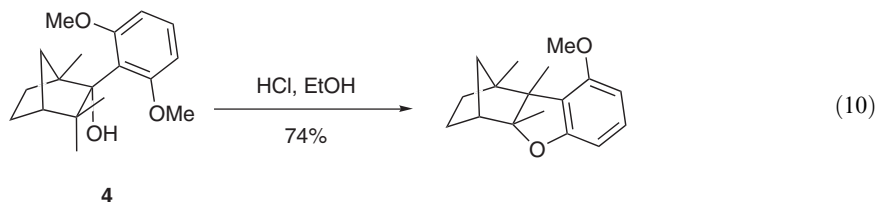
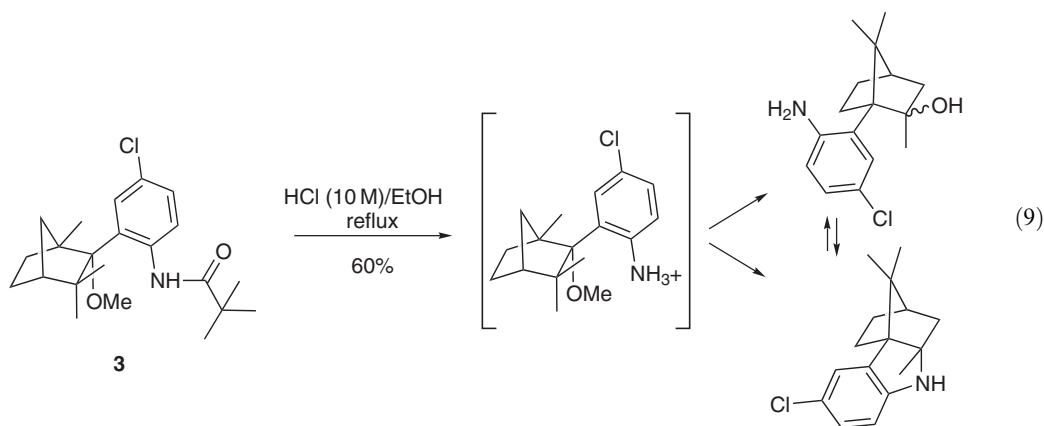


(8)



Scheme 5

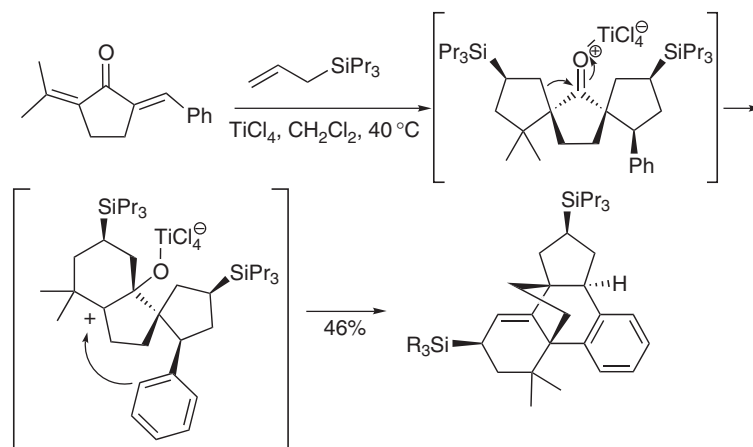
The final step of the reaction, namely the trapping of the final carbocation, is also a source of versatility for the Wagner–Meerwein-type of rearrangements. When the reaction is achieved in alcoholic solution or in the presence of water, the trapping of the carbocation by an oxygen atom is predominant and the deprotonation pathway mostly prohibited. However, the particular structure of the starting material can also be such that an intramolecular trapping can be observed. For example, in the case of the fenchone derivative **3**, the reaction is conducted in an aqueous hydrochloride ethanolic solution and the rearranged carbocation can either be trapped intermolecularly by water or intramolecularly by the nitrogen atom of the chloroaniline moiety. Since the acidic reaction conditions allow a chemical equilibrium between both products, after 1 day, the pyrrolidine is the only thermodynamically preferred product of the reaction, when the kinetic product formed is the amino alcohol <1997TL2159> (Equation (9)). Surprisingly, in the same study, the authors report the preference for the Nametkin rearrangement for derivative **4** (Equation (10)). This result shows the difficulty of predicting the result of such rearrangement reactions when both rearrangements are competitive.



Another spectacular intramolecular trapping is described in the case of a complex reaction sequence involving double allyl silane-mediated [2 + 3]-cycloaddition, Wagner–Meerwein rearrangement, Friedel–Crafts alkylation, and final dehydration to give a pentacyclic structure starting from a cyclopentanone derivative <1999AG(E)2583> (Scheme 6). In this case, the terminal cation produced during the rearrangement plays the role of the electrophile in a Friedel–Crafts-like alkylation.

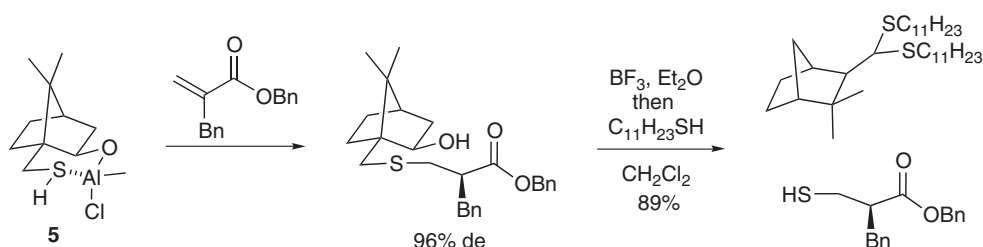
This example emphasizes the ability of the Wagner–Meerwein rearrangement to be included in complex reaction sequences where the driving force of the reaction is the thermodynamic stability of the product formed <1996TL1535, 1998T1615>.

Another important feature of this rearrangement, predominantly used in camphor and fenchone chemistry, is its ability of producing chiral inducers. In this field, the use of a chiral camphor alumino thiol **5** has been proposed to effect a formal asymmetric Michael addition of hydrogen



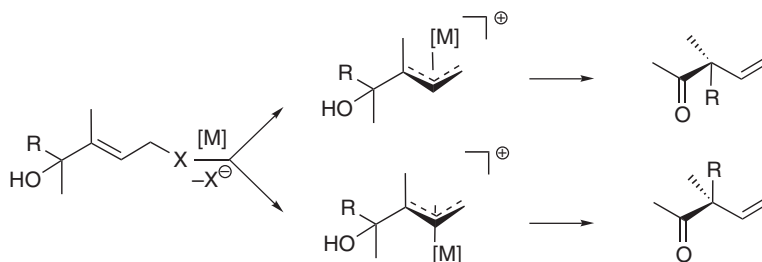
Scheme 6

sulfide to α,β -unsaturated carbonyl compounds in odorless conditions based on the easy Wagner–Meerwein rearrangement of this type of compound allowing a mild release of the chiral inducer <2001OL3121> (Scheme 7).

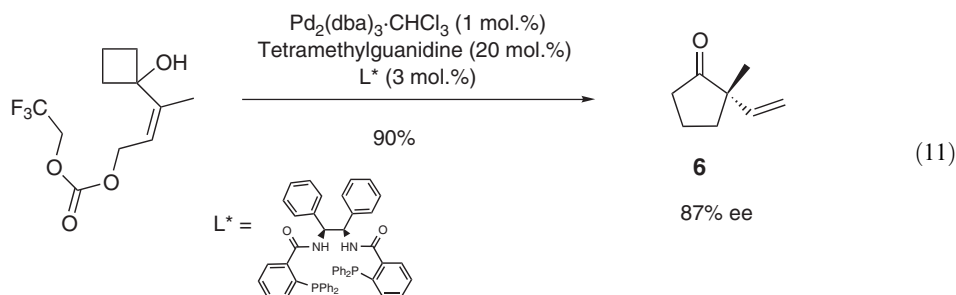


Scheme 7

Alternatively, catalytic metal-mediated Wagner–Meerwein rearrangements have also been proposed <2001JA7162, 1995JA6907, 1999JOC101>. When transition metals are used, due to the potency of the metallic π -allyl complexes, the addition of chiral ligands allows the induction of chirality in the product of the reaction (Scheme 8). The synthesis of optically active cyclopentanone **6** from an achiral hydroxy cyclobutane emphasizes the potential of this methodology <2001JA7162> (Equation (11)).

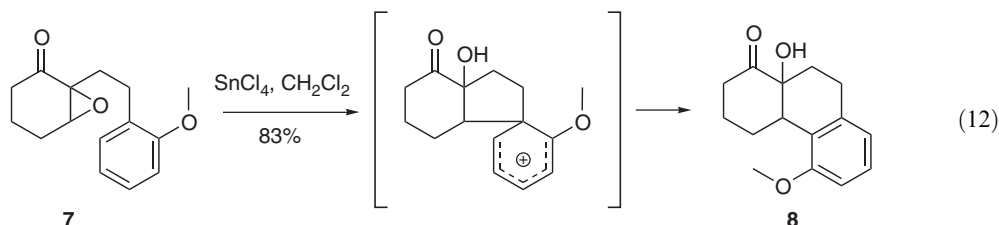


Scheme 8



In conclusion, even if the main area of application of the Wagner–Meerwein (and/or Nametkin) rearrangement remains the field of the camphor–fenchone chemistry, dedicated to design new chiral auxiliaries, it has also been used as a useful transformation for the synthesis of compounds of complex structure (for an example in the triquinane-type skeleton, see reference <1999JOC101>).

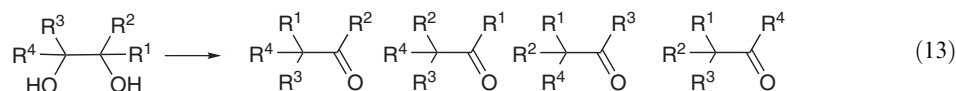
One should also keep in mind that carbocations are often generated in synthetic reactions involving Lewis acids and may rearrange through Wagner–Meerwein or Nametkin-type 1,2-alkyl shift. As an example, the carbocation generated in the Friedel–Crafts-like intramolecular alkylation of compound **7** undergoes a 1,2-alkyl shift to finally afford the tricyclic derivative **8** <1996T15209> (Equation (12)).



1.09.1.2.2 Pinacol rearrangement

The pinacol rearrangement of vicinal diols has been widely used to form quaternary centers α to a carbonyl group. Indeed, associated with a pinacol coupling, it offers a rapid and highly convergent access to this type of carbon arrangement.

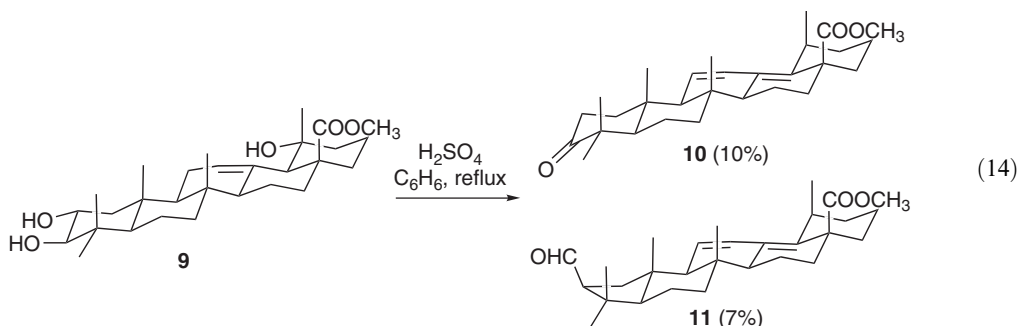
Pinacol rearrangement involves a 1,2-shift of substituent (H, alkyl, or aryl group) with concomitant formation of a C–H or C–C bond α to a carbonyl group. Because of the difficulty of managing the different migrating abilities of the different substituents of the diol subunit, it can lead to the possible formation of a complex mixture of rearranged products (Equation (13)).



However, if the vicinal diol is included in a polycyclic structure, one may expect the regio- and/or stereoselectivity of the rearrangement to be controlled by the stability of the different expected products. Therefore, even if some reports of pinacol rearrangement may be found in acyclic compounds <2000JA1908>, mainly involving aryl-group migration <2000JOC7438, 2000TL1433, 2002TL2161>, most of the publications in this area are now devoted to the use of pinacol rearrangements in cyclic or polycyclic structures.

In acyclic pinacol rearrangements, the selectivity depends on the stability of the carbocation formed in the initial step of the rearrangement (when one of the hydroxy groups is a primary one, the corresponding aldehyde is obviously formed upon 1,2-hydrogen atom migration) and the migrating ability of the different substituents (aryl > H > alkyl). In some cases, the products are different depending on the kinetic or thermodynamic conditions. However, the result of a pinacol rearrangement in almost symmetrical compounds remains difficult to predict <1998T2099>.

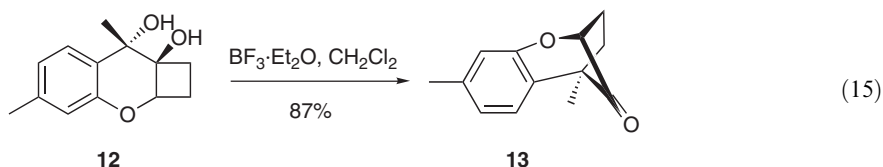
In the case of the ursenoate-type *trans*-diol **9**, treatment with concentrated sulfuric acid led to the formation of both compounds **10** and **11**, respectively, obtained through hydrogen atom and alkyl-group migration (Equation (14)).



The pinacol rearrangement appellation concerns only 1,2-diols, where the selectivity is only dependent on the migrating ability of substituents R^1 – R^4 . Indeed, the alternative pathway for controlling the selectivity in the pinacol rearrangement rises through switching to the “semipinacol” strategy, where both hydroxy groups are clearly differentiated (e.g., through derivation as sulfonic esters), one of them becoming definitely better as leaving group than the other. This strategy has been widely used in the case of tetra-alkyl-substituted diols and will be further described in Section 1.09.1.2.4.

The generally encountered sets of experimental conditions for pinacol rearrangement involve either sulfuric (or hydrobromic <2000JOC7786>) acid treatment <1997JOC1463, 2001JOC3930> or the use of Lewis acids. The most widely used Lewis acid is boron trifluoride etherate <1998JOC3855, 1996JOC4391>.

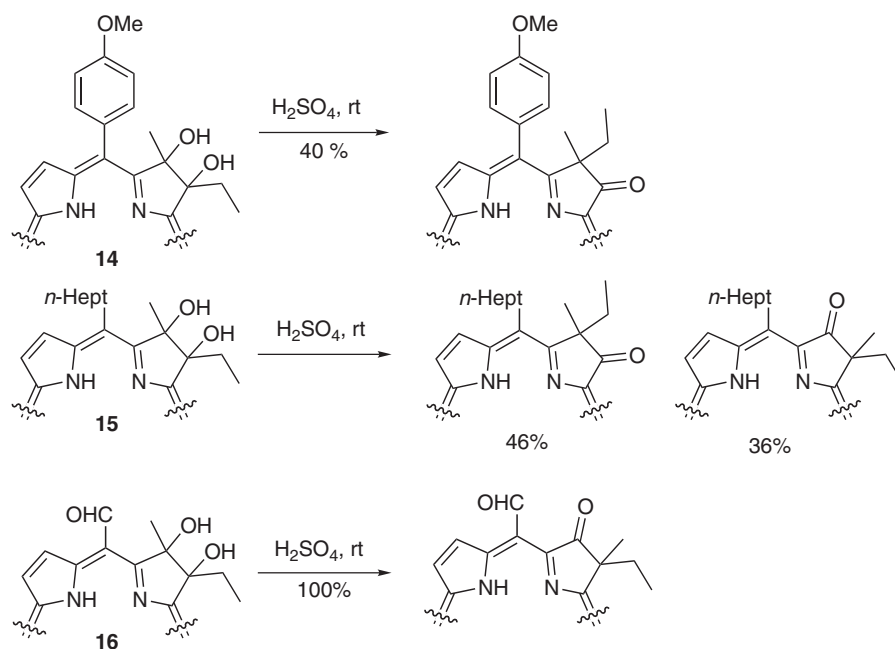
In order to emphasize the potency of the pinacol rearrangement in natural product total synthesis, an example is found in the report of the synthesis of A-ring aromatic trichothecene analogs (Equation (15)) <1998JOC3855>. In this case, treatment of tricyclic diol **12** with boron trifluoride etherate at ambient temperature cleanly afforded the benzooxabicyclo[3.2.1]octanone **13**. Explanation of the selectivity in this case is obviously due to the stabilization of the benzylic cation as well as the stability of the bicyclo[3.2.1]octane compared to the bicyclo[4.2.0]octane (see also reference <2000AG(E)937> for a pinacol-rearrangement-based synthetic approach of diazonamide).



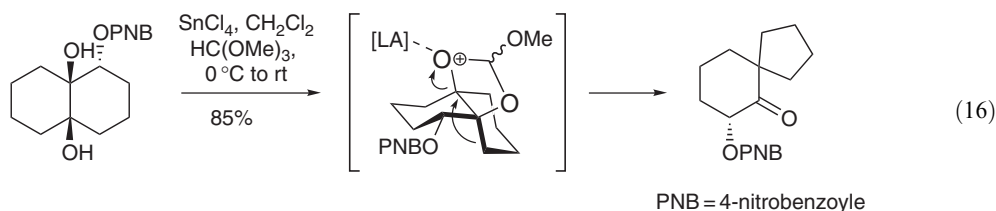
The pinacol rearrangement can be, in some cases, achieved in supercritical water <2000JA1908> or under photochemical conditions <1998JOC7168>.

Examples can also be found, where the regioselectivity encountered in the pinacol rearrangement is related to the presence of substituents remote in the carbon backbone from the reactive centers of the rearrangement. Indeed in the case of porphyrin derivatives **14**–**16**, the *meso*-substituent plays a critical role in the regioselectivity of the alkyl-group migration <2001JOC3930> (Scheme 9).

However, an interesting set of experimental conditions has been described that involves the use of 1 equiv. of triethyl orthoformate or other related ortho esters to achieve the pinacol rearrangement in the presence of a Lewis acid ($BF_3 \cdot Et_2O$ or $SnCl_4$) <1997TL8315, 1998T14689>. This method has the advantage of avoiding by-products eventually generated in the dehydration step and to be compatible with acid-sensitive functional groups on the starting molecule, since the amount of Lewis acid used for the reaction can be reduced to only 1 equiv. However, it presents also the drawback of being dependent on the configurations at the carbon atoms bearing the two hydroxy groups in the ability of forming a cyclic ortho ester intermediate in the case of polycyclic or constrained structures (Equation (16)).



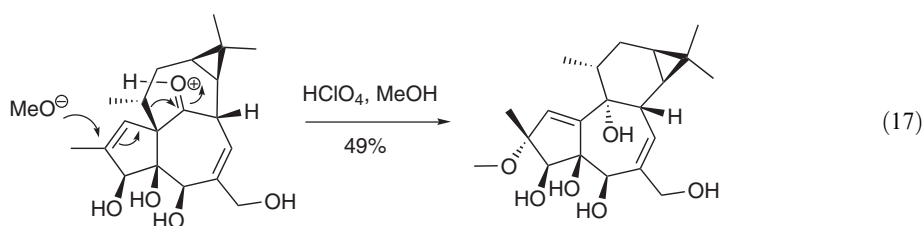
Scheme 9



It is important to note that, in the case described above, the regioselectivity of the pinacolic rearrangement is not affected by the addition of the orthoformate but only the yield of the transformation.

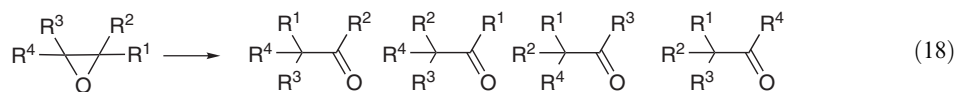
However, if some solutions have been proposed to alleviate the drawbacks of the pinacolic rearrangement, most of the synthetic research using this reaction has preferred to turn to the semipinacolic rearrangement (Section 1.09.1.2.4). Nevertheless, the pinacol rearrangement has also been used in synthetic studies aimed at the synthesis of complex structures, mainly when coupled with other reactions either before <1997T8927, 1995JA10391, 1995ACA107, 2003JOC7143> or after the pinacol rearrangement <1997CC2263, 2000JOC4864>.

Finally, in order to demonstrate once more the importance of the stability of the products in such equilibrated rearrangements, an example of vinylogous retropinacol rearrangement <1999EJO3413>, allowing the transformation of the ingenane to the tigliane skeleton through mild acidic treatment, is shown in Equation (17) (in contrast, for an example of vinylogous pinacol rearrangement suppress see also reference <2000JA10282>). For a similar spontaneous pinacol rearrangement of a strained polycyclic structure driven by the stability of the product formed, see also <1998TL7005>.



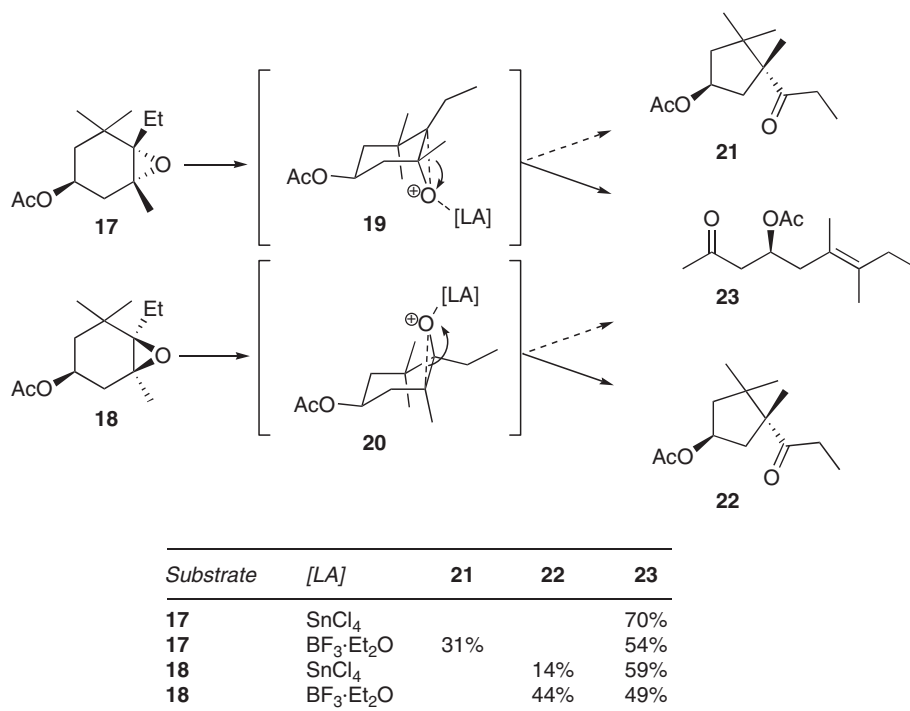
1.09.1.2.3 Rearrangement of epoxides

The rearrangement of epoxides, like the pinacol rearrangement, proceeds via protonation or Lewis acid complexation of the oxygen atom of the epoxide ring and produces a carbocation, which thereafter rearranges through migration of one substituent of the epoxide ring to finally lead to the formation of a new C—C or C—H bond α to a carbonyl group (Equation (18)).



The choice of the experimental conditions is crucial to determine the outcome of the reaction. Indeed, the presence of nucleophilic species may inhibit the occurrence of a rearrangement and preferentially lead to the nucleophilic ring opening of the epoxide. Particularly, in the case of protic acid, the conjugate base may act as a nucleophile. Even in the absence of nucleophiles, the presence of additives may also prevent the rearrangement <2002TL2851>. When the rearrangement is observed, the regioselectivity and the stereoselectivity of the reaction follow the same rules as in the related pinacol rearrangement, depending on the migrating aptitudes of the substituents of the epoxide <1998JOC2699> but may also depend on the experimental procedures <2001JOC8779>.

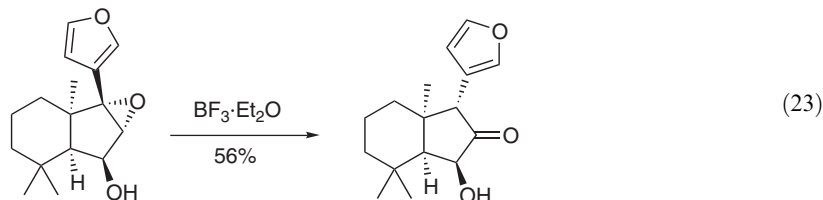
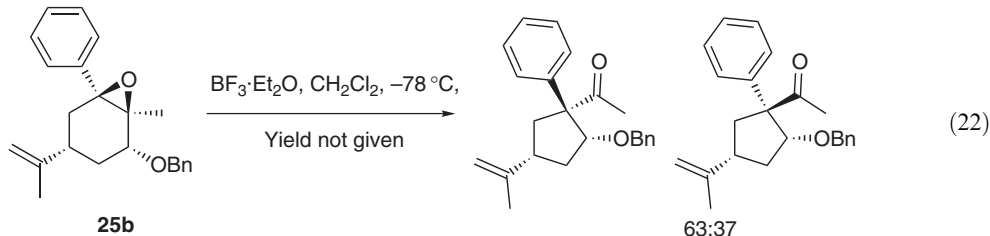
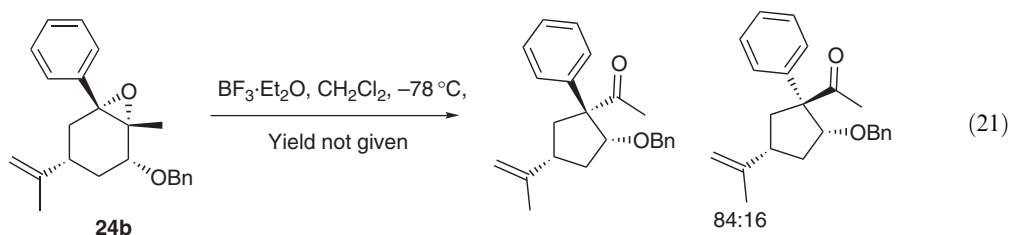
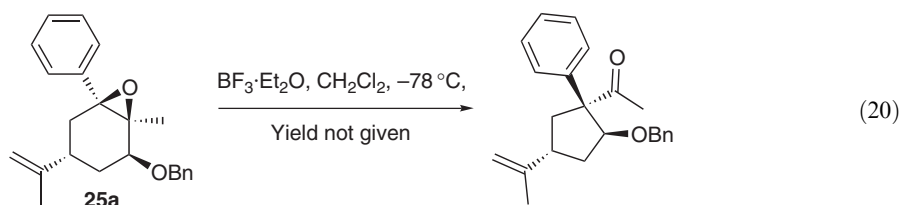
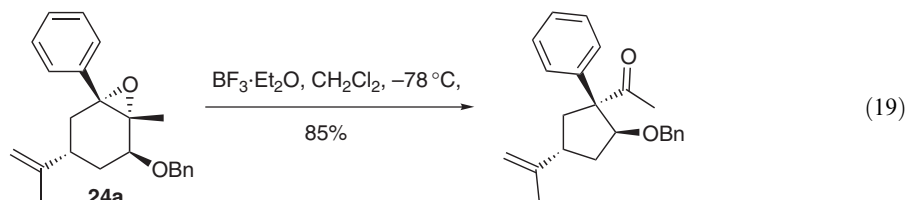
In rigid structures, the stereochemical requirements for substituent migration may also influence the outcome of the reaction as depicted on Scheme 10 for isomeric cyclohexene oxides **17** and **18**. In the same experimental conditions, axial cleavage of the epoxide ring is preferred leading through intermediates **19** and **20** either to the cyclopentyl methyl ketones **21** and **22** or to the acyclic methyl ketone **23** derived from a Nametkin-like rearrangement (Section 1.09.1.2.1) followed by the fragmentation of the six-membered ring in order to allow formation of the carbonyl group. However, the selectivity of the reaction can be managed by changing the Lewis acid catalyst as indicated <1998JCS(P1)2569, 2002JCS(P1)1581>.



Scheme 10

Nevertheless, as this reaction does not proceed by a strictly concerted mechanism, the stereochemical course of the rearrangement may depend on the stability of the isomeric products potentially formed. This assessment is particularly true when stabilized carbocations are formed

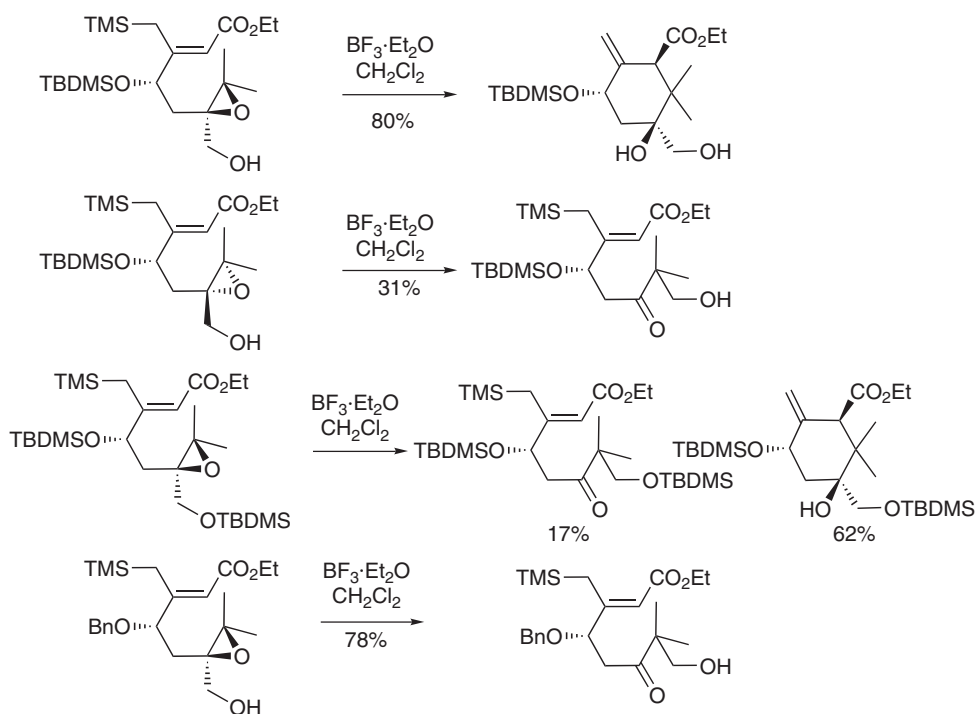
through the opening of the oxirane ring. As an example, treatment of isomeric epoxides **24a** and **25a**, derived from carvone, with boron trifluoride etherate results in the formation of a unique cyclopentyl derivative (Equations (19) and (20)). The configuration of the rearranged product is clearly a consequence of the minimization of the steric interactions between the different substituents during the formation of the five-membered ring, since the related oxiranes **24b** and **25b** both rearrange to a mixture of isomeric cyclopentyl derivatives (Equations (21) and (22)) <1999TL7969, 1999JCS(P1)3393>. Alternatively, the concerted mechanism seems to be preferred in some cases (particularly when the migrating group is a hydrogen) giving formal inversion of configuration at the migration terminus as exemplified in the 1,2-hydrogen shift (Equation (23)) <1997S1381>.



As outlined at the beginning of this section, the use of a Lewis acid as catalyst in this type of epoxide rearrangement has mainly replaced the use of other acidic conditions (Brønsted acids). Different studies have been devoted to the study of the scope of epoxide rearrangement promoted by bismuth- <2001TL8129, 2000TL1527> or antimony-derived Lewis acids <1998JCS(P1)2569, 2002JCS(P1)1581>.

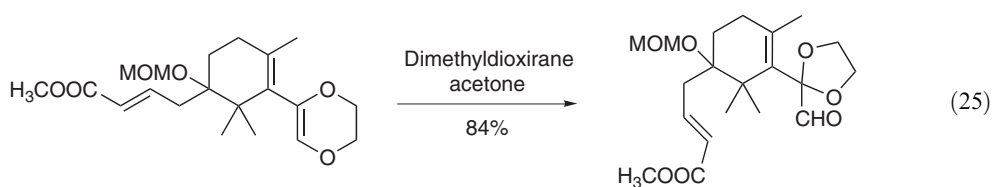
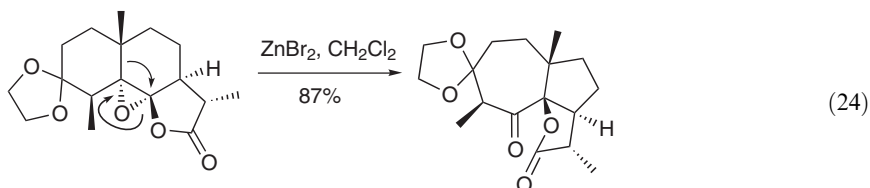
As a consequence of the use of Lewis acids in the initial carbocation formation, one may assume that the presence of nearby chelating groups may have a dramatic influence in the outcome of the reaction. Particularly, the presence of a free hydroxy group on an eventually migrating group may induce a different behavior compared to that obtained with a protected

hydroxy group. In the example shown, substrates can undergo either epoxide rearrangement or carbocyclization due to the presence of the allyl silane moiety (Scheme 11). Authors report the dramatic influence not only of the epoxide configuration but also of the protecting groups of both the primary and the secondary hydroxy groups, which should be related to the formation of cyclic transition states through possible chelation of the boron atom by the oxygens of the molecule <2001JCS(P1)789>.



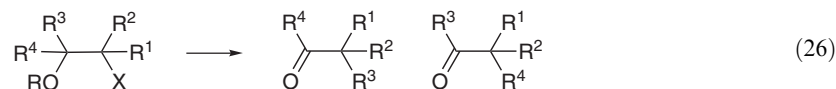
Scheme 11

An important feature of the rearrangement of epoxides is the use of epoxides of enol ethers. This strategy leads to the formation of α -hydroxy carbonyl compounds equivalent to the result of the oxidative ring opening of epoxides <2000CCC490> but with a rearranged carbon skeleton. This methodology allows, for example, an easy entry to the salvialane skeleton starting from an eudesmanolide enol ether epoxide derived from santonin <2001TA1459> (Equation (24)). Furthermore, the rearrangement of epoxides derived from 1,2-dihydroxy alkenes, obtained by the 1,4-dioxene chemistry, allows an easy route to monoprotected 1,2-diketo-building blocks (Equation (25)) <1995TL6475>.



1.09.1.2.4 Semipinacol rearrangement

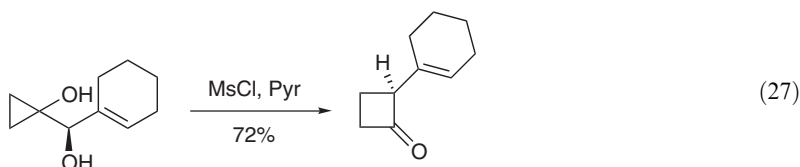
As anticipated in the previous sections, the semipinacol rearrangement has been, when possible, preferred to the pinacol rearrangement, due to the complete control of regioselectivity. The purpose of the semipinacol rearrangement is to induce a differentiation between the two putative reactive centers of the substrate, where a carbocation can be formed (Equation (26)).



In this rearrangement, the regioselectivity of the initial carbocation formation is controlled through the difference in leaving aptitude of the OR and the X groups, and the selectivity in the migrating group is, as in the previous cases, controlled by the migrating abilities of the substituents R^3 and R^4 . The X group may be either an amine (Tiffeneau–Demjanov rearrangement or aza-pinacol rearrangement <2002CC134, 2000JOC5693>) or an oxygen-derived leaving group. In this latter case, two major pathways have been designed consisting in either formation of a sulfonic ester of the hydroxy group (Ts, Ms, or Tf) or in the incorporation of the oxygen atom in a cyclic structure. An alternative strategy is also, while X remains a free hydroxy group, to use a suitable protecting group R for the hydroxyl group so that it will be transformed into the keto group.

The more obvious strategy is the formation of a sulfonic ester of the hydroxy group. This strategy indeed allows a good control of the regioselectivity of the initial carbocation formation since both hydroxy groups may have a different behavior upon esterification. This is the case with a secondary hydroxy group vicinal to a tertiary one <2001T4705, 1997JCS(P1)1707>.

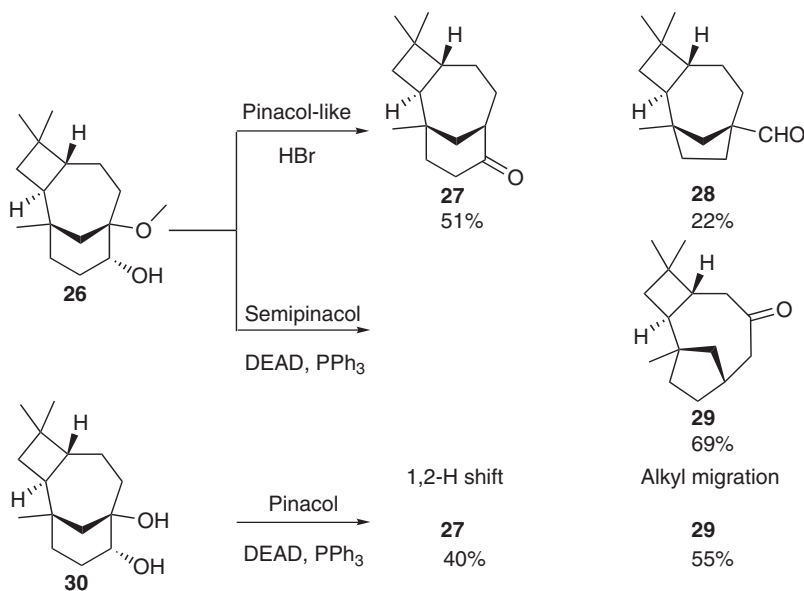
As an example of this possibility, this semipinacol strategy has been used in tandem with the Kulinkovich reaction to afford a general and easy access to α -substituted cyclobutanones from hydroxyesters (Equation (27)) <2000OL1337>.



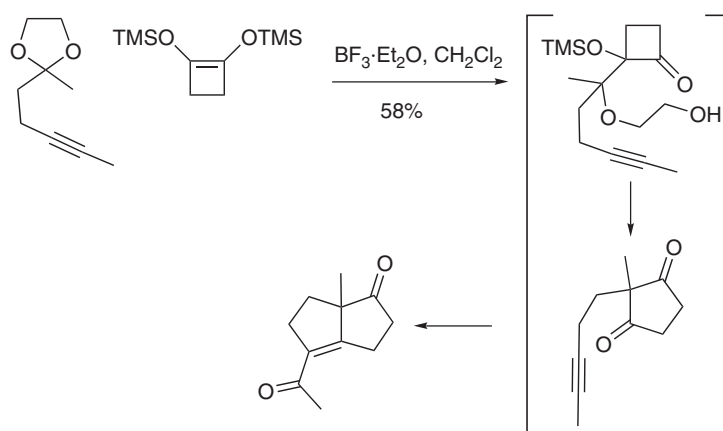
It is important to note that this strategy may invert the regioselectivity that would have been the result of the pinacol rearrangement through formation of the more stable carbocation. This discrepancy has been observed in the case described in Scheme 12 <2000JOC7786>. A pinacol-like rearrangement may be effected through acidic treatment (HBr) of **26** leading, due to these drastic experimental conditions, to the formation of the tertiary carbocation, which thereafter rearranges through either proton migration (compound **27**) or alkyl migration **28** <1999TL6947>. Meanwhile, a semipinacol rearrangement may also occur when **26** is treated under Mitsunobu conditions. In this case, the secondary carbocation is formed, leading exclusively to the formation of ketone **29**. Noteworthy, this set of conditions is obviously only valuable when one of the hydroxy groups is protected. Indeed, when the same reaction is carried out on diol **30**, a mixture of **27** and **29** is formed through an uncontrolled pinacol rearrangement.

The TsOH-initiated semipinacol-like rearrangement of bicyclic substrates incorporating a tertiary methoxy group α to a secondary alcohol has also been the key step for the synthesis of some natural sesquiterpenes <2001TL699, 2002TL265>.

An interesting result has been found in this type of rearrangement, the diol subunit involved in the semipinacol rearrangement being the result of the Mukaiyama addition of bis-trimethylsilyloxy-cyclobutene on dioxolanes and the semipinacol rearrangement leading to the formation of cyclopentadiones (Equation (28)), which may undergo further annulation reactions <1995JOC337>.

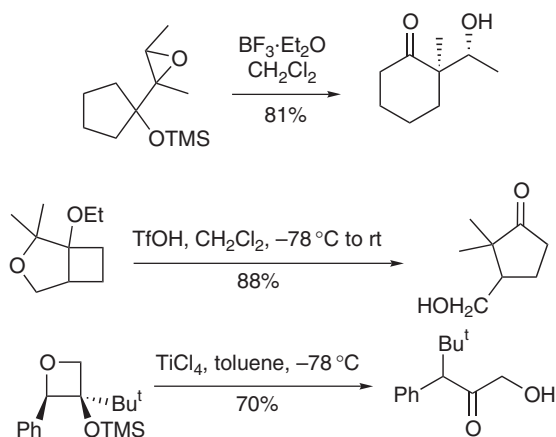


Scheme 12



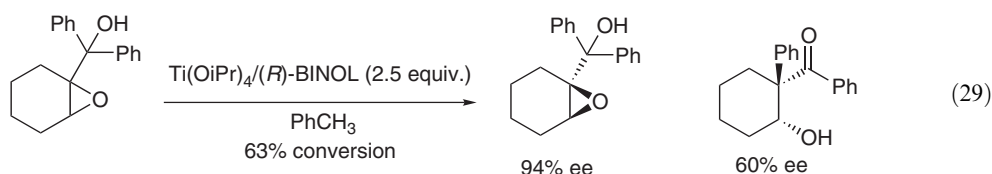
(28)

An alternative strategy widely used in the semipinacol rearrangement consists in incorporating one of the oxygen atoms in a cyclic ether, which may be either an epoxide <2000OL1193, 2002TA395, 2000JCS(P1)3791, 1999TL2149>, an oxetane <1999JOC8041>, or a tetrahydrofuran <1995JOC2526, 1996T14147> (Scheme 13).

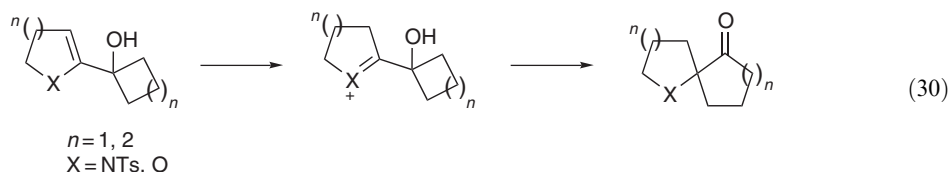


Scheme 13

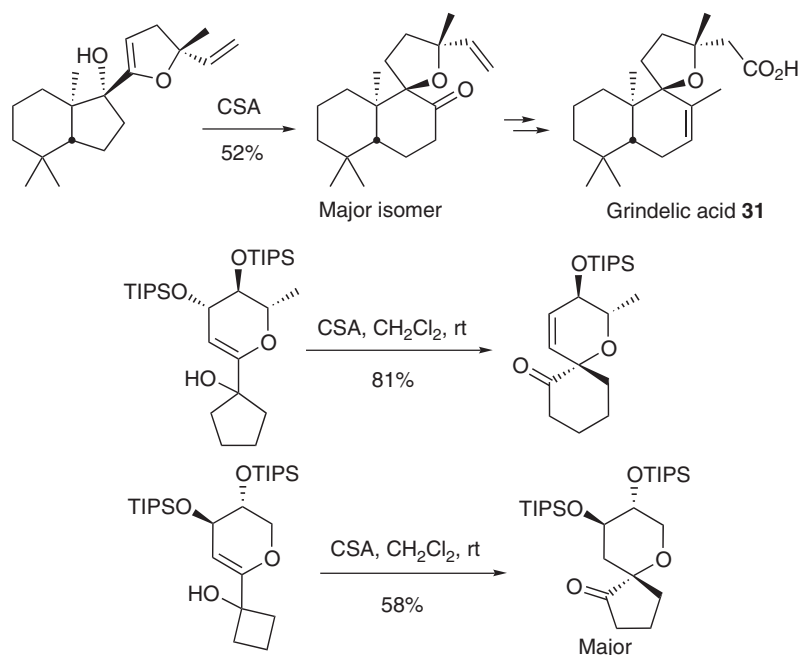
The use of a chiral Lewis acid, which may allow in some cases a kinetic resolution of the starting material, is noteworthy [<2002TA395>](#) (Equation (29)).



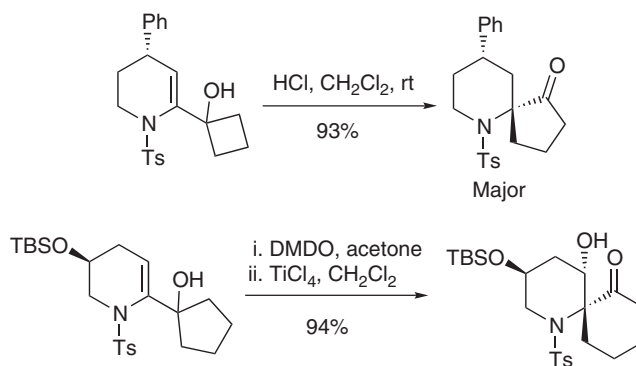
A very promising solution to promote a semipinacol-like rearrangement involves the formation in acidic conditions of either a cyclic oxonium or an iminium ion, which undergoes rearrangement (Equation (30)).



This methodology has been used for the synthesis of some spirocyclic systems and the stereochemical outcome of the rearrangement has been fully investigated. In the case of the rearrangement involving an oxonium ion, cyclobutyl and cyclopentyl carbinols underwent ring expansion by using camphorsulfonic acid [<1996JOC1119, 1997JOC1702, 1997JOC1713, 1995JOC191>](#) (Scheme 14) and grindelic acid **31** was synthesized in a stereocontrolled fashion [<1995TL6005>](#). When X is a nitrogen atom the corresponding rearrangements, involving an iminium ion, are expected to be more difficult [<2001OL2109>](#). Indeed, cyclobutyl carbinols undergo an easy ring expansion due to the ring strain (HCl) while cyclopentylcarbinols only afforded degradation products. However, when the double bond of the starting material is transformed to an epoxide, the reaction proceeds smoothly to afford the expected spirobicyclic compound (Scheme 15). For other related examples of semipinacolic rearrangements, see Chapter 1.18.



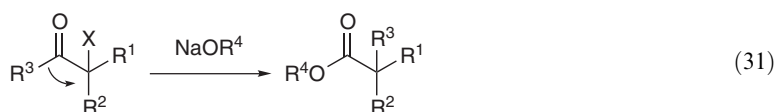
Scheme 14



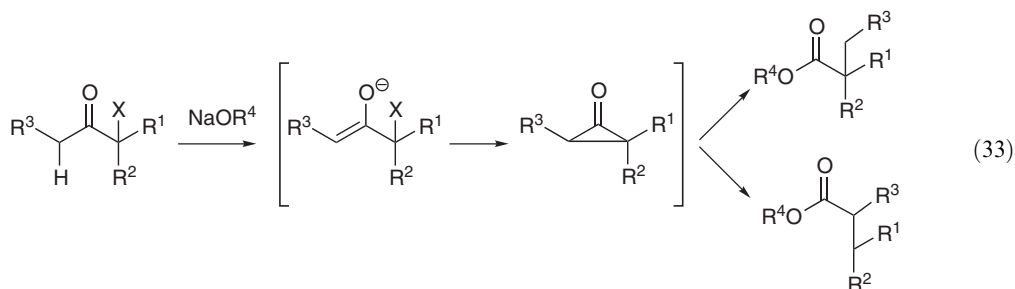
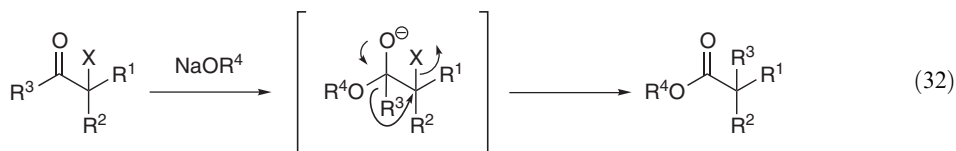
Scheme 15

1.09.1.2.5 Favorskii rearrangement

The nucleophilic Favorskii rearrangement involves a similar 1,2-migration of a substituent as an anion, but, in this case, the initial carbocation is formed from an α -haloketone in basic conditions (Equation (31)). This rearrangement, which may also occur in a modified version [\[2002OL957\]](#) in biosynthetic processes, has been used in syntheses of natural products [\[1996TL1463, 1998JCS\(P1\)3689\]](#) due to its ability of inducing ring contraction in cyclic ketones [\[1995JOC3414\]](#).



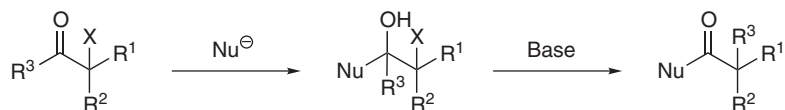
Even if the scope of this rearrangement has been extensively studied, its mechanism remains debated [\[1997JA1941, 2001JPC2453\]](#) in order to explain the regiochemical outcome of the reaction, particularly in the case of α -haloketones presenting a hydrogen atom in the α' -position of the carbonyl group. Two mechanisms are generally accepted and are called the semibenzilic acid mechanism (Equation (32)), also referred to as the quasi-Favorskii rearrangement and the Loftfield mechanism (Equation (33)).



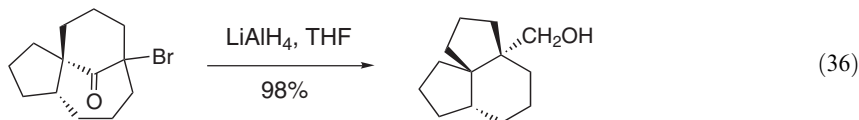
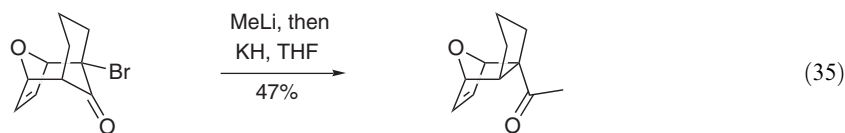
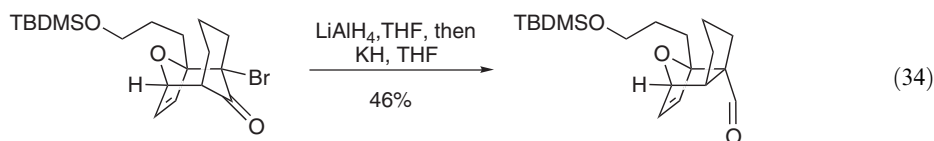
The semibenzilic rearrangement involves at first a nucleophilic attack of the alkoxide on the carbonyl carbon atom of the α -haloketone followed by a concerted displacement of the halide ion by the 1,2-migration of an alkyl group. Alternatively, the Loftfield mechanism involves the formation of the enolate, which is thought to be followed by the cleavage of the carbon-halide bond to form the corresponding cyclopropanone. Then, cleavage of the cyclopropane ring is assumed to occur to form the more stable carbanion that is responsible for the final regiochemical outcome of the rearrangement. The Loftfield mechanism is preferred in the case of α' -enolizable ketones, while the semibenzilic is operative in the absence of α' -hydrogens or in the case where the formation of the cyclopropanone is prohibited due to structural features.

Moreover, one also has to consider the stereochemical outcome of the reaction from this mechanistic point of view. Indeed, the Loftfield mechanism, involving an oxyallyl cation, may result in the formation of a mixture of isomers, while the concerted quasi-Favorskii rearrangement will result in a formal inversion of configuration at the carbon originally bearing the halogen atom. In fact, it has been demonstrated, as reported in the corresponding chapter of the COFGT (1995), that the polarity of the solvent used in the experimental procedure should influence the mechanistic pathway <1995COFGT(1)377>. Both mechanisms have therefore to be taken into consideration.

However, the quasi-Favorskii rearrangement may be achieved through a sequential pathway involving at first the 1,2-addition of an appropriate nucleophilic species on the carbonyl group, followed by treatment with a base leading, through migration of an alkyl group, to the formation of an aldehyde or keto group (Scheme 16) (the nucleophilic species can be either a hydride (Equations (34) and (36)) or an organometallic reagent (Equation (35))).

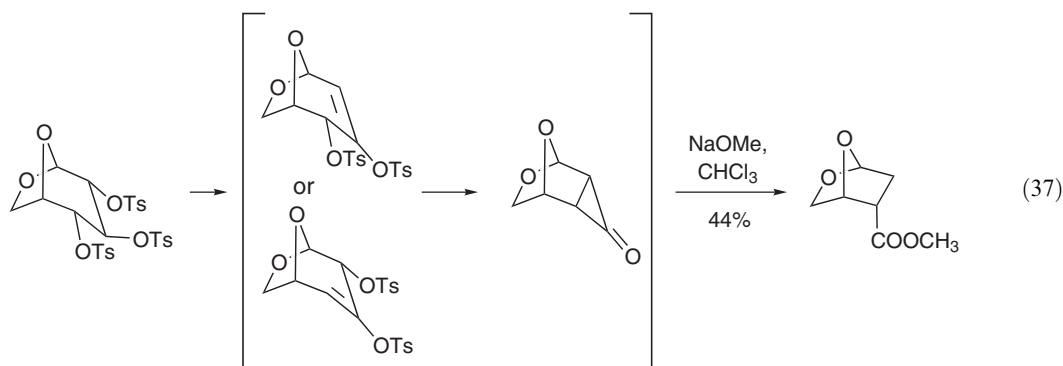


Scheme 16



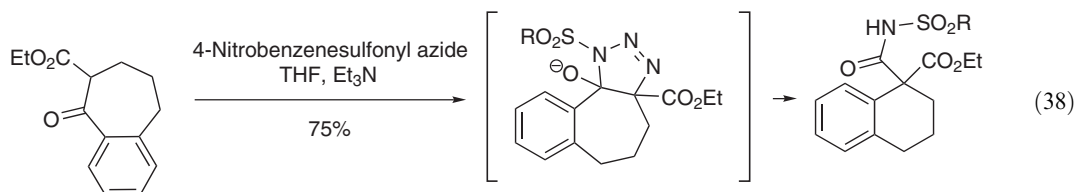
This version of the Favorskii rearrangement has been used on several haloketones and included as a key step in the synthesis of natural products <2001TL5593, 2001OL2533>. It has also been used either in the case of unsymmetrical ketones, the asymmetry of which was not expected to induce a regiochemical control in a normal Favorskii rearrangement <1999TL1075> (Equation (35)), or in the case of nonenolizable ketones <2002TL2347> (Equation (36)).

In the normal Favorskii rearrangement, the regiochemistry is mainly controlled through the stability of the anion formed, which may be managed either by the difference of the substitution patterns of the α - and α' -carbon atoms or by the presence of electron-withdrawing groups. The presence of an acetal moiety can be responsible for the complete regioselectivity of the rearrangement <2002JCS(P1)1297> (Equation (37)).



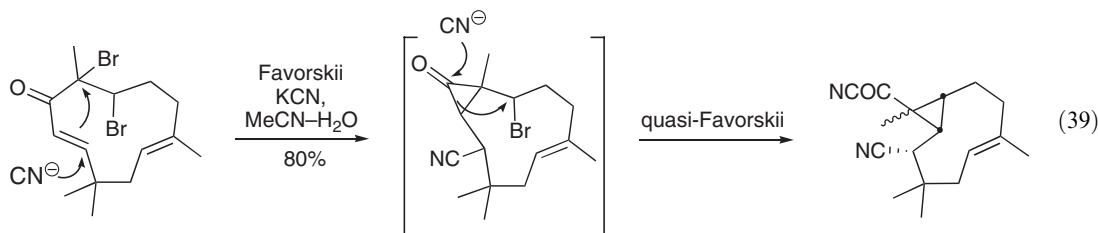
It is important to note, in this example, the use of the tri-tosylate moiety as a haloketone equivalent in the Favorskii-like rearrangement.

In the same area, it has been demonstrated that sulfonyl azides may induce a Favorskii-type rearrangement of benzocyclic β -keto esters with loss of a molecule of nitrogen, through a triazole intermediate (Equation (38)) <1998JOC4679, 1999JOC5132>. In this case, however, the nature of the sulfonyl azide has a considerable influence on the nature of the product of the reaction, due to their ability in forming the triazolic adduct and in inducing different fragmentation pathways for this adduct or by performing preferentially a simple diazo-transfer with fragmentation of the cyclic structure.

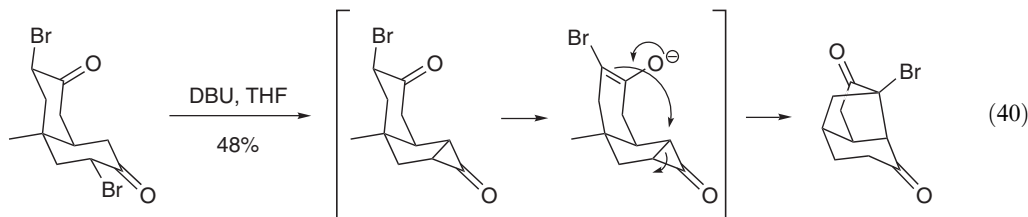


The experimental procedures encountered in the field of the Favorskii rearrangement are mainly based on the classical use of alkoxides of group (I) metals but this rearrangement may also occur under electrochemical <1997T4427, 1996TL5759> or photochemical <1997T16789> conditions. In some cases, the use of non-nucleophilic bases is reported to induce Favorskii-like rearrangements (*vide infra*).

One may also consider the possibility of generating the enolate intermediate through 1,4-addition of an appropriate species on α,β -unsaturated α' -haloketone. This possibility should offer the access to cyclopropanones, since the nucleophilic species used in the 1,4-addition step would not be able to induce fragmentation of the cyclopropane ring. This possibility has been exemplified in a sequential Favorskii, quasi-Favorskii-like sequence using cyanide as nucleophilic species <1999JOC2667> (Equation (39)).



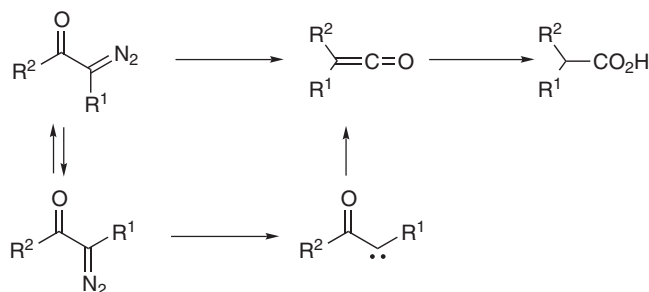
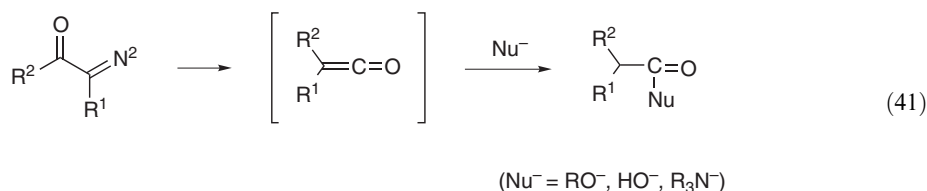
Alternatively, the cyclopropanone may be cleaved intramolecularly by an appropriate nucleophile. It is the case when another enolizable ketone is present in the molecule and the rearrangement achieved in non-nucleophilic basic conditions <1995JOC554>. In the example depicted in Equation (40), the rearrangement is initiated by the DBU-induced formation of the enolate of one keto group of the symmetric starting diketone and the cyclopropanone is thereafter opened in an intramolecular fashion by the enolate of the other carbonyl group, thus affording the more stable carbanion.



1.09.1.2.6 Wolff rearrangement

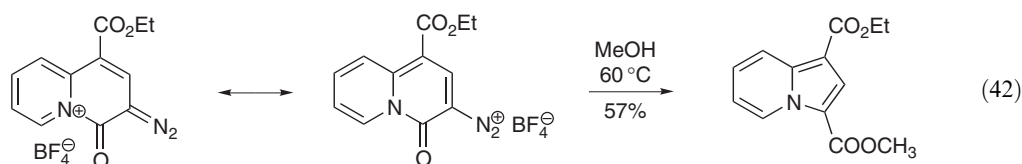
The Wolff rearrangement is the rearrangement of an α -diazoketone-derived carbene, leading, after quenching by an appropriate nucleophilic species, to the corresponding acid derivative as depicted in Equation (41). The whole process involves the formation of a new C—C bond α to a carboxylic acid group. This method has extensively been used for the homologation of carboxylic acids ($R^1 = H$, $Nu = H_2O$) and referred to as the Arndt–Eistert synthesis <2001TL7099, 1995AG1217, 1996LA1121, 1998S837, 1997TL6145, 1997IJC(B)1103, 2000S395>. The mechanism

of this rearrangement has also been studied to know to what extent the nitrogen elimination and substituent migration were concerted or not, allowing or not the trapping of the carbenoid intermediate particularly under photochemical conditions (Scheme 17) <1999JCS(P2)1107, 1999JA2883, 1999JA5930, 1996JA12598, 2001JA6061, 2001JA6069>.



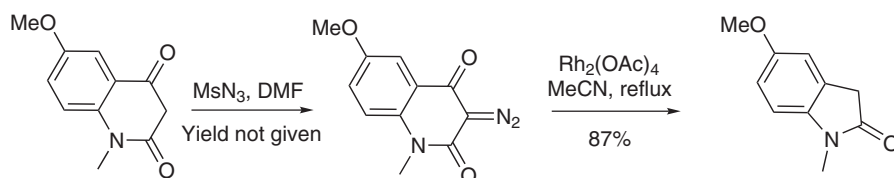
Scheme 17

The Wolff rearrangement is usually initiated through treatment of a diazoketone by either rhodium <1998JOC9828, 1997T8501, 1996T10455, 1999CC1199, 1997TL1397, 2002OL873, 2001TL8455, 1999TL8219>, chromium <1997T7557>, or silver salts <1998JCS(P1)1919, 1998S837>, but may also be achieved either under microwave activation <2002JOC1574>, photochemical conditions <2001JOC2611, 1998JOC8380, 2002OL2465, 1999JCS(P1)1207, 2000TL4053, 1998TL7541, 2001JCS(P1)2194, 2000OL2177, 2003OBC2556>, by heating <2001JCS(P1)2266, 1999TL8219, 1995TL7859>, or ultrasound activation <1998S837>. The rearrangement may also be induced, in the case of the particular aza-Wolff rearrangement by HBF₄ <2001EJO3705> through the rearrangement of the diazonium salt (Equation (42)).



Alternatively, the starting diazoketone may be obtained either by addition of diazomethane or trimethylsilyl diazomethane to the corresponding acid chloride but may also be synthesized by azide transfer using azide sulfonates <2001JCS(P1)2194, 1998JOC4679, 1999JOC5132, 2001TL8455, 1996T6665>.

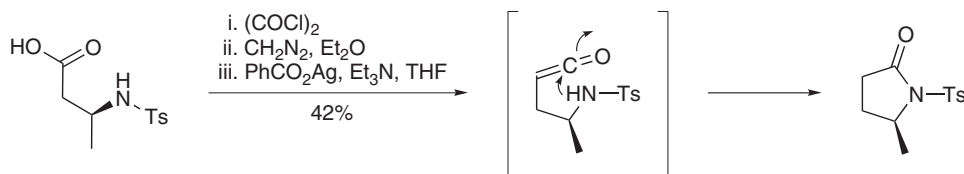
As the product of the rearrangement, in the case of the ring contraction of cyclic ketone exhibits an exocyclic carbonyl group, an additional decarboxylation may also occur after the rearrangement. It is the case of cyclic 2-diazo-1,3-dicarbonylated compounds used for the preparation of substituted oxindoles, as depicted in Scheme 18 <1999TL8219>.



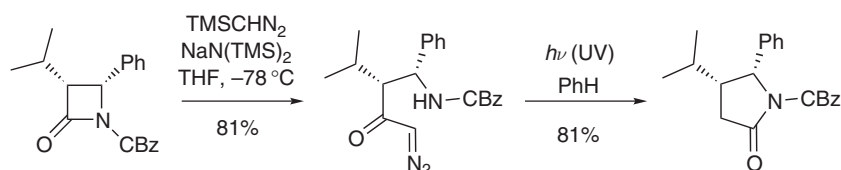
Scheme 18

The stereochemical outcome of the rearrangement ($R^1 \neq H$) has been studied and proved to be very dependent on the experimental conditions. The best results were obtained when the Wolff rearrangement was performed under photochemical conditions at low temperature <2000OL2177>.

Important features nevertheless arise from the recent developments of the Wolff rearrangement. The first one is the possible intramolecular trapping of the ketene intermediate. Indeed, the presence of an extra amino group in the molecule may be used for such purpose, leading to the corresponding lactams. This modification of the Wolff rearrangement may be effected through a classical Arndt–Eistert protocol <1998JCS(P1)1919> (Scheme 19), or as a possible ring-expansion of β -lactams <1998TL7541>. In this latter case, addition of trimethylsilyl diazomethane led to the acyclic β -amino- α' -azido ketone, which thereafter undergoes Wolff rearrangement and an intramolecular amidation (Scheme 20). The outcome of the transformation nevertheless depends on the nature of the starting material, and better results are obtained when γ -lactams are formed.

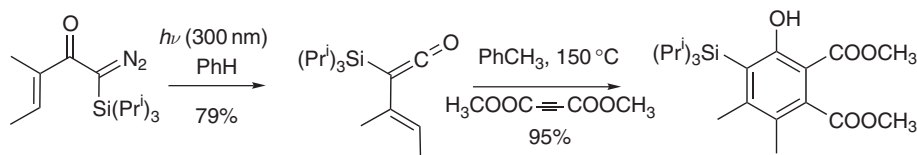


Scheme 19



Scheme 20

The second important feature of the Wolff rearrangement is to induce the formation of ketene derivatives, which can be involved in other reactions <2003T3545, 2001JCS(P1)2266, 2001JOC2611, 1997TL1397>. It is especially the case when starting from α -silyl α -azido ketones <1999CC1199>. Indeed, the silyl ketene intermediates are relatively stable <1998JCS(P1)2105> and may be, for example, engaged in cycloaddition reactions <1998JOC8380, 2002OL2465> (Scheme 21).

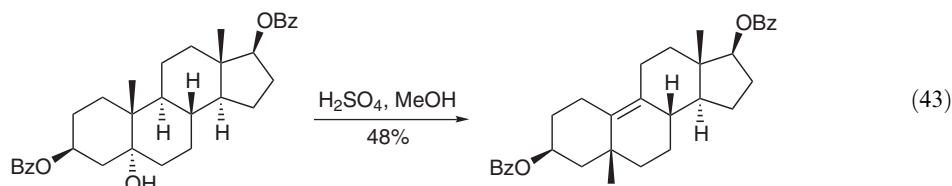


Scheme 21

However, due to the particular structure of the starting material or the conditions used, a competitive reaction may take place between the Wolff rearrangement and other reactions involving carbene chemistry (insertion reactions, etc.) <1996T10455, 1999JPC7145, 1998T6457, 1998JOC9828, 1997T8501>.

1.09.1.2.7 Westphalen–Lettré rearrangement of steroids

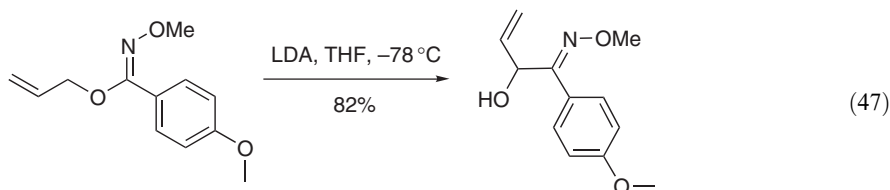
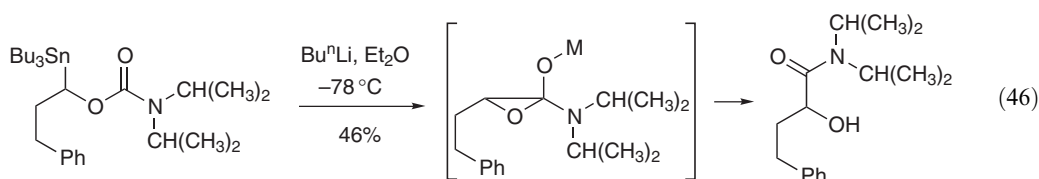
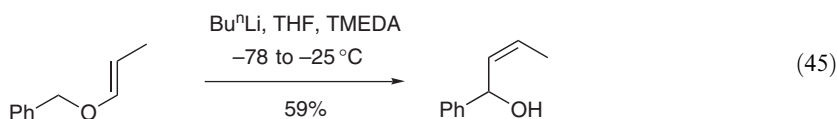
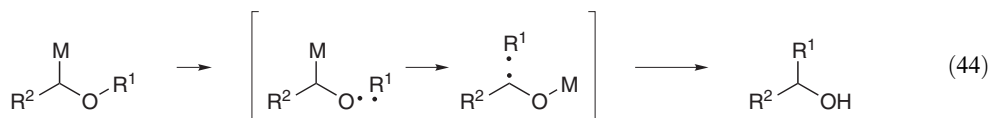
It is worth noting that the well-known Westphalen–Lettré rearrangement of 5-hydroxy-steroids, discovered in the early 1910s and involving dehydration ($\Delta^{9,10}$ -double bond formation) and migration of the methyl group at C-10 to the carbon atom at C-5 with inversion of the configuration at C-5, is still being used in some studies devoted to biological activities of modified steroid derivatives <1996CCC276, 1998CCC1549> (Equation (43)).



1.09.1.3 Substituent Migrates as a Radical

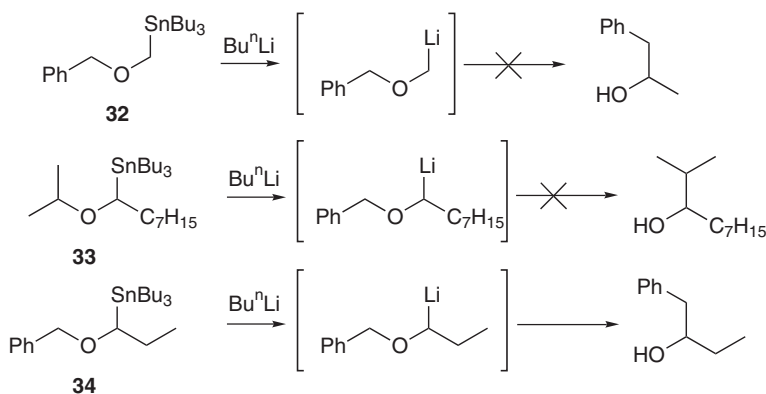
1.09.1.3.1 [1,2]-Wittig rearrangement

The [1,2]-Wittig <2001EG(E)1411> rearrangement corresponds to the 1,2-alkyl migration of an α -metallated ether (Equation (44)). This type of 1,2-alkyl migration is now well recognized to proceed via the radical cleavage–recombination pathway with slight inversion of the configuration at the carbon bearing the metal atom <1996JA3317, 1998JOC9756>. The scope of this rearrangement has been widely reviewed <1997LA1275>. In the gas phase, the same rearrangement has, however, been demonstrated to be an anionic reaction <1998JCS(P2)1435, 1999JCS(P2)333>. Important variants of this rearrangement have also been reported, including the rearrangement of lithioalkyl vinyl ethers <2000CL418> (Equation (45)), 1,2-carbamoyl migration <1999CL759, 1996TL6061> (Equation (46)), and imino rearrangement of hydroximates <1999SL1915> (Equation (47)).



In contrast with the already-presented rearrangements, the scope and limitations of the [1,2]-Wittig rearrangement are not only deduced from the migratory aptitude of the migrating group but also from structural requirements at the carbon atom bearing the metal. Indeed, if the migratory aptitude of the migrating group is roughly consistent with the stability order of the corresponding radical, experimental observations reveal that a radical-stabilizing factor at the carbon atom bearing the metal is required for the rearrangement. This means that the rearrangement requires a good complementarity between the migratory aptitude of the R^1 group and the anion-stabilizing ability of the R^2 group.

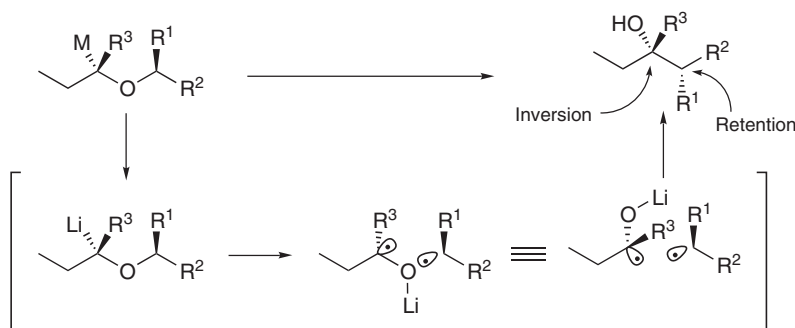
As an illustration of these findings (Scheme 22), upon transmetalation stannane **32** and **33** do not undergo rearrangement, while stannanes **34** does.



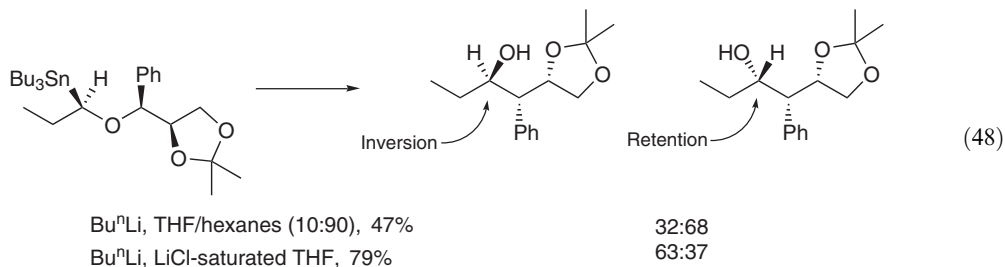
Scheme 22

Although the benzyl group remains the best migrating group in this rearrangement, its application is relatively restricted. Furthermore, the use of an allyl moiety for the formation of the initial carbanion (α -oxyallylic carbanion) induces side reactions such as the formation of 1,4-products prior to the desired 1,2-ones or competitive [2,3]-Wittig rearrangement [<2002EJO478, 2003TL373>](#).

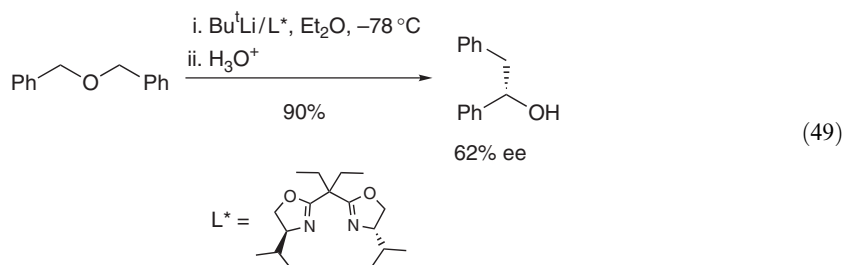
Alternatively, some stereochemical problems are related to the outcome of the rearrangement. Many studies have been devoted to the rationalization of the stereochemical outcome of the [1,2]-Wittig rearrangement [<1997TL8939, 2001TL4865, 1998JA8551>](#). The most adopted assertion, particularly in the case of rearrangement induced by transmetalation of chiral compounds, advocates retention of configuration for the migrating group and inversion of configuration at the metal-bearing carbon atom as depicted on [Scheme 23](#). However, as this is not a concerted mechanism, the stereochemical outcome of the reaction mostly depends on the reaction conditions and on the presence, in the starting material, of an oxygenated function able to chelate the metal atom in the transition state ([Equation \(48\)](#)) [<1998JA8551>](#).



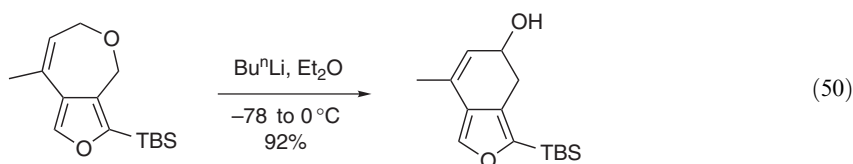
Scheme 23



In a similar manner, the use of external chiral ligands may induce asymmetry in the rearrangement of achiral ethers [<1999AG\(E\)3741>](#) ([Equation \(49\)](#)).



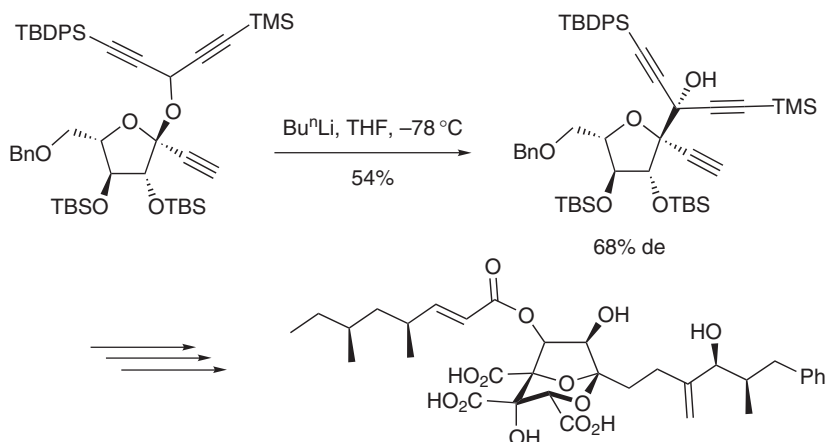
An interesting ring-contraction reaction has been reported in the case of cyclic bisallyl ethers (Equation (50)) <1996JA10766>, the regioselectivity encountered in this rearrangement being attributed to the relative acidity of the different allylic hydrogen atoms.



Examples dedicated to the [1,2]-Wittig rearrangement with aryl migration <1996TL8903>, which are related to the rearrangement of lithioalkyl vinyl ethers <2000CL418>, have also been reported <2002OL1587>.

In order to alleviate the drawbacks of the classic [1,2]-Wittig rearrangement, most examples now involve the rearrangement of acetals. Indeed, the relatively large stability of the α -oxy radical allows them to induce easy [1,2]-Wittig rearrangement. Moreover, the easy preparation of the mixed acetals allows a facile access to the starting material of the reaction. The structural requirements <1999TA4811> as well as the influence of the reaction conditions <2000TA1003> have been studied.

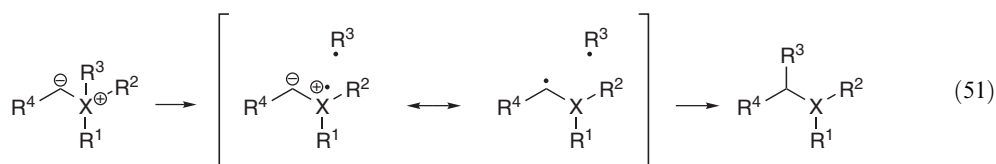
In the same field, the rearrangement of acetals of *O*-glycosides has been used to allow the preparation of the rearranged *C*-glycosides <1996JA3317, 2000AG(E)4500, 1995SL321>. In this case, retention of configuration, generally observed in the migrating radical, allows the configuration of the *C*-glycoside to be fixed in the starting material by the anomeric configuration. This version of the [1,2]-Wittig rearrangement has been used in total syntheses including the synthesis of zaragozic acid <1999TL1917, 2000AG(E)4502> (the key step of the synthesis (Scheme 24) allows the stereocontrol of two vicinal quaternary stereocenters in a [1,2]-Wittig rearrangement). An example of [1,2]-thio-Wittig rearrangement has also been reported <1996JA1398>.



Scheme 24

1.09.1.3.2 [1,2]-Stevens rearrangement

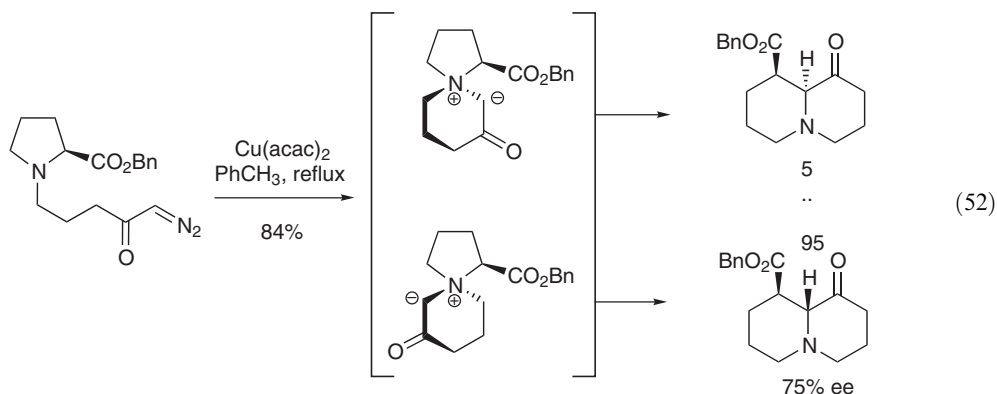
As with the [1,2]-Wittig rearrangement, the Stevens rearrangement involves the 1,2-migration of a group attached to an heteroatom. The initial step of the rearrangement involves the formation of an ylide (generally ammonium, oxonium, or sulfonium). The 1,2-shift thereafter occurs via a radical cleavage of the C—X bond followed by a recombination (Equation (51)). As for the Wittig rearrangement, the configuration of the migrating group is retained. The mechanism of this rearrangement has been studied, particularly in the case of the rearrangement of ammonium ylides <1996JOC7276>, and the absence of competition with a concerted pathway or the formation of ion pairs has been demonstrated. The asymmetric version of the rearrangement of ylides has been reviewed <1997CR2341>.



Most of the recent advances in the field of the Stevens rearrangement, as well as in other related ylide reactions, involve new methods for the formation of the starting ylides based on the use of carbenes from diazo compounds, the features of which have been reviewed <2001CSR50, 1998CR911>.

(i) Rearrangement of ammonium ylides

In the original work of Stevens in the 1930s, the authors mainly reported the rearrangement of ammonium ylides, and for many years, most of the research in this field has been devoted to this type of rearrangement, especially due to the easy access to the starting materials. The main experimental procedures involve treatment of the ammonium salt either with a group (I) metal or with metal alkoxide or amide <2001AG(E)3810, 1997JCS(P1)1491>. However, most of the reported Stevens rearrangements of ammonium ylides now use carbenes generated from diazo-ketones, which allow a one-step procedure <1998TL4159, 2001JOC2414, 1996TL615> involving metallo-carbenoid generation/ylide rearrangement cascade <1997TL3319, 1997JOC78, 1998JOC556, 2000JA8155, 2003TL2895>. In this type of cascade sequence, the reaction is effected by rhodium or copper acetate catalysts. This strategy has been used in the synthesis of some alkaloids <1997T16565, 1995TL2519, 2001JOC2414, 1996TL2165>. In the example shown (Equation (52)) <1997T16565>, the formation of the spirocyclic ylide is demonstrated to be stereoselective under steric control and the rearrangement occurs with a partial retention of configuration at the migrating center.

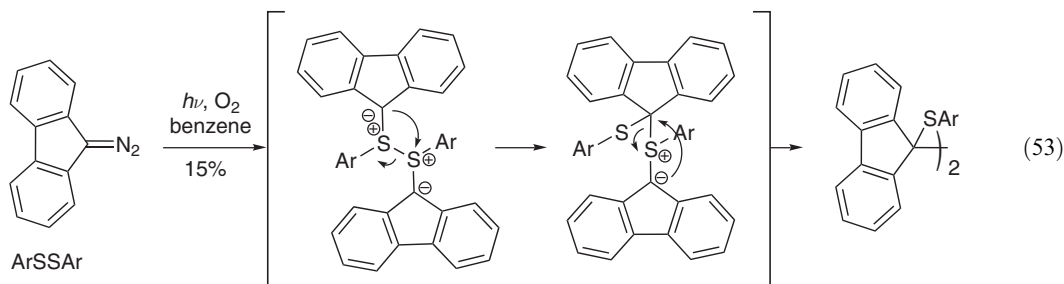


Other sets of experimental conditions have been proposed including Mitsunobu conditions (in the case of ω -hydroxy amines) <1996TL8133> and caesium fluoride <1999JOC581>.

These new features ensure that the Stevens rearrangement of ammonium ylides remains a useful tool in alkaloid synthesis, but it still suffers from the same drawbacks as other related rearrangements, mainly the selectivity for the migrating group <1997TL2113> and competition with other rearrangements (see Section 1.09.4.4.4—the Sommelet–Hauser and the [2,3]-Stevens rearrangement).

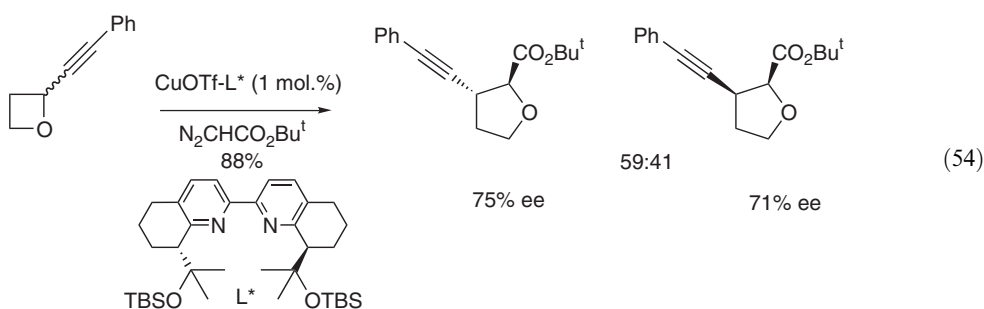
(ii) *Rearrangement of sulfonium ylides*

The rearrangement of sulfonium ylides has not been widely used but has also benefited from advances using carbenoid chemistry under photochemical conditions as proven by the following example of fluorenylidene diinsertion in the S–S bond of an aryl disulfide through two consecutive Stevens rearrangements <1997TL8989> (Equation (53)).



(iii) *Rearrangement of oxonium ylides*

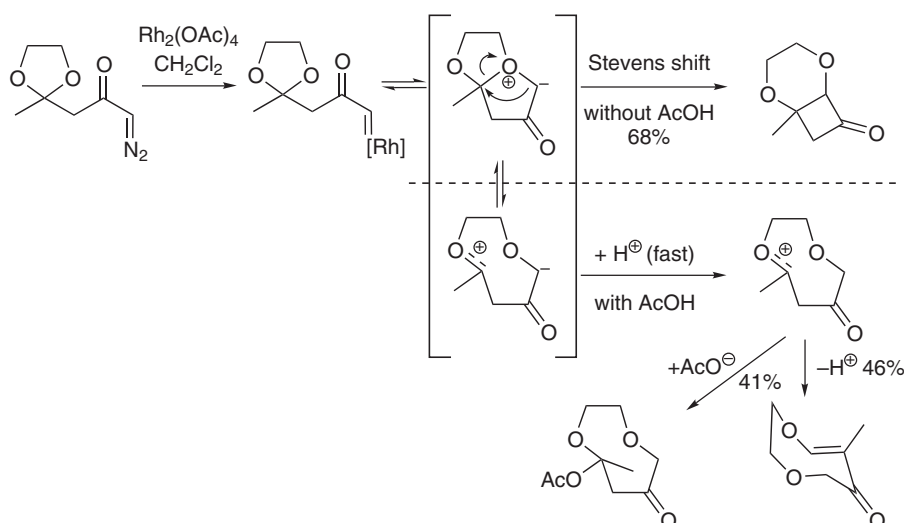
As another consequence of the use of diazo compounds for the formation of ylides, the rearrangement of oxonium ylides becomes easily accessible. In most cases, the diazo precursor and the ether containing the oxygen atom that will be involved in the oxonium are present in the same molecule and the whole process leads to the formation of an α -substituted cyclic ether. The reaction may, however, be achieved in a bimolecular fashion <1996T3905>. In this case, the reaction provides a new method for the ring expansion of cyclic ethers with a good control of the absolute configuration of the inserted carbon when performed in the presence of chiral ligands (Equation (54)), without, nevertheless, kinetic resolution at the racemic migrating center. Asymmetric induction can also be effected in an intramolecular process using chiral ligands <1997TL4367>.



As in the previously reported related Stevens rearrangements, the migrating group is usually a benzyl or an alkyl group but can also be a silyl group <1995TL4845>.

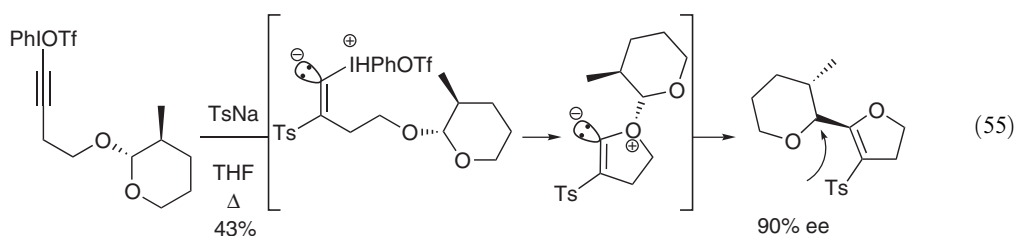
In contrast to the rearrangement of ammonium ylides, the oxonium species may be in some cases trapped either in an intramolecular or in a bimolecular fashion by a dienophile species and therefore involved in a [2 + 3]-reaction <1997TL3319>.

The rearrangement of oxonium ylides has also been studied in the case where the oxygen atom involved in the anion is also included in a cyclic dioxolane <1996TL5053, 1997JOC2123>. The result of the rearrangement has been proven to be largely dependent on the reaction conditions, since acidic conditions allow a rapid addition of H^+ to the initially formed oxonium ion (Scheme 25).



Scheme 25

If the most often reported conditions used for the formation of the oxonium ion remain the use of the diazo-derived cabenoid chemistry [<2003JOC4531>](#), an interesting report has shown in the case of 1-hydroxy 3-ynylidonium ethers that the addition of *p*-toluenesulfate on the triple bond induces an intramolecular cyclization/oxonium formation. The so-formed oxonium thereafter rearranges in a Stevens rearrangement (Equation (55)) [<2000JOC8659, 2000OL2603>](#).



1.09.1.4 Sigmatropic Rearrangements

This section deals with the sigmatropic shift of a σ -bond across one or more double bonds. These rearrangements occur according to the Woodward–Hoffmann rules. In this section, a particular interest will be devoted to the [2,3]- and [3,3]-sigmatropic rearrangements as they have become major tools in the synthetic chemistry of complex natural products. Other sigmatropic rearrangements, namely [1,3]-, [1,5]-, and [1,7]-rearrangements, will be just mentioned but will not be discussed in detail since they are scarcely used.

1.09.1.4.1 [1,3]-Sigmatropic rearrangements

The migration of a carbon atom by a thermal [1,3]-sigmatropic rearrangement proceeds suprafacially with inversion of the configuration at the migrating carbon atom. No major improvement related specifically to this type of rearrangement has occurred since the publication of chapter 1.09.1.4.1 in [<1995COFGT\(1\)377>](#). The rearrangement of vinylcyclopropanes to cyclopentenones, which is to be considered as a [1,3]-sigmatropic rearrangement, has however found some new applications [<1999JA11018, 1999JOC3567>](#) and has been recently reviewed [<2003CR1197>](#).

1.09.1.4.2 [1,5]-Sigmatropic rearrangements

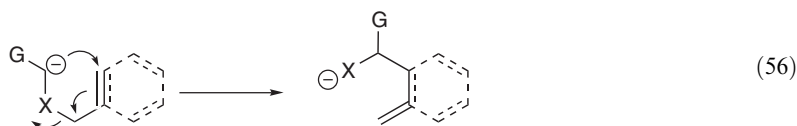
The thermal (or anion assisted) [1,5]-sigmatropic rearrangements have found no further advances since the publication of chapter 1.09.4.2 in <1995COFGT(1)377>. One may, however, consider some research about the mechanism of related rearrangements <2003JPC5479> and their use in the synthesis of natural products <1999OL161>.

1.09.1.4.3 [1,7]-Sigmatropic rearrangements

The thermal [1,7]-sigmatropic rearrangements have found no further advances since the publication of chapter 1.09.4.3 in <1995COFGT(1)377>.

1.09.1.4.4 [2,3]-Sigmatropic rearrangements

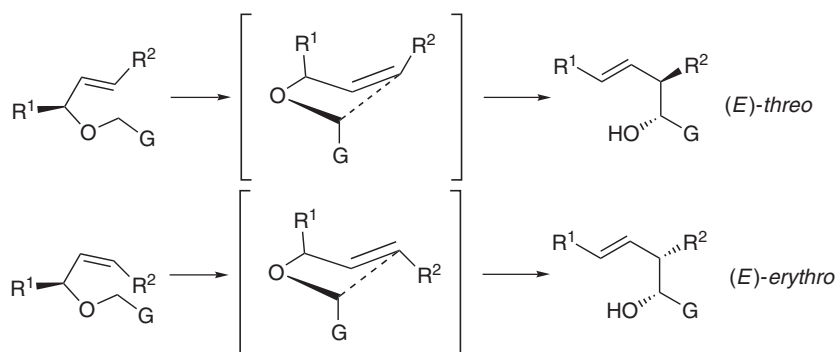
The [2,3]-sigmatropic rearrangement <2000MI535> is widely used in the formation of new C—C bonds via a suprafacial process. At first, carbanion formed in the α position to a heteroatom and the rearrangement thereafter occurs, involving a five-membered envelope-shaped transition state. The rearrangement generally involves an allyl moiety but may be performed with either propargylic or benzylic <2001OL2529> frameworks (Equation (56)).



(i) [2,3]-Wittig

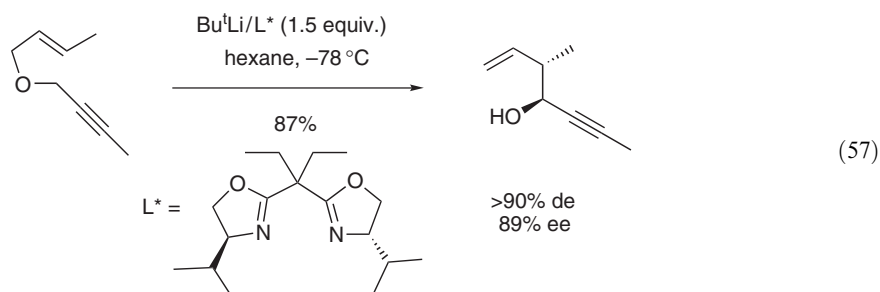
The corresponding rearrangement of ethers (X=O) is known as the [2,3]-Wittig rearrangement <2001AG(E)1411, 1995HOU(E21d)3757, 1995COFGT(1)793, 1997LA2005>. A DFT study of the [2,3]-Wittig rearrangement has been published <2003JOC2310, 1997CL81>. The scope and interest in this type of rearrangement are wide due to the possibility of obtaining a good selectivity for the geometry of the double bond formed in the course of the reaction and on the stereochemistry of the rearrangement, which is mostly dependent on the geometry of the double bond of the allyl moiety in the starting material. The stereochemical features depend on the nature of the G group and will be discussed in each case. Some of the variants modifying the nature of the G group (Scheme 26) provide a diastereoselectivity higher than 95% of either *syn*- and *anti*-diastereomers. Alternatively, as the rearrangement involves a well-defined transition state in a suprafacial process, transfer of chirality across the allylic system is generally observed allowing the formation of enantiopure rearranged products starting from chiral allyl alcohols.

During the 1990s, the number of communications on the [2,3]-Wittig rearrangement and its application in organic synthesis has continued to grow <1997MI1, 2002SL923> and particular emphasis has been given to the design of asymmetric rearrangements <1997PAC595, 2000CL1394, 1995CC2135, 2001OL2529, 2002T2253, 1995SL631, 1996S1438>. Moreover, chiral auxiliaries may be used either in an intramolecular or bimolecular process to induce chirality in the rearranged product, when the starting material does not incorporate asymmetric centers <1995SL321, 1997TL2633, 1999EJO2713, 1995T10699, 1996T1503, 1997CC737, 1998CPB335, 1998SL1429, 1999T6847, 1998TL5513, 2000CHIR505, 1996H(42)423> (Equation (57)).



G = H, aryl, heteroaryl, vinylic, alkynyl, oxazolines, and oxamines, $R-C=O$, $R^3-C=N(R^4)$
 CO_2^- , CO_2R , $CONR_2$, CN , $PO(OR)_2$, $SnBu_3$, SPh , SO_2R , and SiR_3

Scheme 26



(57)

A number of natural or non-natural products have been synthesized featuring a [2,3]-Wittig rearrangement as a key step. This is the case of kallolide A and B [<1995JOC796, 1996JOC5729, 1998JOC5962>](#), cryptophycin [<1999JOC1459>](#), epipatulolide [<1999TL475>](#), conagenin [<1999S243>](#), cyclohexane epoxide arthrinone [<2000TL10013>](#), phomactins [<2003TL2713>](#), tetrionic acids [<2001TL5215>](#), [2,2]-metacyclophanes [<1999JOC7140, 2003TL23>](#), dihydropyr- enes [<1999JCS\(P1\)403>](#), oudemansin A [<1995SL869>](#), brefeldin 1 [<1995SL901>](#), epibrefeldin C [<1996H\(42\)423>](#), amphoterin B [<1995TL2789>](#), β -lactone L-659,699 [<1998H\(47\)671>](#), acetogenins [<1995TL4073>](#), enediynes [<1996BSF987>](#), kedarcidin [<1996H\(43\)945>](#), and difluorinated analogs of eldanolide [<2001MI43>](#).

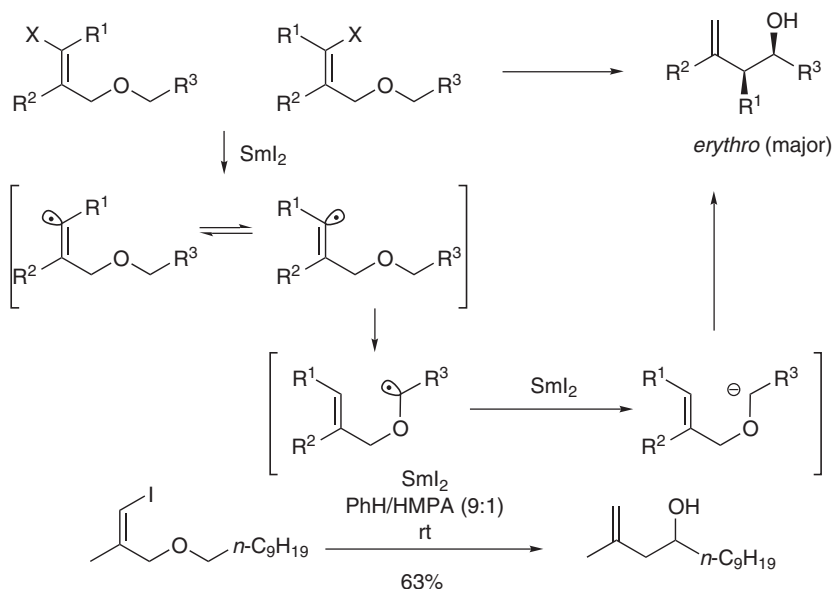
The conditions for the formation of the initial carbanion depend on the nature of the G group. This latter group is most often an anion-stabilizing group (acyl, aryl, allyl, propargyl, etc.), but may also be an unstabilized alkyl group. In this case, the anion has to be formed either through transmetallation of the corresponding stannane (this rearrangement is known as the Wittig–Still rearrangement, [Section 1.09.1.4.4.iv](#)), reductive lithiation of *O,S*-acetals [<2001TL415>](#) or through 1,5-hydrogen transfer from the allylic moiety of the molecule [<1997JOC7542>](#).

This section will therefore be divided according to the nature of the G group.

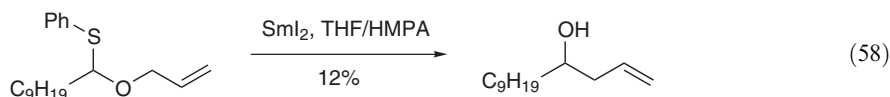
(a) *G as an alkyl group.* As mentioned above, the [2,3]-Wittig rearrangement of unactivated alkyl groups is possible upon several conditions.

An interesting possibility has been found [<1997JOC7542>](#) taking advantage of the samarium iodide-promoted vinyl radical formation, starting from alkyl γ -halogeno-allyl ethers. The vinyl radical initially formed thereafter undergoes 1,5-hydrogen shift in order to generate the oxyalkyl radical, which is further transformed by samarium iodide into the corresponding carbanion, which is then able to undergo a rearrangement ([Scheme 27](#)). In this case, the geometry of the initial double bond obviously did not influence the stereochemical course of the reaction, and the diastereoselectivity ($R^2 = H$, $R^1 \neq H$) is in good correlation with the rearrangement of the (*E*)-isomer although being relatively low (de = 20%).

Samarium iodide has also been used in order to promote the rearrangement of monothioacetals [<2001TL415>](#) ([Equation \(58\)](#)).



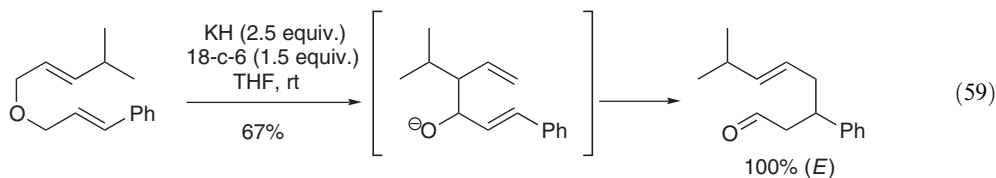
Scheme 27



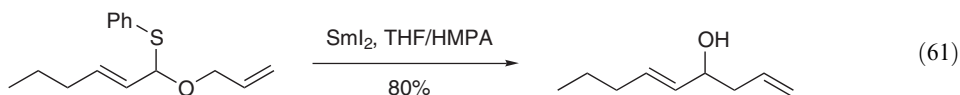
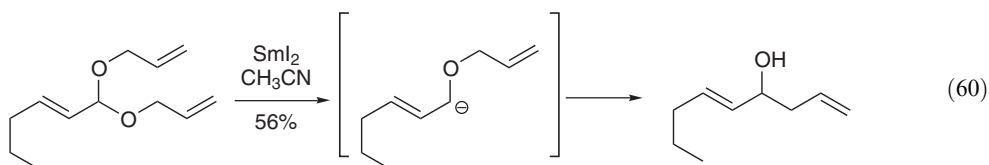
The Wittig–Still rearrangement, however, continues to be the most widely used solution for the formation and rearrangement of unstabilized oxyallyl carbanions (see [Section 1.09.1.4.4.\(iii\)](#)).

(b) *G as an aryl or heteroaryl group.* As mentioned in [Section 1.09.1.3.1](#) for the [1,2]-Wittig rearrangement, aryl groups, because of their ability of stabilizing a carbanion in α -position, have been widely used for such rearrangements. The benzyl group, as one of the best migrating groups, has been used to test enantioselective induction in Wittig rearrangements [<1995TL2789, 1998CC123>](#). Other aromatic groups have also been used, including furyl [<2000TA4725, 1995CC2135, 1999CC2263, 2000TA4725, 2003JOC10183>](#) and benzotriazole [<1996JOC4035>](#). However, due to their high migratory aptitude, the most critical feature to manage is the selectivity between [1,2]- and [2,3]-rearrangements [<2001OL2529, 2002EJO478>](#).

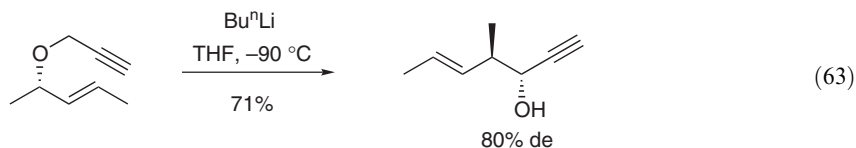
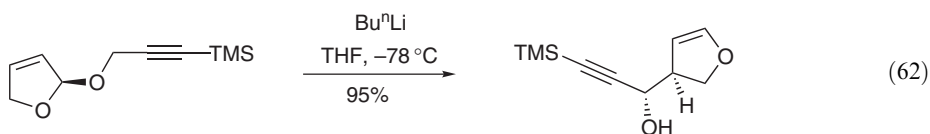
(c) *G as an allyl group.* Allyl groups have also been used in [2,3]-Wittig rearrangements, although in this case, the regioselectivity of the formation of the initial carbanion has to be carefully controlled. An efficient way to control the regioselectivity is to use either γ -phenyl or γ -trialkylsilyl allyl groups [<1997TL6445>](#). Alternatively, since the rearrangement of bis-allylic ethers produces vinyl allyl carbinols, conditions may be carefully adjusted in order to either avoid (Bu^nLi , low temperature) [<1999TL475>](#) or induce a further anionic oxy-Cope rearrangement (KH , 18-C-6, room temperature) [<1997TL6445, 1997TL6449, 1997TL6453>](#) ([Equation \(59\)](#)).



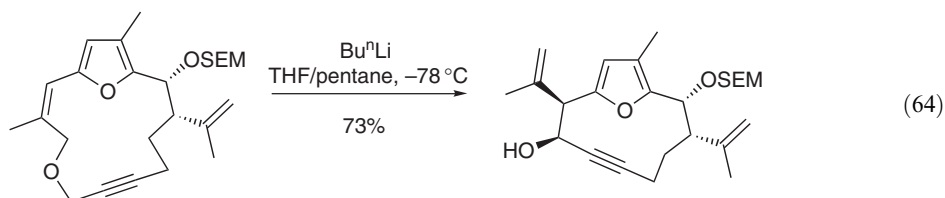
An alternative method for the control of the regioselectivity of anion formation is derived from the radical formation induced by samarium iodide starting from bisallyl acetals derived from α,β -unsaturated aldehydes ([Equation \(60\)](#)) [<1998TL5229>](#), in a similar process to that proposed for the samarium iodide-induced rearrangement of thioacetals ([Equation \(61\)](#)).



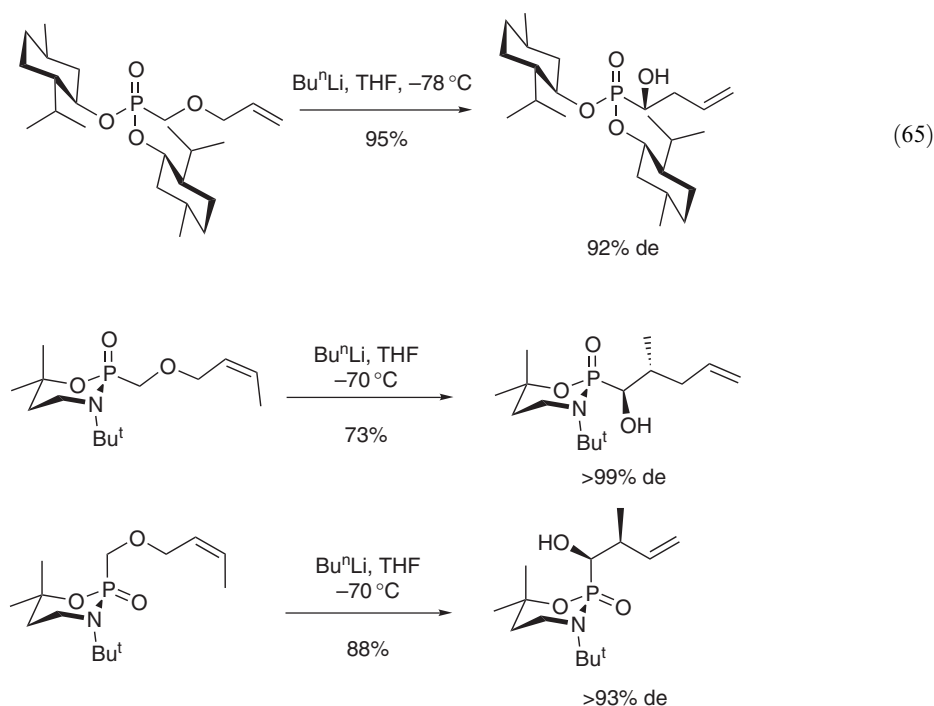
(d) *G as a propargyl group.* The use of propargyl (or γ -trialkylsilyl propargyl) groups for the formation of the carbanion to be involved in the Wittig rearrangement has been extensively studied since it alleviates the drawbacks of regiochemistry of the bisallyl ether rearrangements and produces in most case very good stereochemical control of the stereocenters formed in the course of the reaction, according to the geometry of the double bond of the starting material <2002EJO3465>. These important aspects of this type of reaction have prompted several teams to use this version of the [2,3]-Wittig rearrangement as the key step in the total synthesis of natural products. The double bond of the starting material may be incorporated in a carbocycle <1995TL4073, 2000TL10013> (Equation (62)) or in an acyclic system <1999JOC1459> (Equation (63)).



An exemplary application of this methodology to the total synthesis of natural products has been proposed for the synthesis of macrocyclic pseudopterolides. This synthesis involves the ring contraction of a macrocyclic allyl propargyl ether through a completely stereoselective Wittig rearrangement, leading to the stereocontrolled formation of two adjacent stereocenters <1996JOC5729, 1998JOC5962> (Equation (64)).



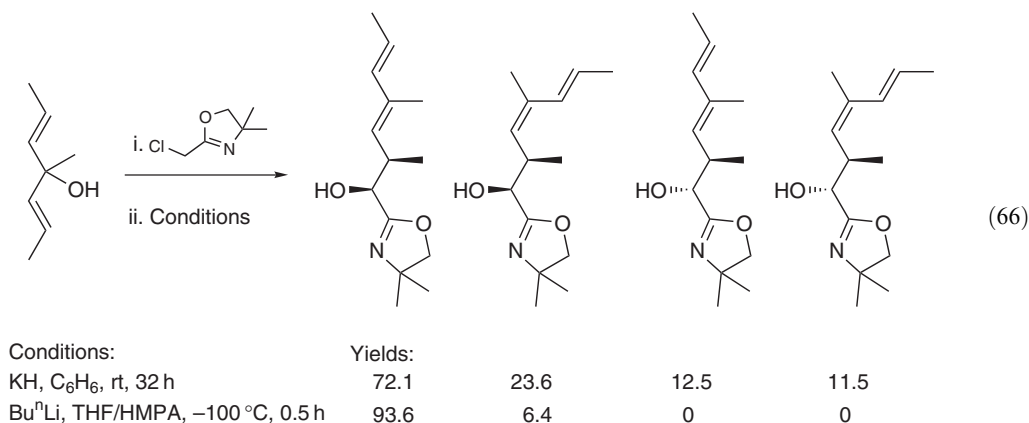
(e) *G as a phosphorus-containing anion-stabilizing group.* Phosphorus anion-stabilizing groups have been envisaged to induce [2,3]-Wittig enantioselective rearrangements. Two methodologies have been developed either by using phosphonates of chiral alcohols <1995TL6635> (Equation (65)) or oxazaphosphorinanes with a chiral phosphorus atom <1995TL6631> (Scheme 28). In both cases the diastereomeric excesses are very good, leading, after removal of the chirality source, to highly enantiopure compounds. Phosphorus groups have also been used in the Stevens rearrangement of sulfonium ylides <1996PS(112)193, 1996PS(109–110)445, 1999HAC281, 1998S1635, 2001SL605>.



Scheme 28

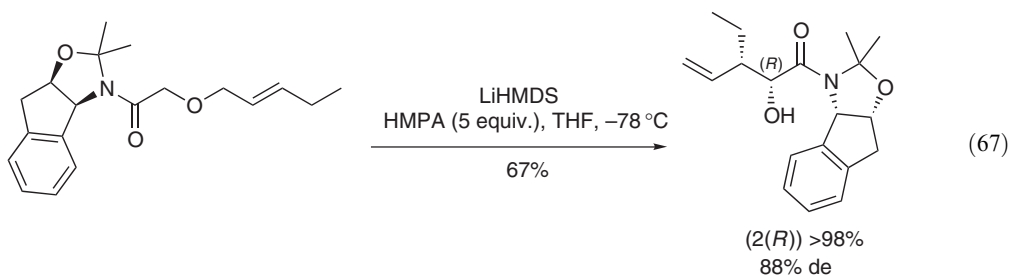
(f) *G as an hydrazone*. In a similar manner, β -oxo-alkyl allyl ethers can be converted into the corresponding chiral hydrazones, which may thereafter undergo a Wittig rearrangement, leading to the corresponding rearranged product with high enantiomeric excess after removal of the chiral auxiliary <1996S1438, 1996T1503, 1999S243>.

(g) *G as an oxazoline*. Oxazolines, as masked acid equivalents, may be used for promoting the Wittig rearrangement. Moreover, the easy access to oxazoliny methyl allyl ethers through alkylation of allyl alcohols by chloromethyl oxazoline allows this rearrangement to be used as the key step in total synthesis. For example, this methodology has been successfully employed for the synthesis of the unsaturated moiety of the sex pheromones of some *Matsuccocus* species <1995TL7197, 1995T10433>. In this example, the stereoselectivity of the rearrangement can be fully controlled according to the experimental conditions used (Equation (66)).



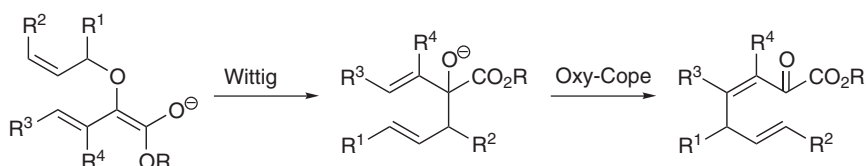
(h) *G as an acid, ester, or amide*. Classically, acids (in a dianionic process <1997CC1469>) or acid derivatives have been widely used in order to induce the [2,3]-Wittig rearrangement, even if it has been generally reported that this rearrangement requires the use of additives (mainly Cp₂ZrCl₂, TMEDA, or DMPU) to be stereospecific <1997JOC137, 1997TL2633>.

However, this methodology presents the possibility of using chiral acid derivatives in order to induce an enantioselective rearrangement. The best results in this field have been reported using a chiral amide [<1997TL2633>](#) (Equation (67)).

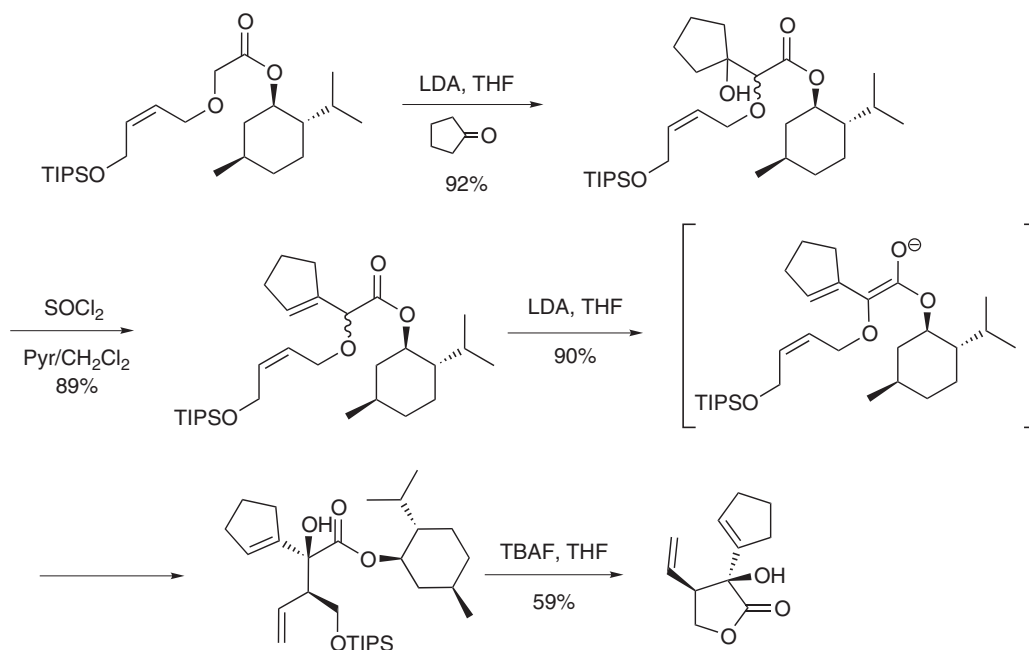


(ii) Rearrangement of dienolates

In the particular case of Wittig rearrangements of acid derivatives, one may pay attention to the potency of the rearrangement of allyl ethers of α -keto esters ([Scheme 29](#)) [<2001EJO483>](#), which, by using a chiral ester, allows an efficient access to α -hydroxy esters ([Scheme 30](#)) with, in general, a satisfying control of the stereogenic centers. The stereochemical outcome of the rearrangement, however, depends on the substituents [<1999T2625, 2000SL415, 2003SL663>](#). This rearrangement, providing vinyl allyl carbinols, may also be associated to a subsequent oxy-Cope rearrangement [<1999EJO2713>](#). This particular [2,3]-Wittig rearrangement of ester dienolates has been reviewed [<2003SL1088>](#).

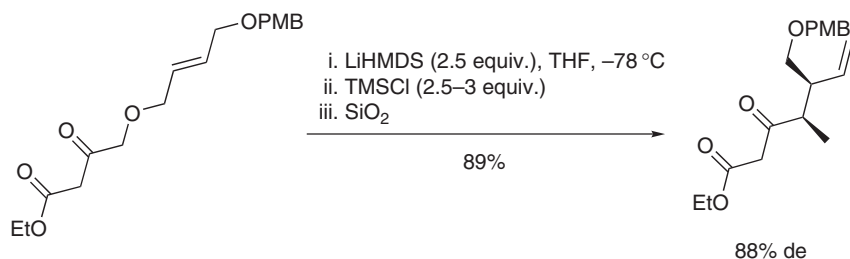


Scheme 29



Scheme 30

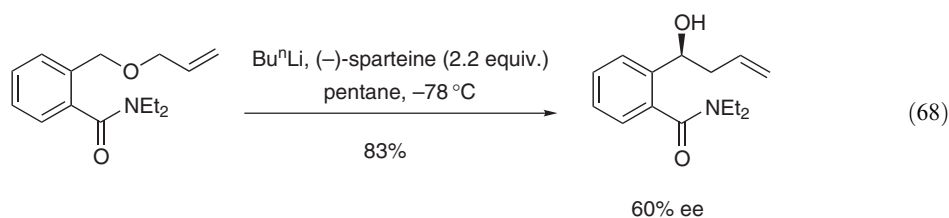
An interesting report has also shown the use of dilithiated hydroxy- β -keto ester enolates to allow a rapid and efficient [2,3]-Wittig rearrangement to occur without addition of polar solvents or transition metal salts <2001TL5215> (Scheme 31).



Scheme 31

In addition to these different examples of [2,3]-Wittig rearrangement, one may also consider the possibility to perform such rearrangement with fluorine-containing compounds. This type of rearrangement may give access to polyfluoro-compounds of biological interest, which would have been difficult to obtain by using other methods involving fluorine chemistry <2000TL4591, 2001TL1317, 1996JOC166, 1995JOC9201, 1995CC1857>.

In conclusion, the [2,3]-Wittig rearrangement, because of its stereochemical characteristics, has widely been used in synthetic strategies. If the enantioselectivity of the rearrangement may be achieved in an intramolecular manner, as depicted in several examples above, the use of bases derived from chiral amines has also been reported <1999T6847, 1998CC83>, yielding good-to-excellent enantiomeric excess in the rearranged products (Equation (68)).



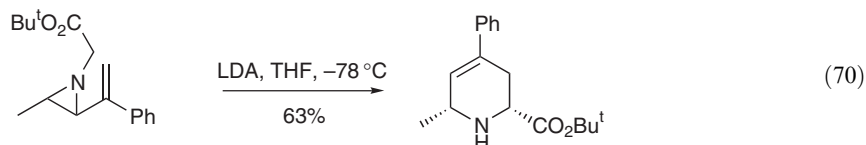
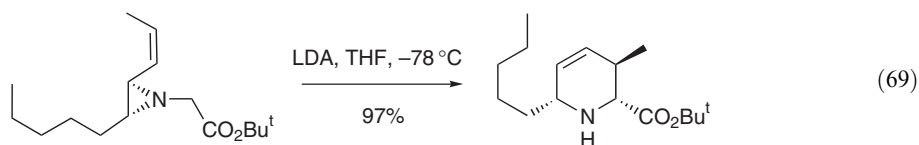
(iii) [2,3]-aza-Wittig rearrangement

The Wittig rearrangement of allyl amines has been reported and is quite similar in scope and limitation to the already reported rearrangement of ethers <1995AHC159, 2001JCS(P1)267, 1997JCS(P1)1517, 2000JOC9152, 1996JOC4820, 1998TL2649, 1995CC1835, 1998JCS(P1)2817, 1997JCS(P1)2951, 2003JOC6160, 2000TL10107>.

Successful [2,3]-aza-Wittig rearrangements have been described using tertiary amines where the nitrogen atom is incorporated into a β -lactam or aziridine ring system, or when protected with a *t*-BOC group or with a phosphoramidate group <1997TL2491>. It seems that the α -amino organolithium species, compared to the oxygenated analogs, are more reluctant to undergo the [2,3]-sigmatropic rearrangement. A solution to this problem has been found in the use of Lewis acids as activators that complex the nitrogen atom favoring the rearrangement <1997S497>. A DFT study of the aza-Wittig reaction and other concerted rearrangements has been published <2003JOC2310>.

In the context of the synthetic applications, this rearrangement has been extensively utilized for the synthesis of nitrogen-containing natural products.

For example, a general rearrangement of allyl aziridines leading to the formation of substituted piperidines in a stereocontrolled process has been reported (Equations (69) and (70)) <1995TL3557, 1998S109, 1995JCS(P1)2739, 1996JOC8148, 1995TL303, 1996TL2495, 1995T9747>.



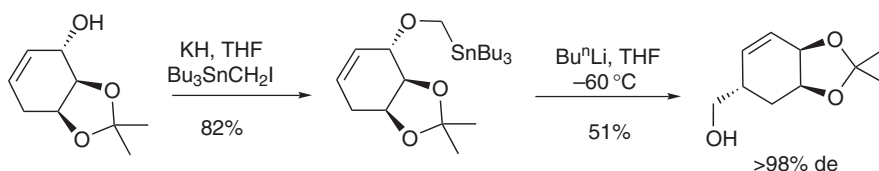
This rearrangement has also been used for the synthesis of some unnatural α -amino acids <2000JOC9152, 2000JCS(P1)3025, 2001JCS(P1)267, 2002JCS(P1)2871> and kainic acid <2003JOC6160>.

(iv) [2,3]-Wittig–Still rearrangement

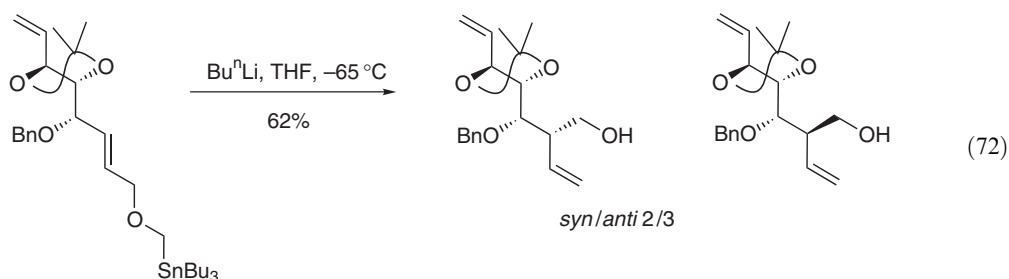
As mentioned in the introduction of the previous section of this chapter, the Still modification of the [2,3]-Wittig rearrangement has been the most used solution to ensure complete regioselectivity in the initial carbanion formation, especially when the G group (cf. Equation (56)) is an alkyl one, through transmetalation of an organostannane (Equation (71)).

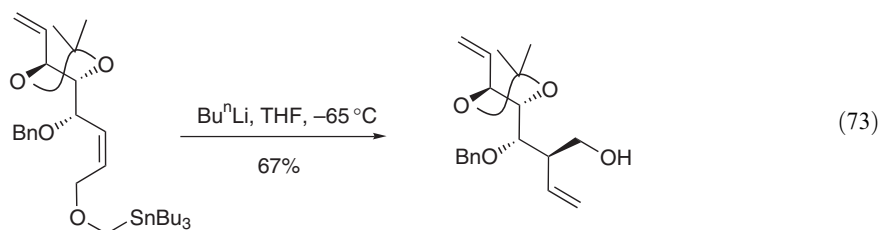


This methodology mostly offers the same stereochemical characteristics as the previously reported Wittig rearrangements. The stereochemistry of the double bond formed in the course of the reaction may depend on the substituent of the initial double bond <1999TL6257>, in the presence of other heteroatoms <1996TL389>, or on the solvent used to perform the reaction <2001OL1789>. The major use of this rearrangement, however, remains the stereoselective introduction of a hydroxymethyl group either on acyclic <1998JOC6735, 1999T13369, 1999TL5063> or cyclic structures <1997TL8841> (Scheme 32) <2001T9727, 2000OL3139, 1999AG(E)129> starting from an allylic alcohol, which is easily derived to its trialkylstannylmethyl ether. In its acyclic version, the *syn*–/*anti*–diastereomeric ratio in the product of the reaction mainly depends, as reported previously, on the geometry of the starting double bond but may be largely dependent on the structure of the whole molecule <1996TL389, 1999TL6257> and therefore difficult to predict (Equations (72) and (73) <1999TL5063>).



Scheme 32





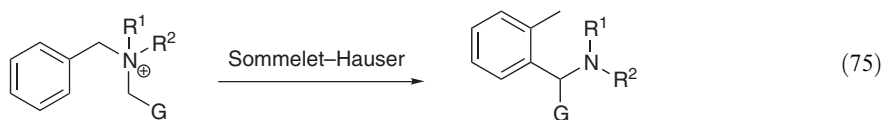
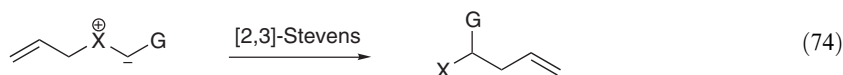
The Wittig–Still rearrangement of enantiomerically defined α -propargyloxystannanes proceeds with complete inversion of configuration at the lithium-bearing carbon atom although important amounts of the competitive [1,2]-rearrangement were also observed [<1997SL1045>](#).

An important variant of this method has been reported, based on silicon–lithium exchange reactions [<1996TL2403>](#).

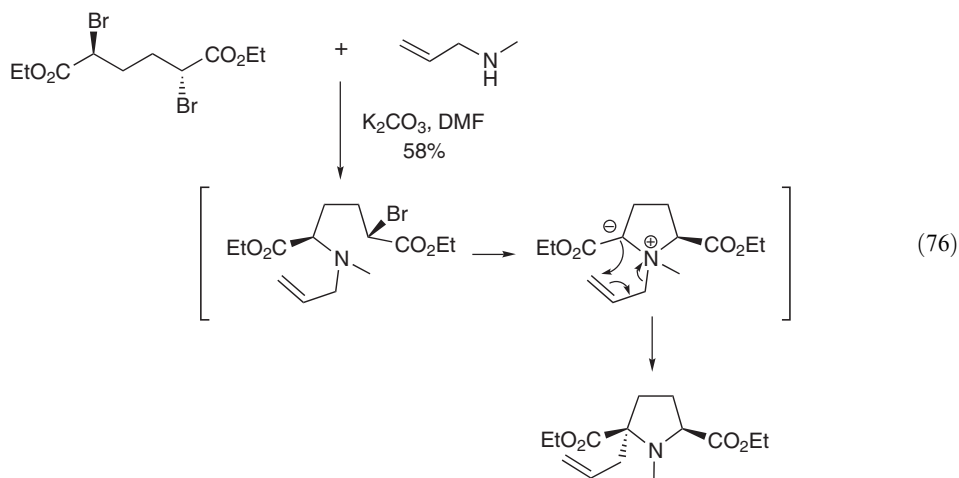
A number of synthetic applications for the synthesis of natural and non-natural products have been reported [<1998JOC7580, 1997JA5512, 2000H\(52\)99, 2002JA9812, 2001T9727, 2001TL4755, 1997SL441, 2001JA12432, 2003T6819, 2003JOC2913, 2003JOC2343, 2002JOC6152>](#).

(v) [2,3]-Stevens rearrangement

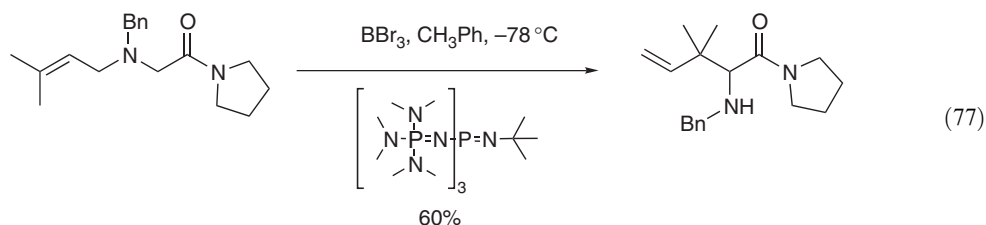
The [2,3]-rearrangement of allyl-substituted ylides, referred to as the [2,3]-Stevens rearrangement, and the related Sommelet–Hauser rearrangement of benzyllammonium ylides [<1997TL2113, 1997JOC2544, 1997JCS\(P1\)25>](#), have been widely studied as competing pathway for the corresponding [1,2]-Stevens rearrangement [<1996JOC7276>](#). Theoretical studies on the Stevens rearrangement [<1995AJC1413>](#) have shown that the reaction proceeds via dissociation to a pair of radicals, followed by recombination to the final product. However, in particular, the rearrangement of ammonium ylides has been often used for the formation of rearranged homoallylic tertiary amines. The specificities of these rearrangements are quite close to those of the [2,3]-Wittig rearrangement (stereochemical features, choice of the G group, etc.) (Equations (74) and (75)). Classical experimental procedures have been extensively discussed in the corresponding section of the COFGT (1995) and include the use of several organic or inorganic bases as well as, in the case of a trimethylsilyl G group, the use of caesium fluoride and the use of carbenes, quite similar to the corresponding methodologies developed for the [1,2]-Stevens rearrangement.



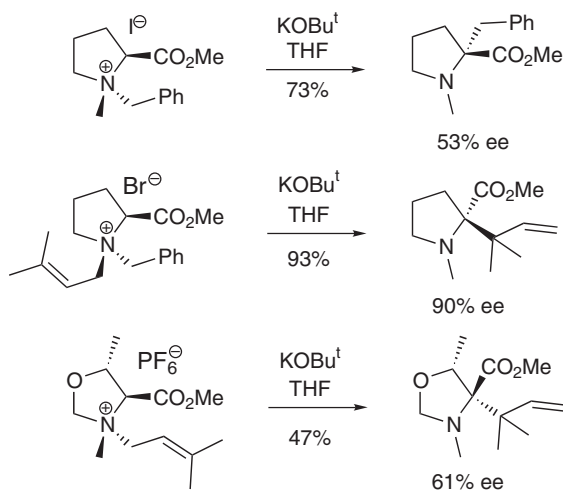
(a) *Rearrangement of ammonium ylides.* The main diversity arising from this type of rearrangement lies in the pathway chosen for the formation of the initial ylide. Indeed, the ylide, when formed through alkylation of the corresponding amine by an appropriate alkyl halide [<1997JCS\(P1\)2951>](#), may be generated by addition of allyl bromide, resulting in a formal allylation of amines [<1996T2075>](#) and has been proven to be compatible with the use of a phosphorus-containing G anion stabilizing group. Moreover, the ylides may be generated directly through treatment of a dihalogeno compound by *N*-methylallylamine [<2002TL899>](#) (Equation (76)) and results in the formation of heterocycles with potentially two stereogenic centers (one being a quaternary) of controlled configurations bearing the heteroatom.



A very promising set of experimental conditions has also allowed the formation of secondary rearranged amines starting from tertiary amines. This procedure involves the formation of ylides through treatment of tertiary amines by an appropriate Lewis acid and a Schwesinger phosphazene base [<2003TL3159>](#). This work has to be considered as the continuation of some pioneering research in the formation of ylides through Lewis acid treatment [<1995TL8481, 1998JCS\(P1\)2817, 1997JCS\(P1\)2951, 2000SL236>](#) (Equation (77)).

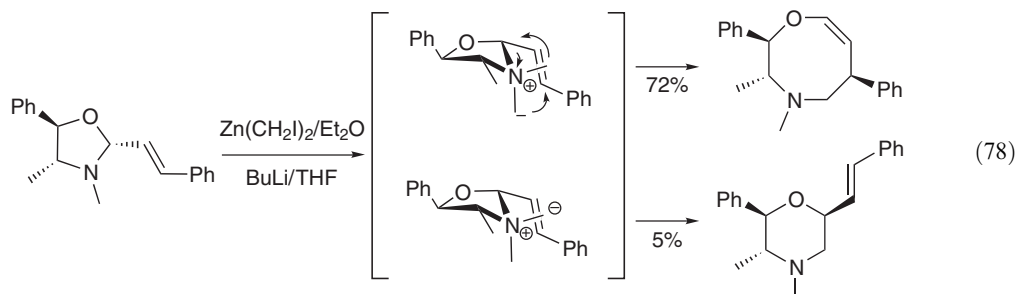


An important aspect of the rearrangement of allylic ammonium ylides, lying in chirality transfer from nitrogen to carbon, has been studied ([Scheme 33](#)). The asymmetric ammonium ylide is formed through stereospecific alkylation of a chiral tertiary amine α to a methyl ester group. Rearrangement is thereafter promoted by treatment with potassium *t*-butoxide [<1999OL31>](#); in this case the methylammonium ylide derived from benzyl proline rearranges through a [1,2]-Stevens shift and the Sommelet–Hauser product is not observed.



Scheme 33

However, most of the reported rearrangements of ammonium ylides involve the formation of the ylide through a carbenoid species, in an intramolecular or bimolecular fashion. The carbene may be derived from a diazo compound <2003JOC4083, 1997TL8283, 2000SL1208, 2002T10113, 2000SL1208> or from the Simmons–Smith reagent <2003OL1757>. In this latter case, the diastereospecificity of the reaction is controlled through the conformation of the five-membered oxazoline ring derived from the condensation of pseudo-ephedrine on cinnamaldehyde. The favored transition state results as expected from the alkylation/ylide formation of the five-membered heterocycle occurring *cis* to the adjacent substituent allowing a nice five-membered envelope-shaped conformation, which is suitable for the [2,3]-rearrangement. However, the minor ylide does not undergo [2,3]-rearrangement, due to its disfavored conformation but undergoes 1,2-alkyl shift (Equation (78)).



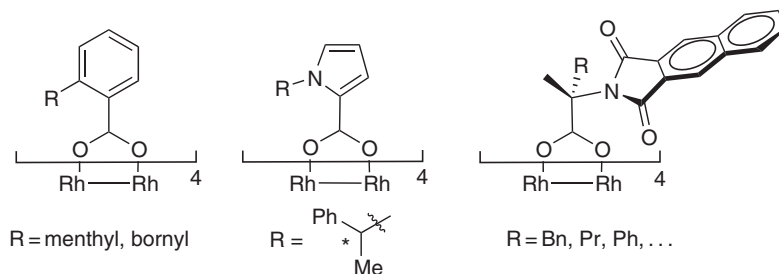
The [2,3]-Stevens rearrangement of ammonium ylides, which may be effected in a Wittig–Still version, is noteworthy <1995JA11817, 1997CUOC71, 2003TL1239>.

The rearrangement of ammonium ylides has been used for the design of efficient methodologies aimed at the total synthesis of natural products such as β -sinensal, *cis*-retinol, and plaunotol <1996CL385, 1996CL671, 1998SL685, 2002JCS(P1)1387>.

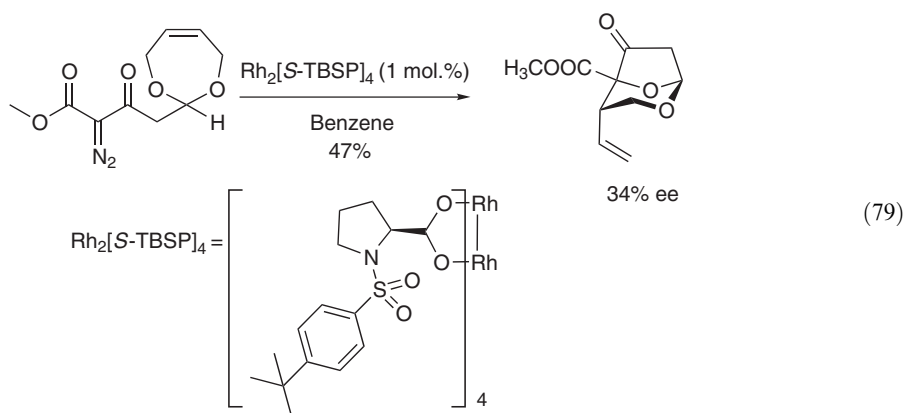
Similarly the Sommelet–Hauser reaction has been applied to an ammonium ylide derived from the HIV-1 reverse transcriptase inhibitor nevirapine <1995JHC1687>.

(b) *Rearrangement of oxonium ylides.* The [2,3]-rearrangement of enantiomerically pure oxonium ylides has been reviewed <1997CRV2341, 1996CRV223, 2001CSR50> and a monograph has recently been published on the chemistry of oxonium ylides <B-2002MI001>, which collects the different methods for their preparation.

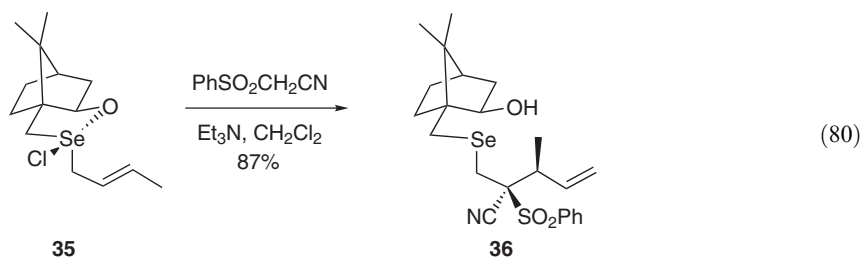
The rearrangement of allyl oxoniums has benefited from the progress of the diazo-derived carbene chemistry <1998CRV911, 2001CSR50, 1995JOC53, 1999T6577>. Many chiral catalysts have been studied (Scheme 34) <1996TL107, 2001TL6361, 1998JA7653, B-1998MI001, 1995JCS(P1)1373, 1997TL4705, 2001TA877> and allow a good enantiocontrol of the rearranged products. The main problem to be managed in this catalytic process is to avoid a competitive cyclopropanation reaction of the allyl moiety <1997TL5265, 2000TL6265>. The main use of this methodology deals with the synthesis of substituted tetrahydrofurans (Equation (79)) <1998TL8813, 1996TL5605>. Other examples of application in the field of synthesis of natural products have been reported <1999CC749, 1998TL97, 2001CC459, 1996TL5053, 1997JOC3902, 1998TL1691, 2002IJ283, 2000TL6265, 2001JA5144>.



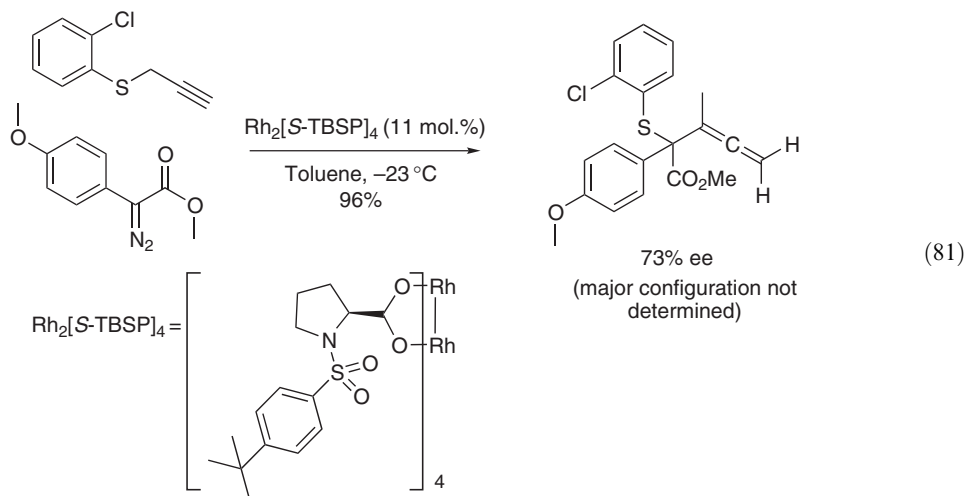
Scheme 34



(c) *Rearrangement of sulfonium and selenonium ylides.* Allylsulfonium <2000JOC2532, 1995CC1245> and selenonium <2000TCC(208)201, 1995CC1243, 1996JOC2932, 1997JOC4562, 1995CC1245, 1997T12115, 2001TL2911> ylides may also undergo [2,3]-Stevens rearrangement. When the selenonium ylides are formed through nucleophilic substitution of the chiral chloroselenurane **35** by (phenylsulfonyl)acetonitrile, the rearranged selenide **36** is obtained in high yield as a single diastereomer (Equation (80)) <1997JOC4562>.



The rearrangement of allylic sulfonium ylides has been, however, the most extensively studied <1996CRV223, 1999RHA117, 1997CRV2341, 1998TA1, 1998PAC1123, 1998CRV911, 2001RCR655>. Catalyzed reactions of α -diazoketones with allyl sulfides led to allylsulfonium ylides that on rearrangement afforded the corresponding thiocarbonyl derivatives. This methodology may be used either in a bimolecular fashion or in an intramolecular process <1996TL6523>. This methodology has been applied to the synthesis of 3-piperidinol alkaloid precursors <2000TL2965> and for the synthesis of the elemanoid type of sesquiterpenes <1995JCS(P1)2989, 1995T7697>. The decomposition of the diazo compound is often effected with chiral metal catalysts. The main metals used are copper <1997TL3435, 1999T649, 1999BCJ603, 2000JOC2532>, rhodium <2001H(54)623, 2002JOC5621, 2003TA891, 2003TA897, 2000JOC2984>, and rhenium <1995JA11730, 1996OM194, 1996OM4695, 1996PAC79> (Equation (81)).

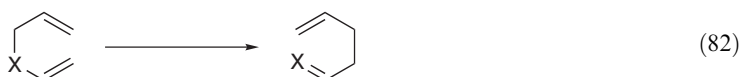


Although the most reported pathway for the generation of the ylides uses the decomposition of an α -diazoketone or ester, the use of trimethylsilyl diazomethane <1999TL8923, 1999TL1617, 2001T5219> or diiodomethane <2001TL2911, 2001JA4508, 1998SL1366> has also been reported.

1.09.1.4.5 [3,3]-Sigmatropic rearrangement

[3,3]-Sigmatropic rearrangements have attracted considerable attention in the 1990s. Indeed, as these rearrangements proceed through a six-membered ring transition state (usually in a chair conformation unless prohibited by strong steric interactions), the stereochemical outcome of the reaction may be predicted and the diastereomeric ratio is usually very good. These rearrangements will only be mentioned in this chapter; their full description will be made in Chapter 1.18.

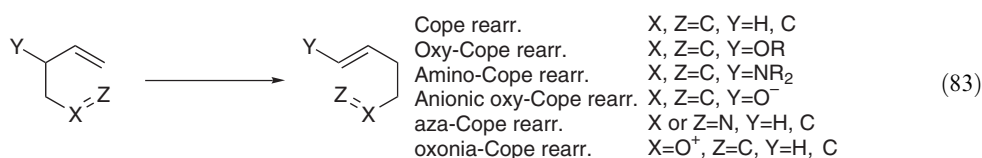
The general [3,3]-sigmatropic rearrangement is depicted in Equation (82). Cope rearrangement deals with the rearrangement of systems with no heteroatoms ($X = CR_2$) and Claisen, aza-Claisen, and thio-Claisen rearrangements are the rearrangements of vinyl allyl ethers, amines, and sulfides, respectively.



(i) Cope rearrangement

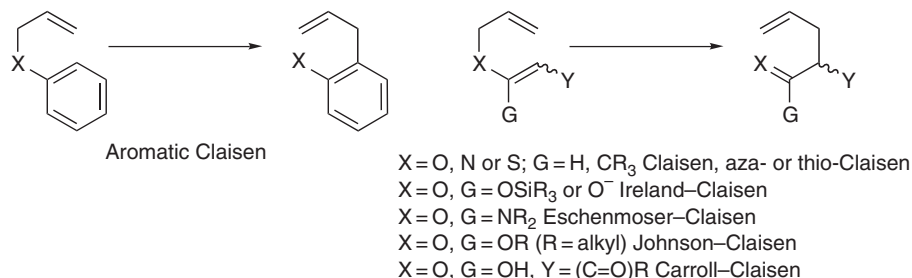
The Cope rearrangement deals with the rearrangement of 1,5-dienes and related compounds (see below) in a reversible process. The experimental conditions and the structure of the starting material therefore considerably influence the position of the equilibrium. In particular the oxy-Cope rearrangement, which finally furnishes a carbonyl group through tautomerization, allows the reaction to become irreversible.

The field of application and the experimental procedure generally used depends on the structure of the starting diene involved in the Cope rearrangement. The different types of Cope rearrangement are discussed in Equation (83).



(ii) Claisen rearrangement

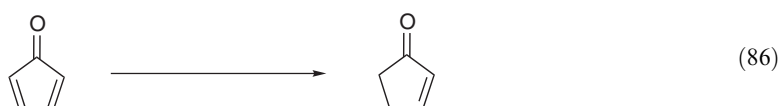
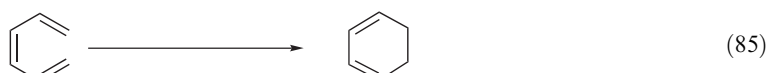
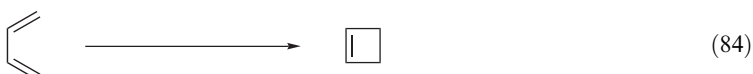
As previously stated, the Claisen rearrangement involves the rearrangement of allyl vinyl (or aryl) ethers, amines, or sulfides (Scheme 35).



Scheme 35

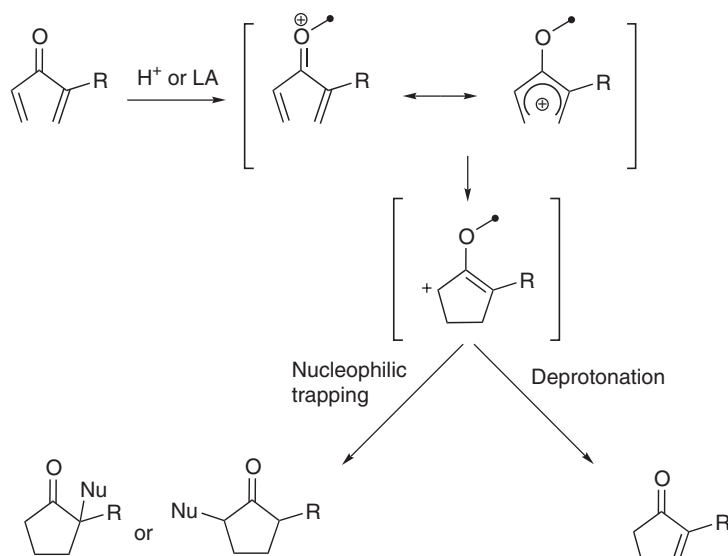
1.09.1.5 Electrocyclic Reactions

This section is devoted to the study of the electrocyclic process allowing the formation of a new C—C σ bond starting from a polyenic compound, the π -system of which is thereby reorganized. The starting material has therefore one more π -bond than the product of the rearrangement. As outlined in the corresponding section of chapter 1.09.1.5 in <1995COFGT(1)377>, the most important of these electrocyclizations are the 1,3-diene cyclobutene interconversion (Equation (84)), the 1,3,5-triene cyclohexadiene interconversion <2000OL3407> (Equation (85)) and the Nazarov cyclization (Equation (86)). As the two first transformations did not find significant improvement in the time schedule covered by this review, the only detailed reaction will be the Nazarov cyclization.



1.09.1.5.1 Nazarov cyclization

Divinyl ketones, although being often unstable, may undergo a rapid cyclization to cyclopentenones under acidic conditions. Both protic (H_2SO_4 , H_3PO_4 , HCl) and Lewis ($\text{BF}_3 \cdot \text{Et}_2\text{O}$, FeCl_3 , TiCl_4 , AlCl_3) acids may be used. Other experimental procedures include superacids <1997JA6774> and photochemical conditions <2001EJO2719>. The reaction proceeds through protonation of the oxygen atom of the carbonyl group, which thereafter generates a pentadienyl cation to be involved in a four-electron electrocyclic cyclization to the expected cyclopentenone (Scheme 36). The intermediate allyl cation may, however, be trapped inter- or intramolecularly by an appropriate nucleophile prior to the loss of a proton. This possibility has been the origin of the main advances in the use of this reaction in the recent years.

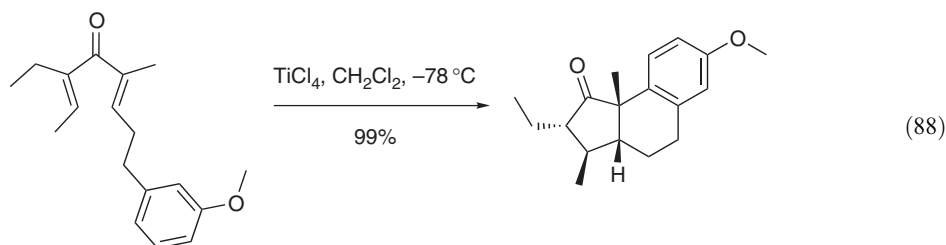
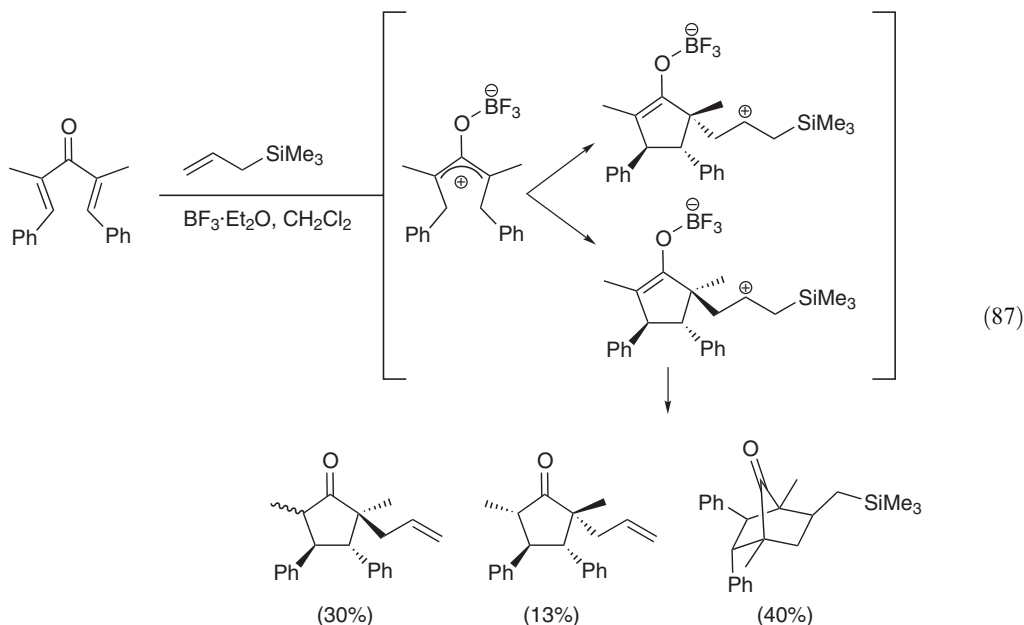


Scheme 36

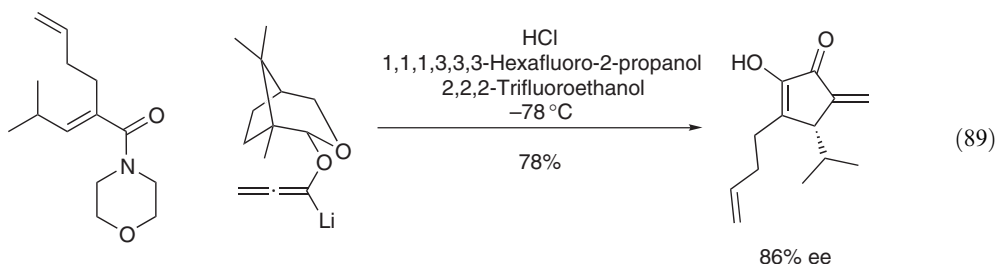
However, when the loss of an electron is allowed to form the cyclopentenone, the more thermodynamically stable isomer is formed with the more substituted double bond. The presence of trialkylsilyl groups β to the carbonyl group may, however, influence the course of the reaction [<1997CC1177>](#). Indeed, desilylation is normally preferred to deprotonation and the stabilization of the carbocation by the silyl group helps to prohibit unwanted side reactions.

Due to the difficulty of obtaining stable divinyl ketones, most of the reported examples of Nazarov cyclization use aromatic vinyl ketones [<2001JOC954, 2000JOM174, 2001JOC7632>](#) or other appropriate precursors of pentadienyl cations [<2000CEJ4021>](#).

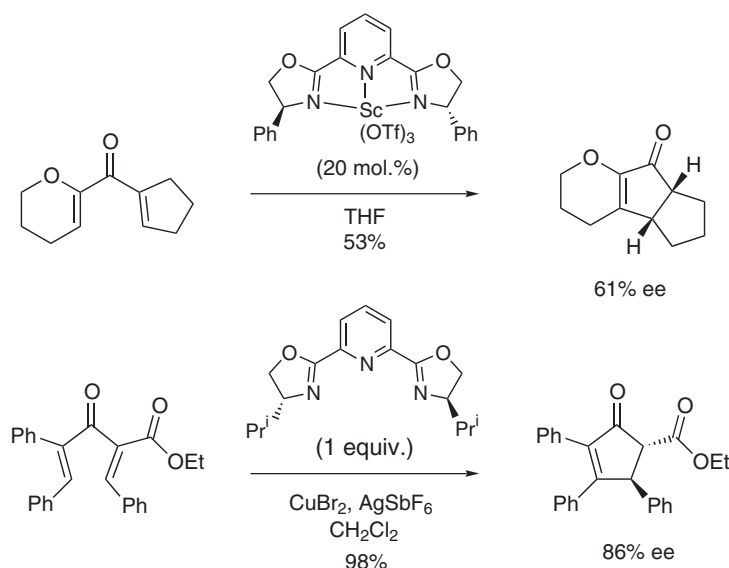
Albeit the deprotonation pathway has been used in some approaches to natural product total syntheses [<1998SL1372, 2001SL1399, 2001T1049>](#), the most promising feature of the Nazarov cyclization remains, as previously stated, the possible trapping of the allyl cation formed after formation of the five-membered ring. In this field, examples have previously demonstrated the solvent or the acid counter-anion to be able to quench the carbocation. However, the use of Lewis acids in aprotic solvents allows the use of other nucleophilic species. Two representative examples are described in [Equations \(87\) and \(88\)](#) using either intermolecular trapping by allyl silanes [<2000AG\(E\)1970>](#) or an intramolecular Friedel–Crafts reaction [<2001OL3033>](#).



An interesting report in the field of the Nazarov cyclization involves the reaction of a chiral 1-lithio 1-alkyloxy allene with a vinylic amide to afford the corresponding allenyl vinyl ketone, which thereafter rearranges to the methylene pentenone with a good enantiomeric excess [<2001JA8509>](#) ([Equation \(89\)](#)).



Alternatively, the use of a Lewis acid with chiral ligand may allow an enantioselective version of the Nazarov cyclization <2003OL5075, 2002OL4931> (Scheme 37).



Scheme 37

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Biographical sketch

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1.10

One or More =CH Bond(s) Formed by Substitution or Addition

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1.10.1 ONE OR MORE =CH BOND(S) BY SUBSTITUTION

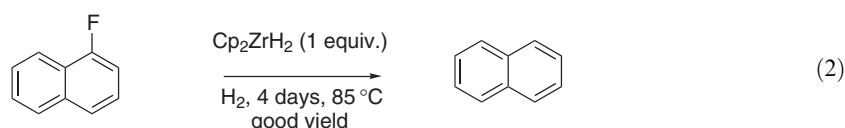
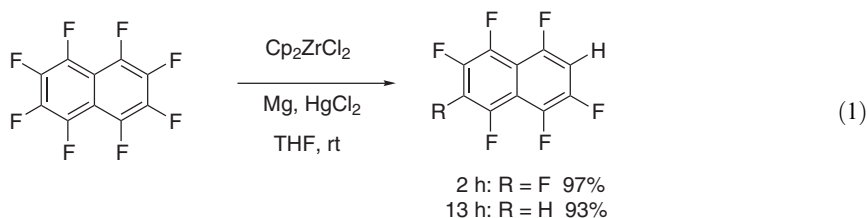
1.10.1.1 Reduction of =C—Halogen Bonds

1.10.1.1.1 Reduction of aryl halides

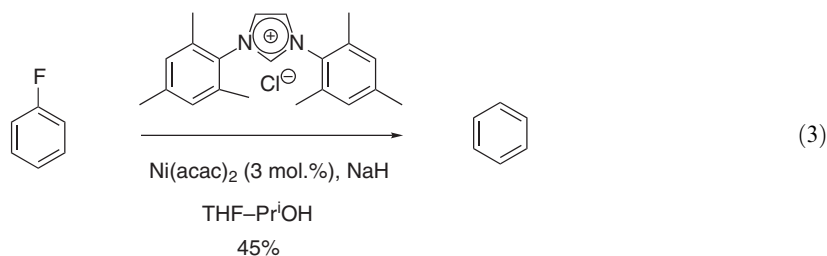
The reduction of aryl halides has been reviewed since COFGT (1995) <2002CRV4009>. The main synthetic methods used to achieve these transformations are always the same and include the use of hydrides, metals, or electrochemistry. However, significant efforts have been made to improve the selectivity of the methods. Selective cleavage of C—X bonds following the order of reactivity $I > Br > Cl > F$ now appear possible.

(i) Reduction of aryl fluorides

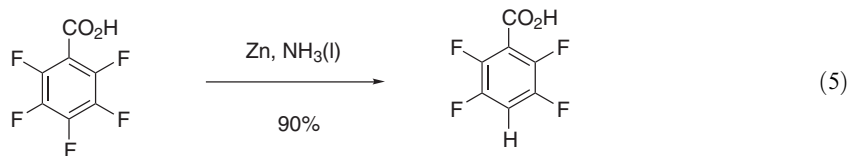
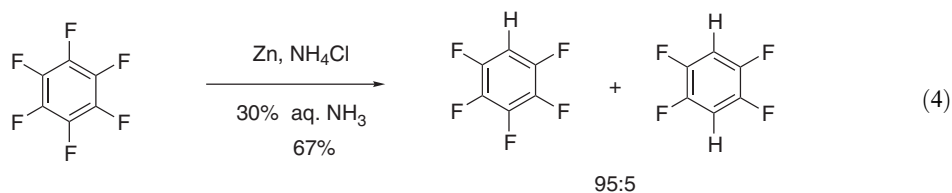
Activation of C—F bonds by metal complexes has been reviewed <1994CRV373>. The use of LAH in the presence of additives ($Bu^tOOH/h\nu$, $CeCl_3$) or the use of $CoCl_2$ in the presence of Grignard reagents has already been reported. Much more efficient reagents have been reported in recent years. For example, Cp_2ZrCl_2 in the presence of magnesium and mercuric chloride allows a selective removal of one fluorine atom from polyfluoride compounds (Equation (1)) <1996CC1115>. Similar results were reported with the homogeneous catalysts $(PMe_3)_3RhC_6F_5$ <1995JA8674>, and Cp_2ZrH_2 used in stoichiometric amounts (Equation (2)) <2000JA8559>.



Reaction of hexafluorobenzene with the complex $NiCl_2$ -2,2'-bipyridine in the presence of zinc in water and NH_4Cl led to a mixture of penta-, tetra-, and trifluorobenzene <2000MC60> (see also <2000JFC(101)65>). Nickel acetylacetonate in the presence of NaH and an imidazolium salt was found to be able to transform fluorobenzene into benzene (Equation (3)) <2002OM1554, 2003MI(345)341>. These conditions were found to be very efficient for the cleavage of other C—X bonds.

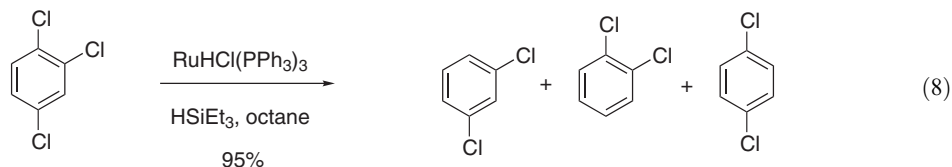
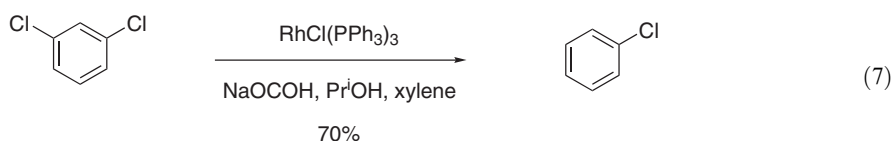
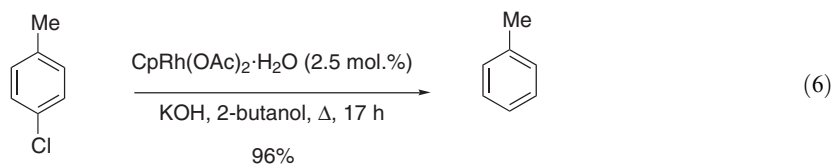


Sodium hydride itself was found to be able to reduce fluorobenzene (29%) if nanometric (23 nm) particles were used. Introduction of lanthanide chlorides increases this yield to 40% <1997SC4327>. Laev <1998JFC(91)21, 2001JFC(110)43> showed that the monodefluorination of polyfluoro compounds can be achieved by the reaction of zinc in 30% aqueous NH_3 (Equation (4)). Replacement of aqueous ammonia by aqueous dimethylformamide (DMF) in the presence of cupric chloride is also possible <2001MI517>. The use of zinc in liquid ammonia gave, in some cases, interesting results. For example, with pentafluorobenzoic acid, the reaction is very chemo-selective, leading to the removal of the fluorine in the *para* position (Equation (5)) <1995TL4655>.

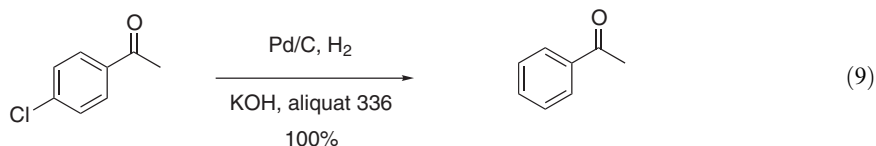


(ii) Reduction of aryl chlorides

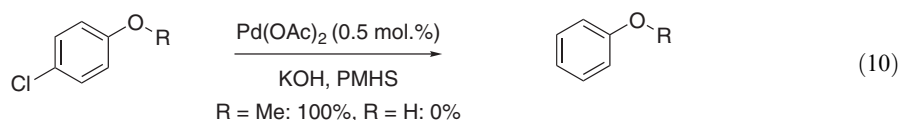
It has been reported in COFGT (1995) that the best methods for the replacement of the chloride of aryl compounds by hydrogen are catalytic hydrogenation and the reduction with Raney nickel, which in turn have led to several new methods. Hydrogenolysis using a rhodium complex of the type $\text{L}_2\text{Rh}(\text{H})\text{Cl}_2$ promoted by Alper <B-1999MI193> was greatly improved using triethylsilane <1999OM1110>, or 2-butanol <1999OM1299, 2002CC2964> as the hydrogen source (Equation (6)). Monohydrogenolysis of polychloroarenes was reported to be effective by using $\text{RhCl}(\text{PPh}_3)_3$ (Equation (7)) <2001NJC775> or $\text{RuHCl}(\text{PPh}_3)_3$ (Equation (8)) <2000MI(195)187>.



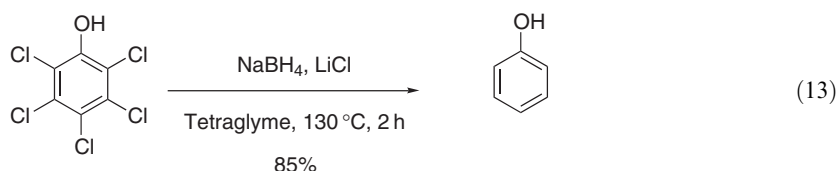
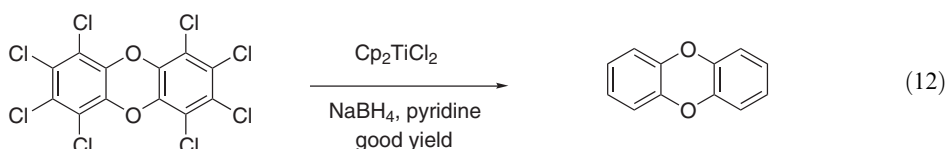
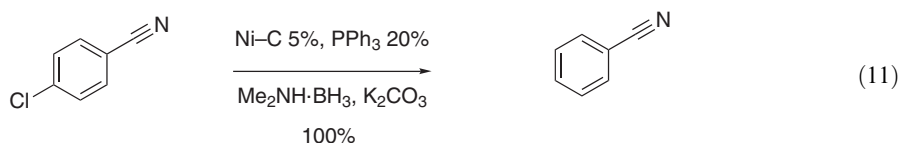
Pd/C and Pd/Si were used for the reduction of chloroaryl compounds in earlier methods. These reductions were improved under phase transfer catalyst conditions. So, in the example reported in Equation (9), the ketone function remained untouched <1996S1109>. Anchored Pd on silica gel also led to improved results <1999SC691>.



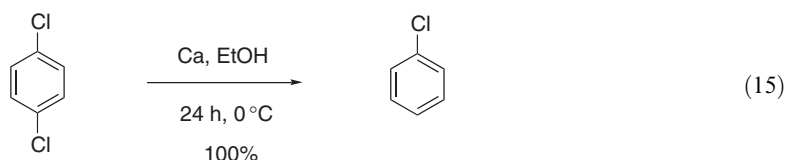
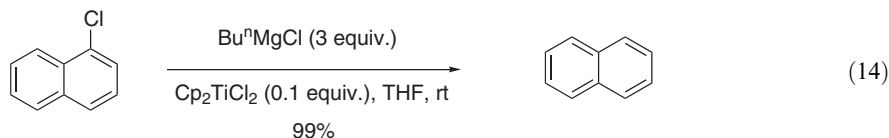
Palladium chloride in the presence of HSiEt_3 was examined. The hydrogenolysis of C-X bonds appears general <1996OM1508>. PdCl_2 anchored on poly(*N*-vinyl-2-pyrrolidinone) in the presence of a base such as KOH <1994TL4599> or sodium formate <2001MI287, 2001MI(175)153> can be used. $\text{Pd}(\text{OAc})_2$ in the presence of polymethylhydrosiloxane (PMHS) led to a very efficient cleavage of the C-Cl bond, with the exception of chlorophenols (Equation (10)) <2002TL8823>.



A Pd(0) complex such as Pd(dba)₂ in the presence of imidazolium salts was found to be a good reagent for dechlorination of aryl halides <2001OM3607>. The use of nickel and its salts was also reported. Raney–nickel–alumina alloy <1998TL5991> and nickel on charcoal in the presence of Me₂NH·BH₃ (Equation (11)) <2001SL970> were efficient, and polychloroaryl compounds were in some cases completely transformed to aryl compounds. Nickel acetate <1995TL6051, 2000T4765> and nickel chloride <1999T4441, 2000MI1017> also appear to be efficient catalysts. However, the prevalent tendency is to use homogeneous catalysts. Excellent results for the cleavage of C–Cl bonds were reported by using (Et₃P)₂NiCl₂ <2000JOM(600)63>, (PPh₃)₂NiCl₂ <2001TL7737>, and Ni(0)·Ime₃ complex <2002OM1554>. NaBH₄ in the presence of Cp₂TiCl₂ appears to be a very powerful solution for dehydrochlorination of perchlorodioxine <1996NJC253> (Equation (12)). NaBH₄ in di- or tetraglyme in the presence of LiCl appeared to be able to reduce pentachlorophenol (Equation (13)) <1997TL6561, 1998SC517>.



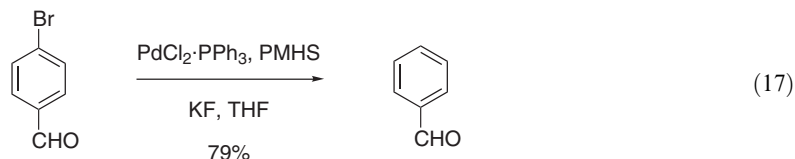
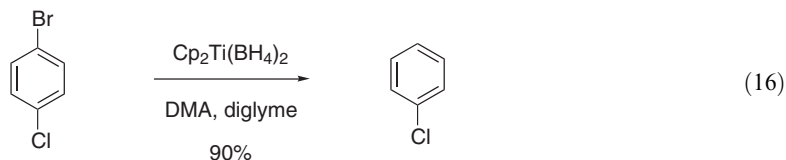
NaH (nanometric size particles) in the presence of LaCl₃ led to a quantitative transformation of chlorobenzene to benzene <1997SC3977>. Use of *n*-butylmagnesium chloride in the presence of Cp₂TiCl₂ in THF (Equation (14)) <1999CC845> or calcium in ethanol (Equation (15)) <2001MI(35)4145> were also reported. Use of microorganisms was also examined <1998MI633> and the results concerning the reduction of the very toxic chlorodioxins was recently reviewed <2003AG(E)3718>.



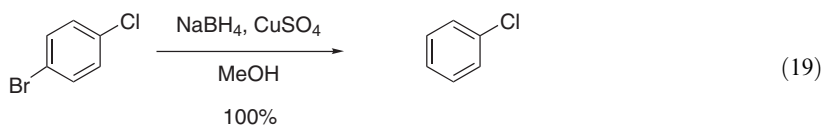
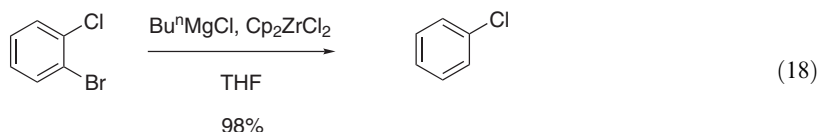
(iii) Reduction of aryl bromides

The use of palladium- and platinum-based catalysts has previously been reported extensively. NaBH₄ and LAH were also found to be powerful reagents. However, more recently a great variety of new reagents have appeared. Very often the reagents used for the cleavage of C–Cl

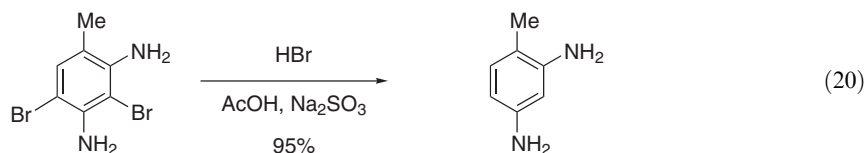
bonds were also tested with success for the cleavage of C—Br bonds (see the preceding section). Some specific reagents have been reported such as $\text{Cp}_2\text{Ti}(\text{BH}_4)_2$ (Equation (16)) <1995T4471>, dichloro[1,1'-bis(phenylphosphine)ferrocene]Pd(II) <1997MI(126)L83>, $\text{PdCl}_2(\text{MeCN})_2$ <1998MI(132)223> in the presence of NaBH_4 , $\text{PdCl}_2[\text{PPh}_3]_2$ in the presence of PMHS (Equation (17)) <2002TL7087>, and $\text{Pd}(\text{OAc})_2$ in DMSO/ H_2O in the presence of HCOOK under microwave irradiation <2001TL331>.



Aromatic bromides have also been reduced selectively using *n*-BuMgCl in the presence of Cp_2ZrCl_2 (Equation (18)) <1997CL1251> or NaBH_4 in the presence CuSO_4 (Equation (19)) <1997BCJ1101>. The less common hydride LiGaH_4 was reported to show reactivity close to that of LAH <1997MI541>.



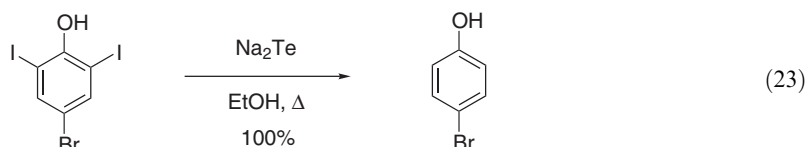
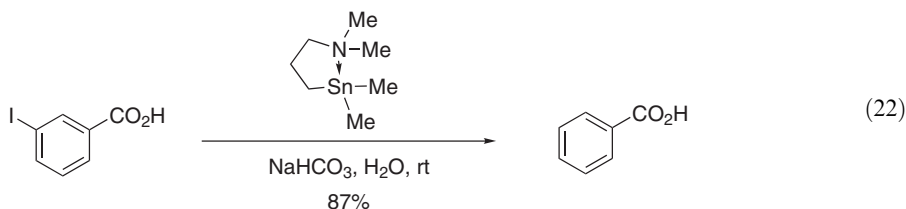
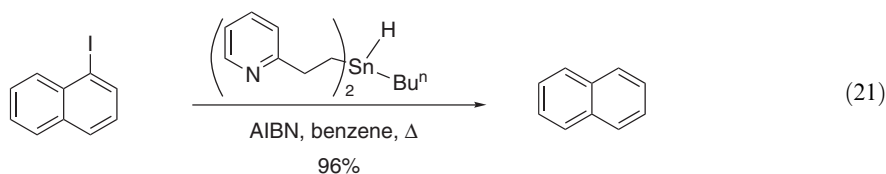
Radical processes were found to be able to induce the dehydrochlorination of aryl compounds. The use of reagents such as Ph_3SnH in the presence of 9-BBN or Et_3B –oxygen <1998TL5437>, PhSiH_3 –AIBN <1997SC1023>, or $(\text{Me}_3\text{Si})_3\text{GeH}$ –AIBN <1995OM5017> has been reported. The radical process can be induced by visible light in the presence of methylene blue as sensitizer <1999TL1441> or at 300 nm in the presence of YbI_2 <1997TL9017>. The use of NaH in the presence of $\text{Ni}(\text{OAc})_2$ <2000T4765> or $\text{Sm}(\text{OiPr})_3$ <1995MI457> also gave interesting results. Chi showed that by using HBr in acetic acid, the bromine atoms of substituted bromo anilines can replace by hydrogens. This unusual method widens the scope of the previously cited methods (Equation (20)) <2001JA9202>. The use of lithium in the presence of polymer supported naphthalene, and NiCl_2 was also examined for the reduction of bromobenzene <2003MI(345)275>.



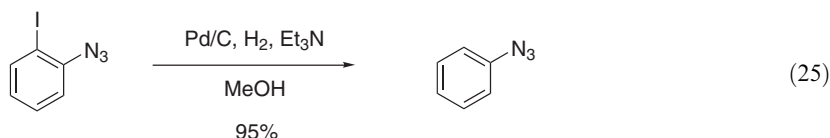
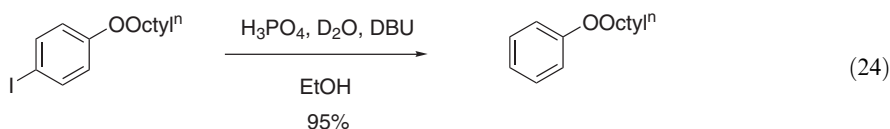
(iv) Reduction of aryl iodides

Since aryl iodides are the most easily reduced halides, most of the methods reported for the reduction of aryl chlorides and aryl bromides can be used. NaBH_4 alone or in the presence of metals is frequently employed. Recently, some specific methods have been reported. Modulation of the reactivity of *n*-Bu₃SnH was obtained by structural modifications. These new reagents allow

specific reduction of aryl iodides (Equation (21)) <1999CC1237, 2001TL5837> (Equation (22)). Na₂Te was found to be efficient for the selective removal of iodide atom (Equation (23)) <1998JOC3911>.



Reduction of iodobenzyl alcohols was reported with NaBH₄ in the presence of Ph₃Ge–AIBN <2001BCJ747> or di-*t*-butylperoxyoxalate <1997JA2628>. Phosphonic acid in the presence of DBU or AIBN in ethanol was also quite useful <2001BCJ225> (Equation (24)). Clean and selective reduction of functionalized aryl iodides was also observed with Pd on charcoal. This selectivity was not observed with aryl bromides or aryl chlorides <2002JOC932> (Equation (25)).



1.10.1.1.2 Reduction of vinyl halides

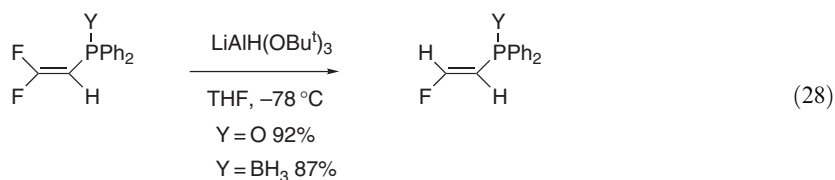
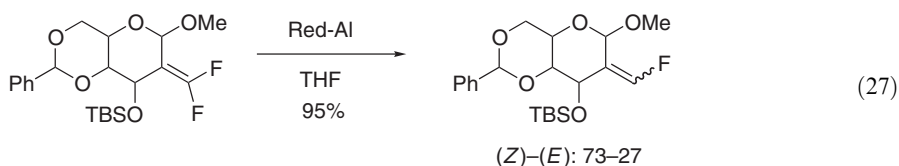
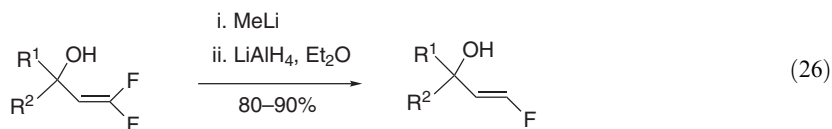
The reduction of vinyl halides to alkenes has been achieved by a large variety of reagents, including metals, complex hydrides, electrochemical reductions, and catalytic hydrogenation. These different methods have been reviewed <2002CRV4009>.

(i) Reduction of vinyl fluorides

The C–F bond appears to be the most difficult one to cleave due to its particular strength. This cleavage can be achieved by catalytic hydrogenation with reagents such as LAH or NaBH₄ (see COFGT (1995)); these reactions correspond in fact to the addition–elimination processes.

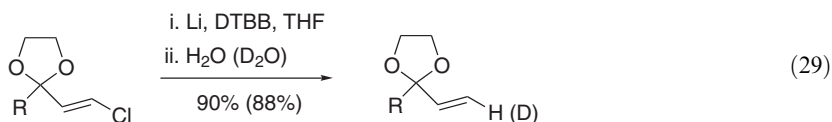
Tellier and Sauv  tre <1996JFC(76)181> found that mono-reduction of lithium alcoholate derivatives from difluoroallylic alcohols could be carried out by using LAH. The stereochemistry of the products was mainly *E* (Equation (26)). Similar monohydrogenolysis was reported for the reduction of β,β-difluoro-α,β-ethylenic esters <2000JOC627>. Monoreduction of polyfluoroalkenes of general formula R–CF=CF–CF₃ was achieved ((*E*)-(*Z*) mixtures) <2001JOC4887>. Monoreduction of trifluorovinyltrimethylsilane was also reported <2002OL1483>. Reductions were observed with

reagents such as Red-Al (Equation (27)) <1997SL669> or $\text{LiAlH}(\text{O}t\text{-Bu})_3$ (Equation (28)) <1999JFC(97)109>. Only catalytic hydrogenolysis allows the complete removal of fluorine atoms from polyfluoro compounds. No improvement of this reaction has been reported since the 1990s.

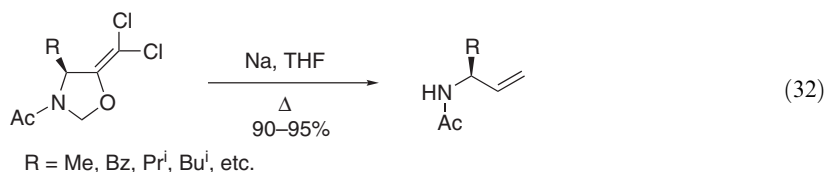
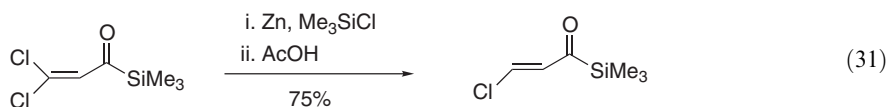
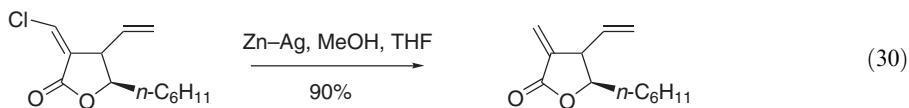


(ii) Reduction of vinyl chlorides

The main reagents used for the reduction of vinyl chlorides are complex hydrides. Good results were reported by the combination of LAH with TiCl_4 or NaH with $\text{Ni}(\text{OAc})_2$ (see COFGT (1995)). Sodium in *t*-BuOH was also reported to be efficient. Yus found that lithium in the presence of 4,4'-di-*t*-butylbiphenyl (DTBB) (or in the presence of naphthalene supported on polymer <2003MI(345)275>) was able to transform vinyl chlorides into vinyl lithium derivatives. Subsequent hydrolysis led to the desired reduction products (Equation (29)) <1994TL7643>.

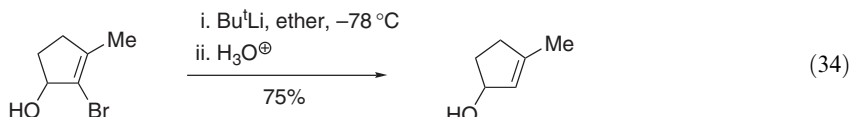
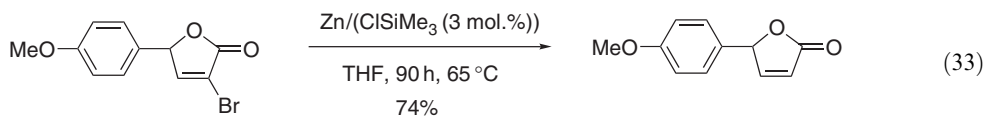


In fact recently, the use of zinc has increased. For example, transformation of hexachloro-1,3-butadiene into 1,3-butadiene was reported by using zinc activated by a mixture NaI-CuCl <1998JA2578>. Heathcock's method <1976JOC636> was used successfully to remove a vinyl chlorine to obtain a carbonyl function (Equation (30)) <1996TA1923>. Zinc activated by ClSiMe_3 was also used <1995T9823> (Equation (31)). Sodium in THF was found to be able to remove two vinylic chlorines fixed on an exocyclic double bond of an oxazoline to lead to the formation of an allylamine <1998CL1237> (Equation (32)).

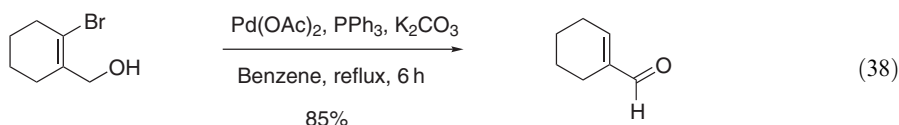
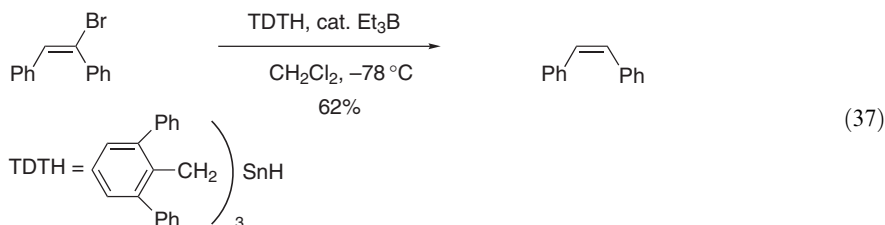
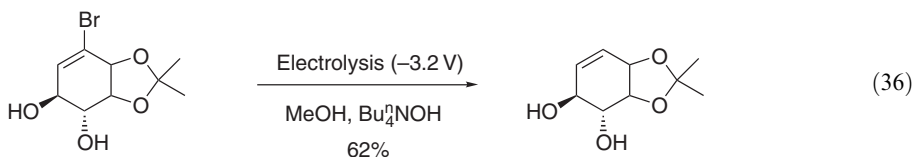
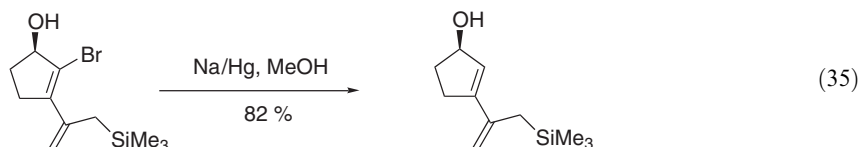


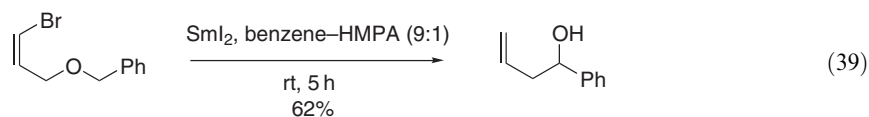
(iii) Reduction of vinyl bromides

The reduction of vinyl bromides is easier than the reduction of vinyl chlorides, so in the majority of cases, the methods reported in the preceding chapter can be used. For instance, reduction of vinyl bromides was reported with the zinc–silver couple [<2002JOC4316>](#) and $\text{Zn}-\text{ClSiMe}_3$ [<2000SL1749>](#) (Equation (33)). Substitution of vinyl bromides by lithium has been extensively studied. Bu^tLi reacted with nonactivated vinyl bromides and the subsequent hydrolysis led to the reduction products [<1995TA1551>](#) (Equation (34)), [<1995JOC7791, 1998T9529, 2002SL607>](#).

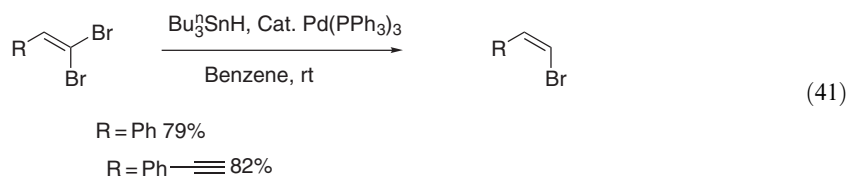
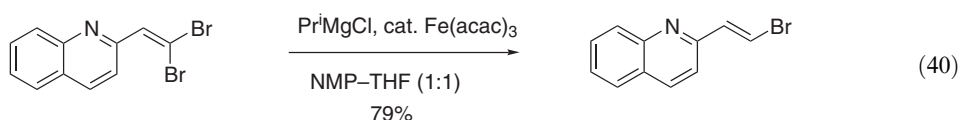


Other methods have been investigated to transform vinyl bromides into alkenes. Corey [<1999JA6771>](#) reported the use of sodium amalgam (Equation (35)). Hudlicky studied the electrochemical reduction (-2.2 to -3.2 V versus Ag/Ag^+ reference electrode) and demonstrated that it can be used as a preparative method [<1999JOC4909, 2003TL1575>](#) (Equation (36)). In these conditions, ring opening of epoxides and aziridines was observed. This method was also found to be efficient with vinyl iodides. Reduction of bromostilbene was found to be stereospecific with tin hydrides such as tris(2,6-diphenylbenzyl)tin hydride (TDTH) (Equation (37)). With this reagent, (*E*)-bromostilbene was reduced to (*Z*)-stilbene exclusively [<2001AG\(E\)411>](#). In the same conditions, (*Z*)-bromostilbene gave 98% of (*E*)-stilbene. In the presence of $\text{Pd}(\text{OAc})_2$, 3-bromoallylic alcohols were transformed into α,β -ethylenic carbonyl compounds (Equation (38)) [<1996T12291>](#). Homoallylic alcohols led to less interesting results. 3-Bromoallylic alcohols protected as benzyl ethers reacted with SmI_2 to generate the products corresponding to 1,5-hydrogen atom transfer, followed by the [2,3]-Wittig rearrangement (Equation (39)) [<1997JOC7542>](#). This reaction was also observed with vinyl iodides.



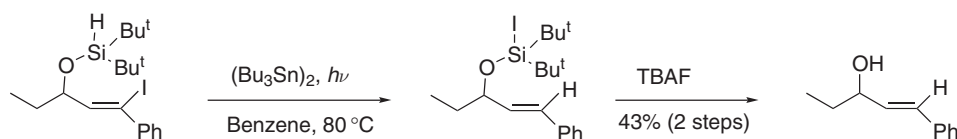
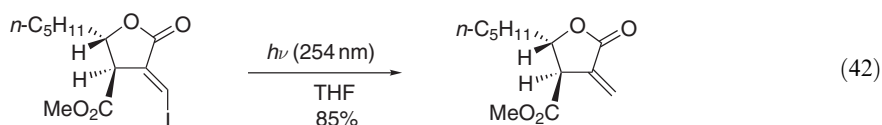


Numerous works have been reported on the monoreduction of 1,1-dibromoalkenes. The (*E*)-isomer was mainly obtained by using indium [\[2001JOC4102\]](#), diethylphosphite in the presence of triethylamine [\[2000TL3215\]](#), diethylphosphite in the presence of sodium ethoxide [\[2002T1491\]](#), Pr^iMgCl in the presence of $\text{Fe}(\text{acac})_3$ [\[2001JOM\(624\)131\]](#) (Equation (40)), or Bu^nLi in pentane at -100°C [\[2000SL1070\]](#). In contrast, the (*Z*)-isomer was mainly formed by the reaction with tributyltin hydride in the presence of a catalytic amount of $\text{Pd}(\text{PPh}_3)_4$ [\[1998JOC8965\]](#) (Equation (41)).

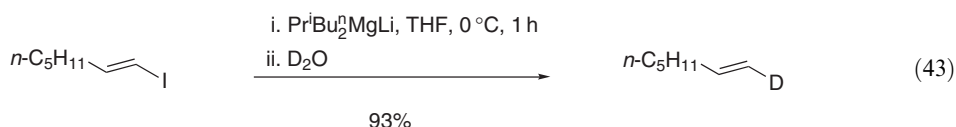


(iv) Reduction of vinyl iodides

Although the cleavage of the C—I bond is the easiest, this reaction appears not to be studied extensively. This is due, in part, to the modest stability of iodides. Methods reported in the above section employing complex hydrides, zinc, or Bu^iLi can be used. Recently, specific methods have been reported. Weavers and co-workers indicated that the reduction of vinyl iodides was observed under irradiation at 254 nm in THF (Equation (42)) [\[1995T11257\]](#). Curran and co-workers also reported a photochemical transformation of 3-iodoallylic alcohols into allylic alcohols (Scheme 1) [\[1997T5679\]](#). Reduction of vinyl iodides was carried out by reaction with magnesium ate complexes, such as $\text{Pr}^i\text{Bu}_2\text{MgLi}$ followed by hydrolysis (Equation (43)) [\[2001JOC4333\]](#). Reduction of 1,1-diiodo-1-alkenes with zinc in a mixture of THF–MeOH was recently reported to lead to the formation of (*Z*)-1-iodo-1-alkenes [\[2003TL8645\]](#).



Scheme 1

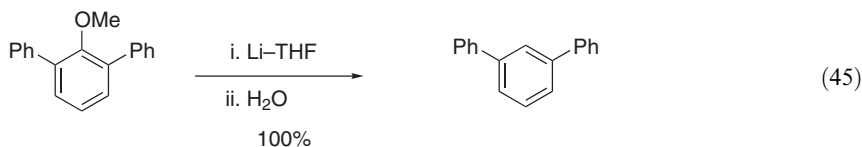
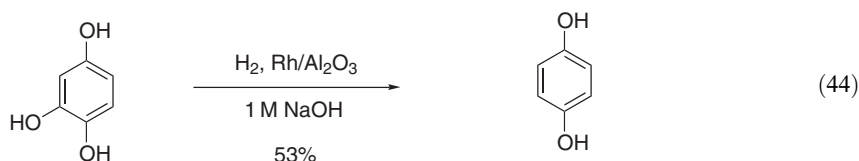


1.10.1.2 Reduction of =C—O Bonds

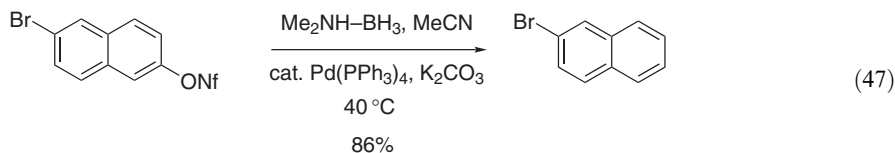
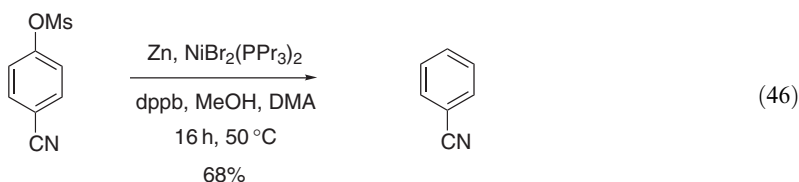
1.10.1.2.1 Reduction of phenols and derivatives

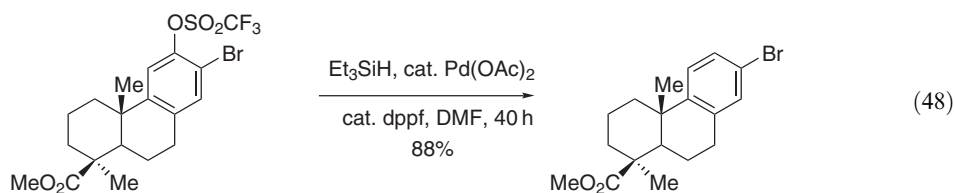
The deoxygenation of phenols to aryl has been carried out by a large variety of reagents. The best methods to achieve this process, rather than the direct deoxygenation of phenols that requires harsh conditions, involves the cleavage of derivatives such as methyl ethers, phosphates esters, 2-chlorobenzooxazoles, 1-phenyl-5-chlorotetrazole, and perfluoroalkylsulfonates (e.g., triflates, nonaflates). The hydrogenolysis can be accomplished with Na in THF (methyl ethers), alkali metals in liquid NH₃ or electrolysis (phosphate esters), or Pd/C (tetrazoles). The mildest conditions were found for the cleavage of triflates and nonaflates due to the use of Pd(OAc)₂ or Ni(0) complex in the presence of phosphines (see COFGT (1995)).

Recently, new results have been reported. The monohydrogenolysis of polyphenols, considered to be difficult, was found to be possible using hydrogen in the presence of Rh on alumina (Equation (44)). Under these conditions, selective cleavage of methyl ethers was observed <2002JA5926>. Pisano and co-workers studied the cleavage of phenolic ethers. A good regioselectivity was observed using Li or K in THF (Equation (45)) <1995JCS(P1)261, 2000JOC322>.



Cleavage of 4-phenoxyphenol to phenol was reported to be effective by electrohydrogenolysis using carbon electrodes entrapped by Raney nickel <1999CJC1225>. Aryl mesylates have been reduced by Zn in the presence of NiBr₂-based catalyst, using MeOH as hydrogen donor. The use of MeOD as deuterium source led to labeled arenes (Equation (46)) <1997CL617>. Lipshutz and co-workers found that aryl nonaflates could be reduced by Me₂NH·BH₃ complex in the presence of a catalytic amount of a Pd(0) complex (Equation (47)). This mixture tolerated amide and ester functions <1999TL6871>. Improvements have also been reported in the hydrogenolysis of triflates by using Pd(OAc)₂ as catalyst. The classical mixture Et₃N·HCOOH, as proton source, can be replaced by HSiEt₃ <1995S1348>. Woodgate found that addition of 5 mol.% of 1,1'-bis(diphenylphosphino)ferrocene (dppf) improved the yields of these reactions in some difficult cases (Equation (48)) <2001JOM(629)114>. A mixture of Li-4,4'-di-*t*-butylbiphenyl and NiCl₂·2H₂O was also used for the hydrogenolysis of aryl triflates. However, these conditions appeared more efficient for the reduction of enol triflates <1999T14479>.

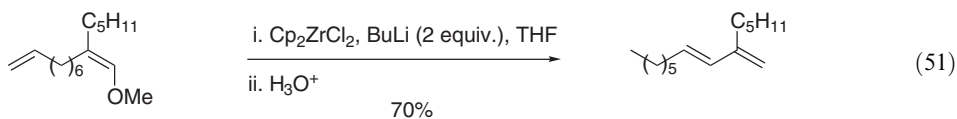
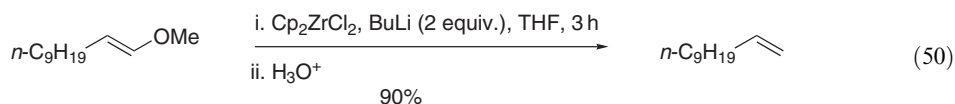
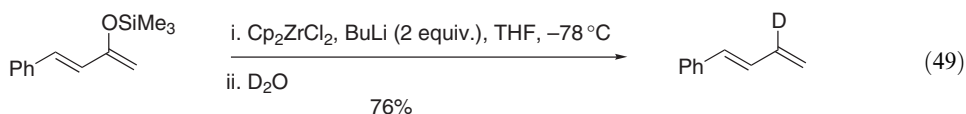




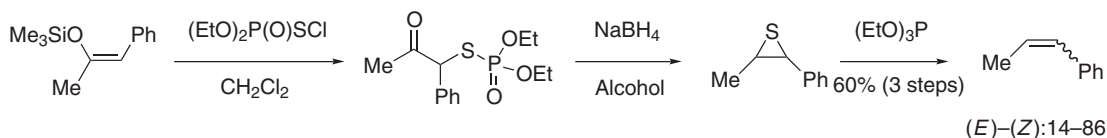
1.10.1.2.2 Reduction of enol ethers and derivatives

The reduction of enol derivatives to the corresponding alkenes has been reported by different methods. This transformation can be carried out from silyl enol ethers (borane reduction) and alkyl enol ethers (DIBAL-H or Na reductions). However, interesting results were found for the reduction of enol phosphates (dissolving metal reductions in liquid ammonia or amines) and vinyl triflates (Pd catalysis in the presence of hydrogen sources such as tin hydrides, silicon hydrides, or formate) (see COFGT (1995)).

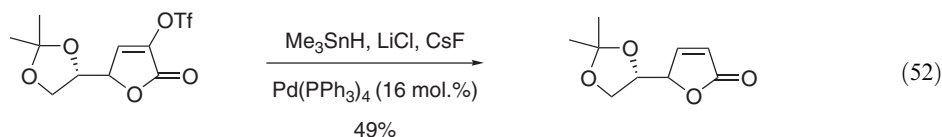
Recently, improved results have been reported in the reduction of these different enol derivatives. Lithium in ethylamine was used for the reduction of enol phosphates to alkenes <1995JOC1856>. Transformation of aryl or 1,3-ethylenic trimethylsilyl enol ethers into styrene or 1,3-diethylenic derivatives was found to be an easy reaction by using the $\text{Cp}_2\text{ZrCl}_2\text{-2BuLi}$ mixture (Equation (49)) <2001SL123>. The same zirconium intermediate was reported by Marek and co-workers to be able to reduce methyl enol ethers (Equation (50)) <2000JOC7218>. This zirconium reagent also reacts with thioenol ethers, vinyl carbamates, vinyl sulfones, and vinyl sulfoxides <2002S2473>. Nonconjugated dienes bearing an enol ether moiety undergo a tandem isomerization–reduction reaction (Equation (51)) <2002JA10282>.



A three-step transformation of silyl enol ethers was reported in moderate overall yields. This transformation can be carried out in a one-pot procedure (Scheme 2) <1997S1134>. New conditions have been reported for the reduction of vinyl triflates. The mixture Li-4,4'-di-*t*-butylbiphenyl in the presence of $\text{NiCl}_2\cdot 2\text{H}_2\text{O}$ was reported to be very efficient <1999T14479>. Lipshutz by using the complex $\text{Me}_2\text{NH}\cdot\text{BH}_3$ in the presence of $\text{Pd}(0)$, also published excellent results <1999TL6871>. Reduction of an enol triflate was also reported by using Me_3SnH in the presence of $\text{Pd}(\text{PPh}_3)_4$ (Equation (52)) <1995H(40)939>.



Scheme 2



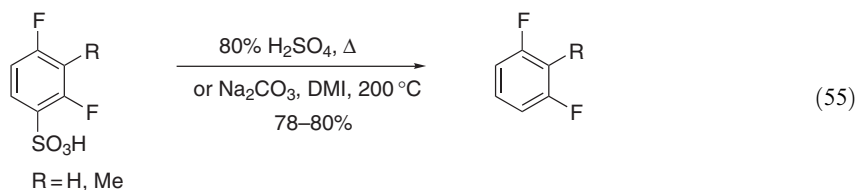
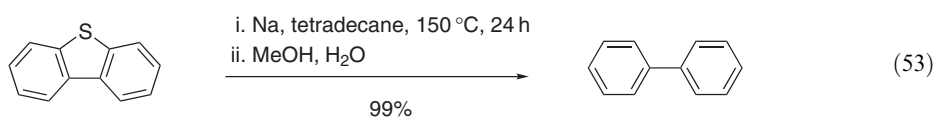
1.10.1.3 Reduction of =C—S, —Se, and —Te Bonds

1.10.1.3.1 Reduction of aryl sulfides, selenides, and tellurides

(i) Reduction of aryl sulfides

Numerous methods have been developed to desulfurize aryl thiols and sulfides. One of the more significant methods is probably the use of Raney nickel, even if its manipulation is not always easy. Nickel boride, formed by the reaction of nickel(II) salts with NaBH_4 , appears to be a useful reagent, allowing more chemoselective reactions than Raney nickel. Homogeneous nickel(0) complexes in combination with hydrides have also been investigated. Metal carbonyls such as $\text{Co}_2(\text{CO})_8$, $\text{Mo}_2(\text{CO})_6$, or $\text{Mn}_2(\text{CO})_{10}$ were found to be effective desulfurization reagents. All these utilizations are reported in COFGT (1995). A review has been published on this topic <1999T10547>.

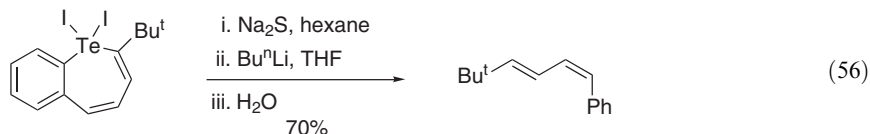
Dibenzothiophene is reported to be one of the more difficult substrates to be desulfurized, and numerous conditions have been tried. In the 1990s, Fort and co-workers found that this compound is transformed into biphenyl by using a mixture $\text{LiH-Ni}(\text{OAc})_2\text{-Bu}^t\text{OH}$ <1995TL6051>, or better a mixture $\text{NaH-Ni}(\text{OAc})_2\text{-Am}^t\text{OH}$ <1998TL8987>. Bianchiri and co-workers found that a mixture of rhodium and tungsten salts also gave interesting results <2001CC479>. Verkade and co-workers utilized Na in a hydrocarbon solvent to obtain the same result (Equation (53)) <1999EF23>. Reductive opening of dibenzothiins with lithium and a catalytic amount of 4,4'-di-*t*-butylbiphenyl (DTBB) in THF led to the formation of thiols <2002CL726> (Equation (54)). A photochemical removal of thiophenyl group was reported to occur in satisfactory yields <1995G315>. Desulfonation of difluorosulfonic acids was reported to occur in acidic as well as in basic conditions. These reactions were conducted on industrial scales (Equation (55)) <2000JFC(101)85>.



(ii) Reduction of aryl selenides and aryl tellurides

Cleavage of aryl-C—Se bonds has been reported to occur in the presence of Ph_3SnH , Raney nickel, Li in liquid NH_3 , or transmetalation with BuLi followed by hydrolysis (see COFGT (1995)). No new procedures have been reported in this field.

Reduction of aryl-C—Te bonds has been reported to occur in the presence of Ph_3SnH , Li in liquid NH_3 , or transmetallation by using BuLi (see COFGT (1995)). In the presence of YbI_2 , a photochemical process was reported to induce this cleavage <1997TL9017>. The transmetallation method was applied to the formation of 1,3-dienes (Equation (56)) <1995CPB19>.

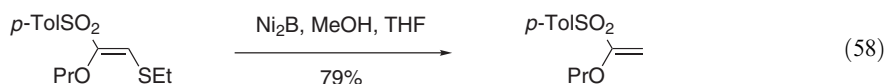
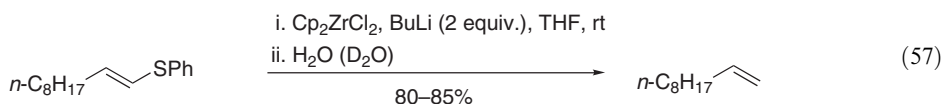


1.10.1.3.2 Reduction of vinyl sulfides, selenides, and tellurides

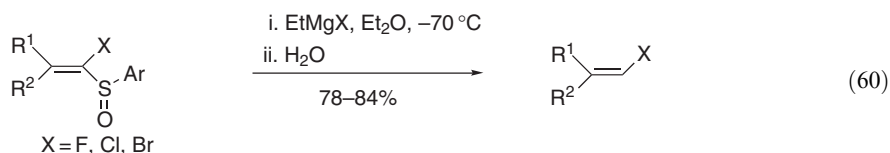
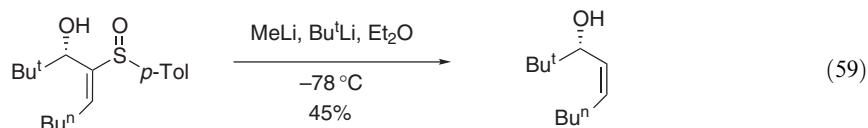
(i) Reduction of vinyl sulfides, sulfoxides, and sulfones

The reduction of vinyl sulfides to alkenes has been reported by using Raney nickel, nickel boride ($\text{NaBH}_4 + \text{Ni(II)}$ salts), and nickel(0) complexes. All these methods gave interesting results reported in COFGT (1995). A review has also been published on this topic <1999T10547>.

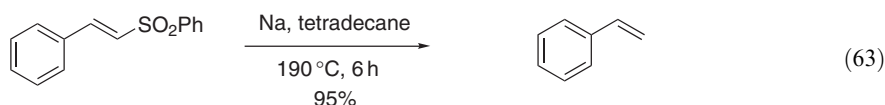
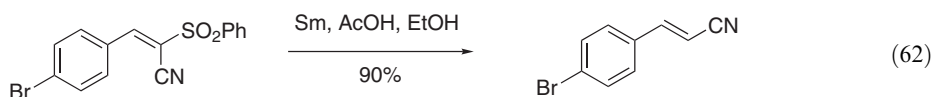
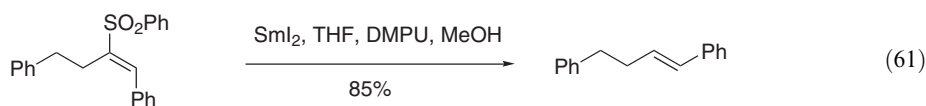
Concerning the reactivity of zirconium salts with ethylenic compounds, Marek shows that vinyl sulfides can be easily transformed into alkenes (Equation (57)) <2002AG(E)1410>. Nickel boride was reported to reduce selectively vinyl sulfides without the cleavage of sulfoxide or sulfone groups (Equation (58)) <1998JOC7908>. A ketene thioacetal was stereospecifically transformed into a vinyl sulfide by reaction with a copper reagent <1995TL1925>.



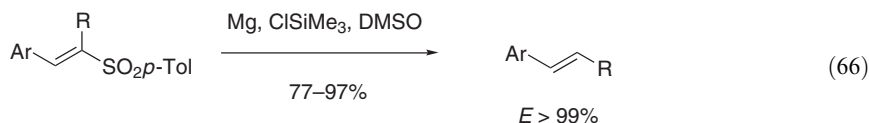
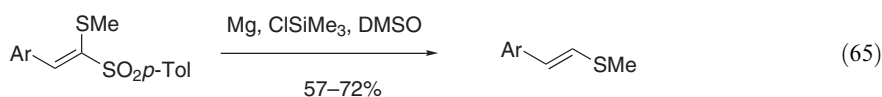
The conversion of vinyl sulfoxides to alkenes is more rarely reported. Use of NaOEt or Bu^tLi has been reported in COFGT (1995). Subsequently, it has been shown that a mixture Bu^tLi – MeLi was more efficient than Bu^tLi alone (Equation (59)) <2002JOC8166>. SmI_2 in a mixture THF–MeOH was also reported to be efficient as a reducing agent <2000OL365>. α -Halovinyl sulfoxides reacted with Grignard reagents to lead, after hydrolysis, to halovinyl compounds (Equation (60)) <1998T5557>.



The reduction of vinyl sulfones has been extensively studied, and reagents such as nickel(0) complexes, palladium(II) salts, Mg, Bu_3SnH , NaTeH , $\text{Na}_2\text{S}_2\text{O}_4$, amalgams (Al or Na), etc. were used (see COFGT (1995)). Recently, new reagents have also been reported to give excellent results. Desulfonation of vinyl sulfones by SmI_2 was shown to lead mainly to (*E*)-alkenes <1995JOC3194> (Equation (61)). Reaction with MeOD gave labeled products. Use of Sm was reported in the case of α,β -ethylenic nitriles and amides (Equation (62)) <2001OPP372, 2001JCR(S)26>. Vinyl sulfones were reduced, as vinyl sulfides, with zirconium salts (see Equation (57)) <2002AG(E)1410>. Cleavage of the vinyl-C—S bonds was reported to be possible with Na in tetradecane at high temperature (Equation (63)) <1998TL2671>.



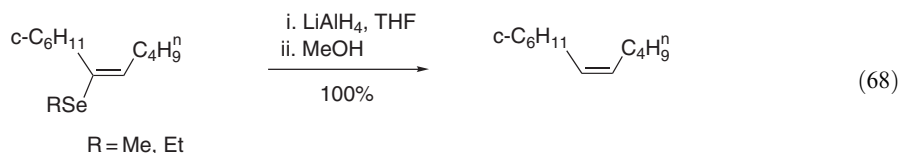
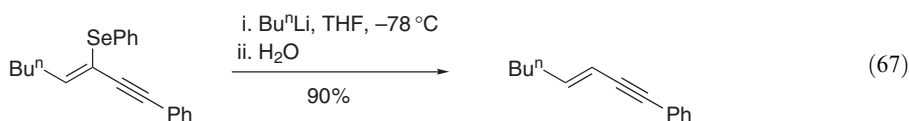
δ -Sulfonyl- γ,δ -ethylenic esters were desulfonated by the reaction with DBU (Equation (64)) <1999TL5957>. Magnesium activated by ClSiMe_3 in DMSO was used to selectively desulfonate α -methylthiovinyl sulfones (Equation (65)) and stereoselectively α -alkyl vinyl sulfones (Equation (66)) <2002CL478>. These cleavages were also observed with sulfoxides. Monodesulfonation of (Z)-1,2-disulfonyl ethylene was reported to be possible with diphenylsilane in the presence of PtCl_2 <1996SC211>.



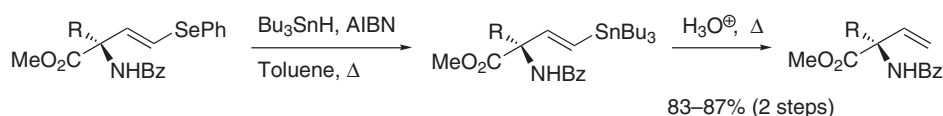
(ii) Reduction of vinyl selenides

Reduction of sp^2 C—Se bonds in vinyl selenides has been reported by the reaction with nickel boride, addition of Bu^nLi followed by protonolysis, and treatment with Bu_3SnH –AIBN or P_2I_4 (see COFGT (1995)).

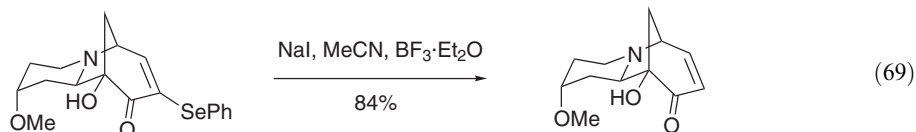
The reaction of vinyl selenides with Bu^nLi was applied to the formation of enynes (Equation (67)) <1998S39, 1998JCR(S)616>. This reduction was also effective with LAH and occurred with retention of configuration (Equation (68)) <1996JOM(523)139>.



In the case of vinyl selenides, γ -functionalized by amino acids, the reaction with Bu_3SnH –AIBN led to substitution of the selenyl group by a tin group, and the reduction products were obtained only after hydrolysis (Scheme 3) <2000JA11031>. It has been reported that an α -selenyl- α,β -enone was reduced by NaI in CH_3CN . However, this reaction does not appear to be general (Equation (69)) <2000JOC6293>.

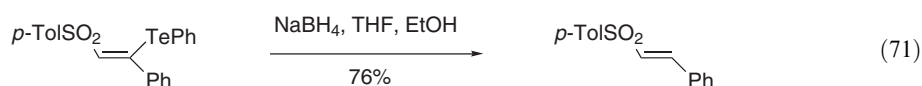
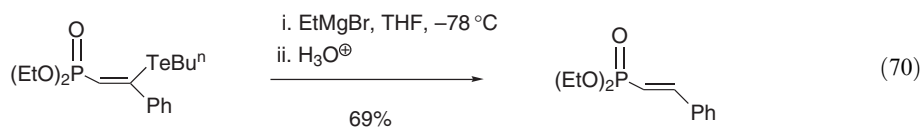


Scheme 3

*(iii) Reduction of vinyl tellurides*

The most usual method used to cleave the sp^2 C—Te bond is transmetalation followed by hydrolysis. This exchange reaction was carried out with Bu^nLi and cuprates. Reduction of vinyl tellurides was also reported with Raney nickel (see COFGT (1995)).

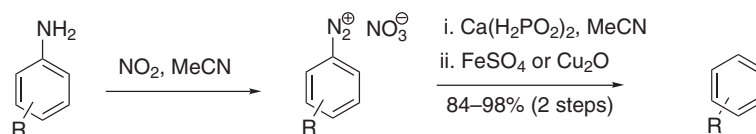
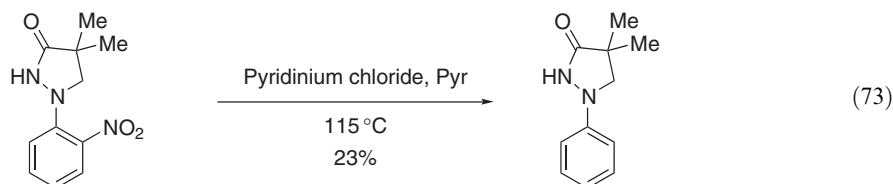
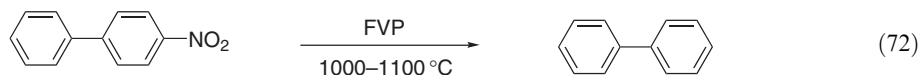
Convenient preparation of vinyl tellurides is reported by addition of diorganoditellurides to acetylenic compounds. Since the subsequent transmetalation is an easy process, these reactions were applied efficiently for the preparations of alkenes <1996JOC4975>. To the previous known methods of transmetalations using Bu^nLi and cuprates, new procedures based on the reactivity of organozinc <1996TL4741> and Grignard reagents were published <2000TL5103> (Equation (70)). A chemoselective reduction of a vinyl telluride using $NaBH_4$ as reducing agent was reported (Equation (71)) <2001JOC74>. This reduction is also possible with Bu_3SnH –AIBN <2002AG(E)1407>.

**1.10.1.4 Reduction of =C—N Bonds****1.10.1.4.1 Reduction of arylcarbon—nitrogen bonds**

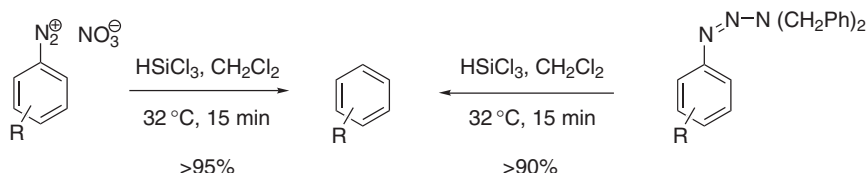
The direct displacement of aromatic nitro group to hydrogen is a rare reaction, and was reported for particular substrates. This substitution is usually carried out after reduction of the nitro compounds to the corresponding amines <1997MI(37)121>. These can then be transformed into diazonium salts (reaction with sodium or potassium nitrite), and cleavage of these salts is possible with a variety of reagents such as H_3PO_2 , EtOH, formaldehyde, Zn, Sn, $NaBH_4$, Bu_3SnH , or Et_3SiH <B-94MI1, 1990HOU(16a)1052>. Cleavage of aryl-C—N bonds is also reported from hydrazines, by oxidation into azo compounds, by using reagents such as HgO or $K_3Fe(CN)_6$.

Since the publication of COFGT (1995) new results have been reported. Flash vacuum pyrolysis at $1000^\circ C$ of some aromatic nitro compounds led to the elimination of the nitro functions (Equation (72)) <1997AJC1159>. Cleavage of aryl nitro functions has also been reported by reaction of nitrophenylpyrazolidinones with pyridine hydrochloride. The mechanism of this reaction seems still unclear (Equation (73)) <2000CC415>. Transformation of electron-deficient arylamines into diazoniums was reported in the presence of NO_2 . The subsequent decomposition occurred easily with $Ca(H_2PO_2)_2$ in the presence of $FeSO_4$ or Cu_2O (Scheme 4) <2000TL5567>. Decomposition of diazoniums with $HSiCl_3$ was found to be a fast and clean reaction. This chlorosilane reacted with the corresponding triazenes to lead to the same products

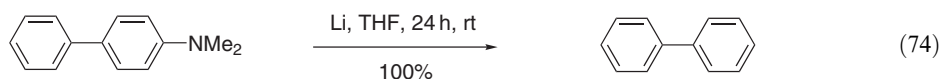
(Scheme 5) <2000TL3813>. Cleavage of triazenes was conducted on solid phase with the same efficiency. Decomposition of diazoniums with Et₃N in MeOH <1996SC1569> or FeSO₄ in DMF was also reported to give excellent results <1995JOC1713>. The direct reduction of arylamines was carried out with Li in THF. This reaction is limited to aryl substituents (Equation (74)) <1999TL8291>.



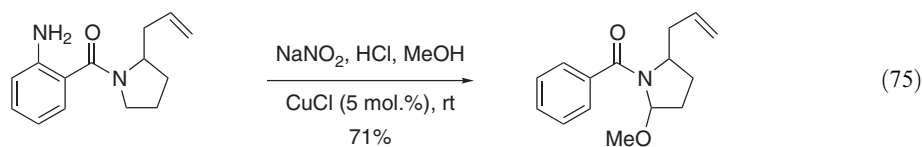
Scheme 4



Scheme 5

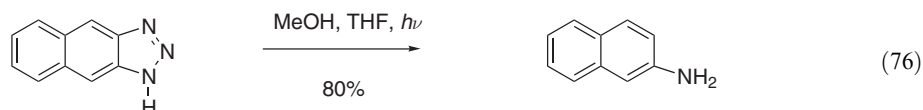


Weinreb and co-workers found that arylamines substituted in the α position by an amide function reacted with NaNO₂ and a catalytic amount of CuCl to lead to α -methoxyamides (Equation (75)) <1996JOC9483>. *N,N*-Dimethylarylamines, after transformation into ammonium salts, were reduced by sodium in liquid NH₃ <2002JA7894>. Primary arylamines, after transformation into sulfonamides, were reduced under alkaline conditions to aryl compounds (Scheme 6) <2001JOC8293>. This cleavage is compatible with the presence of functional groups such as ketones, esters, amides, nitro groups, acids, etc. Aryltriazoles, in a mixture THF–MeOH, were transformed under irradiation into arylamines (Equation (76)) <1996JA6522>.

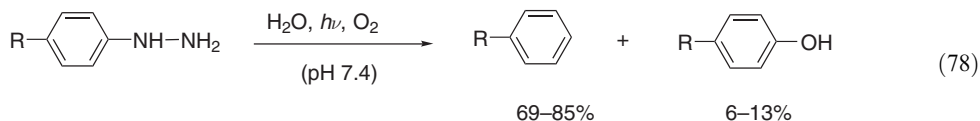
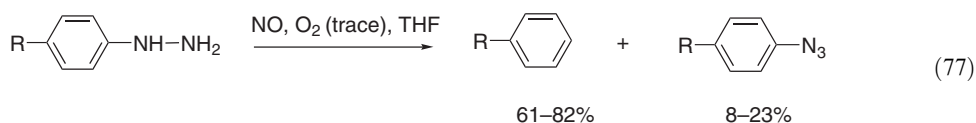




Scheme 6

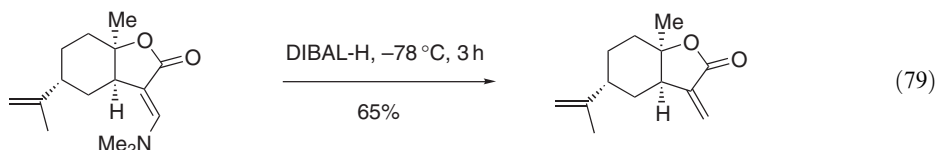


Some interesting results have also been reported in the 1990s, concerning the reduction of aryl hydrazines of type ArNH-NH_2 . Oxidation into azo compounds was reported using PbO_2 . The subsequent decomposition led to the desired arylamines [<1997MI6445>](#). Cleavage of the acyl-C—N bond was also carried out with NO in the presence of a very small amount of O_2 . Aryl azides were formed as side products in small quantities (Equation (77)) [<1997JOC3582>](#). Irradiation of aryl hydrazones at $\lambda \geq 300$ nm in methanol also led to aryl compounds. In this case, phenols were obtained as side products (Equation (78)) [<1997JCS\(P1\)2451>](#).



1.10.1.4.2 Reduction of vinylcarbon—nitrogen bonds

The transformation of nitroalkenes into alkenes has been reported via the formation of β -nitrotrithiocarbonate intermediates, followed by a photochemical elimination (Barton procedure), or directly by reaction with Bu_3SnH . The transformation of enamines into alkenes was reported by reaction with alane, diborane, and 9-BBN. For these two transformations, no new results have been reported since those published in COFGT (1995). 3-Aminomethylene-dihydrofuranone derivatives reacted with DIBAL-H to produce 3-methylene derivatives (Equation (79)) [<2000TL8451>](#). Similar results were reported using NaCNBH_3 as reducing agent [<1997T10633>](#). Reduction of an aminofulvene to fulvene was carried out using DIBAL-H [<1997ZN\(B\)911>](#).



1.10.1.5 Reduction of =C—P, =C—As, =Sb, and =C—Bi Bonds

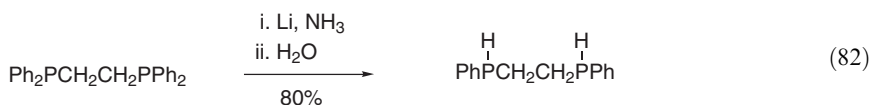
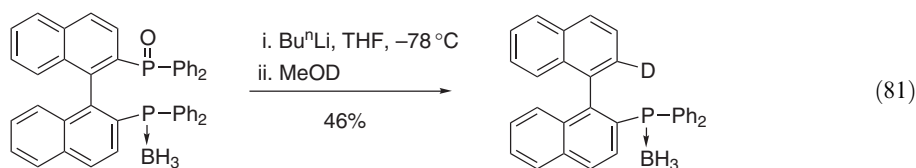
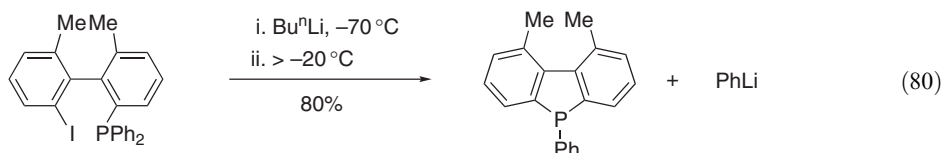
1.10.1.5.1 Reduction of arylcarbon—phosphorus, —arsenic, —antimony, and —bismuth bonds

(i) Reduction of arylcarbon—phosphorus bonds

The most common method to reduce aryl-C—P(III) bonds consists in the use of alkali metals, followed by hydrolysis. Complexes such as $\text{RuH}_2(\text{PPh}_3)_4$ have also been used. The cleavage of arylphosphonium salts can be carried out by hydrolysis (formation of phosphine oxides) or

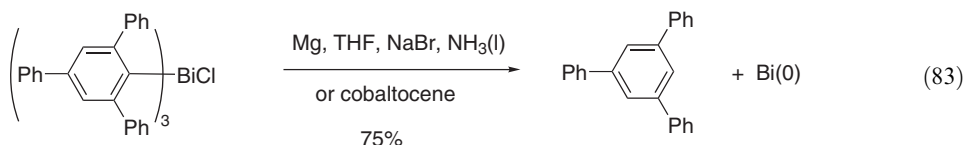
reduction with LAH. The reduction of aryl-C—P(V) bonds is much less widespread. A few examples have been reported using solid KOH or NaH. More information can be found in COFGT (1995).

Recently, it has been reported that lithium derivatives allowed cleavage of aryl-C—P(III) bonds, when an intramolecular attack on the phosphorus atom is possible (Equation (80)) <1996TL5347, 1996JOM(507)257, 2003BCJ1233>. A selective cleavage of the C—P bond between a naphthyl and a diphenylphosphonyl group is also possible in these conditions. This reaction appeared to be reversible, and it was made irreversible by complexation of one of the phosphorus atoms by BH₃ (Equation (81)) <2001JOC8854>. Preparation of 1,2-bis(phenylphosphino)ethane from 1,2-bis(diphenylphosphino)ethane was reported by reaction of Li in THF (Equation (82)) <2000JOC951>. Ru(OAc)₂ in the presence of HBF₄·Et₂O allows the cleavage of aryl-C—P(III) bonds. The main drawback of this reaction is the very low rate of the reaction (2 weeks at rt) <1998OM5213, 2001OM2990>. Degradation of phenylphosphonic acid into benzene and biphenyl with a bacterium (*Rhizobium sp.*) is also reported <1995MI157>.



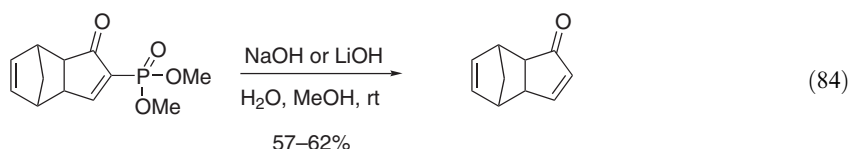
(ii) Reduction of arylcarbon—arsenic, —antimony, and —bismuth bonds

Triorganoarsenic compounds, diarsines, and diorganoarsenic halides are reduced by alkali metals to afford diorganoarsenic species. The cleavage of aryl-C—As bonds has also been achieved using NaHSO₃ and aqueous bases. Pentaorganoantimony and -bismuth compounds were reduced with electrophiles such as HF, HCl, and Br₂ to conduct the formation of organoantimony(IV) and -bismuth(IV) halides. The number of reports concerning these different reactions is limited (see COFGT (1995)). Only one new report, concerning such reactions, has been published. To try to prepare diorganobismuth compounds, reduction of diarylbismuth chloride was attempted. Only cleavage of aryl-C—Bi bonds was observed (Equation (83)) <1995JOM(485)141>.



1.10.1.5.2 Reduction of vinylcarbon—phosphorus bonds

Substituted alkenes and allenes were obtained from vinyl phosphines by metallation with MeLi, followed by hydrolysis of the resultant vinylolithium. Hydrolysis with bases or acids of vinylphosphonium salts is also reported to give the corresponding alkenes (COFGT (1995)). Treatment of a 2-phosphonyl 2,3-cyclopentenone with hot water <1996AG(E)1560>, or alkali bases <1997TL2527>, led to the hydrolyzed product (Equation (84)).

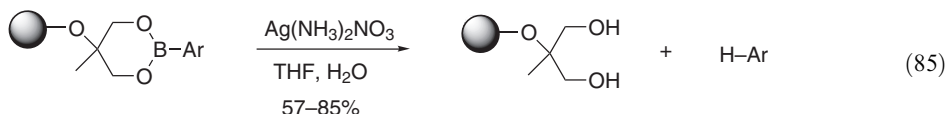


1.10.1.6 Reduction of =C—B, =C—Si, and =C—Ge Bonds

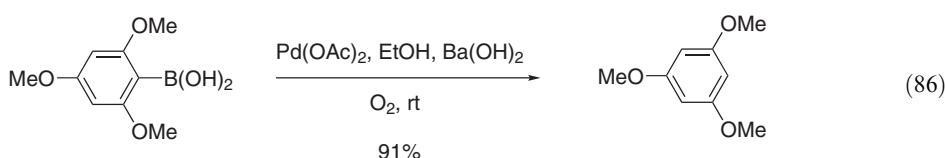
1.10.1.6.1 Reduction of aryl boranes, silanes, and germanes

(i) Reduction of aryl boranes

The aryl-C—B bond cleavage is promoted with acids or bases in drastic conditions. It was found that metal salts (e.g., CuCl_2) catalyze this cleavage and allow milder reaction conditions. Aqueous silver ammonium nitrate and aqueous ethanolic dimethylaminoethanol have also proved effective. In the 1990s, some new results confirmed these previous results. For example, Carboni and co-workers found that aryl compounds were obtained in good yields by cleavage of the aryl-C—B bond using aqueous silver ammonium nitrate in THF. This cleavage was applied to solid phase (Equation (85)) <2000CC1275>.



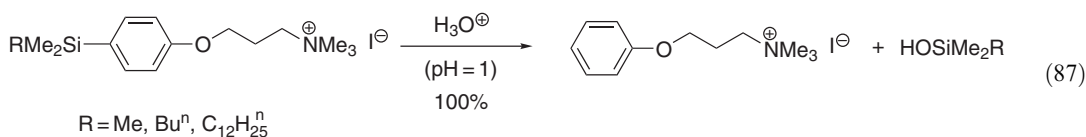
The Suzuki—Miyaura coupling reaction is well documented <1999JOM(576)147> using palladium salts. In the absence of an acceptor (e.g., chloroarenes), this reaction proceeds to the formation of biaryl compounds <1997SL131>. With electron-enriched boronic acids (Equation (86)), no coupling was observed. It seems possible, even if this has not yet been reported, to find conditions that lead to the exclusive substitution of the boron group by hydrogen. The aryl-C—B bond cleavage was also reported with $[\text{Rh}(\text{COD})\text{Cl}]_2$ in basic conditions <2002OL2105>.



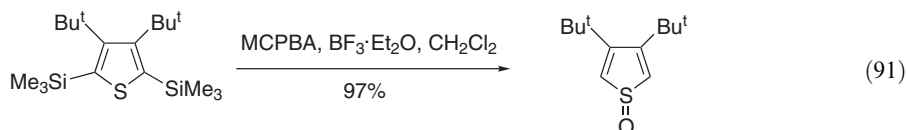
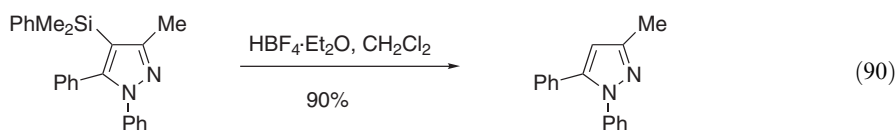
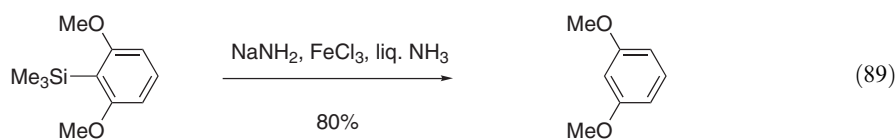
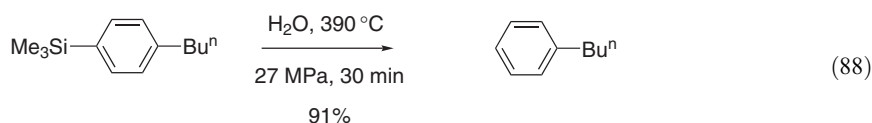
(ii) Reduction of aryl silanes

The *ipso* substitution of silicon by hydrogen in aryl silanes has been extensively studied, and applied in synthesis. This chemistry is largely covered in books and review articles. For a recent example see <B-2002MI685>. The aryl-C—Si bond (as the vinyl-C—Si bond) can be cleaved using electrophilic or nucleophilic reagents (see COFGT (1995)). Cleavage of these bonds, in acidic conditions, is commonly carried out with inorganic acids such as HCl , H_2SO_4 , or carboxylic acids such as CF_3COOH and HCOOH . Nucleophilic reagents such as butoxides, sodium methoxide, NaH , KH , K_2CO_3 , and F^- (CsF , KF , TBAF) are usually used. Desilylation of aromatic compounds is often planned in organic synthesis, and the choice of the reagent depends on the functionalization of the substrates.

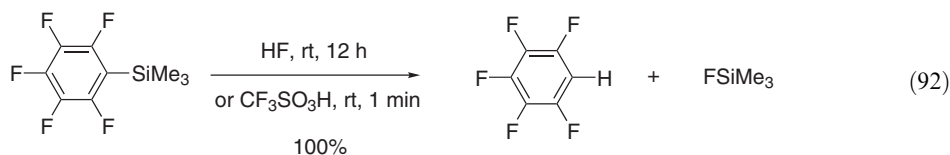
In the 1990s, this cleavage was applied to solid-phase organic synthesis for the preparation of numerous compounds <1995JA11999, 1996TL2703, 1999TL8563, 1997JOC2885, 1997JOC6102, 1997JOC6726, 1998JOC4518, 2001TL1815>. Use of fluorides and TFA led to satisfactory results in these particular conditions. Amphiphilic molecules with silicon are stable in organic solvents and in aqueous solution. However, at pH 1 the cleavage occurred in less than 5 min (Equation (87)) <1999TL4935>.



Some new or particular conditions have been reported for the cleavage of aryl-C—Si bonds. For example, this cleavage was observed in super-critical water (374 °C under 22.1 MPa) (Equation (88)) <2003JA6058>. It has been reported that the reduction was very fast in liquid ammonia (~1 min) using NaNH₂ in the presence of FeCl₃ (Equation (89)) <2000SL619>. In some particular cases, the mixture Me₃SiCl—KI in aqueous MeCN gave interesting results <1995TL5093>. Treatment of a pyrazole with HBF₄ led to the cleavage of the heterocycle C—Si bond instead of the aryl-C—Si bond. No fluorine compound was formed (Equation (90)) <2001S1949>. Heterocyclic C—Si bond cleavage was also observed during the oxidation of a thiophene derivative (Equation (91)) <1997CL499>.



Aryl silanes in which the aryl group is electron poor can be cleaved by using anhydrous HF, FSO₃H, or CF₃SO₃H. These cleavages occurred rapidly under these conditions (Equation (92)) <1998JOM(570)255>. Liquid HI was reported to initiate the cleavage of ethylmesitylsilane to trimethylbenzene and iodoethylsilane in 1 week at -35 °C <2003MI(644)105>. PhSiH₃ was reported to be transformed into SiH₄ in the presence of a stoichiometric amount of a lutetium hydride complex (Equation (93)) <2001OM5598>.



(iii) Reduction of aryl germanes

Germane—carbon bonds are susceptible to react with electrophiles similar to Si—C bonds. Cleavage of these bonds is reported with TFA or HClO₄. In nucleophilic conditions, sodium methoxide was reported to be effective. Aryl germanes are much less used in synthesis than aryl

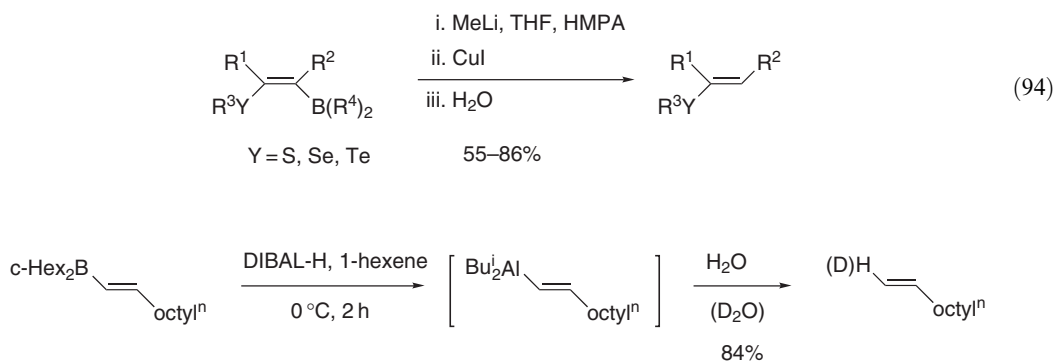
silanes. However, they were examined as linkers in solid-phase synthesis for the preparation of pyrazoles. Cleavage of the aryl-C—Ge bonds was carried out with TFA <2000JOC5253, 1997JOC2885>. Strong acids such as CF₃SO₃H or ClSO₃H were also reported to cleave the aryl-C—Ge bond of electron-poor aromatic compounds <1994HAC91>.

1.10.1.6.2 Reduction of vinyl boranes, silanes, and germanes

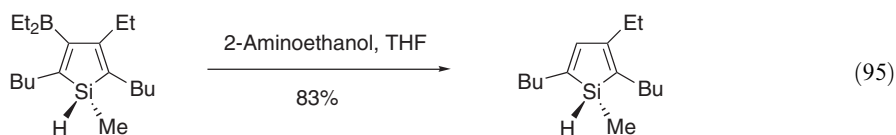
(i) Reduction of vinyl boranes

The hydroboration of alkynes is a method of choice to access vinyl boranes. This reaction has been featured in reviews (e.g., <1997T4957>). Protonolysis of the C—B bond can be carried out under mild conditions, compatible with numerous functional groups owing to the utilization of MeOH, carboxylic acids such as acetic or pivalic acids, or inorganic acids such as HCl. Reaction of alkenyldialkylboranes with BuⁿLi gave borates, which can be hydrolyzed with NaOH. Cleavage of vinyl-C—B bonds with aqueous silver ammonium nitrate or Pd(OAc)₂ has also been reported (see COFGT (1995)).

Hevesi and co-workers found that the hydrolysis of vinyl borates was improved by addition of CuI (Equation (94)) <2001T9109>. Addition of DIBAL-H to vinyl boranes was reported to produce clean B → Al exchanges, and the subsequent hydrolysis can be carried out by simple addition of water (Scheme 7) <2002CC2146>. Selective cleavage of the vinyl-C—B bond of a silacyclopentadiene has been reported with 2-aminoethanol in THF (Equation (95)).



Scheme 7

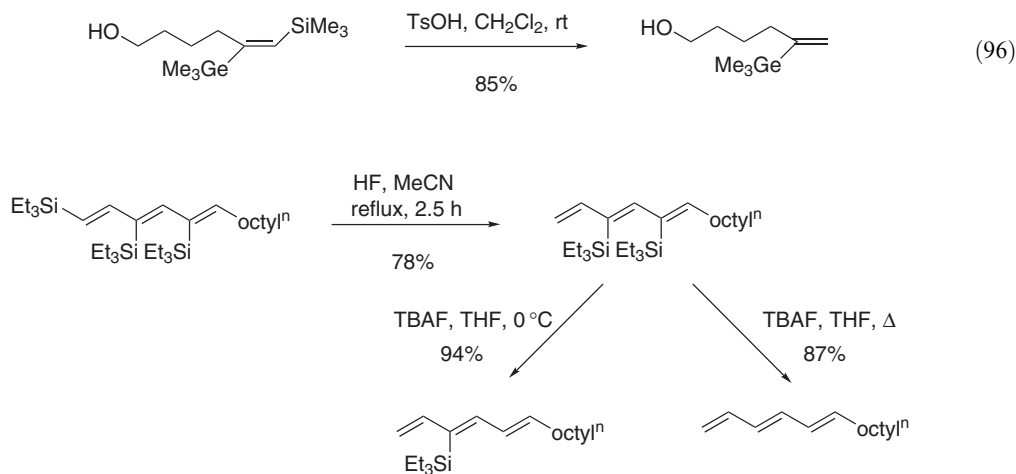


(ii) Reduction of vinyl silanes

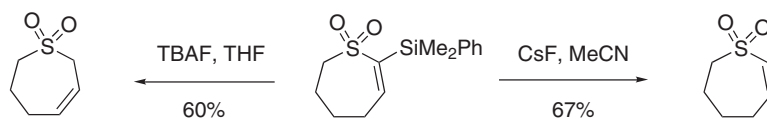
The chemistry of vinyl silanes has been extensively studied <1995CRV1375, B-1998MI1793, B-2002MI713>. The cleavage of vinyl-C—Si bonds can be carried out with electrophilic or nucleophilic reagents (see COFGT (1995)). A large variety of acids has been tested; among the most used acids were HI, HF, HBr, AcOH, HCl (in MeOH, acetone, diethyl ether), TsOH, and CF₃COOH. In nucleophilic conditions, fluorides (TBAF, KF, CsF) or alkoxides are usually used. Cleavage of C—Si bonds with Ag(NH₃)₂NO₃ or Pd(OAc)₂ has also been reported (see COFGT (1995)).

As representative examples concerning reagents used in the 1990s, TBAF in DMSO <2000JOC6508>, CsF in moist DMSO <1996JCS(P1)2803>, K₂CO₃ in EtOH <1999T6739>, HCOOH in MeOH <2000CC569>, MeONa in MeOH <1996TL755>, KH in the presence of 18-crown-6 <1995T4665>, EtSH—BF₃·Et₂O <1998JA7411>, and TFA <2003JOC1929> can be

quoted. Some particular reactions can be emphasized. For example, chemoselective removal of a trimethylsilyl group was reported to occur in the presence of a trimethylgermyl group (Equation (96)) <1995JCS(P1)3>. Yamaguchi found conditions to selectively remove one, two, or three triethylsilyl groups fixed on a 1,3,5-triene (Scheme 8) <1998JOC8086>. Treatment of a tetrahydrothiepine with CsF led to the clean removal of a dimethylphenylsilyl group, while with the more nucleophilic TBAF shift of the C—C double bond was observed (Scheme 9) <1996T4803>.

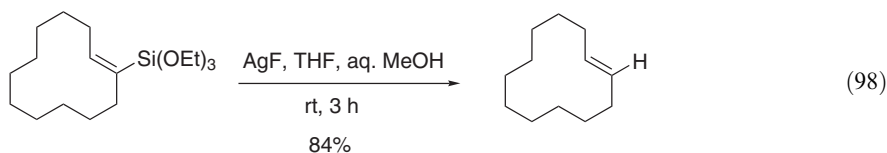
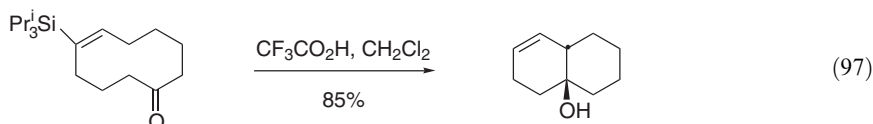


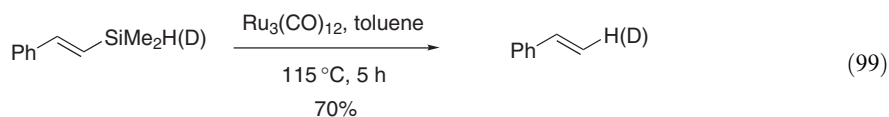
Scheme 8



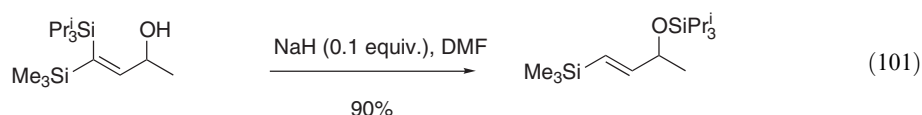
Scheme 9

Cleavage of C—Si bond followed by a transannular 1,6-cyclization was reported when a δ,ϵ -ethylenic decanone was treated with TFA (Equation (97)) <1997T14235>. Fürstner found that AgF cleaved vinyl silanes of (*E*)-stereochemistry, included in large rings, without isomerization. In addition, these conditions are compatible with the presence of a large number of functional groups (Equation (98)) <2002CC2182>. Trost, on the same kind of substrates, reported that the use of the mixture TBAF—CuI also led to excellent results <2002JA7922>. Cleavage of vinyl dimethylsilanes was reported with $\text{Ru}_3(\text{CO})_{12}$ in toluene. This particular reaction seems to take place by elimination of a silylene complex (Equation (99)) <1999CL717>. Chlorovinyltrimethylsilanes were reported to be transformed into chloroethylenes by reaction with HCl in the presence of FeCl_3 . This cleavage was also observed with dimethylchloro- and dichloromethylsilanes (Equation (100)) <1999MI375>.



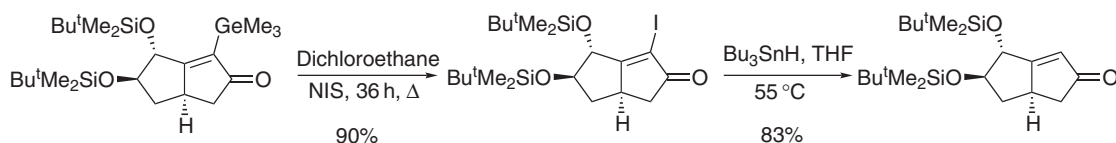
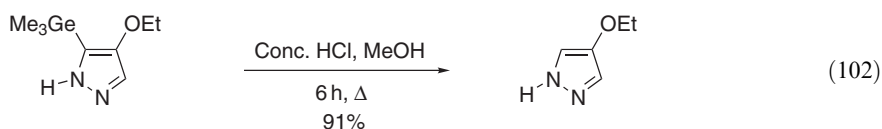


Interesting results have been reported for the removal of the vinyltrialkylsilyl group of allylic or benzylic alcohols. Lautens and co-workers reported that a triethylsilyl group was selectively removed by treatment of an allylic alcohol with NaH (Equation (101)). This result was explained by a C \rightarrow O intramolecular migration of the triethylsilyl group, while the trimethylsilyl group remained unchanged. This migration was not observed when MeLi was used as a base <1995JOC4213>. The same migration of silyl groups was reported with furan and thiophene derivatives <1997JOC8741>. In place of NaH, KF in DMSO at 150 $^\circ\text{C}$ <2001SC3641> or irradiation in benzene <2001JA3638> were also found to be efficient.



(iii) Reduction of vinyl germanes

Preparation of vinyl germanes has been recently reported <2000SL495, 2000TL9981>. Very few results exist which report their reaction with electrophiles. Cleavage of an sp^2 C–Ge bond was reported with conc. HCl (Equation (102)) <1985JGU1853>. Substitution of a vinyltrimethylgermane by a hydrogen was reported to be more effective by the intermediate formation of a vinyl iodide (Scheme 10) <2002TL8575>.

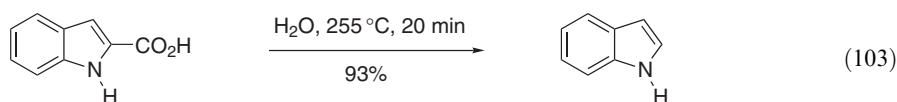


Scheme 10

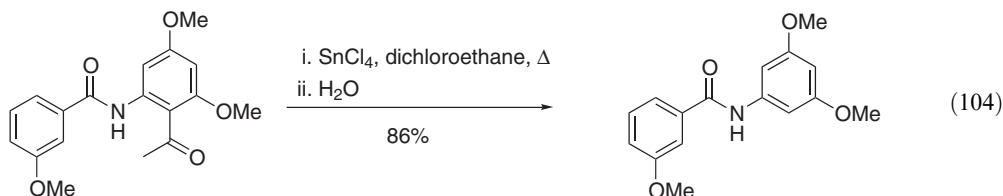
1.10.1.7 Reduction of =C–C Bonds

1.10.1.7.1 Reduction of arylcarbon–carbon bonds

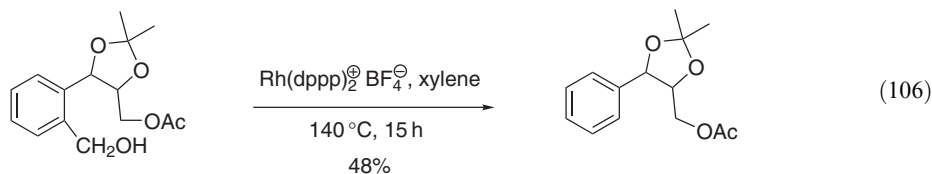
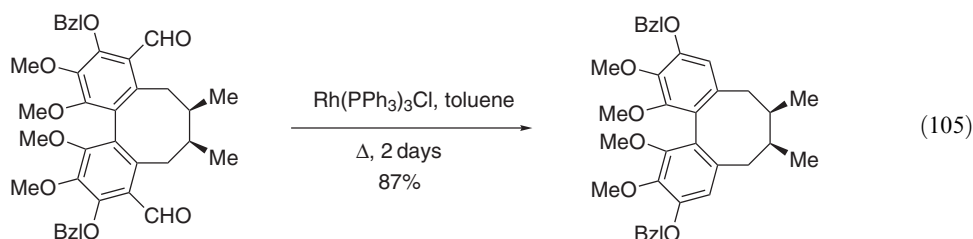
Heating (200–300 $^\circ\text{C}$) in quinoline in the presence of copper salts usually carries out the decarboxylation of benzoic acids <1986TL3045>. Improvements of these reaction conditions have been reported. Microwave irradiation allows the CO_2 elimination at lower temperature, in high yields <2000JCR(S)42>. Heating in CH_3COOH <1998T1943> or in hot water (250–300 $^\circ\text{C}$) (Equation (103)) <1997JOC2505> was reported to lead to clean decarboxylation. Heating of anhydrides at 80 $^\circ\text{C}$ in the presence of $\text{Ba}(\text{OH})_2$ also led to interesting results <1996JOC1136>.



Deacetylation in strong acidic conditions (retro-Friedel–Crafts reaction) was reported by using SnCl_4 (Equation (104)) <2002JCR(S)463> or Nafion-H <1997JCS(P1)1193> (see also <1983JOC3360, 1986S513>).

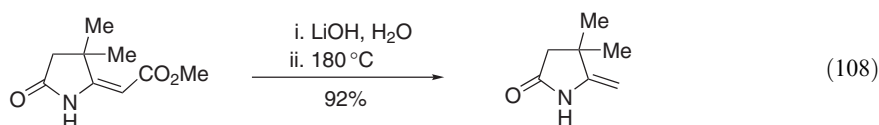
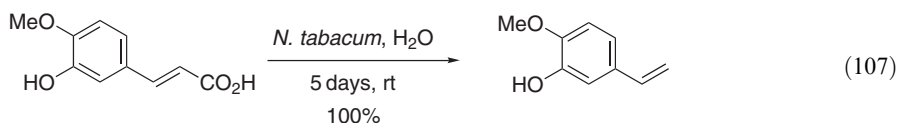


Deformylation of aromatic aldehydes was reported using Nafion-H <1997JCS(P1)1193>, $\text{Sc}(\text{OTf})_3$ <1996T11045>, or the Wilkinson catalyst (Equation (105)) <1995T11693>. A more efficient Rh complex was used with success in a case for which $\text{Rh}(\text{PPh}_3)_3\text{Cl}$ was inefficient (Equation (106)) <2002JCS(P1)1622>.

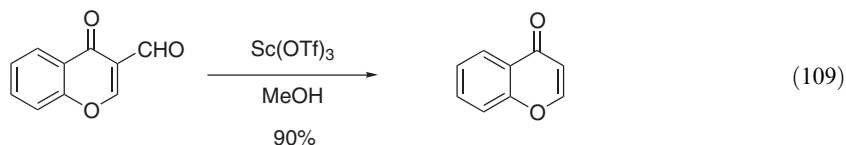


1.10.1.7.2 Reduction of vinylcarbon—carbon bonds

Pyrolysis of cinnamic acids led to the formation of styrenes. However, as in the case of benzoic acids, heating in quinoline in the presence of Cu or its salts led in general to better results. Heating of ethyl cinnamate in H_2O at 220°C led to the formation of styrene in good yield <1997JOC2505>. Decarboxylation of cinnamic acid derivatives was reported by using plant cell cultures. The more efficient plants tested were *Catharanthus roseus* and *Nicotiana tabacum* (Equation (107)) <1999TL6595>. Specific decarboxylation can occur by pyrolysis of the acids without the necessity of heating at high temperature. For example loss of CO_2 for the lithium salts of acid in Equation (108) was reported to occur at 180°C <1996JOC5013>.



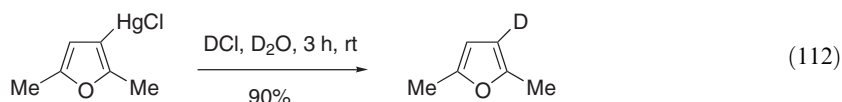
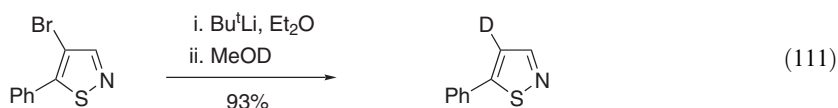
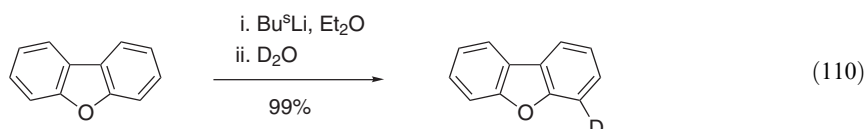
Deformylation of cinnamaldehyde was reported with $\text{RhCl}(\text{PPh}_3)_3$ in the presence of diphenylphosphoryl azide [<1992JOC5075>](#). $\text{Sc}(\text{OTf})_3$ -induced deformylation of an α,β -unsaturated aldehyde to produce chromenone. This reaction was also carried out with $\text{La}(\text{OTf})_3$ or $\text{Y}(\text{OTf})_3$ (Equation (109)) [<1996T11045>](#).



1.10.1.8 Reduction of =C—Metal Bonds

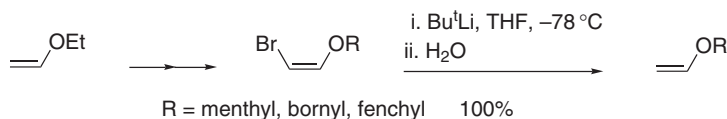
1.10.1.8.1 Reduction of arylcarbon—metal bonds

The substitution of metal by hydrogen atom in aryl metal compounds is mainly carried out with water or inorganic acids diluted in water. Hydrolysis with D_2O provides information on the position of the metal atom. Metallation of dibenzofuran with Bu^sLi (Equation (110)) [<1995TL7657>](#), or reaction of bromoaryls (Equation (111)) [<1997TL355, 2000JOC3626>](#) with Bu^tLi , followed by reaction with D_2O , was used to obtain labeled compounds. Hydrolysis of Grignard reagents gave similar results [<2001MI854>](#). An arylmercurial compound was treated with DCl to also lead cleanly to the labeled product (Equation (112)) [<1997CHE898>](#).

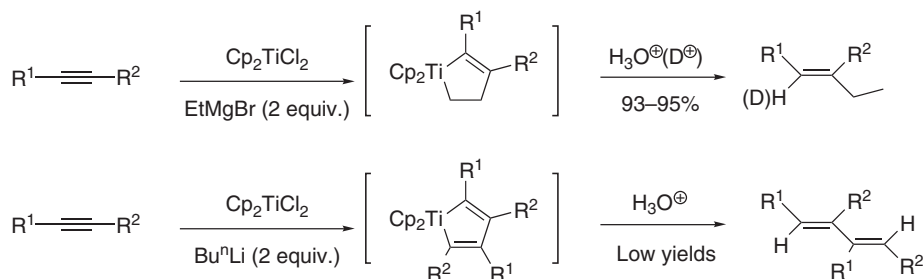


1.10.1.8.2 Reduction of vinylcarbon—metal bonds

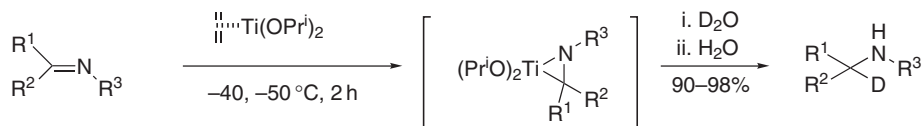
Numerous examples can be found in the literature concerning the reaction of vinyl metal intermediates (Li , Na , Ca , Ba , Cu , Mg , Al , Zr , Ni , etc.) with H_2O or diluted inorganic acids. In the case of vinyl boranes, reaction with acetic acid or transmetalation with alkyllithium (followed by addition of water) is normally used. Vinyl mercurials are cleaved to the corresponding alkenes by protonolysis or reduction (NaBH_4) (see COFGT (1995)). Some new results have appeared concerning the hydrolysis of alkenyllithiums. This reaction was used to prepare vinyl ethers possessing a chiral substituent starting from ethyl vinyl ether (Scheme 11) [<1996TL7255>](#). Addition of D_2O to polyalkenyllithium compounds allowed the elucidation of the mechanism of rearrangement of these compounds [<1998EJO793>](#). Hydrolysis by addition of water to vinyl titanates was used as a stereoselective preparation of alkenes and 1,3-dienes (Scheme 12) [<2001JOM\(633\)18>](#). Reaction of imines by a titanate complex followed by hydrolysis led to amines (Scheme 13) [<1997SL1353>](#).



Scheme 11

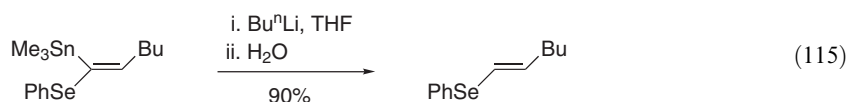
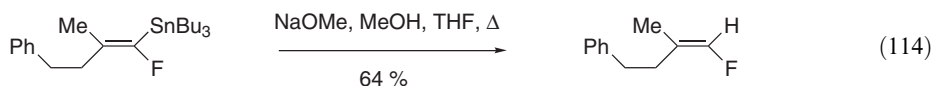
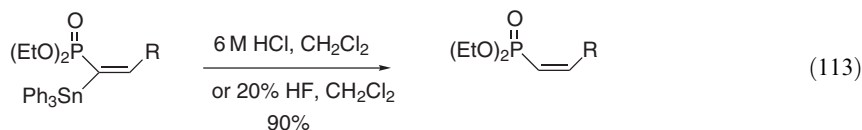


Scheme 12

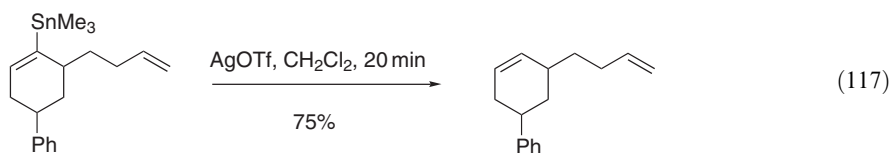
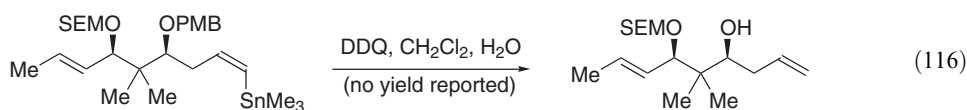


Scheme 13

Numerous works have been reported on the destannylation of vinylstannanes. With compounds stable under acidic conditions, the reaction can be achieved with CF_3COOH <1999JOC1447, 2001JOC7385, 2002T9117>, TsOH <1999JOC5377, 1995JOC4595>, aqueous HCl <1998T12807, 1995SC1921> (Equation (113)), or EtOH , HCl(g) <1996JOC1354>. Nucleophilic conditions using reagents such as K_2CO_3 in MeOH , <1996TL8199>, NaOMe in MeOH , or CsF in MeOH-NH_3 <1996T45> (Equation (114)) were also reported to produce the desired cleavage. In the case of sensitive compounds such as alkyl enol ethers, thioenol ethers <1999JCR(S)290, 1997SL1165>, and seleno-enol ethers (Equation (115)) <1999SL1055> transmetallation followed by hydrolysis appears to be a more appropriate method.



Reduction of a vinylstannane has been reported to occur during the cleavage of a *p*-methoxybenzyl ether by DDQ (Equation (116)) <2000TL2821>. The use of AgOTf was also reported to be efficient (Equation (117)) <1995T3997>.



1.10.2 ONE OR MORE =C—H BONDS BY ADDITION

1.10.2.1 Addition to Alkynes

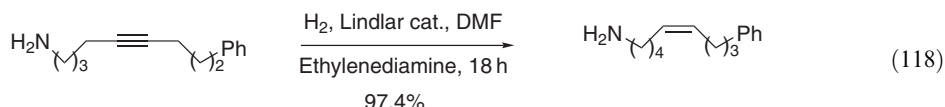
1.10.2.1.1 Addition of hydrogen to alkynes

Numerous methods have been reported for the semihydrogenation of alkynes. The main methods consist in addition of hydrogen to alkynes in the presence of heterogeneous or homogeneous catalysts, or by using dissolving metal reductions. Currently, there is increased interest concerning catalytic transfer of hydrides induced mainly by palladium catalysts or low-valent metals. Transition metal hydride reductions and addition of diimide are much less used.

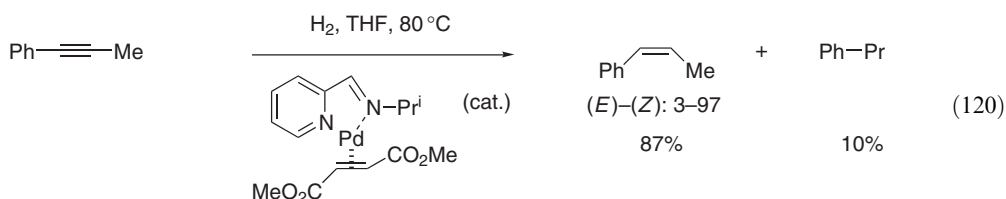
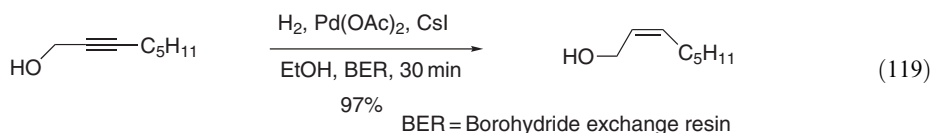
(i) Formation of (*Z*)-alkenes

One of the most popular conditions for the reduction of alkynes to (*Z*)-alkenes is the use of heterogeneous catalysis. Generally, Pd-, Pt-, and Ni-based catalysts are used. Homogeneous catalysts such as the Wilkinson's catalyst ($\text{RhCl}(\text{PPh}_3)_3$), or other Rh-, Ir-, Cr-, Fe, Ti-catalysts are also reported to lead to (*Z*)-alkenes. Transition metal salts such as $\text{CoCl}_3 \cdot 4\text{PPh}_3$, SmI_2 in the presence of alcohols as proton source, or copper(I) hydride gave satisfactory results. Reduction with diimine or hydrometallation with B, Al, and Zr compounds followed by hydrolysis is also interesting in the preparation of (*Z*)-alkenes. All these methods are discussed in COFGT (1995).

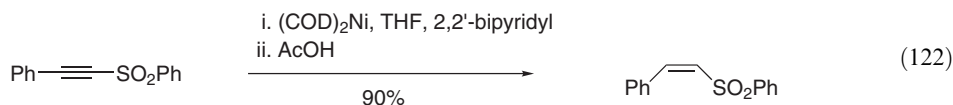
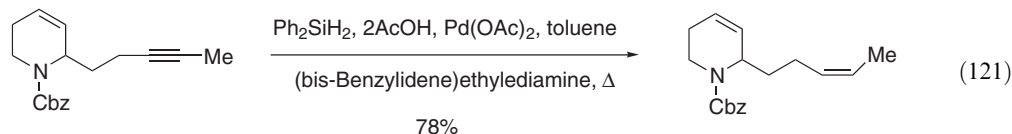
Currently the most frequently used catalysts for the semihydrogenation of alkynes to alkenes are the Lindlar catalysts, usually poisoned with a base such as quinoline and P-2Ni ($\text{Ni}(\text{OAc})_2$ – NaBH_4 mixture) <1973CC553, 1973JOC2226>. Their success is probably due to their availability and the facility to carry out the reactions. New conditions for the use of the Lindlar catalyst have been reported. Ultrasound irradiations are claimed to lower the hydrogenation time <1996SC3809>. In the presence of ethylenediamine, this catalyst was reported to improve the hydrogenation of acetylenic compounds functionalized by free amines (Equation (118)) <2001JOC3634>.



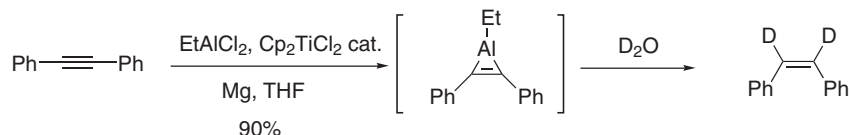
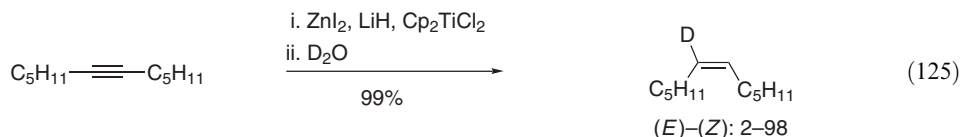
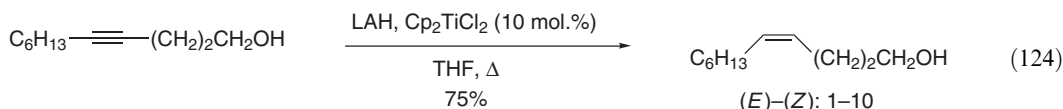
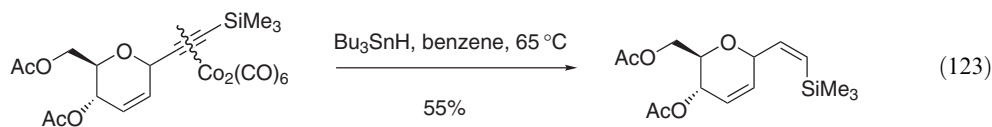
Supported P-2 Ni on Amberlite resin was reported to have increased reactivity when compared to the nonsupported reagent <1996TL1057>. New supported Pd heterogeneous catalysts have been reported to give excellent stereo- and chemoselectivities. $\text{Pd}(\text{OAc})_2$ supported on a borohydride exchange resin (BER) in the presence of CsI led to fast formation of (*Z*)-alkenes (Equation (119)) <1996TL8527>. Excellent stereoselectivity was also reported with a silica-supported Pd–Cu catalyst <2001JOC1647>, and Pd supported on pumice <2001TL2015>. Copper supported on $\gamma\text{-Al}_2\text{O}_3$ led at 150°C under pressure (80 atm) to produce clean (*Z*)-alkenes <1996MI1057>. The reduction of alkynes under homogeneous catalysis is often carried out, using the easily available Wilkinson's catalyst. In this field, new and more or less sophisticated complexes have been tested, based on Pd (Equation (120)) <2002OM1546> or $\text{Rh}(\text{Rh}(\text{dppe})_2(\text{BF}_4)_2)$ <2002AG(E)1607>.



Reductions without hydrogen gas have been reported by using diphenylsilane as hydride source, and $\text{Pd}(\text{OAc})_2$ as catalyst (Equation (121)) <1996TL8787> (see also <1989TL4657>). With diaryl alkynes, utilization of the same catalyst ($\text{Pd}(\text{OAc})_2$) and NaOMe in THF as hydride source also led to the formation of (Z)-alkenes. If the reaction was carried out in MeOH, over-reduction to alkanes was observed <2003TL1879>. Yus found that in the presence of NiCl_2 , Li-naphthalene added to alkynes to produce, after hydrolysis, (Z)-alkenes <1997TL149>. $(\text{COD})_2\text{Ni}$ in the presence of 2,2'-bipyridyl added similarly to alkynes (Equation (122)) <1998T1169>.



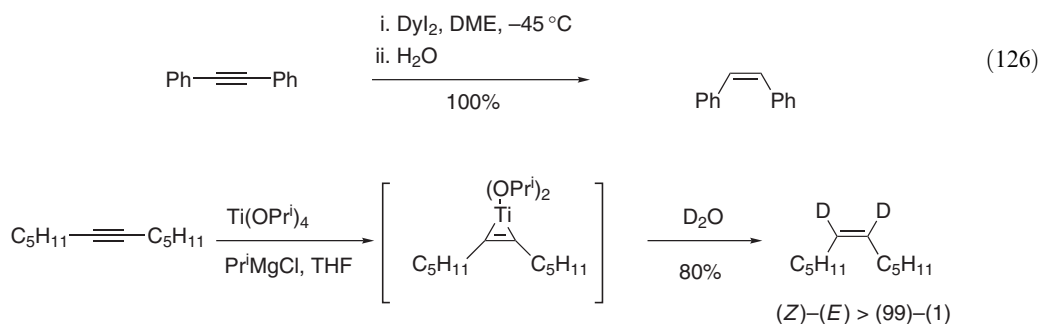
Zn activated by sonoelectrolysis <1999EJO2845>, or by a mixture of Cu–Ag <1994JPR714, 1989TL4951> was found to add to alkynes. This second method appeared particularly interesting for the reduction of polyacetylenic compounds. The use of the homogeneous catalyst $\text{Ru}_2(\mu\text{-CO})(\text{CO})_4(\mu\text{dppm})_2$ in the presence of HCOOH as hydrogen source reduced deactivated alkynes <2001CJC915>. Isobe and co-workers reported that alkynes complexed by $\text{Co}(\text{CO})_6$ reacted with Bu_3SnH to give (Z)-alkenes (Equation (123)) <1998TL2609>. Cp_2TiCl_2 catalyzed the addition of several reagents on alkynes. For example, in the presence of LAH, (Z)-alkenes were mainly formed (Equation (124)) <2002TL1231>. Addition of ZnH_2 (formed *in situ* from a mixture $\text{ZnI}_2\text{--}2\text{LiH}$), followed by hydrolysis with D_2O led to the incorporation of deuterium (Equation (125)) <1995JOC290>. Unsymmetrical alkynes led to regioselective addition. Cp_2TiCl_2 was also reported to catalyze the addition of organoaluminates. In this case, hydrolysis with D_2O led to the incorporation of two deuterium atoms (Scheme 14) <1997MI2150>. In the same way, treatment of alkynes with triallylmanganate led to the formation of manganese–alkyne complexes, which after hydrolysis affords the corresponding (Z)-alkenes <2003T9661>.



Scheme 14

The unusual dysprosium(II) iodide (DyI_2) was found to be a powerful reducing agent allowing the formation of (Z)-stilbene at low temperature (Equation (126)) <2000JA11749>. Sato and co-workers reported that when alkynes were treated with $\text{Ti}(\text{OPr}^i)_4$ in the presence of Pr^iMgCl intermediate titanates were formed, which after hydrolysis led to (Z)-alkenes (Scheme 15)

<1995TL3203>. This method was applied to conjugated polyalkynes (formation of enynes) <2002CC272> and skipped polyene systems <1998JCS(P1)1839> (for reviews on this work, see <2000CRV2835> and <2000SL753>). The well-known hydroboration of alkynes using mainly Cy_2BH is also a useful method for obtaining (*Z*)-alkenes after hydrolysis (see Section 1.10.1.6.2).

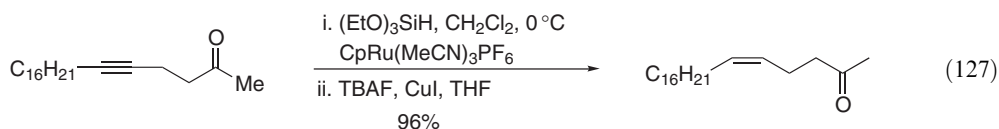


Scheme 15

(ii) Formation of (*E*)-alkenes

The reduction of alkynes to (*E*)-alkenes appears much more difficult and few examples are reported. Reactions of acetylenic alcohols with LAH, Red-Al, or in some cases NaBH_4 are well-known methods to produce functionalized (*E*)-alkenes. This stereoselectivity is observed whatever the relative position of the alcohol function compared to the triple bond in the chain. Similar reductions are possible with acetylenic amines. Another general method is the dissolving metal reduction. Metals such as Li, Na, Ca, and Yb have been used. This method has been recently re-examined and the best conditions, to carry out this reduction, was Li in liquid NH_3 in the presence of Bu^tOH . With skipped diynes, reductions were faster compared to mono-yne, however the addition of $(\text{NH}_4)_2\text{SO}_4$ was necessary to observe clean reactions <1999EJO775>.

To avoid the use of liquid NH_3 , amines such as EtNH_2 are often used with success <1995TL7689>. CrSO_4 in DMF was reported to reduce a triple bond to an (*E*)-alkene (see COFGT (1995)). It was found that $\text{Cr}(\text{OAc})_2$ was in some cases a better reagent <1995JA8106>. Trost and co-workers found that the *trans*-hydrosilylation of acetylenic compounds was catalyzed by $\text{CpRu}(\text{MeCN})_3\text{PF}_6$. Although this addition, in general, produces a mixture of the two regioisomers, the subsequent desilylation using TBAF in the presence of CuI led to (*E*)-alkenes in high yields (Equation (127)) <2002JA7922>, see also <2002CC2182>. The homogeneous catalyst $[\text{IrCl}(\text{H})(\text{BINAP})]_2(\mu\text{-Cl})(\mu\text{OMe})_2\text{Cl}$ was also reported to give the unique formation of (*E*)-alkenes, accompanied by over-reduction products <1999CC1821>.



1.10.2.1.2 Addition of C–H to alkynes

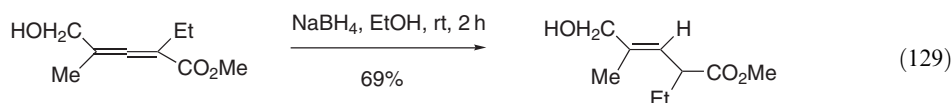
The addition of C–H to alkynes is reviewed in Chapter 1.1.2.

1.10.2.2 Addition to Allenes

1.10.2.2.1 Addition of hydrogen to allenes

Semi-hydrogenation of allenes to alkenes has been achieved by the general methods reported in the preceding chapter concerning the hydrogenation of acetylenic compounds. In general, heterogeneous (e.g., Lindlar catalyst) and homogeneous (e.g., $\text{RhCl}(\text{PPh}_3)_3$) catalysts can be used. In the

case of 1,2-dienes, only the terminal C—C double bond is reduced to give (*Z*)-alkenes. Reduction of these substrates with DIBAL-H led to the formation of the terminal alkenes (reduction of the internal C—C double bond). Dissolving metal reduction (Na in liquid NH₃) of 1,2-dienes led to (*E*)-alkenes by reduction of the terminal double bond. In the case of 1,3-disubstituted allenes, mixtures of reduction products corresponding to addition of hydrogen on the two C—C double bonds are usually observed. Hydrogenation of allenes is much less studied than the reduction of alkynes, and only few new results have been reported in the last period. Addition of LAH to dimethyl 2,3-pentadienoate was found to be *syn* (Equation (128)) <1995SL711>. Similar results were reported using NaBH₄ on a 2,3-pentenoate (Equation (129)) <2000JCS(P1)3188>.



1.10.2.2.2 Addition of C—H to allenes

The addition of C—H to allenes is reviewed in section 1.1.2.

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Biographical sketch

Gérard Rousseau was born in Versailles, France. He studied at the Orsay University, where he obtained his Ph.D. in 1977 under the direction of professor Conia on the reactivity of singlet oxygen with cyclopropanic compounds. After spending a year at Harvard with Professor R. B. Woodward (1978) he returned to Orsay and took a position at CNRS and started his independent research activity. There, his main research fields were the chemistry of ketene acetals, utilization of enzymes in organic synthesis, and, more recently, the preparation of medium-ring compounds. He is presently director of research. His main research interest is currently in the preparation of small- and large-ring heterocyclic compounds by electrophilic cyclization.

1.11

One or More =C—C Bond(s) Formed by Substitution or Addition

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1.11.1 INTRODUCTION

Since COFGT (1995), progress in the area of sp^2 $\text{C}=\text{C}$ bond-forming reactions has been phenomenal, due in a large part to the major developments in transition metal catalysis, particularly involving palladium. In some areas, activity has been so great that the space required to elaborate all aspects of progress would go well beyond the limits of this tome. In such cases, leading reviews are cited, and the reader is encouraged to consult them for more detailed presentations. Many of the methods described here may be applied to other bond-forming reactions covered in other chapters.

The structure of this chapter follows, as closely as possible, that of the corresponding contribution to COFGT (1995). This means that reactions in Section 1.11.2 are classified strictly according to the atom which is replaced, rather than the precise nature of the reactive intermediates involved. Furthermore, many substitution reactions can be regarded in terms of both reacting functions and to avoid repetition they have been treated once only. As far as possible, the “priority order” adopted here is the displacement of H(alkene), B/Si/Ge/Sn, N/O/chalcogen, halogen, H(arene), and finally metal.

In Section 1.11.3, although some of the starting materials appear as propargylic compounds, the intermediacy of an allene is authentic. There are a good number of electrocyclic processes that involve simultaneous creation of an sp^2 $\text{C}=\text{C}$ bond and other multiple bonds and/or functional groups; these reactions are treated in other chapters.

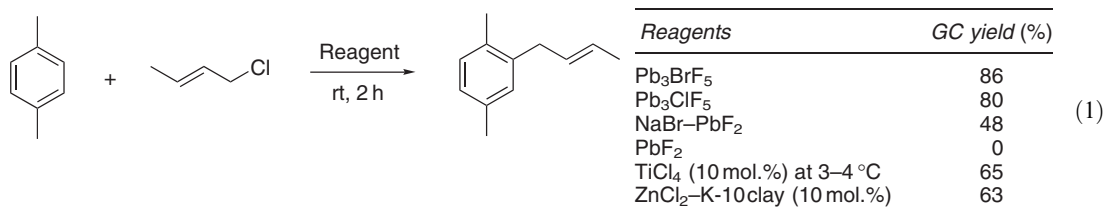
1.11.2 BY SUBSTITUTION

1.11.2.1 Substitution of Halogen

1.11.2.1.1 Substitution of alkyl halides

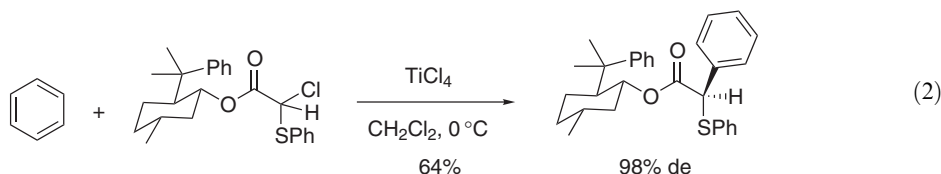
(i) Friedel–Crafts alkylation

Since the 1990s, the Lewis acid-catalyzed alkylation of aromatic hydrocarbons with alkyl halides (and other electrophiles; see appropriate later sections) has continued to enjoy widespread application in organic synthesis. Recent developments in Friedel–Crafts alkylation methodology have been shaped by several important issues: the quest (indeed, requirement) for atom economy, environmental-friendly reagents and reusable materials capable of promoting high-yielding, selective monoalkylation reactions. Particularly in the heavy chemicals industry, traditional Friedel–Crafts catalysts such as AlCl_3 have the disadvantage of being destroyed by aqueous work-up, thus liberating large amounts of hazardous waste. There is also a trend away from the use of alkyl halides, toward “cleaner” alkylating agents such as alcohols or alkenes (see later sections). Although recent advances are of major industrial significance (as testified by a voluminous patent literature), the general synthetic applicability of the new catalyst/operating systems is often uninvestigated—frequently, only one or two simple (albeit industrially important) arene/halide combinations are studied. The potential uses (or limitations) of these new systems in reactions involving multifunctional compounds currently remain largely unexplored. One of the busiest areas of development is in the use of solid catalysts based on acidic clays <1995IJC(B)257, 1997AC(A)(149)257, 1999PJS56, 1999SC4409>, mesoporous zeolites <1998AC(A)(196)29, 2001AC(A)(218)25, 2001MI155, 2001MI509, 2002OPRD256>, and sol–gel-derived silicas, aluminas, or aluminosilicates <1997JCS(F)2439, 1998JCS(F)789, 1998CJC382, 1999MI199, 2000MI164>, optionally modified by the exchange of cations and/or doped with acidic metal halides. These cheap materials promote high selectivity and efficiency under mild conditions, although the surface Lewis acidity and the pore size and shape are critical. Other useful solid catalysts for simple Friedel–Crafts alkylations include iron-containing graphite <2001JCA(201)105>, transition metal-doped phosphates <1996CL721, 2001AC(A)(218)25>, and spinel-type materials <1998AC(A)(166)135, 2001MI331> some of which tolerate the presence of water in the reaction medium. Selective monoalkylation of aromatics with allyl halides, a particularly tricky operation, has been achieved using a solid composite reagent Pb_3BrF_5 (Equation (1)) <1997CC1921> or the solid acid–solid base reagent combination $\text{ZnCl}_2\text{--SiO}_2/\text{K}_2\text{CO}_3\text{--Al}_2\text{O}_3$ <1995CC1895>.



Although rare earth metal triflates have enjoyed greater application in Friedel–Crafts alkylations using oxygen-based electrophile precursors (see Section 1.11.2.2.1(i)), Sc(OTf)₃ and Hf(OTf)₄ are also effective in the reactions involving alkyl halides and can be recovered without loss of activity <1995BCJ2053, 2000BCJ2325>. Yb(OTf)₃ catalyzes the efficient alkylation of benzene aromatics with ethyl α -chloro- α -(ethylthio)acetate; the subsequent desulfuration of the alkylation products represents the formal introduction of an ethyl acetate equivalent onto the aromatic ring in electrophilic form <2000TL9109>. A variety of lanthanide chlorides—themselves poor Friedel–Crafts catalysts—furnish highly active, long-life catalysts for arene alkylation with alkyl chlorides when supported on K-10 clay; silica-based reagents are less reactive <1998CR(C)41>. Gallium triflate is a water-tolerant, reusable, Lewis acid catalyst; it is more active than rare earth metal triflates in the alkylation of toluene with adamantyl bromide <2003MI1>. Other new catalysts include rhenium complexes <2000BCJ2779> and a chlorosilane/InCl₃ combination <2002T8227>, while *p*-toluenesulfonic acid monohydrate compares well with conventional acid reagents in the alkylation of benzene and toluene <1998JOC2858>.

Other areas of activity include the preparation of a wide range of (chlorosilyl)alkyl benzene derivatives from the corresponding chloroalkyl chlorosilanes <2000AOC145> and AlCl₃-induced simultaneous halide exchange/regiospecific alkylation of aromatics with (trifluoromethyl)arenes giving diaryldichloromethanes <1996TL4063>. Microwave irradiation assists the alkylation of naphthalene using halide derivatives; only a small quantity of nitromethane is necessary to initiate the reaction <2001SC3309>. Lewis acid-catalyzed asymmetric Friedel–Crafts alkylation of aromatics with chiral esters of α -chloro- α -(phenylthio)acetic acid allows access to useful chiral 2-aryl-2-thioethanol synthons (Equation (2)) <2000TA2267>.



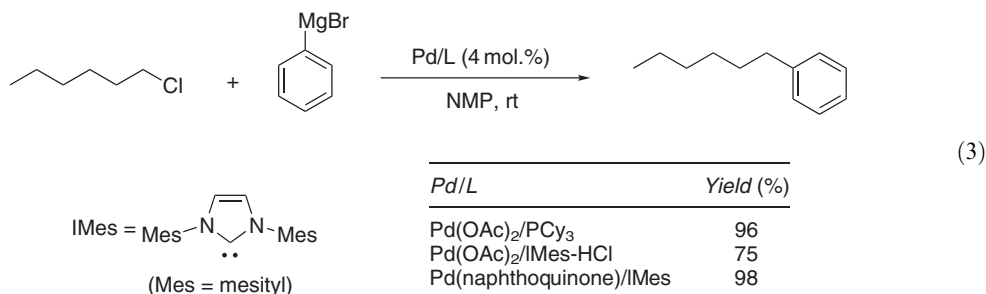
(ii) Substitution by organometallic sp^2 carbanions

Since the 1990s, studies on a wider selection of alkyl halides and vinyl or aryl organometallic reagent combinations have focused on activation, higher functionalization, increased efficiency, use of milder conditions, and improved stereoselectivity and chemoselectivity in their cross-coupling reactions. These improvements have led to widespread application in total synthesis.

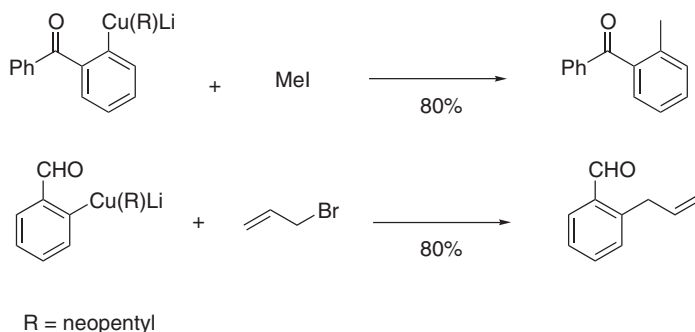
Organolithium species, whose pioneering use by Murahashi is summarized in a historical note <2002JOM(653)27>, have been readily superseded by Grignard reagents <B-1996MI001> and other organometals: B, Si, Sn (see Sections 1.11.2.5 and 1.11.2.6) and Zn, Al, Zr, In <B-2002MI001>. Because of their high intrinsic reactivity, organolithiums do not tolerate many conventional polar functional groups and metal-catalyzed alkenylation or arylation with lithium derivatives remains rather limited.

Grignard reagents, which are more compatible with many functional groups than previously thought, are widely used (both with and without Ni or Pd catalysts) in Kumada–Corriu coupling reactions with alkyl halides, and are well reviewed <2000AG(E)4414, B-2002MI27, 2003AG(E)4302>. Some industrial applications of Grignard cross-coupling reactions are known <2002JOM(653)288, B-2002MI165>. That being said, most alkyl halides involved in such Pd(0)-catalyzed coupling reactions are activated compounds lacking β -hydrogen (benzyl, allyl, propargyl halides) <B-2002MI551>; exceptions are rare. In the catalytic process, Pd(0) undergoes ready oxidative addition to β,γ -unsaturated

alkyl electrophiles, allowing an efficient cross-coupling reaction. In the case of saturated alkyl or even γ,δ -unsaturated alkyl electrophiles, this oxidative addition is more difficult. Furthermore, the metalloalkyl intermediates can readily undergo β -dehydrometallation to give alkenes. These two factors have made it traditionally difficult to achieve metal-catalyzed cross-coupling of sp^3 halides <2000CRV3187>. The ability to couple unactivated alkyl electrophiles has therefore dramatically expanded the scope of the cross-coupling process. Substitution of a wide range of unactivated primary alkyl chlorides, optionally containing various functional groups (ethers, esters, acetals, fluorides, nitriles), by aryl Grignard compounds is achieved with good yield in NMP as solvent in the presence of a $\text{Pd}(\text{OAc})_2/\text{PCy}_3$ catalyst <2002AG(E)4056> and, even more efficiently, by using a palladium/*N*-heterocyclic carbene catalyst (Equation (3)) <2003JOM(687)403>. Even unactivated alkyl fluorides can now be arylated by Grignard reagents via Ni or Cu catalysis <2003JA5646>. However, more sensitive functions (ketones or aldehydes) are, predictably, incompatible with Grignard reagents.



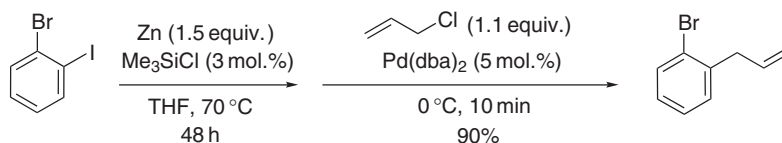
Organocopper reagents attract continued interest <1995JOC2361, B-2002MI002>, including use in industry <2002JOM(653)288>. The most commonly used reagents are obtained by the treatment of aryl or vinyl halides with $\text{CuCN}\cdot 2\text{LiCl}$, in either catalytic or stoichiometric amounts, sometimes in the presence of additives (e.g., trimethylphosphite) <B-1999MI317, 2001OL2871>. Use of the sterically hindered organocuprates, neopentyl $_2\text{CuLi}$ or neophyl $_2\text{CuLi}$, facilitates halide-copper exchange in the presence of sensitive groups, including ketones and aromatic aldehydes (Scheme 1) <2002AG(E)3263>.



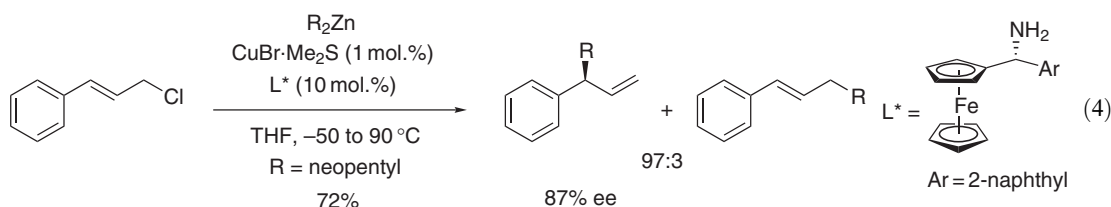
Scheme 1

Progress in metal-catalyzed $\text{C}-\text{C}$ bond formation has been dominated by the Negishi reaction, namely palladium- or nickel-catalyzed cross-coupling through the use of organometals involving metals of intermediate electronegativity (Zn, Al, Zr) <B-2002MI229>. Numerous factors are responsible for this increasing interest: (i) easy access to the required organometals <2002S2473, 2000AG(E)4414>; (ii) the high chemo-, regio-, and stereoselectivities of cross-coupling reactions using these reagents; and (iii) practical advantages deriving from their ease of handling and low cost. Zinc has emerged as a particularly appealing metal since the 1990s <B-1996MI274, B-1999MI213, 2002JOC79>. Organozinc derivatives have an almost covalent $\text{C}-\text{M}$ bond and are therefore less reactive than organolithium or organomagnesium reagents and are compatible with the presence of a large number of other functions in substrates; a wide range of applications are reported <B-2002MI863>. $\text{NiCl}_2(\text{PPh}_3)_2$ is a selective catalyst for the reaction between (monochloro) phenyl zinc chloride and benzylic halides, whereas for more hindered nucleophiles a palladium catalyst is recommended <1998T2953>. One-pot formation of functionalized aryl zinc iodides then

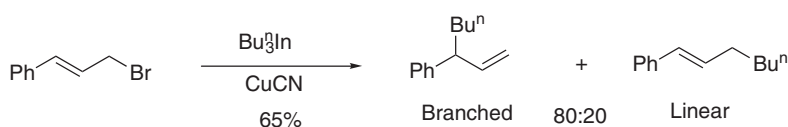
palladium-catalyzed cross-coupling with allylic bromides and chlorides (Scheme 2) <2003JOC2195> or tandem vinyl zinc formation/Cu-mediated vinylation of allylic chlorides <2001SL123> can be performed. Aryl zinc iodides react with methyl iodide under rhodium catalysis in the presence of diverse phosphine ligands <1999CL1241>. Diorganozincs are useful for asymmetric reactions: one of the most significant advances is the copper(I)-catalyzed substitution of unsymmetrical allyl chlorides with diaryl zinc proceeding with S_N2' regioselectivity and moderate-to-good enantioselectivity (up to 87%) using a ferrocenyl amine as a chiral ligand (Equation (4)) <1999AG(E)379>.



Scheme 2



Organoaluminum compounds have useful synthetic applications, their main interest arising from the ease of control of the (*Z*)- or (*E*)-configuration of a substituted alkenyl moiety in such reagents, and the retention of this configuration during cross-coupling with active alkyl halides <B-2002MI863>. Indium also attracts some attention, with its low toxicity and a generally selective reactivity profile <2000EJO2347>. Readily accessible trivinyl and triaryl indium compounds can be used in the substitution of activated allylic halides (as well as acetates and phosphates) with a copper catalyst (Equation (5)) <2003JOC2518> or benzyl bromide using palladium catalyst <2001JA4155>. Cross-coupling reaction between pentaaryl antimony and allylic halides can be performed under palladium or nickel catalysis <1996JOM(525)39>.



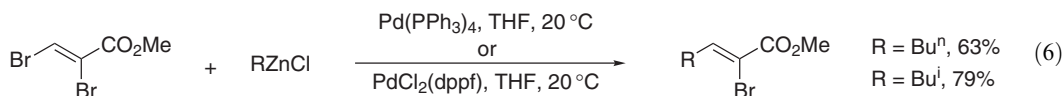
<i>Cu cat., L</i>	<i>Yield (%)</i>	<i>Ratio branched/linear</i>
CuCN	65	80/20
Cu(OTf) ₂	40	72/28
CuBr·SMe ₂ , P(OEt) ₃	33	68/32
CuCN, P(OEt) ₃	50	88/12
Cu(OTf) ₂ , P(OEt) ₃	85	82/18

1.11.2.1.2 Substitution of vinyl halides

(i) Alkyl nucleophiles

Metal-catalyzed cross-coupling reactions between homoallyl, homopropargyl, or homobenzyl metals and alkenyl electrophiles are reviewed <B-2002MI619>. Palladium-catalyzed vinyl halide cross-coupling reactions involving saturated alkyl metals (Li, Mg) are well documented <2002JOM(653)27, B-2002MI597>, although they are often surpassed by other organometals <B-2002MI285>. The high reactivity of organolithium compounds often precludes the need for catalysis. Palladium-catalyzed reactions with alkyl lithiums are in any case rather limited and nickel catalysts are incompatible with organolithium reagents. Alkyl magnesium compounds remain popular alkylating agents.

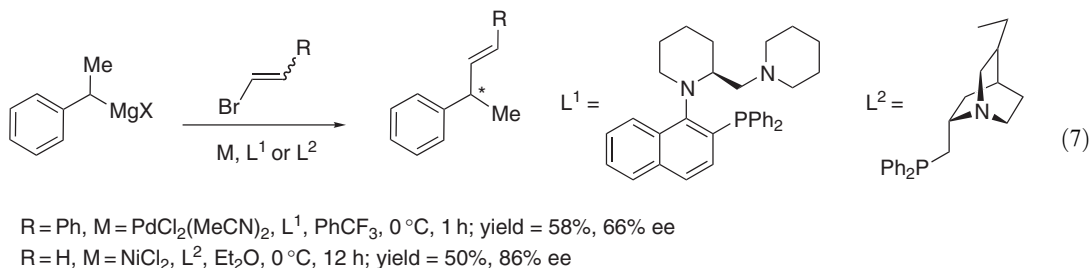
Considerable progress has been made with zinc reagents. Dialkyl zincs show ever-increasing importance and are extensively studied by the Negishi and Knochel groups <1998T8275, B-1998MI387, B-1999MI179, B-2002MI229>. Dialkyl zinc compounds are easily accessible by efficient, chemoselective, and clean carbozincation or hydrozincation of alkenes <1995TL1023, B-1996MI002, B-1999MI77>. Isoalkyl zinc reagents readily undergo palladium-catalyzed cross-coupling reactions with alkenyl halides, in contrast with isoalkyl magnesiums or isoalkyl alanes which react only sluggishly or not at all <2000OM2417>. While α -iodo α,β -unsaturated ketones cross-couple smoothly with alkyl zinc reagents <1999JOM(576)179>, studies by Rossi and co-workers <1998T135> reveal that the reactions between α,β -dibromo α,β -unsaturated esters and organozincs take place preferentially at the β -position (Equation (6)). β -Iodoacrylic acid undergoes efficient substitution by alkyl and allyl zinc bromides without protection of the acid function <2002S543>. Indeed, organozinc reagents tolerate most carbonyl functions, with the exception of acyl halides, anhydrides, and aldehydes. Over a short period of time, they have become versatile tools for synthesis, as illustrated in the preparation of alkenyl cyclopropanes <2002T3673>, pumiliotoxins <2002JOM(653)229>, discodermolide <2001OL3281> as well as various isoprenoids <B-2002MI863>.



While palladium and nickel are the most often used metals for catalysis of cross-coupling reactions involving Grignard and organozinc reagents <B-1998MI227>, other transition metals (Cu, Fe, Co) can also be used. Cobalt-catalyzed cross-coupling of organozinc halides or diorganozincs with (*E*)- or (*Z*)-alkenyl iodides lead to polyfunctional alkenes with complete retention of the stereochemistry of the double bond <1998TL6163>. Grignard reagents undergo efficient and stereoselective cross-coupling reaction with vinyl halides (I, Br as well as Cl) in the presence of a cobalt(II) catalyst and a polar solvent (NMP or DMPU) <1998TL6159>. However, cobalt is less efficient for the introduction of a tertiary alkyl group because of competitive β -elimination. Copper(I) and iron(III) catalysts both give satisfactory results for cross-coupling reactions involving organomanganese or Grignard reagents <1996TL1773, 1998S1199>. There is still much to do in this area.

Progress with group 13 metals is more limited. Heteroatom-stabilized complexes of methyl aluminum and methyl gallium are particularly amenable to the palladium-catalyzed methylation of vinyl halides (Br, I) <1997JOC8681>. Allyl indiums couple with alkenyl halides or *gem*-dibromoalkenes in the presence of Pd(PPh₃)₄/LiCl. S_N2 and S_N2' processes compete, resulting in low selectivity <2002JOC8265>.

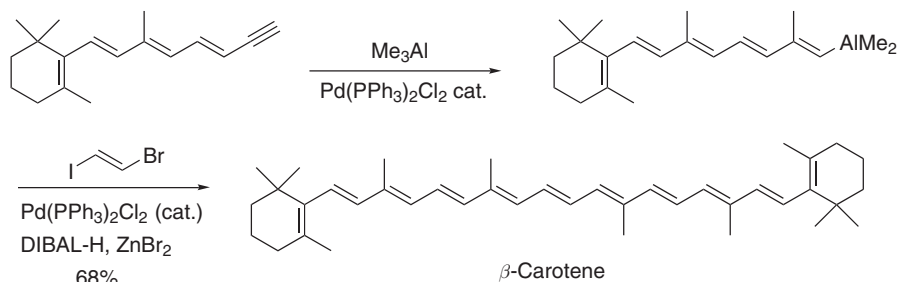
The cross-coupling reaction can be neatly adapted for asymmetric induction at the organometallic *sp*³-carbon center <2002JOM(653)41, B-2002MI791>. Stereoselective protocols are extensively developed for secondary alkyl Grignard reagents in the presence of palladium catalysts bearing chiral phosphine ligands, including ferrocene-based structures <B-1995MI105, 1998CEJ950, 2000AG(E)4414> and β -(dialkylamino)alkylphosphines <1997CB989, B-1999MI887>. *P,N*-Ligands, derived either from axially chiral piperidine-naphthalenes <2003SL2047> or quincorine and quincoridine, in which the nitrogen is a stereogenic center <2002JOM(643)98>, give good results in palladium- or nickel-catalyzed asymmetric cross-coupling reactions (Equation (7)).



(ii) Alkenyl nucleophiles

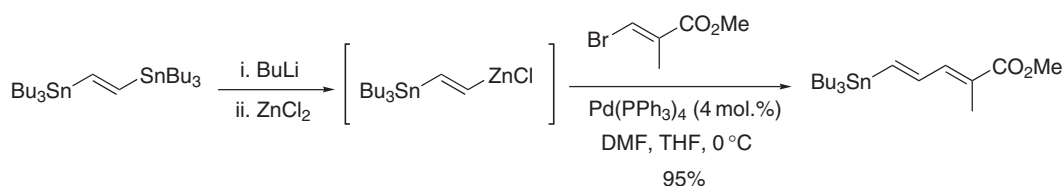
After a slow start, alkenyl–alkenyl coupling now represents a highly efficient, selective methodology for the construction of stereodefined substituted conjugated dienes <B-1998MI1, B-2002MI229, B-2002MI335, 2002JOM(653)34>. Almost all combinations of alkenyl metals

(Li, Mg, Zn, B, Al, Si, Sn, Cu, Zr) and alkenyl electrophiles can be achieved via a Pd- or Ni-catalyzed cross-coupling process, which respects the stereochemistry of each reacting alkenyl moiety. Furthermore, many of the alkenyl metal and alkenyl electrophile reagents can be prepared conveniently with a high degree of stereoselectivity. The reaction proves particularly useful in natural products synthesis [<B-2002MI863>](#) and in the preparation of polyconjugated materials ([Scheme 3](#) [<B-2002MI807>](#)).

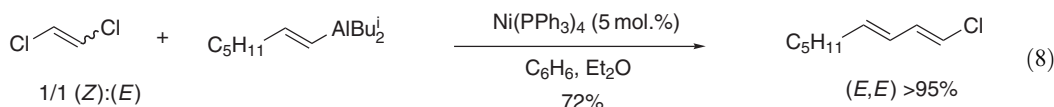


Scheme 3

The methodology is readily extended to 1,1-bimetallic alkenes [<2000CRV2887>](#). Some degree of chemoselectivity is observed when two different metals are present in the same alkene: for example, in the palladium-catalyzed reaction of methyl (*E*)- β -bromomethylacrylate with (*E*)- $\text{Bu}_3\text{SnCH}=\text{CHZnCl}$, reaction occurs exclusively at the zinc center, providing a conjugated dienyl stannane which can be further engaged in a Stille reaction ([Scheme 4](#) [<1999SL1966>](#)). Likewise, the smooth cross-coupling of an α -bromo- α -alkenyl stannane with an alkenyl zirconium gives a 1,3-dienyl stannane [<2003JOM\(687\)462>](#). Di- and trihalogenoalkenes, too, can be coupled, often chemoselectively and with retention of configuration, to provide di-, tri-, or tetrasubstituted alkenes; both 1,1- and 1,2-dihalogenoalkenes are useful in this regard [<2000S1499, B-2002MI649>](#). For example, palladium-catalyzed cross-coupling of an alkenyl zirconium with a 1,1-dibromoalkene provides a key (*Z*)-monobromo intermediate in a total synthesis of the antibiotic lissoclinolide [<1999TL431>](#). Palladium-catalyzed reactions involving alkenyl halides usually proceed with retention of configuration; however, unprecedented inversion of configuration is reported with 2-bromo-1,3-dienes [<2003JA13636>](#). In certain cases, the double bond configuration can be imposed during the cross-coupling reaction; for instance, a (*E,E*)-1-chloro-1,3-diene is obtained when a (*Z*)/(*E*)-1,2-dichloroalkene mixture is cross-coupled with an alkenyl alane under nickel catalysis ([Equation \(8\)](#) [<2002TL3007>](#)).



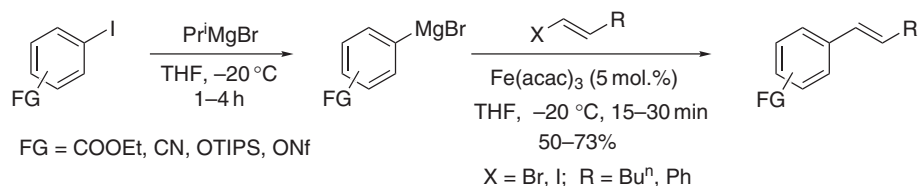
Scheme 4



(iii) Aryl nucleophiles

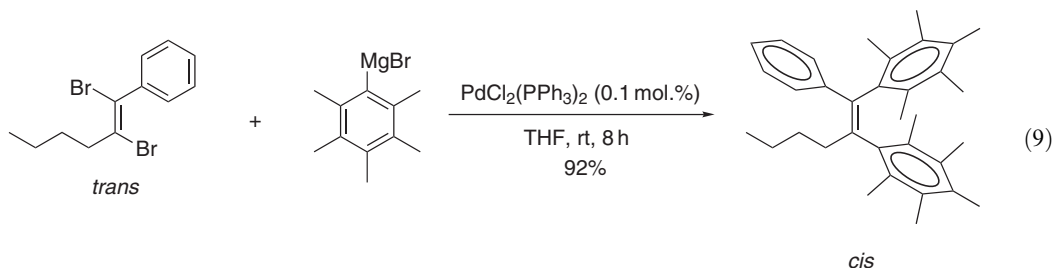
Methodologies for palladium- or nickel-catalyzed aryl metal–alkenyl halide cross-coupling are similar to those used for alkenyl–alkenyl coupling (see [Section 1.11.2.1.2.\(ii\)](#)) and are equally well reviewed [<2002JOM\(653\)23, B-2002MI335>](#). This is one of the two cross-coupling synthetic strategies for the construction of an aryl–alkene bond, the other being aryl halide–alkenyl metal

(see Section 1.11.2.1.3.(ii)). The choice generally comes down to the relative ease of access of the appropriate substrate partners. The majority of aryl nucleophiles containing electropositive metals (Li, Mg, but also Zn) are prepared by oxidative metallation of aryl halides, while those containing metals of intermediate electronegativity (B, Al, Si, Cu, Sn, Zn) are often generated by transmetalation <2000AG(E)4414, 2003AG(E)4302>. New catalysts, such as the commercially available, air-stable complex $\text{Pd}(\text{PBU}_3)_2$, improve the performance of Negishi cross-coupling with sterically demanding vinyl chlorides and aryl zinc reagents <2001JA2719>. Aryl Grignard reagents couple smoothly with alkenyl halides under Fe(III) catalysis (Scheme 5) <2001SL1901>.



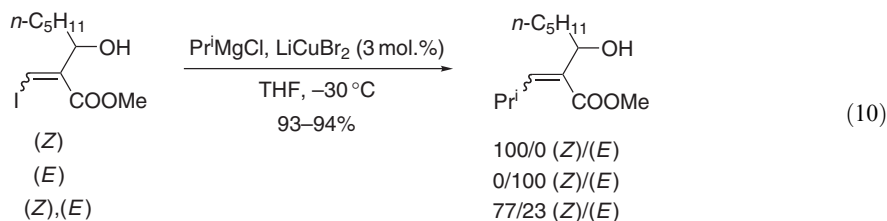
Scheme 5

Dihaloalkenes, again, are versatile synthetic building blocks. For example, efficient stereoselective access to the more hindered *cis*-1,2-diarylalkenes from readily available *trans*-1,2-dibromoalkenes is achieved under palladium catalysis even when sterically demanding electrophiles or nucleophiles are involved (Equation (9)) <2002JA14832>. Intramolecular *o*-alkenylation of phenolates can be achieved with vinyl halides in the presence of a Pd catalyst, allowing access to the substituted heterocycles (indoles, benzofurans, or benzopyrans) <1997TL6379>.



(iv) Addition–elimination displacements of vinyl halides

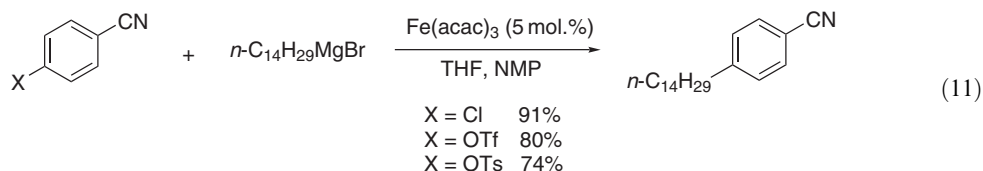
The substitution of haloalkenes by cuprate reagents is facilitated by the presence of a vicinal electron-withdrawing group which permits an addition–elimination process, and generally does not require a catalyst <B-1999MI179, B-2002MI27>. The (*Z*)/(*E*) stereochemistry of the mono-substitution of 3,3-dichloro-1-(trimethylsilyl)-2-propenone using organo(cyano)cuprates such as $\text{RCu}(\text{CN})\text{M}$ or $\text{R}_2\text{Cu}(\text{CN})\text{M}_2$ (where R = alkyl or aryl, M = Li or MgCl) varies with the identity of R; during the second substitution (if carried out), inversion of configuration dominates the reaction profile <1995T9823>. The addition–elimination pathway allows access to rare β -substituted Baylis–Hillman adducts: Grignard reagents in the presence of a catalytic amount of LiCuBr_2 couple efficiently and selectively with β -iodo- α -(hydroxyalkyl)acrylic esters with retention of configuration (Equation (10)) <2000T805>. However, limitations are sometimes encountered: for example, substitution of β -iodoacrylic acid with organocuprate reagents proceeds in low yield and with low selectivity, providing a mixture of (*Z*)- and (*E*)-isomers <2002S543>. In some cases, palladium-catalyzed cross-coupling with organomagnesium halide or organozinc may provide a more rewarding alternative.



1.11.2.1.3 Substitution of aryl halides

(i) Alkyl nucleophiles

This field is largely dominated by the use of palladium- or nickel-complex catalysts. Palladium-catalyzed cross-coupling involving saturated alkyl metals is reviewed <B-2002M1597>. The usual reactivity order is observed for the aryl electrophiles ($I > Br > OTf \gg Cl$), so for successful cross-coupling of aryl chlorides, “high-performance” ligands on palladium are usually required. However, ligand-free iron-catalyzed cross-coupling proceeds very smoothly and rapidly, for a variety of alkyl metals, with a modified order of reactivity for the aryl component ($Cl > OTf > OTs \gg I, Br$) (Equation (11)) <2002JA13856>. Lanthanide salts ($CeCl_3$, $Yb(OTf)_3$) are required as additives in the $PdCl_2(PPh_3)_2$ -catalyzed alkylation of aryl bromides with triethylalane <2003TL8593>. A heterogeneous Ni–C catalyst is described for Kumada–Corriu cross-coupling <2003JOC1177, 2003JOC1190>, although polymer-supported catalysts are not in as much profusion as for other transition metal-catalyzed coupling reactions (Heck, Suzuki, etc.). Ni(0)-catalyzed alkylation (or arylation) of polymer-bound substituted bromophenol by Grignard reagents is described as a means for the development of polymer materials <2000M157>. One example of a solid-supported alkyl zinc and its palladium-catalyzed coupling with aryl iodides is described <2000CC1401>. An interesting practical procedure for efficient removal of phosphine ligands at the end of a preparative reaction by a polymeric scavenger is described <2001OL1869>.



Methyl triisopropoxytitanium cross-couples smoothly with 2-bromonaphthalene in the presence of a Pd/ppfa catalyst (ppfa = *N,N*-dimethyl-1-[2-(diphenylphosphino)ferrocenyl]ethylamine), and also with 2-chloronaphthalene in the presence of $NiCl_2(PPh_3)_2$ <2002SL871>. Dialkyl and trialkyl indium reagents can transfer all their organic groups efficiently <2001JA4155>. *In situ*-generated allyl indium undergoes smooth palladium-catalyzed cross-coupling with aryl iodides <2001OL3201>. Dialkyl indiums couple with functionalized aryl halides (I, Br) under palladium catalysis in aqueous medium <2001OL1997>. To minimize homo-coupling, intramolecular heteroatom-stabilized aluminum, gallium, or indium alkylating reagents are available (Figure 1). In odd cases, reagents like these may substitute an aryl chloride in preference to a bromide <2000S571, 2000TL7555, 2001S591, 2003S302, 2003SL1783>.

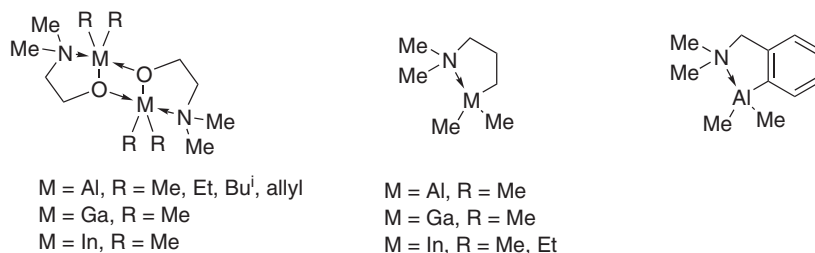


Figure 1 Intramolecular heteroatom-stabilized group 13 organometallic reagents.

Successful multiple-coupling reactions of polyfunctional aromatic compounds lead rapidly to elaborate molecular frameworks: diverse examples include polyhaloarenes <1995TL8565, 1997OPP137>, 2,3,5-tribromobenzofuran <2002TL9125>, and *sym*-pentachlorocorannulene <2003OL713>. Substituted aryl bromides and chlorides can be efficiently coupled with a variety of nitroalkanes in the presence of $Pd_2(dba)_3$ to give monoarylated products in good yield and selectivity <2002JOC106>.

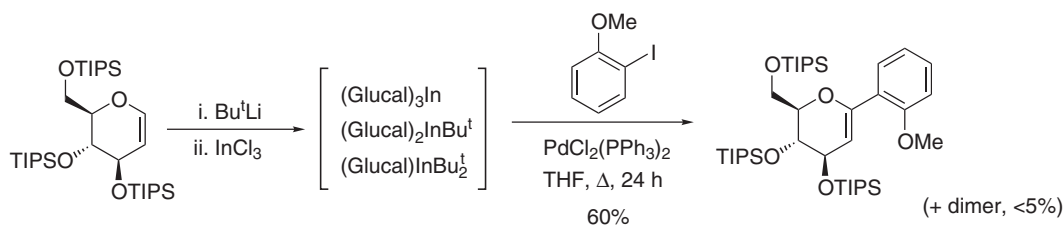
Progress in asymmetric arylation reactions is reviewed <2001AG(E)3284> and matches that described for alkyl metal–vinyl halide asymmetric cross-coupling processes (see Section 1.11.2.1.2.(i)).

In a rare noncatalyzed process, aryl iodides combine with lithium trimethylzincate to give mixed aryl dimethyl intermediates which furnish the corresponding tolyl compounds via oxidative ligand coupling upon treatment with $VO(OEt)Cl_2$ <2001JOC300>.

(ii) Alkenyl nucleophiles

Complementary to the alkenyl halide–aryl metal combination (see [Section 1.11.2.1.2.\(iii\)](#)), the success of this approach to aryl alkenes depends largely on the availability of the alkenyl metal; for Mg, Li, and Zn, most such species are now accessible. The various factors to be weighed up in a palladium- or nickel-catalyzed cross-coupling reaction have been intelligently discussed [<B-2002MI335>](#).

Alkenyl zirconium reagents, prepared *in situ* from terminal alkynes, react with aryl iodonium ions to provide (*E*)- β -substituted styrenes [<1998SC773>](#). Divinyl indium chloride cross-couples with aryl iodides in the presence of $\text{Pd}_2(\text{dba})_3 \cdot \text{CHCl}_3/\text{P}(2\text{-furyl})_3$ in aqueous THF [<2001OL1997>](#). *In situ*-generated tris(dihydropyranyl) indium reagents couple efficiently with aryl halides via $\text{PdCl}_2(\text{PPh}_3)_2$ catalysis to give substituted dihydropyrans ([Scheme 6](#)) [<2003OL2405>](#). Intramolecularly heteroatom-stabilized vinyl aluminum reagents undergo efficient palladium-catalyzed cross-coupling with bromo- and iodoarenes as well as more reactive chloroarene– $\text{Cr}(\text{CO})_3$ complexes [<2003SL1783>](#). *trans*-Alkenyl gallium dichlorides undergo efficient reaction with aryl halides (I, Br), while the *cis*-isomers do not provide coupling products [<2002S1137>](#).

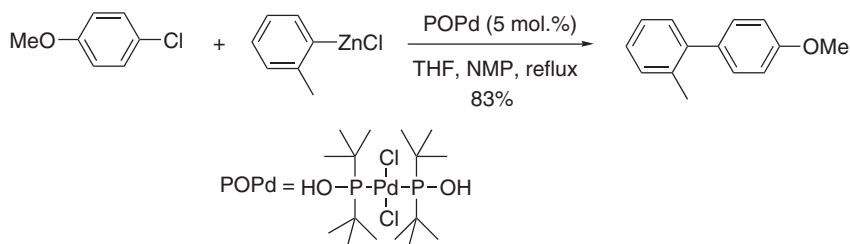


Scheme 6

(iii) Aryl nucleophiles

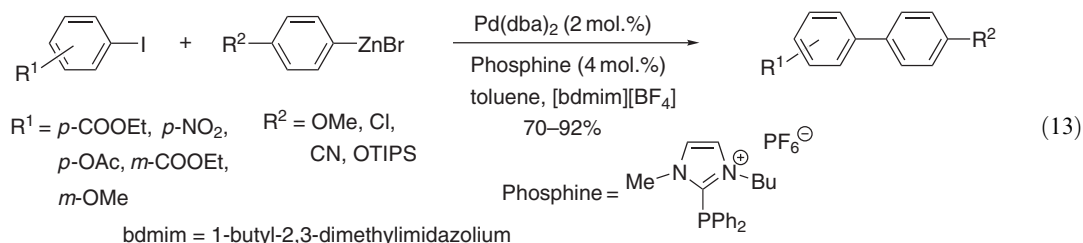
The largest part of those studies devoted to cross-coupling reactions since the 1990s has focused on aryl–aryl bond formation, since biaryls have widespread applications in diverse fields (pharmaceuticals, agrochemicals, dyes, polymers, specialist ligands for asymmetric synthesis, etc.). A vast range of aryl metals (Zn, Mg, Hg, Si, Ge, Pb, Bi, Sb, Cu, Zn, In, B, Sn) can be coupled with aryl halides under Pd, Ni, or Cu catalysis; inventories of, and comparisons between, the various approaches for (and applications of) aryl–aryl coupling techniques are extensively reviewed [<1998T263, 2001MI575, B-2002MI311, 2002CRV1359, 2003CRV3213>](#) along with progress reports in the particular area of axial chirality control [<2001AG\(E\)3284, B-2002MI791>](#).

Development of inexpensive and efficient air-stable ligands for palladium- or nickel-catalyzed cross-coupling reactions involving aryl chlorides is a major challenge: success is achieved with phosphinous acid ligands for palladium-catalyzed cross-coupling of either zinc [<2002JOC3643>](#) or Grignard [<2002JOM\(653\)63>](#) reagents ([Equation \(12\)](#)). Nickelocene is a useful precatalyst, obviating the problems associated with handling the air-sensitive reagents $\text{Ni}(\text{PPh}_3)_4$ and $\text{Ni}(\text{COD})_2$ [<2001JOC7539>](#). Unactivated aryl halides undergo straightforward cross-coupling reactions with aryl Grignard reagents mediated by a palladium/*N*-heterocyclic carbene catalyst [<1999JA9889>](#) or with aryl manganese chlorides in the presence of $\text{PdCl}_2(\text{dppp})$ [<2001JOM\(624\)376>](#). Aryl bismuth reagents cross-couple selectively in the presence of $\text{Pd}(\text{PPh}_3)_4$ with various (bromophenyl)boronic esters to give (biaryl)boronates, ready for consecutive one-pot Suzuki coupling [<2003AG\(E\)1845>](#). Although not often used, aryl lithiums benefit from the reinvestigating of a noncatalyzed coupling protocol [<2003CEJ3209>](#).

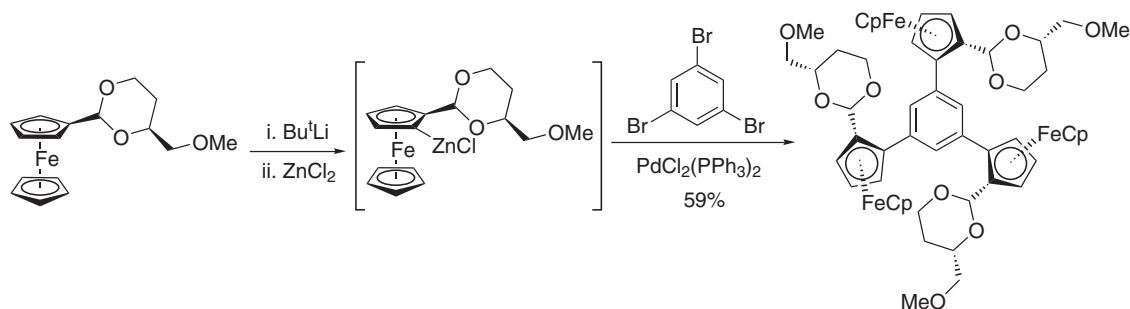


(12)

With appropriate reagents and catalysts, biaryl cross-coupling reactions may be conducted in aqueous medium <2001OL1997, B-2002MI2957>. Complexes derived from $\text{Pd}(\text{dba})_2$ and perfluorinated phosphines successfully catalyze the cross-coupling of aryl zinc bromides and aryl iodides in a biphasic system, thus facilitating catalyst separation and recycling after completion of the reaction <1997AG(E)2623>; similar advantages are observed in the use of an ionic liquid and an ionic phosphine ligand (Equation (13)) <2000SL1613>. Polymer-supported catalysts are viable <2001MI219>, although only a few solid-phase versions of biaryl cross-coupling are described <1996TL5491, 1997SL1084, 1999JCO123>.



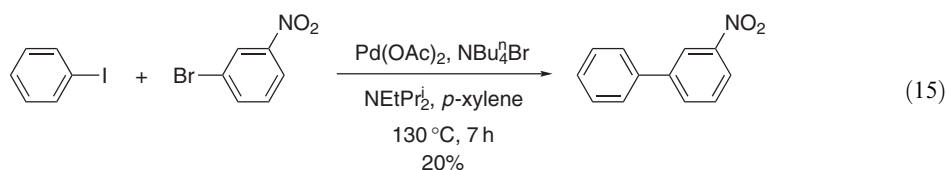
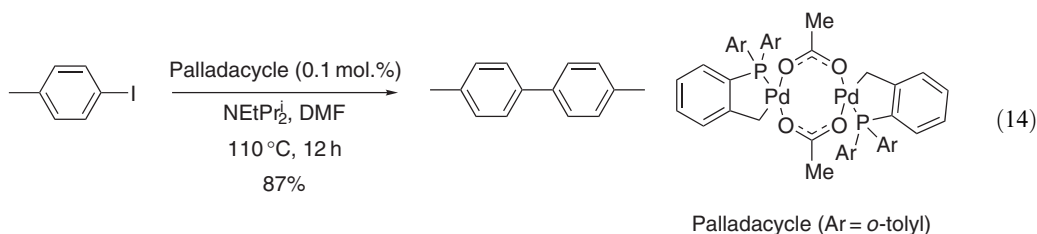
Arylation of heteroaryl halides (and triflates) is also widely practiced <B-2002MI409, 2002JOC8991, 2002TL3547, 2003EJO3948> and is a powerful tool for the synthesis of conjugated polymers <B-2002MI807>. The cross-coupling of ferrocenyl zinc chloride with *s*-tribromobenzene <1997CL35> finds useful application in the construction of molecular octupoles (Scheme 7) <2003S455>.



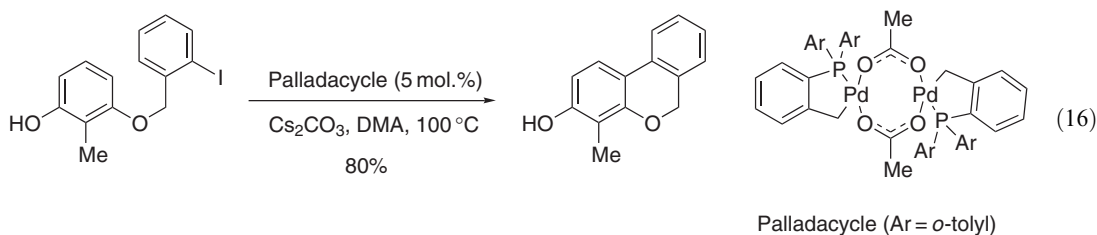
Scheme 7

(iv) Other methods

Recent applications of the reductive homo-coupling of an aryl halide through the action of copper (the Ullman reaction) and its numerous variations are reviewed <2002CRV1359>. Catalyzed aryl halide homo-coupling has several disadvantages: current methodologies are usually only effective with aryl iodides and activated bromides, require a rather large quantity of a catalyst (Pd or Ni, around 2–5%), and have a hard time competing with arene reduction reactions. Resolving these problems remains a challenge; however, efforts to achieve homo-coupling are usually rewarded through the use of a catalyst system derived from $\text{Pd}(\text{OAc})_2$ and phosphines (or arsines and ammonium salts), or a palladacycle (Equation (14)) <1998T13793, 1998TL7939, 2002TL2327>. A marked selectivity for cross-coupling leading to unsymmetrical biaryls is observed in the $\text{Pd}(\text{OAc})_2$ -catalyzed reaction of electron-rich aryl iodides with electron-poor aryl bromides, although isolated yields are moderate (Equation (15)) <2001T7845>. New developments of previously known nickel(0)-based reductive methods are described <1999JCR(S)664, 1999TL5993, 2000TL10319>, including the use of a catalytic amount of a zero-valent nickel complex without an added reducing agent <1999TL4243>. Transient formation of tin or boron metallo-intermediates may facilitate the coupling reaction. For example, binaphthyl formation from 1-iodo-2-methoxynaphthalene can be performed via an *in situ* Suzuki reaction <1996JOC9556> while intramolecular Stille–Kelly cross-coupling of bis(bromoaryls) in the presence of $(\text{Me}_3\text{Sn})_2$ and $\text{Pd}(\text{PPh}_3)_4$ gives a 17-membered biaryl macrocycle, albeit in moderate yield (17%) <2001H(54)259>.

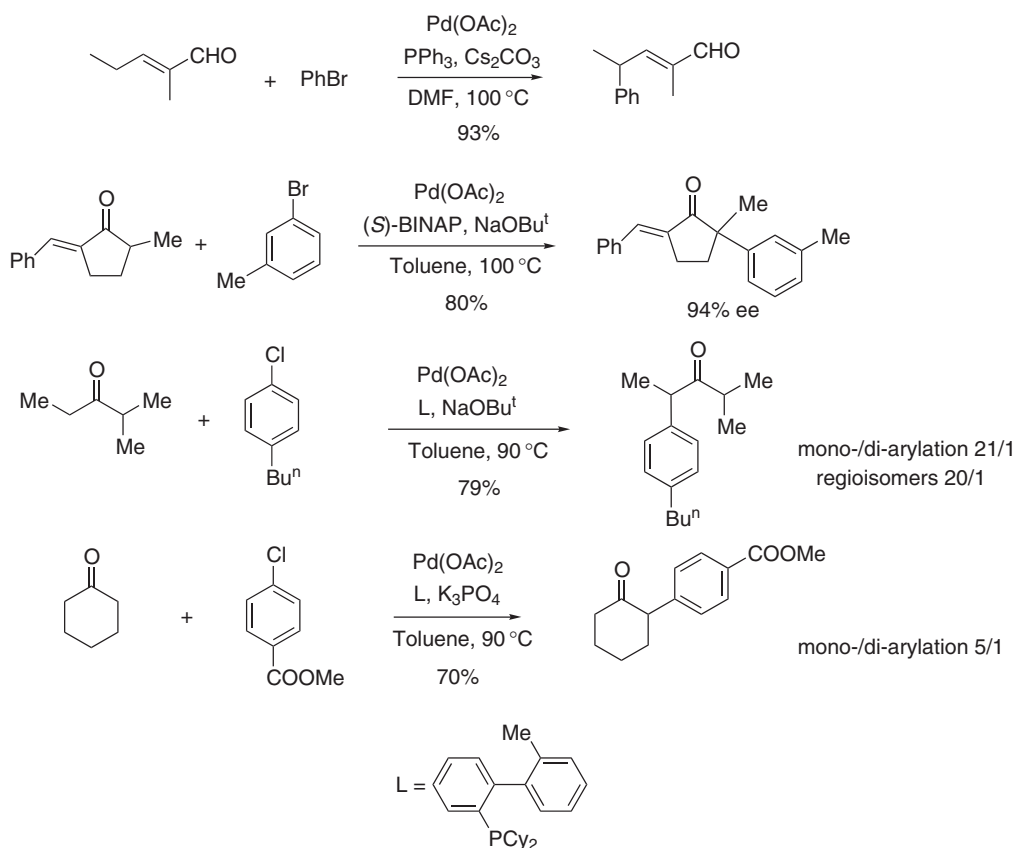


Palladium-catalyzed coupling of an arene and an aryl halide, the formal “arene analog” of the Heck reaction, is reviewed [<B-2002MI1471>](#). Arylation of phenols by aryl halides, in both the *o*-position and then the *o'*-position of the newly introduced aryl substituent, is achieved in the presence of a palladium catalyst and a base (preferably Cs₂CO₃); the same reaction applies for preformed 2-aryl phenols. Coordination of the phenolate oxygen to the intermediate arylpalladium species plays a key role in the process [<1998BCJ2239, 1999CL961>](#). In the same conditions, benzanilides react with aryl bromides to provide the double *o*-arylation products, *N*-(2,6-diarylbenzoyl)anilines, in good-to-excellent yields [<2000TL2655>](#). Rhodium complexes with phosphite or phosphinite ligands catalyze the intermolecular *ortho*-coupling of the substituted phenolates with aryl halides, without further reaction [<2003AG\(E\)112, 2003TL8665>](#). Comparable palladium-catalyzed cross-coupling reactions involving heteroaromatic compounds are known [<1998BCJ467, 1998JOM\(567\)49>](#). The intramolecular process, catalyzed by Herrmann’s palladacycle, provides tricyclic compounds efficiently (Equation (16)) [<1997JOC2>](#), and various extensions of this ring-closing methodology are made for the synthesis of biaryl compounds [<1997JOC1286, 1998H\(49\)191, 1999AG\(E\)1229, 2000JOC2069>](#).

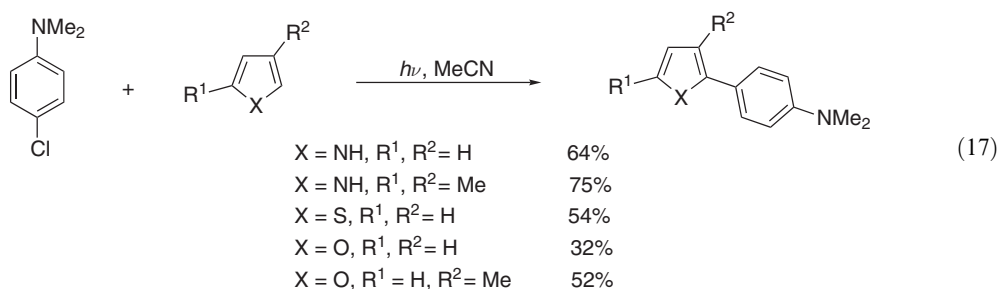


Ketones and α,β -unsaturated carbonyl compounds are arylated by aryl halides at their α - and γ -positions, respectively, under palladium catalysis (Scheme 8) [<1997TL7581, 1997JA12382, 1998JA1918, 1998TL6203>](#); this reaction is reviewed [<2002T2041>](#). A wide range of aryl chlorides couple smoothly with ketones when a Pd(OAc)₂/PCy₂(2-(2-tolyl)phenyl) catalyst is employed in the presence of NaOBu^t, with a high selectivity for monoarylation and for reaction at methylene rather than methine centers. The use of K₃PO₄ as the base allows widening of the functional group compatibility [<2000JA1360>](#). Similarly, efficient monoarylation of carboxylic esters by aryl bromides is achieved at room temperature in basic conditions using a Pd(dba)₂ catalyst in the presence of PBu₃^t or an *N*-heterocyclic carbene ligand [<2002JA12557>](#). Triarylation at the α - and two *o*-positions of benzyl phenyl ketones takes place upon treatment with excess aryl bromides in the presence of Cs₂CO₃ and a catalytic amount of Pd(PPh₃)₄ [<2001T5967>](#). Somewhat unusually, α,α -disubstituted aryl methanols undergo C(sp²)—C(sp³) bond cleavage during their palladium-catalyzed arylation with phenyl bromides [<2001JA10407>](#).

The photochemical formation of biaryl compounds is well reviewed [<2002CRV1359, 2003CRV71>](#). Irradiation of aryl halides (I, Br, Cl) furnishes the corresponding aryl cations that are trapped by arenes substituted by activating groups, via a photo-S_{RN}1 process. Heteroaromatics, e.g., furans, pyrroles, or thiophenes undergo regioselective substitution with aryl halides when irradiated in acetonitrile (Equation (17)) [<2000T9383>](#). Aryl iodides couple regioselectively with azulene at C1 upon irradiation in *n*-hexane [<2001TL715>](#).



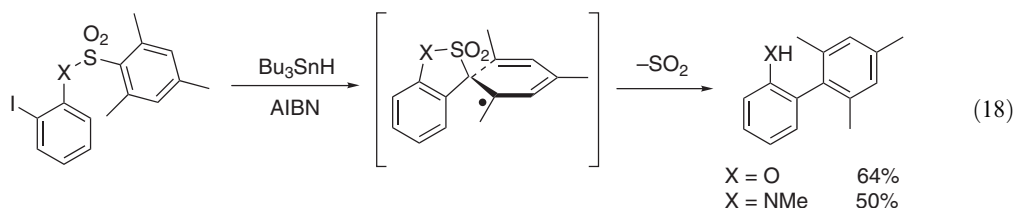
Scheme 8



(17)

Recently, interest has arisen in aryl radical migration for the preparation of biaryls. This new method usually involves intramolecular aryl radical migration from sulfur or silicon to another aryl radical originating from an aryl halide. Motherwell and co-workers first described an intramolecular free radical [1,5]-*ipso*-substitution of an aryl iodide under radical initiation conditions ($\text{Bu}_3\text{SnH/AIBN}$) using sulfonamide and sulfonate tethering chains (Equation (18)) <1997TL137>. The reaction takes place via a spirocyclic intermediate, which rearomatizes through loss of sulfur dioxide to provide α -arylated phenols or *N*-methyl anilines. Hindered biaryls are easily prepared, since the presence of either electron-donating or electron-withdrawing groups *ortho*- to the sulfonyl group facilitates the reaction. *o*-Halogenobenzyl arylsulfonates <1997TL141>, arylphosphinates <2000TL1315>, and diarylsilyl ethers <2000OL985> undergo similar reactions to give *o*-arylbenzyl alcohol derivatives. Studer and co-workers also report the intramolecular 1,5-aryl radical migration from sulfur in sulfonates or sulfonamides to variously substituted alkyl radicals (generated from the corresponding iodide or bromide) with excellent stereocontrol <2002EJO2742>. In the analogous reaction with *o*-iodophenyl benzyl ethers, there is no obvious leaving group, and mixtures of products tend to be formed <2001TL961>. Intermolecular radical additions of aryl or heteroaryl radicals, generated from the corresponding bromides with tris(trimethylsilyl)silane/AIBN, to aromatic solvents (benzene,

toluene, chlorobenzene) can be achieved, although the scope is limited by the fact that the acceptor arene has to be the reaction solvent <2000OL3933>.



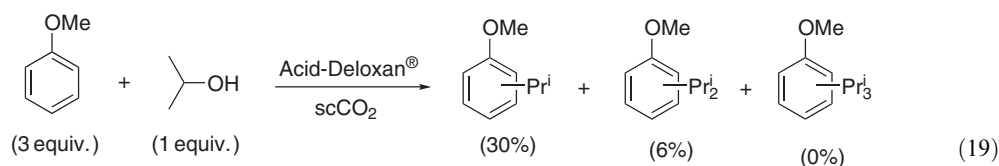
Phenylacetic acid dianions react with aryl halides under photostimulation in liquid ammonia to afford aryl substitution products. The regioselectivity of the arylation depends on the counter ion: with potassium, only *para*-coupling is observed while with the smaller lithium counter ion α -substitution is observed exclusively <2000OL2643>. This methodology is useful for the α -arylation of ketones and is also neatly adapted for the synthesis of substituted indoles by photostimulation of *o*-iodo- or *o*-bromoanilines which undergo substitution with enolates followed by spontaneous ring closure <2003CRV71>.

1.11.2.2 Substitution of Oxygen

1.11.2.2.1 Substitution of alkyl oxygen leaving groups

(i) Friedel–Crafts alkylation and related processes

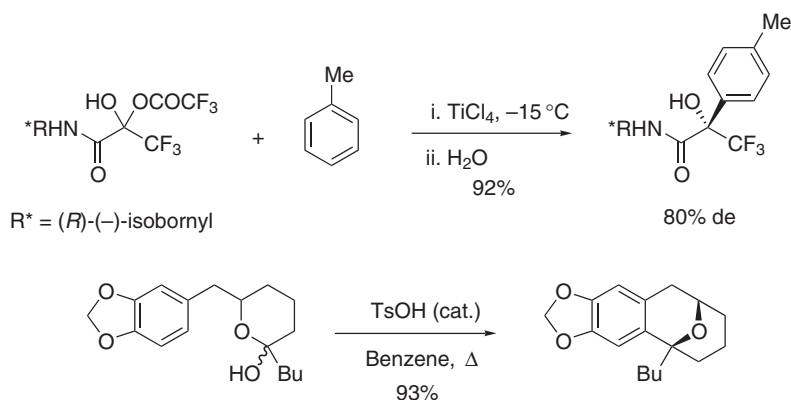
Considerable efforts are now in evidence for the use of more environmental friendly systems for chemical transformations, particularly in the heavy chemicals industry. In this context, alcohols and their derivatives (and also alkenes, see Section 1.11.2.8.1) are attractive alternatives to halides as reagents for Friedel–Crafts alkylation of aromatic compounds, and many new “green” catalyst systems are tested and developed specifically for such reagents <1999AC(A)(181)399>. New solid catalysts for the alkylation of arenes with simple alkyl, allyl, or benzyl alcohols are generally prone the following factors: high selectivity for monoalkylation, efficiency, tolerance to water (which is liberated during alkylations involving alcohols), and recoverability for reuse. They include acidic clays <2002MI363, 1999GC75>, acidic mesoporous zeolites <1999MI55, 1999AC(A)(188)99, 2000JCA(195)237>, iron-containing graphite <2001JCA(201)105>, rare earth triflates <1997JOC6997, 1999CC1331> which can be supported <1998CR(C)41> or micro-encapsulated <2000AC(A)(202)117>, gallium triflate <2003MI1>, and triflamide <1996SL1045, 2000AC(A)(202)117>. An $AlCl_3$ /MCM-41 solid catalyst gives selective 2,6-dialkylation of naphthalene with isopropanol <2003JMOC(A)67>. Friedel–Crafts alkylations can be carried out in supercritical or near-critical fluids. In CO_2 , anisole is alkylated with trityl alcohol using only trifluoroacetic acid as the initiator <2002MI136>; a continuous flow process has been described for the highly selective monoalkylation of anisole (or mesitylene) with isopropanol in supercritical CO_2 in the presence of a solid acid catalyst (Equation (19)) <1998CC359>. The hydronium ion content of near-critical water (perhaps the ideal “green” solvent) is sufficiently high that no other acid additive is required for the efficient alkylation of phenols with tertiary, secondary, and even primary alcohols <1997IEC5175>.



scCO₂ = supercritical CO₂ ($T_c = 31.1^\circ C$, $p_c = 73.8$ bar)

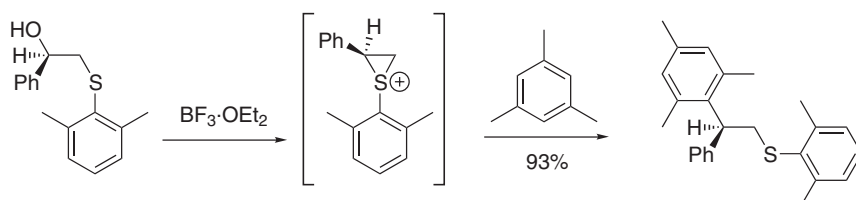
Acid-Deloxan® = polysiloxane-based solid acid formed by sol–gel condensation of alkylsulfonic acid functionalized organosilane monomers

Allylation of active arenes can be performed in high yield and without side reactions by using a variety of transition metal-based catalysts and allylic alcohols, tosylates, or esters <1996SL557, 1996CL1021, 1997CC859, 1997CL137, 1999JOC5308, 2003SL1431>. Other oxygen leaving group electrophile precursors for the alkylation of active arenes include methyl *t*-butyl ether, which is a better *t*-butylating agent than either *t*-butyl alcohol or isobutylene in the presence of solid acid catalysts <2001GC92>, and active silyl ethers <1997SL1145, 2002TL6391> in the presence of triflate-based catalysts. $\text{Sc}(\text{OTf})_3$ <1999S603> and $\text{Cu}(\text{OTf})_2$ <2001T241> also catalyze efficient arene alkylation with mesylates. Ultrasound irradiation improves considerably the efficiency of AlCl_3 -catalyzed reactions of arenes with nonracemic 2-(mesyloxy)propanoates, without loss of stereochemical enrichment <1996BSB755>. Methoxyacetate <1995NJC707> and *N*-sulfamoylcarbamate <2003OL193> benzyl esters are new oxygen-based benzyl cation precursors, allowing highly efficient monobenzylation of benzene and active derivatives; the former works well with lanthanide superacid salt catalysts, while the latter succeeds even under noncatalyzed (thermal) conditions. Ketones and aldehydes have rarely been used successfully in Friedel–Crafts alkylation reactions, due to the nonselective formation of product mixtures. However, the corresponding dioxygenated alkyl systems (that is to say acetals and related functions) have emerged as useful alkylating agents for active aromatic systems, formally by the substitution of oxygen (Scheme 9) <1996TL375, 1997TL7021, 1997JOC151, 1999JCS(P1)1189, 2001HCA163>; in some cases, these reactions can be rendered stereoselective. In the presence of $\text{Sc}(\text{OTf})_3$, acetals of arene carbaldehydes react with active benzenes to give diarylmethanes as the sole products <1997JOC6997>. This remarkable reaction proceeds through a redox process involving a Lewis acid-mediated hydride shift. Indeed, the arene carbaldehyde and the diol can be used as the initial reagents, thus facilitating the operation. Similarly, benzene and other mildly activated aromatics are alkylated with ketones or aldehydes in the presence of hydrosilanes and catalytic amounts of indium(III) salts (many other Lewis acids fail completely); the hydrosilane plays a dual role as both co-catalyst and hydride donor for the redox process <1999T1017>.



Scheme 9

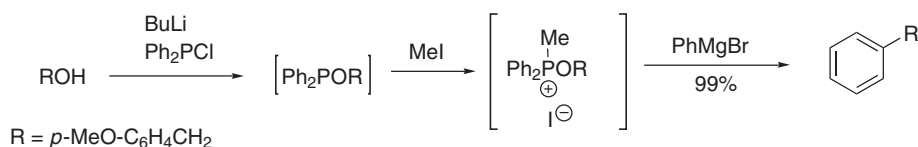
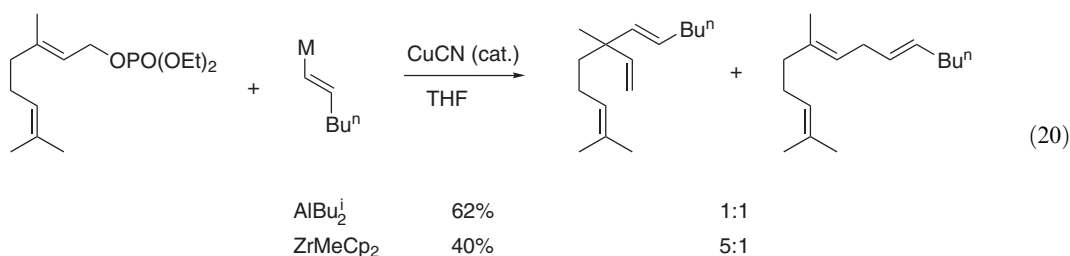
Some novel arene alkylation reactions involving heteroatom systems can be formally explained in terms of substitution of an oxygen leaving group. Alkoxy halo diaziridines react with Lewis acids to give alkoxy halo carbenes, which decompose to give halide, CO, and alkyl cations; these latter alkylate benzene, used as the solvent, in moderate yield <2000JACS9878, 2001OL2305>. Nonracemic β -arythioethanols in which the carbinol center is stereogenic alkylate arenes without loss of enantiomeric excess, in intermolecular or intramolecular fashion <1996SL465, 2002TL351>; in each case, the configuration of the chiral center is controlled by the formation of an episulfonium ion as the reactive electrophilic intermediate (Scheme 10).



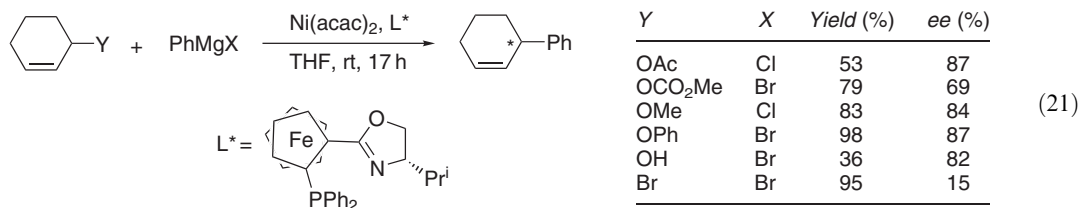
Scheme 10

(ii) Substitution by organometallic sp^2 carbanions

In most cases, alkyl tosylates are as efficient as alkyl halides in the role of electrophiles for the transition metal-catalyzed alkylation of aryl and alkenyl nucleophiles <B-2002MI27, 2002JA4222>. In nickel-catalyzed processes, less expensive 1,3-butadiene can be used as a ligand instead of a phosphine <2002JA4222>. Alkyl tosylates undergo efficient palladium-catalyzed cross-coupling with alkenyl zinc reagents in presence of $P(Cyp)_3$ in THF/NMP as solvents <2003JA12527>. Phosphates are generally poorer leaving groups; isolated examples are described for allylic phosphate arylation using triphenyl indium <2003JOC2518> or alkenylation using zirconium or aluminum reagents <1995SL183> with variable regioselectivity (Equation (20)). The cross-coupling reaction between phenyl magnesium bromide and alkoxy methyl diphenyl phosphonium salts—with the latter prepared *in situ* from an alcohol, methyl iodide, and chloro-diphenyl phosphine—occurs in good yield, with transfer of the alkyl group of the alkoxy function via C—O cleavage, when an excess of Grignard reagent is used without a metal catalyst (Scheme 11) <2003CL676>. An internal phosphine function exerts a regio- and stereo-directing influence during the nickel-catalyzed cross-coupling reaction of allylic methyl ethers with $PhMgBr$ <1995JA7273>. The stereoselective preparation of C-phenyl glycosides by the coupling of 1-aryloxy Δ^2 -carbohydrates with aryl magnesium halides in the presence of $NiCl_2(dppe)$ occurs with inversion of configuration, but with retention when $PdCl_2(dppf)$ is used as catalyst <1998JOM(567)157>. Using chiral oxazolinylferrocenylphosphines as ligands in Ni(0)-catalyzed asymmetric allylic substitution by phenyl Grignard reagents, best results (yield and ee) were obtained with OAc, OMe, and OPh leaving groups; allylic alcohols give low yields while bromides give decreased enantioselectivity (Equation (21)) <2000JCS(P1)2725>.



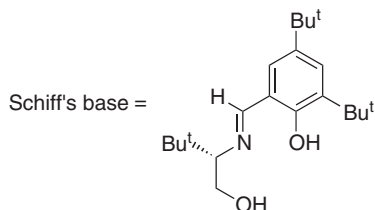
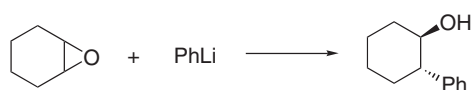
Scheme 11



Epoxide opening by alkenyl or aryl metals has sustained interest and is further developed in its asymmetric form <B-2002MI259, B-1996MI307, B-1996MI274>. As a route to chiral homoallylic alcohols, it is much valued in total synthesis, as exemplified in the preparation of viridifungin A <1998TL877>, fostriecin <2001OL2233>, and 4,5-deoxyneodolabelline <2003JA1843>.

Several recent advances in this field merit particular mention. Aryl lithiocuprates react with oxirane to give homobenzylic alcohols in good yield <2003EJO452>. Sequential nucleophilic addition on C_2 -symmetric 1,2,3,4-diepoxybutane is achieved using high-order cyanocuprates bearing a nontransferable ligand— $R(2\text{-thienyl})Cu(CN)Li_2$ where R is alkenyl group—for the first

epoxide opening, then aryl or vinyl lithium or Grignard reagent in the presence of a copper salt for the second <2002S2138>. Total control of the regiochemistry in epoxide opening of glycidol derivatives with aryl or vinyl Grignard reagents is achieved using a copper halide catalyst (CuI, CuBr) <2003TL2695>. The organozinc reagent PhZnOCOCF₃—prepared *in situ* from diphenyl zinc and trifluoroacetic acid—reacts with 1,3-cyclooctadiene monoepoxide via a regio- and stereo-selective *syn*-1,2-addition, although with 1,3-cyclopentadiene or 1,3-cyclohexadiene monoepoxides, regioisomeric mixtures arising from 1,2- and 1,4-addition are obtained <2002OL905>. Vinyl or phenyl C-glycosides can also be obtained via tandem glycol epoxidation/epoxide opening in a *syn*-fashion using excess of trivinyl- or triarylaluminum; stereochemistry can be controlled by varying the nature of the metal <2000OL2707>. The opening of an epoxide or 2-substituted oxetane by phenyllithium can be performed asymmetrically (Equation (22)). Using a chiral diether ligand in the presence of a Lewis acid (BF₃), *trans*-products are obtained exclusively, with ee up to 47% <1996TA2483, 1997T10699>. Similar success is achieved using (–)-sparteine as a ligand <1998SL1165>. Arylation of cyclic and acyclic symmetrical epoxides (cyclohexene, cyclopentene, or 1,2-dimethylethylene oxides) in the presence of a chiral Schiff's base gives *trans*-adducts with good ee (76–86%) <1998TL9023>. Ring opening of 3-isopropyl-2-phenyl-3-oxetanol by phenyl or vinyl lithium in the presence of BF₃ provides 1,2-diols regio- and stereoselectively <1998EJO2161>.



Ligand/conditions	Yield (%)	ee (%)
(<i>R,R</i>)-1,2-dimethoxy-1,2-diphenylethane, BF ₃ ·OEt ₂ , Et ₂ O, –78 °C	99	43
(–)-sparteine, BF ₃ ·OEt ₂ , Et ₂ O, –78 °C	95	48
Schiff's base, hexane, rt	92	86

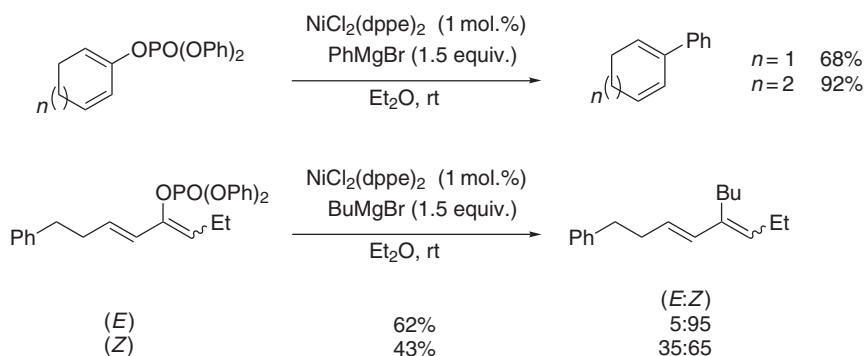
(22)

1.11.2.2.2 Substitution of alkenyl oxygen leaving groups

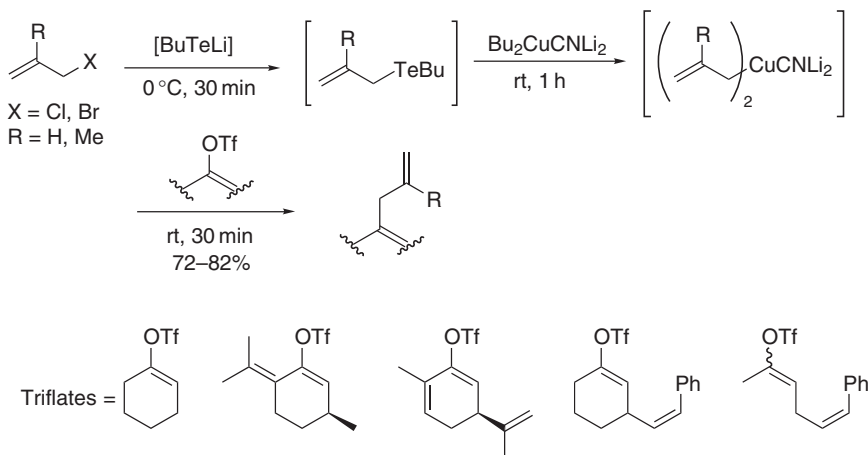
This area remains something of a monopoly for fluorosulfonate and phosphate ester leaving groups. Substitution of enol triflates (or other oxygen leaving groups) by organo nucleophiles is most usually accomplished using boron or tin derivatives; these transformations are discussed later (see Sections 1.11.2.5 and 1.11.2.6.2). Costs and toxicity factors in the preparation of these highly electrophilic substrates (triflic anhydride or exotic triflylating reagents are usually required) are the main drawbacks in the otherwise highly valued enol triflate substitution methodology; partly for these reasons, interest is increasing for the alternative use of enol phosphates, which cross-couple in milder conditions than were previously thought necessary.

The scope, limitations, and ligand effects in the nickel-catalyzed cross-coupling reaction of alkenyl triflates with alkyl Grignard reagents are established; di- and trisubstituted triflates couple readily with a wide range of *sp*³-carbon Grignard reagents, but tetrasubstituted substrates react sluggishly and give low yields of coupled products. Bidentate phosphines with small bite angle (dppe and dppp) are found to be superior to other ligands <1999TL3101>. Cyclic 1,3-dienyl 2-triflates undergo effective copper(I)-catalyzed coupling with Grignard reagents to give 2-substituted conjugated dienes <1998JOC2517> although the corresponding dienyl phosphates fail to react. Success with these electrophiles is achieved using a nickel catalyst, NiCl₂L₂ (L = dppe or dppp). Thus, six- and seven-membered cyclic 1,3-dienyl 2-phosphates couple smoothly with alkyl or phenyl Grignard reagents in ethereal solution; the (*E*)-isomer of an acyclic derivative couples with alkyl Grignards with pronounced inversion of configuration, while the (*Z*)-form provides near-equal mixtures of isomers (Scheme 12) <1999JOC1745>.

The alkylation of enol phosphates with dialkyl cuprates (especially Me₂CuLi) is now a widely used technique, particularly in natural product synthesis, when a ketone function is to be replaced by an alkyl group. The enol phosphate of a β-keto ester reacts particularly well, presumably helped by an addition–elimination mechanism <1998T3279>. Allyl cyanocuprates undergo efficient coupling with alkenyl triflates to give 1,4-dienes (Scheme 13) <2003OM2108>.



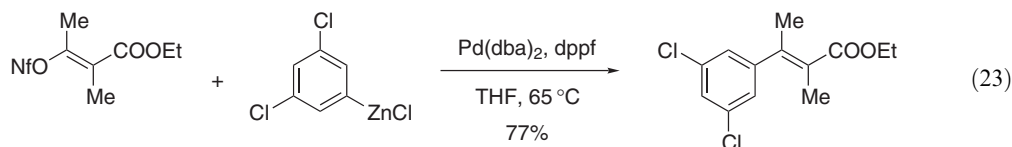
Scheme 12



Scheme 13

Alkylation of lactam-derived enol triflates with lithiocuprates gives variable success, although palladium-catalyzed arylation with phenyl zinc chloride proceeds in excellent yield [<1997JOC8131, 1998CC1757, 1999JA593>](#).

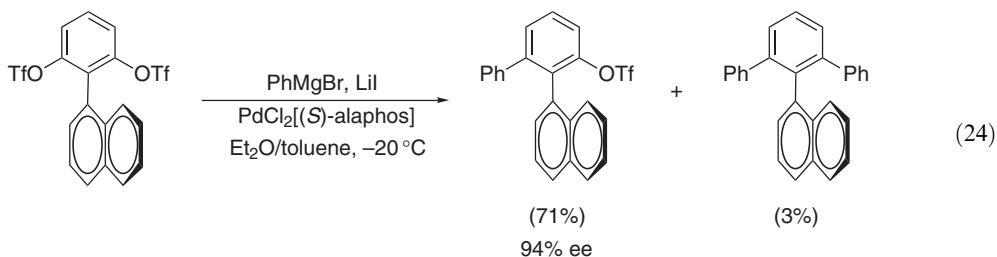
Enol triflates derived from β -keto esters cross-couple successfully with Grignard-based zincate complexes (R_3ZnMgX) under copper catalysis, leading to tri- and tetrasubstituted α,β -unsaturated esters. Zincate complexes are milder than Grignard reagents and therefore avoid hydrogen incorporation in the copper-catalyzed conditions [<2001SL1511>](#). Activated enol triflates, prepared from cyclic α - and β -diketones and cyclic or acyclic β -keto esters and purportedly easier to obtain and handle than triflates, undergo efficient and stereoselective palladium-catalyzed cross-coupling with primary alkyl and aryl zinc chlorides with retention of configuration (Equation (23)) [<1999T2103>](#). Triorganoindium reagents containing alkyl, vinyl, aryl (or alkynyl) groups undergo $\text{PdCl}_2(\text{PPh}_3)_2$ -catalyzed cross-coupling with a representative vinyl triflate in good yield; all three organic groups may be transferred during the reaction [<2001JA4155>](#).



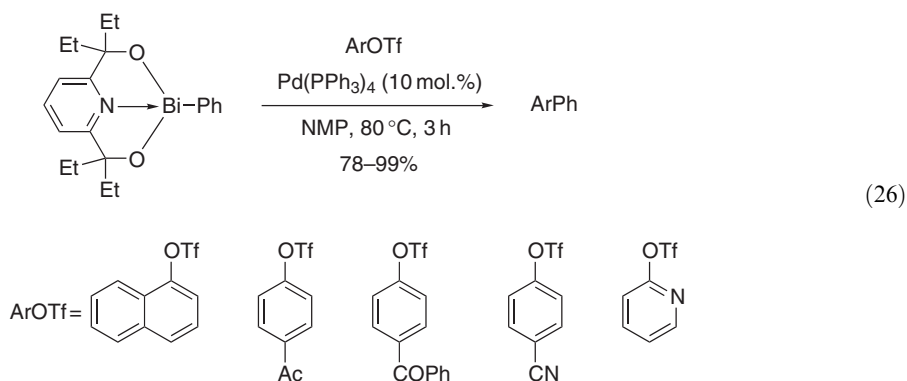
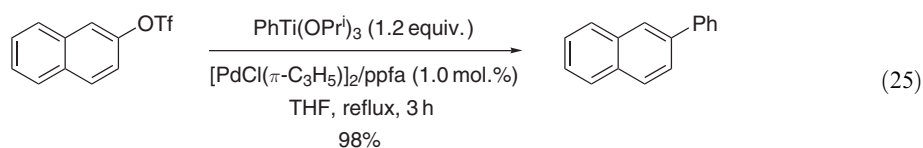
1.11.2.2.3 Substitution of aryl oxygen leaving groups

Much of the methodology developed for cross-coupling reactions with aryl halides can be effectively applied to aryl triflates (see Section 1.11.2.1.3). By careful selection of the phosphine

ligands, metal salt additives, and reaction conditions, as described by Hayashi and co-workers, substitution of one of the two enantiotropic triflate groups of achiral biaryl ditriflates by aryl Grignard reagents can be achieved in the presence of a Pd catalyst; an ee of 94% is obtained with PhMgBr in presence of LiI and the complex PdCl₂[(*S*)-alaphos] (alaphos = (2-dimethylamino)propyldiphenylphosphine) (Equation (24)) <1999T3455>.

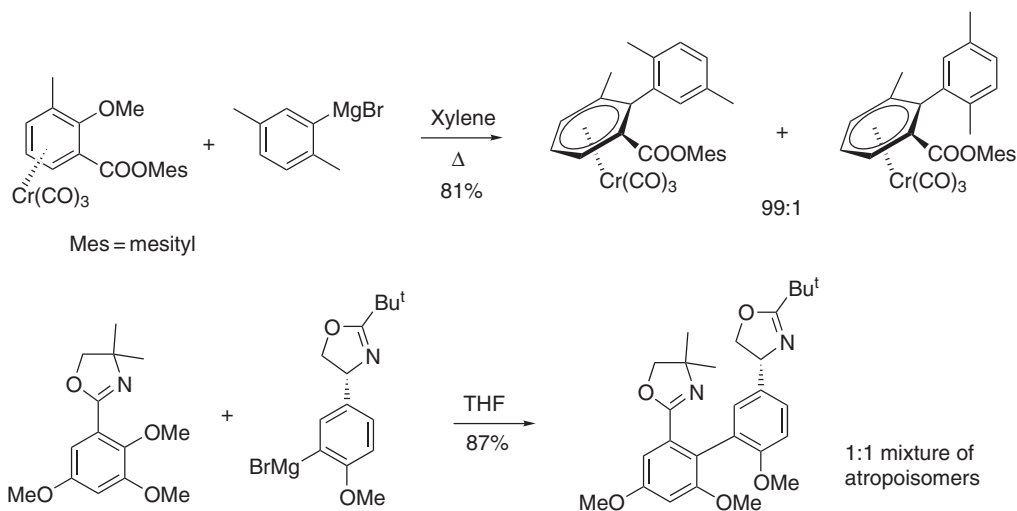


Organozinc reagents are now established as versatile nucleophiles for transition metal-catalyzed cross-coupling reactions <B-1999MI179>. Studies by Knochel and co-workers show that dppf is the required palladium ligand for coupling with aryl triflates; this means that controlled, chemo-selective, sequential coupling of multifunctional arenes (e.g., iodophenyl triflate, or benzyl zinc bromide bearing a triflate) may be performed through simple selection of the catalyst system <1996SL573, 1997TL1749>. This methodology can be extended to sequential polymer-supported aryl skeleton construction <1997SL1084>. Organoindiums are good nucleophiles although they are less exploited. Triorganoindium reagents containing alkyl, vinyl, phenyl (or alkynyl) groups undergo palladium(II)-catalyzed cross-coupling with a representative aryl triflate in good yield and high chemoselectivity; all three organic groups may be transferred <2001JA4155>. This reaction is employed in successive multifold cross-coupling reactions with oligoarene tris-triflates to give dendritic molecules <2002CC2246>. Aryl and alkyl titanium reagents couple smoothly with aryl triflates in the presence of a Pd/ppfa catalyst (ppfa = *N,N*-dimethyl-1-[2-(diphenylphosphino)ferrocenyl]ethylamine) (Equation (25)) <2002SL871> whereas aryl bismuth reagents cross-couple with electron-poor (but not electron-rich) aryl triflates in the presence of Pd(PPh₃)₄ (Equation (26)) <1999OL1271>.



The search for oxygen leaving groups other than triflate for cross-coupling finds some success in aryl nonaflates, which have all the reactivity benefits of triflates (and a few more advantages) for selective palladium-catalyzed reaction with organozinc reagents <1998JOC203>. Aryl tosylates are more attractive than triflates in terms of cost, stability, and availability of reagents, but to compensate for their lower reactivity, higher reaction temperatures and higher catalyst loadings may be required. Nonetheless, efficient cross-coupling has been reported for a variety of organo-metallic nucleophile/catalyst combinations <2001JOC3642, 2002JA13856, 2003JA8704, 2003JA8704>. Aryl sulfonates also undergo nickel- or palladium-catalyzed homo-coupling in mild conditions <1995JOC176, 1997JOC261>.

Cases of methoxy as a leaving group usually remain limited to nucleophilic aromatic substitution of anisoles with aryl Grignard reagents, which may nonetheless lead elegantly to complex axially chiral biaryls. When regioselectivity is an issue, it is often determined by the other substituents present on the anisole; some substitutions are highly diastereoselective, although this is by no means always the case (Scheme 14) <1996TL6359, 2000OL2459>.

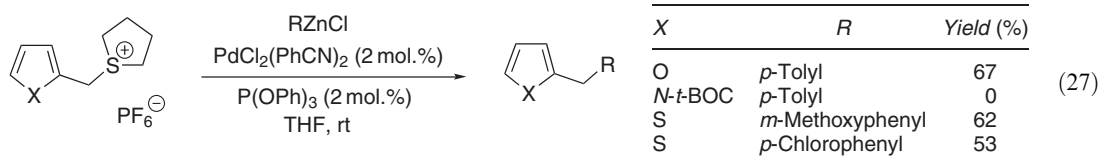


Scheme 14

1.11.2.3 Substitution of Other Chalcogens

1.11.2.3.1 Substitution of alkyl chalcogen leaving groups

Substitution of unactivated alkyl sulfur by aryl or alkenyl nucleophiles remains extremely rare in the literature; the formation of a C(*sp*²)—C(*sp*³) bond by sulfur displacement is often better achieved through an alkyl metal–alkenyl or aryl sulfur reagent combination (see Section 1.11.2.3.2). Partial redress of this situation may be underway, however, through use of sulfonium salt leaving groups, described by Liebeskind and co-workers in palladium-catalyzed cross-coupling reactions with alkenyl, aryl, and heteroaryl zincs. Reactive allylic, benzylic, and heterobenzylic (from furan and thiophene, but not pyrrole) sulfonium salts are known (Equation (27)), and are at least as stable and easy to handle as the corresponding halides <1997JA12376, 1999JOC2796>.



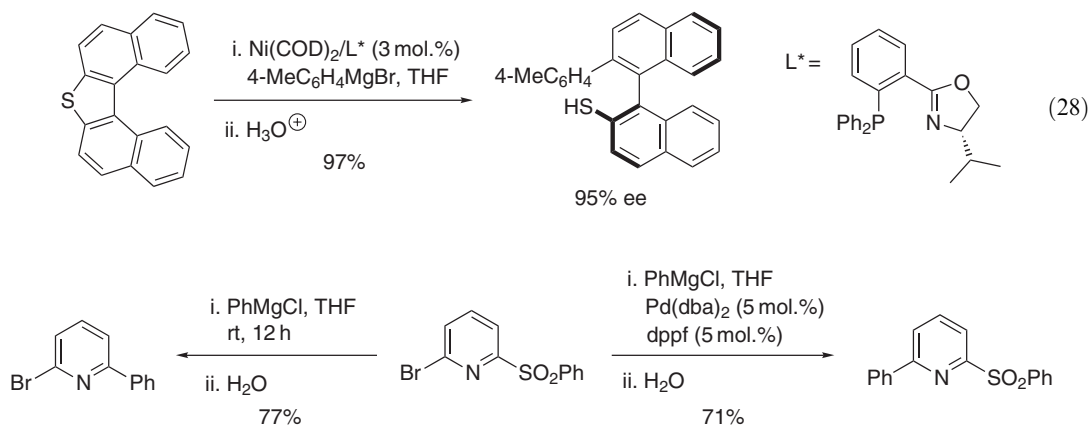
One-pot, high-yield, double functionalization of allyl phenylsulfones can be carried out by sequential base-mediated α -alkylation then palladium-catalyzed nucleophilic arylation with a zinc reagent <1999T2889>, although the regiochemistry of the phenylsulfonyl substitution (S_N versus S_N') is not straightforward.

In the presence of excess triflic acid in benzene, a 4-(phenylthio)tetrahydroisoquinoline derivative (generated *in situ* from a monocyclic precursor in an acid-mediated Pummerer cyclization) undergoes substantial transformation to the 4-phenyl analog, presumably via Lewis acid-induced departure of the phenylthio group to give a benzylic electrophile, which then takes part in a Friedel–Crafts-type alkylation reaction with benzene used as the solvent <2003CPB667>.

1.11.2.3.2 Substitution of alkenyl and aryl chalcogen leaving groups

Sulfur, selenium, and tellurium sp^2 electrophiles undergo cross-coupling reaction with organolithiums, organomagnesium halides, organocuprates, organozincs (also organoboranes and organostannanes) in the presence of Pd, Ni, or Cu catalysts <B-1998MI227, B-1999MI179>. Reaction may occur without a catalyst in the case of lithium reagents (and, to a limited extent, Grignard reagents).

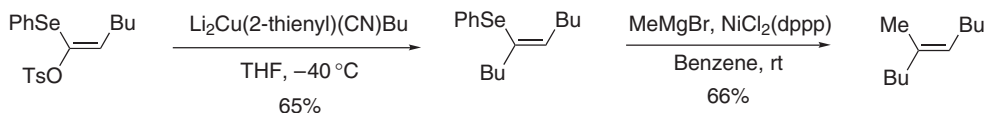
Alkenyl sulfides, sulfoxides, and sulfones can be employed successfully as cross-coupling reaction partners. Addition of alkyl or phenyl lithium to (*Z*)-trifluoromethyl thioenol ethers provides trifluoromethyl alkenes stereoselectively in ~80% yield if the thioenol moiety is conjugated at the β -position <1996TL171>. Nuncatalyzed vinylic nucleophilic substitution of the sulfone group by Grignard reagents in ((*E*),(*E*))-5-tosylpentenamides gives ((*E*),(*E*))-dienamides regio- and stereoselectively but in modest yield (25–60%) <1995TL3901>. The scope for stereoselective Grignard/Cu(I) reagent monosubstitution of α -oxoketene dithioacetals <1995TL1925> and nitroketene dithioacetals <1998T12973> has been widened, along with alkene preparation through nickel-catalyzed alkenyl sulfide cross-coupling with Grignard reagents, although the stereoselectivity is still not totally controlled for the latter <2001SL977, 1999JOC8582>. Attractive chiral 1,1'-binaphthyls can be prepared by ring opening of dinaphthiophene with organomagnesium halides under nickel catalysis in the presence of chiral oxazoline-phosphine (Equation (28)) <2002JA13396, 2003CRV3213>. Alkenyl sulfones couple with aryl or alkyl lithiums to give substituted alkenes in good yield <2000TL8917, 2003JFC195>. $\text{NiCl}_2(\text{dppf})$ catalysis of the cross-coupling reaction of alkyloxysulfonyl arenes with aryl magnesium bromides provides unsymmetrical biaryls in good yield, although alkenyl Grignard reagents are less efficient <2003JOC3017>. Competing electrophile reactivity can be regulated: treatment of 6-bromo-2-pyridyl phenyl sulfone with PhMgCl without catalyst allows selective displacement of the phenyl sulfonyl group, whereas the presence of a catalytic amount of $\text{Pd}(\text{dba})_2/\text{dppf}$ promotes exclusive substitution of bromide (Scheme 15) <2002T4429>.



Scheme 15

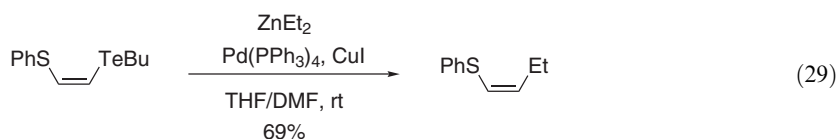
It is possible to play off the reactivities of different alkenyl leaving groups during the regio- and stereoselective preparation of di-, tri-, and tetrasubstituted alkenes (and conjugated dienes). The 1-tosyl moiety is selectively replaced in the $\text{NiCl}_2(\text{PPh}_3)_2$ -catalyzed cross-coupling reaction between 1,4-bis(arylsulfonyl)-2-phenylseleno-1,3-butadienes and a Grignard reagent <1996TL4161>. Conversely, with alkenes of the type *cis*- $\text{TsCH}=\text{CR}(\text{SePh})$, organocopper reagents of the type $\text{RCu}(\text{SePh})\text{Li}$ selectively substitute the phenylseleno group with retention of configuration; no tosyl displacement is observed <1998JOC7908>. Efficient and chemoselective nucleophilic substitution of a phenylselenyl group can be achieved using dimethyl lithiocuprate <1999AG(E)2027>. Nonetheless, α,α -difunctional alkenes of the type (*Z*)- $\text{RCH}=\text{C}(\text{SePh})\text{OTs}$ undergo palladium-catalyzed tosylate group substitution first, with retention of configuration, when treated with an alkyl or aryl cuprate reagent. Subsequent nickel-catalyzed cross-coupling of the resulting (*Z*)-alkenyl selenides with MeMgBr provides stereoselectively trisubstituted alkenes (Scheme 16) <1995T4691>. In a further demonstration of chemoselectivity control, (*E*)-1-(phenylselenyl)alkenylstannanes undergo intermolecular Stille coupling with an aryl iodide electrophile under $\text{Pd}(\text{PPh}_3)_4/\text{CuI}$ catalysis to give the (*Z*)-alkenyl selenides, prior to nickel-catalyzed Grignard reagent coupling <1997S417>. Similar

sequential construction is possible using (*E*)-XCH=CH(SeAr) (X = I, Br) and two different Grignard reagents <1997SC39>. This powerful methodology also allows stereoselective synthesis of conjugated dienes: (*E*)-(ArSe)CH=CHZrCp₂Cl cross-couples with (*E*)-alkenyl halides in the presence of Pd(PPh₃)₄ to give (*E,E*)-1-arylselenyl-1,3-alkadienes, which are then coupled with aryl Grignard reagents, as above <1996T9819>.



Scheme 16

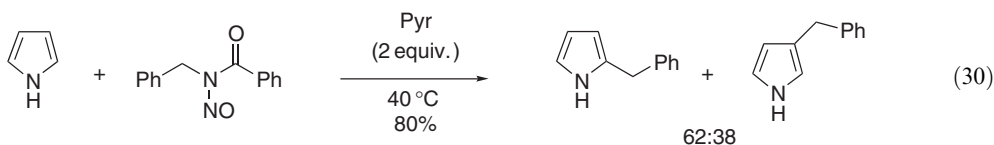
(*Z*)-Alkenyl tellurides undergo efficient and stereoselective cross-coupling with lower-order cyanocuprates leading to (*Z*)-disubstituted olefins; this reaction can be performed in the presence of a vinyl chloride <1995SL671>. Like the phenylselenyl group, phenyltelluryl is substituted by primary alkyl and aryl Grignard reagents under nickel catalysis <1996TL7417>. Dialkyl zincs are also successfully employed for nucleophilic substitution of unsaturated organotellurium compounds in the presence of a Pd(PPh₃)₄/CuI/DMF system (Equation (29)) <2000TL433>. A homo-coupling reaction leading nonstereoselectively to 1,3-dienes is observed for the single case of distyryl tellurides, in the presence of a Pd(OAc)₂ catalyst and silver(I) acetate <1996JOM(526)335>.



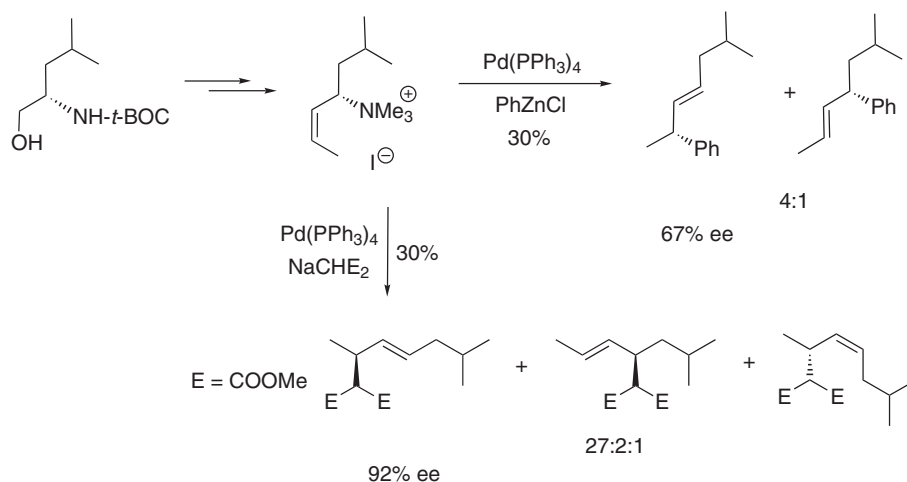
Organotellurium(IV) compounds may behave either as nucleophiles or as electrophiles in metal-catalyzed coupling reactions; diaryl tellurium(IV) dichloride gives biaryl products in good yields in both palladium- or copper-catalyzed Stille cross-coupling with stannanes <1999CC2117> and PdCl₂/NaOMe-mediated reaction with hypervalent aryl iodonium salts <2001SC1721>.

1.11.2.4 Substitution of Nitrogen

Superior Lewis acid catalysis is reported for Sc(OTf)₃ in the alkylation of indole in the 3-position with nonracemic *N*-protected aziridine carboxylates, providing a facile entry to tryptophan derivatives with high ee (up to 96%) <1997SL754>. Benzylation of electron-rich acid-sensitive aromatics can be achieved via simple thermolysis of *N*-benzyl-*N*-nitrosoamides; no catalyst is required (Equation (30)) <1997JOC8091, 1999JOC5966>. The reaction involves a nitrogen-separated ion pair containing an effectively free carbocation intermediate as the reactive species.



Use of ammonium salts as *sp*³-carbon leaving groups in reactions with organometallic reagents is reviewed <B-2002MI27>. Allylammonium salts are precursors for the formation of π -allylpalladiums, which may couple with nucleophiles such as Grignard reagents, cuprates or malonate ester carbanions. Allylic substitution of a chiral amine leaving group by organocuprates in the presence of a Lewis acid via addition–elimination occurs with up to 95% ee using a chiral pyrrolidine auxiliary <B-2002MI259>. Reaction of the trimethylammonium salt of an optically active allyl moiety with PhZnCl in the presence of Pd(PPh₃)₄ proceeds via the π -allylpalladium intermediate with predominant S_N' regioselectivity and 87% retention of configuration, in contrast to expectations based on previous work and on the behavior of a malonate ester carbanion nucleophile under the same conditions (Scheme 17) <1995TA389>.



Scheme 17

The copper-mediated aziridine ring-opening reaction by Grignard reagents is extensively used in synthesis, notably in its asymmetric form using a chiral ligand [<1999OL439>](#), but only a few applications involve vinyl, aryl, or heteroaryl nucleophiles. Diversely substituted *N*-*t*-BOC aziridines react regioselectively with sp^2 -carbon Grignard reagents and copper salts [<1996TL3761, 1997T8237>](#). A catalytic amount of InCl_3 is reported to effect *N*-tosylaziridine ring opening by heteroaromatic nucleophiles with good yield but variable regioselectivity [<2002TL1565>](#).

Arene diazonium tetrafluoroborates are effective electrophiles in cross-coupling reactions with organometallics, and interest in their use has taken an upturn due to their superior reactivity and the low cost of the aniline precursors, compared with aryl halides. Most work involves cross-couplings with arylboronates and is treated later (see [Section 1.11.2.5](#)). With the exception of aryltrimethylammonium salts, which are also useful as Suzuki cross-coupling electrophiles [<2003JA6046>](#), few advances are reported for other nitrogen leaving groups.

p-Dinitrobenzenes undergo rapid, moderate-to-high yielding, selective substitution of one nitro group when treated with a range of alkyl boranes, although the scope of the reaction is rather limited [<2003JOC4388>](#).

1.11.2.5 Substitution of Boron

1.11.2.5.1 General remarks on boron substitution reactions

Aryl radicals generated by the action of $\text{Mn}(\text{OAc})_3$ on arylboronic acids react with aromatic solvents giving unsymmetrical biaryl compounds in reasonable yields, but the scope of this reaction is limited by the narrow range of solvent partners: benzene, thiophene, or furan; the latter gives only moderate success [<2003JOC578>](#). A limited number of alkenyl dialkyl boranes furnish the corresponding alkenyl alkane via “ate” activation and then oxovanadium(V)-induced oxidation [<1998CC1209>](#). However, a recent historical perspective on $\text{C}-\text{C}$ bond formation via boron-mediated (i.e., noncatalyzed) organic group transfer reveals the extent to which this chemistry has really reached its term in synthesis [<2003CUOC1725>](#).

Progress in the area is of course dominated by the Suzuki (or Suzuki–Miyaura) cross-coupling reaction. This process, the palladium- (or other transition metal)-catalyzed reaction of an organic (usually vinyl or aryl) halide or triflate with an organoboron compound (aryl, alkenyl, or alkyl) in the presence of an inorganic base, is one of the most powerful methodologies currently available for $\text{C}-\text{C}$ bond formation. Depending on the reagent combinations, biaryls, styrenes, or conjugated dienes are the usual products, although recent developments allow for the smooth coupling of alkyl reagents. General reviews underline the various features of recent progress [<1995CRV2457, B-1998MI49, 1999JOM\(576\)147, 2002JOM\(653\)83, 2002T9633, B-2002MI249, B-2002MI591>](#). Many factors contribute to its contemporary popularity, including generally mild reaction conditions, wide functional group compatibility, the nontoxic nature of the inorganic byproducts, and

the ease of access to the cheap, easy-to-handle organoborane reagents. Indeed, recent progress in this latter field has allowed some success in “one-pot” tandem borylation/Suzuki cross-coupling processes <2003JOC3729, 2003TL6007>. Some commercial processes now use Suzuki coupling as a key step <2002MI101>. Considerable efforts now turn toward environmental and economic issues. Methods for efficient removal of palladium following Suzuki coupling are described <2003OPRD191, 2003JOC2633>. Solid-phase Suzuki cross-coupling reactions can be carried out, using supported versions of either the boron compound or the halide partner <1999CRV1549, 2003T885>. Microwave acceleration may be observed for homogeneous, heterogeneous, and solid-supported Suzuki reactions. Part of the success of the reaction is due to the continued development of new “tricks” for avoiding problems in specific cases: in recent examples, a CuI additive prevents catalyst deactivation by product chelation in the Suzuki synthesis of di(α -pyridyl)benzene <2001T2991>, while use of Ag_2O as the base suppresses a competing *ipso*-substitution reaction during Suzuki coupling of pentafluorophenylboronic acid <2003TL1503>.

1.11.2.5.2 Substitution of arylboranes

Most work focuses on the preparation of biaryl compounds from arylboronic acids, and the impact of the Suzuki reaction in this area is thoroughly reviewed <1998T263, 2002CRV1359, B-2002MI53>, including the particular field of polyarylene synthesis <2001JPS(A)1533>. A main feature is the emergence of improved, refined (and sometimes air-stable) catalyst systems, allowing greater efficiency, use of milder reaction conditions, and—very importantly—successful coupling reactions with aryl chlorides. A selection of catalysts may achieve this latter objective under mild conditions <2000JPR(342)334, 2002AG(E)4176>, including palladium complexes of bulky electron-rich phosphines (both alkyl and aryl) <1999JA9550, 2000JA4020, 2000CC2475, 2001CC2408>, phosphinous acids <2002JOC3643>, and heterocyclic carbenes <2000TL595, 2000JOM(595)186, 2002JOM(653)69> (Figure 2) or palladacycles (see Equation (14)) <1995AG(E)1848, 2003OM987>. A wide variety of both electron-donating and electron-withdrawing substituents may be tolerated on the chlorobenzene, depending on the catalyst system. A catalyst incorporating Santelli's “tedicyp” ligand (tedicyp = *cis,cis,cis*-1,2,3,4-tetrakis [(diphenylphosphino)methyl]cyclopentane) performs well with electron-deficient chloroarenes <2001SL1458>. Analogous coupling of arylboronates with heteroaryl chlorides <1999SL45, 2001T1323, 2001T2787, 2001TL2115> or with arylsulfonium salts <1997JA12376> is also feasible. Arylboronic acids may even cross-couple with electron-deficient aryl fluorides <2003JA1696, 2003CC578>. Other cross-coupling partners include hypervalent aryl iodides <1996JOC4720>, aryl diazonium salts <1996BSF1095, 2000TL6271>, aryl lead acetates <1998SL771>, and diaryl or di-(*Z*)-styryl tellurium dichlorides <2001JCR(S)283>.

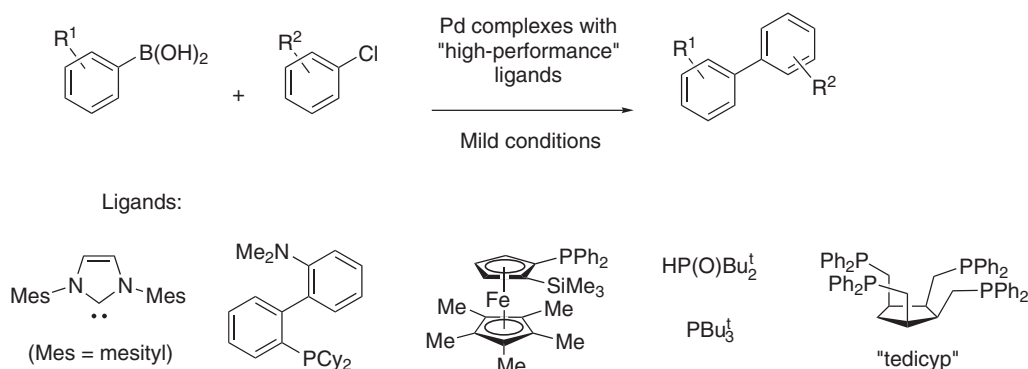
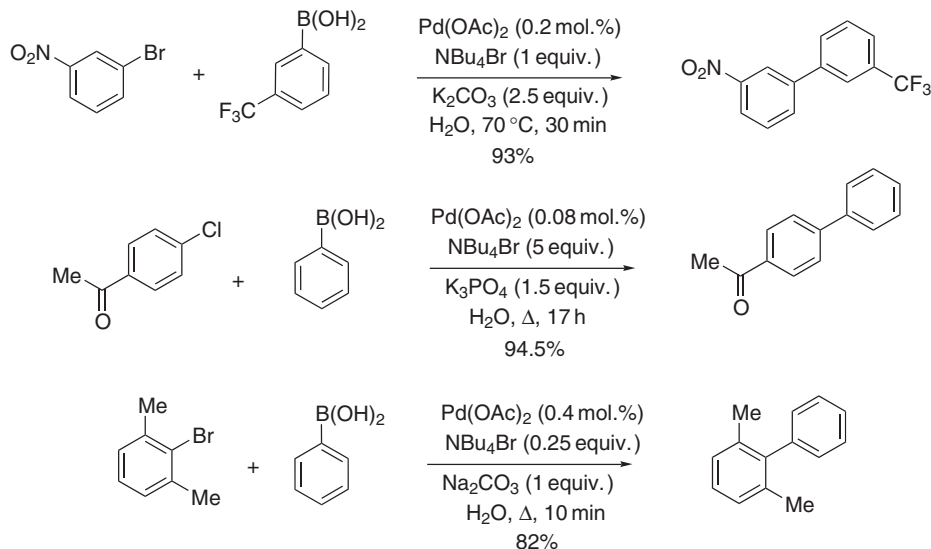


Figure 2 Successful Suzuki coupling with aryl chlorides.

To facilitate extraction after reaction, water-soluble phosphine ligands may be used for the palladium-catalyzed coupling of a wide range of arylboronates and aromatic iodides and bromides <1999JOM(576)305, 2001OL2757, 2003JOC6767>. Some Suzuki biaryl couplings may be performed in ionic liquids <2000CC1249, 2003JMOC(A)(206)193>. For phosphine-free Suzuki reactions, a variety of other types of ligand are available, including certain palladacycles and some

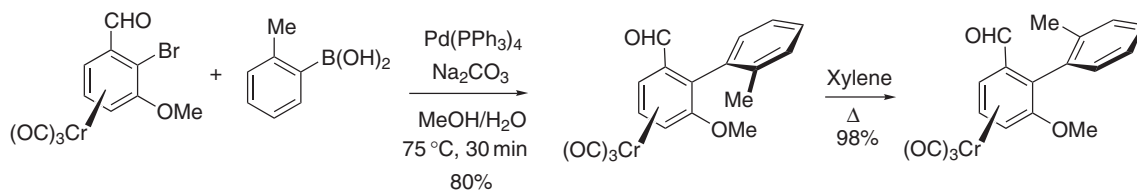
nitrogen heterocycle-based species <2002JOM(653)69, 2003T1837, 2003EJI1161>. $\text{Pd}(\text{OAc})_2$, PdCl_2 , and $\text{PdCl}_2(\text{SEt}_2)_2$ may also be used <2000TL8199, 2003S337>, the first-mentioned giving satisfaction in an aqueous solvent medium if a tetraalkylammonium salt is present (Scheme 18) <1997JOC7170, 1999OL965, 2003CC466, 2003JOC888>. An oxime-derived palladacycle catalyst in conjunction with a tetraalkylammonium salt permits coupling of aryl chlorides with phenylboronic acid in water <2002AG(E)179>.



Scheme 18

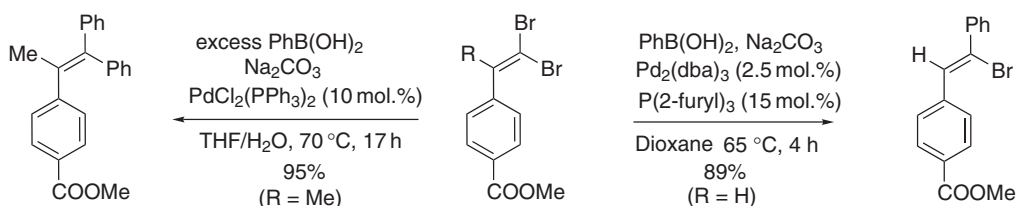
A plethora of heterogeneous catalyst systems for Suzuki biaryl cross-coupling has emerged. Colloidal palladium, Pd nanoparticles, and Pd powder in the presence of KF show some success as catalysts when more active halide partners are used <1996TL4499, 2000OL2385, 2001CC775>. Ligandless heterogeneous Pd-C catalysts allow coupling of aryl chlorides <2001OL1555, 2002SL1118>, whilst more limited application of $\text{Pd}(\text{OH})_2\text{-C}$ has been made <2003JOC1571>. Clay, silica, glass bead, and synthetic polymer supports for catalysts are known <1999TL439, 2001GC23, 2003CC606, 2003TL5095, 2003TL7565, 2003JOC7733> along with a solventless cross-coupling methodology based on a palladium-doped KF/alumina mixture, whose efficiency is improved considerably by microwave irradiation <2003TL3817, 2003S217>. There is still some debate as to the exact nature of the catalytic species derived from heterogeneous palladium reagents, since they may possess a finite homogeneous component <2003MI931>.

One area of particular recent development is the asymmetric Suzuki cross-coupling to give axially chiral biaryl systems. Once again, the key to success is the judicious choice of ligand, which is chiral in this case. Following the first successful diastereoselective application, in the total synthesis of vancomycin <1999CEJ2584>, atropo-enantioselective syntheses of binaphthyl, phenylnaphthyl, and biphenyl compounds, whose structures often derive from the natural product field, have appeared <2001CSR145, 2003JOC4897>. Using a single enantiomerically pure (bromoarene)chromium complex, either enantiomer of certain axially chiral biphenyls can be prepared, through careful control of the reaction conditions (Scheme 19) <2000SL938>.

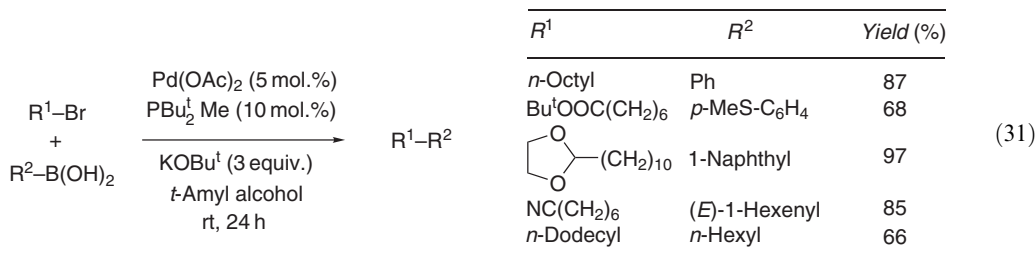


Scheme 19

Not quite so much development has been reported for arylboronic acid coupling with vinyl halides or triflates, although where such reactions are investigated, good results are generally obtained with catalysts which already perform well in cross-coupling with aryl halides. This applies even for highly substituted alkenyl partners, and for chlorides, in some cases. Recent illustrative examples include <2000JA4020, 2002JOC3643, 2003EJO1091, 2003OL3115>. 1,1-Dibromoalkenes may undergo single or double Suzuki cross-coupling, depending on the conditions (Scheme 20) <2001SL254, 2000SL737>, while 1-fluorovinyl bromides or chlorides cross-couple chemoselectively with one arylboronic acid equivalent to give the corresponding α -fluorostyrene derivatives <1999TL827>. Vinyl phosphates may be coupled successfully <2001T6969>, as may the alkenyl or benzyl moieties of the corresponding tetramethylenesulfonium salts <1997JA12376>. New or improved procedures exist for arylboronic acid cross-coupling with cyclopropyl iodides <1996JOC8718>, bromo-derivatives of active sp^3 -carbon compounds <2001CC669, 2002CC622, 2003TL3423, 2003OL1705>, and even with unactivated alkyl bromides, which may react under remarkably mild conditions (Equation (31)) <2002JA13662>.

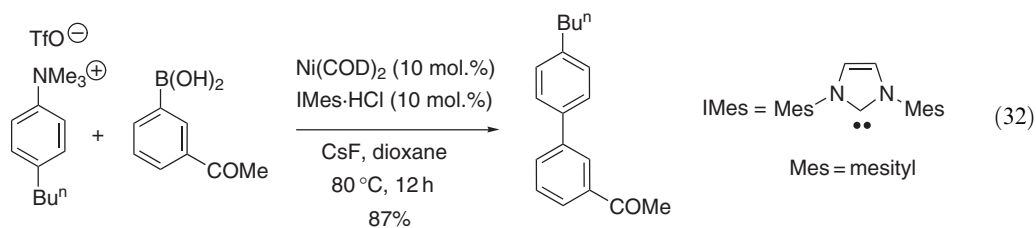


Scheme 20

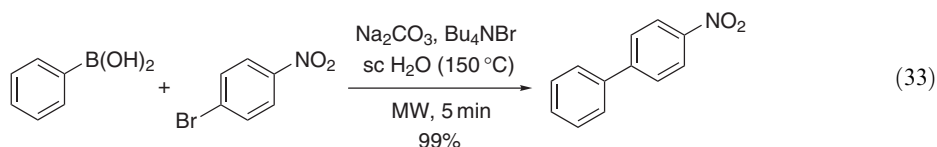


A few alternatives to arylboronic acids have emerged as useful arylboron partners for cross-coupling. Stable, easily prepared aryltrifluoroborate salts give excellent results <1999EJO1875, 2001TL9099> and may function with ligandless palladium catalysts <2003JOC4302>. Diaryl difluoroborate salts react with aryl bromides and activated chlorides, transferring two aryl groups <2003SL1435>. An example of phenyl-BBN coupling with a simple alkyl tosylate is known <2002AG(E)3910>.

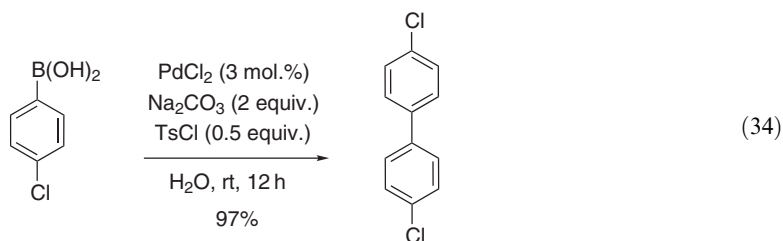
While palladium clearly dominates the center stage, some other useful catalysts for cross-coupling are emerging. The most notable alternative is the use of nickel; advantages include lower cost and the possibility of a better reactivity/selectivity profile. Progress tends to follow the trends set in research on palladium-catalyzed reactions and has been included in a recent review <2002T9633>. Highlights include biaryl formation by cross-coupling of arylboronic acids with aryl chlorides and hindered aryl bromides <1997JOC8024, 1997TL3513, 1999TL2323, 2000T8657>, aryl sulfonate esters <1995JOC1060, 1996TL8531, 2001OL3049>, or aryl trimethylammonium salts (Equation (32)) <2003JA6046> and successful use of phosphine-free <1999T11889>, ligandless <2002TL4009>, or heterogeneous Ni-C <2000T2139> catalysts, although this latter leaches considerable amounts of homogeneous species <2003JOC1177>. Applications to other systems are rare; noteworthy are the observations that nickel-catalyzed coupling reactions of arylboronic acids with vinyl phosphates <1999TL3321> or hindered allylic carbonates <1996JOC5391> succeed where palladium catalysis fails. A chiral oxazolinylferrocenylphosphine ligand permits enantioselective coupling of allylic acetates with arylboronic acids, albeit in moderate ee <2000JCS(P1)15>.



Recently, transition metal-free cross-coupling has been described. In superheated water, in the presence of a base and a tetraalkylammonium salt, a number of arylboronic acids react with aryl bromides (but not aryl iodides) giving biaryls; microwave irradiation improves the scope of the reaction (Equation (33)) <2003JOC5660>.

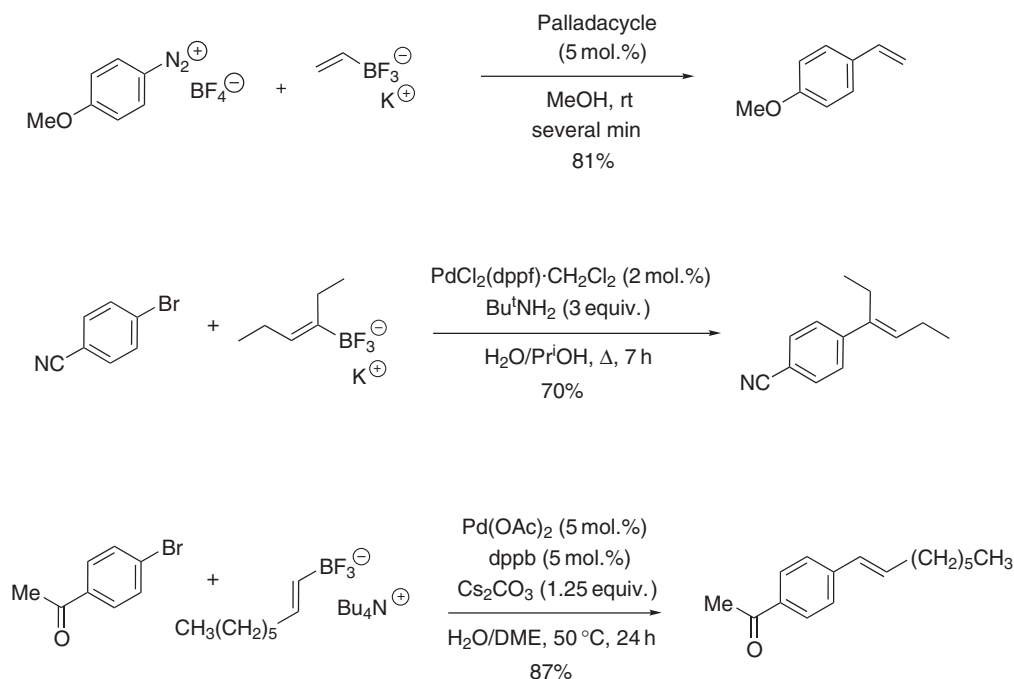


Although other convenient methods exist for the preparation of biaryls, palladium-catalyzed oxidative homo-coupling of arylboronates may be carried out. Sacrificial oxidants can be employed <1997SL1199, 2002TL8149> but usually exposure to air is sufficient <1997SL131, 2002S2183>; a base is not essential for the reaction to proceed <1996JOC2346, 2003TL1541>. The reaction can even be carried out in water with ligandless PdCl_2 as the catalyst (Equation (34)) <2002TL3067>.

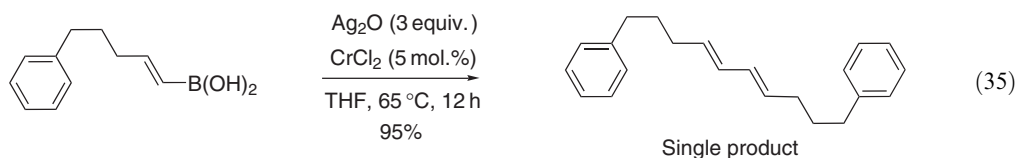


1.11.2.5.3 Substitution of alkenylboranes

Although methodological development has been considerably less, the stereoselective catalytic cross-coupling of an alkenylboron compound with an aryl or vinyl halide or pseudo-halide continues to give great satisfaction, often in natural product synthesis. Usually, the catalyst is a “standard” palladium complex such as $\text{Pd}(\text{PPh}_3)_4$. The limiting factor is perhaps the access to alkenylboron starting materials, although new routes to these compounds are emerging, facilitating one-pot vinylborane formation/coupling procedures <2002SL1880>. A general lack of reactivity with aryl or vinyl chlorides is still evident. In those cases where the studies are actually undertaken, successful new catalyst systems which are developed for arylboron cross-coupling also perform well with alkenylboron reagents too <1997JOC7170, 2003JOC7733, 2003S217>. Alkenyltrifluoroborate salts are new, easy-access, stable reagents for Suzuki cross-coupling with various aryldiazonium salts and aryl halides (Scheme 21) <1999EJO1875, 2001TL9099, 2002JOC8424>. Alkenylboronates couple successfully with cyclopropyl iodides <1996JOC8718> and with certain vinyl phosphates <2003JOC6360>. One example of an $\text{Ag}_2\text{O}/\text{CrCl}_2$ -mediated (*E*)-alkenylboronic acid homo-coupling to give the (*E,E*)-diene is described (Equation (35)) <2002TL8149>.



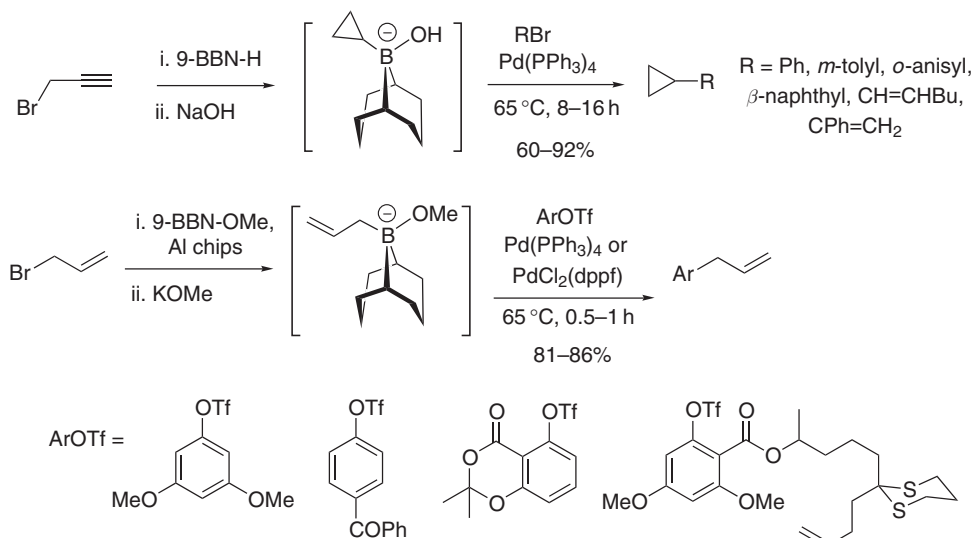
Scheme 21



1.11.2.5.4 Substitution of alkylboranes

Mechanistic aspects, reactivity profiles, and applications of the *B*-alkyl Suzuki cross-coupling reaction are thoroughly reviewed [<2001AG\(E\)4544>](#). Unhindered, electron-rich organoboranes are the most reactive partners and are most conveniently obtained from terminal alkenes as 9-BBN derivatives. Cross-coupling is achieved with a wide variety of vinyl or aryl iodides, bromides, or triflates; other functional groups may be tolerated in either the boron or halogen partner. Recently developed highly active catalysts may give success with aryl chlorides [<1998JA9722, 2001SL290>](#). The base plays a key role in the activation of the borane as a borate species [<1998JOC461>](#); in fact, formation of such an intermediate is a prerequisite for easy handling of allylic or cyclopropyl reagents (Scheme 22) [<1998SL161, 2000TL4251>](#). Intramolecular versions provide cyclic products with variable efficiency. In one case, an asymmetric synthesis of cyclopentanes from prochiral bis(9-BBN-propyl)alkenyl triflates is reported, using a palladium catalyst and chiral phosphine ligands, although the ee is moderate [<1998TA3751>](#).

Apart from the cyclopropane derivatives [<1996SL893, 1998SL198, 2000S1095>](#), whose reactivity results from their significant sp^2 character, alkylboronic acids or esters are generally poor partners for Suzuki cross-coupling. Some recent success is reported for their reaction with aryl halides [<2001TL7213, 2002T1465, 2003CEJ3216>](#) or aryldiazonium salts [<2001OL3761>](#). Reactivity is improved and scope enlarged through Ag(I) promotion [<2001TL7213>](#), or after one-step transformation into alkyltrifluoroboronate salts [<2001OL393, 2003JOC5534>](#) or “ate” complexes [<2001TL5817>](#). Cross-coupling of aryl halides with trimethylboroxine is a convenient way of methylating the aromatic ring [<2000TL6237>](#).



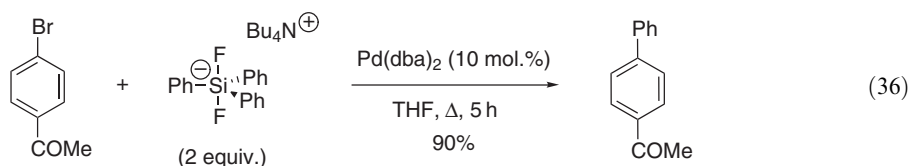
Scheme 22

1.11.2.6 Substitution of Silicon, Germanium, and Tin

1.11.2.6.1 Substitution of silicon and germanium

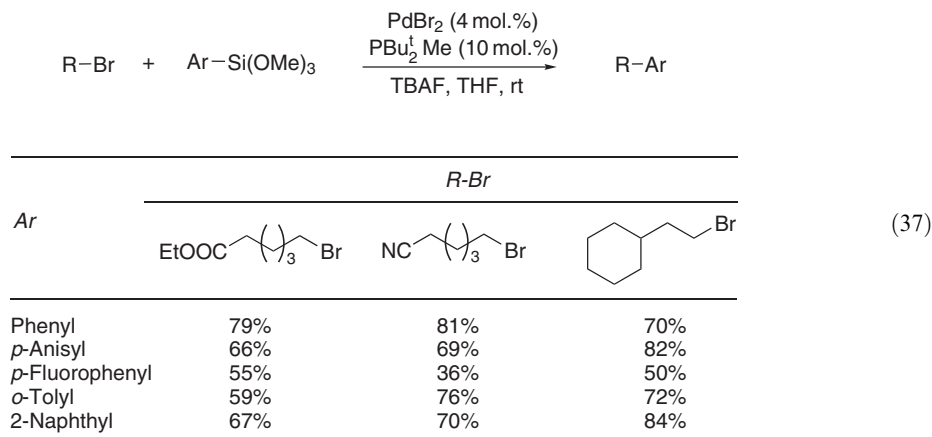
The palladium-catalyzed cross-coupling reaction of an aryl-, alkenyl-, or alkylsilicon reagent with an sp^2 (or active sp^3) halide or triflate, for which the pioneering work by Hiyama engendered the eponymous reaction, was outlined in COFGT (1995). Various general aspects of this reaction—the requirement for the formation of a hypervalent pentacoordinate silicon intermediate, and in this respect the promoting effect of an added fluoride source (usually TBAF), the preferred order of organic group transfer from silicon, the high stereoselectivity, the possibility of *cine*-substitution—have been reviewed periodically since then <1995CRV1317, B-1998MI421, B-2002MI285> while major recent advances, including notably those of Denmark and co-workers, are also highlighted <2002ACR835, 2002CPB1531, 2003ACA75>. The appealing features of silicon—the implication of low-molecular-weight, cheap, readily available, and easy-to-handle reagents, combined with its compatibility with a wide range of functional groups and reaction conditions—have encouraged these developments and improvements. One isolated application of solid-phase Hiyama cross-coupling is described <2001JOM(624)208>.

Tetrabutylammonium triphenyldifluorosilicate (TBAT) is a possible alternative fluoride-promoter source <1996JOC6901> and may even serve as a self-activated phenylating agent (Equation (36)) <1998JOC3156, 1999JOC3266>. However there has been a drift away from fluorosilane substrates, and an initial interest in chlorosilanes has subsided in deference to oxygenated derivatives.

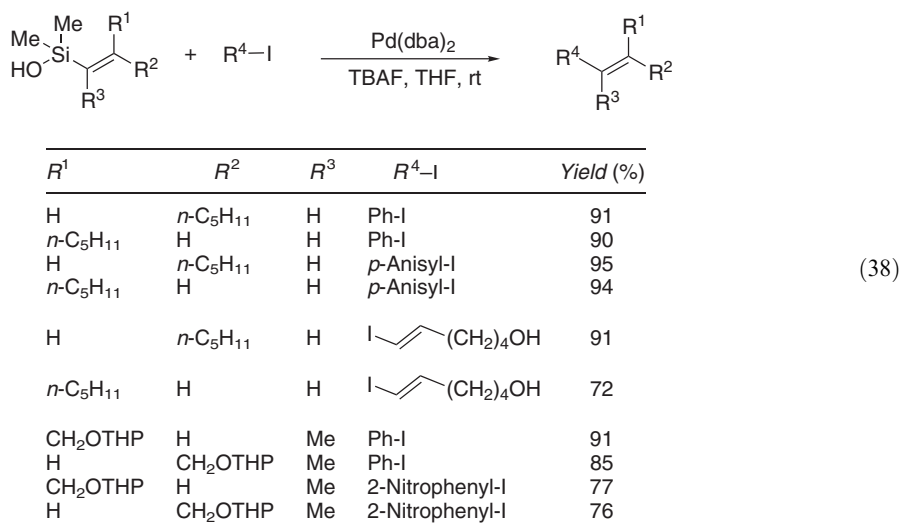


In the presence of TBAF and a palladium catalyst, aryl, ethenyl, and allyl trimethoxysilanes cross-couple smoothly with active aryl halides <1997CC1309, 1999JOC1684>; occasionally, the aryl halide homo-coupling product may present a minor problem. Aryl triethoxysilanes react with allylic benzoates with complete inversion of configuration <2001JOC7159>. The presence of

N-heterocyclic carbene or electron-rich phosphine ligands extends the reaction scope to include aryl chlorides <1999OL2137, 2000OL2053> and unactivated alkyl halides at room temperature (Equation (37)) <2003JA5616>.

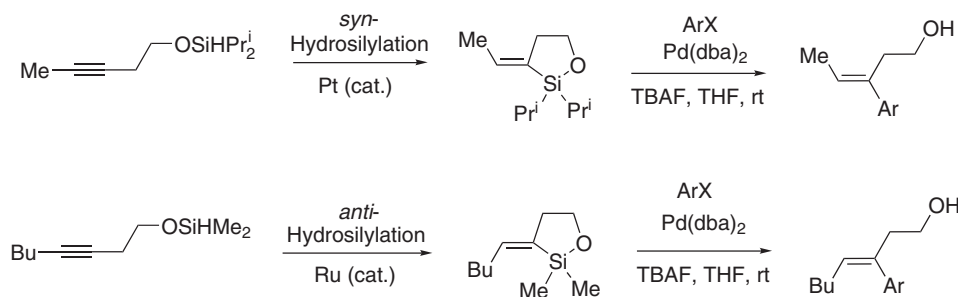


Silicones, too, behave as aryl or alkenyl transfer agents for cross-coupling with aryl halides <2001SL845, 2003SL1850>. Alkenyl silanols undergo highly stereoselective cross-coupling with active aryl or alkenyl halides (Equation (38)) <2000OL565, 2002JOM(653)98>, although with aryl triflates and nonaflates the presence of water seems desirable <2002OL3771>. This latter effect is also prevalent for aryl triflate cross-coupling with aryl trimethoxysilanes; aryl trialkoxysilatrane are suggested as superior reagents, although they are perhaps less easily accessed <2003JOC8106>. Fluoride-free basic conditions (e.g., Ag₂O, Cs₂CO₃) are now available for efficient palladium-catalyzed cross-coupling of aryl and alkenyl silanols with active aryl halides <2000JOC5342, 2001JA6439, 2003OL1357>, rendering this procedure compatible with the presence of silyl ether functions.



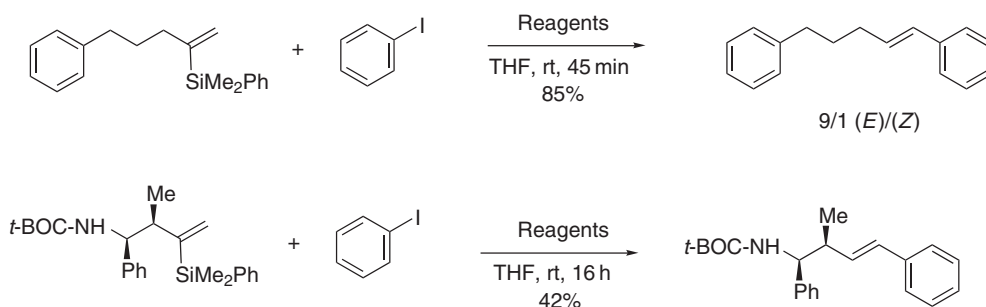
Elegant intramolecular developments of the above chemistry allow the stereospecific construction of highly substituted unsaturated alcohols. Five-, six-, and seven-membered cyclic alkenylsiloxanes undergo TBAF/Pd-mediated coupling with aryl or alkenyl halides giving the corresponding ω -hydroxy styrenes or dienes <2001OL1749>. The intramolecular version, involving coupling with a terminal (*Z*)-iodoalkenyl chain borne α - to the ring oxygen, permits the synthesis of medium-sized rings containing *cis,cis*-1,3-diene units <2002JA2102>, an achievement which has been exploited in a total synthesis of (+)-brasilenyne <2002JA15196>. 5-Alkylidene

oxasilacyclopentanes are transformed into trisubstituted homoallylic alcohols <2001OL61, 2002OL4163> and since the substrates are readily available in either configuration by controlled hydrosilylation of the homopropargylic alcohol, this makes for very attractive tandem reactions (Scheme 23). Adaptation of this technique allows access to geometrically defined 5-hydroxy-2-pentenals <2003JOC5153>. 6-Alkylidene dioxasilacyclohexanes are prepared and cross-coupled with aryl iodides in analogous fashion, giving trisubstituted allylic alcohols <2003OL1119>.



Scheme 23

Silacyclobutanes <1999JA5821, 1999OL1495, 2000S999> are interesting reagents for TBAF-mediated palladium-catalyzed cross-coupling with sp^2 -iodides; there is some evidence that these reactions proceed via ring opening through the same intermediate as that observed in silanol cross-coupling <2000OL2491>. Other new coupling partners include aryl triallylsilanes for aryl transfer <2003JOM(687)570> and alkenyl dimethyl(2-thienyl)silanes for alkenyl transfer <2002CL138>; in the case of alkenyl dimethyl(2-pyridyl)silane, departure of the heteroaryl moiety during the catalytic process protects the system from a competing Heck coupling <2001JA11577>. (α -Substituted)ethenyl dimethyl(phenyl)silane gives almost exclusive *cine*-substitution in its palladium-catalyzed cross-coupling reaction with iodobenzene (Scheme 24) <2002CC2018>. Highly substituted alkenyl benzyldimethylsilanes couple conveniently with aryl iodides in the presence of TBAF and catalytic $\text{Pd}_2(\text{dba})_3 \cdot \text{CHCl}_3$, and have the added advantage of being stable to fluoride-induced silyl ether cleavage conditions <2003OL1895>. α -Alkoxyalkenyl silyl hydrides are transformed into aryl enol ethers upon palladium-catalyzed cross-coupling with aryl iodides <2000OL3221>. Copper(I) salts in conjunction with a promoter (pentafluorophenoxide is recommended) may bring about aryl siloxane cross-coupling with aryl iodides in fluoride-free conditions and without the requirement of a palladium catalyst <1997CL639>.

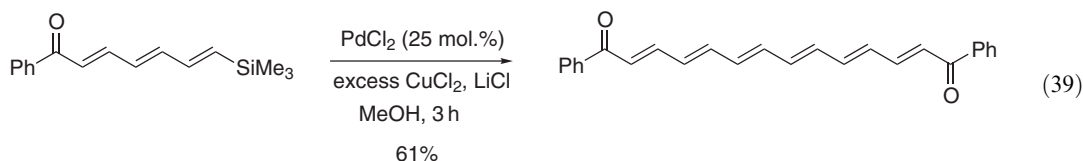


Reagents: $\text{Pd}_2(\text{dba})_3$ (10 mol.%), KOBu^t (2.5 equiv.), 18-c-6 (1.5 equiv.), TBAF (2 equiv.)

Scheme 24

Work with organogermanium compounds is extremely limited. In palladium-catalyzed cross-coupling with aryl iodides, allyl, phenyl, and various alkenyl trioxygermatranes, although slightly more reactive than the corresponding triethoxygermanes, are less so than stannanes, and require TBAF activation <2002OM5911>; they are nonetheless considered more easily accessed than carbagermatranes, which reportedly cross-couple with *p*-tolyl bromide <1996JOM(508)255>.

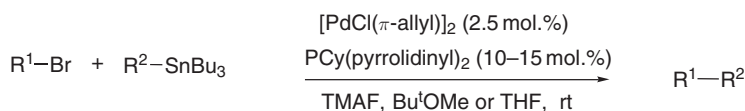
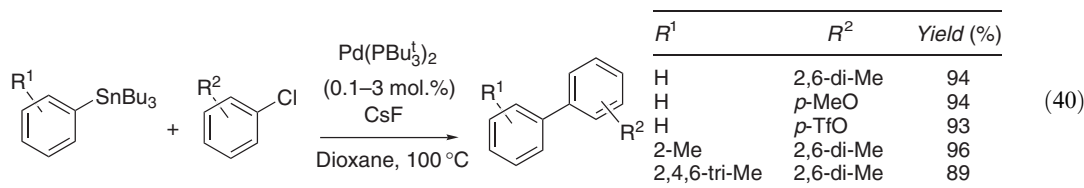
Success is rather limited for Pd(II)/Cu(I) co-catalyzed homo-coupling of $\text{Ar}_n\text{SiF}_{4-n}$ reagents in the presence of a chemical reoxidant <1997SL1199>. However, conjugated polyenes containing up to eight double bonds with *all*-(*E*)-configurations are obtained by the PdCl_2 -mediated homo-coupling of dienyl, trienyl, or tetraenyl trimethylsilanes when an excess of the $\text{CuCl}_2/\text{LiCl}$ couple is present for reoxidation of palladium(0) (Equation (39)) <1997JOC3291>. Stoichiometric quantities of copper(I) salts seem to mediate such reactions in their own right; alkenyl and aryl halogenosilanes homo-couple in good yield in polar aprotic solvents <2000BCJ985> and as little as 5% CuI may suffice, with no other metal involved, providing that 1 equiv. of TBAF is present <1997JCS(P1)797>.



1.11.2.6.2 Substitution of tin

The Stille reaction (not covered as such in the first volume of COFGT (1995)) is the palladium(0)-catalyzed cross-coupling of an organostannane and an organic electrophile; the latter is usually an sp^2 halide or triflate. One organic group is generally transferred from the tin reagent and the order of group transfer is alkynyl > alkenyl > aryl > allyl, benzyl > alkyl. A wide variety of functional groups can be tolerated on both reaction partners, and the reaction proceeds with an excellent degree of retention of the configuration of unsymmetrical alkenyl moieties. The attractive balance between reagent stability and reactivity has made this one of the most popular $\text{C}-\text{C}$ bond-forming protocols. General reviews of historical progress and applications have appeared <1997OR1, B-1998MI167, 2002TCC(219)87, B-2002MI263>. Although sometimes perceived as less sterically tolerant than some other palladium-catalyzed reactions (e.g., Suzuki), it may in fact proceed where other cross-coupling strategies fail. It is a favored tool for the preparation of radiolabeled compounds <2003MI263>, has wide applications in biaryl synthesis <1998T263, 2002CRV1359>, and is a particularly good performer in intramolecular mode, leading to extensive use in macrocyclizations <1999JCS(P1)1235, 2002JOM(653)261>. Stille coupling can be incorporated as one of several mechanistic steps in palladium-catalyzed tandem or cascade processes, notably involving Heck coupling (see Section 1.11.2.8.3.(i)).

The traditional catalyst $\text{Pd}(\text{PPh}_3)_4$ is now joined by several others, with AsPh_3 and $\text{P}(\text{2-furyl})_3$ emerging as particularly successful ligands. A major advance is the discovery of the $\text{Pd}/\text{PBu}_3^t/\text{CsF}$ catalyst system, which promotes the coupling of unactivated aryl chlorides (Equation (40)) <2002JA6343>. This catalyst can also be employed for the smooth coupling of very hindered alkenyl or aryl substrates, even leading to some tetra-*o*-substituted biaryls. Another important breakthrough is the development of the $\text{Pd}/\text{PCy}(\text{pyrrolidinyl})_2/\text{TMAF}$ system (TMAF = tetra-*n*-methylammonium fluoride), which catalyzes the room temperature Stille cross-coupling of alkyl halides possessing β -hydrogens with alkenyl and aryl tin reagents (Equation (41)) <2003AG(E)5079>. The $\text{Pd}/\text{PBu}_3^t\text{Me}/\text{TBAF}$ system is also highly active for sp^3 -electrophile-alkenyl tin cross-coupling <2003JA3718>. Relatively few applications of other “high-performance” ligands are made for Stille cross-coupling; those used for successful biaryl syntheses include iminophosphines <1999JOM(576)169, 2002T6881>, nucleophilic *N*-heterocyclic carbenes <1999JOM(585)348>, palladacycles <1998CC2095>, and phosphinous acid <2003JOC7551>, the latter allowing coupling of aryl chlorides and arylstannanes in neat water. The complex $\text{Pd}(\text{N-succinimide})(\text{PPh}_3)_2\text{Br}$ is a superior catalyst for cross-coupling of benzyl or allyl bromides with alkenylstannanes <2003CC2194>. There are limited but encouraging applications of polymer-supported palladium catalysts <1999SL327, 2003TL639>.

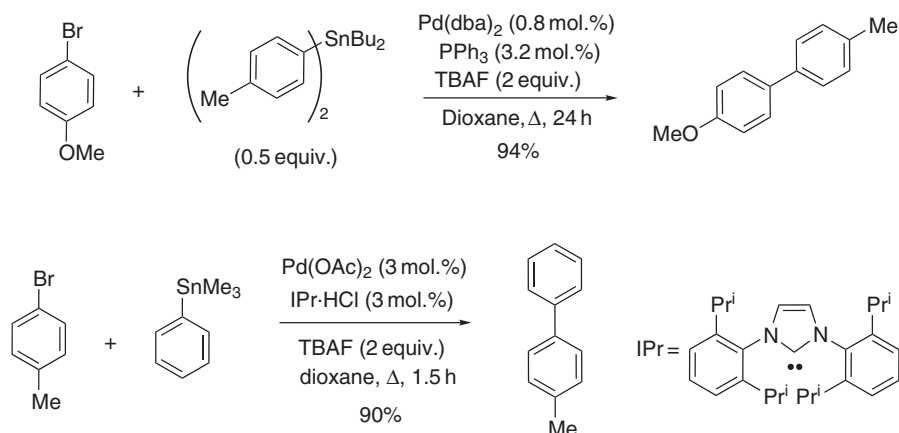


Alkyl bromide	Aryl stannane	Yield (%)	Alkyl bromide	Alkenyl stannane	Yield (%)
$n\text{-C}_{10}\text{H}_{21}\text{—Br}$		72			60
$\text{EtOOC}(\text{CH}_2)_4\text{—Br}$		61			78
$\text{EtOOC}(\text{CH}_2)_4\text{—Br}$		63	$\text{EtOOC}(\text{CH}_2)_4\text{—Br}$		89
$\text{NC}(\text{CH}_2)_5\text{—Br}$		68	$\text{EtOOC}(\text{CH}_2)_4\text{—Br}$		73
$\text{THPOCH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{—Br}$		64	$\text{NC}(\text{CH}_2)_5\text{—Br}$		68

(41)

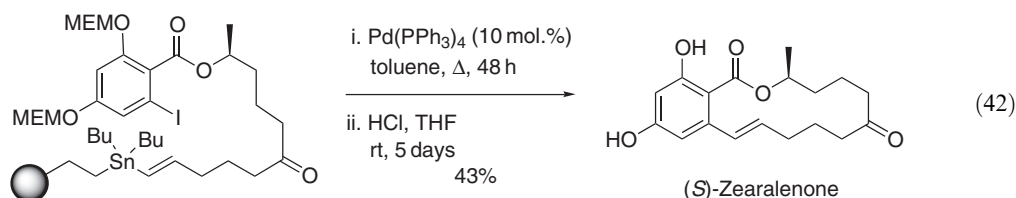
In addition to the often-used halides and triflates, other new electrophile partners are known, including hypervalent iodides [\[1996TL3723, 1996SC4311\]](#), vinyl phosphates [\[1997JA5467, 1998CC1757, 1999TL701\]](#), diaryl- or distyryltellurium(IV) compounds [\[1999CC2117\]](#) along with a variety of sulfur-based reagents [\[1999JOC2796, 2003OL801, 2003JA15292\]](#), although aryl mesylates are unreactive [\[1995JOC6895\]](#). While β -trialkylstannyl- α,β -unsaturated carbonyls remain poor reaction partners, the presence of a heteroatom in the vinylstannane accelerates coupling reactions, possibly due to internal coordination of palladium in the transmetalation step [\[2000JOC5917\]](#). Somewhat unexpectedly, hexaalkyl ditin—normally a stannylating agent—reacts under Pd catalysis with (chloroarene)Cr(CO)₃ complexes to give alkylarenes [\[2001OM1279\]](#). The beneficial effects of certain additives in the Stille reaction, such as LiCl or a Cu(I) co-catalyst, have been known for some time; more recently, the presence of CuCl has been shown to accelerate coupling with sterically congested substrates, and thus suppress *cine*-substitution, occasionally a complication in the Stille reaction [\[1999JA7600\]](#). Other promoters include diethylamine, which may suppress β -elimination in Stille alkylations [\[2001CC1662\]](#), and TBAF, which probably activates the tin reagent as a hypervalent fluoro-stannate; as a result, more than one organic function may be transferred ([Scheme 25](#)) [\[1999SL63, 2001OL119\]](#). Indeed, the designed use of hypervalent tin reagents generally gives good results [\[2001OM1020\]](#). Cross-coupling reactions may also be carried out in aqueous [\[1999JOM\(576\)305\]](#) or supercritical [\[1998CC1397\]](#) media, and can be accelerated by microwave irradiation [\[2002ACR717\]](#).

One of the perceived drawbacks of using organotin reagents is their toxicity, and some efforts have been made to address this issue. The use of fluoros [\[1996JOC6480, 1997JOC5583\]](#), monoorgano [\[1995TL125, 1997JOC5242\]](#), and catalytically regenerated [\[2001JA3194\]](#) tin reagents has been suggested, along with water-soluble, reusable stannatranes [\[2001TL5837\]](#).

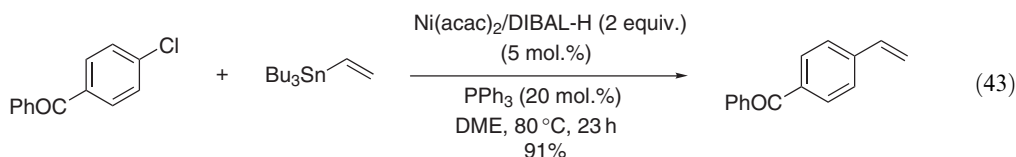


Scheme 25

Indeed, highly elaborate stannatranes may be used as cross-coupling partners [<2000OL1081>](#). Solid-phase Stille coupling can be performed, with either the electrophile or the tin reagent being immobilized [<2003T885>](#); polymer-supported, catalytically regenerated organotin reagents may even be used [<2003TL8601>](#). An elegant solid-phase cyclo-release strategy is used in a synthesis of the macrocyclic natural product (*S*)-zearalenone (Equation (42)) [<1998AG\(E\)2534>](#).



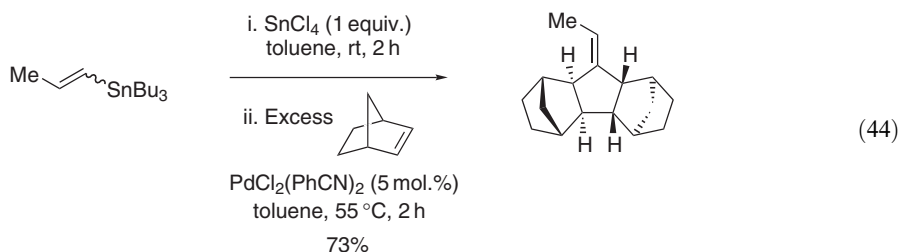
Other transition metals, at one time heralded as potential rivals to palladium, have not emphatically established themselves as catalysts. Despite the beneficial “copper effect” observed for a good number of examples of palladium-catalyzed Stille reactions, copper has only limited success on its own. CuCl catalyzes heteroarylstannane cross-coupling with allylic iodides [<1999SL1942>](#). Otherwise, a fairly large catalytic quantity (10%) of CuI or MnBr₂ effects reaction of aryl or alkenyl stannanes with *sp*² iodides, provided NaCl is present [<1997JOC4208>](#); reactions proceed in milder conditions when more reactive hypervalent iodine substrates are used [<1996JOC9082, 1998TL2131>](#). The use of 1.5 equiv. of copper(I) thiophene-2-carboxylate mediates the very smooth cross-coupling of aryl-, heteroaryl-, and vinylstannanes with aryl and vinyl iodides under mild conditions [<1996JA2748>](#). Nickel catalysts have a few applications: in addition to the “simple” catalysis of biaryl formation from aryltin reagents and iodonium ions by Ni(acac)₂ [<1999JCS\(P1\)2661>](#), a variety of aryl halides, including chlorides, cross-couple with alkenylstannanes in the presence of nickel(0) complexes (Equation (43)) [<1998S1544>](#).



Palladium and copper catalyze cross-coupling of diaryl- or distyryltellurium dichloride with heteroaryl- or β -styrylstannanes in the presence of a base [<1999CC2117>](#). Similarly, aryllead(IV) triacetates cross-couple with organotin reagents under mild conditions in the presence of

$\text{Pd}_2(\text{dba})_3 \cdot \text{CHCl}_3$ catalyst, although an excess of base (NaOMe) is necessary, along with a CuI co-catalyst to suppress homo-coupling <1998CC1317>. PdCl_2 -catalyzed arylation of a number of alkenyl- or arylstannanes can be performed in mild conditions using triaryl antimony(V) <2000JOM(610)38> or triaryl bismuth(V) <2001SC1027> derivatives.

Some aryltin reagents cross-couple with alkenes in Heck reactions <2000BCJ1409>. A cascade process, reminiscent of some applications of the Heck reaction, explains the exclusive formation of the *exo-exo-cis-trans-cis*-pentacycle when alkenyltin trichloride reacts with an excess of norbornene (Equation (44)) <2003JOM(687)567>.



The palladium-mediated homo-coupling of organostannanes is less familiar than cross-coupling reactions, and requires reoxidation of the intervening $\text{Pd}(0)$ complex to render the operation catalytic. Chemical oxidants may be employed <1997SL1199, 1997SC641>, but air may also be a simple alternative. A palladium complex with an iminophosphine ligand is a particularly good catalyst for symmetrical arylstannane homo-coupling <1999JOM(576)169>. In the presence of a $\text{PdCl}_2(\text{MeCN})_2/\text{O}_2$ system, alkenylstannanes undergo efficient homo-coupling and also chemoselective cross-coupling with allylstannanes giving well-defined 1,4-dienes <1997SL791>. CuCl co-catalyzed intramolecular versions of di(alkenyl stannane) coupling are occasionally used for complex cyclic skeletons <1996JA1215, 1996JOC700>. As an alternative to palladium, the use of 10% CuCl_2 or MnBr_2 in the presence of iodine may effect homo-coupling of aryl- and (*E*)-styrylstannanes on heating <1999TL2383>. Similarly, intramolecular coupling of two stannane functions can be achieved through the action of an excess of CuCl <2000OL481>; a double intermolecular $\text{Cu}(\text{NO}_3)_2$ -induced homo-coupling is described in a strained cyclophane synthesis <2000OL2081>.

1.11.2.7 Substitution of a Metal

Organometallic reagents play a fundamental role in many of the C—C bond-forming reactions considered in this chapter, but they are treated throughout the various sections according to the identity of the reaction partner. The exception, treated here, is the $\text{NiCl}_2(\text{PMe}_3)_2$ -catalyzed cross-coupling reaction between aryl or heteroaryl nitriles and alkyl, alkenyl, or aryl Grignard reagents, through C—CN bond cleavage. The direct addition of the organometallic nucleophile to the nitrile is suppressed by prior attenuation with LiOBu^t or LiSPh <2001TL6991, 2003TL1907>.

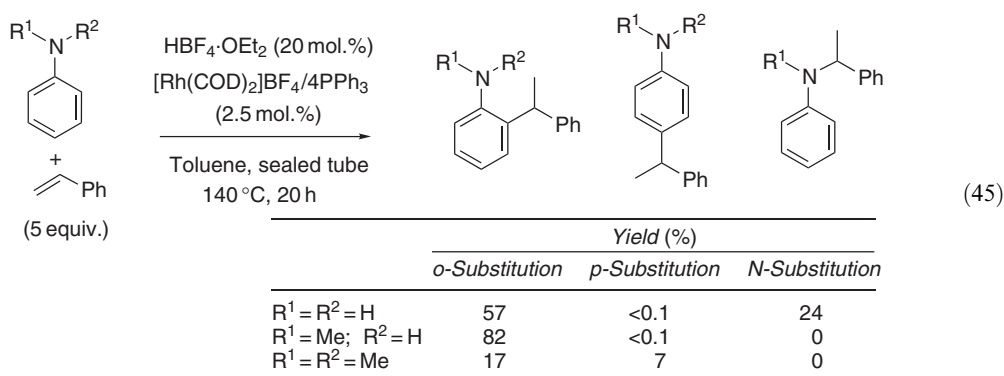
There is very little progress to report on homo-coupling reactions, as can be noted in a recent historical perspective <B-2002MI973>. This is hardly surprising from a synthetic viewpoint since the most common precursors of the organometallic reagents, the corresponding halides, undergo coupling reactions at least as easily. Nonetheless, mild conditions are reported for palladium- and copper-catalyzed dimerization of aryl lead triacetates <1997SC1893>. Air serves as the reoxidant in the room temperature $\text{Pd}(\text{OAc})_2$ -catalyzed homo-coupling of triaryl bismuth reagents; when two different aryl derivatives are used simultaneously, mixtures of homo- and cross-coupled biaryls are obtained <1999BCJ1851>. Oxidative homo-coupling of arylzinc reagents is achieved by the use of NCS or O_2 in the presence of a palladium catalyst <2001BCJ2415>. TiCl_4 <2000T9601> or oxovanadium(V) compounds <1998OM5713> mediate a similar reaction for a range of aryllithium and Grignard reagents.

Aryllithiums react with alkylaluminum halides to give mixed organoaluminum species, which are transformed into the cross-coupled alkyl arenes by treatment with an excess of an oxovanadium(V) reagent <1998JA5124>. Similarly, cross-coupling reactions between an aryl and an alkyl substituent in certain organozinc reagents are preferred to intermolecular homo-coupling reactions in oxidative conditions ($\text{VO}(\text{OEt})\text{Cl}_2$ or AgBF_4) <2000JOC1511>.

1.11.2.8 Substitution of Hydrogen

1.11.2.8.1 Friedel–Crafts alkylations using alkenes and alkanes

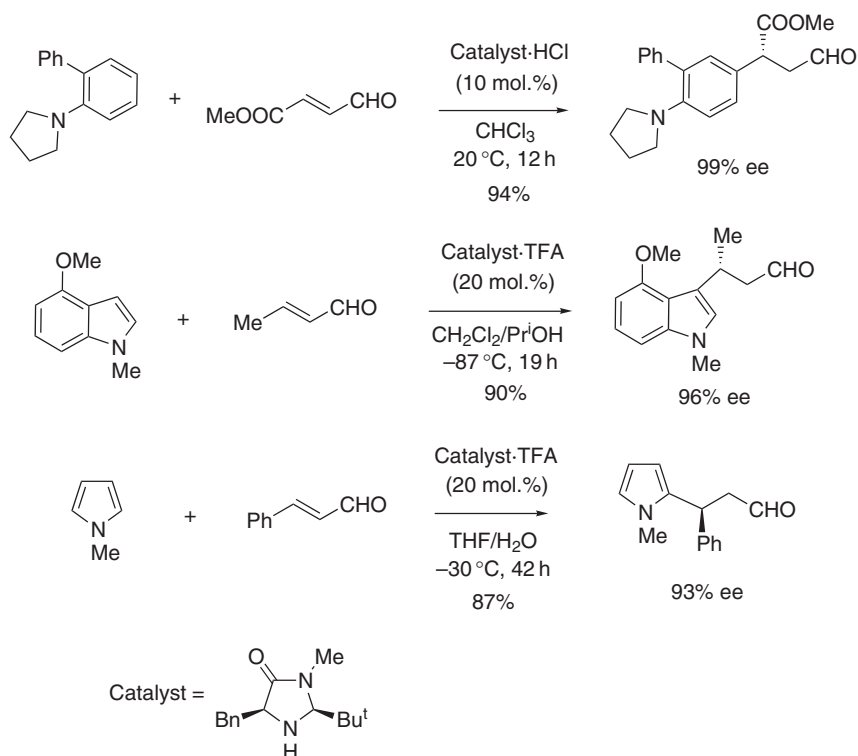
The Friedel–Crafts alkylation of arenes with unactivated alkenes is an important industrial operation <2002MI3>. The search for cleaner, more environment-friendly processes reveals new solid catalysts based on clays <1999JMO(A)(145)237>, zeolites <1999AC(A)(184)231>, or AlCl_3 in immobilized or encapsulated form <1995CC2037, 2000JCA(195)412, 2002TL4555>. In at least one example, triflic acid is a useful catalyst <2002MI37> although $\text{Sc}(\text{OTf})_3$ is active only when immobilized in ionic liquids <2000CC1695>. Halogen-free ionic liquids improve the product yield dramatically in the alkylation of benzene with 1-decene, although a sulfuric acid catalyst is still required <2002GC134>. Supercritical conditions are used to effect efficient, continuous-flow, solid acid-catalyzed alkylation of aromatics with propene <1998CC359>. Significant *ortho*-regioselectivity is observed in the HBF_4 -mediated alkylation of anilines with styrene when a catalytic amount of a rhodium complex is present (Equation (45)) <1999SL243>.



Friedel–Crafts alkylation with alkenyl chlorosilanes is reviewed <2000AOC145>. Michael-acceptor alkenes are convenient partners for Lewis acid-catalyzed alkylation of active aromatic compounds. With furans, $\text{Cu}(\text{OTf})_2$ is the superior catalyst for C2 alkylation with α,β -unsaturated ketones <2000JCR(S)220>. An alternative “green” procedure involves the use of a solventless K-10 clay-catalyzed system under microwave irradiation <1998TL9301>; competing Diels–Alder reactions are disfavored under these conditions. Indoles are easily alkylated at C3 with Michael-acceptor alkenes in the presence of rare earth metal triflates under conventional conditions <1996SL1047> or in supercritical CO_2 in the presence of a fluorinated organic additive as an accelerator <2002OL1115>. Indium tribromide, too, is a useful, reusable catalyst for the addition of indoles to nitro alkenes in aqueous medium <2002S1110>.

A major recent development in this area is the catalytic enantioselective version of the reaction. MacMillan’s enantioselective “organo” catalytic system, which exploits the reversible formation of iminium ions with chiral imidazolidinones, lends itself conveniently to Friedel–Crafts reactions with α,β -unsaturated aldehydes: impressive ee and yields are observed in the alkylation of pyrroles <2001JA4370>, indoles <2002JA1172>, and electron-rich benzenes <2002JA7894> under very mild conditions (Scheme 26). $\text{Cu}(\text{II})$ /chiral bisoxazoline complexes also catalyze the alkylation of indoles, furans, and electron-rich benzenes with β,γ -unsaturated α -keto esters in good yields and with very high ee (above 99% in some cases) <2001AG(E)160>. Similarly, alkylidene malonates alkylate indoles in good yield, although the ee is lower (40–60%) <2001CC347>.

There is little development of the use of alkanes for Friedel–Crafts alkylations. Gallium chloride promotes the alkylation of naphthalene or phenanthrene using cycloalkanes with a notable preference for the formation of the equatorial isomer; yields and regioselectivities (where appropriate) remain modest, however <2003JOC6752>. 1,1-Cyclopropanedicarboxylate esters react by ring opening to alkylate indoles in the presence of $\text{Yb}(\text{OTf})_3 \cdot \text{H}_2\text{O}$, with C—C bond formation occurring specifically at the more hindered position of the cyclopropane ring. However, high-pressure conditions are required to obtain reasonable yields <1997TL5949>.

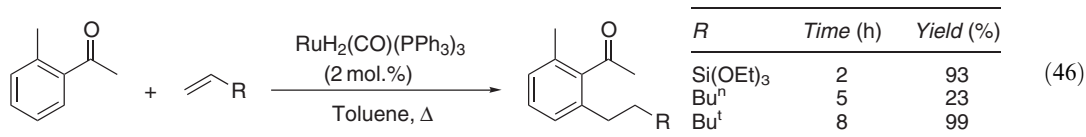


Scheme 26

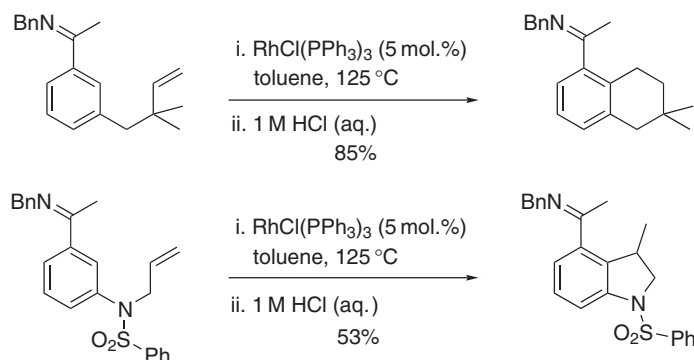
1.11.2.8.2 Transition metal-mediated substitution of arenes using alkenes

Aromatic compounds can be alkylated with alkenes in highly efficient, transition metal-catalyzed processes. Although at a first glance these transformations formally resemble Friedel–Crafts alkylations, the reaction mechanisms are fundamentally different and in consequence so are the various aspects of regioselectivity. The process is best seen as a hydroarylation of (i.e., the addition of an aromatic $\text{C}=\text{H}$ bond across) an alkene. Various applications and discussions of the mechanistic aspects of this exciting new field are reviewed [<1999AG\(E\)1698, 1999EJ11047, 2002CRV1731>](#).

Murai's pioneering work shows that acyl benzenes and related compounds undergo high-yielding, selective alkylation at the *ortho*-position in the presence of ruthenium catalysts—typically $\text{RuH}_2(\text{CO})(\text{PPh}_3)_3$ —with the alkyl moiety being introduced with remarkable regioselectivity, appearing as its anti-Markovnikov isomer [<B-1999MI195>](#). It is likely that pre-coordination of the metal catalyst induces *ortho*-metallation of the arene followed by the insertion at the least hindered end of the olefin then formation of the $\text{C}=\text{C}$ bond by reductive elimination, according to [Equation \(46\)](#). This reaction is quite widely applicable with respect to both the alkene (often a vinyl silane derivative, but simple cases are described too) and the functionalized aromatic component, the latter of which may be an aryl or heteroaryl ketone [<1995BCJ62, 1995JOM\(504\)151, 1997JOM\(530\)211, 1998JA4228>](#), ester [<1996CL109>](#), or aldimine [<1996CL111>](#). The only drawbacks are that dialkylated aromatics may be formed as byproducts (if both *ortho*-positions are free), and the occasional observation of coupled arene–alkene (Heck-type) byproducts. In the $\text{Ru}(\text{I})$ -catalyzed alkylation of ring-oxygenated acetophenones, the success of the reaction may depend on the nature and position of the oxy-substituent(s), the identity of the alkene partner, and even the nature of the catalyst [<1997JOM\(530\)211>](#).



Rhodium-based catalysts effect similar *ortho*-alkylation reactions of aromatic ketones <1999JA6616>, aldimines, and ketimines <2000AG(E)3440, 2001TL4853>, while 2-phenylpyridines are *ortho*-alkylated in the phenyl ring in the presence of Wilkinson's catalyst. In an exception to the regioselectivity trend, $\text{Ru}_3(\text{CO})_{12}$ -catalyzed hydroarylation of styrene with *N*-methylaniline gives exclusively the Markovnikov-coupled product <1999CC1133>; nevertheless, this result is remarkable for its chemoselectivity, since N—H bond insertion is actually a feasible alternative. Intramolecular versions of the Rh-catalyzed reaction, involving hydroarylation of tethered alkenes by aromatic imines (but not ketones) (Scheme 27) <2001JA9692> or nitrogen heterocycles <2001JA2685>, lead to annulated products. Recent results show that an *ortho*-directing group on the aromatic reagent is not a prerequisite: benzene and nonactivated derivatives are alkylated with simple alkenes by an iridium complex catalyst, giving a significant preference for straight-chain alkyl isomers <2002JMOC(A)(180)1>, and a catalytic amount of a ruthenium complex likewise induces addition of benzene to ethene and propene under mild conditions <2003JA7506>.



Scheme 27

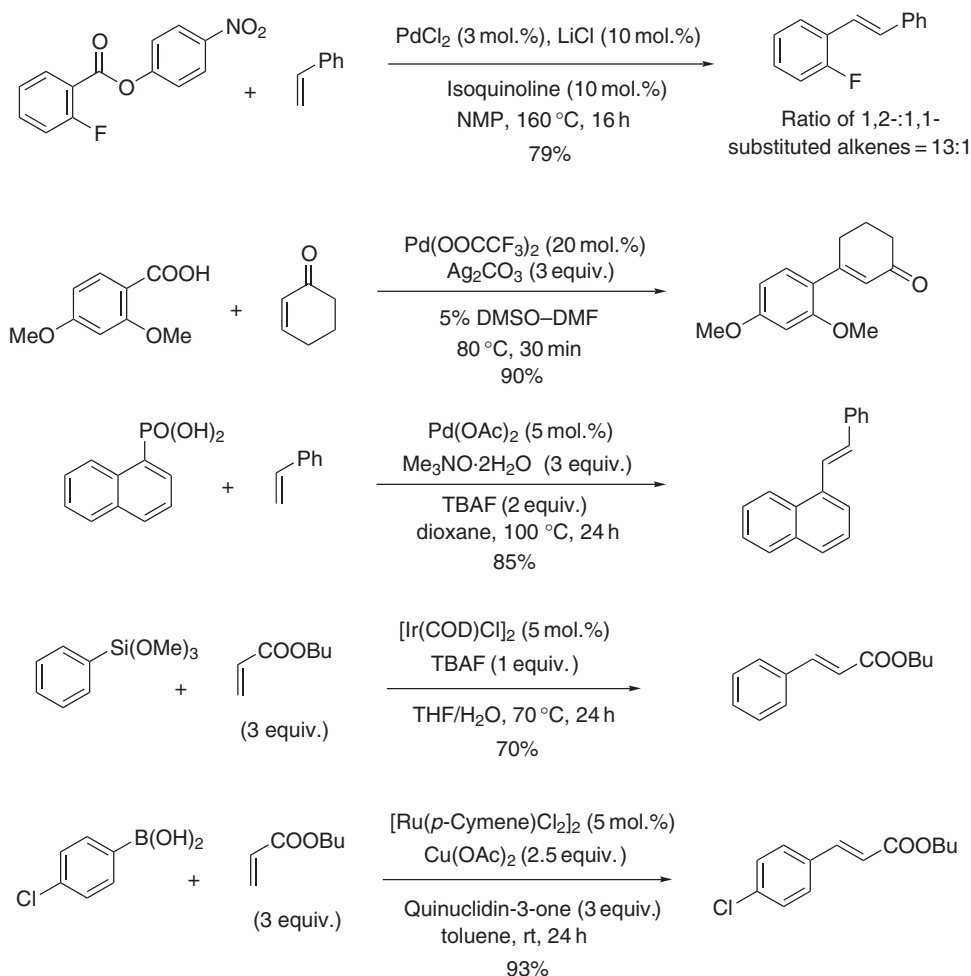
1.11.2.8.3 Transition metal-mediated substitution of alkenes

(i) Initiation by C—X bond insertion

The palladium-catalyzed coupling of an aryl or vinyl halide (or triflate) with an alkene is generally referred to as the Heck reaction. This highly regio- and stereoselective transformation has enjoyed an astonishing number of synthetic applications in recent years and is one of the most powerful methods of C—C bond formation available today, as testified by regular general reviews <B-1996MI153, B-1996MI712, B-1998MI99, B-1998MI208, 2000CRV3009, B-2001RCC315, B-2002MI1133>. Industrial applications are emerging <2001CJC1086, 2002MI101, B-2002MI1209>. Although they are not themselves the subject of this review, mechanistic studies <1998CSR427, 2000ACR314, 2000SL925> have helped to understand the various (often complex, sometimes competing) molecular processes involved and have thus aided the conception and development of new, more efficient catalytic systems.

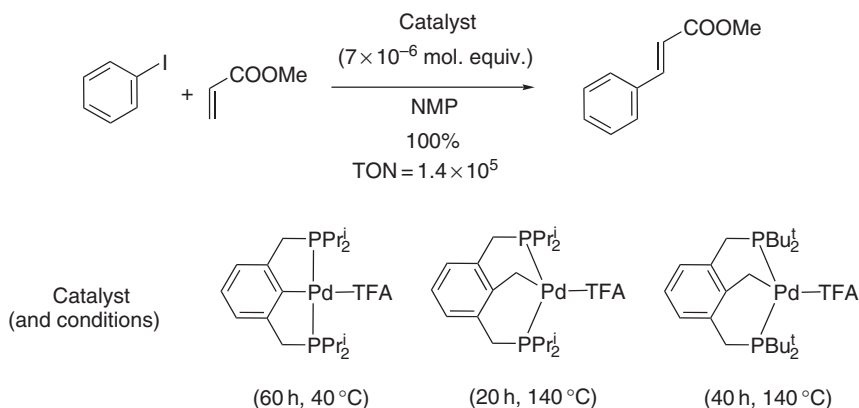
Apart from the mainstay use of iodides and bromides and the increased interest in aryl chlorides as Heck-coupling reaction partners (*vide infra*), a number of other leaving groups may be used successfully (Scheme 28); these include carboxylic acids <2002SL1721, 2002JA11250>, esters <2002AG(E)1237>, anhydrides <1998AG(E)662>, certain tosylates <2002TL573>, and aryl derivatives of the main-group elements: lead <1998JOC5748>, tin <2000BCJ1409>, silicon <2000BCJ1409>, antimony <1999JOM(574)3>, and phosphorus <2003JA1484>. Some of these main-group reagents may prove to be more effective than halides for Heck coupling when rhodium-, ruthenium-, or iridium-based catalysts are used <2001JA5358, 2001JA10774, 2002AG(E)169, 2003AG(E)89>. Generally though, relatively little progress has been made with catalysts based on metals other than palladium; the recognized economic argument for the development of cheaper catalyst systems, based on nickel or cobalt, for example, has inspired only isolated studies <1997TL8533, 2002TL5901, 2002OL2257>.

Phosphine ligands for the active palladium species remain popular and various refinements have been investigated in order to improve catalytic performance, both in terms of catalyst stability and observed turn-over number (TON), notably with a view to performing Heck-coupling reactions with traditionally unreactive aryl chlorides <B-1999MI207, 2001T7449, 2001CEJ2908, 2002AG(E)4176>. A wide range of additives (such as tetraalkylammonium salts, for example) often plays an important



Scheme 28

role, as can the identity of the precatalyst. The most active ligands resemble those which give best results in Suzuki reactions, and include sterically hindered electron-rich monodentate phosphines (e.g., P^tBu_3) [<1999JA2123, 2000SL1589, 2001JA6989>](#), chelating diphosphines [<1998CC1863>](#), rigid tetraphosphanes [<2003EJO1091, 2003TL1221>](#), and phosphinous acids [<2001JOC8677>](#). Palladacycles, “single phosphine” catalysts, have very high reactivity due to their nearly free coordination shell [<1995AG\(E\)1844, 1999JOM\(576\)23, 2003CC1787>](#). Another type of active system containing a metal–carbon σ bond are the so-called “pincer” complexes [<1997JA11687>](#), which display amongst the highest TONs reported for Heck reactions (Equation (47)) [<2003CC1787, 2003T1837>](#); the catalytic mechanism for these complexes may be quite different to the traditional Heck cycle.



(47)

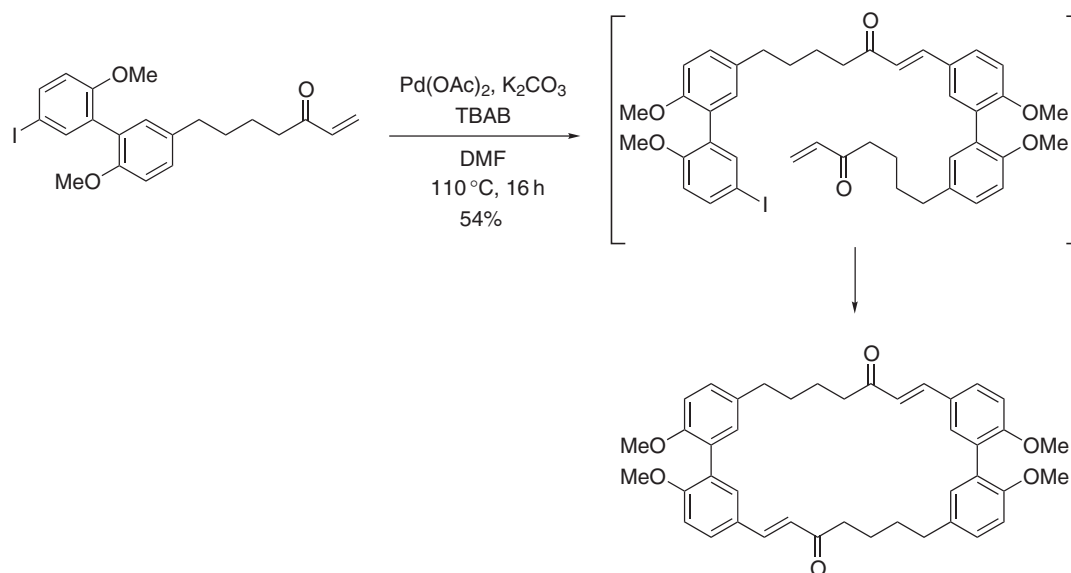
There is a developing interest in phosphine-free ligands for palladium complex catalysts; these include phosphites <1998SL792>, thioethers <2001TL7345>, chelating nitrogen heterocycles <2003OL1451, 2003EJI1161>, diazabutadienes <2003JOM(687)269>, and macrocyclic trienes <2003OL1559>. Stable *N*-heterocyclic carbenes are a recently developed class of catalyst ligands <1995AG(E)2371, 2002JOM(653)69> and can be used in combination with phosphines. Some phosphine-free palladacycles and pincer-type complexes catalyze the Heck coupling of aryl iodides or active aryl bromides with alkenes, and although they are not always as immensely active as their phosphine-based analogs, usually give satisfactory results <2003T1837, 2003OL983>.

Environmental issues have affected other developments of the Heck reaction. Although the general utility of the reaction conditions is often left unexplored, alternative media in which successful reactions may be carried out include: reusable solvent systems <1999OL997, 2000CEJ1017, 2002OL4399>, aqueous solution <1999JOM(576)305, 2002MI393>, and compressed or supercritical fluids <1995OM4023, 1999TL2221, 2001TL8555, 2002JMOC(A)(180)35>, although use of these media is not always beneficial <2000SL1661>; microwave acceleration of the Heck reaction is observed in some cases <2002ACR717, 2002S1611, 2002JOC6243>. A variety of convenient solid supports for the Heck reaction exist, providing for either halide or alkene immobilization <1999CRV1549, 2003T885>. Heterogeneous catalysts based on palladium phosphine complexes are usually limited to reactions involving aryl iodides <1997TL6581, 1998JOM(567)219>, although they can work in aqueous medium <2002SL2045> or supercritical carbon dioxide <2002CC640>; dendritic modification enhances catalytic activity considerably <2003OL1197>. Heterogeneous palladium metal catalysts <2001JMOC(A)(173)249> involving different kinds of supports—carbon, inorganic oxides, molecular sieves, clays, etc.—give satisfactory results, with the obvious advantages of easy catalyst separation and possible recycling; stabilized palladium metal colloids are also active catalysts. Although the substrates are usually aryl iodides (or bromides, to a lesser extent), some catalysts exhibit high activity with aryl chlorides <2002MI348, 2003TL3649>. One problem which remains with immobilized catalysts is leaching; indeed, it may be that, at least in some cases, catalytic activity is due to leached homogeneous species <2000CEJ843, 2002CEJ622>. In any event, palladium nanoparticles may play an important role in catalysis <2000AG(E)165>.

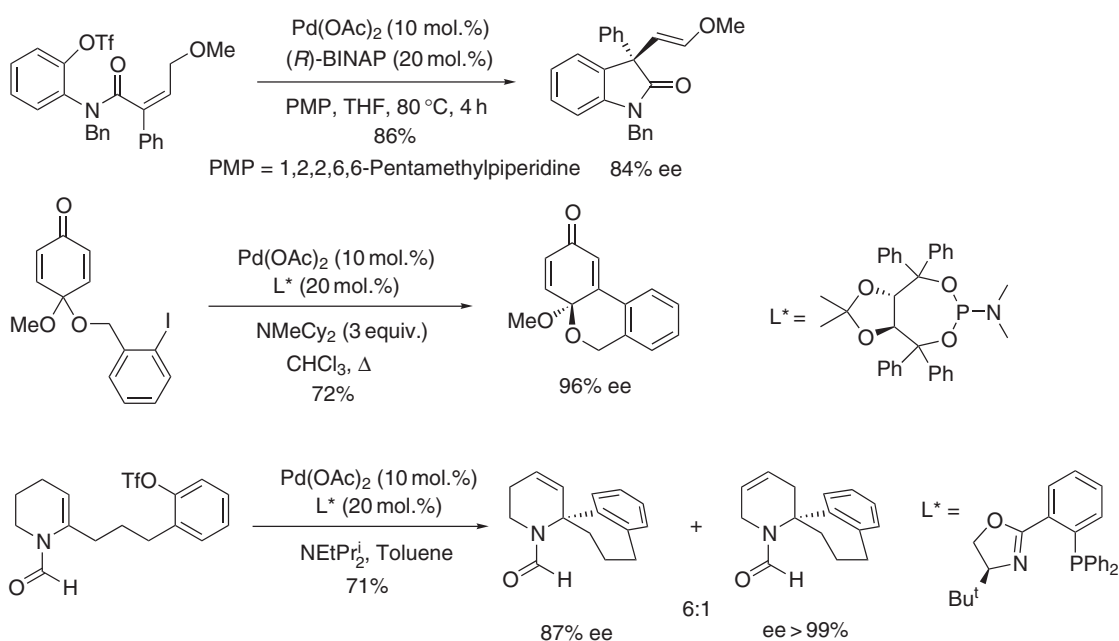
The intramolecular version of the Heck reaction has developed into a particularly useful tool in organic synthesis <1996MI447, B-1998MI231, 2002OR157, B-2002MI1223>. More highly substituted alkene moieties are tolerated than in the intermolecular case, and otherwise difficult-to-form quaternary centers can be constructed effectively. Five-, six-, and seven-membered rings (both carbocyclic and heterocyclic) are formed most efficiently, although smaller and larger rings are also accessible; macrocyclizations well above 20-membered rings can be achieved. For up to six-membered ring closures, the *exo*-mode predominates, while for larger rings the *exo/endo*-selectivity depends on the particular system. The success of the operation depends also on the strain involved in the cyclization process. Thus, with an ω -alkenyl chain borne by an *o,o'*-disubstituted biphenyl, formation of a 13-membered cycle is less favorable than an intermolecular Heck coupling; however, the resulting coupled product suffers no such constraint and undergoes smooth intramolecular reaction to give a 26-membered macrocycle (Scheme 29) <2002TL9327>.

In its original form, the Heck reaction is not stereogenic. However, when the *syn*- β -H elimination from the organopalladium intermediate occurs from a carbon atom not originally part of the alkene system (as in the case of a cyclic alkene), a chiral product is liberated. The success of this operation clearly depends on the selectivity of the β -H elimination. Palladium complexes bearing chiral ligands serve as effective enantioselective catalysts for this, the so-called asymmetric Heck reaction <1996MI119, 1997T7371, 1998MI311, B-1999MI457, 1999JOM(576)1, 1999JOM(576)16, B-2000MI136, B-2002MI1283>. BINAP is the most commonly used ligand, although others sometimes give better results. Intermolecular examples remain limited, for the most part, to simple cyclic alkene substrates (particularly dihydrofurans) with the emphasis being on catalyst optimization <2000JOM(603)40, 2003CEJ3073>. The intramolecular asymmetric Heck reaction has enjoyed much more success for the enantioselective formation of diverse tertiary and quaternary centers <B-2000MI675>, notably in the synthesis of complex natural product structures <2003CRV2945>; illustrative examples are shown in Scheme 30 <1997JOC595, 2003JCS(D)2017, 2003JA6261>.

Perhaps one of the most endearing aspects of the Heck reaction is the facility with which it can be incorporated into tandem, domino, or cascade processes, often leading to highly complex molecular structures from simple components in a very efficient and selective manner. These processes may involve further reactions of the organopalladium intermediate, or of the coupled alkene product, or both. Double or multiple Heck coupling is possible, as are combinations with many other reactions (and in various orders), be they palladium-catalyzed or not <1999JOM(576)65, 1999JOM(576)88, 2000T5959, 2002JOM(653)129, B-2002MI1179,



Scheme 29



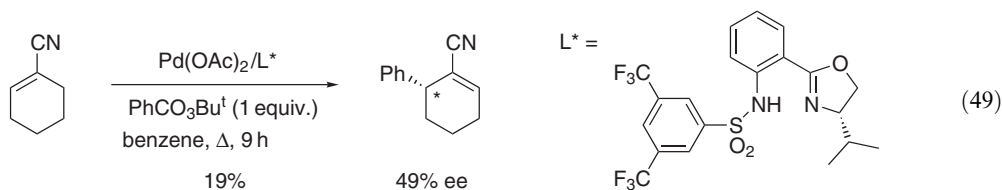
Scheme 30

B-2002MI1369. Recent examples, illustrated in [Scheme 31](#), include Heck/aromatic $\text{C}-\text{H}$ activation [2003CEJ1511](#), Heck/carbonylation [2003OL1523](#), Heck/Suzuki [2003TL267](#), aminocyclization/Heck [2003BCJ1055](#), and Heck/Diels–Alder [2002HCA3161](#).

(ii) Initiation by $\text{C}-\text{H}$ bond insertion

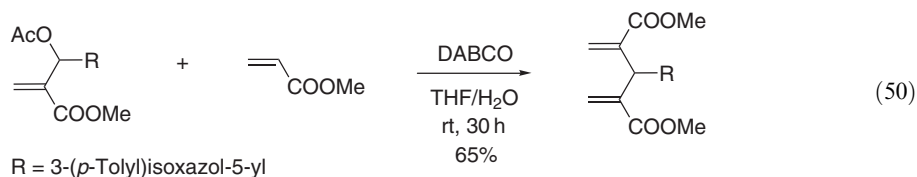
Organometallic species generated by initial metal insertion into vinylic $\text{C}-\text{H}$ bonds may be alkylated by other alkene functions (similar to the reactions seen for arenes in [Section 1.11.2.8.2](#)). α,β -Unsaturated ketones and esters are alkylated by vinyl silanes, styrene, or other alkenes (the latter give variable yields) using ruthenium catalysts [1995JA5371](#), [1995CL679](#) while ruthenium or rhodium

acrylate esters via ruthenium complex catalysis under O_2 <2001JA337> or in the presence of a catalytic quantity of $Pd(OAc)_2$ and a reoxidant <1999OL2097, 2003JA1476>. Intramolecular trapping in the Pd-catalyzed oxidative cross-coupling of 2-phenylphenols with acrylates gives variable yields of the tricyclic dibenzo[*b,d*]pyran systems <1997CL1103>. One asymmetric variant of this type of transformation is described, in which cyclic alkenes react with benzene in the presence of $Pd(OAc)_2$, a chelating, nonracemic oxazoline ligand, and *t*-butyl perbenzoate as the oxidant (Equation (49)). The β -elimination occurs from the opposite side of the entering aryl group, furnishing the coupled products in modest yield and ee up to 49% <1999CL55>.



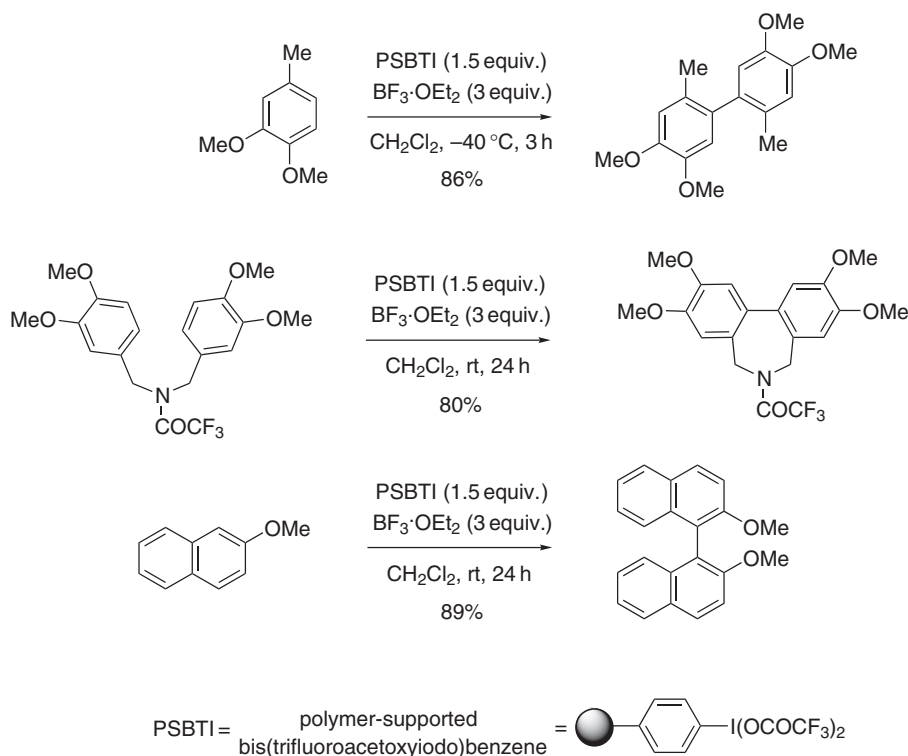
1.11.2.8.4 Miscellaneous methods

Assuming reagent toxicity is not an issue, the asymmetric coupling of phenols with aryllead reagents is quite successful in the presence of brucine; double coupling is observed if both *ortho*-positions are free, with very good *dl:meso* selectivity for the terphenyls thus obtained <1999JA8943>. Heck-type coupling of iodobenzene with styrene can be achieved without a catalyst in supercritical water in the presence of a mild base <2003CC1548>. DABCO catalyzes the reaction of acrylate derivatives with the acetate esters of Baylis–Hillman adducts, in what amounts to a formal hydrogen substitution at the α -carbon. This reaction constitutes an entry to substituted 1,4-pentadienes, although byproducts may also be formed (Equation (50)) <2003SL1439>.



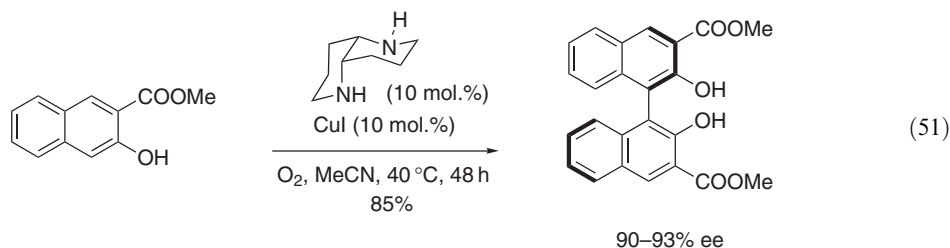
Oxidative (usually symmetrical) aromatic coupling is a useful way of obtaining biaryls, particularly binaphthols <B-2002MI479>. The technique is widely applicable to electron-rich aromatics, but is more challenged in cases of highly substituted aryls and for unsymmetrical coupling. One useful way to overcome these two hurdles simultaneously is to perform the reaction intramolecularly by using a temporary tether between the two reacting arene moieties; this continues to be a valuable tool for natural product synthesis. Various transition metal species can be used as oxidants in either stoichiometric or catalytic amounts, but organic oxidants may be employed instead; the use of hypervalent iodine reagents remains popular <2001OR327>. The nitrosyl cation gives binaphthyls with simple alkyl naphthalenes with minimal ring nitration <1996JOC788>. A few solid-supported metal-based catalysts which function under aerobic conditions have been developed for this reaction <1996SC3075, 1997JOC3194, 1998MI113>. The well-known dehydrogenating agents Pd–C and Pt–C are rarely used, but do induce oxidative dimerization of some aromatic *N*-heterocycles <1997JOC3013, 1998SI596>. A polymer-supported hypervalent iodine reagent is highly efficient and can be recovered and recycled (Scheme 32) <2001T345>.

Most progress appears in the area of catalytic asymmetric reactions, almost exclusively dedicated to the enantioselective coupling of 2-naphthols. Following on from innovative work in the early 1990s, chiral diamine–copper complexes are now available for the enantioselective homo-coupling of 3-hydroxynaphthalene-2-carboxylates in aerobic conditions (Equation (51)) <1999JOC2264, 2001OL1137>. It is noteworthy that the ee falls off considerably if no carboxylate is present, suggesting a metal-coordinating role for this function in the catalytic process. Ruthenium(II)–salen complexes incorporating chiral diamines catalyze the photo-promoted asymmetric aerobic oxidative coupling of several 6-substituted-2-naphthols in decent yield with ee



Scheme 32

values up to 71% [2000SL1433](#). Chiral tridentate oxovanadium(IV) complexes also perform well for 2-naphthols bearing substituents in the 3-, 6-, or 7-positions, giving the corresponding binaphthyls in generally good yield and with ee of nearly 90% in the best cases [2001OL869](#), [2001CC980](#), [2002OL2529](#). More impressive is the treatment of a similar range of 2-naphthols with a catalytic amount (5–10 mol.%) of related binaphthyl- or biphenyl-based chiral bis(oxovanadium(IV)) complexes under mild conditions to give the coupled products in very high yield and ee (often both >90%) [2002CC914](#), [2002AG\(E\)4532](#). On a philosophical note, it is interesting to note the chemical filiation inherent in this approach, since both the catalyst and the engendered reaction products belong to the same family.

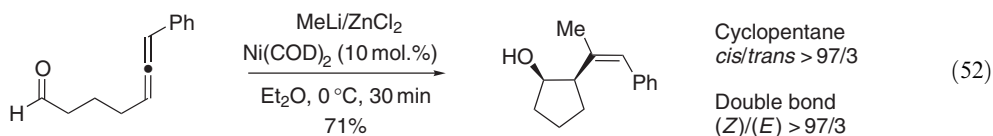


1.11.3 BY ADDITION

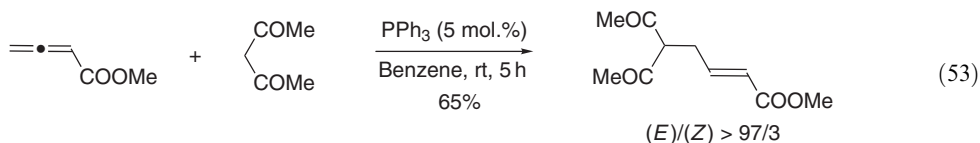
1.11.3.1 Nucleophilic Addition to Allenes

Direct addition of organometallic species to allenes has been little exploited in the 1990s. A reexamination of the exclusive Michael-type attack of α -allenyl ketones (i.e., at the central sp -carbon) by Grignard reagents leads to stereodefined α,β -unsaturated ketones [2002TL6009](#).

Nickel-catalyzed addition of organozincs also takes place at C2, even with unactivated allenes; the resulting metallo-intermediate is trapped intramolecularly with an aldehyde to give well-defined cyclic homoallylic alcohols (Equation (52)) <2002OL4009>. Allylic indium reagents add in a highly regio- and stereoselective fashion to the terminal carbon of allenyl alcohols, via a hydroxy-chelated bicyclic transition state <1996JA4699>.

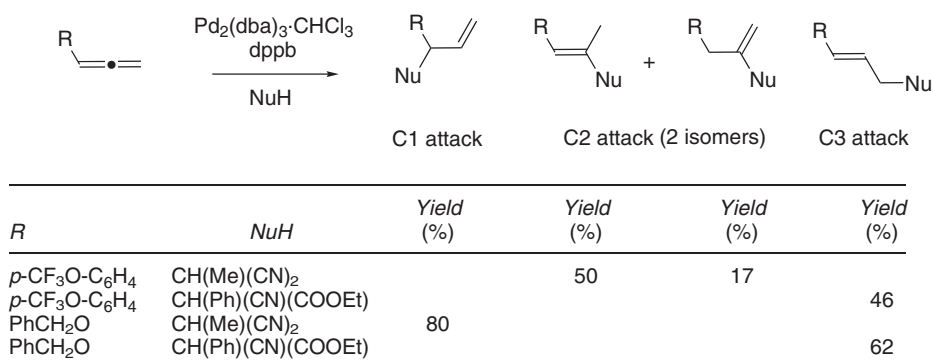


Michael-type addition is also observed in an intramolecular *endo*-mode attack of malonate carbanions on allenyl sulfone functions; decarboxylation ensues, and through appropriate selection of the tether length, functionalized cyclopentene or cyclohexene structures are obtained <2003TL1583>. In an interesting variation on this theme, a tungsten carbonyl complex mediates the intramolecular attack of a silyl enol ether at the terminal carbon of an unactivated allene under photoirradiation; this reaction provides another smooth entry to cyclopentene and cyclohexene compounds <2003OL1725>. In certain conditions, the regioselectivity of nucleophilic attack on an allene bearing an electron-withdrawing group can be completely inverted from the usual Michael-type addition at C2. The key to the success of umpolung addition at C3 is the generation of a 1,3-dipole by initial interaction with a phosphine in a catalytic system (Equation (53)) <1995SL645>.

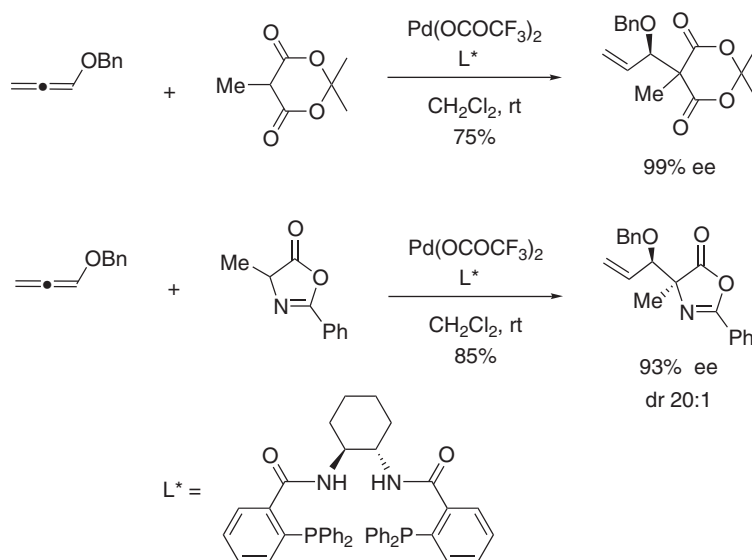


Much more progress is reported for palladium-catalyzed reactions. Whereas previously many transition metal-based species provoked unspecific oligomerization processes with allenes, much-improved catalyst systems now allow highly selective, controlled reactions to take place under mild conditions. Although only carbon nucleophilic and pronucleophilic additions (effectively, additions of C—H bonds across allenes, also called hydrocarboxylations) are treated here, the scope of palladium-mediated reactions involving allenes—including nitrogen, oxygen, and other heteroatom nucleophilic additions, carbonylations, inter- and intramolecular (annulation) processes, cycloisomerizations, and a whole series of tandem and cascade reactions—continues well beyond the confines of this chapter (see, e.g., <2000CRV3067>).

Most palladium-catalyzed allene hydrocarboxylation reactions appear to proceed via a hydro-palladation mechanism, although other possibilities (such as carbopalladation) are not systematically ruled out. The regioselectivity of intermolecular hydrocarboxylation is controlled, predictably, by steric effects in the pronucleophile (bulky reagents add to the least-hindered center) and/or electronic effects in the allene (stabilization of charge distribution in the π -allyl intermediate) (Equation (54)) <1995JA5156, 1995TL2811, 1995SL969, 1996CC831>; with an allenylstannane substrate, an addition–substitution product is obtained <1996CC381>. In general, the olefinic products of γ -additions are often formed with a very high (*E*)-stereoselectivity. Recently, Trost's group has adapted this reaction successfully for asymmetric synthesis, through careful optimization of the reaction conditions and the catalyst system in addition to benzyloxallene <2003JA4438>. Excellent C1 regioselectivity, chemical yields (up to 90%), and ee (up to 99%) are obtained with Meldrum's acid derivatives, while azlactones behave almost as well and display, in addition, high de (up to 20:1) (Scheme 33). Palladium-catalyzed hydrocarboxylation of unactivated allenes with malonate-type methylene or methine carbanions in basic conditions gives mixtures of the C3 (major) and C2 (minor) addition products, although yields are moderate and other processes may compete <1995TL3853>.

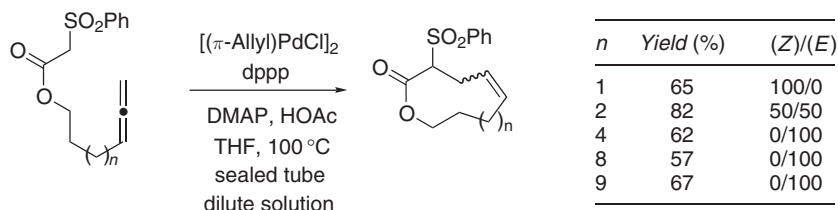


(54)



Scheme 33

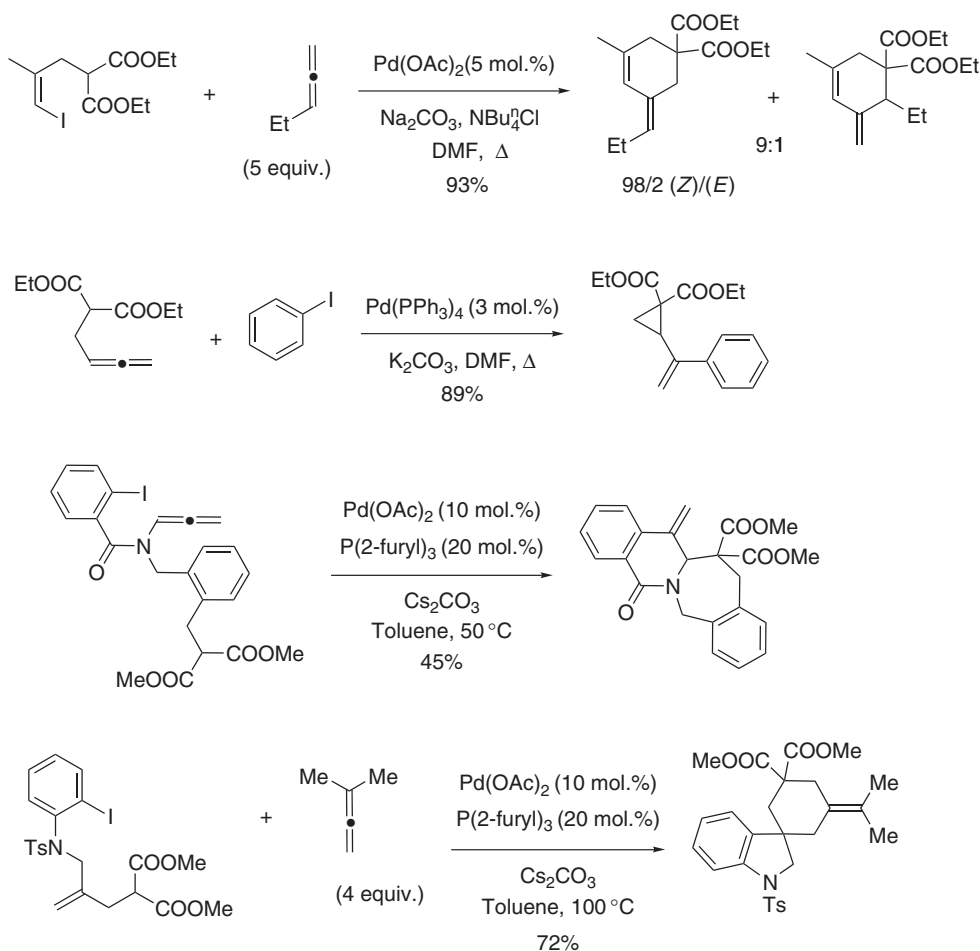
The rewarding extension of this chemistry to the intramolecular case constitutes, formally, a cycloisomerization reaction. Methylene pronucleophiles tethered to terminal allenes undergo palladium-catalyzed *exo*-mode cyclization through addition to the proximal *sp*²-carbon, leading to five- or six-membered carbocycles [<1995JA5156, 1996TL7453>](#). With allenyl ethers, five-, six-, and seven-membered cyclic ethers are formed [<1999TL1747>](#). The system is sensitive to the nature of the catalyst and the reaction conditions, and curiously dimethyl malonate derivatives fail to react. The reactivity profile takes a dramatic change when medium-to-large tethers are involved [<1997AG\(E\)1750>](#). In dilute solution, ring closures take place essentially at the terminal *sp*²-carbon, giving 12- to 17-membered carbocycles and/or macrocyclic lactones; the internal double bond geometry is *trans*. With slightly smaller (nine- to ten-membered) lactone and lactam rings, a *cis*-geometry is progressively imposed, although the regioselectivity remains unaltered. While the origin of the selectivity in these reactions is not clear, the results represent an attractive means of constructing difficult-to-form rings ([Equation \(55\)](#)).



(55)

Tandem reactions are a powerful strategy for the rapid, controlled construction of complex hydrocarbon skeletons, and the scope of palladium-catalyzed processes involving allenes is well

reviewed <B-2002MI1491>. The palladium-catalyzed formal [3+2]-cycloaddition between activated alkenes and allenes actually involves sequential hydropalladation/carbopalladation steps, although the precise mechanism is not established <1999JOC694>. Recent emphasis on tandem carbopalladation reactions involving three distinct partners—an aryl/vinyl halide/triflate, a carbon (pro)nucleophile, and an allene—is on intramolecular combinations of the reaction components (Scheme 34) <1998JOC2154, 2001CC964, 2002JOC2837, 2002CL1140>, although intermolecular examples also work <1995TL5051, 1998CL397, 2003TL7445>. In most cases, the reaction is explained in terms of initial Pd(0) insertion into the aryl/vinyl component then the formation of a π -allylic intermediate by coupling at the allene C2, although the regiochemistry may depend on a variety of factors <1998T14835, 2002JOC2837>. When an additional alkene moiety is included in the structure, a spectacular cascade—Pd(0) insertion, *exo-trig* cyclization, intermolecular allene insertion, nucleophilic π -allyl(palladium) complex capture—creates three new bonds and leads to a spiro-fused ring system <2001CC964>. This kind of palladium-catalyzed tandem/cascade reaction methodology may also incorporate nucleophilic heteroatom attack as one of the steps.



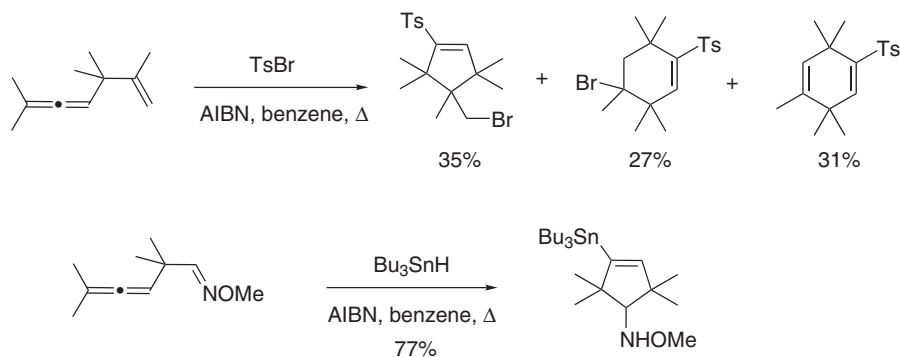
Scheme 34

Related palladium-catalyzed tandem reactions are described in which there is no real carbon pronucleophile (i.e., a center capable of generating a stabilized carbanion). The efficient and selective three-component assembly of a vinyl or aryl halide, an allene, and an arylboronic acid makes use of Suzuki-type cross-coupling for the introduction of the carbon “nucleophile” <2002JOC99>. 2-Iodoaryl allenes undergo formal [4+2]-cycloadditions with alkenes to give naphthalene-derived products; the termination step is β -hydride elimination <1996TL4251>. Aryl iodides react with appropriately spaced allene alkenes to give cyclic products resulting from either β -hydride elimination or a further carbocyclization on the aryl moiety <2003AG(E)2647>.

Other intramolecular metal-catalyzed reactions involving formal additions to allenes include the mercury(II)-mediated spirocyclization of allenyl *p*-methoxybenzyl ketone <1998TL8969> and the ruthenium- or rhodium-catalyzed cycloisomerization of δ -allene alkenes <2002TL6693, 2003TL6335>. Finally, it is worth noting the Pd(II)-catalyzed oxidative carbocyclization reactions of allene alkenes <2001JOC8015, 2003JA6056> and the related Pd(0)-catalyzed carbocyclization of allenic allylic carboxylates <2003JA14140>, in which the allene moiety plays the role of the formal nucleophile. Similarly, an intermolecular amine-catalyzed 1,4-addition reaction of the C1 of allenic esters with α,β -unsaturated carbonyl compounds is described <2003JA12394>; this reactivity contrasts markedly with the [3 + 2]-cycloaddition products obtained from the same substrates under phosphine catalysis (see Section 1.11.3.3.4).

1.11.3.2 Free Radical Addition to Allenes

Allenes are excellent radical acceptors, and recent work exploits radical cyclization reactions in particular. As key steps in natural product syntheses, intramolecularly generated alkyl radical centers undergo 6-*exo-dig* <1996T13181> or 5-*exo-trig* cyclizations <1997LA1155, 1999TL3375>, depending on the substrate. In a remarkable total synthesis of a membranoid natural product, Myers and Condroski <1995JA3057> described the double transannular radical cyclization of a macrocyclic alkene allene to give the tricyclic hydrocarbon skeleton with very good selectivity. Related studies show that addition of an external radical species to the digonal carbon of an allene can be followed by the reaction of this new radical with a suitable acceptor group within the molecule, providing an alternative radical cyclization approach involving creation of unsaturated five- and six-membered carbocycles (Scheme 35) <1995TL6685, 1997JOC1202>.



Scheme 35

Electron-deficient (but not electron-rich) allenes may react with diyls (or diradicals) generated by thermal decomposition of diazene precursors, showing roughly the same diylphilicity as methyl acrylate <1997TL15>. The bicyclic products are obtained as single regioisomers, the 1,2-addition taking place at the electron-deficient end of the allene.

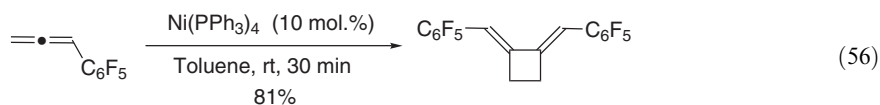
1.11.3.3 Cycloaddition Reactions Involving Allenes

1.11.3.3.1 General observations

Allenes participate in cycloaddition reactions, furnishing two, three, or (in the case of vinyl allenes) four carbon atoms to the new cyclic skeleton. While these transformations are presented formally as cycloadditions, this does not necessarily imply a concerted process; indeed, reactions often proceed in a stepwise manner via identifiable intermediates. Apart from a few useful rules-of-thumb, the reactivity profiles are not easy to generalize, being strongly influenced by complex combinations of steric, electronic, and environmental factors (solvent, catalyst, thermal or photochemical initiation, etc.). In numerous cases, mixtures of products arising from different types of competing reactions are observed.

1.11.3.3.2 [2+2]-Cycloadditions

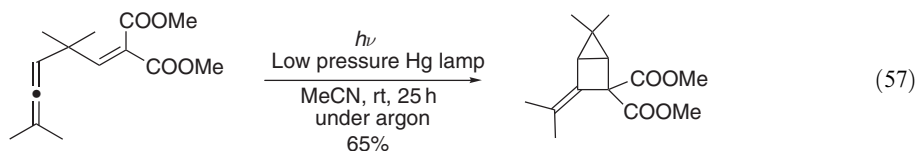
The thermal dimerization to give dimethylenecyclobutanes is described for variously substituted allenes, although the reaction is not particularly regioselective <2000JOC1721, 1997JPR(339)233, 1996JOC8132>. Such reactions are taken as evidence for transiently formed highly strained cyclic allenes <1995T6475, 1997AG(E)1187, 2003JOC1579> even though the cyclobutane products sometimes undergo further rearrangement. A high degree of head-to-head regioselectivity is observed in the [2+2]-dimerization of electron-deficient allenes when an Ni(0) catalyst is used (Equation (56)) <2000JA10776>.



Allene-alkene [2+2]-cycloadditions lead to methylenecyclobutanes, usually via diradical or dipolar intermediates. For successful thermal reactions, electron-rich alkene-electron-deficient allene combinations <2002PS(177)893> and/or Lewis acid promotion <1996TL327, 1998CL331, 2000CPB405> or high pressure <2003EJO894> are typically required, although strained cyclic allenes react rapidly with unactivated alkenes <1995T1973, 1997JOC4998, 1998EJO237>. 4-Ethenylidene oxazolidinones undergo smooth thermal intermolecular [2+2]-cycloadditions with various alkenes (excluding some bearing electron-donating substituents but including, remarkably, conjugated dienes) under unusually mild conditions with excellent regioselectivity at the distal double bond; a concerted mechanism appears to operate <2003CEJ2419>. In contrast, allenamides react with [60]fullerene at the C1—C2 bond <2002S1655>.

Recent efforts reveal particular reagent types, which facilitate smooth intramolecular reactions in mild conditions. A 1-arylsulfonyl substituent activates the allene's C2—C3 bond for highly regio- and stereoselective intramolecular reaction with relatively unreactive alkene centers tethered at either C1 or C3 <1995JA7071, 1995TL4521, 2003JOC6238>, although the regioselectivity is occasionally inversed <2003T3461>. 2-Azetidinone-tethered alkene allenes also display very high stereoselectivity and distal bond regioselectivity in moderate-yielding intramolecular thermal [2+2]-cycloadditions <2003OL3795>.

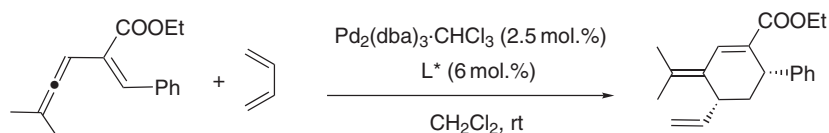
Intramolecular [2+2]-photocycloadditions involving relatively unactivated allenes tethered to enones (or other alkenes bearing electron-withdrawing substituents) proceed in good yield and high stereoselectivity; a high degree of asymmetric induction can be obtained if chiral nonracemic tethers <1995SL776> or 1,3-disubstituted allenes <1997JA2597, 1997T16253> are used. In Tsuno and co-workers' detailed study of the photochemical reactivity of allenyl(vinyl)methane systems in which the vinyl moiety is conjugated with an electron-withdrawing group, the reaction products vary considerably, depending notably on the use of sensitizers, but can lead to significant proportions of the bicyclo[2.1.0]pentane adducts (Equation (57)) <1995BCJ3175, 1999BCJ519, 2001T4831, 2002T7681>.



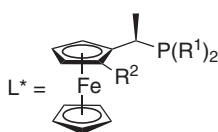
1.11.3.3.3 [4+2]-Cycloadditions

Allene participation in Diels–Alder reactions continues to attract attention. In principle, vinyl allenes as diene components have improved reactivity and selectivity compared to ordinary conjugated dienes. The success of [4+2]-cycloaddition reactions of vinyl allenes appears to depend on the precise nature of the diene unit, and requires a good dienophile, but when reactions proceed they usually do so with a high degree of stereoselectivity and provide an interesting entry to six-membered rings with tetrasubstituted exocyclic double bonds <1996LA1487,

[1998JOC5283](#), [2001EJO1089](#)>. Promising results are reported for metal-catalyzed reactions leading to 3-methylenecyclohexenes, via processes that involve metallacyclic intermediates. Although most work focuses on analogous reactions of alkynes, ethene, a particularly unreactive alkene, can be made to react in the presence of a Rh-based catalyst with an unactivated vinyl allene [<1998AG\(E\)2248>](#), while a palladium-based catalyst directs a [4+2]-cycloaddition between a vinyl allene and an ordinary 1,3-diene, this latter being forced to behave exclusively as a 2 π component [<1997JA7163>](#); variable enantioselectivity is observed when this reaction is carried out in the presence of chiral catalyst ligands (Equation (58)) [<2000CC2293>](#).



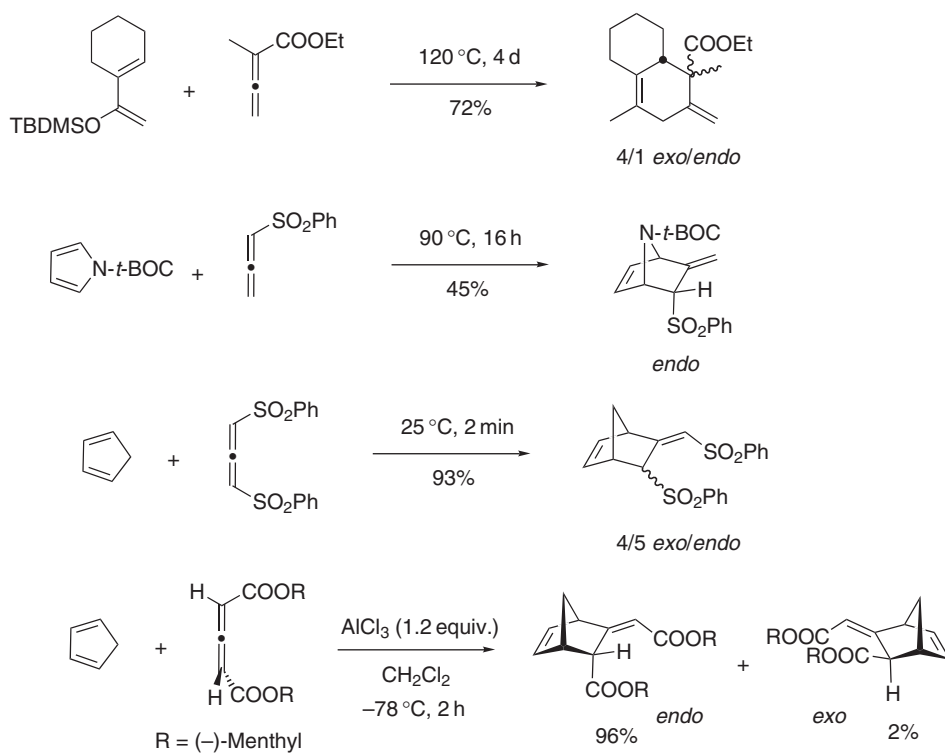
(58)



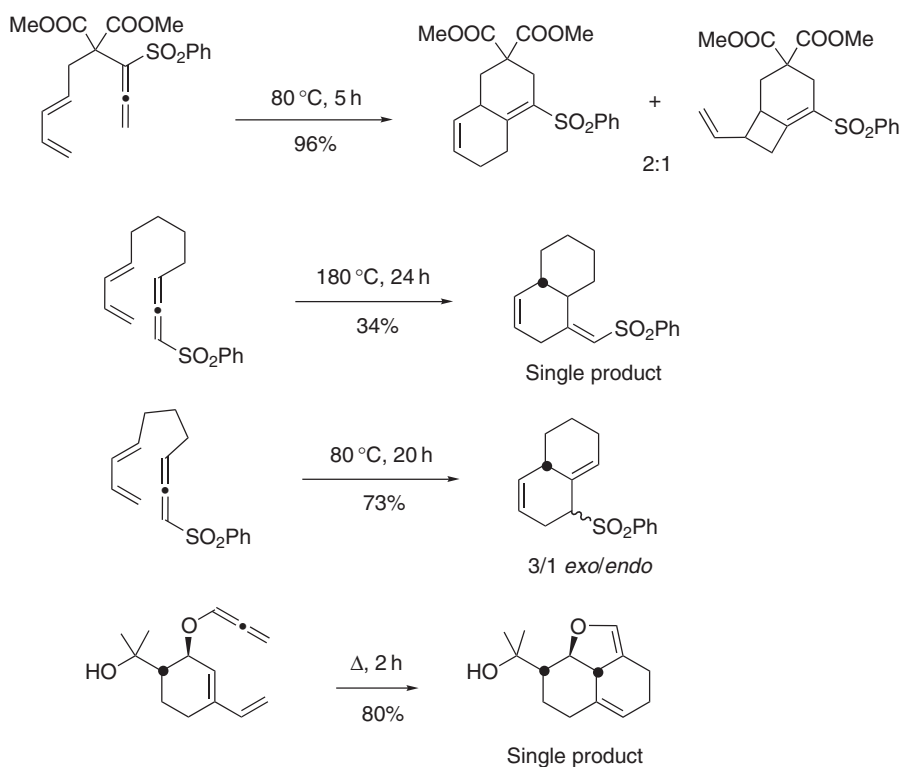
R^1	R^2	Yield (%)	ee (%)
Ph	H	62	6
Ph	SiPh ₃	90	47
Cy	SiPh ₃	80	18
3,5-Bis(trifluoromethyl)phenyl	SiPh ₃	85	83

Unactivated allenes (and 4-ethenylidene oxazolidinones [<2003CEJ2419>](#)) are not good dienophiles. With an electron-withdrawing group at C1, however, allenes participate more readily in intermolecular Diels–Alder cycloaddition reactions with a variety of dienes (Scheme 36). When this group is a carboxylic ester [<1996LA1989, 1999JA3529>](#), a phosphoryl group [<2000EJO3945>](#), or a sulfonyl group [<1997TL7993, 2000EJO3945>](#), addition invariably occurs at the electron-deficient C1—C2 bond; *endo/exo*-stereoselectivity can vary considerably. Curiously, an α -fluoroallenyl phosphonate reacts exclusively at the C2—C3 bond (and with excellent stereoselectivity) [<2000JOC227>](#). Allenyl sulfoxides, normally sluggish dienophiles, display hugely improved reactivity with cyclopentadiene under ultrasound irradiation [<1998TL5413>](#). With a symmetrical 1,3-bis(electron-withdrawing group) allene, [4+2]-cycloadditions with regular dienes are particularly facile, and the question of regioselectivity disappears (Scheme 36). The bis(phenylsulfonyl) derivative behaves appropriately [<1998SL900>](#), while synthetic applications of the dicarboxylate are described [<1997TL7993, 1999AJC1013>](#). In a low-temperature Lewis acid-catalyzed example, enantiomerically pure allene 1,3-dicarboxylates display excellent asymmetric induction in their reaction with cyclopentadiene [<1996JOC2031>](#). Electron-rich allenes give cycloaddition products with pentamethylcyclopentadiene via a stepwise process involving radical cation catalysis [<1995JOC8223, 1996CEJ1031>](#). Predictably, strained cyclic allenes need no particular encouragement to participate in Diels–Alder reactions with unreactive alkenes, although the appearance of [2+2]-dimerization products may understandably compete [<1995T6475, 1997JOC4998, 1998EJO237, 1999JOC976, 2002T3079, 2003JOC1579>](#). To a certain extent, the regioselectivity (if any) can be explained in terms of the participation of the more electron-deficient allene center.

Intramolecular Diels–Alder reactions are often fruitful, although the course of the reaction may depend markedly on the nature and length of the tether (Scheme 37). With a C1-phenylsulfonyl allene bearing an unactivated diene tethered to C3, thermal [4+2]-cycloaddition reactions proceed easily [<2000JCS\(P1\)3129>](#), although with the diene tethered at C1, other processes may compete [<1995JA7071>](#). The distal double bond of allene carboxylate and carboxamide derivatives undergoes intramolecular [4+2]-cycloadditions with cyclic diene systems (including heterocyclic and even carbocyclic aromatics) borne by the heteroatom, leading to elaborate tricyclic structures [<1997LA435, 1997JPR\(339\)233, 2002JA11292>](#). Likewise, an electron-rich allenyl ether undergoes efficient cycloaddition with a diene tethered via the ether oxygen [<1995H\(41\)245, 1998JOC5064>](#). Transition metal catalysis gives spectacular results in the intramolecular [4+2]-cycloadditions of nonactivated allene–diene combinations under mild conditions, leading to 6,5-, 6,6-, or 6,7-fused ring systems [<1995JA1843>](#). Excellent yields and regioselectivities are observed, with the latter being determined by the choice of catalyst.



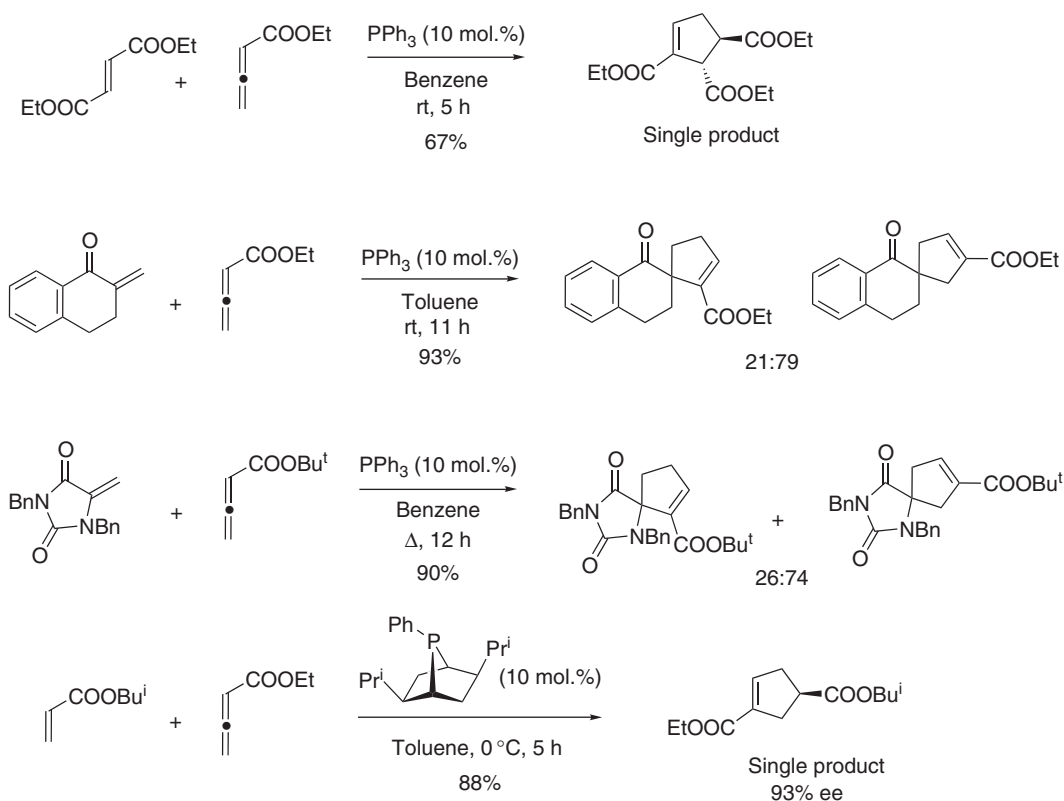
Scheme 36



Scheme 37

1.11.3.4 Other cycloadditions

Rhodium-catalyzed intramolecular [5+2]-cycloadditions of vinyl cyclopropane allenes provide a very efficient entry to bicyclic structures incorporating a seven-membered ring with an exocyclic methylene adjacent to the bridgehead. The reaction works well with variously substituted, non-activated allenes and is highly selective in favor of a *cis*-ring fusion <1999JA5348, 1999OL137, 2000OL2323>. Structurally related, but mechanistically different, the [5+2]-oxopyrylium cycloaddition gives limited success with electron-rich allene partners, and fails with electron-deficient ones <2001TL1695>. A useful phosphine-catalyzed cycloaddition of allenic esters with electron-deficient alkenes has been described (Scheme 38) <1995JOC2906, 1999TL549, 2002JOC8901>. This reaction is in fact a [3+2]-annulation involving a 1,3-dipolar intermediate derived from the allene, and leads to cyclopentenones. [60]Fullerene can participate as the two-carbon component <1997CC79, 1997CC81>. The method has been adapted for asymmetric synthesis using chiral nonracemic alkene partners <1997CC2267> or phosphine catalysts <1997JA3836>. With tropone, allenic esters or ketones undergo unusual phosphine-catalyzed [8+2]-annulation, presumably via the same dipolar intermediate, to give bicyclic trienes, with high selectivity in some cases <2000OL787>. A palladium(0)-catalyzed head-to-head [4+4]-cycloaddition reaction, formally a dimerization, is known for certain vinyl allenes; the process represents an interesting entry to symmetrical cyclooctadienes, although it is of limited scope at present. The contrast with vinyl allene-1,3-diene cycloadditions is noteworthy, since the latter usually proceed in a [4+2]-mode <1999SL951>.



Scheme 38

1.11.3.4 Carbene Addition to Allenes

There is only limited synthetic exploitation of this and related types of reaction, partly due to the existence of alternative, easier methods of obtaining the product methylenecyclopropanes, but also due to a lack of selectivity and (importantly) the ease with which an allene reacts with two carbene equivalents to give a spiropentane system. Thus, in the enantioselective synthesis of

spiropentanes from hydroxymethylallenes using bis(iodomethyl)zinc and a chiral dioxaborolane, only the most sterically hindered substrate adds a single methylene unit; unsurprisingly, this occurs at the least hindered center (with excellent enantioselectivity) <2001OL3293>. Diazoalkane precursors give the required methylenecyclopropane products with selected highly substituted allenes, although with moderate selectivity <2000JOC1721, 2001JOC7202, 2001CEJ4021>. Despite its impressive enantioselectivity, the reaction of singlet (methoxycarbonyl)phenylcarbene with enantiomerically enriched 1,3-dimethylallene gives a mixture of diastereoisomeric methylenecyclopropanes <1996JOC1030>. Dihalogenocarbenes give 1:1 products with substituted allenes, with variable regioselectivity <1997JOC9039, 1999TL1261>. Intramolecular reactions, once again, seem to give the most useful results: the diazoacetates of a range of (hydroxyalkyl)allenes undergo smooth transformation in the presence of a Cu(II) catalyst to give methylenecyclopropyl lactones with excellent yields and regioselectivity; diastereoisomeric excesses, however, remain only moderate <1997TL3833>.

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Biographical sketch



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1.12

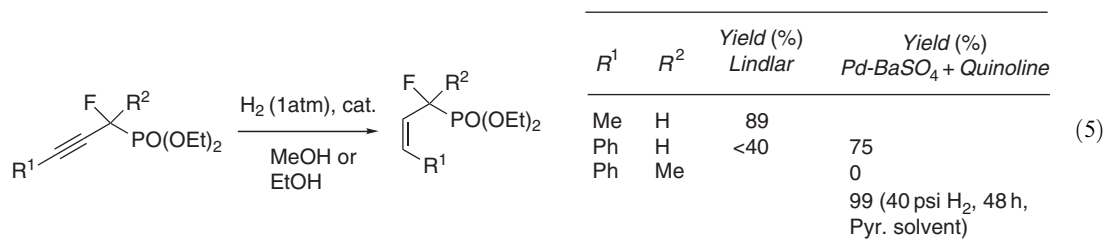
One or More C=C Bond(s) Formed by Addition

A. C. REGAN

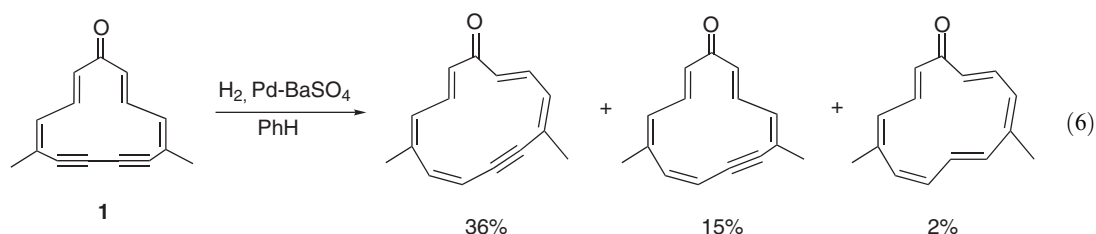
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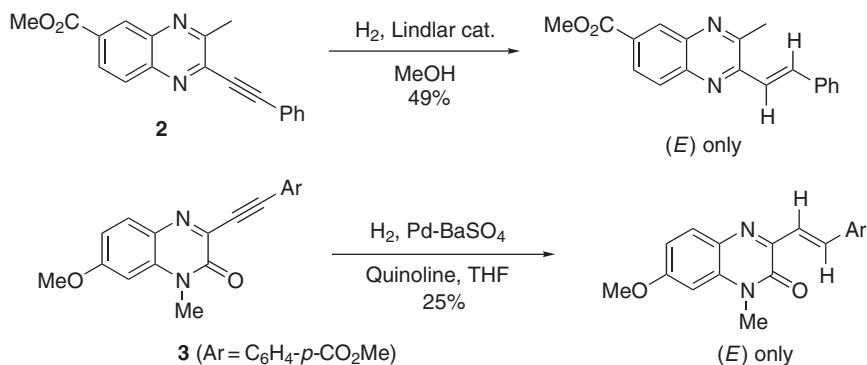
An interesting series of closely related examples is shown in Equation (5), comparing the effectiveness of Lindlar's catalyst and Pd-BaSO₄ + quinoline. In the most difficult reduction, an increased pressure of hydrogen and a change of solvent to pyridine were required <1998T15541>.



In demanding cases, it may be necessary to try several methods of reduction; for example, for the 13-membered cyclic ketone **1** (Equation (6)), only hydrogenation using Pd-BaSO₄ was successful, whereas the use of other catalysts, as well as hydroboration and hydroalumination, all resulted in failure <1998BCSJ221>.



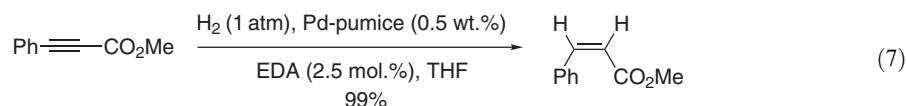
Although heterogeneous catalytic reduction of alkynes over palladium catalysts is usually a reliable method for the synthesis of (*Z*)-1,2-disubstituted alkenes, occasionally this stereoselectivity is reversed. For example, both the quinoxaline substituted alkyne **2** and the related alkyne **3** are reduced to the corresponding (*E*)-alkenes (Scheme 1): the former using Lindlar's catalyst, and the latter using Pd-BaSO₄ <2000H(52)911>.



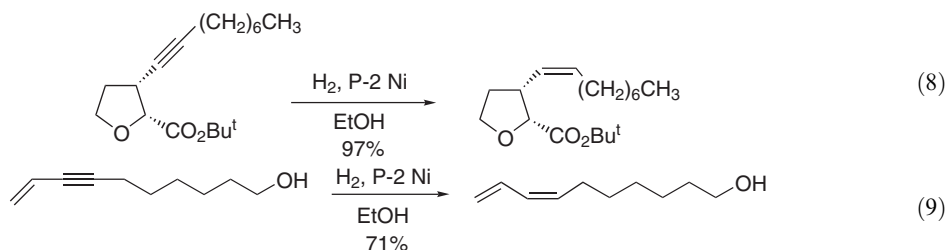
Scheme 1

Other supported palladium catalysts have appeared more recently, including one prepared by adding Pd(OAc)₂ to borohydride exchange resin <1996TL8527>. In the presence of CsI, 1 mol.% of catalyst is effective for the rapid semi-hydrogenation of terminal alkynes at 1 atm pressure, and it is not critical that the uptake of hydrogen is closely monitored since over-reduction of the products is very slow. Hydrogenation of internal alkynes is much slower; however, the (*Z*)-alkene products are readily obtained when 10 mol.% of catalyst is employed.

An interesting new supported catalyst is palladium on pumice <2001TL2015>. The activity of this catalyst varies depending on the catalyst loading on the pumice. A variety of internal alkynes have been reduced, in most cases with excellent stereoselectivity for the (*Z*)-products, and with little over-reduction (Equation (7)).



Apart from palladium, the metal which has been most generally used as a heterogeneous catalyst is nickel <1995COFGT(1)501>. Early work used mainly Raney nickel, and while this is sometimes not very selective, it is still employed. P-2 nickel is a more recent catalyst <1995COFGT(1)501>, and often gives good stereoselectivities when ethylenediamine is used as an additive. Two recent examples of (*Z*)-selective hydrogenations over P-2 nickel are shown in Equations (8) and (9) <1995SC4035, 1997SL387>.

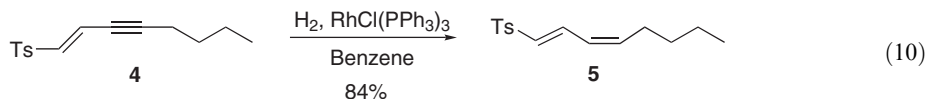


A nickel boride catalyst, prepared from nickel acetate and borohydride exchange resin, is a very effective catalyst for (*Z*)-selective semi-hydrogenation of internal alkynes bearing alkyl, aryl, hydroxyl, or ester groups <1996TL1057>. Conversions are generally quantitative, with excellent stereoselectivities and very slow over-reduction. The selectivity for reduction of alkynes over the product alkenes appears to be steric in origin, since a terminal alkyne underwent considerable over-reduction.

1.12.1.2 Homogeneous Catalytic Hydrogenation

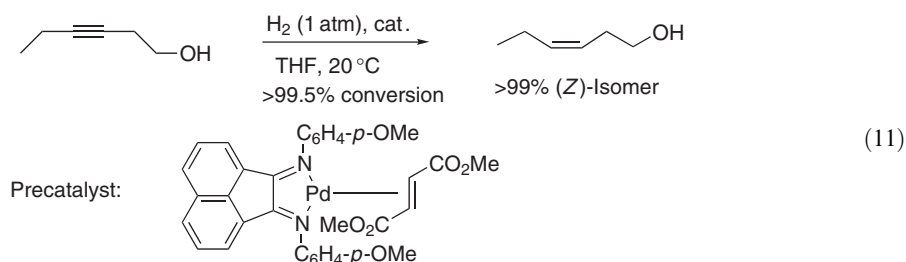
Homogeneous catalysis has been comparatively little used for catalytic hydrogenation of alkynes, compared to heterogeneous catalysis <1995COFGT(1)501, B-1996MI001>. Although Wilkinson's catalyst is the best-known homogeneous hydrogenation catalyst, it usually gives complete reduction of alkyne triple bonds. Nevertheless, in benzene with acidic co-solvents, partial hydrogenation is successful for terminal alkynes. Internal alkynes can be reduced stereoselectively to (*Z*)-alkenes by complexes of the type [(arene)Cr(CO)₃] <1985JOC1147>. It is also possible to obtain (*E*)-selective hydrogenation using rhodium-based complexes, for example [RhH₂(OC(=O)OH) (PPR₃)₂] <1983JA6273>.

A more recent application of Wilkinson's catalyst is in the stereoselective hydrogenation of the (*E*)-tosyl-enyne **4** to the conjugated (*Z*),(*E*)-diene **5** shown in Equation (10) <1997JOC6326>.



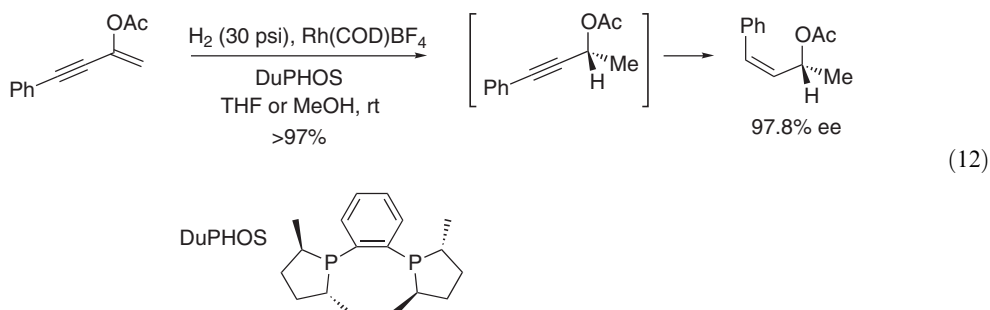
A homogeneous cationic ruthenium complex of the type [Cp*Ru(alkene)]⁺ has been reported to effect the direct *trans*-hydrogenation of alkynes to (*E*)-alkenes <2001NJC423>. *para*-Hydrogen-induced polarization NMR spectroscopy was used to establish the direct pairwise transfer of two *para*-hydrogen atoms, which was rationalized on the basis of a mechanism proceeding via a binuclear rhodium complex.

A new homogeneous palladium(0) catalyst bearing a bidentate nitrogen ligand gave (*Z*)-selective hydrogenation of a wide variety of alkynes (Equation (11)), <1999AG(E)3715>. Very high stereoselectivities (often >99:1) are found for simple alkynes, with superior results in several cases to those obtained with either Lindlar's catalyst or P-2 Ni. The stereoselectivities are not quite as good for phenylalkynes, but still comparable to those of heterogeneous catalysts. Conjugated enynes are reduced cleanly to the corresponding dienes, with uptake of hydrogen stopping after reduction of the triple bond without over-reduction. Several other ligands were tested for generation of the palladium(0) catalyst system, but the bidentate nitrogen ligand shown below gave the best selectivities.



In contrast to the palladium(0) catalyst above, a series of homogeneous palladium(II) catalysts have been prepared with thiosemicarbazone ligands [<1998JCS\(D\)2715>](#), and these show good selectivities toward terminal alkynes.

The relative reactivities of enol ester and alkyne multiple bonds can be seen in [Equation \(12\)](#), where the use of a catalyst prepared from a rhodium(I) salt and methyl DuPHOS results in asymmetric hydrogenation of the enol C—C double bond in the substrate to give an intermediate (which can be isolated by interrupting the reaction), followed by (*Z*)-selective reduction of the alkyne [<1998TL5505>](#).

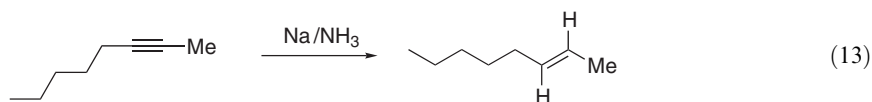


The use of several trinuclear ruthenium carbonyl complexes as catalyst precursors for the homogeneous hydrogenation of diphenylethyne has been reviewed [<1995SL579>](#). In some cases, the clusters retain their trinuclear framework during the catalytic reactions. In general, *cis*-stilbene is the kinetic product, and *trans*-stilbene the thermodynamic product of these hydrogenations.

Transfer hydrogenation of alkynes using homogeneous Pd(0) catalysts can be effected using hydrosilanes and acetic acid as the hydrogen donor, or alternatively, formic acid. These processes usually give the (*Z*)-alkene selectively, and have been reviewed [<B-2002MI002>](#).

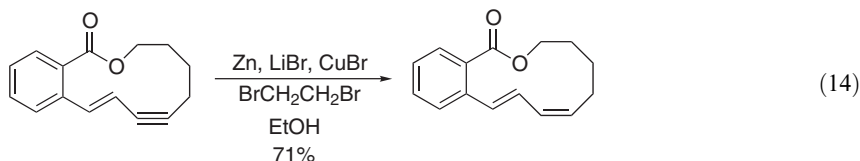
1.12.1.3 Dissolving Metal Reductions

Dissolving metal reductions of alkynes have been widely used as an effective approach for the production of (*E*)-alkenes [<1995COFGT\(1\)501>](#), for which relatively few general methods are available, in contrast to the many methods for reduction to (*Z*)-alkenes. Dissolving metal reductions have been reviewed by [<B-1996MI001>](#), and a detailed experimental protocol is given for the representative reduction of oct-2-yne to (*E*)-oct-2-ene using sodium and liquid ammonia ([Equation \(13\)](#)). Other metals have been used, including lithium, calcium, ytterbium and zinc [<1995COFGT\(1\)501>](#), usually in combination with an amine, although in some cases alcohols can be used as the proton donor.

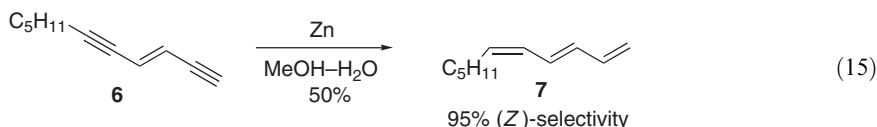


A detailed comparison of the reduction of alkynes of differing alkyl chain lengths using lithium metal shows that the solvent is particularly important [<1999EJOC779>](#). Mono-alkynes with a chain length of 12 or less carbons were easily reduced using *t*-butanol and THF or ether as the solvent. In contrast, for longer chain alkynes, HMPT was found to be necessary. Compounds containing two (nonconjugated) alkyne bonds were reduced much more readily than mono-alkynes.

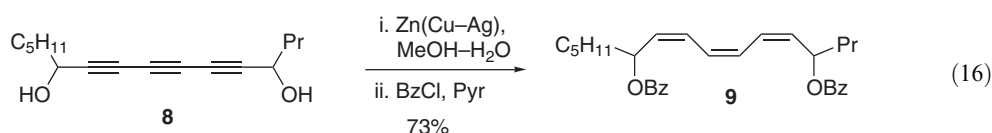
The combination of zinc and 1,2-dibromoethane is unusual in that it gives (*Z*)-selectivity with internal alkynes, and this reagent has been more recently used for the (*Z*)-selective reduction of a conjugated enyne in a macrocyclic lactone (Equation (14)) <2001OL3487>.



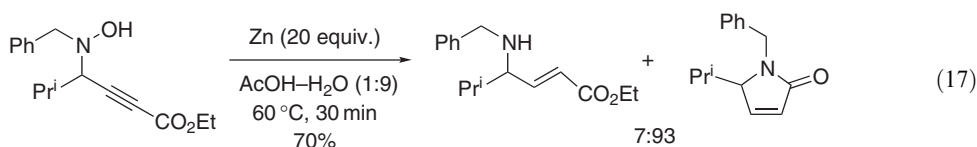
Two alkyne groups in the conjugated ene-diyne **6** are reduced simultaneously by activated zinc in methanol–water, to give the triene **7** with 95% (*Z*)-selectivity (Equation (15)) <1995T1209>.



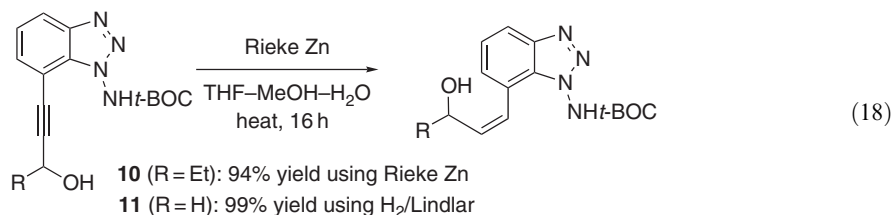
Conjugated trienes can also be prepared by zinc–copper couple reduction of all three alkyne bonds in **8**, in this case affording the all-(*Z*)-triene **9** (Equation (16)) <1997TL6917>.



Zinc in acetic acid–water also gives (*Z*)-selective reduction of the alkynoate ester shown in Equation (17) with concomitant reduction of the hydroxylamine <1997TL5503>. The stereoselectivity is 93:7, but this is highly sensitive to the solvent system used. By raising the proportion of acetic acid to water from 1:9 to 4:1 the selectivity could be reversed, slightly favoring the (*E*)-product. In the presence of di-*t*-butyldicarbonate, the (*Z*)-amine can be trapped out as the *t*-BOC-protected product, preventing cyclization to the lactam <1999SL602>.



Rieke zinc has been used in THF–methanol–water to effect the (*Z*)-selective reduction of the propargylic alcohol **10** in excellent yield (Equation (18)) <2000JCS(P1)2343>, whereas the use of hydrogenation over Lindlar's catalyst was found to be unsatisfactory, and the combination of titanocene dichloride and iso-butylmagnesium chloride reduced the alkyne, but also removed the *t*-BOC group. In contrast, the unsubstituted alcohol **11** was reduced satisfactorily using hydrogenation over Lindlar's catalyst.



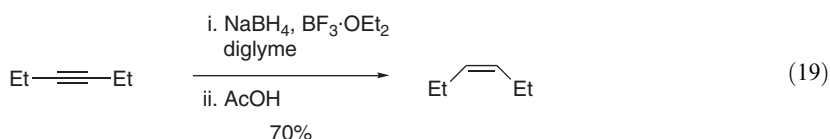
A wide variety of terminal alkynes bearing different propargyl functionalities have been reduced using pulverized indium metal (prepared by sonication) in ethanol <2001JOC5624>. No over-reduction was observed, and a range of reducible functional groups were unaffected.

The combination of nickel chloride dihydrate, lithium metal, and a catalytic amount of naphthalene in THF can be used to reduce alkynes, either completely to the corresponding alkanes, or in some cases partially to the alkenes, depending on the reaction conditions <1997TL149>.

1.12.1.4 Hydride Reducing Agents

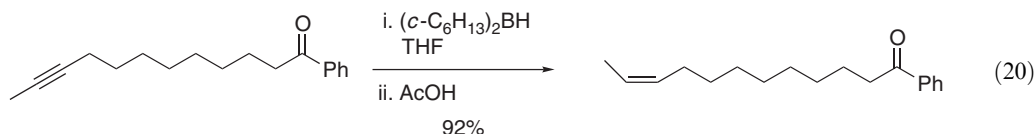
1.12.1.4.1 Boron reagents

The sequence of hydroboration followed by protonolysis of the resulting alkenylborane has become a well-established general method for the overall *cis*-addition of H₂ to alkynes (<1995COFGT(1)501, 1995CRV2457>). In general, bulky dialkylboranes are used to avoid further reaction of the initially formed alkenylboranes, and disiamyl and dicyclohexylborane have been widely employed. A simple experimental protocol for the reduction of 3-hexyne (Equation (19)) using borane generated *in situ* is given in the review by Haworth (<B-1996MI001>).



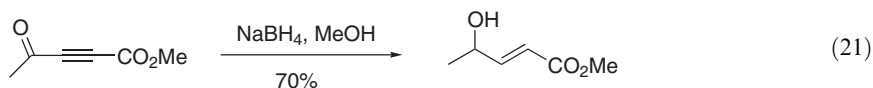
The protonolysis is generally carried out using acetic acid, although other procedures involving hydrolysis under basic or almost neutral conditions have been developed (<1995COFGT(1)501>). 9-BBN-H is a useful reagent for internal alkynes, and other boranes such as catecholborane and haloboranes have also been used (<1995COFGT(1)501, 1995CRV2457>).

Both terminal and internal nonconjugated alkynes can be hydroborated in the presence of aldehyde or ketone carbonyl groups in the same molecule using dicyclohexylborane (<1997TL7681>). After protonolysis, the corresponding alkenes are obtained in good yields, with internal alkynes resulting in (*Z*)-stereoselectivity, as expected (Equation (20)).



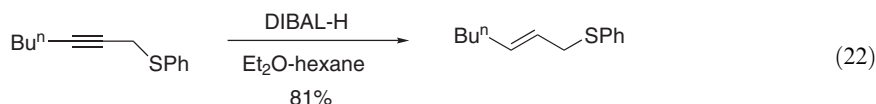
Hydroboration reactions can be catalyzed by transition metal complexes, and these have been reviewed (<1997T4957>). A variety of metals can be utilized, including rhodium, titanium, and zirconium. However, in most cases for the hydroboration of alkynes, the product alkenylboranes have not been converted into the corresponding alkenes, although this should be straightforward in principle.

Sodium borohydride (NaBH₄) is not usually effective as a nucleophilic hydride reducing agent for isolated nonconjugated alkynes, but has been successfully employed to reduce alkynes conjugated with amides, a second alkyne group, and allenes (<1995COFGT(1)501>). Very recently, NaBH₄ has been used to reduce the alkyne triple bond in 4-oxo-ynoate esters to the corresponding (*E*)-allylic alcohols (Equation (21)) (<2003TL443>). When methyl and phenyl ketones are used, none of the lactone resulting from reduction to give the (*Z*)-alkene was detected; however, with more bulky alkyl groups (cyclohexyl and *t*-butyl) some loss of stereoselectivity is observed.

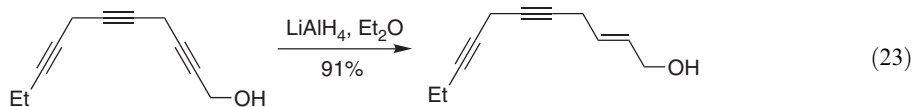


1.12.1.4.2 Aluminum reagents

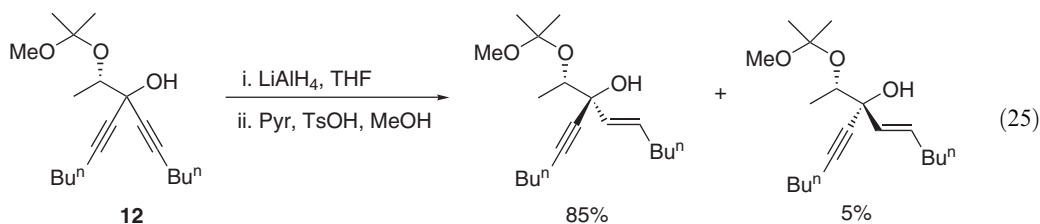
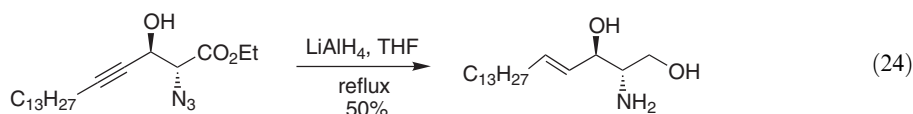
Addition of an aluminum hydride reagent to an alkyne, followed by hydrolysis of the resulting alkenyl aluminum compound, results in overall reduction to an alkene (<1995COFGT(1)501, 84OR375, 1991COS(8)733>). For isolated alkynes, diisobutylaluminum hydride (DIBAL-H) has been often used, and for internal alkynes this generally gives the (*E*)-alkene. Terminal alkynes can give problems with competitive metallation of the alkyne C-H bond. A recent application of DIBAL-H is in the preparation of (*E*)-allylic sulfides, shown in Equation (22) (<1997SC3917>).



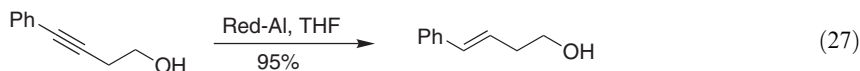
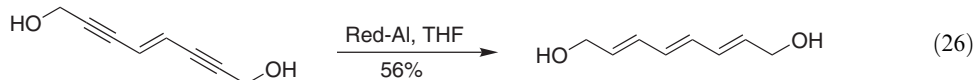
A much more widely used class of alkynes for hydroalumination is that of propargyl alcohols, where reduction to the corresponding (*E*)-allylic alcohols using LiAlH_4 is a standard method (Equation (23)) <1995COFGT(1)501>. This method allows selective reduction of the triple bond of a propargyl alcohol in the presence of another alkyne group in the same molecule.



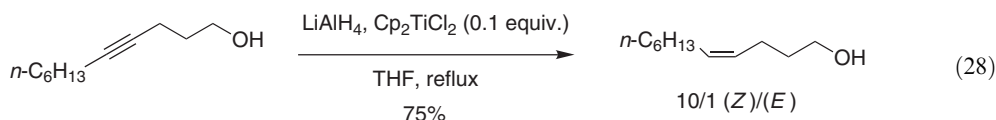
A recent application of LiAlH_4 reduction to a chiral propargylic alcohol is shown in Equation (24), where three functional groups are reduced in the same reaction <2000JOC7627>. In the diynol **12**, the two alkyne groups are rendered non-equivalent by the adjacent chiral center, and selective reduction of one of the alkynes is possible using LiAlH_4 (Equation (25)) <2001OL1057>.



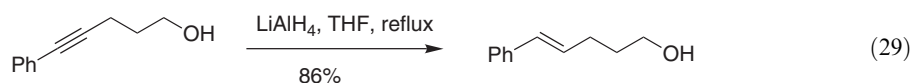
Sodium bis(2-methoxyethoxy)aluminum hydride (Red-Al) also reduces propargyl alcohols to (*E*)-allylic alcohols, and detailed procedures have been published <1986OS(64)182>. Red-Al has been employed in the stereocontrolled synthesis of trienes (Equation (26)) <1996SC2831, 1996TL6547, 1999T4353>, and by the same group for the stereoselective reduction of homo-propargyl alcohols (Equation (27)) <1997SL992>.



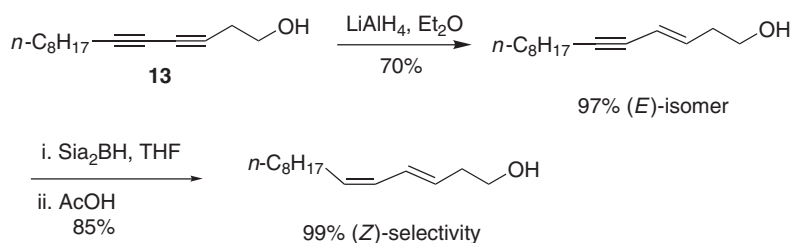
It is also possible to reduce an alkyne, which is remote to a hydroxyl group, using LiAlH_4 in diglyme resulting in (*E*)-alkenols, although the conditions required are often severe (e.g., 150 °C). It has been found recently that the use of titanocene dichloride as a catalyst allows this reaction to be carried out in refluxing THF, and results in the opposite stereoselectivity, giving the (*Z*)-alkenols (Equation (28)) <2002TL1231>. Interestingly, it was also found that a free hydroxyl group is not necessary for the success of this reduction: a benzyl protected alcohol, an acetal, and even a simple dialkylalkyne were reduced to the (*Z*)-alkenes.



No catalysis is required for the (*E*)-selective reduction by LiAlH_4 of alkynes which are remote to a hydroxyl group if they are conjugated with an aromatic ring (Equation (29)). In the seven examples studied, all were reduced in good yield in refluxing THF, and no trace of the opposite stereoisomer was observed <2002TL1735>.



Similarly, a conjugated diyne **13** bearing a remote hydroxyl group has been reduced first with LiAlH_4 in ether to give (*E*)-selective reduction of only the alkyne proximal to the hydroxyl group, and the distal alkyne was then reduced with (*Z*)-selectivity using Si_2BH (Scheme 2) <2001NJC223>.

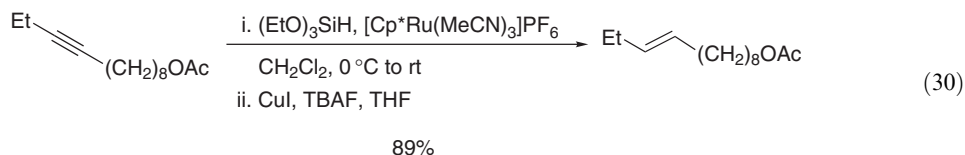


Scheme 2

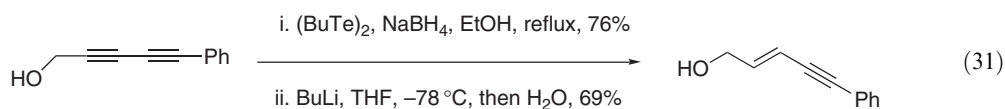
1.12.1.4.3 Other hydride reducing agents

Internal alkynes conjugated to both an ester and a ketone have been reduced using NaBH_4 at low temperature (Equation (21)) <2003TL443>. The reduction is (*E*)-selective, and the ketone is also reduced; however, in some cases a minor amount of (*Z*)-alkenol is produced, which cyclizes to the corresponding unsaturated lactone.

Hydrosilylation of an alkyne followed by protodesilylation, should, in principle, yield the alkene, but the conditions required are usually harsh, and removal of the silicon using TBAF requires elevated temperatures. However, it has been found that ruthenium catalyzed hydrosilylation of internal alkynes, followed by desilylation using TBAF in the presence of a Cu(I) salt is a mild and effective method for the reduction to (*E*)-alkenes (Equation (30)) <2002JA7922>. The same method has been applied to large-ring cycloalkynes, but using AgF for the desilylation step, to give the corresponding (*E*)-cycloalkenes <2002CC2182>.



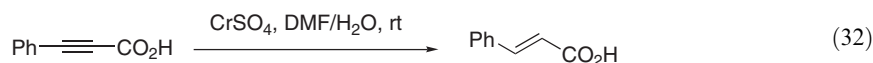
The combination of NaBH_4 and dibutylditelluride effects an unusual chemoselective hydrometallation of only one alkyne group in conjugated terminal and internal diynes <1995T9839>. Subsequent removal of the tellurium atom by transmetalation and protonation gives the corresponding conjugated (*E*)-enynes (Equation (31)).



Hydrozirconation followed by protonolysis is occasionally used for the reduction of alkynes, and it has been found useful for the reduction of a macrocyclic diyne to the corresponding (*E*),(*E*)-diene, where hydrogenation using Lindlar catalyst was ineffective <1997JOC5821>.

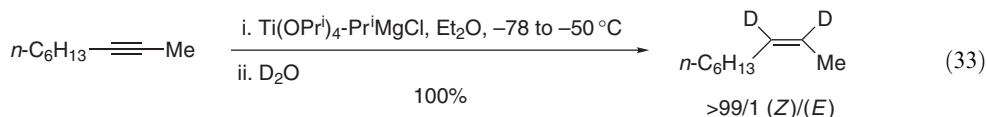
1.12.1.5 Miscellaneous Reducing Agents

Chromium(II) salts have been used to reduce a variety of terminal and internal alkynes, propargyl alcohols, and conjugated ynones <1995COFGT(1)501>, and from internal alkynes (*E*)-alkenes are usually formed. A particularly simple protocol for the reduction of phenylpropynoic acid to (*E*)-cinnamic acid using CrSO_4 has been published (Equation (32)) <B-1996MI001>.



During the synthesis of zaragozic acid C, reduction of a conjugated ynone using either CrSO_4 or CrCl_2 was problematic, possibly because of the air sensitivity of the Cr(II) reagents, and it was found that commercially available chromium acetate monohydrate dimer gave higher yields and more reproducible results [<1995JA8106>](#).

A low-valent titanium alkoxide prepared from Ti(Oi-Pr)_4 and $i\text{-PrMgCl}$ reacts with alkynes to form titanocyclopropene complexes, which can be hydrolyzed by water or acid to the (*Z*)-alkenes with very high stereoselectivity [<1995TL3203>](#) (e.g., [Equation \(33\)](#)). This method has also been used for the selective reduction of conjugated diynes to (*Z*)-enynes [<2002CC272>](#), and for reduction of skipped diynes to the corresponding (*Z*),(*Z*)-dienes [<1998JCS\(P1\)1839>](#).



The combination of sodium methoxide and catalytic amounts of Pd(OAc)_2 and Ph_3P gives partial reduction of internal alkynes to (*Z*)-alkenes in THF, but complete reduction to the corresponding alkanes occurs simply by changing the solvent to MeOH [<2003TL1979>](#).

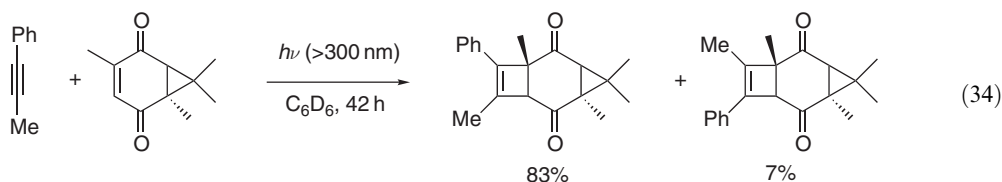
1.12.2 CYCLOADDITION REACTIONS TO ALKYNES

As in the previous review [<1995COFGT\(1\)501>](#), this section includes formal cycloaddition reactions to alkynes, which may be stepwise, as well as concerted electrocyclic additions. Transition metal-catalyzed cyclizations have been reviewed in general, including several cyclizations onto alkynes [<1996CRV49, 1996CRV635>](#).

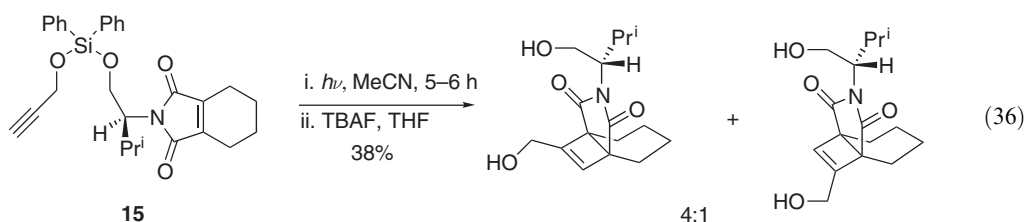
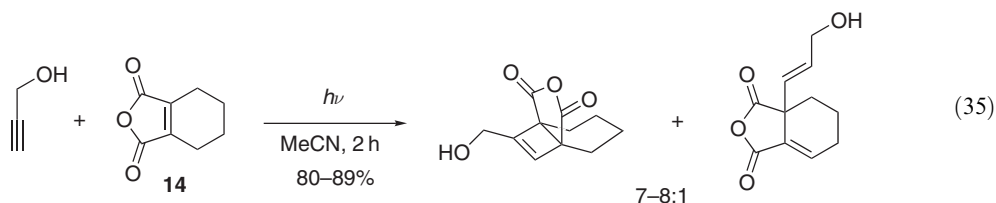
1.12.2.1 [2 + 2]-Cycloaddition Reactions

Cycloaddition reactions of alkynes and alkenes give cyclobutenes, and this reaction may proceed via a photochemical concerted process, or thermally. Photochemical [2 + 2]-cycloaddition is not always a satisfactory method for the formation of cyclobutenes, since the product may undergo either electrocyclic ring opening, or further cycloaddition reactions [<1991COS\(5\)123, 1995COFGT\(1\)501, B-1978MI813>](#). However, photochemical cycloaddition of alkynes to enones works well.

Photochemical cycloadditions of alkynes to quinones are well established [<1995COFGT\(1\)501>](#), and this has been extended to homoquinones ([Equation \(34\)](#)) [<2002JA8912>](#). Unsymmetrical alkynes react regioselectively, with the selectivity being rationalized on the basis of the favored products being formed from the more stable biradicals.

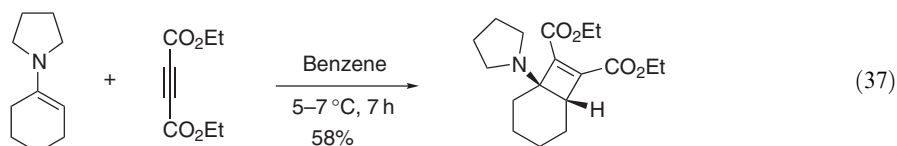


The tetrahydrophthalic anhydride **14** undergoes photochemical [2 + 2]-cycloaddition with a variety of alkynes and alkynols in good yields ([Equation \(35\)](#)) [<1999T5875>](#). Other anhydrides and imides react similarly, and the minor by-product is proposed to arise via a different pathway, rather than from the major cyclobutene product. A structurally related tetrahydrophthalimide **15**, which is linked to an alkyne via a silicon tether incorporating a chiral group, allows an intramolecular cycloaddition, resulting in diastereoselective cyclobutene formation with 4:1 selectivity ([Equation \(36\)](#)) [<1997CC1385>](#). In a simpler achiral system, a similar bis-alkoxysilane tether has been used to control the regioselectivity of an alkyne–alkene cycloaddition [<1995TL4189>](#).



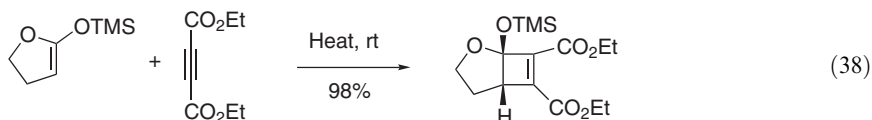
The diastereoselectivities of the photochemical cycloadditions of ethyne to a series of furanones have been studied, and although the less hindered face of the furanone was favored, the selectivities were not as high as with ethene [<2001TL6695>](#).

Uncatalyzed thermal [2 + 2]-cycloadditions usually require a particularly reactive combination of alkyne and alkene. Electron-rich enamines will react successfully with electron-poor acetylenedicarboxylate esters [<1986JOC2004>](#), and several examples have since been reported, some of which proceed at low temperature (e.g., [Equation \(37\)](#)) [<1997OPP541>](#).

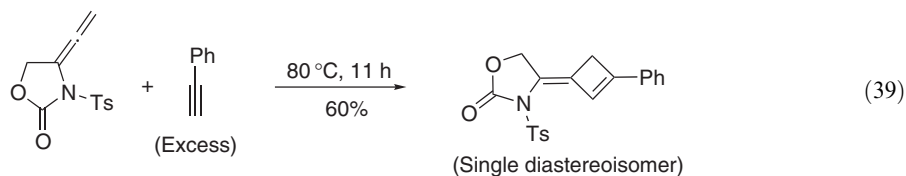


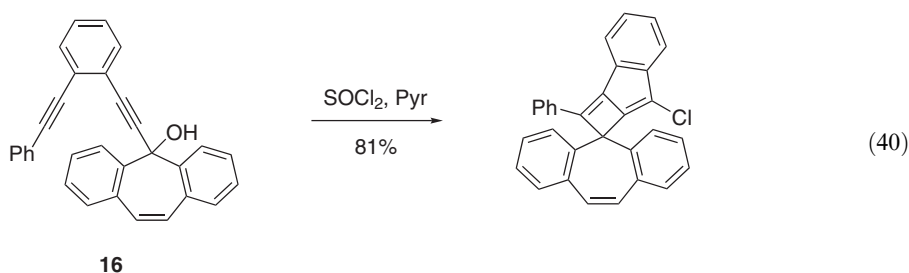
Cyclic enol ethers have also been found to undergo uncatalyzed [2 + 2]-cycloaddition reactions to Fischer alkynyl carbene complexes [<1999JCS\(P1\)197>](#). If the alkyne group is also conjugated with an alkene, the products can be used in thermal benzannulation reactions [<2003JOC537>](#).

Silyl ketene acetals are sufficiently electron rich to add to electrophilic alkynes. In the example shown in [Equation \(38\)](#), the best yields are obtained without the use of any catalyst [<1999TL839>](#). Other workers have found that with acyclic silyl ketene acetals, [2 + 2]-cycloaddition products can be obtained with ethyl propynoate and catalytic ZrCl_4 [<1992JOC6890>](#), whereas DMAD results in ring opening of the cyclobutene products [<1995BCSJ6890>](#).

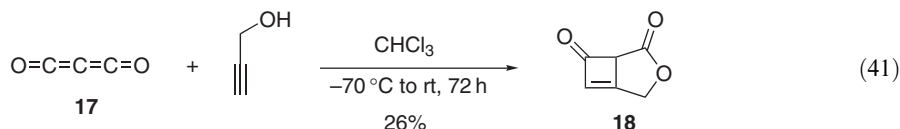


Allenes undergo [2 + 2]-cycloadditions reactions with alkynes, and these can be photochemical, catalyzed by transition metals or Lewis acids, or purely thermal [<1997JA10869>](#). Simple allenes often require high temperatures for thermal cycloaddition; however, oxazolidonones bearing an exocyclic allene group have been found to react at a much lower temperature ([Equation \(39\)](#)) [<1997JA10869>](#). Intramolecular allene–alkyne [2 + 2]-cycloadditions are also possible, and in [Equation \(40\)](#) the propargyl alcohol group in **16** reacts to form a chloro-allene *in situ*, and this then undergoes [2 + 2]-addition to the other alkyne group [<2001JOC6662>](#).

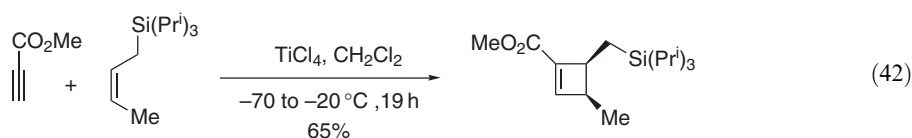




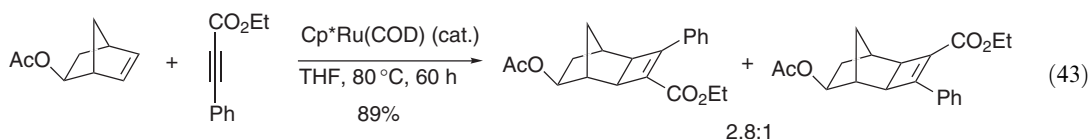
Ketene itself does not generally undergo thermal cycloaddition to alkynes; however, the reaction of dichloroketene is successful, and the chlorine atoms can be removed from the product reductively with zinc, to give the same overall result [\[1990OS\(68\)32\]](#). The generation of dichloroketene for this reaction from trichloroacetyl chloride can also be carried out using zinc and ultrasound, as a convenient alternative to zinc-copper couple [\[1995SC2781\]](#). Thio-substituted ketenes, generated by rhodium-catalyzed rearrangement of α -diazothiol-esters, undergo thermal cycloaddition to internal alkynes in moderate yields [\[2000JOC4375\]](#). Heteroatom-substituted alkynes are required in order to obtain higher yields. Carbon suboxide **17** can be viewed as two cumulated ketene units, and in [Equation \(41\)](#) one of these undergoes cycloaddition to the triple bond of propargyl alcohol, and the other reacts with the alcohol group to give the bicyclic lactone **18** in modest yield [\[1998MI680\]](#). Carbon suboxide has also recently been found to react with internal alkynes to give cyclobutenes fused to α - or γ -pyrones, or bis-pyrones, depending on the molar ratios of reactants used [\[2003JHC321\]](#).



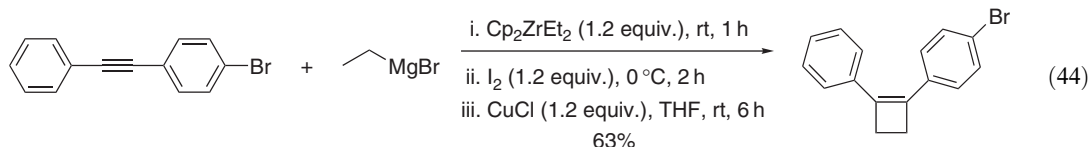
[2+2]-Cycloaddition reactions of alkynes can be promoted by Lewis acids. For example, methyl propynoate undergoes TiCl_4 -promoted addition to both (*Z*)- and (*E*)-disubstituted allyl silanes, with stereospecific formation of the cyclobutene products ([Equation \(42\)](#)) [\[1998TL7705\]](#). Cyclic allyl silanes have also been found to undergo cycloaddition to an electron-deficient alkyne; however both the ring size and the nature of the Lewis acid were critical, with only the combination of a five-membered ring allyl silane and Me_2AlCl being successful [\[1996T6685\]](#). Gallium chloride has been used to catalyze one example of an intramolecular [2+2]-cycloaddition; however, in other related examples isomerized products are obtained, which are proposed to result from cyclobutene intermediates [\[2002JA10294\]](#).



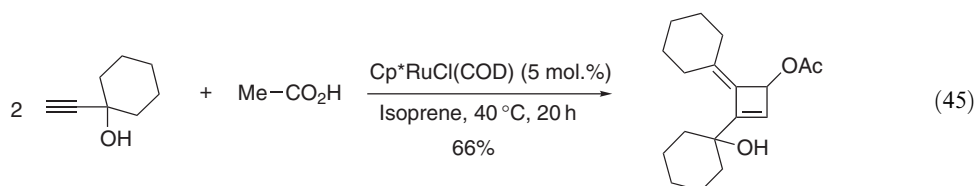
[2+2]-Cycloaddition reactions of alkynes can be catalyzed by transition metal complexes [\[1994AG\(E\)580\]](#), and Jordan and Tam have studied the ruthenium-catalyzed addition of ethyl phenylpropynoate to a number of norbornenes and norbornadienes [\[2000OL3031, 2001OL2367, 2002TL6051\]](#). In general, the *exo*-addition products are favored, and the less-substituted alkene in substituted norbornenes and norbornadienes reacts preferentially. Some regioselectivity is possible with substituted norbornenes and norbornadienes, even though the substituent is remote (e.g., [Equation \(43\)](#)). A similar indenyl Ru complex has also been used to catalyze [2+2]-cycloaddition of norbornene with a range of alkynes [\[2001OM3762\]](#). A cationic Ru-alkylidene complex gives [2+2]-cycloaddition between dimethyl acetylenedicarboxylate and both ethene and norbornene; however, between ethene and other alkynes, hydrovinylation reactions occur [\[1999OM2043\]](#). Cobalt complexes are also active catalysts for the cycloaddition of a wide range of alkynes (not just electron-deficient ones) to benzo-fused oxa- and azanorbornenes [\[2001JOC8804\]](#).



An interesting cyclobutene synthesis, which is equivalent to the overall addition of ethene to aryl acetylenes, is shown in Equation (44), where the ethene equivalent is ultimately derived from an ethyl Grignard reagent, and the reaction proceeds via organozirconium intermediates <1999JOC8706>.



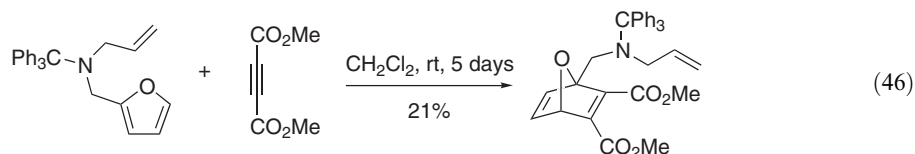
A number of other transition metal-catalyzed reactions result in the formation of cyclobutenes from alkynes, even though the other two carbons in the ring do not arise from direct cycloaddition of an alkene. For example, a ruthenium complex catalyzes cyclodimerization of propargyl alcohols (Equation (45)), with the intermediate complex reacting with a carboxylic acid to give alkylidene cyclobutenes <2001AG(E)2912>.



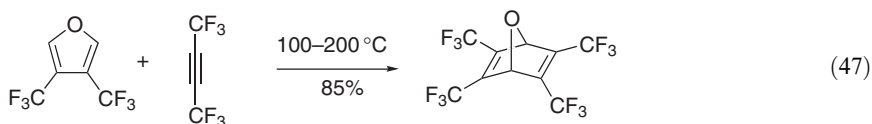
Cyclobutenediones can be formed by transfer of two CO equivalents from iron carbonyls, and both Fe(CO)₅ <1997TL7229> and Fe₃(CO)₁₂ <2000TL2719> can be used as precursors.

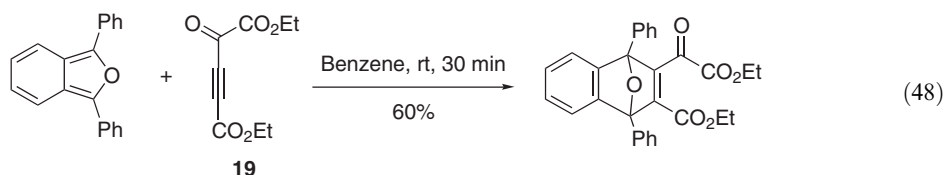
1.12.2.2 Diels–Alder Reactions

Alkynes can react as dienophiles in the Diels–Alder reaction <B-1990MI001>, although isolated alkynes are rather unreactive, and generally need to be combined with unusually reactive dienes <1995COFGT(1)501>. Conjugation of the triple bond, e.g., with phenyl groups, improves the reactivity, and as with alkenes, electron-withdrawing groups are particularly effective. In this respect, diethyl and dimethyl acetylenedicarboxylate have been widely used as dienophiles (e.g., Equation (46)) <2002JCS(P1)1999>.

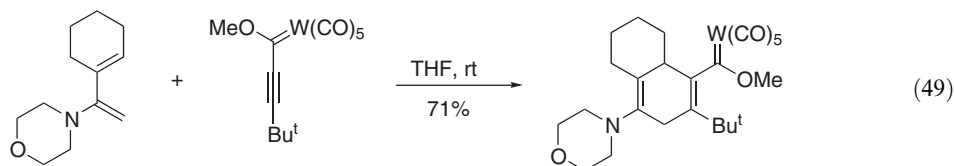


As in the example above, furans are reactive electron-rich dienes, and have been widely employed in Diels–Alder reactions. This has been reviewed <1997T14179>, including the use of both alkynes and benzyne as dienophiles, in both inter- and intramolecular fashion. Hexafluorobutyne is an activated alkyne which has been previously used in Diels–Alder reactions <1995COFGT(1)501>, and it reacts well with furans (Equation (47)) <1996JCS(P1)1095>, and with cyclopentadienes <2001BCSJ1673>. A carbonyl homolog of diethyl acetylenedicarboxylate **19** has been prepared, with an extra carbonyl group between the alkyne and one of the ester groups, and this reacts as a dienophile with an isobenzofuran (Equation (48)) <1995S236>.

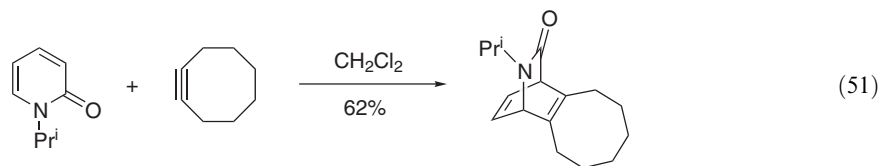
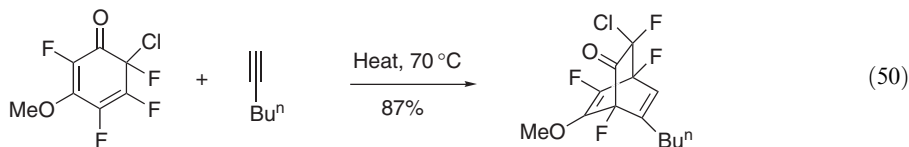




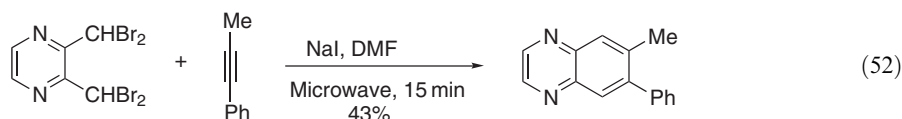
A more recent type of dienophile activating group is a Fischer carbene complex conjugated with the alkyne group, and examples of this kind of dienophile have been reacted with a variety of 2-aminodienes (e.g., [Equation \(49\)](#)) [<1998CEJ2280>](#).



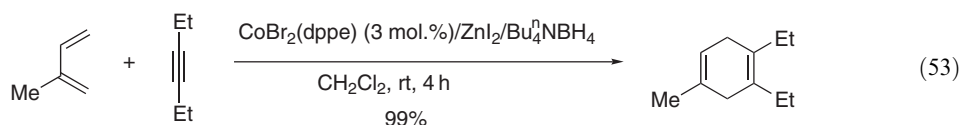
Unactivated alkynes usually require very high temperatures before they will undergo Diels-Alder reactions; however, 1-hexyne reacts with a fluorinated cyclohexadienone at 70 °C ([Equation \(50\)](#)) [<2002RJOC196>](#). The activated dienophile methyl propiolate also reacts in similar yield with a related, but unfluorinated dienone [<1999SL225>](#). A different cyclic diene is the lactam in [Equation \(51\)](#), where a reactive cyclic benzyne is employed as the dienophile [<1997H15>](#). An optimized example of an unactivated alkyne reacting with cyclopentadiene uses a combination of high temperature (260 °C) and elevated pressure (35 bar) [<1995JOC852>](#); attempts to promote the reaction using Lewis acids led to polymeric products.



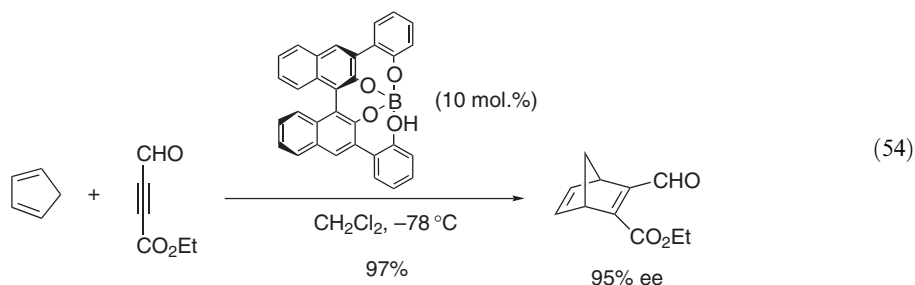
Nonactivated alkynes are normally poor dienophiles; however, 1-arylalkynes have been found to react with *ortho*-quinone dimethanes formed *in situ* under microwave irradiation, to give quinoxalines ([Equation \(52\)](#)) [<2002SL2037>](#).



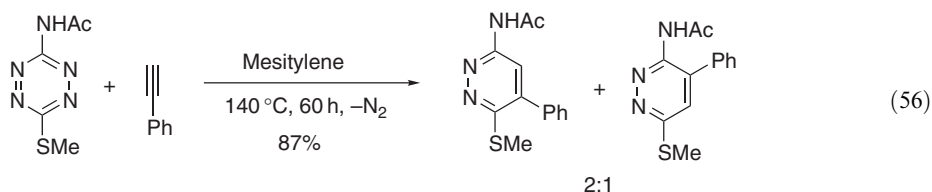
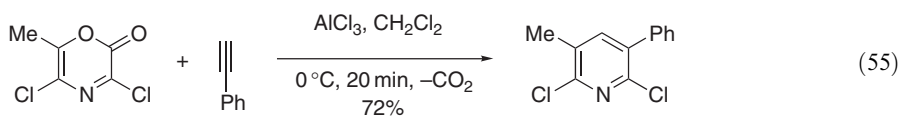
Unactivated internal (e.g., dialkyl) alkynes will react as dienophiles under mild conditions if a transition metal catalyst is employed. Simple dienes react in good yields using a cobalt(I) catalyst ([Equation \(53\)](#)), and the regioselectivity with unsymmetrical alkynes is controlled by steric effects [<2001TL2783>](#). This reaction has been extended to using 1,3-dienes as the dienophile component [<2002S686>](#). Alkoxy-substituted dienes have also been studied and the adducts from 1-alkoxydienes undergo elimination to give aromatic products; however, the adducts from 2-alkoxydienes can be isolated as the 1,4-dihydrobenzenes [<2002SL1081>](#). In related examples, where reductive generation of the cobalt catalyst with borohydride also gives some reduction of the alkyne, zinc powder can be used as the reducing agent [<2003SL241>](#).



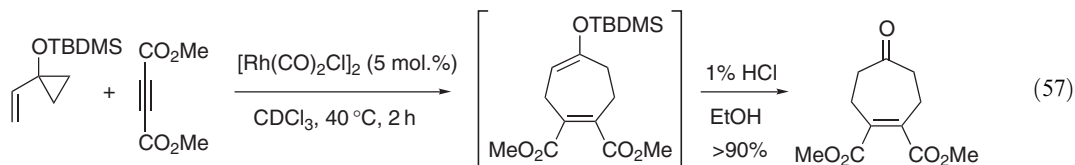
Enantioselective catalysis of Diels–Alder reactions involving alkynals has been achieved using boron coordinated with chiral alkoxy ligands [<1997JOC3026>](#). Three catalysts have been reported, and the best example, in terms of combining high yield with high enantioselectivity, used a doubly activated alkyne, together with a binaphthol-derived ligand ([Equation \(54\)](#)).



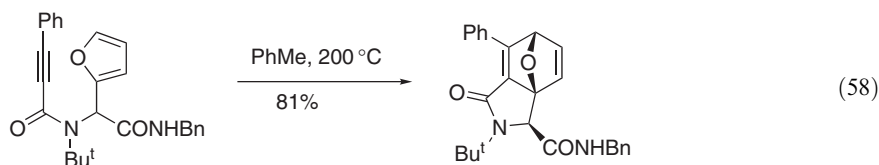
Hetero-Diels–Alder reactions with alkynes are possible, although within the scope of this chapter, the heteroatom is restricted to an internal position of the diene. Acyclic 2-aza-1,3-dienes with electron-donating substituents have been reacted with DMAD [<1996T10095>](#), and conformationally restricted cyclic 2-azadienes react under very mild conditions in the presence of a Lewis acid catalyst ([Equation \(55\)](#)) [<2000SL713>](#). Two heteroatoms are incorporated into the 1,3-diene in the inverse electron demand Diels–Alder reaction of 1,2,3,4-tetrazines with phenylacetylene, where the products also aromatize by loss of nitrogen ([Equation \(56\)](#)) [<1998JOC6329>](#). Intramolecular versions of this reaction have also been achieved.



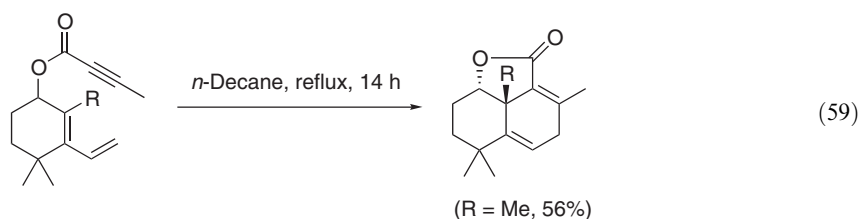
Wender has developed a “homo-Diels–Alder,” or [5 + 2]-cycloaddition of vinylcyclopropanes with alkynes, first in an intramolecular fashion using Wilkinson’s catalyst [<1995JA4720>](#). This catalyst was not successful for intermolecular examples, but these have now been achieved using a rhodium carbonyl catalyst, together with a silyloxycyclopropane as the 5-atom component ([Equation \(57\)](#)) [<1998JA10976>](#).



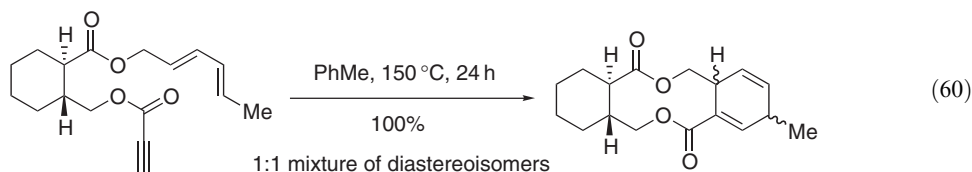
Intramolecular Diels–Alder reactions are possible using alkynes as the dienophile [<1995COFGT\(1\)501>](#). Activation of the alkyne with an electron-withdrawing group is beneficial, as for intermolecular reactions, and so ester and amide linkages of alkynoic acids often work well. An amide linkage was used in the recent example shown in [Equation \(58\)](#), which employs a furan as the diene and proceeds under thermal conditions, whereas Lewis acid catalysis using Me_2AlCl was not successful [<2002TL943>](#). Surprisingly, the ester analogs showed the opposite behavior, with thermal conditions giving only recovered starting materials, but Me_2AlCl resulting in formation of the Diels–Alder adducts in good yield.



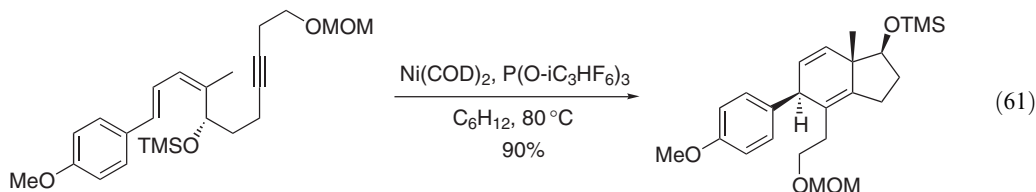
The thermal intramolecular reaction shown in Equation (59) also used an ester linkage, and was used as a key step in the synthesis of forskolin <1996TL1015>. Lewis acid conditions failed here, and carefully developed thermal conditions were required. Other workers found that the closely related reaction with R = H gives only a 10% yield, and this was ascribed to conformational flexibility of the diene, which could adopt the unproductive *s-trans* conformation <1998JCS(P1)1269>. Replacement of the *gem*-dimethyl group on the cyclohexane with a spiro-fused 1,3-dithian improved the yield to 65%, in refluxing THF.



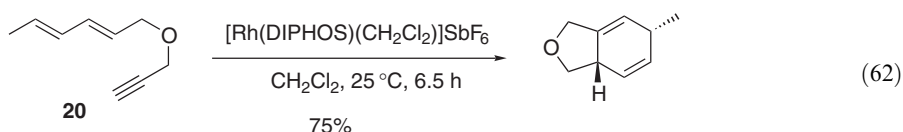
Restriction of available conformations has also been used in the example shown in Equation (60), where the diester linkage reduces conformational flexibility as a result of the *trans*-disubstituted cyclohexane ring, and a quantitative yield is obtained <1999T15045>.



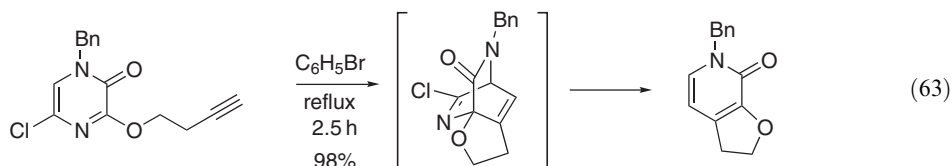
Unactivated alkynes have been found to react thermally with 2-sulfinyldienes, in intramolecular reactions where diastereocontrol is effected by the chiral sulfinyl group <2003CC2476>. Transition metal catalysis can also be used to facilitate the intramolecular reaction of unactivated alkynes. A nickel(0) catalyst was employed by Wender in the reaction shown in Equation (61), which is directed toward steroid synthesis <1995JOC2962>. The single chiral center in the linker completely controlled the formation of the two new chiral centers, and the Ni catalyst was essential, since only decomposition was observed under thermal conditions.



Intramolecular Diels–Alder cyclization of unactivated alkynes can also be catalyzed by rhodium, and substrate **20** shown in Equation (62) has been cyclized using a number of catalysts, with similar yields using either rhodium <1998TL2075> or palladium systems <1998TL3047>. Intramolecular Wender-type [5 + 2]-cycloadditions (see above) are also possible using this substrate. Use of a chiral phosphine ligand on a rhodium catalyst results in asymmetric cyclization of **20** in up to 95% ee <1998JOC10077>. A similar substrate has been cyclized thermally in a low yield whereas an iridium catalyst improved this to 71%, and a chiral phosphine ligand on the iridium complex resulted in enantioselective cyclization <2002SL1681>. The oxygen in **20** can also be replaced by a C, or an N of a sulfonamide <2000TL8041>.



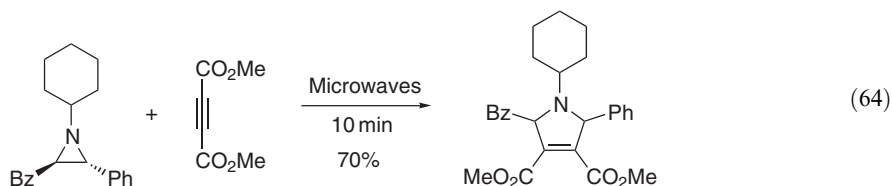
A final example of intramolecular reactions is a hetero-Diels–Alder reaction with inverse electron demand, between a 2-azadiene system in a pyrazinone ring, and an unactivated alkyne attached as a propargyl ether (Equation (63)) <1995T12463>. The pyridinone product is presumably formed by loss of cyanogen chloride from the initial Diels–Alder adduct. Lengthening the linker by one atom, or replacing the alkyne terminal hydrogen by a methyl or phenyl group, all retarded the rate of cyclization.



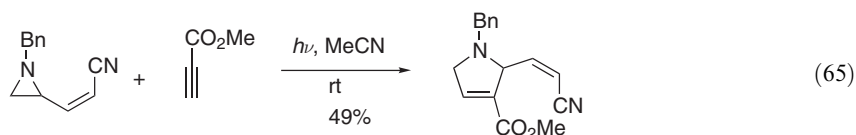
1.12.2.3 1,3-Dipolar Cycloaddition Reactions

1,3-Dipolar cycloadditions which generate alkenes with no attached heteroatoms are restricted to 1,3-dipoles where atoms 1 and 3 are both carbons. The most common examples involve azomethine and carbonyl ylides <1995COFGT(1)501, B-1984MI001>. A recent monograph in the “Practical Approach in Chemistry” series gives detailed protocols for the preparation of several types of azomethine and carbonyl ylides, as well as their addition to alkynes <B-2002MI009>.

Recent developments have been mainly in methods for generations of ylides. Azomethine ylides can be generated by thermal or photochemical ring opening of aziridines, which usually also contain an anion-stabilizing group. Use of microwave irradiation has been found to accelerate the thermal reactions; for example, the cycloaddition shown in Equation (64) requires only 10 min, instead of 18 h using only thermal conditions <1996TL4203>.

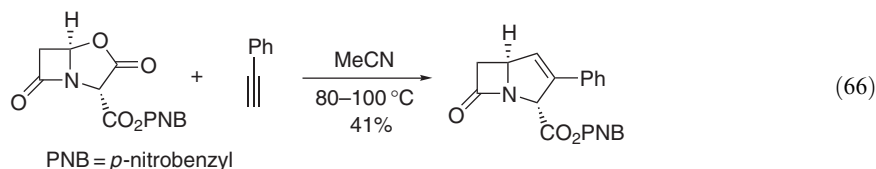


The photochemical ring opening of some 2,3-dibenzoylaziridines has been studied, together with the trapping of the intermediate azomethine ylide with DMAD to give dihydropyrroles <1996JOC4240>. 2-Aryl-3-benzoylaziridines also undergo the same reaction. Similarly, a β -aziridinylacrylonitrile has also been found to undergo photochemical ring opening, and the trapping of the generated azomethine ylide with methyl propiolate is regioselective (Equation (65)) <2000JCS(P1)3022>.

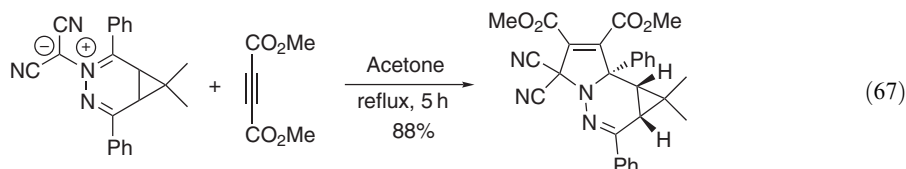


An alternative to direct photochemical ring opening is photoinduced electron transfer (PET) reaction of aziridines, to give a radical cation in the presence of 9,10-dicyanoanthracene as an electron acceptor. Using this method, a 2,3-diphenylaziridine gives a moderate yield of the [3 + 2]-cycloaddition product with DMAD; however, this is much better than with direct irradiation <1997T14297>.

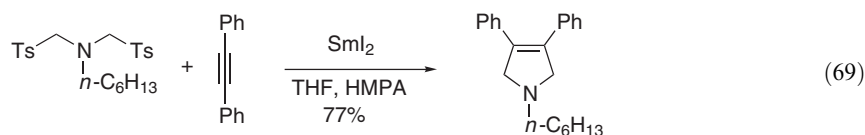
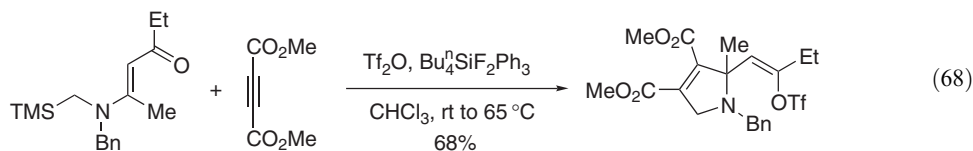
Thermal decarboxylation of β -lactam-based oxazolidinones gives azomethine ylides at relatively low temperatures; these can be trapped by alkenes or alkynes to give carbapenems (Equation (66)) <1997JA2309>.



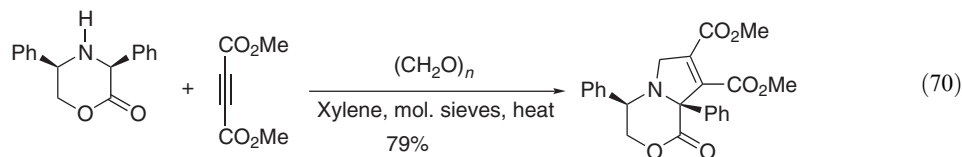
An interesting preparation of azomethine ylides from two neutral species involves the reaction between a diazanorcaradiene and tetracyanoethylene oxide (Equation (67)) <1999T9515>. The ylides undergo cycloaddition to strained alkynes such as cyclooctyne <2000T5443>, and also to DMAD.



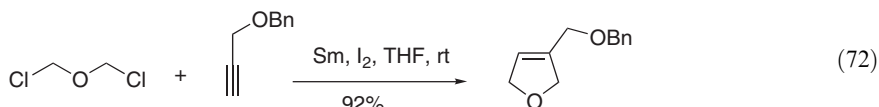
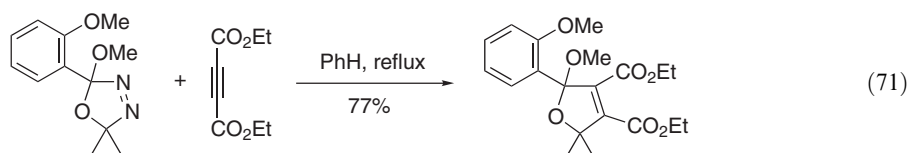
Fluoride-induced desilylation of α -silyliminium ions has often been used to generate azomethine ylides, and a recent example also describes the cycloaddition of the ylide to DMAD <1998JCR(S)82>. In the example shown in Equation (68), *O*-silylation of a vinylogous amide is combined with α -desilylation in order to generate the azomethine ylide <2002AG(E)1778>. Generation of azomethine ylides from neutral imines and trapping by DMAD has been achieved in a one-pot process involving silylation at the C_α , and then on N, followed by *C*-desilylation <2003TL1603>. Most azomethine ylides used synthetically also incorporate an anion-stabilizing group; however, an unstabilized example is shown in Equation (69), generated by SmI_2 -induced loss of two tosyl groups <1999SL590>.



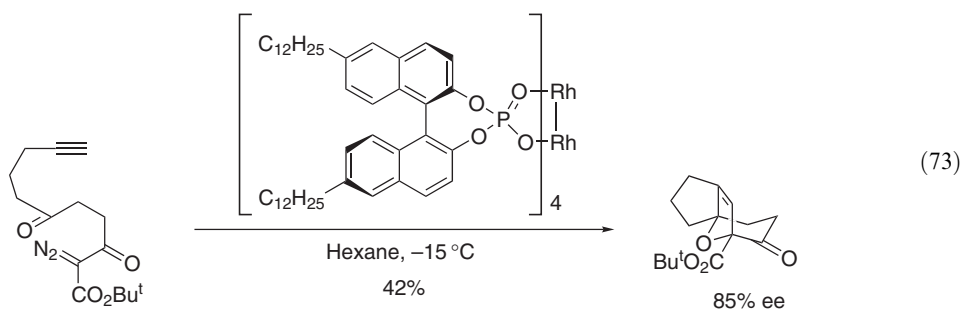
Chiral azomethine ylides generated from morpholin-2-ones and paraformaldehyde react with both DMAD (Equation (70)) and methyl propiolate, with good induction at the newly formed stereocenter <1995TA2465>. In the example shown, phenylglycine is the origin of the template; however, chiral morpholinones derived from alanine also undergo this cycloaddition <2001EJOC3133>.



Carbonyl ylides can be formed thermally at moderate temperatures (refluxing benzene) by extrusion of a nitrogen molecule from silyloxy- or alkoxy-substituted oxadiazolines <1995TL7591, 2003TL5029>, and they readily undergo cycloaddition to acetylenedicarboxylates (e.g., Equation (71)). A symmetrical non-stabilized carbonyl ylide has been generated from an (α -iodoalkyl) silyl ether using a combination of $\text{Sm}(0)$ and HgCl_2 , and reacts stereoselectively with alkynes to give 2,5-dihydrofurans <1996JA3533>. Exactly the same ylide formation and addition to alkynes has also been achieved using Mn and a catalytic amount of PbCl_2 <1997JOC8612>. The simplest possible completely unsubstituted carbonyl ylide can be prepared from bis(chloromethyl) ether (Equation (72)), by the action of either $\text{Sm}(0) + \text{I}_2$ <1996TL9241>, or alternatively $\text{Mn} + \text{catalytic PbCl}_2$ <1997JOC8610>.



Enantioselective cycloaddition of carbonyl ylides to alkynes has been accomplished by generation of the ylides from diazocarbonyl precursors, using chiral rhodium catalysts. Equation (73) shows intramolecular addition to an alkyne, and the same reaction can also be achieved with an extra C atom in the alkyne tether <2003JOC6153>. The corresponding intermolecular cycloaddition to phenylacetylene is also possible, in up to 61% ee <2003TA921>, and the same cycloaddition using a carbonyl ylide generated from an α -aryl- α -diazodiketone proceeds in up to 76% ee <2002TL3927>. Related asymmetric cycloadditions onto DMAD have been achieved by Hashimoto and co-workers, where the carbonyl ylides are generated by rhodium-catalyzed intramolecular cyclization of α -diazodiketone onto ketone or ester groups <1999JA1417, 2000TL5931>.

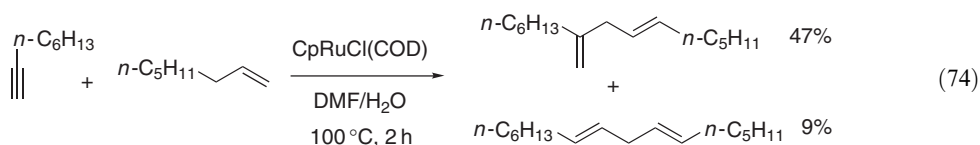


The chemistry of carbonyl ylides generated from rhodium carbenes has been reviewed, including cycloadditions to alkynes <1996CRV223>.

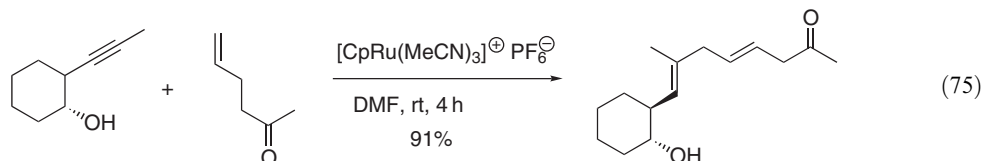
1.12.2.4 Ene Reactions

Ene reactions between an alkyne and an alkene usually involve the alkene component reacting as the enophile, and generate 1,4-dienes <1991COS(5)1, 1995COFGT(1)501>. Alkynes are more reactive than alkenes, although the thermal reaction can still require elevated temperatures of up to 200 °C, which limits the usefulness of this reaction in synthesis. Lewis acid catalysis allows ene reactions to occur at room temperature using alkynes activated with a conjugated carbonyl group, although [2+2]-cycloaddition is then often a competing reaction <1991COS(2)561, 1995COFGT(1)501>. Using Me₂AlCl as a Lewis acid, the reaction of butyn-2-one with allyl silanes has been found to give exclusively the ene product for reaction with a six-membered cyclic allyl silane, but mostly the [2+2] product using a 5-membered analog <1996T6685>.

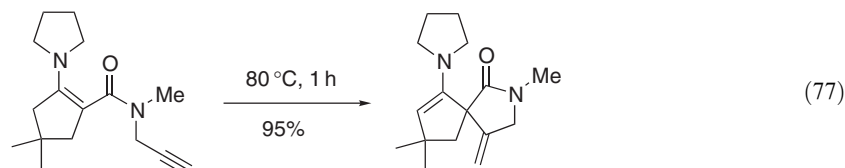
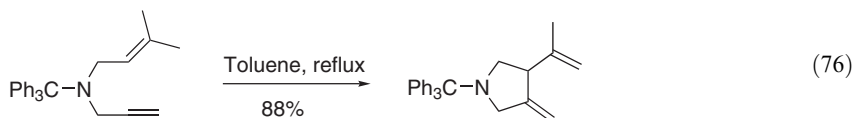
A major development in the ene reaction of alkynes has been the introduction of ruthenium catalysis <1998SL1, 2001CRV2067>, which allows reaction between unactivated alkynes and alkenes. The catalyst initially employed was RuCl(Cp)(COD) <1995JA615>, which allowed reactions to be performed at 65–100 °C, and gave fairly good regioselectivities (typically 3 to 6:1) for branched versus linear products (e.g., Equation (74)).



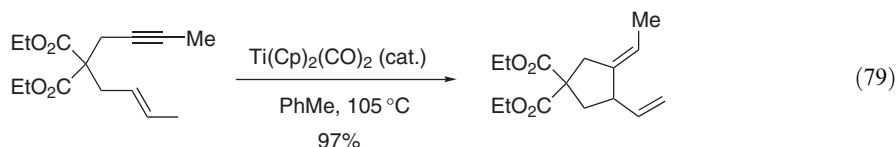
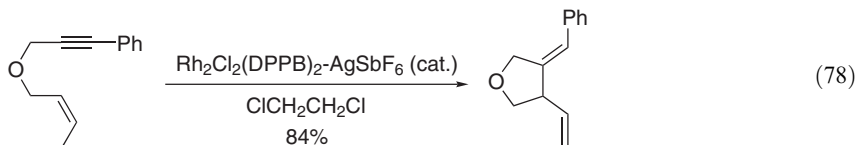
Reactions involving alkynoate esters result in the new C—C bond being formed α to the ester carbonyl group, in contrast to the normal thermal behavior [<1999JA1888>](#). The more reactive cationic Ru complex $[\text{CpRu}(\text{MeCN})_3]^+\text{PF}_6^-$ promotes the reactions at rt, with improved regioselectivities, and also permits reaction with 1,1- and 1,2-disubstituted alkenes, which were unreactive with the original catalyst [<1999TL7743, 2001JA12504>](#). A wide variety of other functional groups can be tolerated within the substrates. The same catalyst can also be used for the reaction between internal alkynes and terminal alkenes, which forms trisubstituted alkenes with good control over the double-bond geometry, and moderate-to-high sterically controlled regioselectivity with respect to the internal alkyne ([Equation \(75\)](#)) [<2002CEJ2341>](#).



Intramolecular ene reactions result in the formation of a new ring, and in most of the reactions involving alkynes, five-membered ring formation has been involved, with relatively few examples of six-membered ring formation [<1978JOC2161>](#). Unactivated alkynes often require very high temperatures for this reaction (e.g., up to 225 °C); however, the allyl amine shown in [Equation \(76\)](#) cyclizes to the pyrrolidine at only 110 °C, and it is proposed that steric buttressing by the bulky trityl group accelerates this reaction [<2002JCS\(P1\)1999>](#). Even milder conditions are successful for the ene reaction of the enamine-amide shown in [Equation \(77\)](#), which cyclizes to a spirolactam at 80 °C [<1997JOC7106>](#).

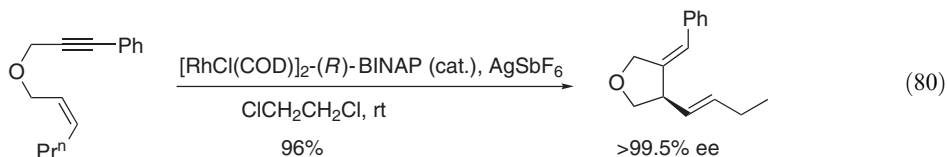


Just as for the intermolecular reaction, intramolecular ene reactions can also be catalyzed by transition metals, and this has been a very active area recently [<1998SL1, 2001CRV2067, 2002CRV813>](#). Ruthenium catalysts are effective for the formation of both carbocyclic [<1999TL7743, 2000JA714>](#) and heterocyclic rings (e.g., [Equation \(78\)](#)) [<2000JA6491>](#). Several other transition metals are also effective catalysts for the ene reaction of 1,6-enynes. The reaction shown in [Equation \(79\)](#) is catalyzed by a titanocene complex [<1999JA1976>](#), and a very similar substrate undergoes the same process using PtCl_2 [<2001JA10511>](#). Ene-type cyclizations of allene-ynes are catalyzed by rhodium complexes, and have been used to form cross-conjugated unsaturated six-membered carbocyclic [<2002JA15186>](#) and heterocyclic rings [<2003SL268>](#).



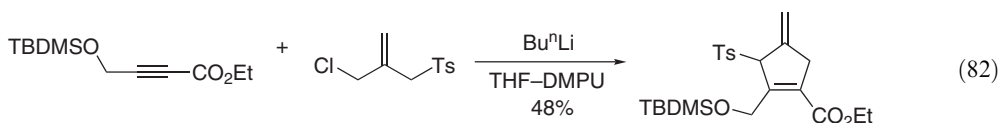
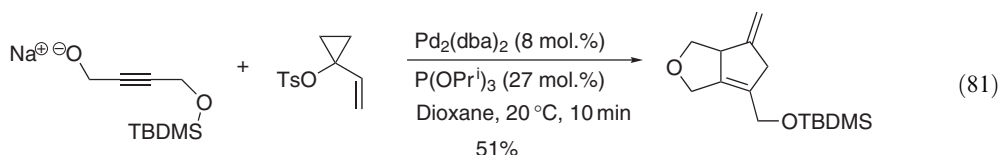
Chiral phosphine ligands are very effective in promoting enantioselective ene-type processes, and BINAP in combination with $\text{RhCl}_2(\text{COD})_2$ and AgSbF_6 , has been used to form tetrahydrofurans [<2002AG\(E\)3457>](#), lactones [<2002JA8198>](#) and lactams [<2002AG\(E\)4526>](#), all in

>99% ee (e.g., Equation (80)). This catalyst system is an improvement on earlier work, which employed DuPHOS, and other phosphine ligands <2000AG(E)4104>. Similar enantioselective cyclizations can also be achieved using a Pd(II) salt, in combination with either BINAP <2001AG(E)249>, or an N,P-ligand containing a chiral oxazoline <2003EJOC2552>.

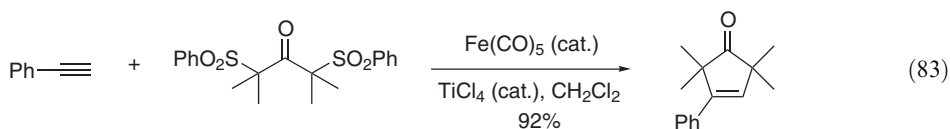


1.12.2.5 [3 + 2]-Cycloaddition Reactions

[3 + 2]-Cycloaddition reactions to alkynes result in cyclopentene formation, and there are several examples of addition of trimethylenemethanes, which are formed by metal-catalyzed ring opening of alkenylcyclopropanes <1995COFGT(1)501>. This approach has recently been developed to realize intramolecular reactions of the type shown in Equation (81), where both the initial alkylation and the subsequent [3 + 2]-cycloaddition are promoted by the same Pd catalyst, in a one-pot tandem sequence <2003JA9282>. An alternative approach to a trimethylenemethane equivalent is to use a phenylsulfonyl-stabilized carbanion, as shown in Equation (82), which undergoes conjugate addition to an activated alkyne, followed by ring closure to the cyclopentene product <2000TL5583>.

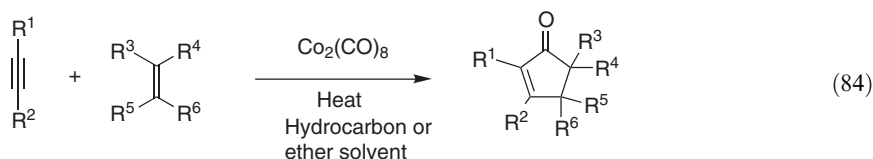


The first example of the [3 + 2]-cycloaddition of an oxyallyl cation to an alkyne has been reported <1995JOC1104>, and this results in the formation of a cyclopentenone (Equation (83)). The reaction works well with activated alkynes such as phenylethyne and diphenylethyne, but gives no cycloaddition product with 1-octyne.

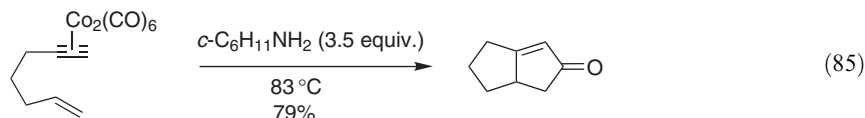


1.12.2.6 The Pauson–Khand Reaction

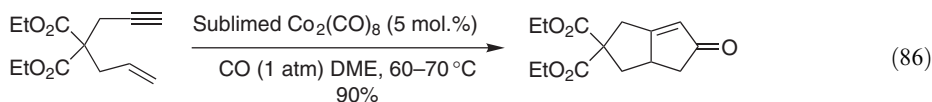
The Pauson–Khand reaction is the formal [2 + 2 + 1]-cycloaddition between an alkyne, an alkene, and carbon monoxide, to yield a cyclopentenone <1991OR1>. Until recently, the reaction was generally promoted by Co₂(CO)₈ at elevated temperatures (Equation (84)), and gave good regioselectivity with respect to terminal alkynes, but little regioselectivity with respect to alkenes in the intermolecular reaction. The intermolecular reaction is also limited in scope with respect to the alkene, with only strained alkenes giving good conversion. Intramolecular reactions work well, usually to give a five- or six-membered ring fused to the cyclopentenone; however, variation of the nature of the tether has also allowed formation of medium rings <2004CSR32>. The Pauson–Khand reaction has been an exceptionally active area of research over the last few years, with several hundred papers appearing since 1995, and only a few highlights are presented here; however, several recent reviews are available <2000T3263, 2003AG(E)1800, 2004CSR32>.



The reaction can be accelerated by adsorption onto dry solid supports, and also by the use of additives such as amine oxides, which have recently been used anchored to a solid support <2000SL1573>. Cyclohexylamine has been found to work particularly well for intramolecular cases (e.g., Equation (85)), whereas sulfides are more effective for intermolecular reactions <1997AG(E)2801, 1999SL771>. The addition of molecular sieves improves conversions <1999OL1187>, and this is also effective in the catalytic reaction <2002TL5763>.

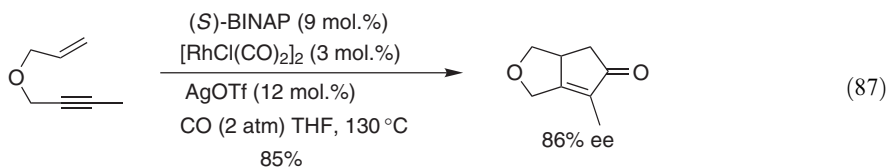


A major goal in this field recently has been to achieve catalytic reactions <2003AG(E)1800>. Livinghouse introduced a significant development with the use of catalytic amounts (0.05 equiv.) of high-purity Co₂(CO)₈ together with only 1 atm of CO, under carefully controlled thermal conditions (Equation (86)) <1998TL7637>. The need to use high-purity Co₂(CO)₈ can be avoided by the use of cyclohexylamine as an additive <2001JOC3004>. A more stable catalyst than Co₂(CO)₈ is obtained when one of the CO ligands is replaced by Ph₃P <2002T4937>; the resulting Ph₃PCo₂(CO)₇ catalyst can be stored in air, and is effective under 1 atm of CO. A polymer-supported version of this catalyst has also been reported <2000CC305>. A variety of heterogeneous catalysts for the Pauson-Khand reaction has been reported by Chung and co-workers, including the use of cobalt nanoparticles on a charcoal support <2002OL3983>, and also an Rh/Co heterobimetallic nanoparticle, which allows the use of unsaturated aldehydes as both the alkene component and also the source of CO <2004OL1183>. Other groups have also reported the use of aldehydes as a source of CO, thus obviating the potentially hazardous use of the toxic gas <2002JA3806, 2002JOC7446>.

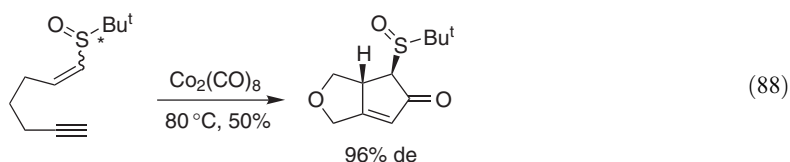


Complexes based on metals other than cobalt can also serve as catalysts for the Pauson-Khand reaction, and a commercially available titanium species, Cp₂Ti(CO)₂, has been found to be effective for intramolecular cyclization of enynes at low pressures of CO <1999JA5881>. A chiral titanocene complex promotes an enantioselective version of this cyclization in selectivities of 87–96% ee <1999JA7026>. The same group has also achieved asymmetric reactions using the original cobalt complex Co₂(CO)₈ together with a chiral chelating bis-phosphite, but the enantioselectivities are more modest (up to 75% ee) <2002JOC3398>.

The rhodium complex [RhCl(CO)₂]₂ is particularly effective for intramolecular cyclizations involving electron-deficient alkenes and alkynes <2001JOMC(624)73>, and several other Rh(I) complexes have also been utilized in the Pauson-Khand reaction by Jeong and co-workers <2002PAC85>. The same group has also reported asymmetric intramolecular reactions using the same Rh(I) complex and (S)-BINAP as the chiral ligand (Equation (87)) <2000JA6771>. An iridium complex Ir(COD)Cl₂ has been used in a very similar asymmetric cyclization to that in Equation (87), with TolBINAP as the chiral ligand, with an enantioselectivity of 93% ee <2000JA9852>.

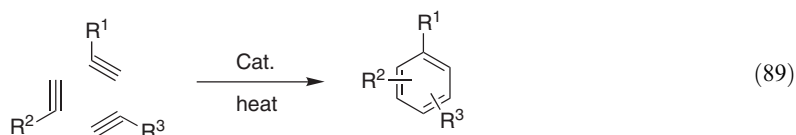


The use of chiral auxiliaries in the Pauson–Khand reaction has been studied for a number of years. Several recent examples lie outside the scope of this chapter, because the alkyne is attached to the auxiliary by a heteroatom, but an intramolecular cyclization of alkenyl sulfoxides gives good diastereoselectivities, although the sulfoxide auxiliary is destroyed by reductive removal (Equation (88)) <2002EJOC2881>.

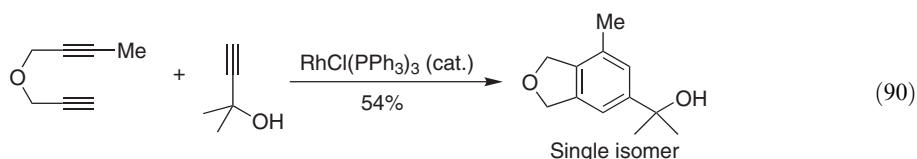


1.12.2.7 Cyclotrimerization of Alkynes

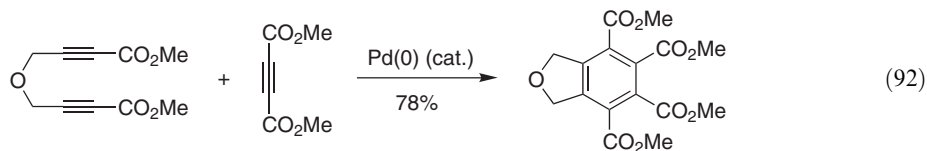
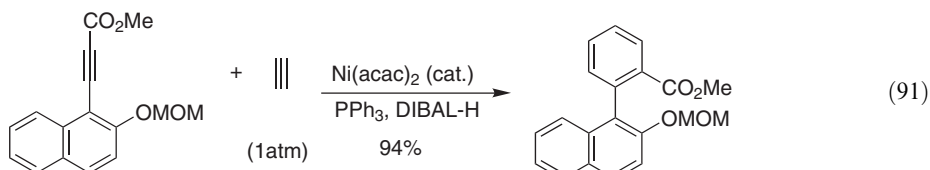
The transition-metal catalyzed [2 + 2 + 2]-trimerization of alkynes is an effective method for the formation of polysubstituted benzene rings (e.g., Equation 89) <1988CRV1081>. Recent developments have concentrated on the problem of regioselectivity in the formation of the benzene ring <2000CRV2901>, which is particularly difficult when starting from three separate alkyne components.



One approach is to make the reaction partially intramolecular, by tethering two of the alkyne units together; for example, aminodiyne with 3- or 4-atom tethers can be cyclized using Ni(PPh₃)₄ <1997H443> or Wilkinson's catalyst <1999AG(E)2426>. Related oxygen-tethered examples cyclizing onto substituted terminal alkynes have been found to be regioselective in generating the *meta*-substituted product (e.g., Equation (90)) <1995JA6605>. The ruthenium catalyst Cp^{*}RuCl(COD) has been shown very recently to catalyze the cyclization of unsymmetrical 1,6-diyne onto alkynes at ambient temperature, to give bicyclic benzenes with very good regioselectivity, and the same catalyst also trimerizes ethyl propiolate in 89% yield, giving a 61:28 ratio of regioisomers (Equation (89), R¹ = R² = R³ = CO₂Et) <2003JA12143>.

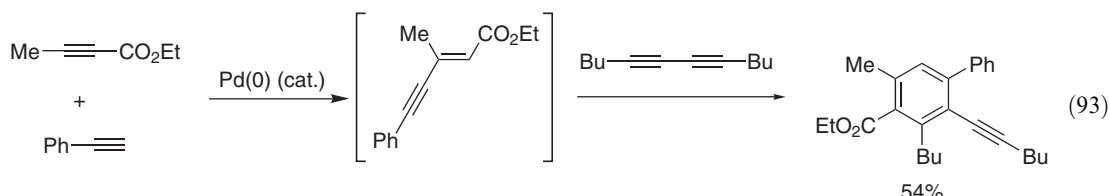


Biaryls have been prepared in good yields using acetylene itself as two of the components, in a nickel(0)-catalyzed reaction (Equation (91)) <1999TL5231>. In the palladium-catalyzed example in Equation (92), all three alkyne units bear electron-withdrawing groups, and this has been extended to a fully intramolecular case, with all three alkyne units tethered together <1999TL5035>.



Benzynes can undergo the cyclotrimerization reaction, and 3-methoxybenzyne undergoes the palladium-catalyzed formation of a triphenylene with high regioselectivity <1998AG(E)2659>.

An alternative approach to the regioselectivity problem is to first form a conjugated enyne, which can then undergo palladium-catalyzed [4 + 2]-cyclization, either with itself, or with another alkyne component. This approach has been extended to a “one-pot” palladium-catalyzed process where the enyne is formed by addition of a terminal alkyne to an ynoate ester, followed by [4 + 2]-cyclization onto a diyne, giving tetrasubstituted benzenes as single products (e.g., Equation (93)) <2001JOC2835>.



Benzenes can also be assembled from three alkyne units using stoichiometric quantities of titanium or zirconium reagents, to generate first a metallocpentaene from two alkyne units, followed by reaction with the third alkyne. A divalent titanium reagent prepared from $\text{Ti}(\text{O}-i\text{Pr})_4$ and $i\text{-PrMgCl}$ has been reacted with three different alkyne units in this manner <2001JA7925>, and has also been used to cyclize unsymmetrical diynes onto another alkyne <2003JOC4980>.

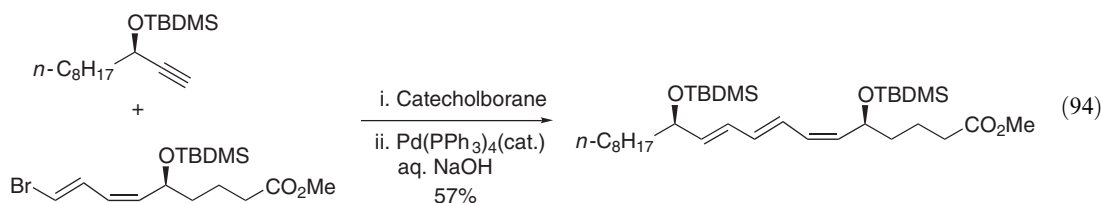
1.12.3 IONIC ADDITIONS

1.12.3.1 Hydrometallation of Alkynes Followed by C—C Bond Formation

Hydrometallation of alkynes generates alkenyl metal species (in the same processes discussed above in Section 1.12.1.4), which can then undergo replacement of the metal atom with C. This section will concentrate on examples where the emphasis is upon formation of a substituted alkene by overall addition of H and C to the alkyne, rather than isolation of the intermediate alkenyl metal compounds.

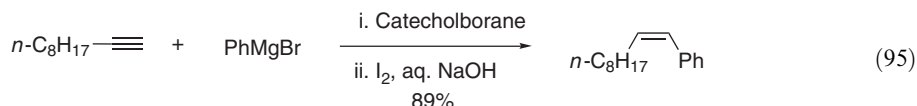
1.12.3.1.1 Hydroboration followed by C—C bond formation

Alkenylboranes formed by hydroboration of alkynes can undergo a variety of reactions replacing the C—B bond with a C—C bond <1995COFGT(1)501>. This process is most often carried out on terminal alkynes, because of problems of regioselectivity in the hydroboration step with internal alkynes. A particularly important class of reactions is that of palladium-catalyzed cross-coupling of alkenylboranes (or boronates) (Miyaura–Suzuki coupling), and this has been reviewed <1995CRV2457>. The coupling is commonly performed with alkenyl halides, resulting in a synthesis of conjugated dienes with retention of configuration of the alkene geometry at both components, although activated (allylic and benzylic) alkyl halides can also be used. A particularly efficient procedure involves hydroboration of a terminal alkyne with catecholborane to give the alkenylborane, followed by palladium-catalyzed coupling with an alkenyl halide <1995CRV2457>, and this has been used in the synthesis of leukotriene B_3 (Equation (94)) <1998T4327>. 1-Bromoalkynes can also be used as the coupling partner to give (*E*)-enynes, and this has been used in the synthesis of sex pheromone components <1999S107>. An alternative method for the preparation of (*E*)-enynes involves the Cu(II)-catalyzed coupling of alkenylboranes with alkynylcopper compounds, both of which are prepared *in situ* <1998CC807>. Recently, satisfactory conditions have been found (using tricyclohexylphosphine as a ligand for Pd) for coupling reactions with α -bromoamides <2003TL7249>, which have proved problematic in the past.

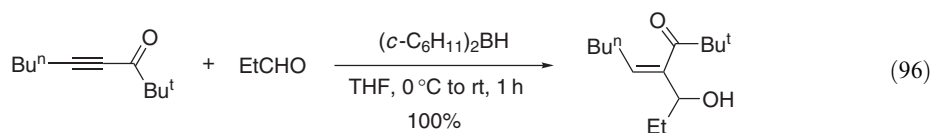


Nickel complexes can also be used as catalysts for the coupling steps. Ni(acac)₂ has been used for the conjugate addition of alkenylboranes to α,β -unsaturated ketones [<1996SC2503>](#), and NiCl₂(PPh₃)₂ has been used for the coupling of alkenylborates to allylic acetates [<1998TL601>](#).

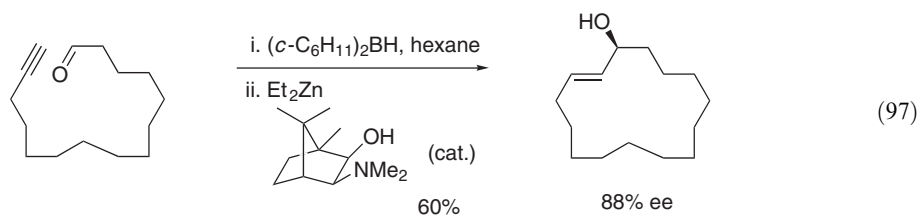
The reaction of (*E*)-alkenyl dialkylboranes with I₂/NaOH, which is known to give (*Z*)-alkenes with migration of an alkyl group from boron, has been extended to the reaction of alkenylboranes (prepared by hydroboration of terminal alkynes using catecholborane) with Grignard reagents and I₂/NaOH ([Equation \(95\)](#)) [<1995T2743>](#). This allows a greater variety of alkyl groups to be incorporated into the product alkene.



Hydroboration of α,β -alkynyl ketones with dicyclohexylborane gives alkenylboranes which rearrange to boron enol ethers. These then undergo further aldol reaction, either with an excess of the starting ketone [<1999TL37>](#), or with an aldehyde, added as a second carbonyl component ([Equation \(96\)](#)) [<1999JOC5822>](#).



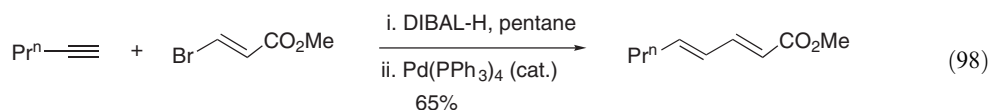
Alkenylboranes can be transmetalated *in situ* by Et₂Zn, and the resulting alkenylzinc compounds undergo asymmetric addition to aldehydes in the presence of chiral ligands. A chiral aminoalcohol derived from isborneol was used for the intramolecular version in [Equation \(97\)](#) [<2001JOC4766>](#), and a similar method was used for intermolecular reactions to generate allylic alcohols for the synthesis of α -amino acids [<2002JA12225>](#). Ligands based upon chiral [2:2]paracyclophanes have also proved to be useful in the intermolecular reaction, particularly with difficult substrates [<2001OL4119>](#).



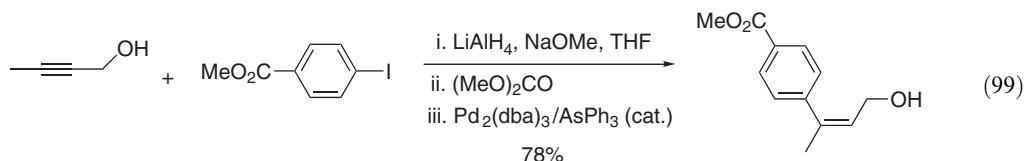
1.12.3.1.2 Hydroalumination followed by C—C bond formation

Alkenylalane intermediates derived from addition of aluminum hydride reagents to alkynes can be reacted with a variety of C-centered electrophiles, with retention of stereochemistry at the alkene [<1984OR375, 1995COFGT\(1\)501>](#). The most often used combination is a terminal alkyne and DIBAL-H, which gives an alkenylalane which reacts well only with reactive electrophiles. Ni- and Pd-catalyzed cross-couplings are also possible. Addition of methyllithium to the alane generates a more reactive alanate, which reacts with a wider range of electrophiles.

The alkenylalane derived from reaction of DIBAL-H with 1-pentyne undergoes Pd(0)-catalyzed coupling with β -bromoacrylates ([Equation \(98\)](#)), and this has been used in the synthesis of pheromones [<1996SC3297>](#).



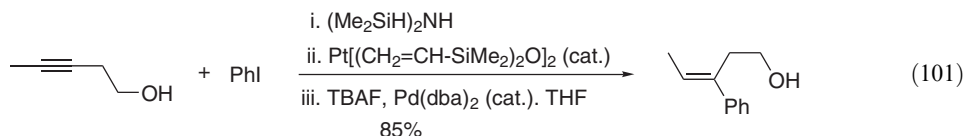
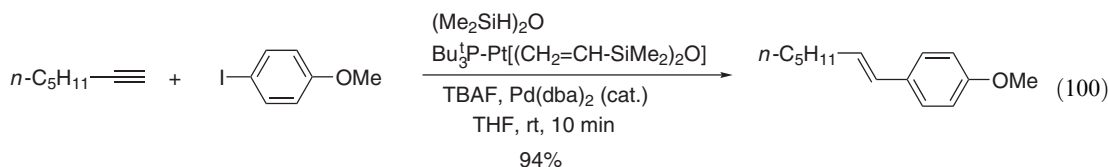
The intermediates formed by hydroxyl-directed LiAlH_4 hydroalumination of propargyl alcohols undergo direct Pd-catalyzed cross-coupling with aryl halides, resulting in a stereoselective synthesis of trisubstituted allylic alcohols (Equation (99)) <2002JOC2125>.



The hydroalumination of propiolate esters with DIBAL-H has recently become more attractive with the finding that the usual requirement for HMPA can be substituted by NMO. The intermediate alane undergoes reaction with a variety of carbonyl-based electrophiles, including aldehydes, pyruvates, and α -halocarbonyl compounds, to give Baylis–Hillman-type products <2003JOC9310>.

1.12.3.1.3 Hydrosilylation followed by C—C bond formation

Terminal alkynes undergo regioselective platinum-catalyzed hydrosilylation to give alkenylsilanes, which are often isolated (see Chapter 2.18.2), rather than reacted directly with electrophiles (see also Chapter 1.11.1.6). Hydrosilylation has been combined with Pd-catalyzed coupling with aryl and alkenyl iodides in a one-pot procedure giving (*E*)-1,2-disubstituted alkenes with good regio- and stereoselectivity (Equation (100)) <2001OL1073>. Interesting results have been obtained in the hydrosilylation/cross-coupling of internal alkynes bearing hydroxyl groups. With a homopropargyl alcohol, overall *cis*-addition was observed, with the phenyl group attached to the carbon nearer the hydroxyl group (Equation (101)) <2001OL61>. However, using a ruthenium catalyst (rather than platinum) for the hydrosilylation step resulted in overall *trans*-addition, with the silyl (and hence aryl) group attached to the carbon remote from the hydroxyl group <2003JA30>.

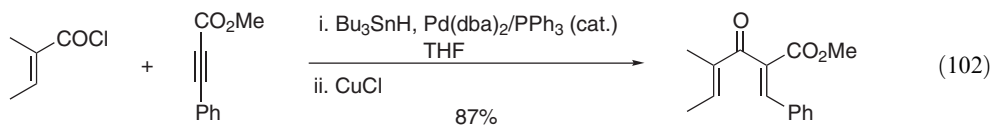


1.12.3.1.4 Hydrostannylation followed by C—C bond formation

Alkenylstannanes can be generated by palladium-catalyzed hydrostannylation of (usually) terminal alkynes, and as with alkenylsilanes, they are often isolated before use (see Chapter 2.19.6).

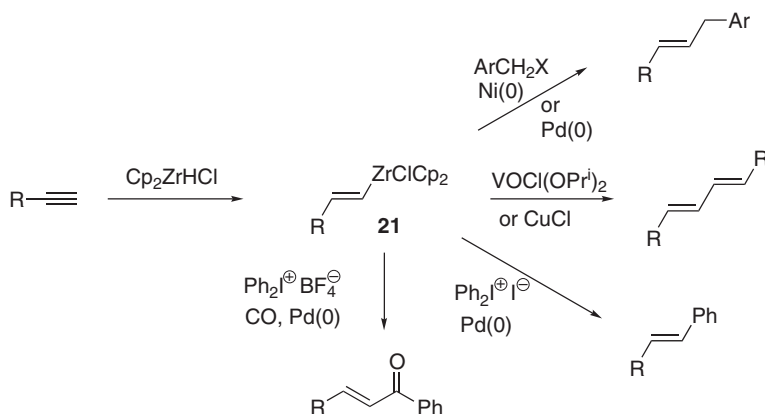
Palladium-catalyzed hydrostannylation of propiolate esters results in the tin atom being introduced α to the carbonyl group, rather than on the terminal carbon, and the alkenyltin intermediates undergo *in situ* Cu(I)-catalyzed coupling with α,β -unsaturated acyl chlorides to give dienones suitable for Nazarov cyclization (Equation (102)) <2003CC1380>. The tin can also be directed to the internal carbon by a nearby nitrogen during hydrostannylation, and this has been utilized in tandem cyclization–Stille couplings, in both intra- and intermolecular fashion

<2000T7451, 2001T607>. Recycling of the tin halide by-product back to tin hydride during one-pot tandem Pd-catalyzed hydrostannylation/Stille couplings allows the overall process to be carried out with only catalytic amounts of tin <2001JA3194>.



1.12.3.1.5 Hydrozirconation followed by C—C bond formation

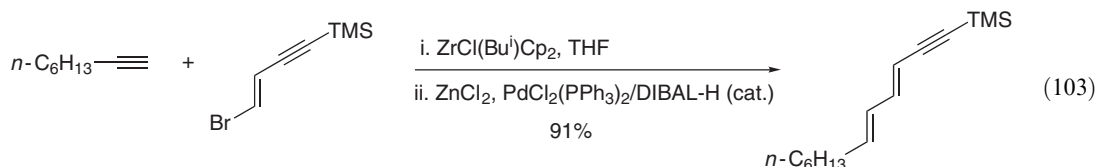
The *syn*-addition of Cp₂ZrHCl (Schwartz reagent) to alkynes gives (*E*)-alkenylzirconium reagents **21** with a high level of stereoselectivity, and many other functional groups are unaffected (Scheme 3) <1996T12853>. The reagent can be prepared from Cl₂ZrCp₂ and reducing agents <B-1996MI002, B-2002MI003>. Terminal alkynes show good regioselectivity for attachment of the zirconium to the terminal carbon. Internal alkynes give mixtures of regioisomers, which can however be equilibrated with excess reagent, to place the zirconium atom on the less hindered carbon, often with high selectivity.



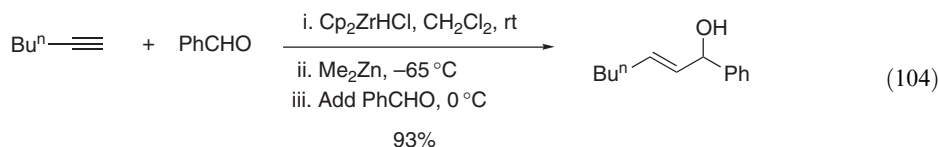
Scheme 3

The alkenylzirconium intermediates **21** can be transformed into alkenes by a range of C-centered electrophiles (Scheme 3) <1995COFGT(1)501, B-2002MI003>. Oxidative homocoupling to symmetrical (*E,E*)-dienes can be mediated by an oxovanadium(V) compound, as an alternative to the previously used CuCl <1999JOMC76>. Cross-coupling with benzyl halides has been found to be catalyzed by Ni(0) more effectively than by Pd(0) <1996T7265>. Palladium(0)-catalyzed coupling with aryl iodide salts gives good yields of alkenylaromatics <1998SC773>, and inclusion of carbon monoxide results in arylalkenyl ketones <2002JCS(P1)459>. The thermal equilibration of the hydrozirconation product of an internal alkyne has been found to improve the regioselectivity, and can be combined with Pd(0)-catalyzed coupling with vinyl iodides in the preparation of unsymmetrical trisubstituted dienes <1997JOC4912>.

Palladium(0)-catalyzed cross-coupling with a four-carbon bromo-ene has been used as a strategy for the iterative stereoselective construction of (*all-E*)-polyenes (Equation (103)) <2002OL703>. Removal of the TMS group from the product allows the process to be repeated on the new terminal alkyne.

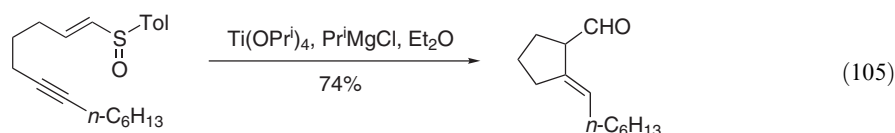


The alkenylzirconium reagents **21** show a low level of nucleophilic reactivity toward carbonyl compounds; however, this can be increased by the addition of either AgClO_4 , or AgAsF_6 (which has been suggested as a safer alternative) <1995T4483>. Another way of increasing the reactivity is to transmetallate the alkenylzirconium intermediate **21** using a dialkylzinc reagent, and this approach has been reviewed <2002CEJ1779>. Reaction with aldehydes gives allyl alcohols in good yields, and catalytic amounts of dialkylzinc can be used (Equation (104)). ZnBr_2 can also be used in place of dialkylzinc. Asymmetric addition of the transmetallated alkenylzinc reagents can be promoted by chiral amino alcohols or more effectively by aminothiols <1998JOC6454>. Transmetallation by dialkylzinc has also been used to aid the addition of alkenylzirconocenes to α -ketoesters and α -iminoesters <2003OL2449> and *N*-phosphinoylimines <2003JA761>. The addition to imines bearing a range of other electron-withdrawing groups on the nitrogen is catalyzed by $\text{RhCl}(\text{COD})_2$ <2003TL923>. Alkenylzirconocenes derived from a range of alkynes have been coupled to α -chloroethers using ZnCl_2 as the additive <1995JOC6260>. Similar types of products can also be obtained by insertion of carbenoids, formed from α -chloroethers, which have been deprotonated by lithium amide bases <2000TL6211>. Lithiated epoxynitriles also undergo insertion reactions with alkenylzirconocenes to give 2-cyano-1,3-dienes <2000TL6201>.



1.12.3.1.6 Formation of alkyne–titanium complexes followed by C—C bond formation

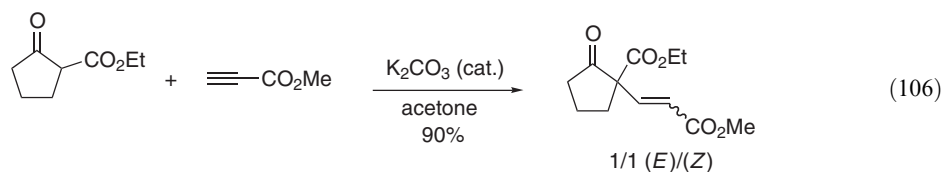
Reaction of alkynes with low valent titanium complexes, generated from $\text{Ti}(\text{Oi-Pr})_4$ and $i\text{-PrMgCl}$, generates titanocyclopropene complexes as mentioned above in Section 1.12.1.5. These complexes can be reacted with carbon-centered electrophiles, resulting in a process which, overall, is equivalent to hydrotitanation of the alkyne followed by C—C bond formation <2000CRV2835, 2000SL753>. An intramolecular version, with an alkenylsulfoxide as the electrophile, is followed by a Pummerer-type process to give cyclic aldehydes (Equation (105)) <2002AG(E)3671>. The titanium complex formed from a symmetrical internal alkyne has been trapped with CO_2 to give an α,β -unsaturated carboxylic acid in good yield <2002JCS(P1)1159>.



1.12.3.2 Ionic Additions of Stabilized Carbanions to Activated Alkynes

Conjugate addition of enolates and other stabilized carbanions to alkynes activated by a conjugated electron-withdrawing group can sometimes be stopped after mono-addition, but can also be complicated by a second addition of the nucleophile, cyclization, or formation of ring-expanded products <1991COS(4)1, 1995COFGT(1)501, B-1992MI001>.

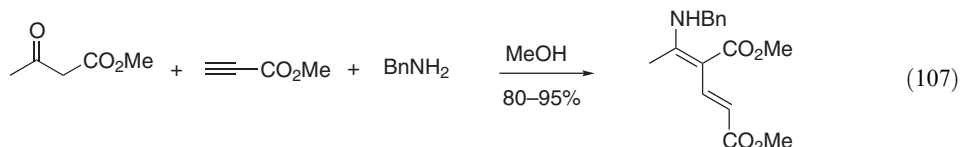
The ruthenium species $\text{RuH}_2(\text{PPh}_3)_2$ catalyzes the Michael addition of a cyanoacetate to both ethyl propynoate and 3-butyne-2-one in up to 90% yield <1995JA12436>. The importance of the reaction conditions is illustrated in Equation (106), where conjugate addition of cyclic β -ketoesters to methyl propynoate or 3-butyne-2-one was achieved using K_2CO_3 in acetone, to give the Michael addition products as a mixture of geometrical isomers in good yield <1998TL6873>. However, changing the solvent to benzene, ether, or THF resulted in significant amounts of ring-expanded products.



An imine-protected ethyl glycinate adds to ethyl propynoate at low temperature using KO^tBu as a base, and this reaction is also successful with α -alkylated glycinatees <1995TL5823>.

In the reaction between various diethyl alkylmalonates and 2-alkynones, further cyclization occurred to give α -pyrones <2003TL2125>, and similar results were obtained with β -ketoesters. Changes in reaction conditions or substrate structure significantly affected the product distribution.

Conjugate addition of β -ketoesters or 1,3-diketones to ethyl propynoate using *N*-methylmorpholine as a base results mainly in attack by the *O* of the enolate rather than the C <2003TL2125>. On the other hand, the enamine formed between methyl acetoacetate and aniline undergoes clean conjugate C-addition to methyl propynoate in 80–95% yield (Equation (107)) <2001SL1440>.



Chiral imines of 2-methylcyclohexanone undergo asymmetric conjugate addition to methyl propynoate on the more substituted side, to give ketones in 43% or 80% ee after hydrolysis, depending upon the conditions for the addition <1996JOC4361, 1996JOC5362>. 2-Methylcyclopentanone reacts similarly, but in a slightly lower selectivity of 71% ee <1997TA2731>.

Triphenylphosphine has also been found to be an effective promoter for selective Michael additions, with an α -cyanoester group reacting in preference to a β -ketoester group within the same molecule, in the addition to 3-butyne-2-one <1999JOC7178>. Several other standard bases were ineffective. The same group has found that the phosphoramidite HMPT catalyzes (at 10 mol.%) the efficient addition of α -cyano- and β -ketoesters to 2-alkynones <2003JOC871>. These reactions often proceed in seconds at room temperature, and without added solvent.

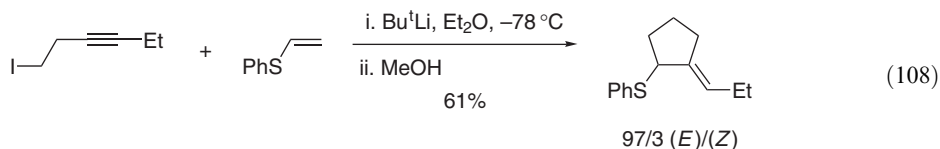
1.12.3.3 Carbometallation of Alkynes

Carbometallation of alkynes generates alkenylmetal compounds <1992COS(4)865, B-1996MI002>, which can be protonated or reacted with C-centered electrophiles to give alkenes <1995COFGT(1)501>. The carbometallation of alkynes containing adjacent heteroatoms has been reviewed recently <2000BCSJ1071>, as has the carbometallation of conjugated alkyne nitriles <2003CRV2035>.

1.12.3.3.1 Additions of organolithium and Grignard reagents to alkynes

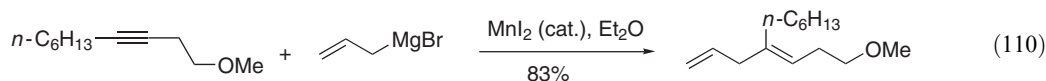
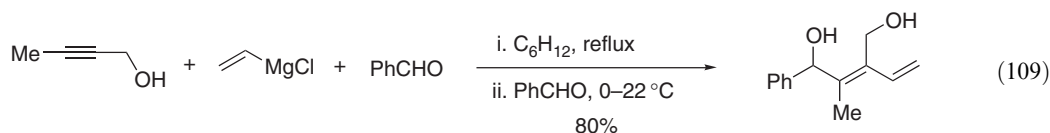
The addition of the reactive and strongly basic organolithium and Grignard reagents to alkynes is often unsatisfactory, and deprotonation of the substrate may occur, either at the terminal C–H, or at propargyl positions for internal alkynes <1992COS(4)865>.

Intramolecular additions often give good yields, and the cyclization of vinylolithiums onto alkynes in a 5-*exo* manner has been used to prepare a range of five-membered cyclic bis-*exo*-dienes <1996JOC8216>. The 5-*exo* cyclization of chiral carbamate-stabilized organolithiums, generated by asymmetric deprotonation in the presence of (–)-sparteine, gives good results if the internal propargyl position is substituted to inhibit deprotonation <1998TL1745>. A tandem process is shown in Equation (108), where an organolithium generated from the homopropargyl iodide adds to the vinyl sulfide, and this is followed by 5-*exo* cyclization <2000AG(E)409>. Cyclopropyllithium species have also been cyclized in a 5-*exo* manner to give spiro-fused bicyclic systems <1996S502>.

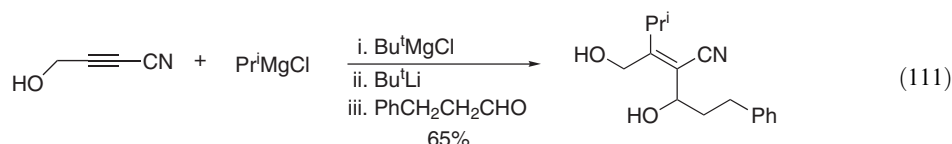


Additions of Grignard and organolithium reagents to propargyl alcohols can also give good results, with overall *trans*-addition of the alkyl group and the metal, and the intermediate alkenyl metal is stabilized by coordination of the alkoxide <1995COFGT(1)501>. This has been extended to addition of vinyl Grignard reagents to propargyl alcohols, and the intermediate dienyilmagnesiums can be

trapped with electrophiles, e.g., aldehydes (Equation (109)) <2000TL11>. The addition of Grignard reagents to homopropargyl methyl ethers is catalyzed by Mn(II), and results in the regio- and stereoselective synthesis of trisubstituted alkenes (Equation (110)) <1996JACS6076>. Addition of organolithiums to homopropargyl ethers gives similar results using catalytic Fe(acac)₃, and trapping with aldehydes is also possible <2001AG(E)621>.

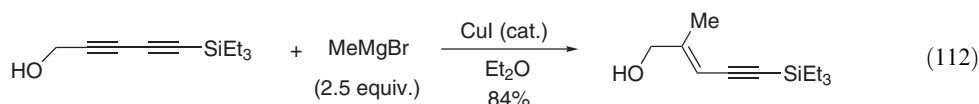


Organolithium and Grignard reagents can be added to conjugated alkynenitriles, in a reaction promoted either by a catalytic amount of a Cu(I) salt <1996JOC3542, 2003CRV2035>, or 1 equiv. of Bu^tMgCl <2003T5585>. The intermediate alkenyl Grignard species can also be activated by Bu^tLi, and then trapped by aldehydes to give tetrasubstituted alkenes (e.g., Equation (111)).



Conjugate addition of BuⁿLi to conjugated alkynones has been mediated by a tris(alkoxyaluminum) compound in excellent yield, and if the additive is changed to a bis(alkoxyaluminum) compound, then 1,2-addition to the carbonyl predominates instead <1995SL719>.

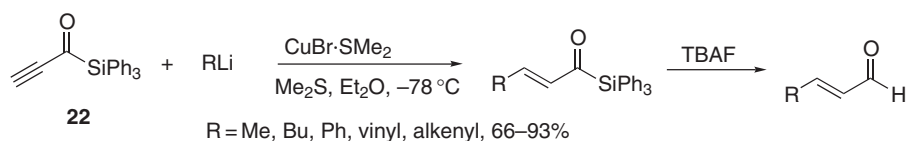
Several groups have studied the regioselective addition of Grignard reagents to conjugated diynes bearing a terminal silyl protecting group. Addition of alkynyl Grignards gives conjugated *cis*-enediynes <2000TL11, 2001JOC2146>, and the regio- and stereoselective addition of alkyl and vinyl Grignards is catalyzed by Cu(I) in good yields (Equation (112)) <2002JOC6844>.



1.12.3.3.2 Addition of organocopper reagents to alkynes

(i) Addition of organocopper reagents to activated alkynes

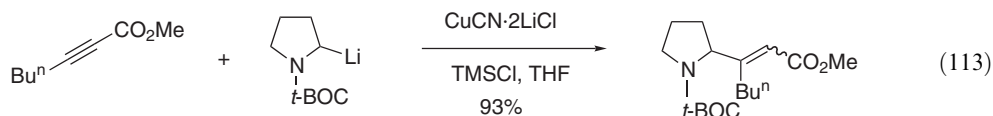
Organocopper reagents are commonly used in conjugate addition reactions, including additions to alkynes conjugated with carbonyl groups <1991COS(4)169>. A variety of cuprates have been added to the alkynylsilyl ketone **22**, and the products can be desilylated to the corresponding α,β -unsaturated aldehydes (Scheme 4) <2001T6267>.



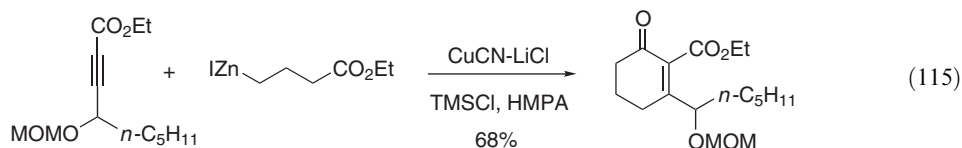
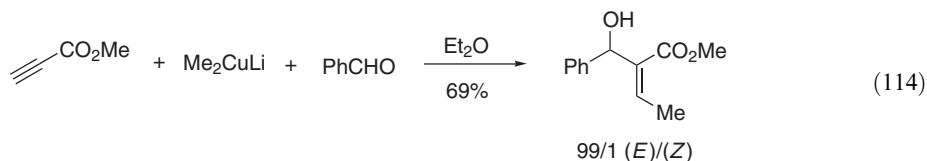
Scheme 4

Unsymmetrical dialkenyl ketones can be prepared by conjugate addition of dialkylcuprates to acetylenic alkenyl ketones, where the addition is completely selective for the conjugated alkyne over the alkene <1999TL7109>. Preparation of an organocopper reagent from lithiated

N-BOC-pyrrolidine failed using the standard copper reagents, but the combination of LiCl-solubilized CuCN and activation by TMSCl allows conjugate addition to an alkyne in excellent yield (Equation (113)) <1997JOC3798>.

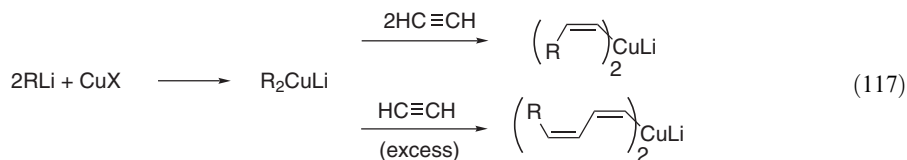
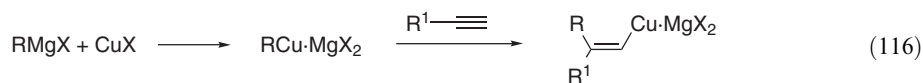


The intermediates formed by conjugate addition of cuprates to alkynes may be trapped by reactive electrophiles, resulting in a three-component coupling. Trapping with aldehydes results in the formation of Baylis–Hillman-type products without any activation of the electrophile (Equation (114)) <1999SC2959>; however, with bulkier menthyl esters activation by Et₂AlCl is necessary <1998TL8203>. Chiral *N*-tosylimines can also serve as the trapping agent if activated by Yb(OTf)₃, resulting in good diastereoselectivities <1999TL4611>. Alkyl halides can be used as trapping agents, and the use of iodomethylboronate esters also introduces extra functionality; however, HMPA is required for successful reaction <2002JA898>. Intramolecular trapping by an ester group, which is incorporated into a zinc-copper nucleophile, results in cyclization to cyclohexenones (Equation (115)) <1995TL7061>.



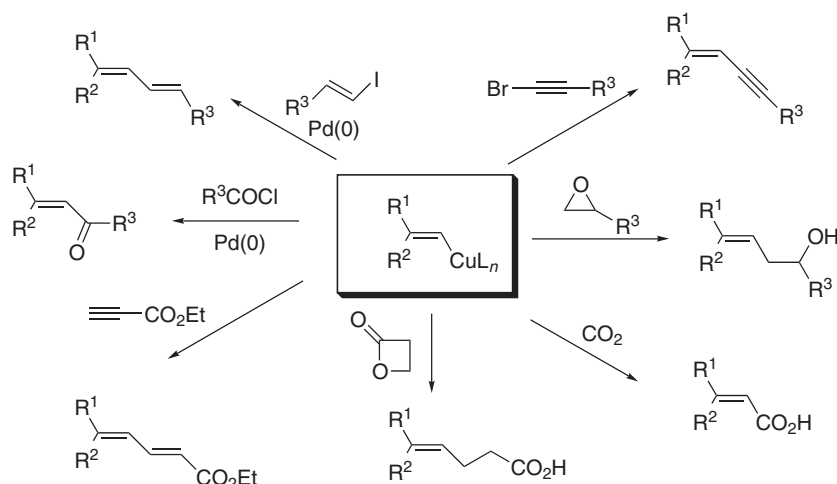
(ii) Additions of organocuprate reagents to unactivated alkynes

Organocupper reagents undergo addition to acetylene and terminal alkynes to give alkenylcopper species with *cis*-addition to the alkyne. Detailed protocols for the mono-insertion of organocupper reagents prepared from Grignard reagents into terminal alkynes (Equation (116)) and the addition of lithium dialkylcuprates to acetylene to give dialkenyl reagents (Equation (117)) are given in the reviews by Normant <B-1994MI002> and Lipshutz <1992OR135, B-2002MI010>. With excess acetylene, dienyl cuprates can be generated instead (Equation (117)), which can be reacted with electrophiles *in situ* <1986JCS(P1)1809>.



The alkenylcopper species can simply be protonated, or alternatively reacted with a wide variety of *C*-centered electrophiles <1992COS(4)865>. These include: coupling with 1-bromoalkynes, ring opening of epoxides, carboxylation to acids, ring opening of butyrolactone, conjugate addition, and palladium-catalyzed coupling with alkenyl iodides and acyl chlorides (Scheme 5). Detailed protocols for all of these conversions are given in the review by Normant <B-1994MI002>.

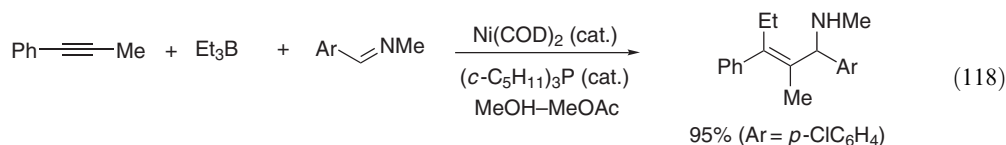
A range of terminal alkynes have been converted into 2-alkyl acrylonitriles by addition of HI generated *in situ*, followed by reaction of the intermediate 2-iodo-1-alkenes with CuCN, in a procedure which is equivalent to overall addition of HCN <1997TL8061>.



Scheme 5

1.12.3.3.3 Addition of organoboron reagents to alkynes

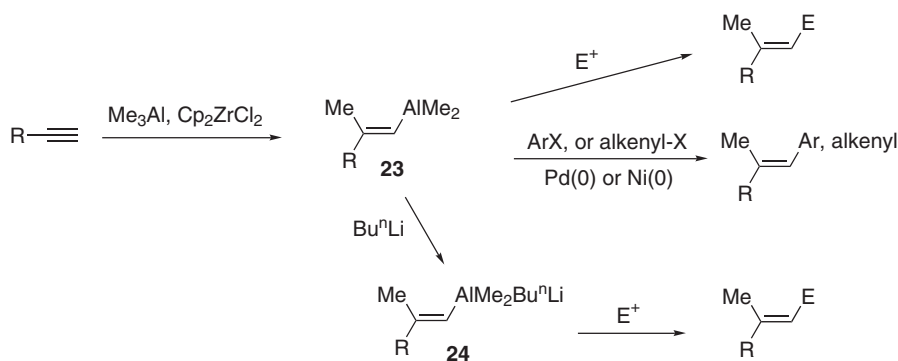
Although the addition of trialkylboranes to alkynes is not a widely used synthetic procedure [<1995COFGT\(1\)501>](#), the three-component coupling shown in [Equation \(118\)](#), involving Ni(0)-catalyzed addition of triethylborane to alkynes and aldimines, gives good yields for several examples [<2003AG\(E\)1364>](#). Boronic acids can also be used in place of triethylborane. Boronic acids also undergo addition to alkynes, catalyzed by rhodium(I) [<2003JOC762>](#) or palladium(0) [<2003AG\(E\)805>](#). This results in overall hydroarylation of the alkyne, and the mechanism may involve formation of an alkenylmetal species, followed by coupling with the boronic acid.



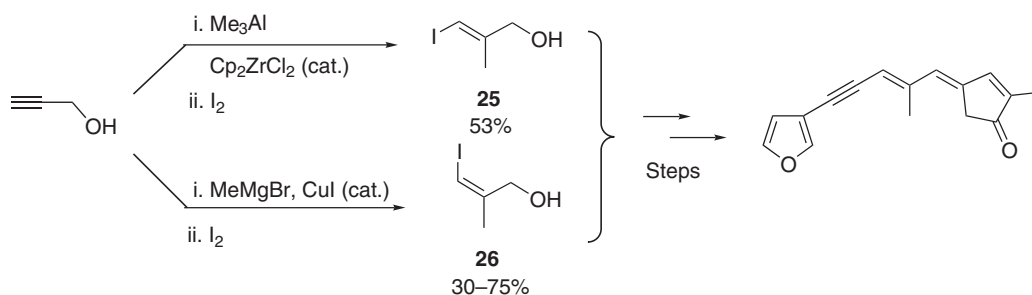
1.12.3.3.4 Addition of organoaluminum reagents to alkynes

The carbometallation of acetylene itself works well with trialkylalanes, but is not satisfactory for terminal or internal alkynes. The most widely used method for carboalumination of terminal alkynes is the zirconocene-catalyzed *syn*-addition of trimethylalane, which is also highly regioselective ([Scheme 6](#)) [<B-1996MI002, B-2002MI003>](#). Internal alkynes are less reactive, and give mixtures of regioisomers if unsymmetrical. Methyl-, allyl-, and benzylalanes all work well, and other combinations of aluminum and zirconium reagents can be used for other alkyl groups. The intermediate alkenylalane **23** undergoes the standard polar reactions with reactive C-centered electrophiles, and also nickel and palladium-catalyzed cross-coupling reactions [<1995COFGT\(1\)501, B-1996MI002, B-2002MI003, B-2002MI004>](#). The reactivity of the alkenylalanes can be increased by forming the alanate **24** with an alkyllithium, which allows reaction with a wider range of electrophiles.

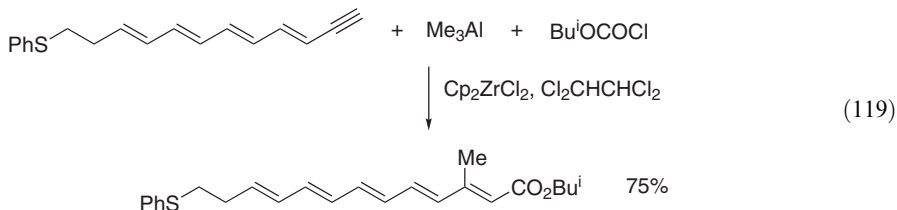
The alkenylalanes **23** can also be reacted with iodine, to give a stereoselective synthesis of alkenyl iodides, which can then be coupled with organometallic reagents to give trisubstituted alkenes. This approach is well suited to the synthesis of isoprenoid units, and has been used often in the synthesis of terpenes (e.g., [Scheme 7](#)) [<1997JOC8591>](#). It is interesting to note that the opposite geometrical isomer **26** of the iodide **25**, required in the same synthesis, was prepared by Cu(I)-catalyzed carbomagnesiation of a common starting material. The direct reaction of alkenylalanes **23** with chloroformates has also been used in natural product syntheses such as polyene antibiotics, e.g., [Equation \(119\)](#) [<1998JOC6092>](#).



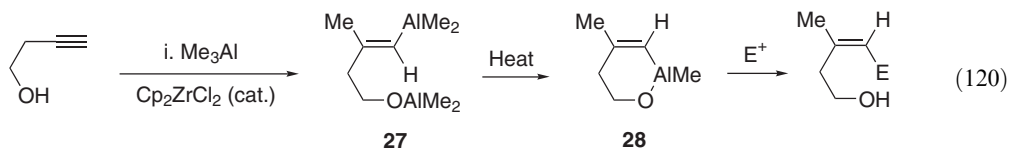
Scheme 6



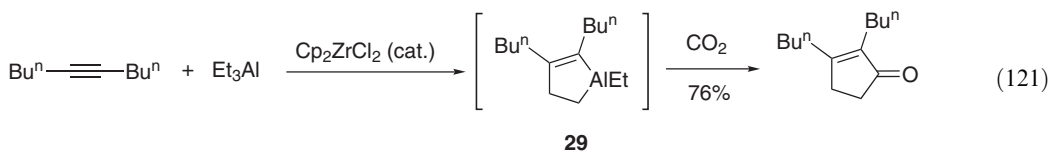
Scheme 7



A useful reversal of the stereoselectivity of methylalumination can be achieved using homopropargyl alcohols (Equation (120)). Initially, the *syn*-adduct **27** is formed as expected, but after heating for 72 h, isomerizes cleanly under chelation control to the *anti*-adduct **28** <1997JOC784>. The homopropargyl alcohol group is essential for the isomerization to occur, and this transformation was exemplified in the synthesis of (3*Z*)- α -farnesene.



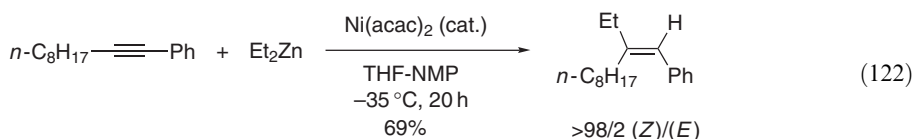
The zirconocene-catalyzed carboalumination of internal alkynes with triethylalane gives a cyclic intermediate, e.g., **29**, and this can be reacted with CO₂ or chloroformates to give cyclopentenones (Equation (121)) [<1998TL2503>](#).



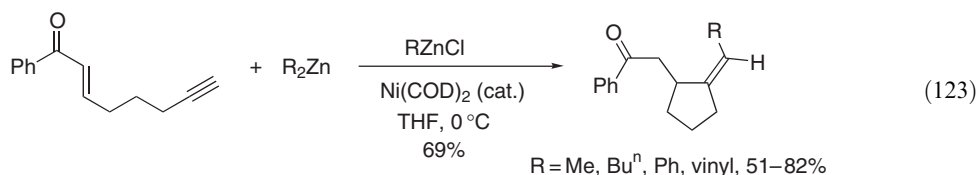
Recently, the stereoselectivity of additions of alkenylalanes **23** to chiral electrophiles has been studied, including additions to chiral aldehydes <2002TL4183> and *N*-tosylimines <2002HCA3478>.

1.12.3.3.5 Addition of organozinc reagents to alkynes

The preparation and reactions of organozinc reagents, including additions to alkynes, has been reviewed <1992COS(4)865, 1998T8275>. Recent developments in the addition of organozinc compounds to alkynes have focused on the use of nickel catalysts <1998T8275, 2000T817>. Dialkyl and diphenyl zinc reagents add to 1-phenylalkynes with high regio- and stereoselectivity (e.g., Equation (122)) <1997AG(E)93, 1998T1299>. The intermediate alkenylzinc reagent can also be quenched with electrophiles (e.g., acyl or allyl halides, and iodine) instead of being protonated, to give tetrasubstituted alkenes. Intramolecular versions are possible, starting from 6-iodo-1-alkynes, resulting in stereoselective 5-*exo*-cyclization. Under an atmosphere of carbon dioxide, terminal alkynes form a cyclic intermediate with the nickel catalyst and the CO₂, which reacts with organozinc reagents to give α,β -unsaturated carboxylic acids <2001OL3345>.

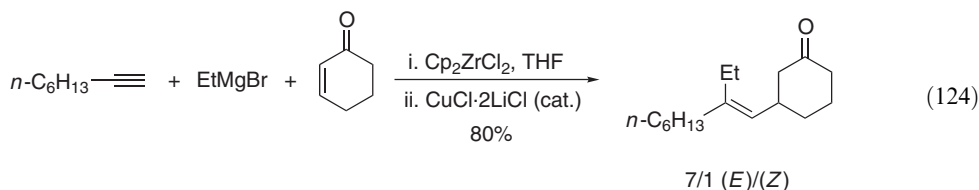


Alkynes bearing a remote enone functionality undergo nickel-catalyzed reaction with dialkylzinc compounds, giving products of cyclization onto the enone (Equation (123)) <1996JA2099>. The mechanism may involve metallacycle formation, rather than carbozincation of the alkyne <1998T1131>. The same reaction can be used to form *O*- and *N*-containing heterocycles <1997T16449>, and cyclization onto a carbonyl group, rather than conjugate addition, has also been achieved <1997JA9065>. Similar cyclizations can be carried out with a diene replacing the enone group, with the intermediate then undergoing trapping by an aldehyde with high 1,5-diastereoselectivity <2002AG(E)2784>.



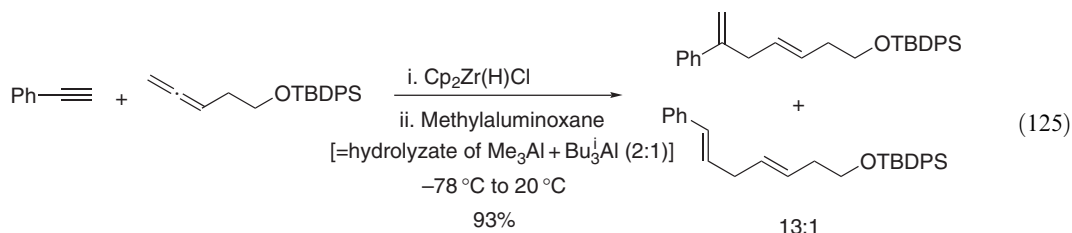
1.12.3.3.6 Other carbometallation reactions of alkynes

Alkynes undergo addition of organozirconium reagents, which can be prepared by *in situ* from EtMgBr and Cp₂ZrCl₂, and conjugate addition of the intermediate zirconacyclopentene to cyclic enones is catalyzed by CuCl·2LiCl (Equation (124)) <1995T4407>. The same type of zirconacyclopentene intermediates reacts with CO/I₂ to give cyclopentenones <1997T9123>. Alternatively, interception of the intermediate by a combination of ethylene and an aldehyde, promoted by AlCl₃, results in an overall 4-component synthesis of γ,δ -unsaturated ketones <2002CC142>.

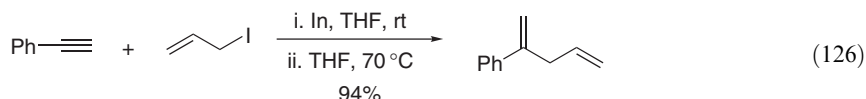


The organozirconium reagent can also be generated by hydrozirconation, and starting from allenes this results in allylzirconium species, which have been used for regioselective carbometallation of terminal alkynes in the presence of methylaluminoxane, leading to 1,4-dienes (Equation (125)) <1997TL3031>. Alkylzirconium reagents, prepared by hydrozirconation of alkenes, react

more slowly, and a trityl salt has been found to be a better catalyst <1999TL8407>. Unsymmetrical internal alkynes can also be used, with the regioselectivity depending upon the steric differences between the two alkyl groups <2001JOMC(624)143>.



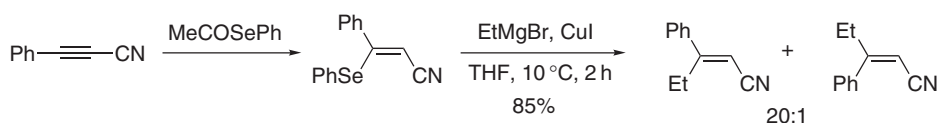
Unactivated terminal alkynes have been found to react with allylindium species in THF to give 1,4-dienes in good yields (Equation (126)) <1997JOC2318>.



1.12.3.4 Addition of Sulfur, Selenium, and Tellurium Reagents to Alkynes

The hydrotelluration of alkynes has usually been performed by the reduction by NaBH₄ of dialkylditellurides, which however, are notorious for their malodorous nature. A recent procedure generates the tellurols by the action of alkyllithiums on elemental tellurium, which avoids this problem <2001JOMC(623)43>. Hydrotelluration of an alkyne forms the alkenyl telluride, which can then be reacted with a variety of C-centered reagents to give the alkene.

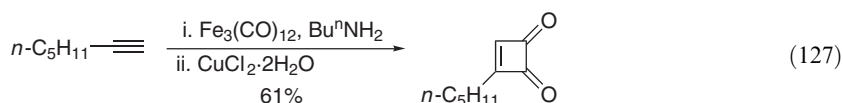
A related strategy for the hydroselenation of alkynes involves the use of a selenoester to form the intermediate alkenyl selenide, which can then be transformed into an alkene by the replacement of the seleno group by a copper-mediated Grignard reagent <1996SC3607> (Scheme 8).



Scheme 8

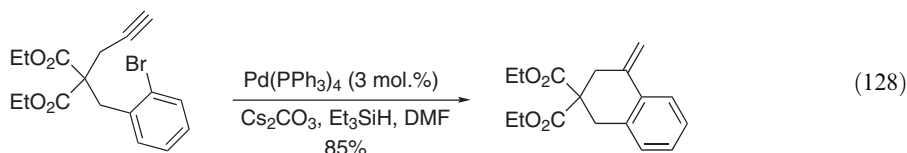
1.12.3.5 Addition of Iron Reagents to Alkynes

The reaction of Fe₃(CO)₁₂ with alkynes in the presence of *n*-butylamine gives the corresponding cyclobutenediones after oxidation by Cu(II) (Equation (127)) <2000TL2719>.

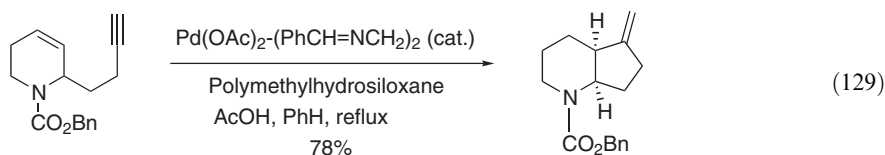


1.12.3.6 Palladium-catalyzed Additions to Alkynes

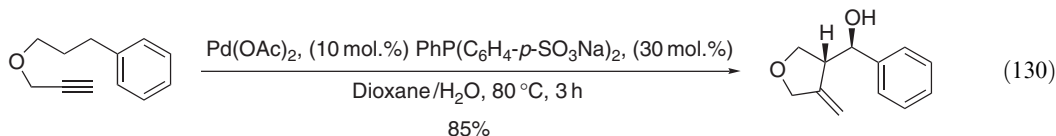
Reaction of alkynes with aryl or alkenyl halides and a palladium(0) catalyst gives alkenylpalladium intermediates, in a Heck-type coupling, and these can be reduced by formate to produce alkenes <B-2002MI005>. With unsymmetrical alkynes the regioselectivity varies, depending upon the nature of the substituents. The intermediate alkenylpalladium species can also be trapped by other nucleophiles <B-2002MI005>, such as carbon monoxide or organometallic reagents. Intramolecular versions can be used to form exocyclic alkenes with five, six, or seven-membered rings, and a recent example is shown in Equation (128), using triethylsilane as the reducing agent, which gives better yields than formate <2003TL3785>.



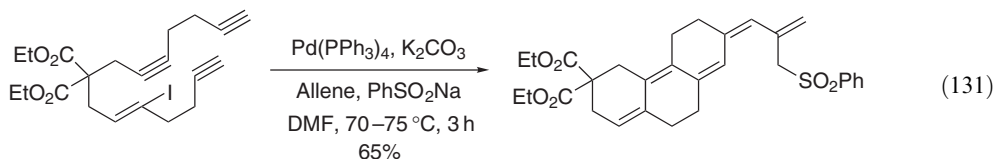
Palladium-catalyzed cycloisomerizations of 1,6- and 1,7-enynes have been developed by Trost as a method for the construction of *bis*-exocyclic 1,3-dienes [<1995AG\(E\)259, 1998SL1>](#). Reductive cyclizations are also possible by addition of a hydride source, giving exocyclic alkenes instead of dienes, and has been used in a natural product synthesis (e.g., [Equation \(129\)](#)) [<1996TL8787>](#). The use of formic acid and triethylsilane has been investigated in reductive cyclizations of 1,6-enynes, and they have been found to give different selectivities [<2000TL8365, 2001T1723>](#).



Reductive cyclization of 1,7-diyne is an alternative to cycloisomerization of the corresponding enynes, since both methods can, in principle, give the same six-membered exocyclic dienes, and this may have advantages where the enyne cyclization fails for steric reasons [<1996JA5146>](#). When electron-rich phosphines are used as ligands for the palladium catalyst, the course of the reaction changes with terminal enynes, and homo-coupling of the terminal alkyne is observed instead. This has been extended to allow intermolecular cross-coupling of terminal alkynes onto internal alkynes bearing electron-withdrawing groups [<1997JA698>](#). The use of palladium catalysts bearing water-soluble phosphine ligands allows cycloisomerization of 1,6-enynes to be carried out in aqueous-organic media, and results in unsaturated alcohols by formal hydration of one of the alkene bonds ([Equation \(130\)](#)) [<2001T5137>](#).



A wide variety tandem and cascade additions and cyclizations onto alkynes are catalyzed by palladium, and these have been extensively investigated by Grigg and co-workers [<1999JOMC\(576\)65>](#). After one or more palladium-catalyzed additions and/or cyclizations, the process can be terminated by reaction of the organopalladium intermediate with C—C π -bonds [<B-2002MI006>](#), nucleophiles [<B-2002MI007>](#), or by carbonylation [<B-2002MI008>](#). This concept is exemplified in [Equation \(131\)](#), where all three alkyne units in the substrate undergo consecutive addition to form alkenes, before capture by allene and a nucleophile [<1997TL1825>](#).



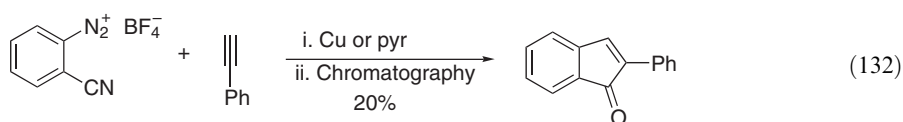
The hydroformylation of symmetrical internal alkynes to α,β -unsaturated aldehydes is catalyzed by $(\text{PCy}_3)_2\text{PdCl}_2$, and the addition of $\text{Co}_2(\text{CO})_8$ markedly improves the catalytic activity [<1997JA6448>](#). Propargyl alcohols undergo a cyclocarbonylation to unsaturated γ -lactones using a palladium(0) catalyst and $\text{CO} + \text{H}_2$ [<1997JOC5684>](#). Other carbonylations of alkynes include the regioselective hydroformylation of enynes [<1999JOC3964>](#), and the carbonylation of ynones [<2000JOC4131>](#); however, both of these are catalyzed by rhodium.

Transition metal cyclizations have been reviewed as a general topic, and this includes several palladium-catalyzed cyclizations of alkynes [<1996CRV635>](#). Other relevant material may be found in a recent review on transition metal-catalyzed reactions of 1,n-enynes [<2002CRV813>](#).

1.12.4 FREE RADICAL ADDITIONS

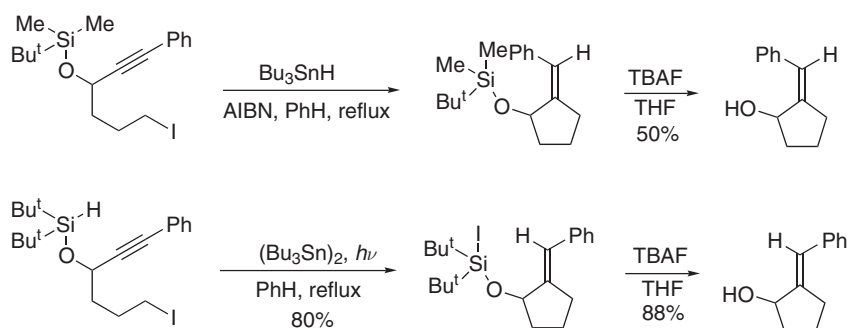
1.12.4.1 Intermolecular Free Radical Additions

The intermolecular addition of *C*-centered free radicals to alkynes is seldom used as a synthetic procedure, compared to additions to alkenes, and yields are often low <1995COFGT(1)501>. A recent review comparing experimental and calculated rate constants for additions to both alkynes and alkenes shows that additions of *C*-centered radicals to ethyne are slower than the corresponding additions to ethene, and have higher activation barriers, even though the additions to ethyne are more exothermic <2001AG(E)1340>. A radical generated by the oxidation of a malonate ester by manganese(III) acetate adds to phenylacetylene, and, under high pressure of carbon monoxide, gives the carboxylated product in moderate yields, which are improved by increasing the pressure of CO <1996JOC5312>. This reaction is more successful when applied to intramolecular additions (see below). Phenylacetylene also undergoes intermolecular addition of a 2-cyanophenyl radical, generated from a diazonium salt, and the alkenyl radical produced is trapped by cyclization onto the nitrile, ultimately giving a cyclic ketone in low yield (Equation (132)) <1998TL2441>.



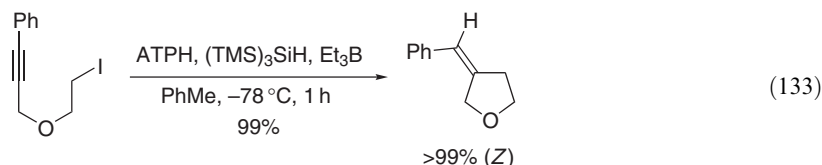
1.12.4.2 Intramolecular Free Radical Additions

The intramolecular addition of a radical to an alkyne generates a new ring, and this process has been surveyed in reviews on radical cyclizations, which include the more often used cyclizations onto alkenes <1996OR301, B-1992MI002>. The most commonly used cyclizations are of 5-hexynyl radicals, which usually close in a 5-*exo-dig* manner, to give alkylidenecyclopentanes (or heterocycles, if a heteroatom is included in the chain). There are several methods of generating the radical for cyclization, and the most widely used is still reaction of a bromide or iodide with a tin radical, formed from a tin hydride and a radical initiator, or by photolysis of a hexa-alkylditin. If the alkyne is not terminal, then the cyclization generates a trisubstituted alkene, often as a mixture of geometrical isomers. In the first example shown in Scheme 9, a high stereoselectivity is obtained by steric shielding of one side of the alkenyl radical during hydrogen transfer <1995JOC8332>. The second example shows that the opposite geometrical isomer can be obtained by internal hydrogen transfer from the silicon.



Scheme 9

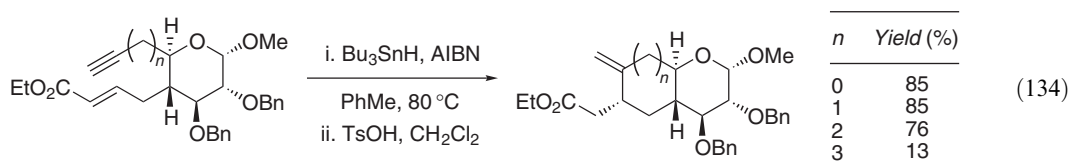
Another way to achieve excellent control of the double bond geometry is to use aluminum tris(2,6-diphenylphenoxide) (ATPH) as a Lewis acid template <2001T135>. This results in complete selectivity for the (*Z*)-isomer of the product shown in Equation (133), whereas standard tin hydride conditions give a 1:1 mixture of geometrical isomers. The Lewis acid also prevents formation of uncyclized reduction product, and these results can be explained by a templating and shielding effect.



Alkenyl radicals, generated from iodoalkenes by tin hydride, also cyclize onto alkynes, and both 5- and 6-(π -*exo*)-*exo*-*dig* modes are observed (depending on the chain length), resulting in bis-exocyclic five and six-membered ring dienes <2000OL2013>.

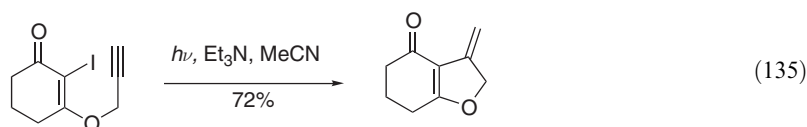
Aryl radicals have also been cyclized onto alkynes linked by an amide group, in 5-*exo*-*dig* mode, and a removable silyl group on the alkyne helps to promote the cyclization <2000JCS(P1)763>. Heterocyclic aryl radicals generated from 3-bromopyridines also undergo 5-*exo* cyclizations onto all-C alkynyl side chains at the 4-position, in good yields <2000T397>.

β -(Alkynyloxy)acrylates undergo tributyltin-mediated radical cyclization, and acidic destannylation yields the *exo*-methylene products (Equation (134)) <2000OL1275>. From five to eight-membered ring sizes could be formed on the sugar derivatives, with the yields remaining high except for the eight-membered ring.

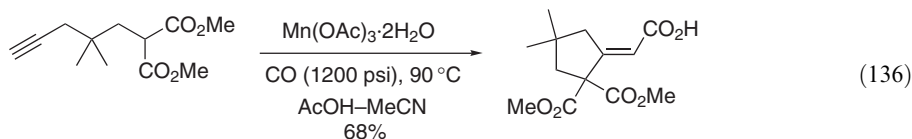


A suitable choice of heteroatom in the chain linking the alkyne to the radical precursor may allow the tether to be cleaved after cyclization, resulting in an acyclic product. Silicon has been used in the past, but a recent method uses tethered α -boryl radicals, and after 5-*exo* cyclization onto an alkyne, the C—B bond can be oxidatively cleaved to give 2-alkylidene-1,3-diols <1999TL9183>.

The use of tin reagents to generate radicals can cause problems with removal of the tin by-products, and with their toxicity and disposal. Radical cyclizations onto alkynes have been carried out on a solid support, which allows the tin by-products to be simply washed away <1997SL61>. Nevertheless, the quest for alternatives to tin reagents for radical generation is an active field of research. Formation of radicals from α -haloacetals by irradiation with UV light in the presence of triethylamine was introduced by Cossy, and successfully applied to cyclization onto alkynes <1994TL8161>. The same method has also been applied to α -iodoenones (e.g., Equation (135)) <1998CC397>. However, cyclization of related alkenyl iodides lacking the carbonyl group was unsuccessful.

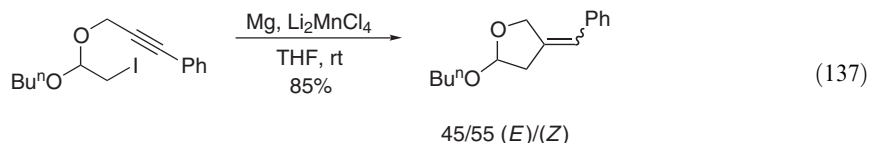


The generation of free radicals by manganese(III) oxidation of β -dicarbonyl compounds and α -cyanoesters has been reviewed by Snider <1996CRV339>, including examples of cyclization onto alkynes. Oxidation of malonates by Mn(OAc)₃ has been mentioned in the previous section, and this has also been applied to cyclization onto alkynes, with trapping of the resulting alkenyl radical by CO (Equation (136)) <1996JOC5312>. A 6-*exo* cyclization was also achieved, but in lower yield.

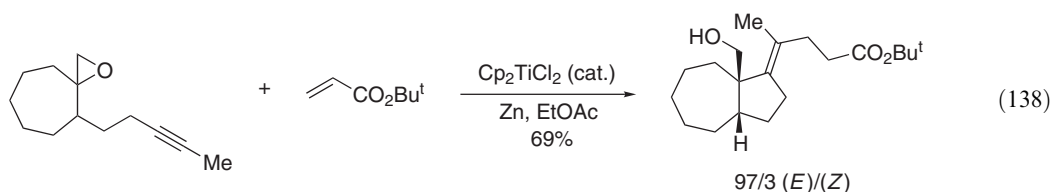


An activated Mn(0) species, generated by the action of Li₂MnCl₄ on magnesium metal, has been used to initiate 5-*exo* radical cyclizations of alkynyl α -haloacetals in good yields (Equation (137)) <1999T1893>. Exactly the same cyclization has also been carried out with radical formation by the combination of BuⁿMgBr and catalytic FeCl₂, but in lower yield <1998TL63>. Using yet another method, the bromo analog has been cyclized with an indium hydride reagent together

with catalytic Et_3B , in 71% yield <2003T6627>. Indium metal has been used together with iodine to mediate radical cyclizations of some other alkynyl iodoacetals, and by changing the ratio of indium to iodine the course of the reaction can be altered from an iodine atom transfer to a reductive cyclization <2002TL4585>.



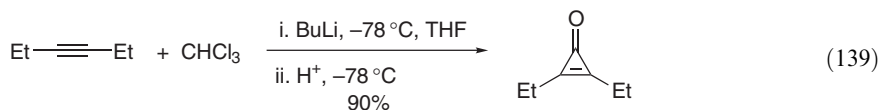
An interesting tandem reaction initiated by a reduced titanocene is shown in Equation (138), where the epoxide is opened to give a radical which cyclizes onto the alkyne, and the resulting alkenyl radical is then trapped by intermolecular addition to an acrylate <2002AG(E)3206>. The tetrasubstituted alkene is formed with very good stereoselectivity.



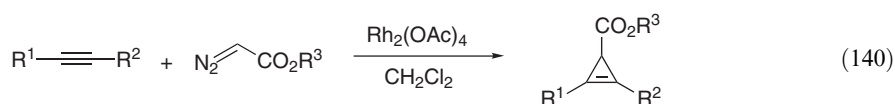
1.12.5 CARBENE AND OTHER ADDITIONS

1.12.5.1 Addition of Simple Carbenes and Carbenoids to Alkynes

The addition of carbenes to alkynes can be used as a method for the synthesis of cyclopropenes <1995COFGT(1)501>; however, there are limitations. Carbenes bearing electron-withdrawing groups have been most generally used, such as dichlorocarbene, and carbenes with an α -carbonyl group. The addition of dichlorocarbene to internal alkynes gives geminal dichlorocyclopropenes, which can be hydrolyzed to cyclopropenones. A recent procedure shown in Equation (139) gives good overall yields <2000SC1767>, and this depends upon quenching the reaction with acid at low temperature, since quenching with water at 0°C results in the formation of ynones.

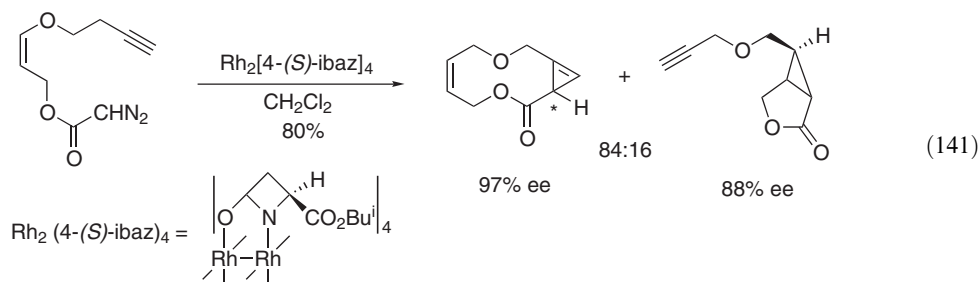


The most widely used carbenes for addition to alkynes are generated from α -diazooesters by rhodium(II) acetate, and the chemistry of these compounds has been reviewed <1994CRV1091, B-1998MI001, B-1999MI001>. The addition is successful with both internal and terminal alkynes (but not phenylacetylene), and gives cyclopropene-3-carboxylic esters, which are stable at room temperature, or even above (Equation (140)). In recent examples of this procedure, the cyclopropenecarboxylates were isolated, and then subjected to further rhodium-catalyzed transformations <1995HCA129>. Similar chemistry can be performed starting from diazomalonates <1995HCA947>. The rhodium acetate procedure is much superior to the previous use of copper catalysts for this reaction, which requires higher temperatures, and leads to further reaction of the products. Conjugated enynes undergo addition to the alkyne, but the vinylcyclopropene products are unstable, and react further, whereas isolated enynes react preferentially on the alkene double bond <B-1998MI001>.

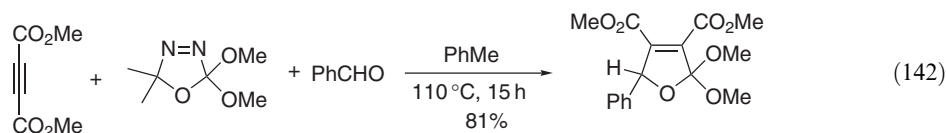


An enantioselective version of this reaction has been achieved by using chiral ligands on the rhodium catalyst, with selectivities of 48 to $\geq 98\%$ ee <1994JA8492>.

Intramolecular addition of acylcarbenes to alkynes is also possible, however the products usually react further, via a vinylcarbene, which may be formed directly or from the cyclopropene <1994CRV1091, 2001JOMC(617)3, B-1999MI001>. In general, the alkyne triple bond in the starting material becomes a C—C single bond, rather than an alkene, although there are a few exceptions <1991JOC2523, 1994CRV1091>. However, cyclizations onto alkynes tethered by a long chain can be successful in producing macrocyclic rings, as in the example shown in Equation (141) <1999AG(E)700>.

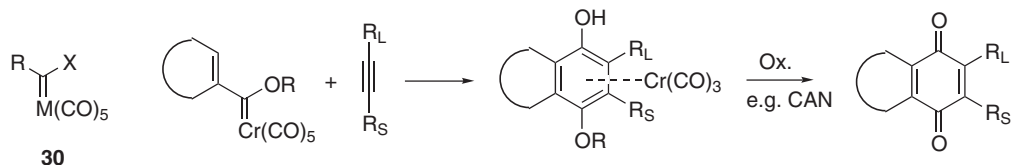


A very different type of carbene addition is shown in Equation (142), where dimethoxycarbene (generated from an oxadiazoline) adds to DMAD, and the intermediate undergoes trapping by benzaldehyde and cyclization <2003SL1446>. Other aromatic aldehydes can also be used.



1.12.5.2 Reaction of Fischer Carbene Complexes with Alkynes: The Dötz Synthesis of Phenols

Fischer carbene complexes **30** are compounds which can be represented as a carbene, which is formally doubly bonded to a transition metal carbonyl fragment, and generally bears an electron donating substituent X, and a group R which can be alkyl, aryl, alkenyl or alkynyl (Scheme 10). They can undergo an extraordinarily rich and diverse range of reactions, as shown in the extensive review by de Meijere and co-workers <2000AG(E)3964>. Fischer carbenes are electron-withdrawing groups, and so an alkene or alkyne conjugated to the carbene will be activated toward [4 + 2]- and [2 + 2]-cycloadditions, as with a carbonyl group <2000AG(E)3964>.



Scheme 10

However, the most widely used synthetic reaction of Fischer carbene complexes is the Dötz reaction, which is the co-cyclization of an alkenyl- or aryl Fischer complex with an alkyne, and one of the CO ligands from the metal (Scheme 10). The reaction results in the formation of a new oxygenated arene complexed to the metal, which can be oxidatively removed to release the product as a quinone. Reductive removal can also be used, to yield phenols. This reaction has received a great deal of attention over the last few years, and several reviews are available <1991COS(5)1065, 1999CSR187, 2000AG(E)3964, B-1999MI001>. Chromium complexes are the most efficient, and the reaction is of broad scope, with many functional groups being tolerated on the alkyne. The yields are usually lower for electron-poor alkynes (e.g., 3-butyne-2-one) <1999CSR187>, although a good yield has been obtained with DMAD, using a (4-methoxyphenyl) iron carbene complex <1993JA9848>. Regioselective incorporation of unsymmetrical alkynes is observed, with the larger group being incorporated next to the phenolic hydroxyl (Scheme 10) and the selectivity is usually complete for terminal alkynes, but lower for internal alkynes.

Originally the reactions were performed thermally, but more recently photochemical conditions have been employed <1995TL1871, 1998EJOC1739>. The use of ultrasound and dry-state absorption on silica allows the reactions to be performed at ambient temperature <1993T5565>, and microwave irradiation has also been used <2002CC2262>.

Intramolecular Dötz reactions are feasible <1999CSR187>, for example a temporary silicon-containing tether has been used to control and reverse the intrinsic regioselectivity of the reactions <1994JA10921>, and the yields were found to be improved by the addition of external alkynes, which were not incorporated into the final product.

A very wide variety of other cyclizations and additions of Fischer carbene complexes onto alkynes have been reported, and these have been reviewed <1996CRV271, 2000AG(E)3964>.

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Biographical sketch



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1.13

One or More C=C Bond(s) by Elimination of Hydrogen, Carbon, Halogen, or Oxygen Functions

O. PIVA

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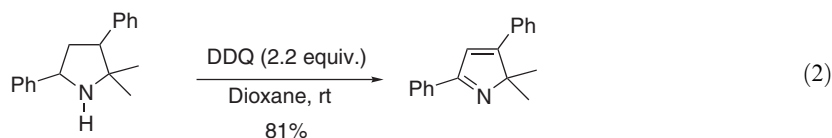
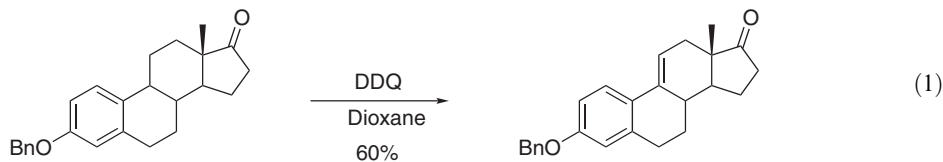
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This chapter concern the formation of alkenes and provides an update to chapter 1.13 in COFGT (1995) covering major advances in the last decade. Numerous procedures including dehydrogenation, dehydration, elimination of hydrogen halide under acidic, basic conditions, or by using more sophisticated reagents are discussed. The access to alkenes from carboxylic acids, ethers, epoxides, 1,2-diols, and derivatives is also described. A special emphasis has been made on methods, which allow the formation of the double bond with high regio- and stereocontrol. Great attention has been paid to processes which are consistent with the use of protective groups. Moreover, numerous examples cited in this review are part of multistep syntheses of complex natural products.

1.13.1 BY ELIMINATION OF HYDROGEN

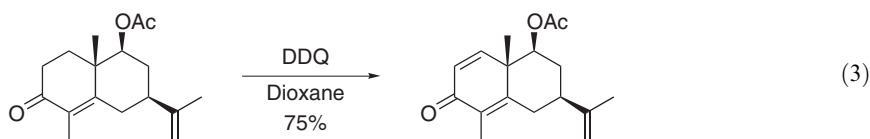
1.13.1.1 Dehydrogenation of Hydrocarbons

Despite their cost and toxicity, 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) and chloranil are the reagents of choice to abstract a hydrogen in the allylic, propargylic, and benzylic positions. The intermediates can be easily trapped by various nucleophiles such as cyanide or water or can be oxidized to the corresponding alkene when the reaction is performed in an inert solvent such as 1,4-dioxane or acetonitrile. The major drawback in these reactions is the formation of a large amount of dihydroquinol, which can be removed by filtration or chromatography on alumina. DDQ is also commonly used to promote aromatization of carbocyclic and heterocyclic compounds but this aspect will be not be covered in this chapter. Representative examples in the field of steroids (Equation (1)) <2000TL1729, 2001CR201> and pyrrolines (Equation (2)) <2003TL3701> are depicted.



1.13.1.2 Dehydrogenation of Ketones and Aldehydes

The direct synthesis of enones or dienones from saturated ketones can be achieved by DDQ <1996SC551>. In the field of natural product synthesis, dehydrogenation of eudesm-4-en-3-ones, for example, gives the corresponding dienones in good yield (Equation (3)).

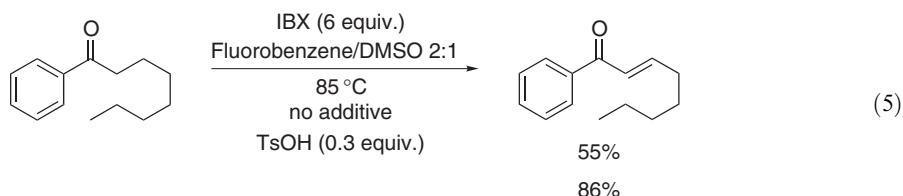
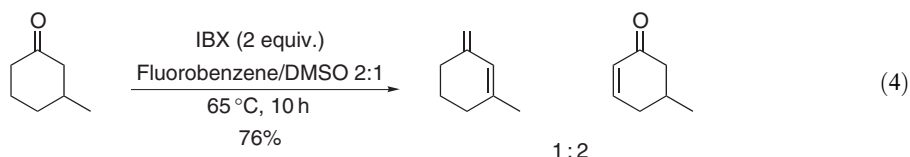


Iodic acid (HIO_3) and its anhydride I_2O_5 , which are commercially available and stable at elevated temperatures, can also be used for the direct conversion of ketones and aldehydes into the corresponding unsaturated compounds <2002AG(E)1386>. Interestingly, these reactions can be carried out in DMSO on substrates bearing sensitive functionalities such as tertiary alcohols (Table 1).

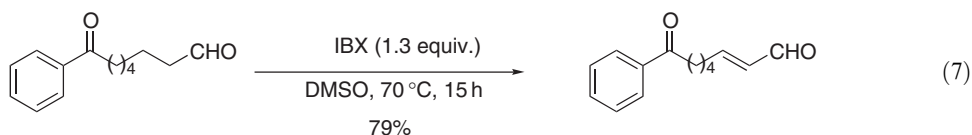
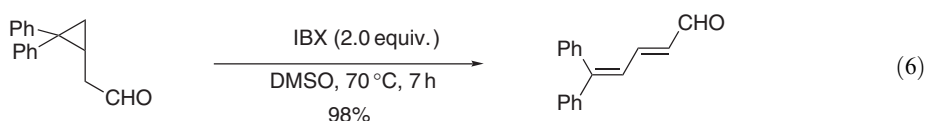
Table 1 Dehydrogenation with HIO_3

Substrate	Temperature ($^{\circ}\text{C}$)	HIO_3 (equiv.)	Product	Yield (%)
	50	1.1		95
	65	2.5		82
	50	1.2		77

o-Iodoxybenzoic acid (IBX) is also of great interest to effect dehydrogenation of carbonyl compounds <2002JA2245>. The reaction time can be dramatically decreased by addition of acids such as TsOH (Equations (4) and (5)).



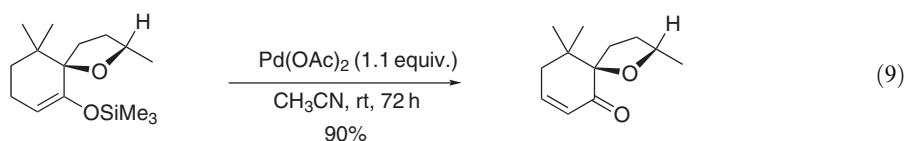
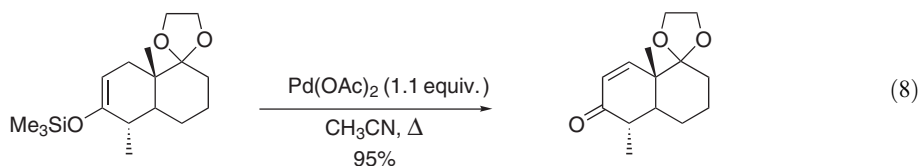
Rearrangement observed on a well-designed cyclopropylaldehyde provides a strong support for a single-electron-transfer (SET) process (Equation (6)). Furthermore, the reaction is highly chemoselective as a ketoaldehyde is only oxidized in the α -position of the aldehyde group (Equation (7)).



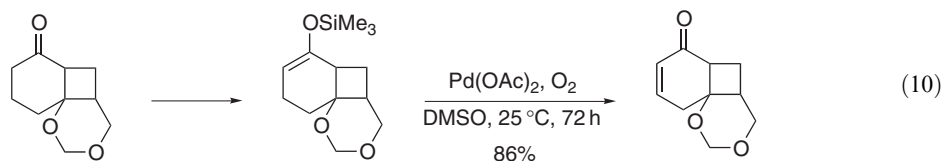
The dehydrogenation of cyclic ketones <1997MI1123> has also been investigated in the presence of palladium(II) trifluoroacetate associated with an appropriate phosphine or sulfide.

1.13.1.3 Dehydrogenation of Silyl Enol Ethers

The scope and applications of palladium species toward the transformation of silyl enol ethers into enones have been covered in a review <B-2002MI001>. Since the 1970s, palladium chemistry has been a cornerstone in organic chemistry and widely applied in natural product synthesis. The tolerance of numerous functionalities, the mildness of the conditions, and the selectivities obtained renders this reaction very appealing. Two significant examples (<1998JOC5890> and <1996JOC1119>) are shown in Equations (8) and (9).



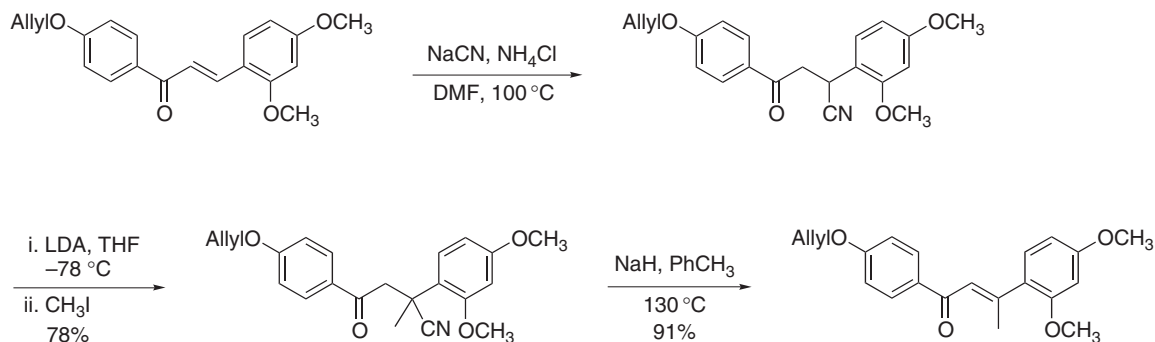
A major improvement for this process has been achieved by performing the reaction with only 10% Pd(OAc)₂ in DMSO as the solvent and under 1 atm of oxygen as the cooxidant. Under these conditions, aldehydes and ketones are converted at room temperature into α,β -unsaturated carbonyl compounds in impressive yields <1995TL2423, 1995TL9449> (Equation (10)).



1.13.2 BY ELIMINATION OF CARBON FUNCTIONS

1.13.2.1 Elimination of Hydrogen Cyanide

Elimination of hydrogen cyanide has been rarely observed. Dihydropyrazoles resulting from 1,3-dipolar cycloadditions of bis-nitrile imides can be aromatized under basic conditions <1997T9293>. Other heterocyclic structures like indoloquinazolines were also obtained via the elimination of HCN by treatment with DBU <2002RCB(E)1869>. A tetracyanoethylene derivative has been engaged in a tandem dimerization to give, after elimination of hydrogen cyanide and ethanol, a bicyclic 2-aminopyridine <1999TL4707>. More interestingly, the functionalization of chalcones can be effectively achieved by using a three-step sequence <1998BMC937> including a Michael addition of HCN, a selective alkylation in the α -position of the nitrile, and a regeneration of the alkene moiety according to an E1cB mechanism (Scheme 1).

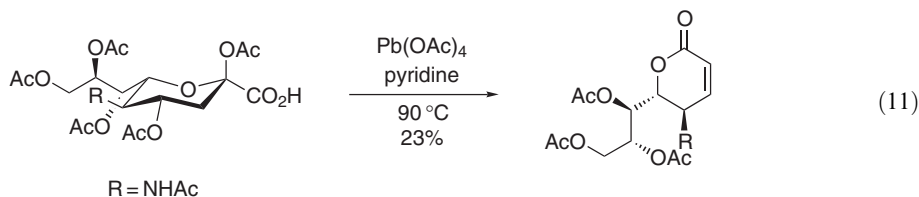


Scheme 1

1.13.2.2 Elimination of Carbon Oxides

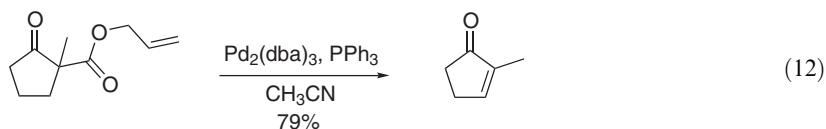
1.13.2.2.1 Decarboxylation

The decarboxylation of acids under oxidative conditions can be achieved in the presence of lead tetraacetate associated with copper(II) acetate. Applied to dipeptides, the resulting *N,O*-acetal intermediates eliminate in the presence of a tertiary amine and lithium perchlorate <2001JOC8215>. *O*-Acetyl sialic acid under similar conditions is converted into a conjugated lactone <1996CAR181> in moderate yield (Equation (11)). Vinylphosphine oxides were also obtained from (carboxyethyl)phosphine oxides by using these conditions <2000MI007>.

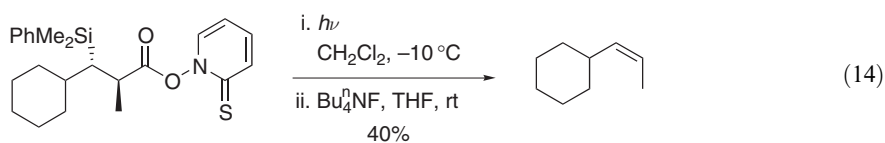
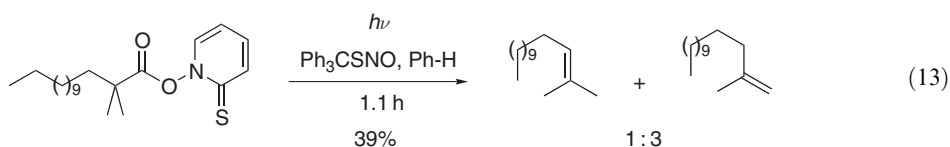


R = NHAc

Of great interest, is the oxidative decarboxylation of allyl β -keto esters promoted by palladium catalysts like $\text{Pd}_2(\text{dba})_3$ in refluxing acetonitrile and in the presence of triphenylphosphine <B-2000MI001> (Equation (12)).



α,α -Disubstituted *O*-acyl thiohydroxamates, under irradiation, are converted into alkenes, unfortunately without noticeable regiocontrol <1999T3573> (Equation (13)). A two-step procedure involving β -silyl Barton esters allows rapid access to alkenes with (*E*)/(*Z*) stereocontrol up to 90/10 <2002OL4253> (Equation (14)).

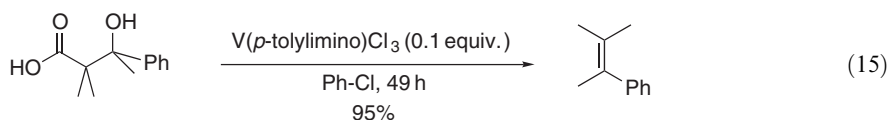


1.13.2.2 Di-decarboxylation

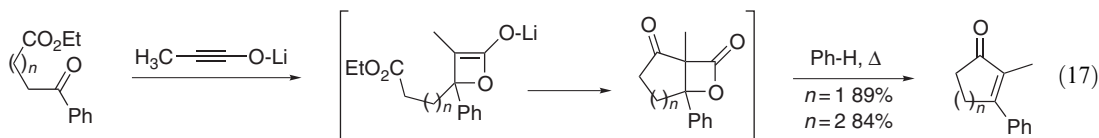
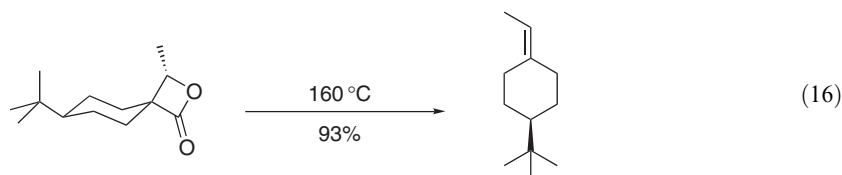
In the recent past, maleic acid and its anhydride have been conveniently implied into [2 + 2]- and [4 + 2]-cycloadditions. A subsequent bis-decarboxylation promoted either by lead tetraacetate, electrochemical conditions, or transition metal complex-mediated reactions allowed the generation of a double bond <1984T2585>. As already mentioned in COFGT (1995) <1995COFGT(1)553>, the impact of this two-step strategy has considerably diminished since the discovery of modern alkyne equivalents.

1.13.2.2.3 Decarboxylation/dehydration

3-Hydroxy carboxylic acids are readily available via aldolization. Their decarboxylation, combined with the loss of the hydroxyl group, has been achieved directly or after formation of the β -lactone. For example, a catalytic amount of vanadium trichloride (10%) and other vanadium(V) complexes, such as trichloro(arylimino)vanadium, can induce this reaction in chlorobenzene, which is the solvent of choice <1997CRV2707> (Equation (15)).

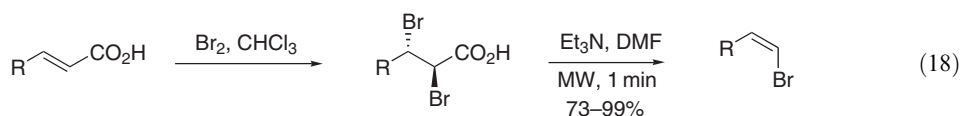


The thermal decarboxylation of β -lactones produces quantitatively and stereospecifically the corresponding alkenes (Equation (16)). It is worth noting that these four-membered rings are easily prepared from 3-hydroxyacids in the presence of benzene sulfonyl chloride <1995TL7643, 1998JCS(P1)2721>. In some cases, the decarboxylation has been also included in tandem processes. For example, a one-pot synthesis of cycloalkenones has been reported <2001JOC7818>. The highly strained bicyclic β -lactones obtained by a [2 + 2]-cycloaddition between a keto ester and an ynoate followed by a Dieckmann condensation underwent a fast decarboxylation to deliver the target molecules in good yields (Equation (17)).



1.13.2.2.4 Decarboxylation/dehalogenation

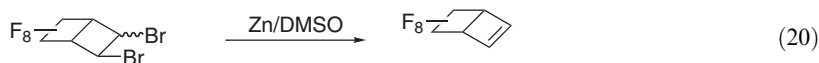
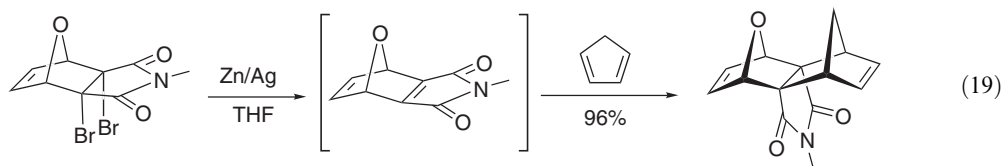
The decarboxylation/dehalogenation has not been widely developed in organic synthesis. A remarkable example is, however, depicted in Equation (18). Microwave irradiation of 2,3-dibromoalkanoic acids in DMF gives exclusively the (*Z*)-bromoalkenes in a very short reaction time and in high yields <2001TL3893>.



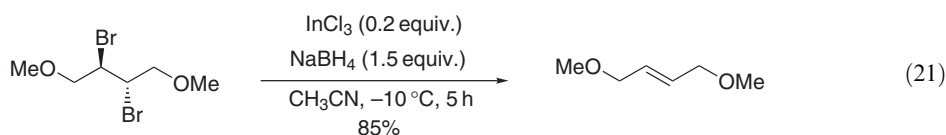
1.13.3 BY ELIMINATION OF HALOGEN (OR H-HAL)

1.13.3.1 Elimination of Dihalides

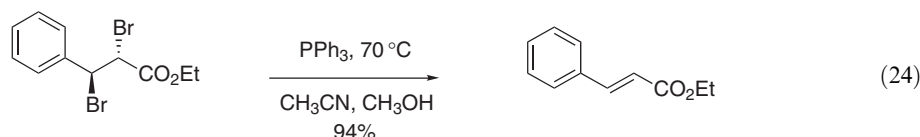
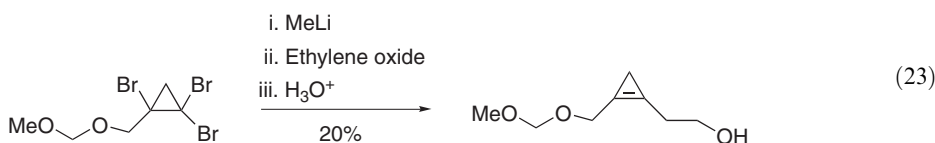
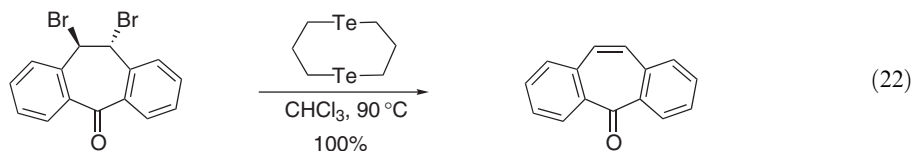
The development of orthogonal protective groups is an important concept and very useful for the total synthesis of complex natural products. Therefore, the protection of an alkene as a 1,2-dibromide is appealing. The regeneration of the alkene functionality can be achieved under various procedures. Most of them require the use of low-valent metals in stoichiometric amount, or as catalysts when combined with a suitable reducing agent. For example, nickel(0) can be generated from the reaction of ethylmagnesium bromide with Ni(dppe)Cl₂ in THF at 0 °C and the bis-dehalogenation is very rapid, tolerant to ketals and THP ethers, and gives mainly quantitative yield in olefins <1995TL9189>. Alternatively, EtMgBr can be replaced by Bu₃SnH to generate nickel(0) <1998T1021>. Zinc has also been used to produce the corresponding alkenes from the 1,2-dibromo compounds <1995TL7753, 1996JA2556> (Equations (19) and (20)).



Dichloroindium hydride (Cl₂InH), easily obtained by mixing InCl₃ and sodium borohydride, can also reduce 1,2-dibromides to (*E*)-alkenes (Equation (21)) presumably by a radical process <2003SL1012>.

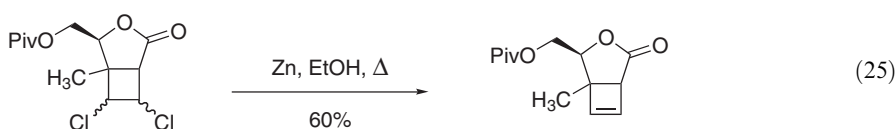


The reductive power of samarium metal has been demonstrated for numerous reactions <2002EJO2431> and advantageously used for the conversion of 1,2-dibromides into alkenes when performed in the presence of a catalytic amount of HCl <1996TL9313> or NH₄Cl <1999T10695>. Miscellaneous conditions (Equations (22)–(24)) were reported including the use of dibutyl telluride <1998JOC169, 1998JOC177> and 1,5-ditelluracyclooctane <1998JCS(P1)3147>, heating in the presence of strong bases such as KOH <2001S2247>, methyllithium <1996T3409> or with phosphorus reagents such as PPh₃ at 70 °C in a mixture of acetonitrile/methanol (10/1) <2001HAC217> or HMPA at 155 °C under inert atmosphere <2001BCJ1089>.

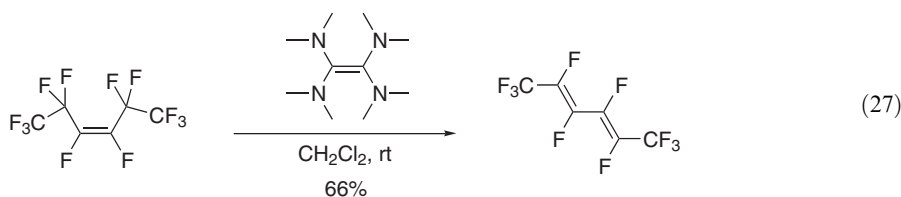


Reductive elimination of *trans*-1,2-dibromocyclohexane has been also carried out by electrochemical catalysis in conductive microemulsions <1996JOC5972> to produce cyclohexene in almost quantitative yield.

The cleavage of two vicinal chlorine atoms has been utilized for the synthesis of cyclobutene derivatives from [2 + 2]-cycloadducts (Equations (25) and (26)). Treatment of *vic*-dichlorocyclobutanes with zinc in refluxing ethanol <2003TL69, 2003JOC3246> or with sodium naphthalenide <1998JOC1379, 2001TL2855> affords unsaturated four-membered rings in good yield.



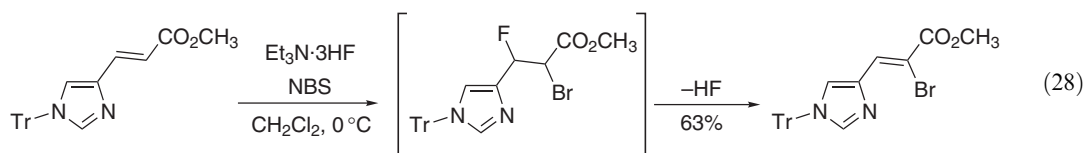
Due to the great strength of the C–F bond, perfluoro compounds are usually inert. However, defluorination and subsequent aromatization has been achieved when perfluorodecalin was stirred at room temperature in the presence of a titanium metallocene associated with aluminum metal <1996JA1805>. As already pointed out in COFGT (1995), sodium/mercury amalgam or tetrakis(dimethylamino)ethene can also be used for the synthesis of perfluoroalkenes <2001JCS(P1)398> from the parent alkanes (Equation (27)).



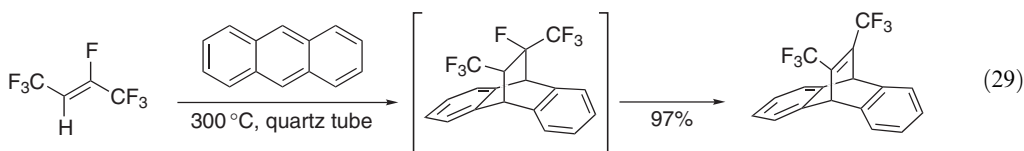
1.13.3.2 Elimination of Hydrogen Halides

1.13.3.2.1 Dehydrofluorination

The introduction of at least one fluorine atom usually has a strong impact on the properties of drugs and biologically active compounds, and consequently, the elimination of HF (the reverse process) has been less studied. The rare mechanistic studies are in favor of a E1cB process [<2001JA2712, 2003JOC718>](#). During the synthesis of modified urocanic acids (Equation (28)), the elimination of HF was preferred to the elimination of HBr [<2002JOC3468>](#).

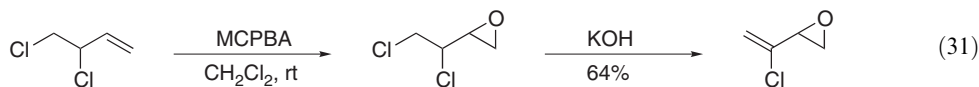
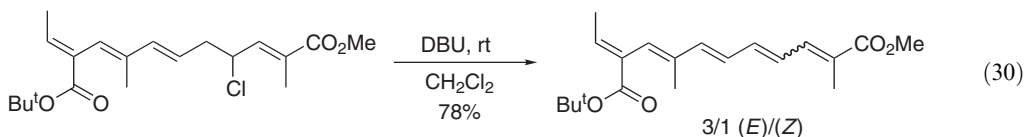


Thermal cycloadditions of highly electrophilic alkenes with anthracene is accompanied by the loss of HF [<1998T4949>](#) (Equation (29)).



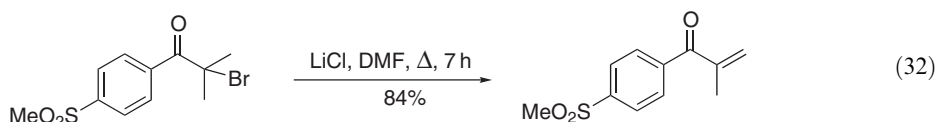
1.13.3.2.2 Dehydrochlorination

Compared to fluorinated compounds, elimination of HCl can be achieved at room temperature with DBU [<2002T9839>](#) (Equation (30)). From dichlorobutene, a two-step sequence MCPBA oxidation/KOH elimination allows a short access to a 1,2-epoxy-3-chloro-3-butene (Equation (31)), a promising synthon for the synthesis of different marine natural products [<2002JOC3847>](#). Potassium hydroxide can also be replaced by stronger base (Bu^tOK in DMSO) [<1999T13205>](#).



1.13.3.2.3 Dehydrobromination

As bromoalkanes are more stable than iodo compounds and more reactive compared to chloroalkanes, the bromo derivatives have been widely used in elimination processes and an astonishing number of methods have been applied to this goal. Simple heating of α -haloketones in DMF and in the presence of lithium chloride (Equation (32)) efficiently induced dehydrobromination [<2002BMCL3317, 2003JNP588>](#).

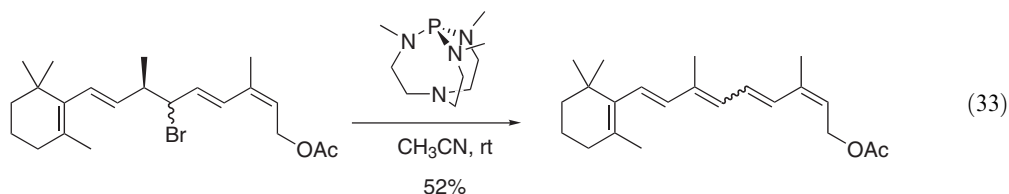


With nonactivated substrates, the use of bases such as DBU, DBN in benzene, toluene, or acetonitrile is required <2001TL4409, 2003JNP810, 1999T13205, 2002H(56)313> (Table 2).

Table 2 Dehydrobromination under basic conditions

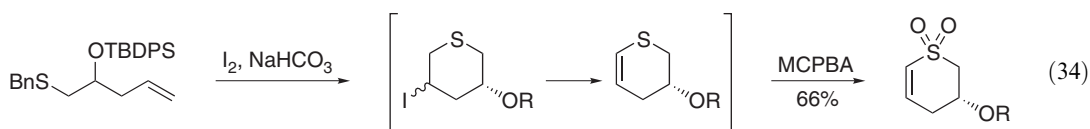
Entry	Substrate	Conditions	Product	Yield (%)
1		DBU, CH ₂ Cl ₂ rt, 12 h		94
2		DBU, benzene rt, 24 h		66
3		TBAF, THF rt, 6 h		76
4		Al ₂ O ₃ , pentane rt, 12 h		91
5		DABCO, CH ₃ CN, 80 °C		>67

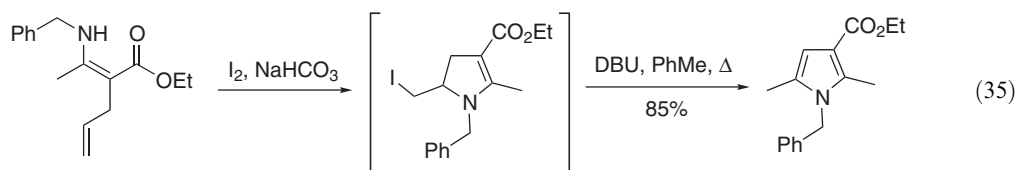
Of interest, proazaphosphatranes reacts faster than DBU or DBN in acetonitrile (Equation (33)). A carbanion, generated by deprotonation of acetonitrile by the phosphorus base could be implicated in this process. This hypothesis is supported by ³¹P-NMR studies <2002JOC420>.



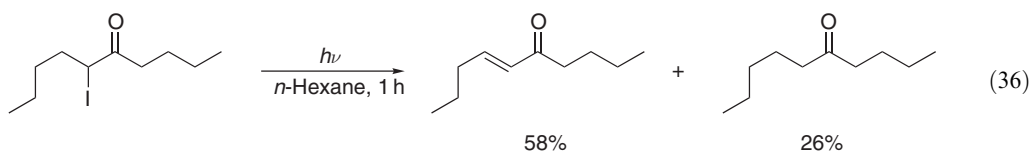
1.13.3.2.4 Dehydroiodination

Elimination of HI has been noticed during the iodine-promoted thioetherification of an unsaturated benzyl sulfide which led, after oxidation, to a cyclic sulfone <2003EJO209> (Equation (34)). Similarly, iododihydropyrroles obtained from β -enamino esters undergo dehydroiodination and an *in situ* aromatization <1995JOC7357> (Equation (35)).





Iodo derivatives are highly sensitive to UV irradiation. α -Iodo ketones can be transformed at 300 nm into α,β -unsaturated ketones (Equation (36)). Unfortunately, the enones are contaminated with the reduced ketones making the purification difficult <1999TL9263>.



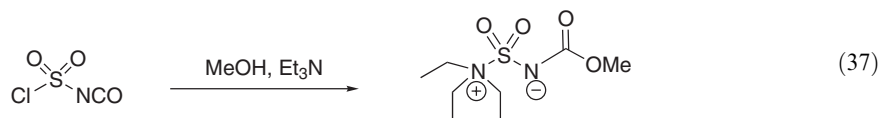
An alternative to this photochemical reaction consists of submitting the same substrates to MCPBA. The supposed iodoso-intermediate can eliminate “HOI” via a *syn*-elimination process. However, this oxidative elimination is much more efficient with α -iodo cycloalkanones than with acyclic ketones <2004S202>.

1.13.4 BY ELIMINATION OF OXYGEN FUNCTIONS

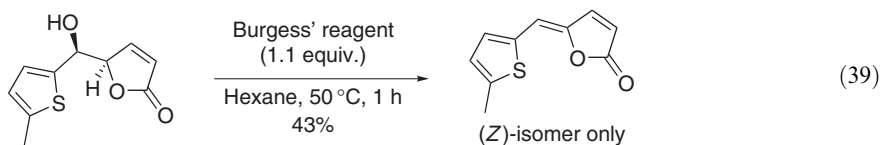
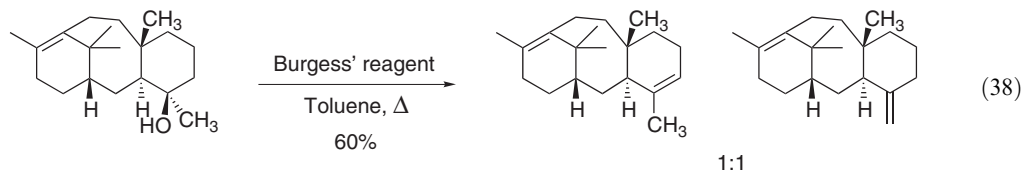
1.13.4.1 Dehydration

1.13.4.1.1 Using Burgess' reagent

The dehydration of alcohols occurs effectively with Burgess' reagent (methoxycarbonylsulfonyl triethylammonium hydroxide). This reagent is commercially available but as reported <2000SL559>, it is better to prepare it just before use, by condensation between chlorosulfonyl isocyanate and triethylamine in methanol (Equation (37)).



Burgess reagent is used with secondary and tertiary alcohols giving the expected alkenes according to a mechanism similar to the Tschugaev *syn*-elimination of xanthates <2000JPR518>. A major drawback for the use of this reagent is the absence of regioselectivity, as pointed out in a total synthesis of naturally occurring taxadienes (Equation (38)). A tertiary alcohol is smoothly converted into a 1:1 mixture of two dienes <1995JOC7215>. Similarly, γ -alkylidene butenolides were prepared by an efficient dehydration with the Burgess' reagent <2000NJC659> (Equation (39)).



A supported-Burgess' reagent has been designed and appears very useful for the cyclodehydration of δ -hydroxythioamides [<1998T6987>](#).

1.13.4.1.2 Using Martin's sulfurane reagent

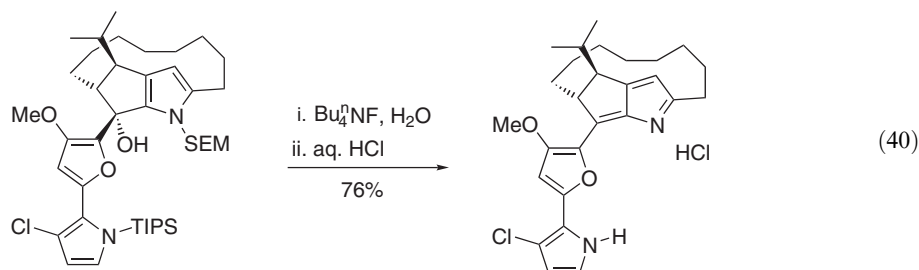
Martin's sulfurane reagent is highly sensitive to moisture and is also expensive. Despite these disadvantages, it has been applied to very sensitive substrates. [Table 3](#) shows representative applications of Martin's sulfurane reagent for the formation of alkene subunits in the presence of functionalities such as an oxazolidinone [<1996TL4317>](#), a ketal [<1997MI487>](#), silyl ethers [<2002SL358>](#), a carbonate, or an epoxide [<2002JA5380>](#).

Table 3 Use of Martin's sulfurane reagent for dehydration of sensitive alcohols

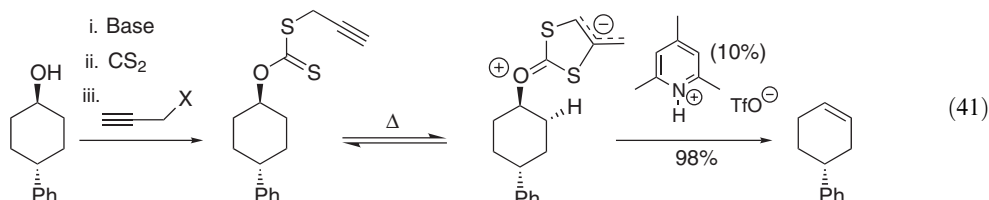
Entry	Substrate	Product	Yield (%)
1			64
2			80
3			79
4			83

1.13.4.1.3 Dehydration by other methods

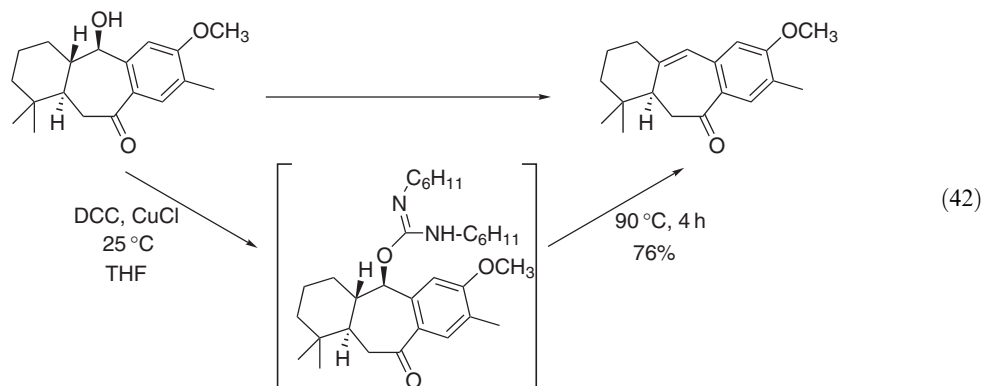
Dehydration of alcohols under acidic conditions is obviously a widely used method to prepare alkenes. The efficiency of this process is correlated to the stability of the carbocationic intermediate. In the last step of the synthesis of roseophilin, dehydration of a tertiary alcohol furnishes the target molecule in good yield ([Equation \(40\)](#)) [<1998JA2817>](#).



A new concept for the formation of C—C double bond takes advantage of the reactivity of *S*-propargylic xanthates under thermal conditions in the presence of a catalytic amount of collidinium trifluoromethanesulfonate [<1999TL1305>](#) (Equation (41)).



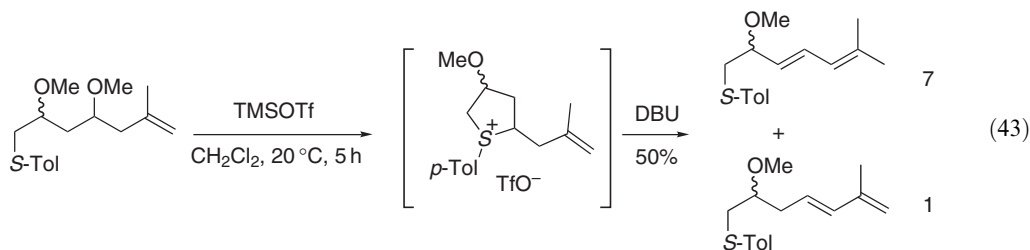
Tertiary and benzylic alcohols can also be converted *in situ* into pseudoureas which presumably undergo an E1 process or an E_i reaction, which is typical of pyrolytic eliminations (Equation (42)) [<1999NJC129>](#). The eliminations of the pseudourea obtained from primary or secondary alcohols were less efficient and required higher temperatures.



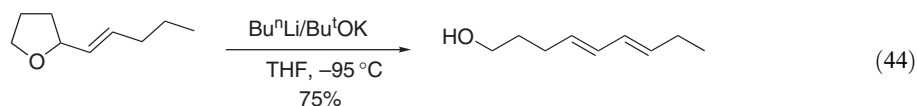
Dehydration of secondary alcohols can be carried out by thermolysis of alkyldiphenylphosphates in the presence of a base such as quinoline or calcium hydride. The phosphorus derivative is prepared just before use with diphenylphosphorochloride or generated *in situ* by simple heating with triphenylphosphate [<1995S1300>](#).

1.13.4.2 Elimination of Alcohols (H—OR)

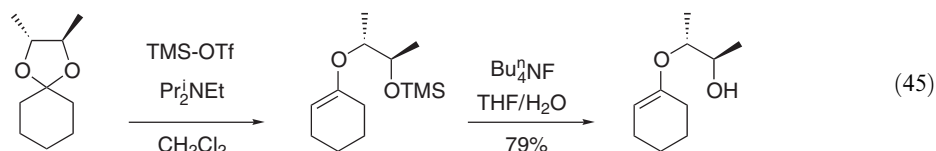
To overcome the poor nucleofugacity of alkoxy groups, the presence of a Lewis acid is usually required to allow the elimination by treatment with bases like DBU. 4,6-Dialkoxy-7-aryltioheptenes were converted into the corresponding dienes as a mixture of two regioisomers (Equation (43)) by first activation with trimethylsilyltriflate followed by the addition of DBU [<2002JOC7957>](#).



The use of strong bases like the superbasic butyllithium/potassium *t*-butoxide mixture (LICKOR) known also as the Schlosser's base is needed for the conversion of α,β -unsaturated acetals or ethers into 1,3-dienes <1998T14603, 2000S1615>. Polyenol ethers were similarly synthesized from γ -phenoxy analogs <1998TL2335, 2002TL8759> (Equation (44)).



Spiro-ketals are also opened by activation with trimethylsilyl triflate to deliver chiral enol ethers, which are very useful for α -functionalization (Equation (45)) <1999EJO2709>.



1.13.4.3 Eliminative Ring Opening of Epoxides

Rearrangement of epoxides into allylic alcohols under basic conditions has been extensively reviewed <2002S1625>. Recent reports are devoted in part to mechanistic studies <2003JA15893> and mainly to asymmetric developments. Desymmetrization of *meso*-epoxides reported a long time ago with chiral bases in stoichiometric amounts <1998JCS(P1)1439>, can now be achieved in a catalytic manner with similar level of induction. Since the first results obtained with proline derivatives by Asami <2002T4655>, or with homochiral C₂-symmetric diamines prepared by Alexakis <1997TA1019>, the rearrangement of epoxides induced by a base has been also applied to the kinetic resolution (Equation (46)) of nonsymmetric epoxides <2002OL3777, 2000JA6610> (Table 4).

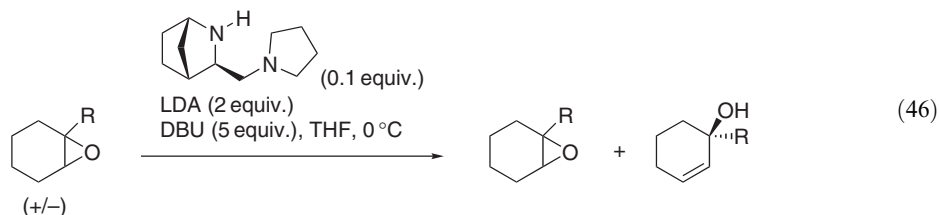
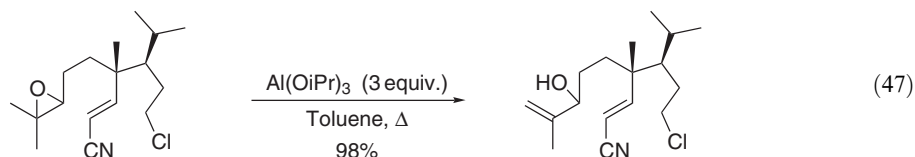


Table 4 Catalytic kinetic resolution of racemic epoxides to allylic alcohols

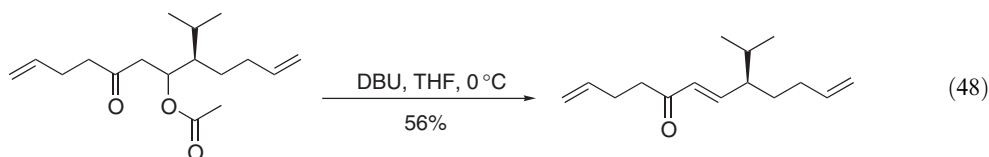
Entry	R	Conversion (%)	Epoxide		Allylic alcohol	
			Yield (%)	ee (%)	Yield (%)	ee (%)
1	Me	52	38	87	40	94
2	Et	63	32	70	37	90
3	Bu ^t	58	36	99	40	99

Promoted by a Lewis acid like aluminum tri(isopropoxide), the rearrangement of epoxides has been included in the total synthesis of natural products such as brassinosteroids <2002TL3181> (Equation (47)).

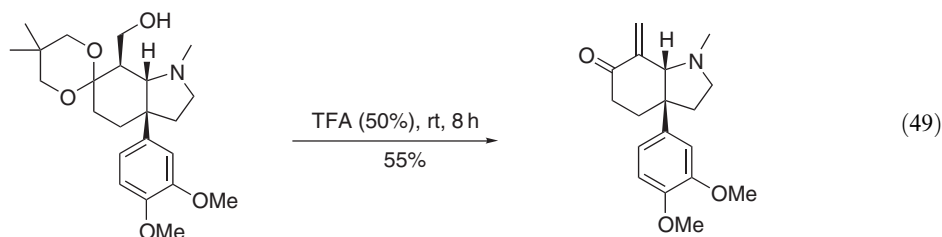


1.13.4.4 Elimination of a Carboxylic Acid (H-OCOR)

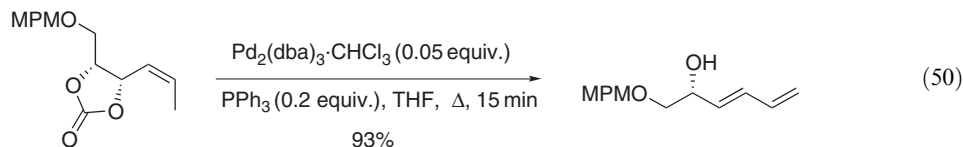
β -Aldols can be easily esterified to acetates or benzoates which under basic conditions are converted into enones in convenient yields via an E1cB mechanism [<1999TL2685>](#). Such a sequence has been included in the total synthesis of 1,6-germacradienols [<2002JOC1554>](#) (Equation (48)).



Compared to other carboxylates, trifluoroacetate is a very good leaving group. Interestingly, treatment of alcohols with trifluoroacetic acid or anhydride can give directly the products resulting from the elimination [<1997JOC1675>](#) (Equation (49)).

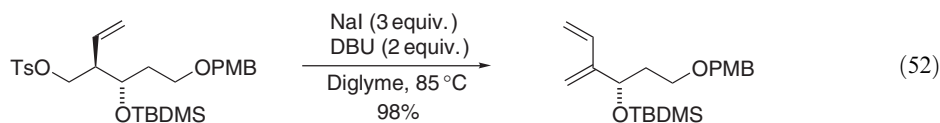
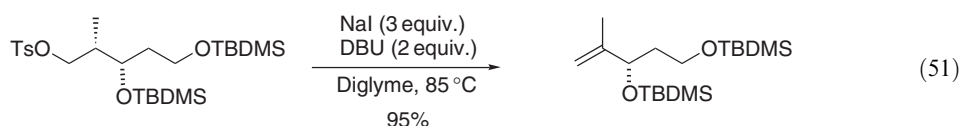


Elimination of nonactivated acetates were reported to proceed by using molybdenum catalysts as noticed in chapter 1.13.4.4 of COFGT (1995) [<1995COFGT\(1\)553>](#). Further investigations in this area have been devoted to the exact nature of the catalyst [<1996JOM\(506\)139>](#). Allylic cyclic carbonates undergo elimination in the presence of a catalytic amount of Pd(0) complex [<1995TL405>](#). A self-coupling process occurs with monosubstituted alkenes (Equation (50)).

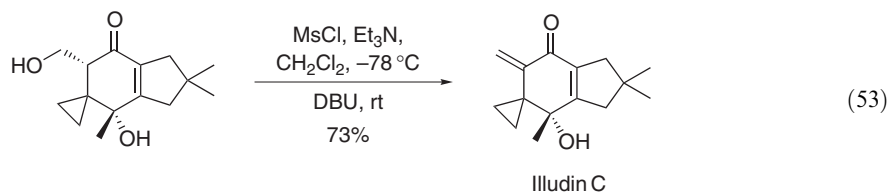


1.13.4.5 Elimination of a Sulfonic Acid

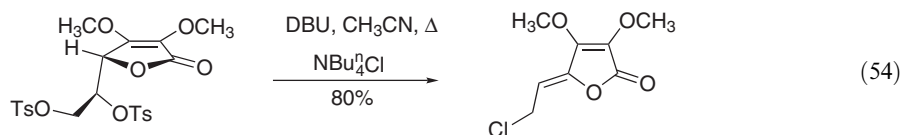
The elimination of mesylates or tosylates is a very popular process for the synthesis of alkenes. Direct heating of primary tosylates in diglyme in the presence of sodium iodide and DBU allows an access to methylene derivatives [<2003S1324>](#) (Equation (51)). The same sequence applied to homoallylic alcohol derivatives gives 1,3-dienes with the same efficiency (Equation (52)). This one-pot procedure avoids the isolation of alkyl iodide intermediates, which are usually unstable.



A similar sequence was reported during the last step of a synthesis of illudin C. The mesylate prepared from the primary alcohol is converted into the alkene by addition of DBU [<2001OL2611>](#) (Equation (53)).

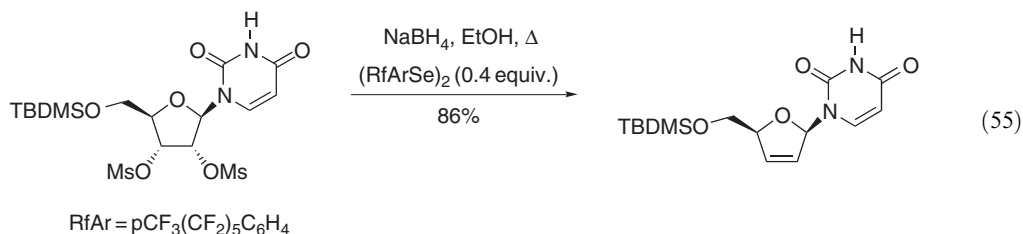


The elimination carried out on a 1,2-bis-tosylate has been combined with a regioselective substitution on the primary tosylate by a chloride anion delivered by the tetrabutylammonium salt [<2001JMC1749>](#) (Equation (54)).

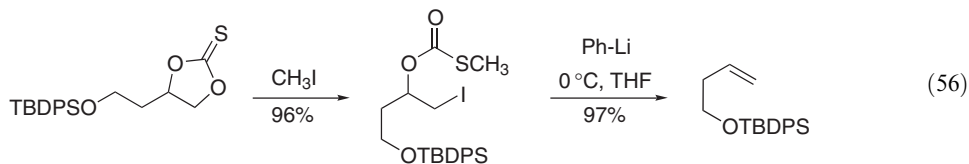


1.13.4.6 Elimination of 1,2-Diols and Derivatives

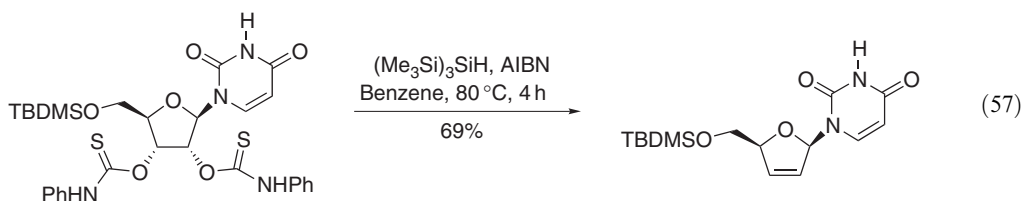
Vicinal dimesylates can be easily converted into alkenes by treatment with arene selenide anions or telluride dianions. The generation of such species requires, however, strong reductive conditions (the use of hydrides or alkali metals in ammonia) [<1996JOC7426, 1997JOC3751>](#) (Equation (55)). Clive and co-workers [<2000OL4029>](#) were the first to develop a catalytic version for this reaction. In order to remove the selenide by-products, Crich and co-workers have taken advantage of a “light” fluororous reagent.



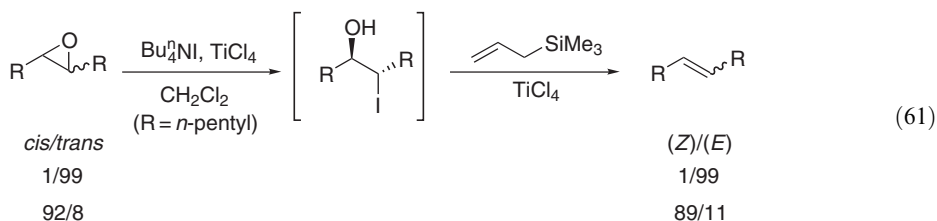
When cyclic sulfates, prepared from 1,2-diols, are treated at room temperature with magnesium iodide in acetonitrile, the corresponding alkenes are formed in high yields [<1998SC871>](#). Iodothiocarbonates submitted to lithium derivatives also afford terminal alkenes in impressive yields [<1999TL4019>](#) (Equation (56)).



Free-radical fragmentation of bis-thioxocarbonates performed with Bu_3SnH , or better with tris(trimethylsilyl)silane (TMSSH), provides access to alkenes and has been applied to the synthesis of 2,3-didehydronucleosides [<2003TL4027>](#) (Equation (57)).



A combination of allyl silane with titanium tetrachloride was able to convert iodohydrins and iodoethers into the corresponding alkenes by a stereospecific *anti*-elimination <1997TL5161> (Equation (61)).



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1.14

One or More C=C Bond(s) by Elimination of S, Se, Te, N, P, As, Sb, Bi, Si, Ge, B, or Metal Functions

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1.14.1 INTRODUCTION

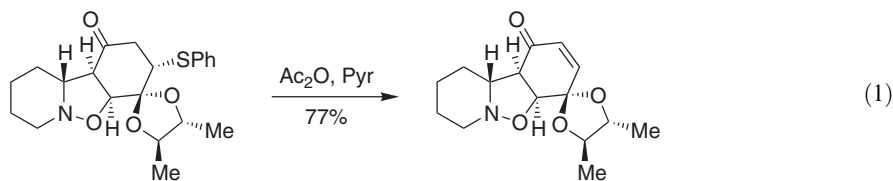
β -Elimination of heteroatoms is one of the most useful methods for the preparation of alkenes. This elimination can be performed either from an isolable precursor (e.g., the β -elimination of sulfoxides) or as a step in a coupling reaction (e.g., the Wittig reaction). The distinction between these two processes is not always clear-cut, however. Whereas in certain coupling reactions the coupling and elimination steps are not readily distinguished (e.g., the Wittig reaction), in others (e.g., the Peterson reaction) coupling intermediates can often be isolated. In the original Horner–Wittig reaction, intermediate β -hydroxyphosphine oxides are generally isolated and can be chemically manipulated before elimination. In this chapter, the focus is on eliminations from isolable precursors. Accordingly, important coupling reactions such as the Wittig, Horner–Wadsworth–Emmons, or Peterson reactions in which spontaneous elimination generally occurs are only briefly mentioned and dealt with in detail in Chapter 1.16. In addition, reactions such as the Julia olefination (in its original version) or the Horner–Wittig reaction involving the formation of well-defined intermediates and their chemical modification are more extensively discussed herein.

1.14.2 BY ELIMINATION OF SULFUR, SELENIUM, OR TELLURIUM FUNCTIONS

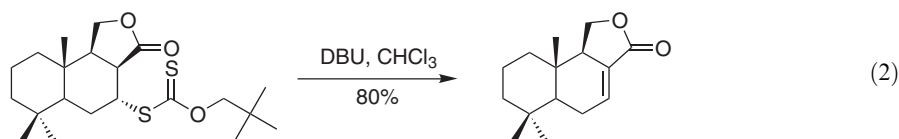
1.14.2.1 Elimination of Sulfide, Selenide, or Telluride Groups

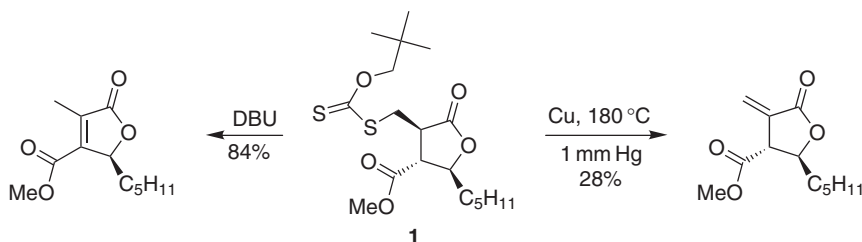
1.14.2.1.1 Elimination of sulfide, thiocyanate, and xanthate groups

Apart from occasional reports where acidic conditions were used [\(<1998H1599>\)](#), elimination of sulfide groups is generally performed under basic conditions. For instance, elimination of thiophenol from a nitrone-derived cycloadduct to form an α,β -unsaturated ketone derivative was efficiently promoted under mild basic conditions by simple heating in the presence of pyridine and acetic anhydride (Equation (1)) [\(<1995TL8665, 1997JOC7781>\)](#). In this particular case, the procedure proceeded in better yield than the alternative pyrolytic elimination of the corresponding sulfoxide (see [Section 1.14.2.2.1](#)).



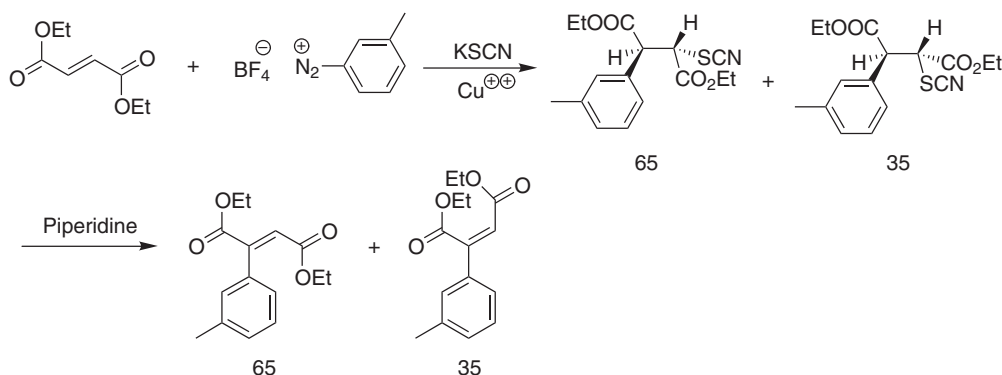
Basic conditions also proved to be very efficient for xanthate removal in the last step of the preparation of the terpenoid cinnamolide (Equation (2)). In contrast, a similar treatment performed on the monocyclic lactone **1** invariably led to the undesired regioisomer possessing an endocyclic double bond. The required *exo*-methylenic compound could however be obtained using a pyrolytic elimination in the presence of copper powder under vacuum, as illustrated in [Scheme 1 \(<1996CC1631, 1999T3791>\)](#).





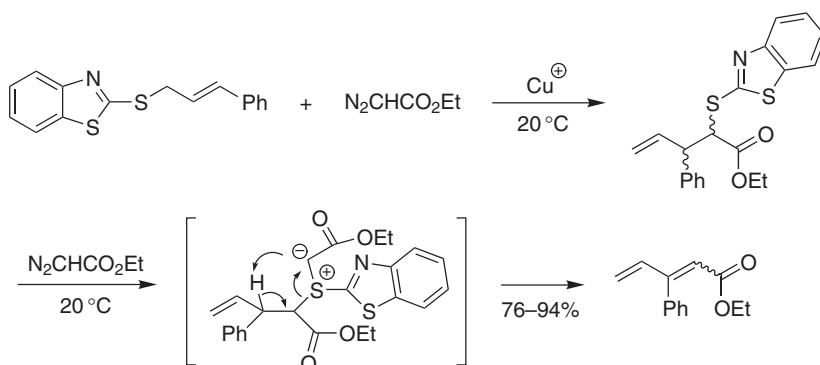
Scheme 1

Stereoselective elimination of HSCN from a diastereoisomeric mixture of thiocyanates resulting from thiocyanatoarylation of diethyl fumarate was also performed under mild basic conditions [<1998ZOR1576>](#) as shown in [Scheme 2](#). The diastereoisomeric ratio in the starting mixture of thiocyanates and the *cis/trans* proportion of the resulting alkenes were similar.



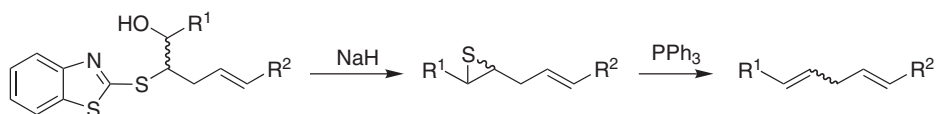
Scheme 2

A new method for high-yield preparation of conjugated dienoic esters has been disclosed. It involves the treatment of heterocyclic allyl sulfides with an excess of ethyl diazoacetate in the presence of a copper(I) complex. A first [2,3]-sigmatropic sulfur ylide rearrangement leads to an intermediate homoallylic sulfide, which can be isolated. This reacts further with ethyl diazoacetate to undergo a formal β -elimination implying the formation of a transient sulfur ylide as shown in [Scheme 3](#) [<1997TL3289>](#).



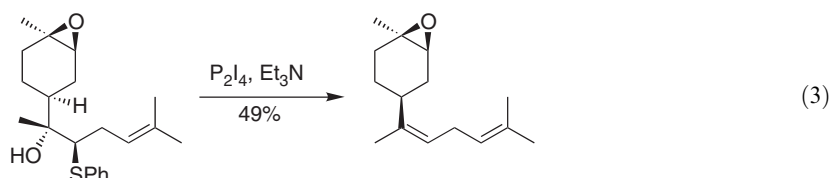
Scheme 3

A synthesis of nonconjugated dienes from β -hydroxy-homoallyl-2-benzothiazolyl sulfides has also been reported. In this case, the elimination of sulfenic acid was accomplished in a two-step procedure involving the formation of an episulfide which was stereospecifically converted to an alkene in the presence of triphenylphosphine ([Scheme 4](#)) [<1998TL3825>](#).

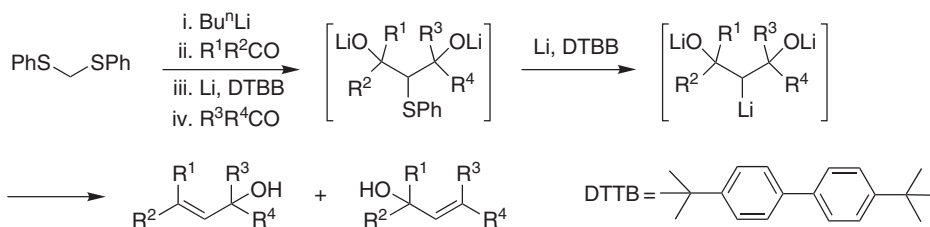


Scheme 4

As shown in Equation (3), the stereospecific *anti*-elimination of benzenesulfenic acid using diphosphorus tetraiodide according to a method originally developed by Krief and co-workers [\[1979TL4111\]](#), allowed access to the sex pheromone of the stink bug *Nezara viridula*, one of the most notorious agricultural pests [\[1998T11421\]](#).

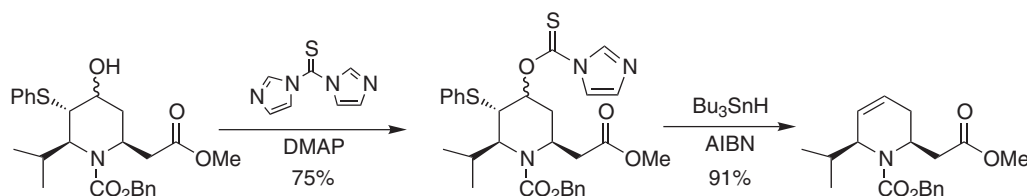


A formally similar elimination was described recently. Sequential deprotonation of bis(phenylthio)methane and reaction with a first carbonyl compound, then repeating the sequence afforded a β,β' -dihydroxysulfide. Desulfurization (Li/di-*t*-butylbiphenyl (DTBB)) and spontaneous elimination of Li₂O led to mixtures of alkenes as illustrated in Scheme 5 [\[1999TL8177\]](#).



Scheme 5

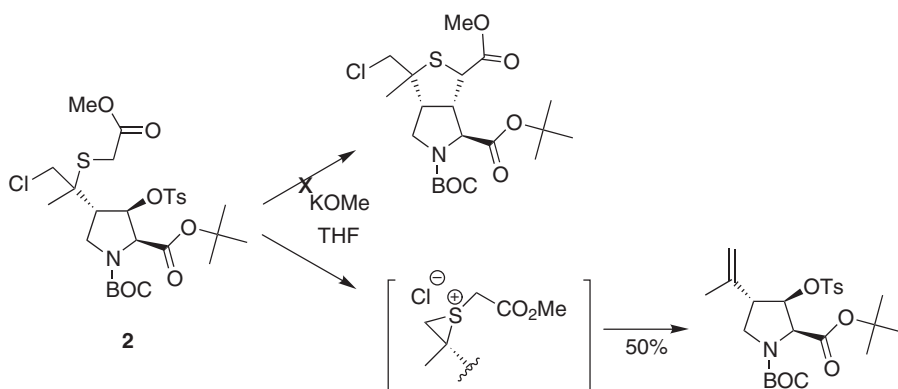
Kueth and Comins [\[1999OL1031\]](#) also used a benzenesulfenic acid elimination for the elaboration of the tetrahydropyridine moiety, encountered in many pharmacologically active agents. As depicted in Scheme 6, this transformation was best realized by first converting the alcohol group of the β -hydroxysulfide to a thiocarbamate. Access to the alkene was effected under reductive radical conditions as previously reported [\[1977TL4223\]](#). The elimination proceeded well regardless of the stereochemistry of the carbon atom bearing the thiocarbamoyl moiety.



Scheme 6

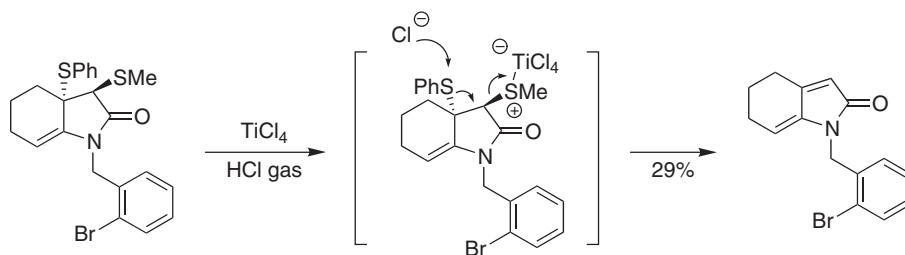
Under basic conditions, β -chloroalkyl sulfides may eliminate to afford terminal olefinic double bonds. This was observed by Bachi and co-workers during a stereoselective synthesis of kainic acid. The strategy relied on the use of a temporary, sulfur-containing linker allowing the directed intramolecular displacement of a tosyloxy group. As shown in Scheme 7, basic treatment of

the kainoid chloroalkyl sulfide **2** did not induce the desired substitution but instead yielded the alkene resulting from formal elimination of sulfenyl chloride (presumably via an episulfonium species) <1996JOC7116>. The approach was successfully modified by prior oxidation of the sulfide to the corresponding sulfone (see Scheme 38).



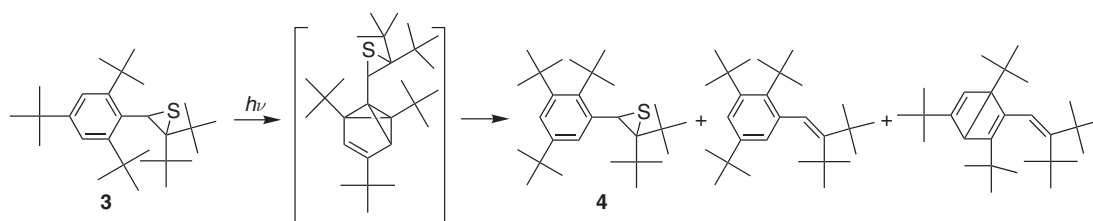
Scheme 7

Elimination of two adjacent sulfide groups, although with a modest yield, was observed during the treatment of an indolone derivative with TiCl_4 in the presence of HCl gas (Scheme 8) <1997H37>. Another related elimination was accomplished with lithium naphthalenide <1995SL628>.



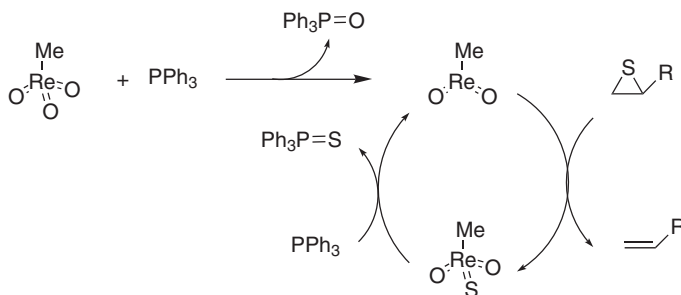
Scheme 8

Treatment of episulfides with phosphines leads to desulfurization and formation of alkenes. The method was recently used for the conversion of vinyl episulfides to conjugated dienes <1999T3791>. Applied to highly sterically congested sulfides, however, desulfurization with trivalent phosphorus compounds only proceeded in low yields or even failed completely in the case of the sulfide **3** <1995BCJ1437>. Other attempts to desulfurize **3**, including the action of strong bases, thermolysis, or irradiation did not give the corresponding styrene. Instead, under irradiation, sulfide **3** was converted into its less-crowded isomer **4**, which then gave the corresponding styrene as well as a rearranged vinyl-substituted Dewar benzene as illustrated in Scheme 9.



Scheme 9

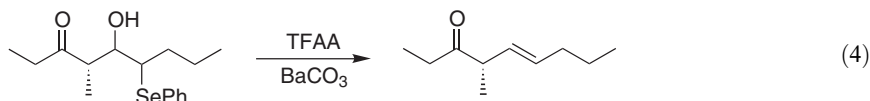
The mechanism of tributyltin hydride-induced desulfurization of episulfides has been thoroughly investigated [<1995JOC470>](#) and new procedures for the elimination of sulfur have appeared. They include the catalytic use of aminium salts [<1995T8935>](#) or of methyltrioxorhenium in the presence of triphenylphosphine [<1999CC1003>](#). The latter procedure is particularly useful for speeding-up desulfurizations, which are otherwise too slow when triphenylphosphine is used alone; as shown in [Scheme 10](#), the mechanism is believed to involve a dioxo Re^{V} as well as a Re^{VII} sulfide species.



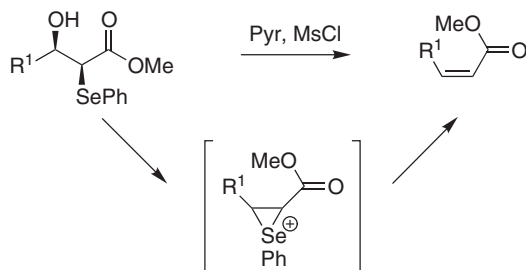
Scheme 10

1.14.2.1.2 Elimination of selenide groups

Elimination of β -hydroxyselenides using the well-established Krief–Reich procedure [<1976TL3743, 1979JA6638>](#) involves the use of mesyl chloride in the presence of triethylamine. The reaction is an *anti*-elimination of the phenylseleno and the mesyloxy groups and proceeds via an episelenonium ion. This method has continued to be widely used recently, for instance in the preparation of sulfinyl butadienes [<1996S1079>](#). The relatively basic conditions required for the elimination may not be suitable for base-sensitive compounds, and in order to synthesize β,γ -unsaturated carbonyl derivatives, Enders and Whitehouse investigated milder elimination conditions [<1996S621>](#). As shown in [Equation \(4\)](#), using trifluoroacetic anhydride in the presence of barium carbonate allowed (*E*)-double bond formation while racemization of the α -stereogenic center was kept to a very low level (<5%). The use of other bases caused considerable racemization (10–20% for K_2CO_3 , 100% for Et_3N).

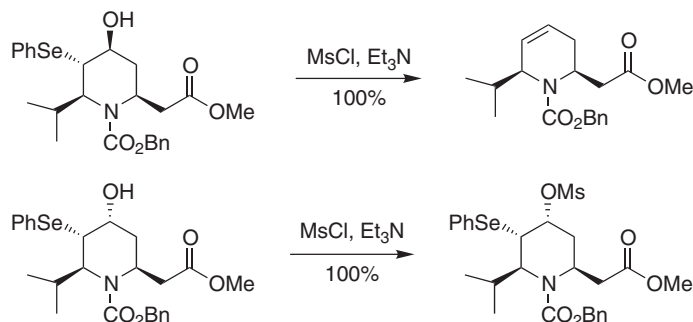


The stereochemical course of the Krief–Reich elimination in the case of the formation of α,β -unsaturated carbonyl derivatives from *syn*-aldol products ([Scheme 11](#)) [<2001T6703>](#) has been carefully investigated, recently. It was noted that pyridine (instead of triethylamine) was required to ensure a good conversion to (*Z*)-isomers. With triethylamine, stereoselectivity dropped considerably due to the formation of *anti*-aldol products via retroaldolization/recombination.



Scheme 11

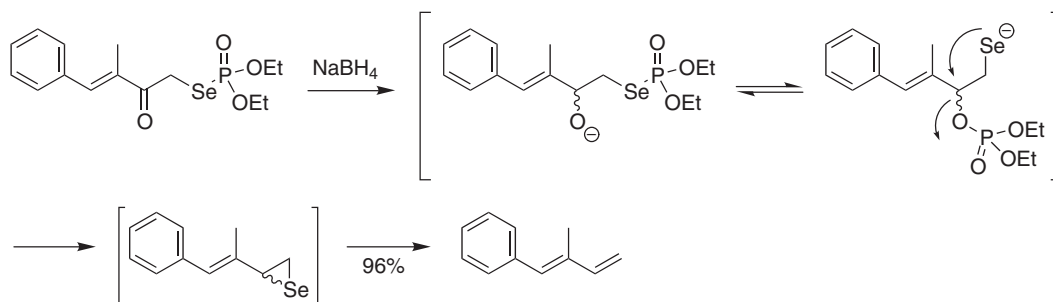
The stereochemical requirements of the Krief elimination were evident in the synthesis of tetrahydropyridine derivatives from cyclic β -hydroxyselenides: as shown in [Scheme 12](#), only the *trans*-isomer yielded the desired unsaturated compound while the mesylate derived from the *cis*-isomer remained unchanged [\[1999OL1031\]](#). Elimination from the *cis*-isomer could be performed using a two-step radical elimination as mentioned earlier (see [Scheme 6](#)).



Scheme 12

A similar radical elimination from a polymer-supported β -bromosulfide has been described by Nicolaou and co-workers [\[1998CC1947\]](#).

A β -hydroxyselenophosphate and an episelenide were key intermediates in the one-pot conversion of β -oxo-selenophosphates to conjugated dienes as shown in [Scheme 13](#) [\[1999TL3791\]](#).

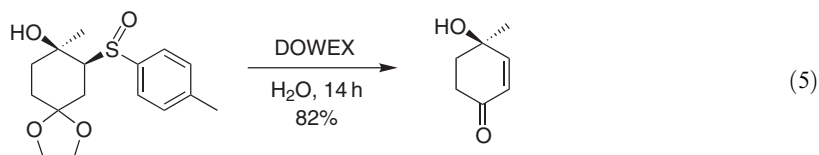


Scheme 13

1.14.2.2 Elimination of Sulfoxide, Selenoxide, or Telluroxide Groups

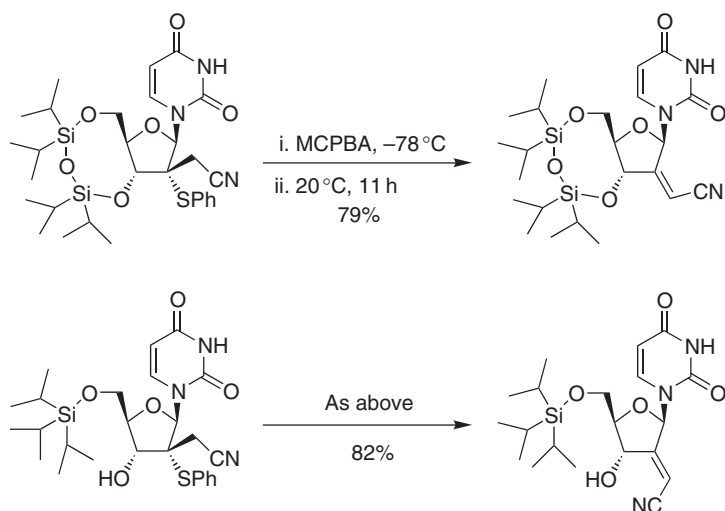
1.14.2.2.1 Elimination of sulfoxide groups

Thermal *syn*-elimination of sulfoxides is a well-established procedure for alkene synthesis, which proceeds particularly well and in mild conditions when conjugated alkenes are formed. For example, a temperature of 40 °C was sufficient for the preparation of butadienyl trifluoromethyl ketones [\[1996CC861\]](#) from α -phenylsulfinyl- γ,δ -unsaturated-trifluoromethyl ketones and elimination occurred at room temperature, along with ketal cleavage, in the one-pot formation of α,β -unsaturated ketones shown in [Equation \(5\)](#) [\[1995TL3737\]](#).



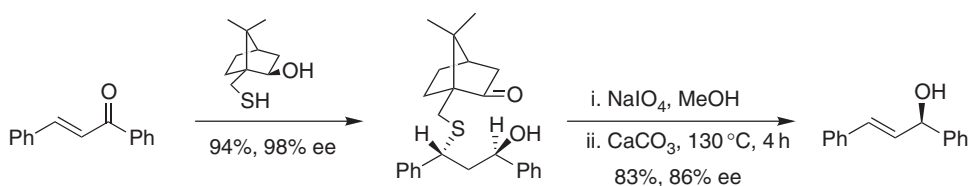
A similar facile elimination in acidic medium, leading to an α,β -unsaturated lactone, has been recently reported by Renard and Ghosez [\[1999TL6237, 2001T2597\]](#).

Sulfenic acid elimination in the nucleoside derivatives shown in [Scheme 14](#) also proceeded at room temperature to afford (*E*)- and (*Z*)-cyanomethylene-deoxyuridine. Interestingly, the stereochemical course of the reaction was dictated by the neighboring 3'-substituent: a free hydroxyl group or the corresponding silyl ether orientated the elimination toward the formation of the (*E*)- or (*Z*)-isomer, respectively [\[1996JOC6261\]](#). Attempts to isolate the intermediate sulfoxides, which appeared to be unstable on silica gel, failed in these cases.



Scheme 14

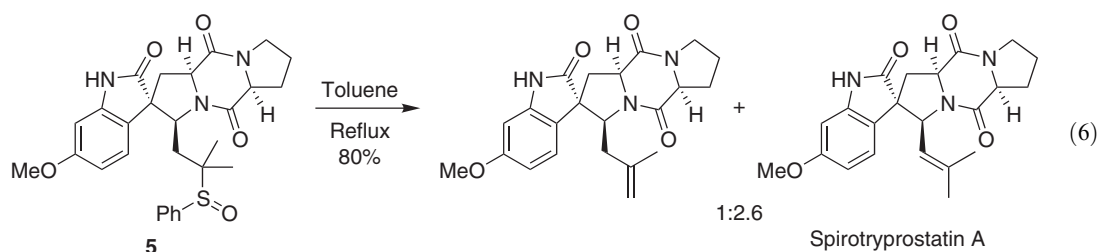
Except for the favorable cases mentioned above, higher temperatures are generally required for the elimination. These conditions may be too harsh in the case of sensitive compounds. For example, Node and co-workers reported a novel preparation of optically active allylic alcohols from α,β -unsaturated ketones involving as a key step a tandem Michael addition/Meerwein–Ponndorf–Verley reduction using 10-mercaptoisoborneol ([Scheme 15](#)) [\[2000JA1927\]](#). After an oxidation step, elimination of sulfenic acid was accomplished with calcium carbonate at 130 °C with a significant decrease of the enantiomeric excess (ee).



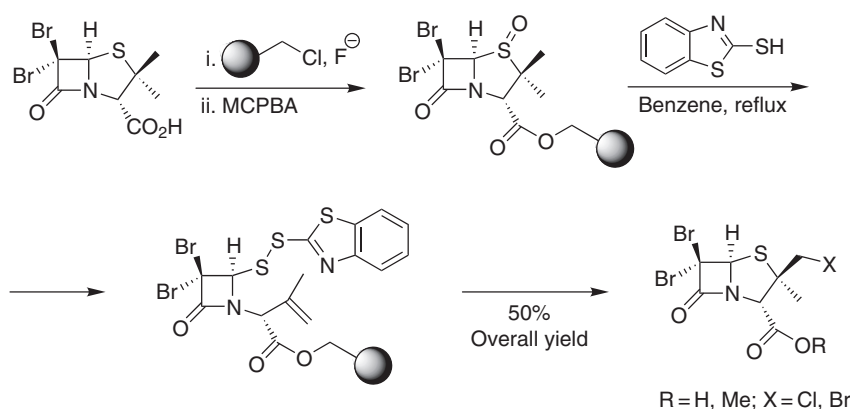
Scheme 15

In such cases, the use of imidazolyl sulfoxides [\[2000SL1725\]](#) (which eliminate more readily than the commonly used aryl sulfoxides), or promotion under microwave irradiation, have been recommended [\[1996TL1855\]](#).

When several possibilities exist for the formation of nonconjugated double bonds, the regioselectivity of the sulfenic acid elimination is often poorly controlled. For instance, the last step of Edmondson and Danishefsky's synthesis of the spiroindolone spirotryprostatin A relied on the thermolysis of the tertiary sulfoxide **5**. As shown in [Equation \(6\)](#), pyrolysis in refluxing toluene led to a mixture of two alkenes. Remarkably, it was possible at this stage to cleanly convert the undesired disubstituted alkene into the target compound by rhodium trichloride treatment. Further migration of the double bond to form an enamide [\[1998AG\(E\)1138\]](#) was not observed.

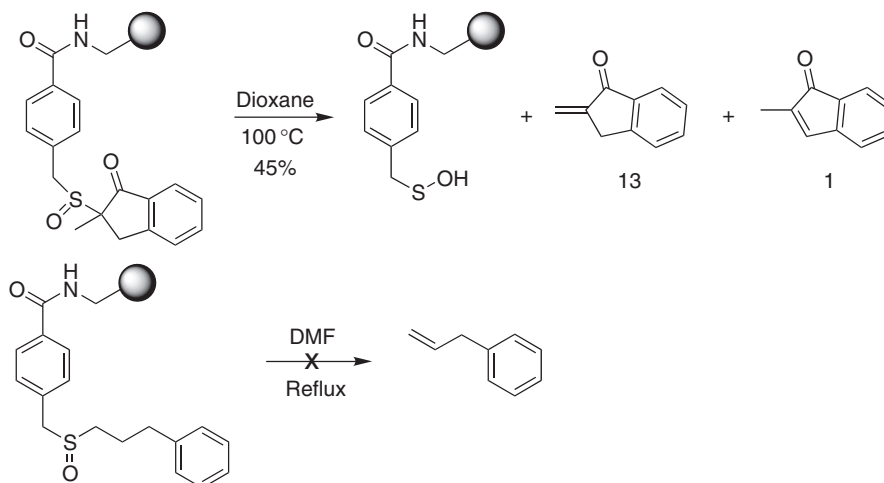


A related elimination was used as a key reaction during the solid-phase preparation of 2- β -halomethyl penam derivatives [<1999TA3893>](#) (Scheme 16). After immobilization of the dibromo precursor onto Merrifield resin and oxidation to obtain a resin-bound sulfoxide, pyrolytic elimination of the sulfenic acid moiety was assisted by mercaptobenzothiazole as reported earlier in solution chemistry [<1973TL3001>](#). As expected, the desired disubstituted alkene was obtained exclusively. The isomeric tetrasubstituted isomer, which would result from a disfavored elimination α to the nitrogen atom, was not observed.



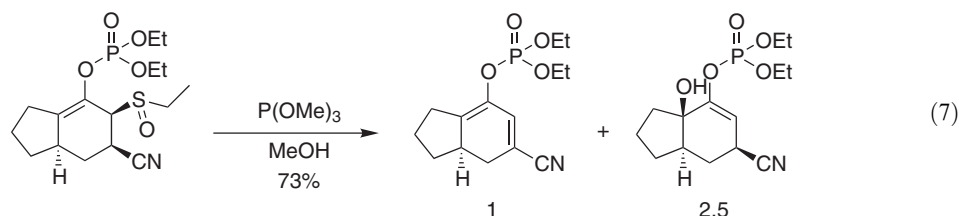
Scheme 16

Still in the active field of solid-phase chemistry, safety-catch linkers based on the sulfoxide/selenoxide *syn*-elimination have been developed recently [<2000TL5287>](#). As expected, compared to sulfoxides, selenoxides underwent elimination under much milder conditions; use of sulfoxides was possible only when conjugated double bonds were formed. Other substrates such as precursors of the sensitive allylbenzene failed to react at low temperature or decomposed upon raising the temperature (Scheme 17).

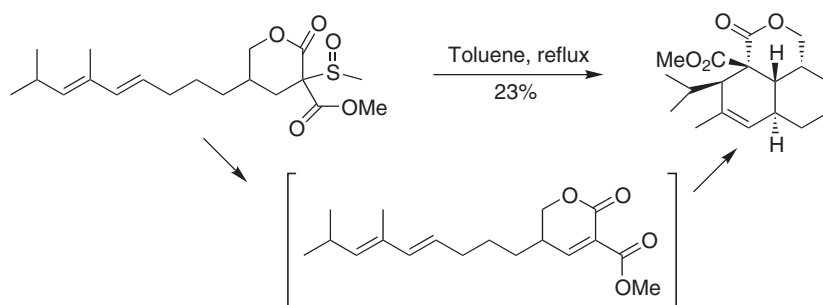


Scheme 17

In allylic sulfoxides, 1,2-elimination to give conjugated dienes competes with the well-known [2,3]-sigmatropic rearrangement. Although the rearrangement pathway is generally favored, there are exceptions. For example, Koprowski and co-workers observed significant amounts of diene formation during a synthesis of tertiary allylic alcohols <2001T1105> (Equation (7)).

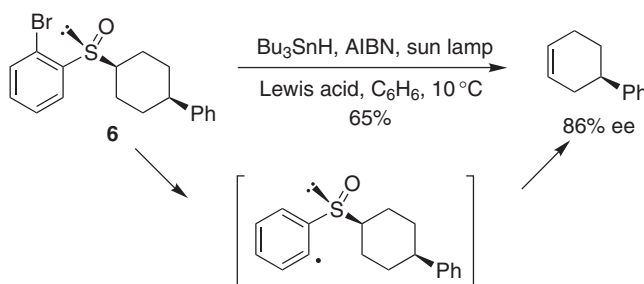


In the reaction shown in Scheme 18, the electron-poor alkene resulting from sulfenic acid elimination was not observed and immediately reacted with a neighboring diene in an intramolecular Diels–Alder cycloaddition to give a *trans*-fused octalin <1995SL909>.



Scheme 18

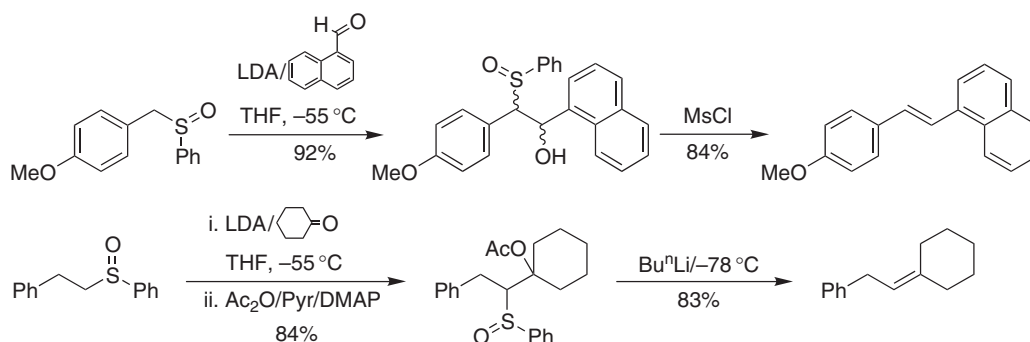
Apart from thermolysis, elimination of sulfoxides has been occasionally carried out by photolysis, sometimes in excellent yield <1995LA1957>. A new very mild procedure based on the radical fragmentation of *o*-bromophenyl sulfoxides has been described by Renaud and co-workers <1999OL873>. As shown in Scheme 19, Bu_3SnH treatment of the representative, optically pure sulfoxide **6** in the presence of a Lewis acid, gave chiral 4-substituted cyclohexenes with very good enantiomeric excesses. The key step of the process involves the abstraction of a hydrogen atom by the initially formed aryl radical. By comparison, thermolysis of **6** gave phenylcyclohexene in only 54% ee and required a temperature of 200 °C.



Scheme 19

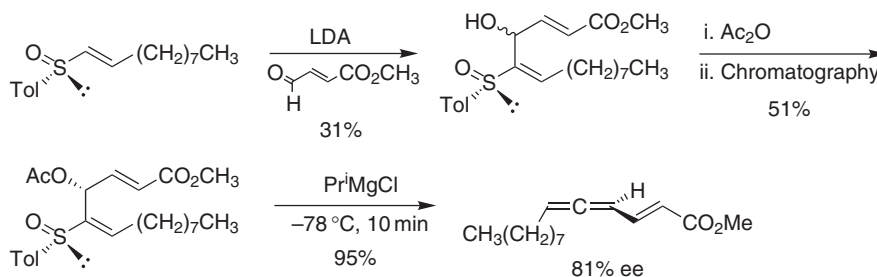
Formation of alkenes (mainly (*E*)) by the elimination of β -chloro-, β -mesyloxy-, or β -acetoxy-sulfoxides has been studied by Satoh and co-workers <1996T2349, 1998TL6935, 2000T6223>. As β -hydroxysulfoxides may be obtained by the condensation of sulfoxides with aldehydes, this method may offer an interesting alternative to the well-known Julia–Lythgoe olefination (see Section 1.14.2.3.1). For example, as shown in Scheme 20, the method could be applied

to the preparation of normally not accessible stilbenes and trisubstituted alkenes. Access to stilbenes was spontaneous while, in other cases, a sulfoxide-metal exchange, after activation of the β -hydroxysulfoxide, was required.



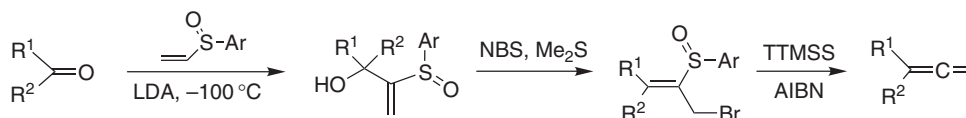
Scheme 20

The same group proposed an extension of the method to the synthesis of allenes from aldehydes and alkenyl aryl sulfoxides <1995T9327, 1999TL8815, 2002T2533>. Starting from optically active sulfoxides, allenes were prepared, usually in high ee values, as exemplified in the synthesis of the chiral allenic pheromone shown in Scheme 21.



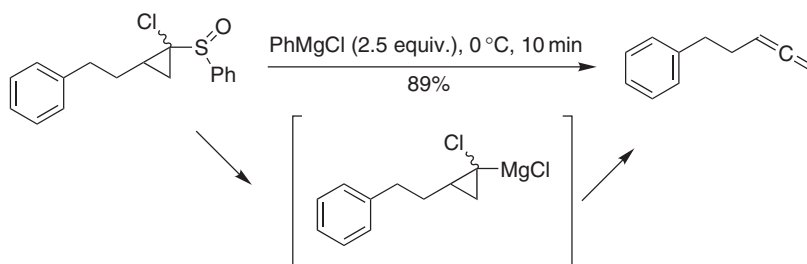
Scheme 21

Malacria's group reported a novel preparation of functionalized allenes using an unprecedented radical β -elimination of vinyl sulfoxides. The radical precursor was obtained in two steps from a carbonyl derivative and a vinyl sulfoxide as indicated in Scheme 22 <1999TL3565, 2002EJO1776>. The radical elimination was best effected by the exposure of the brominated precursor to tris(trimethylsilyl)silane (TTMSS) in refluxing toluene, in the presence of AIBN.



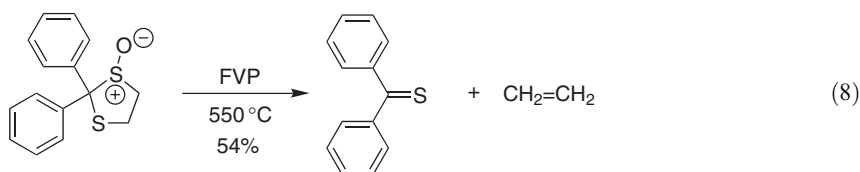
Scheme 22

Allenes have also been prepared by the treatment of 1-chlorocyclopropyl phenyl sulfoxides with Grignard reagents, thus providing an extension of the Doering–LaFlamme reaction based on *gem*-dihalogenated equivalents <1958T75, 2001T5369> (Scheme 23).

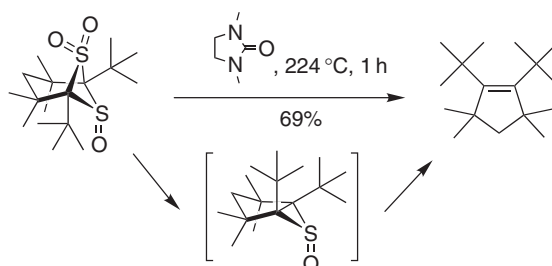


Scheme 23

Dithiolane *S*-oxides were reported to eliminate ethylene under flash vacuum pyrolysis conditions (Equation (8)) <1997ACS527>.



Sterically congested cycloalkenes can be prepared from sulfoxide/sulfone derivatives by pyrolysis in 1,3-dimethyl-2-imidazolidinone (DMI) implying, as shown in Scheme 24, sequential extrusion of SO₂ and SO <2000JOC1799>.



Scheme 24

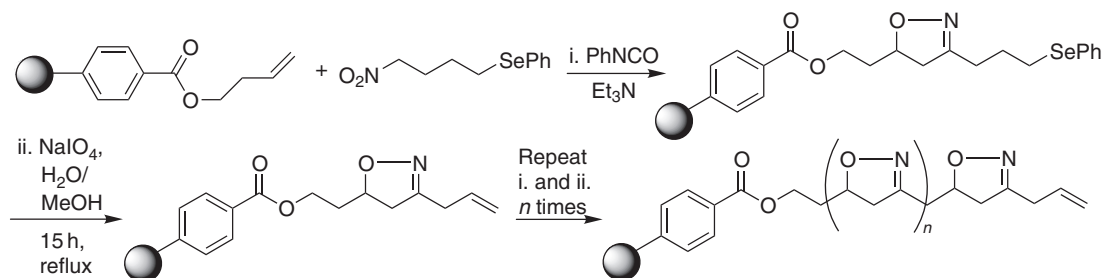
1.14.2.2.2 Elimination of selenoxide groups

Elimination of the selenoxide group in a *syn*-pericyclic fashion resembles the analogous sulfoxide elimination, but proceeds more easily and constitutes a well-established way to prepare alkenes under very mild conditions <1995COFGT(1)589>. It has been widely used in recent years, in particular during the synthesis of many classes of natural substances, both in solution and, since 1996, in polymer-supported chemistry.

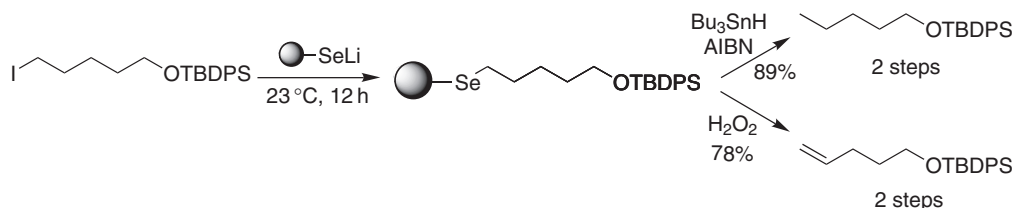
(i) Oxidative elimination from polymer-supported selenide derivatives

Starting from a polymer-bound alkene, an iterative application of nitrile oxide 1,3-dipolar cycloaddition and selenide oxidation/elimination steps was employed in a solid-phase synthesis of polyisoxazolines as shown in Scheme 25 <1996JOC8755>.

Ruhland and co-workers <1998JOC9204> and Nicolaou's group <1998CC1947> reported the use of polymer-supported selenium reagents for organic synthesis. Ruhland's group described selenium-based linkers for traceless solid-phase synthesis. Nicolaou and co-workers used an air-stable, polymer-supported lithium selenide, to investigate a loading onto polymer/release strategy, the substrate being released from the polymer either by free-radical chemistry or under oxidative conditions as shown in Scheme 26.



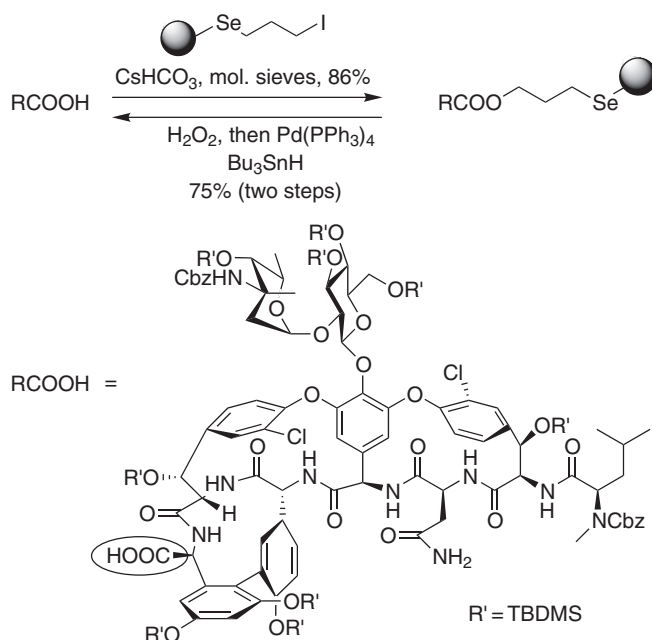
Scheme 25



Scheme 26

Since these preliminary experiments, the oxidation/elimination strategy has been used to cleave selenium linkers from many polymer-supported compounds, including precursors to bicyclic natural products <1999OL807>, polycyclic natural benzopyran derivatives <2000AG(E)734, 2000AG(E)739, 2000JA9939>, deoxysugars <2000AG(E)1089>, cyclic depsipeptide phytotoxins <2001TL8337>, as well as vancomycin analogs <2000AG(E)1084, 2001CEJ3798>.

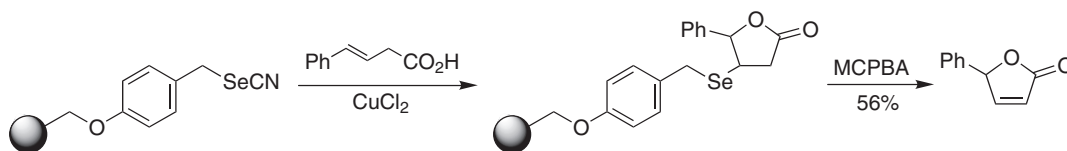
In the latter case, semisynthesis of vancomycin glycosides was developed using a pro-allyl, selenium-based, safety-catch linker strategy. The method was first tested on a protected vancomycin derivative as illustrated in Scheme 27. Loading of the carboxylic group onto the resin was best accomplished in the presence of CsHCO₃ and molecular sieves, whereas the cleavage back to the starting vancomycin derivative was effected by selenoxide elimination and removal of the resulting allyl ester by Pd(PPh₃)₄ and *n*-Bu₃SnH.



Scheme 27

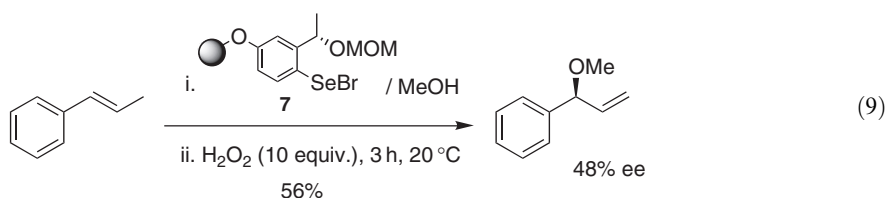
Safety-catch linkers based on the sulfoxide or selenoxide elimination have also been developed for the preparation of simple aromatic compounds <2000TL5287> (see Scheme 17). Selenoxides were preferred as they underwent cleavage under much milder conditions than sulfoxides.

Polymer-supported selenocyanates have been prepared and used for solid-phase selenolactonization <1999SL1760>. Oxidative deselenenylation yielded racemic α,β -unsaturated lactones in fair yields (Scheme 28). The same reaction was also performed in water, employing an amphiphilic polymer-supported selenenyl derivative and H_2O_2 instead of MCPBA as an oxidant <2003TL3793>.



Scheme 28

An asymmetric version of the latter selenolactonization using a chiral, polymer-bound, electrophilic selenium reagent **7** was published by Uehlin and Wirth <2001OL2931>. The deselenenylation step was generally performed under reductive radical conditions except in the experiment shown in Equation (9) where oxidative elimination yielded an allylic ether with a fair enantiomeric excess.



Recently, a new polymer-supported benzyl selenide was prepared and used in a stereocontrolled synthesis of alkenes and allylic alcohols <2002TL5495>.

(ii) Oxidative elimination in solution

Oxidative elimination of selenoxides in solution continues to be frequently used as a convenient way to introduce double bonds in many classes of chemical compounds. In recent reports, various oxidizing agents have been used: H_2O_2 <1995JOC794>, $\text{H}_2\text{O}_2/\text{AcOH}$ <1995NN1227, 1997JOC1501>, NaIO_4 <1997JOC4870>, NBu_4IO_4 <2001OL2737>, dimethyldioxirane <2000JOC6293>, Bu^tOOH <1995CC2519>, MCPBA <1997TL331>.

Although the reaction generally works well, the regioselectivity of the elimination (when several possibilities exist) is sometimes difficult to predict <1997JOC4870> and may fail for labile products and/or substrates <2000AG(E)237>.

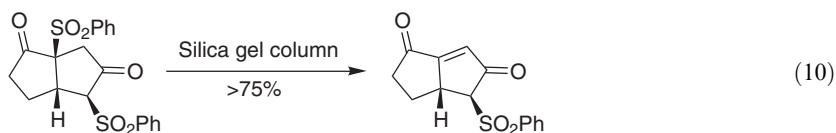
1.14.2.3 Elimination of Sulfone, Selenone, or Tellurone Groups

1.14.2.3.1 Elimination of sulfone groups

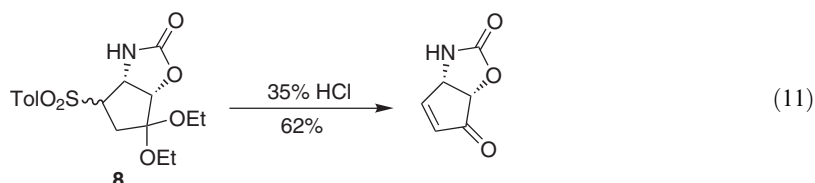
(i) Elimination of sulfones

Although elimination of sulfinic acid from β -ketosulfones is usually performed under basic conditions <1995COFGT(1)589>, there are a few recent reports mentioning elimination under

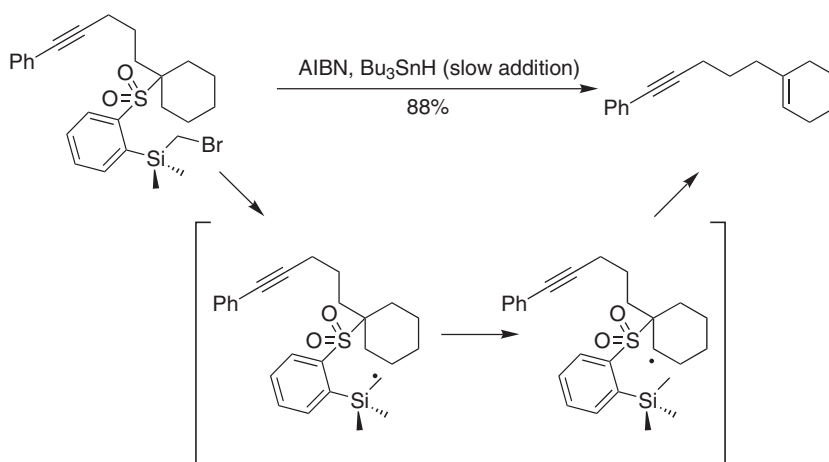
acidic conditions. This was the case for the preparation of the diquinane derivative shown in Equation (10) <1995JOC5135>, which was formed by exposing its bis-sulfonylated precursor to silica gel.



Similarly, the sulfonylated bicyclic oxazolidinone **8** could be converted in one step to the corresponding enone by HCl treatment (Equation (11)), <1997JOC2139>.

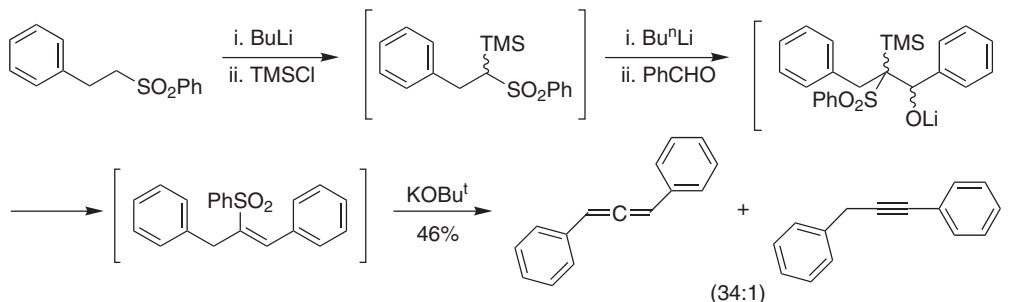


A new method for the elimination of sulfinic acid from aryl sulfones bearing an *o*-(bromomethyl)-dimethylsilyl moiety under mild radical conditions has been disclosed by VanDorst and Fuchs <1997JOC7142>. As shown in Scheme 29, an *o*-silylmethylene radical forms first, followed by intramolecular hydrogen abstraction and collapse of the radical to produce an alkene.



Scheme 29

An impressive integrated chemical process has been reported for the preparation of alkynes and allenes from alkyl sulfones <1997CL1023>. This one-pot preparation involves nearly four quantitative steps, including Peterson elimination and a sulfone elimination. In the example shown in Scheme 30, the allenic derivative was by far the major product.



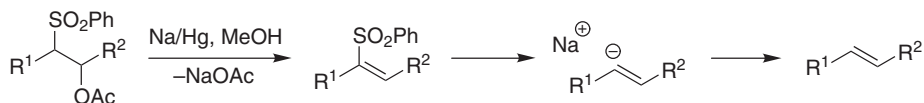
Scheme 30

(ii) Elimination of β -substituted sulfones

(a) *Julia olefination*. Since its discovery in 1973 by Marc Julia and Jean-Marc Paris <1973TL4833> and its development a few years later by Lythgoe and Kocienski (see for instance <1980JCS(P1)1045>), the Julia olefination also commonly called the Julia–Lythgoe olefination has demonstrated a pivotal role in organic synthesis. This reaction which has been reviewed several times <1995COFGT(1)589> consists, in its original form, in four discrete steps involving: the metallation of a phenylsulfone, addition of the metallate to an aldehyde, acylation of the resulting hydroxysulfone to a β -acyloxysulfone, finally reductive elimination with sodium amalgam to afford an (*E*)-alkene. Although this procedure, referred to as the *classical* Julia olefination has proved to be very useful for the synthesis of complex systems (see, e.g., <2002EJO2613>) it suffers from some drawbacks: it requires the use of a toxic and rather aggressive amalgam reagent, it is not generally transposable to ketones and, furthermore, its use, which requires several steps is rather cumbersome.

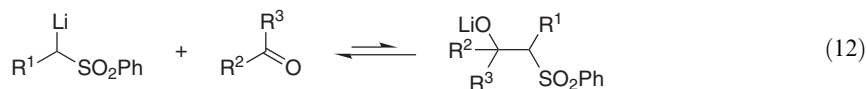
To obviate the first drawback, the use of magnesium in the presence of a few crystals of mercuric chloride <1995TL5607, 1996SC1499> or SmI_2 , instead of sodium amalgam, has been recommended. Based upon a few earlier pieces of work (<1990TL7105, 1992TL8065>), the SmI_2 -induced reductive elimination of β -acyloxysulfones has been much studied since 1995. Keck and co-workers <1995JOC3194> compared $\text{Na}(\text{Hg})$ and SmI_2 -mediated reductions of vinyl as well as β -acetoxysulfones. Use of sodium/mercury amalgam proved unsuitable for preparing highly conjugated alkenes, yielding products of over-reduction. In all cases, SmI_2 in the presence of HMPA (as described by Inanaga <1987CL1485>) or DMPU gave good results. Support to these observations came from independent work from Fukumoto and co-workers <1995T9873>.

A revision of the mechanism of the *classical* Julia olefination using β -acyloxysulfones emerged from deuterium labeling experiments conducted by Keck's group <1995JOC3194>. The new mechanism presented in Scheme 31, which implies a vinyl anion intermediate is proposed instead of the generally accepted mechanism which involves a β -acetoxy anion <1995COFGT(1)589>.

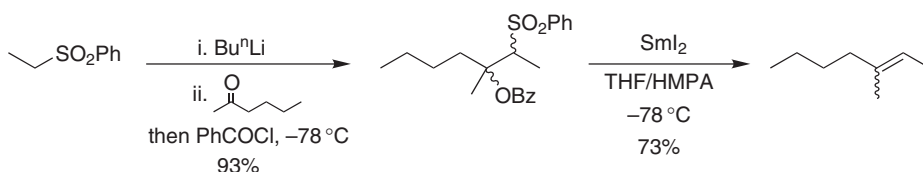


Scheme 31

Marko's group further investigated the SmI_2 variant of the Julia olefination and used it for the preparation of trisubstituted alkenes from ketones <1996TL2089, 2001T2609>. As depicted in Equation (12), the classical Julia–Lythgoe olefination does not generally work with ketones because the first, equilibrated step of the reaction does not favor the formation of the condensation product.

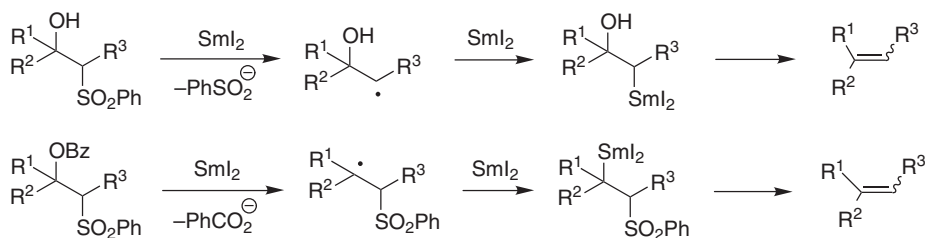


By simply trapping the lithium alkoxides with PhCOCl , nevertheless, it was possible to prepare in excellent yields the corresponding benzoyloxysulfones which were converted to trisubstituted alkenes, often obtained as (*E*)/(*Z*) mixtures, by treatment at -78°C with SmI_2 in the presence of HMPA or DMPU (Scheme 32).



Scheme 32

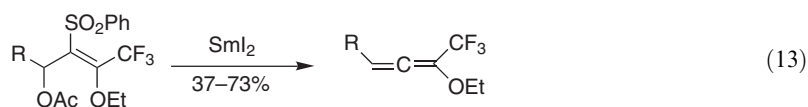
Using TMSCl as a trapping agent instead of PhCOCl also enabled the formation of β -hydroxy-sulfones and their conversion to trisubstituted alkenes with SmI₂/HMPA or SmI₂/DMPU. In this case, however, the elimination only occurred when the temperature was raised to 0 °C. Possible mechanisms for these eliminations are shown in [Scheme 33](#): formation of the β -hydroxy radical from β -hydroxysulfones is particularly slow, which may explain the different kinetics observed.



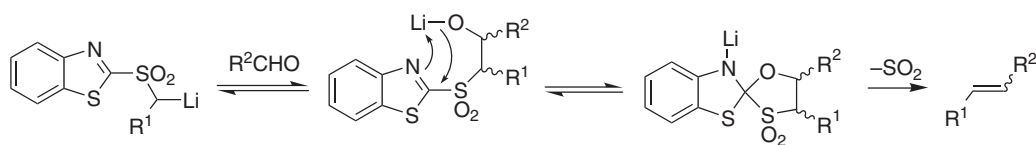
Scheme 33

In addition to the work of Marko's group, trisubstituted alkenes were also prepared from ketones using a sulfoxide version of the Julia olefination as reported before (see [Scheme 20](#) and [<1996T2349, 1998TL6935, 2000T6223>](#)).

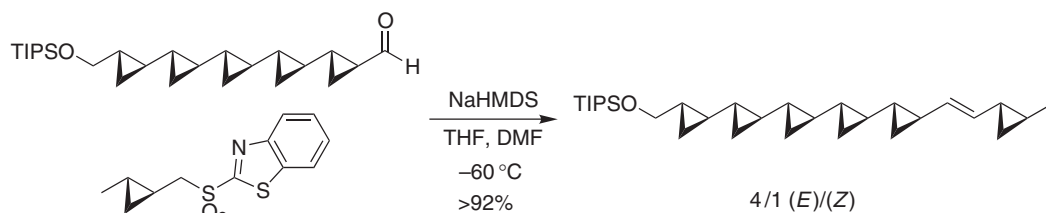
The SmI₂ method allowed the first synthesis of allenes by Julia olefination starting from β -trifluoromethyl vinyl sulfones [<2000CPB1395>](#) ([Equation \(13\)](#)).



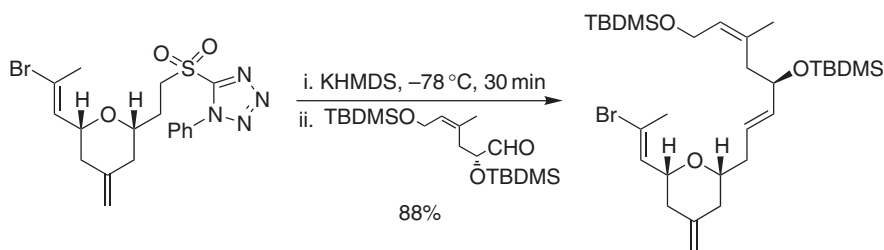
Important improvements to the Julia olefination involve the use of various heteroaryl sulfones among which are benzothiazolyl sulfones (BT-sulfones) ([Scheme 34](#) [<1991TL1175>](#); [Scheme 35](#) [<1996JA10327>](#)), pyridin-2-yl sulfones (PYR-sulfones) [<2001TL5149, 2001TL6619>](#), 1-phenyl-*H*-tetrazol-5-yl sulfones (PT-sulfones) [<1998SL26>](#), and 1-*t*-butyl-1*H*-tetrazol-5-yl sulfones (TBT-sulfones) [<2000SL365, 2002JCS\(P1\)2563, 2002JA11102>](#) ([Scheme 36](#)).



Scheme 34



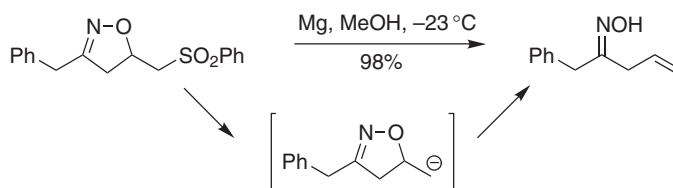
Scheme 35



Scheme 36

These modifications convert the four distinct step sequence of the original Julia reaction to one-step coupling reaction, which will be more extensively treated in chapter 1.16. For a recent exhaustive review on the modified Julia olefination see [<2002JCS\(P1\)2563>](#).

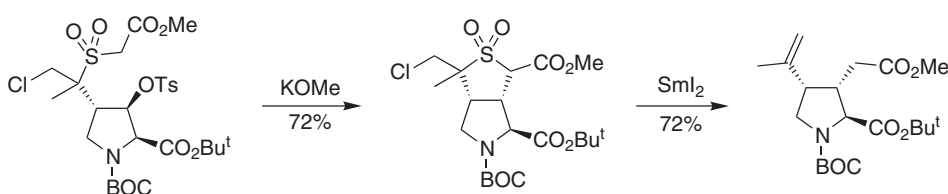
A few reactions related to the final reduction step of Julia olefination have been reported like the ring opening of (phenylsulfonylmethyl)isoxazolines with Mg in MeOH as shown in [Scheme 37](#) [<1999SC3165>](#).



Scheme 37

(b) *Elimination of β -silyl-, stannyl-, chloro-, and sulfonyl sulfones.* New examples of reductive eliminations of 1,2-disulfones, using sodium amalgam, to afford alkenes have been reported recently [<1995COFGT\(1\)589](#), [1995SL628](#), [1997JOC4162](#), [1998EJO2775](#).

β -Chlorosulfones are converted to alkenes upon treatment with tributyltin hydride/AIBN [<1996JOC7116>](#). Reductive elimination of the chlorosulfone can also be performed by using SmI_2 . This was the basis of an elegant strategy, involving a temporary sulfone-containing spacer, used for the synthesis of a kainic acid derivative ([Scheme 38](#)) [<2001TA1101>](#).



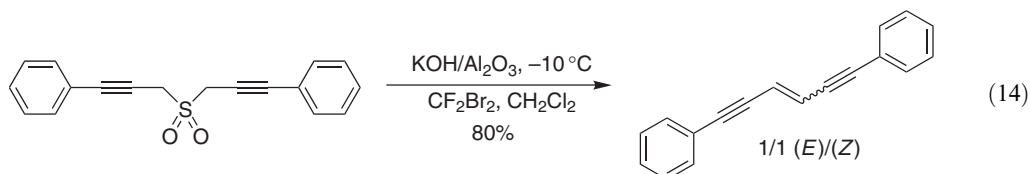
Scheme 38

A few elimination reactions of β -silyl and β -stannyl sulfones have been reported (see [Sections 1.14.5.1.3](#) and [1.14.6.3](#)).

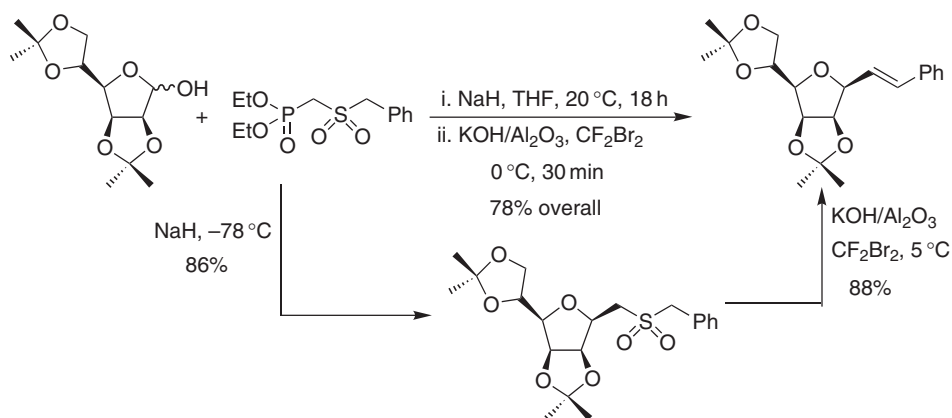
(iii) The Ramberg–Bäcklund reaction

The Ramberg–Bäcklund elimination of α -halo sulfones in the presence of a base leading to alkenes has been extensively investigated. It has been in particular very recently extensively reviewed by Taylor and Casy [<2003OR357>](#). In the Meyers modification, the starting sulfones are chlorinated *in situ* in the presence of KOH, Bu^tOH , and CCl_4 [<1995COFGT\(1\)589>](#). Despite its practical aspects, the Meyers modification suffers from serious drawbacks partly arising from the presence of reactive dichlorocarbene in the reaction medium and its use is essentially limited to the preparation of

stilbenes. Although side reactions can be suppressed by inclusion of a carbene scavenger in the medium, the carbene adducts may be difficult to separate from the desired products. In 1994, Chan and co-workers proposed an improved version of the Meyers method employing alumina-supported KOH, CBr_2F_2 , and Bu^tOH . Using these conditions, a large variety of sulfones were converted into alkenes <1994CC1771>. Key factors for the success of Chan's method are (i) the use of a substitute for CCl_4 , which does not readily form carbenic species and (ii) the serendipitous discovery that alumina-supported KOH, in contrast to KOH alone, does not promote the formation of undesired brominated side-products. Since its discovery, this protocol has been widely used, for example, for the synthesis of paracyclophane derivatives <1997JOC2727>, azamacrocycles <2000JOC8367>, or C_2 -symmetrical diaminodiols <1999TL3917>. The use of CH_2Cl_2 instead of Bu^tOH as a solvent was beneficial for the synthesis of very fragile enediynes (Equation (14)) <1996TL1049>.

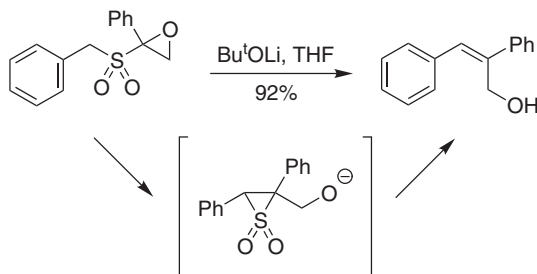


Taylor and co-workers have used both the Meyers and the Chan protocols for the elaboration of C-glycosyl amino acids <1999CC1599>, C-disaccharides <1999AG(E)2939, 2003AG(E)1387> as well as trehalamine derivatives <2001TL1197>. In the example shown in Scheme 39, using a newly described benzyl sulfonylphosphonate reagent enabled a straightforward preparation of a C-glycoside from a suitably protected monosaccharide, either using a two-step or even a one-pot procedure <2003AG(E)1387>.

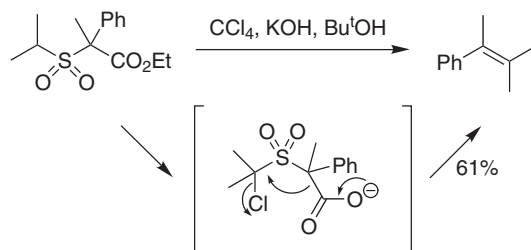


Scheme 39

Two reactions derived from the Ramberg–Bäcklund rearrangement have been published: the epoxy-Ramberg–Bäcklund reaction in which α,β -epoxysulfones are converted into allylic alcohols upon treatment with a base as shown in Scheme 40 <1997TL3055> and the decarboxylative Ramberg–Bäcklund reaction exemplified in Scheme 41 <1995TL8367>.



Scheme 40



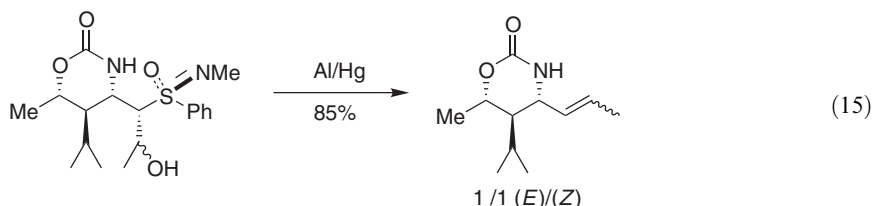
Scheme 41

1.14.2.3.2 Elimination of selenone and tellurone groups

No new examples were reported during the period 1995–2003.

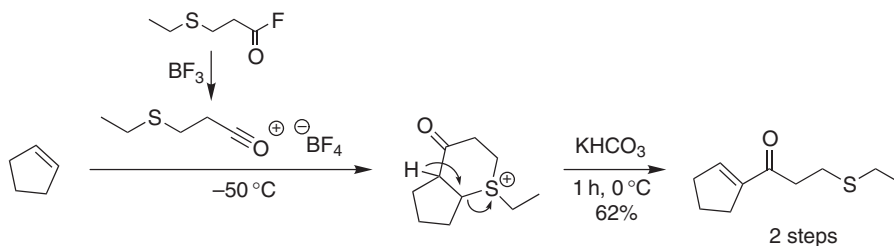
1.14.2.4 Elimination of Sulfinimine, Selenimide, Tellurium Imide, Sulfinamide, Sulfoximine, Sulfonamide, and Sulfonate Groups

In the course of their new asymmetric synthesis of β -amino acid derivatives from allylic sulfoximines and aldehydes, Gais and co-workers [<2003EJO1500>](#) used aluminum/mercury amalgam, as recommended previously [<1973JA6462>](#), to reduce β -hydroxysulfoximines to an equimolar mixture of the corresponding (*E*) and (*Z*) alkenes ([Equation \(15\)](#)). Related vinylic sulfoximines were used by the same group to prepare terminal allenes under basic conditions [<2002JA10427>](#).



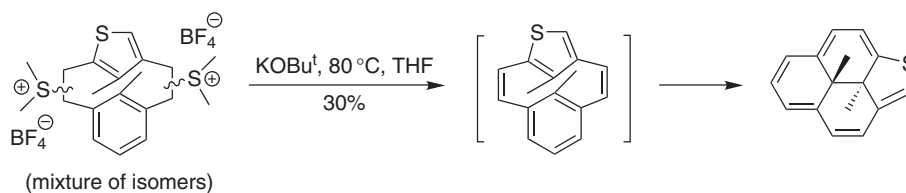
1.14.2.5 Elimination of Sulfonium, Selenonium, and Telluronium Salts and Ylides

Balenkova and co-workers developed a novel reagent quantitatively prepared by reacting BF_3 gas at -60°C with ethylsulfanylpropionyl fluoride. In the presence of alkenes this reagent yielded cyclic sulfonium salts that could be converted under mild basic conditions into alkylthiopentenones as illustrated in [Scheme 42](#) [<1995TL6317>](#). The use of their novel reagent was extended later to a new synthesis of aryl vinyl ketones [<1998S89>](#).



Scheme 42

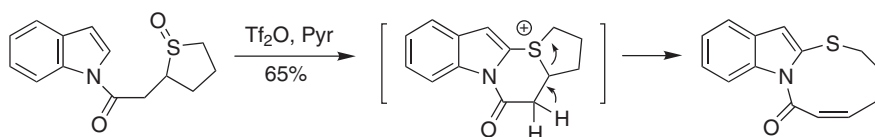
Under drastic basic conditions, novel aromatic thiaannulenes could be prepared from a mixture of bis(dimethylsulfonium)tetrafluoroborates via a strained cyclophanediene as shown in [Scheme 43](#) [<1996JA722>](#).



Scheme 43

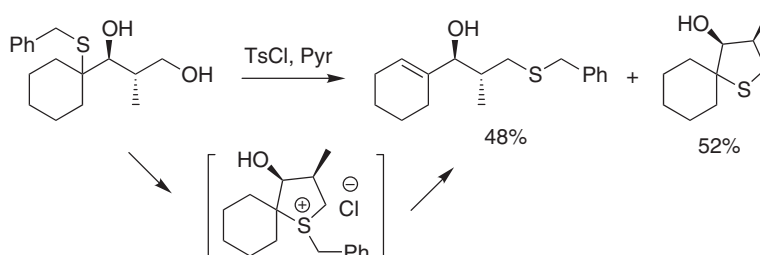
Similar conditions were recently used for the elaboration of novel strained dihydropyrene derivatives [<1999JCS\(P1\)403>](#).

Under Pummerer conditions, the indole sulfoxide shown in [Scheme 44](#) was converted to a bicyclic sulfonium salt which underwent spontaneous β -elimination/ring expansion to give interesting *N,S*-heterocycles [<1998JOC9190>](#).



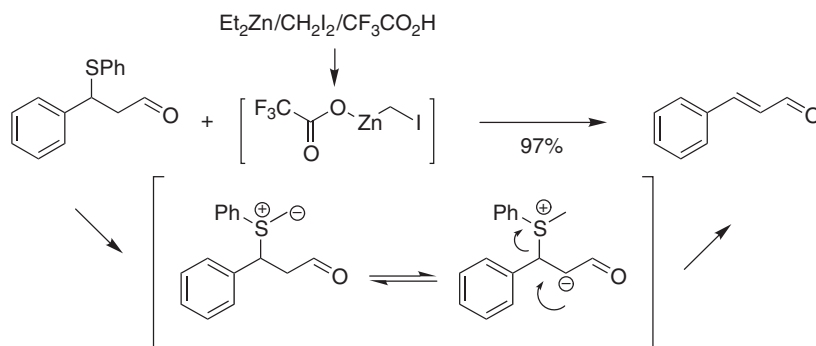
Scheme 44

Warren and co-workers studied the decomposition of intermediate spiro-sulfonium salts, formed by the treatment of 4-benzylsulfanyl-1,3-diols with tosyl chloride, to afford allylic alcohols ([Scheme 45](#)), [<2001JCS\(P1\)1504>](#) and references cited therein.



Scheme 45

Phenyl sulfides or phenyl selenides bearing an electron-withdrawing group at the β -position can be eliminated by treatment with a carbenoid [<2002TL4959>](#). This elimination proceeds via a sulfur ylide intermediate ([Scheme 46](#)).



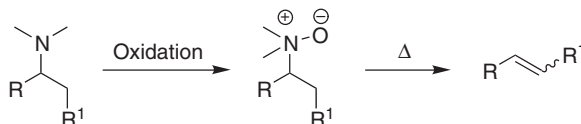
Scheme 46

Other related sulfur ylide eliminations have recently been reported (see e.g., [<1998JCS\(P1\)2181, 1999T10659>](#)).

1.14.3 BY ELIMINATION OF NITROGEN FUNCTIONS

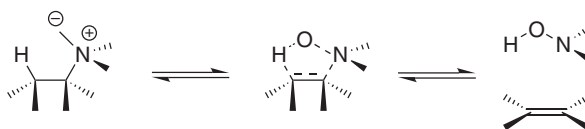
1.14.3.1 Elimination of Amine Oxides—The Cope Reaction

The widely used Cope reaction, which involves the cleavage of amine oxides, usually formed *in situ* from the corresponding amines, leads to alkenes and hydroxylamine derivatives. The reaction conditions are quite mild and there are few side reactions. The amine oxide elimination occurs at temperatures ranging from 100 to 150 °C (neat). In dry DMSO or THF, the reaction can proceed at room temperature. The reaction is useful for the preparation of many alkenes (Scheme 47). A limitation is that it does not open six-membered rings containing nitrogen, though it does open 5- and 7–10 membered rings.



Scheme 47

The elimination of amine oxides involves concerted cyclic transition states in which an intramolecular proton transfer accompanies elimination to form the C—C double bond. A five-membered cyclic synchronous transition state with a 120° (C⋯H⋯O) angle is generally accepted and the elimination proceeds in a *syn*-fashion (Scheme 48). In acyclic systems the (*E*)-alkene is preferentially formed with low selectivity. In cyclic systems, conformational effects and the necessity for a cyclic transition state determine the product composition.



Scheme 48

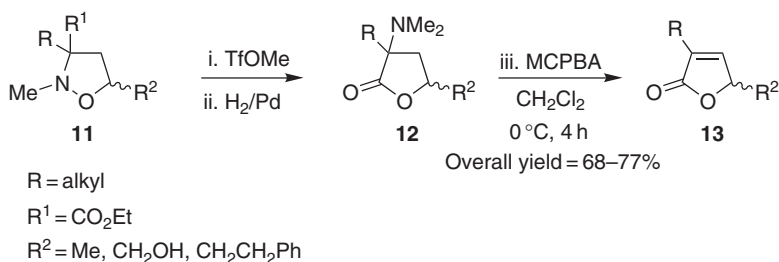
The effect of solvents on equilibrium was briefly studied (Equation (16)) <1995JOC5795>. Solvents that are hydrogen-bond donors favor the formation of *N*-oxides **10a** and **10b**, whereas hydrogen-bond acceptors favor the hydroxylamines **9a** and **9b**.

		Yield (%)			
		9a	10a	9b	10b
 9a R = Me 9b R = Pr ⁱ	 10a R = Me 10b R = Pr ⁱ	0	100	0	100
		0	100	23	77
		15	85	68	32
		55	45	>90	<10
		60	40	>90	<10
		67	33	90	<10

(16)

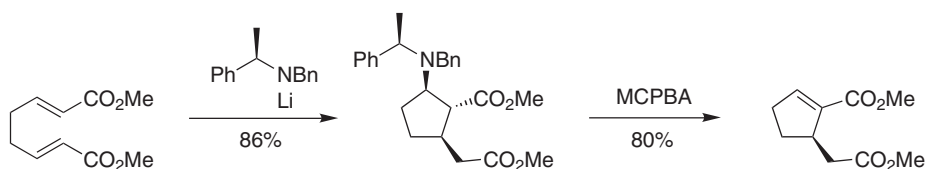
Chiacchio and co-workers developed an efficient access to unsaturated five-membered lactones via 1,3-dipolar addition (Scheme 49). Conversion of isoxazolidines **11** to butenolides **13** has been performed by a three-step sequence involving a Cope elimination as a final step through the intermediate **12** <1998T5695, 1999JOC28>.

The Cope elimination was also used to remove amine-based chiral auxiliaries. The asymmetric synthesis of (*R*)- and (*S*)-methyl (2-methoxycarbonylcyclopent-2-enyl) acetates, which are useful synthons for monoterpene synthesis, was carried out by the addition of the dimethyl ester of

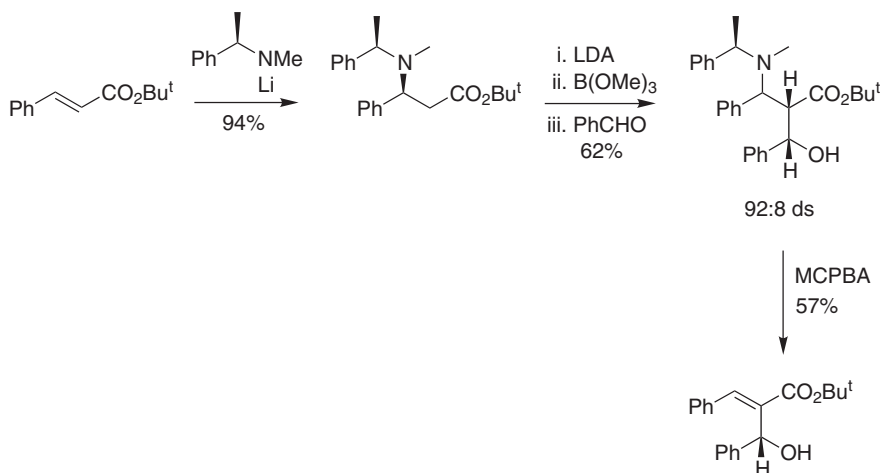


Scheme 49

(*E,E*)-octa-2,6-dienedioic acid to lithiated (*R*)-(α -methylbenzyl)benzylamide followed by a Cope elimination (Scheme 50) <1997TA2683>. By a similar process, the conjugate addition of chiral amides to *t*-butyl cinnamate followed by aldol reaction and Cope elimination affords Baylis–Hillman products (Scheme 51) <2000TA2437>.



Scheme 50

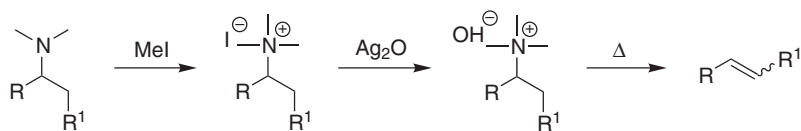


Scheme 51

1.14.3.2 Elimination of Quaternary Ammonium Salts—The Hoffmann Elimination

Elimination of quaternary ammonium salts to afford an alkene and an amine can be achieved either by the thermal decomposition of quaternary ammonium hydroxides or by the treatment of quaternary ammonium halides by bases.

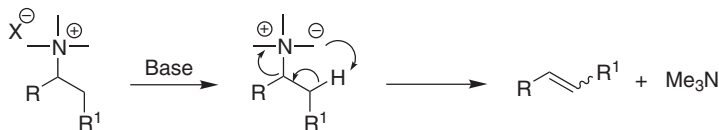
In the former method, known as the Hoffmann degradation, the amine is converted first to a quaternary ammonium iodide which gives the corresponding hydroxide upon treatment with silver oxide. Elimination is induced by heating at temperatures ranging between 100 and 200 °C by distilling an aqueous or alcoholic solution of the hydroxide (Scheme 52).



Scheme 52

The mechanism is usually *E2* leading to the product of *trans*-elimination. In certain cases, for hindered molecules, the reaction proceeds via a five-membered cyclic transition state, similar to that of the Cope reaction.

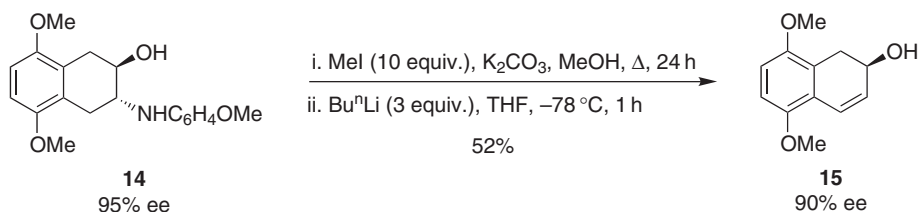
Treatment of quaternary ammonium halides with bases favors the elimination of the amine to form a new C—C double bond. The mechanism is different and involves a 2,3-rearrangement of an ammonium ylide (Scheme 53).



Scheme 53

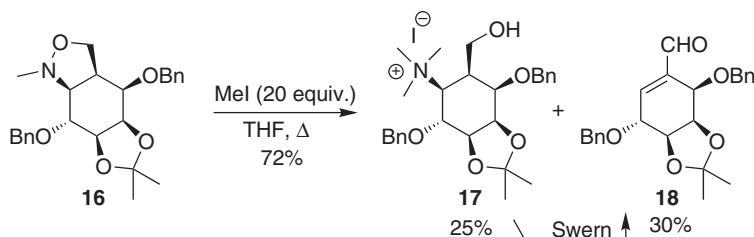
An important difference between this reaction and the Hoffmann degradation is that the products of *syn*-elimination are usually formed. Thus, the two reactions complement each other.

A formal synthesis of 4-demethoxydaunomycin based on the asymmetric catalytic aminolysis of a meso-epoxide followed by Hoffmann elimination was recently described. Methylation of the *trans*- β -amino alcohol **14** affords a quaternary ammonium iodide which is converted to the allylic alcohol **15** by treatment with excess butyllithium (Scheme 54) <2002T75> with only a slight loss of enantiomeric excess.



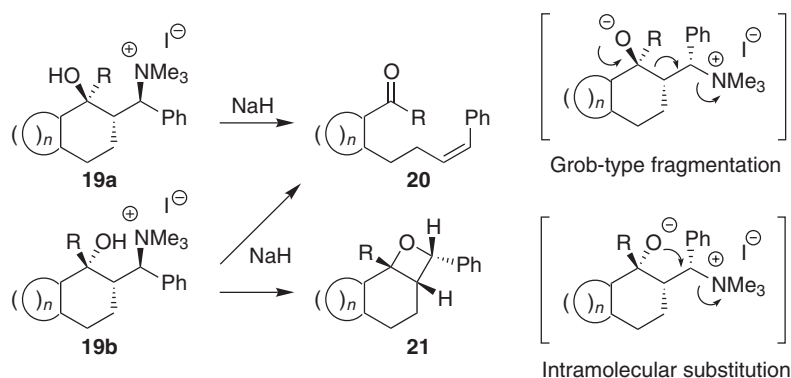
Scheme 54

Isoxazolidines obtained by intramolecular [2+3]-dipolar cycloaddition of nitrones are useful intermediates in synthesis. In the study reported in Scheme 55, two compounds are isolated upon isoxazolidine treatment with methyl iodide (20 equiv.) in THF: the quaternary dimethylammonium salt **17** and the α,β -unsaturated aldehyde **18**. The former could be smoothly converted to the aldehyde under Swern conditions/concomitant β -elimination. A radical fragmentation was suggested to explain the conversion of **16** to **17** <1995TL1899>.



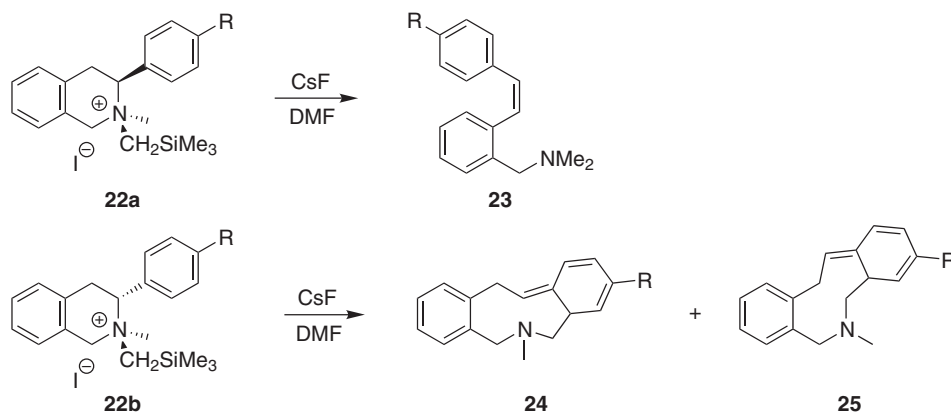
Scheme 55

Treatment of quaternized γ -amino alcohol **19a** with NaH triggers a Grob-type fragmentation leading to the formation of unsaturated aldehydes or ketones **20** in which the newly formed olefinic double bond has the (*Z*)-configuration. The competitive displacement of the ammonium group by the alkoxide, to give an oxetane **21**, was observed only for isomer **19b** (Scheme 56) <1998EJO2185>.



Scheme 56

Caesium fluoride in DMF converts cyclic silylalkylammonium iodides to the corresponding α -arylcycloammonium *N*-methylides which rearrange either via an intramolecular Hoffmann degradation in the case of the *cis*-isomer **22a** or via Sommelet–Hauser or Stevens rearrangements for the *trans*-isomers **22b** to afford the isotoluene derivatives **24** and **25** (Scheme 57) <1995JOC4272>.

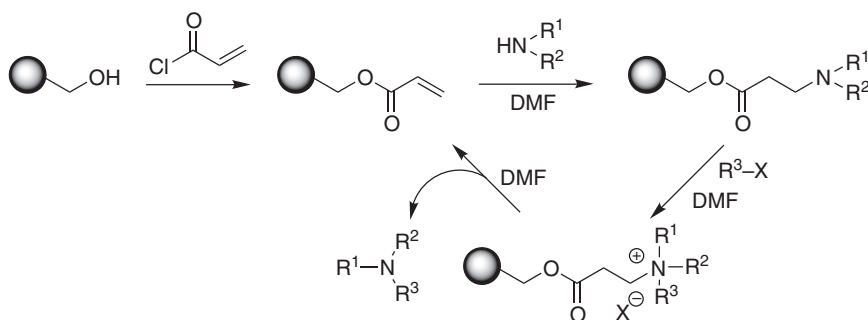


Scheme 57

The use of solid-phase organic synthesis has emerged as a very important tool for the production of combinatorial libraries. The Hoffmann elimination can be used to prepare tertiary amines and separate the products from the resin. Scheme 58 shows the Michael addition of secondary amines to a resin bearing acrylate functionalities. Treatment by alkylating agents introduced both chemical diversity and cleaved the tertiary amines/carrier bond, via Hoffmann elimination, with recovery of the functionalized starting polymer <1997JA3288, 1998JOC1027>. The reaction time was reduced when perfluorinated organic solvents were used instead of DMF <2001TL7509>.

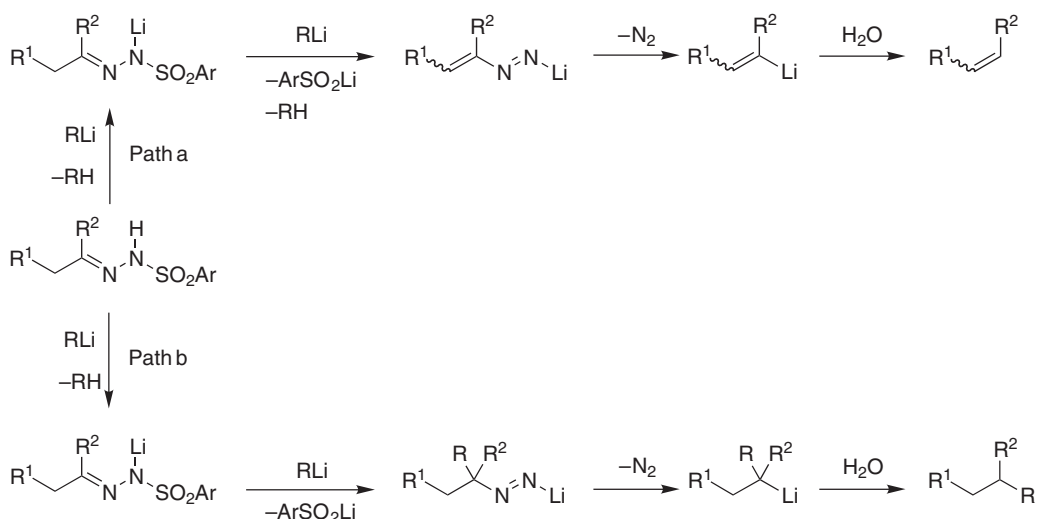
1.14.3.3 Alkenes from Arenesulfonyl Hydrazones

The reaction of arylsulfonylhydrazones, bearing a proton at the β -position, with alkyllithiums affords the corresponding vinylolithium derivatives that can be protonated or used as synthetic



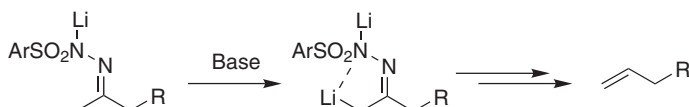
Scheme 58

intermediates. The Shapiro reaction is one of the most powerful methods for regioselective preparation of alkenes via alkenyllithium reagents (Scheme 59—path a). In some cases, reductive alkylation occurs leading to alkanes. This side reaction is observed in particular when $R^2 = \text{H}$ (i.e., for arylsulfonylhydrazones derived from aldehydes) (Scheme 59—path b).



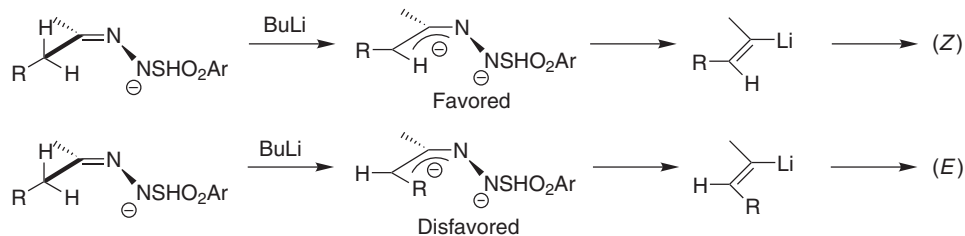
Scheme 59

The Shapiro reaction requires 2 or more equivalents of strong bases such as alkyllithiums or lithium dialkylamides. The mechanism involves the initial formation of a lithiated vinylidene which decomposes to vinyl lithium. The Shapiro reaction works well with cyclic and alicyclic ketones. For unsymmetrical ketones, the regioselectivity of the deprotonation depends on the stereochemistry of the C=N bond in the starting hydrazone, the proton in the *syn*-position to the arylsulfonyl group is preferentially abstracted through chelation with the lithium ion (Scheme 60).

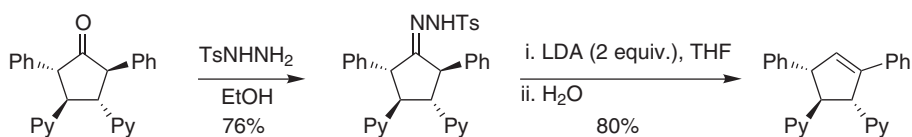


Scheme 60

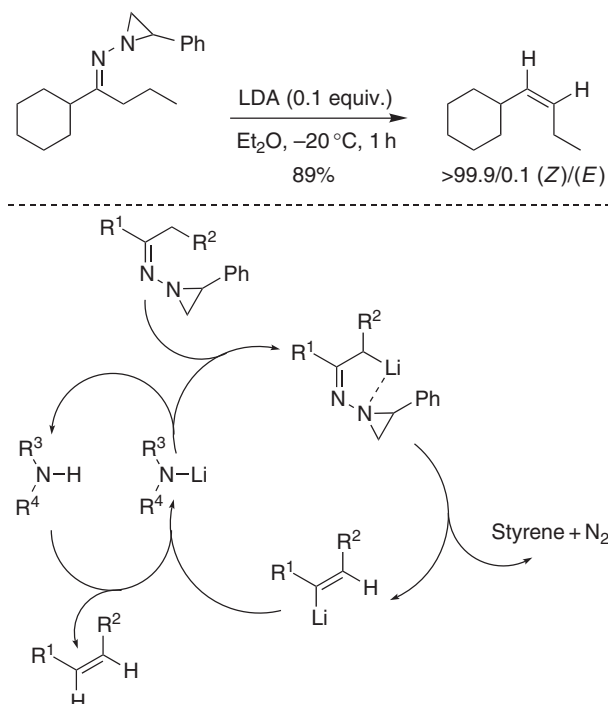
The stereoselectivity of vinyl lithium generation from acyclic arylsulfonylhydrazones has been studied in only a few cases. The Shapiro reaction gives the (*Z*)-alkene as the major product. This result is consistent with the *anti*-position of the α -alkyl group (R) to the hydrazone during dianion formation (Scheme 61).



The Shapiro reaction proceeds in low yield for α,α' -disubstituted substrates because the formation of the dianion intermediate is very slow and substitution at the imino carbon atom competes with elimination. However, when the substituents are phenyl groups, the enhanced acidity of the benzylic hydrogen makes proton abstraction easier and the Shapiro reaction works well, affording the expected elimination product in good yield (Scheme 62) <1997JOC3407>.

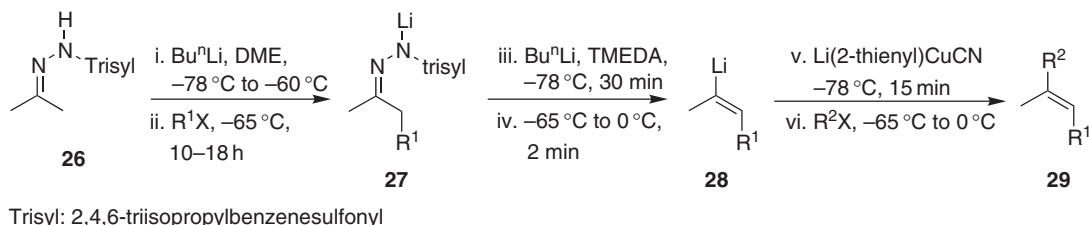


A catalytic version of the Shapiro reaction has been described using a phenylaziridinylhydrazone as arylsulfonylhydrazone equivalent in the presence of 0.1 equiv. of lithium amide; high regioselectivities and stereoselectivities were obtained (Scheme 63) <1996JA2289>.



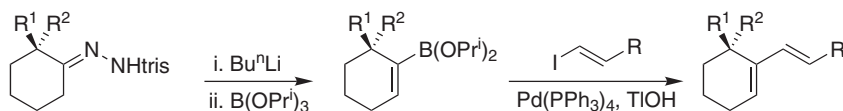
Initially, the Shapiro reaction was used for the formation of simple alkenes by protonation of the intermediate alkenyllithium. Nowadays, major advances in this field exploit the versatility of the vinylolithium intermediates with respect to trapping by electrophiles.

For instance, the Shapiro reaction was applied to the stereoselective synthesis of (*E*)-trisubstituted alkenes by a convergent process: double deprotonation of acetone 2,4,6-triisopropylbenzenesulfonylhydrazone **26** followed by the coupling with R^1X at low temperature produces the hydrazone intermediate **27**. A second deprotonation followed by rapid warm-up at 0°C affords **28** which can be further modified (Scheme 64) <1997TL8915>.



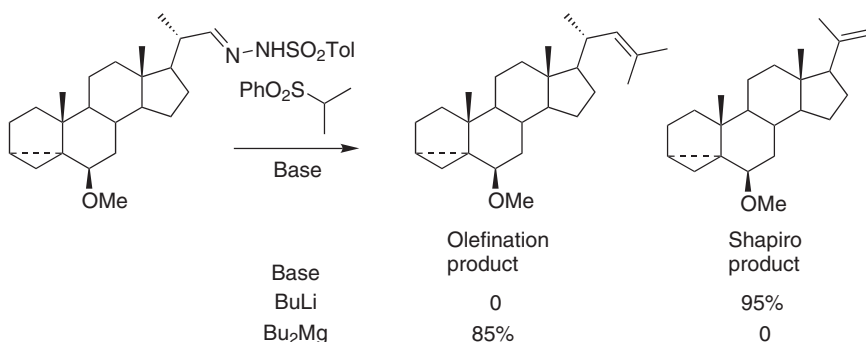
Scheme 64

A one-pot procedure associating the Shapiro and Suzuki reactions was developed for the synthesis of vinyl arenes and conjugated polyenes, including some analogs of retinoic acid. As shown in Scheme 65, treatment of trisyl hydrazones with BuLi at -78°C and warming up to 0°C to give the cyclohexenyllithium was followed by the addition of $B(OPr^i)_3$ to afford the corresponding boronic esters. Then, sequential addition of $Pd(PPh_3)_4$, a vinyl iodide and a base, yielded the coupling product <1996TL429, 1997CJC1163, 2001JOC8483>. A limitation of this procedure is the inefficient generation of cyclohexenyl boronate from α,α' -disubstituted hydrazones.



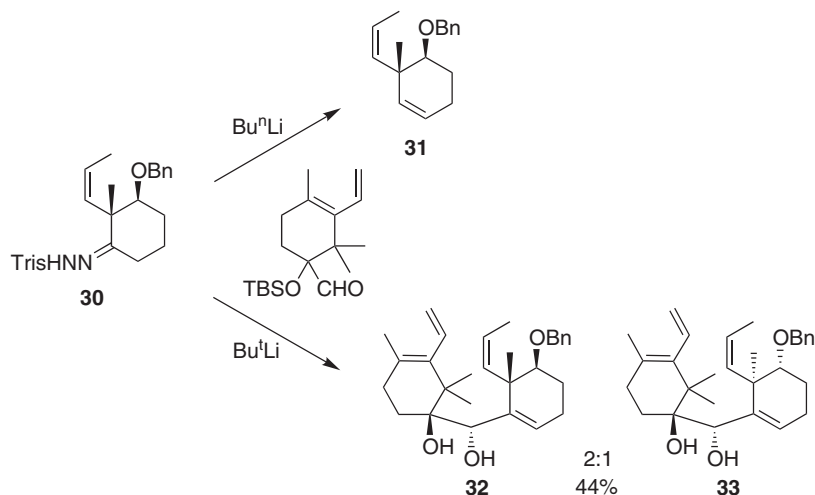
Scheme 65

A useful alternative to the Julia olefination was described involving the reaction between arylsulfonylhydrazones derived from aldehydes and α -metallated sulfones. For example, the reaction of tosylhydrazone with unhindered alkylsulfones in the presence of LDA affords a mixture of (*Z*)/(*E*) olefination products. With hindered alkylsulfones, however, by using butyllithium as a base, the Shapiro products were isolated exclusively. The olefination products could be obtained in good yield by using Bu_2Mg as a base instead of BuLi (Scheme 66) <2000SL547, 2001JOC6994>.



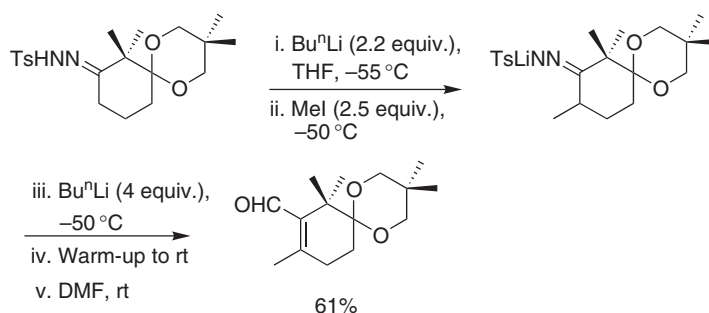
Scheme 66

A synthesis of the C-ring of Taxol based on the coupling between a vinyl lithium intermediate—obtained via a Shapiro reaction—and an aldehyde was described. Using 2 equiv. of BuLi, the alkene **31** was the only isolated product. The problem could be overcome by using Bu^tLi, instead of BuLi (Scheme 67) <1999SL1555>.



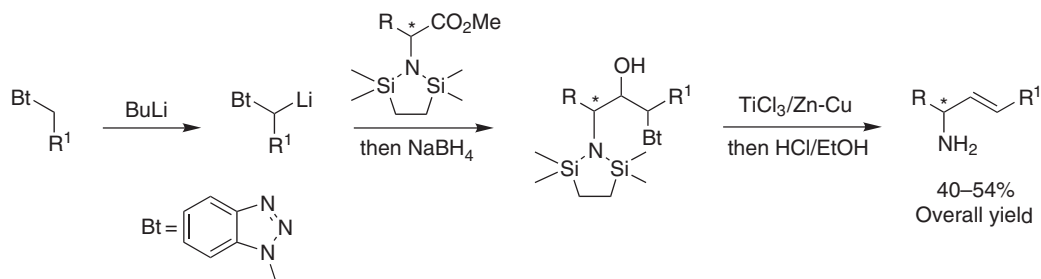
Scheme 67

In the synthesis of the Taxol's A-ring, described by Koskinen and co-workers, the key step is also a Shapiro reaction. Tosylhydrazone gave the best results when compared to other arylsulfonylhydrazones. Scheme 68 proposes a detailed description of the process. The electrophile (DMF) is added immediately when nitrogen evolution has ceased to avoid protonation of the intermediate vinyl lithium by THF <2002T2175>.

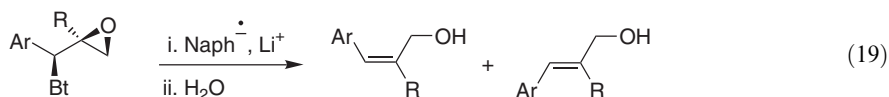


Scheme 68

Nickon and co-workers compared the Shapiro reaction to the thermal and photolytic Bamford–Stevens reactions. The tosylhydrazone derivative prepared in several steps from estrone methyl ether was submitted to different conditions. The Shapiro reaction gave the two alkenes and an unexpected product resulting from ring opening. The Bamford–Stevens reactions (thermal and photolytic) afforded one major alkene in which the proton near the ring oxygen migrates (Scheme 69) <1998T12161>.

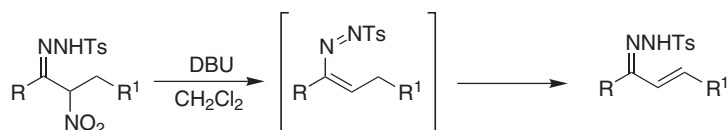


Scheme 70



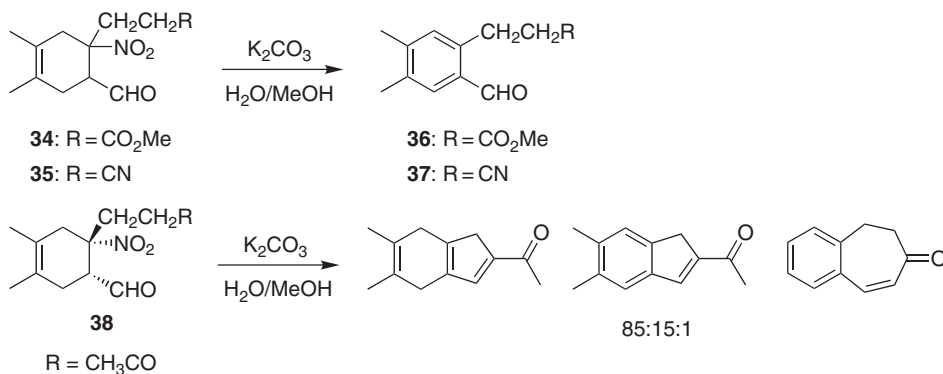
1.14.3.5 Elimination of Nitro Groups

The nitro group is one of the most versatile and useful functional groups in organic synthesis. In particular, it allows the formation of C—C bonds under mild conditions via the Michael and Henry reactions. When β -nitroketones or derivatives thereof are treated under basic conditions, elimination of nitrous acid takes place to give α,β -unsaturated carbonyl compounds. If the nitro group is in the α -position, alkene formation is impossible directly. However, the treatment of α -nitroketone tosylhydrazones with DBU eliminates nitrous acid, affording enone tosylhydrazones exclusively as (*E*)-isomers (Scheme 71) <1995T4173>.



Scheme 71

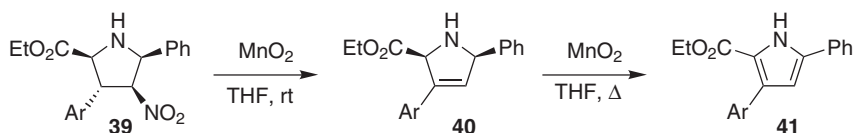
Treatment of nitroaldehydes **34** and **35** (Scheme 72) with aqueous potassium carbonate gave the aromatic derivatives **36** and **37**, respectively. In contrast, under the same conditions, the nitroaldehyde **38** cleanly gave a mixture of compounds resulting from aldol reactions, taking place following nitrous acid elimination and oxidation <2001TL4625>.



Scheme 72

The reductive elimination of tertiary γ -nitro- α,β -unsaturated esters to β,γ -unsaturated esters was described employing Al, Mg, and Zn in methanol. The yields are modest and the best results are obtained using Zn <2001SL857>.

The [2,3]-dipolar cycloaddition of azomethine to nitro-styrenes affords highly substituted pyrrolidines **39**. Oxidative cleavage of the nitro group with MnO_2 at room temperature gives rise to an unsaturated pyrrolidine **40** which could be further oxidized to pyrrole **41** using MnO_2 in refluxing THF (Scheme 73) <1999SL1268, 2000T8545>.

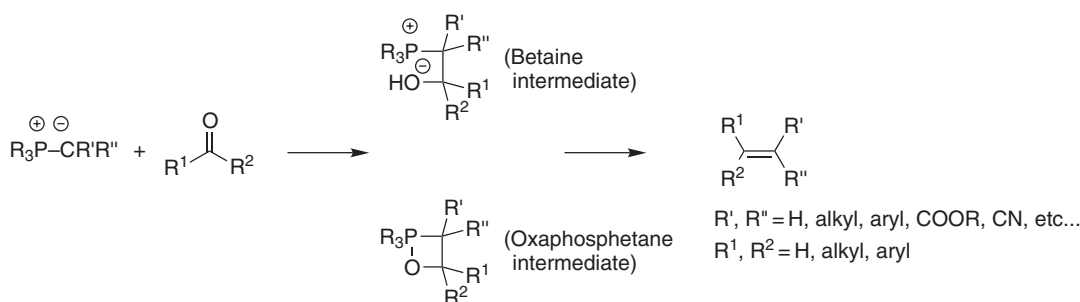


Scheme 73

1.14.4 BY ELIMINATION OF PHOSPHORUS, ARSENIC, ANTIMONY, OR BISMUTH FUNCTIONS

1.14.4.1 Elimination of Phosphorus Groups

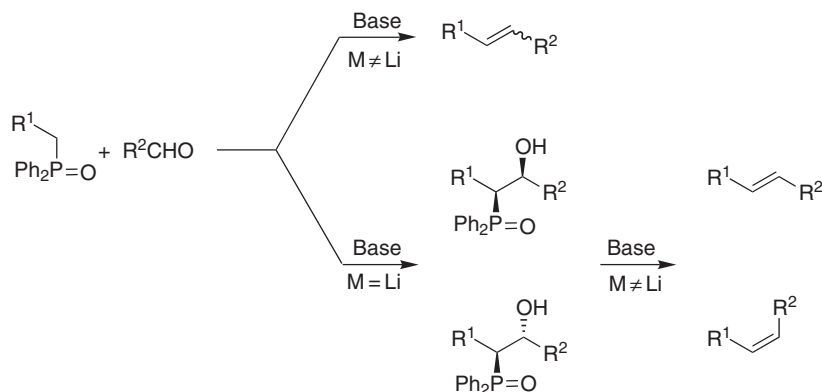
The most widely used method to form C—C double bonds with phosphorus group elimination is the Wittig reaction (and related reactions). The Wittig reaction involves the addition of phosphorus ylides to aldehydes or ketones followed by the elimination of a phosphine oxide and the formation of an alkene. The elimination occurs after the formation of a four-membered oxaphosphetane intermediate or a betaine, depending on the ylide and the conditions used for its formation (Scheme 74). In some cases, oxaphosphetane and betaine intermediates have been observed by dynamic NMR at low temperature <1998JA10653, 1998EJO1085, 2000EJO2601>. Recently a stable oxaphosphetane intermediate was isolated and a crystal structure analysis by X-ray was obtained <2002EJO1143>. In most cases, the Wittig and the related Horner–Wadsworth–Emmons reactions are one-step coupling reactions (the intermediate β -hydroxyphosphonium salts or β -hydroxyphosphonates are not isolated), which are detailed in Chapter 1.16. In contrast, the Wittig–Horner reaction leads to the formation of stable, isolable β -hydroxyphosphane oxides, which can be manipulated in several ways and will be discussed here.



Scheme 74

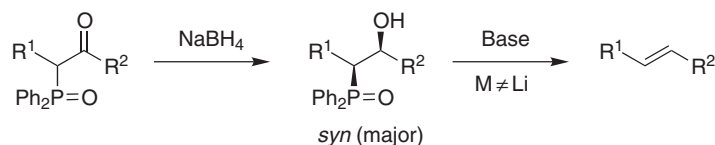
1.14.4.1.1 Elimination of β -hydroxyphosphane oxides and β -hydroxyphosphonates: the Horner–Wittig reaction

With sodium or potassium bases the reaction of metallated phosphane oxides with aldehydes or ketones affords alkenes directly. With lithium bases the reaction stops at the first step, the formation of β -hydroxyphosphane oxides which can be isolated and purified (Scheme 75). The Horner–Wittig elimination from either *syn*- or *anti*- β -hydroxyphosphane oxides is usually carried out with NaH/DMF or KOH/DMSO . The elimination is, in most cases, stereospecific giving pure (*Z*)-alkenes from pure *anti*- β -hydroxyphosphane oxides and pure (*E*)-alkenes from pure *syn*- β -hydroxyphosphane oxides. The Horner–Wittig reaction has been thoroughly studied <1996AG(E)241>.



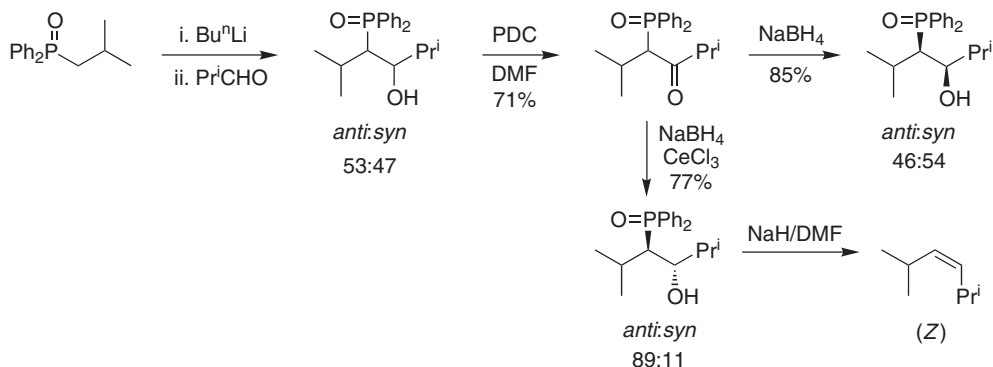
Scheme 75

The Horner–Wittig reaction generally provides predominantly the *anti*- β -hydroxyphosphane oxides, which can be isolated in pure form and in good yield (routinely 60–80%). Therefore, the method is suitable only for the synthesis of (*Z*)-alkenes. In order to prepare (*E*)-alkenes by the Horner–Wittig reaction with acceptable yields, the *syn*- β -hydroxyphosphane oxide must be obtained with a good selectivity. This is usually achieved by reduction (NaBH_4) of β -oxophosphane oxides (Scheme 76), which gives predominantly *syn*- β -hydroxyphosphane oxides. β -Oxophosphane oxides can be obtained either by the oxidation of the original mixture of β -hydroxyphosphane oxides or by the addition of metallated phosphane oxide to acyl chlorides (instead of ketones or aldehydes).



Scheme 76

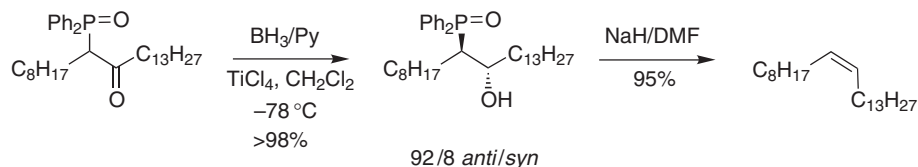
Warren and co-workers reported a general route for the high-yield preparation of branched (*Z*)-alkenes. The Luche reduction of β -oxaphosphane oxides to give *anti*- β -hydroxyphosphane oxides is highly stereoselective and superior to the *anti*-selectivity observed in the Horner–Wittig reaction (Scheme 77) <1995TL7905>.



Scheme 77

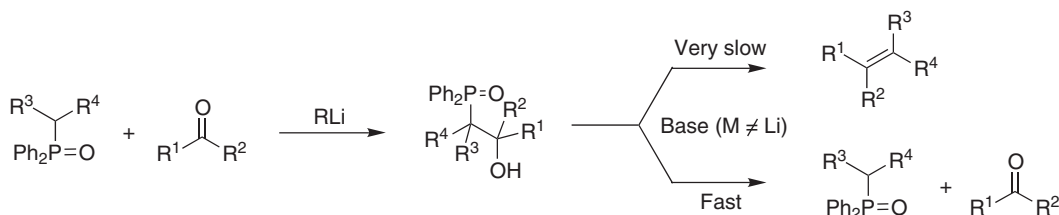
The *anti*-selectivity of the Luche reduction, observed by Warren and co-workers, does not seem to be general, however. In work reported by Bartoli and co-workers, using $\text{LiBH}_4/\text{CeCl}_3$ in THF as the reducing agent, the authors observed in most cases the formation of *syn*- β -hydroxyphosphane oxides. Using BH_3 as a reducing agent and strongly chelating Lewis acids such as TiCl_4 in

dichloromethane, the same authors developed a general and highly efficient methodology for the preparation of *anti*- β -hydroxyphosphane oxides. The method was applied to the total synthesis of stereochemical pure (*Z*)-muscalure (Scheme 78) <1997CEJ1941>.

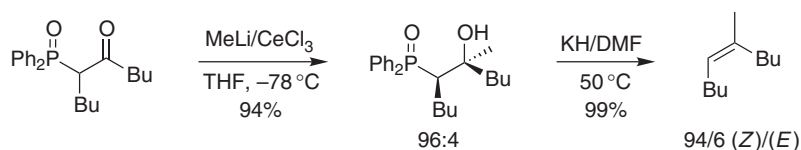


Scheme 78

Trisubstituted or tetrasubstituted alkenes are generally not accessible directly using the classical Horner–Wittig reaction since the intermediate alkoxide undergoes a reverse aldol-type reaction (Scheme 79). However, a useful procedure for preparing trisubstituted alkenes with excellent diastereoselectivity has been described. The addition of RLi–CeCl₃ complexes to β -oxophosphane oxides afforded β -hydroxyphosphane oxides. Treatment of the latter with KH in DMF gave the corresponding alkenes in quantitative yields (Scheme 80) <1995AG(E)2046>.

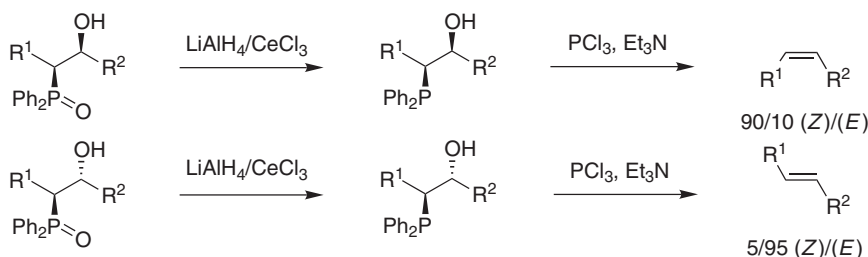


Scheme 79

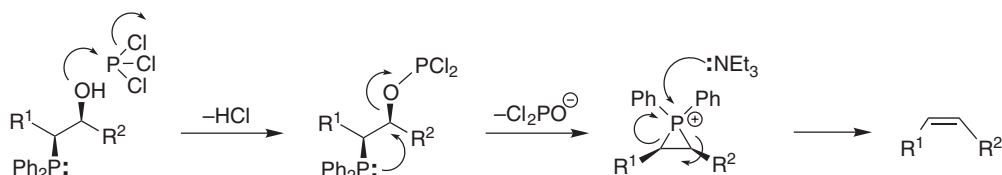


Scheme 80

The classical Horner–Wittig elimination proceeds via a four-membered ring intermediate to yield the alkene. In contrast, the treatment of *anti*- β -hydroxyphosphines and the corresponding *syn*-isomers with PCl₃ and Et₃N gives (*E*)- and (*Z*)-alkenes respectively by an *anti*-elimination (Scheme 81). The reaction proceeds via the formation of an intermediate three-membered cyclic phosphonium salt, followed by extrusion of the phosphorus group induced by triethylamine (Scheme 82) <1998T15345, 1998T15361>.

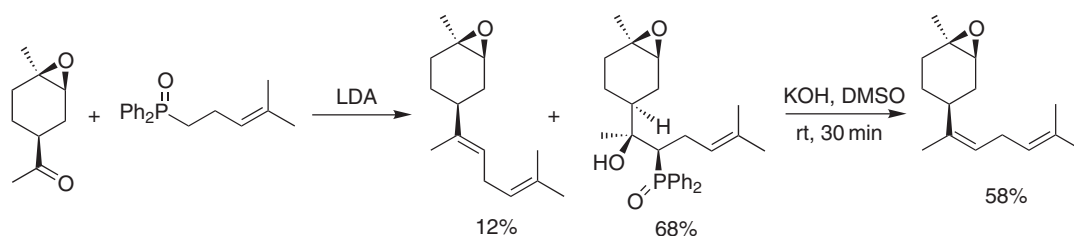


Scheme 81



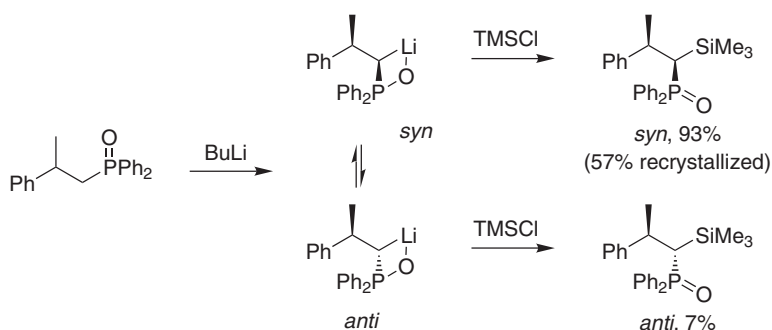
Scheme 82

In most cases, the Horner–Wittig elimination of β -hydroxyphosphane oxides works well by using KOH in DMSO or NaH in DMF as bases. Sometimes, however, these conditions may afford unwanted isomers and degradation products. This was the case during the total synthesis of the *cis*-(*Z*)- and *trans*-(*Z*)-epoxy bisabolenes (Scheme 83), where the use of NaH in DMF resulted in considerable amounts of retro-addition products. The optimal conditions for the elimination were determined to be the addition of powdered KOH to a DMSO solution of the β -hydroxyphosphane oxides at room temperature <2000S269>.

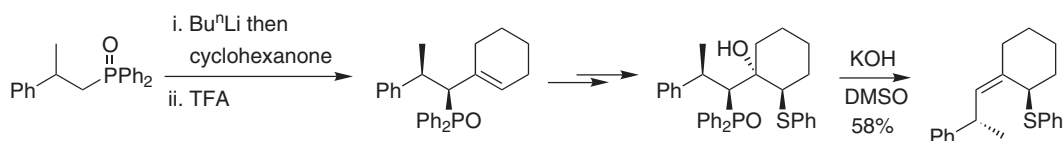


Scheme 83

The Horner–Wittig reaction, in particular the role of the diphenylphosphinoyl group as diastereoselective auxiliary, has been extensively studied by Warren and co-workers. In order to determine the factors which govern the sense and degree of asymmetric induction, the reaction of lithiated chiral phosphine oxides with different electrophiles (Me_3SiCl , MeI , ketones, aldehydes, esters) was examined. The stereoselectivity appeared somewhat variable but *syn*-selectivity predominated in most cases. The authors suggested a dynamic kinetic diastereoselection to explain the results (Scheme 84). The method allowed the stereocontrolled synthesis of 1,4-disubstituted-2-alkenes (Scheme 85) <1998JCS(P1)3405>.

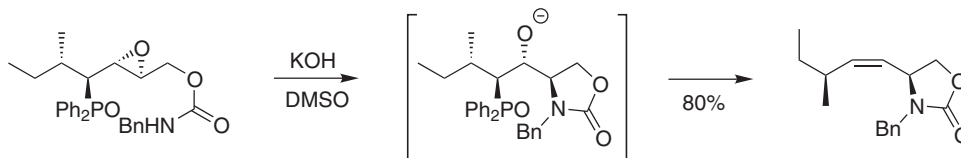


Scheme 84



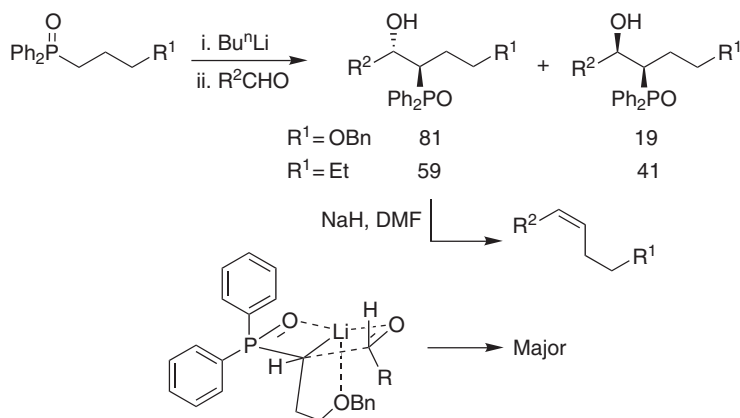
Scheme 85

The treatment of chiral δ -carbamoyloxy- β,γ -epoxy-diphenylphosphine oxides with bases leads to 4-alkenyl-oxazolidin-2-ones resulting from intramolecular nucleophilic attack of the carbamate on the epoxide followed by Horner–Wittig elimination (Scheme 86) <1998JCS(P1)2923>. The starting epoxyurethanes were obtained by kinetic resolution through Sharpless epoxidation of diphenylphosphinoyl allylic alcohols.



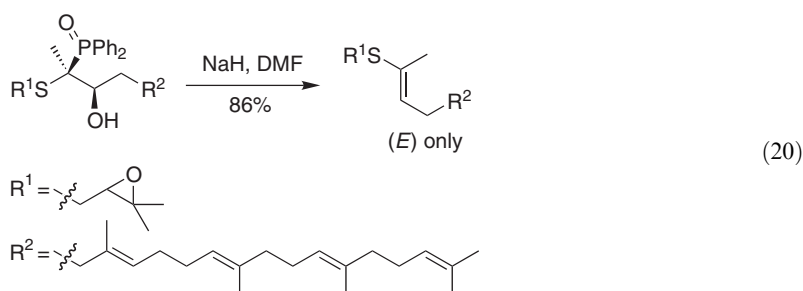
Scheme 86

Synthesis of optically active (*E*)- and (*Z*)-protected homoallylic alcohols was carried out by the addition of phosphine oxides to aldehydes and esters followed by a Wittig–Horner elimination. The reaction of lithiated phosphine oxides with aldehydes afforded β -hydroxyphosphine oxides with moderate-to-good stereoselectivities. The best stereoselectivities were obtained for phosphine oxides featuring a benzyloxy group at the γ -position. These results suggest the formation of a chelate in which the benzyl ether has displaced a solvent molecule from lithium (Scheme 87) <1999JCS(P1)1963>.

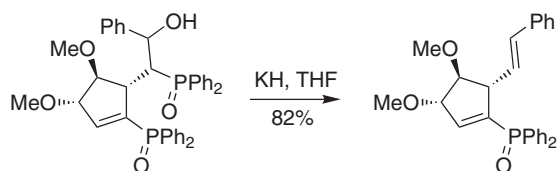


Scheme 87

The Horner–Wittig reaction was also applied to the synthesis of oxidosqualene and analogs. After separation of the two diastereoisomers by chromatography, the *syn*-isomer gives the isomerically pure (*E*)-stereoisomer (Equation (20)) <1995TL5719, 1995T5255>. This reaction was also used to prepare a chiral unsaturated phosphine oxide (Scheme 88) <2002JOC5864>.

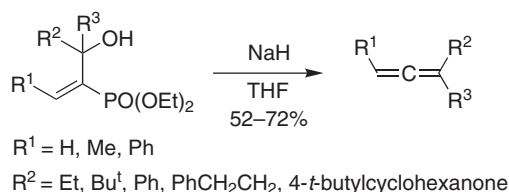


(20)



Scheme 88

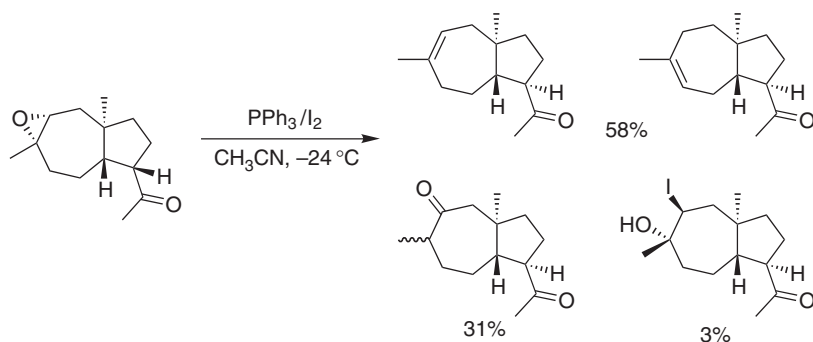
Formation of alkenyl β -hydroxyphosphonates via Baylis–Hillman-type reaction gives versatile intermediates which can be readily converted to allenes by treatment with NaH in THF (Scheme 89) <1998JOC6428>. Dithioallenes, isolated as dimers could also be prepared from phosphonoketene dithioacetals via the Horner–Wittig–Emmons (HWE) reaction and treatment with Bu^tOK in DMF <1996JOC8132>.



Scheme 89

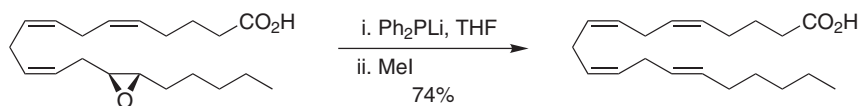
1.14.4.1.2 Via oxirane-opening reactions

A wide variety of nucleophiles can react with epoxides to give β -hydroxy intermediates and in some cases a direct elimination occurs to afford the corresponding alkenes. Epoxides react with triphenylphosphine at elevated temperatures to give alkenes via oxidophosphonium salt intermediates. The sequence alkene epoxidation/opening by triphenylphosphine/elimination results in an inversion of the alkene geometry. In the example shown in Scheme 90, however, where inversion is not possible, oxirane deoxygenation was carried out with PPh₃/I₂ in acetonitrile at low temperature. A mixture of positional isomers of alkenes was isolated along with other compounds <1995T12403>.

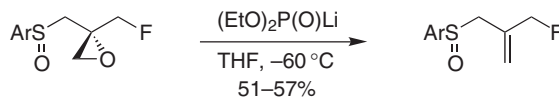


Scheme 90

Stereoselective synthesis of *trans*-arachidonic acid was carried out by the treatment of an epoxide with lithium diphenyl phosphide followed by quaternization with methyl iodide (Scheme 91) <2001BMCL2415>. In the example shown in Scheme 92, addition of lithiated diphenyl phosphite to a 2,2-disubstituted oxirane afforded the corresponding allylic sulfoxide via a four-membered oxaphosphetane ring <1995T8289>.

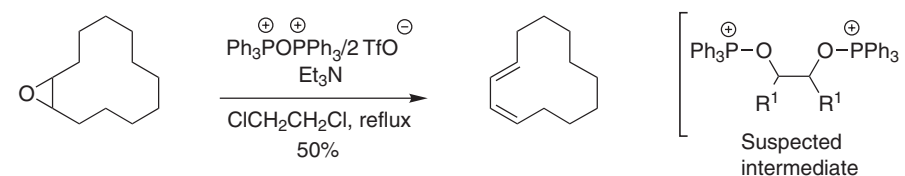


Scheme 91



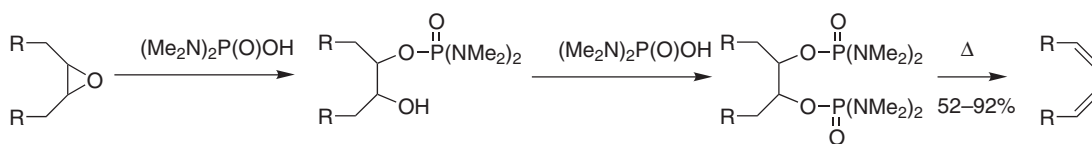
Scheme 92

In 1996, the reaction of triphenylphosphonium anhydride and triethylamine with oxiranes, leading to dienes, was described. A bisphosphonium ether identified by ^{31}P NMR was suspected to be an intermediate in this reaction but the authors were not able to hydrolyze this compound to the corresponding diol, which would have constituted a definite proof (Scheme 93) <1999SL661>.



Scheme 93

Recently, tetramethylphosphordiamidic chloride was used to convert epoxides to dienes. This reaction requires the presence of water to proceed (under anhydrous conditions, only trace amounts of dienes are obtained). In fact, water hydrolyzes the tetramethylphosphordiamidic chloride to the corresponding acid which reacts with epoxides as shown in Scheme 94 <2001T227>.



Scheme 94

1.14.4.2 Elimination of Arsenic, Antimony, and Bismuth Functions

No new references were found between 1995 and 2003.

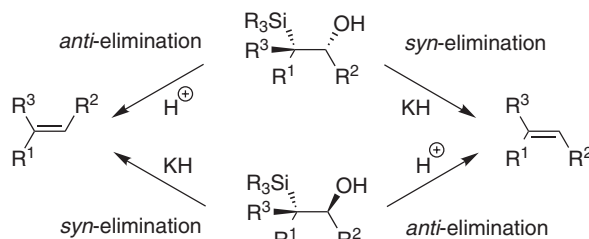
1.14.5 BY ELIMINATION OF SILICON, GERMANIUM, OR BORON FUNCTIONS

1.14.5.1 Elimination of Silicon Groups

β -Elimination in β -substituted organosilanes continues to be an important method for the preparation of alkenes <1995COFGT(1)589>. Besides the well-known elimination of silanols from β -hydroxysilanes (Peterson elimination), other β -substituents suitable for alkene formation include alkoxy or acyloxy groups, halogen, sulfur, and nitrogen.

1.14.5.1.1 Elimination of β -hydroxysilanes and δ -hydroxyallylsilanes

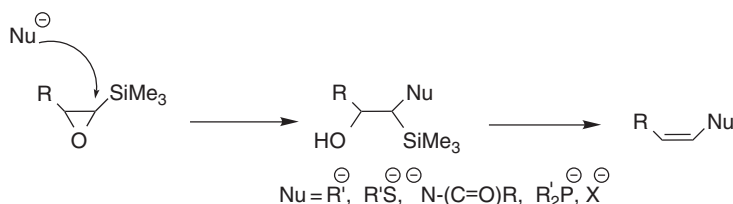
As initially shown [<1968JOC780, 1974TL1133, 1975JA1464>](#), β -hydroxysilanes readily eliminate silanols to afford alkenes (Peterson elimination). The elimination can be carried out under basic or acidic conditions and proceeds in a *syn*- or *anti*-fashion respectively, with almost complete stereoselectivity ([Scheme 95](#)).



Scheme 95

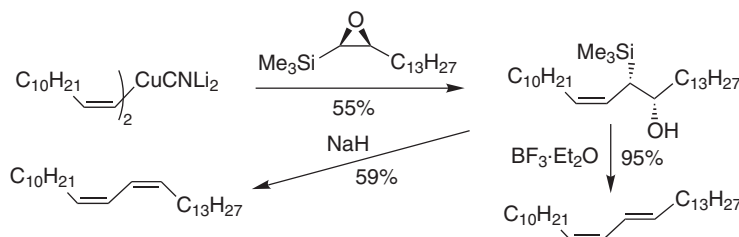
Clean formation of (*E*)- and (*Z*)-alkenes, when possible ($R^2 \neq H$, $R^1 \neq R^3$), will be dictated by the stereochemical purity of the starting β -hydroxysilanes. The latter can be obtained by several methods: condensation of α -silylcarbanions with alicyclic aldehydes or ketones (Peterson olefination) is commonly used for accessing β -hydroxysilanes. This coupling reaction is discussed in Chapter 1.16.

β -Hydroxysilanes can also be conveniently prepared by regioselective nucleophilic opening of α,β -epoxysilanes [<1975JA1464, 1975JA1993, 1992JCS\(P1\)3309>](#). Organocuprates [<1997CCC1457, 1999TA3601, 2000SL1753>](#), phosphides [<1997TL8117>](#), amides [<1999JOC877>](#), thiols [<2000TL1111>](#), and halides [<2001T549>](#) afford α -alkyl-/aryl-, α -phosphino-, α -amido-, α -thio-, and α -halogeno- β -hydroxysilanes which can be converted to the corresponding substituted alkenes, vinyl phosphonium salts, enamides, vinyl sulfides, and vinyl halides, respectively ([Scheme 96](#)).

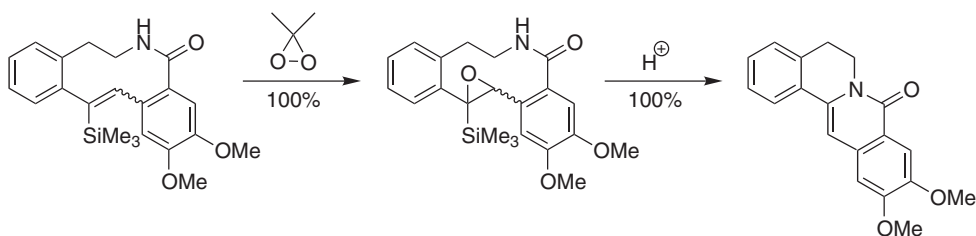


Scheme 96

The method was recently used for the preparation of natural heptacosadienes ([Scheme 97](#)) [<1997CCC1457>](#), and synthetic precursors of isoquinoline alkaloids ([Scheme 98](#)) [<1999JOC877>](#).



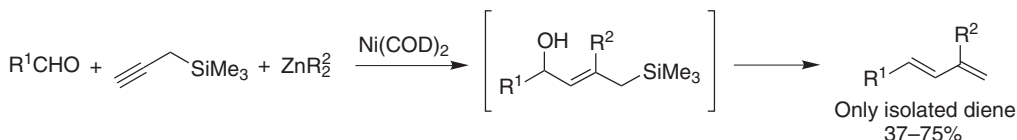
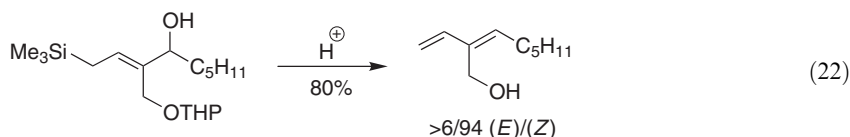
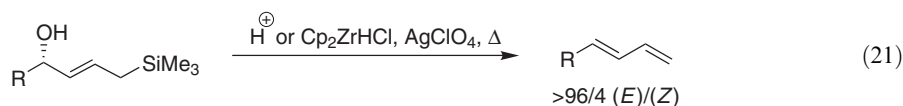
Scheme 97



Scheme 98

Besides the “classical” Peterson elimination, involving β -hydroxysilanes, a vinylogous version was reported earlier [\[1984CC534, 1995COFGT\(1\)589\]](#). In this reaction, 4-trialkylsilyl-2-ene-1-ols undergo base- or acid-induced elimination to afford conjugated dienes. The stereochemical outcome of the reaction has been examined and like its “classical version” the reaction appears to be highly stereoselective.

Under acidic or alkaline conditions, (*Z*)-4-trialkylsilyl-2-ene-1-ols are converted into (*E*)- or (*Z*)-1,3-dienes ([Equation \(21\)](#)) [\[1992TL5969\]](#), ([Equation \(22\)](#)) [\[1996TL7275\]](#). The vinylogous Peterson elimination was a key step in the synthesis of 2,4-disubstituted-1,3-dienes as shown in [Scheme 99](#) [\[1999JOC9310\]](#).

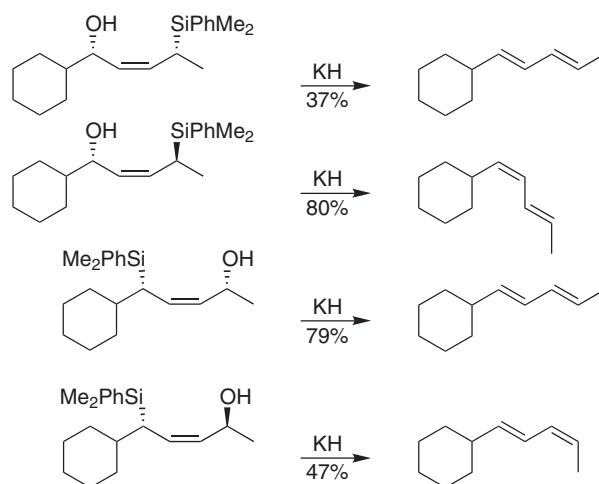


Scheme 99

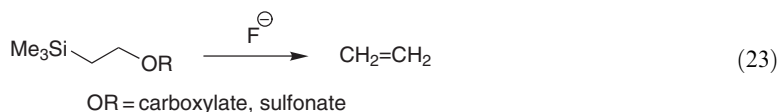
In the base-induced vinylogous Peterson elimination of (*Z*)-4-trialkylsilyl-2-ene-1-ols ([Scheme 100](#)), *syn*- δ -hydroxysilanes afford *trans,trans*-dienes while *anti*- δ -hydroxysilanes provide *cis,trans*-dienes, the newly formed *cis*-double bond being placed at the carbon that previously carried the hydroxy group [\[1998JCS\(P1\)2749\]](#).

1.14.5.1.2 Elimination of β -sulfonyloxy-, β -acyloxy-, and β -alkoxysilanes, and δ -sulfonyloxy-, δ -acyloxy-, and δ -alkoxyallylsilanes

β -Elimination in silanes featuring a leaving-group β to the silicon atom is an alternative to, and in several cases shows distinct advantages over, the Peterson reaction. In particular, the hydroxy group in β -hydroxysilanes can be activated by acylation or sulfonylation, and treatment of the β -sulfonyloxy and β -acyloxysilanes thus obtained with fluoride anion leads to β -elimination ([Equation \(23\)](#)).

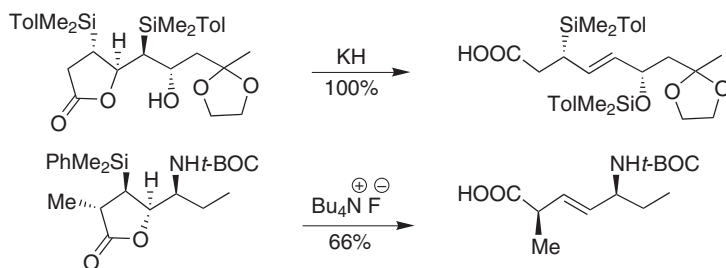


Scheme 100



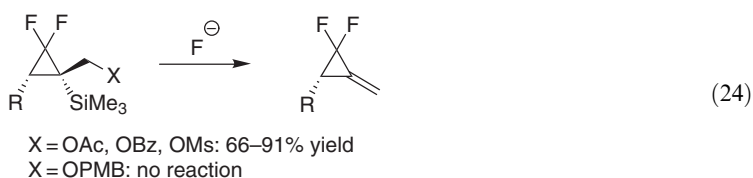
From the mechanistic standpoint the reactions usually proceed in an *anti*-fashion <1995COFGT(1)589>, although deviations from this rule have been observed in several instances <1999T10325>.

Lactones, bearing silyl substituents in the vicinity of the latent hydroxy group, can be opened by treatment with fluoride <1995TL7545> or KH <1998JCS(P1)2733> (Scheme 101) to afford β,γ - or γ,δ -unsaturated carboxylic acids.

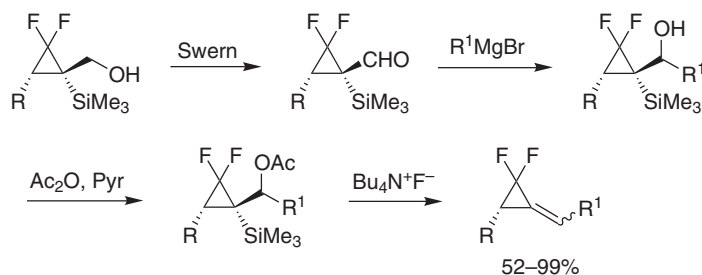


Scheme 101

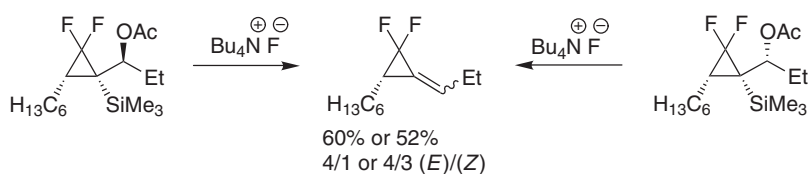
The β -elimination of β -sulfonyloxy- and β -acyloxysilanes allows the preparation of strained systems. This is illustrated in a recently reported preparation of methylenedifluorocyclopropanes (Equation (24)) <1999T10325>. Mesylation or acylation of 3-alkyl-2,2-difluoro-1-hydroxymethyl-1-trimethylsilyl-cyclopropane, followed by fluoride treatment, afforded the corresponding methylenedifluorocyclopropane, whereas silyl ether elimination was ineffective. This contrasts with the successful use of the Peterson reaction for the preparation of nonfluorinated methylenecyclopropanes <1998CRV589>.



The method was successfully extended to the preparation of alkylidenecyclopropanes (Scheme 102). The stereospecificity of the β -elimination was examined using diastereomerically pure substrates and found to be low (Scheme 103).

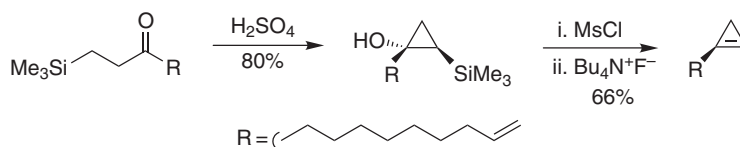


Scheme 102



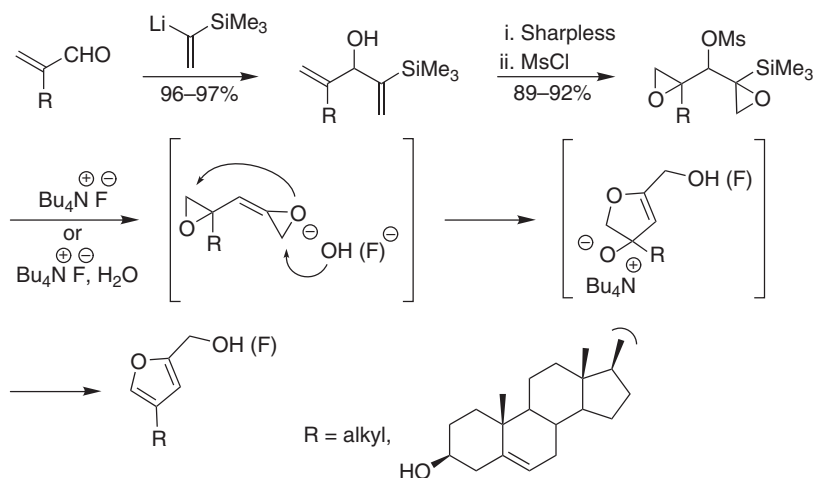
Scheme 103

Acidic treatment of 1-alkyl-2-trimethylsilyl-cyclopropanols gives β -trimethyl silyl ketones while fluoride-induced β -elimination of the corresponding mesylate affords substituted cyclopropanes (Scheme 104) <1999TL2557>.



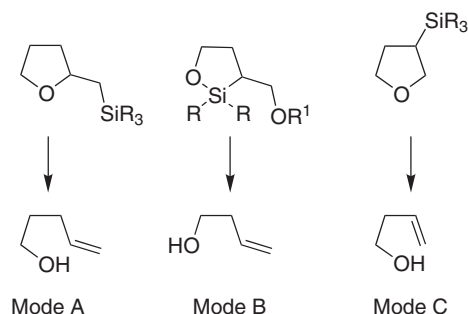
Scheme 104

An elegant preparation of 2,4-disubstituted furans has been developed by Kabat <1996TL7437>. The method relies on a β -elimination of trimethyl silyl mesylate to afford unstable allene oxides, which rearrange to furans. This approach was used for the synthesis of steroidal furans (Scheme 105).



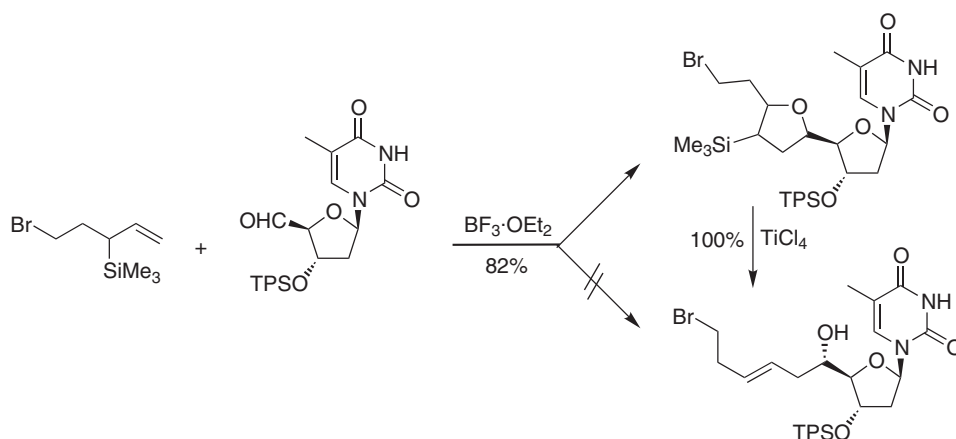
Scheme 105

Double bonds are formed upon exposure of β -alkoxysilanes to Lewis acids as shown in a series of ring-opening reactions affording homoallylic or bishomoallylic alcohols (Scheme 106).

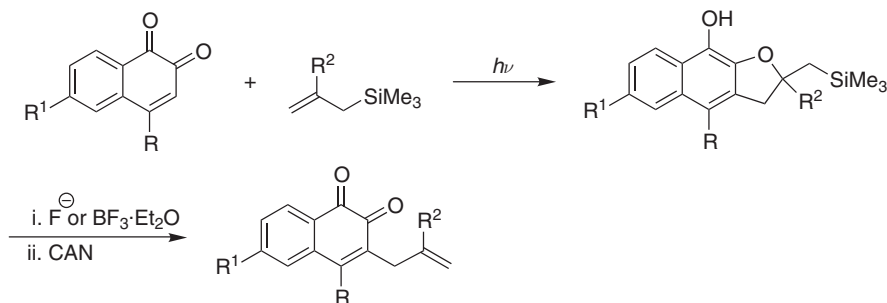


Scheme 106

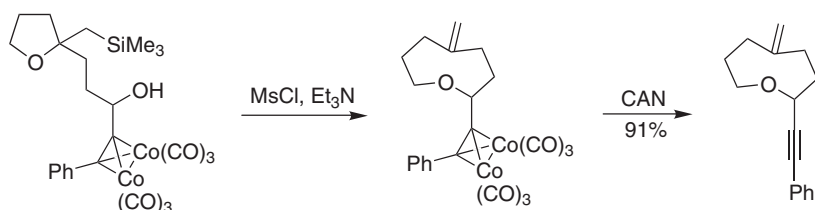
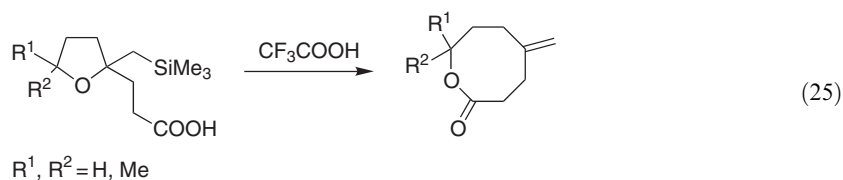
For example, the reaction of substituted allylsilanes with nucleoside-derived aldehydes under Lewis acid catalysis mainly afforded 3-silyl-substituted tetrahydrofurans which could be converted to the originally expected homoallylic alcohols upon treatment with TiCl_4 according to a mode C fragmentation (Scheme 107) <1999T5831>. Similarly, the cycloadducts obtained by photochemical [2+3]-cycloaddition of allylsilanes to 1,2-naphthoquinones suffer fluoride ion- or Lewis acid-induced fragmentation leading, after oxidative treatment, to allylated *o*-naphthoquinones (Scheme 108) <2001S63>. Mode A fragmentation was used for the synthesis of eight-membered lactones (Equation (25)) <1999SL1757>, or eight-membered cyclic ethers (Scheme 109) <2000T2203>. Finally, an example of mode B elimination leading to homoallylic silyl ethers was recently reported (Equation (26)) <2001JOC1966>.



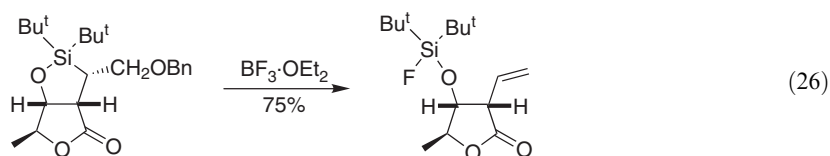
Scheme 107



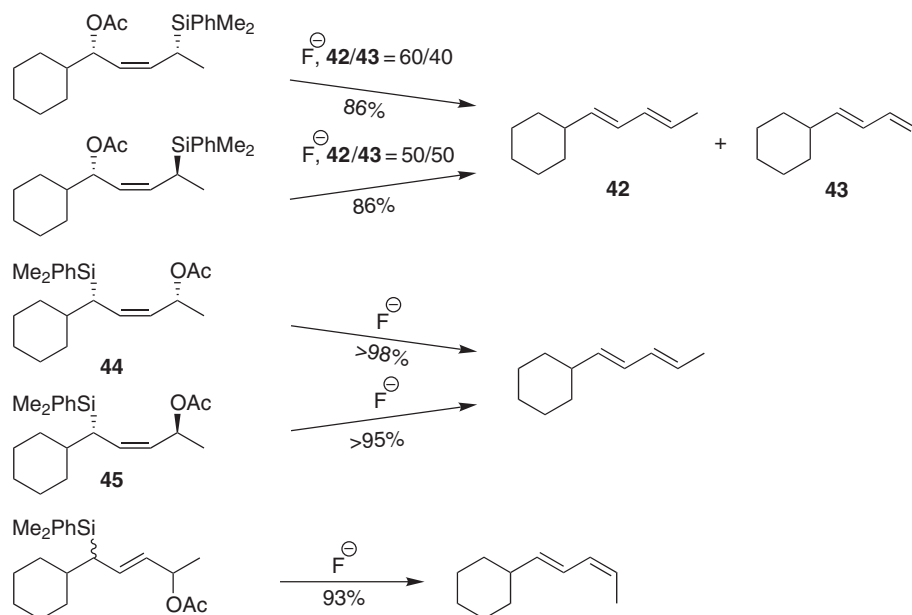
Scheme 108



Scheme 109



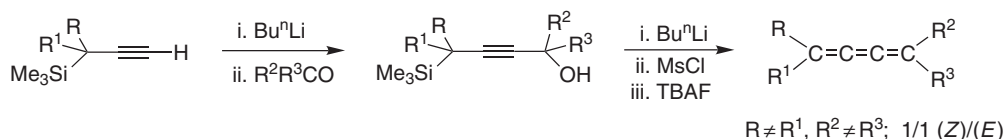
Vinylogous versions of β -acyloxy-, β -sulfonyloxy-, and β -alkoxysilane eliminations have been reported. Acetates derived from (*E*)- and (*Z*)-4-trialkylsilyl-2-ene-1-ols lead to dienes upon treatment with fluoride anion (Scheme 110) <1998JCS(P1)2749>. The stereoselectivity of



Scheme 110

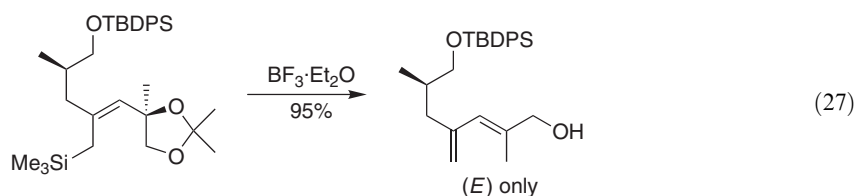
these eliminations differs from that observed for the vinylogous Peterson elimination of the corresponding free alcohols (see [Scheme 100](#)). In some cases the reactions are highly stereoselective affording ((*E*),(*E*))- or ((*Z*),(*E*))-dienes depending on the stereochemistry (*Z*) or (*E*) of the olefinic double bond in the starting material while in other, apparently very similar cases, essentially no stereoselectivity is observed. The factors that govern the degree of selectivity of these reactions are unclear.

A preparation of [3]cumulenes based upon the elimination of 4-(trimethylsilyl)-2-butyne-1-ol mesylates has been reported. While yields are generally good, the reaction is not stereoselective and, when applicable, (*Z*)- and (*E*)-isomers are formed in a 1:1 ratio ([Scheme 111](#)) [<1995JOC1885>](#).

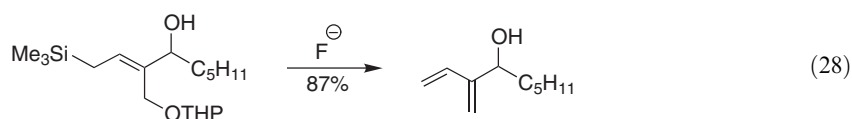


Scheme 111

Elimination of 4-(trimethylsilyl)-2-buten-1-yl ethers can be effected by Lewis acids or fluorides. The method was used in a synthesis of (+)-Prelog–Djerassi lactonic acid ([Equation \(27\)](#)) [<1998T11567>](#). Remarkably, the reaction proceeded in a highly stereoselective fashion to afford exclusively an (*E*)-diene in excellent yield.

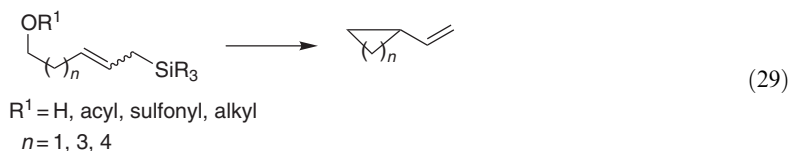


Besides the Lewis acid-induced elimination of silanol (a vinylogous Peterson elimination) mentioned earlier [<1996TL7275>](#) (see [Equation \(22\)](#)), treatment of the THP-monoprotected allylic diol shown in [Equation \(28\)](#) with fluoride leads to the elimination of the OTHP group to furnish a 2-hydroxyalkyl-1,3-butadiene. Therefore, both 1,3-butadienes having an α -hydroxyalkyl moiety at the 2-position and 1,3-alkadienes having a hydroxymethyl group at the 3-position can be obtained from the same intermediate depending on the elimination conditions (compare [Equations \(22\)](#) and [\(28\)](#)).

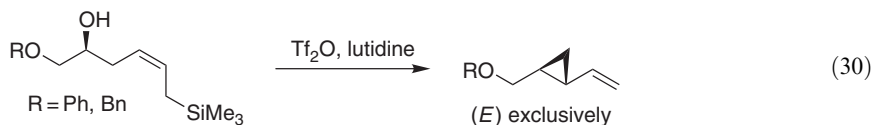


1.14.5.1.3 Long-range elimination of hydroxy-, sulfonyloxy-, acyloxy-, and alkoxyallylsilanes

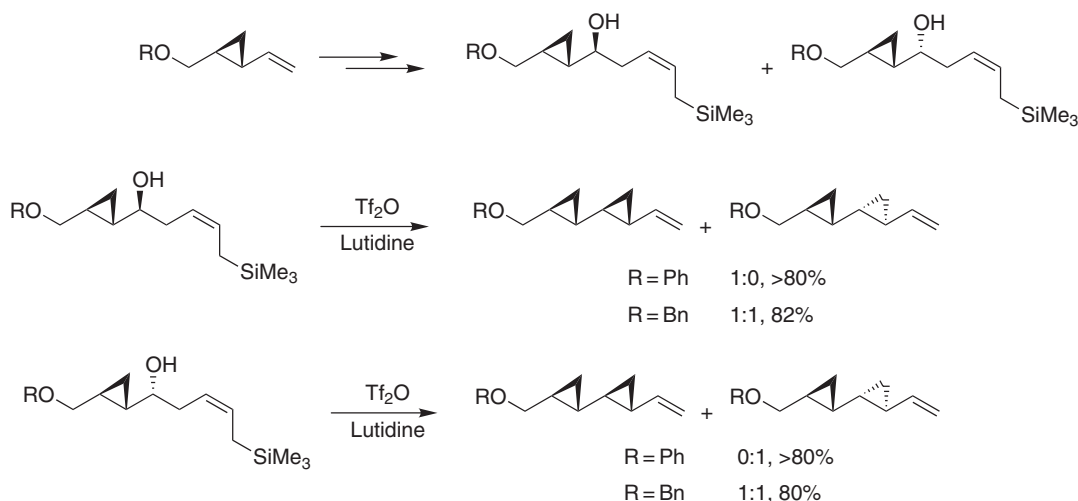
Elimination of silanols from hydroxyallylsilanes or derivatives with concomitant formation of an olefinic double bond and a carbocycle according to [Equation \(29\)](#) have been described previously [<1991T7689, 1989TL4845, 1984CC585>](#).



Accordingly, elimination of ε -sulfonyloxyallylsilanes has been used for the preparation of *trans*-vinylcyclopropanes (Equation (30)) <1997TL2057, 1999OL1257>.

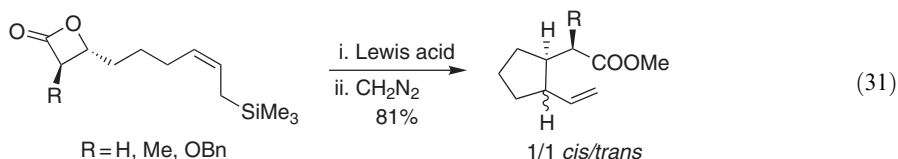


An iterative version of this method was examined as a stereocontrolled approach to oligo-cyclopropane systems as found in certain natural, biologically active compounds <1997TL2057, 1999OL1257>. As shown in Scheme 112, in this study, the outcome of the reaction depends on the nature of the OR group, phenyl ethers leading to the formation of single products whereas benzyl ethers afforded 1:1 mixtures of diastereoisomers.



Scheme 112

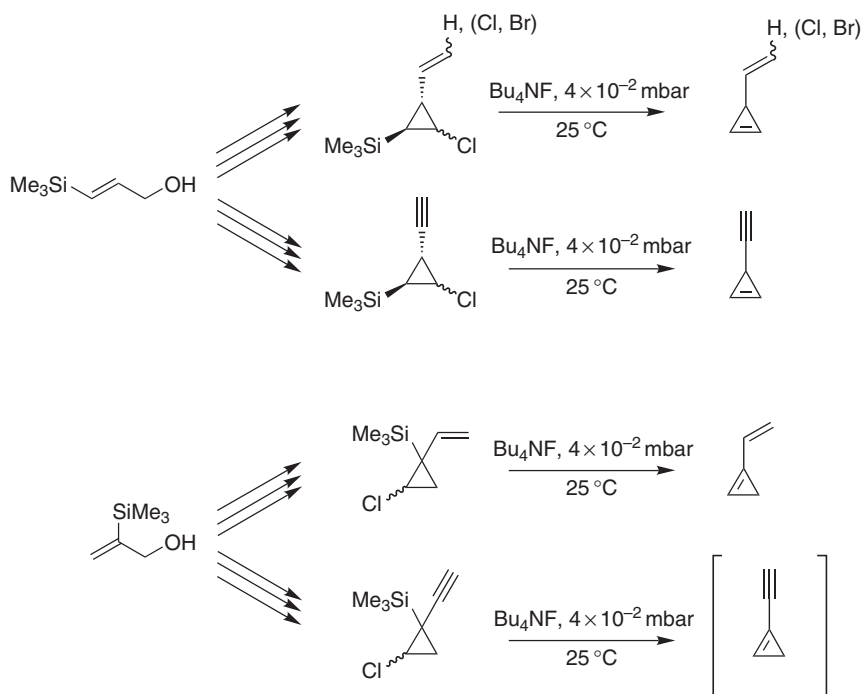
Finally, recent applications of the general process shown in Equation (29) to the preparation of vinyl cyclopentanes have been published (Equation (31)) <1997TL6537>. Here again, the stereo-selectivity of the reaction depends on the nature of the R group, nonsubstituted β -lactams (R = H) leading to nonstereoselective reactions.



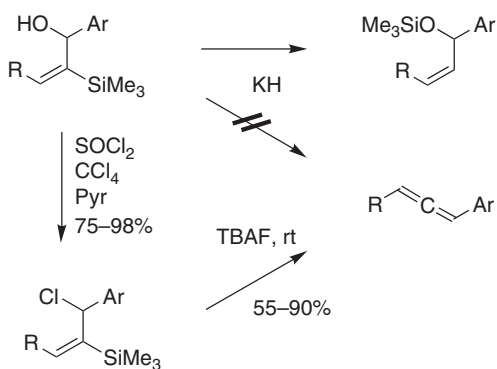
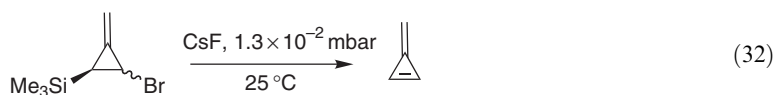
1.14.5.1.4 Elimination of β -halosilanes

β -Halosilanes which can be prepared in various ways are useful synthetic intermediates for the synthesis of strained alkenes <1995COFGT(1)589>. They have been used recently for the preparation of unstable alkenyl- or alkynylcyclopropanes (Scheme 113) <1995TL3457>, methylenecyclopropane (Equation (32)) <1997TL1115>, and allenes (Scheme 114)

<2001TL2605>. In the latter case, a more classical Peterson olefination was attempted with limited success.

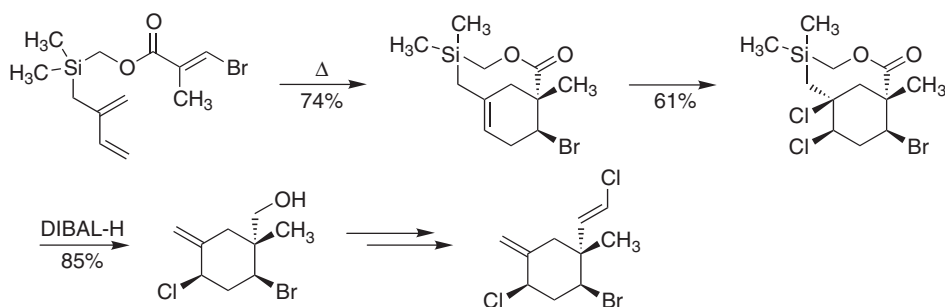


Scheme 113



Scheme 114

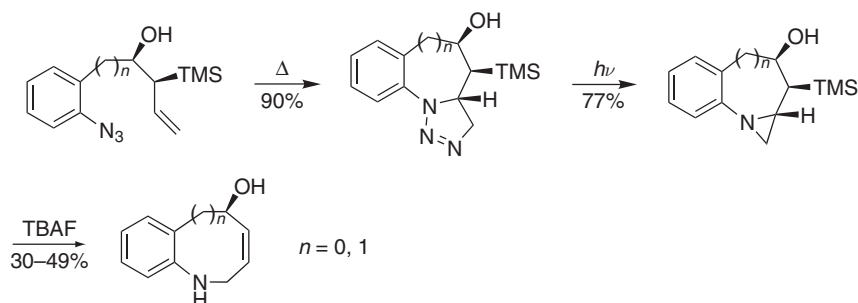
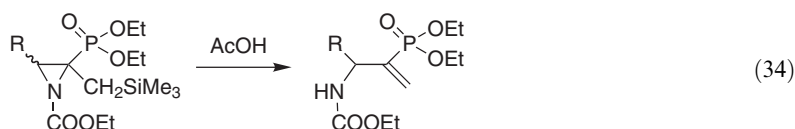
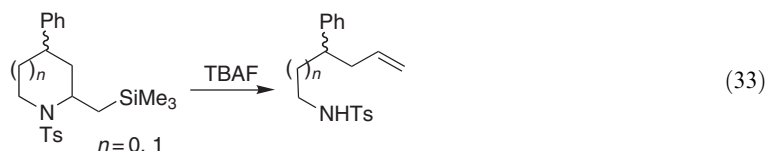
β -Halosilane elimination was used in an elegant synthesis of a naturally occurring, halogenated monoterpene (Scheme 115) <1997JOC8962>. The synthesis involved the use of a silicon tether for the Diels–Alder cycloaddition, the chlorination of the resulting allylsilane, and the removal of the tether with concomitant formation of the required methylene group via β -halosilane elimination.



Scheme 115

1.14.5.1.5 Elimination of β -aminosilanes

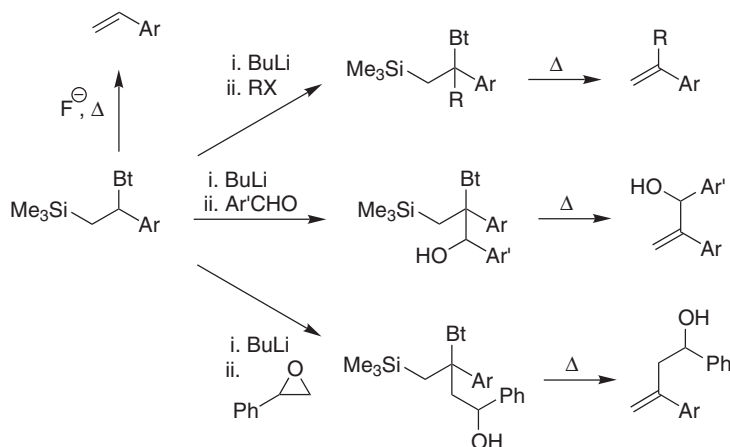
Amides and sulfonamides featuring a β -silyl group readily eliminate upon fluoride treatment to afford olefinic double bonds. The reaction has been applied to the fragmentation of piperidines and pyrrolidines (Equation (33)) <1996TL8493, 2001CC958, 1999TL3873> and aziridines (Equation (34)) <2001T4423>. A new method for the preparation of medium-ring nitrogen heterocycles, involving aziridine fragmentation/ring expansion was recently described. The fused aziridines were prepared via intramolecular [2 + 3]-dipolar cycloaddition of azides (Scheme 116) <2001TL9175>.



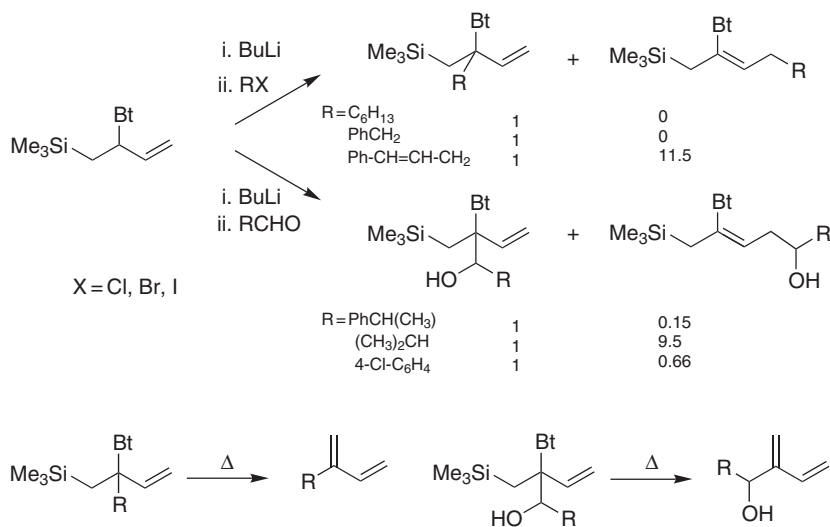
Scheme 116

The 2-benzotriazolyl group behaves both as an activating group toward α -proton abstraction and as a good leaving group for β -elimination. This versatility was exploited in a new preparation of styrenes (Scheme 117) <1997JA9321> and 2-alkyl-substituted 1,3-butadienes (Scheme 118) <1999JOC1888>. A drawback of the latter procedure is the ambident character of the intermediate anion. Whereas the method works well for linear alkyl halides and aldehydes, cinnamyl bromide and hindered aldehydes react with poor regioselectivity resulting in mixtures of α - and γ -substituted products (Scheme 118).

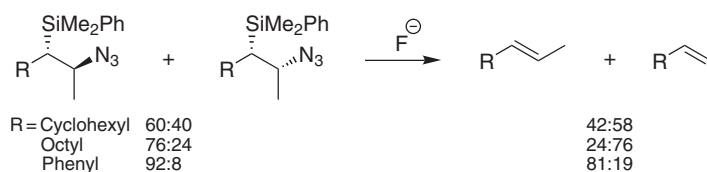
The conversion of β -azido-silanes to alkenes (Scheme 119) <2002OL4253, 2002OL4257> has also been reported. The mechanism of the silylazide elimination was found to vary depending on the substrate used. Whereas aliphatic substituents led to the expected *E2* elimination, an *E1cb* mechanism was suggested for aryl substituents <2002OL4253>.



Scheme 117



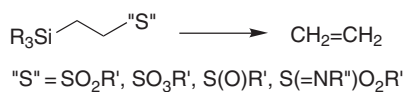
Scheme 118



Scheme 119

1.14.5.1.6 Elimination of sulfur-containing leaving groups

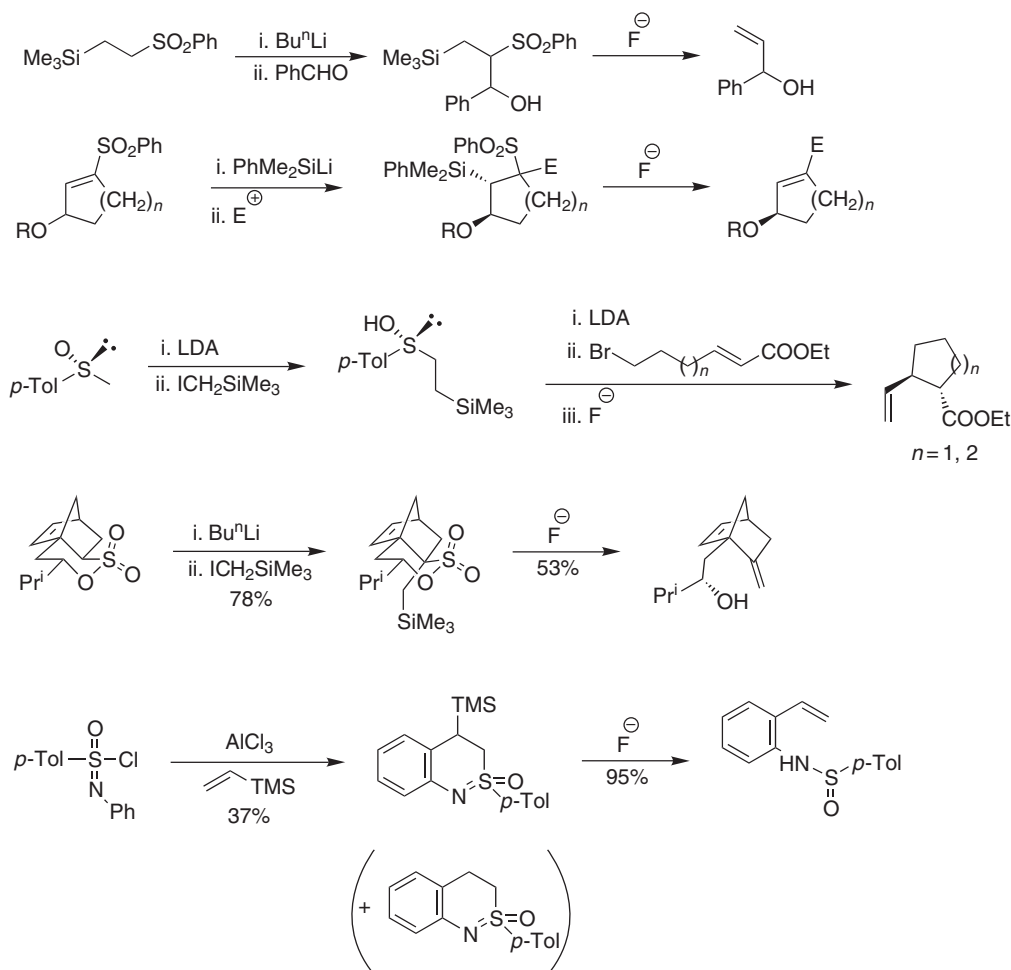
Numerous eliminations in silanes featuring β -sulfur-containing leaving groups are known and have been used for the preparation of alkenes (Equation (35)) <2002TL2381, 1999T2245, 1996TL3841, 2002TL2967, 1995TL4013, 1995TL4769, 1998T9995>.



(35)

The β -sulfur-substituted silanes are prepared by a variety of methods including α -alkylation of sulfones, sulfonates/sultones, sulfonimides, or sulfoxides with R_3SiCH_2X ($X = I, Cl$) <2002TL2967, 1996TL3841, 1999T2245, 1997SL449>, 1,4-addition of R_3SiLi (or derived cuprate) to vinylsulfones <1995TL4013>, or the reaction of *N*-phenylsulfonimidoyl chloride with trimethylsilylethene <1995TL4769, 1998T9995>. The β -sulfur-substituted silanes thus obtained can be deprotonated again, then further functionalized.

Examples of alkene formation by the elimination of silanes featuring a β -sulfur-containing leaving group and the preparation of the latter are shown in Scheme 120.



Scheme 120

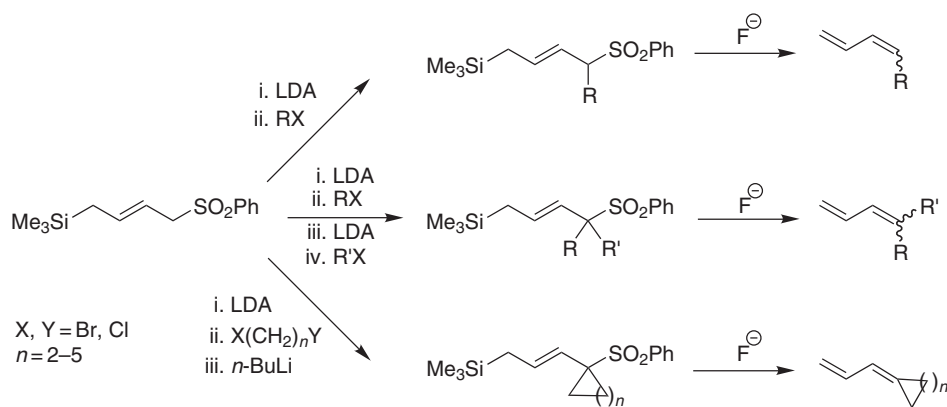
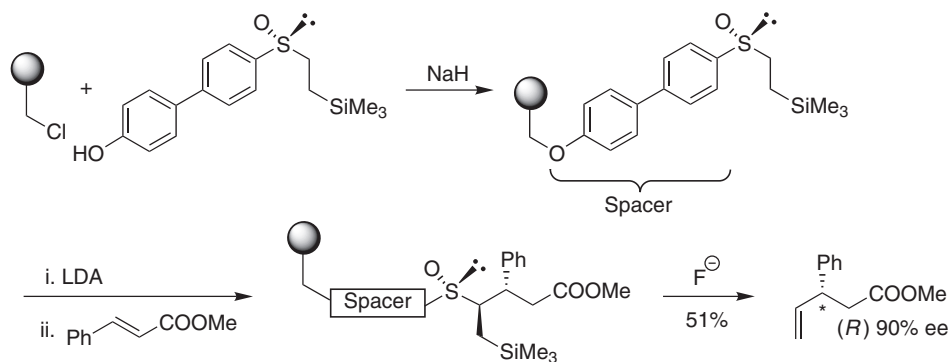
Chiral β -silylsulfoxides have been proposed as new, easily cleaved linkers for solid-phase synthesis (Scheme 121) <2002TL2381>.

Vinylogous equivalents of the above reactions have been described. Thus, fluoride treatment of 1-(phenylsulfonyl)-4-(trimethylsilyl)-2-butenes has been used for preparing a wide variety of substituted butadienes (Scheme 122) <1998JOC4181, 1998JOC4193>.

1.14.5.1.7 Other eliminations of silanes

Besides the widely used reactions of β -substituted silanes mentioned above, there is a number of less common reactions of silanes leading to alkene formation.

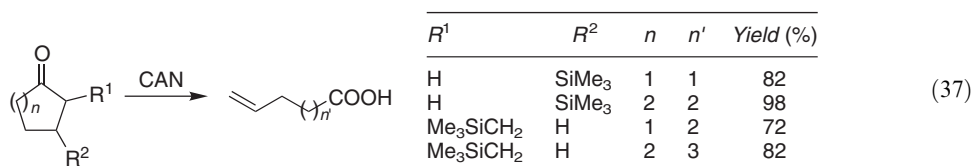
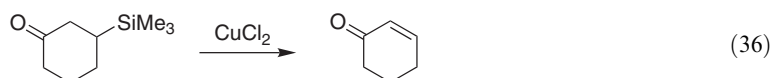
From β -trimethyl silyl ketones, alkenes can be obtained in three ways.



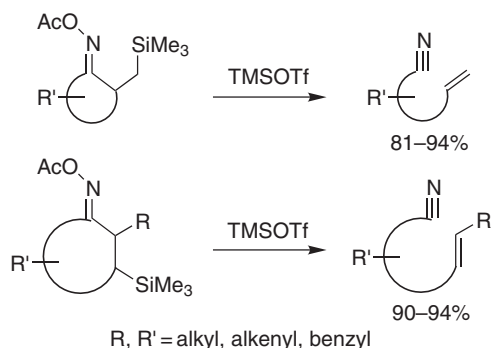
(i) Treatment with CuCl_2 affords α,β -unsaturated ketones (Equation (36)) <1988T4757, 1996TA263>.

(ii) Treatment with CAN induces an oxidative fragmentation leading to ω -alkenylcarboxylic acids (Equation (37)) <2000JA5899>. The excellent regioselectivity of this fragmentation is attributed to the stabilization by the β -silyl group of the radical and cation successively formed during the oxidation. Attempts to apply the CAN-induced fragmentation to the related β -trialkyl stannyl ketones led to formal β -elimination of trialkyltin hydride and formation of conjugated ketones. Successful oxidative fragmentations of β -trialkyl stannyl ketones are discussed in Section 1.14.6.1.2.

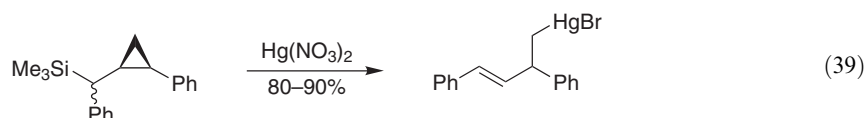
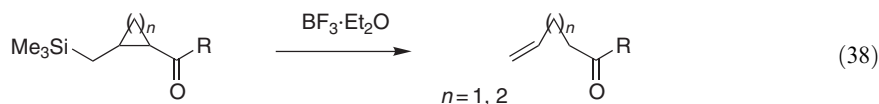
(iii) Conversion of cyclic β -trimethyl silyl ketones to the corresponding β -trimethyl silyl ketoximes and acidic treatment (or, in some cases, fluoride treatment) of the latter leads to a silicon-directed Beckmann fragmentation and constitutes an excellent approach to a variety of alkenyl nitriles (Scheme 123) <1983TL4021, 1984TL223, 1988T2413>.



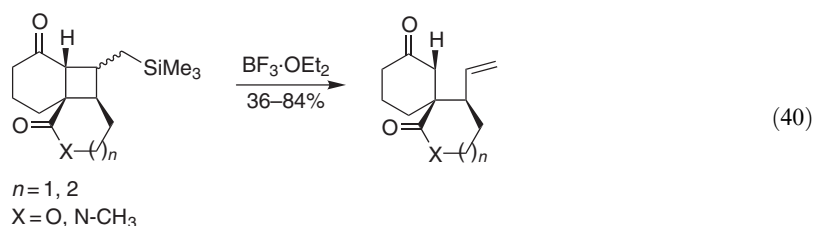
β -Silyl, strained cyclic systems fragment upon Lewis acid treatment (Equation (38)) <1983CPB3931, 1981CC460>, (Equation (39)) <1996TL1209>.



Scheme 123

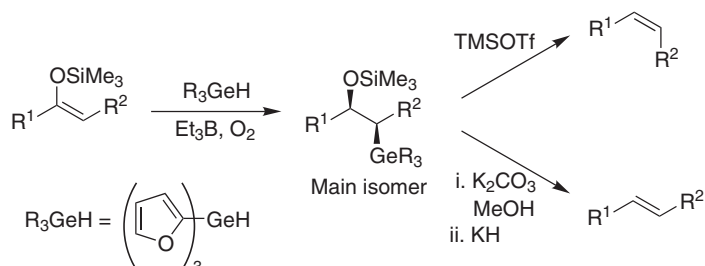


Fragmentation of cyclobutyl ketones was recently used for the synthesis of vinylspirolactones and lactams (Equation (40)) <1999TL6001>.



1.14.5.2 Elimination of Germanium Groups

Germanes bearing leaving groups at the β -position eliminate in a way similar to β -substituted silanes <1995COFGT(1)589>. In particular, 1,2-elimination of β -hydroxy or β -siloxygermanes is analogous to that of β -hydroxysilanes <1994JOC491>. Coupled with the facile radical-mediated hydrogermylation of silyl enol ethers, the reaction was used for the conversion of silyl enol ethers to alkenes (Scheme 124) <2000OL1911>. The elimination is highly stereoselective, following the same rules as the classical Peterson elimination.

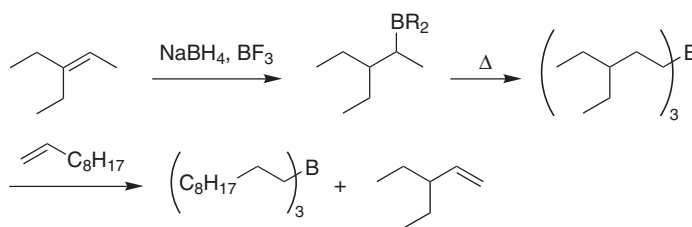


Scheme 124

1.14.5.3 Elimination of Boron Functions

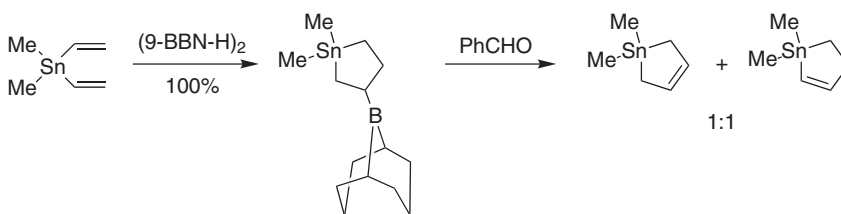
1.14.5.3.1 Elimination of alkylboranes

Alkenes are always formed in conjunction with alcohols upon reduction of ketones/aldehydes by trialkylboranes. For example, reductions with β -(3-pinanyl)-9-borabicyclo[3.3.1]nonane release 3-pinene <1995COFGT(1)589>. The reaction is concerted for aldehydes and acetylenic ketones while a two-step mechanism (the first step being a thermal elimination of 9-BBN) is operative in the other cases <1982JOC1606>. Synthetically, however, the reaction has seldom been used for the purpose of alkene formation. An exception is alkene isomerization via the sequence hydroboration/isomerization/borane elimination in which internal alkenes are converted to their terminal isomers (Scheme 125) <1995COFGT(1)589>.



Scheme 125

Upon attempted hydroboration of divinyltin, an unusual cyclization was observed, leading to a 3-borylstannacyclopentane. Treatment of the latter with benzaldehyde produced a mixture of allyl and vinylstannacycles (Scheme 126) <1998TL2511>.



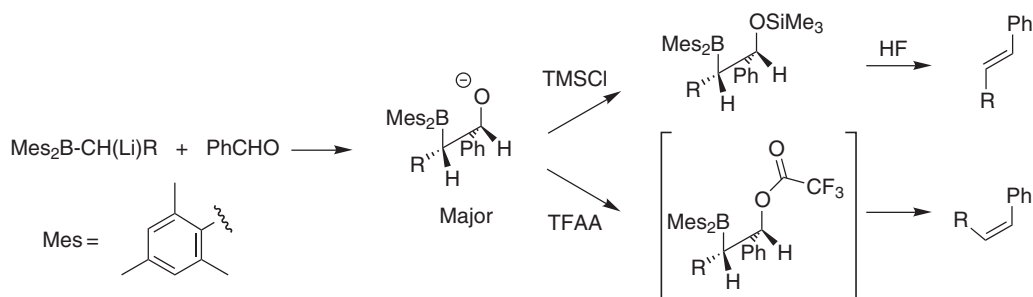
Scheme 126

1.14.5.3.2 Elimination of β -substituted alkylboranes

Elimination of alkylboranes bearing a β -heteroatom to produce alkenes bears some similarities with the elimination of β -substituted silanes. Until now, however, its use in synthetic chemistry has remained limited when compared with its silicon counterpart. The chemistry of boranes substituted with a β -heteroatom has been summarized in the previous edition of this book <1995COFGT(1)589> and several recent reviews are available <1993T7077, 1994PAC223>.

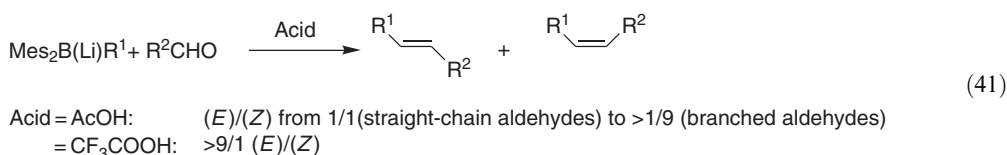
In contrast to the poorly stereoselective addition of α -lithiated silanes to aldehydes (Peterson reaction), the addition of hindered α -lithiated boranes to aromatic aldehydes affords mostly *erythro* β -hydroxyboranes <1993T2965, 1995JA6142>. Subsequent stereospecific *anti*-elimination of the corresponding trimethylsilyl ether under acidic conditions leads to (*E*)-alkenes. The corresponding trifluoroacetates, obtained by trapping of the intermediate lithium alkoxide with trifluoroacetic anhydride eliminate spontaneously to afford mixtures of (*Z*)- and (*E*)-alkenes in which the former isomer predominates (Scheme 127) <1993T7077, 1994PAC223>.

Finally, an example of thermolysis of β -siloxyalkylboronates, giving exclusively a (*Z*)-alkene has been reported <1995CL1107>.

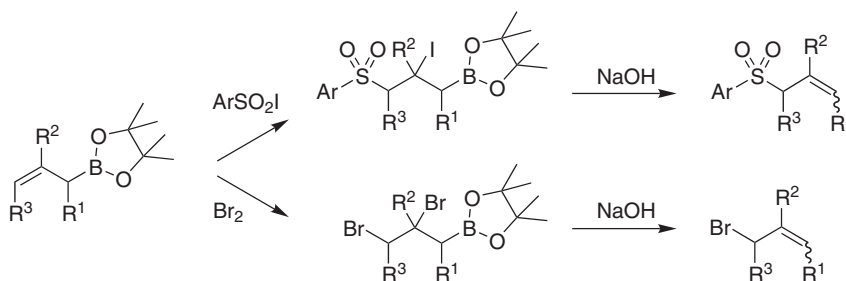


Scheme 127

Aliphatic aldehydes also react with hindered borane anions in the presence of acids leading to mixtures of (*Z*)- and (*E*)-alkenes whose composition depends on the nature of the starting aldehyde and acid used. The reaction, performed in the presence of strong acids, favors the formation of (*E*)-isomers (Equation (41)) <1993T7119>.



Addition of *p*-toluenesulfonyl iodide or bromine across the olefinic double bond of allylborationates, followed by base-induced elimination, produced allylic sulfones or allylic bromides respectively (Scheme 128) <1991SL267>.



Scheme 128

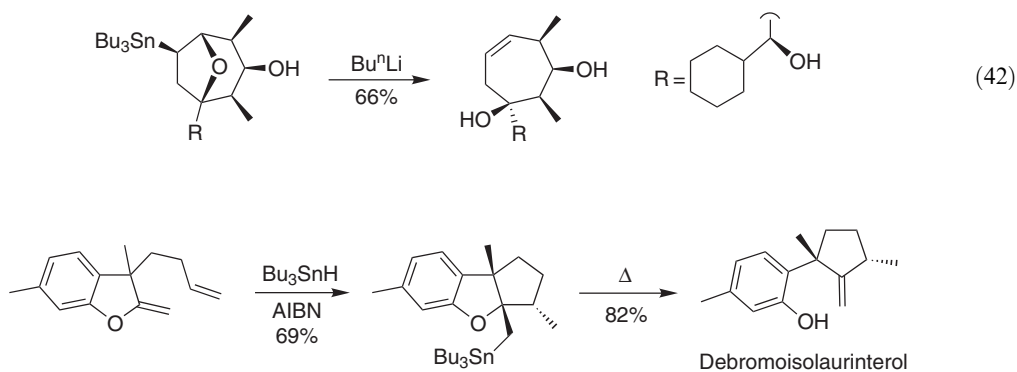
1.14.6 BY ELIMINATION OF METAL FUNCTIONS

1.14.6.1 Elimination of Tin

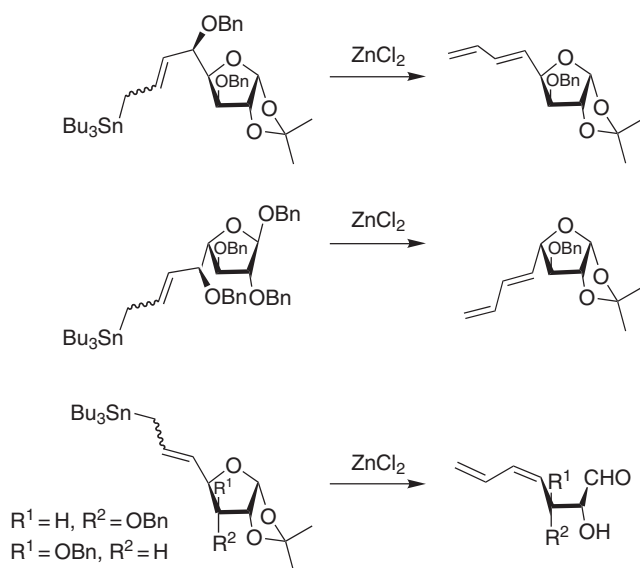
1.14.6.1.1 Elimination of β -hydroxystannanes, derived ethers and esters

The reaction of trialkyl- or triarylstannyl alkylolithiums with aldehydes followed by the elimination of hydroxystannane (tin-Peterson reaction) <1982AG(E)410> resembles the classical silicon-based Peterson reaction. Only the second step is stereoselective and follows an *anti* (via acidic treatment) or *syn* (via thermolysis) mechanism <2001TL8993, 1982CB1818>. β -Hydroxystannanes may also be obtained by the opening of epoxides with trialkylstannylolithiums <1995COFGT(1)589>.

Elimination of β -alkoxystannanes (or of the vinylogous 1-alkoxy-4-trialkylstannyl-alk-2-enes) can be effected under a variety of conditions: by tin-lithium exchange (Equation (42)) <1996JA10930>, thermally (Scheme 129) <2001T791>, or by Lewis acid catalysis <2000TA1997>.



The vinylogous version of the β -alkoxystannane elimination was used for the preparation of carbohydrate-derived conjugated *trans*-1,4-dienes (Scheme 130) <2000TA1997>.

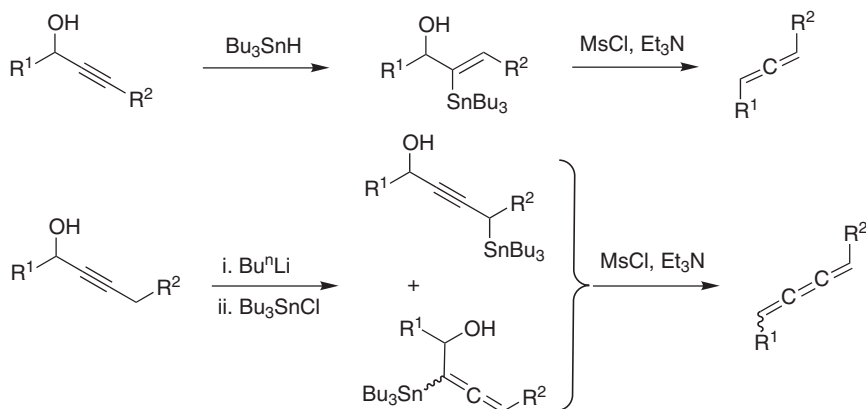


Other useful leaving groups for stannane elimination include mesylates and esters. The method was used for the synthesis of allenes <1992TL5093> and [3]cumulenes (Scheme 131) <1998TL5549>. Elimination of β -mesylates and β -esters was shown to be *anti* by examining the relationship between the chiral allenes and the starting chiral stannyl allylic alcohols (Scheme 132) <1992TL5093>.

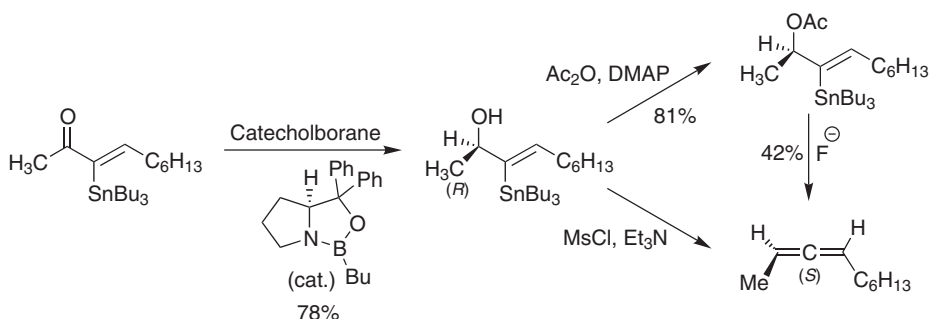
1.14.6.1.2 Other eliminations of stannanes

1,4-Addition of the trialkyltin group to activated olefinic double bonds can be achieved using $R_3SnH/AIBN$, or stannyl cuprates. Upon appropriate treatment, the resulting stannane will eliminate to generate an alkene.

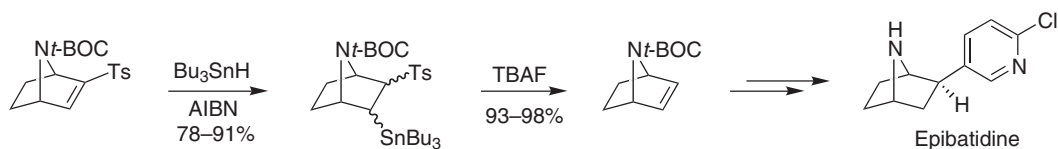
Following this protocol, sequential addition of tributyltin hydride to α,β -unsaturated sulfones and treatment of the resulting β -stannyl sulfones by TBAF has been developed as a good method for the desulfonylation of sulfonyl alkenes (Scheme 133) <1998TL5321>.



Scheme 131



Scheme 132



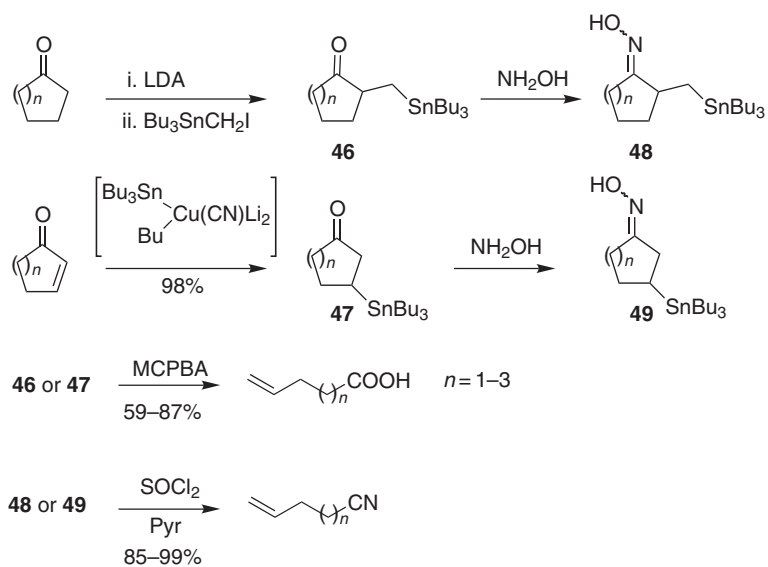
Scheme 133

When applied to cyclic precursors, the tin-directed Bayer–Villiger oxidation of β -tributylstannyl ketones and Beckmann fragmentation of β -tributylstannyl oximes affords unsaturated carboxylic acids and nitriles respectively, obtained in good-to-excellent yields [<1990JA6729, 1993JOC7185, 1995TL43>](#). The stannyl moiety was introduced either by 1,4-addition of stannyl cuprates to α,β -unsaturated ketones or by quenching ketone enolates by trimethylstannyl methyl iodide ([Scheme 134](#)).

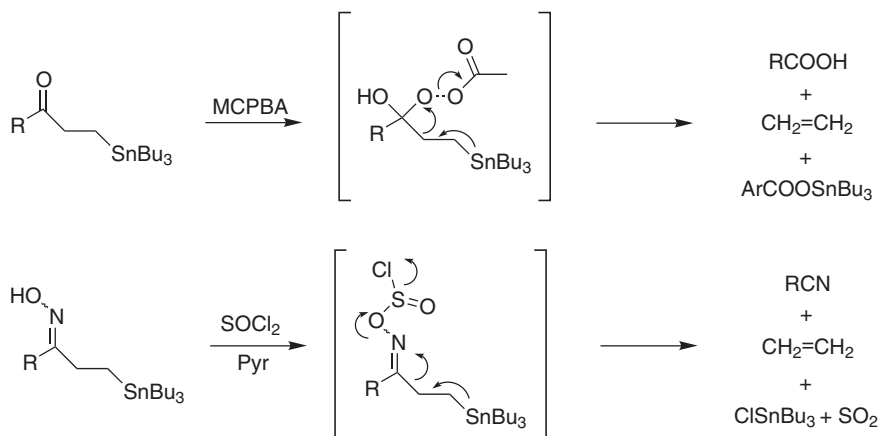
The fragmentations do not involve intermediates typical of normal Bayer–Villiger reactions (lactones). Lactams or amides, the products of classical Beckmann rearrangements were also not observed. The mechanisms are likely to be concerted, the carbonyl (hydroxylamine) function behaving as a leaving group ([Scheme 135](#)).

The closely related fragmentation of β -hydroxystannanes under oxidative conditions generates in good yield alkenes and ketones when the starting material is an alcohol [<1984CC1007, 1985TL2209>](#), or lactones if the starting material is a cyclic hemiketal [<1987CL133, 1994JOC6395, 1995SL543>](#), as summarized in [Scheme 136](#).

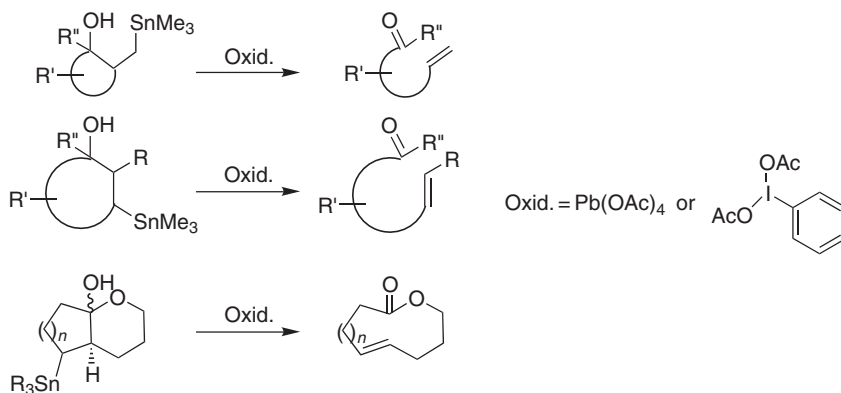
Since their discovery in 1984 and 1987 respectively, the above methodologies have been well exploited. For example, the method was used recently for a ring expansion of conjugated cycloalkenones to homoallylic lactones ([Scheme 137](#)) [<2000TL9655>](#).



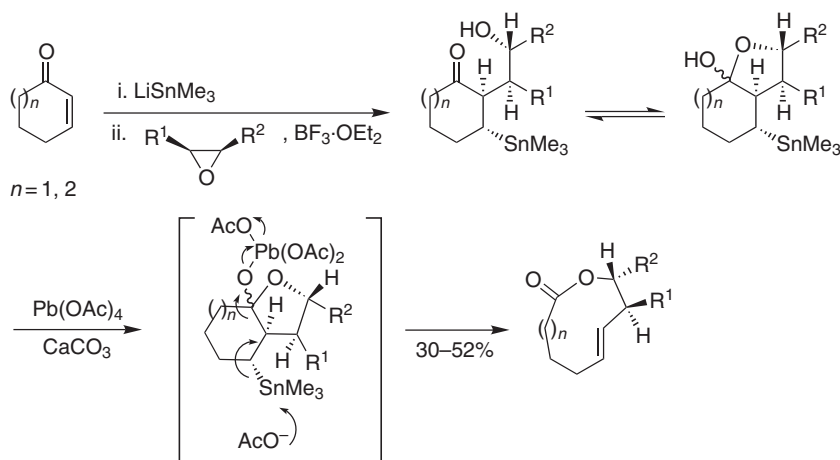
Scheme 134



Scheme 135



Scheme 136

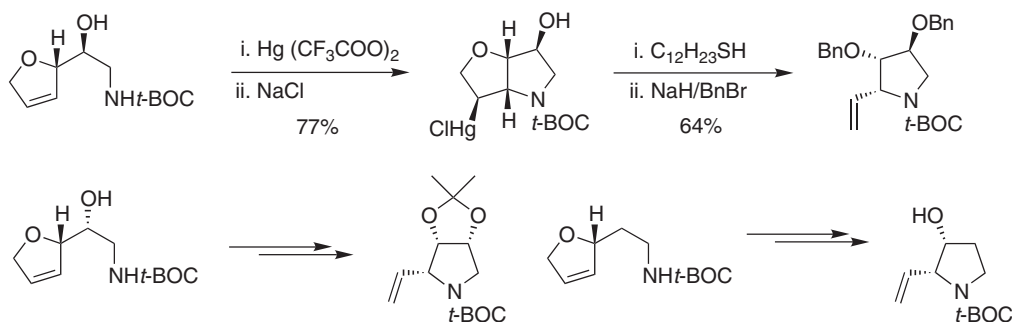


Scheme 137

The scope of this approach was briefly examined. Generally, 1-substituted epoxides are good substrates (an exception is styrene oxide). 1,2-Dimethyloxirane and cyclohexene oxide are also suitable reagents whereas cyclopentene oxide and cycloheptene oxide do not react.

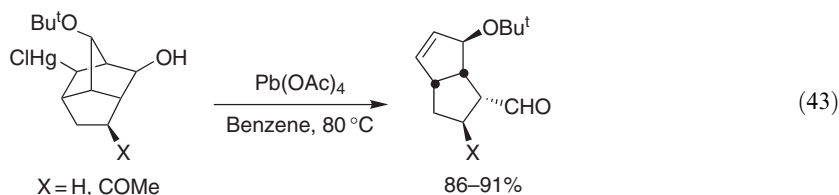
1.14.6.2 Elimination of Mercury

Beta-heterosubstituted organomercurials eliminate under a variety of conditions to afford the corresponding olefinic double bond. Combined with intramolecular amidomercuration the reaction allows the synthesis of sugar-derived vinyl pyrrolidines (Scheme 138) <1995TL8127, 1997S1415, 2001JOC4787>.



Scheme 138

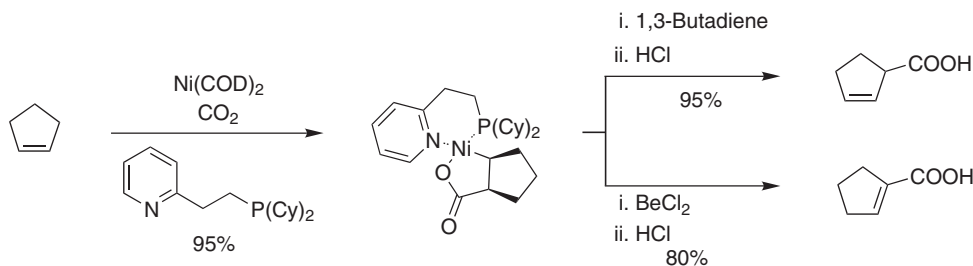
Fragmentation of β -hydroxy organomercurials under oxidative conditions, analogous to that reported earlier for β -hydroxy stannanes, has also been described. The method was used for accessing the diquinane skeleton (Equation (43)) <1998S537>.



1.14.6.3 Elimination of Transition Metals

In this section only “true” β -eliminations whose aim is solely to create an olefinic double bond and not β -eliminations leading to nonisolated intermediates are discussed. For example, the β -hydride eliminations, which are part of the catalytic cycle in coupling reactions, cyclizations, cycloisomerizations catalyzed by weakly electropositive transition metals (e.g., Pd, Rh, Ru) are not considered. There have been occasional reports, however, of β -H elimination induced in isolated organometallic complexes, which may be interesting for synthetic chemists. Representative examples are given below.

Treatment of cyclopentene with Ni(COD)_2 , in the presence of a ligand and under CO_2 atmosphere, affords stable Ni^{II} complexes from which cyclopentene carboxylic acids are obtained by β -hydride elimination (Scheme 139) <1991S395>.

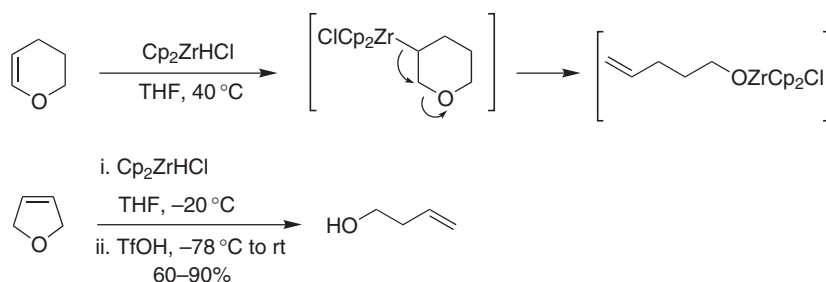


Scheme 139

β -H Elimination in organoiron complexes, to afford alkenes has been thoroughly examined <1980JOC291, 1995COFGT(1)589>. In spite of its fairly broad scope, this reaction has not been used to a significant extent in the recent years.

The elimination of transition metals in complexes featuring electronegative substituents at the β -position is characteristic of group 4 metals. Application of this useful reaction in organic synthesis has been reviewed recently <1995SL299, 1995T4519, 1996T12853>.

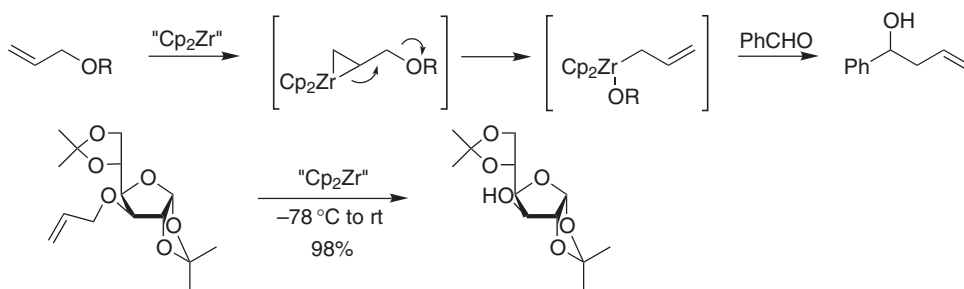
The addition of Cp_2ZrHCl to allyl or vinyl ethers is followed by elimination of zirconium alkoxide and formation of an alkene. The method has been used for the fragmentation of dihydropyrans <1991JOC6494> and five-membered heterocycles including dihydrofurans and pyrrolidines (Scheme 140) <1994OM5166, 1996OM1208>.



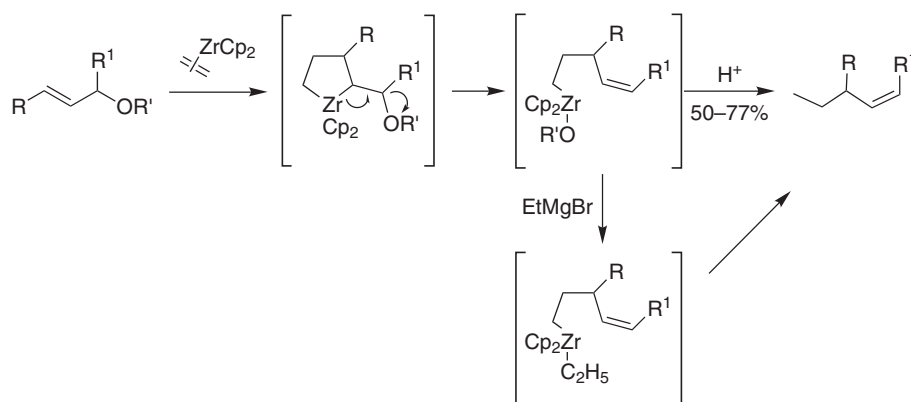
Scheme 140

The reaction of “ Cp_2Zr ” (prepared from $\text{Cp}_2\text{ZrCl}_2/2 \text{ BuLi}$) with allyl or propargyl ethers leads to allylic zirconocenes via β -alkoxy elimination. These intermediates can be further elaborated to more complex molecules. The reaction was used as a new mild deprotection method for allyl ethers (Scheme 141) <1995SL299>.

Treatment of Cp_2ZrCl_2 with ethylmagnesium bromide leads to a zirconocene–ethylene complex, which can be coupled with allyl ethers. Protonolysis of the intermediate zirconium alkoxide affords an alkene. Alternatively, the reaction can be conducted with ethylmagnesium bromide and catalytic amounts of the zirconocene complex. The reaction works with acyclic and cyclic allyl ethers (Scheme 142) <1993JA8485>.



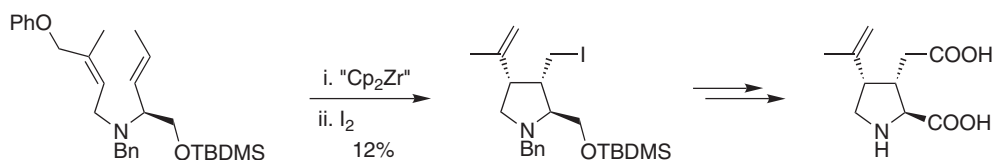
Scheme 141



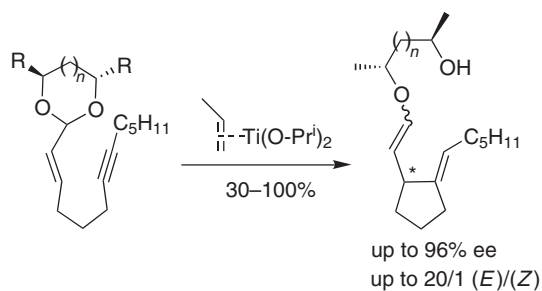
Scheme 142

Intramolecular versions of this reaction have been developed, illustrated for example by a recent synthesis of (–)- α -kainic acid (Scheme 143) <2000JCS(P1)3194>.

Using chiral ketals as chiral auxiliaries, highly enantioselective, Ti(II)-induced reductive coupling of 1,6-enynes has been reported (Equation (44)) <1999JA3559>.

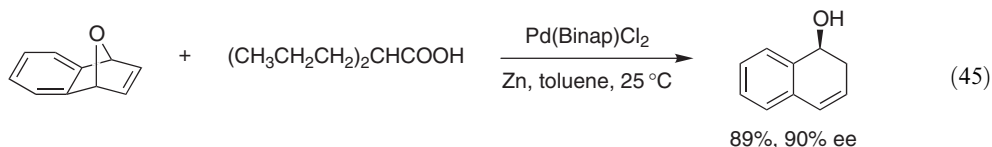


Scheme 143

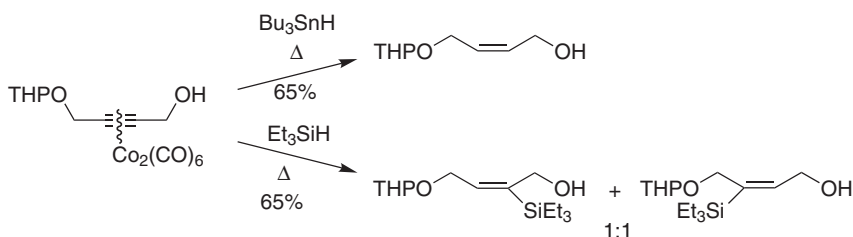


(44)

In the case of strained systems, similar β -alkoxide eliminations also occur with late, non-electropositive transition metals. By using chiral ligands, high enantiomeric excess may be obtained (Equation (45)) <2003OL1621>.



Finally, complexation of alkynes/reductive decomplexation allows a facile stereoselective access to *cis*-olefinic double bonds. Acetylene biscobalthexacarbonyl complexes are widely used for the protection of triple bonds. Under reducing conditions, the metal will eliminate with the reduction of the alkyne to the corresponding alkene. Bu_3SnH is a particularly effective agent for this elimination (Scheme 144) <1998TL2609>. Using R_3SiH instead of Bu_3SnH leads to the formation of vinyl silanes.



Scheme 144

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1973TL3001
1973TL4833
1974TL1133
1975JA1464
1975JA1993
1976TL3743
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1979JA6638
1979TL4111
1980JCS(P1)1045
1980JOC291
1981CC460
1982AG(E)410
1982CB1818
1982JOC1606
1983CPB3931
1983TL4021
1984CC534
1984CC585
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1985TL2209
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Biographical sketch



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1.15

One or More C=C Bond(s) Formed by Condensation: Condensation of Nonheteroatom-linked Functions, Halides, Chalcogen, or Nitrogen Functions

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1.15.1 BY CONDENSATION FROM NONHETEROATOM-LINKED FUNCTIONS

1.15.1.1 Oxidative Coupling of Hydrocarbons

The oxidative coupling of hydrocarbons is mainly reported for the reaction of methane to give ethylene. Since it is of little use in synthesis, only a recent reference <1998MI(171)283> will be mentioned.

1.15.1.2 Metathesis

1.15.1.2.1 General

Alkene metathesis was discovered during early studies on olefin polymerization, and has found several industrial applications (e.g., the shell higher olefin process and the neohexene process <B-1997MI001>). The development of well-defined, highly active catalysts tolerant toward a wide range of functional groups has contributed to the success of this reaction: in the 1990s it has become one of the most powerful synthetic tools in organic chemistry <1997AG(E)2036, B-1998MI002, 2000AG(E)3012>.

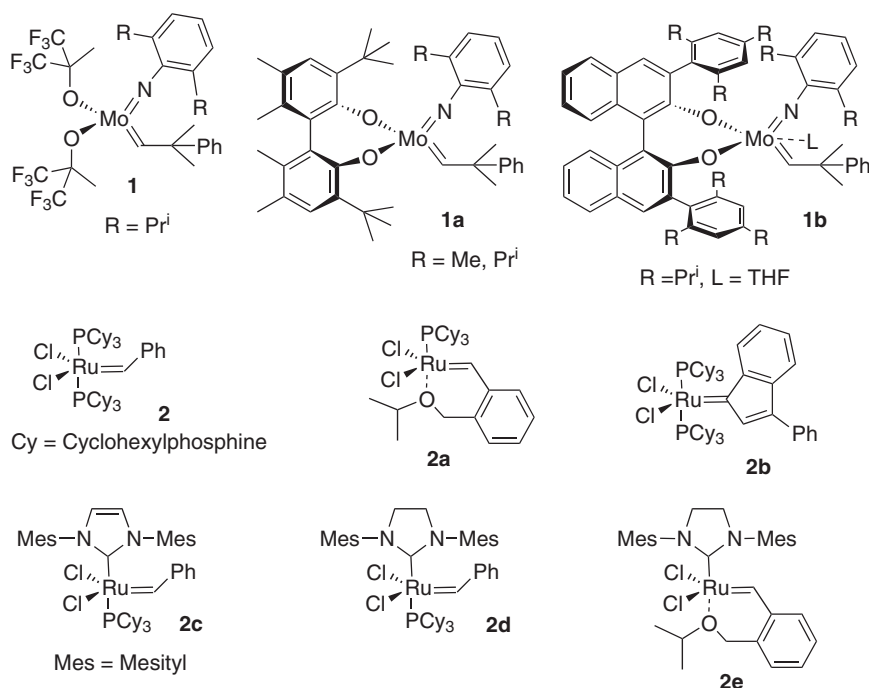
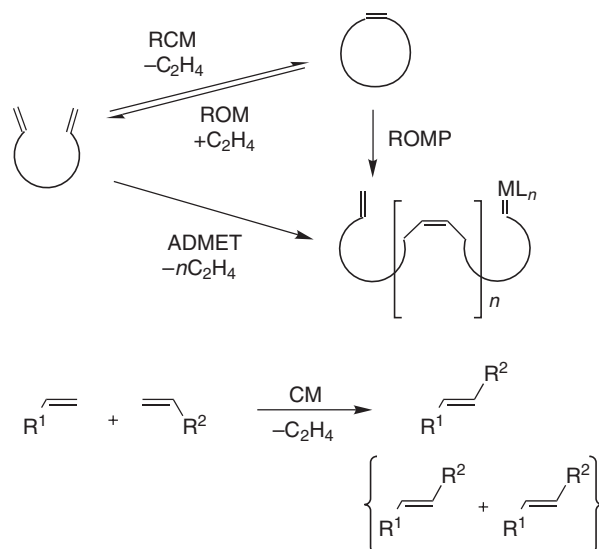
Olefin metathesis refers to the cleavage and reformation of double bonds catalyzed by alkylidene complexes. The mechanism of this reaction was originally proposed by Chauvin <1971MI161> and consists in a sequence of [2+2]-cycloadditions/cycloreversions proceeding via metallacyclobutane intermediates. Each step of the mechanism is reversible, so an equilibrium mixture of olefins is obtained. Five main variations have emerged: ring-closure metathesis (RCM) and the reverse reaction ring-opening metathesis (ROM), ring-opening metathesis polymerization (ROMP) and acyclic diene metathesis polymerization (ADMET) which are beyond the scope of this chapter, and cross-metathesis (CM) (Scheme 1). The inherent competition between RCM and ADMET depends on the size of the ring formed during the reaction and on the conformational constraints present in the acyclic substrate; it can be somewhat shifted toward RCM by using high-dilution conditions. In the case of RCM, the reaction is driven by entropy, because it produces two molecules from one. If one of them is volatile (ethylene, propene, etc.), the equilibrium is generally displaced toward the ring-closed product.

Since metathesis converts one alkene into a new one, tandem processes can be envisaged, which will be discussed later in this chapter.

1.15.1.2.2 Catalysts

The number of catalyst systems that initiate alkene metathesis is very large <B-1997MI001>. Tungsten and rhenium complexes were initially reported in COFGT (1995) <1998JCS(P1)371>. More recently, this reaction has been catalyzed by molybdenum carbenes (for recent reviews, see <1999T8141, 2003AG(E)4592>). Among these, Shrock's catalyst **1** <1990JA3875> has been the most successful and is now commercially available (Figure 1). Until the discovery of the second-generation catalysts, it was the most active carbene which showed tolerance toward some functional groups. Ruthenium carbenes also show high reactivity toward alkenes, and are

excellent candidates for metathesis catalysts (for recent reviews, see <1998T4413, 2001ACR18>). The most widely used in the 1990s has been ruthenium carbene **2** (Figure 1) developed by Grubbs (<1993JA9858, 1995AG(E)2039, 1996JA100>) because of its high activity and its exceptional tolerance toward polar functional groups such as esters, amides, ketones, aldehydes, alcohols, and even acids or water. It is also commercially available and can be handled in air, contrary to the Schrock catalyst which requires the use of a glove box.

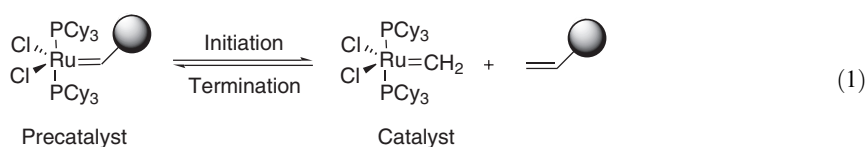


Complexes **1** and **2** have been the basis for many other catalysts. In the case of the molybdenum complex, the most noteworthy application is the design of enantiopure catalysts **1a** derived from biphenol (BIPHEN) and **1b** from binaphthol (BINOL), which open the way to asymmetric olefin metathesis. Catalyst **2a** <1999JA791>, reported by Hoveyda, is stable on silica gel and can be recovered after flash chromatography of the reaction mixture. It possesses a similar activity to that of **2**. Fürstner showed that catalyst **2b** <1999OM5416> is slightly more active than the parent compound <1999CC601, 2001CEJ4811>.

The introduction of *N*-heterocyclic carbenes as Lewis basic ligands to ruthenium alkylidene complexes of Grubbs type <2001CEJ3236> has encouraged the development of new highly active, easy-to-handle catalysts **2c** <1999JA2674, 1999TL2247> (for similar catalysts, see <1999TL4787>), **2d** <1999OL953>, and recyclable second-generation complex **2e** <2000JA8168, 2000TL9973>. These catalysts are compatible with a wide range of functionalities <2003OL2505> and are as active or more active in some cases than Schrock's carbene **1**. In particular, they are able to promote the formation of tetrasubstituted double bonds, which was impossible with catalyst **2**. They possess the same tolerance toward functional groups, and are even more stable: they can be stored on the bench for months. In addition, complexes **2d** and **2e** are commercially available. Grubbs also reported a vinylidene complex of ruthenium made *in situ* from [(*p*-cymene)RuCl₂]₂, 1,3-dimesitylimidazol-2-ylidene hydrochloride, sodium *t*-butoxide, and *t*-butyl acetylene <2001AG(E)247>, which is almost as active as catalysts **2c** and **2d**. Blechert designed a BINOL equivalent of catalyst **2e**, which is more active but shows no asymmetric induction <2002AG(E)794>, and a biphenyl derivative <2002AG(E)2403>, which is even more active than the latter. Very recently, a very active ruthenium catalyst with two alkoxide ligands in place of the chlorides has been reported <2003OM3634>.

Grubbs described water-soluble complexes derived from **2**, which catalyze ROMP of strained cyclic olefins in water <2000JA6601>. RCM has also been performed with ruthenium catalysts in water <2002CC1070>, in ionic liquids <2002CC146, 2003JA9248, 2003AG(E)3395>, and in supercritical CO₂ with catalyst **1** as well <1997AG(E)2466, 2001JA9000>.

Some supported catalysts have been recently reported, based on an earlier result by Grubbs, which describes the immobilization of **2** on a moderately cross-linked polymer functionalized with PCy₂ units <1995JOM(497)195>. More recently, Barrett invented the concept of a "boomerang catalyst," in which the carbene is the anchor group <1999TL8657> (for another example, see <2000OL4075>). The carbene precatalyst becomes soluble during the course of the reaction and is recaptured by the polymer at the end (Equation (1)).

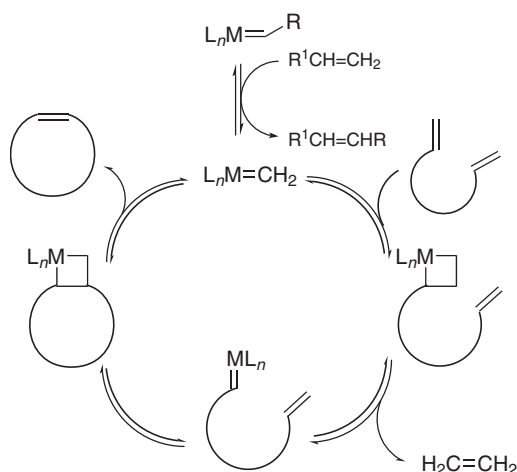


Complexes **2a** and **2e** were attached to various supports, such as a dendrimer <2000JA8168>, monolithic sol-gel <2001AG(E)4251>, a soluble polyethylene glycol resin <2000AG(E)3896>, cross-linked insoluble polystyrene polymers <2001CC37, 2001SL1547>, other polymers <2002AG(E)3835>, as well as polyacrylamide polyethylene glycol (PEGA-NH₂) and butyl-diethylsilyl polystyrene (PS-DES) resins <2002BMCL1873, 2002TL9055>. Hoveyda and Schrock also designed a polymer-supported version of complex **1a**, which gives excellent ee values in asymmetric ring-closing metathesis (ARCM) and AROM/CM reactions <2002AG(E)589>. Immobilized catalysts are in general slightly less active than the parent complexes and can be recycled several times, up to 7 or 8 for the best ones.

1.15.1.2.3 Ring-closing metathesis

The mechanism of RCM has been widely studied by Grubbs <1997JA3887, 2001JA6543>. The individual steps are described in Scheme 2.

RCM is very sensitive to steric hindrance. With the original Grubbs catalyst **2**, only di- and trisubstituted double bonds can be formed, but with molybdenum catalyst **1** and the second-generation catalysts, even tetrasubstituted alkenes are obtained (Table 1) <1997JOC7310, 1999TL2247, 2000JOC2204, 1999OL953>.



Scheme 2

Table 1 Effects of Substitution on RCM

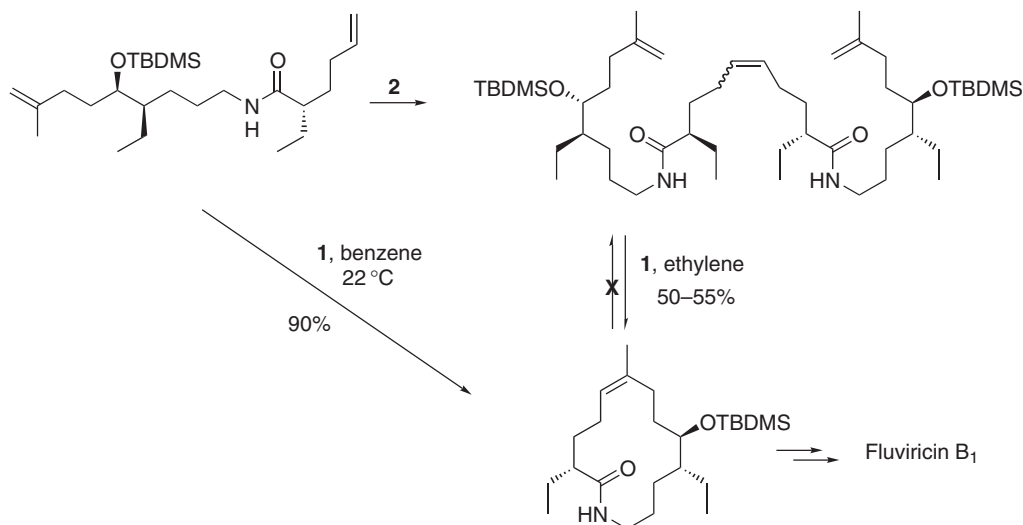
Substrate	Product	Conversion (%) with 2	Conversion (%) with 1	Conversion (%) with 2c	Conversion (%) with 2d
		100	100	100	100
		(93)	100	100	100
		0	37	100	100
		0	93	40	31
		(93)	100		
		0	52	95(89)	90

E = COOEt.

Yields in parenthesis are isolated yields.

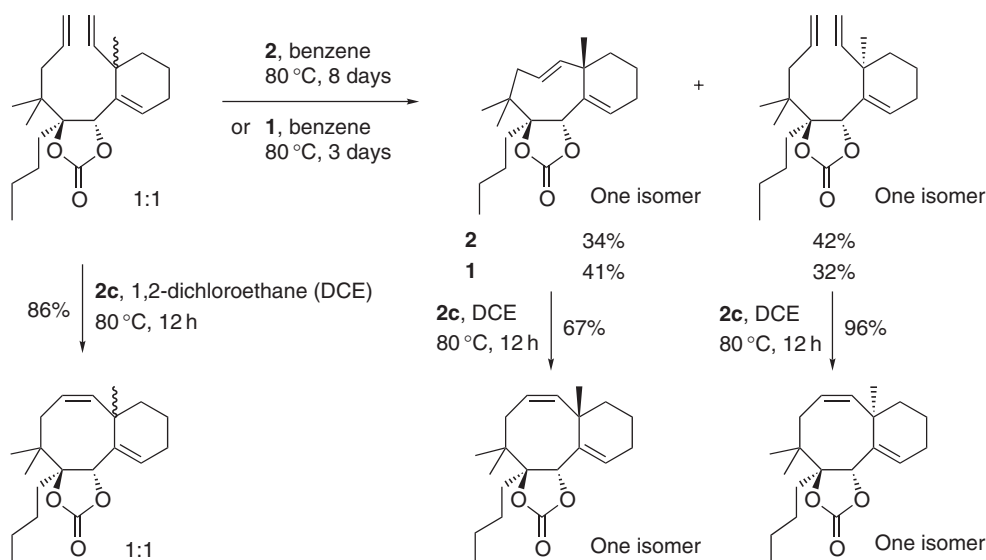
Olefin metathesis is under thermodynamic control. With less active catalysts, the kinetic product can be formed in some cases, then isomerized with molybdenum or second-generation ruthenium catalysts, which are more active. One of the first examples was reported by Hoveyda in the course of the synthesis of 14-membered lactam fluviricin B₁ (Scheme 3) <1997JA10302>.

When treated with ruthenium catalyst **2**, the macrocycle precursor dimerizes through the less substituted double bond. The dimer can be equilibrated to the macrocycle, which is the thermodynamic product, with molybdenum catalyst **1**. Treatment of the linear product with **1** directly furnishes the fluviricin precursor in excellent yield. More recently, Smith illustrated the same fact during his synthesis of cylindrocyclophane precursors <2001JA990>.



Scheme 3

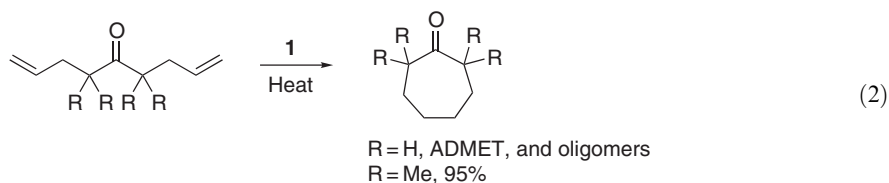
Prunet reported the synthesis of a *trans*-cyclooctene by RCM (Scheme 4) <2000AG(E)725>. Catalysts **1** and **2** lead to the kinetic product in good yields (only one diastereomer of the starting material cyclizes), under very harsh conditions. With complex **2c**, both diastereomers react, and the thermodynamic *cis*-cyclooctene is obtained (which is 7 kcal mol⁻¹ more stable than the *trans*-isomer). Once again, the *trans*-isomer can be transformed into the *cis*-product by treatment with the more active catalyst <2000S869>. Fürstner nicely illustrated the same effect in his synthesis of herbarumin I <2002JA7061>.



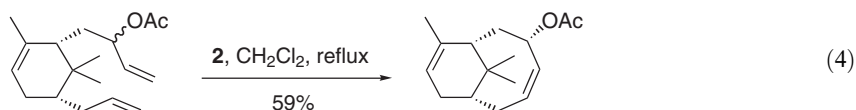
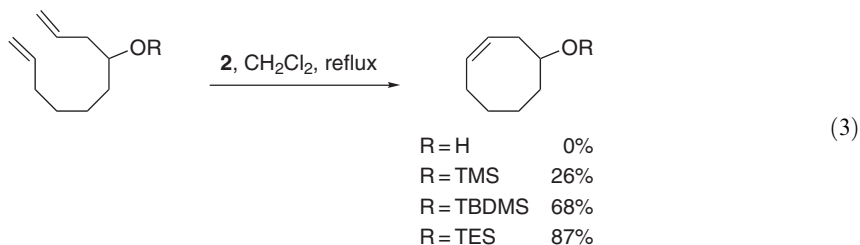
Scheme 4

Closure of small rings is very efficient, including the formation of heterocycles such as oxacycles <1992JA5426, 1993JA9856, 2002TL7263, 1999TL4187>, cyclic enol ethers <1997TL123> and polyethers <2000AG(E)372, 1999JOC3354, 1997TL6299>, azacycles <1992JA7324, 1993JA9856>, silacycles <1997TL4757, 1997TL7861, 1999TL1429, 2002JA15196, 2003AG(E)1734>, boracycles <2002AG(E)152>, phosphacycles <1999TL7333>, and sulfur-containing rings: sulfides and disulfides <1997TL1283>, sulfones <2002OL427>, sultones <2003SL667>, and sulfonamides <2002TL917>.

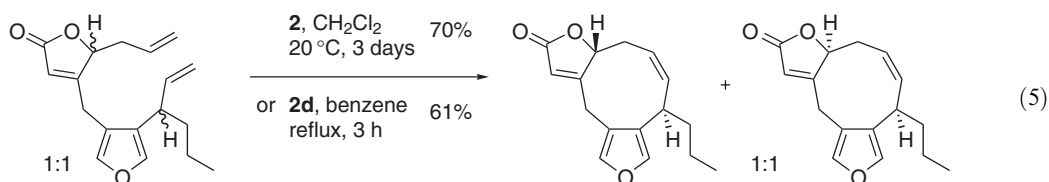
The synthesis of medium-sized rings is more delicate, especially for all-carbon systems (for a review, see <2000AG(E)2073>), and the RCM yields highly depend on the conformational constraint in the starting material <2003OL2883>. Forbes showed the importance of the Thorpe–Ingold effect in RCM (Equation (2)): the cyclization of the ketone bearing geminal dimethyl substituents is possible even without solvent <1992JA10978>.



A similar trend was observed by Taylor and co-workers during their studies toward the synthesis of laureatin (Equation (3)): in this case, it is the bulk of the alcohol protecting group that increases the yield of the RCM reaction <1999TL4267>. Prunet also described the importance of protecting groups: if the secondary alcohol in the taxol precursor (Scheme 4) is protected as a triethylsilyl ether (the tertiary alcohol remaining free), the yield of the cyclization is only 6% with catalyst **2** <2000AG(E)725>, but excellent results are obtained with cyclic protecting groups such as a silylene or an acetonide <2000S869>. Finally, Blechert emphasized the effect of stereochemistry on the outcome of RCM (Equation (4)): only one diastereomer of the taxol AB ring-system precursor cyclizes (the other one dimerizes through the less hindered double bond) <1999S607>.



An advanced precursor of cornexistin was prepared by RCM by Clark (Equation (5)) <2003OL89>. The cyclononene formation proceeds smoothly with both catalysts **2** and **2d**.



Medium-sized heterocycles such as bicyclic lactams <1995JA2108, 1999SL1127, 1999JCS(P1)1695, 2003JOC2728>, silacycles <1997TL4757, 1997TL7861>, azacycles <2002AG(E)2403, 2001SL37>, oxacycles <2000SL1067>, or polyethers <2000AG(E)372, 1997TL6299, 1999TL5405> can also be synthesized by RCM with catalysts **1** and **2** in good yields.

RCM of large rings leads to the desired products in good yields, provided there is a polar substituent properly placed in the linear precursor to function as an anchor group for the catalyst [<2003OL2785>](#). A thorough study by Fürstner and Langemann is illustrated in [Figure 2](#) [<1997S792>](#). Metathesis of hexadeca-2,15-diene with $\text{Cl}_2(\text{PCy}_3)_2\text{Ru}=\text{CHCH}=\text{CPh}_2$ [<1992JA3974>](#) only gives oligomers. When an ester function is present, the cyclized product is formed in decent yield, but the reaction is very sensitive to steric hindrance. A larger distance between the heteroatom and the alkene groups significantly improves the yield. When the ruthenium is too tightly complexed by the polar functional group (five-membered chelate for example), the reaction can be inhibited, as shown in [Figure 3](#).

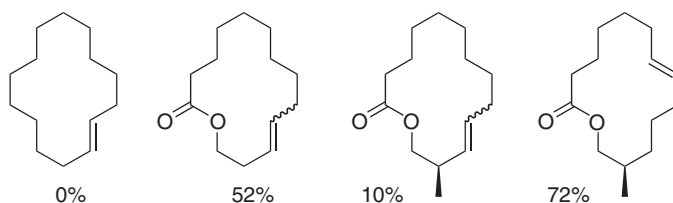


Figure 2

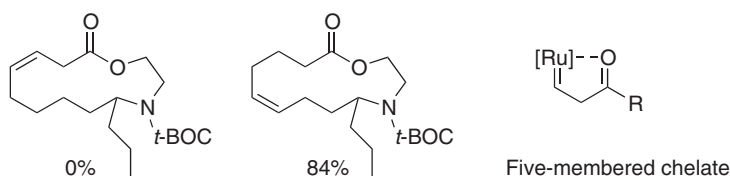
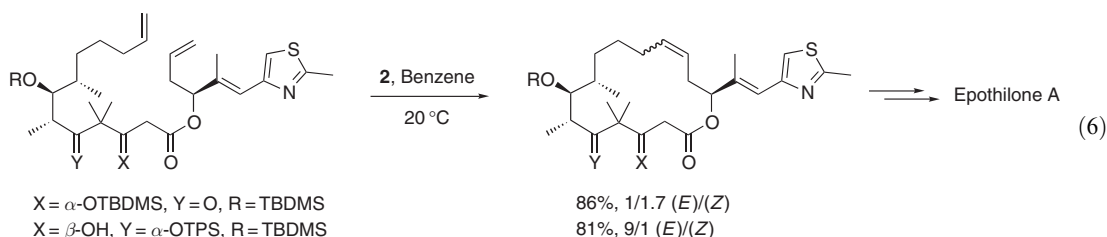


Figure 3

The (*E*)/(*Z*) selectivity of the double bond formation in macrocycles by RCM is rarely predictable, and depends on many factors (for a recent review, see [<2003AG\(E\)2826>](#)): temperature, solvent, catalyst ([Scheme 4](#)), and substrate substituents ([Equation \(6\)](#)). The only example of stereoselective formation of a trisubstituted double bond by RCM was described by Hoveyda ([Scheme 3](#)) in the course of the total synthesis of fluviricin.

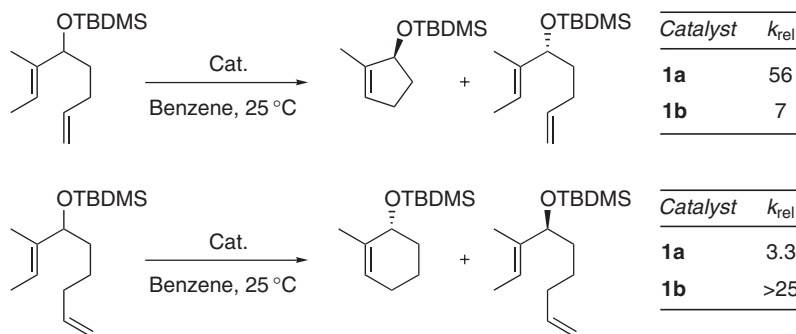
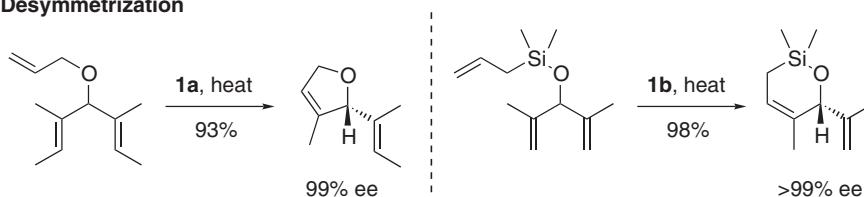


The usual catalysts for asymmetric ring closing metathesis (ARCM) are complexes **1a** and **1b** developed by Schrock and Hoveyda ([Figure 1](#)) [<2001CEJ945>](#). BIPHEN catalyst **1a** (R = Prⁱ) is the reagent of choice for the formation of five-membered rings, whereas BINOL derivative **1b** gives better results for six-membered products ([Scheme 5](#)). This methodology was applied to the total synthesis of (+)-*endo*-brevicommin by Burke [<1999OL1827>](#).

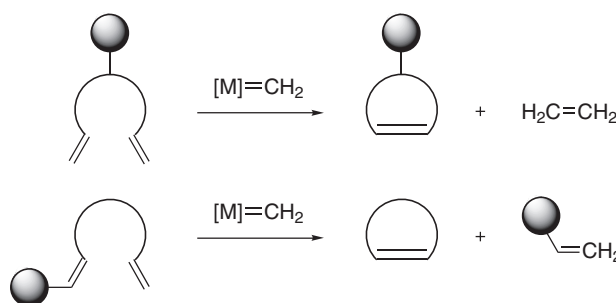
Catalyst **1a** (R = Prⁱ) and a closely related complex were also employed for the ARCM of small- and medium-sized unsaturated amines [<2002JA6991>](#).

Recently, Grubbs reported a chiral ruthenium catalyst derived from **2**, which gives an excellent ee for the RCM of a dihydrofuran when sodium iodide is added to the reaction mixture [<2001OL3225>](#).

RCM has been employed on solid support, either to cyclize or to close/release simultaneously immobilized substrates ([Scheme 6](#)) [<2000AG\(E\)3012>](#). A typical application of the latter method is the synthesis of a library of epothilone analogs by Nicolaou [<1997NAT\(387\)268>](#).

Kinetic resolution**Desymmetrization**

Scheme 5



Scheme 6

RCM has found widespread applications in organic synthesis [<B-1998MI002, 2003MI57, 1998JCS\(P1\)371>](#). Since the metathesis catalysts are very chemoselective and react almost exclusively with alkenes (and alkynes), a new logic of retrosynthesis has emerged, avoiding protecting group manipulations of polar functions. Numerous syntheses of bioactive natural products (laurencin [<1999JA5653, 1999OL2029>](#), dactylol [<1996JOC8746>](#), laulimalide [<2001AG\(E\)3842, 2001JOC8973>](#), macrosphelides A and B [<2003OL2939>](#), ircinal A [<1999JA866>](#), roseophilin [<1997TL2601, 1999JOC2361, 2000OL1157, 2001JA8515, 2001JA8509>](#), gloeosporone [<1997JA9130>](#), ciguatoxin [<2001SCI\(294\)1904>](#), methynolide [<2002SL715>](#), strictifolione [<2003OL1995>](#), fostriecin [<2002OL969, 2002OL4615, 2003OL733>](#), etc.) include RCM as a key step. Complex non-natural products such as catenanes [<1997AG\(E\)1308, 1999JOC5463>](#) or rotaxanes [<2003AG\(E\)3281>](#) have also been prepared by RCM.

1.15.1.2.4 Cross-metathesis

CM reaction has proved to be a powerful tool to link unactivated olefins. Blechert very recently reviewed this field [<2003AG\(E\)1900>](#) (for a previous review, see [<1998MI155>](#)). The first reports were published by Crowe and co-workers [<1993JA10998, 1995JA5162, 1996TL2117>](#). They used molybdenum catalyst **1** in CH_2Cl_2 for the CM of functionalized terminal alkenes with

styrene, acrylonitrile, and allyl silanes (Table 2). An excess of one of the coupling partners is used to drive the reaction to completion. With styrene, there is little self-metathesis, except when electron-withdrawing substituents such as a bromine atom are present in the terminal alkene. The excellent (*E*)/(*Z*)-selectivity in this case is due to the greater stability of the *trans*-disubstituted metallacyclobutane intermediate. However, there is no clear explanation for the fact that CM with acrylonitrile is kinetically controlled. With allyl silanes, the stereoselectivity increases with the size of the silyl substituents. The lack of self-metathesis is due to the steric bulk of the silyl group, while it was due to the electronic properties of styrene and acrylonitrile for the former reactions. Vinylboranes, enones, dienes, enynes, and unsaturated esters do not undergo CM with catalyst **1**, but allylstannanes are good candidates <1997SL129> (Table 2).

Table 2 Examples of CM

Terminal alkene	Alkene (2 equiv.)	Product	Yield (%) ^a	Selectivity
			85	(<i>E</i>)/(<i>Z</i>) > 95:5
			60	(<i>Z</i>)/(<i>E</i>) = 7.6:1
			72	(<i>E</i>)/(<i>Z</i>) = 2.6:1
			77	(<i>E</i>)/(<i>Z</i>) = 7.6:1
			78	(<i>E</i>)/(<i>Z</i>) = 2.7:1

^a Reactions performed with catalyst **1**.

The more recent developments in this field are mainly due to the second-generation complexes: **2d** and **2e** seem to be the catalysts of choice for CM. With these catalysts, terminal alkenes can be coupled with a wide range of olefins such as allyl silanes <2001OL2209>, protected homoallylic alcohols or their dimers <2000JA58>, and α,β -unsaturated carbonyl compounds <2000JA3783, 2001AG(E)1277>. Methylacrylate, acrolein, methyl vinyl ketone, acrylamides, and even acrylic acid give good yields and selectivities with catalyst **2d** (Table 3). The slow rate of dimerization of these substrates, which are used in excess, prevents self-metathesis. Blechert reported the same kind of reactions with catalyst **2e** (the selectivities are consistently over 20:1) <2000TL9973>, and Cossy demonstrated that chiral homoallylic alcohols <2001JOM(624)327> and allyltriphenylsilane (Table 3) <2002MI(344)627> are good candidates for CM with acrylic derivatives.

Reactions with acrylonitrile catalyzed by **2e** lead mainly to the (*Z*)-isomer, and the selectivities range from 2:1 to 9:1 <2001SL430>. Vinyl and allyl phosphonates <2001SL1034>, vinyl- and allylphosphine oxides <2003TL7133>, and phenyl vinyl sulfone also easily undergo CM with terminal alkenes or styrene derivatives. For the latter substrate, Grubbs showed that the CM reactions were not productive with catalyst **2d** <2000JA3783>, but Grela was successful with the same catalyst <2001TL6425>. Blechert found out that better results were obtained with complex **2e** <2003AG(E)1900>.

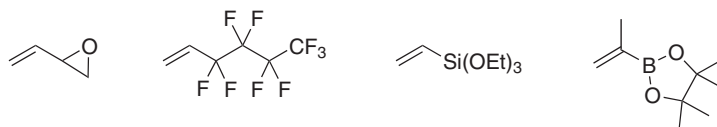
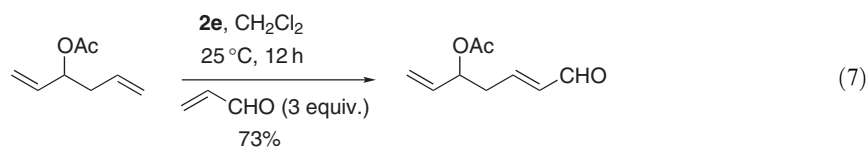
Several functionalized alkenes have been tested successfully in CM reactions with terminal olefins (Figure 4) <2000JA3783, 2002AG(E)3171>. Fischer showed that the reactivity of vinyl silanes toward CM with styrene increases with the number of oxygen substituents ($\text{CH}_2=\text{CHSi}(\text{OR})_3 > \text{CH}_2=\text{CHSiMe}(\text{OR})_2 > \text{CH}_2=\text{CHSiMe}_2\text{OR} > \text{CH}_2=\text{CHSiMe}_3$) <2000OM913> or other electron-withdrawing groups such as chlorides <2003TL7121>.

Cossy reported an interesting chemoselectivity for a CM reaction in the course of the synthesis of the C1–C14 fragment of amphidinol 3 <2001OL1451> (Equation (7)). The allylic acetate double bond does not undergo metathesis, probably because the corresponding metallacyclobutane is deactivated through complexation of the ruthenium by the carbonyl group of the acetate.

Table 3 CM with electron-deficient alkenes

Terminal alkene	Alkene	Product	Yield (%) ^a	Selectivity
BzO-(CH ₂) ₇ -CH=CH ₂	CH ₂ =CHCOOMe	BnO-(CH ₂) ₇ -CH=CHCOOMe	91	(E)/(Z) = 4.5:1
AcO-(CH ₂) ₇ -CH=CH ₂	CH ₂ =CHCHO	AcO-(CH ₂) ₇ -CH=CHCHO	62	(E)/(Z) > 20:1
	CH ₂ =CHC(=O)CH ₃	AcO-(CH ₂) ₇ -CH=CHC(=O)CH ₃	95	(E)/(Z) > 20:1
THPO-(CH ₂) ₃ -CH=CH ₂	CH ₂ =CHC(=O)N(OMe)Me	THPO-(CH ₂) ₃ -CH=CHC(=O)N(OMe)Me	89	(E)/(Z) = 60:1
	CH ₂ =CHC(=O)NHPh	THPO-(CH ₂) ₃ -CH=CHC(=O)NHPh	90	(E)/(Z) = 100:0
	CH ₂ =CHCOOH	THPO-(CH ₂) ₃ -CH=CHCOOH	100	(E)/(Z) = 100:0
Ph ₃ Si-CH ₂ -CH=CH ₂	CH ₂ =CHCOOMe	Ph ₃ Si-CH ₂ -CH=CHCOOMe	86 ^b	(E)/(Z) = 30:1

^a Reactions performed with catalyst **2d**. ^b Reaction performed with catalyst **2e**.

**Figure 4**

There are several examples of CM reactions of alkenes immobilized on solid supports <1996AG(E)1979, 1997CC823>. One of the main advantages of this technique is the suppression of self-metathesis of the bound alkene, and the other olefin need not be used in excess.

CM was applied to the synthesis of the bicyclo[3.3.1]nonane core of garsubellin A <2002OL1943>, the ABC-ring fragment of thyriferol <2002OL593>, antifungal (–)-FR900848 <2000TL8723>, (+)-amphidinolide T1 <2003JA2374>, and to install the side chain of alkaloid (–)-prosophylline <2002JOC1982> and ciguatoxin <1999TL5405>.

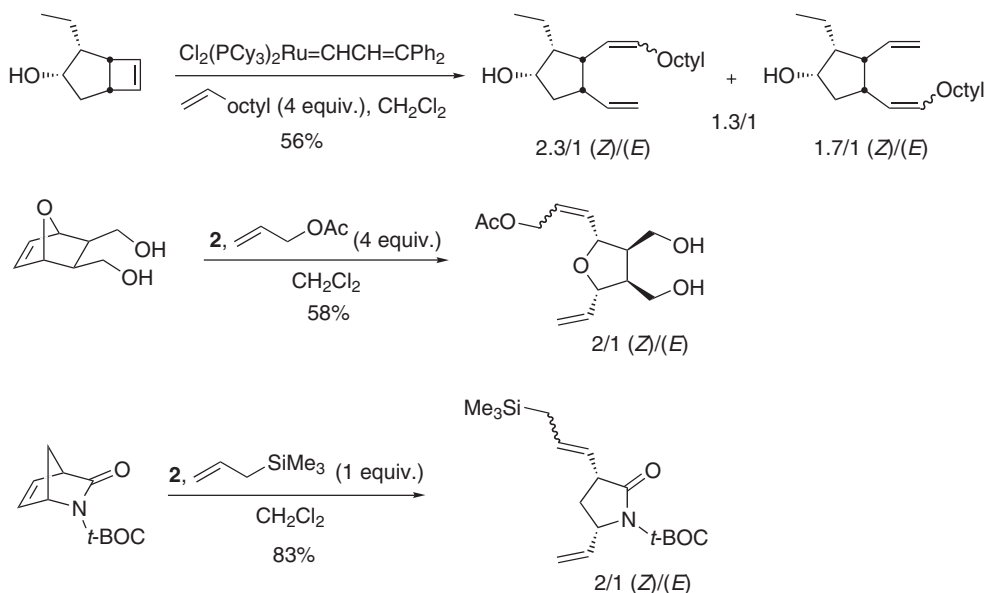
1.15.1.2.5 ROM and tandem reactions

The opposite of RCM is ROM. The ring-opened product either polymerizes (ROMP) or undergoes a CM reaction (for reviews, see <2003AG(E)1900, 1998MI155>). ROM/CM is efficient only if the CM step is faster than the polymerization process, and if the CM partner dimerizes slowly (e.g., styrene, allyltrimethylsilane, or α,β -unsaturated carbonyl compounds). Since ring opening is

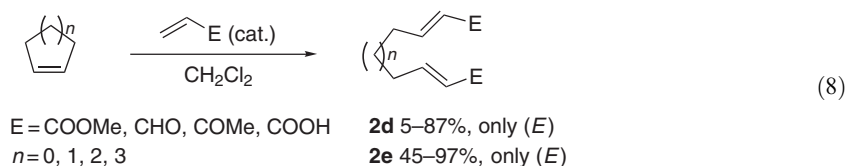
facilitated by release from ring strain, the ROM/CM process was first reported with highly strained cyclic alkenes such as norbornenes and oxanorbornenes (for a review see <2003EJO611> <1996AG(E)411, 1997AG(E)257, 1999JOC9739, 1999T8169>, and cyclobutenes <1995JA9610, 1997JA1478, 1997JA7157>, but a recent publication by Blechert describes ROM/CM of unstrained rings <2001CC1796>.

Two different pathways are possible. Either the ROM step occurs first, and the ring-opened species then undergoes CM (pathway 1), or the catalyst first reacts with the linear alkene and this entity ring-opens the cyclic alkene (pathway 2). It seems that pathway 2 is preferred for cyclobutenes and unstrained olefins, and pathway 1 for the other substrates.

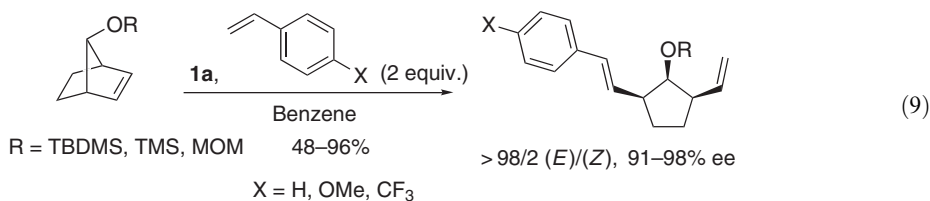
When the substrate is unsymmetrical, the process is not regioselective in general (Scheme 7). The (*E*)/(*Z*) selectivity is rather poor, except when CM is performed with α,β -unsaturated carbonyl compounds (Equation (8)). In this example, double CM is observed in all cases. The order of reactivity of the cyclic alkenes is cycloheptene \geq cyclopentene > cyclohexene, which corresponds to ring strain. Catalyst **2e** is superior to **2d**, as it is the case for simple CM reactions <2003AG(E)1900>.



Scheme 7

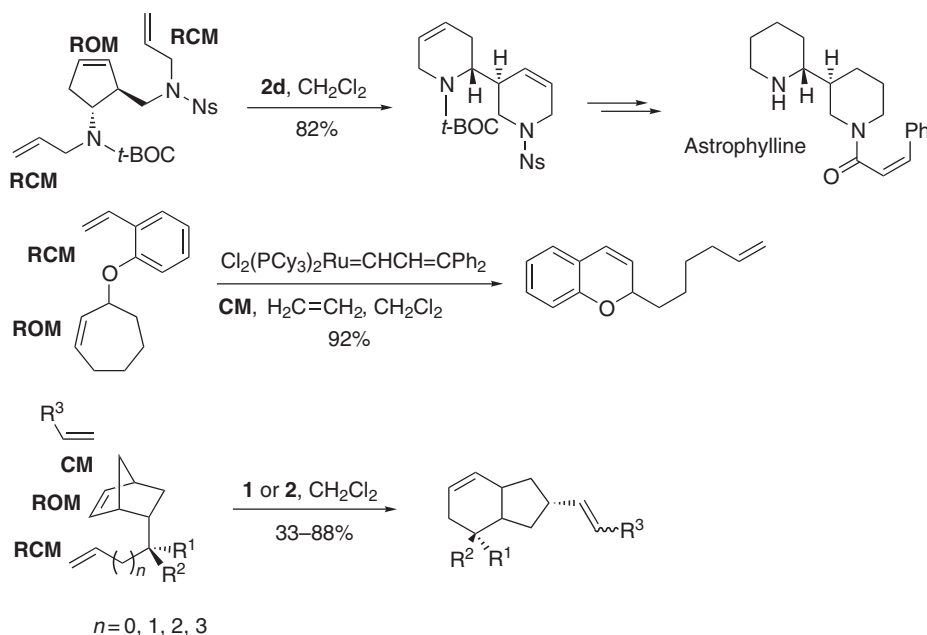


The asymmetric version of this reaction (AROM/CM) was first reported by Schrock and Hoveyda <1999JA11603, 2001JA7767>. *Meso*-norbornenes reacted with styrene derivatives in the presence of catalyst **1a** ($R = Pr^i$) to give the asymmetric ring-opened products in excellent ee values (Equation (9)). Recently, Hoveyda designed a chiral ruthenium complex derived from **2e**, which performs the same reactions with similar results <2002JA4954>. This catalyst is air stable and can be recovered after chromatography.



Cuny applied solid-phase ROM/CM to synthesize a combinatorial library from resin-bound norbornenes and substituted styrenes in the presence of **2** <1997TL5237>.

Numerous tandem reactions are possible. Grubbs described RCM/ROM/RCM of cyclic ethers <1996JA6634>, and Blechert applied the same process to the syntheses of halosalin <1999T8179> and astrophylline <2003JOC2913> (Scheme 8). Hoveyda reported an RCM/ROM/CM (with ethylene) process leading to chromenes <1997JA1488, 1998JA2343>, and Blechert showed that ROM/RCM/CM reactions were possible <1998SL169> (for a similar case, see <2000TL9777>) (Scheme 8).



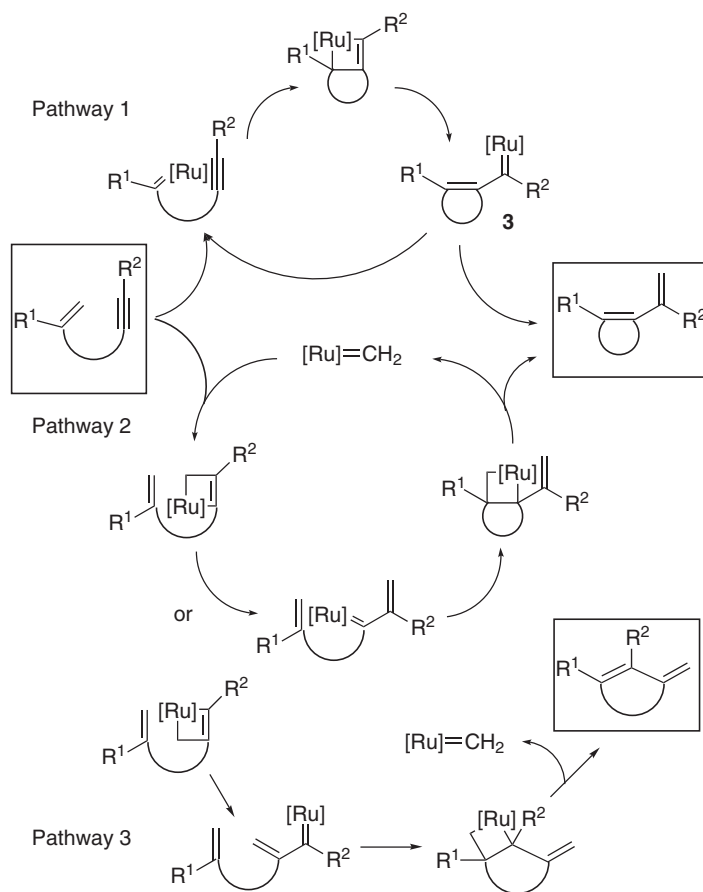
Scheme 8

1.15.1.2.6 Ene-yne metathesis

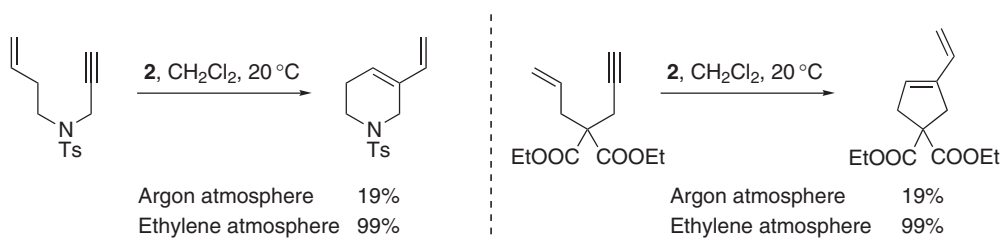
In a similar manner, a new method for 1,3-diene synthesis, resulting from the metathesis coupling between an alkene and an alkyne, was first reported by Mori <1994SL1020>. An excellent review was very recently published by Poulsen and Madsen <2003S1> (for another review, see <1998MI133>). The best catalyst for this reaction seems to be second-generation complex **2d**. The different mechanistic pathways are shown in Scheme 9. In contrast to olefin metathesis, ene-yne metathesis is an irreversible process because 1,3-butadienes are less active than alkenes or alkynes toward the catalysts. No exact proof of a mechanism beginning with the yne or the ene moiety has been established yet, but pathway 1 seems to be the main one for ring-closing processes when the alkene is monosubstituted <1999OL277, 2001AG(E)4274>, and pathways 2 and 3 are preferred if the alkene is *gem*-disubstituted. Moreover, carrying out the reaction under an ethylene atmosphere has an influence on the reaction rate and yield, especially when the alkyne is monosubstituted (Scheme 10) <1998JOC6082>; it seems to help the release of the catalyst from the conjugated carbene **3**.

The substitution pattern of the enyne has a great influence on the yield of metathesis. Enynes having a monosubstituted alkene are more reactive than enynes with a di- or trisubstituted alkene (Scheme 11) <2003S1>.

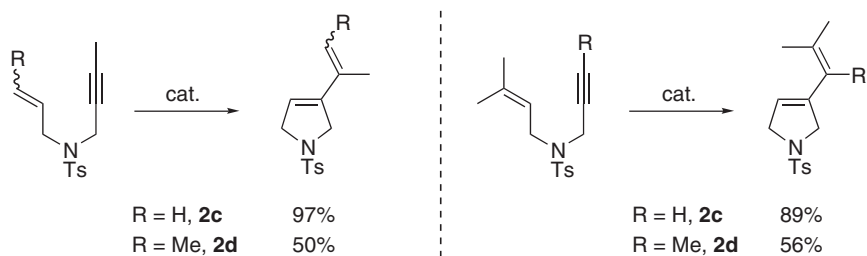
Ene-yne RCM is not driven by entropy so it lacks an inherent driving force. As a consequence, five-, six- (Scheme 11), and seven-membered rings (Scheme 12) <2001CEJ3236> are produced in good yields if a heteroatom or a quaternary center is present in the precursor, but eight-membered rings <2001S654> require two such conformational constraints for their formation (Scheme 12).



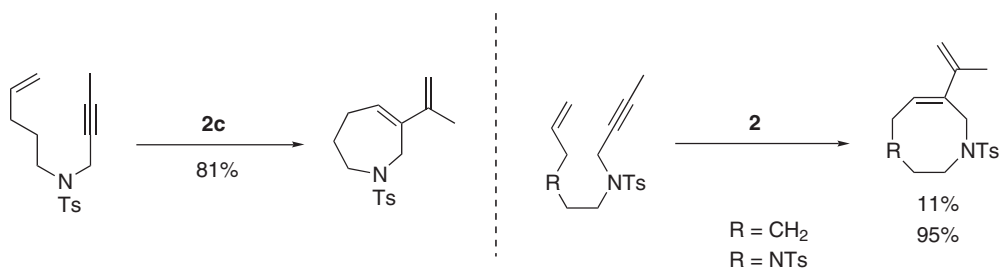
Scheme 9



Scheme 10



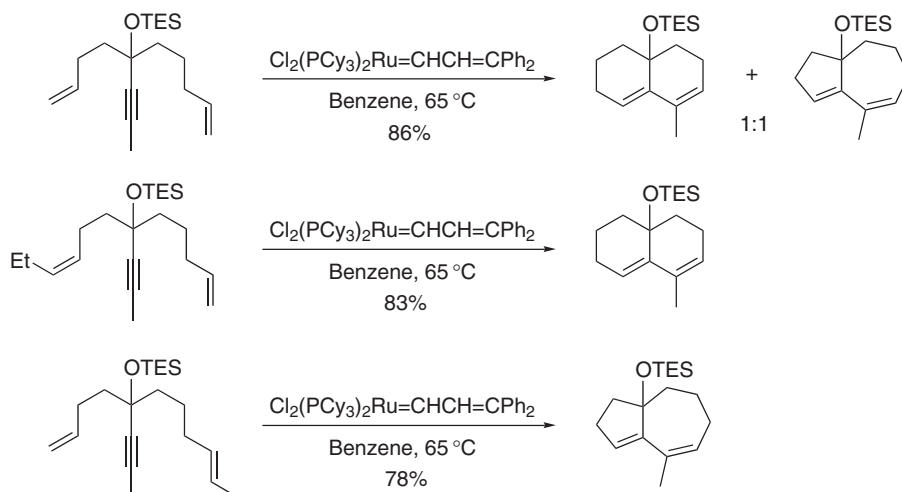
Scheme 11



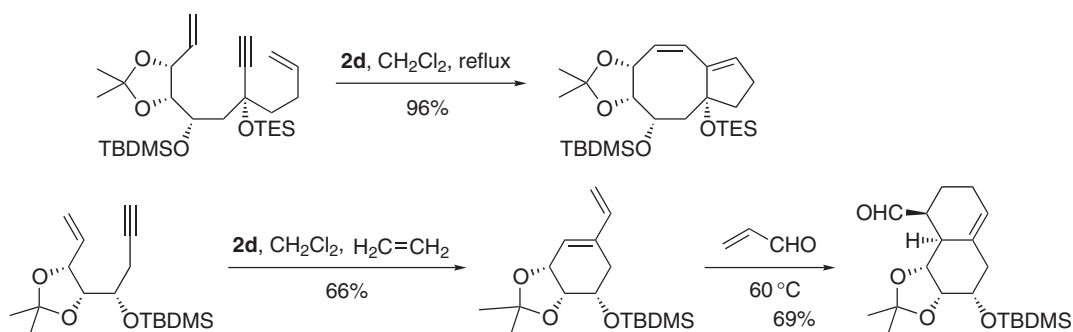
Scheme 12

Other small heterocyclic rings are also easily formed by ene-yne RCM, e.g., boracycles <2002AG(E)3272>, silacycles <2001OL2069>, and polyethers <2000AG(E)372>.

Several tandem ene-yne reactions have been described, first by Grubbs (Scheme 13) <1994JA10801, 1996JOC1073>. In this case, the first metathesis site is the less hindered alkene, so the process can be oriented by selectively hindering one of the double bonds in the starting material. Simple diene RCM is not observed, presumably because it would lead to medium or large rings. Hanna described a carbocyclization of carbohydrate-derived dienynes <2001OL3095>, and Poulsen and Madsen <2002JOC4441> performed an ene-yne RCM on the same kind of substrates followed by a Diels–Alder reaction (Scheme 14).

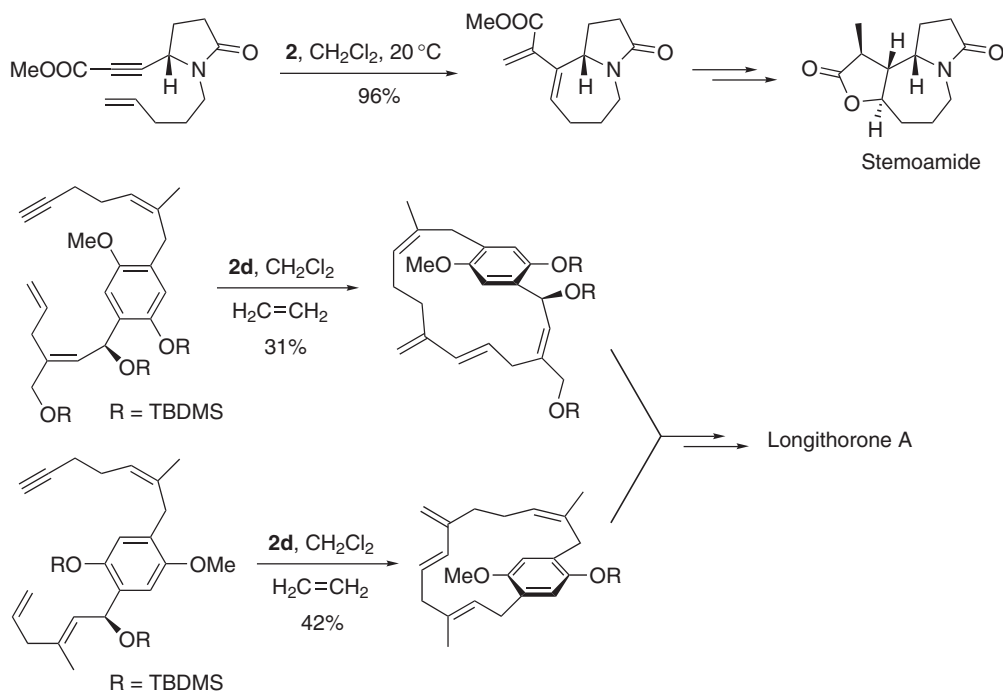


Scheme 13



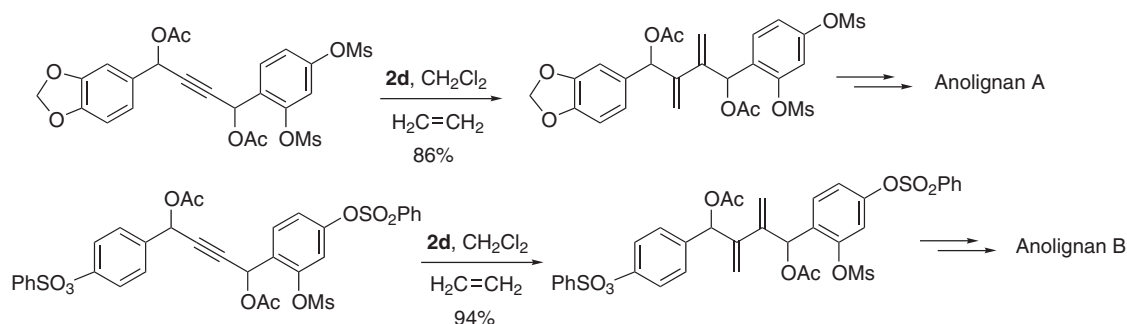
Scheme 14

Ene-yne RCM has been used for the total synthesis of natural products, such as stemoamide <1996JOC8356> and longithorone A <2002JA773> (Scheme 15). In the latter synthesis, both macrocycles bear a 1,3-disubstituted diene (which usually is the preferred CM product), proving that RCM occurred through pathway 3 in Scheme 9.



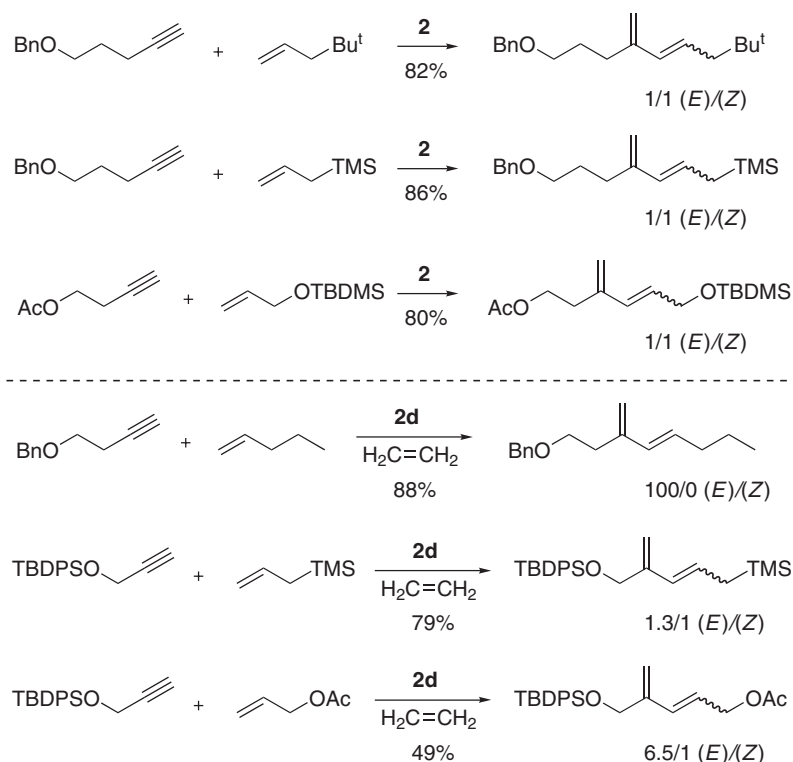
Scheme 15

Ene-yne CM with ethylene was first described by Mori with catalyst **2** <1997JA12388>. Under these conditions, this reaction was limited to alkynes with esters or sulfonamides at the propargylic position. More recently, use of catalyst **2d** circumvented this problem and rendered the reaction general <2000OL2271, 2002TL209, 2002TL2235>. With this transformation, alkynes can be seen as masked 1,3-dienes. HIV-1 reverse transcriptase inhibitors (anolinan A and B) were synthesized by Mori using this reaction as the key step (Scheme 16) <2002JOC224>.

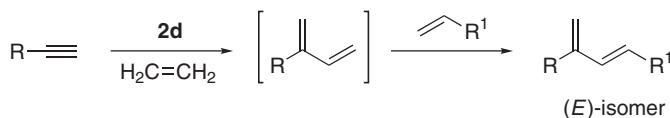


Scheme 16

CM with substituted alkynes gives the 1,3-substituted dienes (Scheme 17) <1997AG(E)2518, 2001TL6699> and is not regioselective if the alkyne is unsymmetrically substituted <2000TL5465>. Generally, 3 equiv. of the alkene are needed to drive the reaction to completion. CM with more substituted olefins has not yet been reported. The (*E*)/(*Z*) ratios of the products are poor, but very recently, an elegant method was designed to render the reaction stereoselectively <2003OL1855>. The ene-yne CM is conducted under an atmosphere of ethylene, so a tandem process is observed: ene-yne CM with ethylene, followed by diene-ene CM (Scheme 18). The (*E*)/(*Z*) ratios are excellent, except in the presence of a polar substituent at the allylic position (Scheme 17).



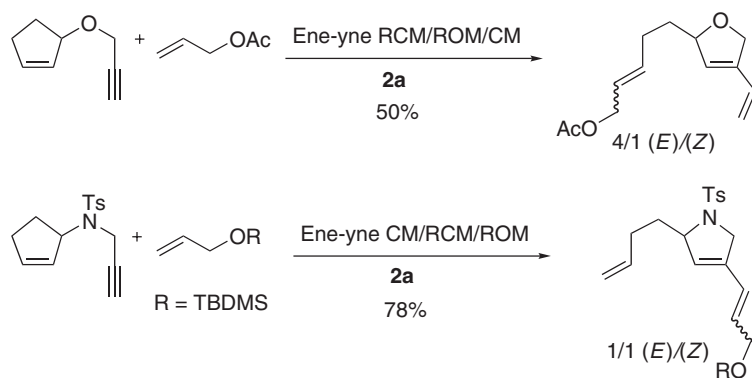
Scheme 17



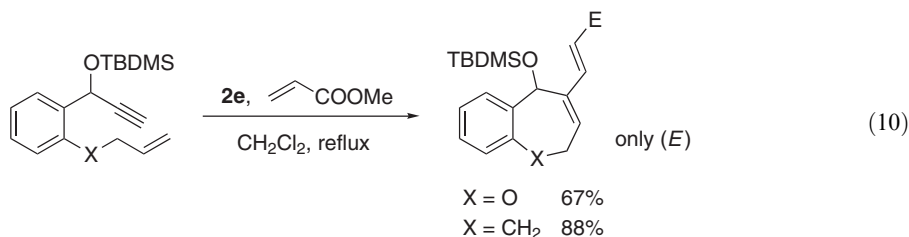
Scheme 18

Blechert reported ene-yne CM reactions of immobilized substrates. Terminal alkynes were reacted with polystyrene-bound allyl silane [<1998TL2295>](#), and a tandem ene-yne CM/Diels–Alder process was effected on an alkyne immobilized on a Merrifield resin [<1999SL1879>](#).

Although 1,3-dienes are not very reactive toward metathesis catalysts, tandem processes involving ene-yne metathesis followed by CM with monosubstituted olefins have been described by Plumet [<2000TL9777>](#) and Blechert [<2001TL5245, 2002MI\(344\)631>](#). Surprisingly, the order of the different metathesis steps depends on the heteroatom present in the substrate, leading to differently substituted dihydrofurans and pyrrolines ([Scheme 19](#)). There is no obvious explanation for this intriguing mechanistic switch.

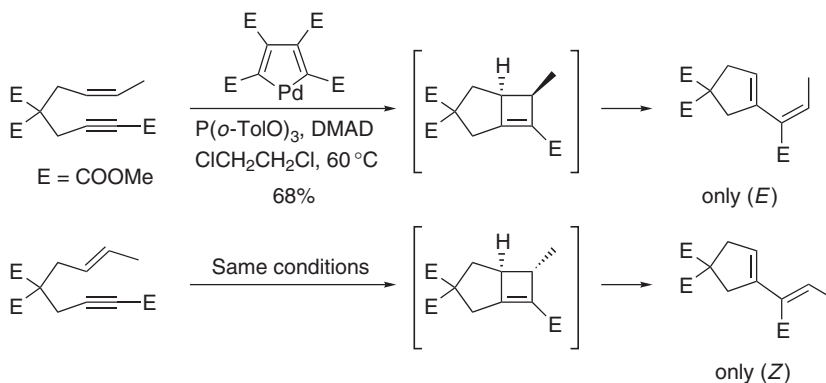


Recently, simple ene-yne RCM/CM sequences were reported by Grimaud (Equation (10)) <2003OL2007>. In this case, the CM reaction is very stereoselective in favor of the (*E*)-olefin.

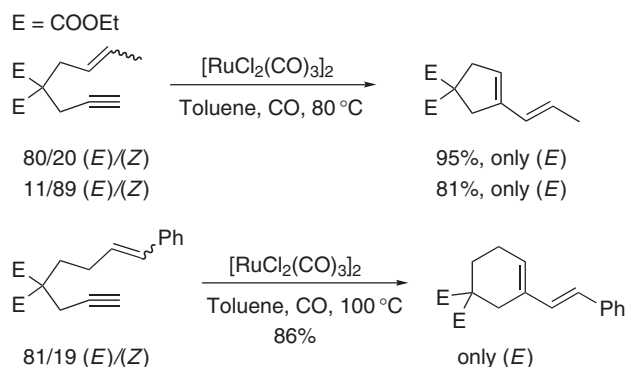


1.15.1.2.7 Non-Chauvin metathesis

Ene-yne metathesis can also be catalyzed by other transition metals, such as Pd(II), Ru(II), Pt(II), and Ir(I). The mechanism is different from the mechanism reported by Chauvin for carbene complexes (hence the name non-Chauvin), involving either an oxidative cyclization to give a metallacyclopentene intermediate which undergoes a reductive elimination followed by a rearrangement, or a cationic intermediate coming from π -complexation of the alkyne moiety (for a review, see <2002CRV813>). Pd(II) complexes effect metathesis of 1,6-enynes, but only if the alkyne is substituted by an ester (COFGT (1995)). The reaction proceeds via an oxidative addition/reductive elimination sequence, giving an intermediate cyclobutene, which undergoes a conrotatory thermal opening (Scheme 20). The overall process is stereospecific, the (*E*)-alkene leading to the (*Z*)-product and vice versa <1993AG(E)1085>. This catalyst does not lead to the desired product for 1,7-enynes.

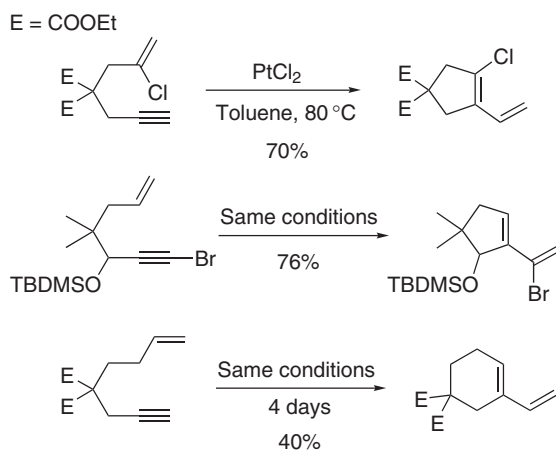


Murai <1994JA6049> has shown that ruthenium complexes other than carbenes can promote ene-yne RCM (Scheme 21). The reaction is stereoconvergent in this case, both isomers of the starting alkene leading to the (*E*)-product. In contrast to Trost's system, 1,7-enynes are good candidates for this reaction, but not enynes substituted with an ester on the alkyne moiety. Substitution of the olefinic portion enhances the reactivity, and even trisubstituted alkenes undergo metathesis in good yields.



Scheme 21

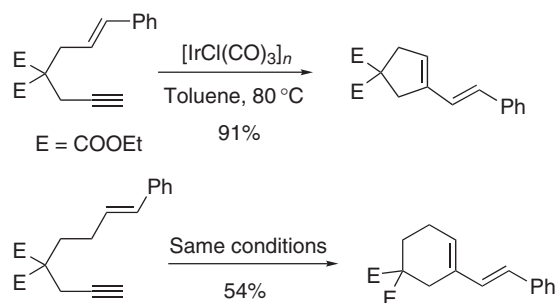
The same group employed PtCl₂ for ene-yne RCM <1996OM901>. No additional ligands are necessary, and the reaction is compatible with a large array of substituents: Cl on the alkene part and Cl, Br, Me, Ph, and even COOMe on the alkyne moiety (Scheme 22), which was not the case with the ruthenium complexes. However, 1,7-enynes react more slowly and give poorer yields.



Scheme 22

They also used iridium complexes for the same reaction <2001JOC4433>. With this metal, the reaction pathway depends on the nature of the catalyst and on the structure of the substrates. The best catalyst for ene-yne metathesis is [IrCl(CO)₃]_n, and monosubstituted alkynes are good substrates (Scheme 23). When the alkene bears a cyclopropyl substituent, no [5 + 2]-cycloaddition occurs and the cyclopropane remains intact in the product.

This methodology was applied to a formal synthesis of roseophilin <2000JA3801> and to the total syntheses of streptorubin B and metacycloprodigiosin <1998JA8305>.

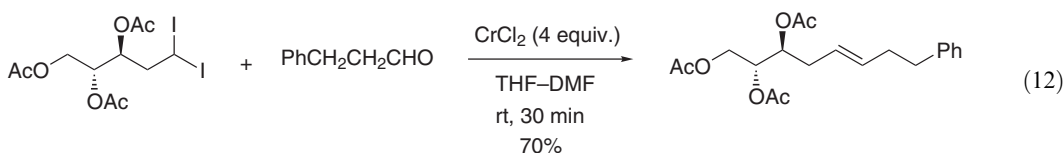
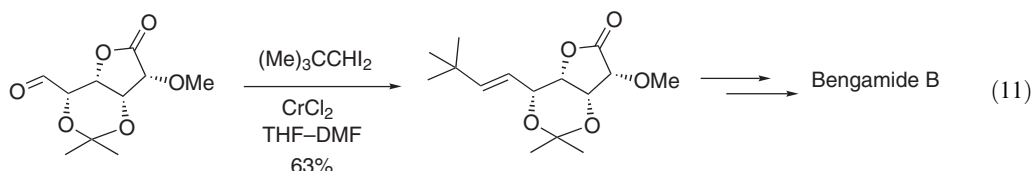


Scheme 23

1.15.2 BY CONDENSATION OF HALIDES: METAL-MEDIATED CONDENSATION OF *gem*-DIHALIDES AND RELATED COMPOUNDS WITH CARBONYL GROUPS

1.15.2.1 Chromium-mediated Condensation

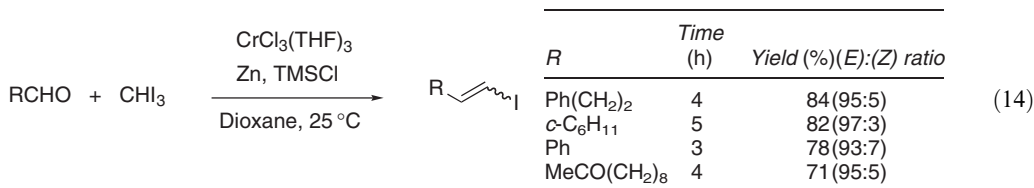
The chromium-mediated condensation of a *gem*-dihalide with a carbonyl compound giving alkenes has been developed by Takai and Utimoto [<1987JA951>](#) (for recent reviews, see [<1999S1, 1999CRV991>](#)). This convenient olefination protocol applicable to readily enolizable substrates provides (*E*)-alkenes with a high selectivity [<2001JMC3692>](#) (Equation (11)). This reaction proceeds under very mild conditions in THF, THF/DMF [<1995T3713>](#), or THF/1,4-dioxane [<1993JA4497, 1992JA2260>](#) and is compatible with a wide range of functionalities [<2001AG\(E\)2326>](#) (Equation (12)). 1,1-Diodoalkanes are the most reactive substrates, especially diiodomethane and diiodoethane, while *gem*-dibromides and dichlorides give poor yields.



It is believed that the reaction proceeds via a *gem*-dichromium nucleophile, which attacks the carbonyl compound (Equation (13)).

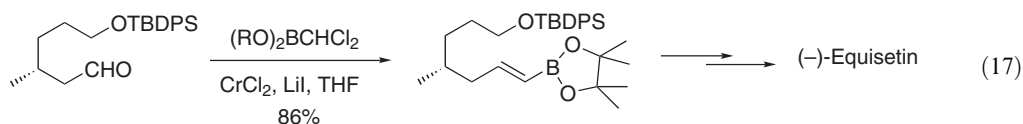
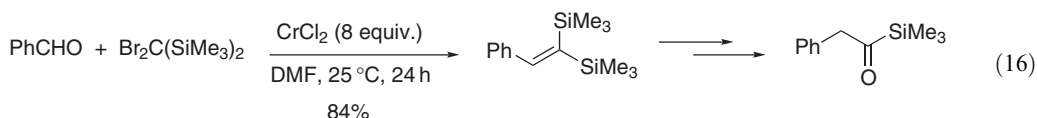
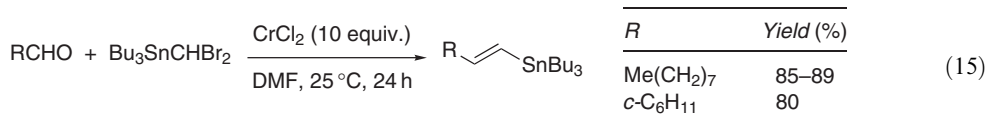


Recent modifications allow the use of catalytic amounts of Cr(III) in the presence of another stoichiometric reducing agent such as Sm/SmI₂ [<1995CL259>](#) or Zn/TMSCl [<1999SL1268>](#) (Equation (14)). This method avoids the use of 6 or 8 equiv. of the air-sensitive and hygroscopic CrCl₂. The reduction power of Cr(II) can be enhanced by complexation with donor ligands such as diamines (TMEDA) [<1998SL253>](#).

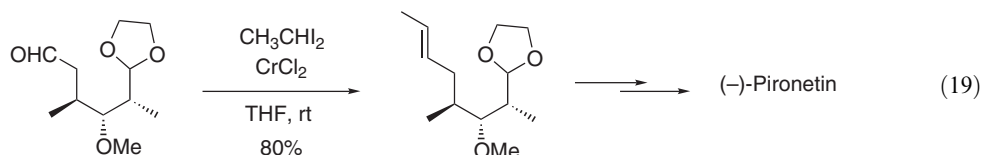
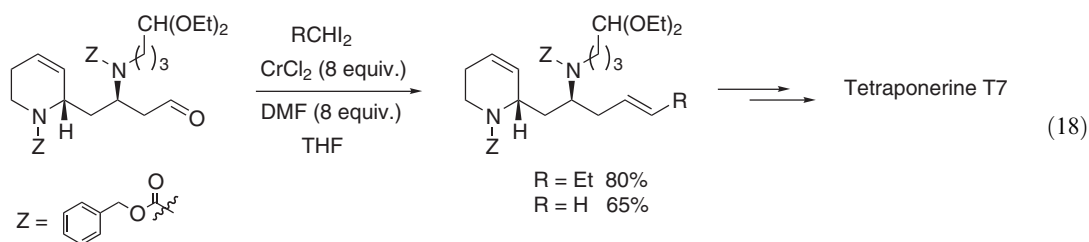


An interesting variant involves α -acetoxy bromides, more readily available than dihalides, with a Cr(II) species prepared *in situ* from CrCl₃ and Zn in the presence of a donor ligand such as DMF or TMEDA (COFGT (1995)) <1993SL837>. Ketones and esters remain unaffected under these conditions.

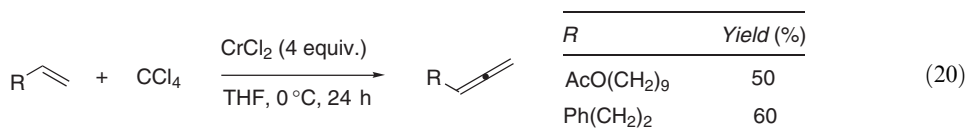
This reaction tolerates other heteroatoms at the geminal position, so functionalized alkenes can be synthesized: Bu₃SnCHI₂ <1998TL6419>, Bu₃SnCHBr₂ <1995T3713, 1999JCS(P1)2911> (Equation (15)), Me₃SnCHBr₂ <1995TL763>, PhSCHCl₂ <1987TL1443>, Me₃SiCHBr₂ <1987TL1443>, (Me₃Si)₂CBr₂ <1997JCS(P1)2279> (Equation (16)), and (RO)₂BCHCl₂ <2001TL2517> (Equation (17)).



The high (*E*)-selectivity and mild conditions make this reaction a powerful tool in organic synthesis <2000JA9584, 1998TL8313, 1997TL4823, 2001OL3487, 2001TL2517, 2001JOC2118, 2001JMC3692, 2001JA12191, 2001AG(E)2326, 2002OL4403, 2002AG(E)4751, 2003JOC1771, 2003JOC1780, 2003CEJ389> (Equations (18)–(19)). The scope of this reaction has been extended by coupling *in situ* the vinyl iodide formed with another carbonyl group to synthesize in one-pot the corresponding allylic alcohol <1999S1, 1999CRV991>.

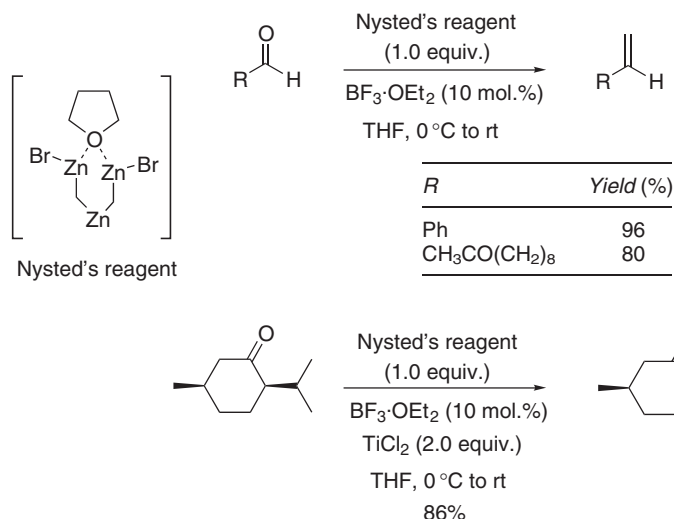


Finally, Takai recently reported the synthesis of allenes from the condensation of a *gem*-dichromium carbenoid with an alkene <2002SL1164> (Equation (20)).



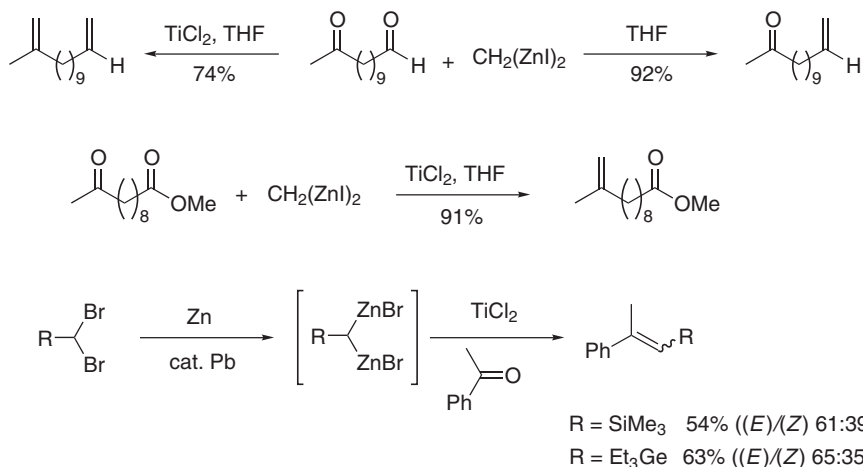
1.15.2.2 Zinc-mediated Condensation

Organozinc reagents have also been successfully applied to such olefinations. Treatment of carbonyl compounds or α,β -unsaturated aldehydes with $\text{CH}_2\text{X}_2\text{-Zn}$ provides methylenated products in good yields in the presence of a Lewis acid such as TiCl_4 [<2001JOM\(617-618\)39>](#). Nysted's reagent (cyclobis(bromodimethylzinc)- μ -methylene(μ -tetrahydrofuran)triazine), a commercially available *gem*-dimetallic compound, reacts with aldehydes in the presence of $\text{BF}_3\cdot\text{OEt}_2$ affording methylenated products, whereas methylenation of ketones proceeds in the presence of $\text{BF}_3\cdot\text{OEt}_2$ and TiCl_2 [<1998SL313>](#) (Scheme 24). This reaction is successful even with readily enolisable carbonyl compounds.

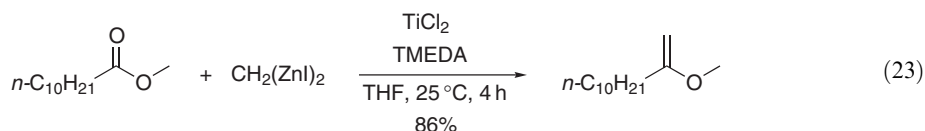
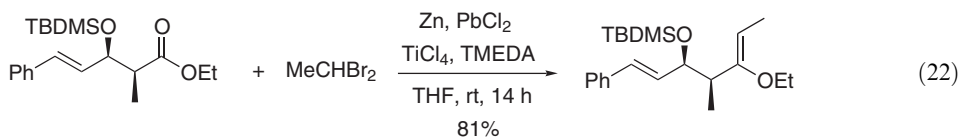
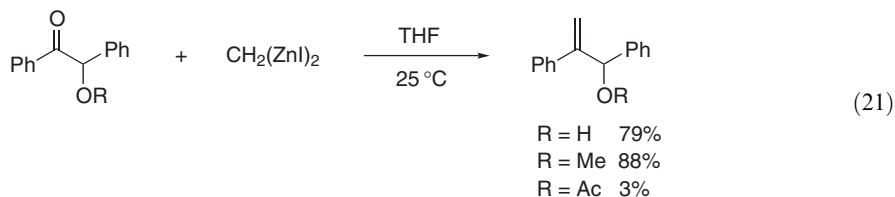


Scheme 24

Condensation of 1,1-bis(halo)zincio)alkanes, prepared with Zn under Pb catalysis, with aldehydes proceeds smoothly without TiCl_2 , although the TiCl_2 -mediated reaction is much faster. One equivalent of TiCl_2 is essential to have good yields with ketones [<1998SL1369, 2000SL495>](#) (Scheme 25) except for α -oxygenated ketones [<2001SL513>](#) (Equation (21)). This method yields poorer stereoselectivity than the chromium coupling. Methylenation of esters is carried out with the *gem*-dihalide Zn in the presence of TiCl_4 and TMEDA [<1996OS73, 1998TL685, 2000SL737, 2001JCS\(P1\)1051>](#) (Equation (22)), or by using 1,1-bis(iodo)zincio)methane with 4 equiv. of TiCl_2 and 8 equiv. of TMEDA [<1999CL825>](#) (Equation (23)).

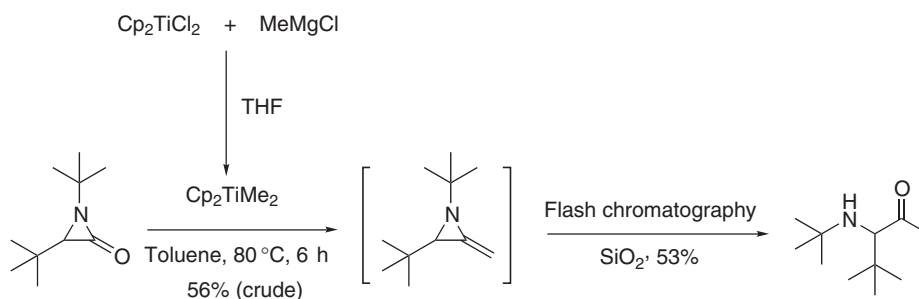


Scheme 25

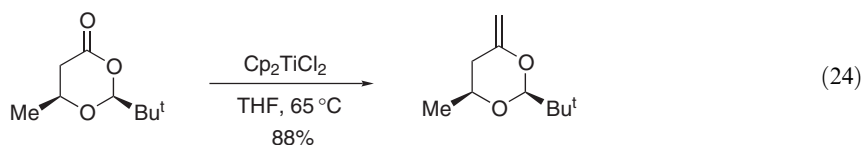


1.15.2.3 Condensations Mediated by Other Metals

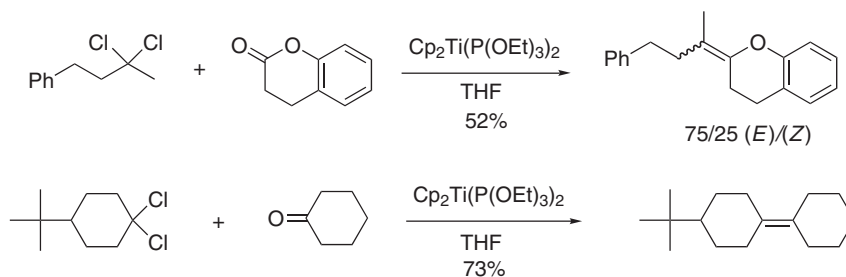
Different titanium-based organometallic derivatives have been developed for olefination of carbonyl compounds, esters or amides: the Tebbe reagent derived from titanocene dichloride and trimethylaluminum <2002T2011> and Grubbs' titanacyclobutanes. Both tolerate no functionality in the titanium reagent allowing thus only methylenation. Petasis reported a more easily handled and a more general titanocene derivative prepared by thermolysis of dialkyltitanocenes, for the mechanism (see <1996OM663, 2003OL1391>). This method is limited because the organolithium or Grignard reagents used (Scheme 26) <2000TL1975> to synthesize the dialkyltitanocene cannot bear a hydrogen β to the metal (Cp_2TiCHR , R = H, Ar, SiMe_3) (Equation (24)) <1993OR1, 1996TL141, 1997TA1115, 2003OL399>.



Scheme 26

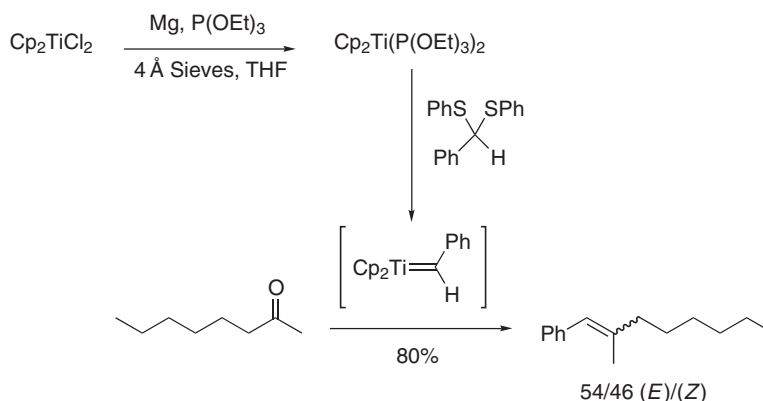


The synthesis of tri- and tetrasubstituted olefins has been performed by using Takeda's titanocene and *gem*-dihalides having two alkyl substituents (Scheme 27) <1998JOC7286> (easily prepared by the treatment of the corresponding hydrazone with $\text{CuX}_2\text{--Et}_3\text{N}$ in methanol <1997T557>).



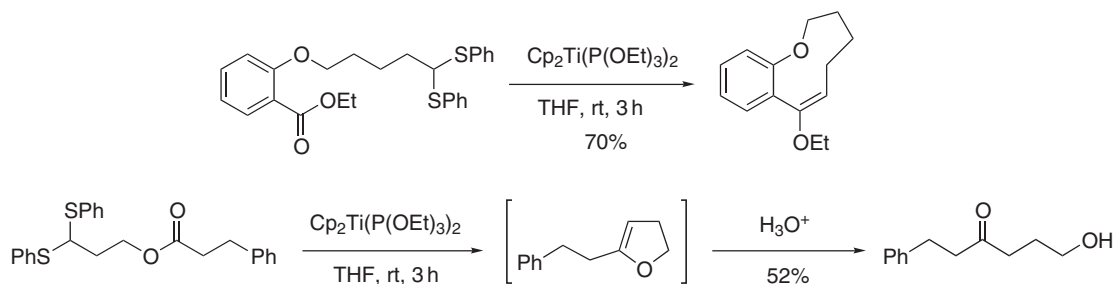
Scheme 27

Desulfurizative titanation of thioketals developed by Takeda constitutes a very convenient olefination reaction of carbonyl compounds (Scheme 28) <1997JA1127, 1998AG(E)453>.

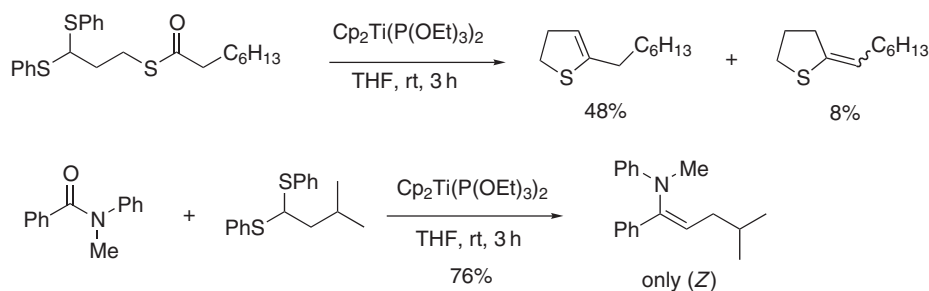


Scheme 28

Dithioketals, easily prepared from the corresponding carbonyl compounds, are treated with a low-valent titanium complex $[\text{Cp}_2\text{Ti}(\text{P}(\text{OEt})_3)_2]$ to form probably a titanium-alkylidene species, which reacts smoothly with aldehydes, ketones, esters (Scheme 29) <1997JA1127, 2000T763, 2001CC625>, thioesters <1999SL1029>, and amides <2003TL5571> (Scheme 30). This reaction gives poor selectivities except in the case of esters and amides.

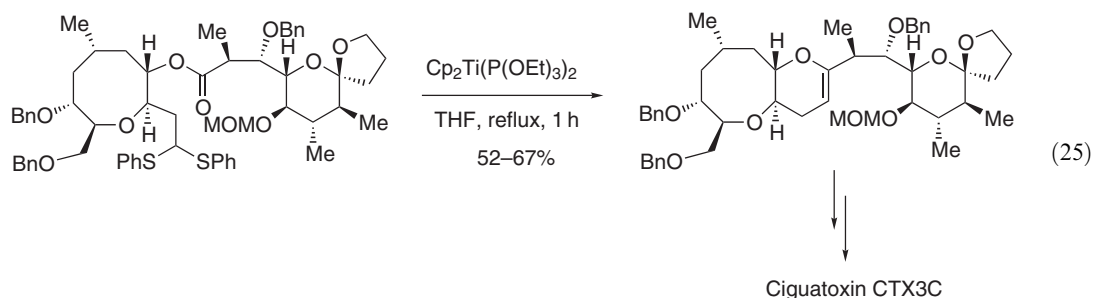


Scheme 29



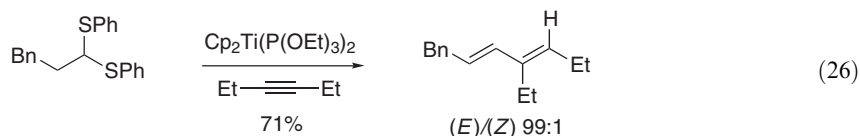
Scheme 30

This convenient method is compatible with various functionalities (Equation (25)) <2001CC381> but is not efficient in the case of thioketals derived from dialkyl ketones (treatment of such thioketals with $\text{Cp}_2\text{Ti}(\text{P}(\text{OEt})_3)_2$ gives the corresponding alkenyl sulfide <1998JOC7286>).

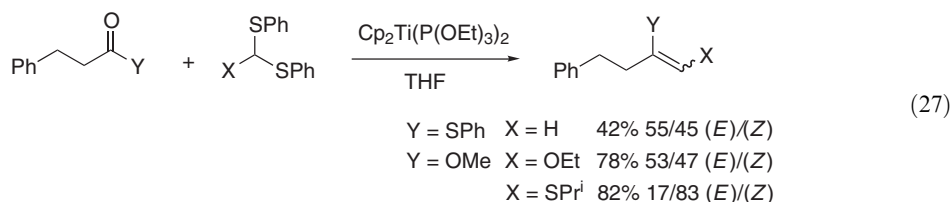


The Takeda olefination of esters has been performed on solid phase toward the synthesis of benzofurans and indoles <2003JOC387, 2000TL4987>.

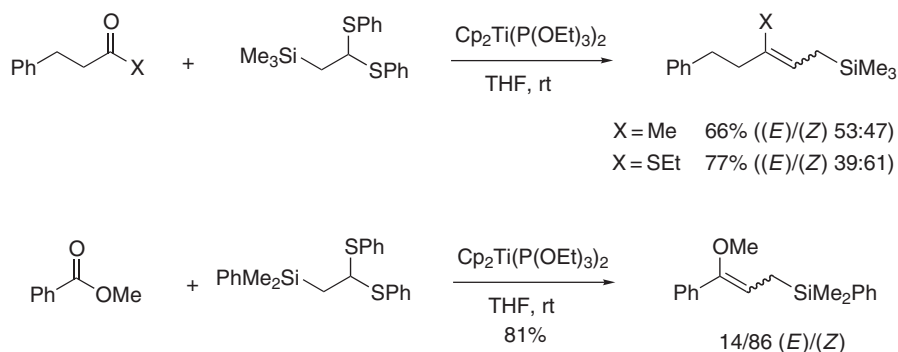
The titanocene-promoted reaction of thioketals with alkynes offers an easy access to conjugated dienes with a high stereoselectivity (Equation (26)) <1997CC1055>.



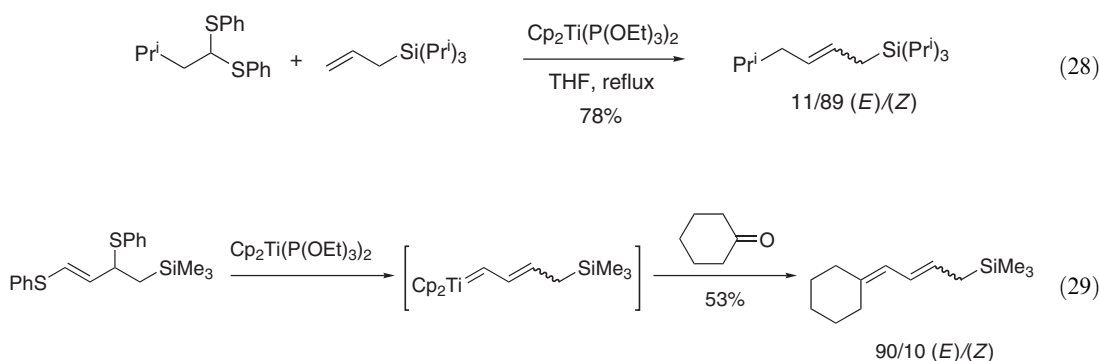
This method has also been applied successfully to the preparation of 1-alkenyl ethers and sulfides by using di- and trithioorthoformates (Equation (27)) <1998TL2153>.



Synthesis of allyl silanes can be performed by using a β -trialkylsilyl thioketal (Scheme 31) <1998TL3753> or by treating a trialkylallylsilane with a thioketal (Equation (28)) <1998CC51>. In the latter case, the γ -substituted allyl silane is obtained with a good (Z)-selectivity. A similar reaction has been developed to prepare allyl silanes from 2,4-bis(phenylthio)but-3-enylsilane (Equation (29)) <2000TL8377>.



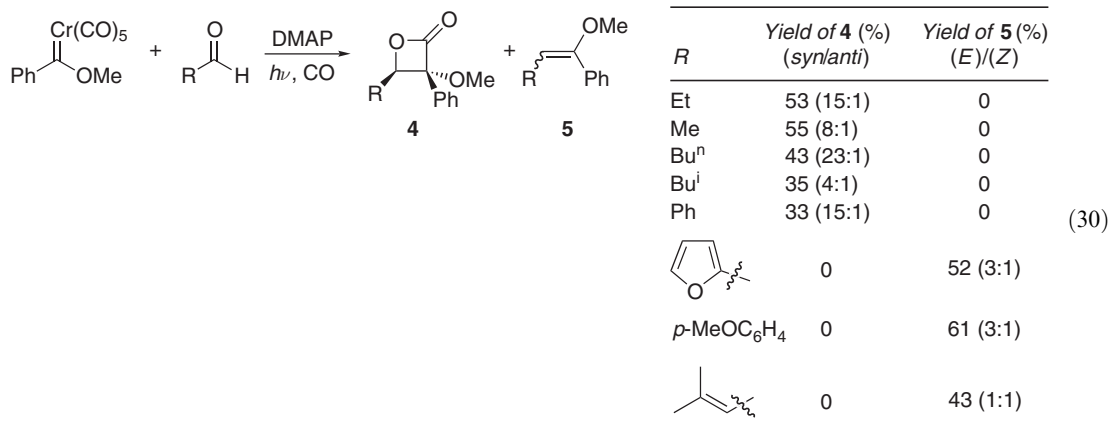
Scheme 31



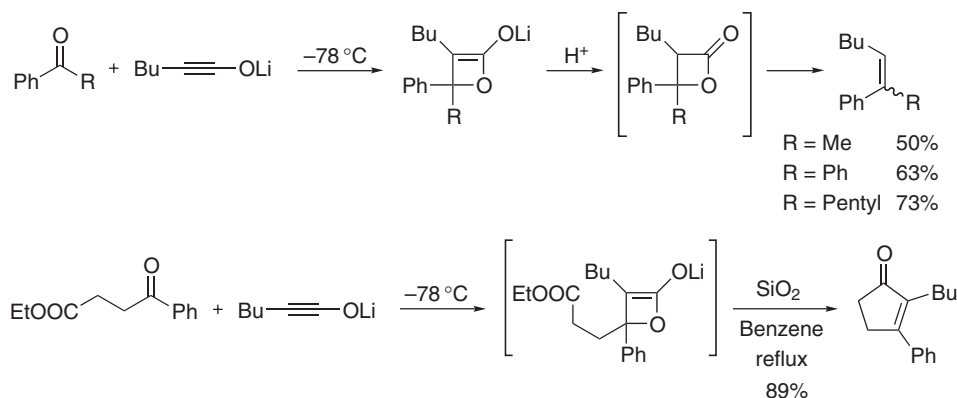
1.15.3 BY CONDENSATION OF OXYGEN FUNCTIONS

1.15.3.1 Synthesis of β -Lactones and Subsequent Decarboxylation

Elimination of carbon dioxide from β -lactones is an efficient route to alkenes. Reactions of aldehydes with ketenes generated from Fischer chromium carbenes lead either to the β -lactones or directly to the enol ethers if the aldehyde is electron deficient (Equation (30)) <2003JOC6056>. The formation of the β -lactones is catalyzed by 4-dimethylaminopyridine (DMAP) and is stereo-selective in favor of the *syn*-isomer.



Addition of ynolate anions, generated from α,α -dibromo esters and *t*-BuLi <1998T2411>, to aldehydes and ketones provides the β -lactone enolates in good yields <2001JOC7818>. These anions can either be hydrolyzed to the corresponding β -lactones which are in turn decarboxylated to furnish alkenes, or involved in a tandem cycloaddition/Dieckmann condensation (Scheme 32).



Scheme 32

1.15.3.2 Conversion of Carbonyl Compounds to 1,3,4-Thia- and 1,3,4-Selenadiazolines and Extrusion of N₂ and S or Se and Related Reactions

Sequential extrusion of nitrogen and sulfur from 1,3,4-thia- or 1,3,4-selenadiazolines gives alkenes. These compounds have been scarcely studied since 1995. A synthesis of spiro 1,3,4-thiadiazolines was reported <1998JCR(S)824>.

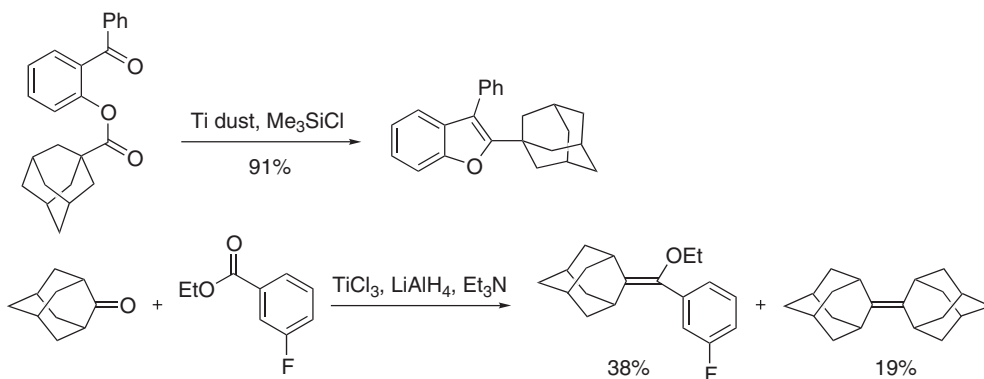
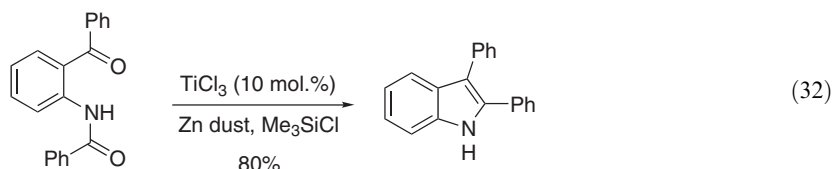
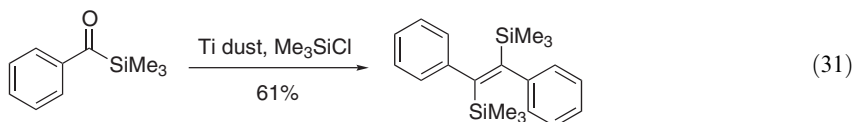
Syntheses of sterically hindered alkenes by extrusion processes were recently described <2000JOC1799>.

1.15.3.3 McMurry Coupling of Carbonyl Compounds

The reductive coupling between two carbonyl compounds in the presence of low-valent titanium compounds to give an alkene is known as the McMurry reaction. It is applicable to a large variety of aldehydes and ketones. It has been widely used in its intramolecular version to synthesize a large array of compounds (for a review, see <1996AG(E)2442>): strained olefins <1996AG(E)2442>, medium- <1995JA645> and large-size rings <1996AG(E)2442, 1995S63, 1996LA655, 1997TL7353, 1998TL7079>, and heterocycles <2003TL3035>. However, the intermolecular coupling was mainly used for homocoupling reactions <1996TL645, 2000TL10277, 2002OM2993, 2002OM2635>. Few examples of efficient cross-coupling reactions have been reported, and they generally require a similar redox potential for both carbonyl compounds and the use of an excess of one of the coupling partners <1997JOM(541)355>.

Previous studies supposed that the reaction proceeds via the formation of zero-valent Ti particles. It is now admitted that the TiCl₃ is reduced to a + (II) oxidation state and that a carbenoid species is a possible intermediate <1995JOM(502)109, 1997AG(E)2234, 1997AG(E)2380, 2001CEJ3043, 2002OM2635>. The classical McMurry conditions are [TiCl₃·(DME)_{1.5}] in combination with a reducing agent such as Zn(Cu), Zn, Mg, Li, C₈K, Na/Al₂O₃ or Na/TiO₂ <1995S63>, LiAlH₄, and metal arene <1991JOC6447, 1996CRV877, 1998JOC5235, 2001JOC2990>. Reactivity of the low-valent titanium species depends on the reducing metal, the solvent, and additives. For example, pyridine stops the reductive coupling at the pinacol stage <1996JA5932>, substoichiometric iodine allows reaction at 0 °C or lower temperatures <1998JOC4925>, and activation with Me₃SiCl renders the reaction catalytic in TiCl₃ <1995JA4468>. The (*E*)/(*Z*)-selectivity is rarely predictable <2002OM2635, 2000JOC7990>.

This reaction has been extended successfully to acyl silanes (Equation (31)) <1995T8875>. Keto amides cyclize to give pyrroles and indoles <1995AG(E)678, 1995JOC6637, 1995JA4468, 1996T7329> (Equation (32)). The McMurry coupling was also used to couple ketones with esters either in the intramolecular version to furnish heterocycles <1995JA4468> or more recently in an intermolecular reaction <2000CA150547, 2000CA207841, 2002TL3645> (Scheme 33). In the latter case, the reaction is limited to hindered ketones and benzoates.



Scheme 33

The McMurry reaction was employed in numerous total syntheses, such as zearalenone <2000JOC7990>, dihydrocembrene and sarcophytol derivatives <2000JCS(P1)4250, 1999TL965>, alkaloid ipalbidin <2003TL3035>, etc.

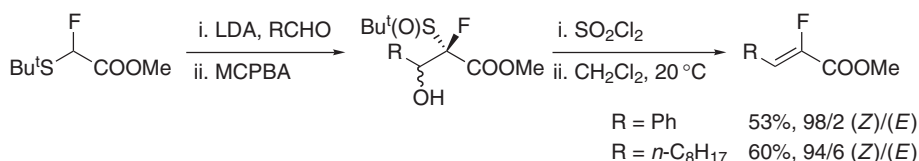
1.15.3.4 Addition of Organometallic Reagents to Carbonyl Compounds and *In Situ* Dehydration

No new significant examples of this process have been reported since COFGT (1995).

1.15.4 BY CONDENSATION OF SULFUR, SELENIUM, OR TELLURIUM FUNCTIONS

1.15.4.1 Alkylation of Sulfur(II)-stabilized Carbanions and Elimination

Addition of anions stabilized by adjacent sulfides to carbonyl compounds <1998T10801>, followed by oxidation and reductive elimination of the resulting β -hydroxysulfoxides, is an efficient access to alkenes. Since 1995, only one example of such a tandem reaction has been reported <1999OL1539>. The reaction is stereoconvergent (Scheme 34), leading to the (*Z*)-isomer from both *syn*- and *anti*- β -hydroxysulfoxides.

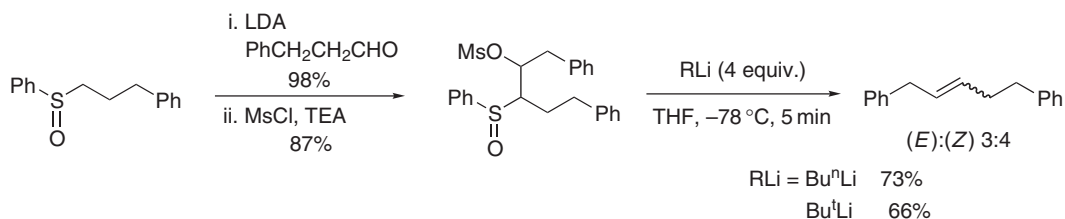


Scheme 34

1.15.4.2 Alkylation of Sulfur(IV)-stabilized Carbanions Followed by Elimination

1.15.4.2.1 Alkylation of sulfoxides and elimination

Addition of sulfoxide-stabilized carbanions to carbonyl compounds has been extensively studied, as well as the *syn*-elimination of the sulfenic acid for the synthesis of alkenes. However, the two procedures have not been linked until recently, when Satoh published a sulfoxide version of the Julia–Lythgoe olefination (Scheme 35) <2000T6223>.



Scheme 35

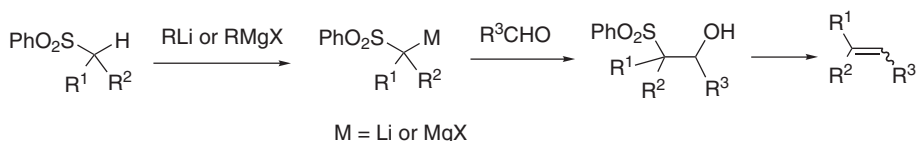
1.15.4.2.2 Alkylation of sulfinamides and elimination

Reaction of α -lithiosulfinamides with carbonyl compounds, followed by thermal elimination of the resulting β -hydroxysulfinamides, furnishes alkenes (COFGT (1995)). No new report has been published since 1995.

1.15.4.3 Alkylation of Sulfur(VI)-stabilized Carbanions Followed by Elimination

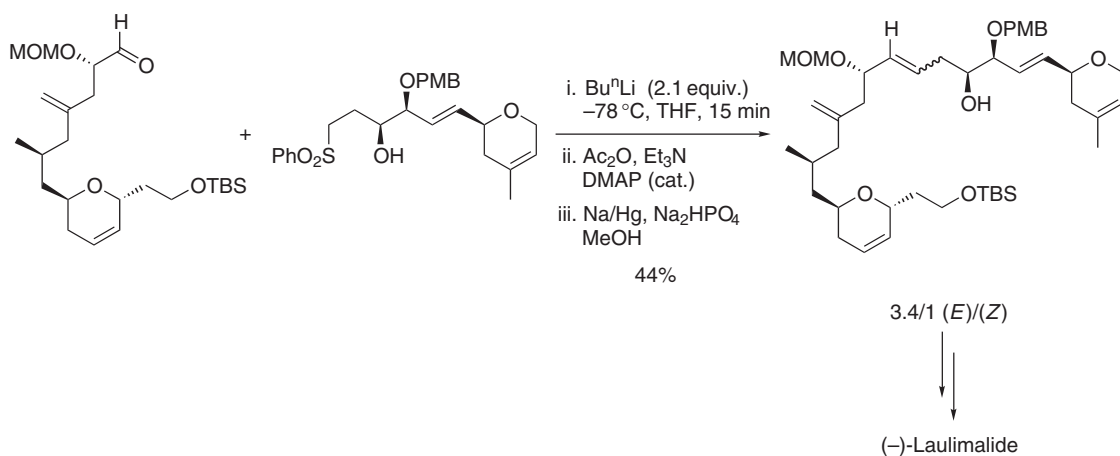
1.15.4.3.1 The Julia reaction and related transformations

The condensation of a sulfone anion with a carbonyl compound and the subsequent reductive elimination is usually referred to as the Julia reaction <1973TL4833>. Further studies have been reported by Lythgoe and Kocienski <1978JCS(P1)829, 1978JCS(P1)834>. This olefination method proceeds as follows: metallation of the sulfone, condensation of the sulfone anion with a carbonyl compound, and reductive elimination of the resulting β -hydroxysulfone (Scheme 36).



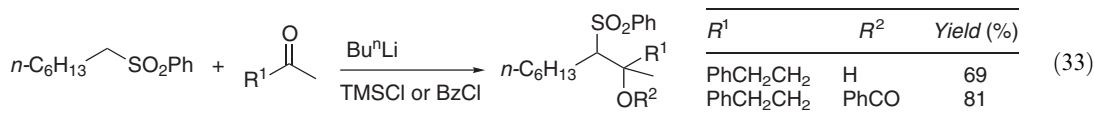
Scheme 36

The sulfone anion is generated by using alkylolithium bases such as BuⁿLi in THF, Bu^tLi <1999S188>, MeLi <1986TL2095>, PhLi <1990JA7407>, lithium diisopropylamide (LDA) <1988JOC4282>, LiHMDS <1995JA8258>, or magnesium bases in the case of easily enolizable carbonyl compounds <1978JCS(P1)829>. Use of the co-solvent HMPA is sometimes required <2003SL393>. For sulfones with additional acidic protons, it is possible to avoid protection with the use of polyanions (Scheme 37) <2001JOC8973>.



Scheme 37

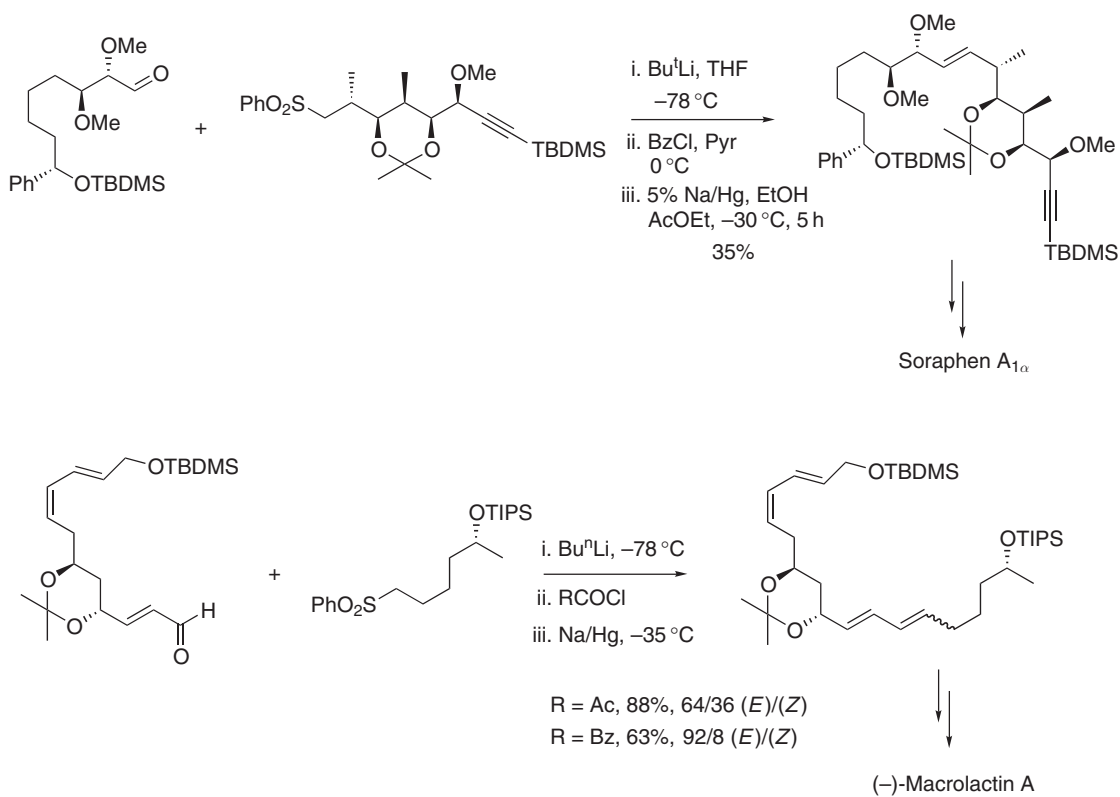
The condensation of the metallated sulfone with the carbonyl is effected at low temperatures (in case M = Li, the equilibrium is in favor of starting materials at high temperatures). It can be promoted by Lewis acids such as BF₃·OEt₂ <2002JOC4346>. The condensation of a sulfone anion and a ketone requires the tertiary alkoxide adduct to be trapped with either TMSCl or PhCOCl to obtain, after aqueous work-up, the corresponding β-hydroxy- or β-benzoyloxysulfone (Equation (33)) <1996TL2089, 1995JA8258>.



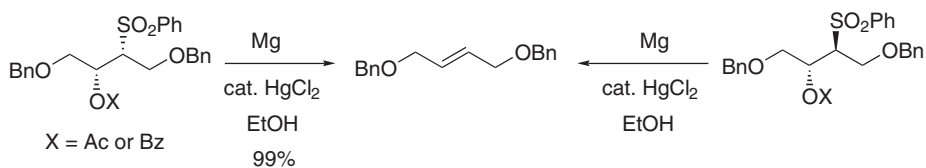
The β-hydroxysulfone can be reduced directly with sodium amalgam <2002JOC4346>. SmI₂ in THF does not effect the reductive elimination except in the case of imidazolyl sulfone <1990TL7105>. The use of Inanaga's conditions (SmI₂ with 1–5 mol.% HMPA in THF at 0°C) provides the desired alkene from the β-hydroxy phenyl sulfone in good yields <1996TL2089, 2001T2609, 1995JOC3194, 1994SL859>. The β-hydroxysulfone is generally converted *in situ* into an ester (Ac <1993BSF256, 2002JA1664>, Bz <1996TL2089>, or trifluoroacetate <1990JA2786>) prior to reduction. Reduction generally proceeds at low temperatures with sodium amalgam in methanol (Scheme 38) <2003SL393, 1999S188, 2002JA1664>, Mg in ethanol (Scheme 39) <1995TL5607>, or SmI₂ in the presence of 0–5 mol.% of HMPA (Scheme 40) <2001T2609, 1996TL2089> to produce mainly the (E)-alkenes. The mechanism of the reduction of both β-hydroxy- and β-benzoyloxysulfone has been discussed by Marko and co-workers <1996TL2089, 2001T2609>.

Generally, the more the chain-branching, the better is the *trans*-selectivity in this reaction (Figure 5) <1980JCS(P1)1045>.

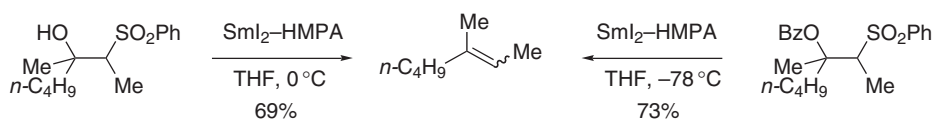
The β-hydroxysulfone can be transformed into a xanthate which is eliminated in good yields and high *trans*-selectivity even when the ester method fails. Elimination is carried out by treating the xanthate with Bu₃SnH <1988JOC4282>.



Scheme 38



Scheme 39



Scheme 40

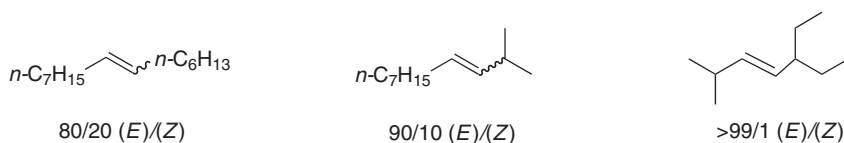
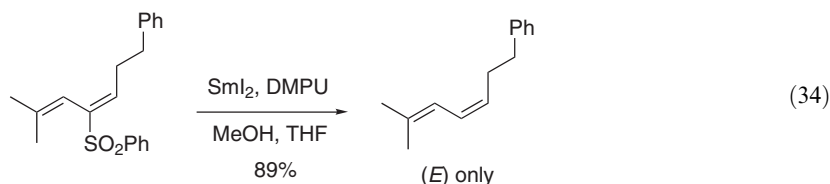
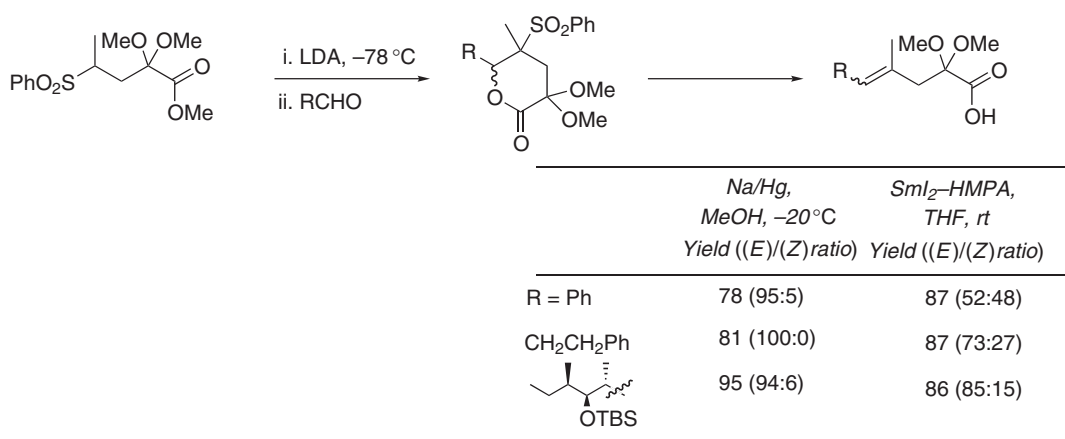


Figure 5

The formation of alkenes can also result from a two-step pathway: prior elimination of the hydroxyl group (elimination of the acetate with LDA or 1,5-diazabicyclo[5.4.0]undec-5-ene (DBU) <1995JOC3194> or Bu^tOK <2002JA1664>) followed by the reduction of a vinyl sulfone with SmI₂ <1995JOC3194>. This method provides (*E*)-alkenes with high selectivities (Equation (34)).

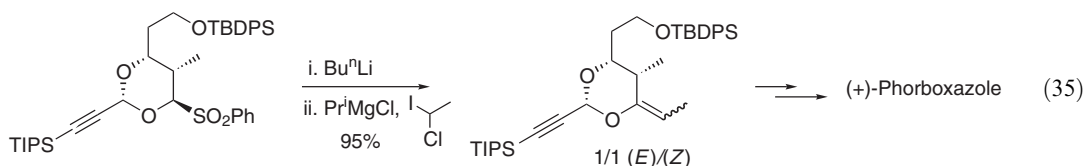


The Julia reaction is an efficient method for the preparation of (*E*)-1,2-disubstituted alkenes, but few examples of trisubstituted alkenes have been described <1990JA2786>. Marko <1996TL2089, 2001T2609> reported an efficient preparation of trisubstituted alkenes from ketones with an (*E*):(*Z*) ratio in a typical range of 2:1 (the ratio is independent of the relative stereochemistry of the starting hydroxy- or benzoyloxysulfone). Férézou obtained an (*E*)-trisubstituted alkene with an excellent diastereoisomeric excess when the reducing agent is Na/Hg, whereas SmI₂ is less selective (Scheme 41). This result suggests a different pathway for the two reducing agents <1998SL1223>.



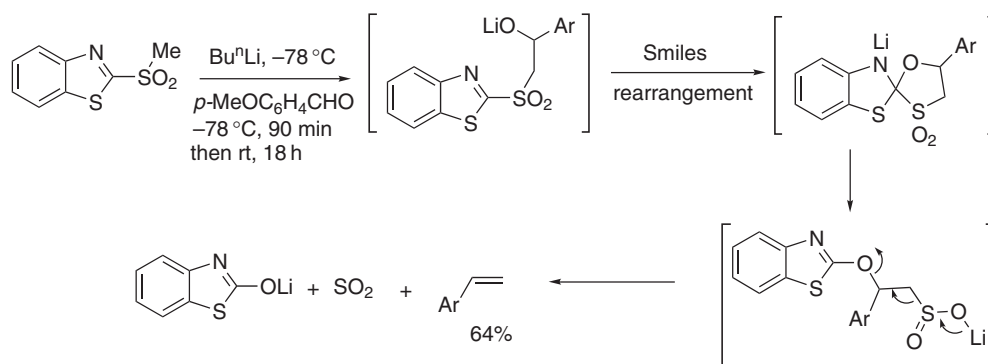
Scheme 41

A similar olefination called Julia type II involves the α -alkylation of a sulfone with an electrophilic α -halo Grignard reagent <1992SL133>. This pathway can be an alternative method in case the classical Julia fails (Equation (35)) <2001JA10942>.



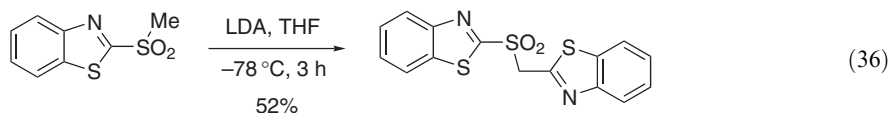
A one-pot procedure, first reported by S. Julia, has been developed by replacing phenyl sulfones with heteroaryl sulfones. The addition of the heteroaryl sulfone anion to a carbonyl proceeds in a fashion analogous to the classical Julia olefination, but because of the heteroaromatic moiety the β -hydroxysulfone is unstable and easily undergoes a Smiles rearrangement <1991TL1175>. This powerful method is compatible with a large range of heteroaromatic sulfones. The three types of sulfones commonly involved in the modified Julia olefination are presented here <2002JCS(P1)2563>.

The first one is benzothiazo-2-yl sulfones (BT-sulfones). The great electrophilicity of the carbon of the thiazolyl moiety renders the Smiles rearrangement very facile (Scheme 42) <1991TL1175, 1993BSF856, 1993BSF336>.

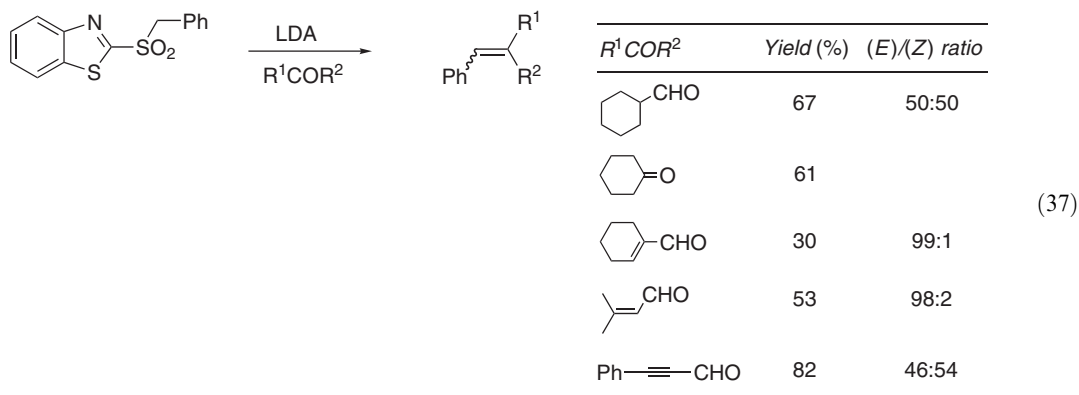


Scheme 42

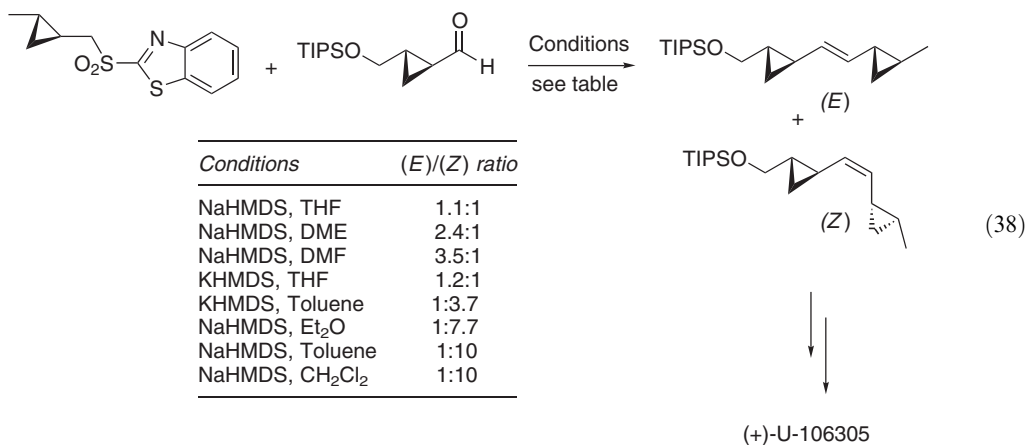
Deprotonation of these sulfones requires non-nucleophilic bases (to avoid *ipso*-substitution on the heteroaromatic moiety) such as LDA <1991TL1175> or LiHMDS <2002TL1373>. This metallation step is quite difficult because of the propensity of the sulfone to self-condense even at low temperatures (Equation (36)).



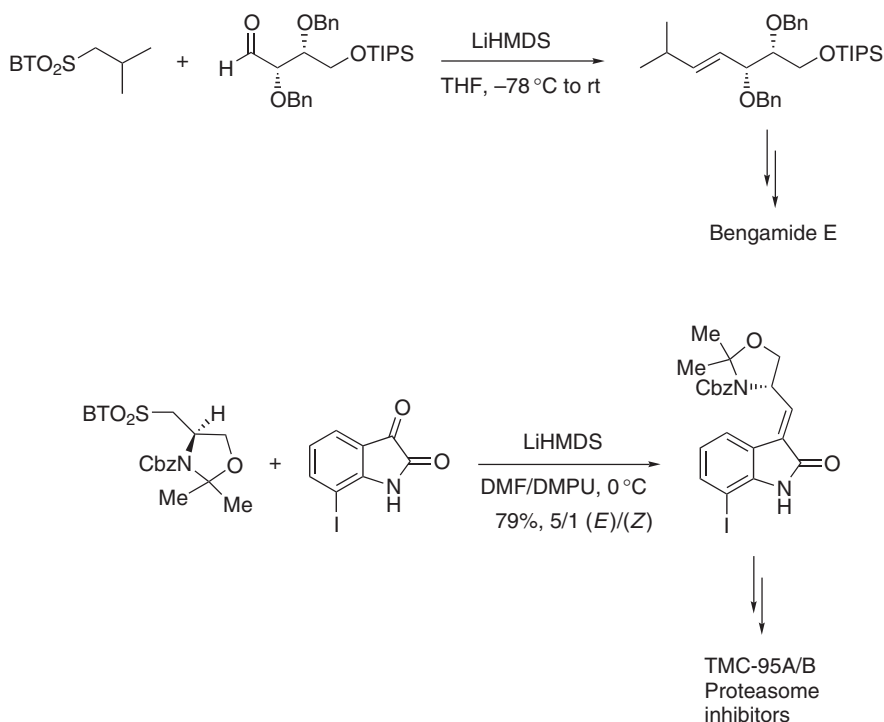
Barbier conditions can improve the olefination yields but are not always compatible with highly functionalized carbonyl compounds. S. Julia reported a systematic study on the stereochemical outcome of the addition/elimination sequence and proposed a mechanism for the equilibration between *syn*- and *anti*- β -hydroxysulfones through retroaddition/addition which dictates the corresponding selectivity of the alkene formation <1993BSF856, 1993BSF336>. This method generally provides 1,2-disubstituted alkenes, favoring the (*E*)-isomer (Equation (37)).



More recently, Charette and co-workers [<1996JA10327>](#) (see also [<2001TL5149>](#)) described the effect of solvent, counterion, and temperature on the selectivity of the alkene. They showed that the (*E*)- or the (*Z*)-isomer can be obtained very efficiently simply by changing the solvent of the reaction ([Equation \(38\)](#)).

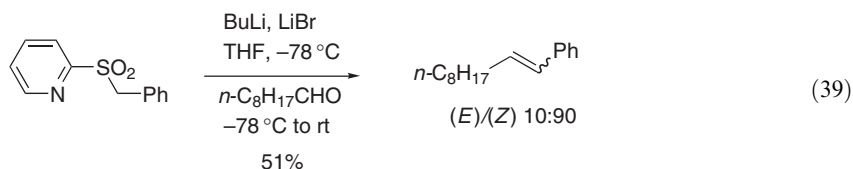


This reaction has been successfully used in various total syntheses such as bengamide E and TMC-95A/B [<1996JA10327, 1998JCS\(P1\)3907, 2003OL197, 2001TA1251, 2002TL1373, 2001T681>](#) ([Scheme 43](#)).

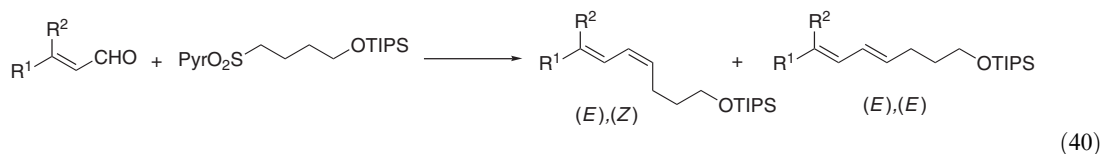


Scheme 43

Pyridin-2-yl sulfones (Pyr-sulfones) constitute the second heteroaromatic sulfone moiety currently used in this one-pot procedure. The metallated sulfones are more stable; they are less susceptible to self-condensation. Pyr-sulfones generally give lower yields of olefin, probably due to a less efficient elimination step, but the *cis*-selectivity is enhanced compared to the analogous BT-sulfones ([Equation \(39\)](#)) [<2002JCS\(P1\)2563>](#).

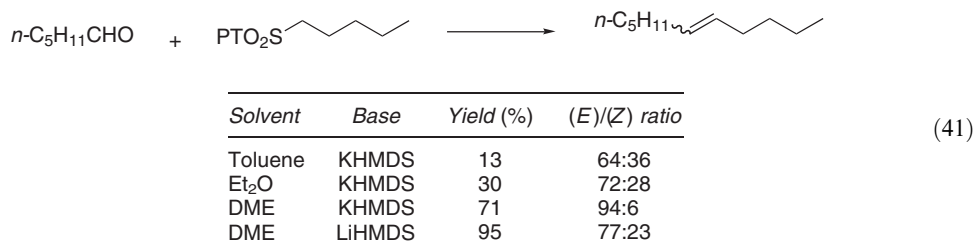


Charette recently reported an efficient synthesis of (*E*),(*Z*)-dienes by coupling a Pyr-sulfone and an α,β -unsaturated aldehyde (Equation (40)) <2001TL5149, 2001TL6619>.

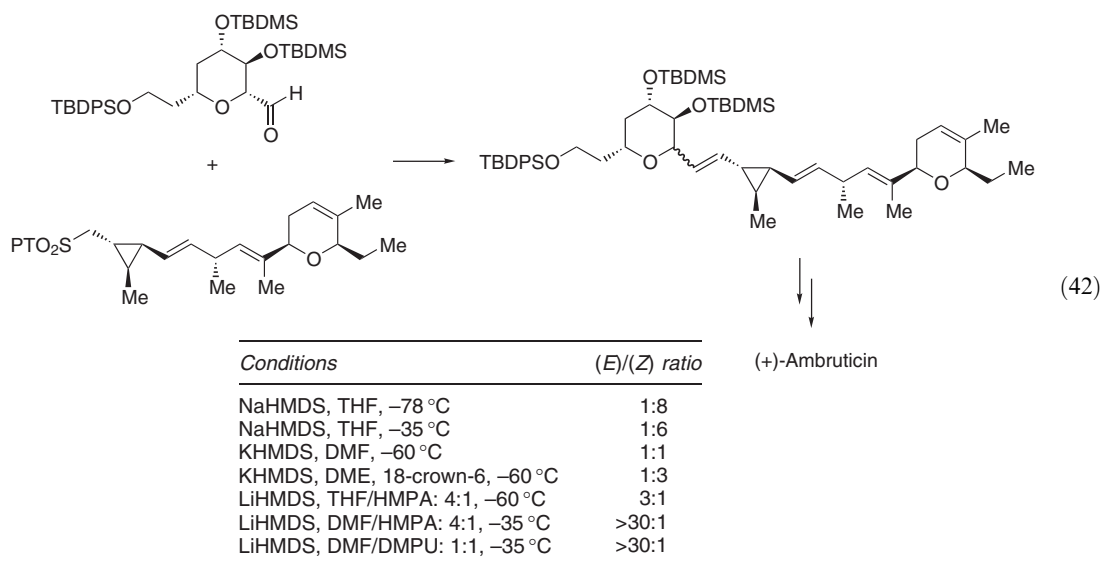


R^1	R^2	Conditions (base, solvent, temp.)	Yield (%)	(<i>E</i>),(<i>Z</i>)/(<i>E</i>),(<i>E</i>) ratio
H	Me	NaHMDS, toluene, 25 °C	54	91:9
H	Pr	KHMDS, toluene, 25 °C	64	90:10
H	Ph	KHMDS, toluene, 25 °C	70	92:8

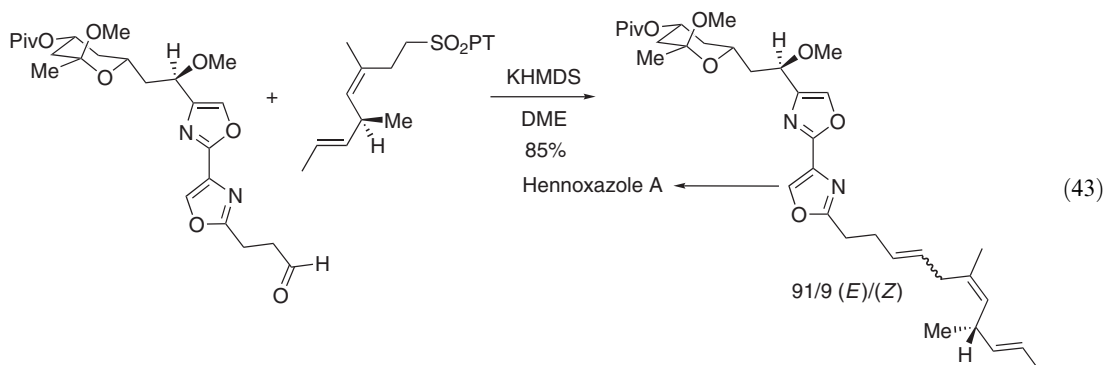
Kocienski has developed tetrazole analogs to achieve the modified Julia olefination. 1-Phenyl-1*H*-tetrazol-5-yl sulfones (PT-sulfones) generally give high yields of *trans*-olefins, in the absence of factors such as α -chain branching or conjugation, with no significant amount of self-condensation. The best conditions for this coupling are DME as solvent and KHMDS as base (Equation (41)) <1998SL26>.



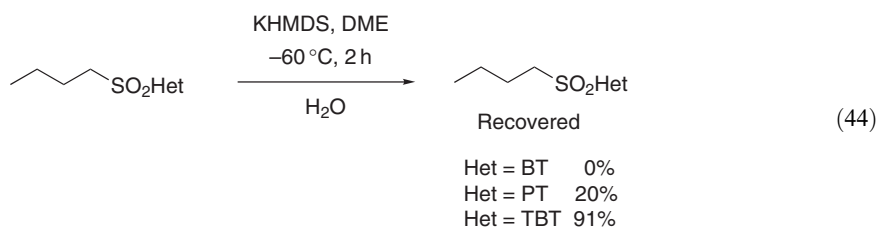
Jacobsen reported the synthesis of (*E*)- or (*Z*)-isomer depending on the solvent/base system used (Equation (42)) <2001JA10772>.



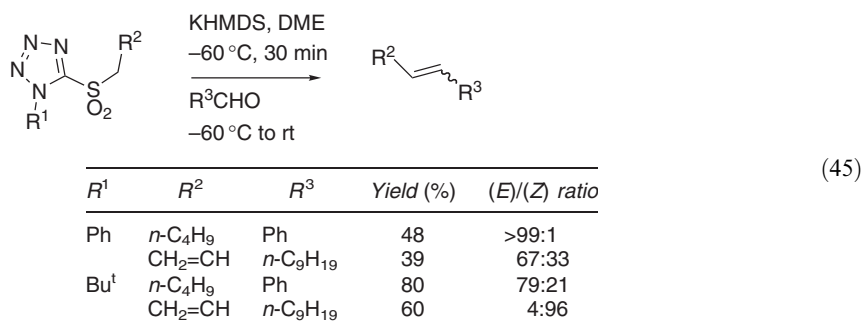
This coupling has been successfully applied to various total syntheses such as hennoxazole A (Equation (43)) <1999JA4924, 2002JA384, 2001JA10772, 2002AG(E)176, 2000TL7373, 2001JA12426, 2002JCS(P1)2563, 2002TL213, 2001T5161, 1999TL4897, 2002T4425, 2001OL2289, 1999JOC9632>.



The efficiency of PT-sulfones, probably due to the steric hindrance generated by the phenyl group, encouraged Kocienski to develop other bulky tetrazole derivatives. 1-*t*-Butyl-1*H*-tetrazol-5-yl sulfones (TBT-sulfones) have shown a low propensity toward self-condensation: this great stability allows premetallation (Equation (44)) of the sulfone thereby broadening the scope of the aldehyde that can be used in this reaction <2000SL365>.



The yields of 1,2-disubstituted alkenes are consistently higher with the TBT-sulfone compared with the corresponding phenyl substituted analog, but the *trans*-selectivity decreases (Equation (45)).



The synthesis of 1,2-disubstituted alkenes can be achieved with the classical or the modified Julia olefination. The PT-variant of the modified reaction seems to be the most efficient to provide (*E*)-alkenes in most cases. When chain branching <1996JA10327> or conjugation <1996S285, 1996S652> is to be considered, both BT- and PT-sulfones are efficient and lead to the desired olefin with high stereoselectivity. Very few trisubstituted olefins have been prepared with the modified Julia olefination. According to these examples, olefins are prepared in good yields but with modest selectivities <1999S1209, 2001OL1491>.

1.15.4.3.2 The Ramberg–Bäcklund reaction

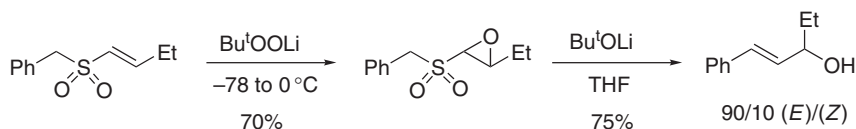
Ramberg and Bäcklund reported in 1940 that the treatment of α -bromoethyl sulfone with aqueous potassium hydroxide provided (*Z*)-but-3-ene as the major product. Since then this reaction has been widely studied <1991COS(3)861> (for a recent review, see <2003OR(62)357>).

The Ramberg–Bäcklund (RB) rearrangement involves the conversion of an α -halo sulfone to an olefin under basic conditions through the formation of the episulfone <1993SL660> and then extrusion of SO₂ (Scheme 44).



Scheme 44

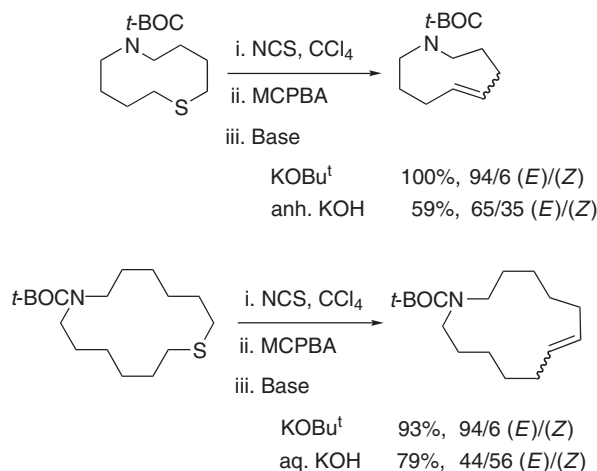
The leaving group is a halogen <1996JOC7644, 1999JA8237, 1991JA9682>, a tosylate <1980JOC1719>, or a sulfinate (*p*-toluenesulfinate <1986CL433>, trifluoromethanesulfinate <1986JA2358>). An epoxide version of the RB reaction has been reported by Taylor to synthesize allylic alcohols (Scheme 45) <1997TL3055>.



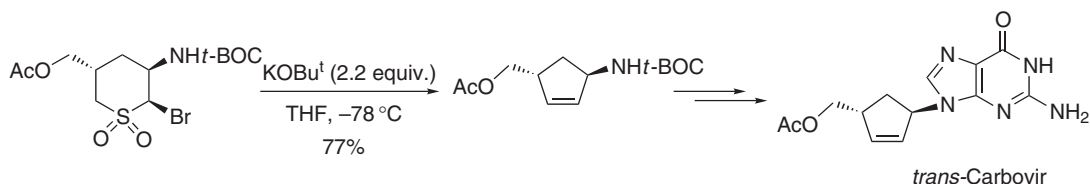
Scheme 45

α -Halo sulfones can be replaced by α -halo sulfides <1973TL4395>, α -halo sulfoxides <1986CB1540>, or α -halo-*N*-*p*-toluenesulfonyl sulfoximines <1978JOC4140>. The RB rearrangement can proceed under milder conditions by using phase transfer catalysts <1982S504>.

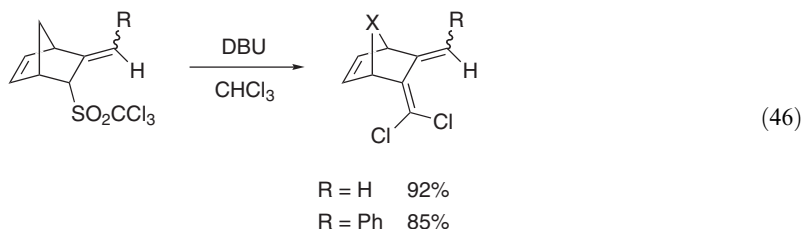
Different bases have been used in this rearrangement: strong hindered bases such as Bu^tOK/Bu^tOH give the best yields of (*E*)-olefin, whereas aqueous KOH favors the (*Z*)-isomer (Scheme 46) <2000JOC8367>. By using a nonprotic solvent, the reaction can be carried out at low temperature under mild conditions (Scheme 47) <1995TL7767, 1989T455>. The RB rearrangement of trichloromethyl sulfones is carried out in dry chloroform in the presence of DBU to furnish 1,1-dichloroalkenes in good yields (under classical conditions, 1,1-dichloroalkenes are only obtained in small amounts) (Equation (46)) <2000TL1501, 1998T1901>.



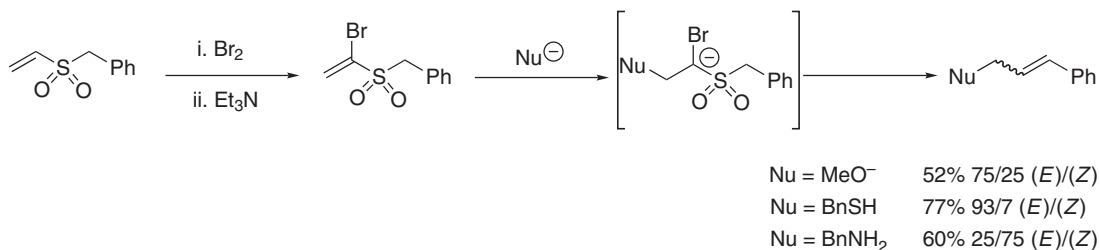
Scheme 46



Scheme 47

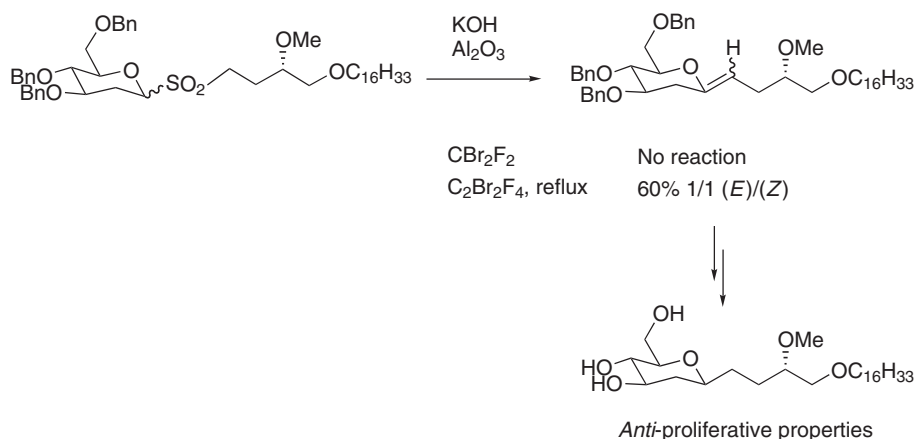


Vinylogous RB provides conjugated dienes. α -Halovinyl sulfones can undergo one-pot tandem conjugate addition-proton exchange-RB process (Scheme 48) <1997SL1043>.



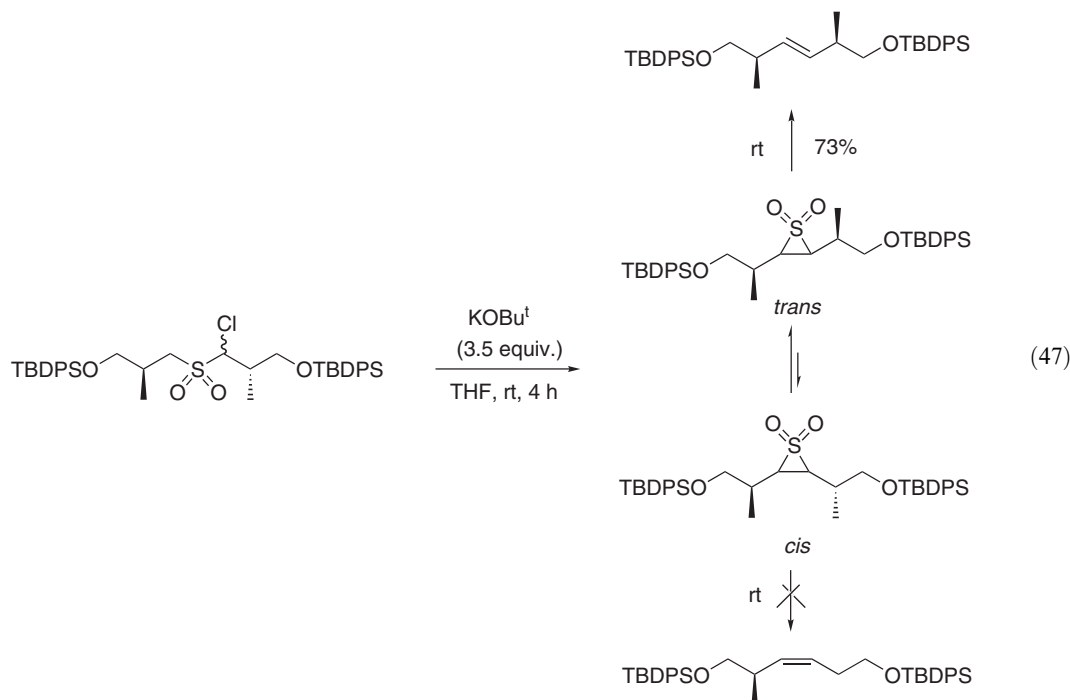
Scheme 48

A one-pot chlorination/RB-rearrangement procedure has been described by Meyers <1969JA7510>. Treatment of the sulfone with KOH, and CCl₄ in a mixture Bu^tOH/H₂O gives the desired olefin in good yields (under these conditions, acyclic dialkyl sulfones can give a significant amount of the dichlorocyclopropane resulting from the addition of the dichlorocarbene to the alkene). More recently, a new one-pot protocol has been developed using CBr₂F₂, KOH on Al₂O₃, and CH₂Cl₂ <1995CC1297>. Replacement of CBr₂F₂ (bp 23 °C) with CCl₄ <1999AG(E)2939> or with CBrF₂CBrF₂ (bp 47 °C) <1999OL2149> at reflux can solve the reactivity problem (Scheme 49).

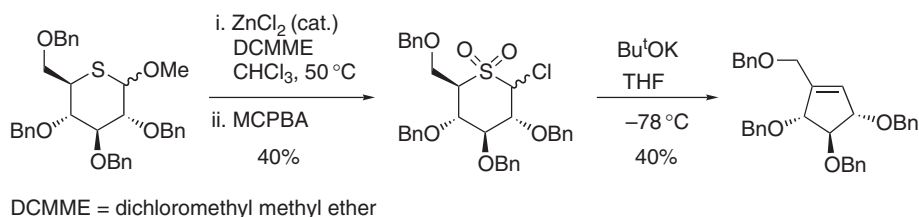


Scheme 49

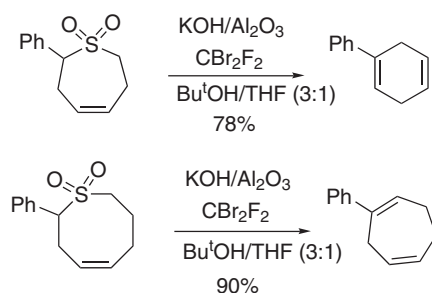
Extrusion of SO₂ proceeds with retention of configuration but the cyclization, which is the rate-determining step, is not normally stereocontrolled. One example of stereocontrol has been reported by Schmittberger and Uguen <1996TL29>. The synthesis of (*E*)-alkenes resulted from the treatment of α -chloro sulfones with an excess of base, which led to both *cis*- and *trans*-episulfones. The lack of reactivity of the *cis*-episulfone at room temperature allows its epimerization into the *trans*-isomer which is quickly transformed into the corresponding (*E*)-alkene (the (*Z*)-alkene is not formed at an appreciable rate below 80 °C) (Equation (47)).



Because of this lack of stereocontrol, the RB rearrangement has been mainly used for cyclization of strained systems <1997JOC2727, 2000TL1501> such as cyclobutenes <1988JA8197>, cyclopentenenes (Scheme 50) <2001TL1197, 1996TL7457>, cyclohexenes <2002OL427>, seven-membered rings (Scheme 51) <2000JOC8367>, and cyclic enediynes (Equation (48)) <2002JCS(P1)2485>. The synthesis of larger rings suffers from low yields and poor selectivities.

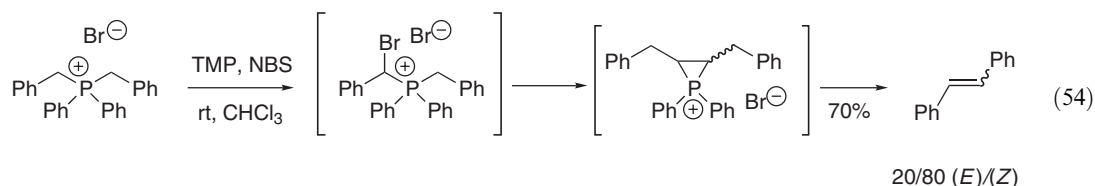


Scheme 50



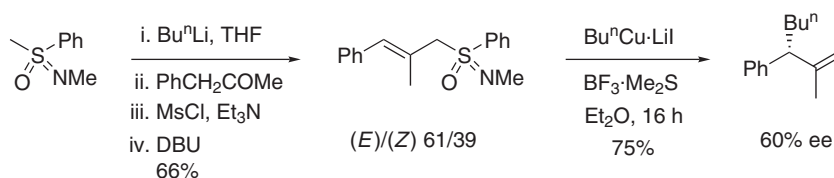
Scheme 51

Recently, a phosphorus version of the RB rearrangement has been described by Lawrence: dibenzylphosphonium bromide, treated with N-bromosuccinimide (NBS) in presence of 2,2,6,6-tetramethylpiperidine, gives stilbene via the corresponding epiphosphonium (Equation (54)) <1998T15345, 1998T15361>.



1.15.4.3 Alkylation of sulfoximine-stabilized carbanions followed by elimination—the Johnson (N-methylphenylsulfonimidoyl)methylolithium method

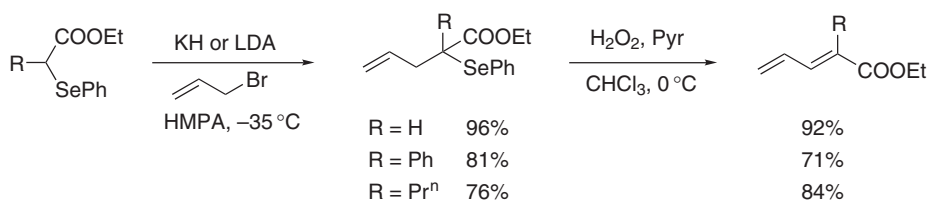
Addition of anions of alkyl aryl sulfoximines to carbonyl compounds gives β -hydroxysulfoximines, which can readily undergo reductive elimination using aluminum amalgam in aqueous THF/acetic acid to give alkenes (COFGT (1995)). β -Hydroxysulfoximines can undergo reductive elimination via the corresponding trimethylsilyl ethers to give chiral alkenyl sulfoximines. This reaction has been applied to the synthesis of isocarbacyclin (COFGT (1995)) <1998EJO1319>. The β -mesyloxysulfoximine derivatives can lead to allylic sulfoximines, which react with organo-copper reagents in the presence of boron triflate and lithium iodide to give substituted alkenes (Scheme 52) <1996JOC4379, 1998EJO1319>.



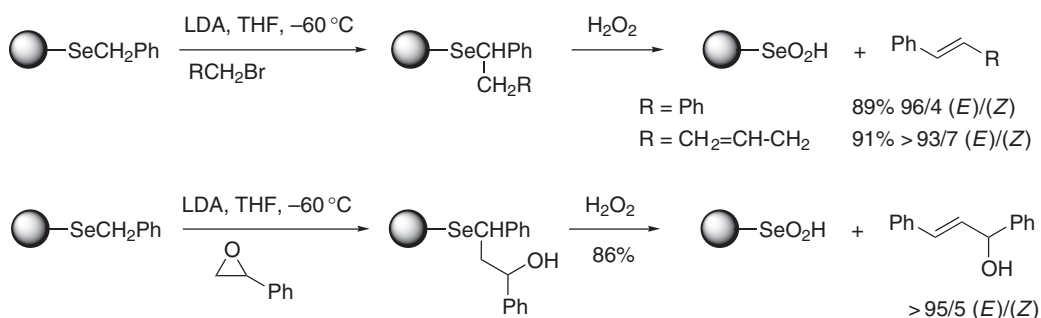
Scheme 52

1.15.4.4 Alkylation of Selenium(II)- and Selenium(IV)-stabilized Carbanions Followed by Elimination

Substituted selenides resulting from alkylation of selenium(II)-stabilized carbanions readily undergo *syn*-elimination after oxidation with H_2O_2 . This method has successfully been applied to the synthesis of 2,4-dienoic esters in good yields from selenium-stabilized ester enolates (Scheme 53) <2000T7483>, and alkenes or homoallylic alcohols from a user-friendly supported selenide anion (Scheme 54) <2002TL5495>.

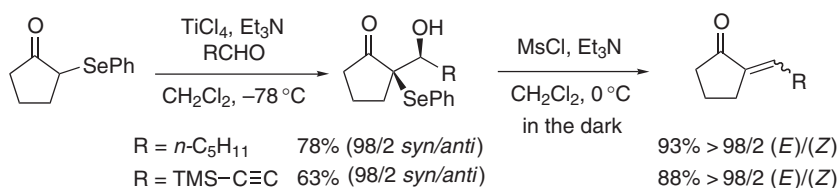


Scheme 53



Scheme 54

Addition of the titanium enolate derived from α -seleno carbonyl compounds or esters to an aldehydes provides α -hydroxyselenides, which are easily transformed into (*Z*)- α,β -unsaturated carbonyl compounds or esters (Scheme 55) <2001T6703>.



Scheme 55

Direct addition of selenoxide α -anions to carbonyl compounds is less synthetically useful (COFGT (1995)).

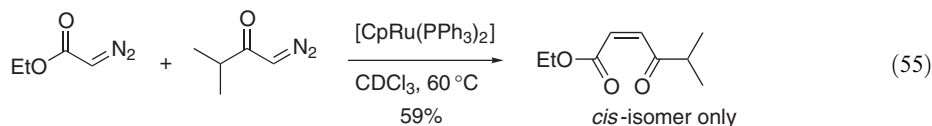
1.15.4.5 Alkylation of Tellurium-stabilized Anions Followed by Elimination

Elimination of telluroxides, which is analogous to that of selenoxides (COFGT (1995)), has not been used for the synthesis of alkenes since 1995, so it is not going to be discussed here.

1.15.5 BY CONDENSATION OF NITROGEN FUNCTIONS

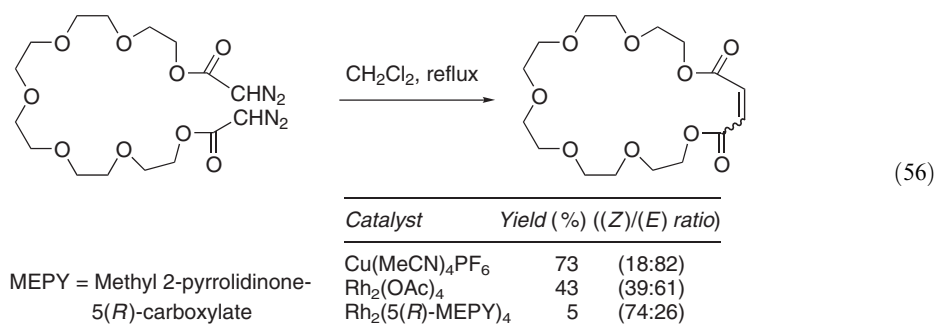
1.15.5.1 Reactions of Diazo Compounds

Alkene synthesis can be carried out by decomposition of diazo compounds catalyzed by rhodium or ruthenium complexes. Recently, symmetrical <1997CC2163> or unsymmetrical <1999OM5091, 2000EJO2795> enediones have been obtained in good yields and excellent *cis*-selectivities by using [RuCl(η^5 -C₅H₅)(PPh₃)₂] (Equation (55)).

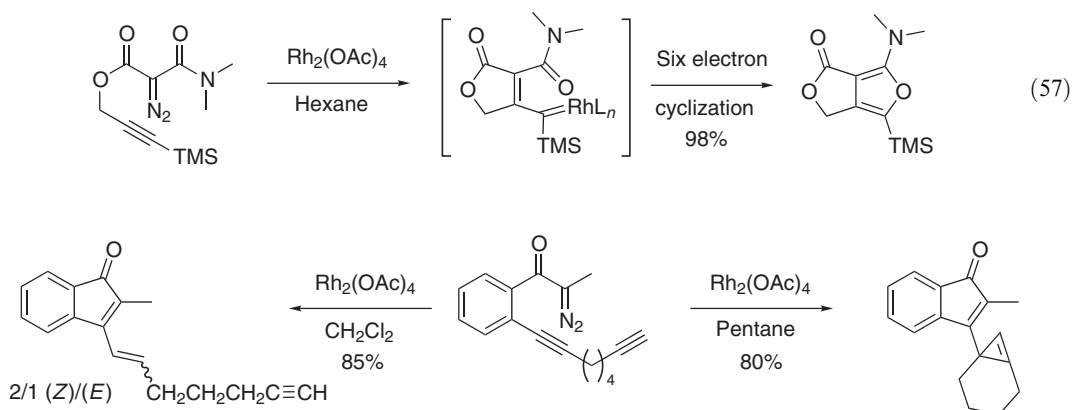


The condensation of α -diazo ketones with trimethylsilyl diazomethane provides *cis*-RCOCH=CHSiMe₃ with high yields (>80%) because only the α -diazo ketone is decomposed by the ruthenium complex <2000EJO2795>.

An intramolecular version of this carbene-carbene coupling gives a macrocyclic *cis*-cycloalkene <2000EJO2795, 2000OL1777>. The stereochemistry of the double bond depends on the catalyst (Equation (56)).

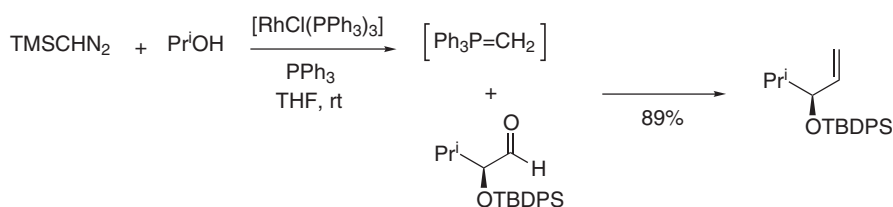


Decomposition of α -diazo ketones bearing a tethered alkyne unit furnishes a rhodium carbenoid, which can lead to the synthesis of cyclic enones [<2000OL2093, 2000JOM\(610\)88, 2001JOM\(617-618\)3, 1996CRV223, 1999OL1327>](#) and bicyclic furans (Equation (57)) [<2003JOC227>](#). The product depends on the metal complex and the solvent employed (Scheme 56). The mechanism has widely been discussed by Padwa [<2001JOM\(617-618\)3, 2000JOM\(610\)88>](#).



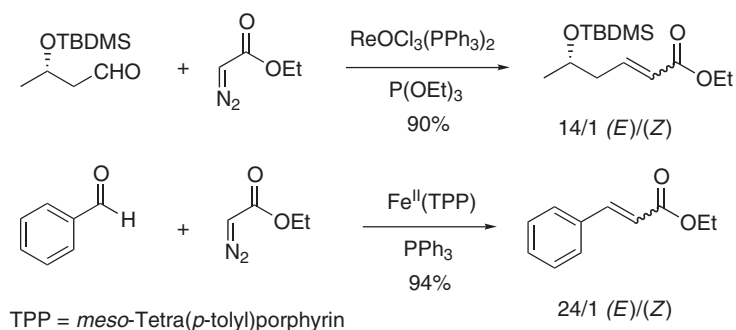
Scheme 56

More recently, Lebel and co-workers [<2001AG\(E\)2887, 2002OL1671, 2002JOM\(658\)126>](#) reported a new methylenation of carbonyl compounds based on the *in situ* generation of methylene triphenylphosphorane from trimethylsilyl diazomethane catalyzed by Rh(I) (Scheme 57). These conditions lead to terminal alkenes in excellent yields and are compatible with sensitive and enolizable carbonyl compounds. This method constitutes a practical alternative to the Wittig reaction under neutral conditions.



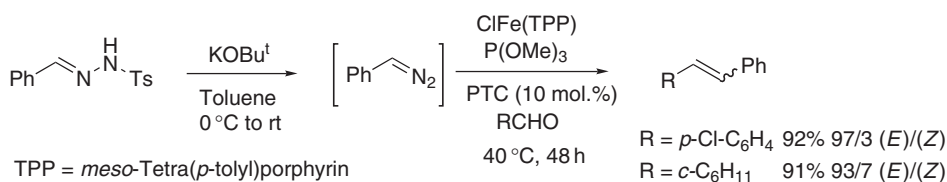
Scheme 57

Olefination of carbonyl compounds with ethyl diazoacetate, catalyzed by $\text{ReOCl}_3(\text{PPh}_3)_2$ with 1 equiv. of $\text{P}(\text{OEt})_3$ [<1997TL8125>](#), by $\text{RuCl}_2(\text{PPh}_3)_3$ [<1998TL625>](#), or by iron(II) porphyrin complex [<2002JA176, 2003OM1468>](#) in the presence of a stoichiometric amount of triphenylphosphine, is very *trans*-selective (Scheme 58). The Fe(II) complex can be replaced by the air-stable and commercially available $\text{ClFe}(\text{TPP})$ or $\text{Ru}(\text{TPP})(\text{CO})$ [<2003JOC3714, 2003OM1468>](#).



Scheme 58

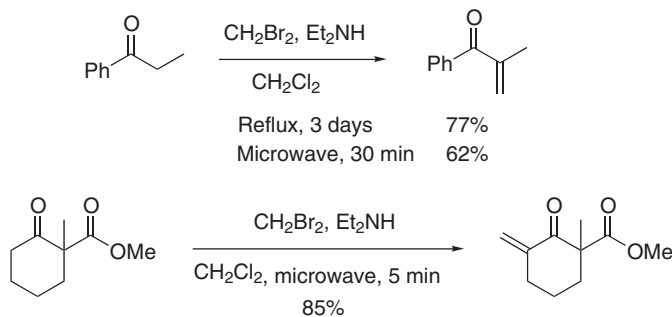
A safe alternative to hazardous diazo compounds is tosylhydrazone [<2003JA6034>](#). In the presence of Bu^tOK, the tosylhydrazone is transformed into the corresponding diazo compound which is decomposed into the alkoxy-substituted phosphorus ylide by treatment with P(OMe)₃ and Fe(III). This new method gives (*E*)-alkenes in high yields and excellent selectivities (Scheme 59).



Scheme 59

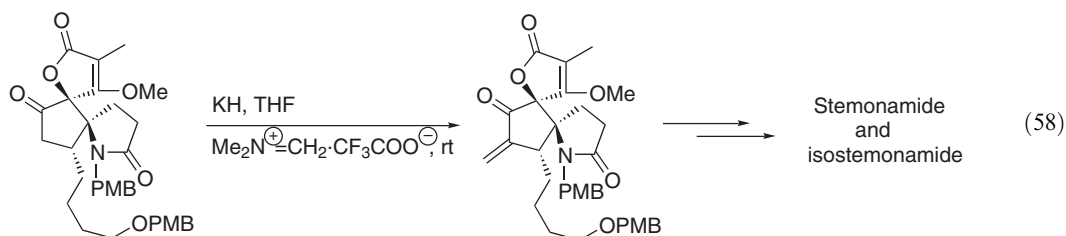
1.15.5.2 The Mannich Reaction

α -Methylene ketones can result from a Mannich reaction followed by deamination. Recently these two steps have been described in a one-pot procedure with Et₂NH/CH₂Br₂ [<1994CC2041, 1998T5223>](#). More recently, it was shown that microwaves increase the rate of the reaction (Scheme 60) [<2003T1509>](#).



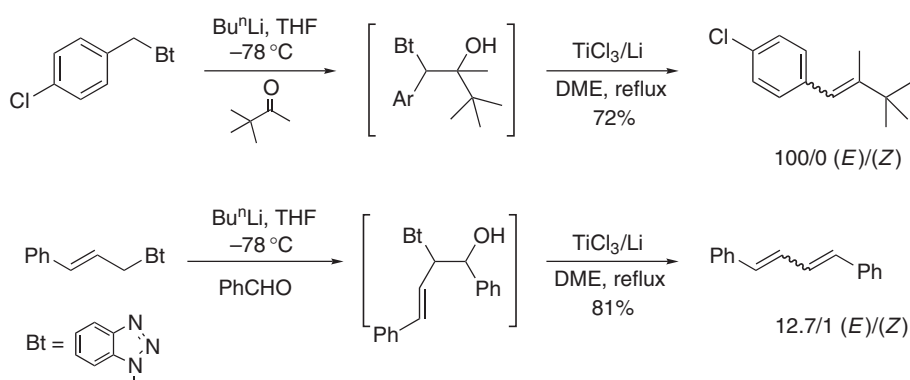
Scheme 60

In a similar way, α -methylene ketones can be obtained by treating enolates of carbonyl compounds with *N,N*-dimethylformaldimmonium trifluoroacetate (Equation (58)) [<2002T61>](#).

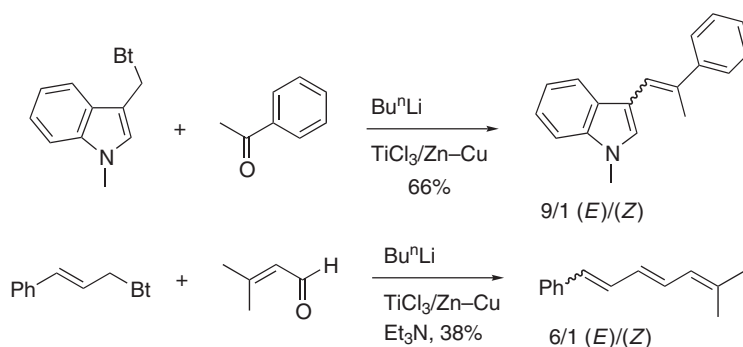


1.15.5.3 The Aza Wittig Reaction

Recently, Katritzky reported an efficient reductive elimination with low-valent titanium of *N*-(α -hydroxyallyl)- or *N*-(α -hydroxybenzyl)benzotriazole, derived from condensation of the *N*-allyl- or *N*-benzylbenzotriazole anion with a carbonyl compound, affording both di- and trisubstituted alkenes in good yields and with excellent (*E*)-selectivities (Scheme 61) <1997JOC238>. This method has been extended to a wide range of benzotriazole derivatives, including those containing heteroaryl groups and tertiary-substituted benzotriazoles <1998JOC6704>. This reaction has also been used successfully for the synthesis of dienes and trienes (Scheme 62).

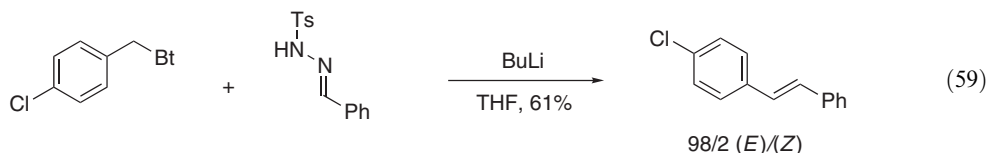


Scheme 61



Scheme 62

A similar olefination can be performed on tosylhydrazones <1999JOC3332>. In the presence of a strong base, condensation of benzotriazole derivatives with tosylhydrazones of carbonyl compounds provides (*E*)-stilbenes (Equation (59)).



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1.16

One or More C=C Bond(s) Formed by Condensation: Condensation of P, As, Sb, Bi, Si, Ge, B, or Metal Functions

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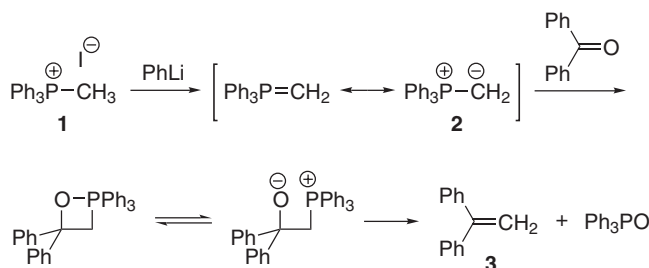
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This chapter intends to give a selective coverage of the recent research (from 1995 to 2003) and some representative examples of early work reported in COFGT (1995) <1995COFGT(1)719>.

1.16.1 C=C BONDS BY CONDENSATION OF P, As, Sb, OR Bi FUNCTIONS

1.16.1.1 Alkenation via the Wittig Reaction

The Wittig reaction is the reaction of phosphonium ylides with carbonyl compounds leading to the formation of alkenes and phosphine oxides by transfer of an alkylidene group to a carbonyl compound with displacement of the carbonyl oxygen. It was discovered in 1953 when Wittig and Geissler treated methyltriphenylphosphonium iodide **1** with phenyllithium and obtained triphenylphosphonium methyllide **2**, which, in reaction with benzophenone, gave 1,1-diphenylethylene **3** and triphenylphosphine oxide (Scheme 1) <1953LA44>.



Scheme 1

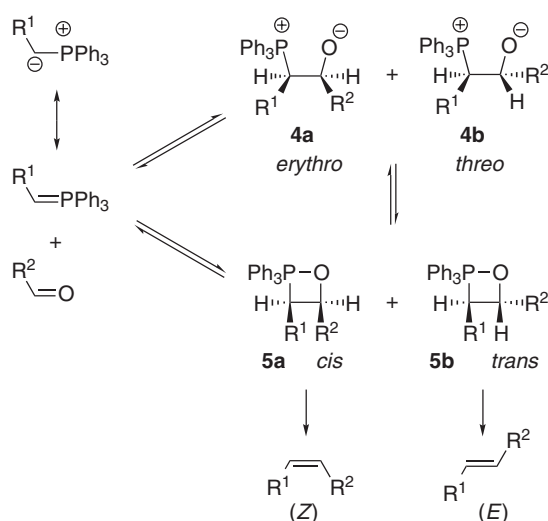
The activity of phosphorus ylides in the Wittig reaction depends on their structure. They can be classified as nonstabilized or reactive ylides, semistabilized or ylides of moderate activity and stabilized or ylides of low activity. The greatest effect on the activity of ylides is that of ylidic carbon atom substituents. Stabilized ylides bear on the ylidic carbon atom at least one electron-withdrawing group such as COR, CHO, CO₂R, CN, P(O)(OR)₂, sulfonyl, etc., or groups capable of delocalizing the negative charge. These ylides, owing to extensive delocalization of negative charge through participation of resonance structures, are less reactive. Semistabilized ylides are those that are functionalized with moderate electron-withdrawing groups such as aryl, thioalkyl, vinyl, and halogen atoms. Non-stabilized ylides are those that are unsubstituted or substituted by electron-donating groups such as alkyl, OAlk, NAlk₂. These ylides, in which the negative charge is localized on the α-carbon, are the more reactive. Introduction of electron-donating substituents on the phosphorus atom such as tri-*n*-butyl or tris(dimethylamino) increases the activity of phosphorus ylides, whereas electron-acceptor halide atoms decrease the activity of ylides. The reaction is very general and the aldehyde or ketone can be aliphatic, aromatic, conjugated cyclic, or heteroaromatic.

The scope, mechanism, and stereochemistry of phosphonium ylides have been extensively reviewed by Schlosser <1970TS1>, Gosney <B-1979MI002>, Maryanoff <1989CRV863>, Johnson <B-1993MI004>, Vedejs <1994TS1, 1996MI1>, Lawrence <B-1996MI007>, Nicolaou <1997LA1283> and Kolodiaznyh <B-1999MI008>. Additionally, a chapter "Ylides and Related Species" is included every year in the *Organophosphorus Chemistry: A Specialist Periodical Reports* published by The Royal Society of Chemistry.

1.16.1.2 Phosphonium Ylides

1.16.1.2.1 Mechanism

The mechanism of the Wittig reaction has been a subject of intensive investigations and the reader is referred to the exhaustive study by Kolodiazny [<B-1999MI008>](#). It seems clear that the Wittig reaction does not proceed by a uniform mechanism and that the structures of the reagents (nonstabilized, semistabilized, stabilized), the reaction medium, the solvents, and the presence of lithium salts have an influence on the reaction mechanism. The Wittig reaction is traditionally explained by assuming that the initial step involves a reversible addition of the ylide at the carbonyl carbon atom to generate two possible diastereomeric betaine intermediates (**4a**, **4b**), the zwitterionic adducts of phosphorus ylides and carbonyl compounds. Subsequent decomposition to the alkene is thought to involve *cis*- and *trans*-oxaphosphetanes (**5a**, **5b**) leading from the betaine to the (*Z*)- or (*E*)-alkenes, via intramolecular attack of the oxygen atom on the phosphonium cation ([Scheme 2](#)). Nonstabilized ylides react with aldehydes to give largely (*Z*)-alkenes, and stabilized ylides give predominantly (*E*)-alkenes, but semistabilized ylides generally give a mixture of (*Z*)- and (*E*)-alkenes with a ratio $\sim 50/50$.



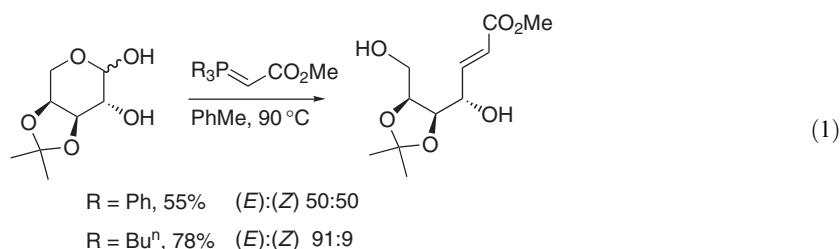
Scheme 2

The mechanism of the Wittig reaction has been the subject of investigations mainly with nonstabilized ylides. In 1973 Vedejs and Snoble confirmed that the Wittig reaction proceeds via the formation of oxaphosphetane intermediates [<1973JA5778>](#). In 1990, McEwen and Ward Jr. studied the metal effects and observed that when lithium was used the product mixture was enriched with the (*Z*)-alkene, while when sodium or potassium ions were present, the (*E*)-alkene dominated [<1990JOC493>](#). In 1996, Borisova and co-workers reported the first experimental evidence of the formation of betaines [<1996MC90>](#). Vedejs and co-workers showed experimentally that the first step of the Wittig reaction proceeds under kinetic control to result in *cis*- and *trans*-oxaphosphetanes. They suggested that oxaphosphetanes were obtained as primary intermediates as a result of an asynchronous [2+2]-cycloaddition of ylides to carbonyl compounds. The mechanism does not take into account the formation of betaines as oxaphosphetane precursors [<1973JA5778>](#). Maryanoff and co-workers discovered the stereochemical drift of *cis*-oxaphosphetanes into their *trans*-isomers. They observed by kinetic studies that the rate of retrodecomposition of *cis*-oxaphosphetanes into ylide and benzaldehydes is 7–15 times faster than the rate of retrodecomposition of *trans*-oxaphosphetanes [<1985TL4587>](#). It was supposed that the first step of the Wittig reaction is reversible for (*Z*)- and (*E*)-olefin and that the second step is rate determining. Decomposition of the oxaphosphetanes proceeds in two directions: to ylide and aldehyde, or to alkene and phosphine oxide.

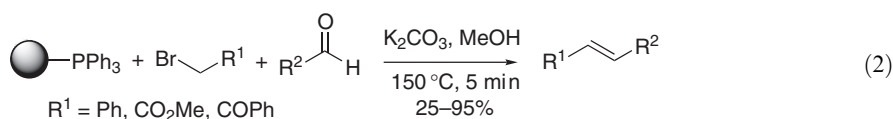
Investigations of the mechanism of the Wittig reaction for semistabilized and stabilized ylides are more difficult because the oxaphosphetanes are much harder to detect, having only transient existence. Detailed analyses of the experimental results from the reaction of stabilized ylides with carbonyl compounds have led to the assumption that a betaine is formed as a primary intermediate and then transformed to oxaphosphetanes. The Wittig reaction of stabilized ylides with aldehydes proceeds under the conditions of kinetic control. (*E*)-Selectivity results from selective formation of *trans*-oxaphosphetanes. The presence of electron-withdrawing substituents destabilizes the intermediary products and accelerates the decomposition of the oxaphosphetane <B-1999MI008>.

1.16.1.2.2 Stabilized ylides

The Wittig reaction of stabilized ylides with aldehydes and unsymmetrical ketones leads stereoselectively to the preferential formation of the (*E*)-alkenes, and the (*E*)-isomer is often produced with almost complete exclusion of the (*Z*)-isomer <1972JOC2579, 1975JA3512>. The degree of stereoselectivity observed may be influenced by the substituents on the ylide. Replacing the phenyl groups on phosphorus by alkyl groups such as butyl or cyclohexyl in the presence of catalytic amounts of benzoic acid in toluene results in an increase in the (*E*)-selectivity and the yield of alkenes (Equation (1)) <1960T130, 1965JOC1296, 2001OL3591>.

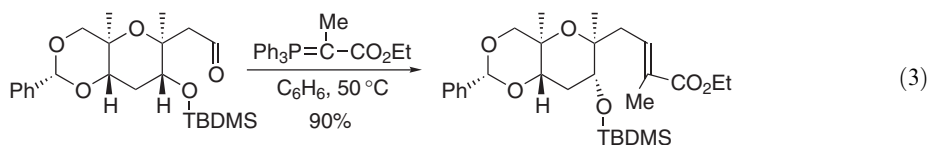


The stereoselectivity of the Wittig reaction depends on the reaction medium and temperature. The highest amount of (*E*)-alkene is obtained below 0 °C in nonpolar aprotic solvents <1987T1895>. The presence of lithium salts in the reaction medium increases the (*Z*)/(*E*) ratio and accelerates the formation of alkene <1964HCA159, 1967CB1144>. There is no limit to the structure of aldehydes used and fullerenes bearing an unsaturated ester have been prepared as the (*E*)-isomer in 89% yield from organofullerenes and methoxycarbonylmethylidenetriphenylphosphorane <1993JOC4796>. Recently, a one-pot Wittig reaction protocol for the production of alkenes by *in situ* formation of the ylide using the efficient combination of solid-supported triphenylphosphine and microwave dielectric heating has been developed (Equation (2)) <2001OL3745>.



The (*E*)-selectivity of the Wittig reaction of stabilized ylides may be affected by the introduction of substituents at the position alpha with respect to the phosphorus atom. If the group is sufficiently large, appreciable quantities of (*Z*)-alkenes are formed in addition to the (*E*)-isomers <1963JA2790, 1974JCS(P1)2470>. For example, the reaction of methoxycarbonylmethylidenetriphenylphosphorane with acetaldehyde gives a 96.5:3.5 mixture of the (*E*)- and (*Z*)-isomers of the methyl ester of tiglic acid <1961JOC4278>.

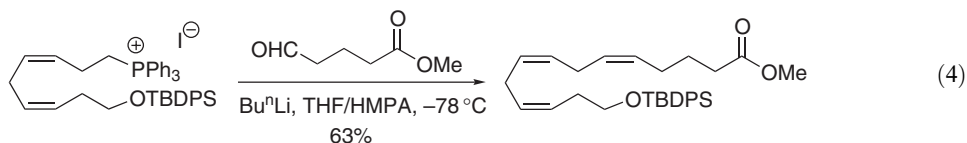
Stabilized ylides are currently used at various stages of multistep syntheses where the need to introduce double bonds in a controlled manner is of importance. For example, alkoxy carbonylmethylidenetriphenylphosphoranes have been used by Nicolaou and co-workers in the synthesis of endiandric acids, ionophore antibiotic X-14547A, calicheamicin γ_1 , zaragozic acid A, brevenoxin B (Equation (3)) and taxol <1997LA1283> and by Lee and co-workers in the synthesis of seselin analogs <1997BMCL2573>. A solid-phase synthesis of epothilone A has been carried out using a Wittig reaction on solid phase, thus demonstrating the value of this kind of operation in solid-phase and combinatorial chemistry <1997LA1283>.



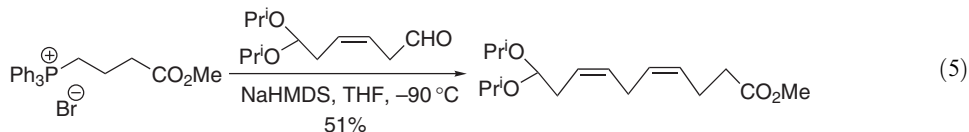
Interaction of stabilized ylides with unsymmetrical ketones almost always leads to a considerable amount of (*Z*)-isomer. For example, treatment of a nucleosidic ketone with ethoxycarbonylmethylidenetriphenylphosphorane in $\text{CH}_2\text{Cl}_2/\text{THF}$ at room temperature gives the (*Z*)-alkene as a single stereoisomer [\[1997JOC11\]](#). Ketones bearing electron-withdrawing substituents are the most reactive. Thus, the Wittig reaction of ethoxycarbonylmethylidenetriphenylphosphorane with fluorinated arylketones proceeds smoothly to give predominantly fluorinated (*Z*)-alkenes [\[1994NJC263\]](#).

1.16.1.2.3 Nonstabilized ylides

In the case of nonstabilized ylides, the thermodynamically less favorable (*Z*)-isomers tend to dominate the mixture of alkenes obtained [\[1963JOC372, 1973HCA1176\]](#). The degree of stereoselectivity varies considerably with the reaction conditions, especially with the nature of the solvent and the base used. In very dipolar aprotic solvents (DMF, DMSO, HMPA) lithium salts have little effect on the stereochemistry of the reaction with carbonyl compounds and a mixture of alkenes containing predominantly the (*Z*)-isomer is obtained both in the presence or in the absence of lithium salts. The use of HMPA [\[1974JOC3793, 1974OPP269, 1998JOC337, 1998TL771\]](#) or DMSO [\[1997S1195\]](#) as co-solvent to THF provides a suitable reaction medium for promoting the formation of (*Z*)-alkenes (Equation (4)).



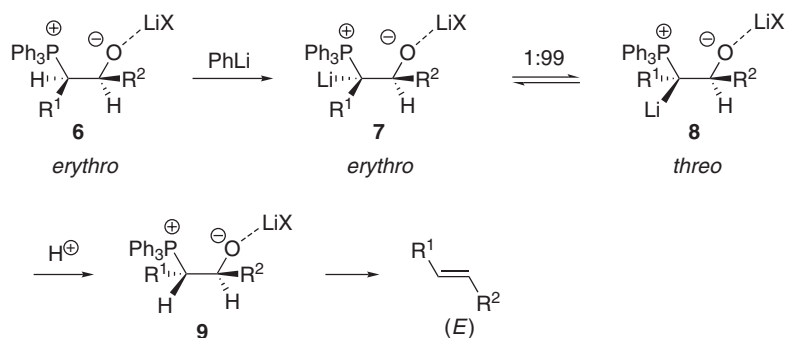
In nonpolar solvents (Et_2O , C_6H_6) containing lithium salts, the Wittig reactions of nonstabilized ylides produce a greater proportion of (*E*)-alkenes. It is argued that in the presence of Li^+ the decomposition of both diastereomeric betaine intermediates to alkene is retarded by complex formation with the cation, thus reducing the proportion of (*Z*)-alkene. When preparing (*Z*)-alkenes in nonpolar media it is important to ensure that salt-free ylide solutions are used. A variety of methods for the preparation of salt-free ylide solutions is accessible from the literature [\[1958LA10, 1965AG\(E\)583, 1970LA211, 1975JA4327, 1976CB1694\]](#). Thus, the salt-free modification of the Wittig reaction provides the simplest access to (*Z*)-alkenes. The highest (*Z*)-selectivity has been reported for the Wittig reaction of tris(2-methoxymethoxyphenyl)-phosphonium ylides which react with unbranched, saturated aliphatic aldehydes to afford olefins with very high (*Z*)-selectivity (99.5%) [\[1990S109, 1993TL1925\]](#). A variation of this method is to prepare the ylide with NaNH_2 in boiling THF and to remove the insoluble inorganic salts by filtration [\[1970LA211\]](#). *t*-BuOK [\[1975JA4327\]](#) and NaHMDS [\[1976CB1694, 1995JOC6627, 1998TL249\]](#) in THF or LiHMDS [\[1996JOC838\]](#) in THF/toluene are frequently employed as bases without the tedious necessity for filtration (Equation (5)).



1.16.1.2.4 Formation of (*E*)-alkenes via Wittig–Schlosser modification

Schlosser described a method leading to alkenes in very high (*E*)-selectivity even with nonstabilized ylides [\[1966AG\(E\)126, 1967LA1, 1970CB2814\]](#). Thus, treatment of the initially formed lithium bromide complexed “phosphorus betaines” **6**, with predominantly the *erythro*-configuration,

with an equivalent of an organolithium reagent, provides an α -lithiated betaine or “betaine ylide” **7**. Whereas the initially formed *erythro*-complex is relatively stable to inversion, its lithium derivative rapidly interconverts. Stereocontrol is accomplished by the spontaneous pyramidal inversion of the α -lithiated betaine to result in the predominant formation of the thermodynamically more stable *threo*-isomer **8**. Addition of a proton donor occurs with remarkable stereospecificity to form the new intermediate in the *threo*-configuration **9**, which decomposes selectively to give pure (*E*)-alkene (Scheme 3). The reaction has recently been reinvestigated by Schlosser and co-workers, who demonstrated that only phenyllithium in ethereal solution containing lithium bromide effects the α -deprotonation rapidly and cleanly. If these conditions are met, the (*E*)-selective modification of the Wittig olefination protocol works with absolute reliability to provide good yields of (*E*)-alkenes from a variety of aliphatic and aromatic aldehydes <2003CEJ570>.



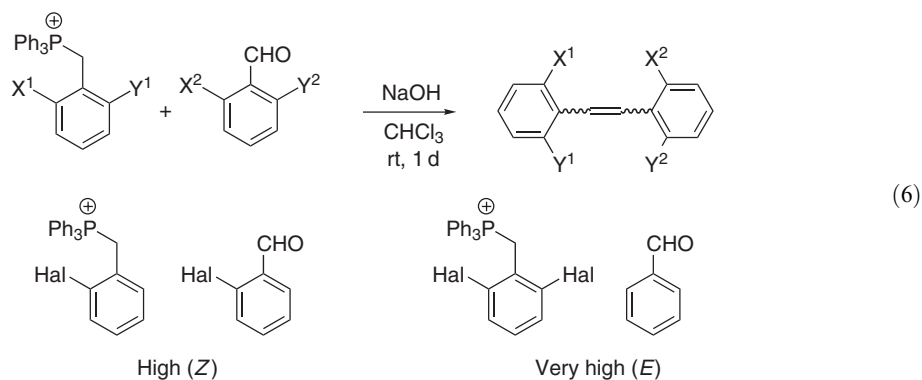
Scheme 3

1.16.1.2.5 Semistabilized ylides

This important class contains ylides of moderate activity stabilized by α -substituents such as vinyl, aryl, or alkynyl groups. They react with carbonyl compounds to give mixtures of (*Z*)- and (*E*)-alkenes. There is little influence of solvent or lithium salts upon the stereoselectivity of the reaction, which essentially depends on structural factors. Under no circumstances are the effects appreciable, and the (*E*)-alkene usually dominates the product composition.

(i) Benzylic ylides

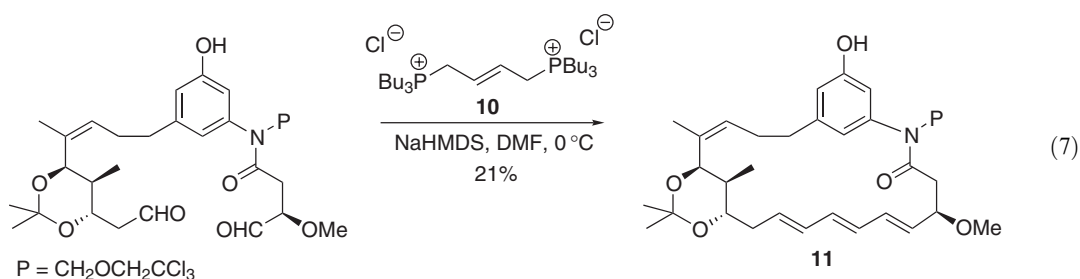
For Wittig reactions effected with triphenylphosphonium benzylides, the stereochemistry of the products depends largely on the nature of the substituents in the aryl ring. For example, in the preparation of 4-nitro-4'-methoxystilbene, the reaction of 4-nitrobenzyltriphenylphosphorane with anisaldehyde leads predominantly to the (*E*)-alkene. By interchanging the ylide and aldehyde substituents, a 1:1 mixture of (*E*)- and (*Z*)-alkenes is obtained <1962JOC4666, 1966JOC334>. Recently, performing the preparation of stilbenes from *ortho*-halo substituted benzyltriphenylphosphonium salts and benzaldehydes, it has been found that there is a cooperative effect of one *ortho*-halo substituent on each of the two reacting partners which increases (*Z*)-selectivity, and by contrast two *ortho*-halo substituents on the same reactant promotes high (*E*)-selectivity <2002TL2449>. So in certain defined cases either (*E*)- or (*Z*)-isomer can be predictably synthesized in good yield (Equation (6)). In the reaction of benzylidenetriphenylphosphorane and benzaldehyde in two-phase organic solvent/water (NaOH) media, the use of polar solvents increases (*Z*)-selectivity for the product stilbene; *ortho*-substituted benzaldehydes bearing heteroatom substituents (CF₃, Cl, Br, MeO, F) also confer a pronounced enhancement of (*Z*)-selectivity <1999JOC(A)(142)125>.



The isomer ratio may be shifted further in favor of the (*E*)-isomer by replacing the phenyl groups on phosphorus by alkyl groups. In an EtOH solution of sodium ethoxide, substitution of alkyl groups for phenyl groups leads to almost pure (*E*)-stilbene and also to better yields [<1962CB1894, 1970TS1>](#). By contrast with the conventional Wittig reaction, the mechanically induced solid-state generation of semistabilized ylides using K_2CO_3 in the presence of stoichiometric amounts of solid organic carbonyl compounds discriminates between (*Z*)- and (*E*)-substituted products in favor of the thermodynamically stable (*E*)-isomer [<2002JA6244>](#). In general, structural changes in the carbonyl co-reactant exert only a minor effect on the stereochemistry of Wittig reaction of benzyldienetriphenylphosphorane. (*E*)-Selectivity is preserved when using a variety of aliphatic, unsaturated, and aromatic aldehydes under aprotic conditions.

(ii) Allylic ylides

Owing to the intrinsic nonstereoselectivity of allylic ylides, formation of conjugated dienes of definite configuration is best conducted by reaction of saturated aliphatic reactive ylide with an α,β -unsaturated aldehyde. This is exemplified by the synthesis of a major component of the sex pheromone of the Egyptian cotton leafworm, which is a (9*Z*),(11*E*)-diene [<1975CL103>](#). Trienomyces A and F have been synthesized using a double Wittig reaction of the diphosphonium salt **10** as a key step. The reaction produces a mixture of isomers including 21% of the required (*E*),(*E*),(*E*)-triene unit **11** (Equation (7)) [<1995JA10777>](#).

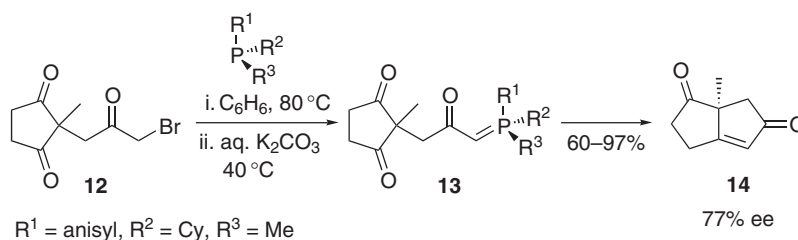


A further stereochemical complication encountered during Wittig reactions with allylic ylides having a terminal substituent is loss of configuration in the allylic double bond [<1966JOC2907, 1972HCA1828>](#). Another difficulty that frequently arises is concurrent condensation at the γ -position [<1974JOC821>](#). As expected, increased steric hindrance at the γ -carbon inhibits γ -condensation [<1973JOC3625, 1973TL4425>](#).

1.16.1.2.6 Asymmetric Wittig reaction

Several articles are available that review asymmetric reactions of phosphorus ylides, written by Rein [<1996ACS369, 2002S579>](#), Li [<1997CR2341>](#), and Kolodiazny [<1998TA1279>](#). Since no new sp^3 stereocenter is formed in the Wittig reaction, the asymmetric version of the Wittig reaction has been focused mainly on alkylidenecycloalkanes with axial chirality. The first desymmetrization of 4-substituted cyclohexanones using a chiral ylide containing a stereogenic phosphorus

center was described by Bestmann and Lienert <1969AG(E)763>. They obtained the axially dissymmetrical 4-substituted alkylidenecycloalkane with reasonable asymmetric induction (43% ee) from 4-methyl cyclohexanone. In 1980, Trost and Curran reported a synthesis of cyclopentanoid natural products based upon the desymmetrization of a *meso*-triketone by the asymmetric intramolecular Wittig reaction depicted in Scheme 4 <1980JA5699>. Thus, a chiral phosphonium salt prepared from (*R*)-CAMP (cyclohexyl-*O*-anisylmethylphosphine) and the bromide **12**, undergoes treatment with aqueous K₂CO₃ to generate the stabilized intermediate ylide **13** which evolves through an intramolecular Wittig reaction to produce the bicyclic ketone **14** (bis-nor-Wieland-Mieschler ketone) in up to 77% ee.



Scheme 4

Desymmetrization has also been realized by the reaction of an achiral stabilized ylide with a symmetrical substituted cyclohexanone in the presence of a chiral host. This approach provides the dissymmetric alkenes in up to 57% ee <1990JOC3446>. The use of a chiral catalyst in an asymmetric Wittig reaction was first reported by Bestmann and Lienert in 1970 <1970CZ487>. Among all the chiral acids investigated as catalysts, they found that mandelic acid was the most effective. However, the levels of induction were low.

1.16.1.3 Arsonium Ylides

In general, arsonium ylides are markedly more reactive than their phosphorus counterparts. Like phosphonium ylides, they may be classified according to their reactivities as stabilized, semistabilized and nonstabilized ylides. Stabilized ylides bear on the ylidic carbon atom at least one electron-withdrawing group such as COR, CO₂R, or CN, semistabilized ylides are functionalized with aryl or vinyl groups, and nonstabilized ylides are unsubstituted or substituted by alkyl groups. Stabilized ylides are inert to air and water at room temperature and isolable. Arsonium ylides differ in behavior from their phosphorus counterparts in that they can react with carbonyl compounds to give either alkenes or epoxides in Wittig-type or Corey-type reactions. The type of product formed depends on the nature of the substituent on both the ylidic carbon atom and the arsenic atom, and of solvent and base effects. The general pattern which has emerged is that stable arsonium ylides provide alkenes whilst nonstabilized arsonium ylides give epoxides. The chemistry of arsonium ylides has been extensively investigated <1987CSR45, 1996CR1641, 2001MI26>.

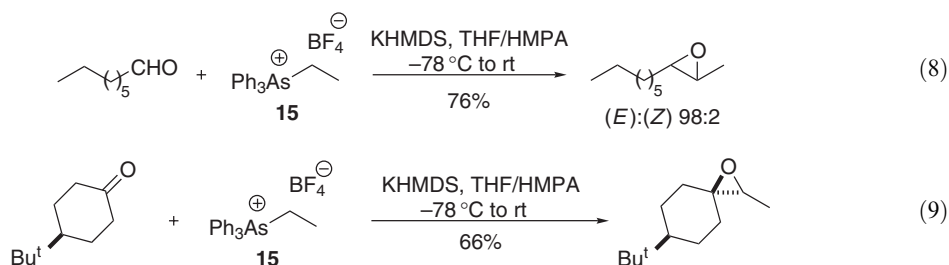
1.16.1.3.1 Comparison of stabilized, nonstabilized, and semistabilized ylides

Arsonium ylides stabilized by COR, CO₂R, and CN groups or cyclopentadiene rings react well with both aldehydes and ketones in Wittig-type processes to afford alkenyl products with predominantly (*E*)-geometry <1982AOC115>. More complex stabilized arsonium ylides such as α-halo ylides react with aromatic aldehydes to give α-halo α,β-unsaturated esters, ketones, and nitriles in excellent yields and (*Z*)-selectivities <1989SC2639, 1996SC677>. Similarly, the reaction has been applied to the preparation of α-phenylselanyl α,β-unsaturated esters, ketones, and nitriles from the corresponding α-phenylselanyl arsonium ylides and aldehydes <1995JCS(P1)95, 2002SC1775>.

Asymmetric Wittig-type olefination of chiral arsonium ylides containing 8-phenylmenthol as the chiral auxiliary has been much less investigated compared to asymmetric reactions of phosphorus ylides. These arsonium ylides give diastereoselectivities of 47–80% in conversions of 4-substituted cyclohexanones to dissymmetric alkenes [<1997TA1979>](#). Under the reaction conditions investigated, the corresponding phosphonates containing the same chiral auxiliary gave lower selectivity. More recently, the first atroposelective Wittig-type reaction of axially chiral 2-formyl-1-naphthamides with chiral arsonium ylides containing the same chiral auxiliary has been reported. The olefination gives (*E*)-alkenes in excellent yields and in up to 88:12 diastereomeric ratio [<2001TL2541>](#).

In contrast to their phosphorus counterparts, stabilized arsonium ylides such as 1-(methoxycarbonyl)methyl- or 1-(trimethylsilyl)methyltriphenylarsonium ylides react with α,β -unsaturated esters <1982AOC115> and α,β -unsaturated ketones <1984TL4425> to give cyclopropanes stereoselectively. Crotonylarsonium ylides react with 2*H*-pyran-5-carboxylates to give divinylcyclopropanecarboxylates <1997JCR(S)130> and with α,β -unsaturated aldehydes or ketones to give 1,3-cyclohexadiene-1-carboxylates and/or acyclic trienes <1997SL126>.

The reactions of nonstabilized arsonium ylides are similar to those observed for the sulfur ylides. Thus, simple nonstabilized ylides on treatment with aldehydes and ketones generally give good yields of (*E*)-epoxides. For example, the ylide derived from an arsonium tetrafluoroborate **15** gives epoxides with >99% (*E*)-selectivity in reactions with aldehydes (Equation (8)), and give good yields of trisubstituted epoxides on reaction with 4-alkylcyclohexanones (Equation (9)) <1981JA1283>.



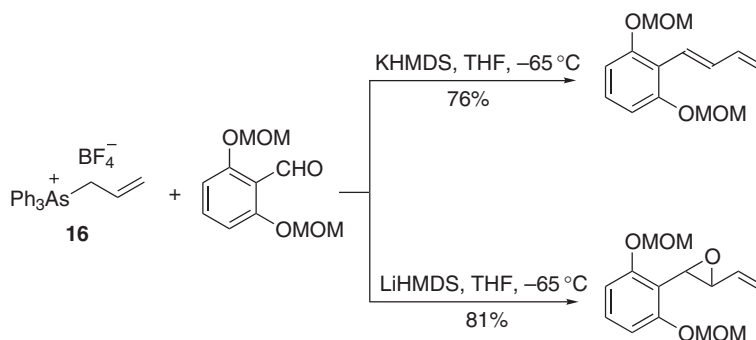
Semistabilized arsonium ylides are intermediate in behavior between stable and reactive ylides. It means that substrate, base, counterion, and solvent are important factors in determining the outcome of their reactions. Reactions with aldehydes and ketones may provide alkenes and/or epoxides, with solvent effects playing an important role. For example, allylic arsonium ylides in reactions with aldehydes and ketones give only vinylic epoxides in high yields when run in THF, whereas pure diene is formed when HMPA is used as co-solvent [<1983SC1193, 1991TL2913>](#). Highly stereoselective (*E*)-alkenation has been achieved through the reaction of a dibenzylic diphenylarsonium ylide with aldehydes, and a significant increase of (*E*)-selectivity is observed in the presence of HMPA [<1989TL5263>](#). Similarly, reactions of the benzylic (2-oxyethyl)diphenylarsonium ylide with aldehydes are completely (*E*)-selective when HMPA is used as co-solvent [<1990AG\(E\)1454>](#). α -Halo-substituted benzylic triphenylarsonium ylides have been prepared and used *in situ* to produce vinylic halides in good yields but with moderate (*E*)/(*Z*)-selectivity [<1998SC633>](#).

The formation of α,β -unsaturated epoxides from allylic arsonium salt **16** and aldehydes has been exploited in the synthesis of an (*E*)-vinyl epoxide, a key intermediate in a stereoselective synthesis of castasterone [<1996T5525>](#). These reactions are sensitive to the reaction conditions and the selectivity for the formation of either epoxides or alkenes is dependent upon the choice of base (LiHMDS or KHMDS) used for generation of the arsonium ylide. Thus, in reactions with aldehydes, the lithium-generated allylic arsonium ylide gives epoxides, whereas the potassium-generated allylic arsonium ylide gives dienes ([Scheme 5](#)) [<1989JOC3229>](#).

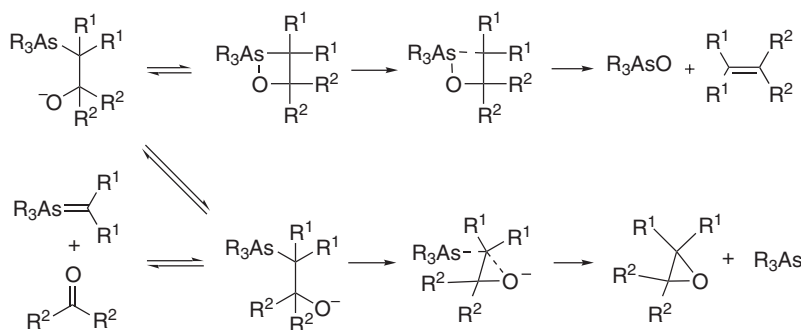
It appears, at least in the case of semistabilized arsonium ylides and possibly for others also, that control over the product can be achieved by suitable choice of substituents on arsenic, and of solvent and base.

(i) *Mechanism*

The behavior of arsonium ylides appears to be intermediate between that of sulphonium and phosphonium ylides. The energetic driving force to generate an arsenic—oxygen bond is not as strong as that to form a phosphorus—oxygen bond, so that there is not the same compulsion to alkene formation in the case of arsonium ylides, allowing the alternative epoxide pathway to compete (Scheme 6).



Scheme 5



Scheme 6

Several observations suggest that the first step, which is slow and reversible, is the rate-determining step and that in alkene formation the reaction goes directly to a four-membered ring transition state without the intermediate formation of a betaine. Formation of an epoxide must involve an intermediate betaine which reacts further by intramolecular displacement of an arsine. The electrons in the arsenic—carbon bond are displaced in an opposite direction in the two mechanisms. In alkene formation, displacement of electrons occurs away from the arsenic atom and in epoxide formation displacement of electrons is towards the arsenic atom. The change in pathway, depending upon the nature of the substituents at arsenic, could be associated with this; electron-donating substituents on arsenic should assist the displacement of the electron away from arsenic and favor alkene formation <1977AG(E)487>. For similar reasons, electron-withdrawing substituents on the ylide carbon atom should favor alkene formation.

1.16.1.4 Stibonium Ylides

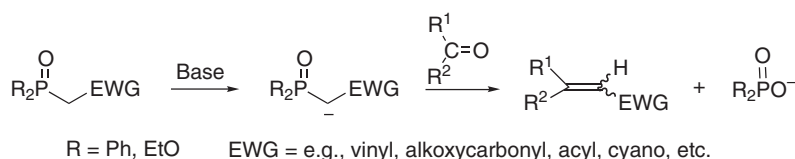
No significant progress has been made in this area since the appearance of chapter 1.16.1.4 in <1995COFGT(1)719>. The chemistry of stibonium ylides has been reviewed recently <2001MI53>.

1.16.1.5 Bismuthonium Ylides

No significant progress has been made in this area since the appearance of chapter 1.16.1.5 in <1995COFGT(1)719>. The chemistry of bismuthonium ylides has been reviewed recently <2001MI105>.

1.16.1.6 P(O)-Activated Alkene Formation

When compared to the Wittig reagents, the P(O)-activated reagents offer a number of advantages, although the lesser stabilizing effect of the neutral phosphonyl group means that electron-withdrawing α -substituents are required at the carbanion center before preparative yields of alkenes can be obtained. These advantages include: (i) greater nucleophilicity than the corresponding phosphonium ylides such that they react with both aldehydes and ketones under mild conditions; (ii) the phosphinic and phosphoric acid derivatives obtained from P(O)-activated syntheses are water-soluble, so separation from the alkene is easily achieved; (iii) considerable control of stereochemistry is possible by change of reaction conditions to yield the alkene with either the (*E*)- or the (*Z*)-geometry. The P(O)-activated reagents are divided into two groups, the phosphinoxy reagents introduced by Horner and co-workers in 1958 <1958CB61> and the phosphonate reagents introduced by Wadsworth and Emmons in 1961 <1961JA1733> (Scheme 7). In the literature the reaction using phosphinoxy reagents is called Horner–Wittig reaction, while the reaction using phosphonate reagents is called Horner–Wadsworth–Emmons (HWE) reaction. Both of them may be regarded as useful supplements to the Wittig reaction.



Scheme 7

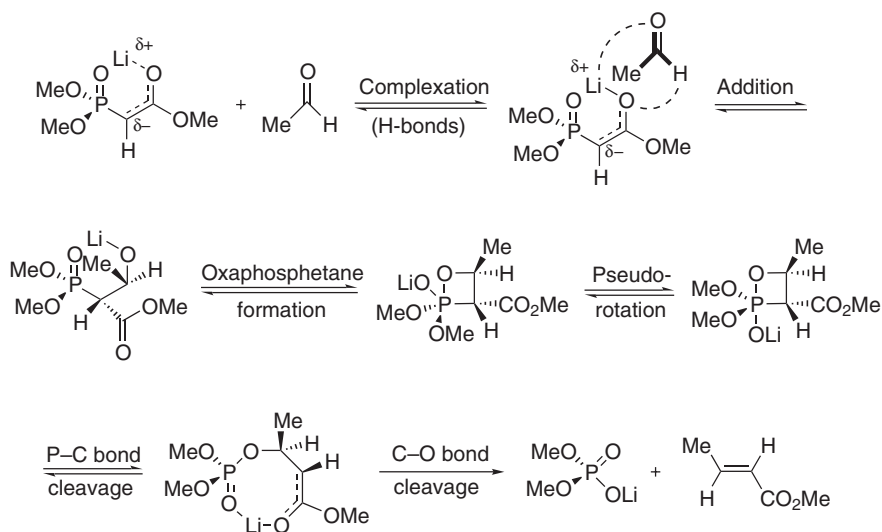
The scope, mechanism, and stereochemistry of these types of reactions have been extensively reviewed by Boutagy <1974CRV87>, Wadsworth <1977OR73>, Walker <B-1979MI001>, Maryanoff <1989CRV863>, Kelly <1991COS(1)761>, Johnson <B-1993MI004>, Vedejs <1994TS1>, Rein <1996ACS369>, Clayden <1996AG(E)241>, Nicolaou <1997LA1283>, Silveira <2001PS(171/172)309>, Minami <2001S349>, Rein <2002S579>, Savignac <B-2003MI010>.

1.16.1.6.1 Mechanism

The accepted mechanism for P(O)-activated alkene synthesis is closely analogous to that of the Wittig reaction. The selectivity is a result of both kinetic and thermodynamic control upon the reversible formation of the *erythro*- and *threo*-adducts and their decomposition to the corresponding (*Z*)- and (*E*)-alkenes, respectively. Some recent sophisticated quantum mechanical calculations, realized in systems with <1999JOC6815> or without <1998JOC1280, 1999JOC5845> lithium countercation, indicate that the reaction occurs with the spontaneous complexation between lithium enolate and aldehyde and the formation of hydrogen bonds between aldehyde hydrogen and enolate or phosphonate oxygen, followed by addition, oxaphosphetane formation, pseudorotation, P—C bond cleavage, and then C—O bond cleavage (Scheme 8). The observed predominance of (*E*)-alkenes is attributed to a reversible addition step followed by a slow, rate-determining, oxaphosphetane formation reaction. The development of an understanding of the various factors affecting these equilibria, including the effect of changing the base, solvent, temperature, and the nature of the associated cation has led to successful attempts to control the stereochemical outcome in P(O)-activated alkene formation.

1.16.1.6.2 Phosphonate-stabilized carbanions (Horner–Wadsworth–Emmons reaction)

The greater reactivity of phosphonate-stabilized carbanions over the corresponding Wittig reagents in alkene-forming reactions is ascribed to the fact that the phosphonyl group has a lower net positive charge and accordingly provides less stabilization for the adjacent carbanion by valence shell expansion. Globally, the phosphonate-stabilized carbanions are more nucleophilic reagents than the corresponding Wittig reagents. Thus, ketones that react sluggishly, or not at all,

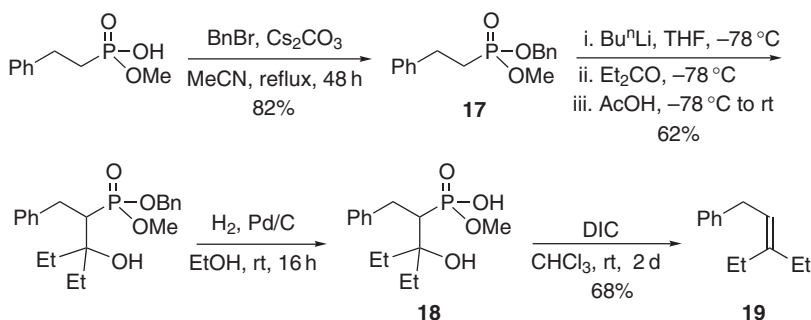


Scheme 8

with Wittig reagents stabilized by an alkoxy carbonyl or acyl group are smoothly converted into the corresponding alkenes by their phosphonate counterparts under mild conditions. Due to a steric effect, ketones are generally less reactive toward phosphonate carbanions than aldehydes, and usually require much more vigorous conditions for alkene formation.

A prerequisite for the use of phosphonate carbanions in alkene synthesis is the presence of an electron-withdrawing α -substituent (Ar, vinyl, OR, SR, NR₂, CO₂⁻, CO₂Et, COR, CN, P(O)(OR)₂), at the carbanion center to promote the spontaneous decomposition of the stabilized β -hydroxyphosphonates. When the β -hydroxyphosphonates do not contain an electron-withdrawing or -stabilizing group, there is no low-energy pathway for collapse to the alkene.

Despite early discouraging results in converting nonstabilized β -hydroxyphosphonates to alkenes, the reaction has recently been re-investigated. Thus, it has been shown that nonstabilized β -hydroxyphosphonic acid monomethyl ester **18**, prepared from benzyl methyl 2-phenylethylphosphonate **17** and diethyl ketone, undergoes dehydration with diisopropylcarbodiimide (DIC) to generate an oxaphosphetane, which is converted to alkene **19** and meta-phosphate by a retro-[2+2]-fragmentation pathway (Scheme 9). The overall sequence can be extended to aliphatic and aromatic aldehydes and executed on multigram scale in ~45% overall yield [\[2003JOC1459\]](#).

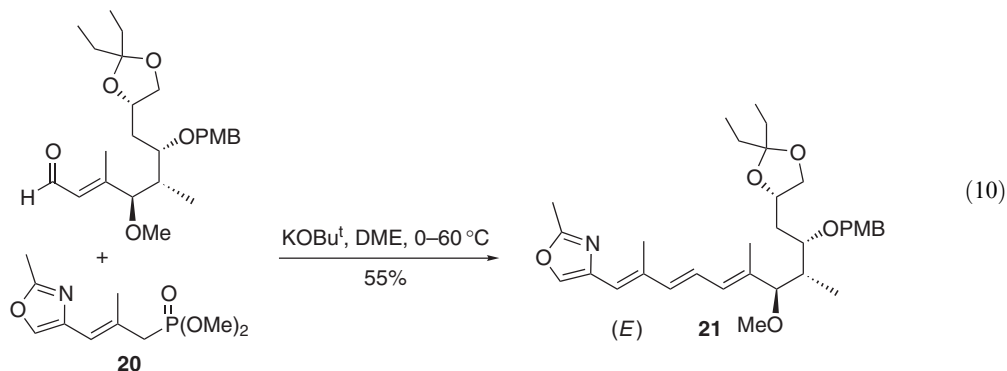


Scheme 9

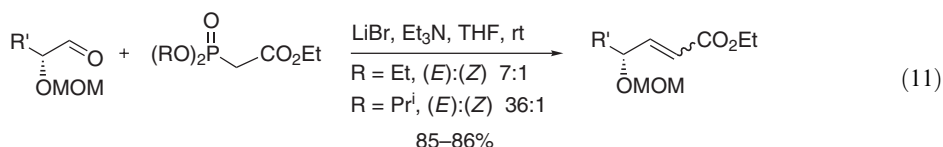
(i) Formation of (E)-alkenes

The use of phosphonate carbanions favors the formation of (*E*)-alkenes when groups capable of conjugating with the incipient double bond are present. Phosphonate carbanions are the

reagents of choice for the preparation of (*E*)- α,β -unsaturated carbonyl compounds, especially in natural product multistep syntheses where they are used at various stages. For example, dialkyl 1-(alkoxycarbonyl)methylphosphonates have been used in the synthesis of (*E*)-Royal Jelly <1975JIC538>, of endiandric acid C and aurodox <1997LA1283>. Extensive use of the (*E*)-stereochemistry has been made when the conjugation is extended by unsaturation. The dehydro derivative of the C18 juvenile hormone of cecropia has been synthesized in 78% yield from the condensation of diethyl 3-(methoxycarbonyl)-2-methyl-2-propenylphosphonate with aldehydes <1971TL1821>. A prominent example can be seen in Nicolaou and co-workers' landmark total synthesis of amphotericin B4, in which three olefination reactions were used to construct the polyene section <1988JA4660, 1988JA4672, 1988JA4685, 1988JA4696>. The first two employed diethyl 5-(ethoxycarbonyl)-2,4-pentadienylphosphonate leading to an acyclic hexenal. Similarly, dimethyl 2-methyl-3-(2-methyl-5-oxazolyl)-2-propenylphosphonate **20** is the key reagent for introduction of the (*E*),(*E*),(*E*)-triene **21** in the partial synthesis of rhizoxin (Equation (10)) <1998JOC6952>, while dimethyl 3-(4-methoxy-5-methyl-2-oxo-2*H*-pyran-2-yl)-2-propenylphosphonate represents another valuable reagent used in the convergent synthesis of (+)-asteltoxin <2003JA5415>.



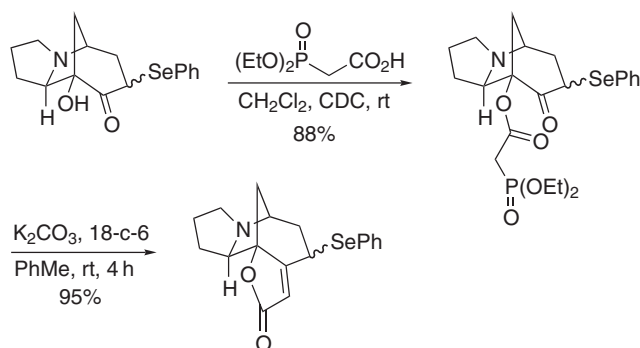
However, significant loss of (*E*)-selectivity occurs when steric interactions in the product become serious <1968BCJ1252, 1968CC1699, 1968CJC2225>. For example, in the reaction of diethyl 1-(ethoxycarbonyl)alkylphosphonates with aldehydes <1968CC1699>, only (*E*)-ester is formed when the α -substituent $R^1 = H$. With the size of R^1 increasing together with the branching of the alkyl group of the aldehyde, the (*Z*)-ester becomes the major product. Loss of (*E*)-stereoselectivity does occur in condensation with unsymmetrical ketones <1965IZV1504, 1967JA5292, 1968JCS(C)543, 1969AJC2145, 1971ABC1116, 1973ACS1401>. Thus, in the first step of the synthesis of racemic β,γ -carotene <1973ACS1401>, condensation of β -ionone with diethyl 1-(methoxycarbonyl)methylphosphonate is not highly stereoselective and a mixture of (*E*)- and (*Z*)-isomers is obtained in the ratio 65:35. Similarly, during the synthesis of the juvenile hormone isolated from the giant silkworm moth *Hyalophora cecropia* <1969AJC1737, 1969AJC2145>, treatment of the methyl ketone with sodium dimethyl 1-(methoxycarbonyl)methylphosphonate in DME led to a mixture of the (*E*),(*E*)- and (*Z*),(*E*)-ester in the ratio 60:40. (*E*)-Selectivity can be maximized by increasing the size of the substituents on the phosphonate group. Homologation of the 2-*O*-(methoxymethyl)-2-hydroxyhexadecanal using diethyl 1-(ethoxycarbonyl)methylphosphonate and LiBr–Et₃N furnishes the unsaturated ester with moderate stereoselectivity ((*E*):(*Z*) = 7:1), but when diisopropyl 1-(ethoxycarbonyl)methylphosphonate is used, the (*E*):(*Z*)-selectivity is increased to 36:1 (Equation (11)) <2000JOC7618>. The best (*E*):(*Z*)-selectivities (up to 120:1) are obtained from diisopropyl 1-(ethoxycarbonyl)methylphosphonate using *t*-BuOK in THF at low temperature <1981T3873, 1982JA1109>.



The same effect is observed with cyanophosphonates, which are usually less stereodemanding than their alkoxycarbonyl counterparts and produce mixtures of (*Z*)- and (*E*)-alkenes in the range

1:4 to 2:1 <1980SC509, 1980ZOB76, 2001JOC1200>. For example, in the reaction with β -ionone, sodium di-isopropyl cyanomethylphosphonate is found to be more (*E*)-selective ((*Z*):(*E*) = 18:82) than the corresponding diethyl ester ((*Z*):(*E*) = 35:65) <1980SC509>. Choice of solvent can also play a role in determining the final product ratios. In benzene, the reaction of diethyl cyanomethylphosphonate with 3,3-dimethylcyclohexanone is (*E*)-selective, whereas in DMF or DMSO, a moderate level of (*Z*)-selectivity is obtained.

The formation of α,β -unsaturated esters and nitriles has been developed in less traditional methods. The search for neutral and mild reaction conditions for generating phosphonate carbanions has promoted the use of simple systems based on the association of an amine and a lithium salt. Thus, LiCl–DBU, LiCl–DEPA, and LiCl–Et₃N in dry MeCN or THF are effective combinations to generate active species in the presence of base-sensitive substrates or reagents <1984TL2183, 1995S920, 2000JOC7618, 2002OL3157>. Under these conditions a solid-phase Horner–Wadsworth–Emmons reaction has been developed to generate α,β -unsaturated amides. Thus, polymer-bound diethyl 1-(acetamidocarbonyl)methylphosphonate was reacted with aldehydes, LiBr, and Et₃N to give the resin-bound unsaturated amides <1994JOC658, 1999CRV1549>. The liquid–liquid two-phase system using aqueous NaOH and C₆H₆, CH₂Cl₂, or CHCl₃ has been employed to prepare (*E*)- and (*Z*)-2-methoxycinnamionitrile and 3-cyclohexyl-2-propenenitrile on large scale in excellent yields <1988JMC37, 1992CPB2391>. Several other solid–liquid two-phase systems have been described, and the system using K₂CO₃ in water <1986TL1577, 1988TL477, 1996T9759> or in toluene <1994JA3367, 2000JOC6293> appears as the most promising (Scheme 10).

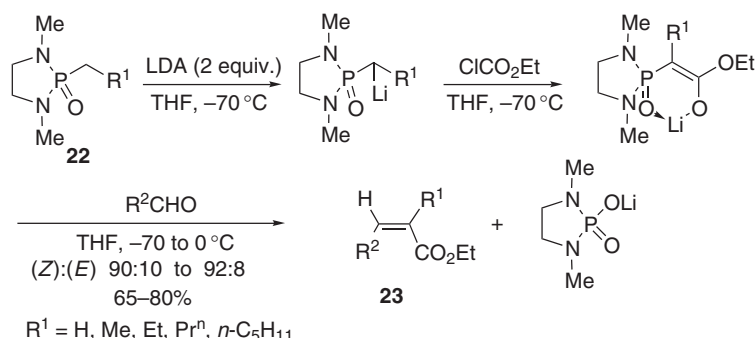


Scheme 10

Recently, the highly stereoselective (*E*)-olefination has been observed in the synthesis of alkenylated chromium carbonyl complexes having nonlinear optical properties, by using Cr(CO)₃-complexed dimethyl benzylphosphonates and heteroaromatic aldehydes <1997TL1025, 1999OM5066>. Analogously, an extensive use has been made of the exclusive (*E*)-configured double bond in the synthesis of poly(phenylenevinylene) dendrimers from new 1,3-bis- or 1,3,5-tris[(diethoxyphosphonyl)methyl]benzene and aromatic aldehydes <2001JOC5664, 2003JOC832>.

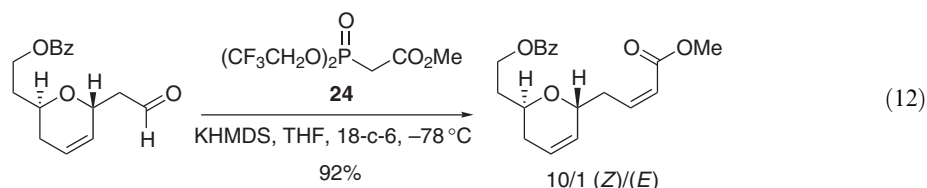
(ii) Formation of (*Z*)-alkenes

Much of the research effort this decade has centered around the development of methods for obtaining almost pure (*Z*)-alkenes from the reaction of phosphonate carbanions with aldehydes. It was first discovered that incorporation of the phosphonyl group into a five-membered <1978T997, 1991TL1317> or six-membered <1978T997, 1991SL517> ring, promotes the (*Z*)-alkenes. The highest (*Z*):(*E*) ratio of alkenes **23** was obtained with the use of 1,3-dimethyl-2-oxo-1,3,2-diazaphospholidines **22** (Scheme 11) <1991TL1317>. This high (*Z*)-selectivity is attributed to a rapid closure to the pentacoordinate intermediate owing to release of strain in the five-membered ring coupled with an increase in the rate of elimination relative to the equilibration of intermediates.



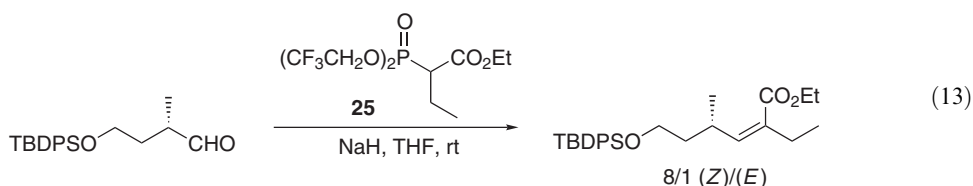
Scheme 11

A decisive modification was introduced in 1983 by Still and Gennari, who obtained high levels of (*Z*)-selectivity with the use of bis(2,2,2-trifluoroethyl) 1-(methoxycarbonyl)methylphosphonate **24** in reaction with aldehydes (Equation (12)) <1983TL4405>. The improved (*Z*)-selectivity is attributed to the electron-withdrawing effect of the trifluoromethyl group that accelerates the elimination of the initially formed β -hydroxyphosphonate adduct such that equilibration to the thermodynamic (*E*)-alkene is severely restricted. Factors that accelerate the elimination step tend to diminish the reversibility of the aldol step thereby favoring (*Z*)-products.



The magnitude of selectivity is dependent on the base and solvent used. KHMDS with 18-crown-6 (18-c-6) in THF appears to be the most effective combination by increasing the rate of elimination relative to equilibration due to minimal complexation of the intermediate with its counterion. Moreover, the conditions of Masamune–Roush <1984TL2183> or Rathke–Nowak <1985JOC2624> (lithium or magnesium halides, 1,5-diazabicyclo[5.4.0]undec-5-ene (DBU), Et_3N , *i*- Pr_2EtN) can be used to achieve (*Z*)-selective olefination of base-sensitive aldehydes <1990JOC128, 1997T1707>. Still's approach has been applied to a variety of carbanion stabilizing groups other than esters, including cyano, which normally exhibits poor selectivity <1988TL419>. Still's method has been extensively used in total synthesis <1988JA2248, 1988JA3929, 1988JOC4274, 1995CRV2041, 2001OL213, 2002JCS(P1)999, 2003EJO2193, 2003AG(E)2711>.

However, the studies of Marshall and co-workers showed that an α -alkyl substituent on the phosphonate moiety can significantly alter the (*Z*)-selectivity of this type of reagent **25** (Equation (13)) <1986JOC1735>. Thus, it has been found that the (*Z*)-selectivity seems unaffected by α -substitution with a methyl group <1983TL4405, 1987JOC3883, 1987TL3075, 1988H(27)2077>, but it is seriously compromised by long-chain α -alkyl substituents <1986JOC1735, 1990JOC128, 2001OL1685, 2002OL1023>.

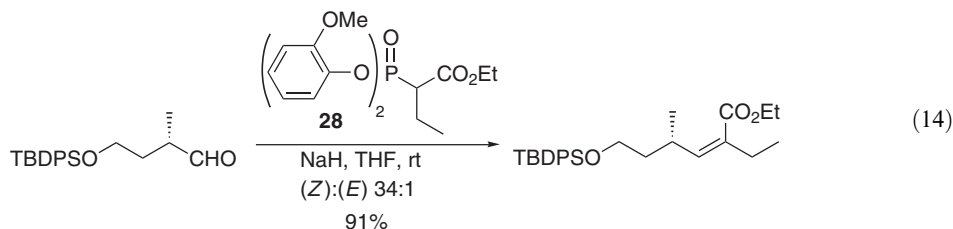


More recently, the diphenyl 1-(ethoxycarbonyl)methylphosphonate **26**, under Still's conditions, has appeared as effective as the bis(2,2,2-trifluoroethyl) 1-(methoxycarbonyl)methylphosphonate for the synthesis of (*Z*)- α,β -unsaturated esters <1995TL4105>. Thus, condensation of diphenyl 1-(ethoxycarbonyl)methylphosphonate with aldehydes using NaI/DBU/THF gives good to excellent yields of (*Z*)- α,β -unsaturated esters in high stereoselectivity <2000JOC4745>. On the other hand, condensation of ring-substituted diaryl phosphonates **27** with aldehydes seems less affected by

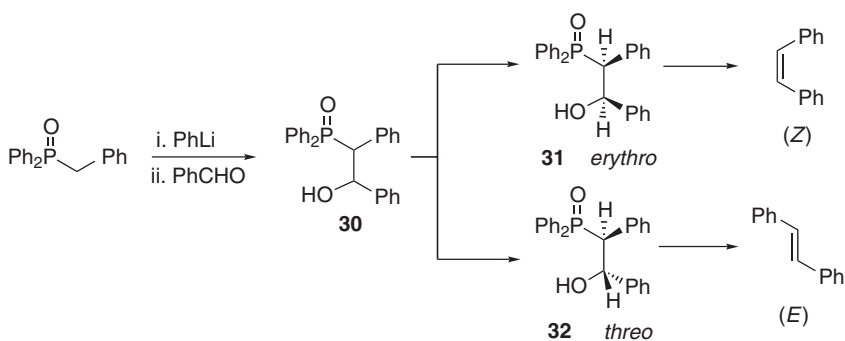
$(\text{PhO})_2\text{P}(=\text{O})\text{CH}_2\text{CO}_2\text{Et}$ **26**

$(\text{R}^2\text{-C}_6\text{H}_2(\text{R}^3, \text{R}^4, \text{R}^5)\text{-O})_2\text{P}(=\text{O})\text{CH}(\text{R}^1)\text{CO}_2\text{Et}$ **27**

$\text{R}^1 = \text{H, Me, Et, Bu}^n$



The first olefinations using phosphinoxy reagents were described by Horner in 1958 [<1958CB61>](#). They involved treating benzyldiphenylphosphine oxide with a potassium base (*t*-BuOK) and then adding a carbonyl compound to give *in situ* an alkene in one step [<1959CB2499, 1962CB581, 1964PAC225>](#). By contrast, when using lithium bases, the same reaction can be stopped at the intermediate adduct and the β -hydroxyphosphine oxide **30** isolated before elimination occurs [<1964TL2467>](#). In this significant discovery, Horner showed that the β -hydroxyphosphine oxide intermediates **30** were stable enough to be isolated, usually as crystalline compounds, and consisted of a mixture of diastereomers that could be separated into a minor isomer with the *erythro*-configuration **31** and a major isomer with the *threo*-configuration **32**. Assignment of configuration was based on subsequent decomposition of the adducts from the reaction of benzyldiphenylphosphine oxide and benzaldehyde by treatment with phenyllithium or lithium hydride to give (*Z*)- and (*E*)-1,2-diphenylethene, respectively, by *syn*-elimination of diphenylphosphinic acid (Scheme 12).



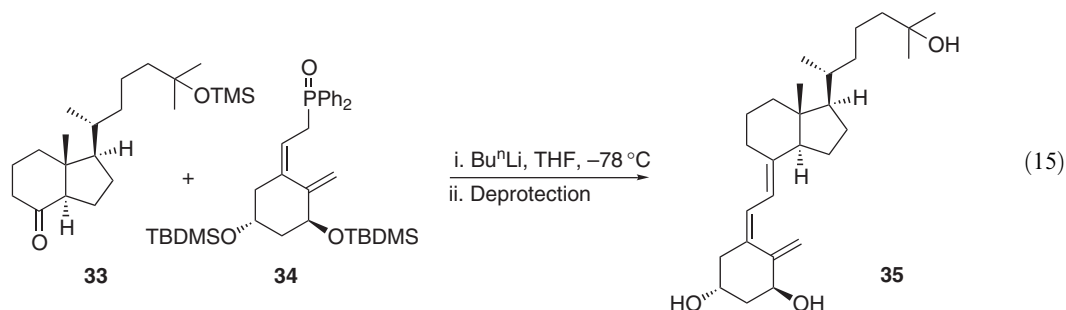
The fact that the Horner reaction can be stopped at the first stage and the intermediate adducts isolated and separated into pure diastereomers provided the basis for the use of phosphine oxide anions to form alkenes of specific geometry [<1996AG\(E\)241>](#). Compounds

containing the $\text{Ph}_2\text{P}(\text{O})$ group are very often crystalline. This property is important for the synthetic application of stereoselective reactions because it allows the separation and purification of stereoisomers by crystallization <1985JCS(P1)2307>. Because of the electronegativity of the $\text{Ph}_2\text{P}(\text{O})$ group, its stereochemical disposition relative to other polar groups in a molecule dominates the overall polarity of the molecule. This aids the separation of diastereomers by flash chromatography <1985JCS(P1)2307>. Recently, the role of the $\text{Ph}_2\text{P}(\text{O})$ group has been reviewed, showing the power of this group to control the stereochemistry of alkenes, and to produce “on demand” either stereoisomer in high stereochemical purity <1996AG(E)241>.

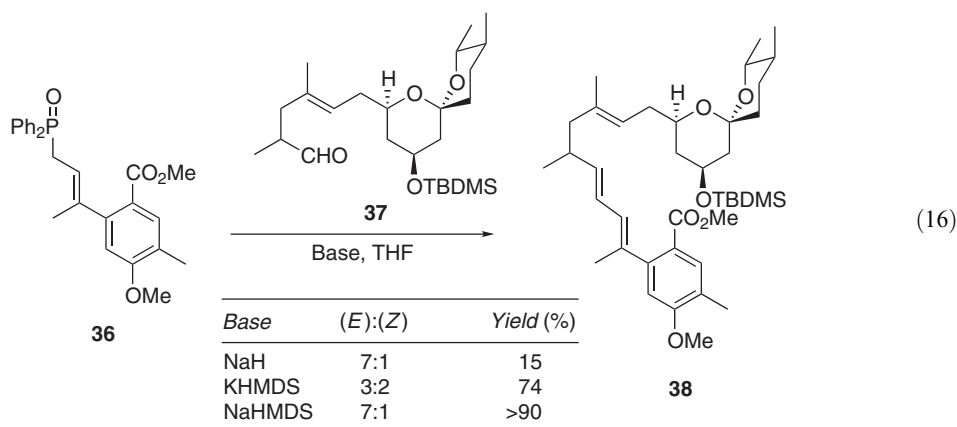
(i) Stereoselective formation of (*E*)- and (*Z*)-alkenes

Metallated alkyldiphenylphosphine oxides bearing functional groups in the α -position (R^1 = benzyl, allyl, OR, SR) undergo a one-step Horner reaction with aldehydes and ketones without isolation of intermediates. As for the Horner–Wadsworth–Emmons reaction, the one-step Horner reaction gives selectively (*E*)-alkenes. The intermediate adduct decomposes easily because the functional group in the α -position provides conjugation or stabilization of the negative charge and lowers the activation energy for the elimination. The (*E*)-selectivity is a result of the reversibility of the addition to a carbonyl compound of an alkyldiphenylphosphine oxide bearing an anion-stabilizing group in the α -position. This reversibility allows interconversion of the two diastereomers of the adduct, and faster elimination from the *threo*-adduct means that the (*E*)-isomer of the product alkene is formed selectively.

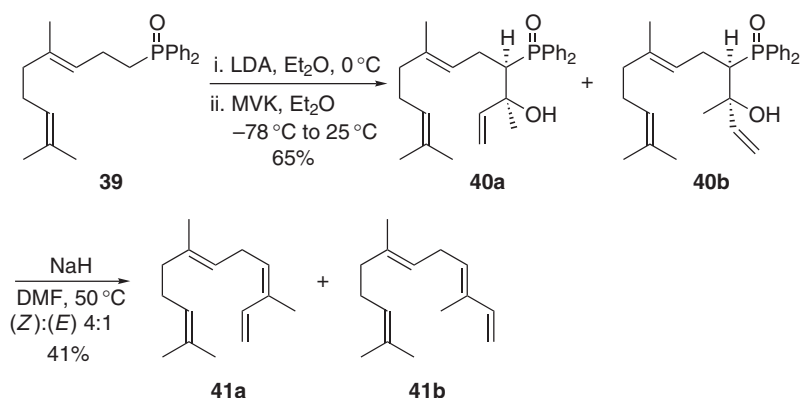
The use of the one-step Horner reaction has been focused with success on the design and synthesis of (*E*)-polyenes and especially of vitamin D and its analogs. This reaction is quite appropriate, since Horner reversal, in conjunction with fast elimination, serves to increase the proportion of (*E*)-product. The strategy of synthesis is based on the Lythgoe-type coupling approach <1976JCS(P1)2386, 1978JCS(P1)590, 1980CSR449, 1991TL4643, 1992TL2937, 1995CR1877, 1997JOC3299, 2000EJO2755, 2001T681, 2002JMC1723, 2002JMC3366, 2003OBC257>. Thus, the reaction of the 25-hydroxy-Grundmann’s ketone **33** with the lithiated carbanion derived from the (*Z*)-allylic diphenylphosphine oxide **34** gave compound **35** containing the newly formed double-bond assuming the natural (*E*)-geometry (Equation (15)). An advantage of this high-yielding coupling approach is its convergency <1995CR1877>. Recently, a solid-phase synthesis of the vitamin D system, obtained by coupling of the solid-supported ketone with modified allylic phosphine oxide has been described. <2001JA3716>.



In the Horner reaction, the choice of base is often critical. For example, in the total synthesis of (\pm)-milbemycin β_3 **38** it has been found that in the reaction of the (*E*)-allylic diphenylphosphine oxide **36** carbanion with aldehyde **37**, the alkene stereochemistry depended profoundly on the choice of the base. In this case, NaHMDS effected the olefination almost quantitatively to give the expected (*E*),(*E*)-diene **38** in a 7:1 ratio with its (*Z*),(*E*)-isomer (Equation (16)) <1986JA2662>. The effects of solvents on the type of product formed have been observed in the reactions of allyldiphenylphosphine oxide with aldehydes. Thus, in the synthesis of natural (+)-digitoxigenin, it has been demonstrated that when (*E*)-2-butenyldiphenylphosphine oxide was treated with *n*-BuLi in THF, the presence of HMPA as co-solvent may be crucial. When the HMPA is used, the desired (*E*),(*E*)-1,3-pentadienyl building block is cleanly isolated with high stereoselectivity <1987T723, 1996JA10660>.



Change of base is often advantageous. For example, synthesis of the mutagenic (*S*)-3-(1,3,5,7,9-pentaenyloxy)propane-1,2-diol with specific (*E*)-geometry has been carried out with LDA in the initial addition followed by the use of *t*-BuOK to effect elimination [<1984CC349>](#). Similarly, (3*Z*,6*E*)- α -farnesene **41a** has been prepared from MVK and 4,8-dimethyl-3,7-nonadienyldiphenylphosphine oxide **39** with LDA. The intermediate β -hydroxyphosphine oxides **40a** and **40b** have been treated with NaH in DMF at 50 °C to induce elimination of sodium diphenylphosphinate (Scheme 13) [<1995JOC6211>](#). The same approach, using two different bases (LDA then NaH), has been employed in the synthesis of (\pm)-16-oxa-2,3-oxidosqualenes [<1995TL5719>](#).

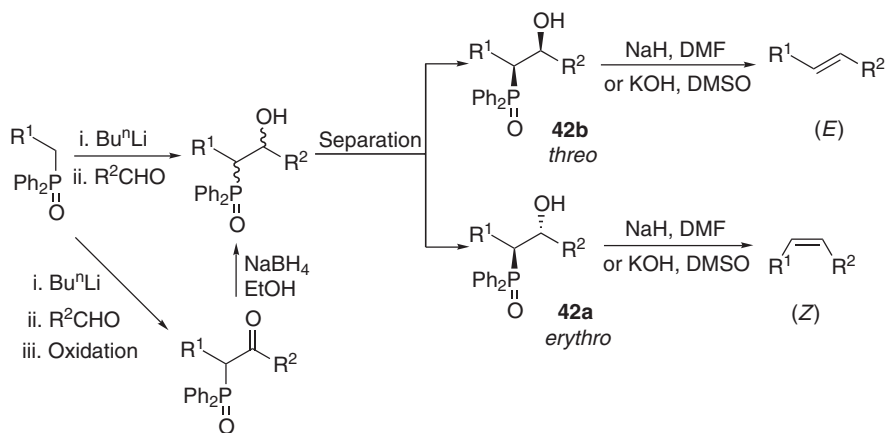


Scheme 13

It is remarkable that most of these one-step reactions specifically make use of the particular properties of the allylic phosphine oxides to prepare dienes and polyenes. These reagents are chosen because the new double bond is usually formed with (*E*)-selectivity and the stereochemistry at the formerly allylic olefin group is retained.

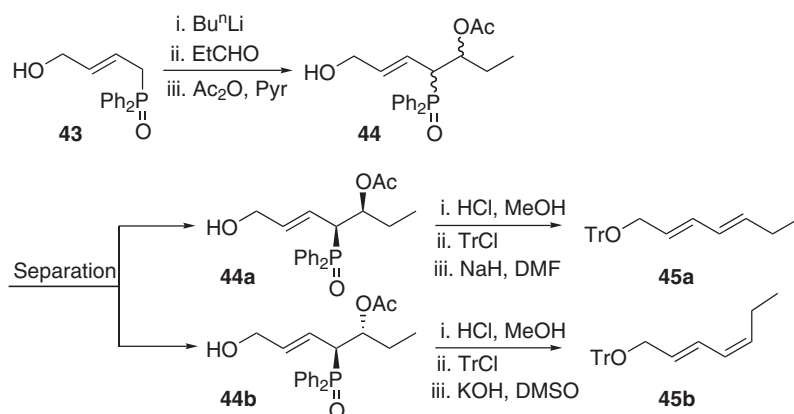
In general, the one-step Horner reaction does not give pure (*E*)- or (*Z*)-alkenes. To obtain stereochemically pure products, the Horner adducts prepared from stabilized lithium derivatives of phosphine oxides (R^1 = benzyl, allyl, OR, SR) are quenched below -50°C under carefully adjusted conditions and isolated before being subjected to elimination [<1994JCS\(P1\)1529>](#). The use of a lithium base is crucial to this control because it slows down the attack of the $\text{Ph}_2\text{P}(\text{O})$ electrophile. The diastereomeric β -hydroxyphosphine oxides **42a** and **42b**, preferentially formed in a ratio of 85:15 *erythro:threo*, are separated by chromatography or crystallization [<1985JCS\(P1\)2307>](#). Treatment of each pure diastereomer with a sodium or potassium base in a dipolar aprotic solvent (NaH/DMF or KOH/DMSO) [<1984JCS\(P1\)243>](#) generates a nucleophilic oxyanion leading to a single stereoisomer by *syn*-elimination of sodium or potassium diphenylphosphinate [<1981JOC459, 1985JCS\(P1\)2307, 1989JOC747, 1989JA1157>](#). The elimination is, in general, 100% stereospecific, giving pure (*Z*)-alkenes from pure *erythro*- β -hydroxyphosphine

oxides **42a**, and (*E*)-alkenes from pure *threo*- β -hydroxyphosphine oxides **42b**. This stepwise sequence has been called by Clayden and Warren the “stereocontrolled Horner–Wittig reaction” (Scheme 14) <1996AG(E)241>.



Scheme 14

Because of the *erythro*-selectivity of the Horner addition, this route is usually suitable only for the synthesis of (*Z*)-alkenes. This methodology has been used with allyldiphenylphosphine oxides to prepare dienes and polyenes in pure form <1979TL5043, 1986JA2662, 1988TL2401>. The synthetic utility of this indirect method is demonstrated by the synthesis of the protected (*E*),(*E*)-dienol **45a** and (*E*),(*Z*)-dienol **45b**, intermediates in the synthesis of some insect pheromones (Scheme 15). Thus, separation of the diastereomeric mixture of diol acetates (**44a**, **44b**), formed from hydroxyallylic phosphine oxide **43** and propionaldehyde, followed by hydrolysis, protection, and elimination (NaH/DMF or KOH/DMSO) gave the protected dienols **45a** and **45b** <1994JCS(P1)1529>. The optimal conditions for the elimination appear to be the use of powdered KOH in DMSO at room temperature. Under these conditions, pure (*Z*)-isomer is obtained free of the undesired (*E*)-isomer <2000S269>.



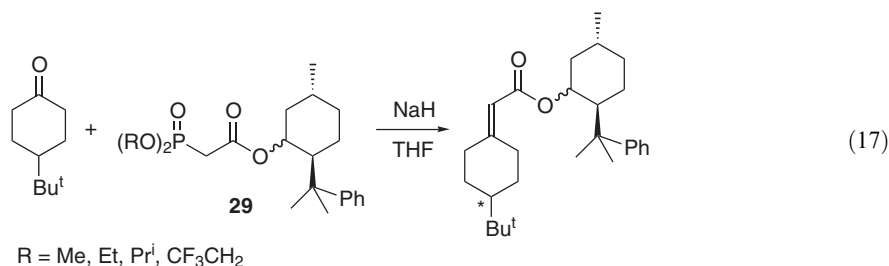
Scheme 15

Unfortunately, this stereospecificity is compromised when conjugating or anion-stabilizing groups are present alpha to the phosphorus <1984JCS(P1)243>, in which case the increased rate of Horner reverse reaction of *erythro*- β -hydroxyphosphine oxide may allow “stereochemical leakage” to produce some of the more rapidly eliminating *threo*-diastereomer, and hence the (*E*)-alkene <1983JCS(P1)2215, 1985JCS(P1)2307>. This leads to contamination of the (*Z*)-alkene, often with predominating amounts of (*E*)-alkene.

The practical synthesis of (*E*)-alkenes by the Horner reaction requires a high-yielding route to the *threo*-diastereomer. In a significant development, Warren <1986TL645, 1989TL601, 1996AG(E)241> introduced the selective reduction of β -ketophosphine oxides to obtain both the *erythro*- and *threo*-isomer adducts separately. Thus, reduction with NaBH₄ in EtOH, which is reported to favor *threo*-selectivity, followed by purification gives rise to the *threo*-diastereomer in a yield of 80–95% (Scheme 14) <1983TL5293, 1985JCS(P1)2307, 1996AG(E)241, 2002SC947>.

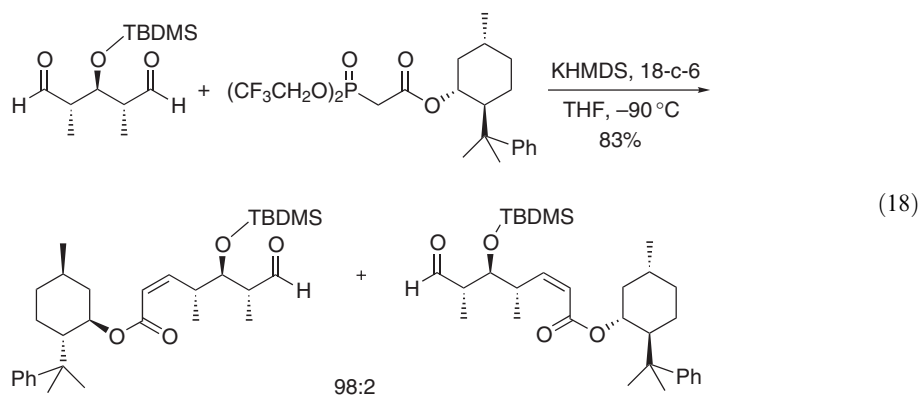
1.16.1.6.4 Asymmetric Horner–Wadsworth–Emmons and Horner reactions

Several articles are available that review asymmetric reactions of phosphonates and phosphine oxides, written by Rein <1996ACS369, 2002S579>, Li <1997CR2341> and Kolodiazny <1998TA1279>. Three types of asymmetric Horner–Wadsworth–Emmons reactions have been achieved: desymmetrization of ketones, kinetic resolution of racemic carbonyl compounds, and preparation of optically active allenes. As for the asymmetric Wittig reaction, the conversion of 4-substituted cyclohexanone to an axially dissymmetric alkene has been the key reaction by which chiral phosphonate reagents have been evaluated. The first desymmetrization of 4-substituted cyclohexanone using diethyl phosphonoacetate containing menthol as chiral auxiliary was reported in 1962 <1962CI(L)2085>. In 1984, Hanessian and co-workers introduced a chiral phosphonamide derived from *N,N*-dimethyl-1,2-diaminocyclohexane giving very high levels of asymmetric induction (>90%) in the desymmetrization of 4-substituted cyclohexanones <1992TL7655, 1992TL7659, 1993JOC100>. Later, several easily available chiral phosphonoacetates derived from menthol **29** <1988TL1773, 1988TL1775, 1997LA2419> or benzopyrano-[4,3-*c*]-isoxazolidine <1996TL1077> as chiral auxiliaries were introduced with success in reaction with symmetric ketones (Equation (17)).



Denmark and co-workers have described two types of chiral phosphonates, an oxazaphospholane and an oxazaphosphorinane, both containing carbon stereocenters and a stereogenic phosphorus center, and demonstrated their utility in asymmetric Horner–Wadsworth–Emmons reactions <1992JA10674>. A chiral phosphinoxy reagent containing 8-phenylmenthol as chiral auxiliary has been compared to the phosphonate analog <1994CC2167>.

As for the Wittig reaction, it has been demonstrated that promising levels of enantioselectivity could be reached in reaction between a phosphonate, a 4-substituted cyclohexanone and a chiral host. For example, chiral bases <1997CPB753>, chiral ligands <1998AG(E)515> and chiral catalysts <1998TL2997> can be used with success. The desymmetrization concept has been extended to *meso*-diketones <1997TL8943> and *meso*-dialdehydes (Equation (18)) <1998JOC8284, 2000OL2611>.



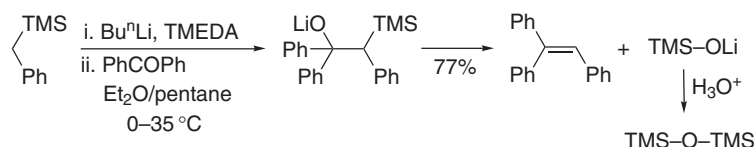
The idea of differentiating two enantiomers of a racemic monocarbonyl compound, which contains one or more stereogenic centers adjacent to the carbonyl group, by kinetic or dynamic kinetic resolution, with a chiral phosphonate reagent was introduced in the 1970s <1975TL437> and developed preparatively in the following years <1984JA5754, 1994JOC6887>. In the standard type of resolution, the racemic carbonyl compound needs to be present in twofold excess in order to allow complete conversion of the chiral phosphonate reagent to a single product isomer. For example, racemic (*Z*)-2,4-dimethylcyclohexanone and 3-*tert*-butylcyclohexanone could be resolved by reaction with chiral phosphoramides with high enantiomeric purity. Similarly, the chiral phosphonoacetate derived from mannitol was used to resolve racemic 2-benzylcyclohexanone to give the corresponding chiral alkene in high ee <1993CC102>.

Kinetic resolution of a racemic aldehyde was not reported until 1994 <1994AG(E)556>. Rein and co-workers then showed that acrolein dimer could be efficiently resolved by reaction with bis(2,2,2-trifluoroethyl) phosphonoacetate containing 8-phenylmenthol as chiral auxiliary. By utilizing the easy equilibration of the two enantiomers of α -amino aldehydes, Rein and co-workers effected the first dynamic kinetic resolution of racemic α -amino aldehydes by reaction with the same chiral phosphonate <1995AG(E)1023>. They also demonstrated the first application of kinetic resolution of an aldehyde to natural product synthesis by the preparation of a subunit of iejimalide A <1997TL6375>. For more detailed information and examples, the reader is referred to the recent review by Rein and Pedersen <2002S579>.

1.16.2 C=C BONDS BY CONDENSATION OF Si, B, Ge, OR Te FUNCTIONS

1.16.2.1 Silicon-mediated Alkenation: The Peterson Reaction

The Peterson olefination involving α -silyl carbanions <1968JOC780> is considered to be the silicon variation of the Wittig and related reactions. The Peterson reagents offer an interesting profile: (i) their reactivity is high enough to allow reaction with both aldehydes and ketones; (ii) the reagents are frequently more (*Z*)-selective than the corresponding stabilized phosphorus reagents; (iii) the silicon reagents are available via several synthetic routes. One practical advantage of the Peterson reaction depicted in Scheme 16 is that the disiloxane by-product, usually a volatile compound, is easily removed from the alkene product. The different aspects of the reaction have been discussed in several papers, especially by Ager <1984S384, 1990OR(38)1, 2001MI789, 2002CSR195>, Colvin <B-1988MI003>, Barrett <1991SL764>, Kelly <1991COS(1)731>, Luh <1993S349>, Kawashima <1996SL600>, Armstrong <B-1996MI005>, Bienz <1997C133>, Iorga <2001SL447> and Savignac <B-2003MI009>.

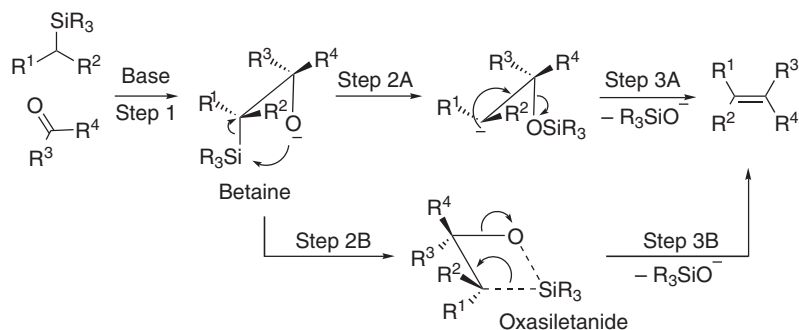


Scheme 16

1.16.2.1.1 Mechanism

Evidence that the reaction mechanism of the Peterson olefination involves the formation of a four-membered intermediate corroborates the theory that this olefination is the silyl variant of the Wittig reaction. Mainly two types of mechanism have been postulated, as depicted in Scheme 17. A stepwise mechanism involves the addition of the carbanion to the carbonyl compound followed by silicon migration from carbon to oxygen to give a carbanion, which then loses the siloxy anion to form the alkene. The elimination of the silanoxide is so rapid that no rotation about the C—C bond is observed during steps 2A and 3A, giving the same outcome as a concerted elimination from the betaine. In the concerted mechanism, steps 1 and 2B proceed simultaneously, leading to the concerted formation of an oxasiletanide intermediate. The elimination of

the silanoxide moiety would proceed in a concerted manner (step 3B). There is experimental evidence in support of both stepwise and concerted mechanisms <1996SL600, 2002CSR195, 2002JOC7378>.



Scheme 17

1.16.2.1.2 Preparation of silicon-stabilized carbanions

The different methods of preparation of α -silyl carbanions have been covered in detail <2001MI481, 2001MI789>. One of the major drawbacks of the Peterson reaction was considered for a long time to be the difficulties experienced in producing α -silyl carbanions. The bases most commonly used for the direct deprotonation of alkylsilanes are either alkyllithiums/PMDTA or TMEDA <2001MI789>. Indirect methods include the addition of an organometallic species to a vinylsilane <1970JA7424>, formation of organometallic reagents from α -halosilanes by metal-halogen exchange <1993TL2111, 1999TL33>, transmetalation <1976AG(E)161, 1980TL3451>, displacement of a phenylsulfanyl group by lithium naphthalenide <1981TL2923, 1986JCS(P1)183> or 1-(dimethylamino)naphthalenide <2002JOC6711> and cleavage of a Si—C bond with alkoxide or fluoride anions <1973TL4193>.

The approaches offering a direct access to β -hydroxysilanes have received a growing attention and represent the most versatile protocols. They involve the reduction of α -silyl carbonyl compounds with complex hydrides <1974TL1133, 1999T1717>, the addition to α -silyl carbonyl compounds of organometallic reagents, alkyllithiums and Grignard reagents, <2000S1223, 2001TL2605>, allyltitanate <1997JOC6326> chromium <1995SL498> or zirconocene <1999TL9325>, and the regio-specific ring-opening of α,β -epoxysilanes with nucleophiles <1975JOC2263, 2001OL3955, 2001T549>.

However, when the alkyl hydrogen of alkylsilanes is further activated by another group (Ar, vinyl, halogen, OR, NR₂, SR, COR, CN, SiR₃, P(O)(OR)₂, sulfonyl), then direct metallation is the method of choice to generate the α -silylalkyl carbanion.

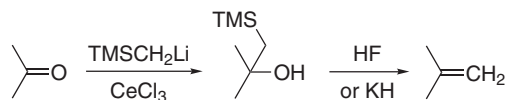
1.16.2.1.3 Methylenation reactions

The Peterson reaction is widely employed in the synthesis of methylene derivatives. (Trimethylsilylmethyl)lithium (TMSCH₂Li) <1973TL4193> has not found application as a consequence of its poor chemoselectivity, which reflects its propensity to behave as a strong base. (Trimethylsilylmethyl)magnesium chloride (TMSCH₂MgCl), a commercial reagent, has proved to be more advantageous for methylenation of aldehydes and enolizable ketones. The reagent is compatible with sterically hindered ketones <1973TL3497> and with a variety of sensitive functionalities, including the anomeric alkoxy group <1982JOC3548>, the thioacetal group <1988TL4521>, and an aziridine moiety <1988JOC3391>.

Hindered ketones can also be converted into an ethylidene unit by the use of α -(trimethylsilyl)-vinyl lithium, which is accessible by metallation of the corresponding bromo compound <1980JA2463>. The same reagent has been used for the preparation of terminal allenes <1978JOC1526>.

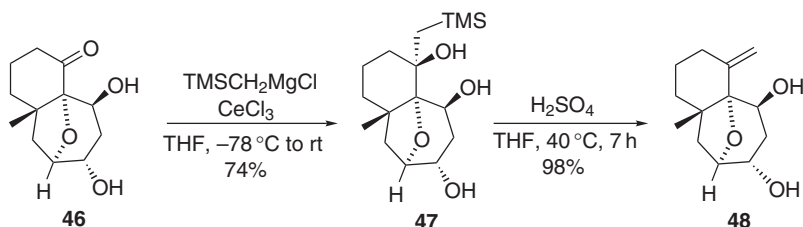
A decisive and efficient modification of the Peterson methylenation involves the use of Lewis acids. In 1987 Johnson and Tait reported that for carbonyl compounds with an easily enolizable α -hydrogen, the β -hydroxysilanes can be prepared in very good yields when TMSCH₂Li in THF

was added to anhydrous CeCl_3 at -78°C followed by the addition of carbonyl compounds [<1987JOC281>](#). As usual, the resulting β -hydroxysilanes were treated with either HF or KH to afford the olefins in good yields ([Scheme 18](#)).



Scheme 18

For example, the enolizable model compound cyclopentanone is methylenated successfully by this protocol in yields superior to those obtained with the related Wittig reactions [<1993JA3855>](#). In another example involving a polyfunctional substrate, the addition of an excess of organocerium reagent prepared from $\text{TMSCH}_2\text{MgCl}$ to the keto diol **46** affords the stable triol **47**, without competing α -deprotonation of the cyclohexanone. Further treatment with concentrated H_2SO_4 converts **47** into the methylene derivative **48** ([Scheme 19](#)) [<1995JOC833>](#). Analogously, the combination $\text{TMSCH}_2\text{MgCl}$ – CeCl_3 is useful for the preparation of allylsilanes [<1997JOC1578>](#).



Scheme 19

Other additives such as TiCl_4 have been used in conjunction with $\text{TMSCH}_2\text{MgCl}$, but yields of methylenated product are inferior [<1981TL5031>](#). In addition, a variety of acetals have been transformed in good yields into the corresponding olefins upon treatment with $\text{TMSCH}_2\text{Cu}\cdot\text{LiI}$, prepared from TMSCH_2Li and CuI in Et_2O [<2000SL859>](#), or with $\text{TMSCH}_2\text{MgCl}$ and ZnI_2 in Et_2O [<2000JOC4694>](#). In these conditions, 2-(2-naphthyl)dioxolane gives the corresponding styrene in 92% yield.

Recently, it has been reported that α -lithiated alkoxy silanes undergo Peterson reaction with carbonyl compounds to yield unstable β -hydroxy alkoxy silanes. On heating in AcOH/AcONa , they eliminate alkoxydimethylsilanol to give alkenes in good yield [<2001JOM\(625\)13>](#).

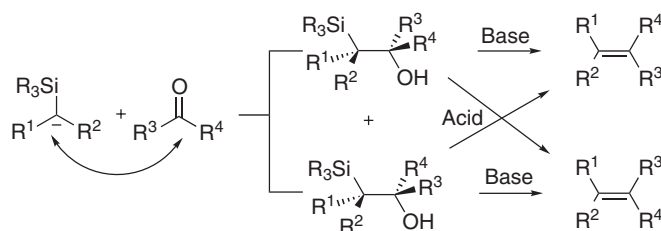
1.16.2.1.4 Stereoselective formation of alkenes

There are two protocols for preparing alkenes from α -silyl carbanions and carbonyl compounds. One employs silyl carbanions where there is no stabilizing group alpha to the carbanion and gives aliphatic alkenes. The other uses silyl carbanions containing a stabilizing group (Ar, CO_2R , SR, SOR, $\text{P}(\text{O})(\text{OR})_2$) alpha to the carbanion and gives functionalized alkenes.

(i) Formation of aliphatic alkenes

In the Peterson reaction of α -silyl carbanions with carbonyl compounds where (Z)- and (E)-alkenes can be produced, both isomers are formed in almost equal amount. This lack of stereo-specificity results from the formation, under kinetic control, of the intermediate β -hydroxysilane as $\sim 1:1$ mixture of *threo*- and *erythro*- β -hydroxysilanes, which decomposes with a high degree of selectivity. The ratio is not affected significantly by any change of the reaction conditions.

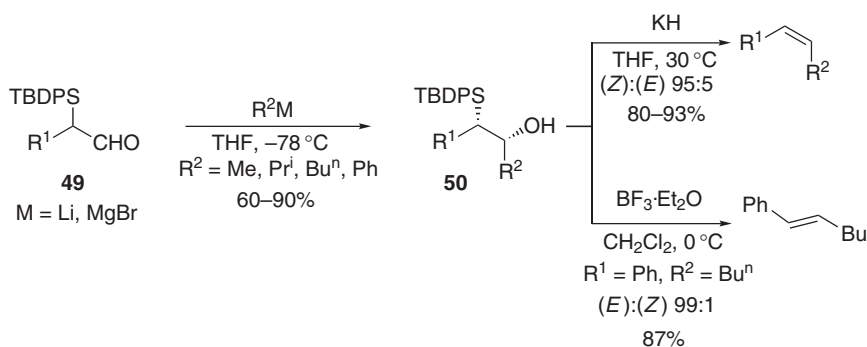
The β -hydroxysilyl intermediates can be treated with either acid or base to form the desired alkenes stereoselectively, as illustrated in Scheme 20. The important feature of the Peterson reaction is that both the (*E*)- and (*Z*)-isomers may be made from the same diastereoisomer. For example, treatment of the *erythro*- β -hydroxysilane under acidic conditions favors the formation of the (*E*)-isomer, whereas the (*Z*)-isomer is formed under basic conditions. Another attribute of this reaction is that the (*E*)-isomer, like the (*Z*)-isomer, can be prepared stereoselectively from both stereoisomers of the β -hydroxysilane (Scheme 20) <2001M1789>.



Scheme 20

For example, reduction with DIBAL-H of the β -ketosilane occurs to give predominantly the *threo*- β -hydroxysilane. On treatment with KH it leads to the stereospecific formation of (*E*)-oct-4-ene (*syn*-elimination), whereas on treatment with $\text{BF}_3 \cdot \text{Et}_2\text{O}$ or H_2SO_4 it leads to the (*Z*)-oct-4-ene (*anti*-elimination) <1975JA1464>. The same basic olefination conditions have been applied to the preparation of (*E*)-configured allylic alcohol from the 2-silylated 1,3-diols generated by reduction of α -silylated β -hydroxy ketones <1999T1717>.

The reaction of α -*tert*-butyldiphenylsilyl aldehydes with organolithium or Grignard reagents provides stereoselectively β -hydroxysilanes following the Felkin–Anh model. The addition takes place to form almost exclusively *erythro*- β -hydroxysilanes. The Peterson olefination can be used in the stereoselective preparation of (*Z*)- or (*E*)-disubstituted alkenes by *syn*- or *anti*-elimination using the standard acidic ($\text{BF}_3 \cdot \text{Et}_2\text{O}$) or basic (KH) conditions <2000S1223> (Scheme 21). The same method has been used to provide a stereoselective synthesis of trisubstituted alkenes by the addition of MeLi to β -ketosilanes <1976JOC2940, 1977TL1807>.



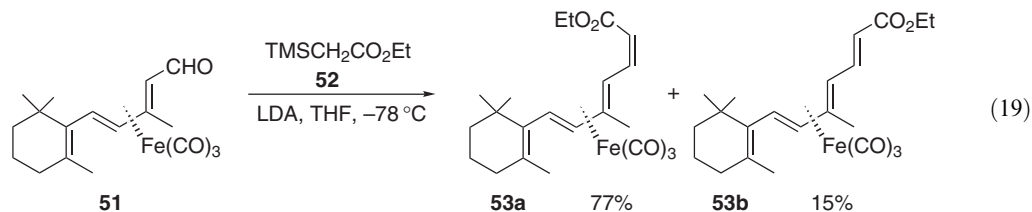
Scheme 21

Synthetic access to diastereoisomeric β -hydroxysilanes can also be obtained from α,β -epoxysilanes. It is known that α,β -epoxysilanes exhibit a regiochemical preference for α -opening of the epoxide ring with a variety of nucleophiles to produce diastereomerically enriched β -hydroxyalkylsilanes <2001OL3955, 2001T549>.

(ii) Formation of functionalized alkenes

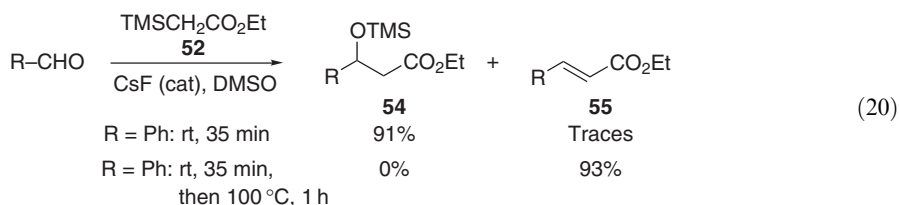
The Peterson reaction can be successfully employed for the synthesis of α,β -unsaturated esters by the addition of α -silyl ester anions to aldehydes. Elimination occurs under the reaction conditions and the

alkene isomer ratio can be influenced by the solvent, the metal counterion, the temperature, the size of the ester group and the nature of the aldehyde <2001MI789>. In search of a stereoselective synthesis of 11(*Z*)-retinal, it was shown that treatment of the β -ionylideneacetaldehyde–tricarbonyliron complex **51** with the lithium enolate of ethyl trimethylsilylacetate **52** affords the (*Z*)-isomer **53a** predominantly (77%) accompanied by the (*E*)-isomer **53b** (15%) (Equation (19)) <2000JOC2438>. The generality of this (*Z*)-stereoselectivity has been confirmed with various aldehyde–tricarbonyliron complexes.

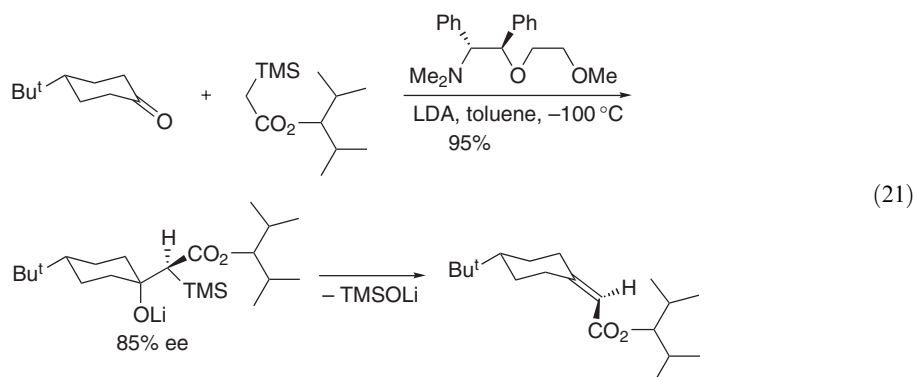


The counteraction effect has been observed in the reaction of aldehydes with *N,N*-dibenzyl(tri-phenylsilyl)acetamide using THF and KHMDS. Whereas the reactions with *n*-BuLi and NaHMDS were unselective, KHMDS gave exclusively the (*Z*)-product <2002JOC4093>. Moreover, it has been shown that the stereoselectivity of the reaction of lithium 1,3-bis(trimethylsilyl)propyne with the monoketal of 1,1-diacetylcyclopropane was temperature dependent. Thus, the (*Z*)-enyne is obtained at low temperature, whereas a mixture of (*E*):(*Z*) enynes is obtained if the reaction is allowed to warm above -40 °C <2000JA4915>.

A simplified version of the Peterson olefination reaction has been introduced using the CsF–DMSO combination. Thus, addition of ethyl trimethylsilylacetate **52** to nonenolizable aldehydes in the presence of catalytic CsF in DMSO at room temperature gives excellent yields of β -siloxy carboxylic esters **54**, which on heating at 100 °C eliminate TMSOH to produce the corresponding α,β -unsaturated esters **55** in high yield with excellent (*E*)-stereoselectivity (Equation (20)) <1995JOC6582>.



The first asymmetric Peterson reaction of an alkyl trimethylsilylacetate with 4-substituted and 3,5-disubstituted cyclohexanones using a chiral host, a tridentate amino diether, has been reported to give the axially dissymmetric alkenes with promising level of enantioselectivity (Equation (21)) <2002OL4329>.

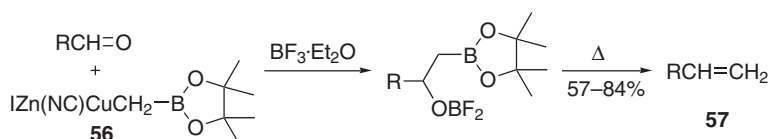


1.16.2.2 Boron-mediated Alkenation

In comparison to the well-established Peterson olefination, the corresponding boron-Wittig olefination using α -boryl carbanions has received little attention. The boron-Wittig olefination has been studied by Matteson and Pelter <1994PAC223, 1996SL600>.

Boron-stabilized carbanions, prepared from alkyldimesitylboranes and bases, react with ketones to give the corresponding alkenes in good yield <1983TL635>. By contrast, in the case of aldehydes, the initially formed and favored *erythro*-adduct has to be decomposed at low temperature with various reagents to promote either *syn*- or *anti*-elimination of the boryl function. Thus, trapping of the adduct at low temperature with TMSCl followed by treatment with aqueous HF gives predominantly the (*E*)-alkene. Alternatively, direct treatment of the adduct with TFAA results in decomposition by a cyclic ester-type elimination to give predominantly the (*Z*)-alkene on warming <1987CC297, 1994PAC223>.

By analogy with the silicon analogs, terminal alkenes are obtained in good yield by the addition of boron-stabilized carbanions to carbonyl compounds <1994PAC223>. For example, the pinacol (1-iodomethyl)boronic ester is converted into non-basic Zn/Cu α -boryl carbanion, which is subsequently reacted with aldehydes in the presence of $\text{BF}_3 \cdot \text{Et}_2\text{O}$ to give the corresponding methylenated product in fair to good yield (Scheme 22). For aromatic or α,β -unsaturated aldehydes, the dehydroxyboronation smoothly occurs on heating. However, lower yields result for the aliphatic aldehydes since the intermediates are quite stable toward elimination. The reaction is available with various functional groups, such as esters and ketones <1996T915>.



Scheme 22

1.16.2.3 Germanium-mediated Alkenation

No further advances have occurred in this area since the publication of chapter 1.16.2.3 in <1995COFGT(1)719>.

1.16.2.4 Tellurium-mediated Alkenation

No further advances have occurred in this area since the publication of chapter 1.16.2.4 in <1995COFGT(1)719>.

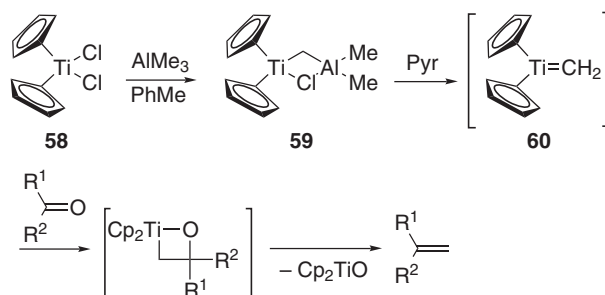
1.16.3 METAL-INDUCED METHYLENATION AND ALKYLIDENATION

One-carbon homologation of carbonyl compounds can be achieved with titanium-based reagents. The use of these reagents in synthesis is limited to the transfer of a methylene unit for the Tebbe reagent but can be extended to alkenation for the other reagents. The methylenation of aldehydes and ketones by these nonbasic, reactive reagents offers some advantages over other methylenation methods, particularly with base-sensitive substrates or with sterically hindered carbonyl compounds. A further advantage of the titanium reagents is their ability to methylenate carboxylic and carbonic acid derivatives. The subject has been previously covered by Pine <1993OR(43)1>, Petasis <1996PAC667>, Hodgson <B-1996MI006>, Takeda <1999RHA93> and Hartley <2002JCS(P1)2763>.

1.16.3.1 Tebbe Reagent

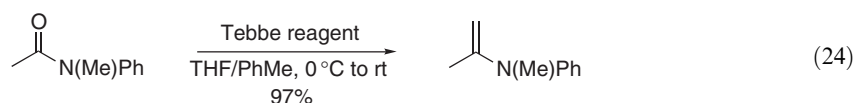
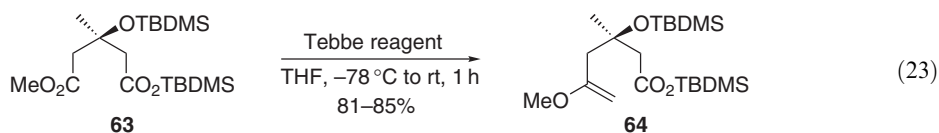
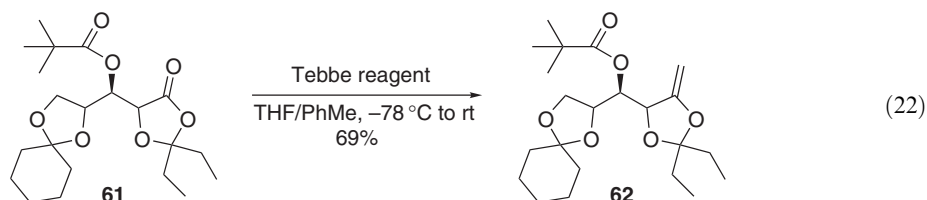
The Tebbe reagent **59** is a titanium–aluminum metallacycle prepared from titanocene dichloride **58** and trimethylaluminum in toluene <1978JA3611, 1990OS72>. The reagent is commercially available as a solution in toluene. When the Tebbe reagent is treated with a Lewis base (Pyr or DMAP), a highly reactive titanocene methylenide **60** is generated by removal of AlMe_2Cl . This

species **60** methylenates cleanly and efficiently a range of carbonyl compounds including easily enolizable aldehydes and ketones. The driving force is probably the formation of the strong titanium–oxygen double bond (Scheme 23) <1984AG(E)587, 1997JA8574>.



Scheme 23

There are a large number of examples of methylenation of esters, lactones, and amides by the Tebbe reagent and an attractive feature of this reagent is its selective methylenation. For example, the lactone **61** is methylenated to give the *exo*-methylene compound **62** without affecting the pivaloate group (Equation (22)) <1994TL2537>, regioselective methylenation of the methyl ester **63** proceeds without affecting the bulky silyl ester group to give enol ether **64** (Equation (23)) <2000JCS(P1)2483>, and the methylenation of tertiary amides gives enamines in high yield (Equation (24)) <1985JOC1212>.



The advantage of the Tebbe reagent is that the reactive titanium methylenide is generated and reacted at low temperature. Its disadvantages are the sensitivity to air and moisture, the Lewis acid character and the fact that it is limited to methylenation.

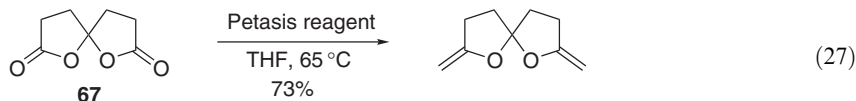
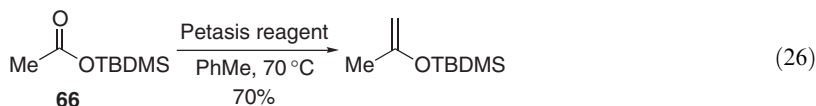
1.16.3.2 Petasis Reagents

Dimethyltitanocene **65**, the Petasis reagent, is prepared from methyl lithium <1990JA6392> or more preferably methylmagnesium chloride <2002OS19> and titanocene dichloride **58**. This reagent is relatively stable to both air and water. It has been shown by Petasis and co-workers that carbonyl compounds are methylenated by dimethyltitanocene **65** on heating at 60–75 °C either in THF or toluene (Equation (25)) <1990JA6392, 1995TL2393>. The reaction proceeds by rate-determining generation of titanocene methylenide **60** by α -elimination and release of methane, followed by reaction with the carbonyl compounds <1996OM663>.

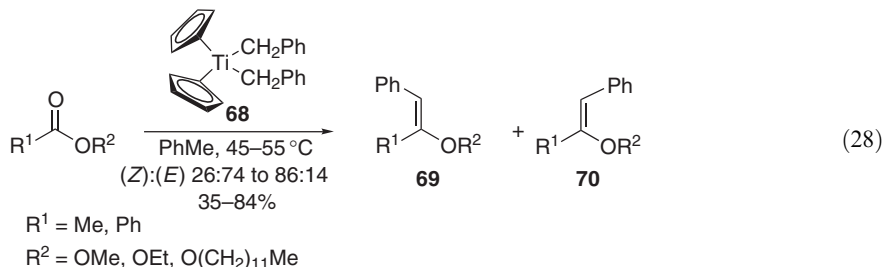


Aldehydes and ketones can be selectively methylenated in the presence of less electrophilic carbonyl compounds such as esters, amides, and carbamates. Examples include the final step in the synthesis of 21-oxogelsemine <1997JA6226> and a key step in the synthesis of an α -alkyl- α -amino acid <1993JOC5918>.

Dimethyltitanocene **65** is also able to methylenate esters with high selectivity, including the silyl ester **66** (Equation (26)) <1995TL2393>, acid anhydrides, lactones, including spirolactone **67** (Equation (27)) <1995TL2393>, thioesters, selenoesters, and acylsilanes. The use of an excess of dimethyltitanocene **65** results in the methylenation of a strained β -lactam to produce 2-methylenazetidine without affecting the ester or the *t*-BOC group <2000TL5607>.



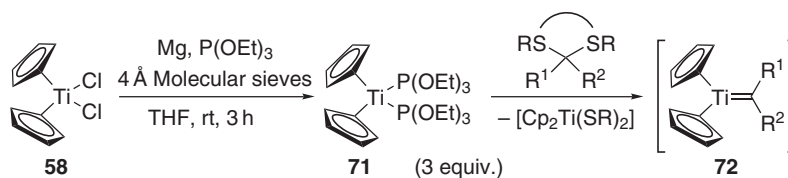
A route to substituted titanium-alkylidene species and their use in carbonyl olefination has been developed. Thus, a range of dialkyltitanocenes such as dibenzyltitanocene (Equation (28)), bis(trimethylsilylmethyl)titanocene, and bis(cyclopropyl)titanocene has been introduced by Petasis and co-workers to alkylidenate carbonyl compounds <1992JOC1327>. When dibenzyltitanocene **68** is heated with esters, (*E*)- and (*Z*)-enol ethers **69** and **70** are formed with good (*Z*)-selectivity.



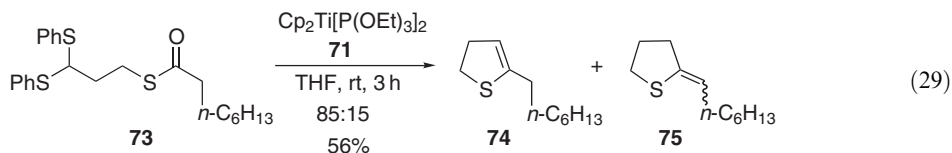
1.16.3.3 Takeda Reagents

In 1997 Takeda reported that dithioacetals can be reduced by low-valent titanium complex **71** to give a reactive titanium alkylidene species **72** presumably by desulfurization. The most important subsequent reaction of **72** is carbonyl olefination, which proceeds smoothly with aldehydes, ketones, esters, and thioesters <1997JA1127>. The low-valent titanium complex **71** is prepared by reduction of titanocene dichloride **58** with Mg in the presence of P(OEt)₃ in THF then added to dithioacetals to generate the titanium alkylidenes **72** (Scheme 24). 4 Å Molecular sieves are essential for rapid reduction. No limitations have been observed with respect to the structure of the dithioacetals. Methylenation is ineffective under Takeda conditions, but allyl, benzyl, or alkyl dithioacetals are suitable substrates for generating alkylidenating reagents. A disadvantage of the reagent **72** is the unsatisfactory stereoselectivity observed for the olefination of aldehydes. Better selectivities have been obtained in the olefination of carboxylic esters <1997JA1127>.

The Takeda reagent has been efficiently used in the synthesis of 5-heptyl-2,3-dihydrothiophene **74**, contaminated by its isomer 2-heptylidenetetrahydrothiophene **75**, by intramolecular carbonyl olefination of the thioester **73** (Equation (29)) <1999SL1029>. Similarly, enol ethers of cyclic ketones have been obtained by intramolecular carbonyl olefination of alkyl ω,ω -bis(phenylthio)alkanoates <2001CC625>.



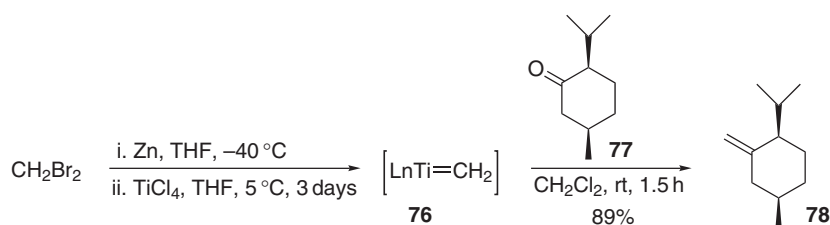
Scheme 24



The advantages of the Takeda reaction are the range of alkylidenating agents that can be generated, the mildness of the conditions and the ease of synthesis of dithioacetal substrates. Moreover, a range of functionality is tolerated within the carboxylic acid derivatives and the alkylidene reagents.

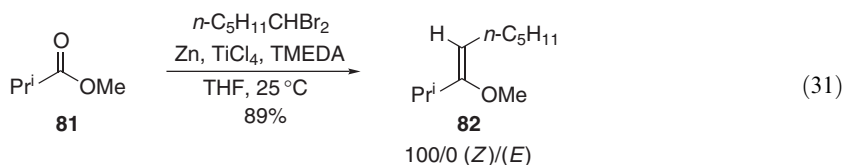
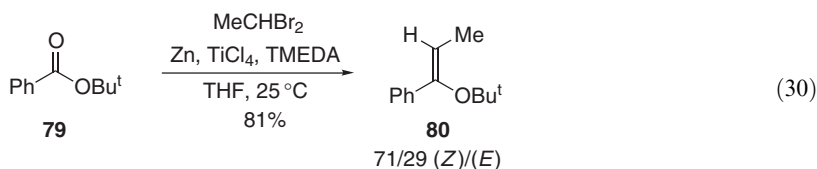
1.16.3.4 Takai–Lombardo Reagents

The Takai–Lombardo methylenation reagent **76** is a titanium-methylidene species prepared from dibromomethane, Zn, and TiCl_4 in THF at 5°C for 3 days. The reagent must be kept cold at all times because the active species slowly decomposes at room temperature. It reacts at room temperature with ketones to give the methylenated product in high yield without enolization. Moreover, the reagent is compatible with a wide variety of functional groups (THP ethers, acetals, esters, carboxylic acids, alcohols, etc.). For example, **76** has been reacted with isomenthone **77** to give the methylenated derivative **78** in 89% yield (Scheme 25) <1987OS81>. The $\text{CH}_2\text{I}_2\text{--Zn--TiCl}_4$ system has also been tested and appears as more reactive than the $\text{CH}_2\text{Br}_2\text{--Zn--TiCl}_4$ system. The reagent is effective for the methylenation of aldehydes, and the ester groups remain unchanged while ketone methylenation proceeds <1985TL5579>.



Scheme 25

A further advantage of the Takai–Lombardo reagents is the possibility, in addition to methylene units, of transferring substituted alkylidene units by using reagents prepared from 1,1-dibromoalkanes, Zn, TiCl_4 , and TMEDA in THF. The presence of trace amounts of lead(II) is reported to be vital to the success of the reaction. Takai and co-workers have published a definitive procedure for the preparation of their reagent <1996OS73>. The reaction proceeds via a *gem*-dizinc compound, which is subsequently transmetallated with TiCl_4 to the titanium-alkylidene species. The use of these reagents allows the general alkylidenation of carboxylic esters. In this transformation, the (*Z*)-enol ethers are obtained with high stereoselectivity. Thus, *t*-butyl ester **79** gives modest selectivity for (*Z*)-enol ether **80** (Equation (30)), but *iso*-butyrate **81** gives solely (*Z*)-enol ether **82** (Equation (31)).



The advantage of the Takai–Lombardo alkylidenation is that it is a mild one-pot procedure that allows the alkylidenation of a range of carboxylic acid and carbonic acid derivatives with good stereoselectivity. The major drawback of this method is the rather cumbersome access to the respective substituted dihalomethane compounds, which prevents a broad application of this reaction in organic synthesis.

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Biographical sketch



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1.17

One or More C=C Bond(s) by Pericyclic Processes

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1.17.1 INTRODUCTION

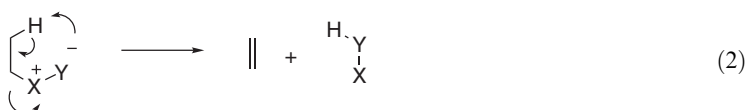
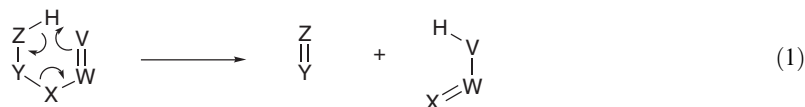
This chapter deals with the creation of the C—C bond by retro-pericyclic cleavage reactions and is intended to provide a selective, rather than exhaustive, survey of these processes. Emphasis is given to papers of recent origin (most of them after 1995) that were not covered in COFGT (1995).

Retro-sigmatropic-shift processes, which are considered first, are characterized by the cleavage of one C—H and one C—X bond to create the alkene, whereas the retro-cycloaddition reactions, which form the next section of the chapter, are characterized by cleavage of two C—C (or C—X) bonds. Formation of dienes and polyenes is considered separately and includes a study of retro-cheletropic reactions. Concerted rearrangements are reported in Chapters 1.09 and 1.18. Within each section, the mechanism and stereochemistry of each process will be covered, together with an assessment of the scope, limitations, and reaction conditions. Finally, attention will be primarily focused on those synthetically useful reactions that have found application, often as key steps, in the field of natural product synthesis.

The majority of the relevant reactions are thermal eliminations that may be carried out either in solution or in gas phase. This chapter describes “flow pyrolyses” as those reactions that are carried out at atmospheric pressure or under low pressure under a stream of inert gas (nitrogen or argon) by feeding a solution of the substrate down a heated tube packed with glass. In contrast, “flash vacuum pyrolysis” (FVP) involves slow addition of the substrate at the top of a quartz column filled with quartz chips and maintained at a high temperature (>500 °C) under ~0.2 mm pressure.

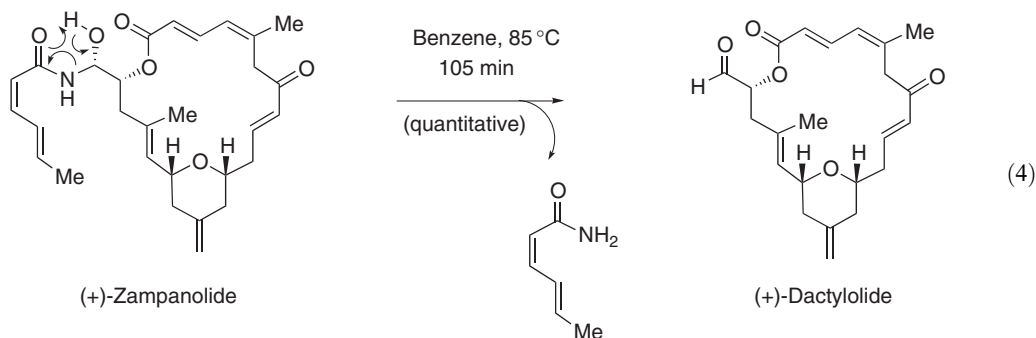
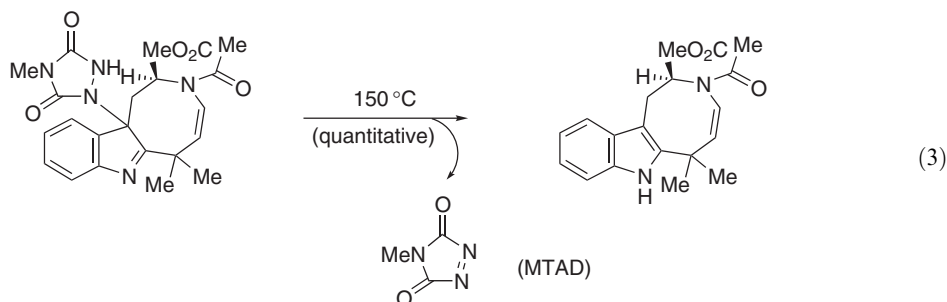
1.17.2 FORMATION OF MONOENES BY RETRO-ENE AND RELATED REACTIONS

The general reactions under consideration are shown in [Equations \(1\) and \(2\)](#). [Equation \(1\)](#) involves hydrogen transfer via a six-membered ring transition state and is formally a $[2\sigma_s + 2\sigma_s + 2\pi_s]$ reaction. [Equation \(2\)](#) is isoelectronic with [Equation \(1\)](#) but involves a five-membered ring transition state $[2\sigma_s + 2\sigma_s + 2\omega_s]$.

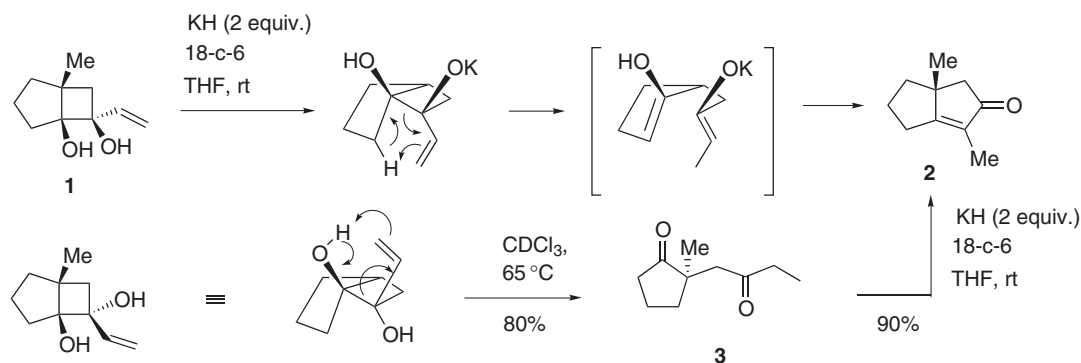


1.17.2.1 Cleavage of One C—H (or One X—H, X = Heteroatom) and One C—C (or One Heteroatomic) Bond

Retro-ene reactions have been principally achieved under FVP conditions and often at very high temperatures to give, in most examples, reactive intermediates that were characterized *in situ* by special techniques such as matrix isolation IR spectroscopy [<1997JOC4240, 1998JOC2619>](#). Such technical constraints have certainly limited the application of this reaction in multistep syntheses. However, several reactions that could be achieved at “reasonable” temperatures have been reported recently in the field of natural product synthesis. Thermal decomposition of urazole–indole adducts can be achieved in good to excellent yields at temperatures ranging from 150 °C to 250 °C [<2003OL1999>](#). Since the adducts are the result of an easily realized ene reaction between indoles and 4-methyl-1,2,4-triazoline-3,5-dione (MTAD), this reaction, which found application in the total synthesis of okaramine A [<2003JA5628>](#), represents the first method for protection–deprotection of the 2,3-indole bond ([Equation \(3\)](#)). The relatively mild temperature required for this reaction to occur is certainly due to the fact that the migrating hydrogen is borne by a heteroatom rather than by a carbon ([Equation \(1\)](#), Z = N). This favorable situation was also exploited to convert (+)-zampanolide into (+)-dactylolide, two cytotoxic macrolides of marine origin ([Equation \(4\)](#)) [<2002OL635>](#).



The accelerating effect of alkoxides on concerted reactions is well recognized. Such an effect on the rate of the retro-ene reaction has recently been demonstrated for the first time <2001OL3025>. Thus, although the *cis*-diol **1** is reluctant to rearrange in toluene at reflux for days, it gives enone **2** when treated with potassium hydride and 18-crown-6 (18-c-6) at room temperature. This transformation was shown to arise via an exceptionally easy anionic oxy-retro-ene reaction to give a potassium enolate that cyclizes to the bicyclic enone **2** (Scheme 1). Interestingly, the diastereoisomeric *trans*-diol, when heated in deuterated chloroform at 60 °C, was transformed to diketone **3**. This dramatic change in reactivity was accounted for by the fact that, in the latter example, the migrating hydrogen is no longer borne by a carbon, as it is in the *cis*-diol, but by an oxygen (Scheme 1).



Scheme 1

Decarboxylation of carboxylic acids containing β,γ -unsaturation is another case, which follows the general mechanism of Equation (1). A well-known and synthetically useful example is represented by the decarboxylation of β -keto acids and 1,3-diacids, which can be accomplished under mild conditions. This operation is often the final stage of the acetoacetic and malonic syntheses of methyl ketones and carboxylic acids.

In a different domain, a detailed kinetic investigation of the allylsulfinic acid desulfination has concluded that a concerted, retro-ene mechanism is involved <1995JOC7166>.

1.17.2.2 Cleavage of One C—H and One C—O Bond

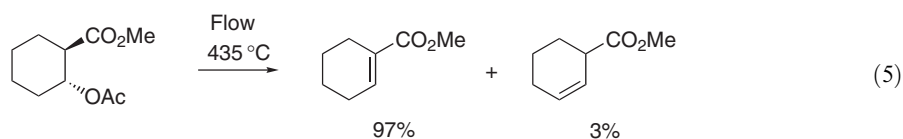
1.17.2.2.1 Pyrolysis of acetates and related esters

Many reviews of this topic (Equation (1); $X = V = O$; $Z = Y = W = C$) are available <1960CRV431, B-1979MI117-001, B-1980MI117-002, 1991COS(6)1011>.

This reaction can be carried out in the gas phase under flow conditions at temperatures of 500–525 °C or in FVP conditions at higher temperatures (600–700 °C). The *syn*-nature of the elimination was proved by pyrolyses of specifically labeled acetates <1953JA6011, 1972JCS(P2)165>.

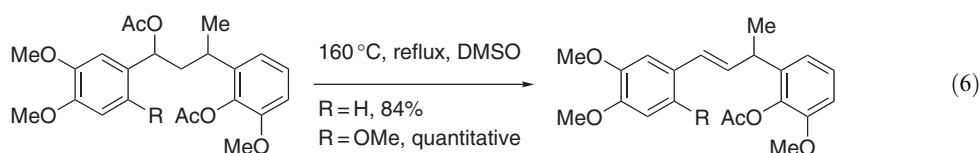
The regioselectivity of the elimination is dependent on a number of factors including statistical effects, thermodynamic stability (arising from steric effects), and electronic effects, and the overall stereochemical outcome can be rather modest <1963RTC1123>. Steric effects promote the formation of the (*E*)- rather than the (*Z*)-alkenes and formation of a double bond *endo*- to a ring is generally favored relative to the *exo*-double bond <B-1979MI117-001, 1959JA651>.

Electronic factors are now recognized as being dominant in governing the rate and direction of alkene formation. The reaction is favored by electron donation at C-1 <1975JCS(P2)1025> and also by electron-withdrawing groups at C-2 (Equation (5)) <1959JA2126>. Bulky electron-donating (alkyl) substituents at C-2 can also cause a small enhancement due to “steric acceleration” <1976JCS(P2)280>.

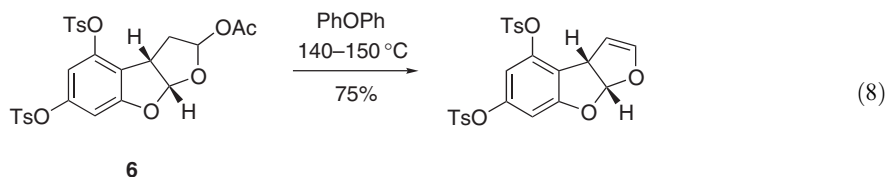
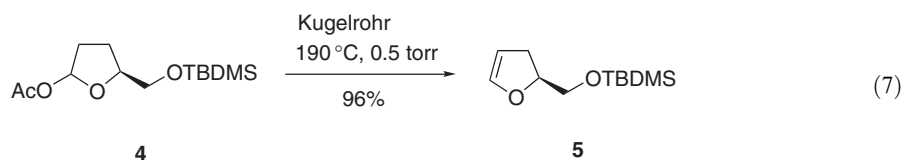


The reaction is also slightly accelerated by electron-withdrawing groups at the carbonyl carbon atom <B-1979MI117-001, 1969JCS(B)187, 1972RTC3>. Thus, cyclohexyl trifluoroacetate is 19 times more reactive than the corresponding acetate <1963JCS1246>. Although the use of benzoates has the advantage that benzoic acid crystallizes at the exit point of the furnace, well away from the more volatile alkene, acetates continue to be the most widely used ester groups <1988ACA58>. FVP conditions are well suited to and particularly effective for the synthesis of alkenes, which readily polymerize or decompose unless kept in the cold.

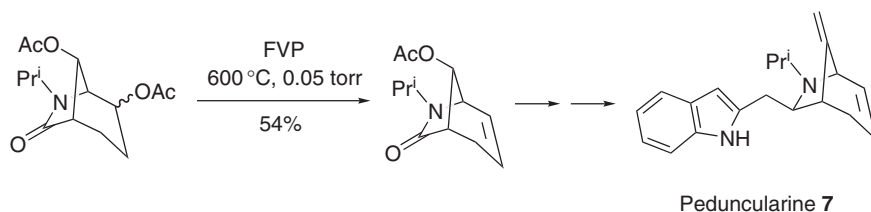
The major drawback of this method arises from the high temperature involved that precludes the presence of sensitive functional groups in the substrates. Consequently, the usefulness of the acetate elimination has been limited to simple substrates and is generally not compatible with sensitive natural product intermediates. However, this method has been successfully used in the total synthesis of natural curcuminoid antioxidants (Equation (6)) <1998JNP609>.



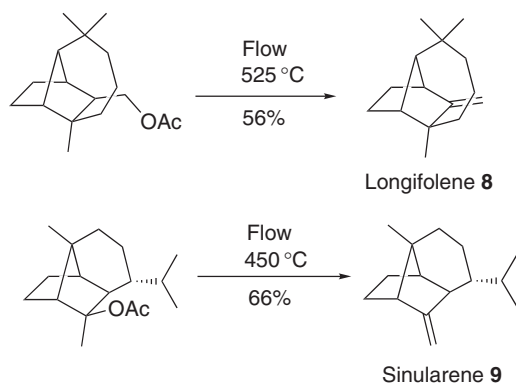
In the course of the enantioselective synthesis of hydantocidin analogs, the chiral dihydrofuran **5** was prepared in excellent yield from the corresponding acetate **4** on a gram scale by heating at 190 °C at 0.5 torr in a Kugelrohr apparatus (Equation (7)) <1999JOC2010>. The ABC tricyclic portion of aflatoxins was obtained by pyrolytic elimination from the acetate intermediate **6**, carried out at 140–150 °C in a high-boiling-point solvent under a stream of nitrogen removing AcOH to prevent side reactions (Equation (8)) <1994JOC3775>.



Acetate pyrolysis was also used in a synthesis of the alkaloid peduncularine **7**, when anionic and cationic eliminations failed (Scheme 2) <1989JA2588>. The exocyclic methylene groups of longifolene **8** <1990JA4609, 1993JOC2186> and sinularene **9** <1979AJC1819> were introduced by classic “flow pyrolysis” methodology using benzene or toluene solutions of the substrates (Scheme 3).



Scheme 2



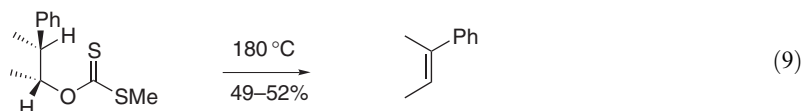
Scheme 3

1.17.2.2.2 Pyrolysis of xanthate esters

This method follows the general mechanism of Equation (1) ($X = O$, $W = C-SR$, $V = S$, $Z = Y = C$); invariably the *S*-methyl derivatives are used. However, earlier work on pyrolysis of steroid xanthates showed that β -cholestanyl-*S*-benzyl xanthate decomposed almost twice as fast as the corresponding *S*-methyl xanthate <1952JA5454>. In addition to the reviews cited in the previous section, a specialized account of this transformation—the Chugaev reaction—is available <1962OR57>.

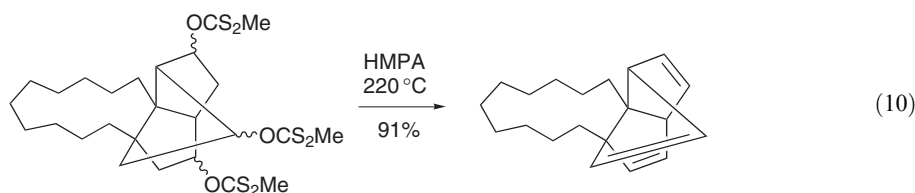
Compared to acetates, the disadvantage of this method is that xanthates are obtained from alcohols via the alkoxides, thus requiring strong basic conditions to be formed; the final products are frequently contaminated with sulfur-containing impurities <1962OR57>. Treatment of the alcohol with strong bases (NaH, KH, $KOBu^t$, Bu^nLi , and MeLi) followed; by subsequent sequential addition of carbon disulfide, and iodomethane (or sometimes dimethyl sulfate) continues to be widely used on a broad range of substrates to prepare xanthate esters. Nevertheless, xanthates are more reactive than acetates so that the reaction can be carried out under relatively mild conditions (typically at a temperature of $\sim 150^\circ C$ for a few hours either at atmospheric pressure or under vacuum), thus minimizing the possible thermal isomerization of the alkene <1962OR57>.

The *syn*-stereochemistry of the process has been demonstrated <1949JA3883> (Equation (9)) and the involvement of the $C=S$ sulfur atom in the elimination was proved by ^{34}S and ^{14}C isotope effects <1961CJC348>.

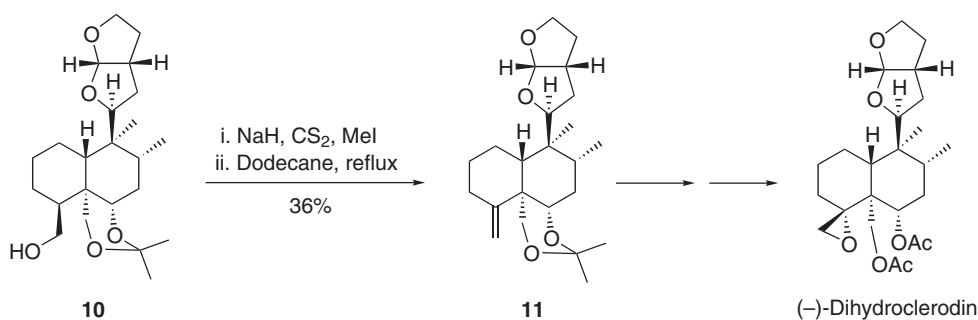


As with acetates, statistical, thermodynamic, and steric factors again govern the direction of the elimination <1962OR57>. In addition, electron-withdrawing groups attached to the sulfur atom further accelerate the reaction <1953JA2118>.

Xanthate pyrolysis is still used substantially in synthesis. A spectacular example in propellane chemistry is represented below <1992JOC5121> (Equation (10)).

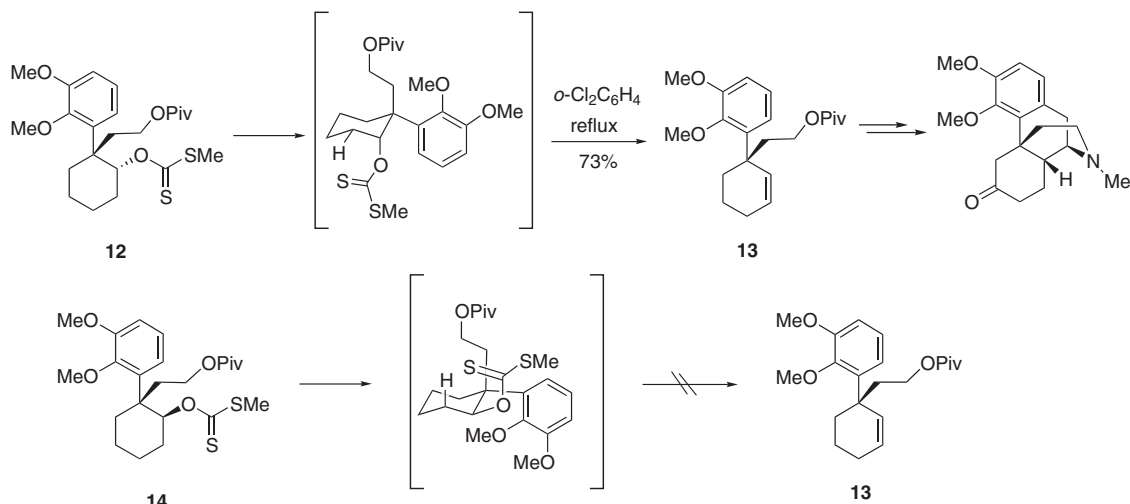


In recent years, a number of applications in natural product synthesis have been found. In the first synthesis of the insect-antifeedant (–)-dihydroclerodin, the alcohol **10** was converted into the xanthate, which under heating at $216^\circ C$ for 48 h gave the desired intermediate **11** with an exocyclic double bond <1999JOC9178> (Scheme 4). It is worth noting that under these conditions the hexahydrofuro[2,3-*b*]-furan motif is stable. All attempts to form the selenide intermediate from the alcohol **10** failed.



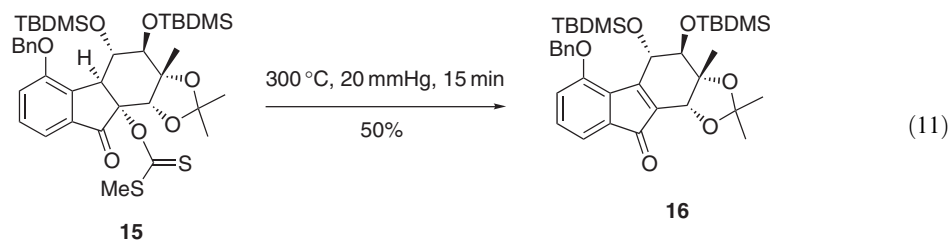
Scheme 4

In the formal synthesis of morphine via the racemic 3,4-dimethoxy-7-morphinanone, thermolysis of the xanthate **12** afforded the desired cyclohexene intermediate **13** (Scheme 5) <2000OL2785>. No elimination occurred when the epimeric xanthate **14** was heated under various conditions but only a complex mixture was obtained. Presumably, this failure could be explained by the fact that the required geometry in the transition state to permit the *syn*-elimination could not be reached in this case due to steric repulsion between the xanthate moiety and the axially disposed alkyl chain.



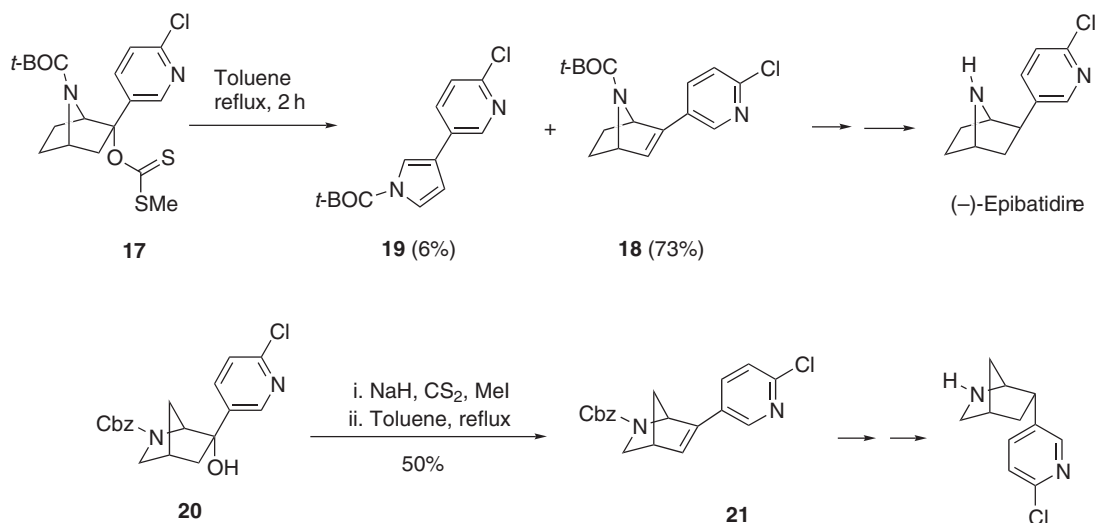
Scheme 5

In the course of synthetic studies on kincamycin antibiotics, the functionalized tetrahydrofuranone intermediate **16** was synthesized by pyrolysis of the xanthate **15** at 300 °C under reduced pressure in a Kugelrohr apparatus (Equation (11)) <2001T2717>.



Xanthate thermolysis ensured an efficient route to (-)-epibatidine and analogs (Scheme 6) <1994JOC1771>. Thus, tertiary xanthate **17** at refluxing toluene afforded the desired olefin **18** along with small amounts of the pyrrole derivative **19** arising from a retro-Diels–Alder reaction. Similarly, thermolysis of the xanthate intermediate prepared from alcohol **20** afforded the racemic

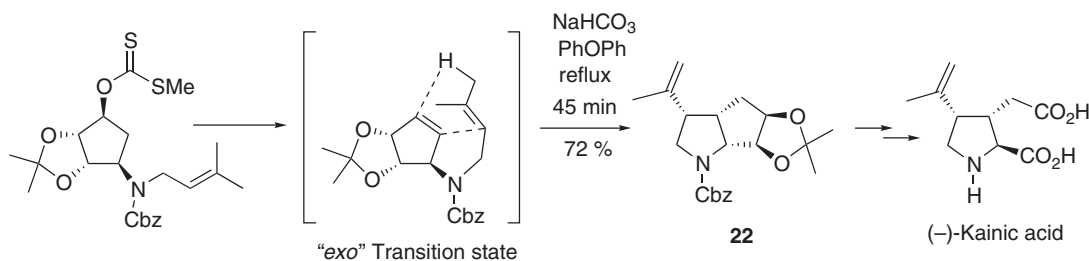
epibatidine analog precursor **21**. All attempts to prepare this compound by a dehydration step proved unsuccessful <2001JCS(P1)2372>.



Scheme 6

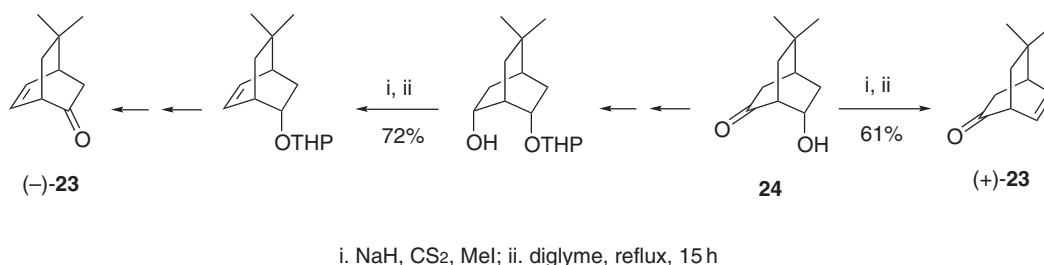
Pyrolysis of xanthates has also been successfully used in the total synthesis of phytotoxins solanapyrones **D** and **E** <2001OL251, 2002JOC5969>, sceletium alkaloids <1998TL7747>, pseudoguaianolides <1998JOC920>, epothilones **B** and **D** from D-glucose <2002TL2895>, and (+)-compactin <1995JCS(P1)777>.

In the course of an elegant and efficient synthesis of (-)-kainic acid, a tandem reaction featuring a Chugaev *syn*-elimination and a subsequent intramolecular ene reaction led to intermediate **22**, isolated in 72% yield as the sole diastereoisomer (Scheme 7) <2000OL3181>.



Scheme 7

An enantioselective synthesis of both enantiomers of bicyclic ketone **23** was achieved from a common intermediate **24** using, in each pathway, a xanthate thermal elimination (Scheme 8) <1996JOC142>.



Scheme 8

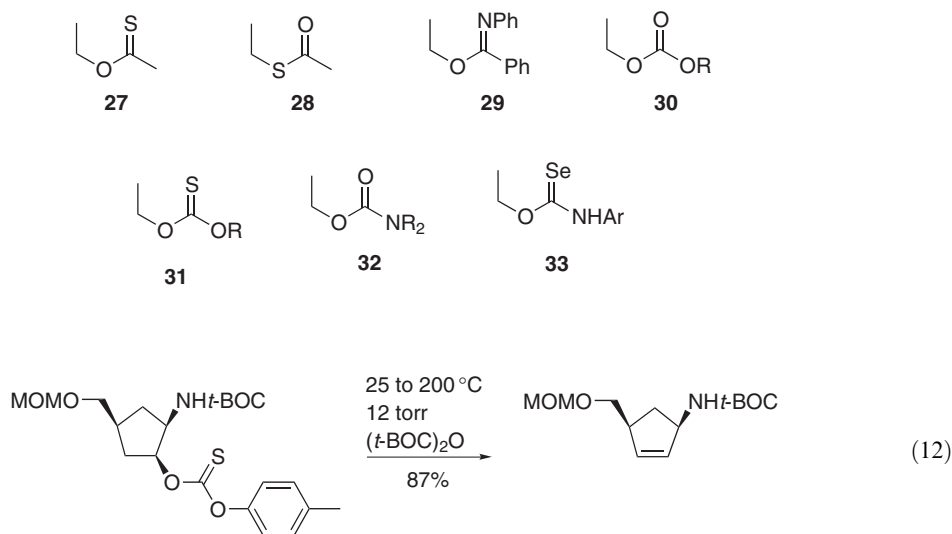
1.17.2.2.3 Other concerted pyrolytic eliminations

Wide structural variation is possible, and some examples have been summarized <1991JOC846>. Variations affecting the nucleophilicity of atom V and the electronegativity of atom W (Equation (1)), although aiding the reaction, have not significantly displaced the acetate or xanthate methods for preparative purposes <1991JCS(P2)1703, B-1979MI117-001>.

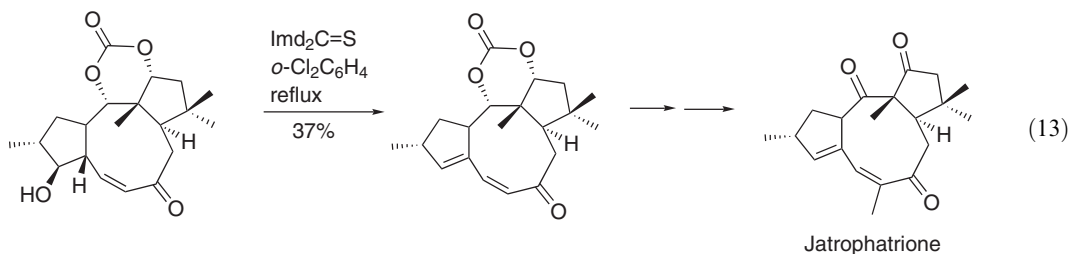
The heteroatom V is not required for a successful pyrolytic elimination and simple vinyl ethers **25** <1977JOC3899, 1982JCS(P2)1175, 1988JCS(P2)737>, 2-alkoxypyridines **26**, and related heterocycles undergo a similar decomposition <1981JOC1969, 1982JCS(P2)1175, 1986JCS(P2)1255>.



Other examples of substrates with two heteroatoms that give alkenes in a similar manner to ester pyrolyses are shown below. They include thionoacetate **27**, the isomeric thioacetate **28** <1973JCS(P2)1293, 1975JCS(P2)317>, and benzimidate **29** <1966TL6279>. Within the series of carbonates of type **30** <1983JCS(P2)291> and their possible sulfur analogs of type **31** <1988JCS(P2)177>, the major rate change occurs when OR is replaced by SR, with the change from carbonyl to thiocarbonyl producing a relatively small effect. The pyrolysis of carbonates has found some applications in total synthesis <1968CJC377, 1983SC559>. It should be noted that, in some cases, *p*-tolylthiocarbamates appeared to be a good alternative to xanthates. An example is shown in Equation (12) <1995JOC4602>.

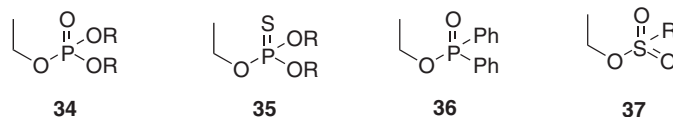


Pyrolysis of *N*-aryl- and *N,N*-diarylcarbamates of type **32** can be carried out in the temperature range of 375–420 °C (lower temperatures than for the acetates) <1981JOC2804>. The thiocarbonyl-diimidazolides offer clear advantages over the corresponding xanthates for those substrates that are sensitive to strong basic conditions. A pertinent example is provided by the synthesis of jatrophatrione, for which initial attempts to form the xanthate failed (Equation (13)) <2002JA6542>.



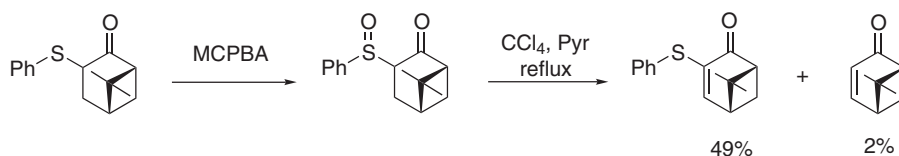
Pyrolysis of *O*-alkylselenocarbamates of type **33** occurred at 80 °C; however, the *syn*-elimination was complicated by a competing bimolecular (E2) mechanism <1994T639>.

Similar observations have been made from phosphates **34**, thiophosphonates **35** <1995TL719>, phosphinates **36**, and sulfonates **37**. Phosphates are much more reactive than the corresponding acetates owing to the greater electronegativity of the phosphorus atom <1961JOC846>. Similarly, tosylates have been found more reactive than either acetates or xanthates in 1,3-eliminations in the adamantane series <1972JCS(P1)2533>. As an alternative to gas-phase methods <1989JOC5811>, 8-quinolylsulfonates or 2-pyridylsulfonates have been found to decompose cleanly at ~150 °C to give good-to-excellent yields of simple alkenes <1989JOC389>.



1.17.2.3 Cleavage of One C—H and One C—S Bond, Including Pyrolysis of Sulfoxides

The pyrolysis of sulfoxides is synthetically an interesting method to form double bonds and has widely been reviewed <1978ACR453, 1978CRV363, 1978S713, 1991COS(6)1011> (Equation (2); X = S, Y = O). Given a ready facility to introduce selectively alkyl or aryl sulfur into many substrates and to oxidize them cleanly to the corresponding sulfoxides, pyrolytic β -elimination of sulfenic acid constitutes a useful method to synthesize unsaturated compounds. The appropriate sulfides are most commonly oxidized with MCPBA, sodium metaperiodate, or dimethyldioxirane <2000EJO4079>. The thermolysis step usually takes place in solution in the temperature range of 80–130 °C as *S*-aryl sulfoxides decompose at lower temperatures <1978ACR453, 2001JOC8722>. In some cases, to be more efficient, the thermal elimination of phenylsulfenic acid in boiling solvents required the presence of NaHCO₃, CaCO₃ <2003JOC7983>, or dihydropyran <2003OL1563>. The Pummerer reaction may be predominant when the reaction mixture is contaminated with protic sources (e.g., Scheme 9) <1993JOC3923, 1998JOC6939>.



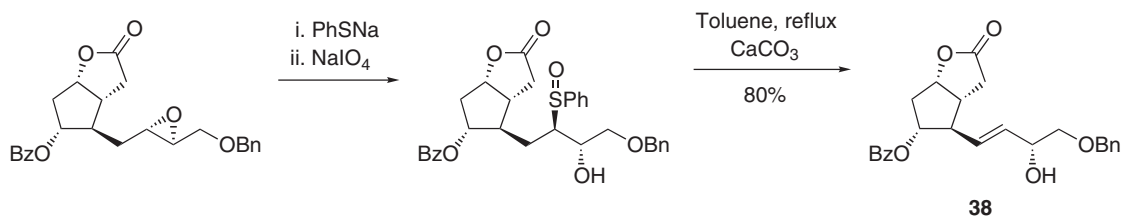
Scheme 9

Electron-withdrawing groups on the *S*-aryl ring also accelerate the reaction <1978CL541>. β -Elimination of alkyl or aryl sulfoxides promoted by microwave irradiation gave excellent yields and was over 1,300 times faster than under thermal conditions <1996TL1855>. The standard *syn*-stereochemistry of the process for acyclic examples has been established and the solvent independence of the reaction rate is consistent with a concerted mechanism <1960JA1810>. Isotope effect studies suggest that the hydrogen transfer occurs via a linear transition state <1978JA2802, 1978JA3927>. Acyclic alkenes are produced with (*E*)-stereochemistry <1973JA6840, 1975JOC148> and fragmentation takes place toward the most acidic β -hydrogen atom <1978TL4903>. With β -hydroxysulfoxides, easily prepared from epoxides by ring opening with thiophenol, the elimination takes place away from the β -hydroxy groups to give allylic alcohols <1975TL2841, 2000TL2895>, as illustrated in Scheme 10 with the synthesis of the prostaglandin analog **38** <1991JOC1329>.

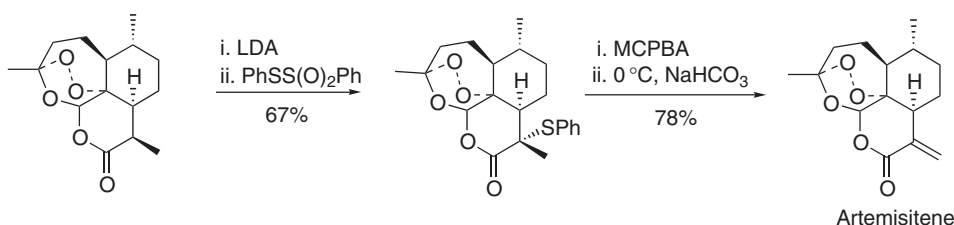
Ring opening of oxiranes with thiophenol without catalysts in hexafluoroisopropanol can be efficiently accomplished. Subsequent *in situ* oxidation under neutral conditions with MCPBA affords a β -hydroxysulfone, which was next converted by pyrolysis to an allylic alcohol <2000TL2895>.

This method has largely been employed for the synthesis of α,β -unsaturated carbonyl and nitrile compounds from the corresponding saturated starting materials by alkylation of the enolates with diphenyl disulfide, phenylsulfenyl chloride, *N*-thiophenylphthalimide <2002SL1308>, or *S*-phenyl

benzenethiosulfonate [<1977JA4405>](#) followed by subsequent oxidation to the sulfoxide and pyrolysis. This sequence has been used extensively in the total synthesis of natural products, as exemplified by the synthesis of artemisitene ([Scheme 11](#) [<2002JMC4321>](#)).

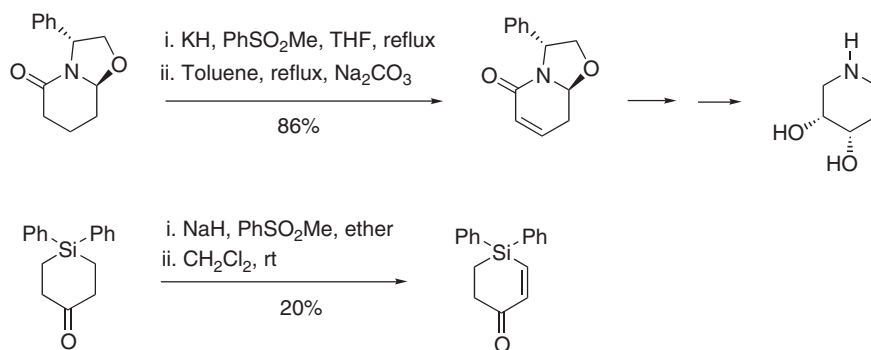


Scheme 10



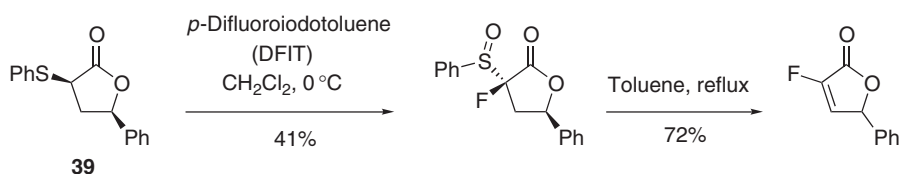
Scheme 11

Direct installation of the α -sulfoxide substituent by trapping the enolate with methylphenylsulfinate [<1995TL7051>](#) or methyl 2-pyridylsulfinate esters [<1993JOC1579>](#) avoids the oxidation step. For instance, this method has been applied to the synthesis of piperidines [<2001OL3257, 2002OL2787>](#) and silacyclohexenones [<1998SL153>](#) ([Scheme 12](#)).



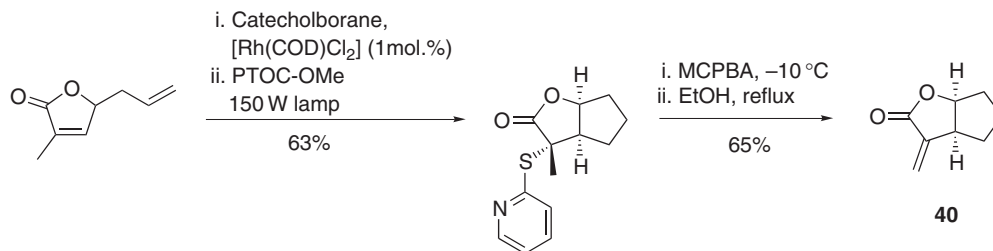
Scheme 12

Difluoroiodotoluene, a hypervalent iodine reagent, has been used as a fluorinating agent, as well as an oxidant, on α -phenylsulfanyllactone **39** to afford after thermolysis the 2-fluoro-2-buten-4-olide ([Scheme 13](#) [<2000TL4463>](#)).



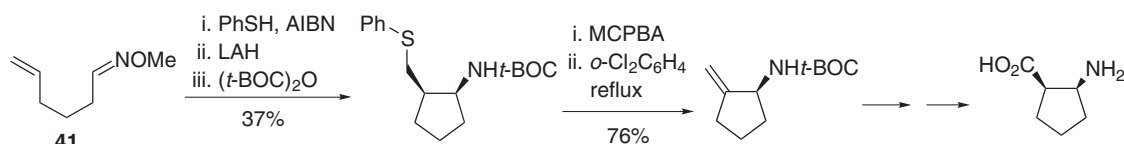
Scheme 13

In this context, free-radical chemistry offers an original synthetic potential to introduce sulfur-containing groups. For instance, intramolecular conjugate addition of a radical to activated olefins, in the presence of Barton carbonate (*N*-methoxycarbonyloxy-pyridine-2-thione, PTOC-OMe) as chain transfer reagent, has been used to synthesize bicyclic α -methylenelactone **40** (Scheme 14) <2003SL1485>. Some similar examples have also been reported in this area using the standard protocol for Barton decarboxylation <1995JOC6237, 1988CC285>.



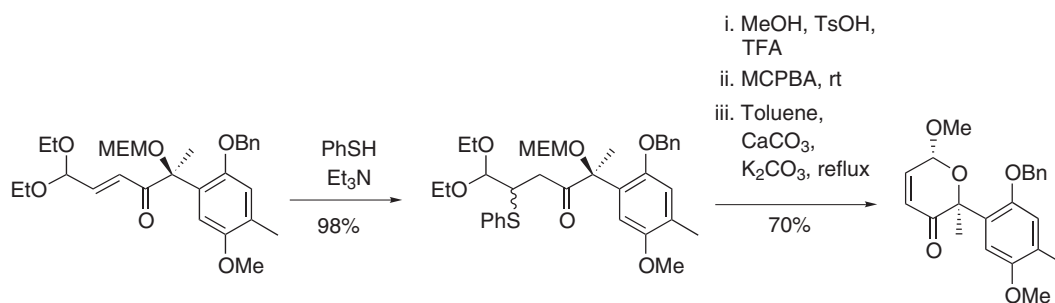
Scheme 14

Sulfanyl radical addition–cyclization on the alkenyl-tethered-oxime ether **41**, coupled with an oxidation/elimination of the resulting sulfoxide, offered a unique opportunity to synthesize cyclic β -amino acids (Scheme 15) <2002T4459>.



Scheme 15

The incorporation of sulfur-containing groups, eliminated as sulfoxide, has also been achieved by conjugate addition of thiophenol <2000JOC1842, 2003JOC4422>, as illustrated by the synthesis of epoxybenzoxocin in the course of synthetic studies on nogarol anthracyclines (Scheme 16) <2000JOC1842>.

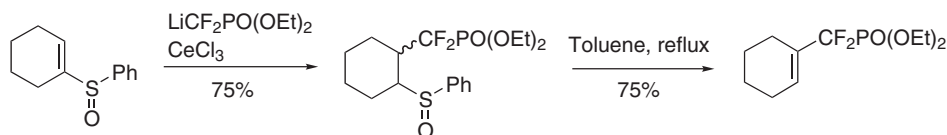


Scheme 16

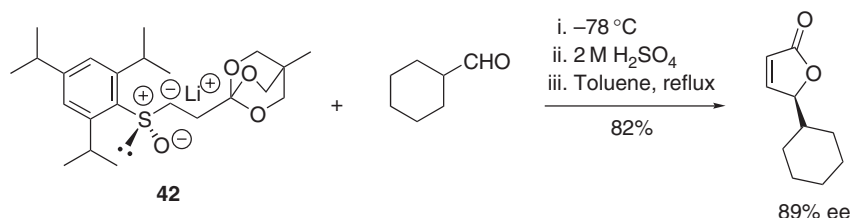
A cerium-mediated conjugate addition of [(diethoxyphosphinyl)difluoromethyl]lithium to vinyl-sulfoxides, followed by sulfoxide elimination, allowed the preparation of allylic difluorophosphate compounds (Scheme 17) <1998TL9085>.

An interesting route to chiral γ -butenolides using a one-pot condensation of enantiomerically pure lithiated sulfoxide **42** to aldehydes, followed by thermal elimination of phenylsulfenic acid, has been reported (Scheme 18) <1999TL6237>.

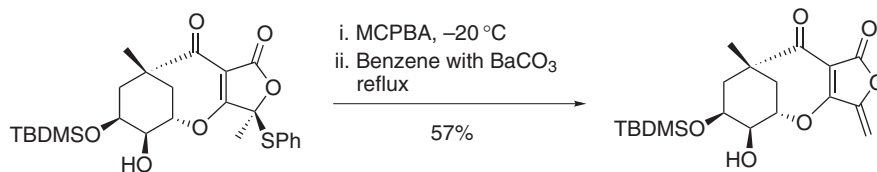
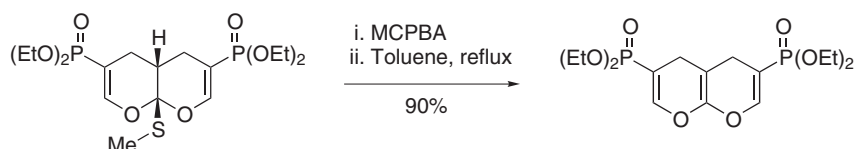
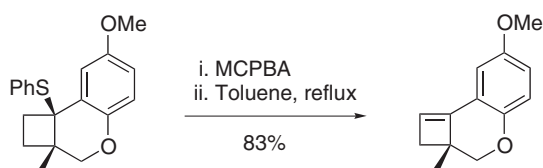
This sulfoxide-based elimination sequence has nicely been exploited in various syntheses. Scheme 19 provides some more examples <2002OL2565, 2002JOC7303, 2002SL1308>.



Scheme 17



Scheme 18



Scheme 19

1.17.2.4 Cleavage of One C—H and One C—Se Bond: Pyrolysis of Selenoxides

During the 1990s, increasing numbers of papers have reported the use of selenoxide elimination in multistep syntheses, pointing out the superiority of this method over others (Equation (2); X = Se, Y = O). A variety of efficient and mild methods using both nucleophilic and electrophilic reagents are available to introduce arylseleno groups (usually phenylseleno), providing a broadly applicable methodology to C—C double bond formation. A number of reviews in this field are available <1978T1049, 1979ACR22, B-1984M117-003, B-1986M117-004, 1991COS(6)1011>.

The phenyl selenide anion turns out to be a good and convenient nucleophile to prepare organoselenium compounds by nucleophilic displacement, and is less basic and more nucleophilic than the corresponding sulfur compound. This air-sensitive anion can be generated *in situ* from diphenyl diselenide by reduction with sodium metal, sodium borohydride, LAH <1996JOC851>, by treatment with NaH (or KH) <1992S933>, or from PhSeH in the presence of bases (KOH, Et₃N).

Selenyl halides (PhSeCl or PhSeBr) and PhSeOTf (generated *in situ* from PhSeBr and AgOTf) are commonly used as efficient sources of electrophilic selenium. In some cases, *N*-phenylselenophthalimide is preferred due to the absence of a nucleophilic counterion [<2001EJO507>](#). Free-radical and organometallic chemistry [<1998SL1432>](#) have also been used to prepare aryl selenides.

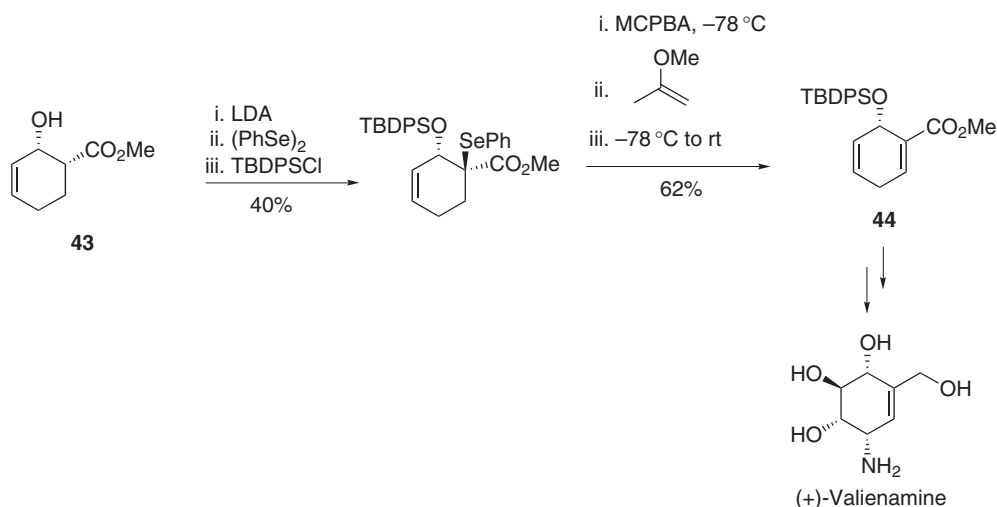
Selenides are oxidized more easily to selenoxides than the corresponding sulfur to sulfoxides. Many oxidative reagents (*t*-butylhydroperoxide, peracetic acid, ozone, and Oxone[®]) have been employed to convert selenides into selenoxides, but hydrogen peroxide, MCPBA, and sodium periodate are, by far, the most frequently used. In some cases, yields have been significantly improved by using dimethyldioxirane [<2000JOC6293>](#) or Davis' reagent [<2001SI356>](#).

Selenoxides undergo a *syn*-elimination reaction about 1,000 times faster than the corresponding sulfoxides. Aryl selenoxides bearing electron-withdrawing substituents (e.g., *o*-NO₂C₆H₄) and pyridylselenoxides have also demonstrated high efficiency in this process [<1980TL5037, 1985T4347>](#). The elimination does not occur [<1992JA10181>](#) or is more difficult [<2000TL7645>](#) if the required *syn*-conformation is not accessible or if the strain from the incipient double bond is too great. Most of the time the selenoxides are not isolated. The elimination reaction occurs in the temperature range from -78°C to boiling toluene, depending on the nature of the substrates. Selenoxide elimination is not free of side reactions and it has proved advantageous, with electron-rich olefin substrates such as enol ethers, to use DHP or 2-methoxypropene as cosolvent in order to trap selenenic acid. Selenenic acid can also be converted into selenamide by the addition of amines.

It should be pointed out that aryl selenides are quite inert to many chemical transformations and consequently could be introduced at the early stage of a synthesis. For example, hydroboration followed by oxidative work-up is compatible with the presence of a phenylselenide group [2001JA30](#). A phenylselenide can also be considered as a temporarily masked double bond. This property has been exploited in the synthesis of peptides containing unstable dehydroamino acids [2002OL1335](#). The oxidation–elimination sequence is compatible with a range of functional groups [2002JA10036](#).

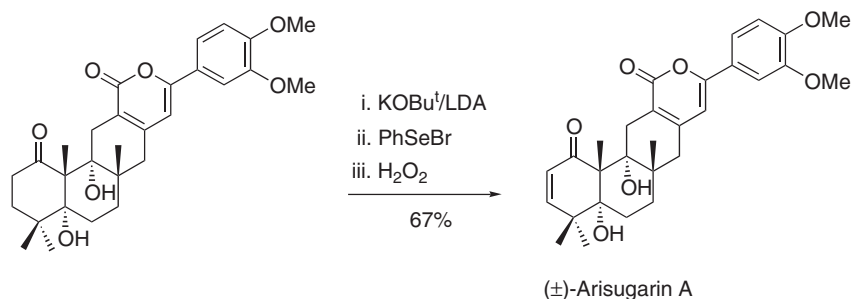
The reaction of lithium ester and ketone enolates with selenyl halides or with diphenyl diselenide leads to α -phenylselenocarbonyl intermediates, which are transformed in high yields to the corresponding α,β -unsaturated compounds following an oxidation–elimination sequence.

In the total synthesis of (+)-valienamine (Scheme 20) <1998JA1732>, selenation of the methyl ester **43** using LDA and diphenyl diselenide followed by oxidation with MCPBA at -78°C gave the desired diene **44**. The oxidation step was performed in the presence of 2-methoxypropene, added as a selenenic acid trap, to avoid the formation of fully aromatized compounds. The same sequence was carried out using 2,2-dipyridyl disulfide in place of the phenylselenide. After thermolysis in toluene of the corresponding 1:1 mixture of sulfoxide diastereoisomers, differing in their configuration at sulfur, it appeared that only one of these diastereoisomers was prone to elimination. Attempts to increase the reaction time and temperature led to aromatized products. This point highlights the fact that selenoxides are more labile compared to sulfoxides and also epimerize at selenium rather rapidly, whereas sulfoxides do not <1993OR1>.



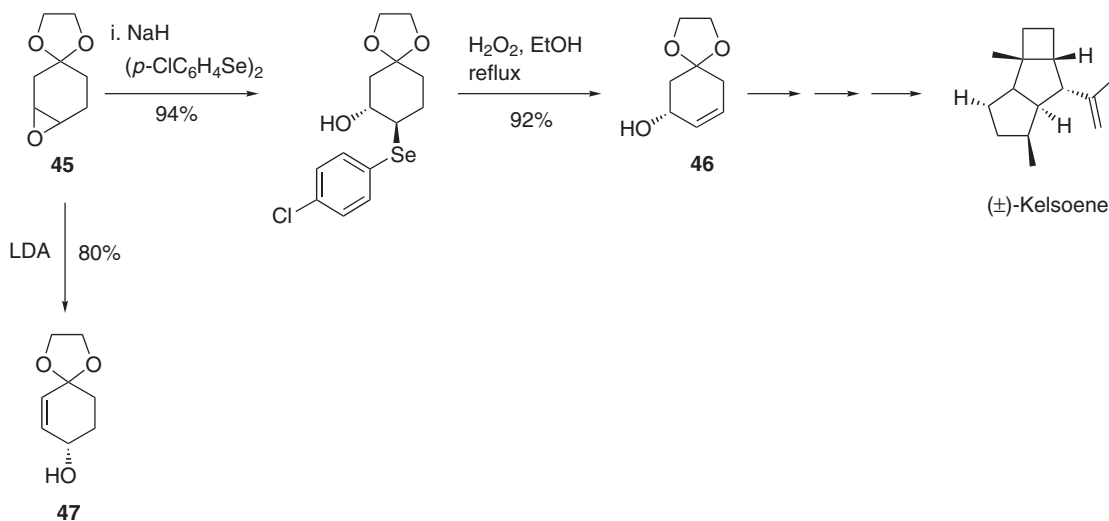
Scheme 20

Introduction of the double bond into the A-ring of (\pm)-arisugarin A was performed at the last stage by the usual α -phenylselenation/oxidation–elimination sequence (Scheme 21) <2003T311>.



Scheme 21

Regioselective ring opening of epoxides with sodium phenylselenide has been routinely used to synthesize allylic alcohols. In the course of the total synthesis of (\pm)-kelsoene (Scheme 22) <2002OL3755>, the allylic alcohol **46** was obtained by a highly regioselective ring opening of epoxide **45** with *p*-chlorophenylselenenolate anion, followed by subsequent oxidative elimination. In contrast, treatment of the same epoxide with LDA afforded exclusively the allylic alcohol **47** <2002OL3755>.

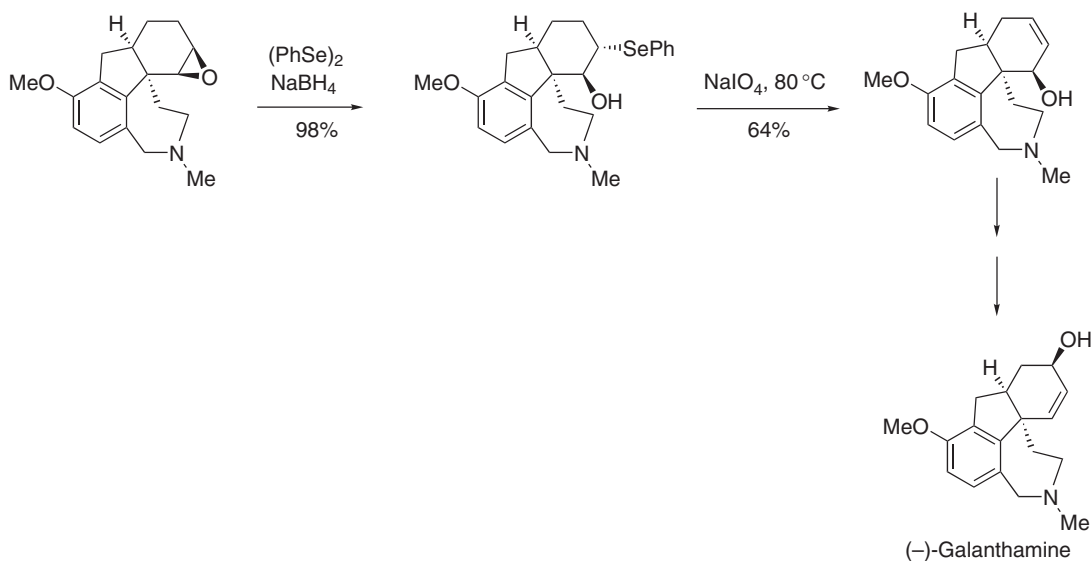


Scheme 22

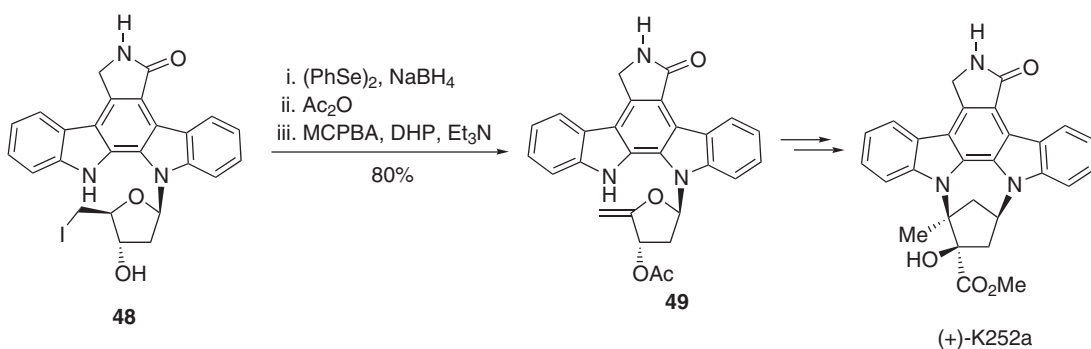
In recent years, this transformation proved to be a powerful tool to deliver, in a stereocontrolled fashion, allylic alcohols from epoxides, and it has been exploited in many total syntheses, e.g., (–)-galanthamine (Scheme 23) <2000JA11262>, (+)-pancratistatin <2000JA6624>, (–)-morphine <2002JA12416>, and the core of agelastatin <2002TL723>.

The introduction of a double bond by highly efficient nucleophilic displacement of a halogen with phenylselenide anion, and subsequent selenoxide elimination, has found extensive application in organic syntheses <2002CC1940, 2002JA10036, 2002OL1335, 2003OL419>. An example is provided by the synthesis of (+)-K252a, in which the iodide **48** is converted into an exocyclic methylene intermediate **49**, in high yield, upon treatment with PhSeNa, acetylation of the resulting alcohol, and a subsequent oxidation–elimination sequence <1999JA6501> (Scheme 24).

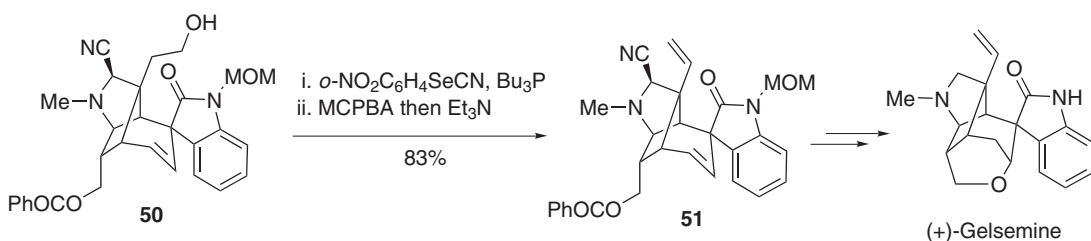
The Grieco procedure <1976JOC1485> provides an easy access to aryl selenides bearing electron-withdrawing groups on the phenyl ring. The efficiency of this procedure is illustrated by the one-pot conversion of the primary alcohol **50** into the corresponding vinyl compound **51** (Scheme 25), an advanced intermediate in the total synthesis of (+)-gelsemine <2000AG(E)4073>.



Scheme 23



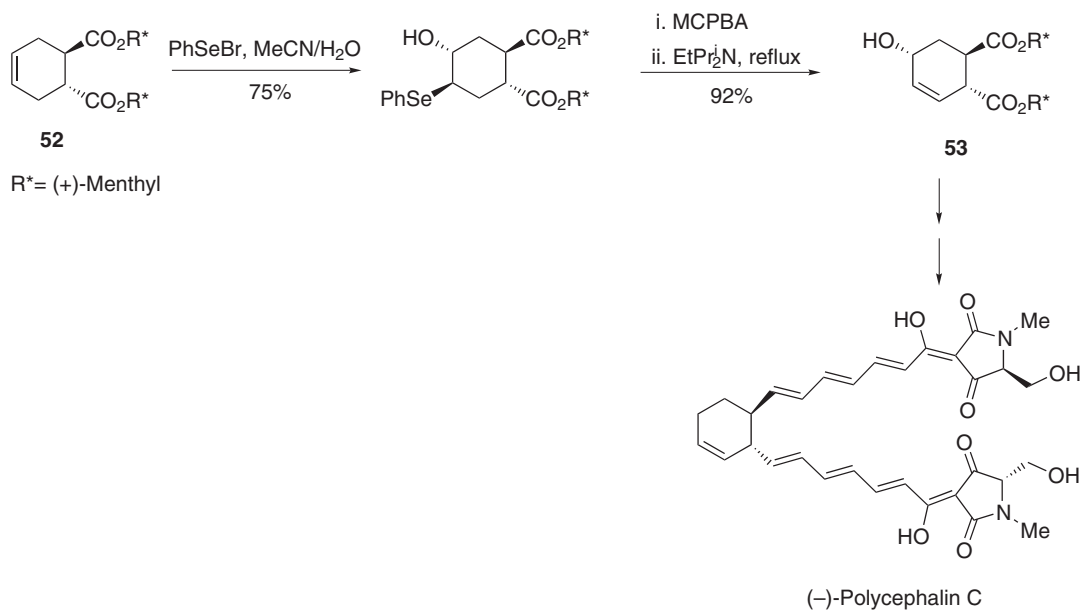
Scheme 24



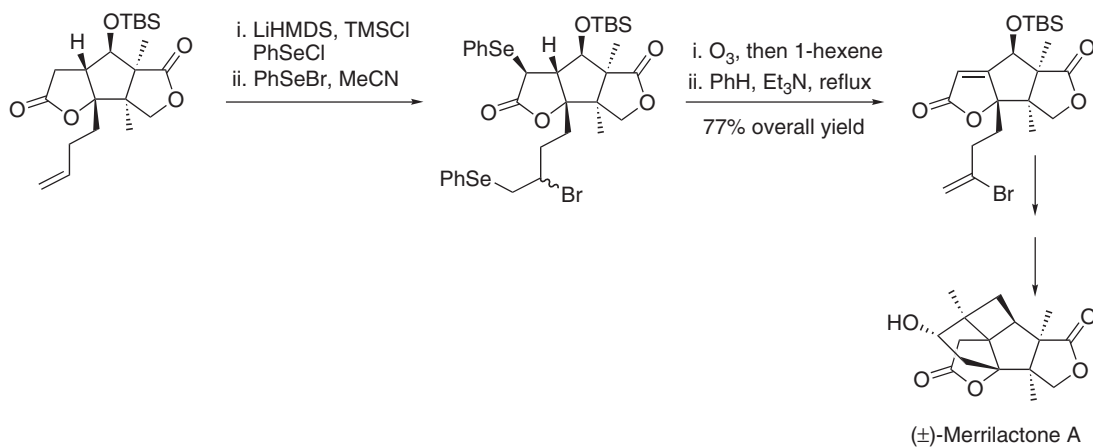
Scheme 25

The electrophilic selenenylation of olefins followed by an oxidation–elimination sequence has found numerous applications in total synthesis [<1996TL275, 1996JOC2882, 2000EJO2145, 2000T309, 2001TA2649, 2002JOC6725, 2003JOC1172>](#). The efficiency of this methodology is illustrated by the double-bond transposition of the Diels–Alder adduct **52** to the chiral allylic alcohol **53**, an intermediate in the total synthesis of (–)-polycéphalin C (Scheme 26) [<2002AG\(E\)2786>](#).

A striking illustration of the power of selenium chemistry to create a double bond is demonstrated by the total synthesis of (±)-merrilactone A (Scheme 27) [<2002JA2080>](#), which features sequential carbonyl α -selenylation and vinyl group bromoselenenylation followed by a double oxidation–elimination reaction.

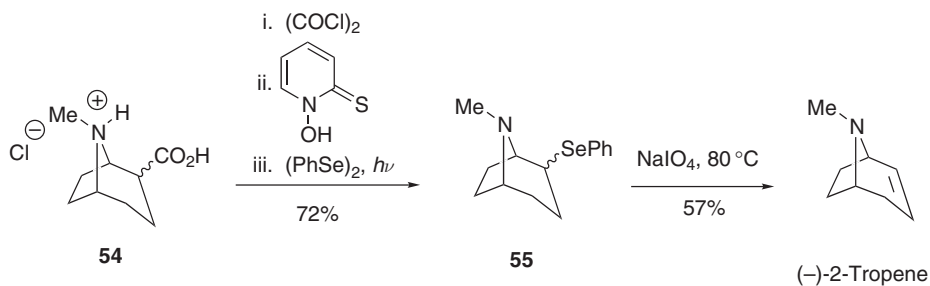


Scheme 26



Scheme 27

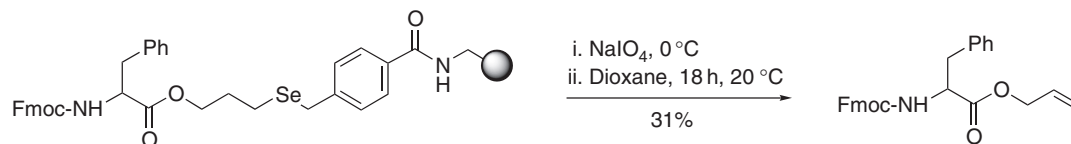
Strategies involving radical reactions to introduce arylselenium have been described in this context. For example, in the course of a total synthesis of both enantiomers of cocaine ([Scheme 28](#)) [<1998JOC4069>](#), phenylselenides **55**, first obtained by photochemical-induced radical decarboxylation of the *O*-thiohydroxamate derivative of the acid **54** in the presence of (PhSe)₂, were next subjected



Scheme 28

to an oxidation–elimination sequence to give the chiral 2-tropene. A similar sequence has also been described in the presence of a pyridylsulfide group. In this latter, it was observed that sulfoxide elimination occurred only when DBU was added to the refluxing toluene solution <1990T2345>.

Efficient thermally cleavable linkers for solid-phase chemistry have been developed based on selenoxide *syn*-elimination (Scheme 29) <2000TL5287>. This process requires an activated substrate and higher reaction temperatures if the selenoxide is replaced by a sulfoxide.

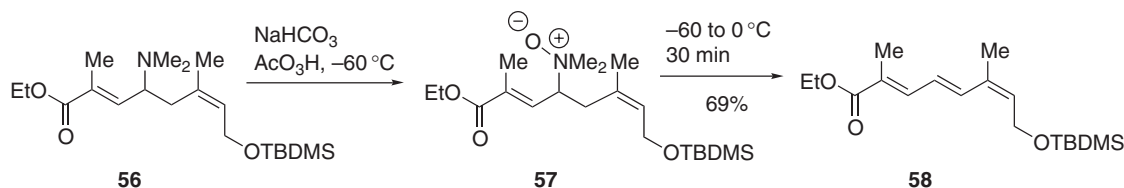


Scheme 29

1.17.2.5 Cleavage of One C—H and One C—N Bond, Including the Cope Elimination

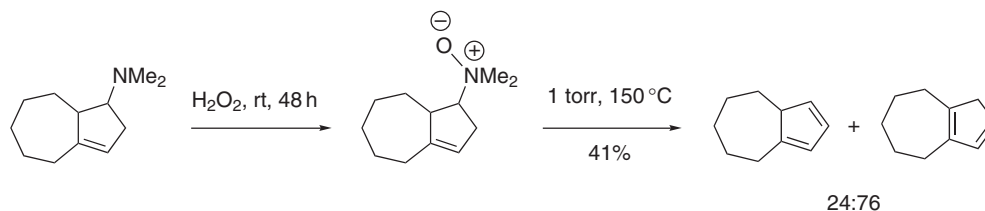
Alkenes may be formed by pyrolysis of suitable amides or thioamides (Equation (1); X = N, V = O or S). Although the temperatures required are higher than those for the corresponding acetate, a similar isomer distribution is obtained <1959JA651, 1960CRV431>. The most important reaction in this section is the Cope elimination <1960OR317, 1960CRV431, 1991COS(6)1011, 1993S263>.

Only a few applications of the Cope elimination to synthesis have been recently reported. In the synthesis of the retinol analog **58**, having a (*Z*)-terminal double bond, the *N,N*-dimethylamine **56** was oxidized with peracetic acid to the corresponding *N*-oxide intermediate **57**. This underwent a Cope elimination during the warm-up of the reaction mixture to 0 °C. The desired triene **58** was accompanied by side products originating from [2,3]- and [1,2]-sigmatropic rearrangements (Scheme 30) <1996CL671>.



Scheme 30

The Cope elimination was used in the synthesis of cyclopentadienyl-annulated cycloalkanes (Scheme 31) <2002S1362> from a dimethylamino precursor. However, Hoffmann elimination of the corresponding ammonium iodide gave a better yield.

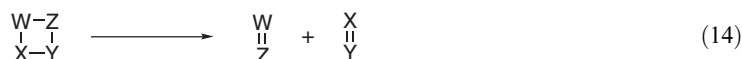


Scheme 31

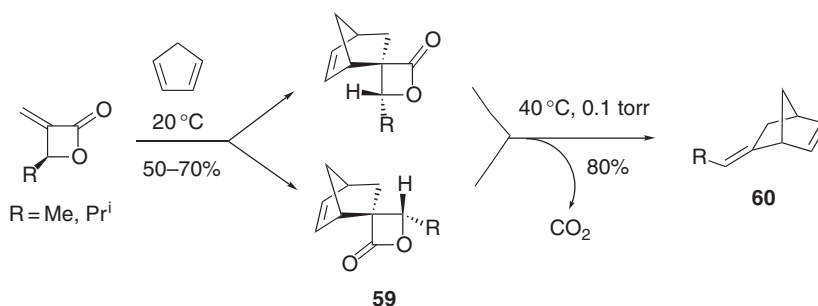
1.17.3 FORMATION OF MONOENES BY RETRO-CYCLOADDITION REACTIONS

1.17.3.1 Retro-[2 + 2]-cycloadditions

Retro-[2 + 2]-cycloadditions would formally be $[2\sigma_s + 2\sigma_a]$ -processes and hence many of these reactions (Equation (14); X = Y = Z = W = C) occur thermally by diradical mechanisms <1986T2135> and will not be considered in detail here.



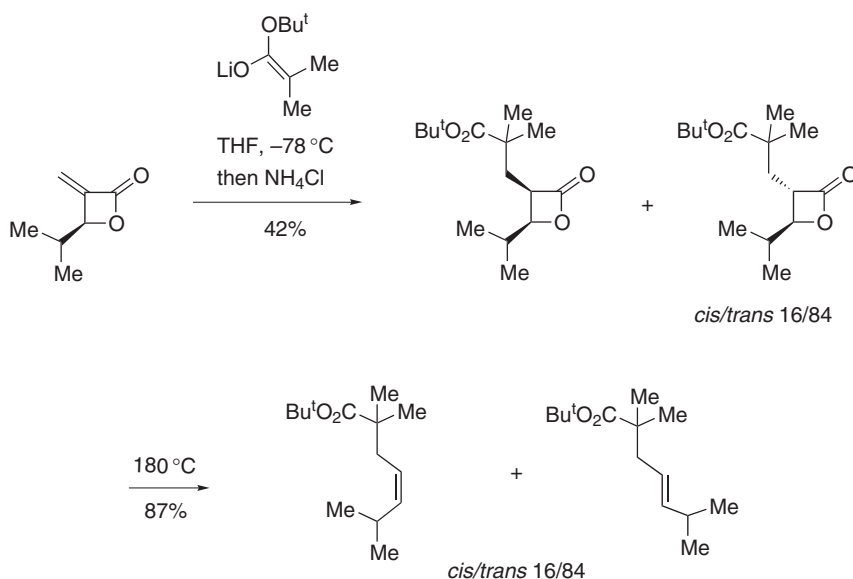
In contrast to the pyrolysis of cyclobutanes, for which experimental evidence is in favor of a diradical mechanism <1994TL2675>, the thermal decomposition of simple cyclobutanones and β -lactams (Equation (14); X = Y = Z = C, W = CO, and X = Y = C, Z = N, W = CO, respectively) to alkenes are believed to follow a concerted mechanism <1982AG(E)225, 1970JA1763>. More synthetically useful than the preceding processes is the decarboxylation reaction of β -lactones (Equation (12); X = Y = C, Z = O, W = CO), which is generally carried out neat or in solution at moderate temperatures (below 200 °C) and with high, if not complete, stereoselectivity. Theoretical and kinetic studies have concluded that, in the gas phase, the reaction can be described as an asynchronous concerted process with little charge separation at the transition state level, whereas, in solution, a polar mechanism with formation of a zwitterionic intermediate is probably involved <1998CPL261, 1997JOC109>. Nevertheless, it has been shown, in several examples, that the thermal decarboxylation of cyclobutanones is stereoselectively controlled when carried out neat or in solution. The pyrolysis of the diastereoisomeric *spiro*- β -lactones **59**, leading to the sole 1,4-diene **60**, provides a good example (Scheme 32) <1991TL7033>. The fact that, in the particularly smooth conditions of the reaction, the retro-[2+2]-cycloaddition is favored over the retro-[4+2]-cycloaddition is noteworthy. Compound **60** can thus be considered as an allene equivalent in which one of the double bond is selectively protected. Overall, the transformation represents an alternative to the classical Wittig reaction which, for the present substrates, works poorly. Thermal decarboxylation of α -aminomethyl and α -thiomethyl β -lactones as well as ester-functionalized β -lactones, all prepared by conjugate addition of suitable nucleophiles to α -methylene β -lactones, are other examples of stereoselective retro-[2+2]-cycloadditions (Scheme 33) <1995JOC578, 1995JOC3879>. Thermal decomposition of β -lactones has also been used for the preparation of enol ethers under FVP conditions <1973CJC981>, allenes, <1991JOC5782, 1993JOC322> and α,α -difluoroalkenes <1995JOC5378, 1998JFC41>. An application in the field of natural products has been reported with the synthesis of cucumin E <2001OL2029, 2002TL5039>.



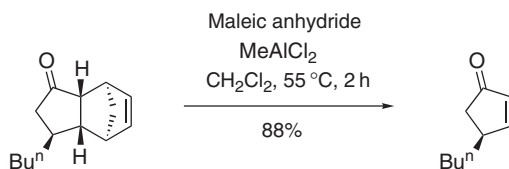
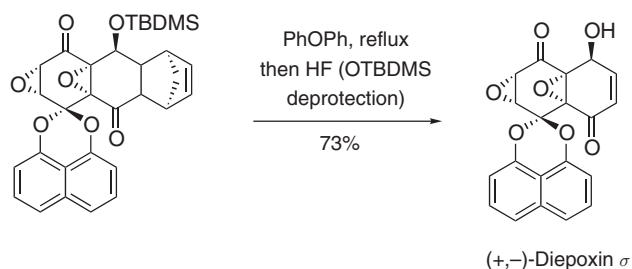
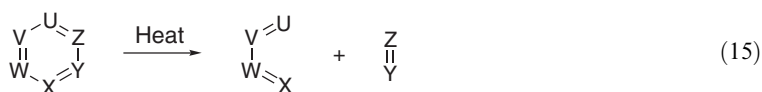
Scheme 32

1.17.3.2 Retro-[4+2]-cycloadditions (Retro-Diels–Alder Reactions)

This $[2\pi_s + 2\sigma_s + 2\sigma_s]$ reaction (Equation (15)) has been used extensively to prepare either alkenes, dienes, heterodienes (Section 1.17.4.1), or other multiple-bonded functional groups containing at least one heteroatom. For the preparation of alkenes (Equation (15); Z = Y = C), which involves cleavage of two C—C single bonds, cyclopentadiene, anthracene, and furan adducts have been commonly used as alkene precursors, the initial choice being dictated mainly by the ease of the final separation between diene and alkene species. The initial Diels–Alder reaction is a commonly used and practical way of temporarily masking a reactive double bond which, in most examples, is released at a later stage of a multistep synthetic transformation. The retro-[4+2]-reaction can be accomplished in solution at elevated temperatures (>200 °C) or at much lower temperatures if the presence of a Lewis acid can be tolerated <1989JOC6008>. The transformations depicted in Scheme 34 illustrate each of these procedures <2000JOC6319, 1998JOC7037, 2001JOC6400>. Both feature the generation of a synthetically versatile α,β -unsaturated carbonyl function. Other examples of the use of the retro-[4+2]-cycloaddition strategy to reach the same structural motif can be found later in this section and in the literature <1995T173, 1996TL8637, 1996TL7841, 1998T12361, 1999TL5593, 2003TL5741>.

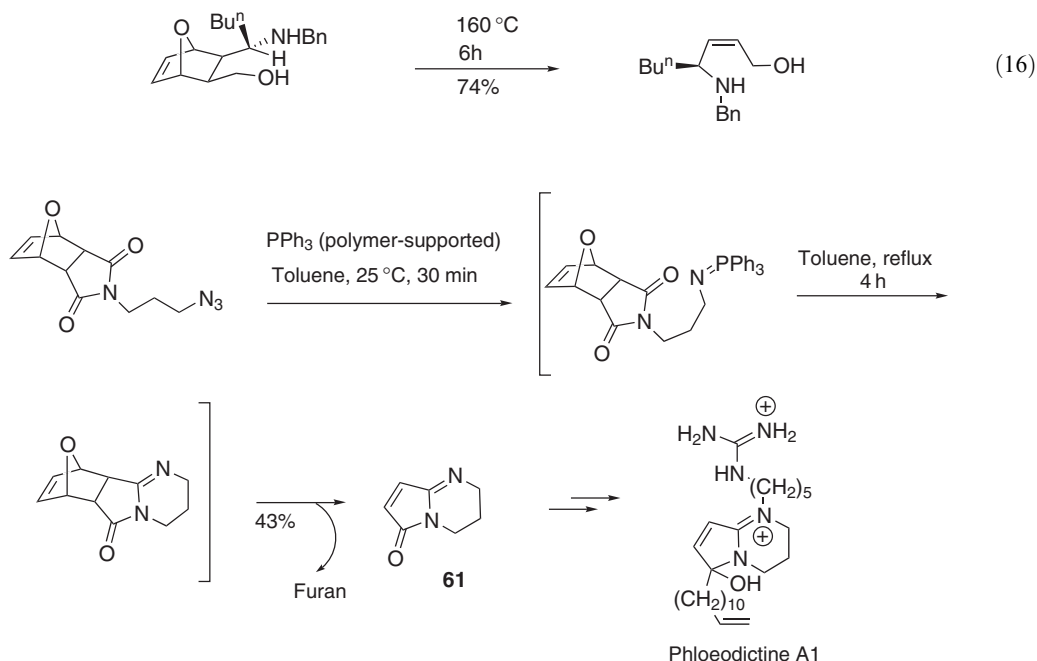


Scheme 33

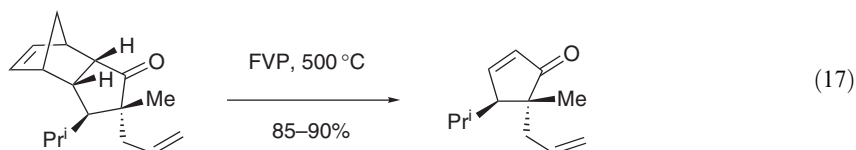
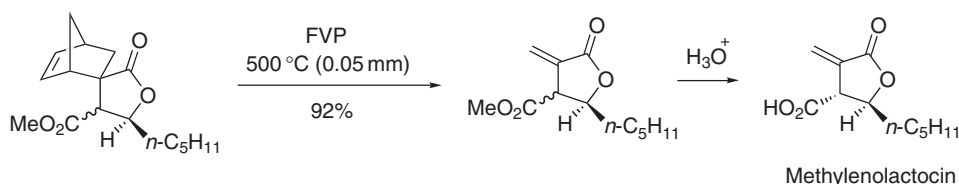


Scheme 34

The concomitant liberation of an aromatic derivative, such as furan, may also help lower the temperature of the retro-[4+2]-cycloaddition reaction as illustrated in the two following examples. Equation (16) shows the preparation of a chiral allylic amino alcohol, which is achieved under relatively mild conditions <1996TL8729>. Scheme 35 depicts a cascade of three reactions (namely, iminophosphorane formation, and Staudinger, then retro-Diels–Alder reactions), which can be carried out in refluxing toluene. The final and rather unstable 3,4-dihydro-2*H*-pyrrolo[1,2-*a*]-pyrimidin-6-one **61** was used as a synthetic precursor of the anti-tumor antibiotic phloeodictine A1 <2003OL765>. A review of the applications of furan Diels–Alder chemistry has been published <1997T14179>.



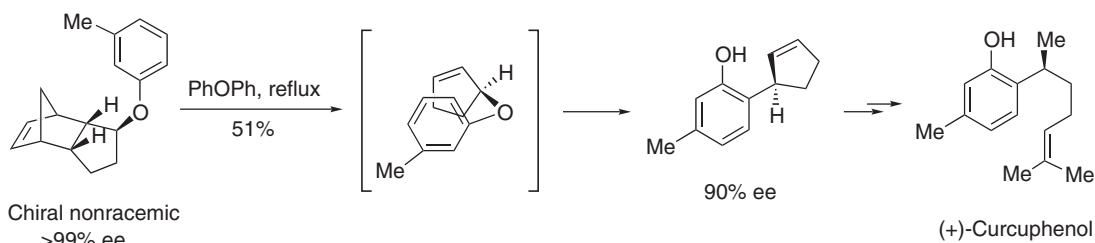
In addition to heating in an appropriate solvent, FVP, which is characterized by very short reaction or contact times, is a very useful means to effect retro-[4 + 2]-cycloaddition reactions. The distinct advantages of this technique allow the formation of highly unstable compounds and minimize the occurrence of secondary reactions such as double bond migration and erosion of selectivity. Two examples of the application of this technique are shown in [Scheme 36](#) <1997T17335> and in [Equation \(17\)](#) <2002OL1063>. Numerous other examples, which conclusively demonstrate the attractiveness of the FVP technique, can be found in a review <1999CRV1163>.



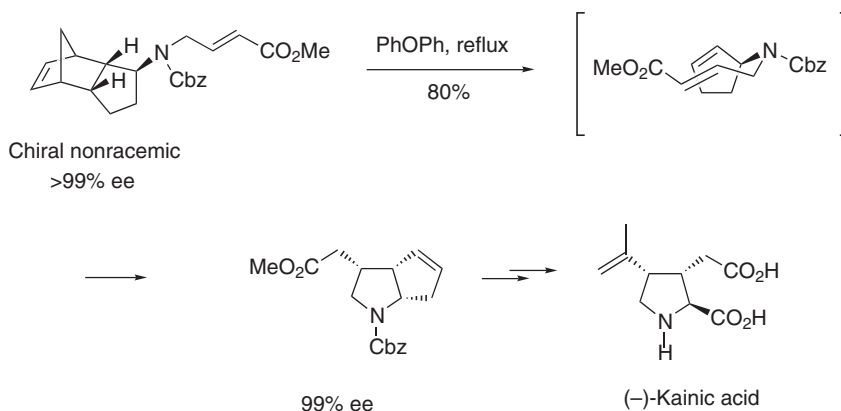
From a synthetic point of view, a particularly attractive situation is found when the released double bond is engaged in a subsequent “one-pot” transformation. Such a cascade reaction, which allows the creation of molecular complexity in a single operation, is of great value for the synthesis of natural compounds. This is well illustrated by the following two examples ([Schemes 37 and 38](#)) in which the released double bond participates in a Claisen rearrangement <1998TA2215> and in an ene reaction, respectively <1997TL857, 2001TL4523>.

In contrast to the preparation of alkenes ([Equation \(15\)](#); Z = Y = C), which involves the cleavage of two single C—C bonds, the preparation of a heteroatomic double bond ([Equation \(15\)](#); Z = C, Y ≠ C) involves the cleavage of one C—C and one C—X single bond (X = heteroatom) or two

C—X single bonds. Examples leading to the formation of highly reactive intermediates such as acylnitroso species [<1996TL9287, 2000TL4265>](#) and selenoaldehydes [<2003TL1179>](#) have been reported.



Scheme 37



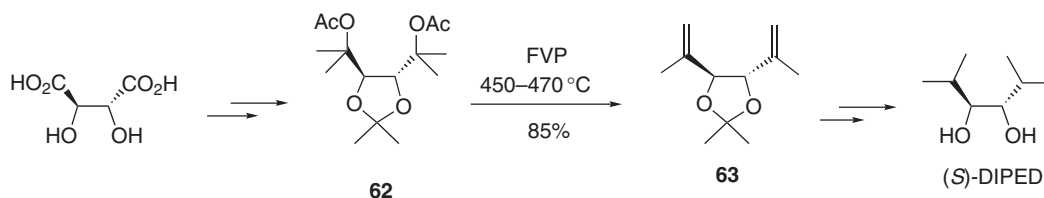
Scheme 38

Thermal equilibration of the primarily formed Diels–Alder adducts with the final production of the more stable adduct(s) is also a process that implies a retro-[4 + 2]-cycloaddition step [<2002TA2003, 2002TL6067>](#).

A number of comprehensive reviews of retro-Diels–Alder processes are available [<1987S207, 1991COS\(5\)551, B-1998MI117-005, 1998OR\(52\)1, 1998OR\(53\)223>](#). The reaction also continues to be the subject of several theoretical studies [<2000OL3505, 2002JA5091>](#).

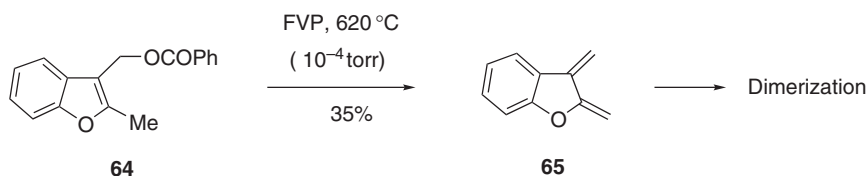
1.17.4 FORMATION OF DIENES AND POLYENES

The methods described in the previous sections may be applied to generate dienes and polyenes. In this section, only those retro-pericyclic reactions that allow the creation of two (or more) double bonds in one single operation will be considered. Such processes are not common in synthesis. An example can be found in the synthetic sequence leading to the formation of (3(*S*),4(*S*))-2,5-dimethyl-3,4-hexanediol [(*S*)-DIPED] from ((*R*),(*R*))-tartaric acid as depicted in [Scheme 39](#). The pyrolysis of diacetate **62** was carried out on a 250 g scale and led to the [(*S*)-DIPED] intermediate **63** in up to 85% yield [<1987JOC5034>](#).



Scheme 39

In a somewhat esoteric example leading to a fully conjugated cyclophane compound, a quadruple sulfoxide elimination was employed to generate four alkene units [<1991AG\(E\)1173>](#). Brief mention will be made also of the case where an already installed double bond participates in the retro-pericyclic reaction. This situation is illustrated by the example of the pyrolysis of furan [<1986JA4138>](#) and benzofuran [<1986JOC4208>](#) derivatives ([Scheme 40](#)). Thus, the FVP of **64** led to the formation of the 2,3-dimethylene-2,3-dihydrobenzofuran **65**, which was characterized by low-temperature NMR spectroscopy. The formation of **65** may involve a direct δ -elimination or a [3,3]-sigmatropic shift of the ester function prior to β -elimination. Compound **65** is not thermally stable and dimerizes at room temperature to give the [4+4]- and [4+2]-dimers.

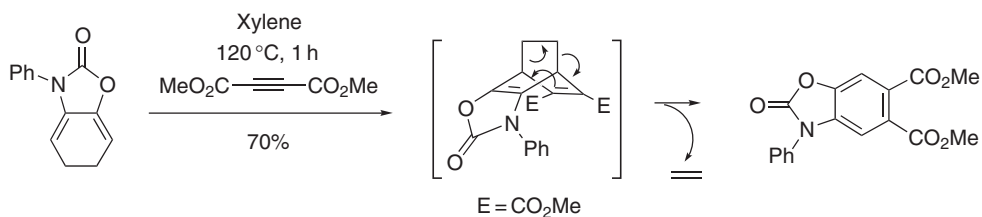


Scheme 40

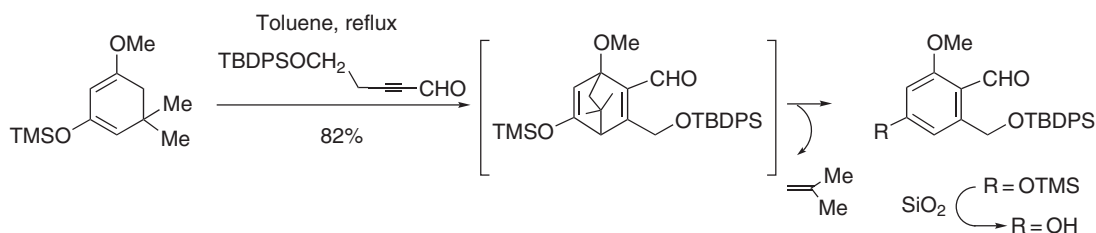
1.17.4.1 Retro-cycloaddition Reactions

As already mentioned, the retro-[4+2]-cycloaddition (retro-Diels–Alder reaction) can also serve to generate a diene or a heterodiene. The general conditions of the reaction are described in [Section 1.17.3](#).

The process is especially simple when the released diene ([Equation \(15\)](#); U = V = W = X = C) is integrated into an aromatic system. The accompanying alkene is most frequently a small stable molecule (e.g., ethylene or isobutylene) although the release of a larger molecule may be encountered [<1989CC1238, 1996TL3487>](#). [4+2]-Cycloaddition and retro-Diels–Alder reactions are often sequential processes. Typical examples are shown in [Schemes 41–43](#) [<2003T481, 2001TL7367, 2003JA9602>](#).



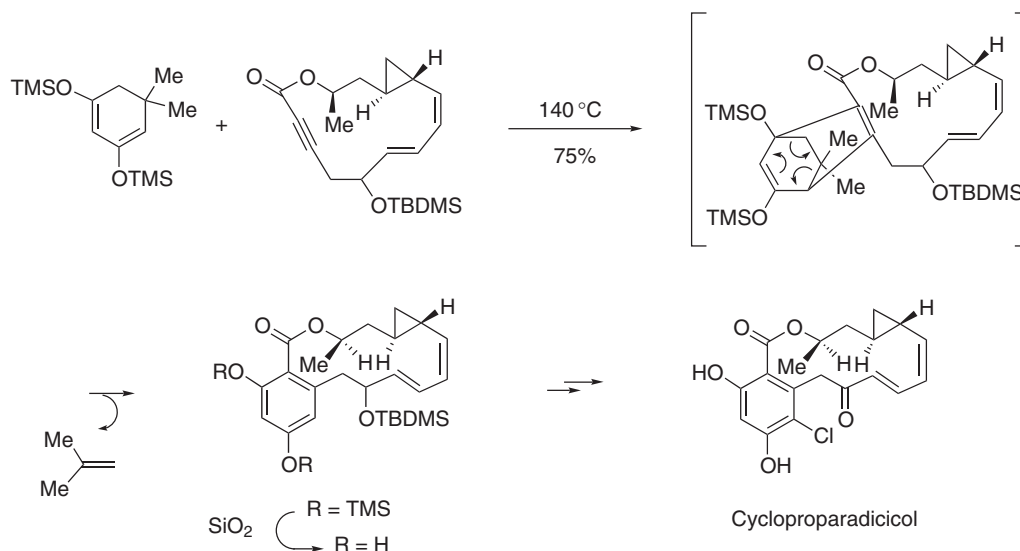
Scheme 41



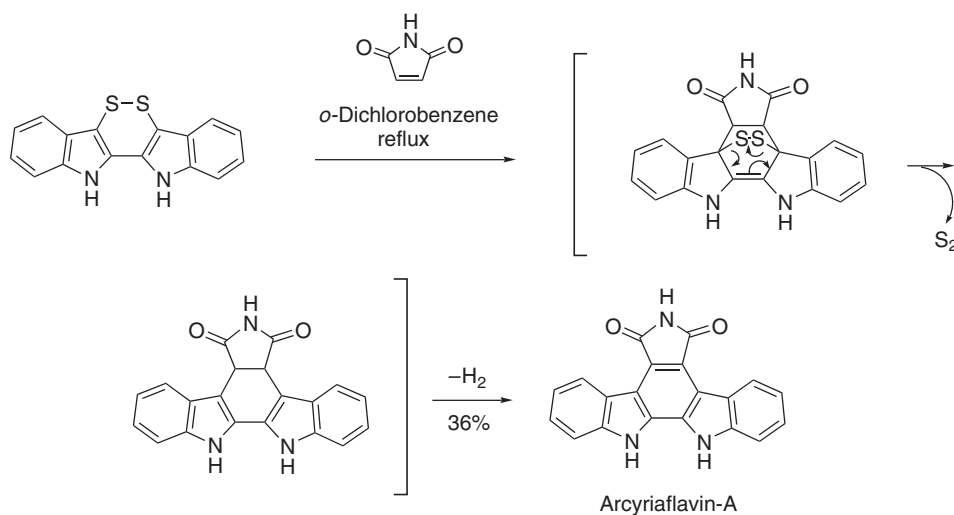
Scheme 42

A diene may be generated by cleavage of two single C—C bonds, as in the examples reported above, or by cleavage of one single C—C bond and one single C—X bond (X = heteroatom) or even by the cleavage of two single C—X bonds. This is illustrated by the examples shown in [Schemes 44](#) [<1999TL3795>](#) and **45** [<1996JOC6028>](#) where two single C—S bonds, on the one hand, and two single C—N bonds, on the other hand, are broken to finally deliver a homodiene. Sulfur and nitrogen

are the accompanying small molecules released. The formation of the cage system **66** is somewhat spectacular as it is the result of a one-pot sequential intermolecular inverse electron-demand Diels–Alder, retro-Diels–Alder, and intramolecular Diels–Alder protocol.



Scheme 43

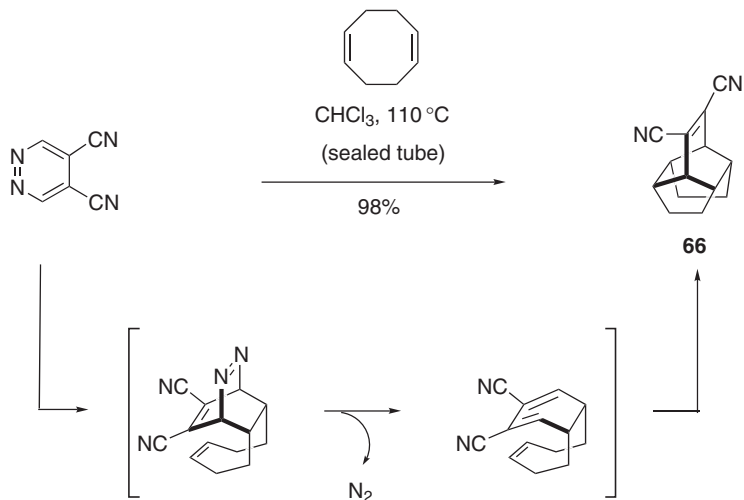


Scheme 44

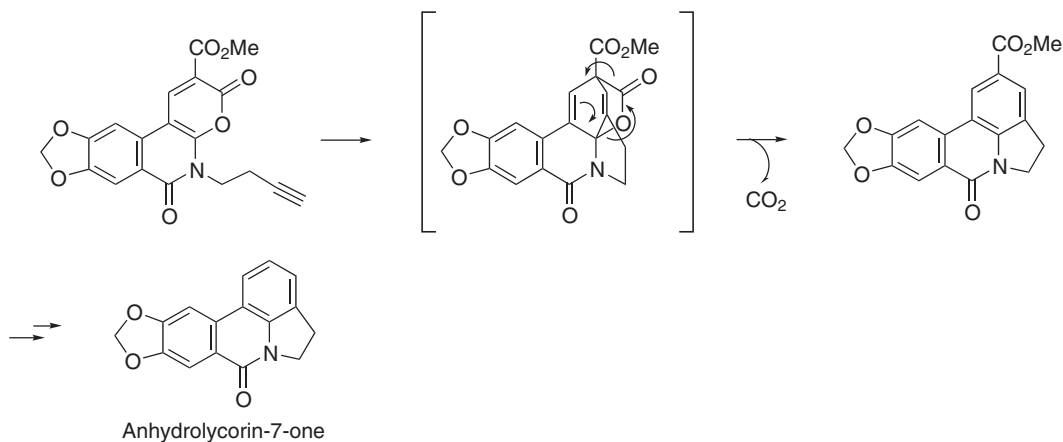
The Diels–Alder–retro-Diels–Alder sequence featuring 2-pyrones has been extensively used in the field of natural product synthesis, both in its inter- and intramolecular version [<1992T9111, B-1999MI117-006>](#). [Scheme 46](#) gives an example with the synthesis of the naturally occurring lycorine alkaloid anhydrolycorine-7-one [<1996JOC1650>](#). Generally, owing to their partial aromatic nature, 2-pyrones need high temperatures to react with dienophiles, although, in the example shown in [Scheme 47](#), the reaction takes place quite easily under the influence of silica [<1998TL4261>](#).

When the dienophile possesses a triple bond, as in the reaction depicted in [Scheme 46](#), and, more generally, when the possibility of forming an aromatic structure exists [<1996JOC7933, 2000OL2049>](#), the tendency is high for the Diels–Alder adduct to experience a retro-[4+2]-cycloaddition with extrusion of CO₂. Similar behavior has been observed for some pyranylene–metal and

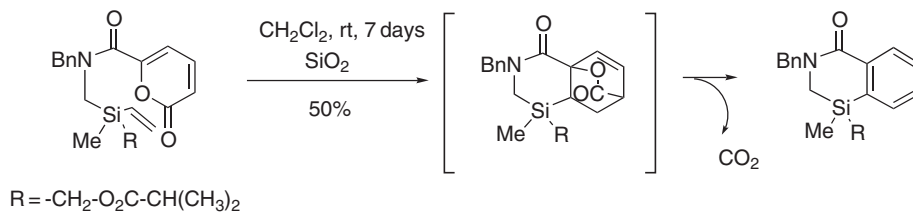
benzopyranylidene-metal complexes, <1990JA4550, 2000OM5525>, which represent the metal analogs of 2-pyrones. For instance, the benzopyranylene-tungsten complex **67** reacted with electron-rich olefins at room temperature to give naphthalene derivatives (e.g., **68**) in good yields (Scheme 48) <2000JA10226>. These reactions have been interpreted as a Diels-Alder condensation followed by a pericyclic demetallation of a tungsten (or a chromium) hexacarbonyl.



Scheme 45



Scheme 46

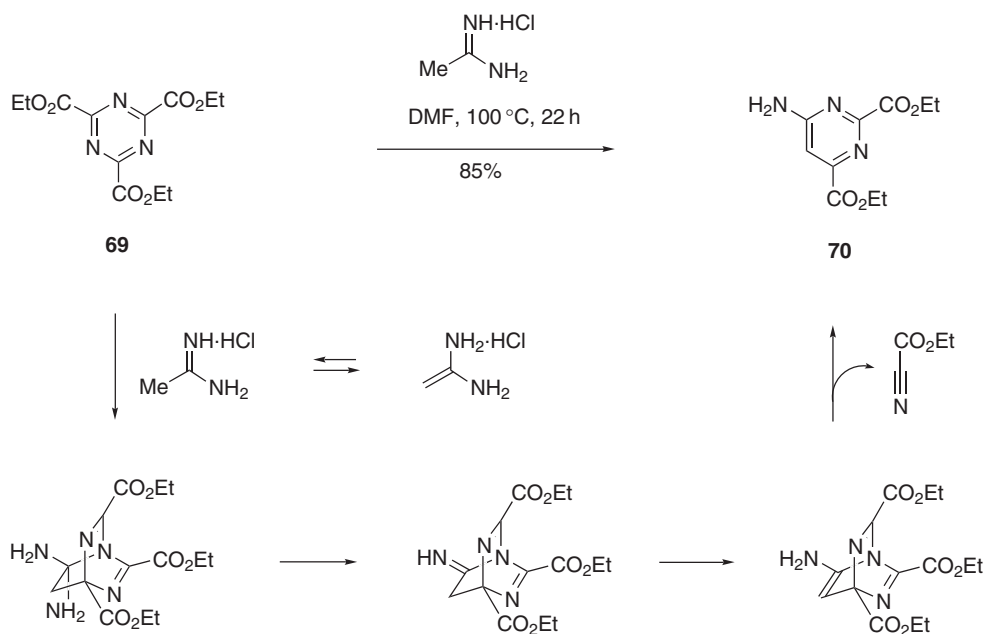


Scheme 47



Scheme 48

Heteroaromatic structures can also be reached by a retro-[4+2]-cycloaddition. In these cases, the process involves the breaking of one C—C and one C—X or two C—X double bonds (X = heteroatom) with the concomitant release of a small stable heteroatomic molecule. In most examples, a tandem Diels–Alder and retro-Diels–Alder sequence occurs. Thus, the condensation of 1,3,5-triazine **69** with acetamidine hydrochloride in DMF afforded the 1,3-diazine **70** in good yield <1994JOC4950>. The reaction cascade proceeds with *in situ* amidine–enamine tautomerization, [4+2]-cycloaddition, loss of ammonia from the Diels–Alder adduct with generation of an imine, imine–enamine tautomerization, and, finally, a retro-Diels–Alder reaction with production of ethyl cyanoformate (Scheme 49). 1,2,4,5-Tetrazines behave similarly to give 1,2-diazines, which are prone to reductive ring contraction to yield synthetically useful pyrroles <2003JOC3593>.

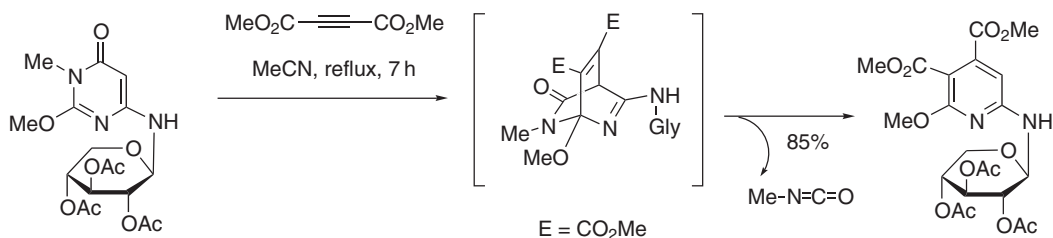


Scheme 49

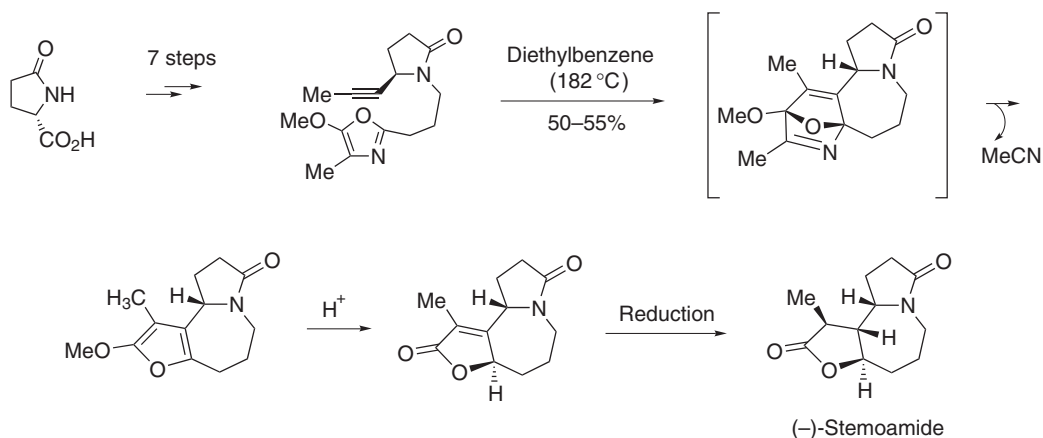
A similar approach was used in the synthesis of purines and purine nucleosides <1996JOC5204, 1999JA5833> and a theoretical study has also been achieved <2001JOC6029>. The synthesis of the 2-glycosylamino pyridine shown in Scheme 50 proceeds with an identical strategy <1996T5845, 1996T13721>.

The Diels–Alder–retro-Diels–Alder sequence is particularly attractive when the cycloaddition reaction occurs intramolecularly since an elaborate structure can be reached in one single operation. An illustration is provided by the synthesis of the alkaloid (–)-stemoamide (Scheme 51) <2000JA4295>.

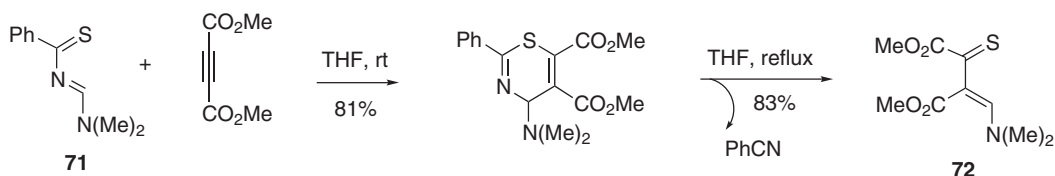
The retro-[4+2]-cycloaddition strategy is also applicable to the formation of heterodienes as illustrated by the transformation of the 1-thia-3-aza-buta-1,3-diene **71** to the 1-thia-buta-1,3-diene **72** under particularly mild conditions (Scheme 52) <1985JOC1545>.



Scheme 50

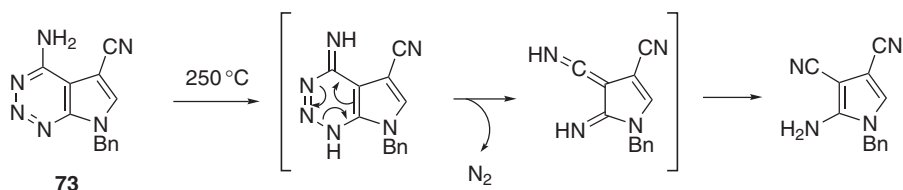


Scheme 51



Scheme 52

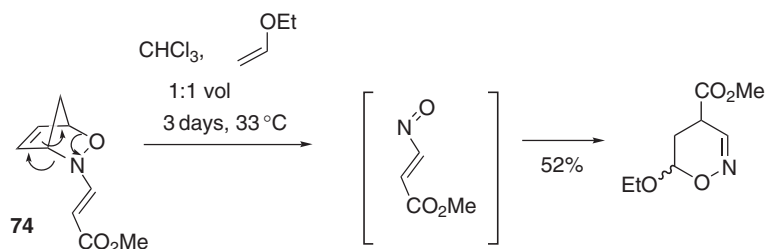
Heterodienes generated by the thermal decomposition of Diels–Alder adducts are sometimes transient species that spontaneously convert to more stable structural forms. Thus, in the transformation depicted in [Scheme 53](#), the pyrolysis of triazine **73** proceeds via a retro-Diels–Alder reaction to give a transient heterodiene that tautomerizes toward a stable 2-aminopyrrole, as firmly demonstrated by ^{15}N -labeling studies [<1999OL537>](#).



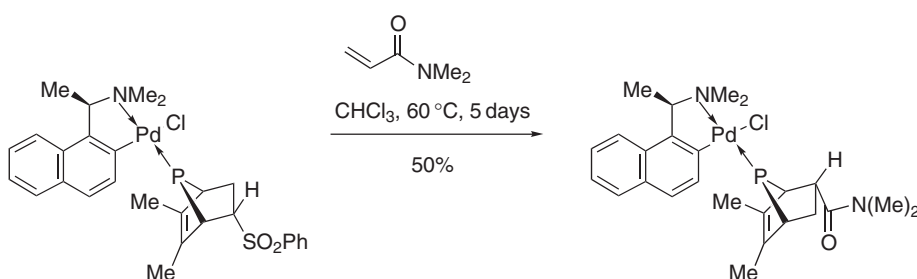
Scheme 53

Capture of an unstable heterodiene by a dienophile present in the reaction medium is also a situation frequently observed. For example, the simple retro-[4+2]-cycloaddition of adduct **74** leads to a nitroso alkene, which is captured by an enol ether in an inverse electron-demand [4+2]-cycloaddition

(Scheme 54) <2000OL1323>. Another example is provided by the transformation shown in Scheme 55 <2000TA2661>. In these two examples, each of the primary Diels–Alder adducts behaves as a source of an unstable diene in neutral medium.

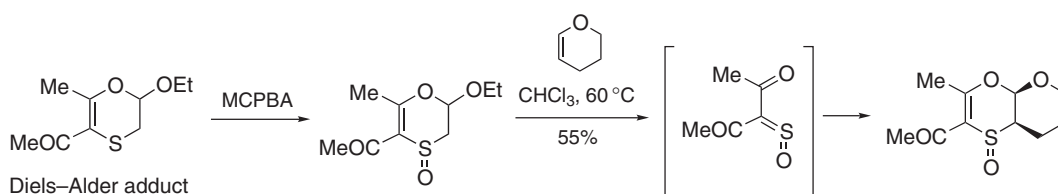


Scheme 54



Scheme 55

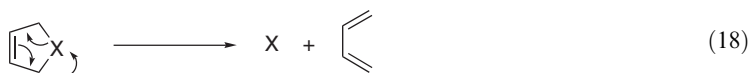
A slightly different situation is shown in Scheme 56. In this case, the primary Diels–Alder adduct is oxidized before being subjected to the conditions of the retro-[4 + 2]-cycloaddition with diene trapping <1995TL5089, 1996T12233, 1996T12247>.



Scheme 56

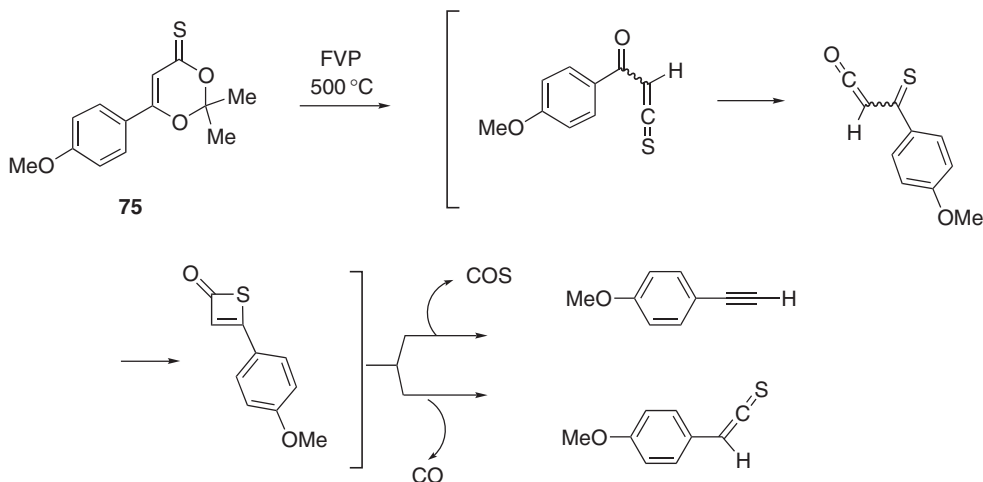
1.17.4.2 Retro-cheletropic Reactions

Retro-cheletropic processes are applicable to the stereospecific synthesis of conjugated dienes (Equation (18)). The extruded group (X) is most often a stable small hetero-molecule such as CO , N_2 , N_2O , S, and SO_2 .



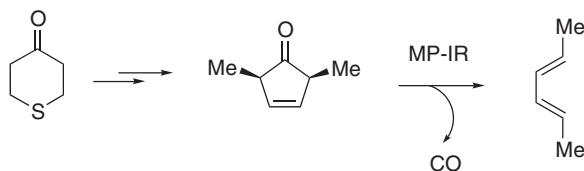
The reaction may be accomplished under FVP conditions or at reflux of appropriate solvents. In most examples performed under FVP conditions, the highly reactive species generated are not isolated but characterized *in situ*. One example is furnished by the pyrolysis of the 1,3-dioxine-4-thione **75**, which gives anisylthio ketene and acetylene as the final products. The transformation was interpreted as shown in Scheme 57 <2000JOC2706>. Loss of acetone from **75** leads to the formation of a thio ketene that rearranges to a thioacyl ketene (anisyl 1,3-shift). The latter then

undergoes electrocyclization to a thiet-2-one which decomposes, following a retro [2+2]-cycloaddition, to give anisylacetylene and, concurrently, by cheletropic extrusion of CO to give anisylthioketene.



Scheme 57

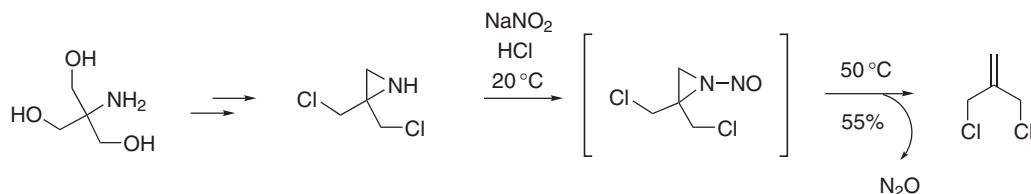
The stereochemistry of the thermal cheletropic decarbonylation of *cis*-2,5-dimethyl-3-cyclopentenone has been determined by multiphoton infrared irradiation <2003JA8529>. In this particular case, the great advantage of the MP-IR photolysis/thermolysis technique over the classic FVP is that the diene product is not prone to isomerization. The reaction leads to the exclusive formation of *trans-trans*-2,4-hexadiene, thereby showing that the cheletropic fragmentation proceeds via the disrotatory pathway as predicted (Scheme 58) <1966JA1335>.



Scheme 58

Photo-mediated cheletropic extrusion of CO has been reported as a route to C-15 mono-substituted semibullvalenes <1998TL4899>.

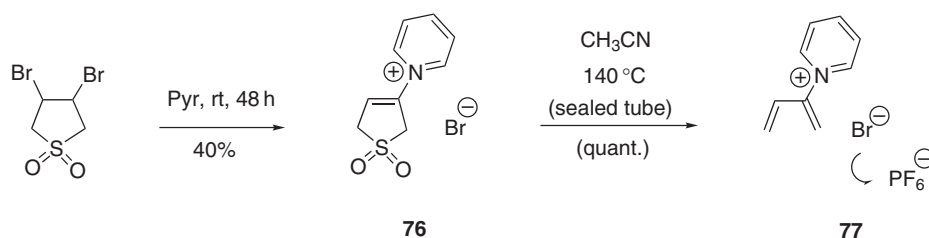
A large-scale one-pot and convenient preparation (55% overall yield) of the useful synthon 3-chloro-2-(chloromethyl)propene by cheletropic extrusion of nitrous oxide from an *N*-nitrosoaziridine (Scheme 59), as well as a theoretical study of the reaction mechanism, has been reported <2000JOC6784, 2000JOC3612>.



Scheme 59

The cleavage of sulfur from 1,3-dipolar cycloaddition adducts to give pyridones has been described but, in that case, it was difficult to make a choice between a cheletropic extrusion or a stepwise mechanism to account for the departure of sulfur [<2000T1247>](#).

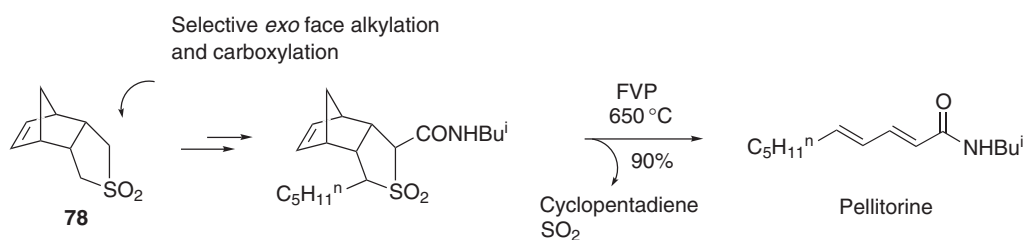
The cleavage of SO₂ from 3-sulfolene is, by far, the most synthetically useful retro-cheletropic reaction and this topic has been reviewed [<1993PHC1>](#). This reaction has been widely used to synthesize diversely substituted electron-rich and electron-poor 1,3-butadienes. An example is the cation-substituted diene **77**, which was isolated after thermolysis of the 3-sulfolene **76**, particularly in mild conditions (Scheme 60) [<1997JOC7812>](#). Despite its electron-deficient character, diene **77** reacts in normal demand with electron-poor dienophiles.



Scheme 60

Thermolytic extrusion of SO₂ from polymer-bound 3-(phenylsulphonyl)-3-sulfolene followed by trapping of polymer-bound 2-(phenylsulphonyl)-1,3-butadiene with various dienophiles has been recorded [<2001JOC5528>](#). Due to the relatively simple thermal extrusion of SO₂, 3-sulfolenes may also serve to temporarily protect a reactive diene. This strategy has been exploited in a synthesis of 19-fluoro vitamin D derivatives [<1996TL6753>](#). The effect of solvent polarity on the cheletropic extrusion of SO₂ from 3,4-dimethyl-3-sulfolene has been investigated [<1996T6241>](#).

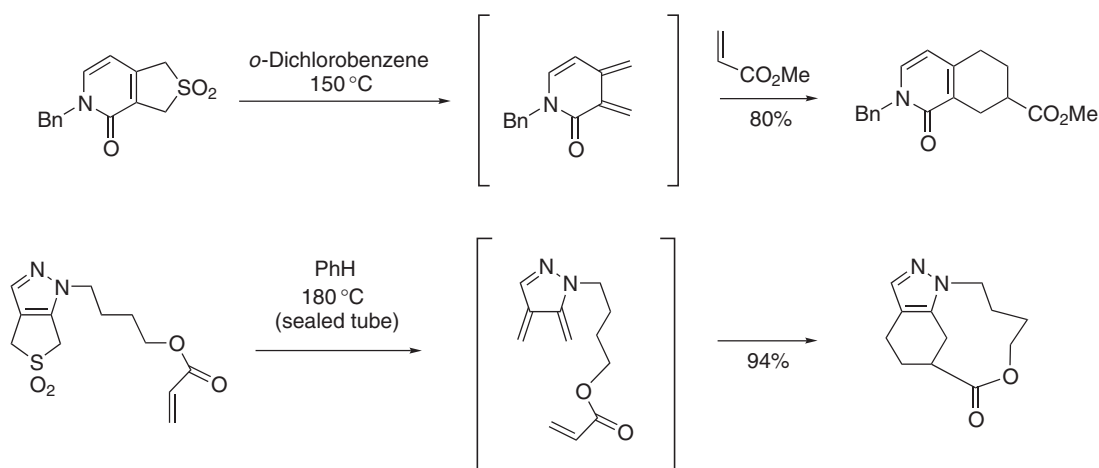
The sulfone **78** resulting from the Diels–Alder cycloaddition between 3-sulfolene and cyclopentadiene may be stereoselectively alkylated at its C-2 and C-5 positions. After pyrolysis, effecting both retro-[4+2]-cycloaddition and cheletropic extrusion of sulfur dioxide, a diene substituted at each of its termini may be selectively isolated. An example of this protocol [<1986T4975>](#) is presented in Scheme 61 with the synthesis of pellitorine, an insect sex pheromone.



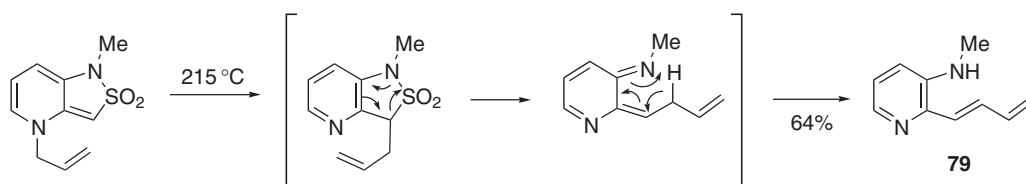
Scheme 61

The pyrolysis of 1,3-sulfolenes with the formation of reactive *o*-quinodimethanes [<1999CRV3199, 2002T5367>](#) has been employed in the preparation of natural products such as alkaloids [<1994TL1071>](#) and steroids [<1980HCA1703>](#). The pyrolysis of heteroaromatic sulfolenes leads to heteroaromatic *o*-quinodimethanes, which are generally trapped by dienophiles in both an intermolecular or intramolecular mode. Scheme 62 gives an example of each of these modes [<2002TL799, 2000JOC5760, 1998T12609>](#).

The extrusion of SO₂ may be part of a cascade of reactions as in the example depicted in Scheme 63. The sequence consists of three pericyclic reactions, namely, a Cope rearrangement followed by cheletropic extrusion of SO₂ leading to a heterodiene in which a [1,5]-sigmatropic hydrogen shift leads finally to the 1,3-diene **79** [<2001T5009>](#).

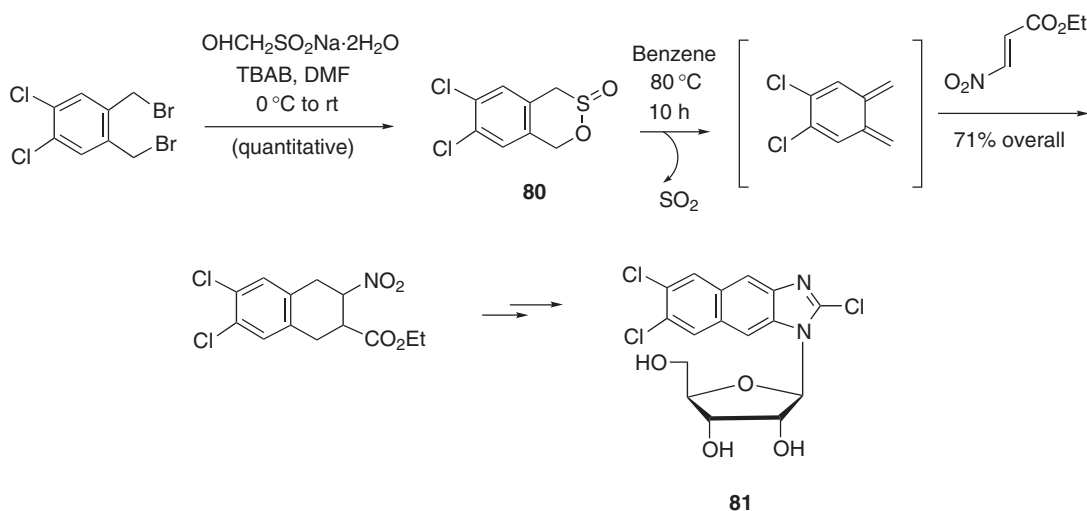


Scheme 62



Scheme 63

The pyrolysis of sultines is sometimes more advantageous for the generation of heterocyclic-fused *o*-quinodimethane species. For instance, the easily prepared sultine **80** undergoes cheletropic extrusion of SO₂ smoothly at reflux in benzene, whereas the corresponding sulfolene requires a temperature of 230 °C to generate the same *o*-quinodimethane intermediate [<1998JOC977>](#). The reaction has been applied to the synthesis of the nucleoside **81** (Scheme 64) with the aim of finding new antiviral drugs. Other syntheses of heterocycles, using the pyrolysis of sultines as the key step, have been reported [<2000JOC3395, 2002JOC9267>](#).



Scheme 64

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Biographical sketch



Jacques Lebreton was born in Guérande (France) in 1960. He received his Ph.D. degree (1986) from the University of Paris XI-Orsay under the supervision of Professor Eric Brown (Le Mans). His thesis work included the total synthesis of C-nor D-homosteroids. In 1986, he started his first postdoctoral fellowship with Professor James A. Marshall at the University of South Carolina working on the [2,3]-Wittig rearrangement and its application in total synthesis. Following a second postdoctoral fellowship with Professor Robert E. Ireland at the University of Virginia working on the total synthesis of monensine, he joined in 1990 the laboratories of CIBA-GEIGY (Novartis) in Basle, where he worked in Dr. Alain De Mesmaeker's group in antisense oligonucleotides. In 1994, he joined the CNRS and spent a few years in the group of Dr. Jean Villéras (UMR-CNRS 6513, Nantes) exposed to organometallic chemistry. In 1998, he was promoted to Professor at the University of Nantes. His major research interests are organometallic chemistry, synthesis of bioactive molecules, and synthesis of labeled molecules to study biological processes.



André Y. Guingant is a director of research at the French National Center for Scientific Research (CNRS) and works in the Organic Synthesis Laboratory at the University of Nantes. He attended the Pierre et Marie Curie University (Paris) and received his Ph.D. degree in 1979 under the supervision of the late Professor J. Ficini. After pursuing research as a postdoctoral fellow with Professor Samuel J. Danishefsky at the Universities of Pittsburgh and Yale, he joined the laboratory of Dr. Jean d'Angelo at the "Ecole Supérieure de Physique et Chimie Industrielles" (ESPCI, Paris) in 1982. In 1992, he moved to the University of Nantes. His research interests involve the development of stereoselective methods, the total synthesis of natural products, and medicinal chemistry investigations in the field of nitrogen-containing heterocycles.

In 2000, A. Guingant and J. Lebreton set up a research group, named Symbiose, devoted to develop research at the interface between chemistry and biology. The Symbiose group is a member of a network that aims to develop new pharmacological strategies and design new antagonists to specifically target small G protein signaling.

1.18

One or More =CH, =CC, and/or C=C Bond(s) Formed by Rearrangement

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1.18.1 GENERAL INTRODUCTION AND METHOD OF CATEGORIZATION

Rearrangement reactions play a central role in functional group transformations and in the state of the art in modern organic synthesis. The present chapter complements other parts in this work devoted to rearrangements, Chapters 1.09 and 1.17. Allylic rearrangement during substitution, aromatic rearrangements, and reductive transposition will not be examined within this chapter. The reader is referred to the two books edited by de Mayo <B-1963MI001, B-1980MI001>, to the corresponding chapter on rearrangements in the annual series *Organic Reaction Mechanisms* edited by Kniepe and Watts <B-1966MI001, B-2001MI001>, and to some other specific reviews and relevant papers on sigmatropic rearrangements <1996TA1847, 1998S227, 2001CUOC1133, 2002ACR279>.

The order of discussion is based on the formation of compound type **2** from precursor **1** (Equation (1)).



In this section the same order that has been used in the excellent account by Murphy on the present subject is followed <1995COFGT(1)793>. Accordingly, the rearrangements for [1,*j*]-processes (*j* = odd number) for Y = hydrogen, carbon-, chalcogen-, or heteroatom-containing substituents are described. These are not necessarily sigmatropic and the cases for Y = hydrogen are discussed first, followed by Y = carbon and hetero- or chalcogen-containing substituents.

1.18.2 REARRANGEMENTS INVOLVING [1,2]-SHIFTS AND [1,*j*]-MIGRATION

This section deals with rearrangements involving a [1,2]-shift of a double bond and migration of the group X across the alkene moiety to give the new function Y (Equation (1)). These reactions have been covered in a recent book <B-2000MI001> and in general texts <B-1970MI001, B-1976MI001>; they are discussed in the following order: sigmatropic, acid- and base-catalyzed, metal-catalyzed, and anion accelerated migrations of hydrogen atoms.

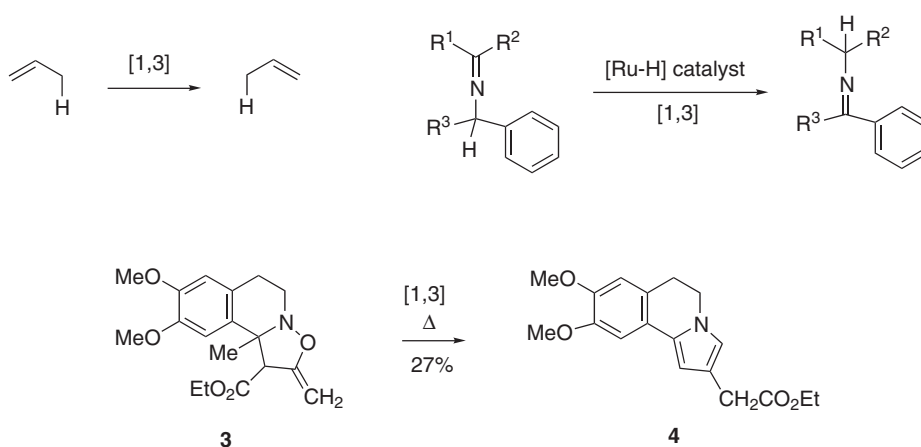
1.18.2.1 Where Y = H

1.18.2.1.1 [1,*j*]-Migrations of hydrogen

(i) Sigmatropic migrations of hydrogen

The photochemical or thermal migration of hydrogen across a π -system has been reviewed several times <1976CRV187, 1981MI1272, 1995HOU(E21d)4421, 1995COFGT(1)793> and has interesting consequences from the synthetic point of view. The most common migrations are the photochemical [1,3]-, thermal [1,5]-, and the photochemical or thermal [1,7]-hydrogen shifts. According to the Woodward–Hoffmann rules, the simplest thermally allowed [1,3]-process should take place antarafacially along the allylic carbon skeleton (Scheme 1). The photooxidation of phenyl allyl sulfide gives α,β -unsaturated sulfones in a typical [1,3]-H shift <2002JOC1036>. The isomerization of imines proceeds via a [1,3]-hydrogen shift catalyzed by ruthenium-hydride complexes in toluene, under a hydrogen atmosphere (Scheme 1) <1998CL1255>. The reaction of $\text{Fe}_2(\text{CO})_9$ with imine ligands derived from α - or β -naphthylcarbaldehydes gives new iron complexes as the result of C–H activation in the *ortho*-position with respect to the exocyclic

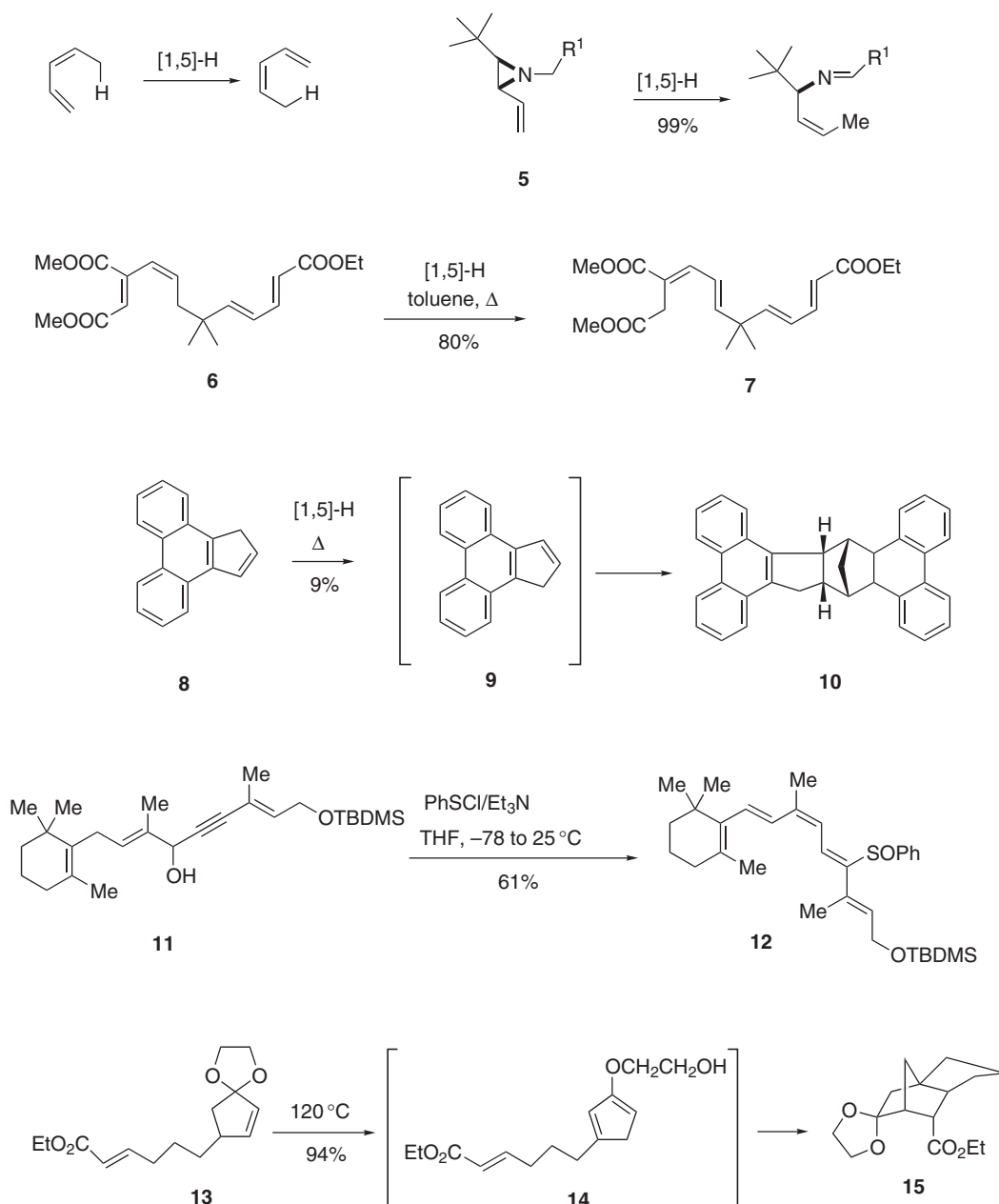
imine function; the reaction then proceeds via subsequent [1,3]-hydrogen shift toward the former imine carbon <1999OM4845>. A [1,3]-sigmatropic shift has been detected in the photo-Fries rearranged intermediate of 2,4-dimethoxy-6-(*p*-tolylxy)-*s*-triazine <1998JCS(F)3077>. The thermal rearrangement of 5-methyleneisoxazolidines **3** afforded two isomers of 5,6-dihydropyrrolo [2,1-*a*]isoquinolines **4** (Scheme 1) <1997JCS(P1)2973>. A new planar-chiral bidentate phosphoferrocene ligand coupled to a rhodium complex, [Rh(COD)₂]BF₄, has proved to be an efficient catalytic system for the asymmetric isomerization of allylic alcohols to aldehydes; the isomerization proceeds via an intramolecular [1,3]-hydrogen migration <2001JOC8177>. The thermal and photochemical isomerization of tetraaryl tetrakis(trifluoromethyl)[4]radialenes has been shown to take place by [1,3]-hydrogen migration <2000JOC1615>. (Cyclobutenyl)carbene tungsten complexes are shown to rearrange to 1-tungsta-1,3,5-hexatrienes by ring opening of the cyclobutene ring and subsequent [1,3]-hydrogen migration <1998OM1197>. A new highly efficient enantioselective entry to versatile chiral building blocks such as tetrahydro-*endo*-1,4-methano- and tetrahydro-*endo*-1,4-ethanonaphthalenones was achieved by desymmetrization of *meso*-allylic 1,4-enediyls using a cationic chiral Binap–Rh(I) catalyst; the reaction mechanism includes a suprafacial [1,3]-hydrogen migration pathway <1995AG(E)2287>.



Scheme 1

In contrast, the thermal antarafacial [1,5]-hydrogen shift is one of the best studied reactions within the group of pericyclic rearrangements <1976CRV187> (Scheme 2). The general features include a *cisoid*-geometry of a 1,3-pentadiene structural moiety, intramolecular process and first-order kinetics, being independent of solvent polarity <1982T567> (Scheme 2). Density functional calculations have been carried out for [1,5]-hydrogen shifts in 1,3-cycloalkadienes <2001JOC8902, 2002JOC6025>, pyrroles, furans, thiophenes <1997CEJ523>, pyrazoles, and related systems <1998JCS(P2)2497>. A thermal [1,5]-hydrogen shift results in the synthesis of conjugated linoleic acid isomers <2003MI3, 2002MI435, 2003T567>. A [1,5]-sigmatropic proton shift has been observed in the oxidation behavior of oxatocopherol-type oxidants <2002JOC3607>, and in the FVP of *N*-mesityl-*C*-acylketenimines leading to quinolines <1998JOC5779>. New annelation methods for the synthesis of 8*H*-heptaleno[1,10-*bc*]furans, -pyrroles, and -thiophenes have been described making use of [1,5]-hydrogen migrations <1997HCA2520>.

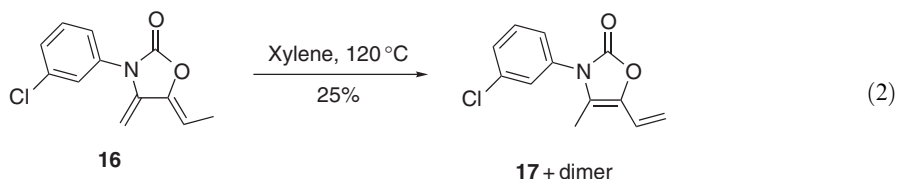
[1,5]-Hydrogen shifts have been involved in the conversions of [*o*-(1-halo-1-(*p*-tolylsulfonyl)alkyl)benzyl]trimethylsilanes to *o*-quinodimethanes and benzocyclobutenes <1998JOC2086>, and in the synthesis of chiral indenyl ligands derived from verbenone <2002OM144>. The secondary products obtained in the heptalene-forming reaction of azulene and acetylenedicarboxylates are formed via [1,5]-hydrogen shifts <2002HCA27>. The thermal [1,5]-hydrogen shift of 7-alkoxy-carbonyl tropyliene was found to be accelerated by conformational regulation at the carbonyl group, which mainly affected the activation energy <1999CL1143>. Somfai reported that in addition to the aza-[2,3]-Wittig rearrangement products, vinylaziridines were good substrates for the homodienyl [1,5]-hydrogen migration, specially with substituents capable of conjugation in the starting product **5** (R¹ = CO₂Bu, Ph) (Scheme 2) <1995TL1953, 1996JPO623, 1999T11595>. In a synthetic approach to mniopetals, it was found that compound **6** produces stereospecifically itaconic acid derivative **7** via a thermal [1,5]-hydrogen shift <1999IJC(B)269>.



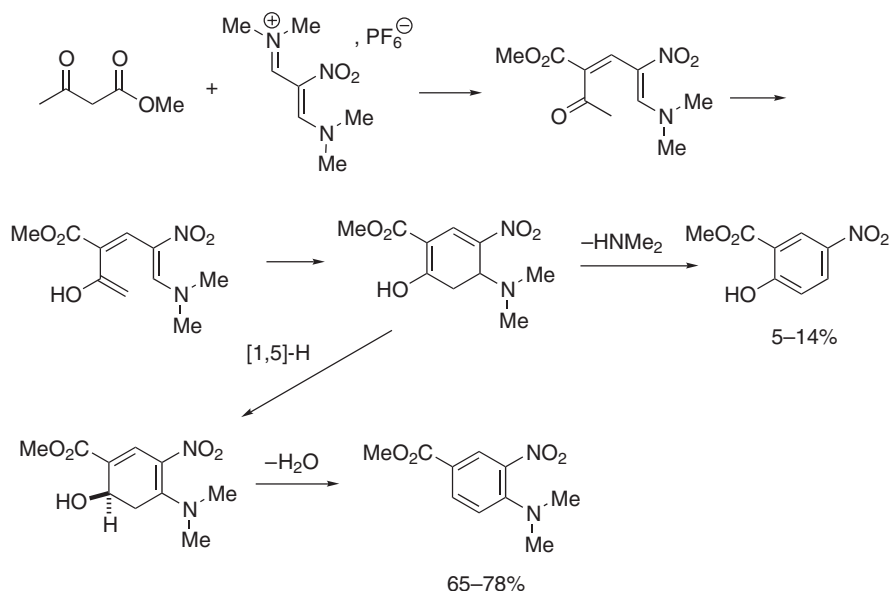
Scheme 2

(Scheme 2). Thermolysis of cyclopenta[*l*]phenanthrene **8** afforded the Diels–Alder adduct **10** via intermediate **9** as the result of a [1,5]-sigmatropic hydrogen migration in the precursor [<1998JOC3735>](#) (Scheme 2). De Lera and co-workers have described a pericyclic cascade reaction for the stereocontrolled synthesis of 9-*cis*-retinoids. The transformation of alkenynol **11** to polyene **12** is a process that comprises an ordered sequence of sigmatropic rearrangements: a reversible [2,3]-allyl sulfonate to allyl sulfoxide shift, followed by a [2,3]-propargyl sulfonate to allenyl sulfoxide rearrangement, and finally a stereodifferentiating [1,5]-sigmatropic hydrogen shift (Scheme 2) [<2000JOC2696>](#). In the first synthesis of mono- and dipyrrole-substituted cyclopentadienes, it was observed that at higher temperatures substituted cyclopentadiene systems interconvert via sigmatropic [1,5]-hydrogen migration [<1997JOC7877>](#). UV irradiation of 2-(1-adamantylidene-1-phenylmethyl)-3,3,3,4,4,5,5-hexafluoro-1-(3-thienyl)cyclopentene gave 4',5'-hexafluoropropano-6'-phenylspiro[adamantane-2,7'-(6*H*)-benzothiophene] via a photochemical 6 π -electrocyclization followed by the thermal [1,5]-hydrogen migration [<2003BCJ355>](#).

Electrochemical oxidation of 1-tosyl-3-aryl-1,3-dihydro-1,3-diazaazulanones at room temperature afforded double-bond isomers, 1-tosyl-3-aryl-1,3-diazaazulanones via [1,5]-hydrogen migration, together with 3-aryl-6-tosyl-1,3-dihydro-1,3-diazaazulanones <1999H(50)63, 2002H(58)63>. It has been reported that heating at 120 °C promoted the dioxolane ring opening followed by [1,5]-hydrogen migration in enone ketal **13** yielding intermediate **14**, ready for the intramolecular Diels–Alder reaction to give cycloadduct **15** <2002JCS(P1)366> (Scheme 2). Compound 3',3',9,9-tetrachlorospiro(bicyclo[5.2.0]nona-2,4-diene-8,2'-oxetan)-4'-one underwent intramolecular [1,5]-hydrogen migration in the seven-membered ring at 115 °C <2001JCS(P1)2257>. Stabilized azomethine ylides with electron-withdrawing substituents react via a [1,7]-electrocyclization with phenyl rings followed by [1,5]-hydrogen shift to yield dihydrobenzazepines <2003TL793>. In the dimerization of product **16**, compound **17** resulting from the [1,5]-hydrogen migration was also detected in low, but significant yield (Equation (2)) <1997JOC4105>.



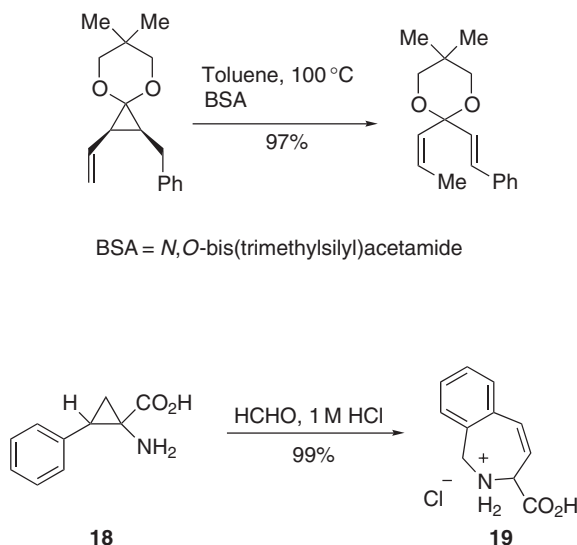
The reaction of 2-nitrovinamidinium hexafluorophosphate with methyl acetoacetate gives unexpectedly phenols or anilines in very good yield; the surprising formation of these anilines can be rationalized by a keto-enol tautomerism of the initial adduct followed by an electrocyclic ring-closure and a [1,5]-H shift; elimination of water restores the aromaticity (Scheme 3) <2002OL439>. Chiral methyl groups in the form of chiral acetic acids substituted with hydrogen, deuterium, and tritium atoms at the α -carbon have been prepared by using a [1,5]-H shift <1999JA10848>. A [1,5]-hydrogen shift has been invoked in a thermal sigmatropic rearrangement of 4-(4-aryloxybut-2-ynyloxy)[1]benzopyran-2-ones to the corresponding thiones <2001S924>.



Scheme 3

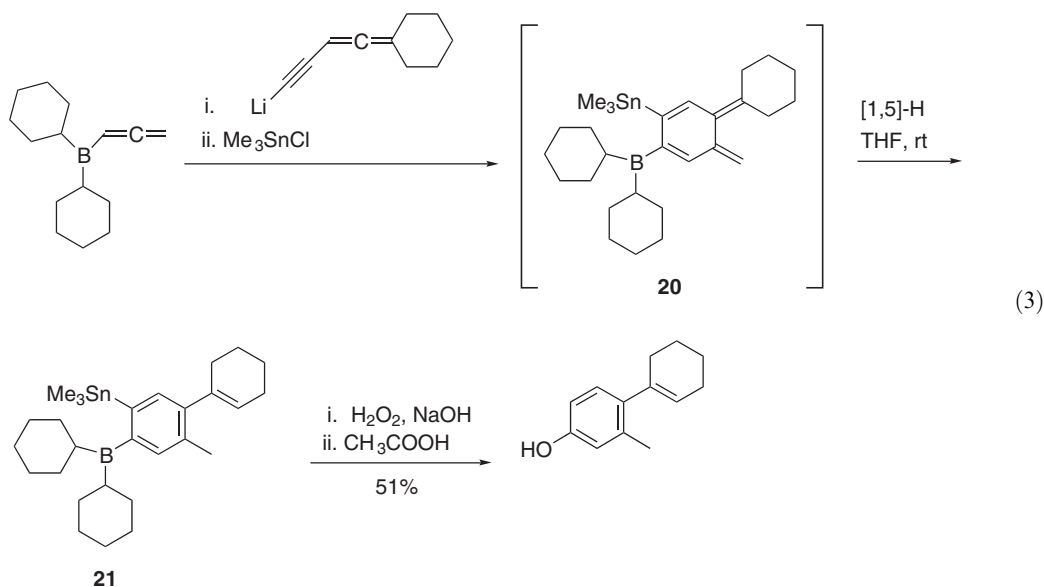
The reaction of 1-triphenylphosphoranylidene-2-propanone with *cis*-2,3-bis(trimethylsilyl)-cyclopropanone gave products arising from the unexpected [1,5]-sigmatropic rearrangement featuring cyclopropane ring opening <2000TL3399>. Substituted vinyl cyclopropanes undergo [1,5]-hydrogen shift in competition <2001JOC8751> with sigmatropic rearrangement to cyclopentenes (see Section 1.18.2.2.1(ii)). The [1,5]-hydrogen shift generally occurs at lower temperatures than cyclopentene formation. The *cis*-configuration of the product from the *cis*-cyclopropane coupled to the low activation energy suggests that this hydrogen rearrangement occurs by a suprafacial, concerted homodienyl [1,5]-hydrogen shift <1997JOC1532>. The [1,5]-hydrogen shift

in *cis*- and *trans*-*N*-acyl-2-alkylcyclopropylamines has been described <1997JOC1532>. *cis*-1-Alkyl-2-vinylcyclopropane acetal underwent a thermal [1,5]-hydrogen migration reaction to give the acetal of a (*Z*),(*E*)-dienone (Scheme 4) <1996H(42)565>. The reaction of α,α' -cyclopropyl amino acid **18** with formaldehyde in hydrochloric acid gave the heterocyclic ring system 2,3-dihydro-1*H*-2-benzazepine-3-carboxylic acid **19** in a process that involves a novel [3,3]-sigmatropic rearrangement of the iminium ion of the *N*-methylene derivative followed by a [1,5]-hydrogen shift (Scheme 4) <2001JOC2884>.



Scheme 4

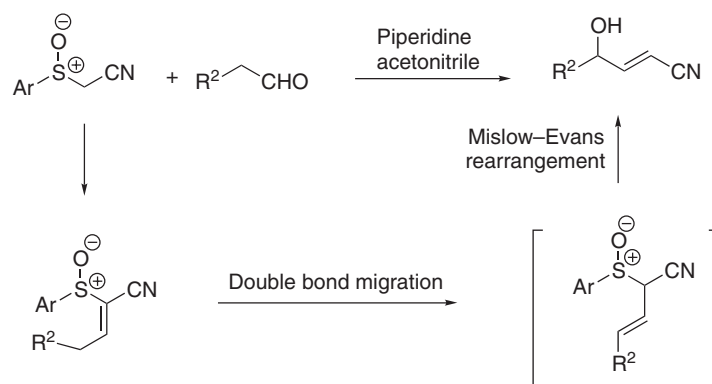
The adducts from the [4 + 2]-cycloaddition of 4-dialkylamino substituted 1,3-diazabuta-1,3-dienes with butadienylketenes undergo [1,5]-hydrogen shifts <2002JCS(P1)774>. It has been reported that the intermediate reactive *o*-quinodimethane **20** underwent [1,5]-hydrogen shift to give organoborane **21** (yield not given) (Equation (3)) <1999JOM(581)108>. A [1,5]-hydrogen shift has been invoked as the crucial step in the reaction of ammonia with 3-pyrrolidino-1,2,4-triazine-4-oxide to give 5-amino-1,2,4-triazine-4-oxide <1999TL6099>.



Regarding the [1,7]-sigmatropic hydrogen shift, several examples have been recorded in the literature. In a project directed to the study of anaerobic photocyclization of 3-styryl pyridines, it was observed that the formation of 2-azaphenanthrenes in the absence of oxygen is attributed to the conversion of the 4a,4b-dihydroazaphenanthrene primary photoproduct to a 1,4-dihydropyridine intermediate by means of a formal [1,7]-hydrogen migration [\[2001JA3878\]](#). Methylene-propenylidene cyclohexadiene derivatives show competing [1,7]-hydrogen migrations with 1,6-electrocyclic reactions [\[1996JA10311\]](#).

(ii) *Acid- and base-catalyzed migrations of a hydrogen atom*

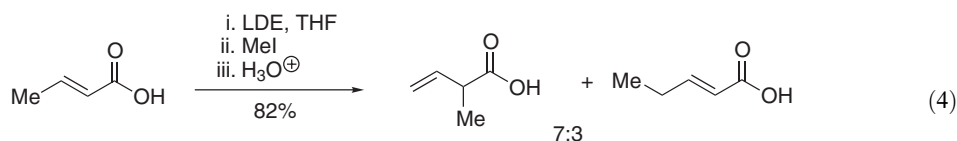
Double-bond rearrangement is possible under mild basic conditions, as in the piperidine-mediated conjugation of a β,γ -unsaturated ester to give the corresponding α,β -unsaturated ester [\[1998SL81\]](#). The reaction of aldehydes or ketones with 2-arylsulfinyl acetonitrile gives the highly functionalized four-carbon unit 5-hydroxyalk-2-enenitrile, in a very useful transformation that is assumed to proceed by a double-bond isomerization (Scheme 5) [\[2001JOC1228\]](#). A new method for α -pyrone synthesis has been proposed based on the base-catalyzed reaction of 1,2-allenyl ketones and conveniently substituted acetates with electron-withdrawing groups; the reaction seems to proceed by a cascade Michael addition, carbon-carbon double-bond migration, and lactonization [\[2002OL505\]](#).



Scheme 5

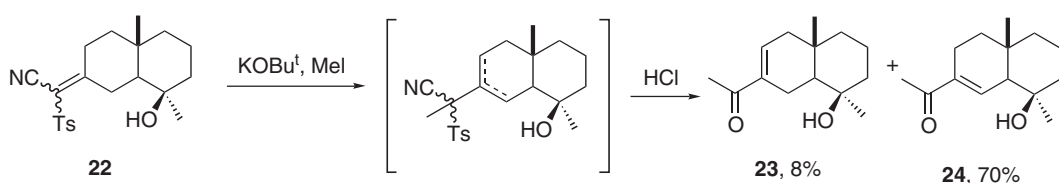
Unusual double-bond migration in the formation of saturated isoprenoid chains in the biosynthesis of core membrane lipids has been reported [\[2000CC1545\]](#). Acid-catalyzed double-bond migration in steroid chemistry has been widely documented in recent years. The transformation of cholesta-5,7-dien-3 β -ol to 5 α -cholesta-8,14-dien-3 β -ol is a well-known reaction that has been used to prepare the biosynthetic intermediates for the investigation of steroid biosynthesis [\[1995MI290, 1999TL8863, 2000JCS\(P1\)1697, 2002JCS\(P1\)2395\]](#).

α,β -Unsaturated carboxylic acids are synthetically useful building blocks, because upon deprotonation by 2 equiv. of lithium dialkylamides they give dianion intermediates, dienediolates, as ambident nucleophiles through their α - or γ -carbon, and whose regioselectivity depends on the electrophile as well as on the reaction conditions [\[1991COS\(2\)99, 1991COS\(3\)1, B-1994MI001\]](#). Thus, it has been observed that α -attack predominates in the irreversible reaction with alkyl halides and protonation, while γ -attack has been attained by counterion interchange with copper(I) salts or with allylic halides (Equation (4)) [\[2002CUOC283\]](#). A number of theoretical [\[1996T11105\]](#) and experimental studies have been conducted in order to determine the influence of the halides [\[1998T15305\]](#), the type of solvent [\[2001SL156\]](#), effect of the leaving groups [\[1998T4357\]](#), and the use of chiral bases [\[2001TA915\]](#) in the regioselectivity of the reaction. Practical applications have been documented in the synthesis of pyridones [\[1999SL1088, 2000S273\]](#) and natural products [\[1996SC1309\]](#).



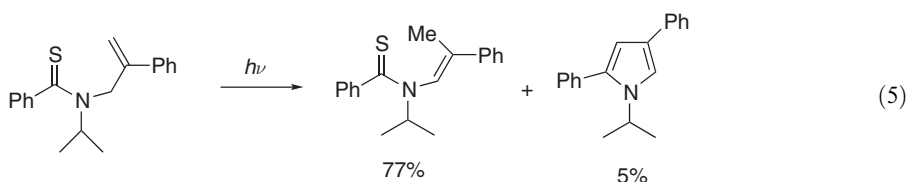
(LDE = lithium diethylamide)

Intramolecular Diels–Alder reaction of 1-(pentenoyl)-3-(tetrahydropyridinyl)indoles followed by acid-catalyzed double-bond migration results in the aromatization of the intermediate and formation of pentaheterocyclic ring systems related to those found in *Strychnos* alkaloids <1998JOC1974>. The same type of acid-catalyzed rearrangement has been found between 1,2,3,9a-tetrahydro-9*H*-carbazoles and 1,2,3,4-tetrahydro-9*H*-carbazoles <2000JCS(P1)2395> and in the synthesis of β,β' -fused metallocenoporphyrins <2001CC2646>. The base-promoted methylation of α,β -unsaturated nitrile **22** followed by acid hydrolysis gives a mixture of double-migration products **23/24** <1995JOC2188> (Scheme 6).

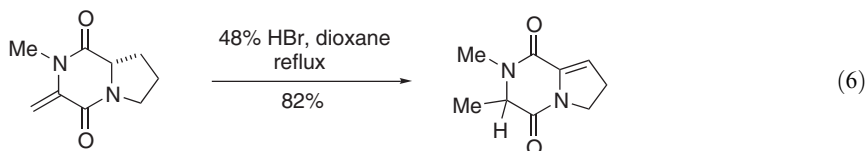


Scheme 6

The photochemical irradiation of *N*-(2-phenylprop-2-enyl)thiobenzamides gives *N*-(2-phenylprop-1-enyl)thiobenzamides after double-bond migration via two consecutive [1,4]- and [1,6]-hydrogen transfers <1997JCS(P1)1851> (Equation (5)).

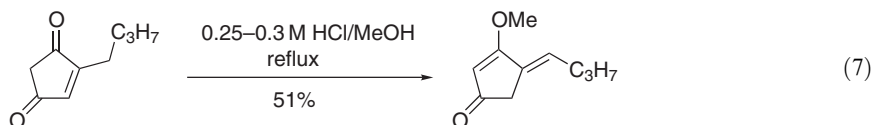


The reaction of allylic tosylamides with propynyl(phenyl)iodonium triflate in the presence of lithium hexamethyldisilylamide affords azabicyclo[3.1.0]hexanes in a process that involves double-bond migration driven by the high strain energy of endocyclic methylenecyclopropane-containing fused bicyclic systems <1998TL4781, 1998JA4027>. The isomerization of but-1-ene with alumina catalysts <2001CC701> and the photooxidation of 1-alkenes in the presence of zeolites <1999JA5063> have been reported. The well-known base-catalyzed isomerization of allyl phosphonates to vinyl phosphonates has been applied in pyranosyl phosphonates <1996JMC1321>. A nice example of transfer of central to axial chirality involving the base-mediated double migration in enantiomerically pure (1*R*)-menthyl (*R*)- and (*S*)-1-(1'-indenyl)naphthalene-2-carboxylates has been published <1996CC2571>. An unusual carbon–carbon double-bond migration has been reported in the acid-catalyzed isomerization of 3-ylidine-2,5-piperazinediones (Equation (6)) <2000EJO1993>.

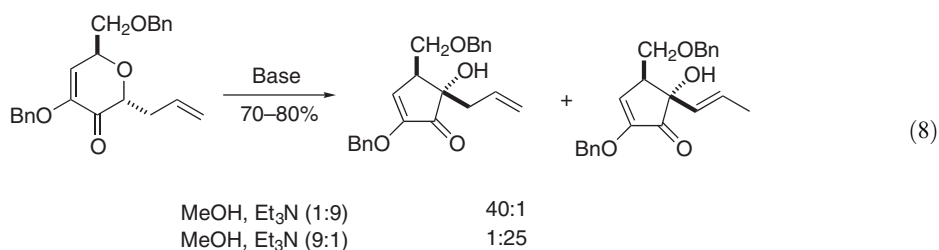


The synthesis of C-11 methyl-substituted benzocycloheptapyridine inhibitors of farnesyl protein transferase has been achieved by base-mediated double-bond deconjugation followed

by methylation <1999OL1371>. The regioselective enolization of 4-substituted cyclopentene 1,3-diones, under basic or acid conditions, gives enol ethers with simultaneous endocyclic double-bond migration in the side-chain (Equation (7)) <1998T1589>.



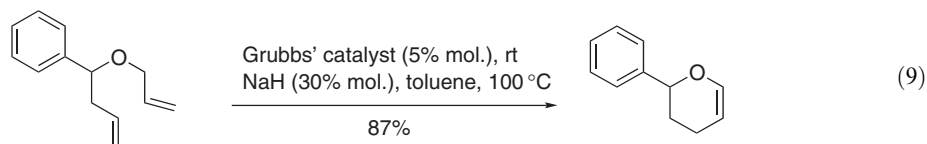
(*E*)-3-Penten-2-one has been prepared in large scale by 1,5-diazabicyclo[5.4.0]undec-5-ene (DBU)-promoted isomerization of the corresponding γ,δ -unsaturated ketone <1998SC4513>. The triethylamine-promoted double migration of 1,5-anhydro-3-*C-p*-tolylsulfonyl-D-hex-2-enitol derivatives and the corresponding 5a-carba-*DL*-sulfonyl sugar has been investigated from the theoretical and experimental standpoint <2000MI783>. A new synthesis of α,β -cyclopentenones has been described using a base-mediated rearrangement of *C*-4-ulopyranosyl compounds; depending on the basic conditions, variable mixtures of the double-bond migration derivatives have been obtained (Equation (8)) <2001CAR(334)223>.



(iii) Metal-catalyzed migrations of hydrogen

The well-known double-bond migration of allyl ethers and allyl acetals to vinyl ethers (prop-1-enyl ethers) or vinyl acetals, respectively, has found many applications in organic chemistry <1993HOU(E15a)1>. For instance, the allyl and the but-3-en-2-yl moieties have been used traditionally as protective groups in carbohydrates, which are easily removed via isomerization and hydrolysis of the respective vinyl ether <1996CC141>. This reactivity has been used with advantage in tandem processes coupled to Claisen rearrangements for the synthesis of γ,δ -unsaturated carbonyl compounds from allyl homoallyl ethers using iridium catalysts <2000OL4193>, or from diallyl ethers with nickel catalysts <1998S305>.

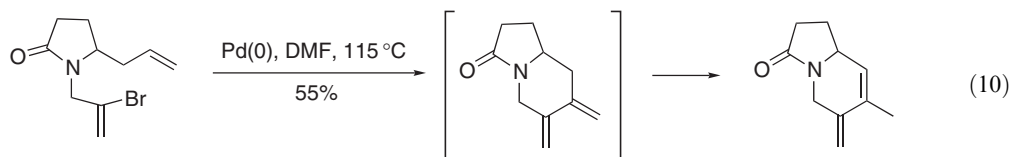
A polymer-supported iridium catalyst has been found to efficiently catalyze the double migration in a number of allyl to vinyl ethers, and in the isomerization of *C*-substituted allyl aromatic derivatives to the corresponding *C*-vinyl compounds <2002SL516>. Ruthenium-mediated metathesis reactions leading to cyclic allyl ethers have been very often accompanied by double-bond isomerization products to give cyclic enol ethers as undesired by-products <1997TL8635, 1999OL1123, 2000JOC2204, 2002TL1839>. Some authors have reported that the *in situ* generated ruthenium hydride species accelerates the isomerization process, after the metathesis reaction (Equation (9)) <2002JA13390, 2003EJO816>.



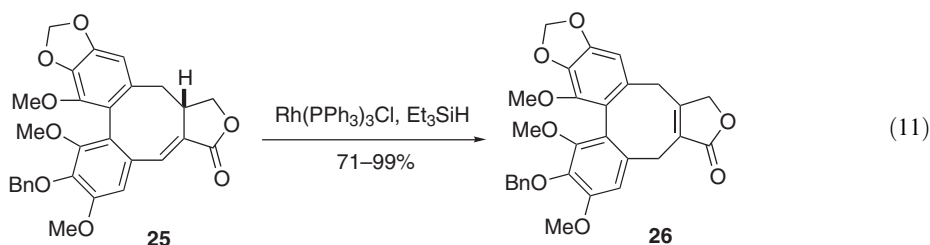
The deconjugation of thermodynamically more stable α,β -unsaturated esters is possible using Ru complexes <2000JOC3966>. (*E*)-3-Dialkoxyphosphorylbut-2-enoates are conveniently transformed into the deconjugated 3-dialkoxyphosphorylbut-3-enoates by palladium(II) assisted photochemical double-bond migration <1999S1056>. The synthesis of 2-bicyclo[3.2.1]oct-2-en-8-ones by carbonylation of cycloheptadiene-derived iron carbonyl complexes bearing alkyl-allyl subunits proceeds by double-bond migration <1995S587>.

The oxidation of 5-unsaturated 3 β -hydroxy steroids to the corresponding 4-en-3-one derivatives can be performed under Oppenauer oxidation conditions by using (PPh₃)₃RuCl₂ and potassium carbonate; the reaction proceeds by ruthenium-catalyzed dehydrogenation and subsequent hydrogen transfer to the acetone used as solvent, with simultaneous double-bond migration <1996JOC6587>. Double-bond migrations have been detected in the hydrogenation of arylalkenes by using iridium metal complexes <2001CEJ5391>. Double-bond migration of allylamines in the presence of transition metal complexes provides an efficient approach to the preparation of aldimines of the aliphatic alkyl group <1999OL2161>. S-Allylic systems rearrange to the sulfur-containing vinyl groups under [RuClH(CO)(PPh₃)₃] catalysis <2003JOM(665)167>.

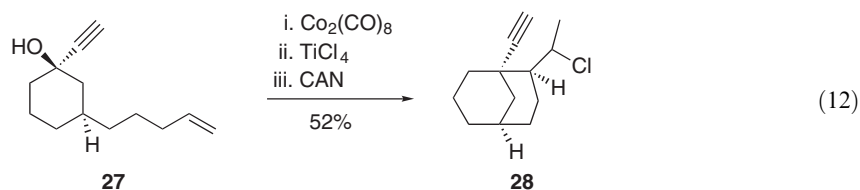
In the course of Heck reaction, a number of double-bond isomerizations have been described in the resulting products <1996JOC7147>. For example, in the Pd(BINAP)-catalyzed Heck reaction of 2,3-dihydrofuran with 1-cyclohexenyl triflate substantial amounts of 2,3-dihydrofuran derivatives have been found by C—C double-bond migration, a process that can be minimized by using chiral phosphinooxazoline/palladium complexes <1997SI338, 1999JOM(576)16>. The Heck reaction of aryl iodides and trimethyl silane has been investigated, and conditions have been found to prevent the desilylation and double-bond migration <2000TL8445>. The intramolecular Heck reaction of *N*-allyl (aryl or benzyl)-5-allyl-pyrrolidones or *N*-allyl (aryl or benzyl)-6-allyl-piperidones catalyzed by Pd(II) salts gave the corresponding indolizidinones, quinolizidinones, and benzoazepinones in moderate yields (56–90%), and exclusive 6-*exo-trig* mode of cyclization accompanied by double bond migration (Equation (10)) <2002S87>.



Ruthenium complexes allow the easy and synthetically useful rearrangement of *N*-allyl ethanamides to (*E*)-*N*-aryl-*N*-(1-propenyl)ethanamides <2001TL7095>. An allyl, branched-chain sugar has been isomerized in high yield to the corresponding vinyl analog by treatment with rhodium trichloride in basic medium <2003JOC2123>. During the reductive decomplexation reaction of acetylene–cobalt complexes with triethyl silane to produce the corresponding vinyl silanes, partial olefin isomerization in a terminal isolated double bond contained in the substrate was observed <2002T6485, 1998TL2609>. In the total synthesis of the lignan schizandrin <1995T11703> and the major metabolites of gomisins A <1996H(42)359>, the key step is the rhodium complex triethyl silane catalyzed reaction of α,β -unsaturated lactones **25** to butenolides **26** (Equation (11)).

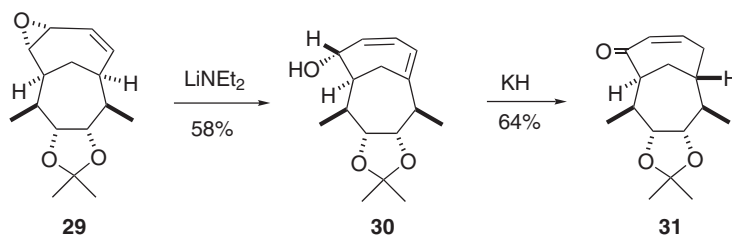


The pyridinium chlorochromate (PCC) oxidation of homoallylic alcohols gives α,β -unsaturated aldehydes by carbon–carbon double bond migration <2003TL1275>. The electrochemical, nickel-catalyzed addition of carbon dioxide to (perfluoroalkyl)alkenes affords γ -fluoro- γ -(perfluoroalkyl)- β -alkenyl carboxylic acids in a process that involves a double-bond migration with loss of a fluorine atom <1998TL4831>. Alkylidene malonates have been described to lead to double-bond migration products under electrochemical conditions <1998T14529>. Isomerization of homoallylic amines promoted by catalytic iron carbene complexes <2001OM5419>, or of *N*-allylic substrates in the presence of osmium clusters have been described <2002JOM(658)147>. Intramolecular Nicholas reaction of compound **27** followed by reaction with titanium tetrachloride gives the bicyclic derivative **28** through a mechanism that involves double-bond migration (Equation (12)) <2001SL1929>.



(iv) Anion-accelerated migrations of hydrogen atoms

Rigby has reported the first example describing the stereochemical course of alkoxide-accelerated suprafacial [1,5]-hydrogen sigmatropic rearrangement [<1996JOC7992>](#). In a project directed to the synthesis of ingenane diterpenes, allylic epoxide **29** was opened with lithium diethylamide to give a dienol **30** that on treatment with potassium hydride in the presence of 18-crown-6 ether afforded the α,β -unsaturated ketone **31**, in a sigmatropic process where the proton β to the carbon bearing the hydroxy group was transferred with complete retention of stereochemistry to the opposite bridgehead position [<1998TL2265>](#) (Scheme 7).



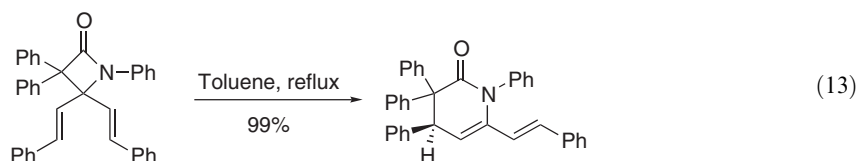
Scheme 7

1.18.2.2 Where Y = C

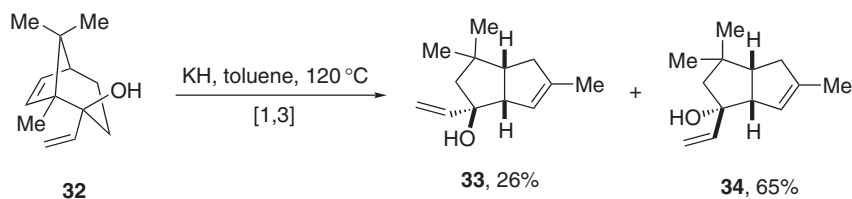
1.18.2.2.1 [1,j]-Rearrangements involving C—C bond migration

(i) Sigmatropic migrations of C—C bonds

Sigmatropic rearrangements involving C—C bond migration are well known. These migrations occur with retention or inversion of configuration at the migrating carbon atom depending on whether it is a thermal suprafacial [1,5]- or a thermal suprafacial [1,3]-rearrangement, respectively [<1995COFGT\(1\)793>](#). The thermal [1,3]-sigmatropic shift of methyl across an allylic structure has been studied by *ab initio* methods [<2002JPC\(A\)5709>](#). A [1,3]-sigmatropic shift has been invoked to explain the norbornene to norcarene rearrangement [<2000PJC1645>](#) in the thermal rearrangement of compounds with the 7-methylbicyclo[3.2.0]hept-2-ene skeleton [<2000JOC5396>](#) and in the amine-promoted transformation of 8-bromo-3,9-dimethylxanthine [<1998JHC949>](#). Photochemical [1,3]-sigmatropic shifts of carbon—carbon bonds have been described in the rearrangement of longipinene derivatives [<1996TL8093>](#) or in the migration of allylic carbons in the cembrane-pseudopterane cycloisomerization and in some transformations of the antifungal macrolactam ascomycin [<1999IJC\(B\)1159, 1998JOC420>](#). The [1,3]-sigmatropic rearrangement of carbon—carbon bonds in an azetidinone nucleus is an interesting example that shows the synthetic potential of this type of rearrangement for the preparation of more advanced molecules in a highly stereocontrolled manner (Equation (13)) [<2002TL2627>](#).



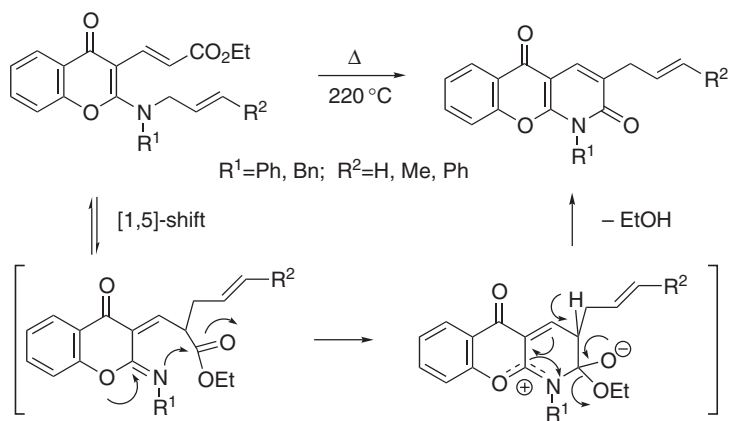
Anion-accelerated examples of thermal [1,3]-rearrangements have been investigated <1996CC2369, 1996MI3, 1997T13971>. In a series of studies directed to the synthesis of fused-ring skeletons through anionic [1,3]-rearrangements of bridged bicyclic compounds, the conversion of alcohol **32** into diquinanes **33** and **34** has been described (Scheme 8) <1996CL389, 1996CL1035>.



Scheme 8

The necessary structural requirements and parameters for the photochemical promoted [1,3]-migration of a hydroxyimino or an acetoxyimino group in a β,γ -unsaturated oxime or oxime acetate have been reported. The molecules undergoing the rearrangement should have a quaternary carbon separating the two π -systems and one of the radical centers in the cyclobutyl 1,4-biradical should be stabilized by conjugation with a phenyl ring <1996JCS(P1)107>.

The reaction of thallium 5-methyl-1,2,3,4-tetrakis(methoxycarbonyl)-cyclopentadienide with *p*-nitrobenzyl bromide gave a mixture of isomeric *p*-nitrobenzylcyclopentadienes featuring a [1,5]-sigmatropic shift of a *p*-nitrobenzyl group <2002MI1449>. Heating xylene solutions of 2-(*N*-allylanilino) or 2-[allyl(benzyl)amino]-substituted ((*E*)-oxochromenyl)propenoates at 220 °C leads to a [1,5]-shift of the allylic moiety, which is followed by intramolecular cyclization involving the nitrogen atom and the ester function to give the 3-allyl substituted-1-phenyl or 1-benzyl-2*H*-[1]benzopyrano[2,3-*b*]pyridine-2,5(1*H*)diones (more examples have also been described with crotyl cinnamyl residues) (Scheme 9) <2003HCA169>. A consecutive [1,5]-sigmatropic rearrangement of the phenyl ring is proposed for the transformation of 2-substituted benzo[*b*]thiophenium triflates to give 3-phenyl-benzo[*b*]thiophenes <2002TL2239>. It is known that the [1,5]-alkyl migration in a 4*a*-alkyl-4*a*-hydrocarbazol-4-one yields a 3-alkylcarbazol-4-one with a rearomatized indole nucleus <1999OL161>.



Scheme 9

Further examples of thermal [1,5]-sigmatropic rearrangements on 3,3-spiroalkylated pyrazole ring systems featuring the so-called Alphen–Huettel rearrangement have been reported <2001H(55)1859>. A nitrogen ylide complex is the key intermediate in the reaction of aminocarbenes with acetylenes to give pyrrolinones; a final [1,5]-migration of an alkyl group from nitrogen to carbon accounts for the final result <1998JOM(567)101>. [1,5]-Sigmatropic rearrangements of carbon–carbon bond have been detected in the thermolysis of a fluorinated indolyl-fulgide featuring a novel [1,5]-indolyl shift, <2001JOC4739> as well as in some pyrazole derivatives <1997CJC523>.

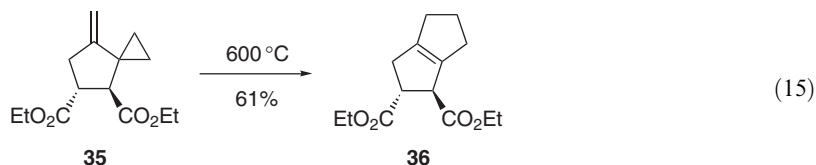
(ii) Rearrangement of vinylcyclopropanes

The rearrangement of vinylcyclopropanes to cyclopentenes is popular and has found diverse applications in the synthesis of natural products. This rearrangement can be considered as a formal [1,3]-shift of a carbon–carbon bond (Equation (14)). The subject has been covered in previous reviews <1985OR247, 1991COS(5)899, 1996RHA21, 1997HOU(E17c)2538, B-2000MI001>. The reaction can be conducted under thermal, photochemical, and metal-catalyzed conditions.



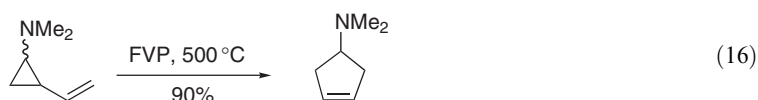
(a) *Thermal rearrangements of vinylcyclopropanes.* A recent review <2003CRV1197> gives a clear picture of the currently accepted ideas on the mechanisms <1996JA299, 1997JA10543, 1997JA10545, 1998MI222, 1999JA11018, 2000JOC6791>, reaction stereochemistry <1995JA10672, 1999JOC3567>, reaction kinetics <1997JPC(A)4097>, dynamics <1999JA4720>, computational studies, and substituent effects <2001EJO3559, 2003CRV1151>. To summarize, two models account for the experimental results; in one model, the vinylcyclopropane rearrangement involves a short-lived family of diradical intermediates; in the other, the vinylcyclopropane rearrangement may take place by either or both two-step diradical and orbital-symmetry-controlled pericyclic mechanisms.

A number of synthetic applications of the thermal rearrangement of vinylcyclopropanes have been published. 1-Methylene-2-vinylcyclopropane rearranges to 3-methylenecyclopentene via the cross-conjugated 4-methylene-2-(Z)-pentene-1,5-diyl diradical <1997JA5857>. Bicyclopropylidene undergoes a Pd(0) and Ni(0) [3 + 2]-co-cyclization reaction with alkenes to give 4-methylenespiro[2.4]heptane derivatives **35** that on thermal rearrangement afforded compound **36** in moderate yield (Equation (15)) <1998EJO113>.



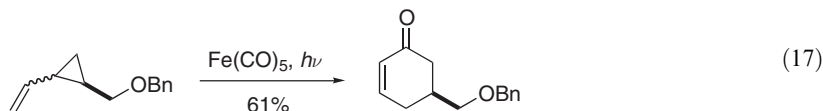
De Meijere has reported the rearrangement of cyclopropylketimines as the route for dihydropyrrole- and dihydrofuran-fused bicyclic diazepine-2,5-diones <2000OL4249>, and the high-yielding thermal isomerization of 1-cyclopropylidene-2-vinylcyclopropane to 4-methylenespiro[2.4]hept-5-ene <2001EJO3607>. The vinylcyclopropane–cyclopentene rearrangement has been successfully applied in a series of highly functionalized heteroaromatic substrates <1997CJC1256, 1997JCS(P1)835, 1998CPB151, 1999JOC6347, 2000MI209, 2001JOC3182>. The thermal rearrangement of α,β -unsaturated vinylcyclopropanes is possible and has been documented <2001SL433>. The thermal rearrangement can also be accelerated by suitable catalysts. In this context, diethylaluminum chloride or tin tetrachloride have been extensively and successfully investigated <1996TL3565, 1998JOC6586>.

Related *N*-cyclopropylketimines and vinyl phosphiranes rearrange thermally to 1-pyrrolines <1997JOC1532, 1999JA856, 1996JA1690, 2000JA3033, 2002JA13903>. Perfluorinated vinylcyclopropanes rearrange easily under thermal conditions <2002JFC(117)199>; a kinetic study is also available <1995JFC(70)249>. The rearrangement of donor–acceptor vinylcyclopropanes to functionalized cyclopentene derivatives has been discussed <1996LA2007> and a theoretical study concerning the substituent effects using density functional theory has been published <1999EJO215>. The thermal rearrangement of 2-ethenyl-substituted cyclopropylamines leading to 4-aminocyclopentenenes has been investigated by de Meijere (Equation (16)) <1998TL7695, 1998JCS(P1)3699, 2002SL1362>.

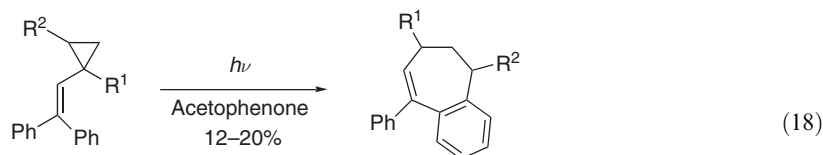


(b) *Photochemical rearrangement of vinylcyclopropanes.* The rearrangement of vinylcyclopropanes has been reported under photochemical conditions and has found useful synthetic

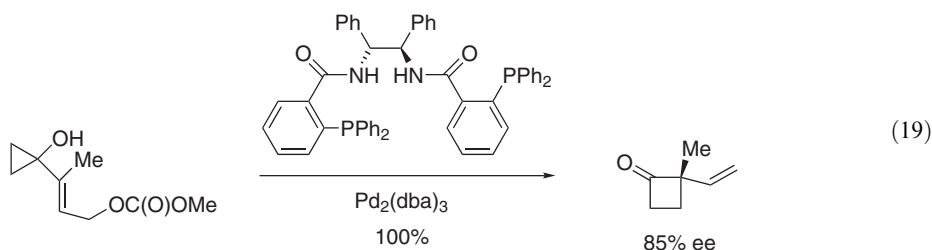
applications. The mechanism has been discussed by arguing that the rearrangement in these conditions is a case where spin-inversion and orbital-symmetry requirements produce the same product; the rearrangement is stereospecific and proceeds via a concerted process <1995T5871>. The photochemically initiated $\text{Fe}(\text{CO})_5$ carbonylation of alkenyl cyclopropanes is known <1996TL357, 1996JOM(525)155> and has been applied to the synthesis of enantiomerically pure cyclohexanones <2000JA6807> (Equation (17)).



Related *N*-cyclopropylketimines rearrange under photochemical conditions to 1-pyrrolines <2001OL4087>. Rearrangements of vinylcyclopropanes under photochemical conditions where a transition metal—Cr, Mo, W—has been incorporated into the basic template are known <1996SL806, 1996JA7873>. Armesto's group has been very active on this subject, and they have reported the photochemical rearrangement of 1-substituted-3-(2,2-diphenylvinyl)-2,2-dimethylcyclopropanes to cyclopentenones or heterocycles <1999JOC1056>, and a novel vinylcyclopropane rearrangement affording 6,7-dihydro-5*H*-benzocycloheptene was observed when electron-withdrawing groups are located at C-1 <2000OL183> (Equation (18)). Irradiation of a polyunsaturated cyclohexane derivative yielded a complex polycyclic structure implicating a vinylcyclopropane–cyclopentene rearrangement <2002EJO1708>.

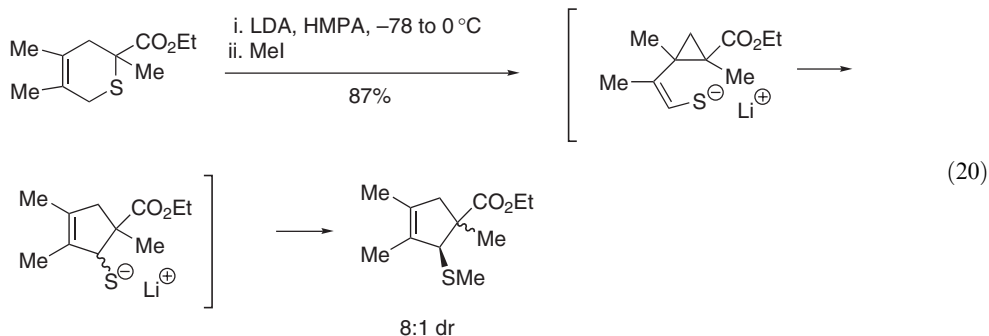


(c) *Acid or metal-catalyzed rearrangement of vinylcyclopropanes.* The reaction of a mixture of C_{60} with dimethyl acetylenedicarboxylate (DMAD) in the presence of tricyclohexylphosphine does not afford the expected product, but a new molecule whose structure was assigned and justified in terms of acid-catalyzed (silica gel or AcOH) ring-expansion of the vinylfullerene intermediate—not isolated—to give the corresponding fused-cyclopentafullerene derivative <2003JOC3811>. The metal-catalyzed rearrangement of vinylcyclopropanes has been used with success and advantage as the reaction takes place under mild conditions. Iwasawa has reported the $\text{Co}_2(\text{CO})_8$ -mediated rearrangement of 1-(1-alkynyl)cyclopropanols to 2-cyclopentenones <1998JA3903, 1999SL13, 2000TCC(207)69>. Ma and co-workers reported that the Pd(0)-catalyzed coupling-cyclization of 2-(2',3'-allenyl)malonates with organic iodides gives mixtures of vinylcyclopropanes and the rearranged cyclopentene derivatives <2002JOC2837>. The ring expansion of 1-alkenylcyclopropanols to give 2-alkenylcyclobutanones can also proceed by transition metal catalysis. The enantioselective transformation using a chiral palladium catalyst has been reported <2001JA7162> leading to substituted cyclobutanones with high ee (Equation (19)).

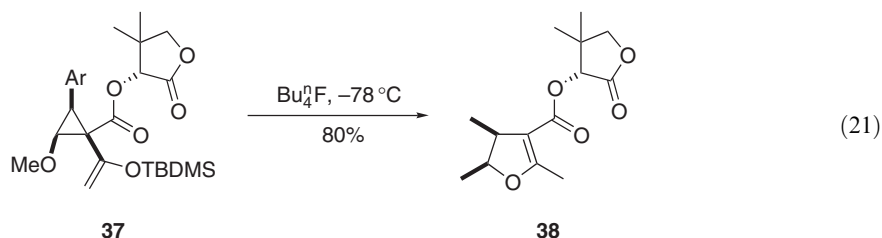


The intermolecular palladium-catalyzed annulation of vinylic cyclopropanes and cyclobutanes with aryl halides bearing functionality (hydroxyl, amino, tosylamino, etc.) in the *ortho*-position provides a novel and efficient process for the synthesis of a wide variety of five- and six-membered ring heterocycles and carbocycles <1996T2743>.

(d) *Charge-accelerated rearrangement of vinylcyclopropanes.* The thermal vinylcyclopropane rearrangement suffers from serious limitations, as the reaction only proceeds at high temperatures. However, it was found that charged substituents on the vinylcyclopropane accelerate the rearrangement <1991COS(5)999>. It has been postulated that the base-induced ring-contraction of 3,6-dihydro-2*H*-thiopyrans to give cyclopentenones proceeds via sulfur-charged vinylcyclopropanes <1996JOC4725> (Equation (20)).



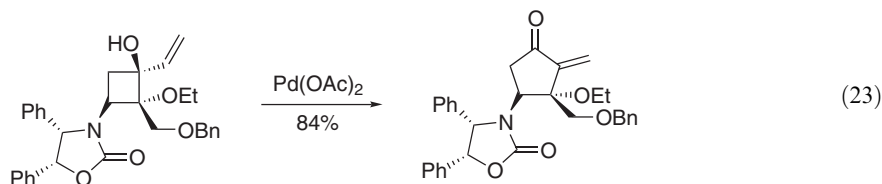
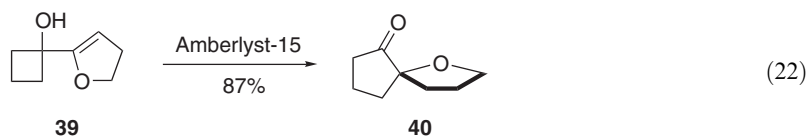
Simple 2-(2-trimethylsilyl)ethenyl)cyclopropyl acetates on treatment with methyllithium at low temperatures cleanly rearrange to polyfunctionalized cyclopentenones via the corresponding cyclopropanolates <1997TL3257, 2002JOC1786>. An anion-accelerated vinylcyclopropane–cyclopentene rearrangement has been demonstrated by the treatment of **37** with tetrabutylammonium fluoride at -78°C , as **38** was isolated in good yield <1998JOC2641> (Equation (21)).



The rearrangement of vinylcyclopropanes to cyclopentenones has been shown to be greatly accelerated by triarylammonium ($(p\text{-ClC}_6\text{H}_4)_3\text{N}^+\cdot\text{SbF}_6^-$) catalysis, and a stepwise, cation radical mechanism seems to be the origin of the rate enhancement <1995TL7415>.

(iii) Rearrangement of vinylcyclobutanes

The rearrangement of vinylcyclobutanes <B-2000MI001, 2001JA6718, 2002ACR279> to cycloalkanes is a similar and useful functional group transformation with interesting and practical synthetic features <1986TCC(133)83>. A recent account on the application of cyclobutane derivatives in organic synthesis <2003CRV1485> gives an updated summary for most of the recent contributions in this area. Regarding the expansion to five-membered ring systems, acid treatment of vinylcyclobutanol **39** afforded the expanded ring system **40** <1997JOC1713, 2001JOC2828> (Equation (22)). Different examples of vinylcyclobutanols and vinylcyclobutanones giving expanded products and using different promoters (Lewis acids, palladium complexes) have been reported <1996JA12541, 1997JOC7850, 1999JA10842, 2000JOC504, 2001JOC1455>. Hegedus reported the ring expansion of α -alkoxy-1-vinylcyclobutanols shown in Equation (23) <2000S953>. Uemura has described the oxidative transformation of vinyl *t*-cyclobutanols by palladium catalysis under oxygen atmosphere <2001JOC1455>. The ring expansion of 1-alkenylcyclobutanols to give 2-alkenylcyclopentanones using a chiral palladium catalyst has been reported <2001JA7162>; facial selectivity for alkene complexation in some examples is greater than 89% (Equation (24)).



Medium-sized ring systems have been obtained using the vinylcyclobutane rearrangement. Cyclobutanol **41** gave the bifunctional benzocyclooctadienone **42** in 47% yield upon treatment with HgO/I₂ under irradiation conditions (Scheme 10) <1995JCS(P1)49>. Oxidation of vinylcyclobutanediols **43** afforded the dihydrooxacenes **44** in good yield (Scheme 10) <1997JOC6456, 2000OS141, 2002OL3891>.

Using the vinylcyclobutane rearrangement in the synthetic sequence, a number of natural products, as gloiosipnone <1997T8913>, laurene <1997SL863>, and precapnelladiene <1998JOC6905> have been prepared.

1.18.2.3 Where Y = C—C

Baldwin has reported an anionic [2,3]-rearrangement of an all-carbon system <1970CC165>, but in the period covered by this review no other major advances have been published.

1.18.2.4 Where Y = C—C—C

1.18.2.4.1 Cope rearrangement

Extensive and excellent full accounts have been published in the recent years covering the different aspects and modifications of [3,3]-sigmatropic rearrangements, such as the Cope and Claisen reactions <1995HOU(E21d)3301, 1996TA1847, 2001CUOC395, 2003S961>. A review is available reporting the evolution of the accepted mechanisms of the Cope sigmatropic rearrangement <1995ACR81>, and a number of papers have been published dealing with different aspects of the mechanisms <1999JCS(P2)2357, 1999JA169, 2000JA186, 2002JOC1419>.

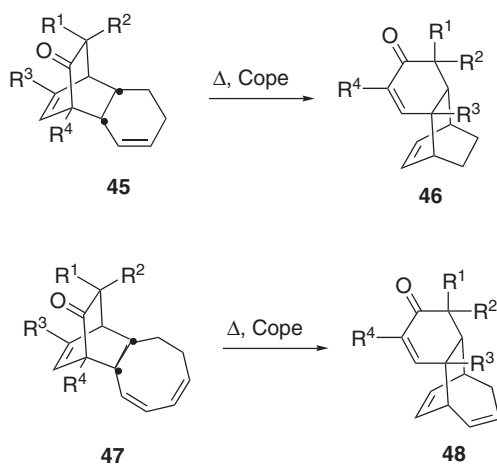
The Cope rearrangement is an important carbon—carbon bond forming reaction in modern organic synthesis <1975OR1, 1984CRV205, 1991COS(5)785>. Some new aspects of the Cope rearrangement have been reviewed <2000MI1033>, including the effect of pressure <2000JPR609>. The rearrangement of unsubstituted hexa-1,5-dienes is reversible to form preferentially highly substituted olefins in an equilibrium mixture (Equation (25)).



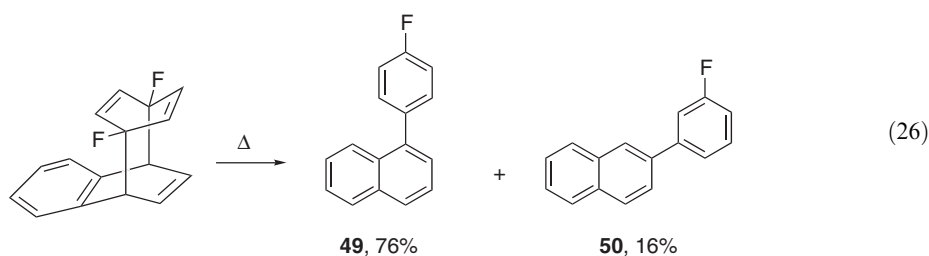
Since the pioneering work of Doering and co-workers, the Cope rearrangement of acyclic 1,5-dienes is generally considered to proceed via a highly ordered, six-membered, chair-like transition state <1962T67>. In spite of its potential for chirality transfer processes, Cope rearrangements have rarely been investigated in the context of acyclic stereoselection. In order to gain new insights in this aspect, the Cope rearrangement of *syn*- and *anti*-aldols installed in differently substituted acyclic 1,5-hexadienes has been investigated, showing that the reaction is more stereoselective for the *syn*- than for the *anti*-precursors <1996SL212, 1996TL4471, 1996TL8899, 1997T133>. In this process a series of highly flexible and versatile intermediates have been obtained for the synthesis of heterocyclic ring systems such as tetrahydrofurans <1997SL815> and piperidines <1998SL652>.

1.18.2.4.2 Thermal/photochemical Cope rearrangement

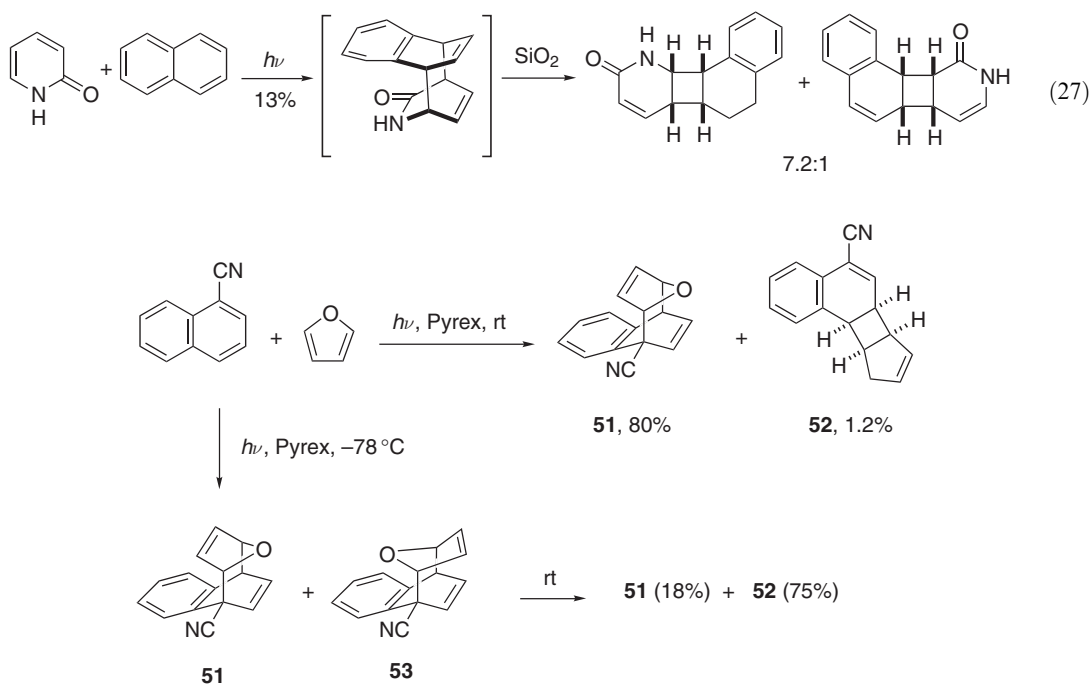
Cyclohexadienones **45** and **47** give compounds **46** and **48**, respectively, after thermal Cope rearrangements (yields not given) (Scheme 11) <1995T6015>. It has been published that a 1,4-difluorobenzene-naphthalene underwent a facile Cope rearrangement followed by dehydrofluorination to give 1-(4-fluorophenyl)naphthalene **49** and 2-(3-fluorophenyl)naphthalene **50** in 76% and 16% yield, respectively (Equation (26)) <1995BCJ3557>. The Cope rearrangement of 3-ylidene-piperazine-2,5-diones has been reported <2002ZN377>. Functionalized *cis*-decalins have been prepared by thermal Cope rearrangement of bicyclo[2.2.2]octenones <2001CC2578>.



Scheme 11

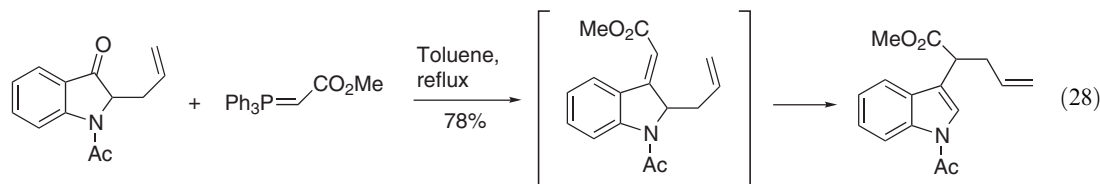


The photochemical reaction of 2-pyridone and naphthalene gives an unstable intermediate that slowly affords Cope rearrangement products on contact with silica gel (Equation (27)) <1999OL1775, 2000JOC1972, 2001SI1185>. The photochemical reaction of furan with 1-naphthalenecarbonitrile at room temperature afforded a mixture of [4,4]-adduct **51** and compound **52** that has proved to be the Cope rearrangement product of the other possible [4,4]-adduct **53** (Scheme 12) <1996TL9329, 1998JOC1212, 1998JCS(P1)2501>.



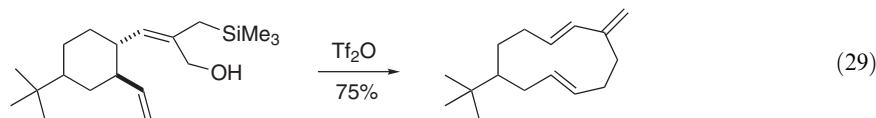
Scheme 12

The tandem Wittig reaction and reverse aromatic Cope rearrangement of 2-allyl-1,2-dihydroindol-3-ones gives good yields of 3-indole acetates after heating under reflux in toluene (Equation (28)) <1995CC381, 2001JOC1200>. A facile tandem Wolff–Cope rearrangement has been used for the synthesis of fused carbocyclic skeletons <2003JA13624>.



The allylation of a chiral dienolate combined with a Cope rearrangement has resulted in an excellent method for the preparation of γ -chiral α,β -unsaturated acid derivatives, that has found application in the synthesis of the C6 side chain of zaragozic acid A <1996TL8895>. 3-Phosphorylated 1,5-hexadienes rearrange to the expected unsaturated 5-vinyl phosphonates under strong thermal conditions <1997CJC1131>.

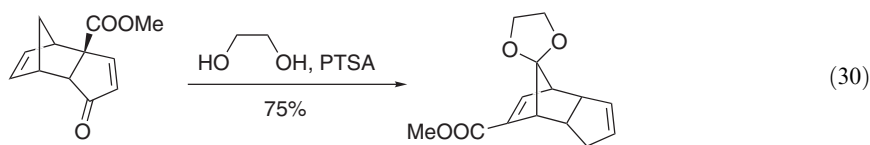
The homo-Cope rearrangement is a subtle variant of the usual Cope rearrangement where one of the terminal double bonds of the 1,5-hexadiene is disubstituted with a trimethylsilylmethyl at C-1 and with a hydroxymethyl group at the same carbon; on treatment with triflic anhydride not only the Cope rearrangement takes place, but ring closing occurs to form 11-membered carbocycles by a new five-carbon ring-expansion reaction (Equation (29)) <1995LA745, 2001TL1915, 2003T3157>.



Applications of the thermal Cope rearrangement to the synthesis of natural products have been reported several times, as in the hemi-synthesis of sesquiterpenes vernolepin and 8-*epi*-vernolepin from natural products salonitenolide and cnicin <1995TL311, 1998JCS(P1)4107, 2000TL7639>, and cnicin has also been the starting material in a recent synthesis of elemene and heliangolane derivatives <2003EJO2690>. Other applications of the Cope rearrangement can be found in the preparation of naphthofurans and phenanthrofurans related to morphine <1998CC65>, in the first synthesis of floerkein B and barbilycopodin <1997H(46)123>, in the synthesis of racemic diterpene obtunone <1999SC537>, in synthetic approaches to $\Delta^{3,8}$ -taxane tricyclobicycles <1999TL4235>, in the synthesis of the racemic tetracyclic core of the complex and in biological attractive molecule CP-225,917 <2002TL4559>. In addition to the standard spectroscopic analysis, the absolute structures of natural products vibsanin B and C have been established by chemical correlation between them through thermal Cope rearrangement <1997TL1435>.

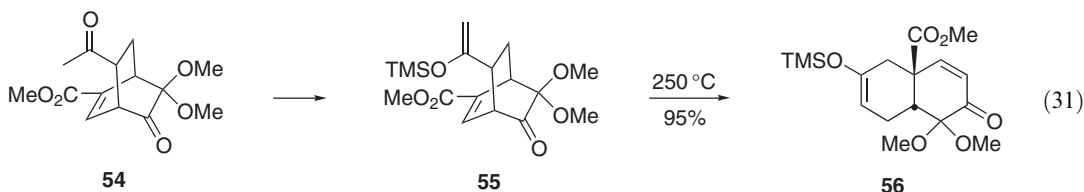
1.18.2.4.3 Catalysis of the Cope rearrangement

The Cope rearrangement is often accelerated by the presence of catalysts <1984CRV205>. Palladium(0)-catalyzes the Cope rearrangement of acyclic 1,5-dienes <1999JA10850>. The rate of Cope isomerization of germacranolides to elemanolides has been shown to be enhanced by catalytic amounts of bis(benzonitrile)palladium(II). This observation made possible an efficient approach from natural and commercially available costunolide to sesquiterpene lactones, stoebe-nolide and dehydromelitensin <1998TL1401>. In the palladium-catalyzed Heck reaction on *N*-methyl-*N*-(1,5-hexadiene-3-yl)-2-iodo-benzoic acid amide, some secondary products were detected probably arising via chelation assisted Pd-catalyzed Cope rearrangement <1997JMOC(116)99>. The Cope rearrangement can be accelerated by catalytic amounts of acids. This was the case of the example shown in (Equation (30)); reaction of 2-*exo*-carbomethoxy-tricyclo[5.2.1.0^{2,6}]deca-3,8-dien-5-one with ethylene glycol in the presence of PTSA gave 1-carbomethoxy *endo*-dicyclopenta-1,4-diene-8-one 8-ethylene acetal <1996TL7827>.

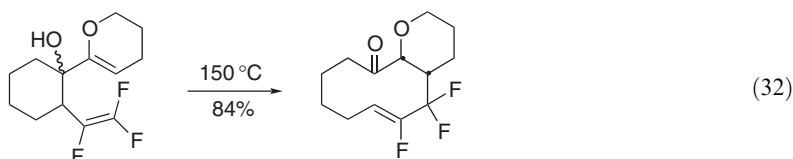


1.18.2.4.4 Oxy-Cope rearrangement

The oxy-Cope rearrangement [<1991COS\(5\)785>](#) has been reviewed [<1995CRV9>](#). A full and comprehensive analysis of the oxy-Cope rearrangement using density functional theory has been published [<2001HCA124>](#). The oxy-Cope rearrangement has become one of the methods of choice for the synthesis of carbon–carbon bonds in a simple and efficient manner [<1995T9767, 1997T13971, 1998TL9>](#). Diketone **54** was converted into the Cope rearrangement product **56** via silyl enol ether **55** after heating at 250 °C [<1998TL659, 1998CC155>](#) (Equation (31)).



The oxy-Cope rearrangement of fluorinated divinylcyclohexanols is a practical route for the synthesis of cyclodecenones (Equation (32)) [<1999CC2535>](#). The sigmatropic rearrangement in fluorinated molecules has been reviewed [<1992JFC\(56\)165, 1997TCC\(193\)131>](#).



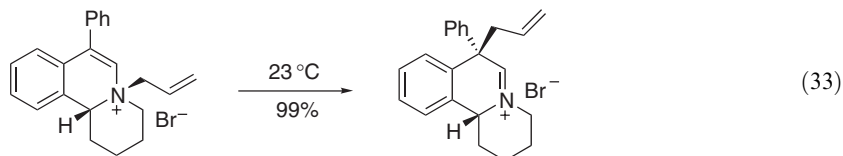
The synthetic applications of the siloxy (or silyloxy)-Cope rearrangement have been reviewed [<2001SL1079>](#). In a number of examples, the protection of the alcohol moiety accelerates or improves the chemical yield of the rearrangement process. Schneider's group has made some practical applications, such as the stereoselective synthesis of highly substituted piperidines [<1999EJO3353>](#), the asymmetric synthesis of protected 1,3,5-triols [<1999CEJ2850>](#), the preparation of highly substituted tetrahydropyrans [<2000EJO73>](#), the efficient synthesis of functionalized cyclohexanes [<2002CEJ2585>](#), or bicyclic medium-ring-containing compounds [<2003JA14901>](#).

The siloxy-Cope rearrangement has been used as a key step in the synthesis of (+)-lasiol [<1998EJO1661>](#) and in the synthesis of the core structure of Ras farnesyl transferase inhibitors CP-225,917 and CP-263,114 [<1999TL4605, 2000TL6259>](#). Leighton and Bio have also reported on the application of the siloxy-Cope rearrangement in synthetic sequences leading to these potential antitumor molecules [<1999JA890, 2000OL2905, 2003JOC1693>](#). The siloxy-Cope rearrangement of *syn*- and *anti*-aldols installed in differently substituted acyclic 1,5-hexadienes has been reported, showing that the reaction is more stereoselective for the *syn*- than for the *anti*-precursors [<1996SL212, 1996TL4471, 1996TL8899, 1997T133>](#).

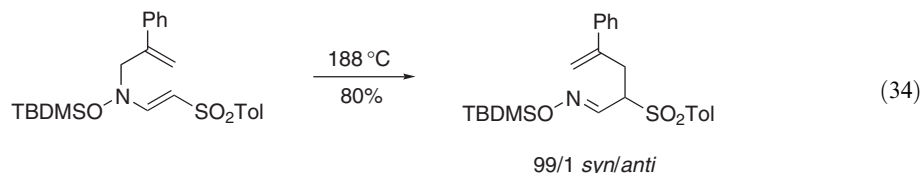
1.18.2.4.5 Aza-Cope rearrangement

The subject has been reviewed [<1987RCR477>](#) and updated recently [<1996JOC978>](#). The aza-Cope (also called the amino-Claisen rearrangement) reaction is the [3,3]-sigmatropic rearrangement of an *N*-allyl enamine. Whereas neutral allylic enamines rearrange to δ -ene imines at rather elevated temperatures, analogous protonated substrates, Lewis acid-coordinated or quaternarized

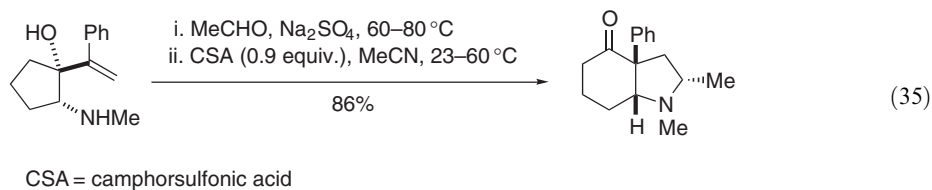
molecules rearrange in milder conditions <1997OM4248>. 3-Alkylideneindolin-2-ones have been prepared from propargylbenzotriazoles in two steps via reaction of an allene dianion followed by 3-aza-Cope rearrangement and [1,3]-hydrogen shift <1997BSB419>. The aza-Cope rearrangement has been applied to the synthesis of chain-extended amino sugar derivatives from *N*-glycosyl homoallylamines <1998TL791> and has also been the key step in the synthesis of 2,3-dihydro-1*H*-2-benzazepine-3-carboxylic acid derivatives, which are conformationally constrained peptide analogs <2001JOC2884>. The aza-Cope reaction has been used for the synthesis of 5,6,7-trisubstituted 4-aminopyrido[2,3-*d*]pyrimidines as novel inhibitors of adenosine kinase <2003JMC5249>. Reissig has applied a Cope-type rearrangement of vinylcyclopropylisocyanates to the preparation of highly substituted azepinones, this reaction being accelerated by a 2-silyloxy substituent <2000SL725>. An interesting example of a 3-aza-Cope rearrangement of a quaternary *N*-allyl enammonium salt featuring a stereospecific 1,3-allyl migration from nitrogen to carbon has been reported (Equation (33)) <2000JOC4938>.



An exotic extension of the aza-Cope rearrangement is the 1,3,4-triaza Cope rearrangement, a process that starts with the reaction of 1-alkyl-1-cyanohydrazone with methyl triflates giving 2-(methylamino)-1-alkyl imidazoles as their triflate salts <1997BSB553>. The pericyclic process involving 1,5-hexadienes usually proceeds under high temperatures and prolonged reaction times. The analogous aza-Cope rearrangement also proceeds under drastic conditions <1996TA1847>, but it has recently been found that the *N*-silyloxy iminoethers rearrange under milder conditions in good yields, featuring the first 3-oxy-assisted 3-aza-Cope rearrangement (Equation (34)) <2002CC746>.



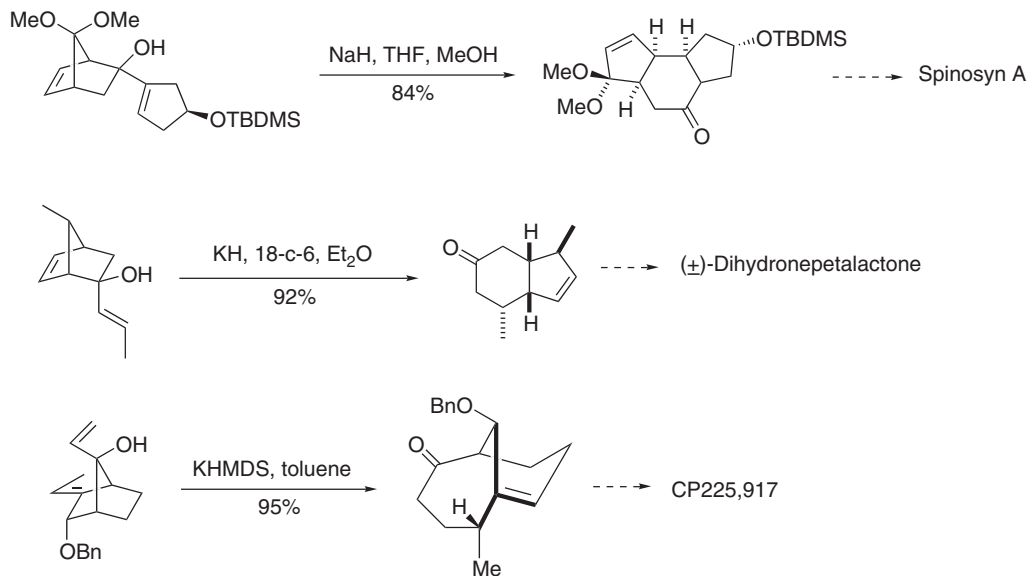
An interesting variant of the aza-Cope is the aza-Cope–Mannich, a powerful method for assembling nitrogen heterocycles based on the acid-promoted condensation of an acyclic homoallylic amine containing an allylic hydroxyl (or alkoxy) group with an aldehyde or ketone. When the amine and alcohol substituents are vicinally located on a ring, the aza-Cope–Mannich reaction affords a product in which pyrrolidine annulation is combined with one-carbon ring-expansion (Equation (35)) <1997IJ23>.



1.18.2.4.6 Anionic oxy-Cope rearrangements

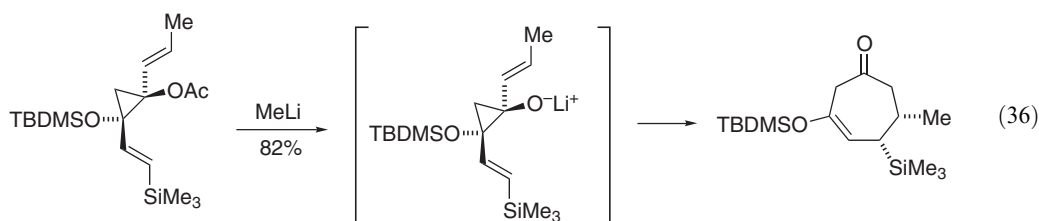
The anionic oxy-Cope rearrangement has been reviewed <1995CRV9, 1997T13971, 1998EJO1709>. The mechanistic aspects concerning the variations and rate effects of alkoxy and thioalkoxy substituents in the anionic oxy-Cope rearrangements have been investigated <1999JA11880, 2000JCS(P1)1423, 2000JA10788>. Paquette's group has made a number of contributions in this subject showing the power of this methodology for the assembly of complex polycyclic arrays from hydroxyl-substituted, 1,5-hexadienes; treatment of these substrates with bases (sodium or potassium hydride, potassium hexamethyldisilazide, or potassium carbonate) at

room temperature allowed these authors to reach these objectives in a simple and efficient manner (Scheme 13) <1997TL1271, 1998SC1509>. Paquette has extensively reported on the squarate ester-polyquinane connection using the oxy-anion Cope rearrangement as the key step <1995JOC889, 1995JOC897, 1995JOC7849, 1995JOC7857, 1997JA1230, 1997JA3038, 1997JOC627, 1997T8913>.

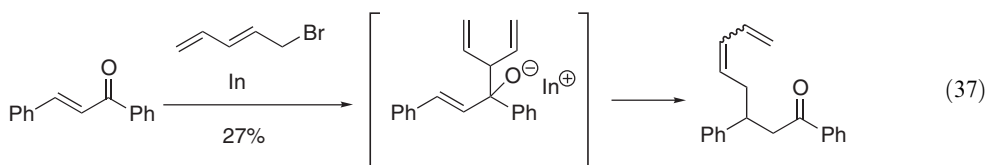


Scheme 13

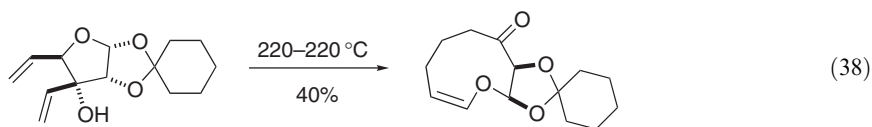
The anionic oxy-Cope rearrangement of 1,2-divinylcyclohexanol derivatives give the corresponding 2-methyl and 10-methyl-5-cyclodecenones <2001TL3815>. The anionic oxy-Cope rearrangement of divinyl cyclopropanes has been investigated and constitutes an excellent synthetic method for the preparation of medium-sized carbocycles (Equation (36)) <1998JA4947, 2000S1327>. The effect of trialkylsilyl groups attached to the alkene moieties has been investigated, and it has been observed that due to its bulkiness, this group modifies the stereochemical course of the oxy-Cope rearrangement <1997T14235>.



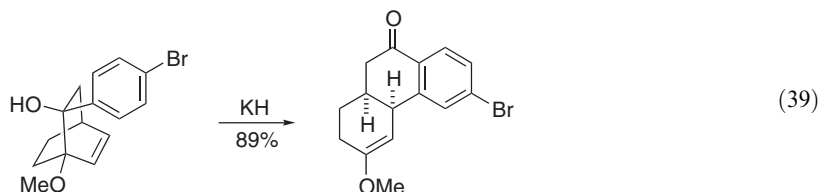
The addition of γ -pentadienyllindium(I) to unsaturated ketones afforded the conjugate addition product preferentially via tandem carbonyl addition In(I)oxy-Cope rearrangement pathway (Equation (37)) <2003S790, 2000POL533, 1999TL7867>. The Grignard addition to 2-arylidene-1-tetralone—Cr(CO)₃ complex gave a tertiary homoallyl alcohol that on treatment with potassium hydride underwent anionic oxy-Cope rearrangement to give the homoallylic α -alkylated 1-tetralone Cr(CO)₃ complex <1996JOC8362, 2001IJC(B)1063, 2002JCS(P1)669>. Trimethyl borate has been used to promote the thermal cycloaromatization of 1-aryl-1-(prop-2-ynyl)-3,3-bis(alkylthio)-2-propen-1-ols <1996TL2817>.



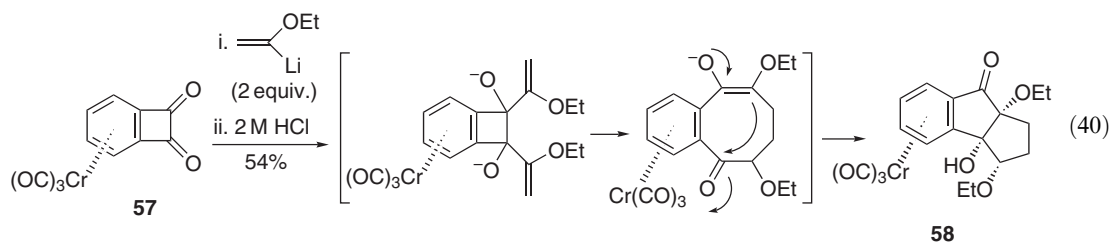
The anionic oxy-Cope rearrangement has been investigated in furanoside templates for the synthesis of nine-membered ethers with moderate success (Equation (38)) <1996CC1359>. The charge-accelerated oxy-Cope rearrangement <1990AG(E)609, 1993OR93, 2000JA740, 2000TL747> has been used with advantage in a number of synthetic approaches for useful group/structure transformations, as in model studies for the synthesis of antitumor compounds CP-263,114 <1998JA10784, 2001OL2431> and CP-225,917 <1999T12059>, inhibitors of Ras farnesyltransferase; in the synthesis of β -hydroxycyclohexanones <1998TL685, 2000TL737, 2001JCS(P1)1051>; in enantioselective routes to highly functionalized steroidal nuclei <1996TL6103, 1999SL1491>; the hydroazulenoid skeleton <1998TL4133>; enantiopure *cis*-decalins <1996AJC639, 1996CC869, 1996TL5897>; for the synthesis of the dicyclopenta[*a,d*]-cyclooctene core of ceroplastin sesterterpenes <1996JOC3268>; in studies directed to the synthesis of taxane diterpenes <1995T3455, 2000S921, 1998SL897, 2000EJO2187, 1998H(48)235>; for the synthesis of the sesterpenic acids bilosespens A and B <2003OL4741> or the limonoid triterpene dumsin <2003JOC6905>; for the synthesis of (\pm)-dihydronepetalactone (Scheme 13) <1998JCS(P1)2645>; the carbobicyclic substructure of CP-225,917 and CP-263,114 (phomoidrides A and B) (Scheme 13) <1997CC2157, 2001JCS(P1)2194>; the alkaloid norsuaveoline <1998TL8009>; in the preparation of (\pm)-palominol or (\pm)-dolabellatrienone <1998TL741>, (–)-salsolene oxide <1997JA2767, 1997JOC8155> and (+)-taxusin <1998JA5203, 1998JOC9968>; in the synthesis of paclitaxel <1998JOC6432>; ajmaline/sarpagine-related alkaloids such as (+)-ajmaline, norsuaveoline, talpinine, talarpine, and epiaffinisine <1998JOC9160, 1999JA6998, 2000JOC3173, 2001OL345, 2003JOC5852>; in the synthesis of an advanced intermediate for the obtention of fungal metabolite penitrem D <1995JOC7837>, spinosyn A (Scheme 13) <1998JA2543>, the antifungal antibiotic aleurodiscal <1998S495>; in studies directed to vinigrol <1996SL625, 1997JOC5062, 2003OL1139, 2003OL3631, 2003JOC6096>; in highly stereoselective approaches to *cis*-clerodanes <1998SL912>; in the total synthesis of (\pm)-precapnelladiene <1998JOC6905>; in the synthesis of bioactive mesotricyclic diterpenoids jatrophatriene <1999JOC3244> and citlaltirone <2003JA1567>; in the total synthesis of (–)-*o*-methylshikoccin and (+)-*o*-(methylepoxy)shikoccin <1996JA11990, 1997JA9662>; in the synthesis of a tetracyclic lactone structurally related to the kaurane diterpenoids <1996SL129>; in the total synthesis of racemic tetracyclic diterpenoid scopadulin <2001JOC4831>, the sesquiterpene (–)-patchoulone <2003NJC50>, in the synthesis of *Cyathin* diterpene skeleton <1999T3553>, the insect antifeedant (–)-homogynolide A <1995S845>, natural sesquiterpene lactones as vulgarylides <1995TL673, 1996JA5620> and deoxocrispolide <1996JA5620>.



The aromatic oxy-Cope rearrangement has been applied to the synthesis of aromatic compounds such as helicenes (Equation (39)) <2002TL7827, 2003TL2167>.



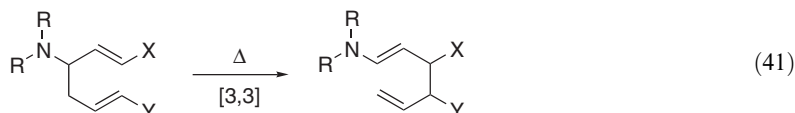
An interesting case of a dianionic oxy-Cope rearrangement <1996CEJ182, 1999SL680, 2001EJO2519, 2001EJO93, 2002PAC57, 2002EJO1972> followed by intramolecular aldol reaction has been observed after the nucleophilic attack of 1-ethoxy-1-lithioethene to the α -diketone **57** to give compound **58** (Equation (40)) <1998EJO2719>.



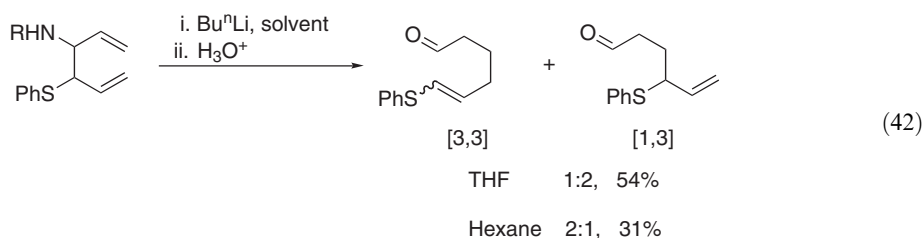
Finally, the oxy-Cope rearrangement of substrates incorporating a C-alkynyl or C-allenyl onto the tertiary alcohol moiety is also known [<1996SC2119, 1996T7737>](#), and the effect of halogen substitution on the alkynyl group has been investigated [<1997T12637>](#).

1.18.2.4.7 Anionic amino-Cope rearrangements

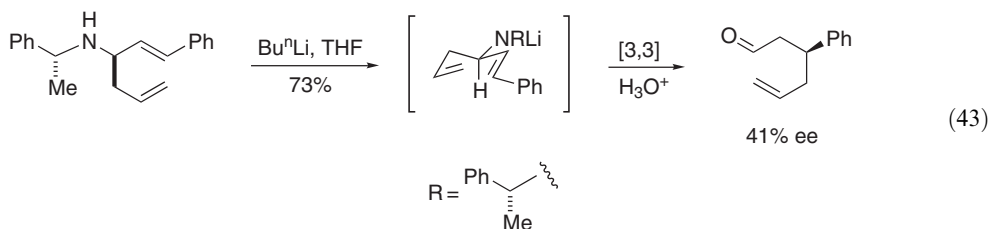
The anionic amino-Cope reaction has been the subject of some interest in recent years. Some *ab initio* theoretical calculations have been performed [<1998JA205>](#), and recent results show that a concerted mechanism is operating [<1998TL3345, 1998SL1117>](#), although evidence has been presented for an alternative stepwise mechanism [<1999TL3801>](#). Thermally induced [3,3]-sigmatropic amino-Cope rearrangement of 3-amino-1,5-dienes occurs to furnish enamine products in high yield and with excellent (*E*)/(*Z*)-enamine selectivity; these resulting final products are useful building blocks for further synthetic development (Equation (41)) [<1997SL725>](#).



In the anionic amino-Cope rearrangement of 3-amino-1,5-hexadienes, depending on the solvent/additives used, in addition to the [3,3]-rearranged products, it has claimed the formation of [1,3]-compounds, showing the complexity of this useful functional group transformation (Equation (42)) [<1999TL3119>](#).

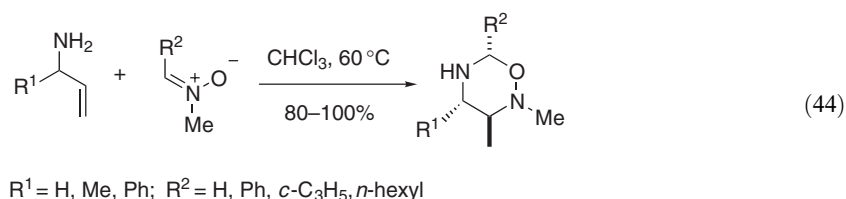


In 1998, the first example of asymmetric induction in an anionic amino-Cope rearrangement using enantiomerically pure amines as chiral inductors was reported (Equation (43)) [<1998TL3345>](#); this methodology was applied later for the enantioselective synthesis of tetrahydropyrans [<2002TL4195>](#).



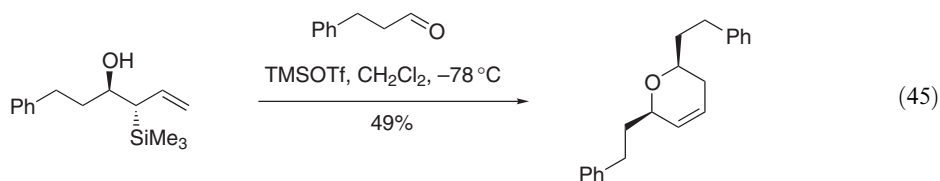
Nitrogen-charged intermediates have been invoked in the mechanism for the reverse-Cope elimination-Meisenheimer reaction [<1995JOC5795, 1995JOC5803>](#) of allyl amines or thiols

with nitrones for the synthesis of oxadiazinanes or thiazolidine-*N*-oxides (Equation (44)) <1997TL8545, 1997TL8549>.

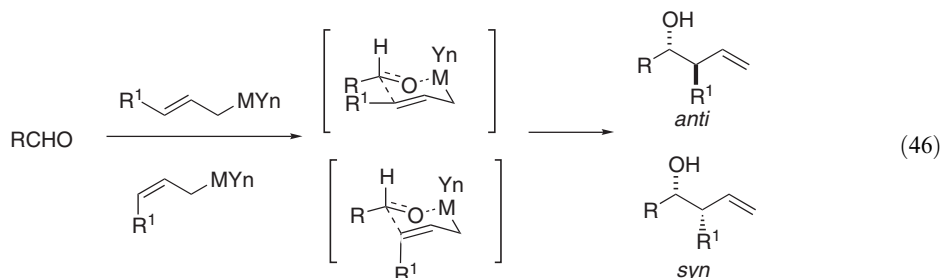


1.18.2.4.8 2-Oxonia-Cope rearrangement

The 2-oxonia-Cope rearrangement has been invoked as a competitive pathway in Prins cyclizations and related transformations <2000TL9431, 2001CC835, 2001JOC4679, 2001OL3815, 2002OL577>. The rearrangement has been used in the synthesis of *cis*- and *trans*-2,6-disubstituted tetrahydropyrans (Equation (45)) <1997JOC3426, 2000JA9836, 2001SL955>.



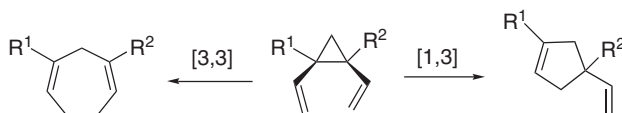
The 2-oxonia [3,3]-sigmatropic rearrangement is a new concept that has been introduced recently as a mechanistic rationale for a simple functional group transformation such as the allylation of aldehydes for the synthesis of homoallylic alcohols (Equation (46)) <1998JA6609, 2000JA1310, 2000CEJ2909, 2001JA9168, 2003AG(E)1273>, or for the synthesis of tetrahydrofurans from homoallylic alcohols <2001AG(E)2921, 2001JA2450>.



The 2-oxonia-Cope rearrangement has been applied in the total synthesis of the natural *cis*-2,6-disubstituted tetrahydropyran (–)-centrolobine <2002OL3919>, and in the stereocontrolled synthesis of linear 22*R*-homoallylic sterols via triflic acid promoted rearrangement <2002OL2389>.

1.18.2.4.9 Cope rearrangement of divinyl cycloalkanes

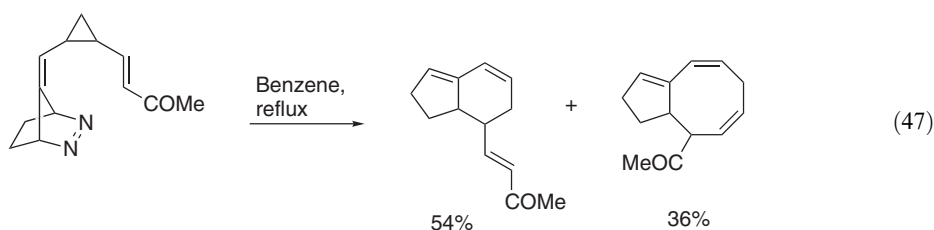
Divinyl cyclopropane derivatives may undergo rearrangements <1991COS(5)971> following two different routes. One way is the [3,3]-sigmatropic-Cope rearrangement leading to 1,4-cycloheptadienes <1997HOU(E17c)2589>, and the other is a [1,3]-sigmatropic rearrangement giving vinyl-substituted cyclopentenenes (Scheme 14) <1997HOU(E17c)2538>. A DFT study on these



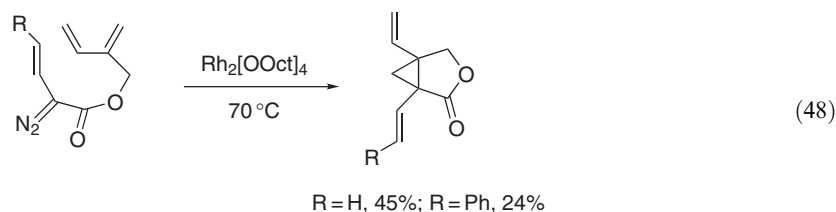
Scheme 14

competitive reactions <1999EJO1107> and an *ab initio* study on the transition structures and energetics <2003JST(625)251> have been published. The mechanism of the rearrangement of 7-vinylnorcaradienes has been investigated <1996TL7761>.

Piers has described an efficient synthesis of 1,2-bisalkenylcyclopropanes by Pd(0)-catalyzed cross-coupling of the cyclopropylzinc chlorides and alkenyl iodides; the compounds prepared in such a way thermally rearrange to the corresponding cycloheptadiene derivatives <2001S251>. Chiral ethyl cyclohepta-2,5-diene carboxylates have been synthesized from suitable divinylcyclopropane derivatives via Cope rearrangement; these compounds are intermediates in the asymmetric synthesis of natural products such as lamoxirene, isolated from a marine brown algae <2000JOC2458>. Takeda and co-workers have reported a new [3+4]-annulation strategy in the reaction of [β -(trimethylsilyl)acryloyl]silanes with lithium enolates of α,β -unsaturated methyl ketones for the synthesis of diversely functionalized cycloheptanes <1995JA6400, 1998JA4947> and they have proposed a mechanism via Cope rearrangement of the presumed divinylcyclopropane intermediates. 1,2-*cis*-Divinylcyclopropyl derivatives, obtained by reaction on propenoyl-chromium carbenes and conveniently functionalized 1,3-dienes, undergo Cope rearrangement to give the expected cycloheptadiene <2002OL2719>. Very interesting differences have been observed in the thermal rearrangement of C7-substituted divinylcyclopropyl[2.2.1]diazenes; substrates with only one electron-withdrawing substituent (ketone or carboxylic ester) afford Cope rearrangement products (Equation (47)) <1998TL1893, 2003TL2109>. 1-Silyloxy-2,3-divinylcyclopropanes undergo thermal Cope rearrangement to give the corresponding cycloheptane unsaturated silyl enol ethers in good yield; these compounds are good intermediates for further elaboration <1995JA9919>.

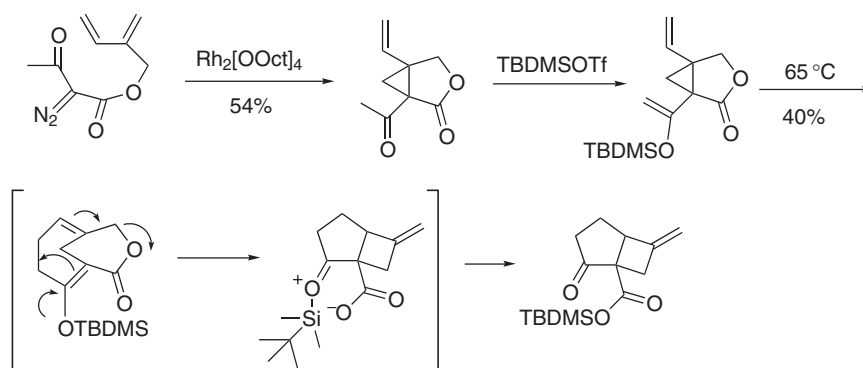


The intermolecular reaction of diazo compounds with conveniently substituted furan <1996JA10774, 1996JOC2305, 2000JOC4261, 2001T7337>, 2-pyridone <2002JOC5683> or pyrrole heterocyclic ring systems <1997JOC1095>, the intermolecular reaction of diazo compounds with dienes <1998JOC657, 1998JA3326, 1999JOC8501> or rhodium octanoate [$\text{Rh}_2(\text{OOOct})_4$]-mediated intramolecular reaction of diene, diazo compounds <1996TL3967, 1997TL1737> result in the formation of divinylcyclopropane intermediates (Equation (48)) that undergo *in situ* Cope rearrangement, affording highly functionalized 8-oxabicyclo[3.2.1]octane derivatives or polycyclic arrays of complex molecules (Scheme 15). Following these strategies, the synthesis of sesquiterpenes tremulenolide A and tremulenediol A has been achieved <1998JOC657>.

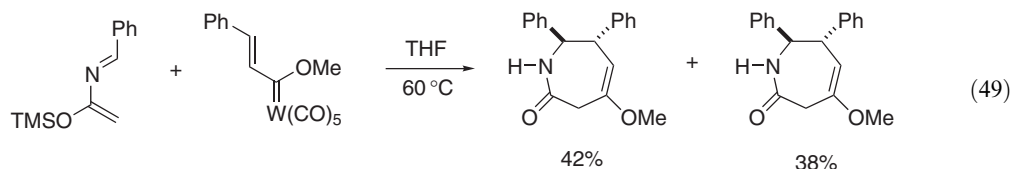


R = H, 45%; R = Ph, 24%

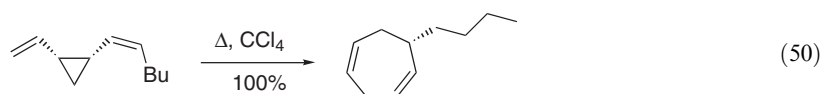
The reactions of 2-aza-1,3-butadienes with alkenyl Fischer complexes yield seven-membered unsaturated lactams in moderate yield with no stereoselectivity, possibly via a novel vinyl-imino cyclopropyl [3,3]-sigmatropic rearrangement (Equation (49)) <1997JOC9229>. The cyclization of triene-conjugated nitrile ylides gives complex heterocyclic architectures such as 1,4-prop[2]-enoisoquinolines via sigmatropic rearrangement of the presumed analogous vinyl-imino cyclopropyl intermediates <1999JCS(P1)443>. In an approach to the synthesis of α,α' -cyclopropyl aminonitriles, Salaün and co-workers have reported the formation of a series of azepines arising via aza-Cope expansion of 1,2-*cis*-vinyl-imino cyclopropyl intermediates <1999JOC4712>.



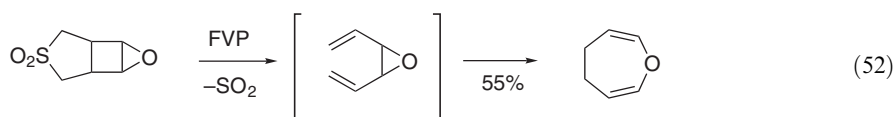
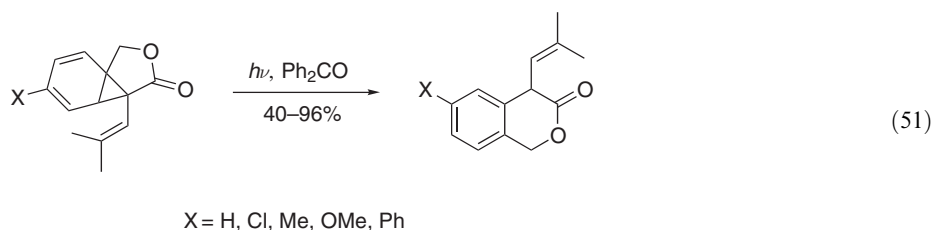
Scheme 15

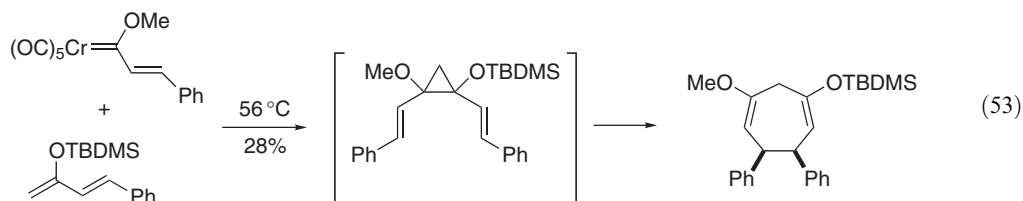


The asymmetric synthesis of (+)-dictyopterene C' has been accomplished via Cope rearrangement of an appropriately substituted divinylcyclopropane intermediate (Equation (50)) <1998HCA1754>; the analogous aza-Cope rearrangement has also been described <1999HCA315, 2000HCA1525, 2002TA551>.

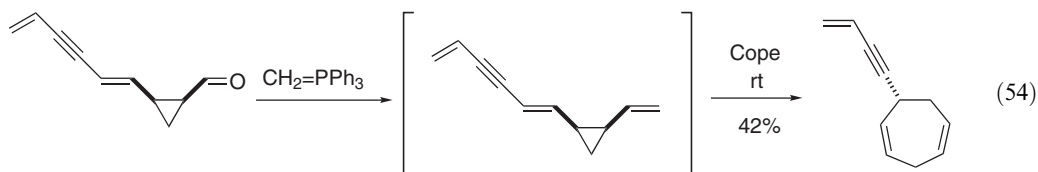


In an interesting report, the benzophenone-sensitized photochemical reaction of vinylnorcaradienes gave isochroman-3-one derivatives in good yields (Equation (51)) <1997CC1973>. The pyrolysis of tricyclic cyclobutane-fused sulfolanes gives *cis*-1,2-divinyl compounds that rearrange to the Cope-derived products (Equation (52)) <1999JCS(P1)605>. Thermal reactions of α,β -unsaturated Fischer carbene complexes with silyoxydienes give cyclohepta-1,4-dienes through a mechanism that involves the Cope rearrangement of the presumed *cis*-1,2-divinyl intermediates (Equation (53)) <1999CEJ876>. The reaction of α -diazoesters with cycloalkanedienes affords bicyclic derivatives in good yield as a result of cyclopropane formation and subsequent Cope rearrangement of the intermediate divinyl cyclopropyl derivatives <2000TL2035>; this strategy has been used to produce useful intermediates in a synthetic approach to the formal asymmetric synthesis of sertraline <1999OL233>. The hydroxyl-directed zinc carbenoid addition to a substituted cycloheptatriene results in a sequential cyclopropanation/Cope rearrangement/cyclopropanation process leading to a stereochemically pure tricyclic compound in good yield <2001TA2727>.

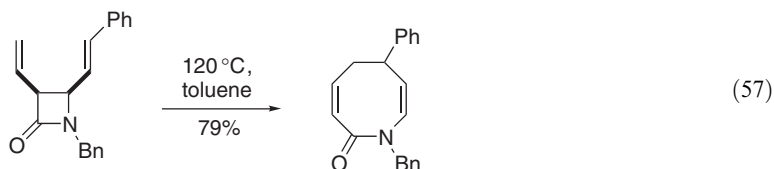
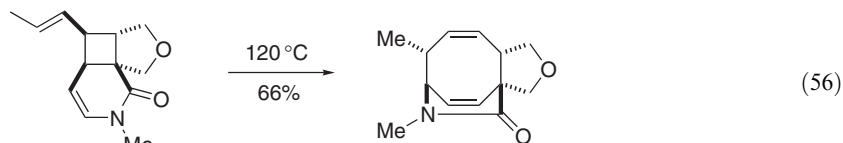
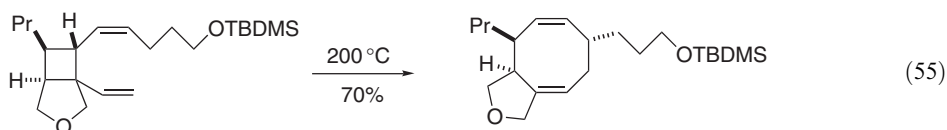




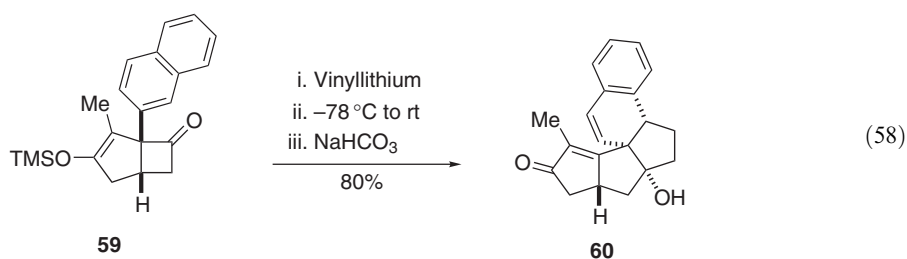
The synthesis and absolute configuration of desmarestene, the gamete-releasing and gamete-attracting pheromone of the brown algae *Desmarestia aculeate*, has been reported using as the key step the Cope rearrangement of 1,2-*cis*-vinylalkenylcyclopropanes (Equation (54)) <1995AG(E)1602, 1995T7927, 1997T13681>.



Some examples of Cope rearrangement are known for divinylcyclobutanes, as for instance in the synthesis of functionalized bicyclo[6.3.0] ring system (Equation (55)) <1997JA1478>, its application to the synthesis of both enantiomers of asteriscanolide <2000JA8071>, and to the synthesis of bicyclo[5.8.5] ring systems <2001OL2819>. The intramolecular photochemical cycloaddition of 1,3-dienes with 2-pyridones affords 1,2-divinylcyclobutanes that undergo thermal Cope rearrangement to give a polycyclic cyclooctadiene (Equation (56)) <1999TL3527>. β -Lactams have been used as templates for the divinylcyclobutane Cope rearrangement reaction leading to azocinones (Equation (57)) <2001TL3081>. An AM1 study for the oxycyclobuta-Cope aromatic rearrangement <2000JST(531)301> has been published.

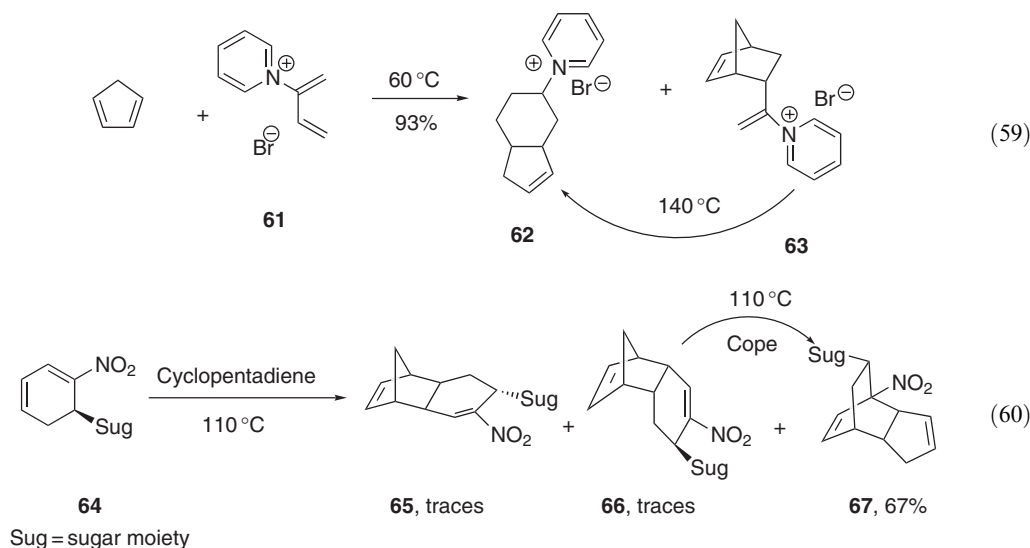


Moore has extensively reported on the oxy-Cope variant of the divinylcyclobutane rearrangement <1995JA8486, 1996JOC7976, 1997JOC3792, 1998JOC6905, 2000JOC3379, 2000JOC8564>. For example, the addition of vinyl lithium to cyclobutanone **59** gives an intermediate that after ring expansion via divinylcyclobutane rearrangement and transannular ring-closure affords the polycyclic ring system **60** in good yield (Equation (58)) <1996JOC7976>.



1.18.2.4.10 Cope rearrangement of vinyl bicycloalkenes

The Cope rearrangement of vinyl bicycloalkenes leads to the formation of fused bicyclic dienes <1997SC841>. The reaction of cyclopentadiene with pyridinium salt **61** affords two Diels–Alder products **62** and **63**; it has been found that compound **63** is transformed into product **62** under thermal conditions featuring a Cope rearrangement process <1996JOC9293> (Equation (59)). A similar reactivity has been discovered in the reaction of cyclopentadiene with 2-nitro-3-methyl-1,3-butadiene <1996T9275> and with 1',2',3',4',5'-penta-*O*-acetyl-1'-*C*-[(1*R*)-2-nitrocyclohexa-2,4-dienyl]-*D*-manno-pentitol **64** to give adducts **65–67** (Equation (60)) <1998TA449>.



The Cope rearrangement of vinyl bicycloalkenes such as bicyclo[2.2.2]octenones is a general and stereoselective entry into functionalized *cis*-decalins <1997CC1085>. This strategy has been efficiently applied into the synthesis of the norsesquiterpenoid eremopetasidione <2001OL263>. The intramolecular Diels–Alder adducts from *o*-quinonoid monoketals give bicyclic ring systems that after Cope rearrangement afford polycyclic complex arrays, that have culminated in the synthesis of xestoquinone <1997JOC2330>. 1,2-Dialkenylcyclohexene epoxides undergo thermal Cope rearrangement to furnish 1,6-oxygen-bridged cyclodeca-1,5-dienes <1999JOC3806>.

1.18.2.5 Where Y = C–Z (Z = Heteroatom)

For Z = chalcogen, Y = C–O (Wittig rearrangement, rearrangement of oxonium ylides), Y = C–S (thia-Wittig rearrangement); for Z = nitrogen, Y = C–N (aza-Wittig rearrangement, rearrangement of nitrogen ylides) or miscellaneous rearrangements (Y = Hal, C–Se, C–Si), see Chapter 1.09.

1.18.2.6 Where Y = C–C–Z

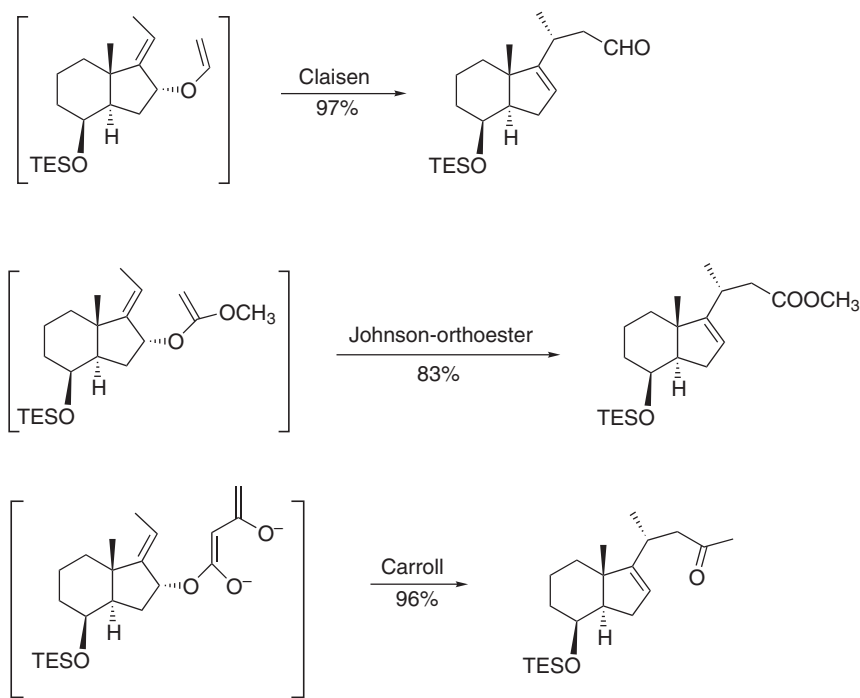
1.18.2.6.1 Where Z = chalcogen

Extensive and excellent full accounts have been published in the last years covering the different aspects and modifications of the [3,3]-sigmatropic Claisen and Cope reactions <1996TA1847, 2003S961, B-2000MI001>.

(i) Claisen rearrangement (Y = C–C–O)

The Claisen rearrangement of allyl vinyl ethers is one of the most important sigmatropic reactions. The Claisen rearrangement has been extensively reviewed in recent years covering different

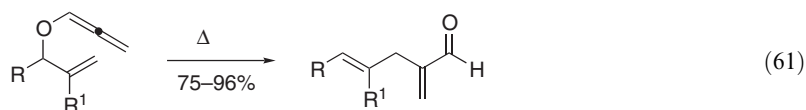
aspects, such as theoretical studies on the nature of the transition states <1999JA10865, 1997JA2877>, the effect of the substituents <2001JPC383>, the asymmetric Claisen rearrangement <1999CSR43>, the effect of pressure <2000JPR609>, the use of water as solvent <1997JCS(P2)71, 1997JOC2505, 2002CRV2751>, or Claisen rearrangements in carbohydrates <B-2001MI001, 2001TCC(215)293>. It has found widespread synthetic application due to the simplicity of the process and the high degree of stereoselectivity and functional group reorganization <1991COS(5)827, 1996AG(E)936, 1996T5461>. The effect of solvent and substituents has been reviewed <1997ACR219>. This synthetic transformation has been the subject of a series of different modifications that have contributed to enhance the value of the original proposal. As an example, in a synthetic study directed to prepare functionalized vitamin D₃ side-chain intermediates, Hatcher and Posner synthesized suitable precursors and compared the results of some of these variants of the Claisen rearrangement (Scheme 16) <2002TL5009>. These rearrangements proceed in high yield and excellent stereocontrol. A series of β -fluoro and β,β -difluoro allylic alcohols have been submitted to typical [3,3]-sigmatropic rearrangements such as the classical allyl vinyl ether, Johnson–Claisen and Eschenmoser–Claisen reactions to give the expected β -fluoro and β,β -difluoro-carbonyl derivatives <1995T11327>. A review showing the applications of the Claisen rearrangement in the synthesis of bioactive marine terpenoids has been published <2002BCJ203>.



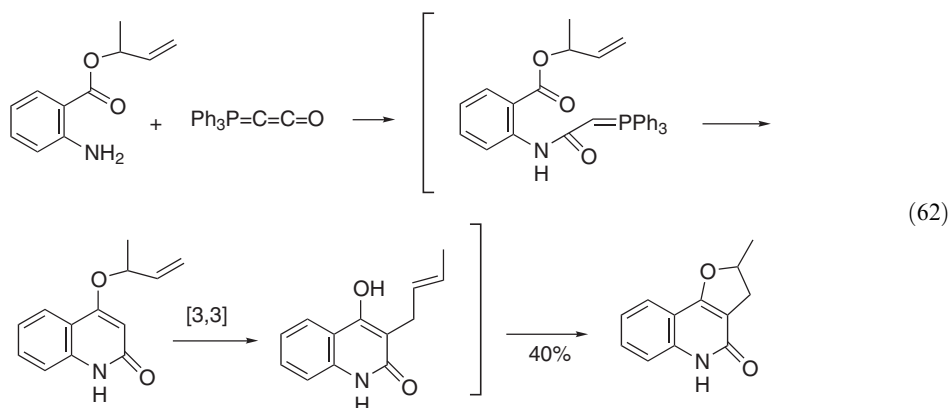
Scheme 16

(a) *Claisen rearrangement of allyl/propargyl vinyl ethers*. A recent account reviewing the catalysis on the Claisen rearrangement of allyl/propargyl vinyl ethers has been published <2002EJO1461>. The use of *n*-butyl vinyl ether in reaction with allylic alcohols for the synthesis of substrates of the Claisen rearrangement, the allyl vinyl ethers, has been documented <2002SC869>.

The thermal allene-Claisen rearrangement of allyl, allenyl ethers has been reported to be a simple and facile entry to α,β -unsaturated aldehydes <2000OL571> (Equation (61)). Analogous propargyl, vinyl ethers also give the corresponding homoallenyl aldehydes <1995M1151, 1997BSB645>. In the case of simple allyl vinyl ethers the expected homoallyl aldehydes are obtained in good yield <1996SL67, 1999JIC521>. This approach has been used for the preparation of the key aldehyde intermediate in a synthetic approach for faveline dimethyl ether <1995T5819>, for the total synthesis of (\pm)-myltayl-8(12)-ene and (\pm)-6-epijunicedranol <1999JCS(P1)2877>, or the preparation of chiral bicyclo[4.3.1]decanes, a structural motif present in a number of natural products, such as ingenol or sanadaol <1999TL1031>.

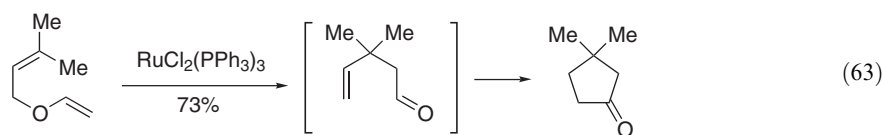


The synthesis of a number of heterocyclic ring systems (tetronic acids, tetronates <1995SL425, 2001EJO1951>, coumarins, benzoxepinones) has been approached in two steps by Wittig olefination reaction with the readily available ketylenylidene(triphenyl)phosphorane and carboxylic acids bearing OH or NH groups followed by *in situ* Claisen rearrangement (Equation (62)) <1996JCS(P1)2799>. Sequential Wittig reaction of a conveniently functionalized benzaldehyde or acetophenone derivatives followed by Claisen rearrangement of the resulting allyl vinyl ether <1997S1420> has been efficiently applied to the synthesis of racemic sesquiterpene laurene <1997JCS(P1)3127> and α -cuparenone <1997T3167>.



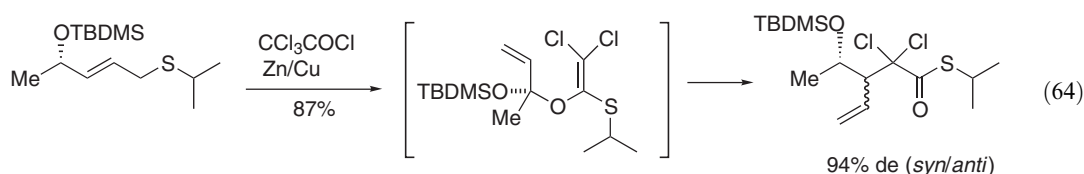
Allyl vinyl ethers can also be prepared by Lewis acid (TMSOTf, AlCl_3 , TMSI/HMDS, etc.) cleavage of 3-vinyl-substituted 1,3-dioxolane acetals, and rearranged on heating to give the expected γ,δ -unsaturated carbonyl derivatives <1997SC663, 2002TL7757>. In a large series of papers, Majumdar and co-workers have extensively exploited a diverse array of simple or tandem [2,3]- <1998T11603, 1999T1449, 1998TL7147, 1998JOC9997, 1998JOC3550> or [3,3]-sigmatropic rearrangements on conveniently functionalized heteropropargyl precursors <2001S1568, 2002S669> for the synthesis of heterocycles <1997JIC884, 1999H(50)1227>. The observed diastereoselectivities in the Claisen rearrangement of cyclohexenyl allyl ethers are governed by the Lewis acid catalysis employed rather than the thermal rearrangement conditions <1995TL803>. Curran has reported on the accelerated Claisen rearrangement of 6-methoxy allyl vinyl ether in the presence of a soluble diaryl urea <1995TL6647>.

The tin-mediated Claisen rearrangement of 2-allyloxycyclohexenone has been proved to be a stannyloxy-accelerated Claisen rearrangement <1999JA8955, 1998JA3807>. Triisobutylaluminum <1996SL475> or aluminum tris(4-bromo-2,6-diphenylphenoxide) are effective catalysts for the Claisen rearrangement of various allyl vinyl ethers, the reaction proceeding at low temperature, in good yield and with high diastereoselectivity <1995JA1165, 1996SL720>. Palladium(II) catalysts efficiently promote the Claisen rearrangement of differently substituted allyl vinyl ethers <1995BSF696, 1995SL447, 1995CL697, 1996TL7991>, as 2-alkoxycarbonyl-substituted allyl vinyl ethers to give the β,γ -alkyl-substituted α -keto esters in good yield and excellent *syn/anti*-diastereoselectivity <1999SL1823>. Rhodium(II) complexes catalyze the reaction of allyl α -diazoacetates with di-*t*-butylthio ketene affording 4-allyl-2-methylene-1,3-oxathiolan-5-ones through the 1,5-cyclization of a thiocarbonyl ylide followed by Claisen rearrangement <1995BCJ1393>. Eilbracht has extensively reported on an elegant and useful tandem ruthenium-promoted Claisen rearrangement and hydroacylation reaction that allows the cyclization reaction of differently substituted allyl vinyl ethers <1995S330, 1996SL1221, 1998TL1905, 1998TL9647> (Equation (63)). Iridium(I)-phosphine precatalysts promoted olefin isomerization processes in conveniently functionalized bis(allyl) ethers leading to highly stereoselective Claisen rearrangements of the resulting aliphatic allyl vinyl ethers <2003JA13000>.

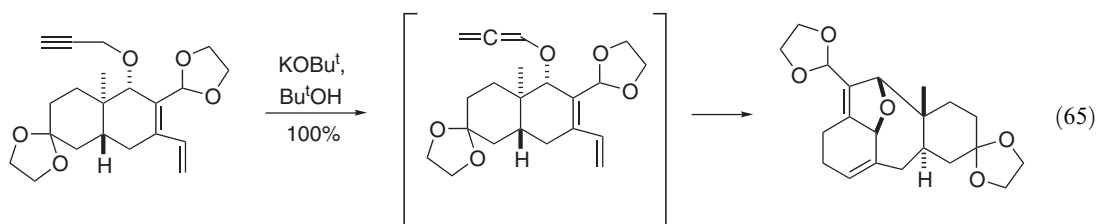


Looking for a chiral catalyst, it was found that the combination of copper(II) triflate plus molecular sieves promoted efficiently the Claisen rearrangement of 2-alkoxycarbonyl substituted allyl vinyl ethers [<2001OL49>](#); as an extension the use of chiral copper(II) bis(oxazoline) complexes as catalysts for the enantioselective Claisen rearrangement has been documented [<2001AG\(E\)4700, 2003T4031>](#).

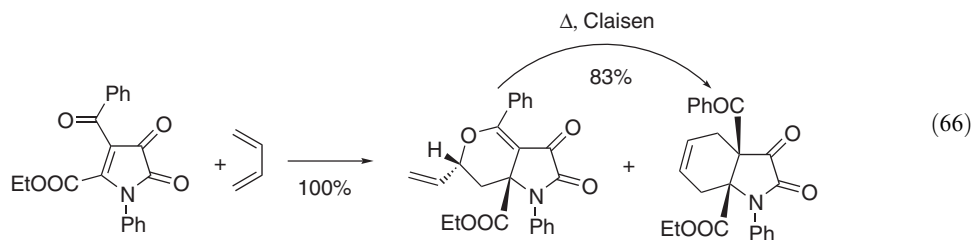
4-(*O*- or *N*-)Substituted (*E*)-allyl sulfides upon reaction with trichloroacetyl chloride in the presence of Zn/Cu couple are transformed *in situ* into the corresponding allyl thioethers that after Claisen rearrangement afford the expected γ,δ -unsaturated esters (Equation (64)) [<1997HCA876, 2001T5607>](#). The thermally induced Claisen rearrangement of various isomeric diethylphosphorylallyl vinyl ethers yields 1-alkenylphosphates and 2-alkenylphosphonates [<1995SC2533>](#).



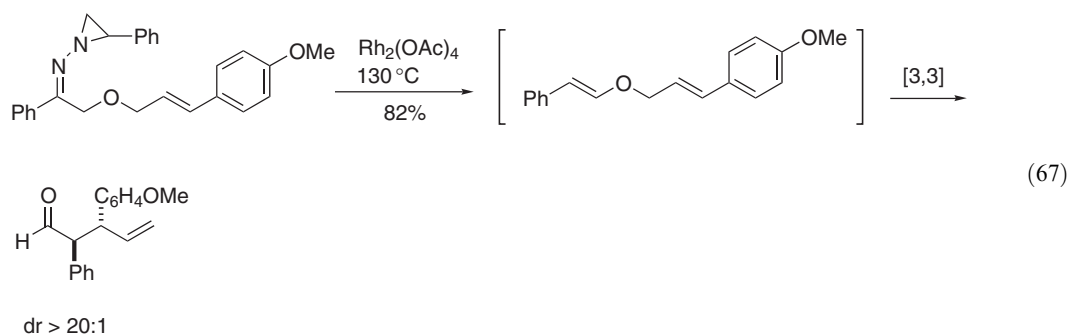
Tandem intramolecular [2+2]-cycloaddition and [3,3]-sigmatropic rearrangement of allenyl ethers have been used in a novel synthetic strategy for the synthesis of oxa-taxane skeleton [<1995T3499>](#) (Equation (65)), and for the α -ketol isoprene unit elongation in a synthetic approach to the natural product sarcophytol A [<1995JCS\(P1\)751>](#).



Products arising from hetero-Diels–Alder reactions have been shown to rearrange to the normal Diels–Alder adducts via Claisen rearrangements (Equation (66)) [<1996CPB681>](#). Hetero-Diels–Alder adducts from the reaction of cyclopentadiene with substituted ketenes also react in the same way via Claisen rearrangements [<1999JA4771>](#).

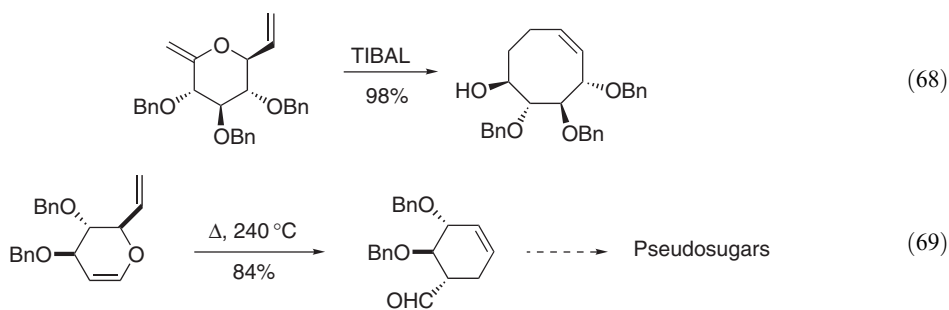


The Claisen rearrangement of allyl or propargyl fluorovinyl ethers for the synthesis of α -tri-fluoromethyl unsaturated acids and derivatives has been extensively investigated in different laboratories [<1995JOC6289, 1996CC861, 1998TL305, 1998TL5041, 1998CC2441, 1999JFC\(94\)27, 2000EJO1933, 2000CC1691, 2001TL2665, 2001JOC4887, 2002JFC\(113\)167, 2003T4641>](#). α -*O*-Substituted *N*-aziridinyl imines on treatment with rhodium(II) catalyst afford carbenoid species that give enol ethers in a Bamford–Stevens-type reaction in good yields; for similar *O*-allyl derivatives this intermediate isomerizes to give the Claisen rearrangement products in a simple and efficient process (Equation (67)) [<2002JA12426>](#).



The copper-catalyzed reaction of allylic alcohols with vinyl iodides gives allyl vinyl ethers that rearrange *in situ* to the γ,δ -unsaturated aldehydes in good yield and moderate diastereomeric excess [<2003JA4978>](#).

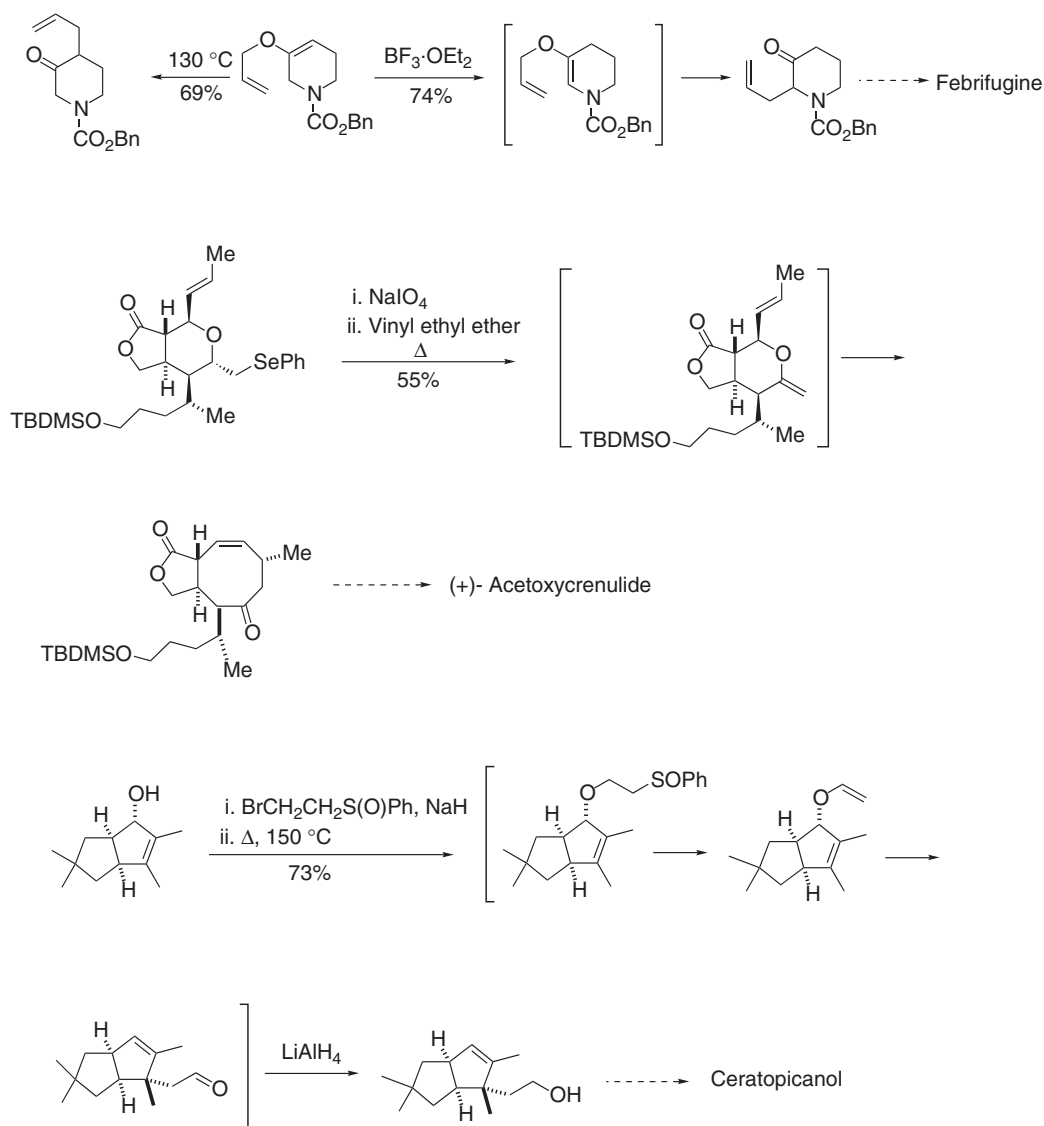
Paquette has shown that the Claisen rearrangement of 2-methylene-6-vinyltetrahydropyran is a convenient method for the synthesis of medium-sized carbocycles [<1995JOC1435, 1998TL5705, 1997JA8438>](#). The same methodology applied to 2-methylene-5-vinyl tetrahydrofuran has proved to be successful for the total synthesis of sesquiterpenoid 7-*epi*-bulnesene [<2002TL1939>](#). Following these trends, the thermal or triisobutylaluminum (TIBAL)-promoted Claisen rearrangement has been set up for the synthesis of bridged bicyclic [4.*n*.1] ring systems [<1997S1258>](#), and in sugar templates for the synthesis of cyclooctane carbagluco derivatives as a new class of carbohydrate mimetics [<1997AG\(E\)2793, 2000AG\(E\)362, 2000AG\(E\)2466, 2000TA283, 2001EJO1053, 2002T10189>](#) (Equation (68)). Zhang has applied the same protocol for the stereoselective preparation of seven-membered carbasugars [<2003TA2195>](#) and also a similar process involving ring expansion in fluorinated precursors [<2000JCS\(P1\)2339>](#) has been reported. Still in the sugar domain a new method for the synthesis of C-glycosides has been developed using 3-*O*-allyl glucals as suitable precursors [<2000TL7589, 2003TL3631, 2003OBC3772>](#); a similar analysis has been previously documented for the synthesis of *cis*-2,6-disubstituted pyrans using the Ireland–Claisen rearrangement in suitable precursors on nonsugar-substrates [<1997AJC43>](#). A new strategy has been advanced for the synthesis of pseudo-sugars, based on the thermal Claisen rearrangement of allyl vinyl ethers installed in a pyranose template (Equation (69)) [<1998CC925>](#).



The asymmetric Claisen rearrangement of allyl vinyl ethers in the presence of chiral bis(organoaluminum) Lewis acids gives the corresponding γ,δ -unsaturated aldehydes in good chemical yield, but moderate enantioselectivity [<2002T8307>](#).

The synthesis of D/L-febrifugine and D/L isofebrifugine is an interesting case, where, depending on the reaction conditions, the initial vinyl allyl ether rearranges normally to the expected product (thermal conditions) or to a new vinyl allyl ether (Lewis acid catalysis $\text{-BF}_3\cdot\text{OEt}_2$ —at room temperature), that after Claisen rearrangement gives the key intermediate (Scheme 17) [<1999S1814, 1999CPB905>](#). Application of the Claisen rearrangement has been reported in studies directed to the synthesis of natural products such as azadirachtin [<1999SL1295, 2002OL3847>](#), in the asymmetric synthesis of cycloalkenones [<2000JA3785>](#), in the synthetic study on amphidinolide B [<1998BCJ2433>](#), in the formal total synthesis of racemic acorones [<2001SL1986>](#), or in the promising compound for the treatment of Alzheimer's disease garsubellin A and related phloroglucins [<2002OL1943>](#).

Among the natural products synthesized using the Claisen rearrangement of allyl vinyl ethers we can cite flavor and fragrance compounds [<2000MI1033>](#), acetoxycrenulide [<1995JA1455, 1995JOC1435, 1996JA1309>](#) (Scheme 17), anti-inflammatory sesquiterpene furoic acids



Scheme 17

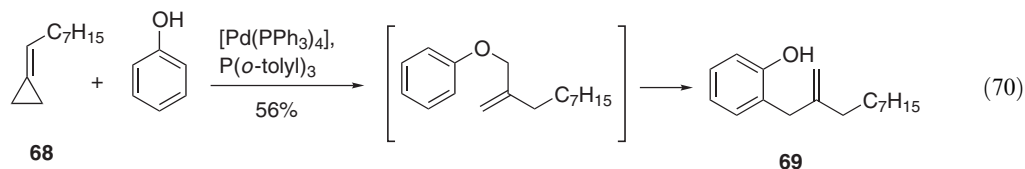
<1996T4245>, key intermediates such as 3a-(*o*-nitrophenyl)octahydroindol-4-ones for the synthesis of indole alkaloids <1996T4013>, the antitumor compound FR900482 <1996TL3475>, sesquiterpene ceratopicanol <1995TL15, 1996JOC2095> (Scheme 17), the cardiotoxic agent kalmanol <1996JA727>, (+)-cassiol <1999H(51)1321>, C(16),C(18)-bis-*epi*-cytochalasin D <2000JOC6073>, in the stereoselective total synthesis of racemic tochuinyl and dihydrotochuinyl acetates <1998T8133>, the asymmetric synthesis of the cytotoxic diterpenoid (–)-sclerophytin <2001JA9021>, the first enantioselective total synthesis of the sesquiterpene cyclomyttalane-5 α -ol <2002JCS(P1)583>, pancratistatin <2002OL1343>, 12-oxo-phytodienoic acid <2002TL4361>, the enantioselective synthesis of both enantiomers of labdane diterpene saudin <2002JA190>, sesquiterpenes of the herbertane family <2002SL340>, nerylgeraniol-18-oic acid <2001SC2549>, and the alkaloid mesembrine <2002TL2297>.

(b) *Aromatic Claisen rearrangement*. The transition state structures for the aromatic Claisen rearrangement have been calculated by the molecular orbital method <1996JOC6218>. The aromatic Claisen rearrangement is a [3,3]-sigmatropic transformation where an allyl ether gives an *o*-dienone, which on enolization affords an *o*-allylphenol <1995IJC(B)1043, 1995AJC531, 2000CL116, 2000TL2039, 2000JCS(P1)1731, 2001T7965, 2002IJC(B)1460>. These rearrangements have been extended to *O*-allylazulenes <2000EJO193> and to perfluoroallyloxy derivatives

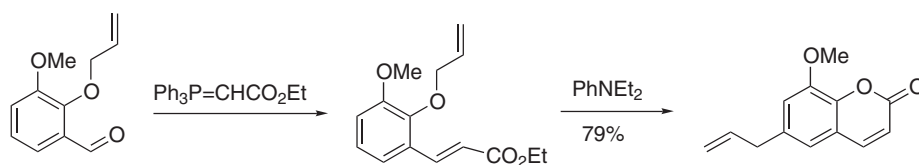
<2001JFC(108)57>. Using enantiomerically pure *O*-allyl phenyl ethers it is possible to prepare chiral *C*-alkylated phenols <1998JA815>. ^1H NMR techniques are available in order to predict the Claisen rearrangement regioselectivity in allylindanyl and allyltetrahydronaphthalenyl ether derivatives <2000MRC970, 2003JOC5493>. The enantioselective aromatic Claisen rearrangement on catechol mono allylic substituted ethers, using chiral boron reagents, has been described <1997TL4815>.

Allyl aryl ethers undergo accelerated Claisen rearrangement in the presence of water <2002MI434>. Sodium metabisulfite promotes the effective reductive Claisen rearrangement of allyloxyanthraquinones <1996SC715, 1997AJC379, 1997OPP365>. The silver/potassium iodide couple also efficiently promotes the Claisen rearrangement of allyloxyanthraquinones <2000JOC2813>. It has been reported that the photo-aromatic Claisen <2002JA9768> rearrangement in zeolites as solid supports affords a mixture of the expected hydrogenolysis, *ortho*- and *para*-rearrangement products <1996JA9428, 1998JMOC(134)129, 2001CL252>, and the effects of β -cyclodextrin on the photo-Claisen rearrangement of allyl phenyl ether have been published <1997CJC1151>.

Different types of montmorillonites catalyze the regiospecific rearrangement of benzyl phenyl ether to a mixture of the *ortho*- (major), *para*- (minor), and the debenzylated (traces) products <1998IJC(B)301, 2001SL269>. The catalytic system nafion-H/silica nanocomposite has been tested in the Claisen rearrangement of *O*-allyl phenol <2000JCA(193)132>. It has been reported that florisol catalyzes the aromatic Claisen rearrangement and this can be applied to suitable precursors for the synthesis of mycophenolic acid analogs <1997TL4725>. *O*-Allylsalicylic acids rapidly rearrange in the presence of Merrifield resins under microwave irradiation <2000SL1129>. Lewis acids such as $\text{Yb}(\text{OTf})_3$ or DIBAL-H are reported to efficiently catalyze the Claisen rearrangement of allyl, crotyl, and prenyl aryl ethers <2000SL615>. The palladium-catalyzed reaction of methylenecyclopropane **68** with phenol gives an intermediate that after Claisen rearrangement leads to compound **69** (Equation (70)) <1999AG(E)3365>, and the synthesis of *N*-allyl-2(1*H*)pyridones from 2-(allyloxy)pyridines has also been disclosed <1996TL2829>.

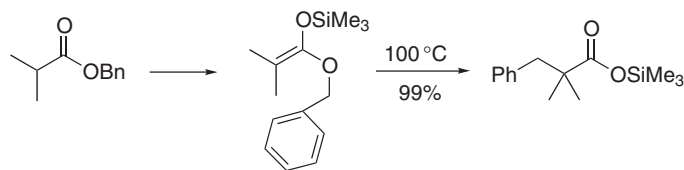


Benzyl vinyl ethers do not undergo the Claisen rearrangement, but in the presence of lithium perchlorate in diethyl ether, the 2-furyl and 2-thienylmethyl vinyl ethers give 1,3-rearrangement products, being a convenient entry to γ -heteroaryl propanals <1995TL9527>. Even since the early days of this reaction, rearrangements of certain allyl vinyl ethers have been observed which deviate from the normal [3,3]-pattern which are called “abnormal” Claisen reactions <1996TL21, 2000JA8131, 2002IJC(B)868>. The transformation of allyloxybenzenes into *p*-allylphenols or *o*-allylphenols and the 2,3-rearrangement of 4-allyloxyhydroazepin-2-ones are typical processes <2001SL228, 2001TL4561, 2000JA8131, 2000TL6893, 2000TL6901>. Wittig reaction of 2-allyloxybenzaldehydes give the corresponding alkyl cinnamates, which on Claisen rearrangement go to the *o*- or *p*-allylcoumarins <1995IJC(B)686, 1995H(40)817> (Scheme 18). The rearrangement of differently substituted *O*-allyloxy-coumarins <1998IJC(B)662, 1999IJC(B)1242>, isocoumarins <2000TL29>, flavones <2001TL7241, 2002T3589>, and flavanones <1998IJC(B)596> has been reported.



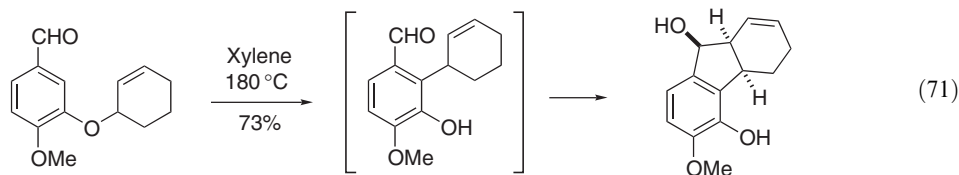
Scheme 18

The synthesis of aromatic crown ethers ("crownphanes"), 2:2 macrocycles <2002SL1874> or alkoxy-calix[4]arenes <1995TL5567, 1996T13189, 1997JA12677, 1997TL8993, 1998CL307, 1998JA12226, 1999TL8007, 1999POL1153, 2000CC2197, 2000TL9261, 2000CC343, 2000TL8111, 2001CC595, 2001JCS(P1)588, 2002EJO1996>, rotaxanes <2002TL5747>, polymers <2001MM6545>, tripodal hexadentate ligands <1998TL6211, 1998TL6215, 2002JA9988>, or 16-membered farnesylated *p*-benzoquinone derivatives <1999TL1941> have been reported from conveniently functionalized aromatic-*O*-allyl derivatives. Thermal Claisen rearrangement of allyloxy perfluorobenzene derivatives gives intermediates that finally afford intramolecular Diels–Alder products <2002JFC(113)123>. The Claisen rearrangement of *O*-allyl or *O*-propargyl benzothiophenes has also been documented to give after sequential ring closure tricyclic fused thiophenes <1999JCS(P1)3705>. The synthesis of furocoumarins by Claisen rearrangement of di-*O*-allyloxy coumarins has been reported <1999JCB(5)545>. Sakamoto's group has also reported the aromatic Claisen rearrangement in the adduct formed in the reaction of 2,3-dihydro-1*H*-indol-3-ones with allyl alcohols in the presence of camphorsulfonic acid and magnesium sulphate to give 2-allyl-2,3-dihydro-1*H*-indol-3-ones in good yields and under thermal conditions <1996JCS(P1)729>. Alternatively, 2-*O*-allyl-indol-3-ones upon Wittig reaction and Claisen rearrangement afford the 3,3-disubstituted-indol-2-ones in good yield <1996TL7525, 1998JCR(S)594, 2000TL4657>. An interesting variant of the conventional aromatic rearrangement includes examples where a ketene silyl acetal is the necessary "vinyl" functional moiety in the precursor <2002TL5837> (Scheme 19). Similar processes have been described in trifluoromethyl substituted *O*-allyl furans and thiophenes in a reaction that affords trifluoromethyl substituted butenolides and their thio analogs <2001TL1657, 1995SUL173>. The Claisen rearrangement of 3-(prop-2-ynylsulfanyl)-1,2,4-triazine is an efficient synthetic route to 2-methyl-thiazolo[3,2-*b*][1,2,4]triazinone <1998JCB(5)590>.

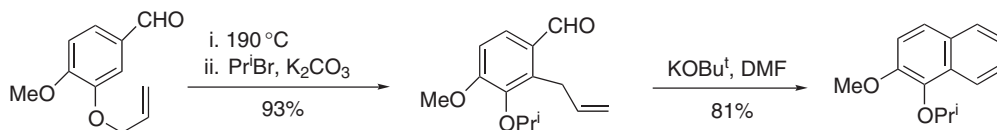


Scheme 19

A new method for the synthesis of tetrahydrofluorene has been reported via thermal domino Claisen rearrangement on conveniently functionalized 3-(*O*-cyclohexyl) benzaldehydes <1996SL283> (Equation (71)).

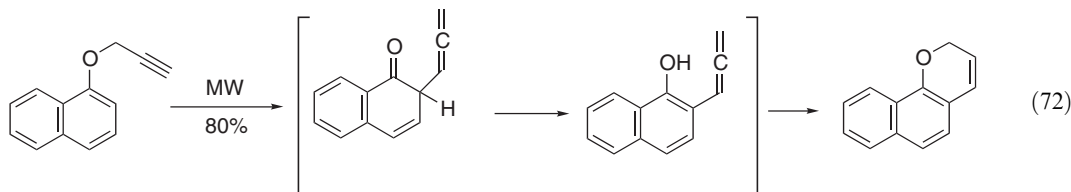


A new method for the synthesis of substituted naphthalenes based on the sequential Claisen rearrangement of *O*-allyl acylbenzenes followed by photochemical irradiation in the presence of potassium *t*-butoxide has been reported (Scheme 20) <2000JCS(P1)787>. Also a novel synthesis of substituted naphthalenes has been developed in three steps from *O*-allylbenzaldehydes, via Claisen rearrangement, Grignard addition to the aldehyde followed by a ring-closing metathesis reaction <2001TL6155>. A sequential Claisen/ring-closing metathesis approach has been described for the synthesis of spirocyclic cyclopentanes and cyclohexanes <2003TL8883>.

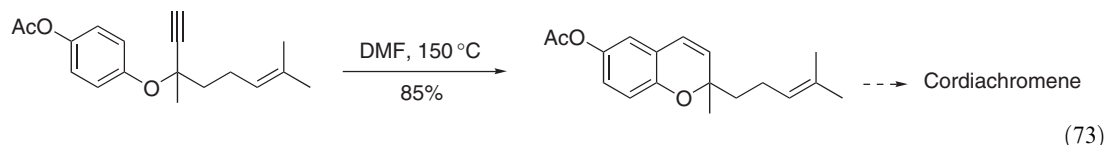


Scheme 20

O-Allyl and propargyl phenyl derivatives, naphthalenes, or indoles rearrange and cyclize, via allenyl intermediates, to give a number of benzofuran <1998H(48)2173, 2000IJC(B)958, 2003H(59)237>, benzopyran <1995JHC219>, naphthopyran <1996H(43)751>, or pyrano[3,2-*e*]-indole derivatives, respectively <2001BCJ675, 1995TL7019, 1996JCR(S)338, 2000TL3541, 2000JNP245> (Equation (72)). This strategy has been used for the synthesis of 1,7-dihydro-pyrano[2,3-*g*]indole ring system of the natural indole alkaloid paraherquamide F <2002TL2149>.



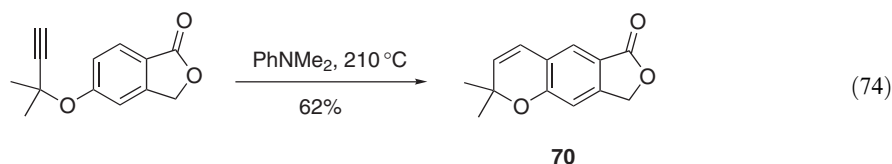
Molybdenum hexacarbonyl [Mo(CO)₆] catalyzes the rearrangement of allyl aryl ethers and the subsequent dihydrobenzofuran formation <1997SL585, 1997S41, 1998S256, 2001JOC4965>. This strategy has been used for the preparation of pyrano[6,5-*h*]quinolin-2-one heterocyclic ring systems <1999TL4505>, and in a short synthesis of cordiachromene <1999TL8113> starting from an *O*-propargyl aryl derivative (Equation (73)), for the synthesis of furo-fused 2*H*-chromenes <1996CJC1649>, or the preparation of oxo-analogs of isopsoralen <2002T2831>. Caesium fluoride (CsF) has been found to promote efficiently the Claisen rearrangement of *O*-propargyl benzene derivatives <1997H(45)2261, 1997H(45)2273>.



Synthetic studies directed to the preparation of 1-*O*-methylforbesione <2001AG(E)4264> and to the bridged tricyclic core in *Garcinia* natural products <2002OL909> have been published featuring a cascade biomimetic aromatic Claisen rearrangement and Diels–Alder reaction. The Claisen rearrangement of *O*-allyl aryl ethers followed by ozonolysis is a convenient method for the synthesis of *O*-hydroxyaldehydes <1997SC4235>.

Ogasawara and co-workers have reported the synthesis of 2-(cycloalk-2-enyl)phenols by Claisen rearrangement of *O*-allylphenols obtained *in situ* by retro-Diels–Alder reaction of conveniently functionalized unsaturated bicyclic derivatives. They have applied this elegant strategy to the synthesis of (+)-curcuphenol <1998TA2215> and (+)-curcudiol <1998SL1004>. Practical use and application of the aromatic Claisen rearrangement has been reported in the synthesis of new cardanol and cardol derivatives <2002S2749>, in the synthesis of prenylated phthalides such as salfredin B₁₁ **70** <1998JCR(S)292> (Equation (74)), in the synthesis of the di-*O*-methyl ether of the aglycone of cesternoside A <1996JCR(S)342>, *o*-methoxylated phenyl-isopropylamines <1996TL7889>, differently substituted flavones <1996IJC(B)1253>, 2,3',3'-trimethyl-2',3'-dihydroangelicins, seselin and other angelicin derivatives <1996JCR(S)148, 1995TL7109>, 4-allyl-2,6-dimethoxyphenol, a naturally occurring compound with interesting biological activities <1996SC2569>, 8-(1,1-dimethylallyl)-apigenin <1996H(43)277>, maxima flavanone A <1999IJC(B)596>, the enantioselective synthesis of (*S,R,R,R*)-nebevicolol <2000T6339>, subellipitenone F, an inhibitor of topoisomerase II <2000CL464>, neurotrophic illicinones <1998JA12684, 2000JA6160>, the potent phytoestrogens 8-prenylnaringenin and 6-(1,1-dimethylallyl)naringenin <2001T1015>, (–)-aplysin and (–)-debromoaplysin <2001TL4913>, the coumarin trachyleuranin-A <2001TL6491>, in the synthesis of the prenylated flavonoid lupiwighteone <2003T4177>, in the asymmetric synthesis of the antitumoral metabolite FR900482 <1997T10239>, 6-*C*-prenylflavanones <1997S1246>, the enantioselective synthesis of the alkaloid (–)-pseudophrynaminol <2003TL1591>, the natural product carpanone <2001SL1482, 2002JCS(P1)1850>, tricyclic indane derivatives as melatonin receptor agonists <2002JMC4222>, a series of oxepin- and oxocin-annulated coumarins, 6-prenylcoumarins and pyranocoumarins, such as suberosin and toddaculin <2002JCS(P1)371, 2002TL7781>, enantioselective synthesis of chroman-2-ylmethanol <2002JCS(P1)496>, 3,6-dihydro-1*H*-benzo[*c*]oxocines <2002H(57)2021>, 2,5-dihydro[*b*]oxepines <2002H(57)1997>, the neolignans usiderin K and J <2001SC861>.

N-arylpiperazines as high-affinity 5-HT_{1A} receptor ligands <1995JMC1942>, in synthetic studies directed to the antitumoral diazonamide A <1997JCS(P1)2413>, analogs of antibiotic frenolicin B <1995S780>, a high-yielding synthesis of racemic hongconin <1996SC867>, puraquinonic acid ethyl ester, and deliquinone <2002JOC5857>.

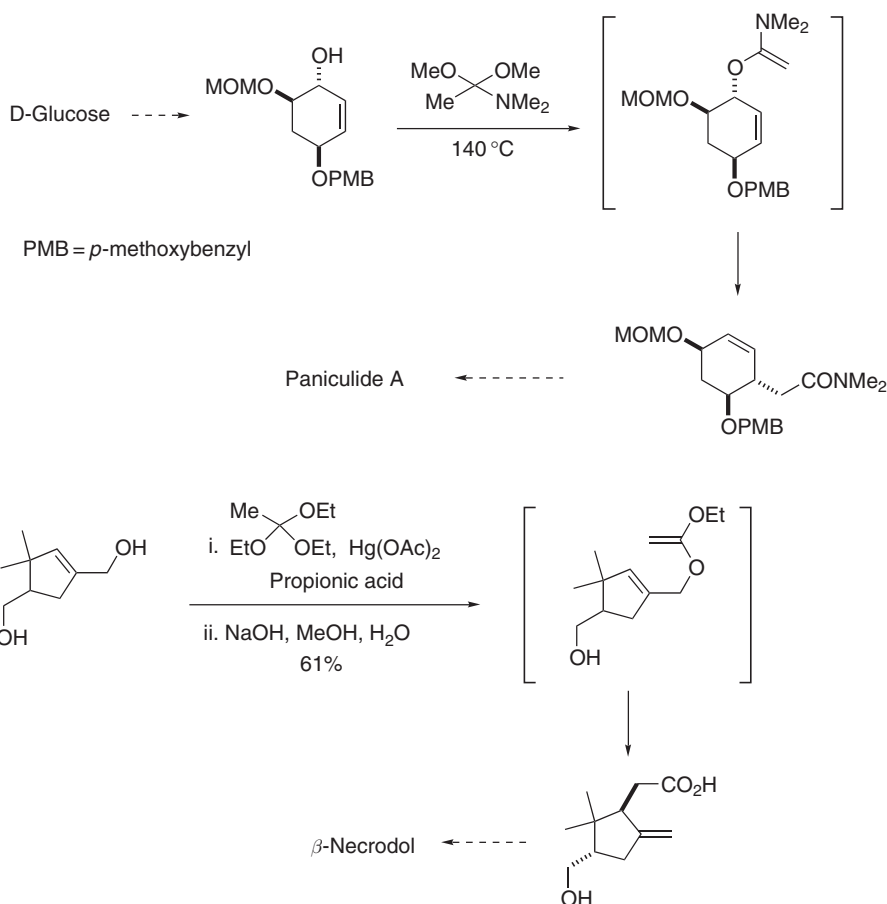


(c) *The Eschenmoser amide acetal and Johnson orthoester Claisen rearrangements.* The Eschenmoser amide acetal <1964HCA2425, 1969HCA1030> and Johnson orthoester Claisen rearrangements <1970JA741> are major developments of the original Claisen reaction of great importance in synthetic organic chemistry in view of the number of examples documented in the literature <2000TL8301, 1995JCS(P1)2033>. The use of microwave irradiation accelerates the classical and conventional thermal orthoacetate rearrangement <1995T1809>.

The Johnson–Claisen rearrangement of trisubstituted allylic alcohols has been investigated and it has been found that substrates with (*E*)- or (*Z*)-geometry at the double bond afford high levels of *syn/anti*-diastereoselection <1997JOC1976>. Using the Johnson–Claisen rearrangement, the stereoselective synthesis of trisubstituted alkenes <1995TL757, 1996SL747>, the synthesis of *threo*-3,4-divinyladipic acid <1997JOC1906>, the preparation of substituted allenic esters <1995SC4087, 2001JA12466>, and its application to 2-adamantanone substrates have been reported <1998T11899>. Fluorinated succinic acid derivatives or trifluoromethylated compounds have been prepared from fluoro and difluoro allylic alcohols via Johnson–Claisen or chelated enolate Claisen rearrangements; these reactions occurred with moderate yield but with the expected high diastereoselectivity <1996SL82, 1999JCS(P1)3345, 2000TL5269, 2000JCS(P1)3217, 2000JOC2104, 1997JFC(86)81, 2000JOC6231>. Allylic alcohols installed in *N,N*-dialkyl naphthamides have been submitted to these [3,3]-sigmatropic rearrangements showing that the Johnson orthoester Claisen rearrangement affords a better diastereoselectivity compared to the Eschenmoser amide rearrangement, the chemical yields being similar <2000TL3279>. Examples of the application of the Claisen–Johnson rearrangement in synthetic transformations in the area of steroids <1997JCR(S)134, 2000CPB1480, 2000T9575, 2002MI597> and vitamin D analogs <2002JMC1825> have been documented, and for the synthesis of versatile chiral intermediates for fused cyclopentanoid natural products <2001ZN1227>.

The Johnson–Claisen rearrangement has been used in the efficient synthesis of β,β' -disubstituted γ,δ -unsaturated esters containing quaternary centers <1999JOC8945>, in the synthesis of both enantiomers of bicyclo[4.3.0]nonane-3,8-dione <2001JCS(P1)2040>, and in the synthesis of γ -hydroxy α,β -unsaturated ketones and nitriles <2001EJO713>. An enantioselective method for the generation of benzylic stereocenters featuring the Johnson–Claisen rearrangement of a number of allylic alcohols was applied to the preparation of both enantiomers of 3-methyl-2-phenylbutylamine, an important resolving agent <2003TA2401>. The effect of an allylic located sulfur atom in the stereoselectivity of the Claisen–Johnson rearrangement has been investigated <1999JOC2928>. 1-Dimethyl phenylsilyl (or 1-phenylsulfonyl) substituted allylic alcohol derivatives have been submitted to the standard Claisen–Johnson conditions to give the unsaturated β -silyl esters <1995TL8723, 2000T10263> or unsaturated β -sulfonyl esters <1998TL5827>.

The Eschenmoser amide acetal rearrangement has been used as key steps for the synthesis of natural products such as (\pm)-ambrox <1996JOC2215>, morphine <1997SL441>, (–)-carbovir <2003TL4125>, paniculide A from D-glucose <1999T3855> (Scheme 21), the enantiomeric forms of paraconic acids starting from D-mannitol <1999TL4829>, in a synthetic approach to 4,5-epoxyhasubanans, a type of morphine compound <2000M997>, in the synthesis of branched-chain cyclitols or pyranosides <1997CAR(300)183, 1997LA1983, 2002MI431>, in the preparation of 4-(2-aminoethyl)indoles through an orthoamide rearrangement of 3-hydroxy-2-methoxyindolines <1998H(47)367>, in the obtention of azachlorins, a novel type of hydrophorphyrin <1995LA1509, 1995AG(E)784, 1995LA1033>, in the synthesis of 5-oxaprostanoid derivatives <1995H(40)93>, and 13-alkylmilbemycins <1995H(41)2027>, racemic sesquicillin, a C29 isoprenoid-related fermentation product <2002AG(E)1434>, unsaturated morpholine amides <2002SL411>, and in the synthesis of gelsemine <2002TL545, 2002TL549>.



Scheme 21

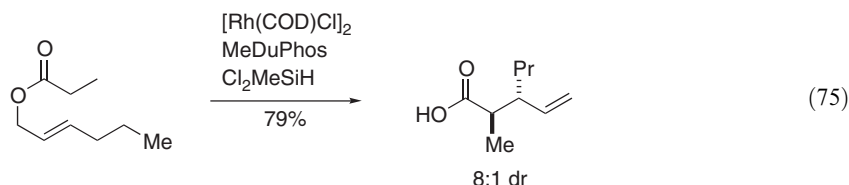
The orthoester Claisen rearrangement applied onto 1-hydroxymethyl-substituted cyclohexenes has provided key intermediates for the synthesis of sesquiterpene AM6898D <2000TL4173>, antifeedant terpenoid lactones <2000MI4973>, in the preparation of highly functionalized dienes <2001T6261>, in the synthesis of intermediates toward indacene ring systems <1996TL8065>, intermediates en route to thapsane type of sesquiterpenes <2002TL2765, 2002TL2769>, in synthetic studies directed to analogs of the alkaloid deplancheine <1996H(43)1981>, and in the enantioselective synthesis of the C1–C28 portion of the cytotoxic natural product amphidinolide B1 <1997TL7909>. The orthoester Claisen rearrangement applied onto 1-hydroxy-3-cyclohexenes has afforded key intermediates for the synthesis of (+)-valerane <1996TL2863, 2000JCS(P1)4321> and (+)-pinguisenol <2000JCS(P1)2583>. Using allylic alcohols, obtained by base-promoted epoxide rearrangement, derived from enantiomerically pure limonene, the orthoacetate Claisen rearrangement afforded intermediates for the synthesis of spirolactones <1998EJO2677>, tetracyclopropylmethane, a unique hydrocarbon with S₄-symmetry <2001AGE(E)180, 2002JA6706>, and the ABC rings of the alkaloid manzamine A <2002JOC6181>. The Claisen rearrangement on allylic and propargylic alcohols in substrates containing the *t*-BOC-2-acyloxazolidine chiral moiety has been reported <2002EJO29>.

The orthoester Claisen rearrangement has been used as a key step in a number of synthetic sequences leading to natural or non-natural products, as in the total synthesis of (±)-albene <1995P1699>, in the transformation of sugar templates <1998TA4203, 2000TA453, 2001MI57>, in the synthesis of carbocyclic nucleosides <2002TL6399>, in the synthesis of novel indole analogs of mycophenolic acid as potential antineoplastic agents <2000T2583>, in the total synthesis of *R*-(–)-baclofen <1997TA3801>, γ,δ-unsaturated acid and aldehydes <1995CL565>, modified prostaglandins <1995MI337>, non-natural nucleosides

<1998TL3443, 1999TL231, 2000CAR(328)37>, mono- and bis-tetrahydrofuran intermediates for the synthesis of acetogenins <1999TL193>, (\pm)- β -necrodol <1999TL4401, 2001T2011> (Scheme 21), (\pm)-*trans*-2-butyl-5-heptyl-1-methylpyrrolidine, an ant venom alkaloid, <1999H(50)333>, immunosuppressant FR65814 <1999T2205>, (2*S*,4*R*)-4-propyl-glutamic acid <1999TL6577>, homogynolide <1999JCS(P1)2069>, α -pinguisene and pinguisenol <1997JCS(P1)3295, 1999JCS(P1)1265>, in the preparation of pseudopterane analogs <1999JOC5193>, L-glutamic acid analogs <2000MI91>, synthetic studies directed to spinosyn A <2000CJC757>, racemic acorone <2000T8189>, 1,14-herbertenediol and 11-*epi*-herbertenolide <2002TL151>, 1,13-herbertenediol, α - and β -herbertenol <2003TL1027>, synthesis of 26-norbrassinolide, 26-norcastasterone and 26-nor-6-deoxocastasterone <2001P343>, sphingosines <1995S868>, trail pheromone mimic of the subterranean termite *Reticulitermes virginicus* <1998JCR(S)706>, the antibiotic macrodiolide tartrolon <1998TL803>, the antitumor agent halomon <1998AG(E)2085>, the glycoprotein processing enzyme swainsonine <1996JOC7217> or 3-(hydroxymethyl)swainsonine <1997T11021>, the synthesis of RS-97613, a potent immunosuppressive and anti-inflammatory agent <1996JOC2236>, racemic pseudomonic acid A <1995TL7631>, (3*R*)-(-)-A-factor, an autoregulator of cytodifferentiation <1995CC437>, enantiomerically pure (-)-tubifoline and related alkaloids <1996TA2775, 1997TA935>, the alkaloids geissoschizine and isositsirikine <1995T8623>, (+)-arenarol <1997TL7769>, (-)-mesembranol from D-glucose <1997JCS(P1)275>, the synthesis of quadrilure, the pheromone of square-necked grain beetle <1995TA463>, the preparation of capsaicin and analogs, a series of well-known pungent principles of hot red pepper <1996T8451>, the synthesis of potential anticonvulsants 3-substituted alkenyl GABA derivatives <1998BMCL2599>, the naturally occurring pyrrole compound porphobilinogen <2001JA9307>, the alkylidene cyclopentenone prostaglandin TEI 9826 <2003TL2579>, in a general approach to the synthesis of α -substituted 3-bisaryloxy propionic acid derivatives as specific matrix metalloproteinase inhibitors <2001BMCL295>, and the sesquiterpenes AM6898A and AM6898D <2002T2513>.

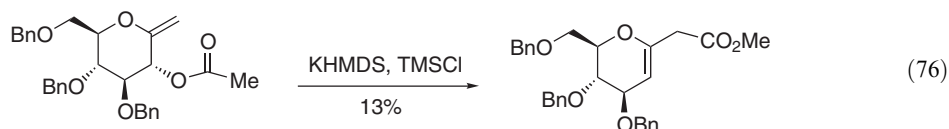
(d) *The Ireland ester enolate Claisen rearrangement.* Some new aspects of the Ireland–Claisen rearrangement and related processes have been reviewed recently <2002T2905>. The origins of boat and chair preferences in the Ireland–Claisen rearrangement on cyclohexenyl esters have been studied <2003JOC572>. The rearrangement of simple enolates from allylic esters is a practical variant of the Claisen rearrangement <1999T3723> that usually proceeds with high stereochemical control <1996TL3005, 2001JA3687>. The chelation-controlled Claisen rearrangement yields (*Z*)-trisubstituted alkenes with high selectivity; this (*Z*)-selectivity has been rationalized by postulation of a seven-membered ring chelate in the transition state prior to rearrangement <1995JOC5093>.

The catalytic diastereoselective reductive Claisen rearrangement has been reported in the reaction of allylic acrylates in the presence of chiral phosphine inductors <2002OL2743> (Equation (75)) or different Lewis acids <2002TL4837>. The possibility to perform the Ireland ester enolate Claisen rearrangement using a polymer-supported silyl triflate has been communicated, an important result that opens the way to carry out this reaction using the solid-phase technique <1999TL3289>. An elegant implementation of the Ireland ester enolate Claisen rearrangement has been set up in the total synthesis of naturally occurring dolabellane, featuring an unprecedented enantioselective Claisen rearrangement of an achiral 15-membered macrocyclic lactone <1996JA1229>, and in synthetic studies directed to the synthesis of dihydroxyvitamin D analogs <1999JMC3539>.



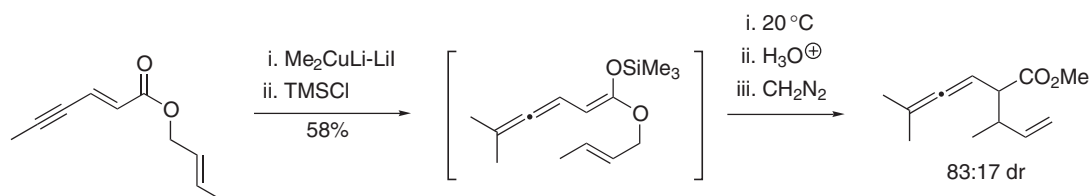
Using the Ireland ester enolate accelerated Claisen rearrangement, α -silylated allyl alcohols were transformed into the corresponding acetates or propionates, that after deprotonation and silylation afforded α,δ -silylated- γ,δ -unsaturated carboxylic acids <1996HCA391>. The Ireland–Claisen rearrangement has been used as a probe for the diastereoselectivity of nucleophilic attack on a double bond adjacent to a stereogenic center carrying a silyl group <2003OBC4005>. Polycyclic aromatic compounds have been prepared from benzannulated enyne-allene derivatives

obtained from Ireland–Claisen rearrangements <2003JOC8545>. In the sugar field, a full account has been published on the stereochemistry and structural limitations of the Ireland–Claisen rearrangement <1999S121>, and a new method for the synthesis of C-glycosides (Equation (76)) <1999TL5677>. Using conveniently functionalized *N*-(allyloxyacetates) β -lactam templates, the Ireland–Claisen rearrangement has given dienes that, under the ring-closing metathesis reaction conditions using Grubbs' catalyst, afforded medium-sized annulated β -lactams <2000JOC3716>. In the steroid area, the Ireland–Claisen rearrangement has been used with advantage in Δ^{23} -22-alcohols to perform $\Delta^{22,25}$ -24-alkyl chain elongation <2000TL5765>. The Ireland–Claisen rearrangement has been tested in differently substituted tricarbonyliron complexes <1996CB427, 1997TL351>, in the synthesis of α -methoxy- β -trifluoromethyl- γ,δ -unsaturated carboxylic acid derivatives <1997TA223>, in a synthetic approach toward ciguatoxin <1997CL845>, toward quartromicin spirotetronic acid subunits <1997TL8785>, in the stereoselective synthesis of alkylidene cyclohexenes <1998TL7043>, in the construction of 1,3-dienes containing an (*E*)-double bond and an *exo*-methylene group <1995CC1497>, in a new route to substituted glutaric acid derivatives <1995SC183>, and in the preparation of 2,3-disubstituted succinates <1998SL531>.



The Ireland–Claisen rearrangement has also been applied in synthetic studies directed to the synthesis of sarcodictyins and eleutherobin <1999TL153>, in the stereoselective formation of C2–C3 bond in taxanes <1999TL4659>, in the preparation of key synthetic intermediates for fumagillin and ovalicin <1999TL4797>, in the synthesis of C29–C44 fragment of spongistatin <2000JOC4145>, fluoroalkylated <2001TA2743> or allyl silane-containing <2001TL191> amino acids, in synthetic studies directed to forskolin <1997JOC6985>, in the stereoselective synthesis of the rhizoxin C1–C9 and C12–C26 subunits <1998TL2239, 1998JOC6952>, in the synthesis of novel matrix metalloproteinase inhibitors <1998BMCL1359, 2002JMC2289>, in a synthetic approach to azadirachtin <2002OL2877>, or eupomatilones <2002OL19, 2002JOC2042>. The Still–Wittig and the Ireland–Claisen rearrangements have been used in the synthetic sequences leading to serine *cis*- or *trans*-proline isosteres <2003JOC2343>. Recently, chemists at Merck have disclosed the preparation of a series of highly potent benzodiazepine γ -secretase inhibitors, with potential activity in Alzheimer's disease, which were prepared using a modified Corey asymmetric Ireland–Claisen rearrangement <2003JMC2275>, the enantiomeric excess being higher than 99%.

In a new synthetic approach, the formation of the key enolate intermediates in the Ireland–Claisen rearrangement has been promoted by Michael addition of organocuprates, or lithium enolates, to α,β -unsaturated esters; the enolates formed rearrange *in situ* or are trapped by silyl chlorides before rearrangement <1995T12631, 1995JOC8140>. The 1,6-conjugate addition of organocuprates to 2-propen-1-yl and 2-buten-1-yl 2-en-4-ynoates followed by *in situ* enolate capture with silyl electrophiles is followed by a quick [3,3]-sigmatropic rearrangement that yields 2-substituted methyl 3,4-dienoates <1997LA725> (Scheme 22).

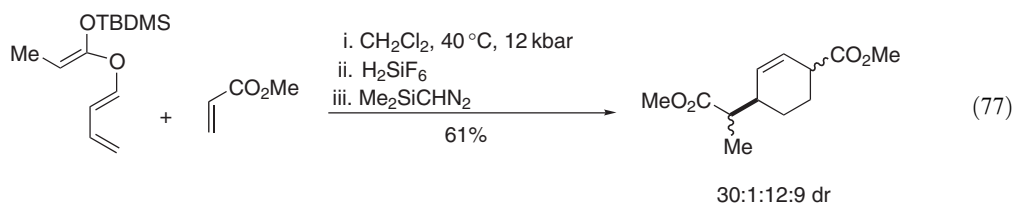


Scheme 22

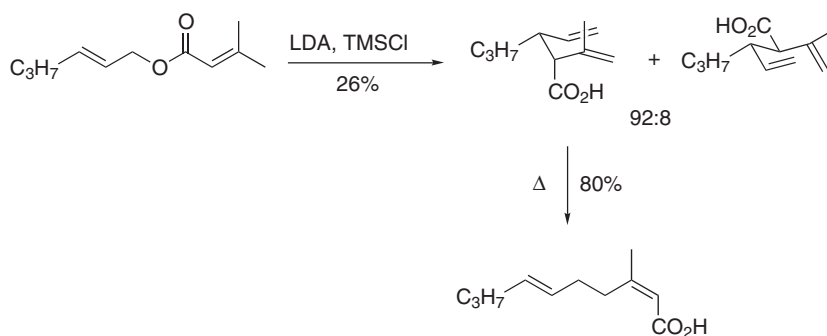
This attractive strategy has also been proposed but using a radical-based Michael addition to a suitably functionalized allylic ester acrylate promoted by a combination of reagents such as manganese, lead dichloride, and trimethylsilyl chloride <1996JOC8728>.

In two consecutive articles in the same journal issue, Piscopio <1998JOC3158> and Burke <1998JOC3160> reported enolate Claisen rearrangement and Ireland–Claisen rearrangement, respectively, on allyl-heteroatom-(C, O, S, N)- α -substituted acetates for the synthesis of intermediates that were transformed into carbocycles or heterocycles via ring-closing metathesis carbocyclization strategies.

A tandem sequence based on the Diels–Alder reaction of dienes and acyclic dienophiles such as methyl acrylate followed by *in situ* Ireland–Claisen rearrangement of the resulting adduct has been reported <1999SL925, 2000HCA2712>; the whole process allows the synthesis of carbocycles in good yield and stereoselectivity (Equation (77)). The same procedure has been applied to *N*-butadienyl-*N*-alkyl-*N*,*O*-trimethylsilyl ketene acetals for the synthesis of fused heterocyclic ring systems <1996SI239, 1996T11643, 2000HCA2266>.



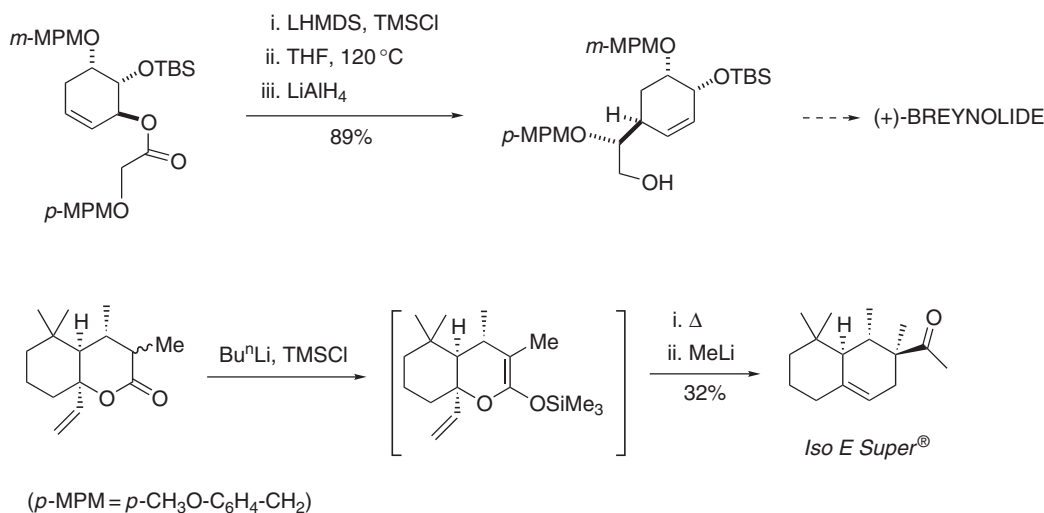
Recently, a simple variant of the Carroll rearrangement has been proposed where instead of a β -keto ester a mixed allyloxy malonate has been used as template; this structural and functional arrangement allows the incorporation of chirality on one of the ester moieties for asymmetric synthesis; after trimethylsilyl ketene acetal formation the Ireland–Claisen rearrangement affords the expected γ,δ -unsaturated esters; this strategy has been applied to the synthesis of (+)-methyl dihydroepijasmonate and (+)-methyl epijasmonate <2000AG(E)569>. Tandem Ireland–Claisen rearrangement followed by Cope rearrangement of the resulting crude reaction mixture has been described in the treatment of 2-hexenyl 3-methyl-2-butenates with bases [LDA, LDE (lithium diethylamide), LHMDs] followed by quenching with TMSCl; an Ireland–Claisen rearrangement product was obtained that on heating afforded the Cope compound in good yield (Scheme 23) <1998SL70>.



Scheme 23

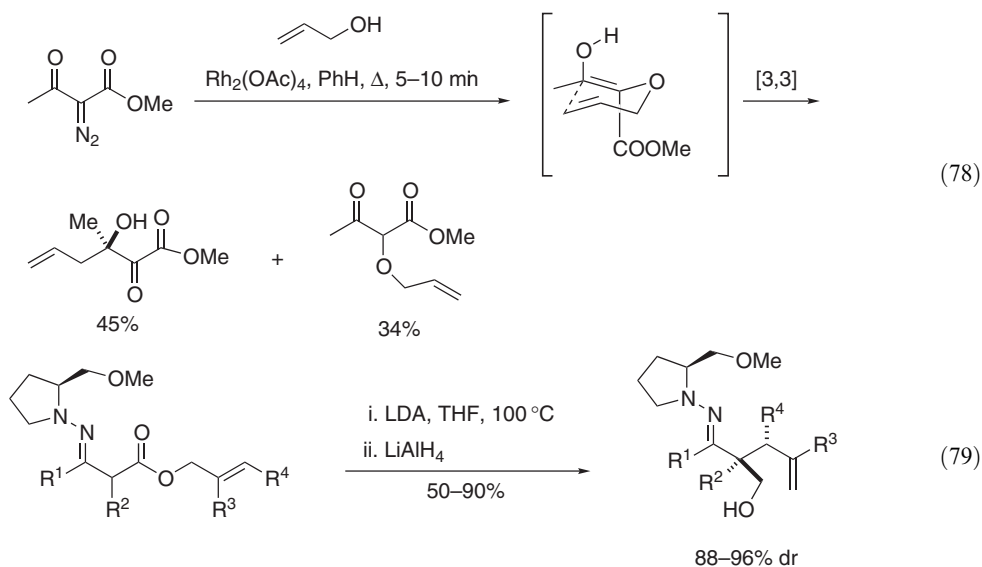
Many applications to the synthesis of natural products have been described using the Ireland ester-enolate Claisen rearrangement, as in the synthesis of (*S*)- and (*R*)-verapamil <2001EJO1349>, long-chain unsaturated dienoic acids <1996TL2349>, for the synthesis of useful intermediates for the preparation of substituted tetrahydrofurans <2002T1865>, (+)-breynolide (Scheme 24) <1999TL9>, myxalamide A <1999JOC23>, aspidophytine <1999JA6771>, herboxidiene <1999JCS(P1)955>, racemic patulolide <1999TL471>, the fragrant molecule *Iso E Super*[®] used in perfumery <1999HCA1016> (Scheme 24), epothilones B and D <2001TL8373>, the potent toxin atractyligenin <1997JA11769>, the asymmetric synthesis of (–)-methyl palustramine <1998JOC7490>, sphydrofuran <1998JOC8595>, the hemiacetal pheromone of the spined citrus bug *Biprorulus bibax* <1995LA1451>, (+)-Prelog-Djerassi lactone <1998T11567>, racemic samin and other furanofuran lignans <1997JCS(P1)857, 1998JCS(P1)1779>, 14-membered macrolide galbonolide B <1998JCS(P1)3541>, in synthetic approaches to 1- α -fluoro-25-hydroxy-vitamin D₃ analogs <1998JOC6984>, total synthesis of β -elemene and fuscil <1995JA193>, β -lactone enzyme

inhibitor (–)-ebelactone <1995JOC3288>, (–)-indolizidine 167B <1997JOC8549>, total synthesis of (+)-iridomyrmecin <1997SL657, 1999JCS(P1)3579>, an asymmetric synthesis of (–)-fumagillol <1997TL4437>, the alkaloids (–)-trachelanthamidine, (–)-iso-retronecanol, and racemic turneforcine <1997JCS(P1)2089>, in the formal total synthesis of the alkaloid magellanine <2001CL546, 2003TL6029>, in the total synthesis of the antitumor antibiotics (–)-methylenolactocin and (–)-phaseolinic acid <2001SL120>, a practical synthesis of (+)-discodermolide <2001JA9535>, the synthesis of (–)-ciantrin B, a phospholipase A₂ inhibitor <2002JOC4392> and in the synthesis of brassinosteroids <2002TL3169>.

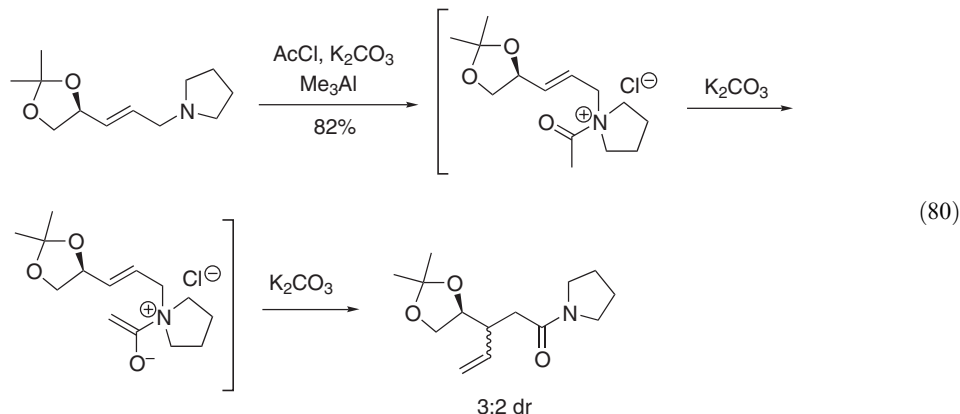


Scheme 24

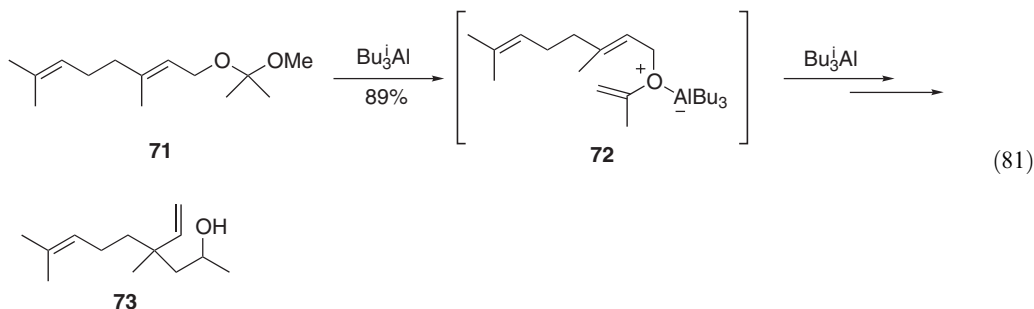
(e) *The Carroll rearrangement.* The Carroll reaction is a useful method for preparing γ,δ -unsaturated ketones from allylic acetoacetates <1940JCS704, 1940JCS1266, 1943JA1992>. A facile entry to the synthesis of arylacetones and related derivatives has been communicated using the Carroll rearrangement <1995TL3597>. A variant of the classical Carroll rearrangement has been reported in the rhodium(II)-catalyzed reaction of α -diazo-ketoesters with allylic alcohols; under these conditions the intermediate O–H insertion products rearrange to give α -hydroxy- α -ketoesters and insertion products in good overall yield (Equation (78)) <1999OL371, 1999JA1748>. The first asymmetric Carroll rearrangement using chiral auxiliaries was reported in 1995 by Enders <1995AG(E)2278, 1996LA1095> (Equation (79)).



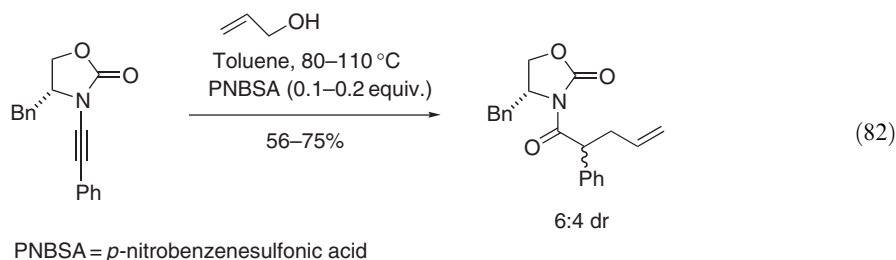
(f) *Charge-accelerated Claisen rearrangement.* A zwitterionic intermediate species has been invoked in the mechanism for the Claisen rearrangement leading to γ,δ -unsaturated amides from allylic amides and acetyl chloride (Equation (80)); the reaction proceeds in good yield and moderate diastereoselectivity <1995JOC3773>. Esterification of *N*-*t*-BOC glycine with enantio-merically pure unsaturated alcohols gives intermediates that on treatment with LDA and zinc chloride gives Claisen rearranged products, presumably via nitrogen charged intermediates, in good yield (70%) and with complete transfer of chirality <1996CC1683>.



The Bu_3Al -catalyzed formation of the enol ether **72** from alcohol **71** also promoted the unexpected Claisen charged accelerated rearrangement to give product **73** in good yield; the reaction has been extended to other alcohols showing the scope and limitations of the method (Equation (81)) <1995JOC4318>.

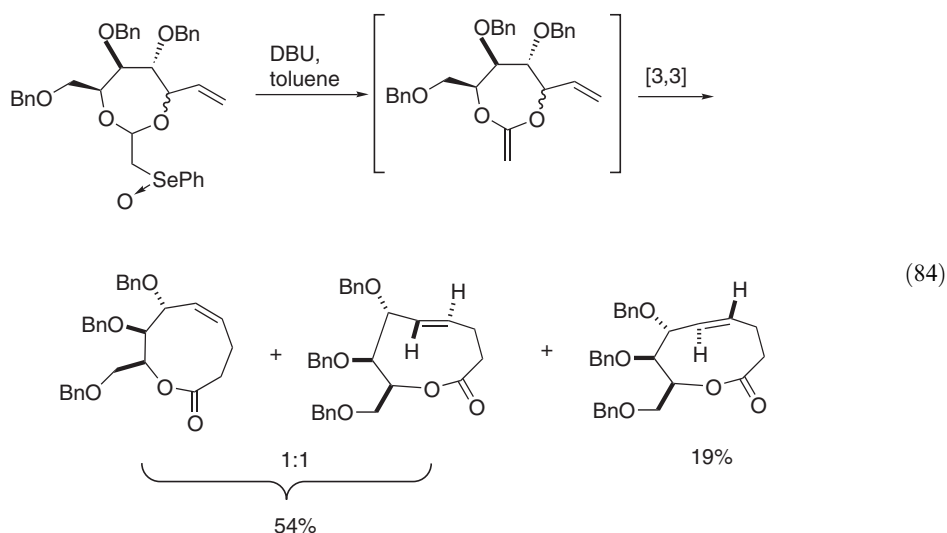
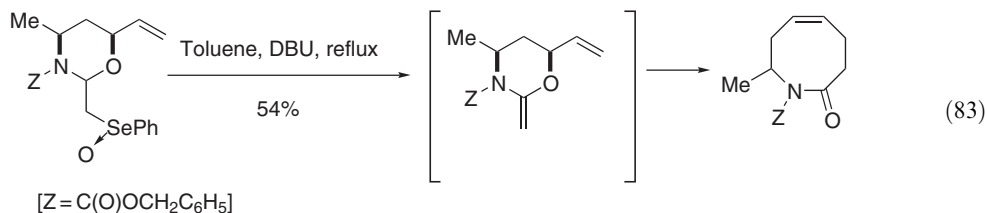


(g) *The Ficini–Claisen rearrangement.* In spite of the long-known seminal works by Ficini and co-workers on the ynamine–Claisen reaction <1966TL6425, 1968TL4139>, it was only recently that the first efficient and stereoselective acid-promoted Ficini–Claisen rearrangement has been reported using chiral ynamides <2003SL1379>, under mild conditions, at low temperatures <2002OL1383> (Equation (82)).



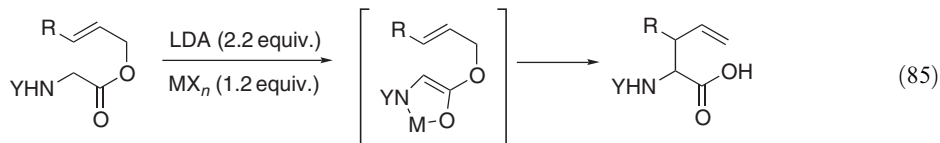
(h) *The Holmes–Claisen rearrangement.* This is a variant of Claisen rearrangement based on the rearrangement of vinyl-substituted ketene acetals and enol ethers that has proved to be an efficient method for the synthesis of unsaturated medium ring ketones and medium ring lactones <1986CC325, 1991T7171, 2000CC629, 2000CC631, 2000TL117, 2002T1943>. In recent developments the Claisen rearrangement of 2-methylene-5-vinyl tetrahydrooxazoles has afforded unsaturated seven-membered lactams (azepin-2-ones) <1994JCS(P1)3397>, studies that have been

extended to the synthesis of unsaturated eight-, nine- and ten-membered medium ring lactams ($n = 1, 2, 3$) from vinyl-substituted precursors in the presence of DBU (Equation (83)) <1995CC2325, 1996JCS(P1)123>. Pearson has applied this methodology for the synthesis of nine-membered ring lactones from suitable intermediate ketene acetals (Equation (84)) <1996JOC5546>. A related Claisen rearrangement was published by Petrzilka in 1978, and applied to the synthesis of macrolides, such as racemic phoracantholide <1978HCA3075>.



(ii) The Kazmaier–Claisen rearrangement

The allylic ester of protected amino acids undergo asymmetric chelate Claisen rearrangement in the presence of cinchona alkaloids leading to γ,δ -unsaturated amino acids, peptides, and aza-heterocycles in a highly stereoselective manner <1995MI77, 1995MI283, 1997LA285, 1998CC2535, 1999JIC631, 1999JOC4574, 1999S1671, 1999TL479, 2000EJO1241, 2000S914, 2000SL1004, 2000SL1523, 2001S487, 2001CEJ456, 2001EJO4067, 2001CHIR357> (Equation (85)).



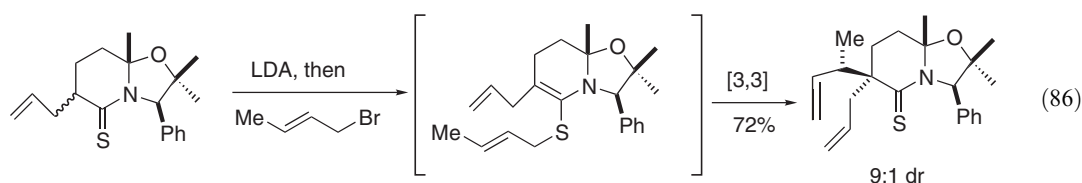
The asymmetric chelate-enolate Claisen rearrangement <2002CEJ1850> has been applied to the synthesis of allenic amino acids <1996S1489, 1998SL434>, quaternary amino acids containing β,γ - as well as γ,δ -unsaturated side chains <1995AG(E)2012, 1995CC1991, 1995SL1138, 1996TL5351>, 5-*epi*-isofagomine <1998TL817, 1998EJO1155>, to the synthesis of unsaturated polyhydroxylated amino acids <1996SL975, 1998S1321>, and highly demanding α -alkylated amino acids <1996TL7945, 1996T941, 1996JOC3694>. This strategy has also been used for the synthesis of an α -cyclohexyl glycine substituted intermediate en route to morphine <1997JOC1194, 2001BMCL627>, and for the synthesis and determination of the stereochemistry of 2-amino-3-cyclopropylbutanoic acid, a plant regulator <2002CC42>, in the synthesis of furanomyacin derivatives <2002BMC3905>, and in the preparation of the C-glycoside α -D-C-mannosyl-(R)-alanine <2002T9381>.

Recently, a modified Kazmaier–Claisen rearrangement has been investigated where the allylic alcohol bears a trialkylsilyl substituent at C1, leading to final allyl silane modified amino acids in good yield and excellent *syn/anti*-diastereoselectivity <2002HCA4165>.

1.18.2.6.2 Thia-Claisen rearrangement

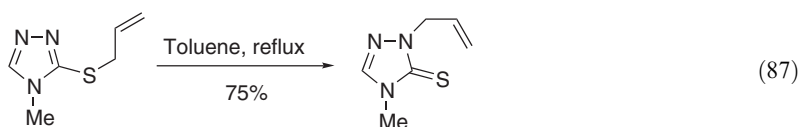
The thia-Claisen rearrangement of allyl, vinyl sulphide and its applications in organic synthesis have recently been investigated <1995HAC559>, reviewed <1997BCJ2571, 1999TCC(204)127, 2003T7251>, and attracted some synthetic interest in the last years <1995JOC2692, 1995CC2345, 1997TL2413, 1997T17253, 2000EJO3463>. Some theoretical studies have been advanced <1996JCS(P2)2065, 1997JCS(P2)2737>.

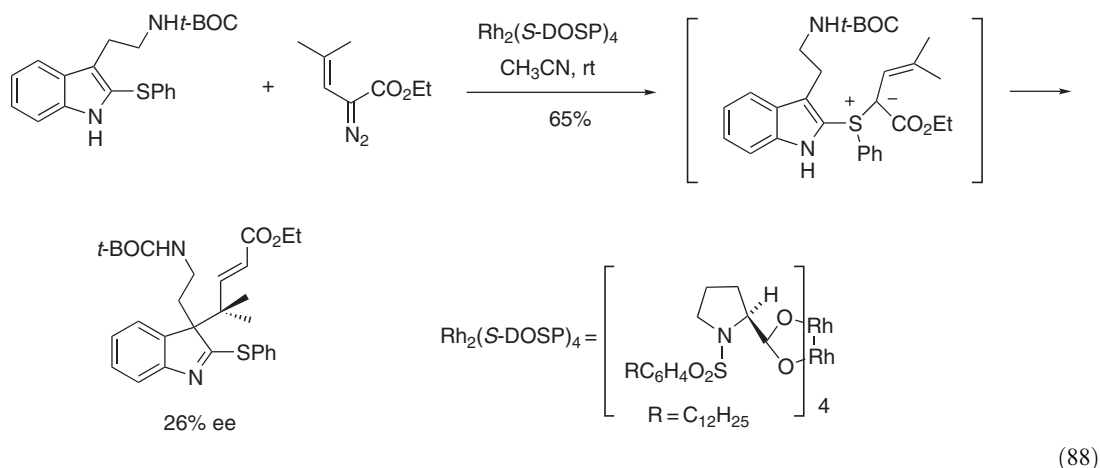
The thia-Claisen rearrangement of *S*-allyl ketene dithioacetals gives the expected allylated dithioesters with excellent diastereoselectivity <1996PAC863>. The thia-Claisen rearrangement has been applied in *S*-allyl, propargyl, methylallyl thioiminium salts prepared from *N*-benzyl thiopyroglutamates to give 4-substituted thioxoprolinates in a facile process and in good yield <1995TL8467, 2003JOC993>. Meyers' group has been particularly active in this subject <1997CC1> (Equation (86)), and has reported the total synthesis of (–)-trichodiene <1998JA5453>, the synthesis of chiral cyclohexenones with vicinal stereogenic quaternary centers <1999JOC3585> and the palladium and nickel catalyzed thia-Claisen rearrangement of chiral bicyclic thiolactams via *N,S*-ketene acetals <2000TL815, 2000TL1363>. Rawal and co-workers have reported an efficient and highly diastereoselective version of the thia-Claisen rearrangement using *C*₂-symmetric pyrrolidine as chiral inductor and removable chiral auxiliary <2000JA190>. The use of chiral bicyclic proline derivatives as chiral auxiliaries for the asymmetric thio-Claisen rearrangement has been described <1996LA927>. Metzner and associates have reported on the asymmetric Claisen rearrangement promoted by a sulfinyl group in a new method for the synthesis of α -sulfinyl dithioesters <1997AG(E)371, 2001JOC7841, 2002CEJ632>.



The thia-Claisen rearrangement has also been documented in the rearrangement of camphor-derived 1,3-oxathianes; this strategy allows the synthesis of macrocyclic thiolactones in high yield and with complete control of the absolute configuration at tertiary and quaternary stereocenters <2002CC2534>. Majumdar has described a thia-Claisen rearrangement example in the synthesis of [6,6]pyranothiopyran ring system by refluxing conveniently functionalized 4-(4'-aryloxybut-2'-ynylthio)[1]benzopyran-2-ones <1997JIC884, 2002OL2629, 2002TL2111, 2002TL2115>, and in the synthesis of thieno[2,3-*b*]thiochromen-4-one derivatives <2002SC1271>.

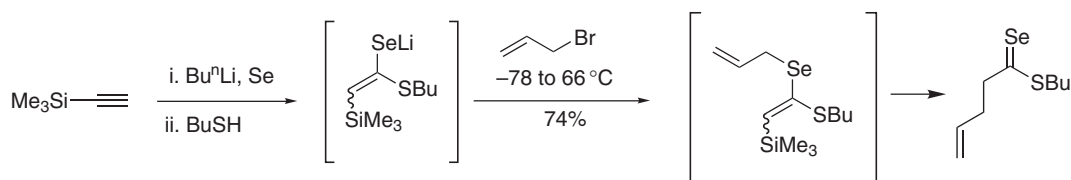
Allylic *S*-methyl thiocarbonates (xanthates) rearrange in a thia-Claisen-like reaction to give allylic thiols after basic hydrolysis <2000TL1703>. 3-Allylthioallyl triazoles rearrange to the corresponding *N*-allyl derivatives (Equation (87)) <1999H(51)475>. Thioallenylidene complexes have been prepared for the first time via thia-Claisen rearrangement of sulfonium salts formed *in situ* from ruthenium-butatrienylidene intermediates <1999EJO2121>. Reports have highlighted moderate chirality transfer in intramolecular [3,3]-sigmatropic thia-Claisen rearrangements with sulfonium salts obtained upon treatment of 2-thioindoles with vinyl diazoacetates in the presence of chiral rhodium(II) catalysts <1999EJO2459> (Equation (88)) <2003TA911>.



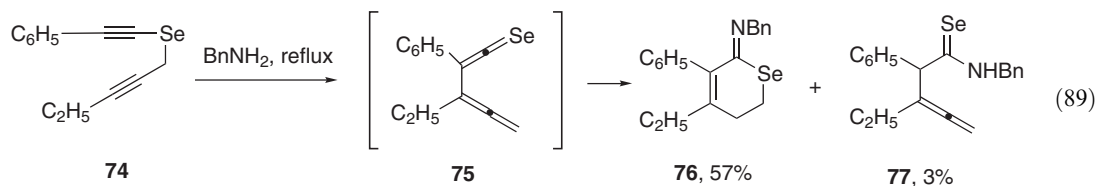


1.18.2.6.3 Seleno-Claisen rearrangement

The reaction of lithium alkynyl selenolates generated from terminal acetylenes with thiols gave rise to lithium selenolates with high stereoselectivity, that on trapping with allylic bromides afforded γ,δ -unsaturated selenothioesters via seleno-Claisen rearrangement (Scheme 25) <1996TL2839, 1997T12237>. The [3,3]-sigmatropic seleno-Claisen rearrangement of 2-pentynyl phenylethynyl selenide **74** in the presence of amines gave compounds **76** and **77** via intermediate **75** (Equation (89)) <2001JOC4099>.

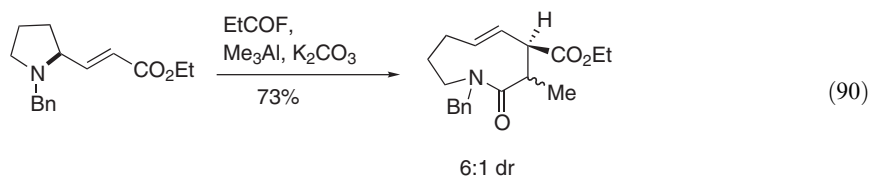


Scheme 25



1.18.2.6.4 Where Z = N; the aza-Claisen rearrangement and related processes

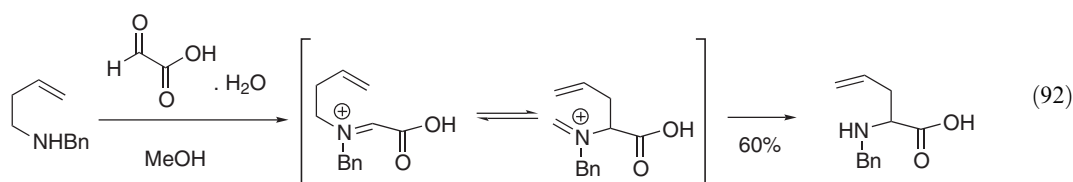
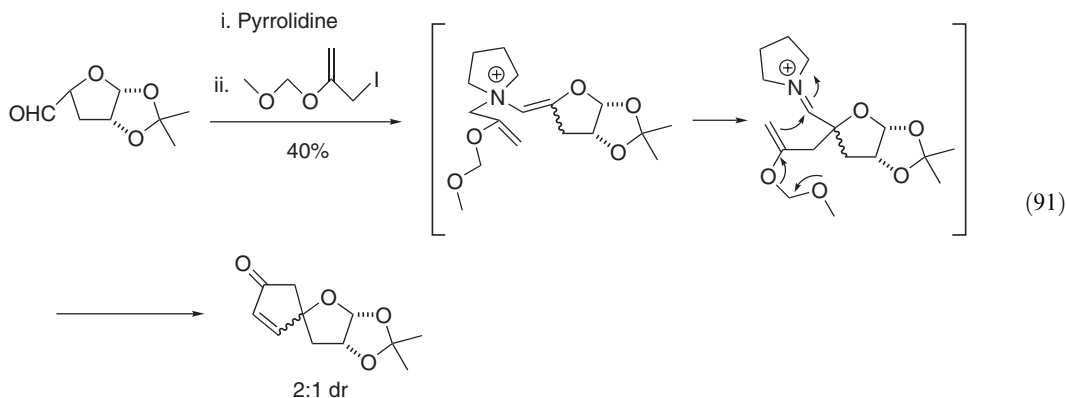
Ab initio calculations and computational studies on the aza-Claisen rearrangement have been published <1996JOC978, 2002CEJ641>. The aza-Claisen rearrangement has been reviewed <B-2000MI001, 2001MI89> covering essentially its application to the synthesis of unnatural α -amino acids for complex molecule preparation. The zwitterionic aza-Claisen rearrangement of various *N*-allyl amines with carboxylic acid chlorides has been developed as a mild and efficient method to form γ,δ -unsaturated amides or lactams <1995AG(E)1026, 1996CEJ894, 1996JCS(P1)115, 1998AG(E)1140, 1996JOC3677, 2002T1317>. A significant improvement has been observed by replacing the carboxylic acid chlorides by the corresponding fluorides (Equation (90)) <1999SL25, 2000JOC1710>.



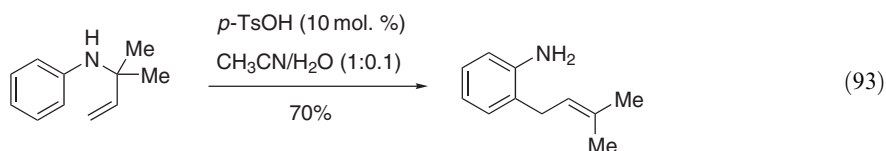
Davies has just reported a double diastereoselective [3,3]-sigmatropic aza-Claisen rearrangement which takes place on *N*-allyl-*N,O*-silylketene aminals <2003CC2134>, the diastereoselectivity obtained depends on the configuration of the starting amina.

The Mukaiyama reaction of the trimethylsilyl enol ether of [1,4]oxazin-2-ones with α -alkynyl ketones gives intermediates that on heating afford bicyclic adducts via 2-aza-Cope rearrangement <1999JOC6891>. A 2-aza-Cope rearrangement was invoked to rationalize the observed epimerization in the enolate *C*-allylation of phenylglycine-derived oxazaborolidinones <1999JA2460>.

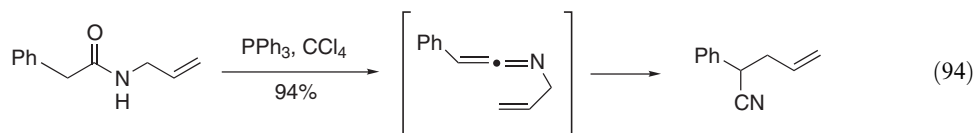
The sequence, Mannich reaction followed by *in situ* 3-aza-Cope rearrangement of the ammonium salt, has been used in several instances for the preparation of chiral cyclopentenones from sugar templates <1995TL3137> (Equation (91)) in the total asymmetric synthesis of both enantiomers of strychnine <1995JA5776>, in a synthetic approach to the *Stemona* alkaloids <2001JOC7751>, and in a novel synthetic approach to carbapenems <1995CC2527>. The same synthetic sequence in related substrates leading to 2-aza-Cope rearrangement (also called “the Agami aza-Cope/iminium hydrolysis tandem reaction” <1993T7239>) has been applied in the synthesis of *N*-benzyl allylglycine (Equation (92)) <2000TL7961>, *N*-benzyl-4-acetylproline <2002TL903>, and in a synthetic approach to the core structure of the immunosuppressant FR901483 <2001OL1347>.



The amino aromatic Claisen rearrangement (also called 3-aza-Cope rearrangement) is a variant of the aromatic Claisen rearrangement where, instead of an *O*-allyl or an *O*-propargyl derivative, an *N*-(allyl)aniline substrate was submitted to the rearrangement conditions to give the corresponding *o*-allylanilines <1995TL4787, 2001S621, 1995MI508> (Equation (93)). The aromatic aza-Cope reaction of *N*-allylic anilines is accelerated by zeolites, proceeding at low temperatures and leading to mixtures of the *o*-*C*-allyl anilines and the corresponding indolines <1996TL5281>. This transformation has been used for the synthesis of intermediates in a synthetic sequence leading to conformationally fixed analogs of the antitumor indolactam-V <1995BMCL453>. The usually harsh thermal conditions (200–350 °C) have been changed to milder reaction parameters using Lewis acids or protic acids as promoters <1995S1287>. For example, these *o*-allyl aniline intermediates cyclize to the corresponding indolines in the presence of zinc montmorillonite under microwave irradiation <2000SL487>.



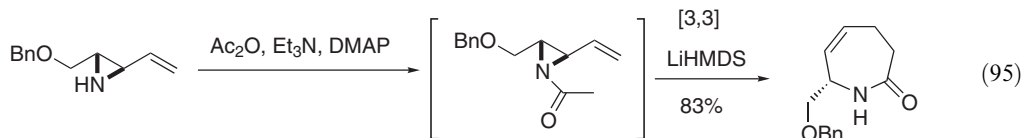
Examples document that the aza-Cope rearrangement is a highly competitive process in respect to the Mannich cyclizations in systems containing allyl silane π -nucleophiles <1996TL571, 1998JOC841>. Compounds with a non-nucleoside adenosine kinase inhibitor profile, having the heterocyclic ring system pyrido[2,3-d]pyrimidine have been prepared via aza-Cope rearrangement of intermediates obtained by imine formation between the corresponding benzaldehydes and 4,6-diamino-5-vinylpyrimidines <2001JMC2133>. The sigmatropic rearrangement of *N*-allylenamines is a useful method for the synthesis of γ,δ -unsaturated carbonyl compounds and δ,ϵ -unsaturated amines; this rearrangement is accelerated by the use of Lewis acids such as zinc chloride <1995JOC2807>. The rearrangement of 3-aza-1,2,5-hexatrienes, contrary to the normal forcing conditions that have been employed in the Cope transformations, takes place at room temperature, under essentially neutral conditions and with excellent chemical yields; these intermediate species allow the easy and efficient transformation of *N*-allyl amides into γ,δ -unsaturated nitriles using a number of reagents, the best being triphenylphosphine in carbon tetrachloride (Equation (94)) <1996JOC55>.



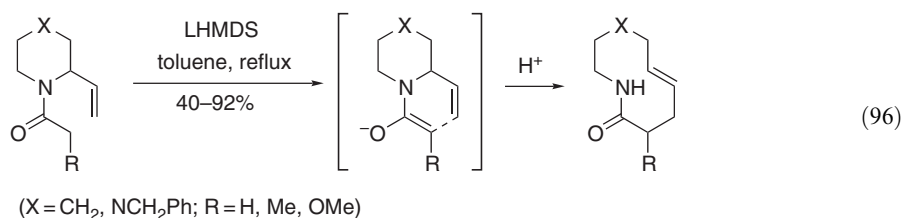
In a series of papers Majumdar and associates have reported the synthesis of unusual nitrogen-containing heterocycles using aza- or amino-Claisen rearrangements <2002S121, 2001TL4231, 2001T4955, 2001M633, 1996CJC1592>. This author has recently reviewed his contributions on this subject <2002JIC112>. The late transition-metal-catalyzed aza-Claisen [3,3]-sigmatropic rearrangement is a convenient method for the synthesis of various allylic amides from the corresponding alcohols <1999TL1449>. An aza-Claisen rearrangement was the invoked mechanism for the Lewis-acid-catalyzed Claisen rearrangement for the synthesis of β -amino- $\alpha,\beta,\epsilon,\gamma$ -unsaturated esters from simple allylic amines and allenolate esters <2002JA13646, 2001JA2448, 2001JA2911, 1999JA9726>. Using a chiral external ligand (ph-ambox) can form a cationic Pd(II) catalyst for the chiral aza-Claisen of allylic imidates to allylic amides in high enantioselectivity (up to 83% ee) <1999TL1449>.

The photochemical reaction between tertiary allylic amines and chromium complexes, in the presence of Lewis acids in a carbon monoxide atmosphere, affords γ,δ -unsaturated amides (or lactams), via a zwitterionic aza-Cope rearrangement <1996JOC2871>.

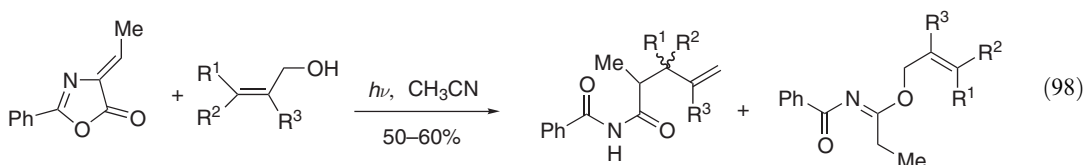
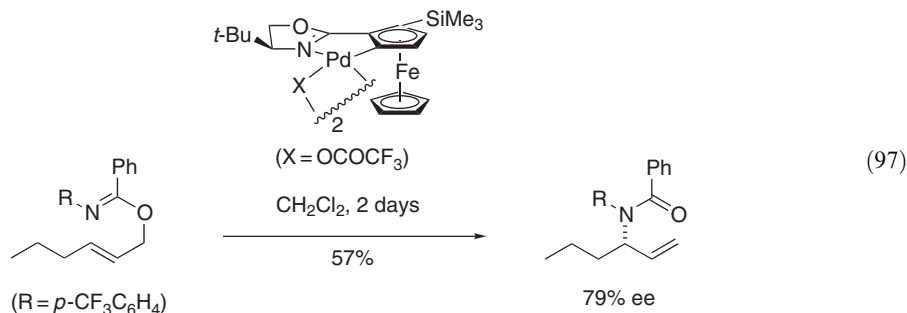
The aza-[3,3]-Claisen enolate rearrangement of vinylaziridines is a convenient method for the synthesis of mono-, di- and trisubstituted seven-membered lactams (Equation (95)) <1997JA8385, 1998S109, 2001CEJ94>.



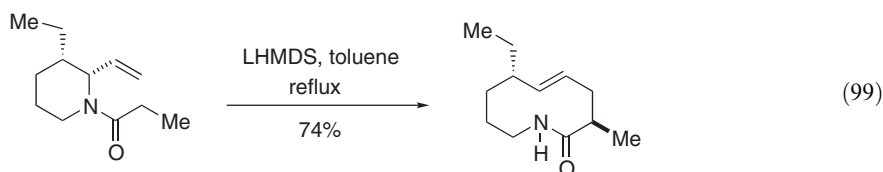
A new ring expansion reaction of 1-acyl-2-vinylpiperidine and the corresponding piperazine via aza-Claisen rearrangement of amide enolates has been described (Equation (96)) <1996SC1675>.



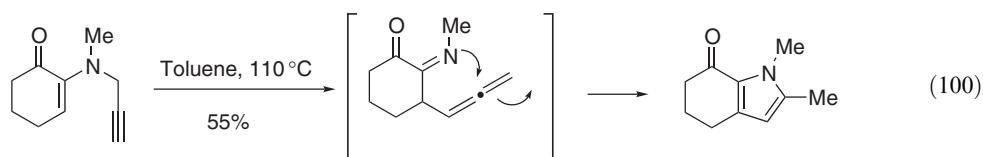
The imidate rearrangement is a variant of the aza-Claisen process. The asymmetric base-catalyzed imidate rearrangement gives γ,δ -unsaturated amides in moderate yield and high enantiomeric excess [<1997JOC4442, 1999T14941, 2003TA415>](#). The palladium-catalyzed rearrangement allows the transformation of an allylic imidate into an allylic amide [<1984AG\(E\)579, 1997JOC1449, 1997TL8837, 1998TA3213, 1998TA1065>](#); the use of chiral ligands has been reported to produce the final product in a very enantioselective manner [<1999JA2933, 1999CC2435, 2002TL9509>](#) (Equation (97)). The photochemical rearrangement of a series of *O*-allyl, *N*-benzoyl imidates has been reported (Equation (98)) [<1996TL4019, 1998TL9711>](#).



An aza-Claisen [3,3]-sigmatropic rearrangement has been the key step for the macrocycle formation in the synthesis of fluvirucinine A₁ [\(Equation \(99\)\) <1999AG\(E\)3545>](#), in the total synthesis of enantiomerically pure (–)-antimycin A_{3b} [<2000TL7667>](#), in the preparation of the tricyclic core of the cytotoxic marine alkaloid madangamine A [<1997JOC1920>](#), and in the synthesis of modified nucleosides such as 5'-branched 5'-aminothymidines [<1997HCA1589>](#), in synthetic studies directed to the preparation of inhibitors of protein kinase C isozymes [<1996JA10733, 1997BMC1725>](#), in the synthesis of the bicyclic core of the pumiliotoxin alkaloids [<2002EJO3304>](#), in the synthesis of *C*-allylglycines for the preparation of isoquinolones [<2002S242>](#), in the total synthesis of racemic gelsemine [<1999AG\(E\)2934>](#), in the highly enantioselective formal synthesis of indole alkaloid tryprostatin B [<2000TL3611>](#), and in the total synthesis of another indole alkaloid, okaramine J [<2003OL2825>](#).

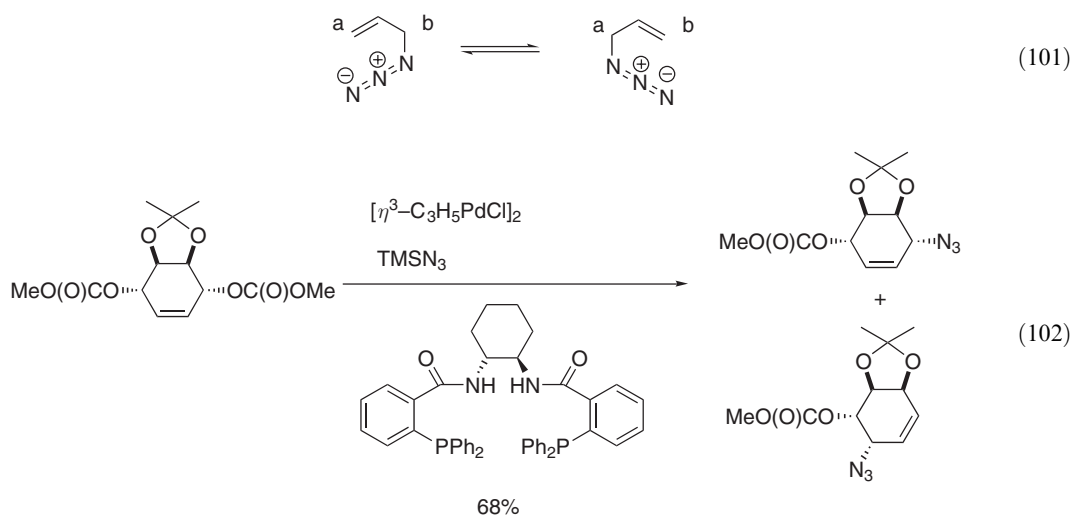


A new variant (the aza-Bergman) of the classical aza-Claisen rearrangement has been described in the thermal rearrangement of *C,N*-dialkynyl imines for the synthesis of 2,5-didehydropyridines [<1997JA1464>](#). The [3,3]-sigmatropic rearrangement of a *N*-vinyl-*O*-acetylhydroxylamine, obtained by acetylation of the corresponding nitron, has been documented in the critical quaternary center formation in the synthetic sequence for fumagillol, fumagillin, and TNP-470 [<1999AG\(E\)971, 2003CHIR156>](#). The thermal rearrangement of *N*-alkyl-*N*-vinyl-propargylamines leads to annulated[*b*]pyrroles with moderate to good yields via a tandem aza-Claisen rearrangement–cyclization reaction (Equation (100)) [<1996TL6709>](#).



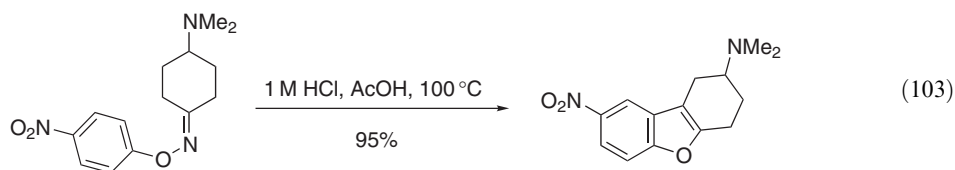
1.18.2.7 Other Heteroatom Variants

Many heteroatom variants of the Claisen rearrangement (3-hetero-Cope rearrangement) have been reported, playing an important role in the stereocontrolled introduction of allylic functionality involving secondary hydroxyl groups [<1971CC328, 1984AG\(E\)579, 1996T13919>](#). The mechanism of the addition of allyl metal (Zn, Sn, Li, Mg, etc.) to vinyl metal has been theoretically investigated by density-functional methods showing a dichotomy between the metallo-ene reaction and metallo-Claisen rearrangement [<1997AG\(E\)2469, 2000JA11791>](#). The stereoselective hetero-Claisen rearrangement of camphor-derived oxazoline *N*-oxides upon treatment with acylating agents give α -acyloxyoxazolines [<1998TL2107, 1996SL297>](#). A new thiazole synthesis has been discovered via the polyhetero-Claisen rearrangement in the intermediate resulting from the cyclocondensation of thioamides with alkynyl(aryl)iodonium reagents [<1996JOC8004>](#). A similar iodonium-Claisen rearrangement has been investigated in allenyl(*p*-methoxyphenyl)iodine substrates [<1995JOC2274>](#). A very remarkable case is the [3,3]-sigmatropic rearrangement of allylic azides ([Equation \(101\)](#)), a process that has proved to be of synthetic interest for the preparation of advanced intermediates, useful in the preparation of natural products (pancratistatin, conduramine-E) ([Equation \(102\)](#)) [<1995TL8737>](#).



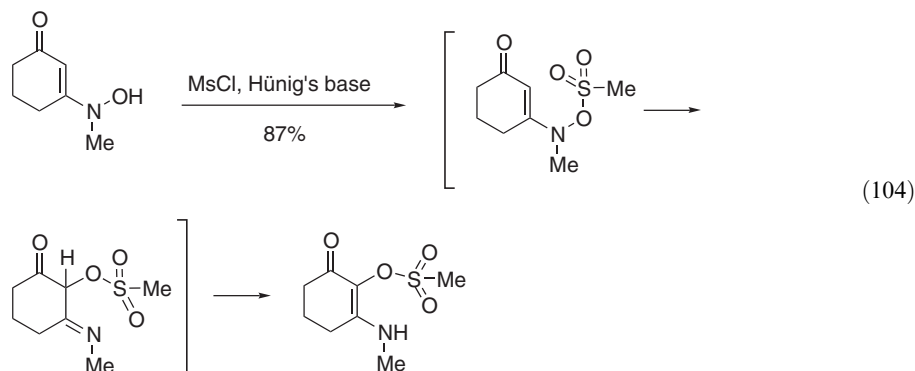
Ab initio studies have been published on the phospho-Cope rearrangement [<1995JOC7101>](#). An oxa-Cope rearrangement has been reported for the synthesis of silenes from 1,2-bis[tris(trimethylsilyl)silylcarbonyl]alkanes [<2001JA8400>](#).

The acid-catalyzed [3,3]-sigmatropic rearrangement of *O*-aryloximes [<1998BMCL2099, 2003JOC770>](#) ([Equation \(103\)](#)) and the thermal rearrangement of allyloxytetrazoles to *N*-allyltetrazolones [<1997JCS\(P2\)489, 2002JCS\(P1\)1213>](#) are interesting cases of hetero-[3,3]-sigmatropic rearrangements.



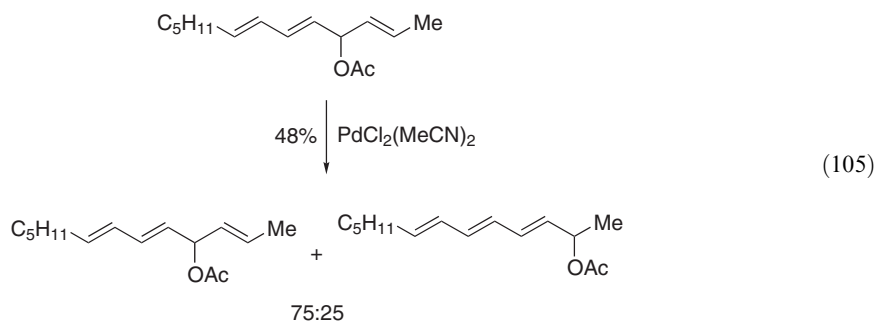
1.18.2.8 Where Y = Z—C—Z'

Polyhetero substituted precursors have been reported to rearrange in [3,3]-sigmatropic Cope processes <1980T3, 1984AG(E)579, 1984CRV205, 1988CRV1423, 1989S71>. This is the case of differently substituted ene hydroxylamines derived from carbocyclic or heterocyclic 1,3-dioxo compounds; these substrates rearrange spontaneously or upon heating in good yields <2003EJO190> (Equation (104)).



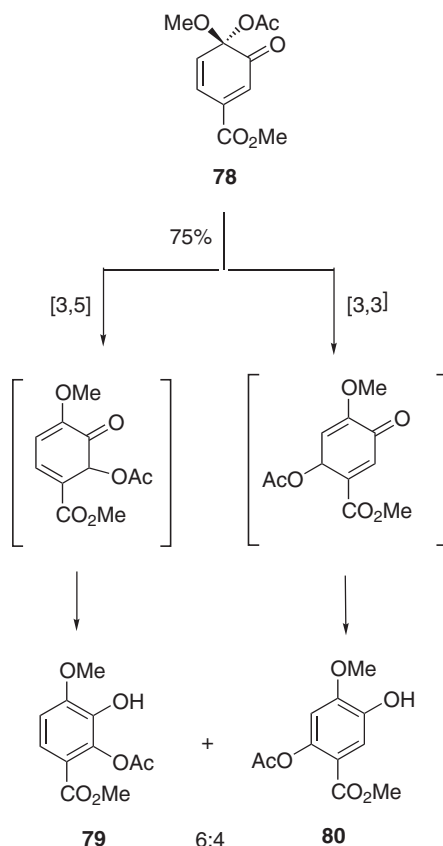
1.18.2.8.1 Where Z and Z' = chalcogen

$\text{PdCl}_2(\text{MeCN})_2$ <1999T4353> (Equation (105)) or $\text{Eu}(\text{fod})_3$ <2001TL4215> catalyze the [3,3]-sigmatropic rearrangement of allylic acetates. CoCl_2 also catalyzes the allylic rearrangement of allylic acetates: tertiary acetates completely rearrange, whereas secondary acetates afford mixtures of isomers. As a practical example, the synthesis of chiral 3*E*,5*E*-octadiene-1,2*R*,7*R*,8-tetraol structural motifs by palladium-promoted hetero-Claisen rearrangement of allylic acetates has been reported <1996T13919>. It has also been found that in the presence of catalytic amounts of cobalt dichloride, acetic anhydride, and acetonitrile, allylic alcohols gave in a one-pot process mixtures of allylic acetamides in moderate yield. Regarding the mechanism it seems that a π -allyl complex is the key reactive species rather than a [3,3]-sigmatropic rearrangement of an acetamdate obtained in a Pinner reaction <1995JOC2670>.

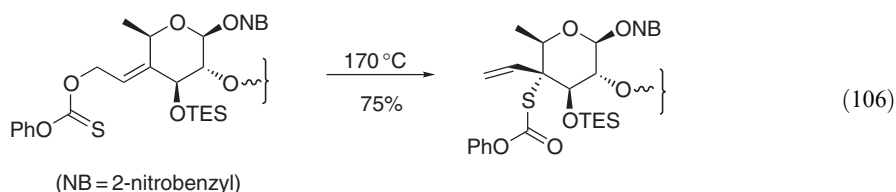


Allylic bromides upon treatment with sodium acetate in boiling acetonitrile gave the rearranged allylic acetates <2000JCS(P1)1753>. The sigmatropic rearrangement of allylic acetates in ortho-quinone monoketals derived from 3-hydroxy-4-methoxybenzoate, such as **78**, has been investigated, showing that after treatment with silica gel in dichloromethane, compounds **79** and **80** were isolated in a 6:4 ratio in 75% total yield (Scheme 26) <1999TL615>.

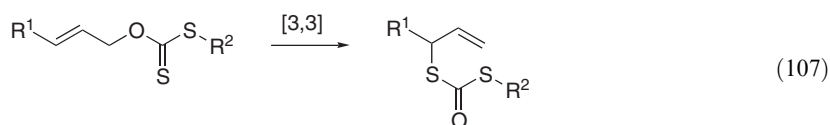
Allylic acrylates also rearrange to the corresponding isomer <2000EJO219>, and 6-fumaryl 1,3,8-nonatrienes substituted at the C-5 position by an unsaturated unit undergo [3,3]-sigmatropic rearrangements which compete with the Diels–Alder cyclization <2002TL2753>. In a progress report on the total synthesis of the enediyne antitumor antibiotic namenamicin, Nicolaou described the [3,3]-sigmatropic rearrangement of allyl thiocarbonates (Equation (106)) <1999JCS(P1)545>.



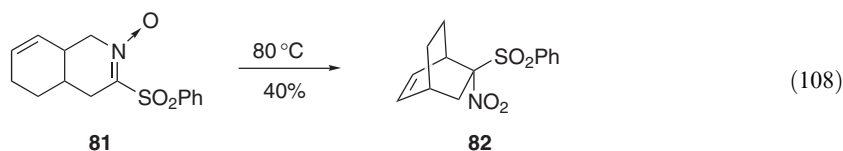
Scheme 26



The thiono-thiolo rearrangement [<1997MI137>](#) has been investigated in the case of the reaction of allylic alcohols with thiophosgene in pyridine, which gives the corresponding thiono chloroformates that spontaneously rearrange at room temperature to the thio chloroformates in yields ranging from 54% to 77% [<1999TL8059>](#). The [3,3]-sigmatropic rearrangement of *O*-(2-alkenyl) *S*-alkyl dithiocarbonates (allylic xanthates) to *S*-(2-alkenyl) *S*-alkyl dithiocarbonates (dithiolcarbonates) [<1996TL2445, 2002CC2394>](#) (Equation (107)) constitutes one of the key steps in the total synthesis of (5*S*)-thiolactomycin [<1997JCS\(P1\)417>](#).

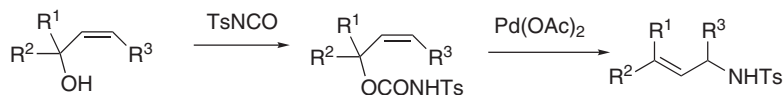


The thermal transformation of nitronic ester **81** at 80 °C in benzene or ethanol into the nitrosulfone **82** appears to be the first reported example of the [3,3]-sigmatropic rearrangement of an *O*-allyl nitronic ester [<2002CC1090>](#) (Equation (108)).



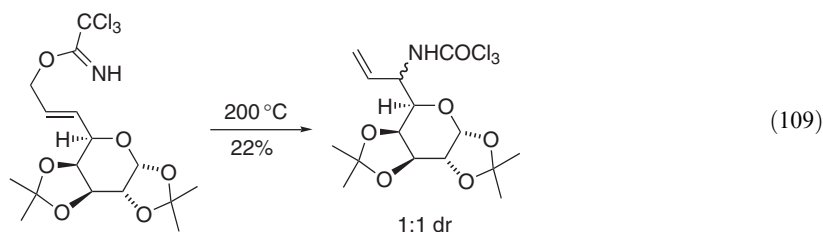
1.18.2.8.2 Where Z and/or Z' = nitrogen

The synthesis of *N*-tosyl allylic amines from allylic alcohols has been carried out via *N*-tosylcarbamates in a very stereoselective process catalyzed by palladium(II) <2000OL2357> (Scheme 27).

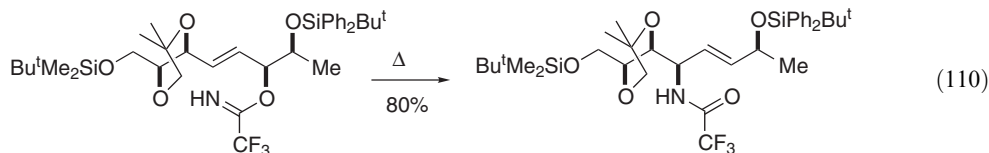


Scheme 27

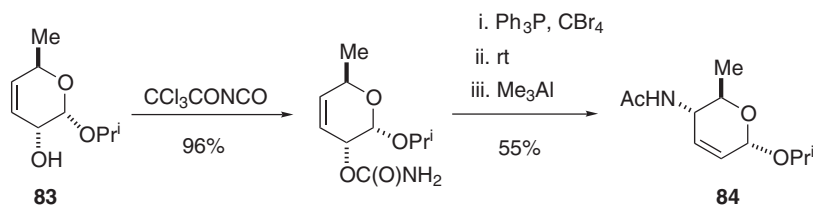
The rearrangement of trichloroacetimidates (Overman's methodology) is one of the methods for the synthesis of allylic amines from allylic alcohols. The Overman rearrangement in sugar templates has been reviewed <B-2001MI001>. It has found many synthetic applications <1998TL1465>, e.g., in the stereocontrolled synthesis of α -amino aldehydes and α -amino acids <1996TL2573, 2002JA12225, 2003JA12412>, in the synthesis of 1-aminocyclopropanecarboxylic acids <1995TL2975>, in the preparation of novel 2',3'-dideoxynucleoside precursors <1995TL4311>, in the synthesis of lincosamine and 7-*epi*-lincosamine precursors from D-galactose as starting material (Equation (109)) <2000TL525>, and in the synthesis of *cis*-4-amino-2-cyclopentene-1-methanol, a key intermediate for the synthesis of carbocyclic nucleosides <2002MI65>.



Allylic trifluoroacetimidates undergo [3,3]-sigmatropic rearrangement to the isomeric allylic trifluoroacetamides, as in the example shown in Equation (110), a key step in the stereoselective synthesis of polyoxamic acid <1999JCS(P1)3291>. This is an efficient process with total 1,3-transfer of chirality coherent with a chair-like transition structure. This rearrangement seems faster than the trichloroacetimidate rearrangement and has been applied to the total synthesis of thymine polyoxin C <1999JCS(P1)3305>.



The [3,3]-sigmatropic rearrangement of allyl cyanates to isocyanates is an organic transformation that converts allylic alcohols into allylamines in a highly stereospecific manner. The synthetic sequence starts from alcohols, followed by dehydration of the allyl carbamates to form the allyl cyanates, rearrangement to the isocyanates and functionalization to the ureas or acetamides <2001TL6133>. Its application in the carbohydrate **83** arena is a simple and efficient entry to aminosugars **84** (Scheme 28) <1996JCS(P1)377, 1997JCS(P1)1449, 1997CEJ453>. It has also been used in the total synthesis of blastidic acid and cytosine, two components of the antibiotic blastidicidin S <2001SL1763>. A similar [3,3]-sigmatropic rearrangement has been reported using thiocyanates as precursors <1997TL875, 2000TL525, 2001TL4401, 2002T1611>.

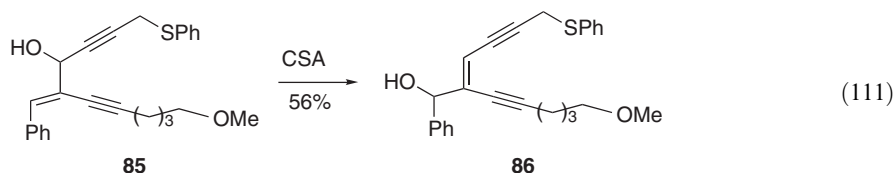


Scheme 28

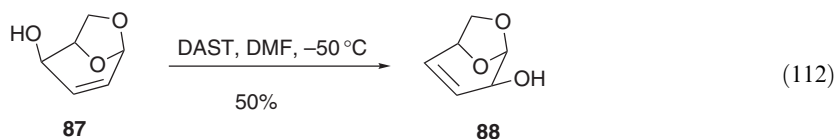
A related [3,3]-sigmatropic rearrangement of isothiocyanates represents a new entry into vinyl thiocyanates <2001EJO1089>.

1.18.2.9 Where Y = Z

The acid-catalyzed isomerization of allylic alcohols is a simple and ubiquitous reaction in organic synthesis, whose efficient application has been usually hampered by the number of secondary reactions leading to geometrical stereoisomers and skeletal rearrangements, typical of reactions proceeding by cationic intermediates. This is the case of the camphorsulfonic-acid-catalyzed allylic rearrangement of alcohol **85** to the *cis*-enediynes **86**, isolated in 56% yield along with other isomers (Equation (111)) <1996TL8413, 1999JOC5062>. Alternatively, the transformation of compound **86** into isomer **85** has been carried out in two steps by a reaction with methane-sulfonyl chloride followed by basic hydrolysis <1996AG(E)779>. However, the ability of allylic alcohols to undergo allylic isomerization or 1,3-transposition reactions has been exploited in organic synthesis <1991COS(6)829>.

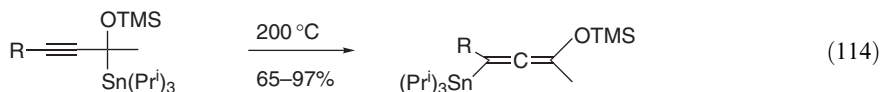
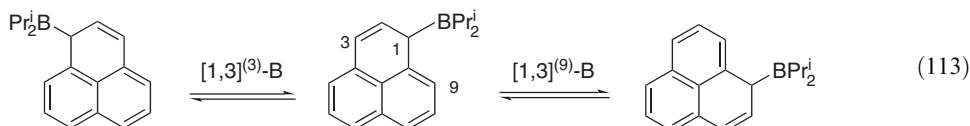


In the presence of pyridinium *p*-toluenesulfonate an allylic alcohol moiety exocyclic to a lactam ring undergoes stereo-controlled allylic isomerization <2001SC1753>. It has been reported that the allylic alcohol **87** in a sugar template isomerizes to product **88** on treatment with DAST in DMF as solvent; a hetero-Cope rearrangement has been invoked on an intermediate formate species to account for this transformation <1998S201> (Equation (112)).



B3LYP computations and NMR data showed that [1,3]-dialkylboryl shifts in cyclononatetraenyl(dipropyl)borane is facile and slightly favored over [1,2]-shifts <1998CC2507>. The study of the dynamic behavior of [1-4- η^4 -exo-7-dipropylborylcyclohepta-1,3,5-triene]tricarbonyliron and cycloheptatrienyl(dipropyl)borane allowed the authors to describe the first observation of a [1,7]-boron shift <1996CEJ1483, 1998JA1034>. Using NMR techniques the kinetics of this isomerization has been investigated. Both possible [1,3]-boron shifts are observed in phenalenyl(dipropyl)borane, but the benzylic rearrangement to position C9 is much faster than allylic migration to position C3 <2000CC311> (Equation (113)). The transition state structures for the chlorine [1,7]- and [1,5]-shifts in 1,7,7-trichlorocycloheptatrienes have been calculated <2002JOC625>. A review has been published covering the chemistry of germoles, stannoles, and siloles, based on progress in the period 1993–1998 <B-1998MI001>. The [1,5]-silicon shifts in indenyl silanes have been extensively studied by X-ray and NMR techniques <2000JCS(P2)611, 2000OM590, 1999NJC317, 1998MI105>. *Ab initio* molecular orbital calculations of the C=C–C–Si torsion angle and the [1,3]-sigmatropic silyl shift in allyl silane have been performed <1997JA807>. Theoretical studies on the 1,3-silyl migration in allyl silane have been

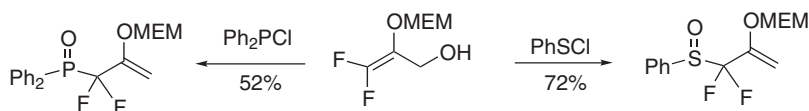
reported <1997JA1948, 1999JA8597>. Regarding migrations of tin-containing groups, a [1,9]-sigmatropic SnMe_3 migration has been observed in cyclononatetraenyl(trimethyl)tin <1999CEJ2828>, and the thermolysis of $[\alpha\text{-(silyloxy)propargyl}]$ stannanes afford 1,3-rearranged $[\gamma\text{-(silyloxy)allenyl}]$ -stannanes <1997JOC8955> (Equation (114)).



1.18.2.10 Where $Y = Z-Z'$

1.18.2.10.1 Where $Z, Z' = \text{chalcogen}$

The reversible [2,3]-sulfoxide/sulfenate rearrangement (the Mislow–Evans rearrangement) is an interesting functional group transformation that converts allylic sulfides into allylic alcohols <2000TL10107>. Theoretical studies and the elucidation of the transition structures and solvent effects for the sulfenate–sulfoxide rearrangement have been published <1995JA9077, 1998JOC6061>, a homolytic scission giving a radical pair being the most likely mechanism for the rearrangement. Hilvert has analyzed the antibody-catalyzed Mislow–Evans rearrangement <1999JOC8334>. A number of examples have been recorded in the literature. Percy and co-workers have reported the 2,3-rearrangement of a series of sulfenates and phosphinates prepared, and transformed *in situ*, from the corresponding difluorinated primary, secondary, and tertiary allylic alcohols in good yields (Scheme 29) <1996TL6403>.



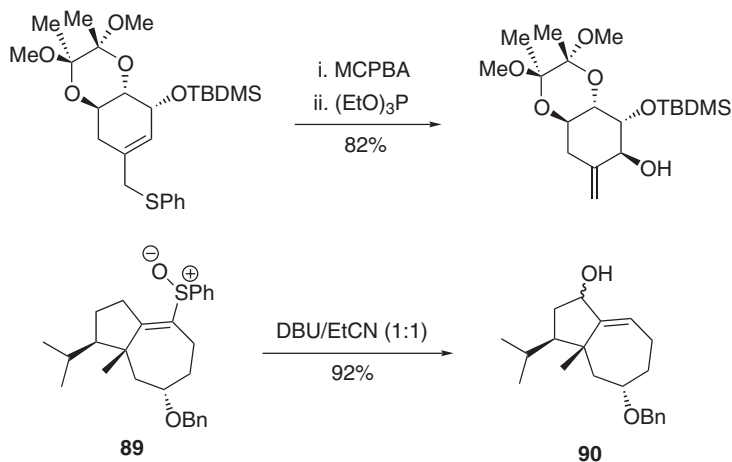
Scheme 29

The enantioselective synthesis of gabosines A, B, D, and E from (–)-quinic acid <2002SL1341> (Scheme 30), and the synthesis of model compounds from carbohydrate precursors <1998MI323> used this rearrangement as a key step. A sulfoxide–sulfenate rearrangement was also described in a synthetic approach to the hydroazulene portion of guanacastepene A; the vinylsulfoxide **89** is isomerized to the corresponding allylic sulfoxide in basic medium and the [2,3]-sigmatropic rearrangement takes place *in situ* to give the allylic alcohol **90** <2002TL9605> (Scheme 30).

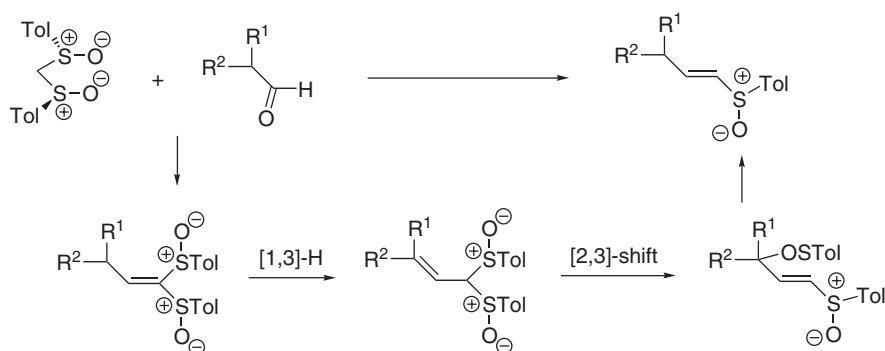
In the one-pot synthesis of (*E*)- γ -hydroxy and (*E*)- γ -keto- α,β -unsaturated sulfoxides from bis-sulfoxides, described by Llera, a [1,3]-H shift and a [2,3]-sulfoxide/sulfenate rearrangement were the key steps <1995TL4889> (Scheme 31). Carreño and co-workers have extensively used the sulfoxide–sulfenate rearrangement on Diels–Alder adducts from conveniently functionalized dienophiles and *p*-tolylsulfenyl-1,3-pentadienes <1996TA2151, 1998TL1405, 1999TA3473, 2000TA1217>.

Propargylic dialkoxo disulfides undergo a double [2,3]-sigmatropic rearrangement to diallenic *vic*-disulfoxides <2003TL777>. The reverse sulfenate–sulfoxide rearrangement has also been described in a series of propargyl sulfenates leading to diallenic disulfoxides <2000TL6923>.

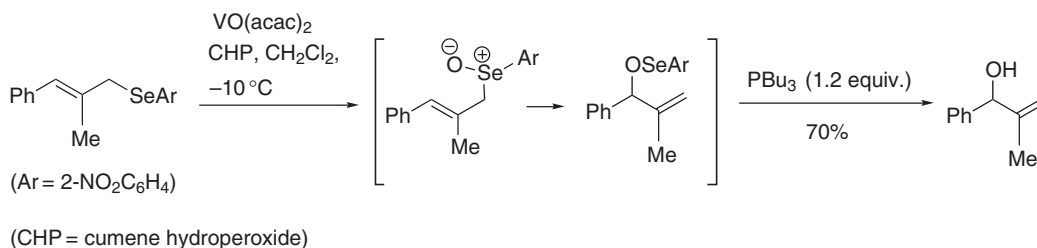
A similar process has been observed and documented for the [2,3]-sigmatropic-selenoxide/selenate rearrangement <B-1999MI001, 1998SL987, 1995MI220, 2002CC558>. Recently, the first catalytic method for this rearrangement using vanadyl(IV)acetylacetonate (10%) has been reported (Scheme 32); final reaction with phosphines results in allylic alcohols in good overall yield <2000CC2031>. Uemura has reported the synthesis of chiral ferrocenyl diselenides and has prepared enantiomerically pure allylic selenides that upon oxidation produced asymmetric [2,3]-sigmatropic rearrangement giving allylic alcohols in high enantiomeric excess <1995JOC4114>.



Scheme 30



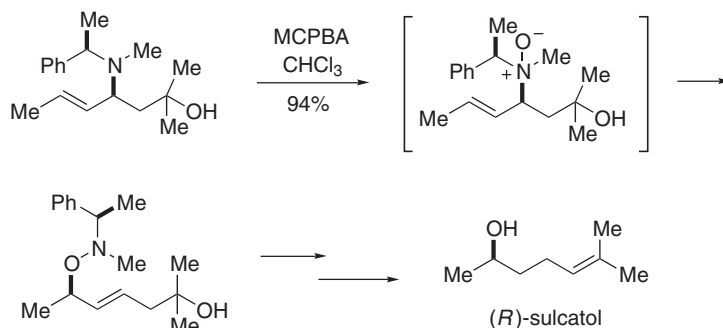
Scheme 31



Scheme 32

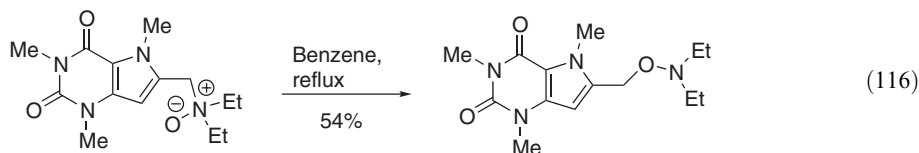
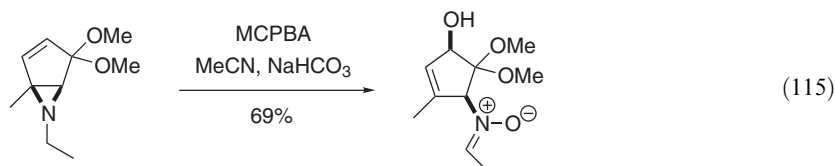
1.18.2.10.2 Where Z and/or Z' = nitrogen, phosphorus

The Meisenheimer rearrangement of allylic amine *N*-oxides to the corresponding *N,N,O*-trisubstituted hydroxylamines is a [2,3]-sigmatropic rearrangement that, after cleavage of the N—O bond, gives secondary or tertiary allylic alcohols <1919CB1667>. Enantiomerically pure substrates for the asymmetric transfer in the Meisenheimer rearrangement have been described <2000TL8279>. Davies reported the synthesis and *in situ* Meisenheimer rearrangement of the *N*-oxides obtained by oxidation of the tertiary amine where the (*R*)-1-phenylethyl-*N*-methyl amine has been incorporated as a chiral inductor <1996TA1001>. He has applied this strategy for the enantioselective synthesis of (*R*)-sulcatol <1996TA1005, 1996JCS(P1)2467>; the [2,3]-rearrangement was completely stereoselective, affording only one compound at the newly formed stereocenter, having the *E*-stereochemistry at the double bond (Scheme 33).

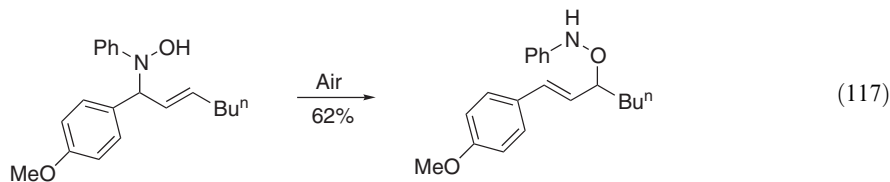


Scheme 33

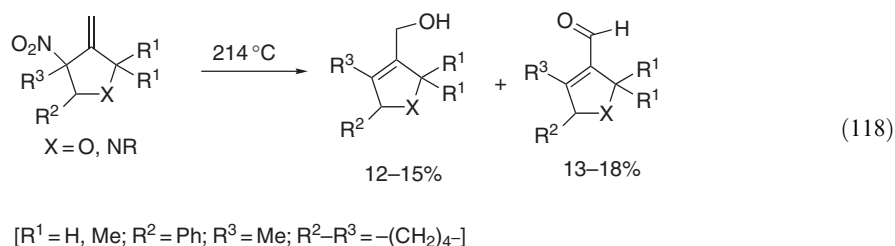
Coldham has also reported moderate levels of stereoselectivity in the chirality transfer from nitrogen to carbon in the [2,3]-amine oxide rearrangement, by using camphor-like amines or *N*-allyl prolinol derivatives [\[1997SL322, 1998TA1995, 1999JCS\(P1\)2327\]](#). Various BTAA's (bicycles derived from tartaric acid and α -amino acids) employed as chiral auxiliaries did not afford a high level of asymmetric induction [\[2000TA4227\]](#). The interesting transformation of a bicyclic 2-alkenyl aziridine into a δ -hydroxynitrone (Equation (115)) involves a [2,3]-Meisenheimer rearrangement to give an *endo*-*N*-oxide which undergoes a rapid sigmatropic rearrangement followed by *in situ* oxidation to the final nitron [\[2001TL3029\]](#). *N*-Oxides of 8-[(dialkylamino)methyl] caffeines undergo the expected Meisenheimer rearrangement to the corresponding *O*-(8-caffeinylmethyl)-*N,N*-dialkylhydroxylamines in moderate yields [\[1999EJO2419\]](#) (Equation (116)). Finally, Cossy has reported the synthesis of unsaturated [1,2]oxazines by sequential Meisenheimer rearrangement of unsaturated *N*-acryloyl-*N*-oxides followed by ring closing metathesis reaction [\[2003TL8577\]](#).



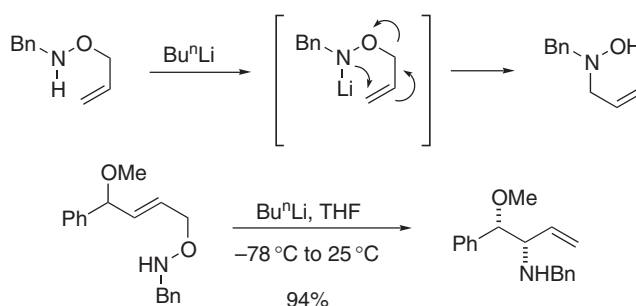
Related rearrangements of *N*-aryl-*N*-allylhydroxylamines to *O*-allylhydroxylamines have been communicated recently [\[2001CC1806\]](#) (Equation (117)). This rearrangement takes place spontaneously (initiated by air), by simply allowing the compound to stand at room temperature; it was observed that the rate of the rearrangement depended on the type of the substituent on the nitrogen atom, the most favorable being aryl.



In spite of previous reports [\[1998SL939\]](#) showing that allylic nitro compounds did not undergo [2,3]-sigmatropic rearrangements at 110°C in toluene, in 1999 French authors reported the first [2,3]-sigmatropic rearrangement of this type of compound (Equation (118)). Working under harsher conditions (1,2,4-trichlorobenzene, reflux), the thermal reaction affords rearranged alcohols and carbonyl compounds in almost equal amounts, in poor chemical yield [\[1999CC2009\]](#).

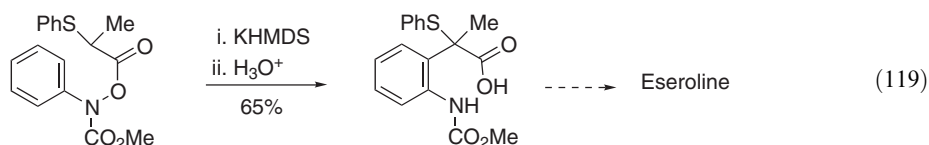


In 1998, Davies reported a new [2,3]-sigmatropic rearrangement when *N*-benzyl-*O*-allylhydroxylamine afforded *N*-allylhydroxylamine on treatment with Bu^nLi (Scheme 34) <1998CC2235, 2002JCS(P1)1757>; the reaction was shown to be very stereoselective when (*E*)-*N*-benzyl-*O*-(methoxy-4-phenylbut-2-enyl)-hydroxylamine afforded *syn*-3-benzylamino-4-methoxy-4-phenylbut-1-ene as a single diastereomer via a chelated transition state <1999CC2079, 2002JCS(P1)2141> (Scheme 34). In an independent study published few years later, Saito *et al.* reported similar results on closely related substrates <2001JA7734, 2001JA9724>.

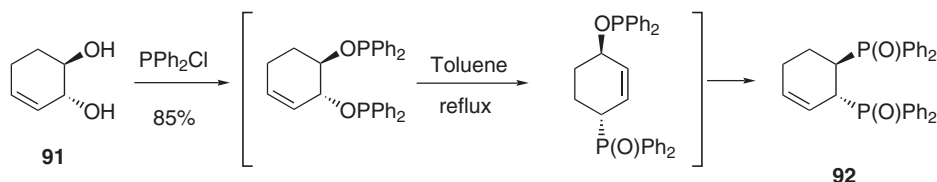


Scheme 34

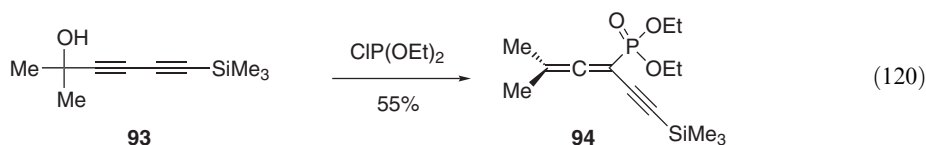
The [3,3]-sigmatropic rearrangement of enolates derived from hydroxamic acid derivatives has been used in a synthesis of the alkaloid eseroline (Equation (119)) <2001H(55)1029>.



The analogous *phospha*-[2,3]-sigmatropic rearrangement has also been reported. This protocol allows the formation of cyclic 1,2-diphosphane oxides **92** from diphenylphosphinites that are readily prepared from the corresponding 1,2-diols **91** (Scheme 35) <1999TL4981, 2001AG(E)1235>. Allene phosphane oxides have been obtained by a similar [2,3]-sigmatropic rearrangement of phenylphosphinites prepared and rearranged *in situ* from propargylic alcohols <1995AG(E)2037, 1997JOC603>. The reaction of bisalkynol **93** with diethoxychlorophosphane in the presence of triethylamine in dichloromethane gives phosphorylyne-allene **94** via a [2,3]-sigmatropic rearrangement (Equation (120)) <1999EJO2367>.



Scheme 35



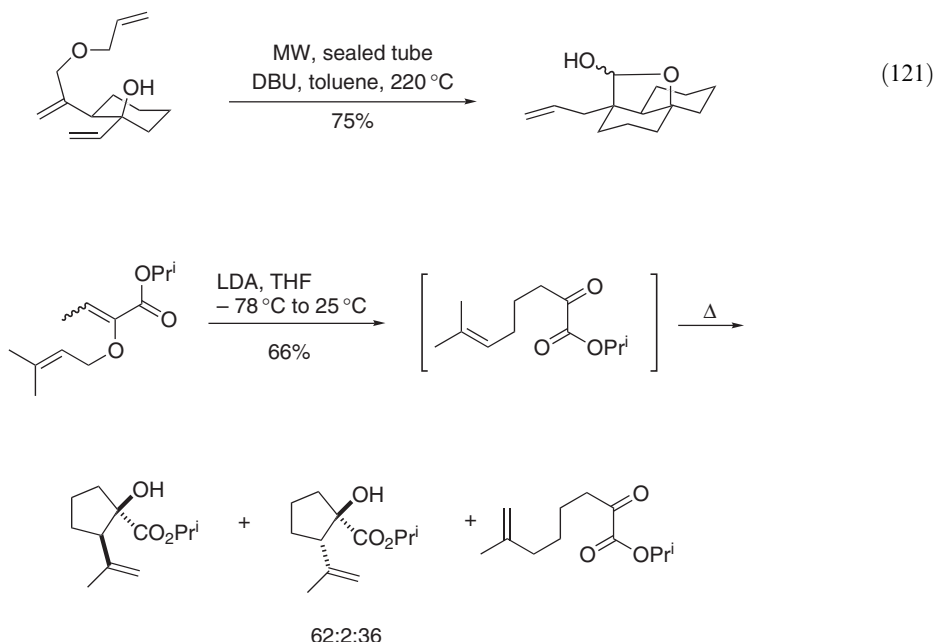
1.18.3 OTHER REARRANGEMENTS

1.18.3.1 Tandem and Higher Sigmatropic Rearrangements

Tandem sigmatropic rearrangement processes are usually found in the current literature and have been reviewed [<B-1992MI001, 1998S227, 2000MI1033>](#). This strategy has been applied in organic synthesis by taking advantage of putting together in the same protocol functional group transformations that can be achieved separately [<1991COS\(5\)875>](#).

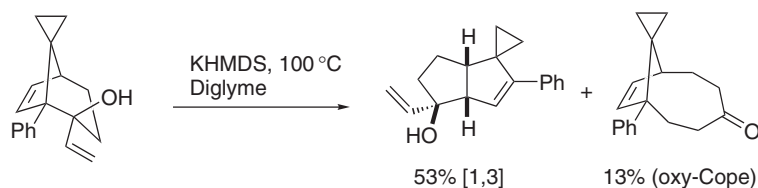
The aromatic Claisen rearrangement of *O*-allyl-1-naphthols followed by the tandem *o*-phenol oxygenation and oxy-Cope rearrangement has resulted in a convenient method for the synthesis of 4-allyl-substituted 1,2-naphthoquinones [<1996S699>](#). A tandem thio-Claisen-Claisen rearrangement of thiochromene derivatives has been efficiently applied by Majumdar in the preparation of pentacyclic heterocycles [<2003T5289>](#). Tandem [2,3]-Wittig/anionic-oxy-Cope rearrangements have been used for the synthesis of a series of bis-allylic ether substrates [<1997TL4679>](#), the stereoselective synthesis of trisubstituted δ -lactones and tetrahydropyrans [<1997TL6449, 1997TL6453>](#). The ester-enolate/dienolate [2,3]-Wittig rearrangements have been described in tandem processes with other sigmatropic rearrangements, such as the anionic-oxy-Cope [<1997TL6445>](#) or the Ireland-Claisen or ring-closing metathesis reactions [<2000JCS\(P1\)2916, 1997JOC137>](#). For the synthesis of the kinamycin core a tandem Copecheletropic reaction has been applied [<1996CC1181>](#).

Tandem oxy-Cope/ene/Claisen rearrangements have been shown to furnish a highly diastereoselective synthesis of decalin skeletons containing quaternary carbon centers (Equation (121)) [<2002OL1371, 2000OL663>](#). An efficient sequence based on pericyclic reactions comprising the ester dienolate [2,3]-Wittig/oxy-Cope rearrangement followed by a carbonyl ene reaction has been described as a new entry to polyfunctionalized carbocycles [<2001EJO483>](#) (Scheme 36).



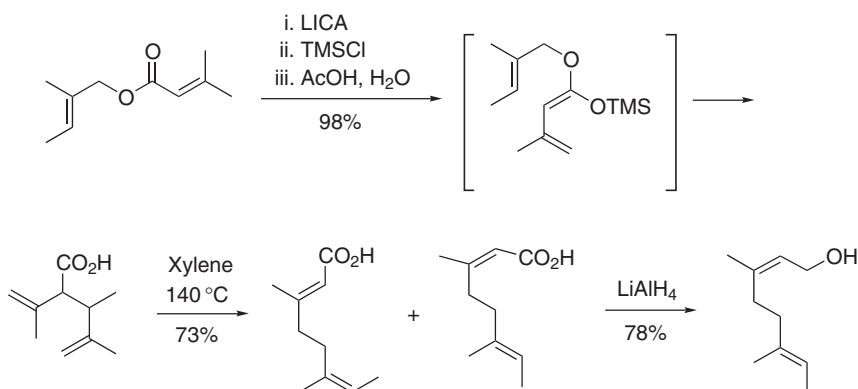
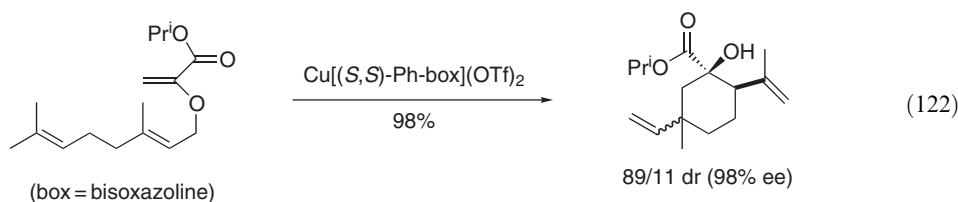
Scheme 36

In a series of studies directed to the synthesis of fused-ring skeletons, the synthesis of a ring-expanded ketone in good yield through tandem [1,3]- and oxy-Cope rearrangements has been reported [<1999TL511, 2002TL3633>](#) (Scheme 37). The same strategy has been applied for the preparation of useful intermediates in the total synthesis of (\pm)-junicedranol [<2000TL1939>](#).



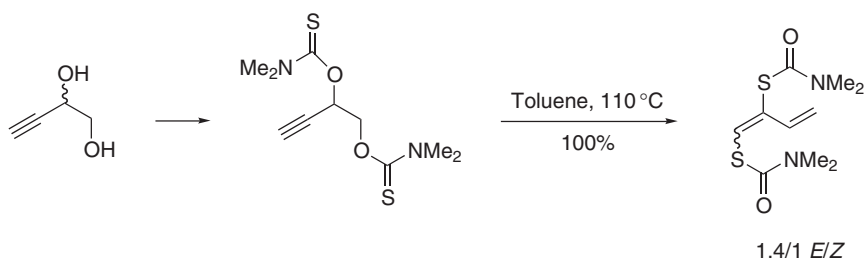
Scheme 37

The tandem allyl vinyl ether isomerization of a di-*O*-allyl ether followed by *in situ* Claisen rearrangement is catalyzed by the system $\text{Ru}_3(\text{CO})_{12}$ /imidazolinium salt/caesium carbonate [<2002CC1772>](#). A catalytic and enantioselective tandem Claisen rearrangement plus intramolecular carbonyl ene reaction has been elegantly applied in the synthesis of densely functionalized carbocycles from open-chain molecules [<2002SL1999>](#) (Equation (122)). A tandem [3,3]-sigmatropic rearrangement/[1,2]-allyl shift has been applied by Wood to an efficient synthesis of (+)-latifolic acid and (+)-latifoline [<2001JOC7025>](#). A structural isomer of nerol has been elegantly prepared by sequential tandem Ireland–Claisen and Cope rearrangement (Scheme 38) [<1999EJO2781>](#).



Scheme 38

Propargylic dialkoxy disulfides undergo an unprecedented sequence of three [2,3]- and one [3,3]-sigmatropic rearrangements followed by an intramolecular [2+2] cycloaddition affording bicyclic derivatives [<2003TL777>](#). Thermolysis of bis-thiocarbamates derived from but-3-yn-1,2-diols gave buta-1,3-dienes with carbamoylthio groups in positions C1 and C2 with good yields via tandem [3,3]-[3,3]-sigmatropic rearrangements [<1995AG\(E\)1627, 1998AG\(E\)3289, 2000T5413>](#) (Scheme 39).



Scheme 39

An elegant sequential tandem process has been described starting from Claisen rearrangement of the adducts from 2-methoxyphenols and functionalized dienes, followed by *in situ* Diels–Alder reaction of these intermediates, and further Cope rearrangement; this is a convenient method for the synthesis of highly functionalized *cis*-decalins [<1997CC1085>](#). A beautiful example of “biomimetic” cascade reactions, the tandem Claisen rearrangement/intramolecular Diels–Alder reaction, has been achieved in the construction of bridged tricyclic scaffolds present in complex natural products isolated from *Garcinia*. This strategy pioneered by Nicolaou [<2001AG\(E\)4264>](#) has been extensively applied by Theodorakis [<2002OL909>](#) to the synthesis of this family of natural products, including lateriflorone and derivatives [<2003OL1491, 2003T6873>](#).

Numerous higher-order sigmatropic rearrangements are known and have been the subject of some theoretical studies [<1998JA10490>](#). In preliminary efforts directed to the synthesis of natural products thiarubrine A and B, [3,4]- and [3,5]-sigmatropic rearrangements have been reported [<1997TL799>](#). The synthesis of phytochrome and related tetrapyrroles featured a [3,5]-sigmatropic rearrangement of an *N*-pyrrolo enamide as the key step [<1997JOC2894>](#). A very unusual [9,9]-sigmatropic shift in a benzidine-type rearrangement has been described [<1997JOC3794>](#).

1.18.3.2 Rearrangements Involving Ring Opening

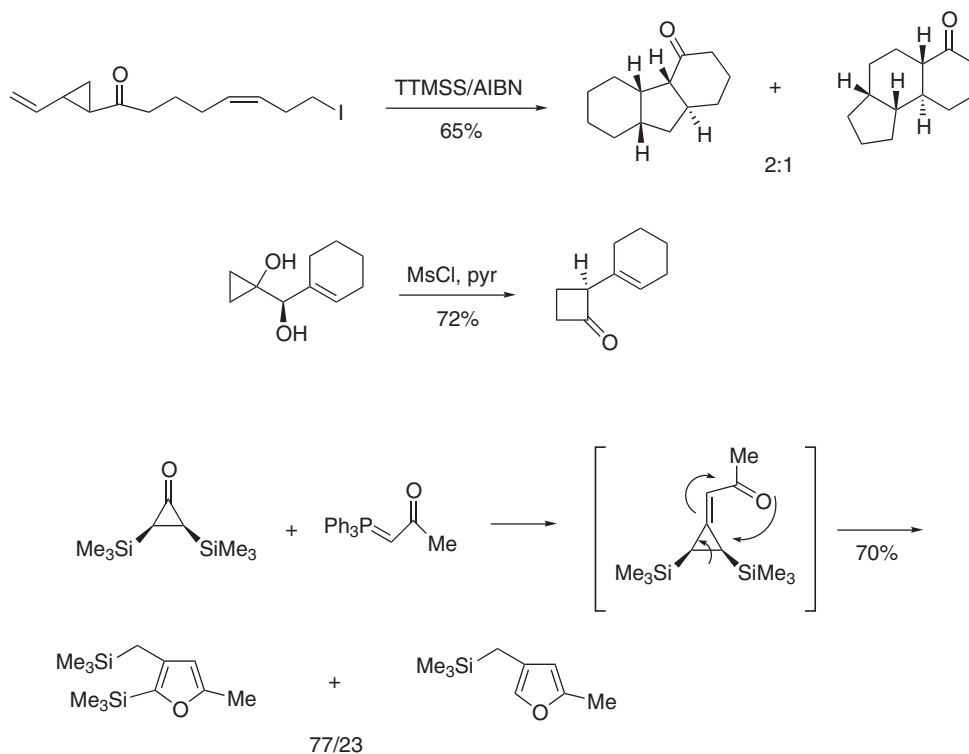
1.18.3.2.1 Ring opening of cyclopropanes

The cyclopropane ring is extremely sensitive to reactants and/or experimental conditions (thermal, photochemical, metal-catalyzed, free radicals) leading to rearranged or opened products.

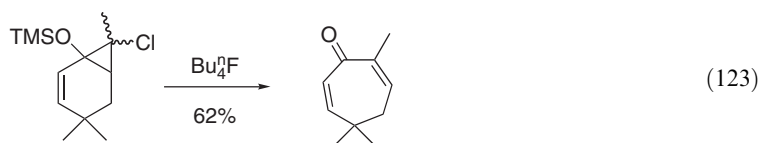
A convenient preparation of 2-fluoro-3-alkoxy-1,3-butadienes by thermolysis in quinoline solution of 1-chloro-1-fluoro-2-alkoxy-2-methylcyclopropane has been reported [<2002OL3155>](#). The kinetics of thermal cyclopropane ring opening of a series of diaryl homonaphthoquinones have been examined [<2000JCS\(P2\)135>](#). Free-radical conditions have been investigated and reported in the literature concerning the ring opening of vinylcyclopropanes [<2000T8959, 2001CSR94, 1996JCS\(P1\)57, 1998TL1893, 1999TL3431>](#). The reaction of alkylthio radicals with alkenyl cyclopropanes opens the cyclopropyl ring and generates a homoallylic radical that is captured by a radical trap to give a new radical that adds back to the thioalkyl allylic system to form, after elimination of the alkylthio radical, a polycyclic ring system [<1997JOC4601>](#).

There are many examples in the literature on the photochemical ring opening of cyclopropanes. Thus, the photochemical ring opening of cyclopropyl *p*-benzoquinones has been reported [<1996JA1233>](#). The sensitized photochemical oxa-di- π -methane (ODPM) rearrangement of tetracyclo[3.3.0.0^{2,8}.0^{2,8}]octane derivatives produces cyclopropane ring opening leading to cyclopentanoid molecules, useful in organic synthesis [<1997T13053>](#). The UV irradiation of dibenzonorcaradienes bearing an acyl or alkoxycarbonyl substituent in the C7 position yields a number of substituted phenanthrenes [<2001OL1885>](#). Usually, these reactions proceed through a 1,3-diradical species [<2001OL1885, 1998JOC3176>](#). 2-Aminocyclopropanols undergo an oxidative ring-opening reaction leading to enamines in moderate yields [<1997T7855>](#). Density-functional theory has been applied to study the effects of fluorine substitution on the kinetics of the cyclopropylcarbinyl radical ring opening [<1999JOC540>](#). Tandem free-radical processes have

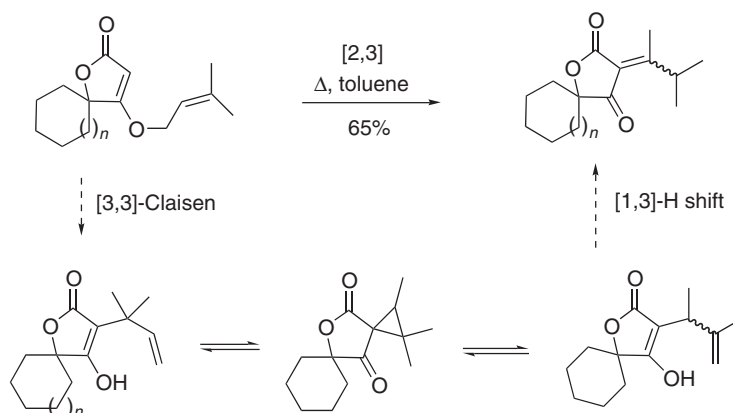
been described giving complex carbocyclic arrays <1997TL3647> (Scheme 40). Reissig has published a full account of the synthesis and reactivity of donor-acceptor-substituted cyclopropanes, highlighting the methods for their cleavage <2003CRV1151>. In particular, their ring opening reactions for the preparation of substituted and functionalized 1,4-dicarbonyl compounds and derivatives are of special interest. Pinacol rearrangement of α -hydroxycyclopropylcarbinols promoted by Lewis acids, in acid medium <1998T6903> or in the presence of methanesulfonyl chloride/pyridine <2000OL1337>, gives 2-substituted cyclobutanones (Scheme 40), that have been used in the asymmetric synthesis of 4-deoxyverrucarol <2000JOC504>. The reaction of commercially available 1-triphenylphosphoranylidene-2-propa-none with *cis*-2,3-bis(trimethylsilyl)cyclopropanone gave products arising from the unexpected [1,5]-sigmatropic rearrangement featuring a clean cyclopropane ring opening (Scheme 40) <2000TL3399>. Six-membered ring-fused trimethylsilyl-substituted cyclopropanols expand to medium-sized carbocycles when treated with tetrabutylammonium fluoride (Equation (123)) <2002T9279>.



Scheme 40

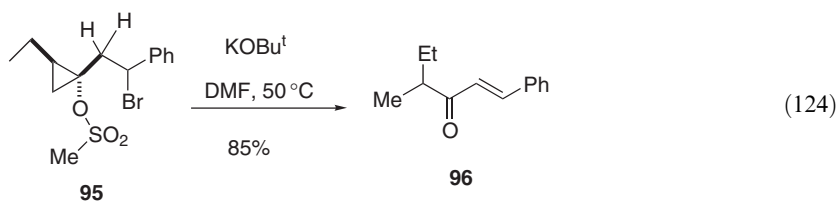


The thermal [2,3]-sigmatropic rearrangement of allyl tetronates proceeds via 3-(spirocyclopropyl)dihydrofuran-2,4-diones (Scheme 41). In some cases these intermediates have been isolated and submitted to cyclopropane ring opening with alcohols or water <2001TL4561>. Jasmonoids have been prepared by pyrolysis of a spiroannulated cyclopentanone <1998MI319>. The procedure involves a retro-Diels–Alder reaction and a homo-1,5-hydrogen shift with concomitant cyclopropane ring opening.



Scheme 41

The intramolecular hydroxyl-mediated opening of a cyclopropyl ring has been used in a model study for the synthesis of the diterpenoid harringtonolide [<1998JCS\(P1\)1555>](#). Vinylcyclopropanes are opened in free radical-mediated three-component reactions with alkynes and diphenyl diselenide [<2000JOC7682>](#). Mesylate **95** on treatment with Bu^tOK in DMF afforded the ring-opening product **96** in preference to the elimination of HBr or MeOH ([Equation \(124\)](#)) [<2002EJO2160>](#).

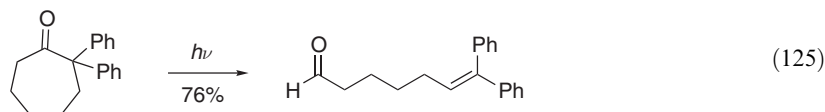


Rhodium compounds are the typical catalysts to accomplish the opening reactions of the cyclopropane ring and it has been reported that treatment with rhodium(II) acetate of different diazo propanones results first in a cyclopropanation reaction, followed by acid-catalyzed ring-cleavage of the cyclopropyl moiety [<1997TL5081>](#). A rhodium carbonyl complex catalyst allowed the transformation of 4-pentynyl cyclopropanes into bicyclo[4.3.0]nonenones, which proceeds by cleavage of the cyclopropane ring in moderate yields [<1999CL705>](#).

Alexakis has reported the tandem enantioselective conjugate addition–cyclopropanation reaction leading to trimethylsilyl-protected 3-cyclopropanols, a series of useful intermediates, that have been submitted to a variety of experimental conditions for opening the cyclopropane ring [<2002JOC8753>](#). Tricyclo[3.3.0.0^{2,8}]octane-3-one ring systems upon treatment with tributyltin hydride afforded open cyclopropane derivatives [<1995TL6819, 2002AG\(E\)4090>](#). Similarly, tricyclo[4.3.0.0^{2,9}]nonan-3-one systems reacted with different agents such as *t*-butyldimethylsilyl iodide or trimethylsilyl trifluoroacetate to give cyclopropane cleavage products [<1999T847>](#). The hemi-synthesis of erythrolide K has been achieved by a cyclopropane ring opening involving a [1,5]-sigmatropic hydrogen shift from erythrolide A [<1998TL1469>](#).

1.18.3.2.2 Photochemical ring opening of cyclic ketones

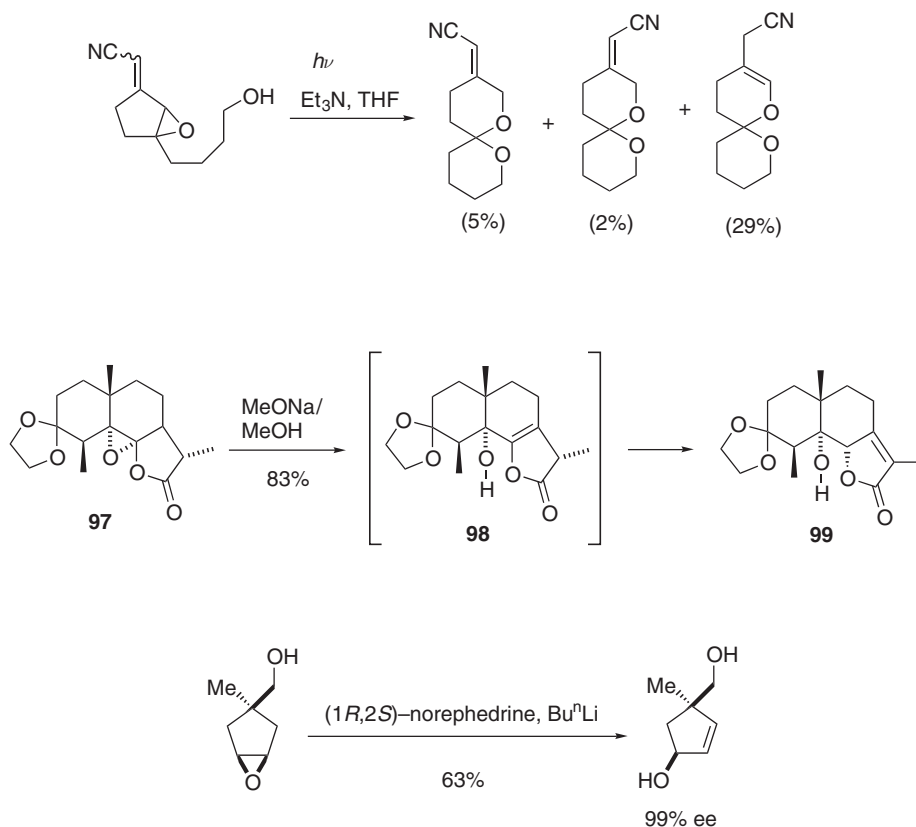
The photochemical ring cleavage of cyclic ketones has found limited use in organic synthesis due to the fact that usually several compounds are formed in the photolysis, in addition to the expected ω-unsaturated aldehyde. An interesting exception is the photolysis of 2,2-diphenylcycloheptanone, which cleanly afforded 7,7-diphenyl-hept-7-en-1-al in 76% yield ([Equation \(125\)](#)) [<1999BCJ103>](#).



1.18.3.2.3 Rearrangement of epoxides

The acid- or base-promoted rearrangement of epoxides into allylic alcohols is an extremely useful functional group transformation that has found extensive application in organic synthesis <1991COS(3)733, 1991TA1> and a number of reviews have been published in the last years showing the interest in this reaction <1996T14361, 1996MI188, 1998JCS(P1)1439>. A recent review on the asymmetric base-mediated epoxide isomerization is also available covering the literature from 1997 up to 2001 <2002CSR223>, and the reader is directed to this excellent account for all the relevant references on the subject for this period.

The opening of epoxides to give unsaturated alcohols is a functional group transformation with a number of interesting synthetic applications, either using bases, as in the preparation of sesquiterpenes <2002TL627>, or using acids, bases or hydroperoxides, as in the case of steroids <2001T2185>. The acid-catalyzed rearrangement of caryophyllene oxide has been investigated <1996JCS(P1)2507>. Palladium complexes have been reported to promote the ring opening of trisubstituted epoxides giving mixtures of allylic alcohols and α,β -unsaturated ketones <2002JOC1580>. The first total synthesis of (+)-chrysanthemol included in the synthetic sequence the cleavage of an epoxide to give an allylic alcohol using Lewis acids (boron trifluoride etherate or aluminum isopropoxide) as promoters <1997CL1289>. Other Lewis acids such as Et_3Al have been shown to promote the ring opening of β -hydroxy epoxides leading to α -hydroxy alkenes <2003TA2189>. An interesting example of photocyclization of δ -hydroxybutyl α,β -unsaturated γ,δ -epoxynitriles has been described <1995LA19> (Scheme 42).



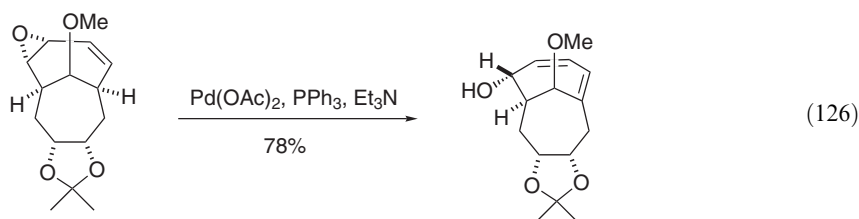
Scheme 42

However, the base-promoted rearrangement of epoxides account for the largest amount of the published work in this area. The influence of the solvent and the structure of the substrate in the mechanism of the base-mediated isomerization of cycloalkene epoxides has been discussed

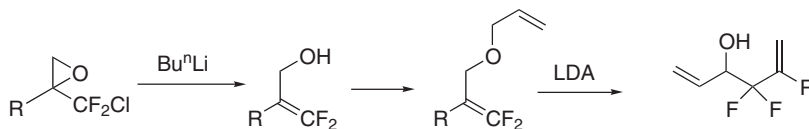
<1996JOC820, 2000JOC1461>. The lithium diethylamide/lithium *tert*-butoxide reaction with 1,5-cyclooctene diepoxide has been revisited, but not without problems of structure assignment <1997T1855> and further correction <1998T13323>. Hodgson has studied the mechanism of the base-mediated rearrangement in simple cyclopentene oxides and also in bicyclo[2.2.1] and bicyclo[2.2.2]alkene-derived epoxides to give ketones and alcohols, giving new insights in the mechanisms that operate following α -lithiation in such systems <1997TL887, 1997TL8907>. His group has also screened a number of external ligands, (–)-sparteine, bisoxazolines, ..., to accomplish the synthesis of enantio-enriched unsaturated diols arising from the double ring opening of epoxytetrahydrofurans <2003OBC1139>. The opening of epoxide intermediates with magnesium amides provides valuable compounds for the synthesis of vitamin D₃ derivatives <1998JOC6984>. In a general synthetic route to the dihydroagarofuran sesquiterpenoid from α -(–)-santonin, the homoallylic alcohol **99** was obtained by sodium methoxide-promoted rearrangement of epoxide **97** (Scheme 42); presumably the intermediate allylic alcohol **98**, after a [1,3]-hydrogen shift, gave the α,β -unsaturated lactone <1998TL7935, 1998SC3751, 2002TL627>.

The use of chiral lithium bases in the rearrangement of epoxides has been intensively explored in recent years as reviewed by Andersson <2002CSR223, 2000SL1092> and some theoretical calculations have been performed <2003CL150>. Camps has disclosed a regio- and stereoselective synthesis of highly functionalized cyclopentanols using lithiated alkylidiphenyl phosphine oxides as chiral bases <2002T3473>. Quaternary carbon-containing *meso*-epoxides were enantioselectively transformed into the corresponding allylic alcohols <1995TL1893> by treatment with (1*R*,2*S*)-norephedrine and BuⁿLi <1996TA407> (Scheme 42).

In a reported total synthesis of (+)-iridomyrmecin, a key step was a highly enantioselective ring opening of a racemic epoxide promoted by a chiral base <1997SL657>. In his synthetic approach to the ingenane type of diterpenes, Rigby has reported an improved method for the opening of the key allylic epoxide leading to a dienol intermediate <2002OL799> (Equation (126)).

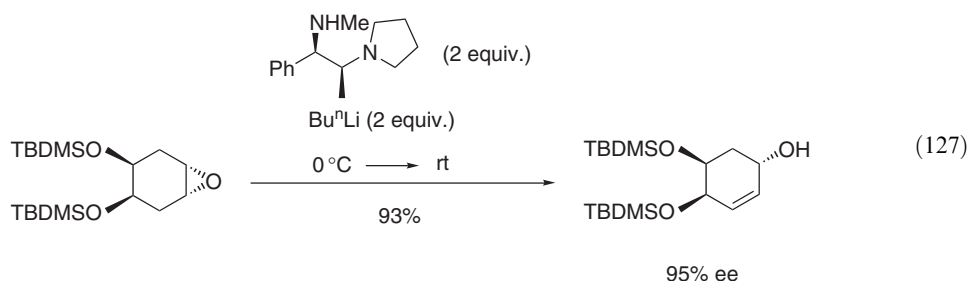


The epoxidation of commercially available sesquiterpene (+)-ledene with MCPBA afforded a rearranged allylic alcohol as the major compound in a mixture that included epoxy derivatives along with other rearranged products <1996MI1840>. *gem*-Difluoroalkenes, obtained by epoxide rearrangement, were submitted to LDA-promoted [2,3]-Wittig rearrangement to give the expected *gem*-difluoro allylic alkenes in good yield (Scheme 43) <1995CC1857>.

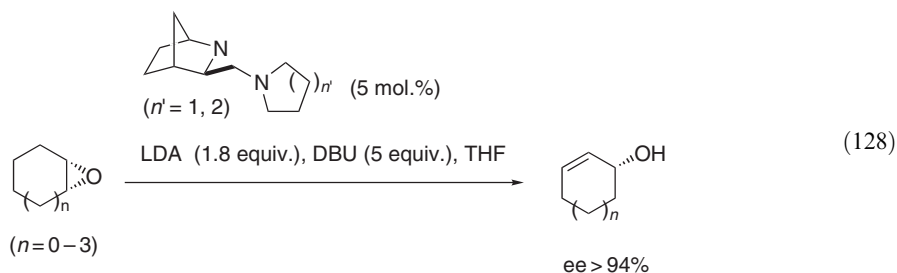


Scheme 43

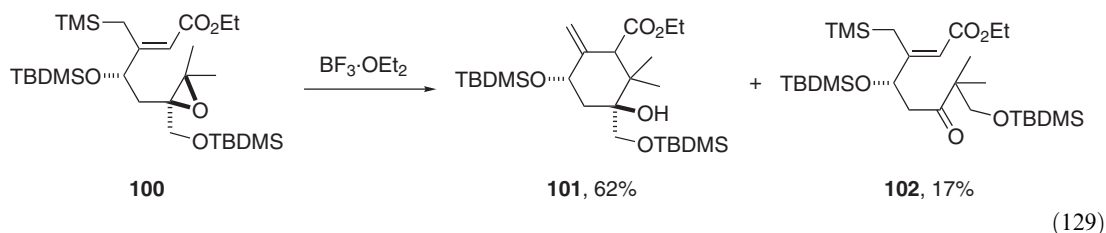
O'Brien has carried out exhaustive studies on the enantioselective base-mediated rearrangement of numerous 4-amino-substituted cyclopentene oxides <1998TL8175, 2000T9633> and substituted hydroxycyclohexene oxides leading to a plethora of carbocyclic nucleoside analogs, conduritols (Equation (127)) <2002T4643>, aziridinocyclohexenols <2003OBC523> and densely functionalized cyclohexenones <1998JCS(P1)2435>. A norephedrine-derived chiral base was found to be very efficient in these transformations.



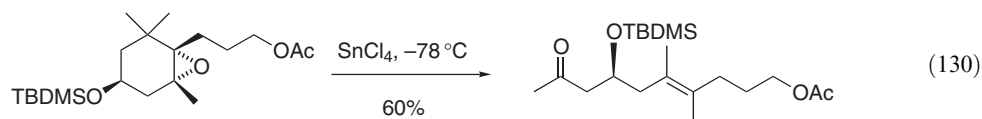
Andersson has implemented the use of 3-substituted 2-azanorbornyl ligands as catalysts in the preparation of several allylic alcohols (precursors of the prostaglandin core unit, epibatidine, carbovir, faranil, lasiol) [<1998JA10760, 2000JA6610, 2000SL1092, 2002CSR223>](#) by reaction of different epoxides with LDA in stoichiometric amount (Equation (128)), the enantioselectivity being higher than 94% ee in most cases.



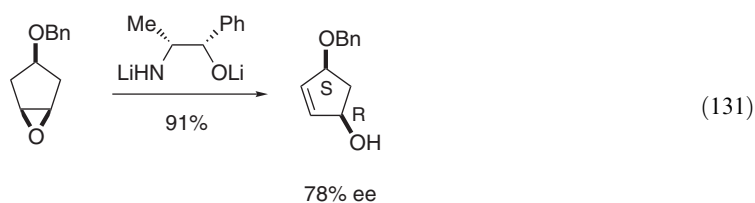
The boron trifluoride-etherate-promoted electrophilic cyclization of tetrasubstituted epoxides containing a trimethylsilyl allyl moiety has been described [100 <1996JOC2075, 2001JCS\(P1\)789>](#) to give a major carbocyclic derivative [101](#) and a 1,3-hydroxyketone as a rearranged carbonyl compound [102 <1998JOC8212>](#) (Equation (129)).



The Lewis acid-promoted stereoselective rearrangement of the epoxy group of 5,6-epoxy carotenoids gives open-chain molecules that can be considered as key intermediates for the synthesis of the crassostreaxanthin type of natural product (Equation (130)) [<1999JCS\(P1\)1625>](#).



Murphy has reported the enantioselective epoxide ring opening of cyclic epoxides using dilithiated bases, obtaining the best results in terms of substrate conversion, but with low enantioselectivity, with dilithiated ephedrine [<2002T4675>](#) (Equation (131)).



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1.19

Tricoordinate Carbanions, Cations, and Radicals

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1.19.1 TRICOORDINATE CARBANIONS (P. PALE, UNIVERSITY DE LOUIS PASTEUR)

1.19.1.1 General Aspects

In COFGT (1995), this section was mainly devoted to proton abstraction. Although deprotonation is a useful method, it requires rather harsh conditions and has a relative lack of selectivity. The increasing selectivity requirements in organic synthesis due to the increasing complexity of targets have promoted the development of more selective and milder access to carbanions. Since most organic syntheses deal with bioactive compounds, chirality and its control have also become

very important issues. For these reasons, this section will emphasize selective carbanion formation and when possible, stereoselectivity control.

1.19.1.2 Literature Survey

Since COFGT (1995), several reviews dealing with the formation and reactivity of carbanions have been published. The selective preparation of organolithiums and some of their selective reactions have been recently collected by Clayden <B-2002MI001>. Another book deals with the structures and mechanisms associated with carbanions <B-2003MI002>. The formation of allylic carbanions and the regioselectivity of their reactions have been reviewed <B-1996MI003>. The formation and stability of carbanions in water have been addressed <2001ACR981>.

Asymmetric reactions using carbanions have been reviewed <1999MI1121>. Enantiocontrol in carbanion formation and reaction have been detailed <1997AG(E)2282> as well as enantiomerically enriched carbanions <2002AG(E)716, 2002JOMC149>.

Some reactions of carbanions have also been reviewed, such as electrophilic aliphatic substitutions <2003MI349>, reactions with carbon tetrahalides <1999OPP359> and with electrophilic amino reagents <2000EJO1281>.

1.19.1.3 Carbanions and Organometallic Species

Although carbanions can be produced by a large variety of methods, their formation generally implies a metal counter-ion, except for a few methods in which the counter-ion is different from a metal, usually an ammonium ion.

Carbanions and organometallic species exhibit nucleophilic and basic properties, which render them useful intermediates for organic synthesis. One property can be increased relative to the other by changing the solvent, the counter-ion, and the temperature. However, organometallics offer a further element of control, which is the nature of the metal and of its ligands. Depending on the nature of the metal and its oxidation state, the carbon–metal bond can vary from ionic to polar or apolar covalent, and cluster formation can occur. The reactivity obviously varies according to these phenomena. Moreover, the metal ligands other than carbon ligands can strongly influence the electronic properties of the metal, which in turn alter the property of the carbon–metal bond and thus affect the reactivity. In the last decades, an impressive amount of work has been devoted to the formation and use of carbanions having metals other than Li, Mg, and Zn as counter-ions.

1.19.2 CARBANIONS BY PROTON LOSS

1.19.2.1 Deprotonation: General Aspects

The formation of carbanions by proton abstraction has been extensively described in COFGT (1995) and no significant improvement has been made in this area.

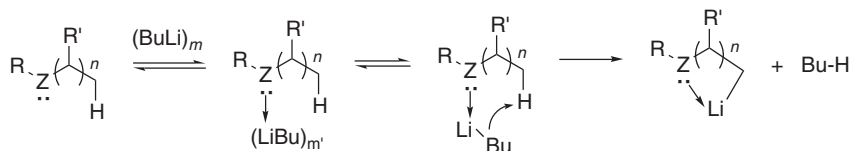
Nevertheless, it is worth noting that high regioselectivity can be achieved if deprotonation can be directed by the coordinating and chelating groups. This process, initially developed for aromatic compounds, is often referred as orthometallation <1990CRV879> or lateral lithiation <1995OR1>.

It is also worth mentioning the development of stereoselective deprotonations, which can be either diastereo- or enantioselective <1997AG(E)2282, B-2002MI001>. New chiral enolates have been produced, allowing the efficient formation of any aldol stereoisomer.

1.19.2.2 Directed Deprotonation

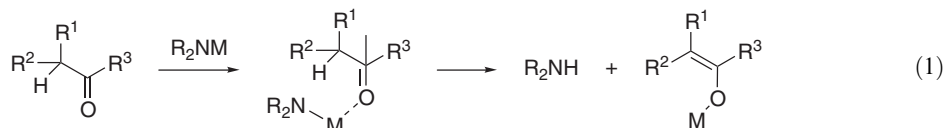
The presence of a Lewis base heteroatom in a molecular structure at an appropriate distance from a proton can facilitate the abstraction by a two-step process if the deprotonating reagent is an organometal. At first, the heteroatom will coordinate the organometallic base, usually an organolithium, and this induces a change in the cluster structure of the base and therefore its reactivity (steps 1–2, Scheme 1). Upon coordination, the deprotonation becomes entropically favored and thus kinetically fast due to the proximity of the proton and the base. Secondly, once formed,

the new organometallic species is stabilized by chelation, which thermodynamically favors its formation (step 3, [Scheme 1](#)).

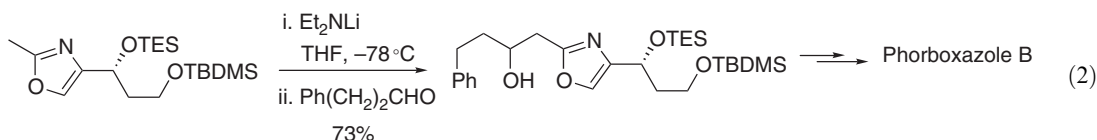


Scheme 1

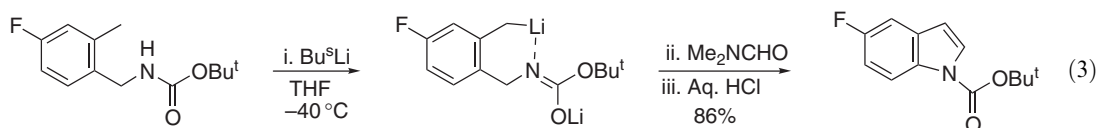
It is worth noting that the same process is operative for enolate formation by amide bases and is responsible for the highly organized transition state, which allows the stereoselective formation of either *Z*- or *E*-enolates [<1995COFGT869>](#) and subsequent stereoselective reactions ([Equation \(1\)](#)).



Numerous synthetic applications benefit from this process. Applied to 2-methyl oxazoles, this method allows a convenient access to marine natural products containing 2,4-disubstituted oxazoles [<1999OL87>](#) such as phorboxazole B [<2000JA10033>](#) ([Equation \(2\)](#)).



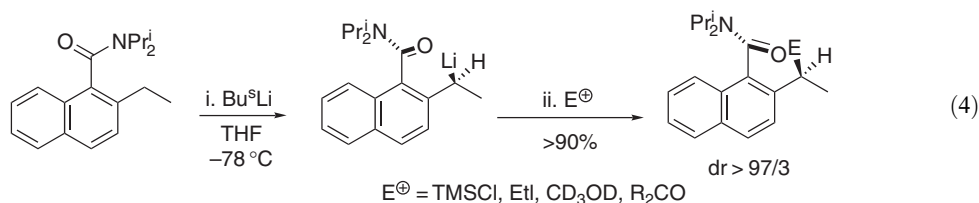
An efficient synthesis of substituted indoles has been achieved using directed metallation as the key step [<1990SL207>](#) ([Equation \(3\)](#)).

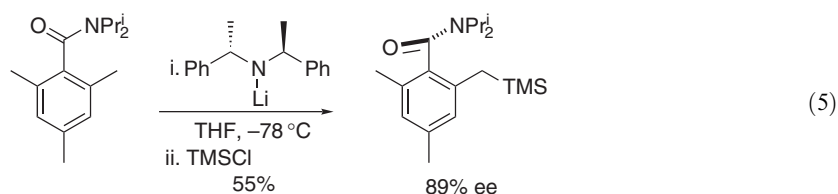


1.19.2.3 Stereoselectivity Issues

1.19.2.3.1 Diastereo- and enantioselective deprotonation

Enantioselective syntheses with lithium–sparteine carbanion pairs have been achieved and have been reviewed [<1997AG\(E\)2282>](#). Racemic benzylic carbanions produced by directed deprotonation can, in the presence of (–)-sparteine, give products with high enantioselectivity upon alkylation. The enantioselectivity as well as the sense of induction are strongly related to the nature of the electrophile [<1994JA9755>](#). Atropoisomerism of the lithiated intermediate can actually control such stereoselectivity [<1997TL2561>](#). Atroposelectivity was then developed as a new tool for stereocontrol and was used *inter alia* in diastereoselective deprotonation ([Equation \(4\)](#)) [<1997TL2561>](#), desymmetrization ([Equation \(5\)](#)) [<2001JCS\(P1\)371>](#), and dynamic resolution [<2000ACR715>](#).

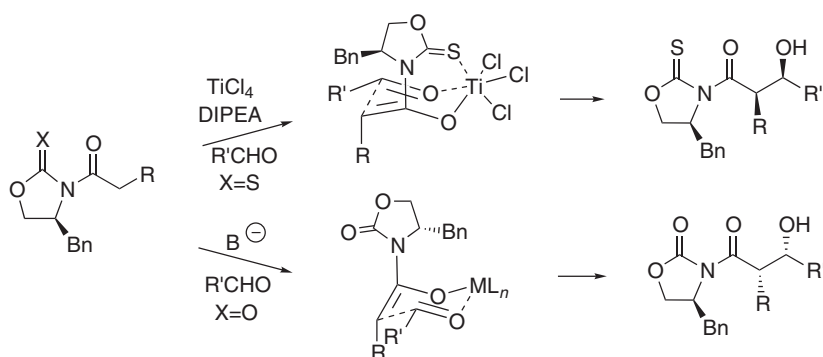




1.19.2.3.2 Chiral enolates

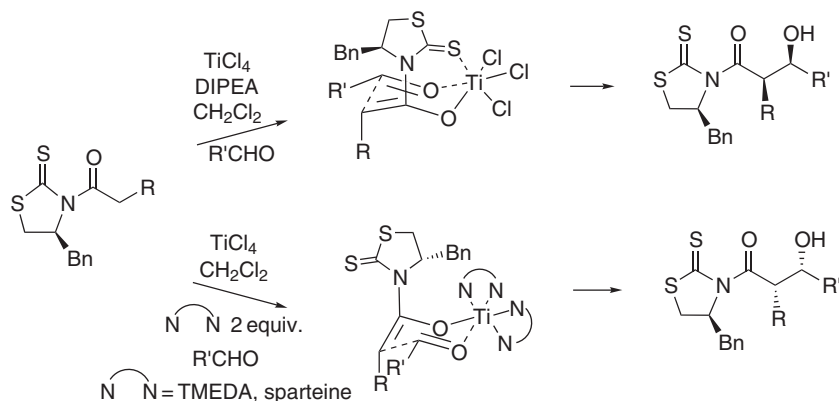
Enolate formations were well described in COFGT (1995) <1995COFGT869>, and no significant advances can be noticed in this area. However, concerning their applications, some improvements have since been made, especially in stereoselective aldolizations. Two major advances were enantioselective aldolization by the Crimmins' and Evans' groups, while direct catalytic asymmetric aldolizations were developed using Shibasaki-type catalysts or amino acids. The latter aspects have been reviewed <2002EJO1595>.

With enolates bearing a chiral auxiliary group, Crimmins and co-workers demonstrated that enantioselectivity can be reversed by using more coordinating auxiliaries together with an appropriate metal <1997JA7883>. Oxazolidinethiones give rise to a highly organized transition state, the sulfur atom being coordinated to titanium (Scheme 2, top), as compared to the now classical Evans oxazolidinones, which leads to a Zimmerman–Traxler transition state (Scheme 2, bottom).



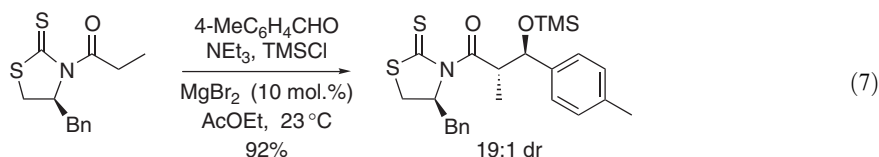
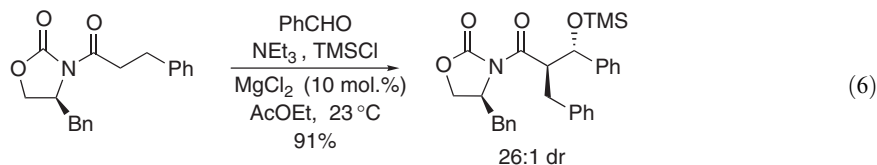
Scheme 2

Further research showed that, everything being equal, the nature of the base alone can reverse the enantioface selection <2001JOC894>. Indeed, using 2 equiv. of a double-coordinating base, such as tetramethylethylenediamine (TMEDA) or sparteine, completes the titanium coordination sphere and thus avoids further coordination of the chiral auxiliary, preventing the formation of the highly coordinated transition state (Scheme 3).



Scheme 3

Similarly, Evans showed that each enantiomer of *anti*-aldol adducts can be obtained from optically pure *N*-acyloxazolidinones (Equation (6)) <2002JA392> or thiazolidinethiones (Equation (7)) <2002OL1127> in the presence of magnesium salt. Only catalytic amounts of Mg^{2+} are required for these general reactions.



All aldol stereoisomers are thus now available with high enantioselectivity through one of these methods.

1.19.3 CARBANIONS BY SCISSION OF C—C OR C—X BONDS

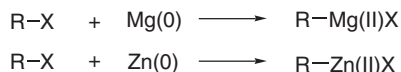
1.19.3.1 General Considerations

Carbanion formations by scission of C—C, C—O, and C—N bonds were well described in COFGT (1995) <1995COFGT883> and no significant advance has been made in this area. However, in the last decade carbanions have been produced through the rupture of carbon–halogen and carbon–chalcogen bonds, mainly due to the development of organometallics derived from transition metals. Three main processes were used to achieve carbanion formation by scission of carbon–halogen bonds and are discussed below.

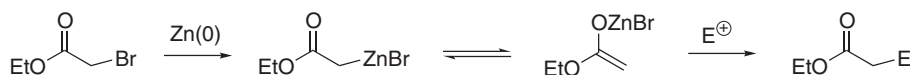
1.19.3.2 Oxidative Addition

Organohalides and related compounds act as oxidants toward metals, usually in a low oxidation state. The resulting compounds correspond to a formal addition of the oxidant to the metal, although such oxidative addition processes can be explained by three mechanisms <B-2000MI003>.

Oxidative addition encompasses several well-known formations of metallic carbanions, such as Grignard and organozinc reagents (Scheme 4), as well as the Reformatsky and Simmons–Smith reactions (Scheme 5), but this process is more general and is the major entry to organometallics derived from transition metals <B-2000MI004>.



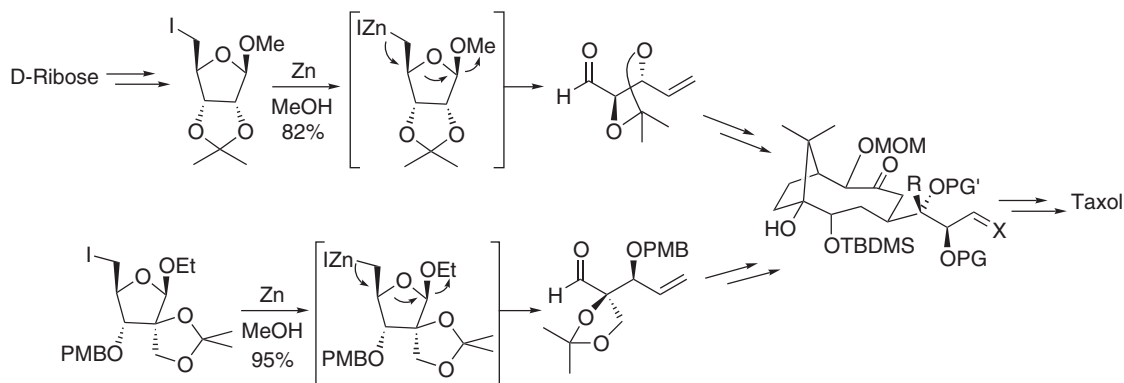
Scheme 4



Scheme 5

Oxidative addition sometimes fails, the bulk metal (powder, turning, etc.) being unable to react with some organohalides. To overcome this problem, Rieke developed highly reactive forms of magnesium and zinc, often written Mg^* and Zn^* , <1997T1925> and hundreds of Rieke organomagnesiums and organozincs are now commercially available.

Zinc insertion into halides has gained interest in carbohydrate chemistry and in organic synthesis since fragmentation of the intermediate organozinc reagents derived from halocarbohydrates leads to enantiopure synthons, such as in Paquette's approach toward Taxol (Scheme 6) <1995JOC7849, 1995JOC7857>.



Scheme 6

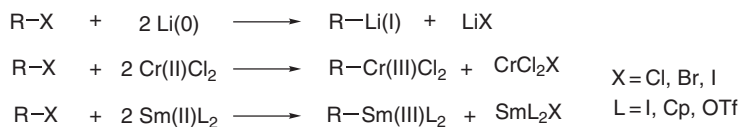
1.19.3.3 Halogen–Metal Exchange and Related Processes

1.19.3.3.1 General aspects

Two processes account for the formal substitution of halogen by metal: reduction of organohalides by metals or low-valent transition metals or lanthanide compounds, and organohalide–organometallic equilibria (halogen–metal exchanges *sensu stricto*). The reduction of halides can either be direct or mediated by arenes. A few atoms other than halogen can also be substituted by a metal (see also Chapter 1.01).

1.19.3.3.2 Direct reduction of organohalides

Simple organolithium reagents are obtained by treatment of organohalides by lithium metal through two successive single-electron transfer (SET) processes. Several other metals, such as, Na, Sn, Sm, and In, behave in the same way. The formation of organochromium and organosamarium species proceeds similarly by addition of the corresponding divalent salt to the halide (Scheme 7).

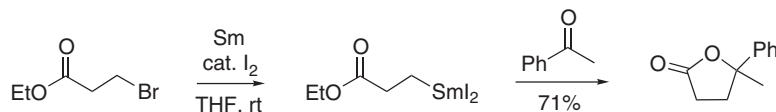


Scheme 7

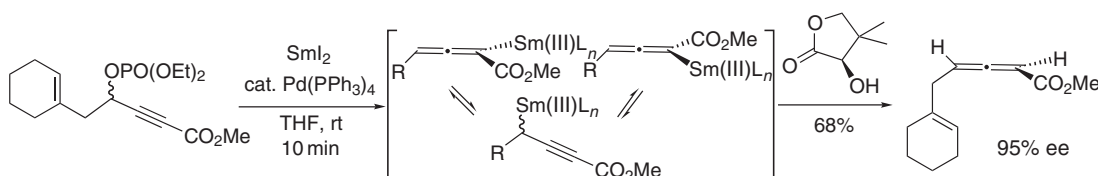
Organochromium compounds, usually obtained from the commercially available chromous chloride, behave as mild and selective carbanions. Their applications in organic synthesis are thus growing and have been reviewed <1999S1, 1999CR991>.

Organosamarium species exhibit more complex reactivity with a dual pattern typical of carbanions and radicals. Their instability has precluded the development of synthetic applications other than radical reactions until recently, where new methods for their preparation improved their stability and reactivity as carbanions <1997TL6585>. Homo-enolates can be obtained from

3-halo esters and added to ketones yielding lactones (Scheme 8) <1990JOC1628>. Interestingly, dynamic kinetic resolution has been achieved by protonation of samarium propargylic carbanions with chiral proton sources (Scheme 9) <2001T889,>.



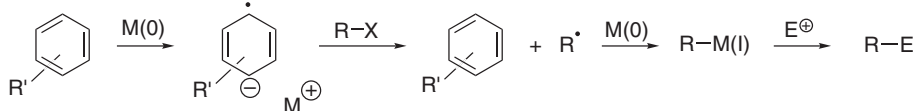
Scheme 8



Scheme 9

1.19.3.3.3 Reduction of organohalides mediated by arenes

The direct reaction of lithium metal with complex substrates is difficult and usually nonselective, leading to complex mixtures and side-products. However, lithium–arene reagents or arene catalysts have allowed a wider range of organolithiums to be prepared by reduction not only of halides but also of sulfides and various ethers (Scheme 10).



Scheme 10

Naphthalene <Np> was first used with sodium or lithium <1974CR243> but to solve some reactivity and selectivity problems other arenes have been proposed and 4,4'-di-*t*-butylbiphenyl (DTBB) and 1-dimethylaminonaphthalene (DMAN) emerged to be the most efficient reagents (Figure 1) <1996CSR155>. DTBB reacts with lithium to give a blue-violet solution, acting as colored indicator, and reacts rapidly even at very low temperatures (down to -100°C), especially with alkyl halides. DMAN in turn gave a greenish solution but its radical-anion decomposed at -45°C . Its major advantage lies in its amino group, which facilitates reaction work-up through acidic treatment.

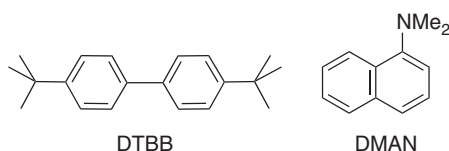
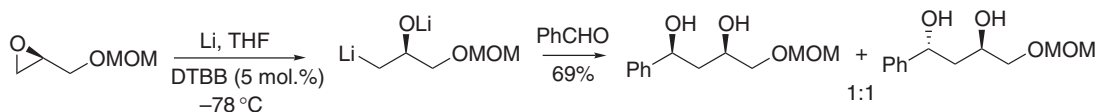


Figure 1 Arenes used for the lithiation of organohalides.

It has been shown that a catalytic amount of arenes can be used in most cases <1991CC398>. Either used in stoichiometric or catalytic amount, these reagents exhibit a similar reactivity pattern. This reactivity follows the stability order of the intermediate radicals: alkyl halides react faster (tertiary > secondary > primary alkyl) than alkenyl halides, which react faster than

aryl halides <1989ACR152>. The catalytic version proved to be a very useful method to prepare functionalized organolithiums. Indeed, amido, amino, and acetal groups are compatible with this reductive lithiation, but ethers and thioethers (sulfides) are not, since C—O and C—S bonds can also be reductively cleaved in these conditions <1987AG(E)9727>. Nevertheless, such cleavages can be another useful entry to organolithiums, as exemplified by the reaction of chiral epoxides <1995TA1907> and even aziridines <1994JOC3210> (Scheme 11). The generation of carbanions by reductive cleavage of alkoxy-substituted aromatic compounds has been reviewed <1997MI55>.



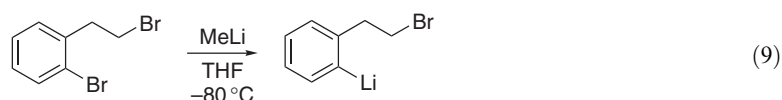
Scheme 11

1.19.3.3.4 Organohalide–organometallic equilibria

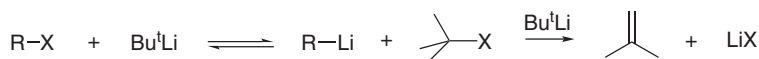
The treatment of organohalides by organolithiums promotes a metathesis reaction. This reaction, however, is in equilibrium since the nature of the compounds is the same before and after the reaction (Equation (8)).



The equilibrium is driven by the stability of the newly formed organolithium and, indeed, the following reactivity order has been observed with regard to the starting halide: $\text{C}_{\text{sp}^2}\text{-X} \approx \text{C}_{\text{sp}^2}\text{-X} > \text{C}_{\text{sp}^3}\text{-X}$, and for alkyl halides: primary > secondary > tertiary (Equation (9)).

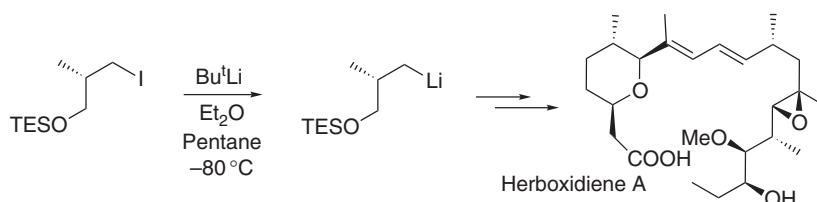


The equilibrium can also be shifted if one of the newly formed species is trapped *in situ*. This is usually achieved by using 2 equiv. of Bu^tLi as reagent. Upon exchange, *t*-butyl halide is formed, which is converted into *i*-butene and lithium halide by the second equivalent of Bu^tLi (Scheme 12).



Scheme 12

A synthesis of (+)-herboxidiene A relies on such halogen–lithium exchange and on several directed deprotonations (Scheme 13) <1996S652>.

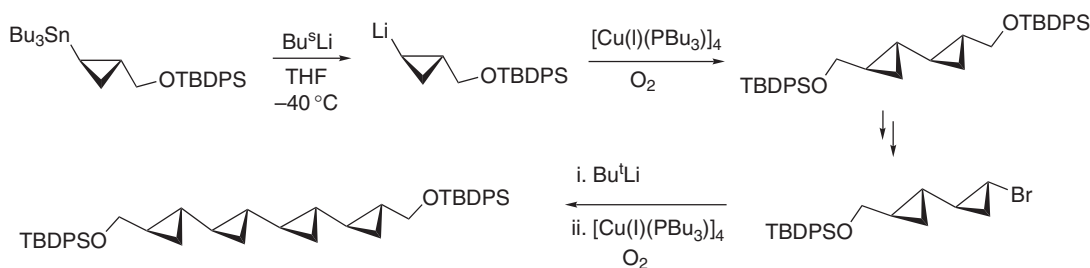


Scheme 13

1.19.3.3.5 Organometalloid–organolithium exchange

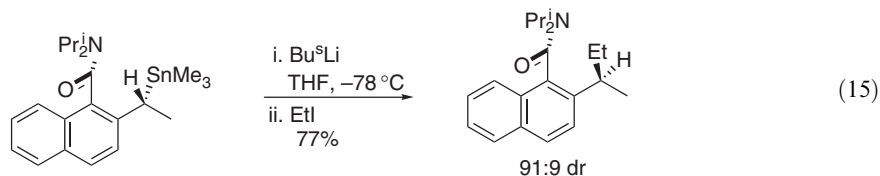
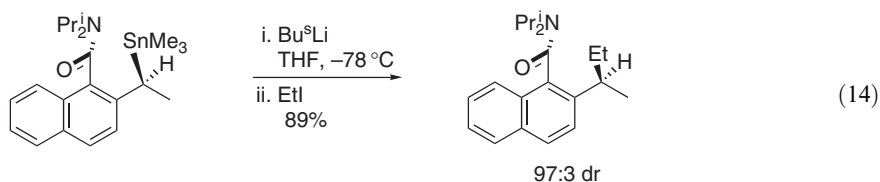
Organic compounds bearing a chalcogen or a main group metal atom from the third, fourth, or fifth row react with organolithiums yielding new organolithiums. Due to its similarity to the process discussed above, this reaction is often referred to as the lithium–metalloid exchange. Mechanisms involve “ate” complexes [<2002HCA3748, 1998EJO1851>](#). Organic selenides, tellurides, and tin have mostly been used.

This process is gaining importance in organic synthesis as a mild and efficient alternative to halogen–lithium exchanges. Moreover, the conversion of C–Sn to C–Li bonds by Sn–Li exchange is now one of the most important general methods of making configurationally defined organolithiums. It has, for example, been applied in carbohydrate chemistry [<1997TL1903>](#) and in the synthesis of the polycyclopropane antibiotic FR-900848 ([Scheme 15](#) [<1996JA6096>](#)).



Scheme 15

A lack of stereospecificity has nevertheless been observed in the case of atropoisomeric naphthamides, as seen from the comparison of [Equations \(14\)](#) and [\(15\)](#) [<2001JA12449>](#).



1.19.4 CARBANIONS BY ADDITION TO C=C BONDS

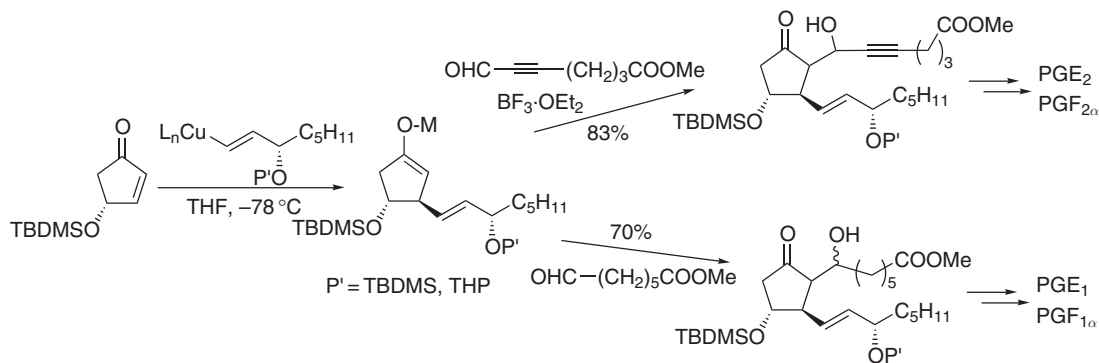
1.19.4.1 General Aspects

These additions have been well described in COFGT (1995) [<1995COFGT888>](#); nevertheless, some aspects deserve to be discussed further, such as the catalytic and asymmetric versions of Michael additions and the Baylis–Hillman reaction. Other processes such as carbo- and hydro-metallations are gaining interest.

1.19.4.2 Addition to Enones and Related Compounds

1.19.4.2.1 1,4-Additions (Michael-type reactions)

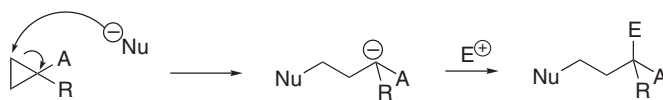
1,4-Addition to an alkene or alkyne conjugate with a π -accepting group leads to the formation of a stabilized carbanion, which can be trapped by electrophiles. The conjugate addition of carbanions to α,β -unsaturated carbonyl compounds is a powerful strategy for C—C bond formation and their numerous applications to synthesis are well known [<B-1992MI005>](#). One of the most illustrative applications is probably the three-component prostaglandin synthesis described by Noyori [<1984AC\(E\)847>](#), which has been scaled up for industrial production [<1992TL6393>](#) (Scheme 16).



Scheme 16

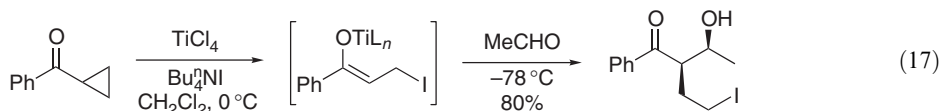
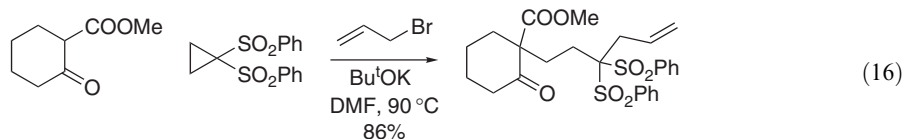
A large number of stoichiometric reagents are known to induce high stereocontrol in 1,4-additions [<1992CR771, B-1992MI004>](#) but chiral catalysts able to perform enantioselective additions have now been discovered [<2002JA13362, 2002JOC7244, 2000T2879, 2001JA4358, 2002JA5262, 2002JOC7244, 2003CR2829>](#).

A similar reaction has been developed starting from cyclopropanes bearing at least one accepting group. Nucleophilic addition occurs and a stabilized carbanion is produced, which can be quenched by various electrophiles (Scheme 17). The overall process offers a unique three-carbon homologation [<1985JOC2378>](#).



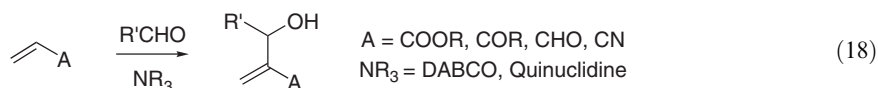
Scheme 17

Even if useful, this process has not yet gained much interest in organic synthesis, but a three-component reaction has nevertheless been developed (Equation (16)) [<1983JA1052>](#) as well as a tandem opening-aldol reaction (Equation (17)) [<2001T987>](#).

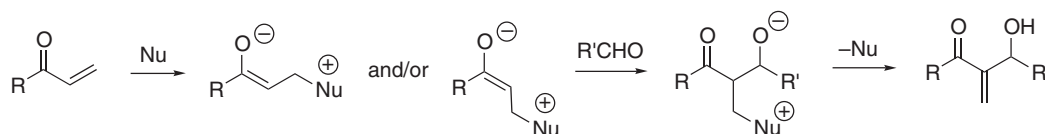
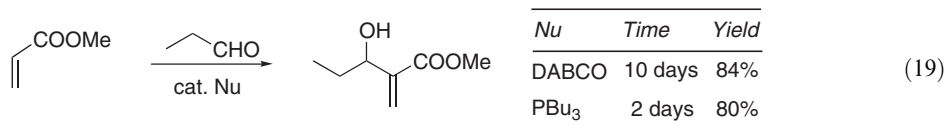


1.19.4.2.2 The Baylis–Hillman reaction

Although not recent, the Baylis–Hillman reaction is an interesting C—C bond formation reaction providing useful building blocks that have recently stimulated a lot of research [<1997OR201, 2003CR811>](#). It is a base-catalyzed condensation of aldehydes with activated alkenes ([Equation \(18\)](#)).

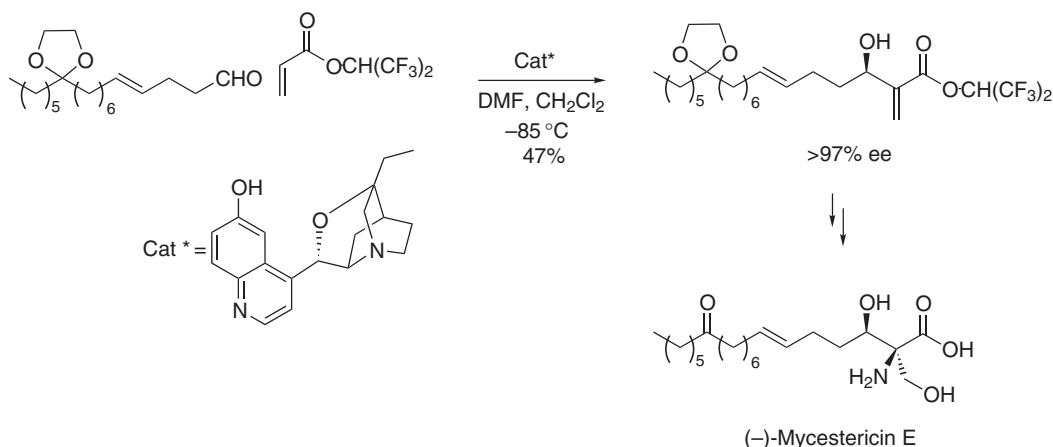


Being quite slow with the tertiary amines normally used as catalysts, the reaction was recently improved either by using tributylphosphine ([Equation \(19\)](#)) as catalyst at room temperature or by cooling, which probably led to a better stabilization of the Z-enolate ([Scheme 18](#)) [<1997JOC1521>](#).



Scheme 18

Asymmetric versions have been developed and applied to total synthesis, as illustrated by the synthesis of the immunosuppressive reagent (–)-mycestericin E ([Scheme 19](#)) [<2001CC2030>](#).



Scheme 19

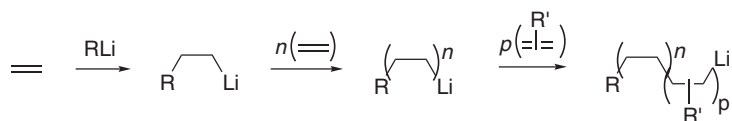
1.19.4.3 Carbometallation

Organometallics can add across alkenes or alkynes in a highly stereo- and regioselective process by [Equation \(20\)](#).



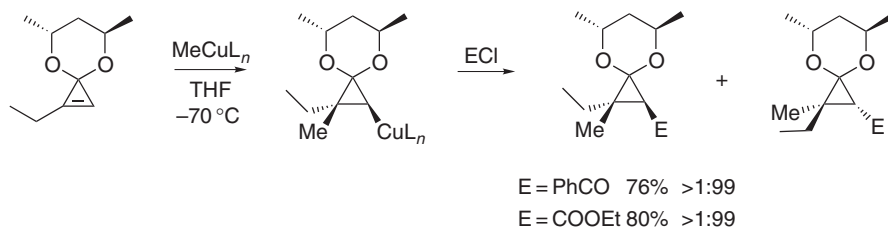
Since a new organometal is produced through this reaction, further addition is possible. What could be a drawback turned out to be an advantage for making the so-called “living” polymers.

Organolithiums can add across alkenes in excess, yielding a new long-chain organolithium, which can be trapped by another alkene to form a new elongated organolithium, which can react again. Such successive trapping allows for formation of block-copolymers (Scheme 20) <B-1983MI006>.



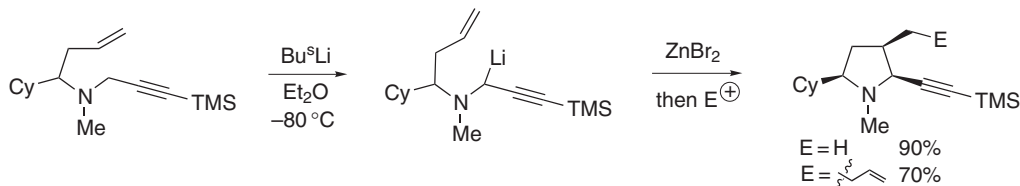
Scheme 20

In organic synthesis <1991COS865, B-1998MI007>, carbometallations have been mostly applied to alkynes due to the very high stereoselectivity. Nevertheless, interesting and useful methods have been developed with alkenes, especially for ring formation and as an efficient access to 1,1-bimetallic species, equivalent to dicarbanions <B-1998MI007>. Carbometallation proceeds with *syn*-stereoselectivity, which can be nicely exemplified by Nakamura's addition of organocuprates to cyclopropanes (Scheme 21) <1990JA7428, 2000JA978>.



Scheme 21

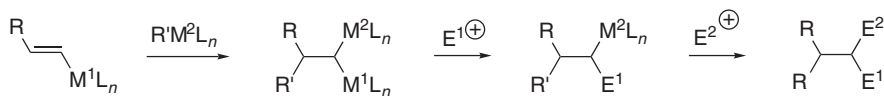
In a series of papers, Normant demonstrated that compounds bearing an acidifying group (A = alkyne, ester; Scheme 22) and an allyl group at the β -position are easily cyclized after deprotonation by organolithiums and treatment with zinc bromide. The cyclic organometallic produced after carbometallation can then be trapped with various electrophiles, providing a very efficient and highly diastereoselective synthesis of carbocycles <1996TL857> and heterocycles <1995TL1263, 1997TL89>.



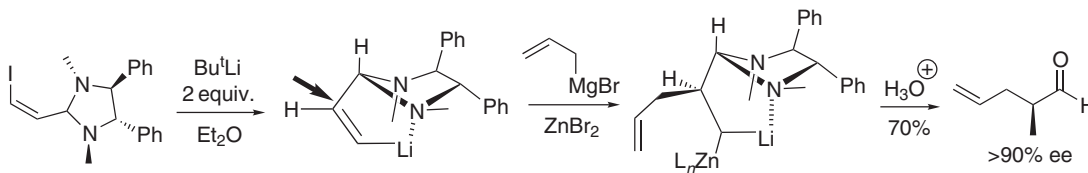
Scheme 22

Carbometallation of metallated alkenes provides 1,1-bimetallic species, which can react successively with different electrophiles, depending on the nature of the metal (Scheme 23). The formation and reactivity of 1,1-bimetallic species have been reviewed <1996CR3241>.

High diastereoselectivity can be achieved if chelation can organize the first intermediate. Using chiral auxiliaries, Normant and co-workers were able to obtain chiral adducts with excellent enantioselectivity (er >95:5) (Scheme 24) <1998TL4821>.



Scheme 23



Scheme 24

The synthetic potential of alkene carbometallation has promoted the development of enantioselective versions, which has been reviewed [<1999JCS\(P1\)535>](#).

1.19.4.4 Hydrometallation

In a process similar to carbometallation, compounds carrying a hydrogen–metal bond can stereo- and regioselectively add to alkenes and alkynes ([Equation \(21\)](#)). As with carbometallation, this process offers a direct entry to organometallics without prior deprotonation or lithiation; however only a few stable reagents are able to stereoselectively add across unsaturated C—C bonds. Among them, organoboranes such as disiamylborane and catecholborane, DIBAL-H, and the Schwartz's reagent are the most useful ([Figure 2](#)).

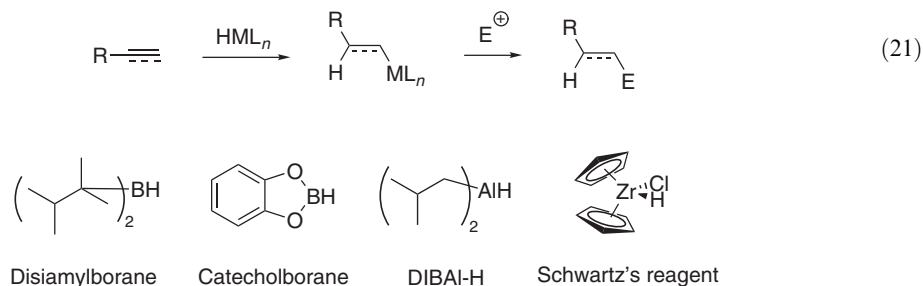
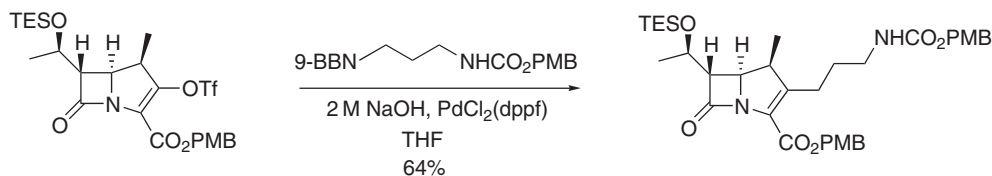


Figure 2 Common reagents for hydrometallation.

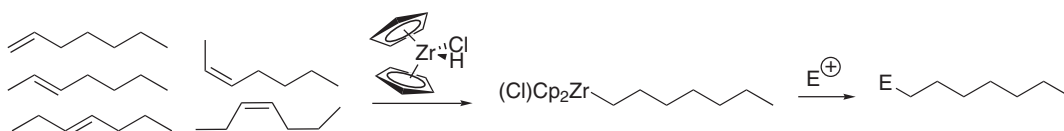
Hydroboration of alkenes produces organoboranes with high regioselectivity, but the latter cannot be considered as carbanions due to the low polarization of the C—B bond. However, upon activation by a Lewis base, some carbanionic character is observed in the presence of electrophiles [<B-2001MI008>](#). Organoborons have gained significant importance with the emergence of the Suzuki reaction [<1995CR2457>](#). This palladium-catalyzed cross-coupling reaction allows for very mild C—C bond formation without the requirement of basic and highly reactive organometallics. In palladium-catalyzed cross-coupling, a nucleophilic organometallic formally displaces an electrophilic vinyl or aryl halides. In Suzuki coupling, the nucleophile is an organoborane; but, as for other organoborane reactions, it must be activated. This is usually realized by running the reaction in the presence of mild bases, such as hydroxides, alkoxides, or carbonates, which play a critical role in the reaction mechanism [<1998JOC458, 1998JOC461>](#). Under these mild conditions, sensitive systems such as carbapenems can be alkylated ([Scheme 25](#)) [<1997T539>](#).

Hydrozirconation is of increasing importance in organic synthesis, providing a convenient entry to organometallic species without using strongly basic organolithiums. The reaction is compatible with various functional groups such as ethers, silyls, and some esters. Moreover, the huge volume

occupied by the zirconocene moiety ensures a very high regioselectivity upon addition of Schwartz's reagent. For example, a single organozirconium is obtained after treatment of a regio- and stereo-isomeric mixture of alkenes by Schwartz's reagent. Successive hydrozirconations and β -eliminations lead to isomerization of the less bulky organometallic (Scheme 26). The formation and the organic chemistry of organozirconium reagents have been reviewed <1996T12854>.



Scheme 25

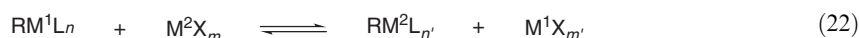


Scheme 26

1.19.5 CARBANIONS BY METAL–METAL EXCHANGE

1.19.5.1 General Aspects of Transmetallation: Tuning the Reactivity

Once produced, the metallic part of a carbanion can be modified by a transmetallation reaction, where a preformed organometallic is treated by a salt or a complex of another metal. This treatment leads to an equilibrium (Equation (22)), which is shifted according to the stability of the newly produced compounds.



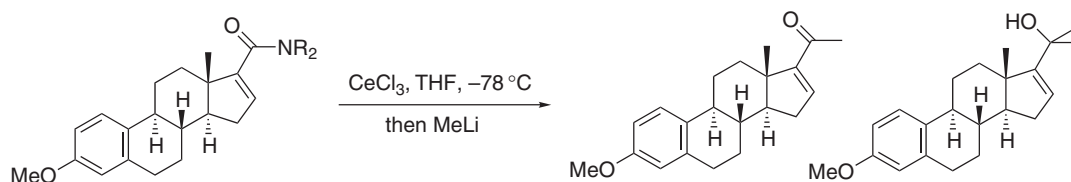
For example, going from a main group organometallic to a transition metal derivative can increase carbon–metal bonding due to overlap with *d*-orbitals.

Transmetallation is often used to modulate carbanion reactivity. Indeed, organolithiums, organomagnesiums, and some other organometallics are strongly basic entities; they can also lead to electron transfer. These basic or redox properties obviously compete with the nucleophilic character, useful for C–C bond formation. Changing the metal nature can minimize properties other than nucleophilicity, and some reactivity and selectivity problems have thus been solved.

Organocopper derivatives are probably the best-known example: they are commonly prepared from organolithiums, organomagnesiums, or organozincs and exhibit high nucleophilicity without the basicity of their progenitors <B-1999MI009>.

Organoceriums exhibit an even lower basicity, being, for example, able to add to the ketone of β -ketoesters without deprotonating them despite their high acidity <1989H703>. En route to batrachotoxin, Kishi and co-workers were unable to displace Weinreb amides with organolithium reagents. But transmetallation with CeCl_3 overcame these difficulties and offered a mild and direct method for the formation of saturated and α,β -saturated ketones from tertiary amides (Scheme 27) <1998TL4793>.

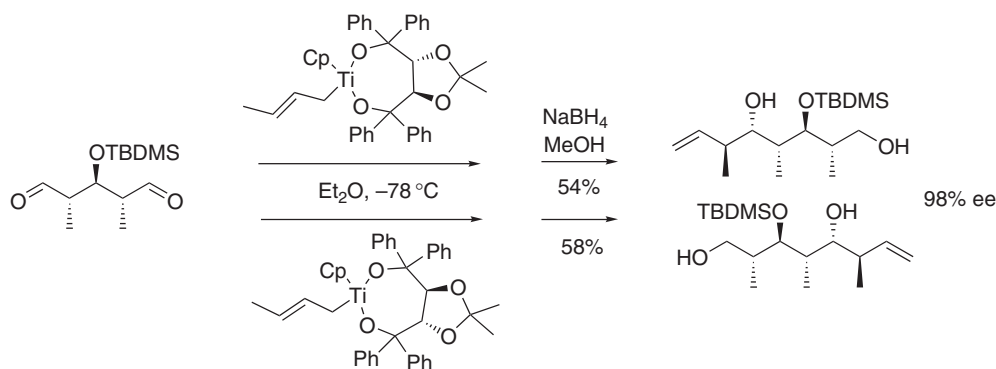
Alternatively, some carbanions are not reactive enough; transmetallation to a more reactive organometallic can solve this problem. As mentioned above, hydrozirconation provides a direct and efficient way to prepare metallic carbanions. However, the carbanionic reactivity of organozirconiums is not always high, but transmetallation affords a way to more nucleophilic reagents. Treatment with copper or zinc derivatives furnishes the corresponding organocoppers <B-1999MI009> or organozincs and even allows for asymmetric addition to aldehydes <1998JOC6454>.



NR_2	$MeCeCl_2$	Time	Yield (%)	Ketone/alcohol
	3 equiv.	1 h	40	100/0
	3 equiv.	1 h	40	100/0
	3 equiv.	5 min	95	100/0
	10 equiv.	15 min	95	100/0

Scheme 27

Transmetallation also offers the opportunity to switch from one organometallic to another having a larger coordination sphere in which chiral ligands can be introduced. This method has become very fruitful in asymmetric synthesis, specially in allylation reactions [<2003CR2763>](#). For example, the very efficient Duthaler's reagent [<1992JA2321>](#) has been applied to the syntheses of various natural products including the C_{14} – C_{25} fragment of (+)-discodermolide (Scheme 28) [<1992CR807, 2001OL3995, 2003OL3029>](#).



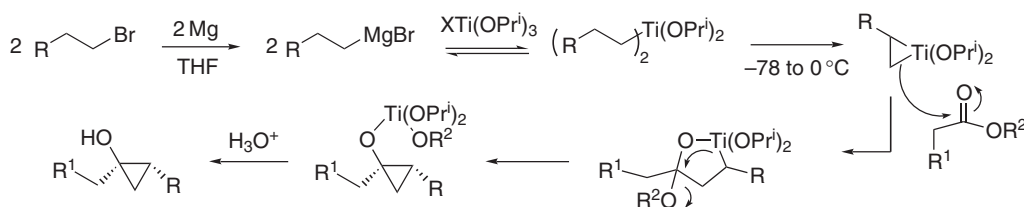
Scheme 28

1.19.5.2 Dicarbanions–Metallacycles

Transmetallation also affords an entry toward dicarbanionic reagents. Indeed, the behavior of some titanium and zirconium organometallics allows for the formation of metallacycles, which act as dicarbanions [<B-2002MI010>](#).

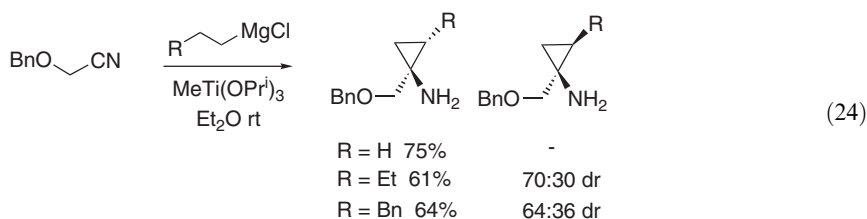
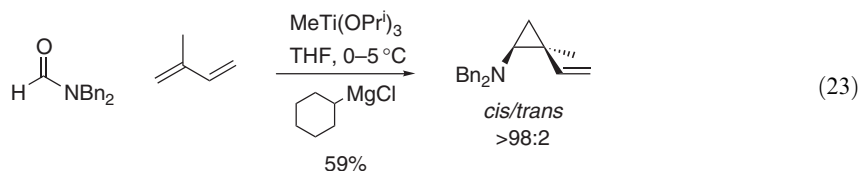
1.19.5.2.1 Titanium dicarbanions (the Kulinkovich reaction)

A formal diethylene dianion is produced by mixing alkylmagnesium bromide with titanium isopropoxide [<1991S234, 1993MI55>](#) or chlorotitanium triisopropoxide [<1994JA9345>](#). After transmetallation and β -elimination, an organotitanium is formed which is best described as a titanacyclopentane. The two C–Ti bonds of this species can successively add to esters giving *cis*-1,2-disubstituted cyclopropanols (Scheme 29). This reaction, referred to as the Kulinkovich reaction, is gaining interest due to its complete diastereoselectivity and the usefulness of cyclopropane derivatives [<2000CR2789>](#).



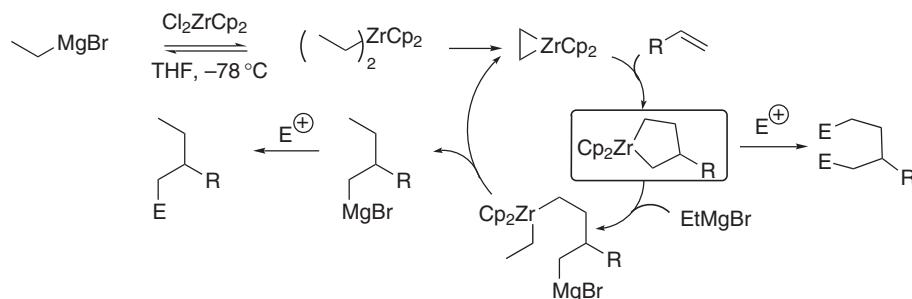
Scheme 29

This reaction has been extended to amides (Equation (23)) <1998TL7695> and to cyanides (Equation (24)) <2002JOC3965, 2003JOC7133>. Enantioselective versions <1994JA9345, 2000OL1337> as well as intramolecular versions <1996JA291, 2003OL2137> have been developed.



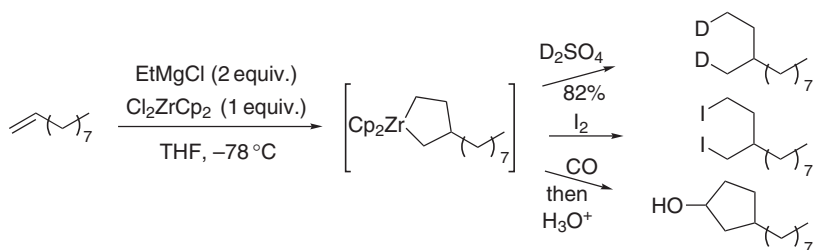
1.19.5.2.2 Zirconium dicarbanions and the Dzhemilev reaction

Zirconium species allow the addition of Grignard reagents to unactivated alkenes. In stoichiometric reactions, a zirconacyclopentane is formed, which reacts as a dicarbanion with a few electrophiles (H^+ or D^+ , Br_2 or I_2 , CO , O_2) (Scheme 30 right, Scheme 31) <1991JA6266>. If a catalytic amount of zirconium species is used, the intermediate zirconacyclopentane reacts further with the starting Grignard reagent giving a new organomagnesium, which can be trapped with various electrophiles (Scheme 30, left) <1985JOM43>. Known as the Dzhemilev reaction, this process may look like a carbometallation; however, the mechanism proceeds through transmetallations, β -elimination, and insertion as depicted in Scheme 30.

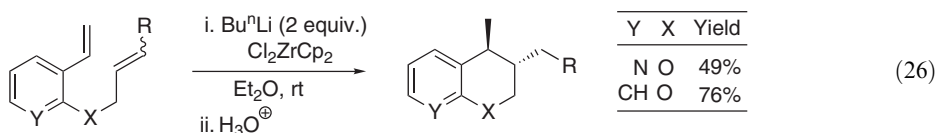
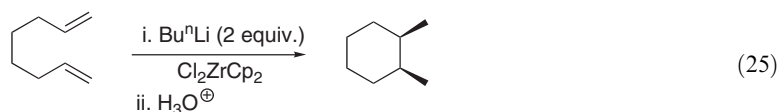


Scheme 30

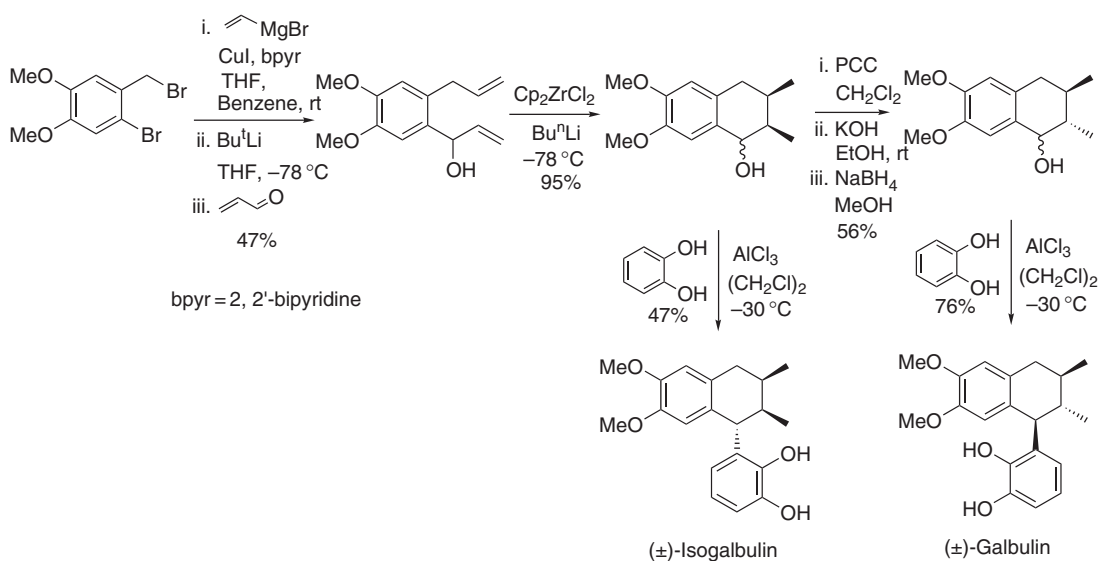
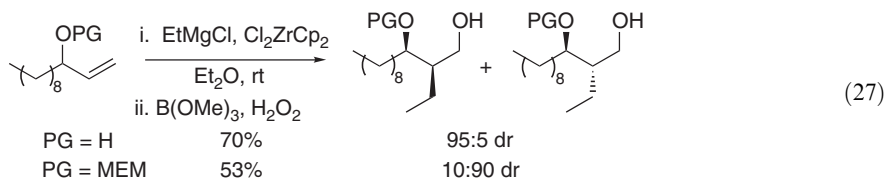
The intramolecular version of the stoichiometric reaction produces either carbocycles with a predominant *cis*-stereoselectivity (Equation (25)) <1994ACR124> or heterocycles but with *trans*-stereoselectivity (Equation (26)) <1995SL1237>.



Scheme 31

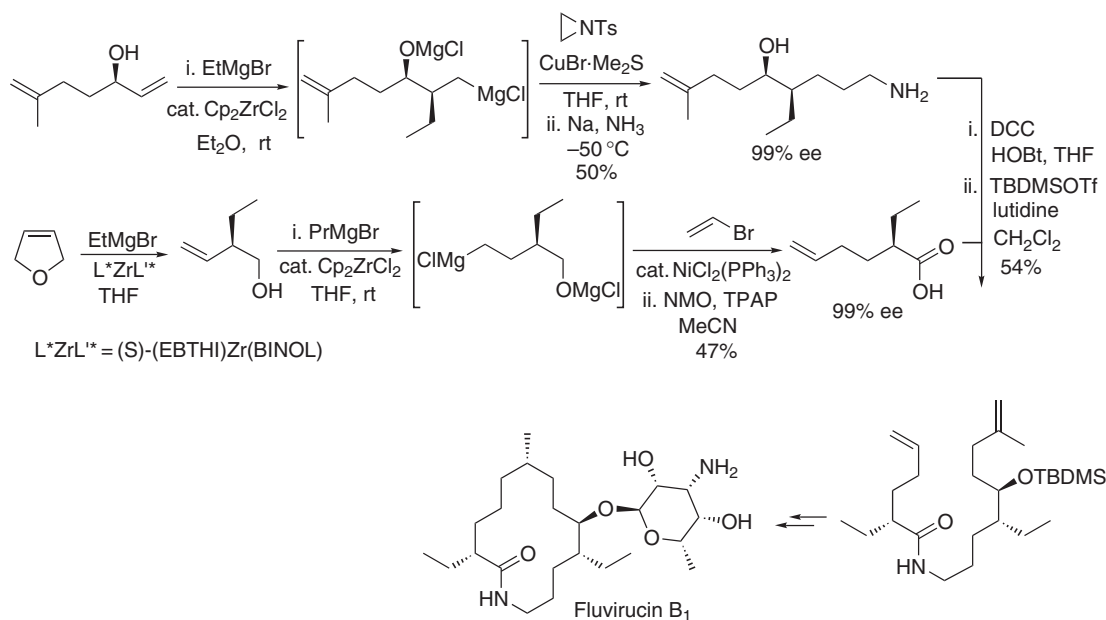


In the Dzhemilev reaction, high diastereoselectivity is observed when a hydroxy or alkoxy group is present next to the double bond. Moreover, either *syn*- or *anti*-adducts can be formed, depending on the nature of the adjacent oxygenated group (Equation (27)). With chiral zirconium catalysts, Hoveyda and co-workers were even able to get enantio-enriched adducts (Scheme 33) <1996AG(E)1262, 1995JA2943>.



Scheme 32

These diastereo- and enantioselective reactions have been applied to total syntheses <1996JA1028, 1996JA10926, 1997JOC3263, 1997JA10302, 1998TL6525, 2000JOC3236> as exemplified in Schemes 32 and 33.



Scheme 33

1.19.6 TRICOORDINATE CARBOCATIONS (P. VOGEL, EPFL, LAUSANNE, SWITZERLAND)

Carbocations as stable species are found everywhere, from interstellar space to your glass of wine. The color of red wine, as well as that of many flowers, fruits, and leaves, is due in part to the anthocyanins. They intervene as reactive intermediates in a large number of reactions including in living systems. Over 30 000 natural isoprenoids have been characterized. They play important roles in stabilizing membranes, and in the construction of signal transduction networks, visual pigments, antibiotics, etc. [<B-1994MI11>](#). Various polycyclic isoprenoids are generated from simple linear polyene substrates such as geranyl pyrophosphate, farnesyl pyrophosphate, and geranylgeranyl pyrophosphate in processes that involve cationic intermediates.

The study of carbocations is not only relevant to the understanding of organic reactivity and biochemistry, but it has also helped us to develop better models for the chemical bonding in organic and organometallic compounds.

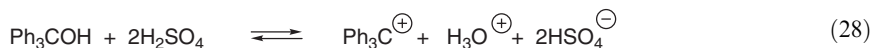
1.19.6.1 General Literature Survey

Between 1968 and 1976, a five-volume treatise edited by Olah and von R. Schleyer was published [<B-1968MI001, B-1970MI002, B-1972MI003, B-1973MI004, B-1976MI005>](#). Monographs have been written by Bethell and Gold [<B-1967MI006>](#) and Vogel [<B-1985MI007>](#) and reviews have been published [<1973AG\(E\)173, 1973TS253, B-1974MI008, B-1974MI92, 1979TCC1, 1979TCC19, 1981MI211, 1981CS97, 1991CRV375, B-1990MI287>](#). For a review of carbocations in super-acid solutions, see Olah *et al.* [<B-1985MI009>](#).

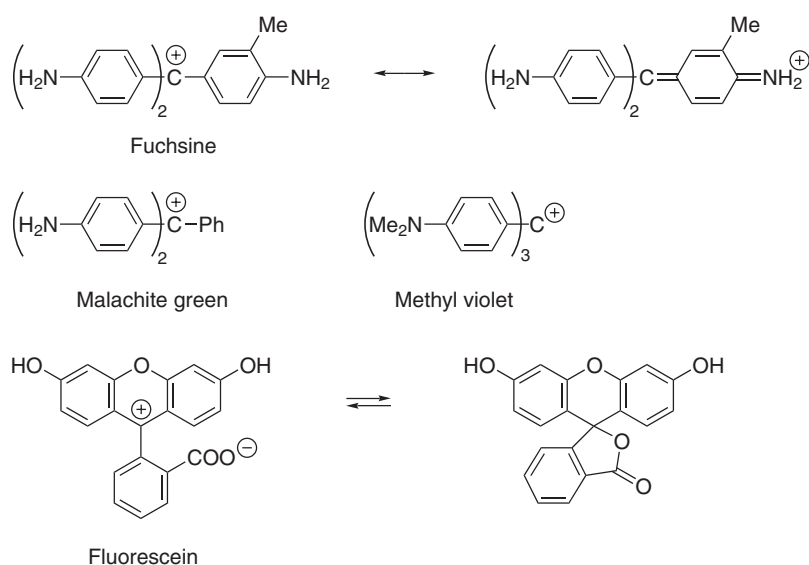
Olah [<2001JOC5943>](#) described 100 years of carbocations and of their significance in chemistry. Reviews on thermodynamic stabilities of carbocations [<2002APO57>](#) and on interactions between carbocations and anions in crystals have appeared [<1998CRV1277>](#). A general reactivity scale for *n*-, π -, and σ - nucleophiles [<2003JA286>](#) has been proposed by Mayr and co-workers. Carbocation stability in water can be evaluated by their intrinsic barriers to their reactions [<2001ACR981>](#). Monofunctionalized C₆₀ ions have been reviewed by Takeuchi [<2001BCJ785>](#). An overview on isoprenoid biosynthesis, which also implies carbocation intermediates, has been presented by Cane [<1999CONAP1>](#). Managing and manipulating carbocations in biology has been illustrated by reviewing the structures of terpenoid cyclases and the mechanisms of the reaction they catalyze [<1998MI695>](#). Dicarbocations have also been reviewed [<1983AG\(E\)390, B-1987MI425, B-1990MI439, 1995JA12005, 1997JA3407>](#).

1.19.6.2 Historical Background

In 1899, Stieglitz raised the possibility of ionic hydrocarbon compounds while studying salts of imido ethers. In 1901, Norris, as well as Kehrman and Wentzel [<1901CB3815>](#), independently discovered that colorless triphenylmethyl alcohol gave deep yellow solutions in concentrated H_2SO_4 (Equation (28)). Triphenylmethyl chloride similarly formed orange complexes with AlCl_3 and SnCl_2 .

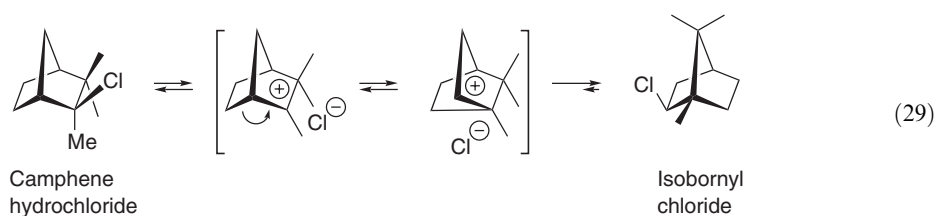


Baeyer and co-workers [<1902CB3013>](#) in 1902 recognized the salt-like character of these compounds. The same year, Gomberg [<1902CB3914>](#) noted that triphenylmethyl chloride gives colorless solutions in ether and benzene, whereas deep yellow solutions are obtained with SO_2 , CH_3COCl , or SO_2Cl_2 . Walden [<1902CB2018>](#) also contributed to the understanding of the ionic character of dyes such as fuchsine, malachite green, methyl violet, and fluorescein (Scheme 34).

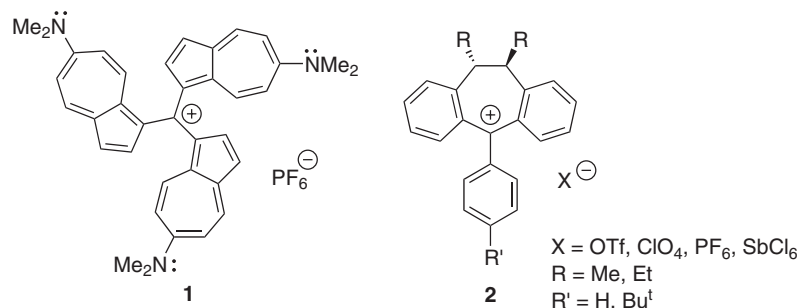


Scheme 34

Hantzsch in 1908 demonstrated that the yellow solutions of triphenylcarbinol in H_2SO_4 conduct electricity and established the existence of the equilibrium shown in Equation (28). The trityl cations were considered an isolated curiosity of chemistry and their fleeting existence was doubted until 1922 when Meerwein found that the rate of the Wagner rearrangement of camphene hydrochloride to isobornyl chloride (Equation (29) [<1899CB2302>](#)) increased with the dielectric constant of the solvent [<1922CB2500, 1927LA16>](#). Furthermore, he found that certain Lewis acids such as SbCl_5 , SnCl_4 , AlCl_3 , and SbCl_3 , as well as dry HCl , which promote the ionization of triphenylmethyl chloride by formation of carbocations [<1921CB2573>](#) also considerably accelerated the rearrangement. Meerwein concluded the existence of cationic intermediates capable of undergoing skeletal rearrangement, a concept that has become a milestone of physical organic chemistry. For a recent study of the historic camphenyl cation, see [<2001JOC7294>](#).

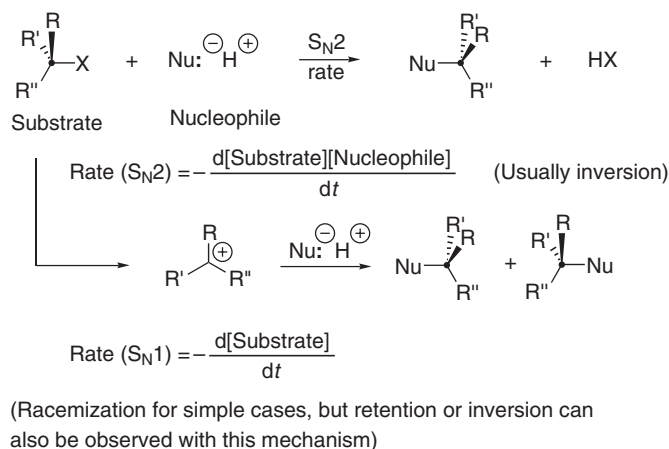


Analogues of trityl (triphenylmethyl) cation continue to be of interest today. For instance, Ito and co-workers [<1999JOC5815>](#) have prepared tris[6-(dimethylamino)-1-azulenyl]methyl hexafluorophosphate **1**, which is an extremely stable methyl cation in DMSO/H₂O as its pK_{R^+} value has been determined to be 24.3 ± 0.3 . The extreme stability of **1** is attributed to the dipolar property of the azulene rings, in addition to the contribution of the mesomeric effect of the three dimethylamino groups. Homochiral triarylcarbenium ions such as **2** have been prepared. They have been used to induce asymmetric Mukaiyama aldol additions [<1997JA11341>](#) (Scheme 35).



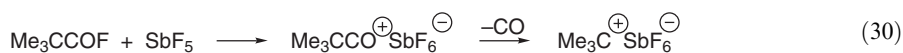
Scheme 35

During the 1930s, Ingold and Hughes carried out detailed kinetic and stereochemical investigations on nucleophilic substitution at saturated carbon and polar elimination reactions [<1933JCS526>](#). Their work relating to unimolecular nucleophilic substitution and elimination, called S_N1 (Scheme 36) and $E1$ reactions, in which formation of carbocations is the slow rate-determining step, laid the foundation for the role of electron-deficient carbocationic intermediates in chemistry and biochemistry.



Scheme 36

With the advent of mass spectrometry, the existence of carbocations in the gas phase was proven and their reactions in the absence of solvent could be studied [<B-1979MI010>](#) and results compared with predictions based on quantum calculations [<B-1986MI011>](#). A decisive breakthrough was realized by Olah with the direct observation by IR and NMR spectroscopy of alkyl cations in solution. An earlier case was the observation of the decarbonylation of the complex of pivaloyl fluoride with SbF_5 that generates the long-lived *t*-butyl hexafluoroantimonate (Equation (30)) [<1962JA2733, 1963JA1328>](#).



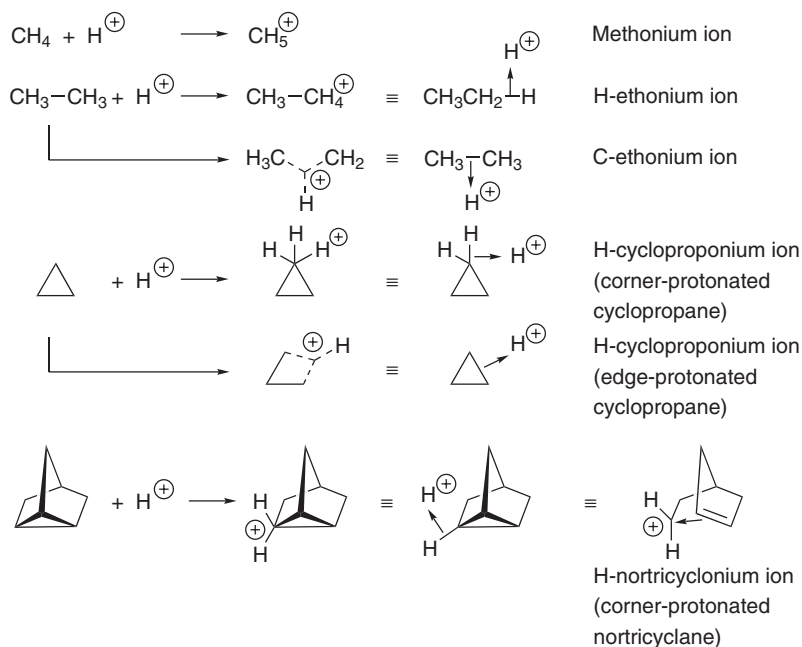
1.19.6.3 Carbenium and Carbonium Ion Nomenclature

Trivalent ions of type R_3C^+ may be regarded as being derived from carbenes by addition of a proton or a sextet ionic species R^+ , and it is logical, therefore, to call them carbenium ions <1972JA808, 1972JA6371, 1972JA7859>.

Examples are given as follows:

- (i) CH_3^+ carbenium ion or methylenium ion (methyl cation)
- (ii) CH_3CH_2^+ methylcarbenium ion or ethylenium ion (ethyl cation)
- (iii) Ph_3C^+ triphenylcarbenium ion or triphenylmethylenium ion (trityl cation)
- (iv) R_2NCH_2^+ *N,N*-dialkylaminocarbenium ion

The real “carbonium ions” are derivatives of a five-coordinated carbocation: CH_5^+ . With respect to the pentavalent carbocations, especially for the bridged structure of the 2-norbornyl cation (Scheme 37), the terminology used was “nonclassical” carbonium ion <1951JA5009, B-1965MI012>. As we shall see, they can be derived by formal complexation of a C—H or a C—C bond with a proton or an electrophile. They are denoted by the prefixes H— or C—; for instance:



Scheme 37

Radical cations that are considered to be formed by addition of a proton to a trivalent radical may be named as follows:

- (a) by adding the word “cation” to the name of the neutral compound having the same empirical formula, or
- (b) by adding the suffix “yl” to the name of the cation, for example:

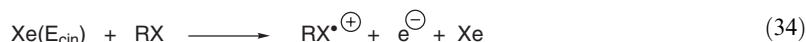
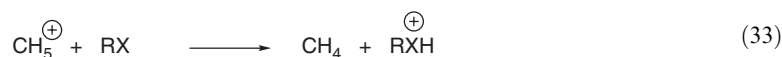
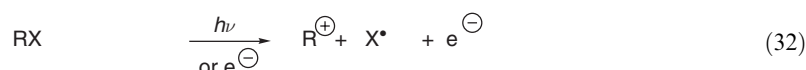
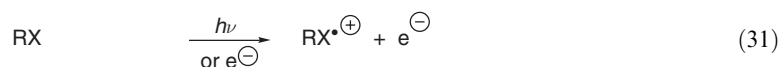
$\text{C}_2\text{H}_6^{\bullet+}$	(a) ethane cation	(b) ethaniumyl cation
$\text{C}_6\text{H}_6^{\bullet+}$	(a) benzene cation	(b) benzeniumyl cation
$\text{Me}_2\text{S}^{\bullet+}$	(a) dimethylsulfane cation	(b) dimethylsulfoniumyl cation
$\text{Ph}_3\text{N}^{\bullet+}$	(a) triphenylamine cation	(b) triphenylammoniumyl cation

1.19.7 CARBOCATIONS IN THE GAS PHASE

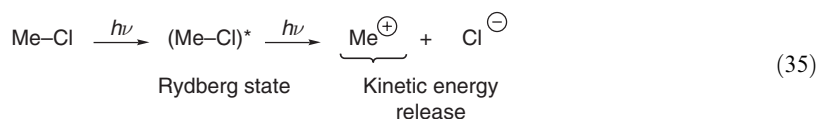
1.19.7.1 Methods for Generating and Investigating Ions in the Gas Phase

The direct heterolysis of a neutral molecule A–B is not a feasible process in the gas-phase, because the standard heteropolar bond dissociation enthalpies, $\text{DH}^\circ(\text{R}^+/\text{X}^-)$, are much too high. Although heterolysis can, in principle, occur at extreme temperatures, it must compete with the much more favorable homolytic fragmentation. Thermal ionization is, therefore, not a practical technique for generating carbocations in the gas phase.

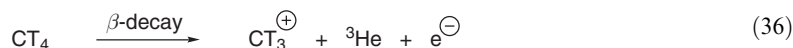
Classical methods used for the gas phase generation of ions involve the ionization of a neutral molecule and subsequent detection of molecular and/or fragment ions by the techniques of mass spectrometry (MS) <B-1978MI013> including the ion cyclotron resonance (ICR) method <1971ACR114, B-1976MI014>. For gaseous precursors, ionization is generally induced by interaction with protons (photoionization mass spectrometry: PIMS) or electrons (EI: electron ionization; e.g., Equations (31) and (32)). Chemical ionization (CI: e.g., Equation (33)) and fast atom (Xe or Cs) bombardment (FAB; e.g., Equation (34)) are also extremely useful, especially for the generation of ions with relatively high molecular masses.



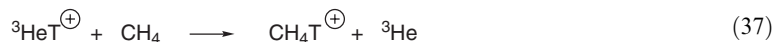
More recently <2001SCI2527> a technique called “heavy electron” photoelectron spectroscopy has been applied to measure vibrational frequencies and rotational constants of CH_3^+ . Methyl chloride is excited by vacuum ultraviolet photons that lead to Rydberg states of CH_3Cl . They couple with the long-range ion-pair state. Dissociation of this state gives rise to momentum-matched Cl^- and CH_3^+ products, either of which may be detected with velocity map imaging. For a structureless atomic anion such as Cl^- , the kinetic energy release directly reflects the internal energy levels in the cation, a situation similar to what occurs during photoionization spectroscopy (PES) of radicals into carbenium ions ($\text{R}^\bullet + h\nu \rightarrow \text{R}^+ + e^-$ (energy)). In the case of the photoionization of $\text{Me}-\text{Cl}$ into $\text{Me}^+ + \text{Cl}^-$, it is the chloride anion that plays the role of a “heavy electron” (Equation (35)).



Ionization can also be generated by β -decay of tritiated compounds. Labeled methyl cations are formed by spontaneous radioactive β -decay of tritium atom contained in CT_4 giving CT_3^+ in 82% yield (Equation (36)) <1970APO79, 1977JA5477, 1979JA4276>.



Tritium, T_2 , generates ${}^3\text{HeT}^+$ by β -decay which is a powerful Brønstedt acid and for which a heat of formation of $\sim 1339 \text{ kJ mol}^{-1}$ has been evaluated <1969JCP5426>. It can thus tritiate gaseous organic compounds such as methane (Equation (37)) <1984JA37>.



In all these techniques, an ion is usually recognized according to its mass/charge ratio (m/z) and its kinetic energy. In most cases, gas-phase ion structures are based on indirect observables, and on their reactivity, i.e., their degradations into smaller ions and their reactions with neutral

molecules. The measurement of the kinetic energy release in a fragment ion <1979AG(E)451> can be done, for example, by analysis of the metastable peaks due to ions having rate constants for fragmentation appropriate for decomposition within the field-free region of the mass spectrometer <B-1978MI1115>. Depending on the type of instrument, ions with lifetime of 10^{-11} to 10^{-3} s can be analyzed. More recently, infrared fingerprints of small gaseous cations such as CH_3^+ <1999SCI135>, CH_3^+ <2001SCI2527>, and protonated benzene (cyclohexa-2,4-dien-1-yl cation) <2003AG(E)2057> have been reported.

ICR spectrometry adds another dimension to ion analysis as it can store circulating ions in reservoirs and cool them or warm them by ion–molecule interactions. Thus, relatively high pressure and long residence time can be realized in these machines. This has allowed the measurement of accurate thermodynamic data for all kinds of ion/molecule reactions. Quantum calculations have proved extremely useful for the interpretation of the results obtained by mass spectroscopy techniques as they deal with free, nonsolvated ions.

1.19.7.2 Gas-phase Thermochemical Data

The assignment of absolute proton affinities (PA(A)) and standard heats of formation of carbocations ($\Delta H_f^\circ(\text{R}^+)$) relies on the use of suitable reference standards. The latter are usually derived from spectroscopic measurements of ionization energies or appearance energies. For carbenium ion, $\Delta H_f^\circ(\text{R}^+) = \Delta H_f^\circ(\text{R}^\bullet) + \text{IE}(\text{R}^\bullet)$. They have been reviewed by McMahon <2001JM187>. Examples of thermochemical data are given in Tables 1 and 2.

Table 1 Thermochemical parameters for selected carbenium ions and related radicals in the gas phase, in kJ mol^{-1} . $\text{DH}^\circ(\text{R}^+/\text{H}^-)$: hydride affinity = $\Delta H_r^\circ(\text{R}-\text{H} \rightleftharpoons \text{R}^+ + \text{H}^-)$; $\Delta H_f^\circ(\text{R}^+)$: standard heat of formation of carbenium ion R^+ , $\Delta H_f^\circ(\text{R}^\bullet)$: standard heat of formation of radical R^\bullet , $\Delta H_f^\circ(\text{RH})$: standard heat of formation of RH, $\text{DH}^\circ(\text{R}^\bullet/\text{H}^\bullet)$: heat of the homolytic dissociation: $\Delta H_r^\circ(\text{R}-\text{H} \rightleftharpoons \text{R}^\bullet + \text{H}^\bullet)$



R^+	$\text{DH}^\circ(\text{R}^+/\text{H}^-)$	$\Delta H_f^\circ(\text{R}^+)^b$	$\Delta H_f^\circ(\text{R}^\bullet)$	$\Delta H_f^\circ(\text{RH})$ gas	$\text{DH}^\circ(\text{R}^\bullet/\text{H}^\bullet)$
H^+	1673.6	1530.0	218.0		436.0
CH^+	1368.2	1619.2	595.8	392.9	418.4
CH_2^+	1397.5	1397.5	389.1	145.6	460.2
CH_3^+	1311.3	1093.3	145.6	−74.5	438.1
$\text{CH}_2=\text{CH}^+$	1217.5	~1125.5	265.3	52.3	431.0
CH_3CH_2^+	1129.7	903.7	117.2	−784.5	418.8
$\text{HC}\equiv\text{C}-\text{CH}_2^+$	1133.9	1175.7	343.1	187.0	374.0
$\text{CH}_2=\text{CH}-\text{CH}_2^+$	1079.5	~945.6	163.2	20.5	361.1
$\text{CH}_2=\text{C}^+-\text{CH}_3$	1112.9	991.6	238.5	20.5	435.1
$\text{CH}_3\text{CH}_2\text{CH}_2^+$	1117.1	882.8	100.4	−103.8	423.0
$\text{CH}_3-\text{C}^+\text{H}-\text{CH}_3$	1050.2	798.7	93.3	−103.8	415.9
$\text{CH}_3\text{CH}_2\text{CH}_2\text{CH}_2^+$	1108.8	836.8	75.3	−127.2	423.0
$\text{CH}_3\text{CH}_2\text{C}^+\text{HCH}_3$	1037.6	765.7	71.1	−127.2	414.6
$(\text{CH}_3)_2\text{CHCH}_2^+$	1108.8	828.4	66.9	−135.6	418.8
$(\text{CH}_3)_3\text{C}^+$	974.9	698.7	46.0	−135.6	398.3
$\text{CH}_2=\text{C}(\text{CH}_3)\text{CH}_2^+$	1037.6	882.8	121.3	−16.7	355.6
	1041.8	928.8	213.4	23.8	405.8
$\text{CH}_3\text{C}^+\text{HCH}_2\text{CH}_3$					
CH_3^+	1008.3	723.8		−146.9	
$\text{H}_2\text{N}-\text{CH}_2^+$	912.1	744.8	159.0	−23.0	400.0
$\text{NC}-\text{CH}_2^+$	1330.5	1262.7	246.9	73.6	389.1
$\text{O}=\text{CH}^+$	1066.9	815.9	41.8	−108.8	368.2
$\text{HO}-\text{CH}_2^+$	1062.7	719.6	−25.9	−200.8	393.7
CH_3CO^+	937.2	631.8	−25.1	−166.1	359.8
$(\text{CH}_3\text{O})\text{CH}_2^+$	1016.7	682.0	−12.6	−184.1	−389.5
Ph^+	1200.8	1138.0	330.5	82.8	466.1
	1016.7	815.9		−62.8	405.8

Table 1 (continued)





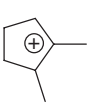

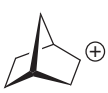
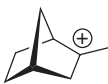





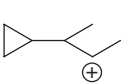
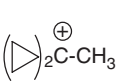


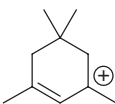
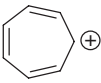
R^+	$DH^\circ(R^+/H^-)$	$\Delta H_f^\circ(R^+)^b$	$\Delta H_f^\circ(R^\bullet)$	$\Delta H_f^\circ(RH)$ gas	$DH^\circ(R^\bullet/H^\bullet)$
	966.5	811.7		-170.3	
	949.8	774.0		-37.7	
	1045.2	829.3	101.7	-77.0	396.6
	947.7	702.9		-105.9	
	945.6	669.4		-136.8	
	951.9	656.9		-154.8	
	970.7	782.4		-51.9	
	941.4	719.6		-82.0	
	978.2	700.8			401.7
	938.5	661.1			412.1
	1008.3	895.4		25.1	407.5
	962.3	824.2		4.2	
	912.1	748.9		-25.1	
	924.7	761.5		-25.1	
	866.1	820.1		92.0	
	941.4	832.6		36.0	343.1
	1069.4	1054.4		129.7	338.9

Table 1 (continued)

R^+	$DH^\circ(R^+/H^-)$	$\Delta H_f^\circ(R^+)^b$	$\Delta H_f^\circ(R^\bullet)$	$\Delta H_f^\circ(RH)$ gas	$DH^\circ(R^\bullet/H^\bullet)$
	866.1	623.4		-104.6	
	811.7	849.4	246.9	182.8	282.0
PhCH_2^+	979.1	891.2		50.2	368.2
PhC^+HCH_3	945.6	836.8		30.1	
$\text{PhC}^+(\text{CH}_3)_2$	920.5	786.6		4.2	
$\text{Ph}_2\text{C}^+\text{CH}_3$	899.6	893.7		133.9	
FCH_2^+	1211.7	838.1		-233.9	431.4
F_2CH^+	1187.8	595.8		-452.3	422.6
F_3C^+	1251.0	415.5		-695.8	444.3

^a National Institute of Standards and Technology chemistry WebBook, NIST Standard Reference Data-base Number 69, Mallard, W. G.; Linstrom, P. G., Eds.; Gaithersburg, MD, 2000 (<http://webbook.nist.gov>). ^b $\Delta H_f^\circ(\text{H}^-) = 143.1 \text{ kJ mol}^{-1}$ used.

^c $\Delta H_f^\circ(\text{Bu}^+) = 678.2 \pm 2.5 \text{ kJ mol}^{-1}$ is obtained by photoionization coupled with MS; $\Delta H_f^\circ(\text{Bu}^+) = 711 \text{ kJ mol}^{-1}$ by proton affinity of isobutene.

Table 2 Proton affinities of compounds **B**, 1 atm 25°C, gas phase. Substituent effects on the relative stability of cations BH^+ given by $\text{PA}(\text{substituted B}) - \text{PA}(\text{unsubstituted B})$. Reference is $\text{PA}(\text{NH}_3) = 846.4 \pm 8 \text{ kJ mol}^{-1}$, $\Delta H_f^\circ(\text{H}^+) = 1,530 \text{ kJ mol}^{-1}$. Proton affinities are the heat of reactions $\text{BH}^+ \rightleftharpoons \text{H}^+ + \text{B}$

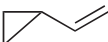
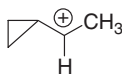

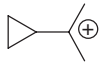
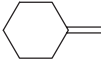
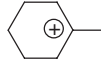

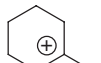

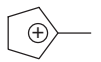

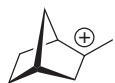
<i>Substituent effects</i>			
$\text{CH}_2=\text{CH}_2$	\rightarrow	CH_3CH_2^+	672.0
$\text{CH}_3-\text{CH}=\text{CH}_2$	\rightarrow	$\text{CH}_3-\text{C}^+\text{H}-\text{CH}_3$	754.8
$(\text{CH}_3)_2\text{C}=\text{CH}_2$	\rightarrow	$(\text{CH}_3)_3\text{C}^+$	809.6
	\rightarrow		816.7
	\rightarrow		866.5
$\text{Ph}-\text{CH}=\text{CH}_2$	\rightarrow	$\text{Ph}-\text{C}^+\text{H}-\text{CH}_3$	833.5
$\text{Ph}-\text{C}(\text{CH}_3)=\text{CH}_2$	\rightarrow	$\text{Ph}-\text{C}^+(\text{CH}_3)_2$	858.6
	\rightarrow		822.6
	\rightarrow		836.8
	\rightarrow		819.6
 ($\Delta H_f^\circ: 12$)	\rightarrow		866.1

Table 2 (continued)


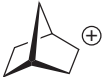


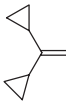
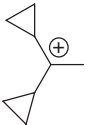

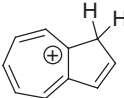
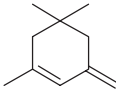
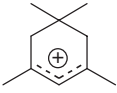



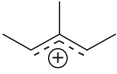



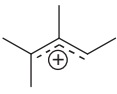

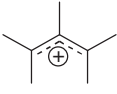









			Substituent effects	
 (ΔH_f° : 21)	\rightarrow		843.5	
	\rightarrow		799.1	
 (ΔH_f° : 46)	\rightarrow		910.0	
 (ΔH_f° : 73.5)	\rightarrow		939.3	
 (ΔH_f° : -2)	\rightarrow		904.2	
 (ΔH_f° : 18.1)	\rightarrow		844.3	
 (ΔH_f° : 11)	\rightarrow		860.6	16.3
 (ΔH_f° : 18.1)	\rightarrow		838.5	
 (ΔH_f° : 10.8)	\rightarrow		845.6	
 (ΔH_f° : 11)	\rightarrow		869.9	
 (ΔH_f° : 4)	\rightarrow		891.6	
 (ΔH_f° : -3)	\rightarrow		881.2	
 (ΔH_f° : +48.3)	\rightarrow		887.0	

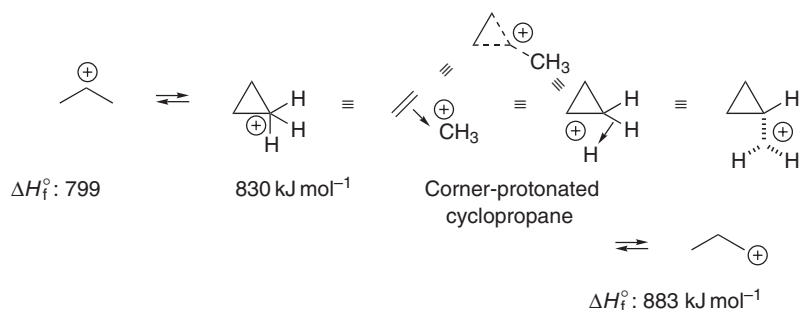
Table 2 (continued)

			Substituent effects	
	→		836.8	
O=CH ₂	→	HO—CH ₂ ⁺ ↔ HO ⁺ =CH ₂	730.5	
O=CH(CH ₃)	→	HO—C ⁺ H(CH ₃) ↔ HO ⁺ CH(CH ₃)	774.0	43.5
O=C(CH ₃) ₂	→	HO—C ⁺ (CH ₃) ₂	811.3	80.8
O=C=CH ₂	→	⁺ O≡C—CH ₃	818.4	
HCOOH	→	HC ⁺ (OH) ₂	753.5	
CH ₃ COOH	→	CH ₃ C ⁺ (OH) ₂	789.5	36.0
CF ₃ COOH	→	CF ₃ C ⁺ (OH) ₂	725.1	−28.5
HCON(CH ₃) ₂	→	H—C ⁺ (OH)[N(CH ₃) ₂]	877.8	
CH ₃ CON(CH ₃) ₂	→	CH ₃ C ⁺ (OH)[N(CH ₃) ₂]	894.5	16.7
CH ₂ =NH	→	CH ₂ =N ⁺ H ₂	846.4	
Ph—H	→	C ₆ H ₇ ⁺ = 	774.0	
Ph—CH ₃	→	C ₆ H ₆ CH ₃ ⁺	801.2	27.2
PhF	→	C ₆ H ₆ F ⁺	770.3	−3.8
PhCl	→	C ₆ H ₆ Cl ⁺	769.9	−4.2

^a see footnote ^a of Table 1.

1.19.7.3 Examples of Carbenium Ions in the Gas Phase

Applying the new technique called “heavy electron” photoelectron spectroscopy, CH₃⁺ has been characterized by vibrational and rotational energy levels <2001SCI2527>. Among C₃H₇⁺ cations, isopropyl cation, *i*-Pr⁺, is the most stable isomer. In between lay the corner-protonated cyclopropane, or H-cyclopropenium ion as shown in Scheme 38 <1976JA6834>.

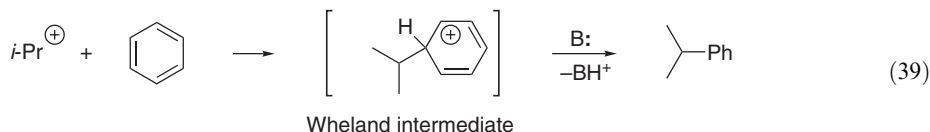
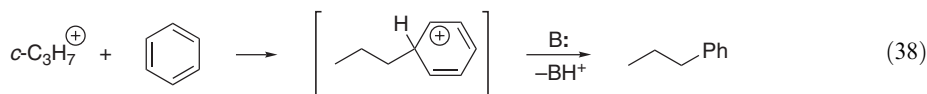


Scheme 38

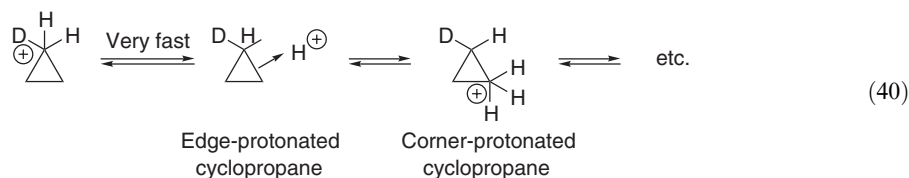
Lifetime for *c*-C₃H₇⁺ in the gas phase is estimated to exceed 10^{−7} s. It isomerizes to *i*-Pr⁺. H-Cyclopropenium ion has been suggested to be an intermediate in the gaseous reaction of methyl cation with ethylene <1981JM7> and as a possible product of the H₂ loss from C-proponium ion <1998JPC(A)10798>. The metastable dissociation of propane molecules from cluster ions of C₃H₇⁺ with neat propane or Ar/propane gas has been ascribed to the ionization of *c*-C₃H₇⁺ core to give *i*-Pr⁺ proceeding by way of a transient *n*-Pr⁺ <1995MI415>. All attempts to trap *n*-Pr⁺ in a gas phase reaction have failed, suggesting that it rearranges into *c*-C₃H₇⁺ and *i*-Pr⁺ in less than 10^{−10} s <1984JA3917>.

The protonation of cyclopropane by gaseous Brønsted acids such as H₃⁺, D₃⁺, CH₅⁺, and C₂H₅⁺ generates *c*-C₃H₇⁺, which isomerizes into *i*-Pr⁺ competitively by its reaction with benzene, giving *n*-propylbenzene (Friedel–Crafts alkylation Equation (38)), whereas *i*-Pr⁺ reacts with benzene given *i*-propylbenzene (Equation (39)). The relative abundance of these two products

varies with the nature of the Brønsted acid (the more energetic the protonation reaction of cyclopropane, the more $c\text{-C}_3\text{H}_7^+$ is isomerized into $i\text{-Pr}^+$), the pressure (up to 1 atm), temperature and the presence of additives in the gaseous systems. Isomerization of $c\text{-C}_3\text{H}_7^+ \rightarrow i\text{-Pr}^+$ requires more than 10^{-8} s. The reaction of $c\text{-C}_3\text{H}_7^+$ with benzene occurs within the lifetime estimated to be ca. 10^{-10} s.



Using deuterated acids, it could be demonstrated that complete hydrogen scrambling in $c\text{-C}_3\text{H}_7^+$ occurs during that short time, thus showing that the energy barrier for migration of hydrogen around the protonated cyclopropane (Equation (40)) must be very low, in agreement with quantum calculations <2001MI2916>.



Using adequate precursors and ionization techniques, thermal (ion without excess energy than RT) s -butyl, $s\text{-Bu}^+$, and t -butyl, $t\text{-Bu}^+$, ions can be prepared. Although the isomerization $s\text{-Bu}^+ \rightarrow t\text{-Bu}^+$ is exothermic by -67 kJ mol^{-1} , a high activation energy retards this reaction and allows the study of various reactions of these ions in the gas phase. Irrespective of their origins, both $i\text{-Bu}^+$ and $t\text{-Bu}^+$ dissociate into methane and propen-2-yl cation ($\text{CH}_3\text{C}^+=\text{CH}_2$). Another minor fragmentation process is the loss of ethylene with generation of ethyl cation (Figure 3), a cation that adopts the structure of a π -complex of ethylene and a proton in its most stable form. Quantum calculations

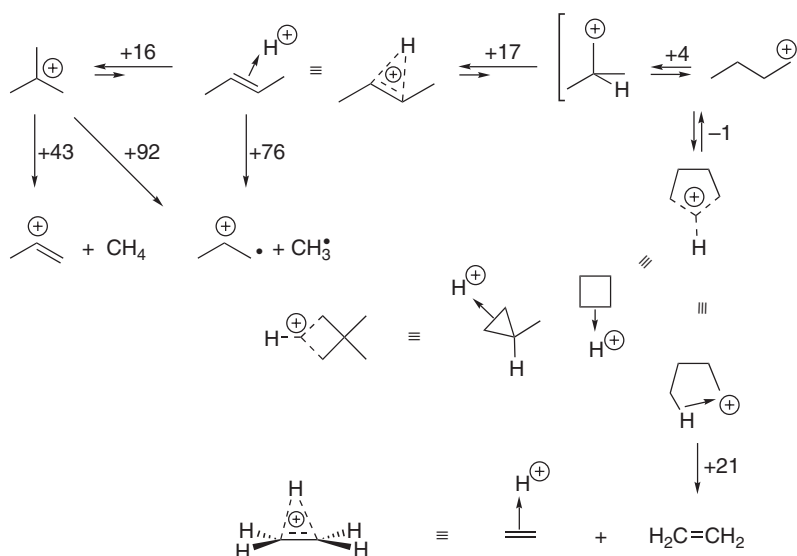
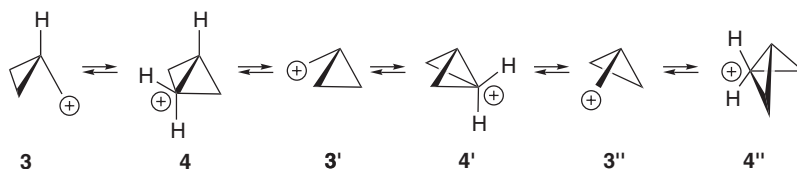


Figure 3

estimate the bridged pH^+ -ethenium ion to be 25–33 kJ mol^{-1} more stable than the classical ethyl cation structure <1995JA8476>. Quantum calculations also predict a bridged structure for $s\text{-Bu}^+$ of the type pH^+ -(*E*)-but-2-enium <1993JA259>. The mechanism of the fragmentation $\text{C}_4\text{H}_7^+ \rightarrow \text{C}_2\text{H}_5^+ + \text{CH}_2 = \text{CH}_2$ is calculated to involve the protonated cyclobutane, which is 150 kJ mol^{-1} higher in energy than $t\text{-Bu}^+$. The primary $n\text{-Bu}^+$ and isobutyl cation are not energy minima.

Distinction between $t\text{-Bu}^+$ and $s\text{-Bu}^+$ can be realized by collision-induced dissociation (CID) using O_2 as target gas. This activates the loss of methyl radical from these ions. The kinetic energy release when $s\text{-Bu}^+$ is activated by O_2 to lose CH_3^\bullet is ca. 500 meV, whereas it amounts to ca. 90 meV when $t\text{-Bu}^+$ is used. The resulting $\text{C}_3\text{H}_6^{\bullet+}$ fragment has the propene-radical/cation structure <1998JPC(A)6441>.

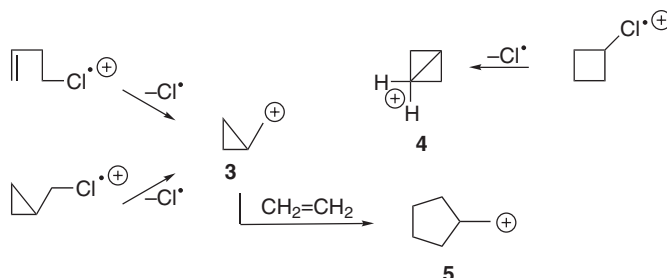
The structure of the C_4H_7^+ ions is still under debate after five decades of extensive investigation. Based on experimental and theoretical studies, the current consensus is that C_4H_7^+ exists as rapidly equilibrating species of nearly equal stabilities that are the bisected cyclopropylmethyl cation **3** and the symmetrical 1H-bicyclobutonium ion **4** as shown in Scheme 39. The barrier of **3** \rightleftharpoons **4** interconversion does not exceed few tenths of a kcal mol^{-1} <1978JA8018, 1979JA5537, 1998JA7652> (Scheme 39).



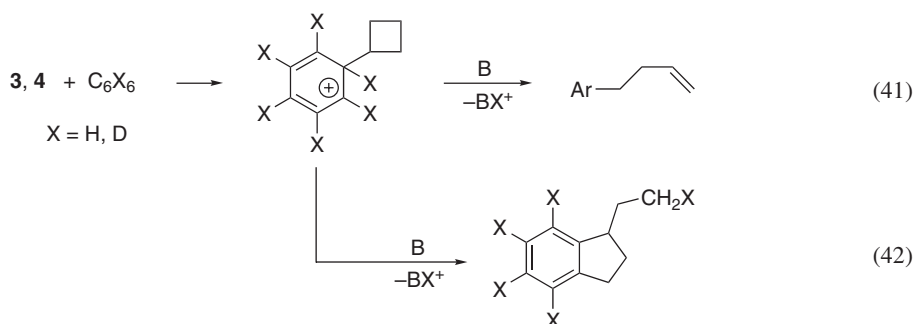
Scheme 39

When **3** and **4** produced from cyclobutanol or cyclopropylmethanol were dispersed in the bulk gas containing benzene or hexadeuterobenzene and H_2O , irrespective of the source of the ion and of the intermolecular or intramolecular nature of the Friedel–Crafts alkylation (Equation (41) and (42)), the C_4H_7^+ ions undergo equilibration before they are trapped. The equilibrium constant **3/4** is close to unity at 300 K and equilibration occurs within a time interval of $\leq 10^{-10}$ s <2001MI2024>.

In another study, cyclopropylmethyl cation **3** was generated by the loss of chlorine atom from cyclopropyl chloride radical-cation or from homoallyl chloride radical-cation. Cyclobutyl chloride radical-cation generates bicyclobutonium ion **4** preferentially. Under dilute gas phase conditions, it was found that the reactions of cations **3** and **4** with ethylene do not give the same products. Whereas **4** reacted with multiple competing reaction pathways, **3** underwent a cycloaddition with ethylene generating cyclopentylmethyl cation **5**, as shown in Scheme 40 <2001JPO17>.



Scheme 40

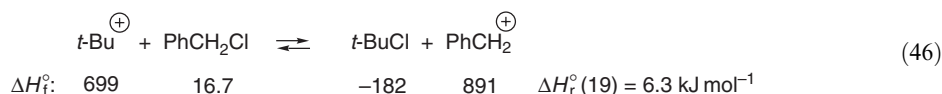
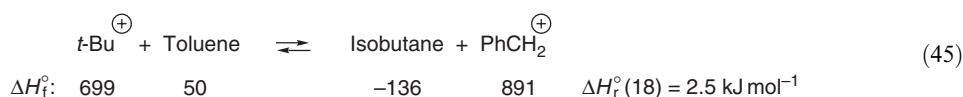
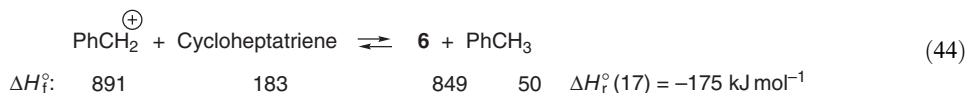
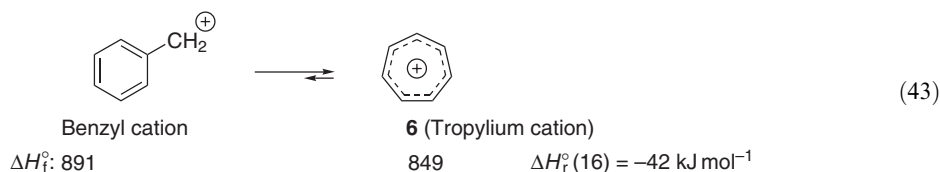


Scheme 41

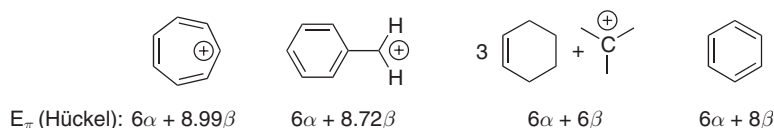
Contrary to quantum calculations and the results described above, (Equations (41) and (42), Scheme 41), these results suggest that the energy barrier separating **3** and **4** cannot be neglected.

1.19.7.4 “Aromatic” Carbenium Ions

The tropylium ion (cycloheptatrienyl cation) is a typical aromatic cation or 7C-6 π Hückel system ($4n + 2$, $n = 1$) that can be readily prepared in solution. In the gas phase, the tropylium ion **6** is more stable than the isomeric benzyl cation (PhCH_2^+) as shown by Equations (43) and (44). It is noteworthy that the latter ion has about the same stability as the *t*-butyl cation (Equations (45) and (46)).



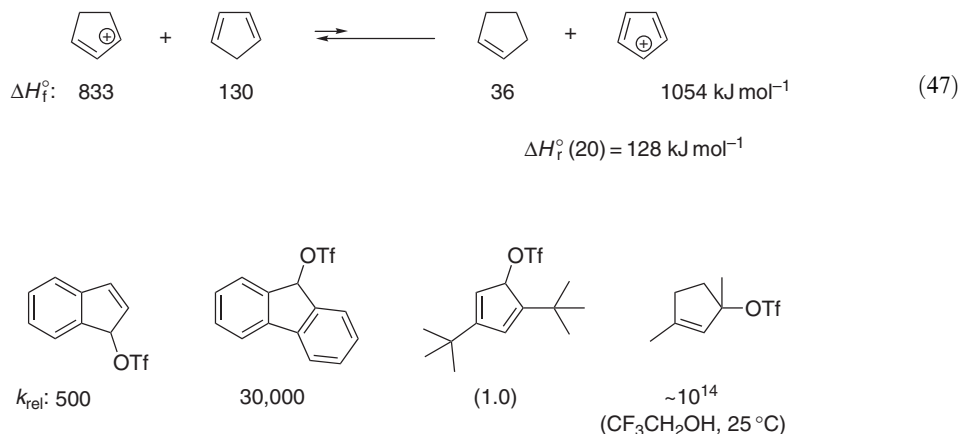
In the gas phase, the “thermal” tropylium ion is an unreactive species, whereas the benzyl cation undergoes a number of reactions, e.g., hydrogen and chloride transfers, additions, and condensations with aromatic hydrocarbons. The benzyl \rightarrow tropylium rearrangement could be observed only at high internal energies <1981CJC1592, 1976JA6072, 1982JA5249> in contrast with the facile toluene \rightarrow cycloheptatriene radical-cation rearrangement. The Hückel approximation gives the following π -energies for tropylium ion and benzyl cation, to be compared with the π -energies of 3 ethylene + methyl cation and of benzene (Scheme 42). The difference in Hückel π -energies between tropylium ion and benzyl cation thus amounts to $\Delta H_p = 0.27\beta$. Considering a β value of -134 kJ mol^{-1} as estimated from the rotational barrier in ethylene, one calculates a stability difference of 36 kJ mol^{-1} between these carbocations, what is not significantly different to the experimental value given by the equilibrium shown in Equation (43).



Scheme 42

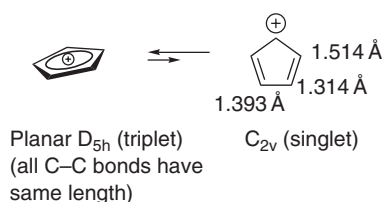
1.19.7.5 “Antiaromatic” Carbenium Ions

Thermochemical data give $\Delta H_f(20) = 128 \text{ kJ mol}^{-1}$, which demonstrates that cyclopentadienyl cation is a destabilized species compared with allyl cation (Equation (47)) <2001CRV1333>. In open-chain analogs, conjugation of an allyl cation with a vinyl group stabilizes the carbocation (cf. $\text{DH}^\circ(\text{c-cyclohex-2-en-1-yl}^+/\text{H}^-) = 937 \text{ kJ mol}^{-1}$ with $\text{DH}^\circ(\text{c-cyclohexa-2,4-dienyl}^+/\text{H}^-) = 891 \text{ kJ mol}^{-1}$). Quantum calculations predict the cyclopentadienyl cation to be destabilized by “antiaromaticity” as much as cyclobutadiene. Similarly, benzocyclopentadienyl cation (indenyl cation) is predicted to be as antiaromatic as benzocyclobutadiene, but not as much as fluorenyl cation <1997JA7075>. The following $\text{S}_{\text{N}}1$ solvolysis relative rate constants (Scheme 43) are consistent with the above hypothesis <1997JA2371>.



Scheme 43

The cyclopentadienyl cation was generated in a matrix and observed to have a triplet ground state as predicted by simple Hückel theory <1977ACR27> and by *ab initio* quantum calculations <1997JA7075, 2001JCP9243>. It has a planar $\text{D}_{5\text{h}}$ geometry. The calculations indicate a $\text{C}_{2\text{v}}$ singlet structure about 10 kJ mol^{-1} higher in energy than the triplet $\text{D}_{5\text{h}}$ structure <1998CPH1, 1998MI1402> (Scheme 44).

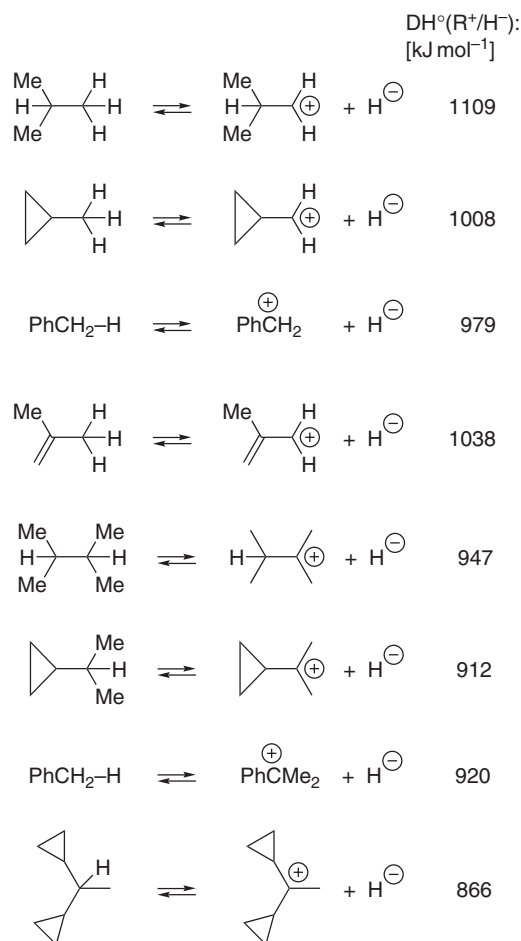


Scheme 44

The IR spectrum of the pentachlorocyclopentadienyl cation, C_5Cl_5^+ has been measured in SbF_5 matrix and is consistent with a $\text{D}_{5\text{h}}$ structure <1997JPC(A)1523>.

1.19.7.6 The Cyclopropyl Substituent Effect

Hydride affinities given below (Scheme 45) show that the cyclopropyl substituent stabilizes carbenium ions much better than the isopropyl group. It stabilizes almost as much as a phenyl group <1991CB165>. For a long time it has been recognized that a cyclopropyl group resembles more a vinyl group than a cyclobutyl group, although cyclopropane and cyclobutane have almost the same strain energy.



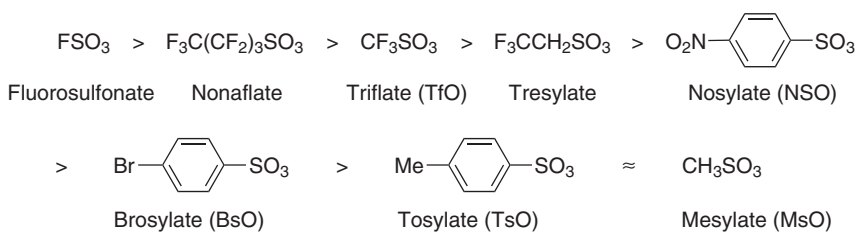
Scheme 45

1.19.8 CARBOCATIONS IN THE CONDENSED PHASE

Because charged species are more strongly solvated than neutral molecules, one expects the heterolytic dissociation enthalpies to decrease significantly on going from the gas phase to the condensed phase (solution, solid, surfaces). Ease of heterolytic $\text{R}_3\text{C}-\text{X}$ bond cleavage into a carbocation R_3C^+ and an anion X^- (counter-ion X^-) will depend on the intrinsic stability of these ions in the gas phase (as expressed by $\text{DH}^\circ(\text{R}_3\text{C}^+/\text{X}^-)$) and on the general and specific interactions they have with the surrounding molecules. Heterolysis ($\text{S}_{\text{N}}1$ mechanism according to Ingold) is not the unique reaction generating carbocation intermediates. Protonation of, or electrophile addition to, a neutral compound is a general method to generate cationic species. Other methods involve oxidation of neutral molecule, electrooxidation at the anode and by photoinduced electron transfer (PET), fragmentation of carbenium ions or of alkoxychlorocarbenes.

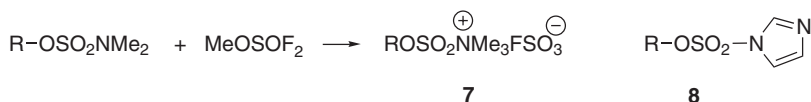
1.19.8.1 The Effect of the Nature of the Nucleofugal Group

Some of the more common leaving groups, X , in the order of their decreasing ease of displacement by a nucleophile are as follows: $\text{N}_2^+ > \text{N} = \text{NOSO}_2\text{R} > \text{PhI}^+ > \text{OSO}_2\text{R} > \text{OP}(\text{O})\text{OR}_2 > \text{I} > \text{Br} > \text{OCOR} > \text{NO}_2 \sim \text{Cl} > \text{OH}_2^+ > \text{S}^+ \text{Me}_2 > \text{F} > \text{OSO}_3^- > \text{R}_3\text{N}^+ > \text{OR} > \text{NR}_2$. It is opposite to the order of basicity <1979ACR198>. For the sulfonates, the following order of decreasing nucleofugacity can be retained (Scheme 46) <1978ACR107>.



Scheme 46

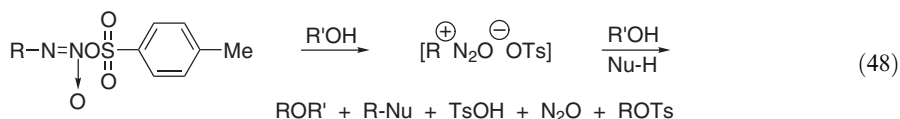
Fluorosulfonate salts of trimethylammonium sulfonyl esters (*O*-besylate **7**, Scheme 47) <1981CJC362> are ca. 10^5 times more reactive than the corresponding trifluoromethanesulfonates (triflates).



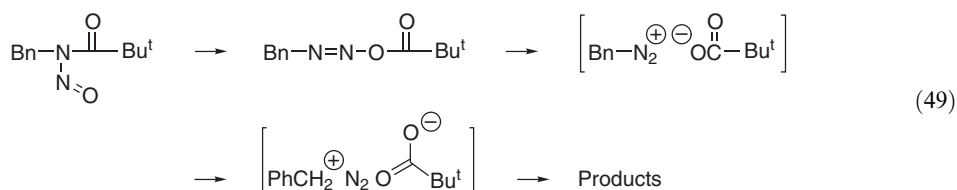
Scheme 47

Primary and secondary sulfonates are obtained readily by esterification of the corresponding alcohols. However, problems arise with the esterification of tertiary alcohols. In some cases, imidazolysulfonates (imidazylates **8**) may be obtained. The latter are quite useful for $\text{S}_{\text{N}}2$ -type substitutions <1981THL3579>.

In polar solvents (1,1,1,3,3,3-hexafluoroisopropanol, CH_3CN) the lifetimes of dialkylcarbocations arising from the decomposition of corresponding diazonium ion intermediates range from 100 ps to 40 ns at 22°C <1999JA6589>. Solvolytic formation of aryl cations as intermediates has been demonstrated in the dediazonation of arene diazonium ions, indicating the special properties of the nitrogen leaving group <1992JCS266, B-1995MI015>. Somewhat related to the diazonium ions are the tosylazoxyalkanes and -arenes <1983HCA1710> and the nonafluorobutylsulfonyloxyazoxyarenes ("azoxynonaflates" <1984CB3004, 1984CB3021>). Their solvolyses follow mechanisms involving unimolecular fragmentation and the formation of carbenium ion intermediates (Equation (48)).



Diazoalkanes are protonated into diazonium ions. They intervene in the carcinogenicity and mutagenicity of *N*-alkyl-*N*-nitroso compounds <B-1992MI016>. *N*-Benzyl-*N*-nitrosopivalamide decomposes to produce very short-lived nitrogen-separated ion pairs, which is essentially unsolvated (Equation (49)) <2000JOC1115>.



Salts derived from carbocations and carbanions are known. For instance, the reaction of Bu^tC_{60} anion (1,2-dihydro-[60]fullerenes has a pK_a of 4.7 <1994JPC13093>) with tricyclopropylcyclopropenyl cation in tetrahydrofuran (THF) gives 1-*t*-butyl-4-(tricyclopropyl-2-cyclopropen-1-yl)-1,4-dihydro[60]fullerene with C—C covalent bond formation. This compound equilibrates with the original cation and anion in a polar solvent such as dimethylsulfoxide (DMSO) <2001T3537>.

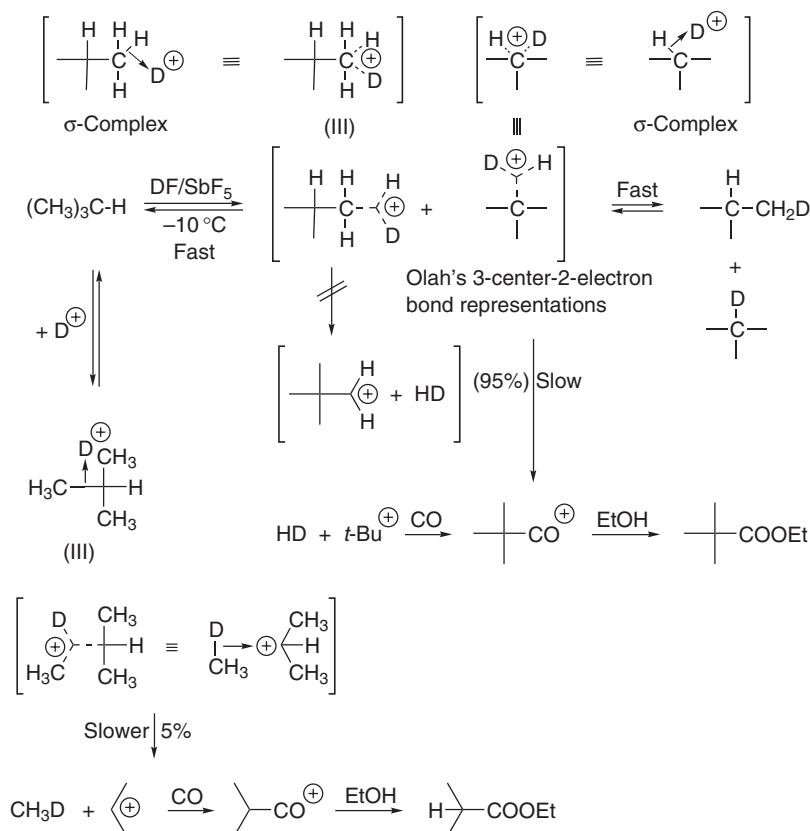
1.19.8.2 The Use of "Super-Acids"

Nonaqueous systems containing species of considerably higher acidity than H_3O^+ are called super-acids <B-1985MI009>. In such media, it is possible to completely protonate many organic compounds and to observe the corresponding ions directly by spectroscopic techniques.

ESCA studies <1997ACR245> of solid matrices of $\text{FSO}_3\text{H}/\text{SbF}_5$ or HF/SbF_5 saturated with CH_4 at -180°C and in high vacuum (10^{-9} Torr) showed that the 1s ESCA shift differed by less than 1 eV (the limit of resolution) from that of CH_4 . This is considered to be that due to CH_5^+ .

Ethane has been shown to undergo C—C bond protolysis in preference to C—H bond protolysis <1973JA4960>. The ratio of CH_4 and H_2 formed as the gaseous cleavage products of the reaction of C_2H_6 with HF/SbF_5 1:1 in SO_2ClF is about 15:1. Protonation of the C—C bond is followed by cleavage of the ethonium ion intermediate, induced by attack of a molecule of ethane. The σ base (in this case, probably the C—H bond of ethane) attacks the developing methyl cation in C_2H_7^+ and generates a C—proponium intermediate, which then cleaves into Et^+ intermediate and CH_4 . Oligomerization reactions ensure the involvement of more molecules of ethane, giving finally stable carbocations such as *t*-butyl and *t*-hexyl cations.

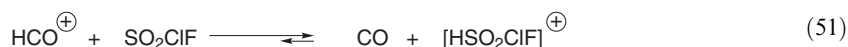
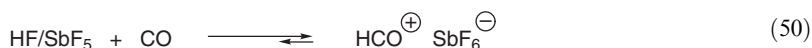
Propane bubbled into DF/SbF_5 is slightly ionized but extensively deuterated at the primary and secondary positions <1999JA10628>. Isobutane in DF/SbF_5 at 0°C undergoes fast H/D exchange at all C—H bonds before being converted into *t*-butyl cation and dihydrogen (Scheme 48). In the presence of carbon monoxide, *t*-butyl cation gives the acylium ion (Koch–Haaf reaction <1964OS1>) that can be generated with ethanol to give ethyl pivalate (95%). A secondary product is isolated, ethyl isobutyrate (5%), resulting from the concurrent fragmentation of the C–isobutonium ion into methane and isopropyl cation <1997JA3274, 2000PAC2309>.



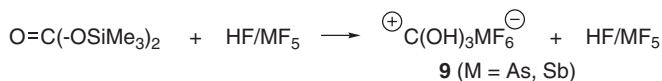
Scheme 48

The strongest known member of the super-acid family, 1:1 mixture of HF and SbF_5 , can protonate carbon monoxide at 85 atm. and to the formyl cation, HCO^+ can be characterized by ^1H -, ^{13}C -NMR and IR spectroscopy <1997SCI776, 1998AG(E)603>.

In the presence of SO_2ClF , the acidity of HF/SbF_5 is weaker and the equilibrium shown in Equation (51) competes with the addition (Equation (50)).

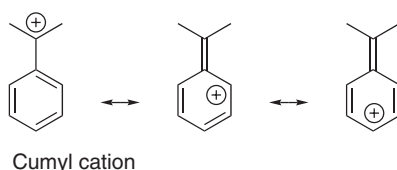


The Olah group has prepared cations ClCO^+ , BrCO^+ , and ICO^+ in $\text{HSO}_3\text{F/SbF}_5/\text{SO}_2\text{ClF}$ solutions <1991JA3205>. On treating *t*-butyl fluoroformate in a SO_2ClF solution of $\text{HSO}_3\text{F/SbF}_5$ (1:1) at -78°C , they obtained FCO^+ , FC(OH)_2^+ , and $t\text{-Bu}^+$ <1997AG(E)1875>. Crystalline salts **9** have been obtained and characterized by X-ray diffraction studies (Scheme 49) <1999AG(E)714>.



Scheme 49

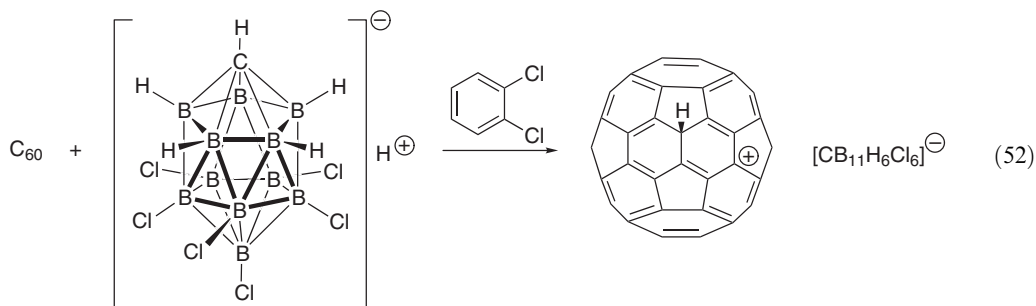
The X-ray crystal structure of the cumyl cation has been determined as the SbF_6^- salt. The relatively short $\text{C}^+-\text{C}_{\text{ipso}}$ bond and bond lengths within the benzene ring are consistent with strong benzylic delocalization (Scheme 50) <1997JA3087>.



Scheme 50

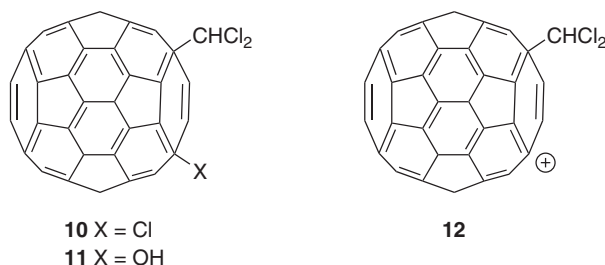
1.19.8.3 Carboranes as Super-Acids

Most current super-acids are still nucleophilic (SbF_6^- , HSO_4^- , CF_3SO_2^- , fluorine, and oxygen have a high affinity for silicon) and do not allow free silylium ion, R_3Si^+ , to exist. Attempts to protonate fullerene C_{60} with these super-acids lead to decomposition. The solid acid $\text{H}(\text{CB}_{11}\text{H}_6\text{Cl}_6)$ obtained by condensing liquid HCl onto solid $(\text{C}_2\text{H}_5)_3\text{Si}(\text{CB}_{11}\text{H}_6\text{Cl}_6)$ and removal of the volatiles under vacuum is capable of protonating C_{60} quantitatively without decomposition (Equation (52)). In contrast to many super acids such as HF/Sb_5 , $\text{HSO}_3\text{F/SbF}_5$, etc., carborane $\text{H}(\text{CB}_{11}\text{H}_6\text{Cl}_6)$ (and $\text{H}(\text{CB}_{11}\text{H}_6\text{Br}_6)$, which is also available) is not a mixture of Brønsted and Lewis acids <2000SCI101>. Salts such as [cyclohexadienyl] $^+$ [$\text{CB}_{11}\text{H}(\text{Me})_5\text{Br}_6^-$], [toluenium] $^+$ [$\text{CB}_{11}\text{H}_6\text{Br}_6^-$], and [hexamethylbenzenium] $^+$ [$\text{CB}_{11}\text{H}_6\text{Br}_6^-$] have been obtained as stable crystalline materials by treatment of benzene, toluene, and hexamethylbenzene, respectively, with acids of type $\text{H}[\text{CB}_{11}\text{R}_6\text{Br}_6]$. Thus, the Wheland intermediates (σ -complexes) postulated as intermediates in aromatic electrophilic substitutions are now reagents. They have been used to bracket the solution phase basicity of C_{60} between that of mesitylene (1,3,5-trimethylbenzene) and xylene <2003JA1796>. The azafullerenium cation C_{59}N^+ has been isolated in good yield as the carborane salt $[\text{C}_{59}\text{N}]^+[\text{Ag}(\text{CB}_{11}\text{H}_6\text{Cl}_6)_2]^-$ <2003JA4024>.



Likewise, treatment of fullerene C_{76} with $[Ar_3N^{\bullet+}][CB_{11}H_6Br_6^-]$ ($Ar = 2,4$ -dibromophenyl) in 1,2-dichlorobenzene or 1,1',2,2'-tetrachloroethane leads to $[C_{76}^+][CB_{11}H_6Br_6^-] + Ar_3N$ <1996JA13093>.

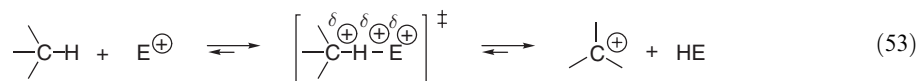
Substituted fullerene derivatives form fullerene carbocations much more readily and under less acidic conditions. For instance, $C_{60}Ar_5Cl$ ($Ar = Ph$, or 4-F- C_6H_4) reacts with $AlCl_3$ in CH_2Cl_2 , $CHCl_3$, or CS_2 at 25°C to give intense purple-red solutions of salts of $C_{60}Ar_5^+$ <1998CC2153>. Treatment of C_{60} with $AlCl_3$ in $CHCl_3$ at 20°C results in the addition of 1 equiv. of $CHCl_3$ giving **10**, which is hydrolyzed into alcohol **11** in the presence of silica gel. Fullerol **11** dissolves in CF_3SO_3H giving a reddish purple solution of alkylfullerenyl cation **12** (Scheme 51).



Scheme 51

1.19.8.4 Intermolecular Hydride Transfer Reactions

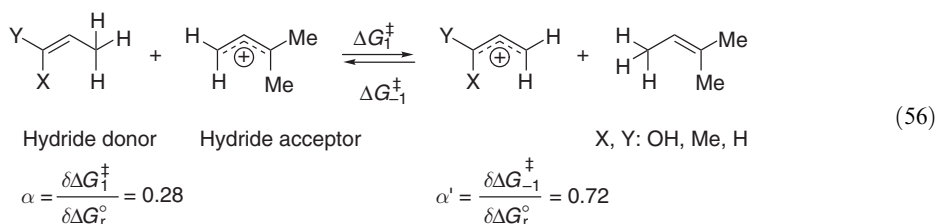
A possible mechanism for the oxidation of an alkane is the transfer of a hydride to the electrophilic agent, E^+ , with the formation of a carbenium ion intermediate (Equation (53)). The hydride abstraction process might be the preferred mechanism if the resulting carbenium ion is a stable species, for instance, a tertiary alkyl cation, thus making the carbonium ion intermediate energetically disfavored. Competition between electrophilic addition to the C—H bond and hydride transfer to the electrophile may also be affected by the nature of the hydrocarbon (σ -nucleophilicity, steric factors, etc.), the nature of the electrophile, and the medium <1997JCS(F1)515, 1995CC121>.



The Bell–Evans–Polanyi theory gives the relationship (Equation (54)) between activation enthalpies and the heat of the reaction, where α varies between 0 and 1 depending on the type of one-step, concerted reaction. Looking at an ensemble of similar reactions in which structural parameters are varied, Hammond and Leffler have derived the relationship shown in Equation (55) from Equation (54), in which $\delta\Delta G_r^\circ$ expresses the change of the reaction-free enthalpy induced by structural variation, and the proportionality constant α reflects the fraction of this effect observable in the activation free enthalpy ΔG^\ddagger . The magnitude of α has often been used for localizing transition states <B-1963MI017>. A study on the kinetics of hydride abstractions from CH groups by carbocations revealed that the variation of the hydride acceptor affects the rate constants of the hydride transfer to a considerably greater extent than an equal change of the thermodynamic driving force (exergonicity) caused by variation of the hydride donor (Equation (56)). Substitution in the donor influences the heat of reaction (X, Y electron-releasing groups increase the exothermicity) and the intrinsic barrier of the hydride migration (opposite effect predicted by Equation (54)), while substituent variation in the acceptor affects both terms in the same sense (in agreement with Equation (54)). For the reactions shown in Equation (56), a value of 0.72 is found for Hammond–Leffler's $\alpha = \delta\Delta G^\ddagger / \delta\Delta G_r^\circ$ when the hydride acceptor is varied, while $\alpha = 0.28$ is found (quantum calculations) when the hydride donor is varied. These findings are interpreted in terms of a partial positive charge of the migrating hydrogen in the transition state as shown in Equation (53) <2002JA4084>.

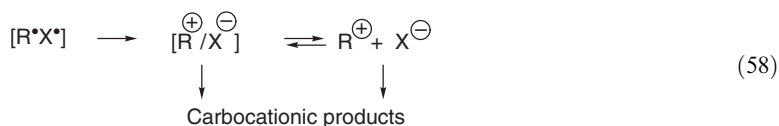
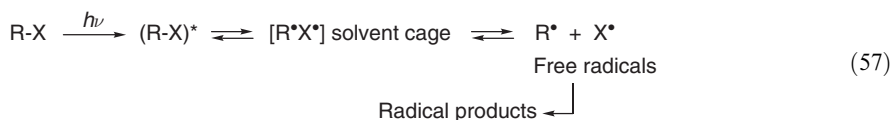
$$\Delta H^\ddagger = \alpha \Delta H_r^\circ + \beta \quad (54)$$

$$\delta\Delta G^\ddagger = \alpha\delta\Delta G_r^\circ \quad (55)$$

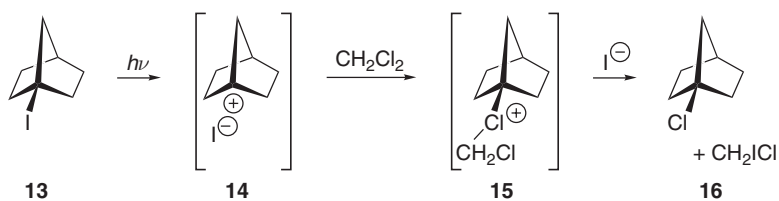


1.19.8.5 Carbocations Generated upon Irradiation

The absorption of light by alkyl halides, RX, generally results in initial homolytic cleavage of the carbon–halogen bond (Equation (57)) <B-1973MI018>. Depending upon the substrate and solvent, the initially formed radical pairs can undergo subsequent electron transfer to afford an ion pair and, ultimately, carbocationic products (Equation (58)).



Irradiation of 1-iodonorbornane **13** in CH₂Cl₂ (quartz vessel, 254 nm UV light) results in the formation of 1-chloronorbornane (**14**, 80% yield) and chloriodomethane (Scheme 52). The proposed mechanism for this photoreaction involves the generation of 1-norbornyl bridgehead cation **14**, which reacts with CH₂Cl₂ giving the chloronium ion intermediate **15**. The latter undergoes displacement by iodide anion to give the observed products <1996JA8135>. Irradiation of **13** thus affords an opportunity to explore the behavior of the unusually unstable and reactive 1-norbornyl cation. The contrasting reluctance of iodide **13** to undergo ionic C–I bond cleavage under nonphotochemical conditions is emphasized by its quantitative recovery from extended treatment with refluxing methanolic silver nitrate. Irradiation of **13** in methanol, ethanol, or tetrahydrofuran gives the corresponding 1-norbornyl ethers together with small amounts of norbornane, a reduction product of 1-iodonorbornane believed to arise principally via the 1-norbornyl radical, which can abstract a hydrogen atom from the solvent. Irradiation of **13** in acetonitrile, followed by aqueous work-up, afforded 1-acetaminonorbornane (Ritter reaction).

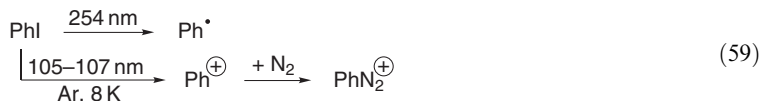


Scheme 52

Under usual solvolytic conditions, the generation of simple vinyl cations requires the presence of a super-leaving group such as triflate (CF₃SO₃) or nonaflate (C₄F₉SO₃) <1972CB1465>. Irradiation of vinyl iodides affords mixtures of ionic and radical products.

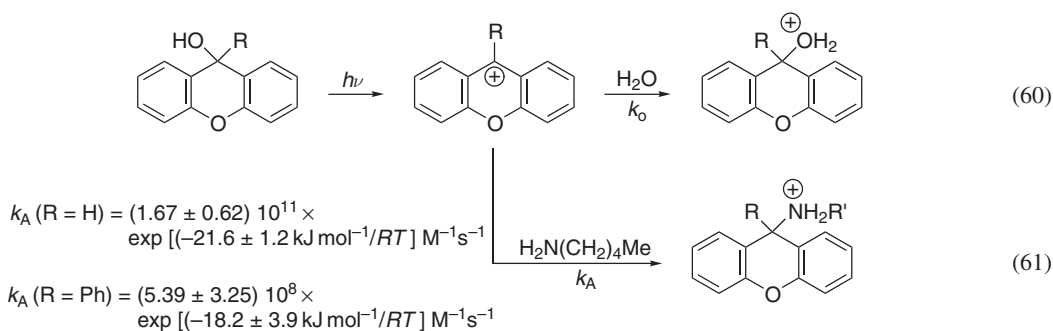
Irradiation with a UV light at 254 nm of iodobenzene generates the phenyl radical. When PhI was sublimed with a large excess of Ar and deposited on a cold spectroscopic window of CsI at 8 K, a matrix was formed. Its irradiation with the light of an argon discharge lamp (105–105 nm)

generated the phenyl cation (Equation (59)) and its IR spectrum could be recorded, showing typical bands at 3110 and 713 cm⁻¹. If the argon matrix is doped with 5–10% N₂, the phenyl-diazonium ion is formed at the expense of Ph⁺ (the 3110 cm⁻¹ band decreases and the typical stretching frequency of the diazonium ion appears at 2325 cm⁻¹). The IR data of phenyl cation and of deuterated derivatives were in agreement with quantum calculations predicting a symmetrical singlet ground state of phenyl cation <2000AG(E)2014>.



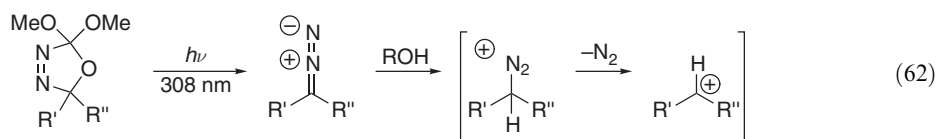
Photolysis of 4-chloro (and -fluoro) anilines in a polar solvent generates the corresponding 4-aminophenyl cation, an intermediate otherwise difficult to access in solution <B-1997MI451>, and that adds to alkenes, not to *n*-nucleophiles such as alcohols. Under nonacidic conditions, irradiation of *N,N*-dimethyl-4-chloroaniline in CH₃CN containing 1 M norbornene (bicyclo[2.2.1]hept-2-ene) gives a single major product, which is isolated in 33% yield and recognized as 2-arylnortricyclene. In the presence of protic solvents such as alcohols, and arylalkoxynorbornanes are produced concurrently with 2-arylnortricyclene <2003CC738>.

Laser flash photolysis (LFP) has been employed for the observation of reactive intermediates and for the direct measurement of rate constants of their decay reactions. Photolyzing some precursor with a laser pulse initiates a rapid photochemical transformation to the reactive species of interest. This is detected, usually, by absorption (UV, visible, IR) spectroscopy, and the decay is directly monitored. A number of applications involving carbocations have appeared, with the intermediate being generated and directly studied under normal solvolytic conditions, i.e., H₂O or alcohols as solvent <1993CRV119, 1996T6823>. Detailed studies have been reported involving species such as xanthylium, triarylmethyl, diarylmethyl, fluorenyl, benzyl, phenethyl, cumyl, and substituted vinyl cations (Equations (60) and (61)) (Scheme 53) <1999CJC2069>. Laser flash photolysis was used to generate 9-*R*-xanthenium cations (R = H, Ph) in subcritical water to demonstrate the importance of ionic chemistry under these conditions. The carbocations were generated at temperatures up to 330 °C. At higher temperatures, the decrease of the dielectric constant of H₂O resulted in weak cation signals with short lifetimes. The temperature effect on the intrinsic solvent decay (*k*₀) followed the Arrhenius law and could be extrapolated all the way from 25 to 300 °C. The bimolecular rate constant *k*_A for the reactions of xanthenium and 9-phenylxanthenium cations with *n*-pentylamine also followed the Arrhenius law between 100 and 300 °C <2001JPC(A)8046>.



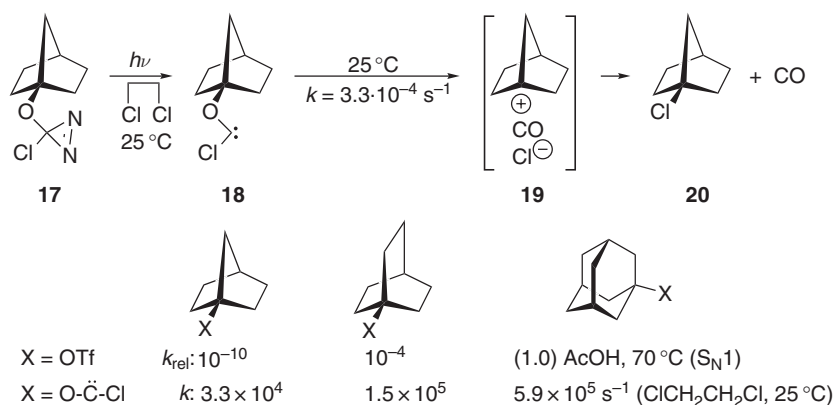
Scheme 53

Estimates of the lifetimes of the 2-propyl cation, cyclobutonium ion, cyclopropylethyl cation, and 2-adamantyl cation in HFIP (1,1,1,3,3,3-hexafluoro-2-propanol), TFE (2,2,2-trifluoroethanol), and acetonitrile (MeCN) have been obtained using electrophilic aromatic addition to 1,3,5-trimethoxybenzene as a kinetic probe reaction in LFP experiments (Equations (62)). The lifetimes range from ~100 ps to ~40 ns at 22 °C. The precursors of the carbocations were oxadiazolines <1999JA6589>.

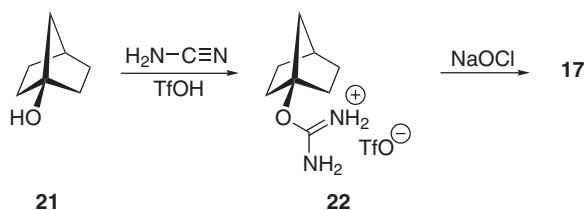


1.19.8.6 Carbocations by Fragmentation of Alkoxy(chloro)carbenes

Because of the ring strain increase imposed on the intermediate bridgehead carbenium ion, heterolysis of 1-bicyclo[2.2.1]heptyl (1-norbornyl) tosylate or triflate ($k = 6.5 \times 10^{-8} \text{ s}^{-1}$ at 70°C , $\Delta H^\ddagger = 118 \text{ kJ mol}^{-1}$ <1971JA3189>) is very difficult. For instance, the acetolysis of bicyclo[2.2.1]hept-1-yl tosylate is 10^{-10} times slower than that of adamant-1-yl tosylate (AcOH, 70°C). On irradiating the alkoxychlorodiazine **17** ($>320 \text{ nm}$, 25°C) in 1,2-dichloroethane, carbene **18** is generated (Scheme 54). It fragmentates into ion pair **19** (as demonstrated by interception by methanol) that collapses into carbon monoxide and 1-chloronorbornane **20**. Laser flash photolysis of **17** at 351 nm allows to measure the rate constant for the fragmentation **18** \rightarrow **19** to be measured. Doing that at various temperatures between 0 and 50°C allowed the activation parameters E_a (**18** \rightarrow **19**) = $37.6 \pm 0.8 \text{ kJ mol}^{-1}$, $\log A = 11.2 \pm 0.1 \text{ s}^{-1}$, with k (**18** \rightarrow **19**) = $3.3 \pm 0.4 \cdot 10^4 \text{ s}^{-1}$ at 25°C to be estimated. This is 3×10^{15} times faster than acetolysis of norbornyl tosylate at 70°C ! Similar measurements with the carbenes derived from bicyclo[2.2.2]oct-1-yl and adamant-1-yloxychlorodiazirines (Scheme 55) led to rate constants for the carbene fragmentation that are nearly the same, in contrast with the acetolysis of the corresponding tosylates or triflates <2001TL6045>. For instance, (2,2-diphenylethoxy)chlorocarbene fragments in MeCN at 25°C with a rate constant $k = 2.1 \times 10^6 \text{ s}^{-1}$ <2002JA5258>. The alkoxychlorodiazine **17** was obtained by treatment of norbonan-1-ol (**21**: bicyclo[2.2.1]heptan-1-ol) with an equivalent of cyanamide and one equivalent of trifluoromethanesulfonic acid. This gave the isouronium salt **22**, which is oxidized with 12% aq. NaOCl to give diazirine **17** (see also <2002OL2341>).



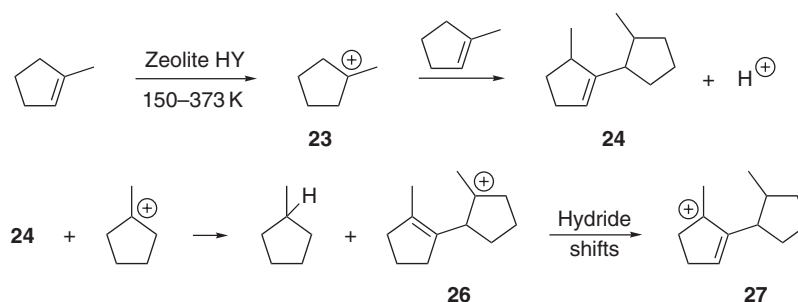
Scheme 54



Scheme 55

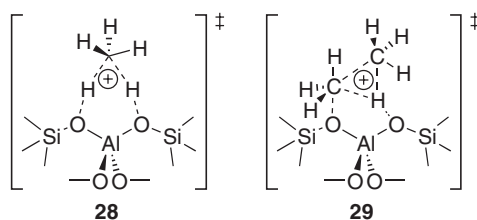
1.19.8.7 Hydrocarbon Alkylation and Cracking with Zeolites

Zeolites (molecular sieves) are important solid catalysts. They are crystalline aluminosilicates of group IA and group IIA elements, such as Na, K, Mg, and Ca. They are represented by the empirical formula $M_{x/n}^{x+}[Al_xSi_yO_{2(x+y)}]^{x-} \cdot nH_2O$. They are used in petroleum refining, synfuel production, and petroleum production <1994CRV2095, 1995CRV637>; (see also <2003JA2136, 1998JA11804>). The Brønsted acid site has been established as the primary active site for zeolite catalysts. Using *in situ* NMR spectroscopy, Haw and co-workers <1989JA2052, 1992JPC8106, 1994JA7753> observed the formation of cyclopentenyl cations on zeolites through propene oligomerization. These cations are believed to be the true intermediates in aromatic formation and coke deposition, which are undesirable in some reactions. The same authors <2000JA4763> also found that cyclopentenyl cations not only play a catalytic role but also act as reactive intermediates in methanol-to-olefin (MTO)/methanol-to-gasoline (MTG) chemistry. A study with methylcyclopentene (Scheme 56) has shown that this compound is protonated already at 150 K to generate 1-methylcyclopentyl cation **23**. It adds to methylcyclopentene to give **24**. Hydride abstraction by **23** then generates cation **26**, which after a number of hydride shifts is isomerized into the observable, stable allyl cation **27** <2001CC2008>. Inclusion of 4,4'-dimethylaminodiphenylethylene and related alkenes within activated CaY zeolites results in the formation of persistent monomeric carbocations. Their structure and consequently the color of the zeolite is controlled by the water content within the zeolite <2003TL1615>. Stable carbocations formed by absorption of alkenes on zeolite Y can be characterized by an IR band near 1510 cm^{-1} <2001MI1870, 2000JOC3947>.



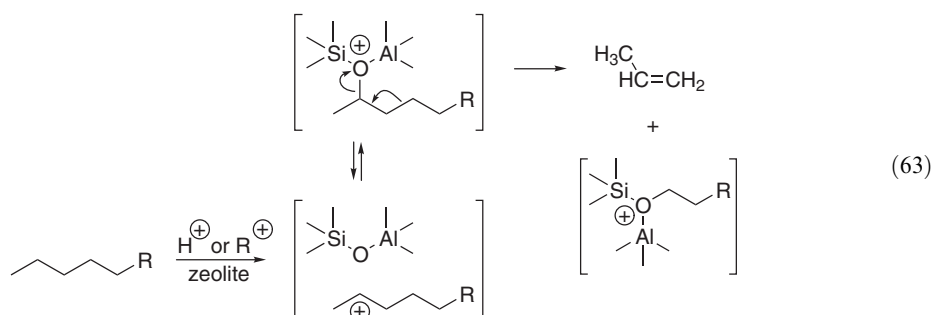
Scheme 56

In 1984, Haag and Dessau <1984MI305, 2000MI11> proposed that alkane cracking catalyzed by zeolites follows mechanisms analogous to those proposed by Olah and co-workers for the reactions of alkanes in super-acidic, liquid media. They postulated that the solid acid catalysts protonate alkanes to give H- and C-alkonium ions that collapse to give the products of cracking, thus establishing an important link between solution-phase and surface chemistry and between homogeneous and heterogeneous catalysis. Quantum calculations have suggested the transition structure **28** for the H/D exchange of methane with zeolites <2000JPC(B)6308> and **29** for the process leading to cracking to ethane (Scheme 57) <1998MI1>.

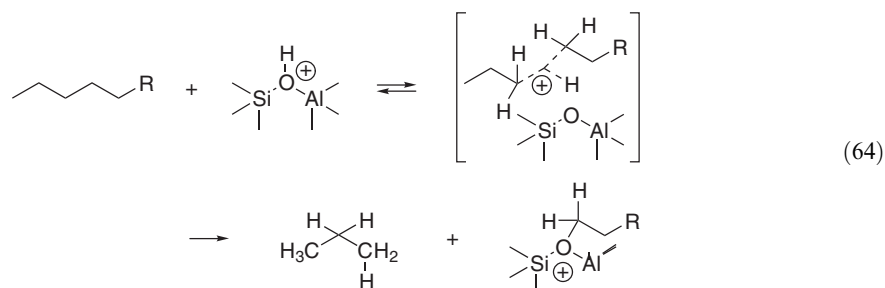


Scheme 57

Most acid-catalyzed alkane cracking occurs following the β -scission rule <B-1995MI019> (Equation (63)).



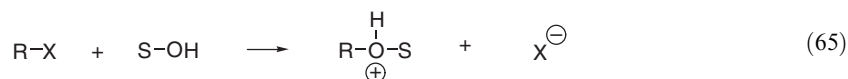
An alternative mechanism is the C—C bond protonation via carbonium ion formation, Equation (64) <1989MI611, 1998MI235>.



1.19.9 CARBOCATION REACTIONS

1.19.9.1 As Intermediates in Heterolysis

For the reaction shown in Equation (65), the two main reaction coordinates are the distance R...X and the distance O...R. One can draw the diagram shown in Figure 4 for possible mechanisms of this reaction.



The associative mechanism S_N2 is preferred for primary alkyl derivatives that cannot generate stable carbocations such as benzyl, allyl, cyclopropylcarbinyl, or organometallomethyl systems. With secondary alkyl systems, depending on the nucleophile and the medium, the displacement reaction can either obey the S_N2 or the S_N1 mechanism. With tertiary alkyl derivatives, electron and steric reasons make the S_N1 mechanism preferred.

The S_N1 solvolysis rates for a series of similar compounds under similar reaction conditions reflect directly the stability of their carbocationic intermediates <1979JA522>. This hypothesis developed slowly over the last 50 years. It grew out of the observations of parallel reactivity profiles for solvolysis reactions and reactions involving *sp*³–*sp*² interconversions at the reacting carbon atom, such as alcohol oxidation with chromic acid <1967JOC2003> or ketone reduction with sodium borohydride <1957T221>. The lack of solvolytic reactivity of bridgehead derivatives of the 1-norbornyl and trypticene type <1939JA3184, 1954CRV1066, 1960AG147> was taken as indicative for the preferentially planar structure of carbenium ions, long before the planar structure of the *t*-butyl cation was experimentally determined by X-ray crystallography <1993JA7240>. The first attempt to rationalize rate constants of solvolysis of secondary derivatives used strain estimates for carbenium ions, based on IR-stretching frequencies of carbonyl groups and nonbonded interactions <1964JA1853, 1964JA1854, 1964JA1856>. These qualitative estimates were subsequently replaced by empirical force-field calculations, which were particularly successful in the context of bridgehead solvolysis <1971JA3189,

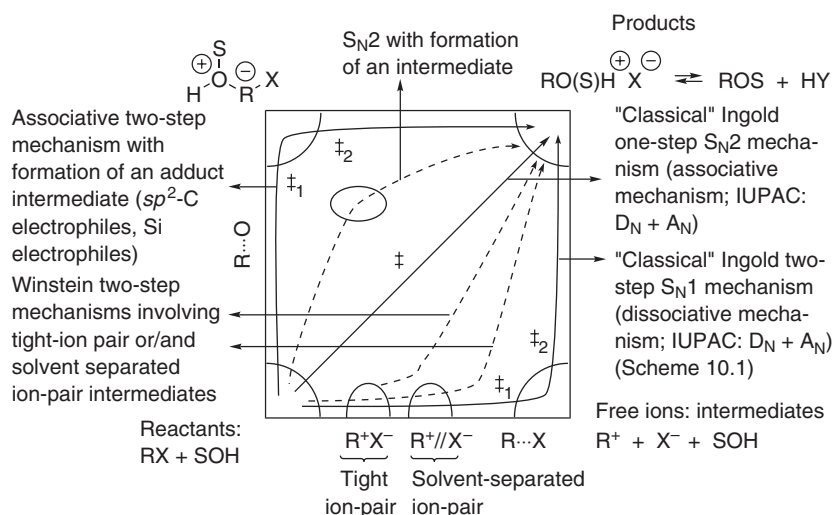


Figure 4

1974JA7121, 1984C389, 1986HCA635, 1987HCA1017, 1989MI863, 1991HCA1808>, but were also applied with various degrees of sophistication toward the solvolysis of secondary aliphatic derivatives <1978JOC3588, 1980JA1424, 1983JA3356, 1982HCA1418, 1984TL1703, 1985HCA119, 1978JOC3878, 1981CB3336>. Arnet and co-workers <1939JA3184, 1954CRV1066, 1960AG147, 1978JA5408, 1983JA2889> reported heats of ionization (ΔH_i) of secondary and tertiary alkyl and aralkyl chlorides to stable carbocations in SbF_5 – solvent mixtures. Correlation of the heats of ionization with the respective free energies of activation for ethanolysis afforded a straight line over a range of 92 kJ mol^{-1} for ΔH_i . These results established the near energetic equivalency of carbocations in solution and the transition state for solvolysis.

Abboud and co-workers <1999JOC6401, 1997JA2262> developed the dissociative proton attachment method (DPA) based on Fourier transform ion cyclotron resonance spectroscopy (FTICR) to determine the stability of carbocations in the gas phase. Comparison of the experimental ion stabilities with ion stabilities calculated by *ab initio* methods at the MP2/6-311G** level indicated the absence of rearrangements. In addition, correlation of the experimental ion stabilities with the rate constants for solvolysis under standard conditions afforded a straight line covering the full rate range of bridgehead derivatives. It was found that even 2-adamantyl derivatives that are typical representatives of secondary derivatives solvolyzing without nucleophilic solvent participation fit the correlation between ion stability and solvolytic reactivity, as established for bridgehead derivatives <2002JOC1057>. The same applies to tertiary aliphatic derivatives in the absence of nucleophilic solvent participation <2000JA7351>. The relative rate constants for solvolysis ($\log(k/k_0)$) of the bicyclic secondary derivatives correlate with the stabilities of the respective carbocations in the same manner as tertiary bridgehead derivatives, but simple monoderivatives and acyclic derivatives solvolyze faster than predicted on the grounds of the ion stabilities. The corresponding stabilities of cyclopropyl- and benzyl-substituted carbocations have been obtained by a combination of experimental and computational data available in the literature with computational methods. Correlation of the rate constants for solvolysis versus ion stabilities for these compounds reveals a trend similar to that observed for bridgehead derivatives, but with much more scatter, which is attributed to nucleophilic solvent participation and/or nucleophilic solvation <2003JOC3786>.

1.19.9.2 Heterolyses of Substrates α -Substituted by Electron-withdrawing Groups

The chemistry of carbocations containing a strongly electron-withdrawing α -substituent such as a trifluoromethyl, a cyano, or a carbonyl group has been actively studied. The electronic effects of the cyano and carbonyl groups are generally interpreted to include the mesomeric effect ($-M$) as

well as the inductive/field effect ($-I$), both being electron withdrawing, as formulated by the resonance structures **30** \leftrightarrow **30'** and **31** \leftrightarrow **31'** (Scheme 58). The $-M$ effect of the cyano group is reflected in its more positive value of σ_p (0.67) than σ_m (0.62) <1994PAC2451>. This is also true when the cyano group is conjugated with a carbocationic center through a benzene ring as shown by σ_m^+ (0.562) <1958JA4979>.



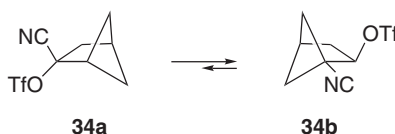
Scheme 58

A number of solvolysis rate data relevant to α -cyano and α -carbonyl substrates have been interpreted as supporting the notion that the α -cyano and α -carbonyl carbocations are stabilized by electron-donating π conjugation ($+M$) to an extent as to partly offset their destabilizing inductive effect <1984AG16, 1985ACR3, 1991CRV1625>. In resonance formulations, the positive charge is designated to distribute on the electronegative nitrogen or oxygen atom as shown by **32** \leftrightarrow **32'** and **33** \leftrightarrow **33'** (Scheme 59).



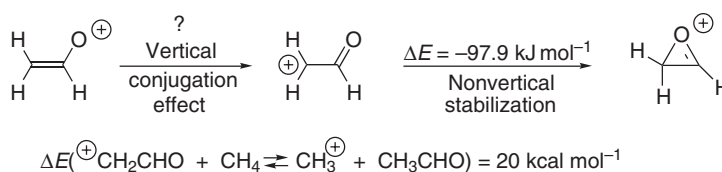
Scheme 59

The effect of geminal group interaction that destabilizes the ground state and enhances the solvolysis rates has been pointed out by several groups <1990JA4556, 1990JA4557, 1993JA2522, 1993JA2523>. A typical example is the marked destabilization of **34a** in comparison with **34b** by 38–42 kJ mol⁻¹ (Scheme 60).



Scheme 60

Quantum calculations (MP2) 6-31G** <1988JA3788> on the 2-oxoethylcation suggest this ion to be significantly less stable (by about 97.9 kJ mol⁻¹) than the oxiranyl cation. In other words, the best way for 2-oxoethyl cation to profit from the α -acyl substituent is a nonvertical effect (a rearrangement) leading to the oxiranyl cation. The calculations predicted that the isodesmic equilibrium of 2-oxoethyl cation and methane with methyl cation and ethanal favors the 2-oxoethyl cation by about 20 kJ mol⁻¹ only (Scheme 61).

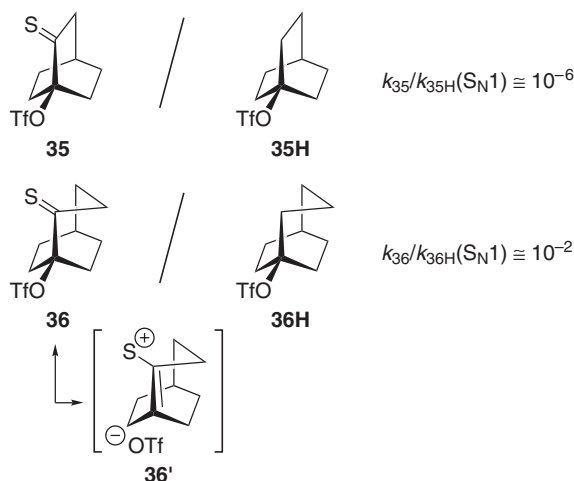


Scheme 61

This suggests that the hypothetical π -electron donating effect of the α -formyl substituent is relatively small for the intrinsically unstable methyl cation. One thus expects it to be very small or nonexistent for more stable benzyl or secondary alkyl cations (the polarizability effect V_1 of the substituent diminishes faster with the charge delocalization than its inductive effect V_C).

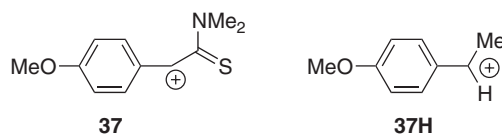
According to Creary <1982JA4151>, the carbenium destabilizing effect of a β -carbonyl function due to its permanent dipole moment ($\sigma_P^+(\text{PhCO}) = 0.406$) can be offset by a stabilizing conjugative (polarizability) effect. Similarly, the electron-withdrawing diethyl phosphonate substituent ($\sigma_P^+ = 0.505$) may be less destabilizing than expected due to its polarizability <1983JA2851>. Alternatively, Takeuchi and co-workers, studying the solvolyses of 2-oxo bridge-head substrates, conclude that the π -conjugative stabilization of tertiary α -carbonyl carbocation intermediates is negligibly small, if present <1997JOC5696>. (For the trifluoromethyl substituent effects, see <1984AG(E)20, 1985ACR3, 1991CRV1625, 1994JOC7185>; for the α -thiocarbonyl substituent effects see <1998JOC2209, 1998JA10372, 1998JPO701>.)

The solvolysis of bicyclic triflates **35** and **36** has been studied (Scheme 62). The ratio of S_N1 reactivity between α -thiocarbonyl-substituted compound and the unsubstituted compound (**35H**, **36H**) increases from 10^{-6} to 10^{-2} when going from **35** to **36**. This is consistent with stabilization of the cationic transition state for solvolysis by conjugation **36** \leftrightarrow **36'**. This effect is more efficient for large rings than for less flexible systems <1998JOC2209>.



Scheme 62

The α -thioamide cation **37** is 10^{-7} -fold less reactive toward 1:1 MeOH/H₂O than cation **37H**, indicating strong stabilizing interactions of the α -thiocarbonyl group (Scheme 63) <1998JA10372, 1998CJC1910, 1998JPO701, 2001ACR981>.

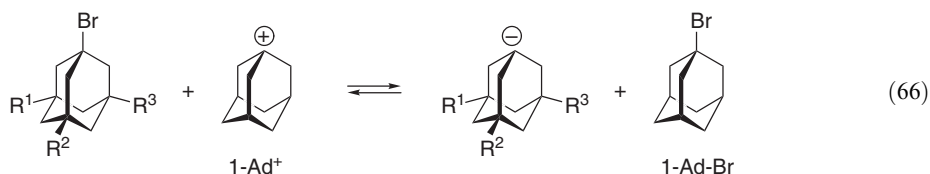


Scheme 63

1.19.9.3 Remote Allyl Substituent Effects

In the gas phase, the replacement of a methyl group of a methyl-substituted tertiary carbenium ion by an ethyl, propyl, or isopropyl group leads to an extra stabilization of the carbocation by ca. 12, 19, and 21 kJ mol⁻¹, respectively. Thus, the larger the alkyl substituent, the better it stabilizes the cation. This effect corresponds to the “normal inductive order” of the alkyl substituent effects on the stabilities of carbenium ions, i.e., H \ll Me < Et < *n*-Prop < *i*-Prop < Bu^t <1975JA5714, 1997JOC5374>.

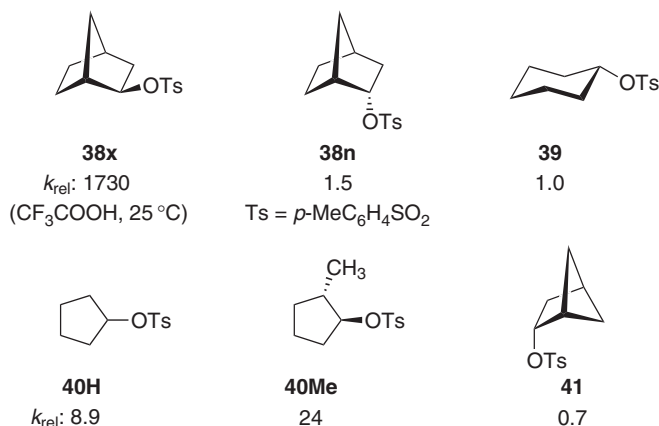
Applying the FTICR technique to measure the differential bromide affinities ΔG° **39**, Takeuchi and co-workers [<2001JOC2034>](#) found that the relative stabilities of 1-adamantyl cation increases by alkyl substitution at tertiary centers C(3), C(5), and C(7) (Equation (66)). Their relative stability increases with the number of isopropyl substituents. The relative stabilities calculated by the PM3 quantum calculation method were in good agreement with the experimental results in the gas phase.



In contrast, the sequence of the rates for the solvolysis in nonaqueous solvents are 3,5,7-(Me)₃-1-AdBr < 1-bromoadamantane (1-AdBr) < 3,5,7-(Prⁿ)₃-1-AdBr < 3,5,7-(Prⁱ)₃-1-AdBr. The rates of solvolysis of 3,5,7-(Prⁱ)₃-1-AdBr and 3,5,7-(Prⁿ)₃-1-AdBr relative to 1-AdBr at 25 °C are 15 and 3.8 in EtOH, respectively, but markedly decrease with the increase in the amount of added water, reaching 0.84 and 0.15, respectively, in 60% EtOH. Reflecting these effects of water, the Grunwald–Winstein (GW) relationship for 3,5,7-(Prⁱ)₃-1-AdBr and 3,5,7-(Prⁿ)₃-1-AdBr against Y_{Br} is linear for nonaqueous alcohols (EtOH, MeOH, TFE-EtOH, TFE, 97% HFIP), but marked downward deviations are observed for aqueous organic solvents, in particular, aqueous ethanol and aqueous acetone. The effect of the alkyl substituents to diminish relative solvolytic reactivity in EtOH–H₂O mixtures may be ascribed to a blend of steric hindrance to Brønsted base-type hydration to the β -hydrogens and hydrophobic interaction of the alkyl groups with ethanol to make the primary solvation shell less ionizing. The introduction of one nonyl group to the 3-position showed much smaller deviations in the GW relationship than the case of 3,5,7-(Prⁿ)₃-1-AdBr. The markedly decelerated solvolysis of alkylated 1-bromoadamantanes in aqueous organic solvents is a kinetic version of anomalously diminished dissociation of alkylbenzoic acids in aqueous ethanol and aqueous *t*-butyl alcohol that was demonstrated by Wepster and co-workers earlier [<1989JCS\(P2\)977, 1990RTC455, 1992RTC22>](#) and ascribed to hydrophobic effects.

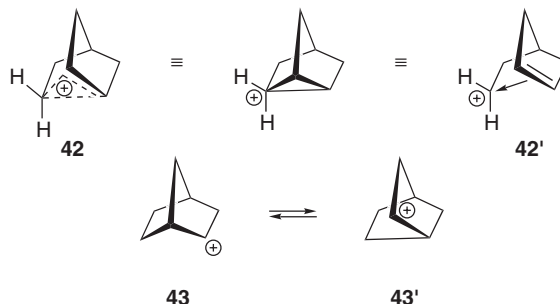
1.19.9.4 Anchimeric Assistance versus $\sigma(\text{C},\text{C})$ Hyperconjugation

The S_N1 solvolysis of bicyclo[2.2.1]hept-2-*exo*-yl (2-*exo*-norbornyl) tosylate **38x** is significantly faster than that of its *endo* isomer **38n** (Scheme 64). The rate constant ratio $k_{\text{exo}}/k_{\text{endo}}$ varies from 350 in AcOH to 1120 in CF₃COOH [<1974JA181, 1978JA3143>](#) and 1700 in HCOOH [<1978JA3143>](#).



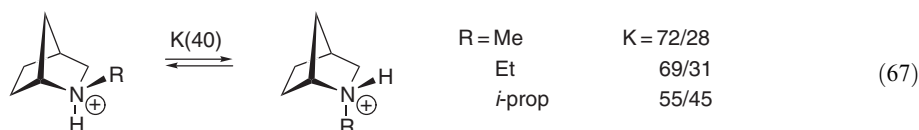
Scheme 64

The products of solvolyses of both 2-*exo* and 2-*endo*-norbornyl derivatives are exclusively *exo*. Furthermore, the solvolyses of labeled or optically active 2-*exo*-norbornyl esters yield completely racemized products, thus suggesting a symmetrical structure (C_s) for the secondary bicyclo[2.2.1]-hept-2-yl (2-norbornyl) cation intermediate. Winstein proposed the “nonclassical” bridged structure **42** <1952JA1147, 1952JA1154>, which can be seen as the π -complex **42'** (Scheme 65) <1999MI225>.

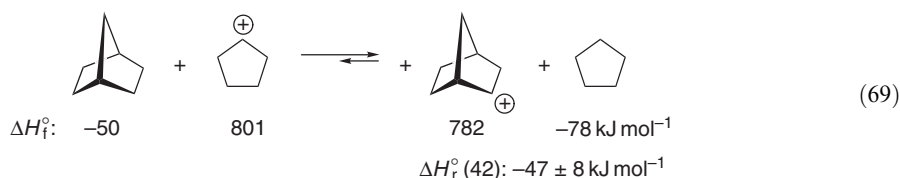
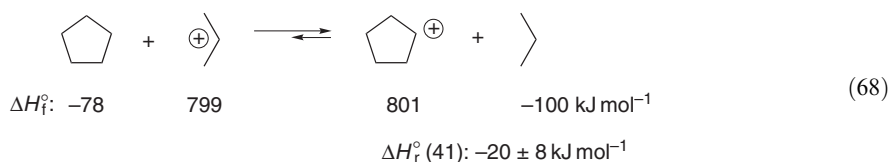


Scheme 65

Brown and co-workers have argued that the attack of the nucleophile on the *endo* face of a “classical” C_1 2-norbornyl cation **43** is difficult for steric reasons <1978JA1865>. This hypothesis has been challenged by several experiments. For instance, it is found that the N proton and the methyl, ethyl, and isopropyl group have similar ability to usurp the *exo* position in protonated *N*-alkyl-2-azanorbornanes (Equation (67)) <1978JA1503>.

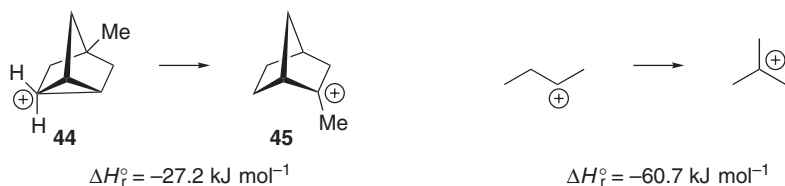


In the gas phase, the 2-norbornyl cation is about 24 kJ mol⁻¹ more stable than simpler acyclic and cyclic secondary carbenium ions. This is illustrated by comparison of the hydride transfer equilibria shown in Equations (68) and (69) <1984JA6917, 1979AG(E)951>.



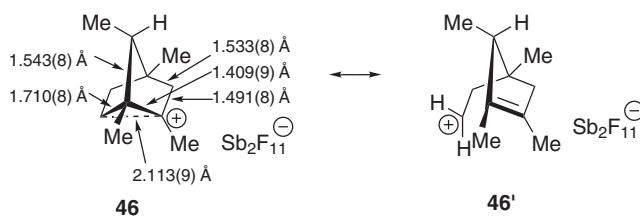
The heats of ionization of 2-chloronorbornane, 4-methyl-, and 2-methyl-2-chloronorbornane in SbF_5/SO_2ClF amounts to 96.2, 92.0, and 125 kJ mol⁻¹, respectively <1980JA398>. The rearrangement of secondary 4-methylbicyclo[2.2.1]hept-2-yl cation **44** into the tertiary 2-methylbicyclo[2.2.1]hept-2-yl cation **45** in Sb_5/SO_2ClF releases 27.2 kJ mol⁻¹. In contrast, the rearrangement of but-2-yl cation into *t*-butyl cation releases 60.7 kJ mol⁻¹, confirming that the secondary 2-norbornyl cations enjoy a special stabilization compared to simpler carbenium ions (Scheme 66).

This fact could be interpreted in terms of a symmetrically bridged ion **42** or fast equilibrating ions **43** ⇌ **43'** whose extra stability would arise from the enhanced polarizability (hyperconjugation) of the norbornane skeleton. An “enhanced” vertical stabilization effect might also be accompanied by partial σ -bridging. A relatively small stability difference between the secondary



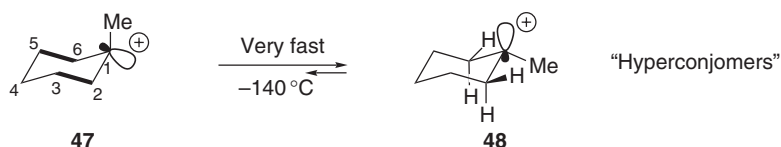
Scheme 66

and tertiary 2-norbornyl ions cannot be considered as evidence for the symmetrical structure **42** since it is found that the stability difference between 2- and 1-adamantyl cations in the gas phase differ by only at most 16 kJ mol^{-1} <1979JA951>. At the present time, a variety of experimental studies (e.g., NMR spectra at 4 K for ion in $\text{SbF}_5/\text{SO}_2\text{ClF}$ <1996JA7849>; deuterium isotopic substitution and its effect on the NMR data) as well as high-level quantum mechanics strongly support the conclusion that the stable structure of bicyclo[2.2.1]hept-2-yl cation is the C_s bridged (“nonclassical”) structure **42** (potential energy hypersurface with a single energy minimum) <1983ACR440, 1991CR375, 1995AG(E)1393>. Tertiary 2-norbornyl cations remain “classical” carbenium ions but may undergo deformation of their skeletons, compared with their precursors, due to the $\sigma\text{C}(1,6)$ bond participation to the positive charge delocalization. Laube <1995HCA943> has obtained monocystals for the Sb_2F_{11} salt of 1,2,4,7-*anti*-tetramethylbicyclo[2.2.1]hept-2-yl cation **46** and has measured its structure by X-ray diffraction studies at 110 K (Scheme 67). The data show an extra-long $\sigma\text{C}(1,6)$ bond of 1.71 \AA and relatively short $\sigma\text{C}(2,1)$ bond of 1.41 \AA and interatomic distance (2.11 \AA) between C(2) and C(6). Thus, although this tertiary carbenium ion has a much weaker electron demand than secondary 2-norbornyl cation, its deformed structure reveals the importance of limiting structure **46'** arising from the $\sigma\text{C}(1,6)$ bond participation to the charge delocalization (hyperconjugation $\mathbf{46} \leftrightarrow \mathbf{46'}$).



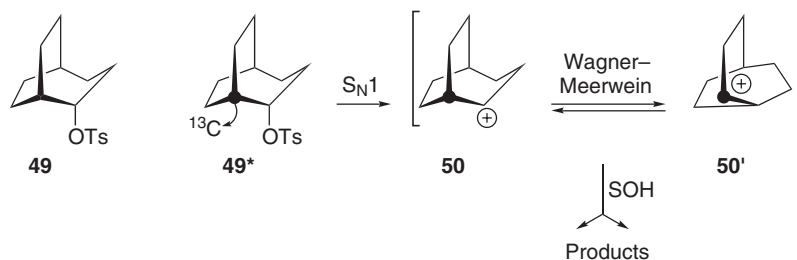
Scheme 67

In super-acid solution 1-methylcyclohexyl cation exists as a rapidly equilibrating pair of structures **47** and **48** (Scheme 68). In conformer **47**, distortion about C(1) renders the $2p(\text{C}^+)$ hyperconjugation with the $\sigma(\text{C}(2)-\text{C}(3))$ and $\sigma(\text{C}(5)-\text{C}(6))$ bonds optimal, whereas in conformer **48**, bending of the methyl substituent in a “more equatorial position” renders the $2p(\text{C}^+)$ hyperconjugation with the two axial $\sigma(\text{C}(2)-\text{H})$ and $\sigma(\text{C}(6)-\text{H})$ bonds optimal <1987JA7811>. In agreement with the data given above for acyclic carbenium ions in the gas phase, quantum calculations predict **47** to be slightly more stable ($0.96\text{--}3.3 \text{ kJ mol}^{-1}$) than **48**, whereas the experimental results for the ion in solution show that **48** is more stable than **47**. Using the SCI-PCM solvation model in Gaussian 94, solvated **48** becomes the preferred conformer. The two isomeric structures **47** and **48** have been called hyperconjomers <2001JCS(P2)869>.



Scheme 68

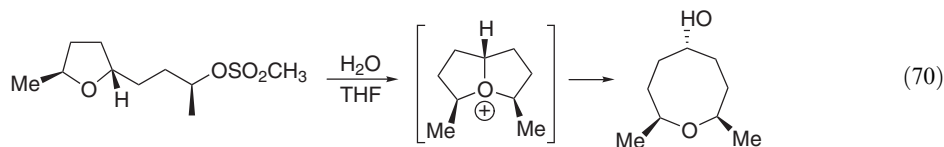
The secondary 2-norbornyl cation is a secondary carbenium ion substituted by a cyclopentyl moiety, which makes it so special compared with other bicyclic and tricyclic secondary cations such as 4-homoadamantyl cation <1993JOC7891> or 2-bicyclo[3.2.1]octyl cation <1961JA1397>. Takeuchi and co-workers <2000JOC1680> have reported the solvolysis of 2-bicyclo[3.2.2]nonyl *p*-toluenesulfonate **49** and [$1\text{-}^{13}\text{C}$]-2-bicyclo[3.2.2]nonyl *p*-toluenesulfonate **49*** (Scheme 69). The solvolysis rate constant of **49** was nearly equal to that of cycloheptyl *p*-toluenesulfonate in TFE (2,2,2-trifluoroethanol). This indicates that the ethano bridge in **49** does not significantly enhance the rate and that **49** ionizes without anchimeric assistance. The solvolysis of **49*** in MeOH or TFE gave 2-substituted bicyclo[3.2.2]nonane, *exo*-2-substituted bicyclo[3.3.1]nonane, 2-bicyclo[3.2.2]nonene and 2-bicyclo[3.3.2]nonene whose ^{13}C labels were exclusively found at only two positions with proportions different from unity. These results were interpreted in terms of equilibrating classical secondary 2-bicyclo[3.2.2]nonyl cations **50** \rightleftharpoons **50'**.



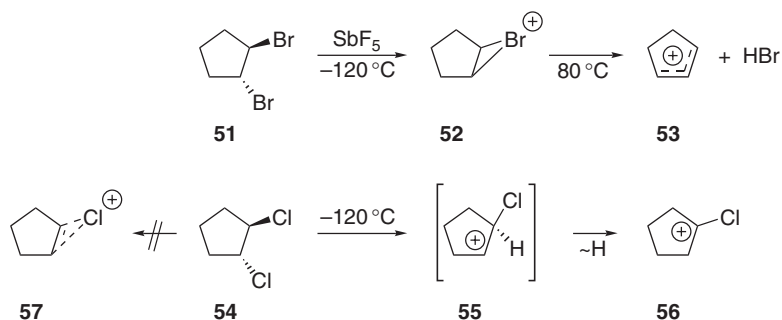
Scheme 69

1.19.9.5 Anchimeric Assistance by Heteroelements

The replacement of a CH_2 group by a heteroatom can cause changes in rates and mechanism of a solvolysis due to inductive effects (electronegativity difference), changes in ring strain, and nonvertical participation by the n electrons. The stereoselective 1,4-rearrangement-ring expansion of tetrahydrofurans via bicyclo[3.3.0]oxonium ion intermediates has been developed to prepare oxocanes, as exemplified with the solvolysis shown in Equation (70) <2002OL675>.

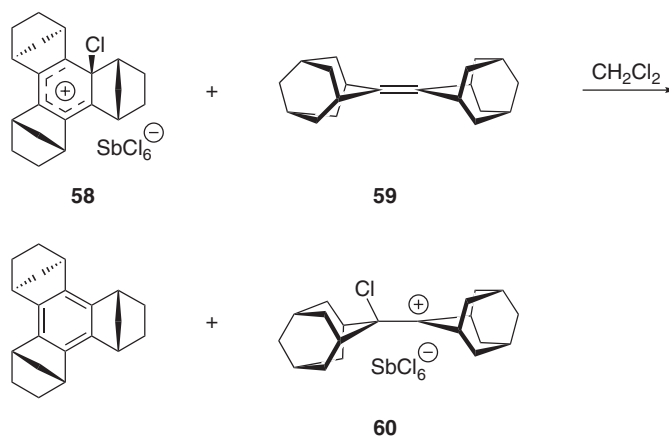


Ionization of *trans*-1,2-dibromocyclopentane **51** in $\text{SbF}_5/\text{SO}_2\text{ClF}$ at -120°C gives the bicyclic bromonium ion **52**, which undergoes HBr elimination at -80°C to yield cyclopentenyl cation **53** (Scheme 70). Under the same conditions, *trans*-1,2-dichlorocyclopentane **54** gives 1-chlorocyclopentyl cation **56** arising from intermediate **55** followed by hydride shift. The participation of the chlorine atom to give the bicyclic chloronium ion **57** is less favored than participation by the larger bromine atom giving **52**. Due to this, hydride transfer **55** \rightarrow **56** becomes the dominant process <1974JA8112>.



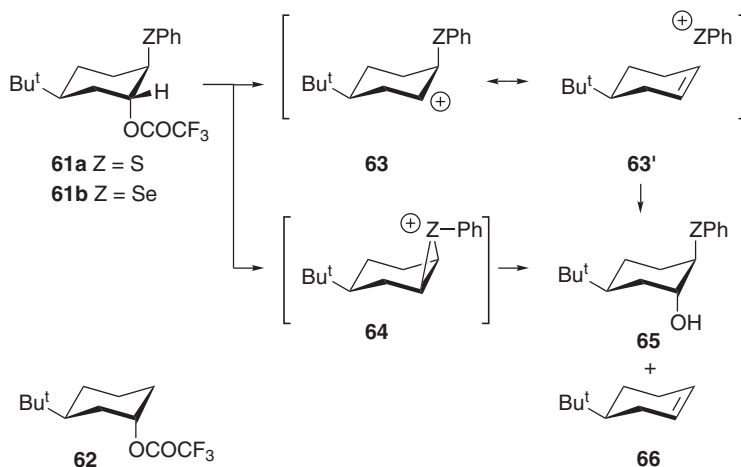
Scheme 70

Chloronium ion transfer from **58** to alkene **59** generates the nonbridged, tertiary carbenium ion **60** (Scheme 71) <1998CC927>. Bridging by the chloro substituent is not observed.



Scheme 71

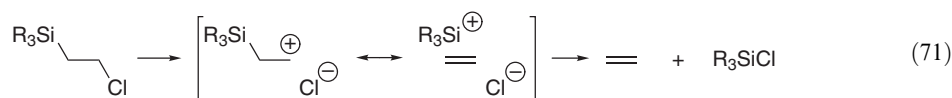
In aqueous trifluoroethanol trifluoroacetates **61a** and **61b** that are constrained to have antiperiplanar relationship between the nucleofugal (CF_3COO) and the 2-phenylthio and 2-phenylseleno substituents, respectively, are solvolyzed 10^5 and 10^6 times faster than the analogous trifluoroacetate **62** (Scheme 72). Results are consistent with either vertical (hyperconjugative **63** \leftrightarrow **63'**) or nonvertical (heteroatom participation: **64**) mechanisms <2002MI2799>.



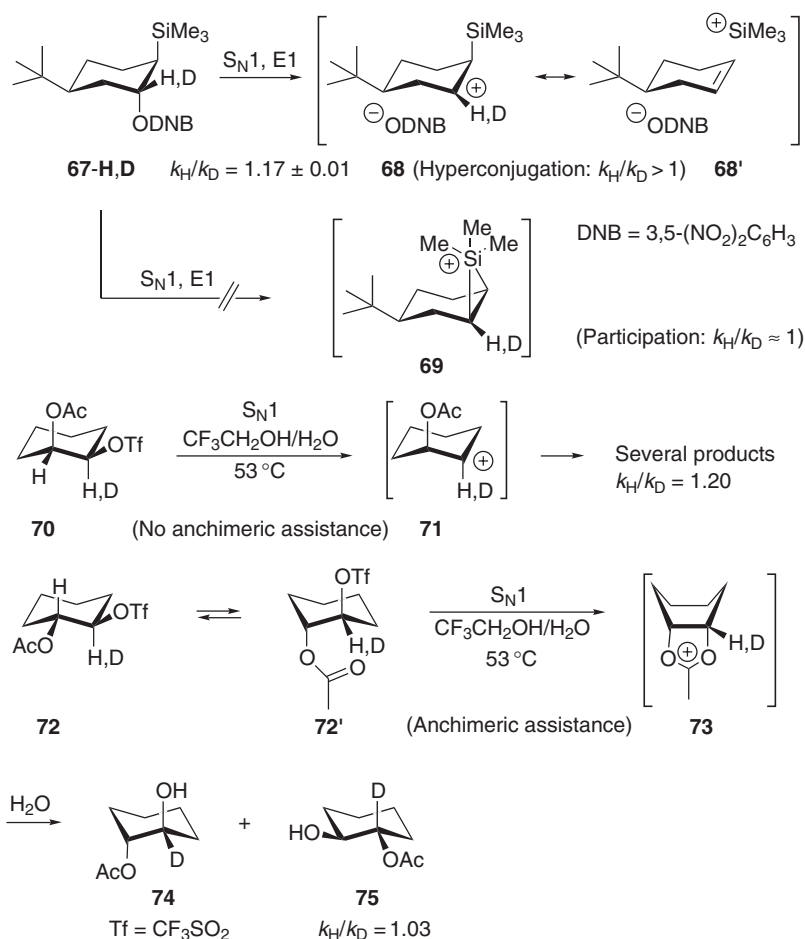
Scheme 72

1.19.9.6 Hyperconjugation and Participation by Metals

In 1946, Sommer and co-workers <1946JA488, 1946JA485> found that β -chlorosilanes are much more reactive than the corresponding α - and γ -chlorinated derivatives under ionizing conditions and that the products of reaction are mostly alkenes (e.g., Equation (71)) resulting from an E1-type of elimination. Compared with nonsilylated systems, the β -chlorosilanes generate alkenes 10^{12} times as fast as the corresponding chloroalkanes. In the gas phase and for secondary carbenium ions, β - Me_3Si substitution introduces a stabilization of nearly -126 kJ mol^{-1} <1989JA5586, 1990T2677>.

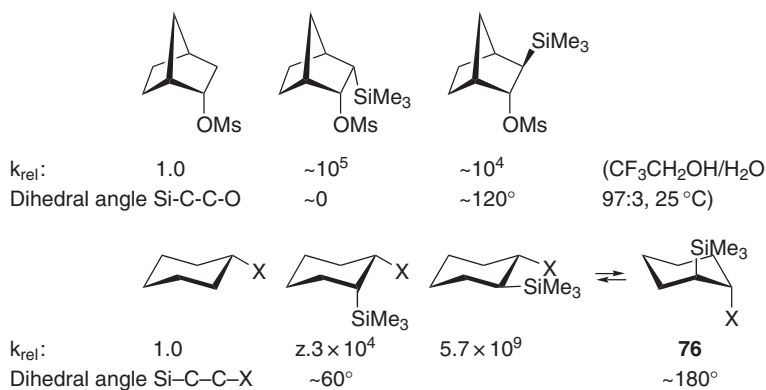


In order to determine whether the β -silicon effect is a vertical (hyperconjugative) or a non-vertical (anchimeric effect) participation by the metallic center, Lambert and co-workers <1993JA1317> have measured the kinetic isotope effect $k_{\text{H}}/k_{\text{D}}$ of the $\text{S}_{\text{N}}1$ trifluoroacetolyses of 3,5-dinitrobenzoates **67-H** and **67-D**. At 25 °C, $k_{\text{H}}/k_{\text{D}} = 1.17 \pm 0.01$ typical for an $\text{S}_{\text{N}}1$ or $\text{E}1$ process was found, which is consistent only with a vertical β - Me_3Si substituent effect (intermediates **68** \leftrightarrow **68'**) and not with the formation of a bridged cationic intermediate of the type **69**. In the latter hypothesis, $k_{\text{H}}/k_{\text{D}}$ would have been close to unity, by analogy with what is found for the $\text{S}_{\text{N}}1$ solvolyses of trifluoromethanesulfonates **70** and **72** (Scheme 73). When participation of the β -acetoxy group is prohibited for geometrical reasons, as in the solvolysis of **70**, $k_{\text{H}}/k_{\text{D}} = 1.20$. In contrast, in the case of the solvolysis of **72** for which participation by the neighboring acetoxy group intervenes, $k_{\text{H}}/k_{\text{D}} = 1.03$ is observed.

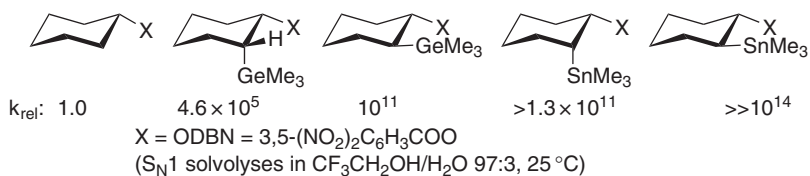


Scheme 73

The vertical, hyperconjugative β -silicon stabilizing effect depends on the dihedral angle between the β -silyl substituent and the leaving group as exemplified by the relative rate constants of the $\text{S}_{\text{N}}1$ hydrolyses given in Scheme 74. The strongest hyperconjugative interaction intervenes when these groups can adopt an antiperiplanar orientation as in **76**. β -Substituents R_3Ge , R_3Sn , and R_3Pb are even better than β - R_3Si in accelerating $\text{S}_{\text{N}}1$ solvolysis and $\text{E}1$ eliminations, provided they can be oriented antiperiplanar to the nucleofugal group (Scheme 75). The protolysis of aryltrialkyl metals generate cyclohexadienyl cation intermediates in their rate-determining steps.

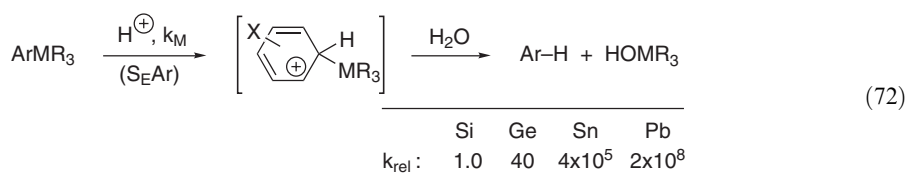


Scheme 74

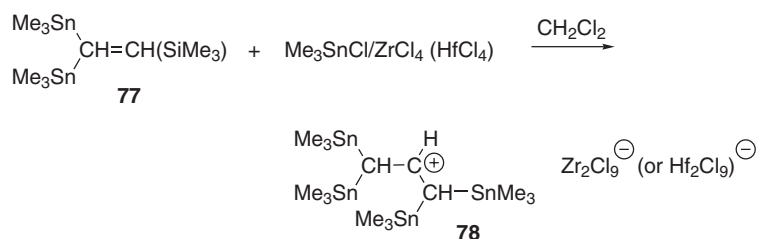


Scheme 75

The latter have relative stabilities following the sequence $\text{Si} < \text{Ge} < \text{Sn} < \text{Pb}$ as suggested by the kinetic data given in Equation (72) <1990JA8120, 1988JOC5422>. for γ -silyl, γ -germyl, and γ -stannyl substituent effects on the relative stability of tertiary carbenium ions, see <1999JPO564, 2000JOC3135>.



The stabilizing effect of β -tin groups on carbenium ions is significantly stronger than that of β -silicon groups. This is verified with the isolation and the characterization (X-ray structure) of the secondary cation salts **78** obtained below by the reaction of Me_3SnCl and ZrCl_4 (or HfCl_4) onto a disubstituted alkene. The isolation of the salt does not require superacidic media (Scheme 76) <2002JA11266>.



Scheme 76

1.19.9.7 Characterization of Cationic Electrophiles and Their Reactivity with Nucleophiles

For pure S_N2 displacement reactions empirical measures of nucleophilicity may be obtained by comparing relative rates of reaction of a standard electrophile with various nucleophiles (Scheme 77). One of the measures of nucleophilicity is the nucleophilic constant n_{CH_3I} defined by Swain and Scott <1953JA141> by $n_{CH_3I} = \log[k_{\text{nucleophile}}/k_{\text{MeOH}}]$ (in MeOH at 25°C), using methyl iodide as electrophile. Interestingly the values n_{CH_3I} do not correlate with the basicity of the nucleophile. An explanation is given by the hard-soft-acid-base (HSAB) concept <1967JA1827, 1975CRVI>.

	MeOH	NO_3^-	F^-	AcO^-	Cl^-	NH_3^-	N_3^-	Br^-	MeO^-
n_{MeI} :	0.0	1.5	2.7	4.3	4.4	5.5	5.8	5.8	6.3
pK_a of conjugate acid:	-1.7	-1.3	3.45	4.8	-5.7	9.2	4.7	-7.7	15.7

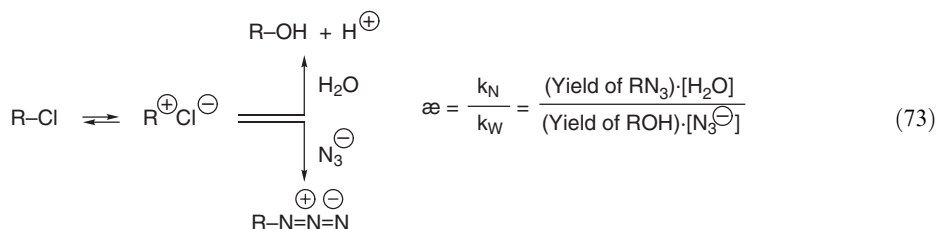
	HO^-	NH_2OH	$\text{NH}_2\text{-NH}_2$	Et_3N	CN^-	I^-	Ph_3P	PhS^-
n_{MeI} :	6.5	6.6	6.6	6.7	6.7	7.4	8.7	9.9
pK_a of conjugate acid:	15.7	5.8	7.9	10.7	9.3	-10.7	8.7	6.5

Scheme 77

The activation barrier of an S_N2 reaction depends on the exothermicity of the reaction (Dimroth principle) and on the ease by which the nucleophile can transfer an electron to the electrophile (Bell–Evans–Polanyi theory, $\Delta H^\ddagger = \alpha\Delta H_r + \beta$).

For S_N1 displacement reactions, the reactivity of the carbocationic intermediates depends on their relative stability, steric factors (bulk of the cation and of the nucleophile), solvation effects (solvent stabilization of ion-pairs, desolvation of the nucleophile and ion-pair) and on the relative stability of the products (Dimroth principle).

Relative stabilities of intermediates may be evaluated by competition experiments. Less stable intermediates are expected to be more reactive and less selective. Hence, a very reactive (unstable) carbocation will exhibit almost equal affinity for strong or weak nucleophiles, and in the limit the rates are diffusion controlled. A more stable cation will lie in a deeper energy well and will preferentially undergo reactions, which have low activation energies, assuming kinetic control. This usually means that reactions with the strongest nucleophiles will be the fastest. The competition between the highly nucleophilic azide ion and water is often used. The competition constant α is given by the relation shown in Equation (73) if the concentration of N_3^- is in large excess over that of the starting material RCl . It is defined as the ratio of second-order rate constants for reaction with azide (k_N) and water (k_W). A value of $\alpha \cong 1$ signifies a very unselective and hence reactive species. A large value of α denotes a high degree of selectivity and thus a carbocationic intermediate of high stability.



Linear relationships between α and the relative solvolysis rates for a number of chlorides have been reported. The substrates which solvolyze rapidly are the ones which yield stable cations, and they show large selectivities of α . The slowest substrates, for example those giving unstable secondary cations show small α values <1971JA4821, 1974JOC3085>.

Selectivity–reactivity relationships can be observed and interpreted provided the same type of intermediates are responsible for the product formation in the investigated series of substrates. As seen above, at least three kinds of discrete ionized species are formed in the S_N1 solvolysis process. These intermediates can have different selectivities toward various nucleophiles

<1980JA7039> and thus, make an apparent selectivity–reactivity relationship not representative of the relative stabilities of the carbocation intermediates. Ritchie and co-workers <1972ACR348> have found that the reactivities of a large number of nucleophiles toward triarylcarbenium ions can be correlated by Equation (74).

$$\log k = \log k_0 + N_+ \quad (74)$$

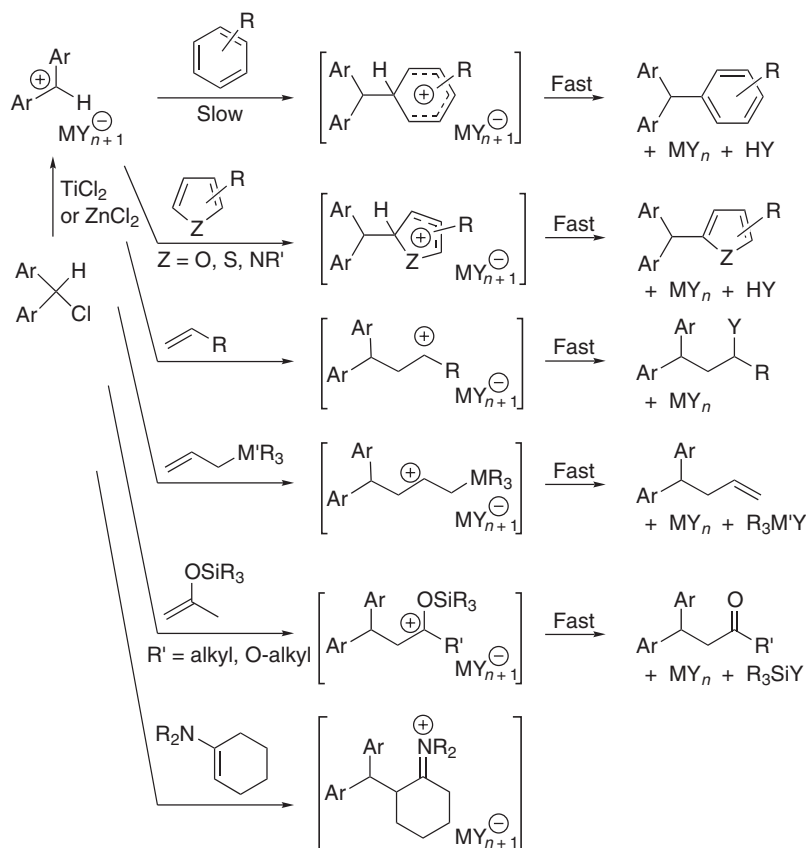
where k is the rate constant for the reaction of an electrophile with a given nucleophile in a given solvent, k_0 is dependent solely on the electrophile, and N_+ is a parameter characteristic of the nucleophilic system. This correlation represents an apparent failure of the reactivity–selectivity principle because the N_+ values are independent of the nature of the electrophile! In other words, different carbocation intermediates of different intrinsic stabilities can exhibit constant selectivity. This is due to solvation effects which modify the relative stabilities of the ion pairs, of the nucleophiles, and of the transition states of the nucleophile–electrophile combination reaction <1976JA776>. In the cases studied by Ritchie and co-workers <1972JA4966> the selectivity, k_N/k_W , is essentially constant ($\sim 10^6 \text{ M}^{-1}$) because the azide ion and the solvent respond similarly to changes in carbocation stability; the nucleophile-trapping processes are activation limited (desolvation of the nucleophile, the diffusional rate constant $\cong 5.10^9 \text{ M}^{-1}\text{s}^{-1}$ for N_3^-) <1982JA4689, 2001ACR381, 2003JA286>. A downward selectivity break is expected when the azide-trapping rate constant reaches an invariant, diffusional value, because the rate constant of solvent trapping remains activation limited and continues to increase as the carbocation becomes less stable. With stable carbocations, direct observation of recombination barriers of ion pairs by dynamic NMR spectroscopy has been possible in some cases <1982ACR2>. An energy barrier to recombination of $(\text{CH}_3\text{OC}_6\text{H}_4)_3\text{C}^+$ and NCS^- of 70 kJ mol^{-1} has been measured in $\text{SO}_2/\text{CD}_2\text{Cl}_2$ <1978CB1659>.

Mayr and Patz <1994AG(E)938, 2003ACR66> have found that the second-order rate constants k of the electrophilic additions to alkenes (uncharged nucleophiles) are correlated by Equation (75), where electrophiles are represented by a single electrophilicity parameter E , while nucleophiles are characterized by the nucleophilicity parameter N and the slope parameter s , which is usually close to unity.

$$\log K (20^\circ\text{C}, \text{CH}_2\text{Cl}_2) = s(N + E) \quad (75)$$

The reactivity scales so-obtained cover more than 16 orders of magnitude; the individual rate constants are reproduced with a standard deviation of a factor of 1.19. The reactivity parameter E derived from the reaction of diarylcarbenium ions with π -nucleophiles (Scheme 78) are also suitable for characterizing the nucleophile reactivities of alkynes, metal- π -complexes, hydride donors (Table 3) and for characterizing the electrophilic reactivities of heterosubstituted and metal-coordinated carbenium ion (Table 4) <1995AG(E)2250, 2001JA9500>.

The kinetics of 82 reactions of benzhydrylium ions (Ar_2CH^+) with n -nucleophiles (their reactive centers bear nonbonded electron pairs) has also been determined at 20°C . Evaluation by the Equation $\log k = s(N + E)$ delivered the reactivity parameters N and s for 15 n -nucleophiles (water, hydroxide, amines, etc.). All nucleophiles except water ($s = 0.89$) and $^-\text{SCH}_2\text{CO}_2^-$ ($s = 0.43$) have closely similar slope parameters ($0.52 < s < 0.71$), indicating that the reactions of most n -nucleophiles approximately follow Ritchie's constant selectivity relationship ($s = \text{constant}$). The different slope parameter for water is recognized as the main reason for the deviations from the Ritchie relationship. Correlation analysis of the rate constants for the reactions of benzhydrylium ions with the n -nucleophiles (except H_2) on the basis of Ritchie's Equation $\log k = N_+ + \log k_0$ yields a statistically validated set of N_+ parameters for Ritchie-type nucleophiles and $\log k_0$ parameters for benzhydrylium ions. The N and s parameters of the n -nucleophiles derived from their reactions with benzhydrylium ions were combined with the literature data for the reactions of these nucleophiles with other carbocations to yield electrophilicity parameters E for tritylium, tropylium, and xanthylium ions. While the E parameters for tropylium and xanthylium ions appear to be generally applicable, it is demonstrated that the E parameters of tritylium ions can be used to predict reactivities toward n -nucleophiles as well as hydride transfer rate constants but not rates for the reactions of tritylium ions with π -nucleophiles. It is now possible to merge the large data sets determined by Ritchie and others with those of Mayr and co-workers and present a nucleophilicity scale comprising n - (e.g., amines), π - (e.g., alkenes and arenes), and σ -nucleophiles (e.g., hydrides) <2003JA286>.



Scheme 78

Values given in [Tables 3](#) and [4](#) can help a rational design of organic transformations and of carbocationic polymerizations (see Section 1.19.2.4.5). The electrophilicity parameters E and the nucleophilicity parameters N can be employed for elucidating reaction mechanisms. For instance, 1,1,3-triarylallyl cations **79** react with isoprene **80** to give Diels–Alder adducts **82** ([Scheme 79](#)). The second-order rate constants agree with those calculated for the stepwise process by the correlation shown in [Equation \(75\)](#). Thus, cycloaddition **79** + **80** \rightarrow **83** implies the formation of allyl cations **81A** + **81B** in its rate-determining step. If the reaction would be a one-step, concerted [4 + 2]-cycloaddition, its rate constant would be greater than that calculated with $\log k = s(N + E)$.

In the case of the reaction of iminium ion **84** with cyclopentadiene, giving adduct **85**, the second-order rate constant is $2 \cdot 10^4$ times larger than predicted for the stepwise cycloaddition (applying [Equation \(75\)](#)). This suggests a concerted Diels–Alder addition with a degree of concertedness corresponding to ca. 27 kJ mol^{-1} ([Scheme 80](#)) [<2000EJO2013>](#).

1.19.9.8 Carbocation Rearrangements

The intermediacy of carbocations in molecular rearrangements was first suggested by Meerwein and van Emster [<1922CB2500, 1922LA16>](#) in 1922. These authors studied the conversion of camphene hydrochloride into isobornyl chloride, discovered by Wagner [<1899CB2302>](#) in 1899. Analogous rearrangements in acyclic systems were extensively studied by Whitmore and co-workers [<1932JA3274>](#).

In simple, acyclic carbenium ions, the energy barriers for hydride and alkyl group migration are only $8\text{--}16 \text{ kJ mol}^{-1}$ higher than the energy difference between the rearranging ions. The energy barrier for the 1,2-hydride shift in the but-2-yl cation ($\Delta G^\ddagger < 10 \text{ kJ mol}^{-1}$) is lower than that in the 2,3-dimethylbut-2-yl cation (**87**) ($\Delta G^\ddagger = 13 \text{ kJ mol}^{-1}$) and is attributed to the intrinsic stability difference between secondary and tertiary carbenium ion ([Scheme 81](#)). In the case of

Table 3 Nucleophilic parameters N for neutral nucleophiles.^a The s parameter is shown in parenthesis when it deviates from unity

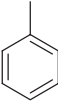
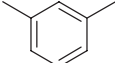


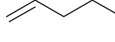
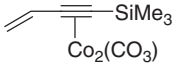
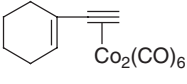
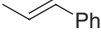
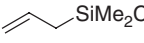
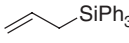

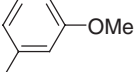



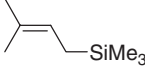
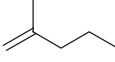




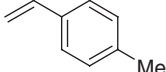
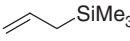
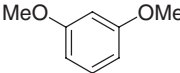

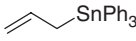
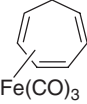



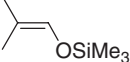
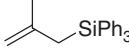
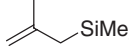
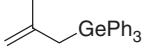
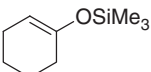
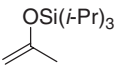
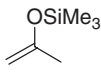
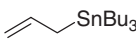
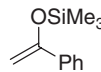
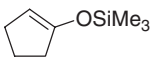
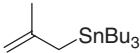

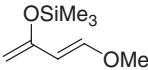
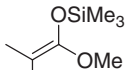
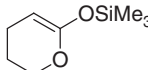
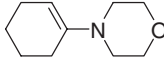
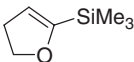
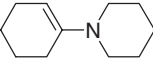
π -Nucleophiles					
					
N: -4.47 (1.32)	-3.5 (1.62)	-3.5	-2.4 (1.09)	-2.2	-1.11 (0.92)
					
-0.44 (1.06)	-0.4	-0.4	-0.13		
Low reactive nucleophiles:					
					
-0.2	0.13 (1.27)	PhC \equiv CH 0.34 (0.65)	0.5	0.78 (0.95)	0.7
					
0.96 (1.0)	1.1	1.1	1.26 (0.96)	1.4	1.7
					
1.8 (0.94)	2.48 (1.09)	2.82 (0.90)	3.09 (0.90)	3.42 (0.94)	3.44 (0.94)
					
3.61 (1.11)	3.8 (0.79)	3.9	4.17 (0.83)	4.41 (0.96)	4.8
					
5.21 (1.0)	5.38 (0.85)	5.41 (0.91)	5.46 (0.89)	6.22 (0.96)	6.57 (0.93)

Table 3 (continued)

					
7.48 (0.89)	8.23 (0.81)	8.57 (0.84)	9.1	10.6 (0.86)	11.4 (0.83)
		most reactive nucleophiles			
12.56 (0.70)	13.36 (0.81)				
Hydride donors					
PhSiH ₃	Ph ₃ SiH	PhMe ₂ SiH	Et ₃ SiH	Ph ₃ GeH	Bu ₃ SiH
0.25 (0.67)	2.06 (0.68)	3.27 (0.73)	3.64 (0.65)	3.99 (0.62)	4.45 (0.64)
Ph ₃ SnH	Bu ₃ GeH	Et ₃ N → BH ₃	Bu ₃ SnH		
5.64 (0.59)	5.92 (0.73)	8.90 (0.75)	9.96 (0.55)		

^a Taken from <2001JA9500>.

the β -phenyl cations **88**, **90**, the phenyl group migrates faster than the hydride and leads to the corresponding stable ethylenebenzenium ions **89**, respectively. In these examples, the bridged structures are more stable than the classical carbenium ions. In the case of diphenyl-substituted derivatives, the bridged ions **91** are less stable than the classical benzyl cations **90**. Thus, the energy barrier of 1,2-shifts is a function of the stability of the ions involved and of the nature of the migrating groups (phenyl vs. H or CH₃).

The rates of Wagner–Meerwein rearrangements are higher for carbenium ions in which the positive charge is highly localized, since the charge then interacts more efficiently with the potential migration group. Conversely, for carbenium ions in which the charge delocalization occurs either by vertical or nonvertical stabilization, the rearrangement is relatively slow.

Apart from the 6,2-hydride shift ($\Delta G^\ddagger \cong 25 \text{ kJ mol}^{-1}$), the secondary 2-norbornyl cation **42** undergoes an *exo*-3,2-hydride shift with a relatively high energy barrier ($\Delta G^\ddagger \cong 50 \text{ kJ mol}^{-1}$) <1975JA1133, 1974JA189>. These two processes result in a scrambling of all the hydrogen and carbon atoms in this cation (Scheme 82). In contrast, the energy barrier to the *exo*-3,2-hydride shift in the 2,3-dimethylbicyclo[2.2.1]hept-2-yl **92** is only 27.5 kJ mol^{-1} <1982JA7105>. This result is expected as σ -delocalization of the positive charge in the classical tertiary carbenium ion **92** is expected to be less important than in the nonclassical, bridged secondary ion **42**. The energy barrier for **92**, remains significantly higher than that measured ($\Delta G^\ddagger = 13 \text{ kcal mol}^{-1}$) for the 1,2-dimethylcyclopent-1-yl cation <1978JA7082, 2002AG(E)3628>. This difference can likewise be attributed to the higher degree of σ -delocalization in cation **92** compared to the cyclopentyl cation **93**. Conformational effects and ring strain effects may also affect the magnitude of the energy barrier for degenerate 1,2-shifts. Indeed, the *endo*-3,2-hydride shift in 2,3-*exo*-dimethylbicyclo[2.2.1]hept-2-yl **94** must have an energy barrier higher than 50 kJ mol^{-1} <1975JA1133, 1974JA189>. The nonamethylcyclopentyl cation **95** in SbF₅/SO₂ClF shows two types of methyl substituents in its ¹H- and ¹³C-NMR spectra at low temperatures. Four Me groups undergo rapid circumbulatory migration with a barrier <8 kJ mol⁻¹ while five Me groups are fixed to ring carbon centers. The process that equalizes the two sets of Me groups has a barrier of 29.3 kJ mol^{-1} . Quantum calculations reveal a classical trivalent carbenium ion, but stabilized by hyperconjugation and partial bridging of two quasi-axial β -Me groups. This bridging is related to the unique dynamic behavior of the nonamethylcyclopentyl cation. In agreement with the calculations, the ¹³C-NMR spectra of (methyl-d₃)-octamethylcyclopentyl cation in SbF₅/SO₂ClF at -133°C showed four ring carbon atoms with the proportions 2:2:5:1 indicating that the minimum energy structure of this ion is not symmetrically bridged <2000JA8067>.

The relatively high energy barrier ($\Delta G^\ddagger \cong 33.5 \text{ kJ mol}^{-1}$) measured for the degenerate hydrogen scrambling in the benzenium in **96** <1978JA6299> compared with that for the 1,2-hydride shift in 1,2-dimethyl-1-cyclohexyl cation ($\Delta G^\ddagger \cong 15.5 \text{ kJ mol}^{-1}$) <1978JA7082> can be attributed to π -delocalization of the positive charge in **96** (Scheme 83). In the case of the stable heptamethylbenzenium tetrachloroaluminate **98**, an energy barrier $E_a = 69 \pm 0.8 \text{ kJ mol}^{-1}$ ($\log A = 11.5 \pm 0.1$) was measured in CH₂Cl₂ solution <1983CC1533>. Permethylation of **96** (giving **98**) is expected

Table 4 Electrophilic parameters E for carbocationic electrophiles^a

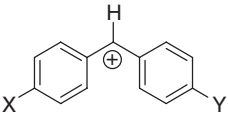


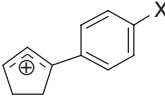
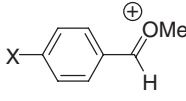
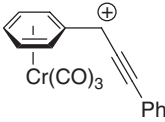
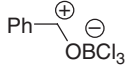
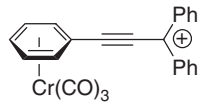
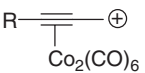
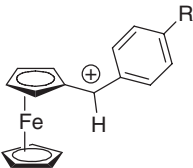
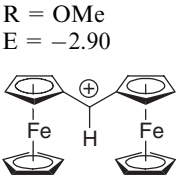
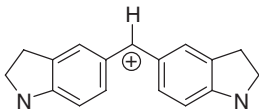
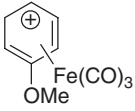
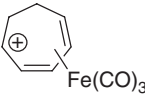
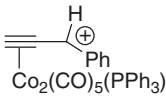
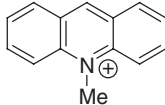
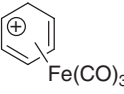
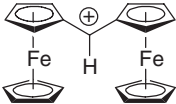
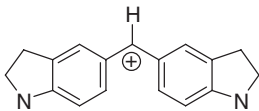
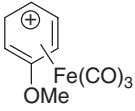
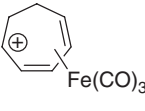
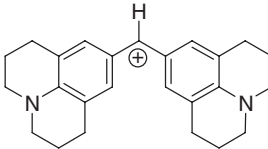
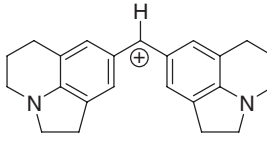
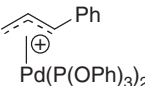
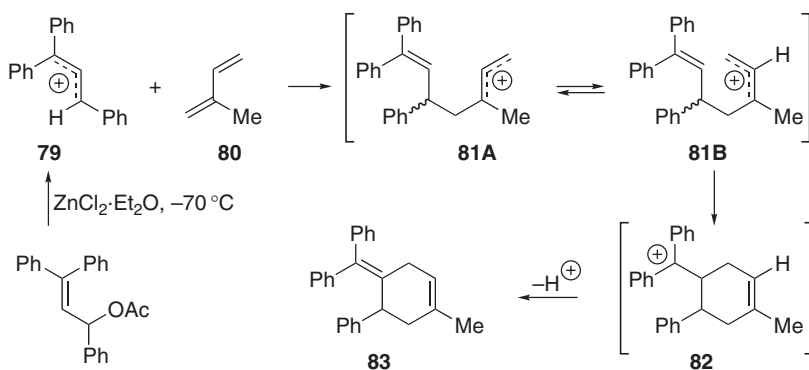
						
X = Y = Cl	X = Y = H	H = F, H = H	X = Y = F	X = Me, Y = H	X = Y = Me	X = OPh, Y = H
E = 6.02	E = 5.90	E = 5.60	E = 5.39	E = 4.59	E = 3.63	E = 2.90
X = OPh, Y = Me	X = OMe, Y = H	X = OMe, X = Me	X = Y =	X = Y = OMe	X = Y =	X = Y =
E = 2.16	E = 2.11	E = 1.48	Oph E = 0.61	0.0	N(Ph)CH ₂ CF ₃ E = -3.14	N(Me)CH ₂ CF ₃ E = -3.85
X = Y = Ph ₂ N	X = Y = 	X = Y = PhNMe	X = Y = Me ₂ N	X = Y = 		
E = -4.72	E = -5.53	E = -5.89	E = -7.02	E = -7.69		
						
X = Cl	X = H	X = Me	X = OMe			
E = 3.25	E = 2.93	E = 1.95	E = 0.14	E = 1.06	E = 0.93	E = -0.28
						
						
						
						
						
R = H	R = Ph	R = Me ₃ Si				
E = -0.83	E = -1.55	E = -1.59	E = -0.98	E = -1.36	E = -2.14	

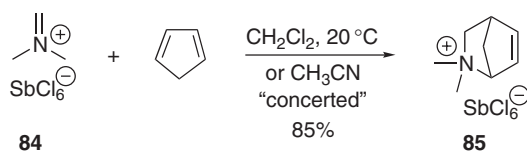
Table 4 (continued)

 <p>R = H E = -2.67</p>	 <p>R = OMe E = -2.90</p>	 <p>E = -3.50</p>	 <p>E = -3.72</p>	 <p>E = -5.88</p>	 <p>E = -6.15</p>	 <p>E = -7.14</p>
 <p>E = -7.78</p>	 <p>E = -8.54</p>	 <p>E = -8.76</p>	 <p>E = -8.94</p>	 <p>E = -9.19</p>	 <p>E = -9.45</p>	 <p>E = -10.04</p>
 <p>E = -10.33 (slow-reacting electrophiles)</p>						

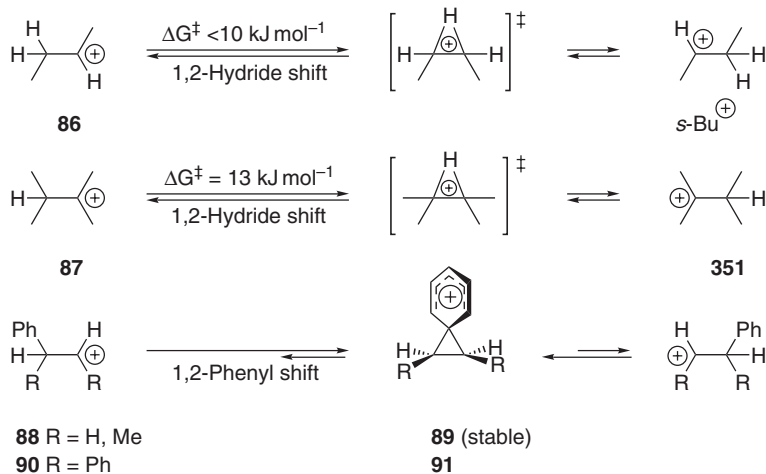
^a Taken from <2001JA9500>.



Scheme 79



Scheme 80



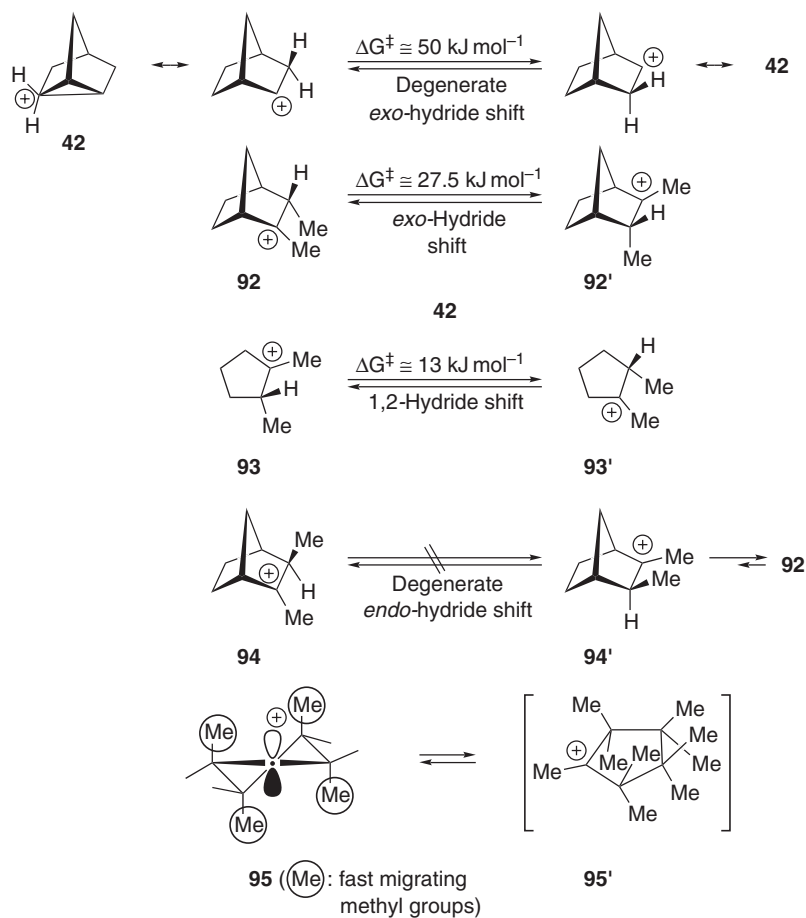
Scheme 81

to enhance the charge delocalization, thus making the 1,2-shift more difficult. Kinetic measurements on the degenerate rearrangements of acyclic carbenium ions suggest that 1,2-methyl shifts are not much easier than the corresponding 1,2-hydride shifts [<1978JA7082>](#).

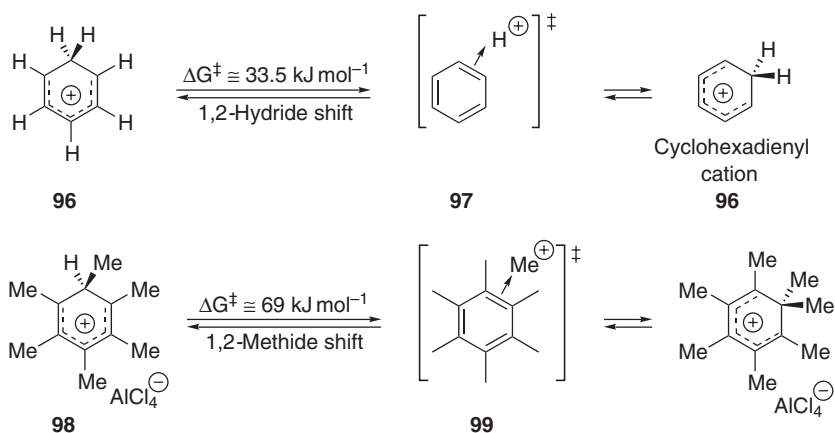
1.19.10 CARBODI- AND POLYCATIONS

Small carbocations are abundant in the mass spectra of hydrocarbons. Well characterized (with the help of *ab initio* quantum calculations) are CH_4^{++} , $\text{C}_2\text{H}_6^{++}$, $\text{C}_3\text{H}_6^{++}$, and $\text{C}_4\text{H}_2^{++}$ <1989JA1155, 1989JA8995>. The parent six-coordinate diprotonated methane, CH_6^{++} , has a C_{2v} structure <1996JA8503>. Quantum calculations predict the seven-coordinate triprotonated methane, CH_7^{+++} , to be an energy minimum with a C_{3v} -structure <2001JOC5943>.

A large number of di- and polycarbenium ions have been obtained in super-ionizing media. Examples as shown in [Scheme 84](#) [<1995JA12005, 1997JA3407>](#).



Scheme 82

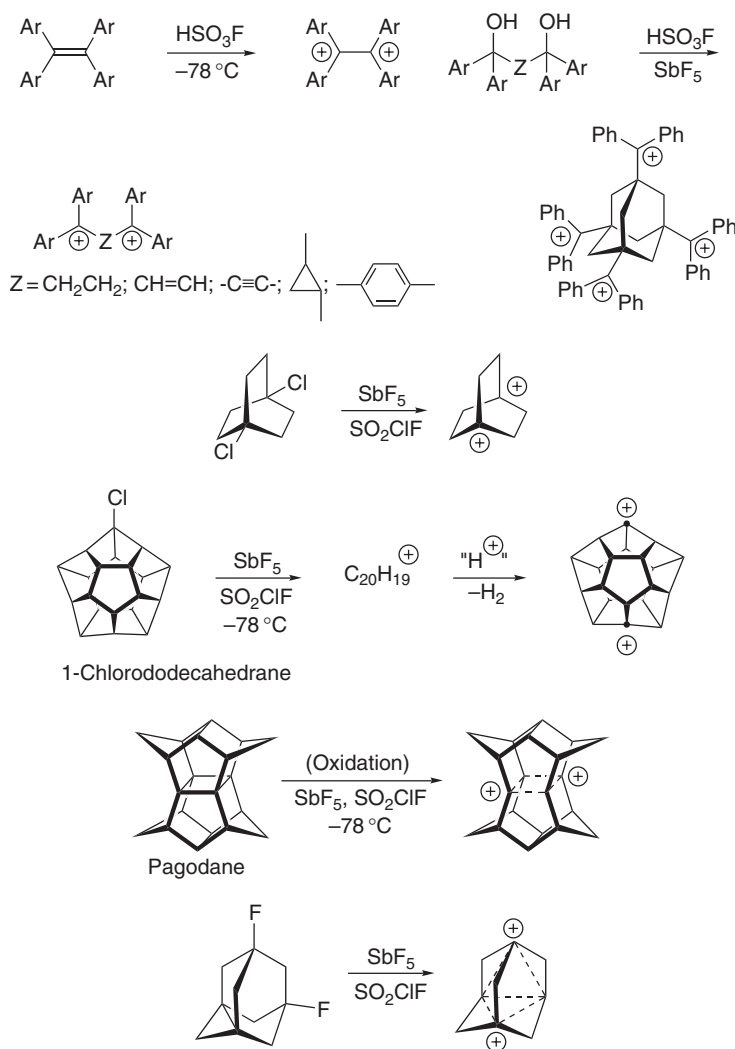


Scheme 83

1.19.11 CARBOCATIONS IN LIVING SYSTEMS

Wallach noted that many compounds, especially the fragrant principles of plants (essential oils) could be formally dissected into branched C₅ units called isopentenyl or isoprene units. For instance, terpenes are multiples of C₅ units linked together head to tail (isoprene rule <1953E357>). Several modes of cyclization are conceivable and lead to various skeletons. The

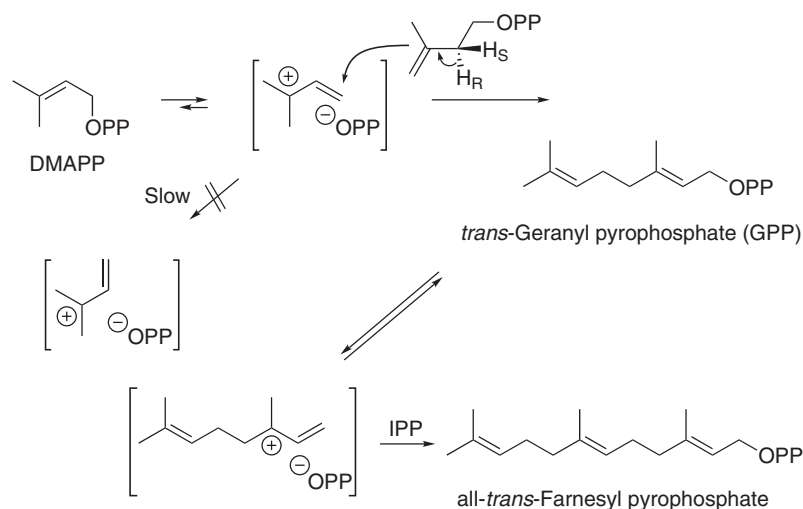
terpenes are classified according to the number of C₅ units: monoterpenes: C₁₀, sesquiterpenes: C₁₅, diterpenes: C₂₀, sesterterpenes: C₂₅, triterpenes: C₃₀, and tetraterpenes: C₄₀. In 1956 Folkers and co-workers <1956JA4499> isolated the easily incorporated mevalonic acid, and subsequently Cornforth and co-workers <1966JBC3970, 1969NAT1212> showed how it functions as a building block during the biosynthesis of the terpenes. They demonstrated that isopentenyl diphosphate (IPP) and dimethylallyl diphosphate (DMAPP) derived from mevalonic acid are the universal precursors of terpenes, one of the largest group of natural products comprising numerous medically relevant compounds such as vitamins, hormones, and antitumor agents (Taxol) <B-1992MI020>.



Scheme 84

1.19.11.1 Mechanism of the Prenyl Transfer Reaction and Monoterpene Biosynthesis

Using fluorinated analogs of IPP and DMAPP, it could be shown that prenyl transfer takes place by an ionization/condensation/elimination mechanism (Scheme 85). The exact timing of condensation with regard to ionization is not known, but the presence of C(3)–C(4) double bond of the isopentenyl pyrophosphate is not required for the enzyme to trigger ionization of the allylic pyrophosphate <1978ACR307>.



Scheme 85

trans-Geranyl pyrophosphate (GPP) is the precursor of most monoterpenes. It is isomerized first into (3*R*) or (3*S*)-linalyl pyrophosphate (LLP) and neryl pyrophosphate (NPP) before cyclization [<1985ACR220, 1987CRV929>](#) as summarized in [Schemes 86 and 87](#). These bioreactions involve the intermediacy of tertiary carbenium ions.

Prenylation is not only a reaction limited to the biosynthesis of terpenes. Many important proteins, nucleic acids, and cell wall components are prenylated within the cell. The reaction are catalyzed by prenyltransferases using prenyl pyrophosphate as reagent [<1990NAT425>](#).

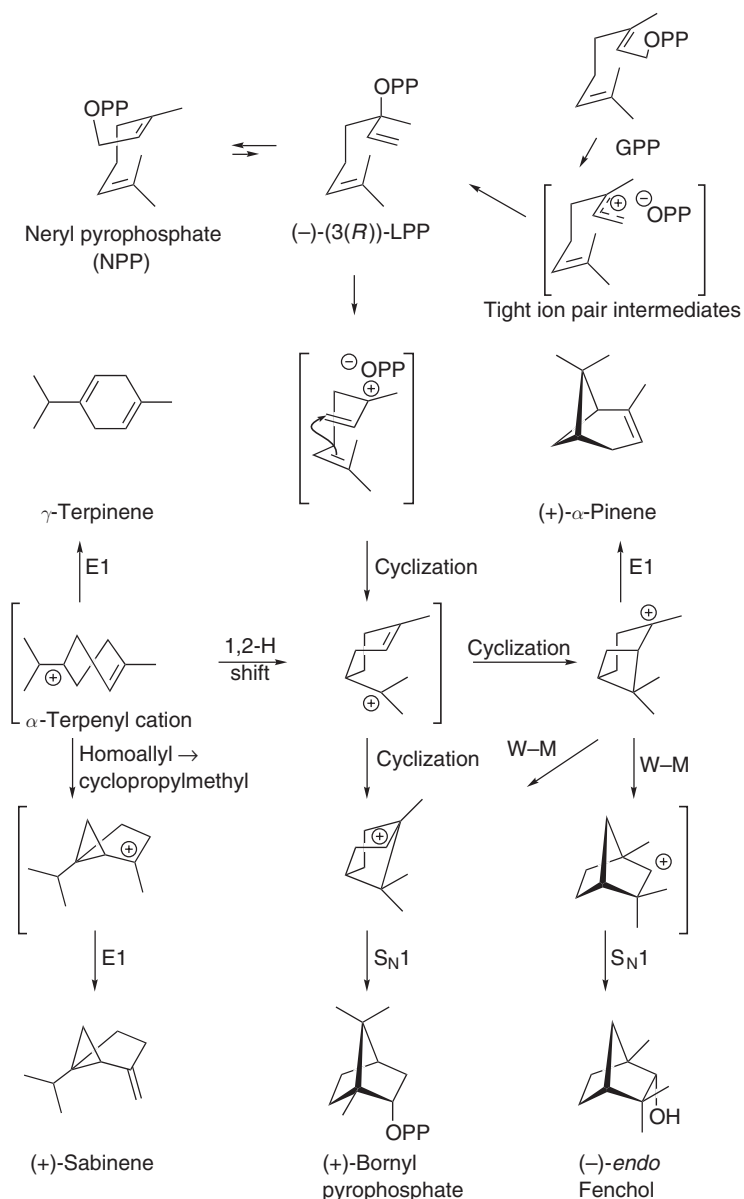
Prenylation of aromatic substrates generates valuable compounds that can be catalyzed *in vitro* by prenyltransferases isolated from rat liver, plant, yeast, bacteria, or from cloned *E. coli* strains overproducing these enzymes [<B-1999MI79>](#).

1.19.11.2 Biosynthesis of Sesquiterpenes, Diterpenes

Prenylation of all-*trans*-geranyl pyrophosphate generates all-*trans*-farnesyl pyrophosphate, [Schemes 86 and 87](#), the common precursor of sesquiterpenes. The latter is isomerized into *cis*, *trans*-farnesyl pyrophosphate and finally into nerolidyl pyrophosphate. For instance, cyclization of *cis*, *trans*-farnesyl pyrophosphate generates bisabolyl cation intermediate that can be rearranged into various bicyclic cationic intermediates that react with H₂O or eliminate a proton to give sesquiterpenes such as β -bergamotene, camphenol, sirenin, α -acordadiene, and α -cedrene ([Scheme 88](#)).

Geranylgeranyl pyrophosphate is the precursor of the diterpenes. Phytol, 6,7,10,11,14,15-hexahydrogeranylgeraniol, forming the lipophilic side chain of chlorophyll, is the most prominent member of linear diterpenes. The biosynthesis of the majority of diterpenes is initiated by electrophilic attack of the terminal double bond. This triggers a series of cyclizations leading to mono, di-, tri-, and tetracyclic derivatives [<1971MI395, 1976MI73>](#). The most important monocyclic diterpene is Vitamin A (or retinol), essential in the process of vision. More often the cyclization progresses to the bicyclic cation **100** (*trans*-decalin system), which eliminates a proton to give labdadienyl pyrophosphate or reacts with water to furnish sclareol. Intramolecular alkylation of the latter may generate 8-pimarenyl cation, the precursor of abietic acid and rosenonolactone. The bicyclic cation **100** can also undergo 1,2-hydride and 1,2-methide shifts to produce products such as hardwickiic acid ([Scheme 89](#)) [<2002JA6998>](#).

Many proteins are modified in the cell by farnesylation and geranylgeranylation [<1996MI241>](#). The finding that the Ras protein is farnesylated and that inhibition of the enzyme that catalyses this process (protein farnesyltransferase) in a variety of mutant Ras-induced cancer models arrests the growth of tumor cells has resulted in the intense search of inhibitors that prevent farnesylation [<1997MI437, 1997MI2971>](#). In the case of Rat protein farnesyltransferase an associative transition state has been proposed. This protein farnesyltransferase is a zinc metalloenzyme that catalyzes the transfer of a 15-carbon farnesyl group to a conserved cysteine

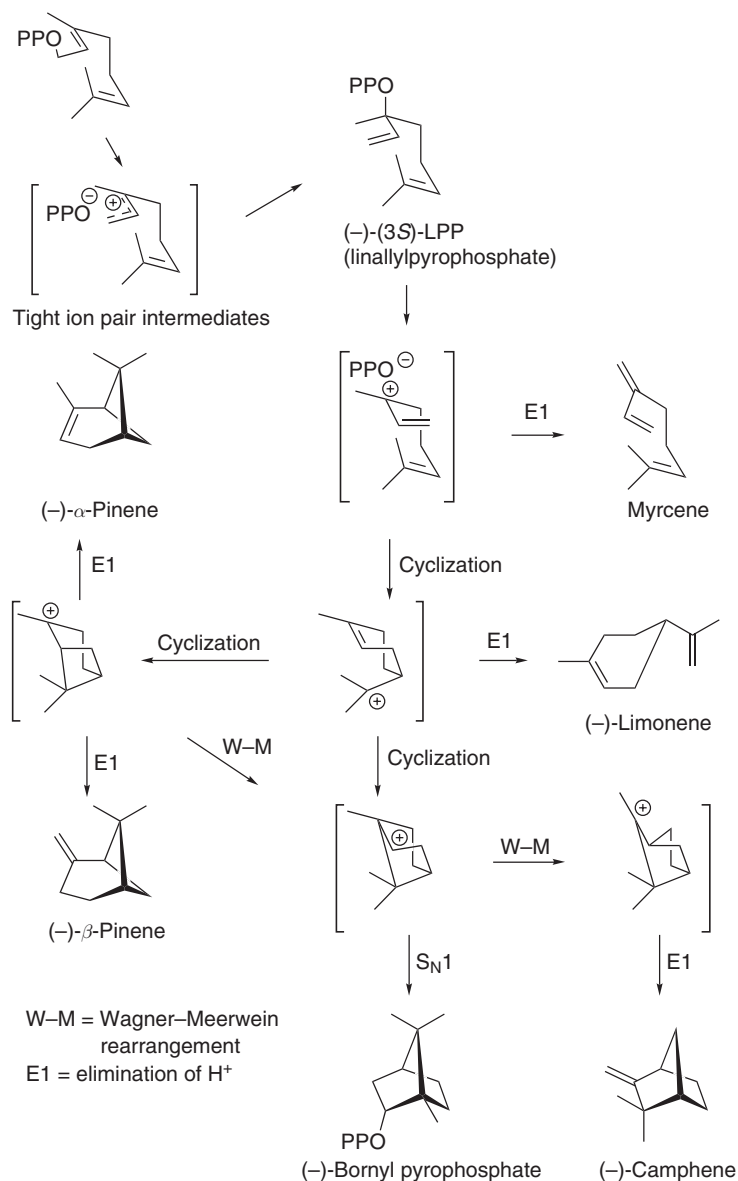


Scheme 86

residue of a protein substrate. By changing the metal and using modified substrates the mechanism that best fits the data implies an “exploded” transition state where the metal-bound peptide/protein sulfur has a partial negative charge and carbon center C(1) of farnesyl pyrophosphate (FPP) has a partial positive charge, and the bridge oxygen between C(1) and the α -phosphate of (FPP) has a partial negative charge. This transition state suggests that stabilization of the developing charge on the carbocation and pyrophosphate oxygen centers is an important catalytic feature [2000B2593](#).

1.19.11.3 Squalene and Triterpenes

Squalene was first isolated from shark liver, but was later found to be ubiquitously distributed. By folding this compound in certain modes one can construct the basic triterpenoid skeletons with angular methyl groups and side chain in correct positions. Squalene is the precursor of

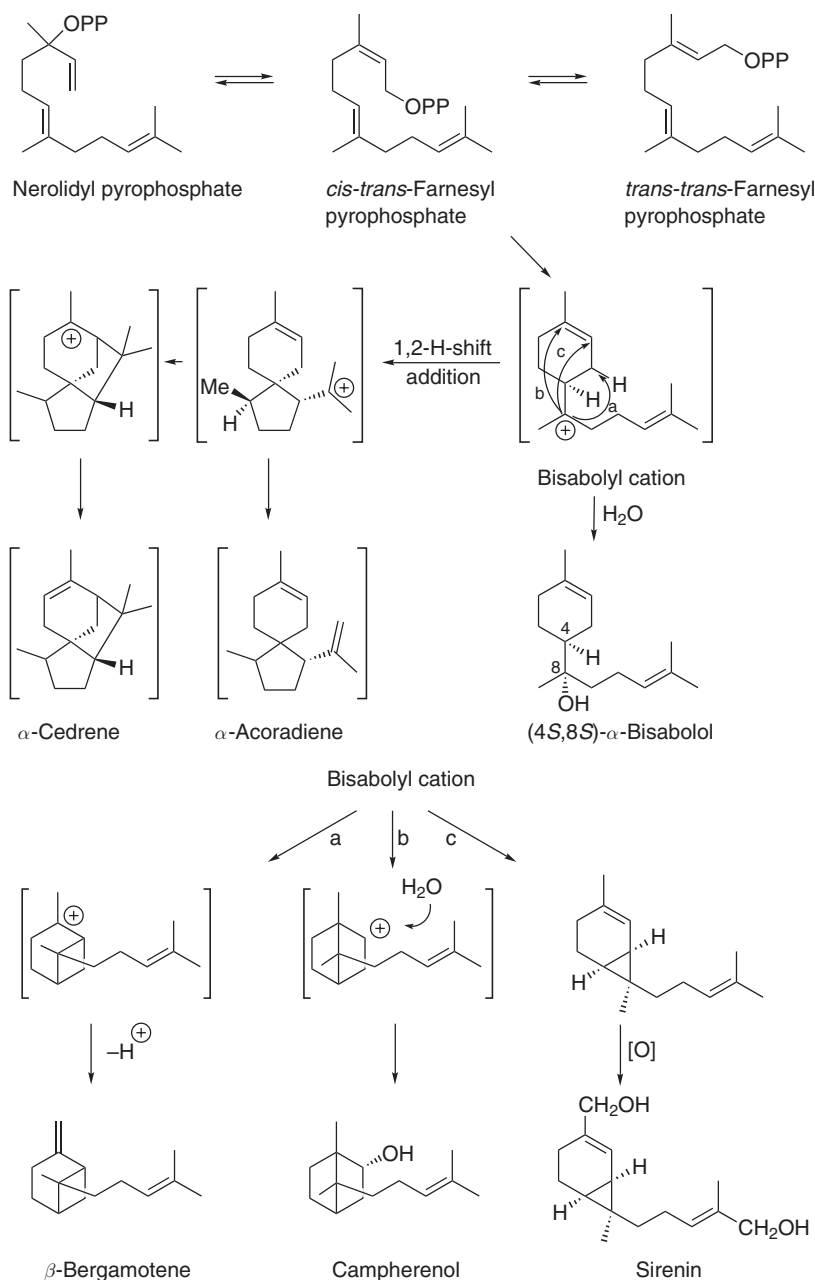


Scheme 87

cholesterol. It consists of two all-*trans* farnesyl groups joined tail to tail. The mechanism of this coupling was indicated by the isolation of presqualene pyrophosphate that has a cyclopropane unit (Scheme 90).

Squalene can be folded in a number of ways both with regards to ring size, start and terminus of the cyclization [<1993CR2189, 2000AG\(E\)2812, 2002JA10286>](#). There is also the possibility that the naturally occurring all-*trans* form isomerizes at olefinic centers at one or the other stage of the cyclization. With a few exceptions, the A, B, and C rings are six-membered rings and the cyclization is always initiated at the terminal alkene unit. After the first cyclizations generating carbocation intermediates, the latter can undergo Wagner–Meerwein rearrangements or/and proton elimination.

In 1955, Stork and Burgstahler [<1955JA5068>](#) and Eschenmoser and co-workers [<1955HCA1890>](#) suggested that the conversion of squalene into lanosterol implies the intermediacy of cation **102** that initiates a stereospecific polycyclization in which all the alkene moieties are oriented *trans*-antiparallel (Scheme 91). In 1966, van Tamelen [<1966JA4752>](#) and Corey [<1966JA4751>](#) demonstrated that squalene-2,3-oxide **101** is an intermediate for the biosynthesis of lanosterol and dammaradienol **103**. These biotransformations are simpler than

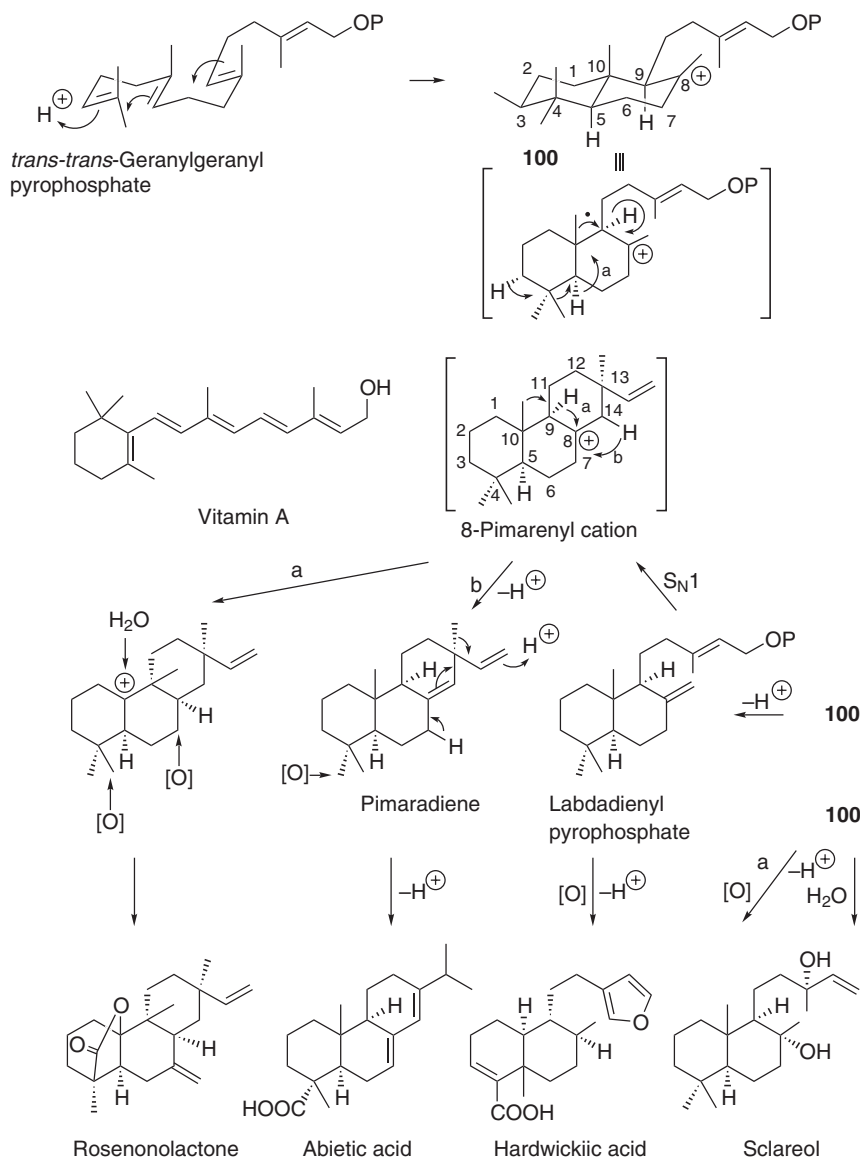


Scheme 88

conversion of **101** into lanosterol as the carbon skeleton is not rearranged. Corey and co-workers <1991JA8172> have isolated an enzyme called 2,3-oxidosqualene-lanosterol cyclase (sterol cyclase) from Baker's yeast (*Saccharomyces cerevisiae*) and have demonstrated that the C(10) methylene group of **101** plays a key role in the required folding of this compound for its transformation into lanosterol <1992JA1524>. It was shown that sterol cyclase isolated from pig liver catalyzes the isomerization of (20*E*)-20,21-didehydro-18-tritio-2,3-oxidosqualene **104** into protostanediol **106**.

In this case, cation **106** is postulated as an intermediate (Scheme 91). Its quenching with H_2O is stereospecific and is faster than rotation about the $\sigma(C(17),C(20))$ bond in **105**, and faster than migration of hydrides.

The synthetic analog of **106**, benzoate **107** <1990JA6429> was treated with BF_3 at $-90^\circ C$ in CH_2Cl_2 , 94% of alkene **108** was isolated (Scheme 92). Similarly, the 20-epimer of **106** was

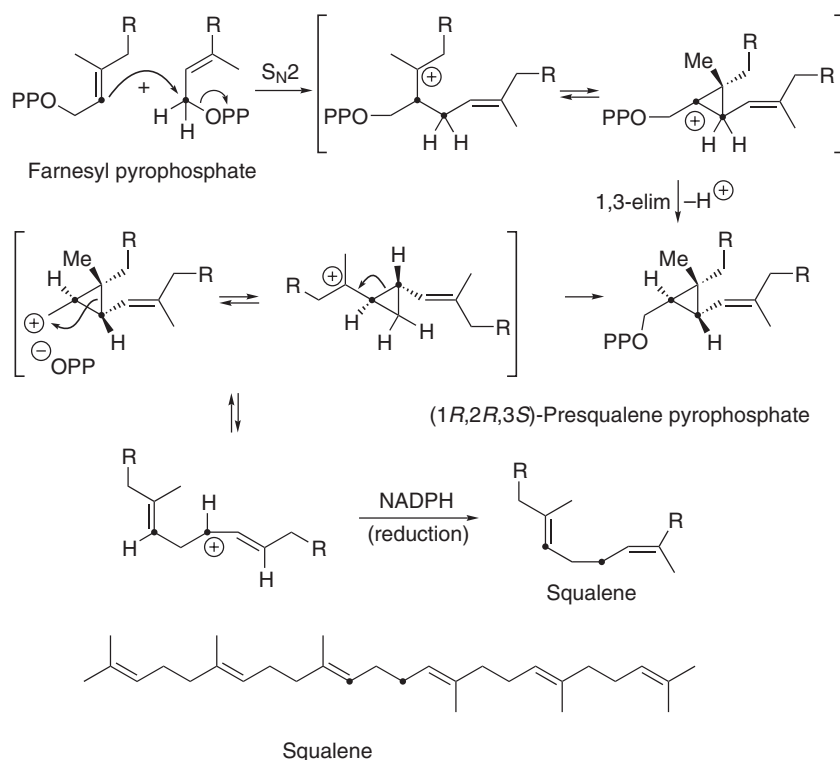


Scheme 89

converted chemically into the 20-epimer of **108**, with high stereoselectivity. These reactions imply highly stereoselective ionization of alcohol at C(20), giving a tertiary cation that subsequently undergoes a 1,2-hydride shift to give tertiary cation **109**, which then undergoes four successive (or concerted) migrations of hydride and methide groups (Wagner–Meerwein rearrangements). Wagner–Meerwein rearrangements are suprafacial. When two 1,2-shifts are coupled, the migrating groups must adopt an antiperiplanar relationship for a facile, concerted reaction (Scheme 92).

1.19.11.4 Nonmetal Hydrogenase-catalyzed Hydrogenation

The formation and consumption of H_2 by microorganisms (anerobic protozoa, anerobic archaea) is catalyzed by enzymes named hydrogenases that are iron–sulfur proteins, most of them additionally containing nickel. Hydrogenase without nickel and iron–sulfur has been found in some methanogenic archaea <1996CRV3031>. It catalyzes the reversible reduction of



Scheme 90

N^5,N^{10} -methenyltetrahydromethanopterin ($\text{CH}\equiv\text{H}_4\text{MPT}^+$) with H_2 to N^5,N^{10} -methylene-5,6,7,8-tetrahydromethanopterin ($\text{CH}_2=\text{H}_4\text{MPT}$) and a proton, an intermediate step in the formation of CH_4 from $\text{CO}_2 + \text{H}$ (Scheme 92).

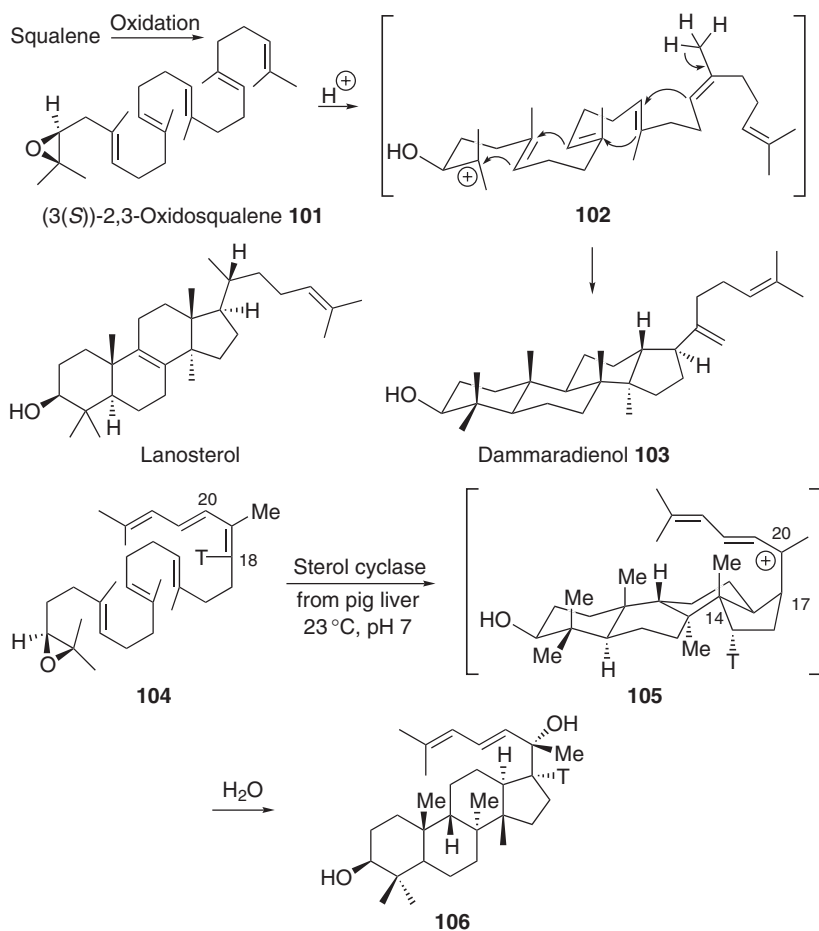
It has been proposed that the reaction involves the formation of a σ complex between dihydrogen and the diaminomethyl cation of $\text{CH}\equiv\text{H}_4\text{HMPT}^+$, in an analogous manner to the hydrogenation of *t*-butyl cation in super-acidic media that equilibrates with isobutene and proton <1995AG(E)2247>.

1.19.11.5 Carbocations and Medicinal Chemistry

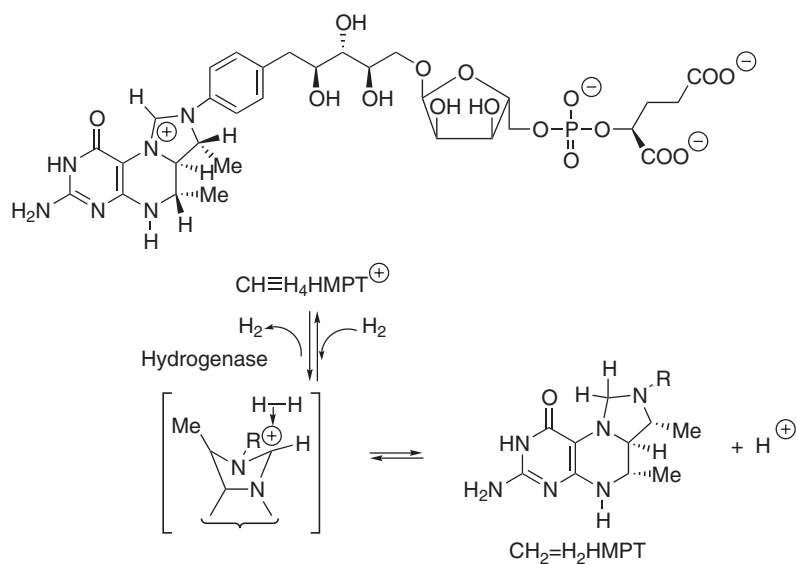
The antiestrogen Tamoxifen **111** is widely used in the treatment of breast cancer <1993BJP507>, and has received considerable recent publicity as a prophylactic agent for women considered at risk of this disease. Like most carcinogens, Tamoxifen gives rise to DNA adducts <1996MI4374, 1998MI201>. Metabolic activation is required before adduct formation, and the key intermediate is α -hydroxytamoxifene (**112**; Scheme 93). As a further activation event, sulfation into **113**, is also invoked as shown in Scheme 94. Sulfate **113** solvolyses in $\text{H}_2\text{O}/\text{CH}_3\text{CN}$ to generate the Tamoxifen carbocation **114** \rightleftharpoons **115** that has a lifetime of ca. $100\ \mu\text{s}$ <2000CJC1186>.

The carcinogenic activity of polycyclic aromatic hydrocarbons is due to their initial epoxidation by cytochrome P-450 monooxygenases <1967MI1, 1980MI1107>, followed by epoxide hydrase enzyme-mediated hydrolysis to the corresponding *trans*-diol, and a second epoxidation at the adjacent double bond (Scheme 95). This metabolic process yields a diol epoxide **116** able to alkylate DNA <B-1991MI021>. A critical step in the mechanism of carcinogenesis is the epoxide ring opening to yield a carbocation **117** <1999JOC7738>.

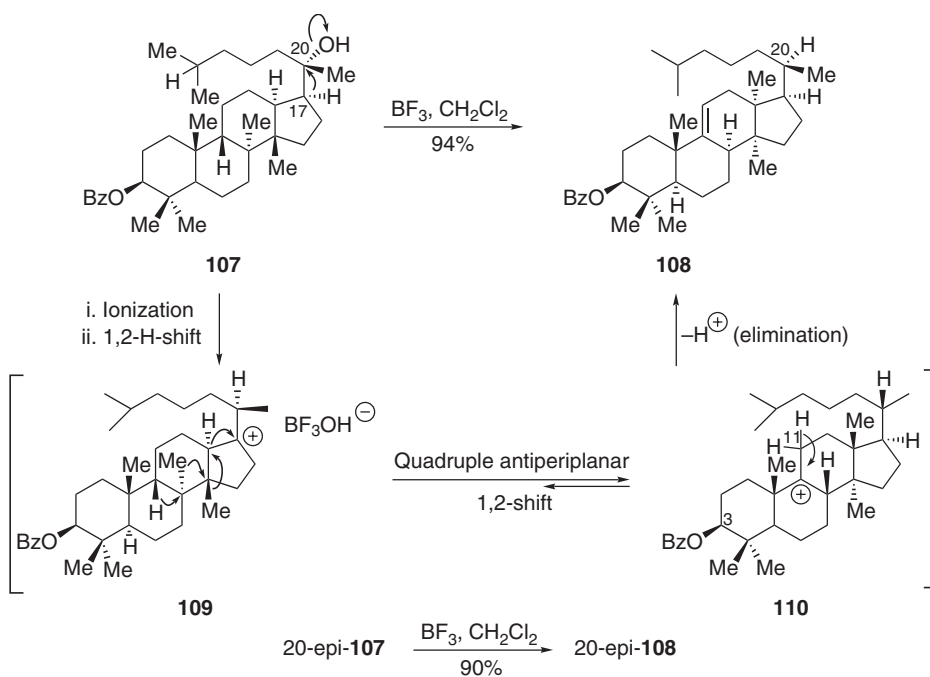
The cytotoxicity of carbocations can be exploited to fight parasites (Scheme 96). For instance, the antimalarial β -sulfonylendoperoxide **118** undergoes a Fe(II) -induced degradation that generates cationic species **119** responsible for the alkylation of vital biomolecules of the parasite <2001JOC5943>.



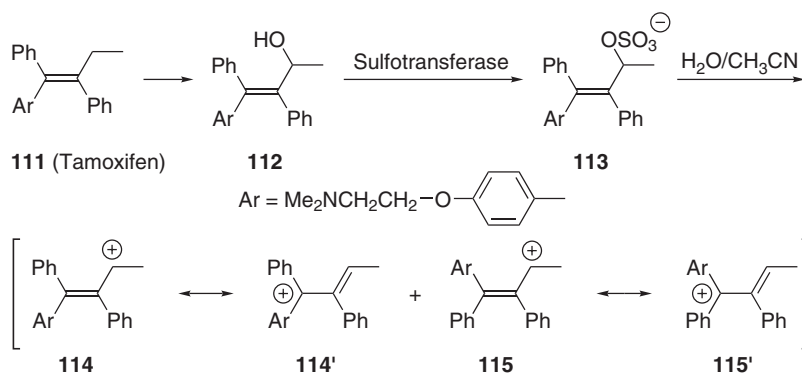
Scheme 91



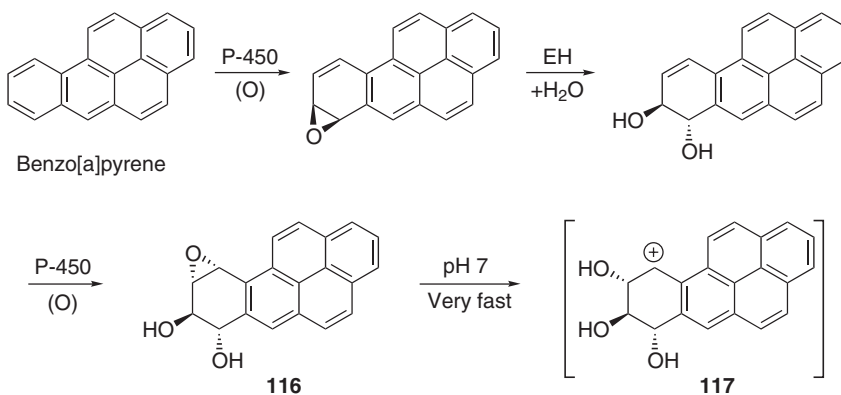
Scheme 92



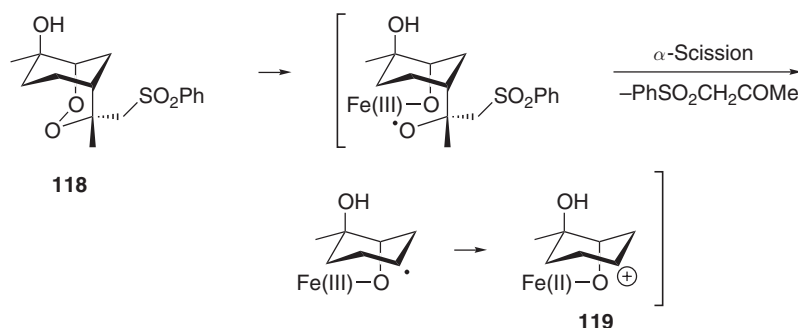
Scheme 93



Scheme 94



Scheme 95



Scheme 96

1.19.12 CARBOCATIONIC POLYMERIZATION OF ALKENES

Alkenes may be polymerized to their corresponding homopolymers via a variety of processes, of which the most important are free-radical polymerization (see Section 1.19.3.4.9), anionic polymerization, coordination/migration (Ziegler–Natta) polymerization and carbocationic polymerization <B-1999MI022>. Several well-characterized Ziegler–Natta catalysts (e.g., $\text{TiCl}_4/\text{Et}_3\text{Al}$) can also induce carbocationic polymerization of styrene, isobutene, vinyl ethers, and *N*-vinyl carbazole <2000CRV1471>.

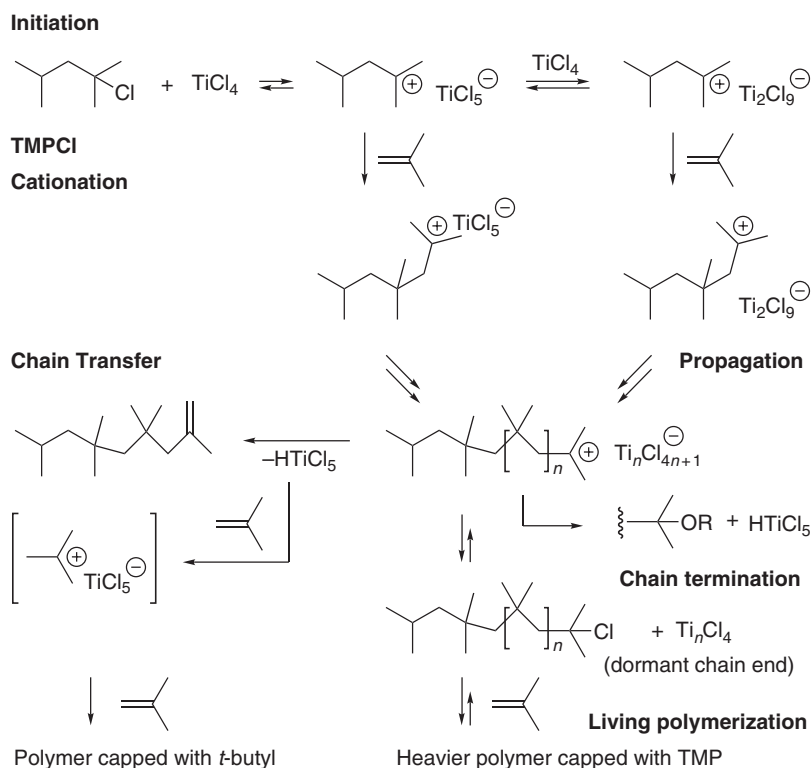
The first polymer of isobutylene was reported in 1873 <1873MI146>. During the 1980s Kennedy and co-workers described the living cationic polymerization of isobutylene producing high molecular weight polyisobutylene (PIB, $M_n = 120\,000\text{ g/mol}$) with relatively narrow distribution ($M_w/M_n = 1.1$) <1988MI473>. PIB-based materials are of interest due to a unique combination of properties such as low air permeability, high damping, and environmental and chemical stability. These materials have been used in applications such as tubes, tyre inner liner, shoe sole, adhesive components, motor oil additives, and polyethylene additives to improve resistance to environmental stress cracking. The living polymerization of isobutylene made possible the synthesis of PIB-based thermoplastic elastomers <1996MI462> and other architectures such as star-branched <1981MI67>, brush <1998MI85> or hyperbranched structures <1998MI1117, 2001MI565>.

The active sites of carbocationic initiation of alkene polymerization may be generated in a number of ways including protonation of the alkene and electrophilic addition of $\text{R}_3\text{Si}^+\text{X}^-$ or $\text{R}_3\text{C}^+\text{X}^-$. The counter-ion X^- must be a very poor nucleophile, otherwise carbocations will combine to give neutral compounds. Propagation involves repeated additions of alkene molecules to the carbocationic intermediate, which migrates well away from the site of initial attack. Thus the $\text{C}=\text{C}$ double bond must be the most nucleophilic species of the system. Chain-transfer may involve deprotonation of the carbocationic end group by a monomer. Chain transfer is often the limiting factor on molecular weights and thus the nature of the Lewis base X^- is very important. Chain termination occurs if trace amounts of good nucleophiles are present (e.g., H_2O , ROH) and can quench the carbocationic site irreversibly. To obtain polymers of high molecular weights, it is essential to carry out cationic polymerizations at low temperature (-80 to -100°C). A comprehensive mechanism for living isobutylene polymerization is given in Scheme 97. A typical initiator is 2-chloro-2,4,4-trimethylpentane (TMPCl) with the Lewis acid TiCl_4 (co-initiator). Solvent can be hexane, MeCl , or methylcyclohexane/ MeCl mixtures. Kinetic measurements show second-order dependence on the effective TiCl_4 concentration <1999MI553, 2000MM53>.

1.19.13 TRICOORDINATE RADICALS (P. VOGEL, EPFL, LAUSANNE, SWITZERLAND)

1.19.13.1 General Features of Radical Formation

Radical reactions are now an important tool of organic synthesis, driven in part by the good understanding of their dynamics and their structures. We restrict ourselves to gas phase and solution phase studies, but realize the important contributions of studies in heterogeneous systems and ordered environments, including living systems <2003JA13443, 2003CC2843>.



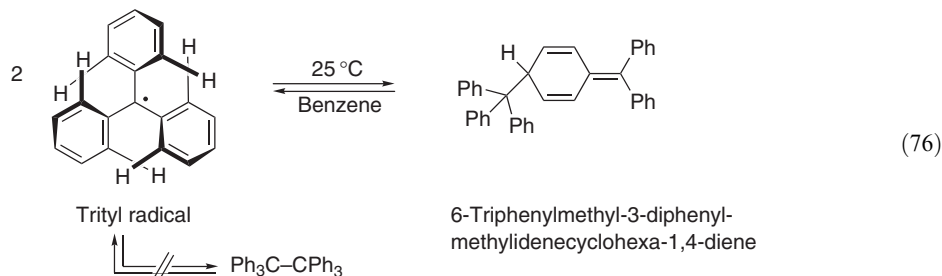
Scheme 97

1.19.13.1.1 General literature survey

Since 1970 there has been a dramatic increase in the generation, understanding, and use of radicals in synthesis and this is reflected in the number of literature reviews. General texts in the field include: Williams and Kelly <B-1995MI001> and Gilchrist <B-1995MI002>. Reviews on atom transfer addition to alkenes and atom transfer in radical polymerization <2002CUOC67>, on the prediction of reactivity in radical polymerization <2002CUOC83>, on free-radical carbonylations <1996AG(E)1051> and acyl radical chemistry <1999CRV1991>, on the chemistry of β -(acyloxy)alkyl and β -(phosphatoxy)alkyl radicals <1997CRV3273>, on radical reactions as key steps in natural product synthesis <1996AG(E)405, 1997CRV53, 1996CRV177, 1996CRV195, 1996CRV207, 1996CRV289, 1996CRV339, B-2002MI003>, on the factors controlling the addition of carbon-centered radicals to alkenes <2001AG(E)1340>, on the persistent radical effect <2001CRV3581> and its role in alkene polymerization <2001CRV3611>, on living radical polymerization <2001CRV3661, 2001CRV3689> have been published. Thermochemical data obtained by mass spectrometry methods have been summarized recently <2002CRV2855>. Reviews on more specific topics are: bridgehead radicals <1989CRV975, 1992CSR105>, the captodative—or synergistic <1989JA7558>—effect <1985ACR148, 1988PAC1635>, cyclopropyl methyl radicals <1992MI71, 1993CSR347>, diastereofacial selection in intermolecular reactions <1991ACR296, 1994SL1>, organosilane <1992ACR188> and organotin reagents <B-1986MI004, 1987S665>, retrosynthetic planning <1991SL63>, and ring expansions <1993CRV2091>. Recent advances on radical nucleophilic reactions <2003CUOC747>, the discovery and development of cyclobutanone-based free radical ring expansion and annulation reactions <2002CUOC1015>, tin hydride-induced intramolecular aryl radical cyclizations <1999CUOC469>, addition of free radicals to C_{60} <1998ACR63>, homogeneous gas phase polymerization <1997ACR297>, the use of xanthates in radical reactions <1997AG(E)673>, and the activation of alkanes with radicals <2002CRV1551> have been reviewed. For annual reports, see <2002AR(B)317, 2001AR(B)3, 2000AR(B)3, 1999AR(B)3, 1998AR(B)321, 1997AR(B)55, 1996AR(B)51, 1996AR(B)103>.

1.19.13.1.2 Historical background

In the middle of the nineteenth century it was believed that the ethyl radical, $\text{CH}_3\text{CH}_2^\bullet$, could be liberated, for instance by reaction of ethyl bromide with certain metals. However, it was soon realized that the gaseous products so-obtained are mixtures of ethane, ethane (Equation (76)) and butane, forcing the conclusion that carbon is tetravalent in all its compounds. In 1900, Gomberg <1900CB3150> at the University of Michigan demonstrated that triphenylmethyl (trityl) radical equilibrates with 6-triphenylmethyl-3-diphenylmethylenecyclohexa-1,4-diene, then believed to be hexaphenylethane (Equation (76)). The combination of two trityl radicals into hexaphenylethane is impeded by Front- and Back-strain between the phenyl substituents. Conjugation between the carbon-centered radical and the π -electrons of the phenyl ring is not optimal in the trityl radical due to gauche interactions between the *o*-hydrogen atoms of the phenyl groups that force the radical to deviate from planarity and to adopt a propeller shape.



During the 1920s, Paneth <1929CB1335> demonstrated that alkyl radicals exist as reactive intermediates. During the 1930s, Hey and Waters <1937CB169> observed that the decomposition of aromatic peroxides and azocompounds led to the phenylation of benzene derivatives, reactions with regioselectivities quite different from those expected for aromatic electrophilic substitutions, thus forcing the conclusion that the reaction species is the electrically neutral phenyl free radical.

In Chicago, Kharasch <1937JOC393> discovered in 1937 that the addition of HBr to alkenes does not always follow the Markovnikov regioselectivity rule. Especially when initiated by the decomposition of peroxide, the reaction of HBr with an alkene implies a radical chain process. The addition of HBr to the alkene might be accompanied by the formation of a homopolymer of the alkene. In 1937, Flory <1937JA241> described the kinetics of the radical-induced polymerization of alkenes. Of all the various type of polymerization processes that are available today, the free-radical polymerization process is probably the most popular. It is easy to perform, requires minimal purification of the monomers (alkenes, dienes, etc.), can be performed under a wide variety of conditions (including in water) and is economical (see Section 1.19.3.6).

1.19.13.2 Radical Initiators in Organic Chemistry

The most common methods used today to engender radicals and a selection of their reactions with applications in modern organic synthesis is described. The long-lived tricoordinate carbon radicals have paramagnetic properties and thus can be detected by electron spin resonance (ESR) spectroscopy <2000MI55>. When a reaction that generates radical intermediates (transient radicals with a given concentration) is run in the probe of an NMR machine, unusual signals might be seen with enhanced intensities or negative intensities (emission). The phenomena are inferred as the chemically induced dynamic nuclear polarization (CIDNP) <1975MI319, 1972ACR18> and thus can be used to detect transient radicals.

The chemistry of radical reactions has made fantastic progress as a consequence of the discovery of new initiators. Radical reactions at low temperature using highly active initiators facilitate the generation of radicals at specific positions in the molecule and thus lead to high stereocontrol.

1.19.13.2.1 Thermal radical production

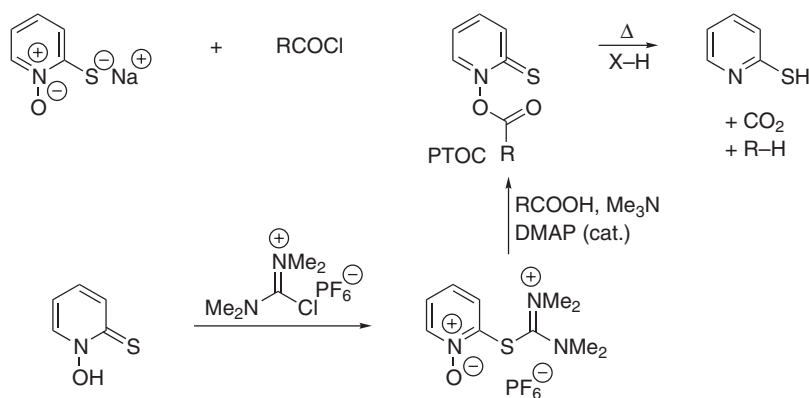
Compounds with homolytical bond dissociation enthalpies $\text{DH}^\circ(\text{R}^\bullet/\text{X}^\bullet) < 140 \text{ kJ mol}^{-1}$ can be used for the thermal generation of radicals; they are the peroxides, azo compounds (Table 5), nitrite esters, and esters of *N*-hydroxy-2-thiopyridone (PTOC: pyridine thiocarbonyl esters;

Table 5 Approximate half-lives ($\tau_{1/2}$) for the unimolar decomposition of peroxides and azocompounds and other radical initiators at 80 °C unless indicated otherwise

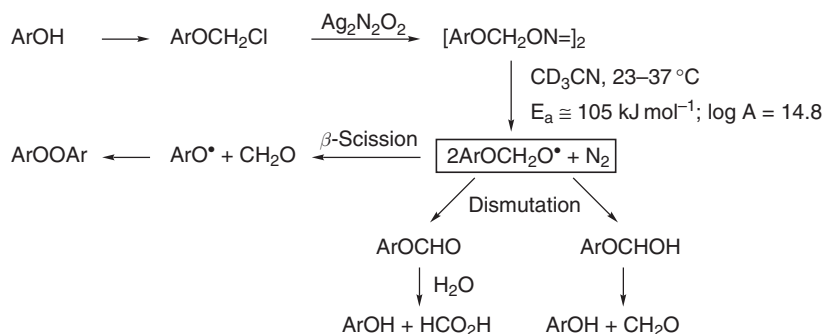
$\text{X}-\text{C}(\text{Me})_2-\text{N}=\text{N}-\text{C}(\text{Me})_2-\text{X} \xrightarrow{80\text{ }^\circ\text{C}} \text{N} + 2 \text{X}-\text{C}(\text{Me})_2^\bullet$						
X =	Me	Bn	Pho	N≡C (AIBN)	EtOOC	Ph
$\tau_{1/2}$:	~10 ⁶ h	~117000 h	~36200 h	1.5 h	~3 min	~2 min
$\text{Bu}^t\text{O}-\text{O}-\overset{\text{O}}{\parallel}-\overset{\text{O}}{\parallel}-\text{O}-\text{Bu}^t \xrightarrow{\Delta} 2\text{Bu}^t\text{O}^\bullet + 2\text{CO}_2$						
DPBO (di- <i>t</i> -butyl peroxyoxalate)				24 h at 20 °C (PhH) ^a 0.7 h at 45 °C (PhH)		
$\text{Bu}^t\text{O}-\text{N}=\text{N}-\text{O}-\text{Bu}^t \xrightarrow{\Delta} 2\text{Bu}^t\text{O}^\bullet + \text{N}_2$						
DTNB (di- <i>t</i> -butyl hyponitrite)				7 h at 45 °C (isooctane)		
<hr/>						
(Bu ^t O) ₂	⇌	2 Bu ^t O [•]			~3000 h	
Bu ^t OO ₂ CMe	⇌	Bu ^t O [•] + AcO [•]			~600 h	
PhCO ₂ O-Bu ^t	⇌	Bu ^t O [•] + PhCO ₂ [•]			~120 h	
(PhCO ₂) ₂	⇌	2 PhCOO [•] → Ph [•] + PhCO ₂ [•] + CO ₂			~3 h	
(MeCOO) ₂	⇌	2 AcO [•] → Me [•] + MeCO ₂ [•] + CO ₂			~3 h	
BnCO ₂ O-Bu ^t	→	Bn [•] + CO ₂ + Bu ^t O [•]			~0.5 h	
PhOCMe ₂ CO ₂ O-Bu ^t	→	Bu ^t [•] + CO ₂ + Bu ^t O [•]			~0.2 h	
PhOCMe ₂ CO ₂ O-Bu ^t	→	PhOCMe ₂ [•] + CO ₂ + Bu ^t O [•]			~1.2·10 ⁻⁵ h	

^a Taken from the reference <B-1994MI010, B-1998MI1610>.

Scheme 98). For precursors with higher homolytical bond dissociation enthalpies, flash pyrolysis is a means to general radicals in a rare gas <1992MI4003, 2003CSR59, B-1994MI005, B-1998MI1610>.

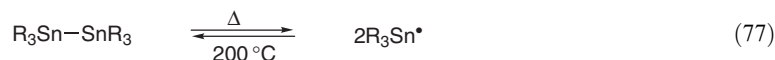
**Scheme 98**

The introduction of *O*-acyl thiohydroxamates (mixed anhydrides of carboxylic acids and thiohydroxamic acids) by the Barton group in 1983 <1983CC939> has provided one of the mildest and versatile sources of carbon-centered radicals. Their preparation consists in reacting the sodium salt of 2-mercaptopyridine-*N*-oxide with the corresponding acyl chloride using dimethyl formamide-catalyzed reaction with oxalyl chloride (Scheme 98) <1985T3901, 1986PAC675, 1989CRV1413, 1992T2529, 1994PAC1943> Other methods are also available (Scheme 99) <B-2001MI109>.



Scheme 99

Tin-centered radicals are used routinely to initiate radical transformations (Equation (77)). These radicals can be generated by heating hexaalkylditin or hexaarylditin above 200°C (or by photolysis) ($\text{DH}^\circ(\text{Me}_3\text{Sn}^\bullet/\text{Me}_3\text{Sn}^\bullet) \cong 251 \text{ kJ mol}^{-1}$; standard dissociation enthalpy = heat of reaction $\text{Me}_3\text{Sn-SnMe}_3 \rightleftharpoons 2 \text{ Me}_3\text{Sn}^\bullet$).



The strength of metal-carbon bonds and of metal-metal bonds decreases as the size of the element increases. Tetraethyllead (Et_4Pb) has a particularly weak Pb-C bond (standard dissociation enthalpy: $\text{DH}^\circ(\text{Et}^\bullet/\text{EtPb}^\bullet) \cong 125 \text{ kJ mol}^{-1}$), which accounts for the ease of homolysis and hence the effectiveness of this reagent as an anti-knock agent in gasoline <2002JCS(P2)367>.

Homolytic bond cleavage of the Mn-Mn bond in decacarbonyldimanganese ($\text{Mn}_2(\text{CO})_{10}$) can be achieved by heating or by photolysis (standard dissociation enthalpy: $\text{DH}^\circ(\text{Mn}(\text{CO})_5^\bullet/\text{Mn}(\text{CO})_5^\bullet) \cong 159 \pm 20 \text{ kJ mol}^{-1}$ <1998JOM123, 1990CRV629>) (Equation (78)).



Hyponitrites decompose at ambient temperature to give N_2 and alkoxy radicals. In the case of aryloxyalkoxy radicals, very fast β -scission occurs yielding aryloxy radicals (Scheme 99) <2002AG(E)804>.

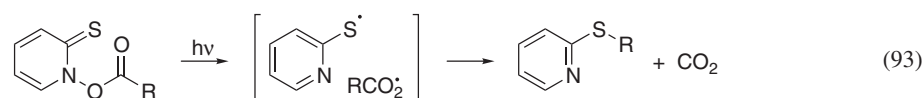
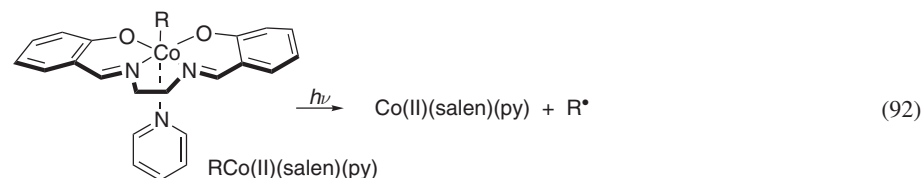
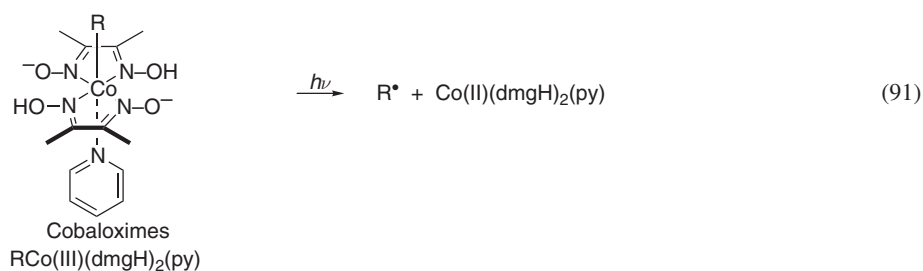
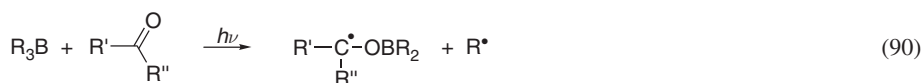
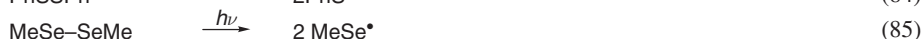
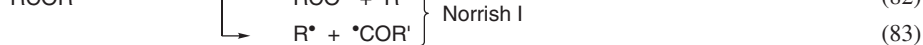
1.19.13.2.2 Photo-induced homolyses

Photolysis (UV, visible light) or high-energy radiation (e.g., X-rays, γ -rays) of organic, organo-metallic, and inorganic compounds generates radicals. For example, azo compounds and peroxides (Table 5) that absorb UV light are photolyzed into the same radicals as those engendered on heating. Other examples of light-induced homolyses are given in Scheme 100.

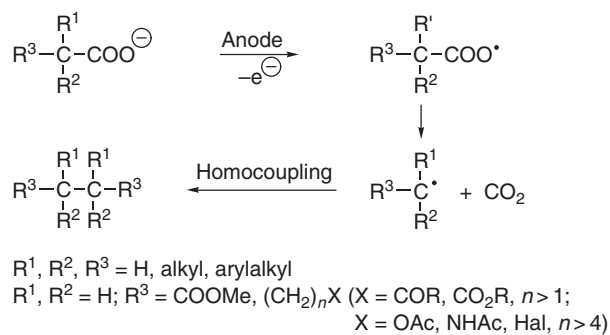
1.19.13.2.3 Electrochemical generation of radicals

The first important electrochemical reaction of C-C bond formation was discovered by Kolbe in 1849 when he electrolyzed carboxylates and obtained homocoupling of their alkyl groups <1849LA257, 1860LA125>. This reaction generates alkyl radicals by anodic decarboxylation (Scheme 101).

Heterocoupling (cross coupling) of two different carboxylates (mixed Kolbe electrolysis) is a method to prepare unsymmetrical compounds. However, as the intermediate radicals combine statistically, the mixed coupling product is always accompanied by two symmetrical products resulting from the homocoupling. If the less costly carboxylate is used in excess, the yield of the product of heterocoupling can be satisfactory and the method has been applied to prepare a large number of important fatty acids, pheromones, and other natural products of biological interest <1990TCC91>.



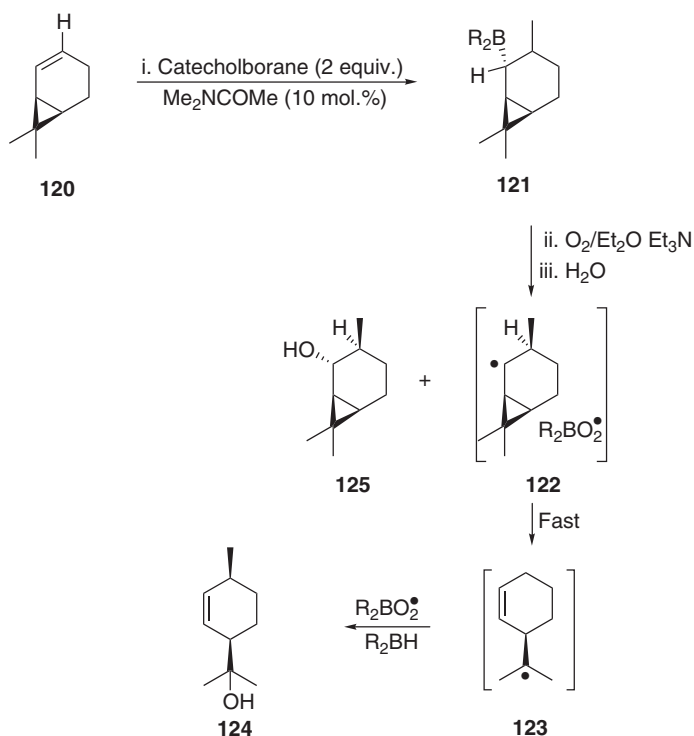
Scheme 100



Scheme 101

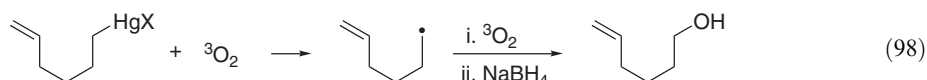
Radicals can be generated by cathodic reduction of carbocations, protonated C=X bonds, and by reduction of halides or onium salts (Schemes 102 and 103).

When (+)-2-carene **120** was hydroborated with catecholborane in the presence of 10% of Me₂NCOMe, the so-obtained B-alkylcatecholborane **121** reacted with O₂ (in the presence of Et₃N) giving a 2:1 mixture **124** and **125** (Scheme 104). The results can be interpreted in terms of parallel radical and polar paths in the oxidation step, the first path giving the product of cyclopropylalkyl → homoallyl radical rearrangement **122** → **123**, the second path giving the unrearranged alcohol **125** <2002JOC7193>.



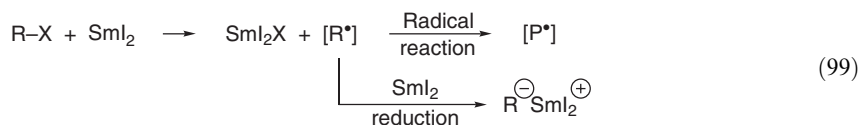
Scheme 104

The reaction of O₂ with organomercurial compounds can also generate alkyl radicals (Equation (98)).

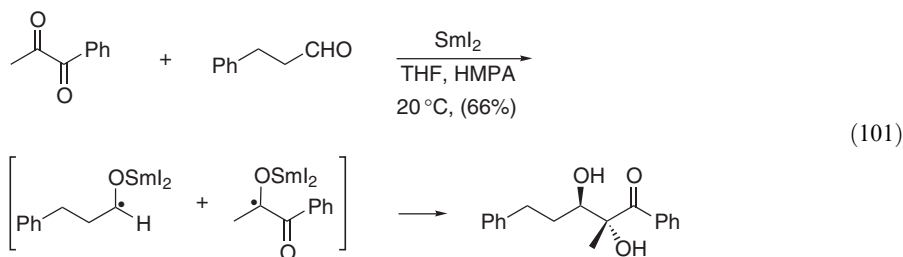
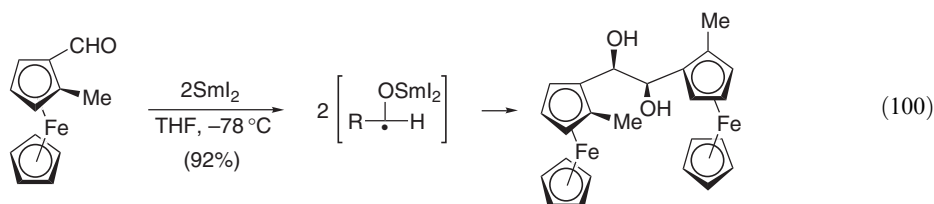


1.19.13.2.5 Single-electron chemical reductions

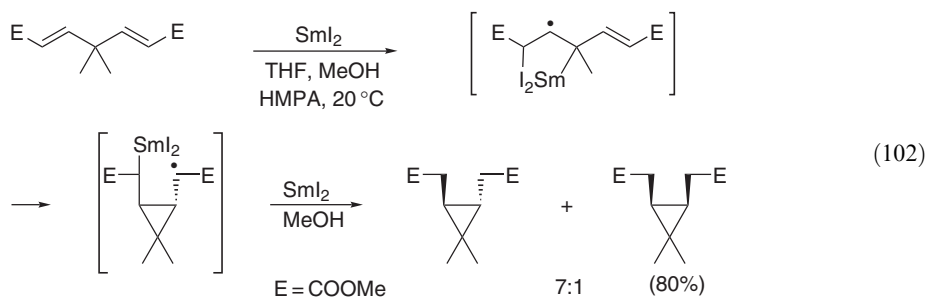
The seminal report on samarium(II) iodide by Kagan and co-workers <1980JA2693> outlined numerous applications for this remarkable reducing agent. The recognition that SmI₂ can complement other reducing agents such as Bu₃SnH, CrCl₂, Na/NH₃, and Zn(Hg) in the mediation of radical reactions has led to the development of very powerful synthetic methods <1996CRV307, B-2001MI153>. In a THF/HMPA mixture, the rate constant for the reduction of a primary alkyl radical is ca. 6·10⁶ M⁻¹ s⁻¹. This sets an inherent limit to the types of radical process that can be carried out in the presence of SmI₂ (Equation (99)). Bimolecular radical reactions are thus limited and the method will give better results for intramolecular radical reactions.



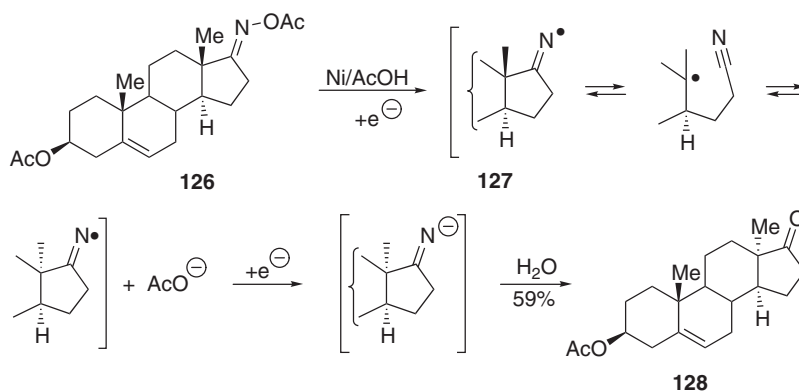
The pinacol coupling reaction, traditionally carried out with active metals such as sodium, magnesium, or aluminum, can also be accomplished with SmI_2 <1999MI565>. Diastereoselective pinacol homo- and heterocouplings have been realized as exemplified by Equations (100) <1999CC2051> and (101) <1993CL959, 1993CL2129>.



Conjugated, electron-deficient alkenes can be reductively coupled in the presence of SmI_2 , providing hydrodimerized products. Both intermolecular and intramolecular versions of the reaction have been established as exemplified for the latter case by Equation (102) <1991TL6557, 1999TL7499>.

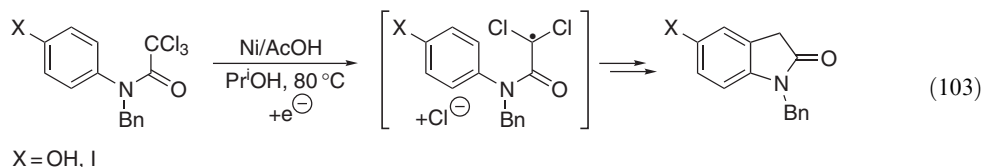


The use of nickel powder in combination with acetic acid has been introduced in 1992 by Zard and co-workers <1992TL7849, 1994TL5629> to cleave an oxime ester (e.g., **126**) into a carboxylate anion and an iminyl radical (e.g., **127**). The iminyl radical reacts as illustrated in Scheme 105 with the conversion of **126** into ketone **128**.

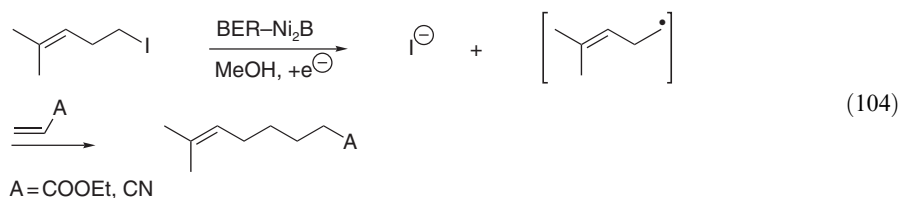


Scheme 105

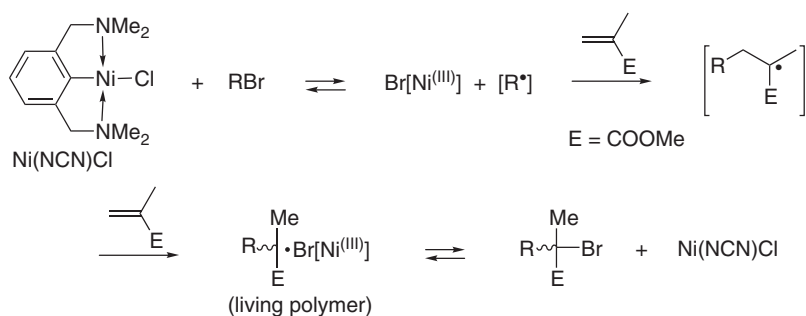
Nickel powder in AcOH and isopropanol is an efficient means to generate alkyl radicals from trichloroacetamides <1994TL9553, 1994TL1719, 1996TL1397>. A wide variety of functional groups are compatible with these reducing conditions as shown in Equation (103).



Nickel boride (Ni_2B) has been utilized as catalyst in many reactions. It is prepared by reducing nickel salts with NaBH_4 <1986CRV763, 1997OPP1>. When a catalytic amount of $\text{Ni}(\text{OAc})_2$ is reduced with borohydride exchange resin (BER) in methanol, BER is covered immediately with a black precipitate of nickel boride. The $\text{BER}-\text{Ni}_2\text{B}$ (cat.) has been used to catalyze the reduction of nitro, halogeno, and azido compounds <B-2001MI183>. It can be used also for the semi-hydrogenation of alkynes into alkenes <1996TL1057>. Secondary and tertiary alkyl bromides are reduced by $\text{BER}-\text{Ni}_2\text{B}/\text{MeOH}$ with rates comparable to those of primary bromides, suggesting that the reductions proceed via radical intermediates <1997JOC2357>. For instance (Equation (104)) the radical addition of alkyl iodides with α,β -unsaturated esters, nitriles, and ketones can be carried out with BER (3–5 equiv.)– Ni_2B (0.05–0.2 equiv.) in methanol. This system is a good alternative to tributyltin hydride for the coupling alkyl iodides with electro-deficient alkenes (Equation (104)).



The Kharasch addition of alkyl halides to alkenes can be catalyzed by the nickel complex $\text{Ni}(\text{NCN})\text{Cl}$ (0.01–10 mol.%) <1998MM6756, 1996MM8576> as illustrated in Scheme 106.

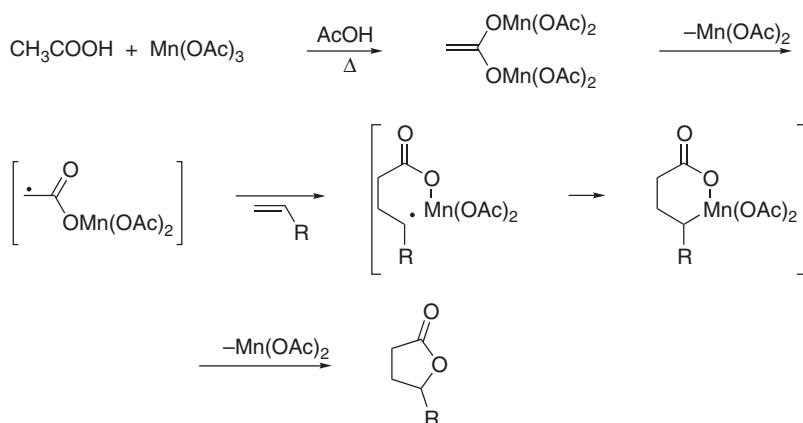


Scheme 106

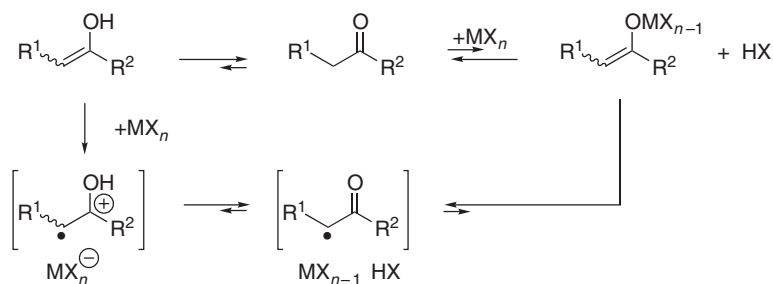
1.19.13.2.6 Single-electron chemical oxidations

The oxidative addition of acetic acid to alkenes to give γ -butyrolactones (Scheme 107) was first reported by Heiba and co-workers <1968JA5905> and Bush and Finkbeiner <1968JA5903> in 1968. This method which uses manganese triacetate as oxidant and generates free-radical intermediates has been applied intensively in organic synthesis <B-2001MI198>.

A wide variety of CH-acidic compounds (1,3-dicarbonyl compounds, nitroalkanes) may serve as precursors for the oxidative metal-mediated generation of radicals. Apart from $\text{Mn}(\text{OAc})_3$, cerium(IV) ammonium nitrate (CAN) serves as a convenient oxidant. Both oxidants have comparable oxidation potentials (CAN: +1.61 V, $\text{Mn}(\text{OAc})_3$: +1.54 V vs. NHE (normal hydrogen electrode)). CAN can be used at lower temperature than $\text{Mn}(\text{OAc})_3$ in MeOH/MeCN (Scheme 108) <1997CSR127, 1999SL834>. Oxidation of a mixture of diketene and 1,1-diarylethene with $\text{Mn}(\text{OAc})_3 \cdot \text{H}_2\text{O}$ gives the corresponding 5,5-diaryl-5-hydroxypentan-2-one <1996JOC8264>.

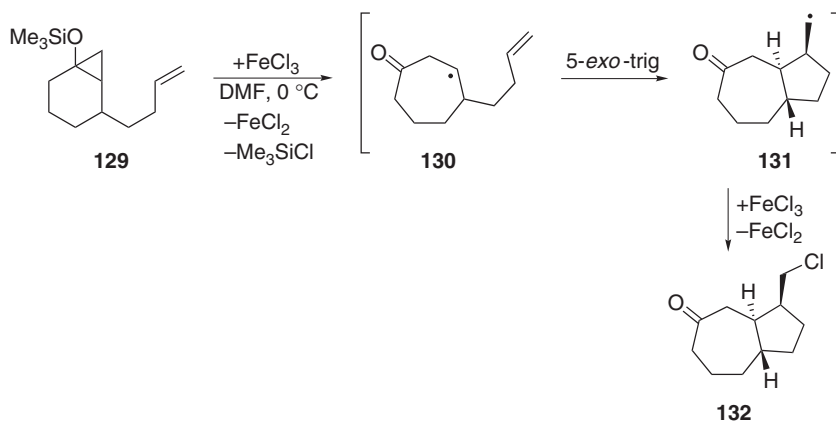


Scheme 107



Scheme 108

Like cerium(IV), iron(III) salts can oxidize electron-rich centers by single-electron transfer to form radicals [<1980JOC749, 1985TL5923, 1998CC209>](#). An example is shown in [Scheme 107](#). Single-electron oxidation and ring opening of cyclopropyl silyl enol ether **129** by FeCl_3 affords radical **130** as intermediate. The latter undergoes *5-exo-trig* cyclization into radical **131** that is trapped by FeCl_3 to provide chloride **132** [<1995JCS\(P1\)2315, 1997PAC601>](#) ([Scheme 109](#)).

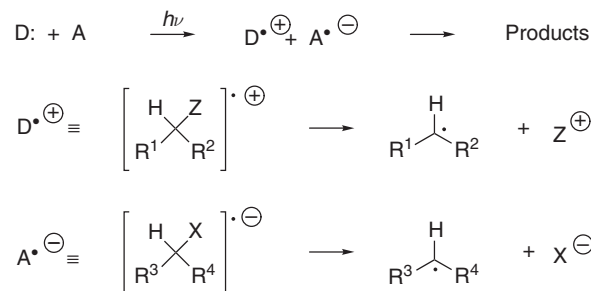


Scheme 109

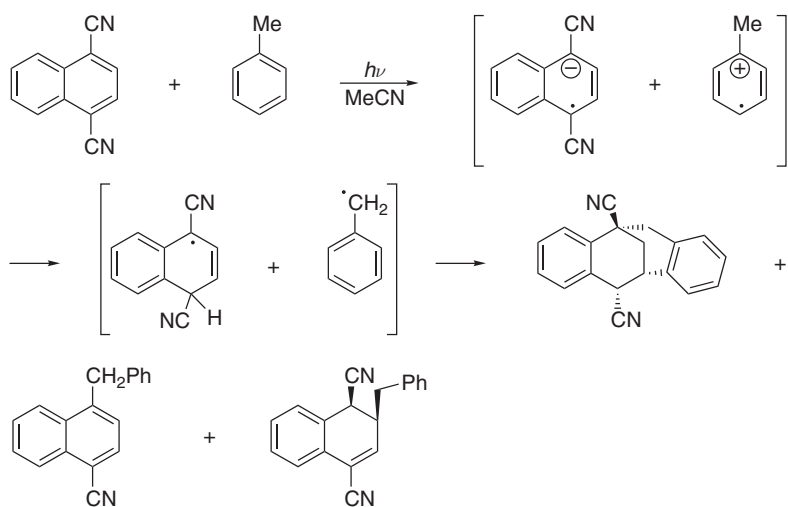
Copper(II), cobalt(III), silver(I), and vanadium(V) salts have also been applied to generate radicals by one-electron oxidations [<1994CRV519, 1995T7579, 1998T3321>](#).

1.19.13.2.7 Photoinduced electron transfer for the generation of radicals

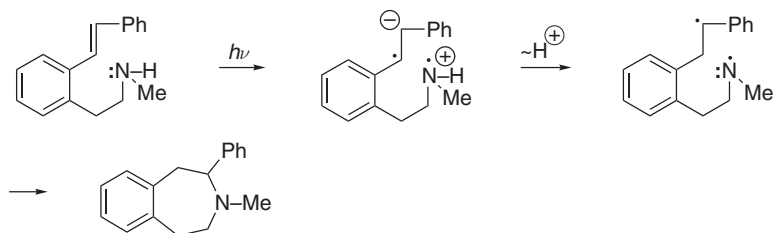
The photoinduced electron transfer (PET) process involves a donor D and an acceptor A. Upon light absorption of either A, D, or a complex $A \leftarrow D$, radical-ions $D^{\bullet+}$ and $A^{\bullet-}$ may form [<1970IL259, 1983CRV425>](#). Both radical ions may generate radicals as shown in [Scheme 110](#). Examples of reactions are given in [Schemes 111–114](#) [<B-2001MI229>](#).



Scheme 110



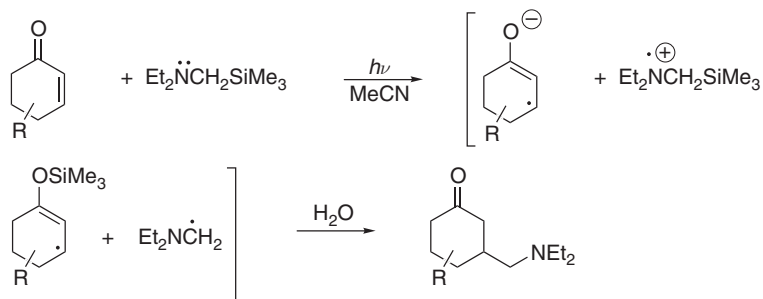
Scheme 111



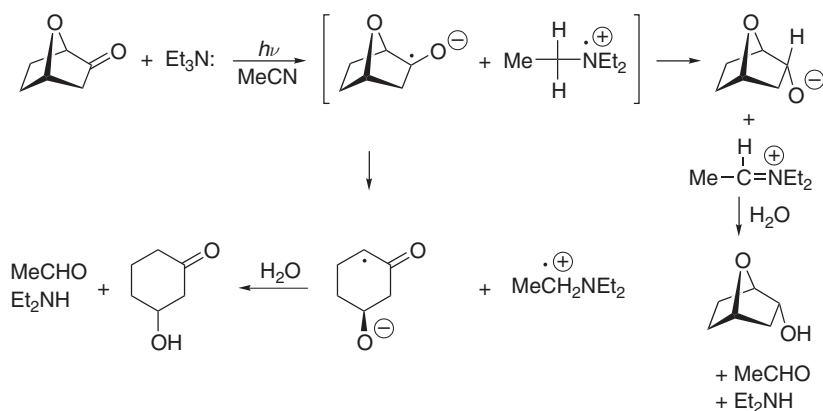
Scheme 112

1.19.13.2.8 The radical-polar crossover reaction

An easily oxidized sulfide can undergo single-electron transfer (SET) to an appropriate electrophile, generating a radical-cation/radical-anion pair. Fragmentation of the radical-anion may afford an organic radical R^{\bullet} that can directly recombine with the radical-cation or undergo further reaction before recombining with the radical-cation to afford a sulfonium salt. The latter

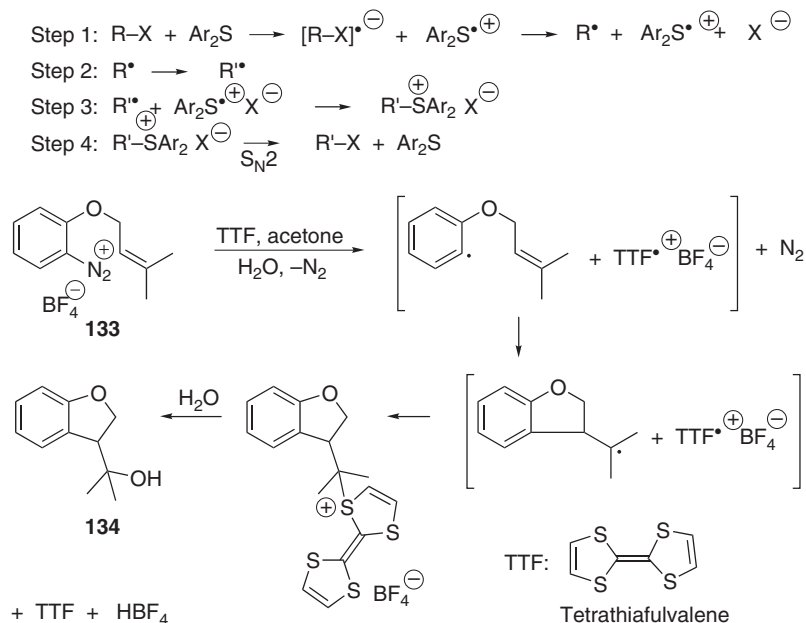


Scheme 113



Scheme 114

undergoes the usual polar reactions such as elimination and substitution, liberating the initial sulfide and a new molecule (Scheme 115). The term “radical-polar crossover” arises since the scheme involves a transition from radical to polar chemistry. An example is given for the



Scheme 115

diazonium salt **133** that is converted into the rearranged alcohol **134** in acetone/water in the presence of a catalytic amount of tetrathiafulvene (TTF) <1993CC295, B-1999MI123>.

1.19.13.3 Reactions of Radicals

Radicals react by atom or molecular group transfer, generating other radicals (bimolecular homolytic substitutions S_H2). They can add to unsaturated compounds generating other radicals. They can also rearrange or fragment without undergoing the above reactions. Two radicals can react giving a stable compound (termination of chain processes); they can also be reduced into anionic species, or oxidized into cationic species by single-electron transfer, on dismutate (transfer of an atom or a molecular group from one radical to another).

1.19.13.3.1 Rate constants for abstractions

A considerable range of alkyl and aryl iodides, bromides, and to a lesser extent chlorides react in bimolecular homolytic substitution (S_H2) reactions with tin-centered radicals to form carbon-centered radicals (Equation (105)).



The rate of reactions (Equation (105)) depends, as predicted by the Bell–Evans–Polanyi theory, on the exothermicity of the reactions and on the polarizability of the reactants. In general, the weaker the C—X bonds the faster are the reactions. In the case of alkyl halides, iodides react faster than bromides and chlorides, as illustrated with the kinetic data summarized in Table 6 <2002JCS(P2)367>.

Table 6 Absolute rate constants (k in $\text{dm}^3 \text{mol}^{-1} \text{s}^{-1}$) for reactions of organohalides with Bu_3Sn^\bullet , Bu_3Ge^\bullet , Et_3Si^\bullet , and $(Me_3Si)_3Si^\bullet$ radicals^a

	Bu_3Sn^\bullet	Bu_3Ge^\bullet	Et_3Si^\bullet	$(Me_3Si)_3Si^\bullet$
Me—I	4.3×10^9			
Bn—Br	1.5×10^9	8.0×10^8	2.4×10^9	9.6×10^8
Bu ^t —Br	1.5×10^8	8.6×10^7	1.1×10^9	1.2×10^8
EtOOCCH ₂ —SePh	1.0×10^8			
<i>n</i> -Pent—Br	2.6×10^7			
EtOOCCH ₂ —Cl	1.0×10^6			
Bn—Cl	1.1×10^6	1.9×10^6	2.0×10^7	4.6×10^6
EtOOCCH ₂ —SPh	2.0×10^5			
Bu ^t —Cl	2.7×10^4			

^a Taken from <2002JCS(P2)367>.

The rate constants are usually greater than $10^9 \text{dm}^3 \text{mol}^{-1} \text{s}^{-1}$ for alkyl iodides, around 10^7 – $10^8 \text{dm}^3 \text{mol}^{-1} \text{s}^{-1}$ for alkyl bromides, and around $10^5 \text{dm}^3 \text{mol}^{-1} \text{s}^{-1}$ for alkyl chlorides, while alkyl fluorides do not react. The more stable the carbon-centered radical formed, the faster is the reaction. Thus the following reactivity sequence can be obtained: benzyl \approx allyl $>$ alkyl $>$ aryl \approx vinyl (Dimroth principle). Sulfides and selenides undergo similar S_H2 reactions and the order of reactivity toward tin radicals is typically as follows: $R-I > R-Br > R-SePh \approx R-OC(\equiv S)SMe$ (xanthates) $> R-Cl > R-SPh$ <1984JA343, 1986AJC1151>.

Similar reactions are observed for related germanium- and silicon-centered radicals (Table 6). The tris(trimethylsilyl)silyl radical is 4–10 times less reactive than Et_3Si^\bullet (steric effect). For hydrogen atom abstractions, the rate constants given in Figure 5 can be retained for the reactions of primary alkyl radicals. As expected from the Bell–Evans–Polanyi theory (or the Dimroth principle <1936TFS1340, 1938TFS11, 1936PRS414, 1933AG571, 1969JA7224, 1996JA12878>), the less exothermic reaction (which implies the hydrogen donor with the strongest $R'-H$ bond (Et_3SiH)) is the slowest.

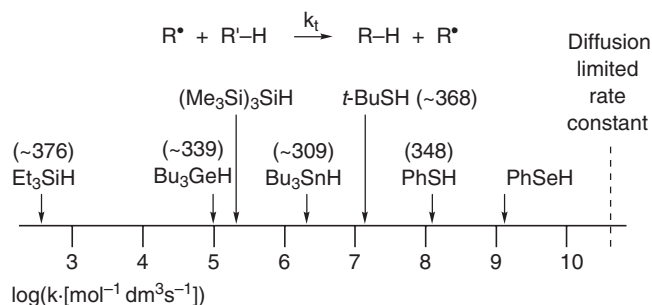


Figure 5 Rate constants for the bimolecular S_H2 hydrogen atom abstractions from hydrogen donor $R'-H$ by a primary alkyl radical R^\bullet (standard homolytic dissociation enthalpy: $DH^\circ(R^\bullet/H^\bullet) = \Delta H^\circ_r(RH \rightleftharpoons R^\bullet + H^\bullet)$) values are given in kJ mol^{-1} in parenthesis).

The pentacarbonylmanganese radical, $^\bullet\text{Mn}(\text{CO})_5$, undergoes hydrogen- or halogen-atom abstraction reactions, the driving force being the formation of the stronger $\text{H}-\text{Mn}$ ($DH^\circ(\text{H}^\bullet/^\bullet\text{Mn}(\text{CO})_5) \cong 272 \text{ kJ mol}^{-1}$) and halide- Mn bond ($DH^\circ(\text{Cl}^\bullet/^\bullet\text{Mn}(\text{CO})_5) \cong 293 \text{ kJ mol}^{-1}$; $DH^\circ(\text{Br}^\bullet/^\bullet\text{Mn}(\text{CO})_5) = 243 \text{ kJ mol}^{-1}$) compared with the $\text{Mn}-\text{Mn}$ bond in decacarbonyldimanganese ($DH^\circ((\text{CO})_5\text{Mn}^\bullet/^\bullet\text{Mn}(\text{CO})_5) = 159 \pm 20 \text{ kJ mol}^{-1}$). Alkyl bromides react more rapidly than alkyl chlorides. The former have lower bond dissociation enthalpies than the latter (e.g., $DH^\circ(\text{Et}^\bullet/\text{Br}) = 283 \text{ kJ mol}^{-1}$ vs. $DH^\circ(\text{Et}^\bullet/\text{Cl}) = 338 \text{ kJ mol}^{-1}$), which does not compensate for the difference in bond energy of $\text{Mn}-\text{Cl}$ vs. $\text{Mn}-\text{Br}$.

The higher reactivity of alkyl bromides compared with alkyl chlorides results from the higher electron affinity of the former compared with the latter <1983JA4359>, which makes the charge-transfer configurations $\text{R}-\text{Br}^{\bullet-} + \text{Mn}(\text{CO})_5^+$ relatively more stable than configurations $\text{RCl}^{\bullet-} + \text{Mn}(\text{CO})_5^+$. It is the greater polarizability of the bromides that makes them react faster than the corresponding chlorides toward the $^\bullet\text{Mn}(\text{CO})_5$ radical.

For the S_H2 reactions of various radicals with benzyl bromides, the absolute rate constants are shown in Figure 6 <1997JOM545, 1996JA7367, 1991JPO485, 1997T8479, 1992PAC1473, 1988JA281>.

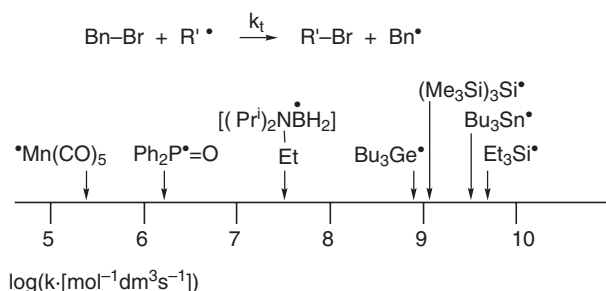


Figure 6 Rate constants for the bimolecular reactions $\text{Bn}-\text{Br} + \text{R}'^\bullet \rightarrow \text{R}'-\text{Br} + \text{Bn}^\bullet$.

1.19.13.3.2 Intermolecular addition reactions of radicals

Radicals (carbon-centered, metal-centered, oxygen-centered, and nitrogen-centered) can add to multiple-bonded systems such as alkenes, alkynes, carbon monoxide, ketones, aldehydes, imines, oximes, nitriles, isonitriles, azides, $^\bullet\text{N}=\text{O}$, O_2 , SO_2 , etc.... As predicted by the Bell-Evans-Polanyi theory (Figure 7), the rates of the additions depend on steric factors, on the exothermicity of the reactions (ΔH_r) and on the polarizability of the reactants as demonstrated for the additions (Equation (106)) of benzyl radical to alkenes ($\text{X} = \text{H}, \text{Me}, \text{Cl}, \text{Ph}$; $\text{Y} = \text{Cl}, \text{OAc}, \text{SiMe}_3, \text{C}_5\text{H}_{11}, \text{OR}, \text{OCOR}, \text{CHO}, \text{SO}_2\text{Ph}, \text{CN}, \text{COOMe}, \text{Ph}, \text{Bu}^t, \text{Si}(\text{OEt})_3, \text{pyridin-2-yl}$) for which Equations (107) and (108) hold.

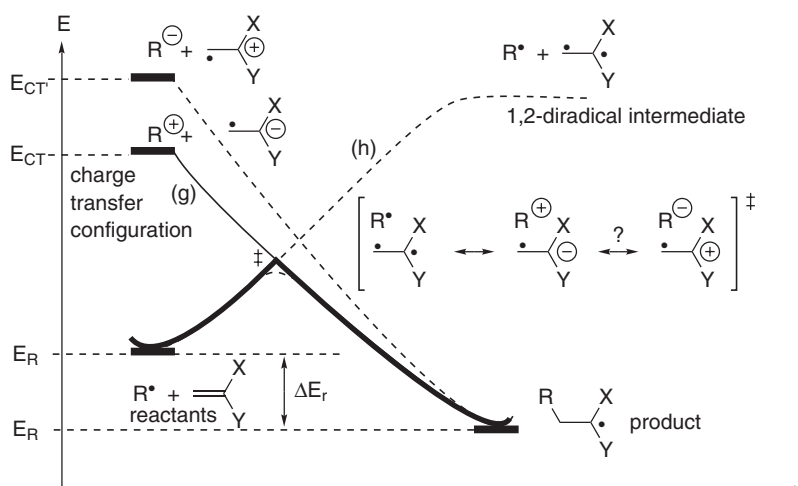
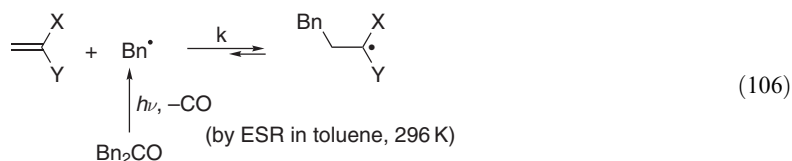


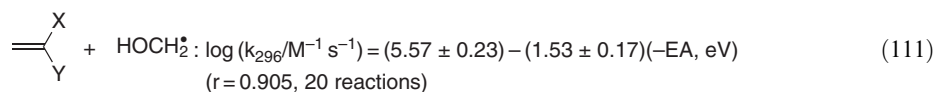
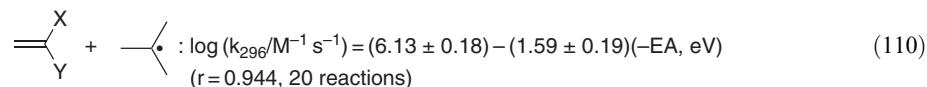
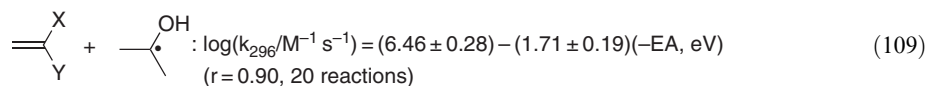
Figure 7 Bell-Evans-Polanyi diagram for the addition of radical R^\bullet to alkenes. The transition state of this process implies an electron transfer from the radical to the alkene. An hypothetical, nonconcerted mechanism (h) implies the rotation about the $\pi(\text{C}=\text{C})$ bond of the alkene to generate a 1,2-diradical. This process requires a high-energy barrier. It does not occur because the reactants give a charge-transfer configuration (g) that crosses the π bond dissociation potential energy hypersurface before it reaches the 1,2-diradical intermediate.



$$\log(k_{296}/\text{M}^{-1}\text{s}^{-1}) = (2.07 \pm 0.40) - (0.037 \pm 0.004) \cdot H_r^\circ (\text{kJ mol}^{-1}) \quad (r = 0.894) \quad (107)$$

$$\log(k_{296}/\text{M}^{-1}\text{s}^{-1}) = (3.26 \pm 0.15) - (1.03 \pm 0.13)(-\text{EA}(\text{alkene}), \text{eV}) \quad (r = 0.886) \quad (108)$$

For the additions of 2-hydroxyprop-2-yl, *t*-butyl, and hydroxymethyl radicals to the same alkenes, the linear relationships of Equations (109), (110), and (111) have been found <1995HCA910, 2001AG(E)1340>.



A qualitative description of the polarizability effect (ability for the reactants to exchange electrons) on the rates of radical additions to π -systems (alkenes, alkynes, imines, carbonyl derivatives, etc.) can be given by the FMO (frontier molecular orbital) theory. In this theory (Figure 8), the better the stabilization arising from the overlap of the SOMO (single-occupied molecular orbital) of the radical with the LUMO (lowest-unoccupied molecular orbital) and with the HOMO (highest-occupied molecular orbital) of the π -system, the lower the activation enthalpy of the reaction. One can distinguish several situations, for instance that of an alkyl radical (e.g., Me^\bullet , Et^\bullet), which has a relatively high-lying SOMO (α_{C} in the Hückel MO theory) adding to electron-poor π -systems such as acrylic esters, acrylonitrile, imines, or ketones that are characterized by relatively low-lying LUMOs. Thus, the larger the overlap between these orbitals

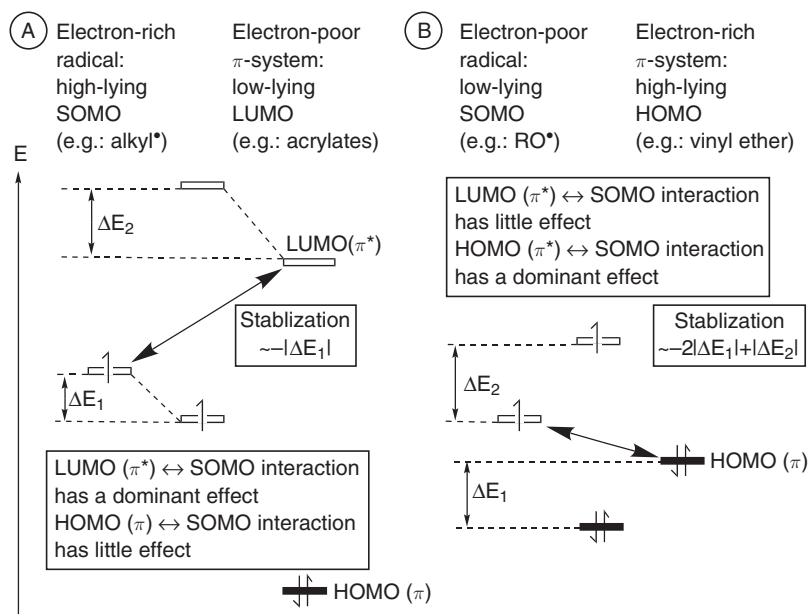
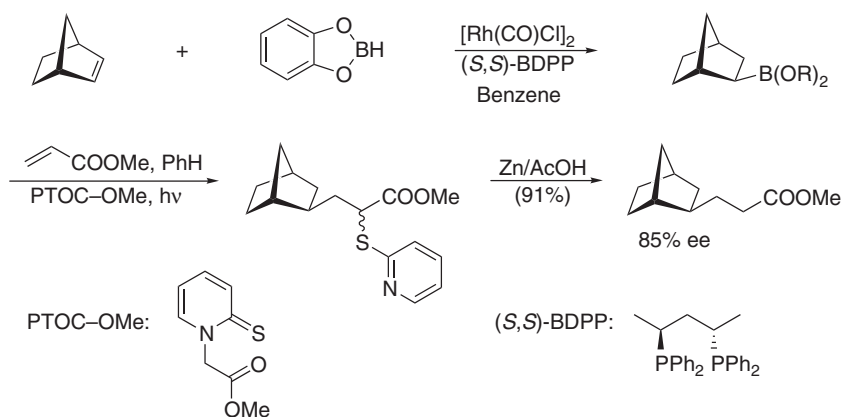


Figure 8 FMO theory applied to the transition state of the radical additions to π -systems: (A) electron-rich radical adding to an electron-poor π -system; (B) electron-poor radical adding to an electron-rich π -system. The relative importance of the orbital overlap diminishes as the energy difference between these orbitals increases.

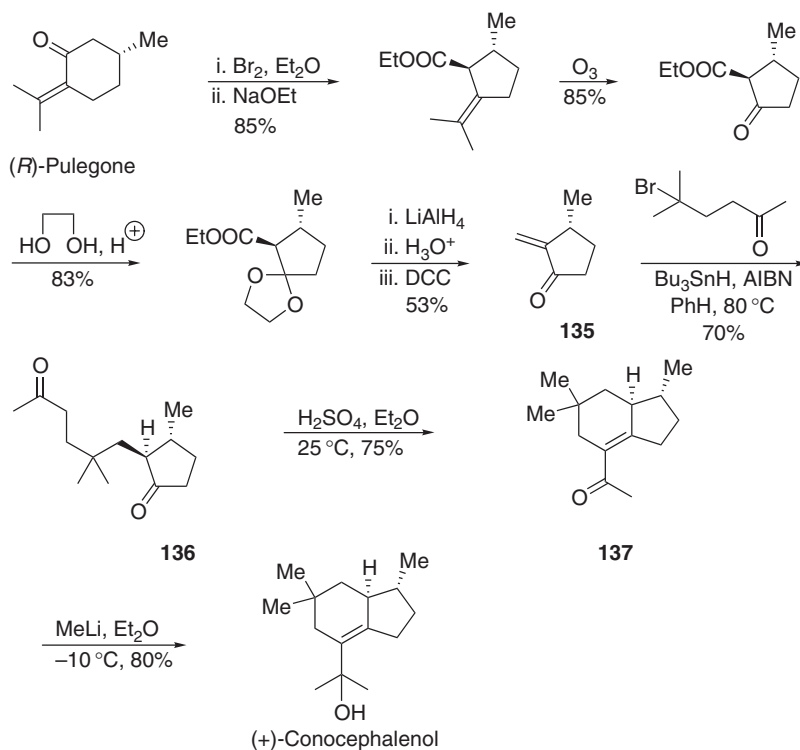
and the smaller the energy gap between these orbitals (SOMO \leftrightarrow LUMO (π^*)) the better the stabilization and thus the faster will be the reaction. Alternatively, an electron-poor radical such as an oxygen-centered radical ($\alpha_o = \alpha_c + \beta$ in the Hückel theory) or an α -ketoalkyl radical, which has a relatively low-lying SOMO will prefer to add to electron-rich π -systems such as vinyl ethers, conjugated π -systems, vinyl sulfides, etc. as they are characterized by relatively high-lying HOMOs, making the SOMO \leftrightarrow HOMO interaction to dominate and to stabilize the transition states of their additions. This qualitative theory treats the polarizability contribution of the reaction, not the enthalpic term (ΔH_r , Dimroth principle).

B-Alkylcatecholboranes prepared by Rh(I)-catalyzed hydroboration of alkenes are suitable radical precursors for conjugate addition to activate alkenes. This procedure is particularly useful to control the enantioselective hydroboration that can be coupled with the radical-chain reaction in a one-pot operation (Scheme 116) <2003JOC5769>.



Scheme 116

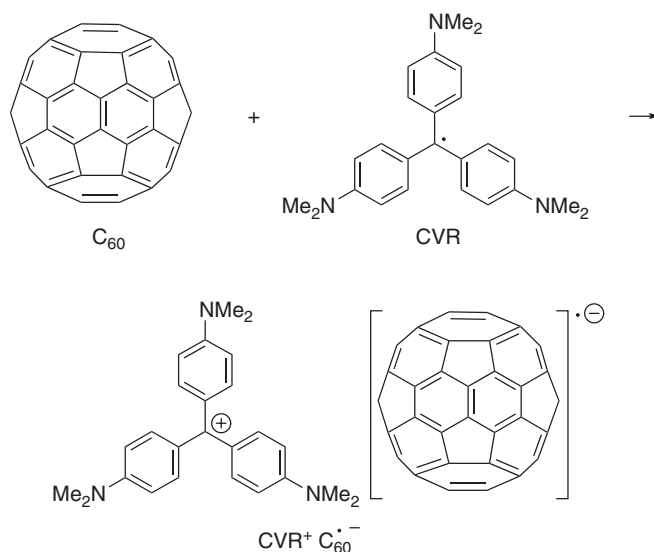
Radical additions of enantiomerically pure B-alkylcatecholborane to α,β -unsaturated ketones, aldehydes <1999CEJ1468>, esters, and carbonitriles <2000CC1017> have also been reported. (+)-Conocephalenol has been derived from (*R*)-pulegone (Scheme 117). The key steps **135** \rightarrow **136**



Scheme 117

is an addition of a tertiary radical to enone **135** (Scheme 117) and an intramolecular aldol cyclization **136** \rightarrow **137** under acidic conditions <1999T11289>.

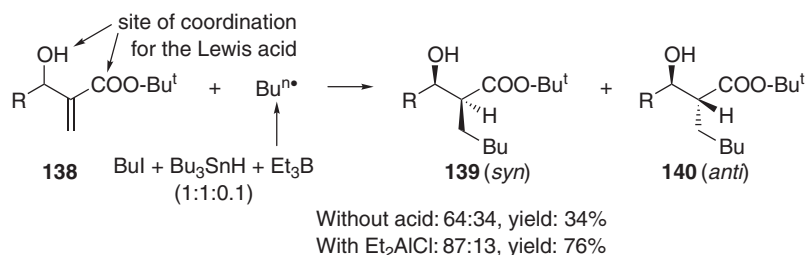
The addition of reactive carbon-centered radicals to buckminsterfullerene (C_{60}) produces R-C_{60}^\bullet as well as multiple-addition fullerenyl radicals <1998ACR63>. The high affinity of C_{60} toward radicals has been demonstrated by its ability to absorb up to 34 methyl radicals, 15 benzyl radicals <1991SCI1183>, 11 phenyl radicals <1991JA6274>, and 16 perfluoroethyl radicals <1993SCI404>. Another possibility in the reaction of an alkyl radical with C_{60} is electron transfer from the radical to C_{60} . This has been observed with Crystal Violet radical (CVR), which reduces C_{60} with the formation of $\text{CVR}^+\text{C}_{60}^{\bullet-}$ as a solid (Scheme 118) <1999CC1529>.



Scheme 118

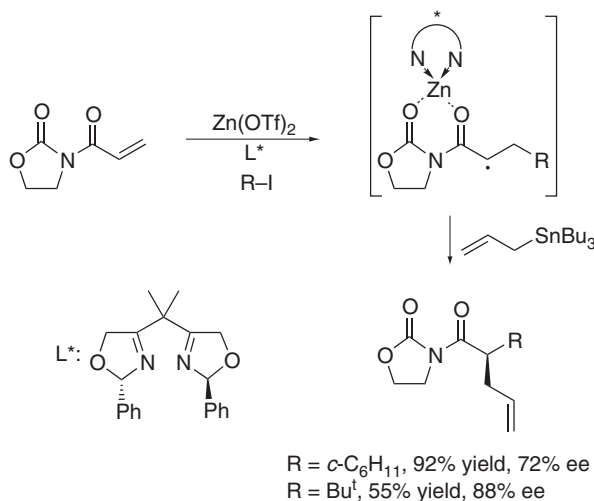
1.19.13.3 Enhancement of alkene electron affinity by coordination with a Lewis acid

Acrylate derivatives can be complexed by protic and Lewis acids on their carboxylic moieties. This enhances the electron affinity ($-EA$) of the alkene, thus accelerating its reaction with a radical R^\bullet . This principle has been applied by Sato and co-workers [<1995JOC3576>](#) to improve the yield and the *syn/anti*-diastereoselectivity (product ratio **139:140**) of the addition of *n*-butyl radical to α -substituted acrylic esters **138** (Scheme 119).



Scheme 119

The use of achiral auxiliaries as templates for chiral, nonracemic promoters is a valuable strategy for asymmetric synthesis. Porter and co-workers have applied this approach to effect relative and absolute stereocontrol in radical reactions as shown in [Scheme 120](#) [<1995TL8183, 1995JA11029>](#).

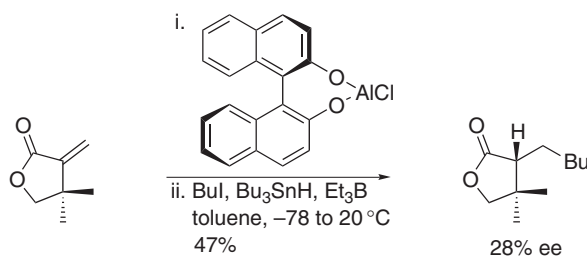


Scheme 120

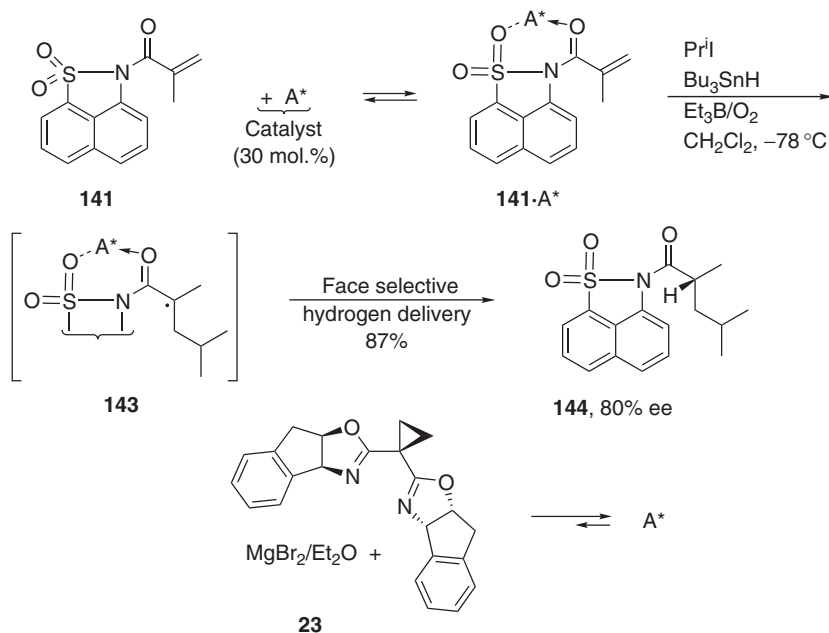
Hoshino and co-workers [<1995CC481>](#) have used enantioselective halide reduction using a magnesium-based system with good yields and promising ee values. The use of a chiral, non-racemic aluminum-based Lewis acid to effect a similar asymmetric hydrogen atom transfer to an enolate radical (Scheme 121) has also been reported by Sato and co-workers [<1995JOC3576>](#).

Using a naphthosultam template **141** and a homochiral Lewis acid derived from MgBr_2 and bisoxazoline **142**, the addition of isopropyl radical generates a radical adduct **143** that abstracts an atom of hydrogen from tributylstannane with high facial selectivity (stereoselectivity), producing **144** with 87% yield and 80% enantiomeric excess. It is an elegant example of an enantioselective hydrocarbonation reaction (Scheme 122), the enantioselectivity of it being induced by a catalytic amount of ligand **142** [<2002JA948>](#).

An enantioselective conjugate radical addition to β -acyloxy acrylates has been reported by Sibi and co-workers [<2003AG\(E\)4521>](#). Nucleophilic radicals generated from alkyl halides add to β -acyloxy acrylates **143** ($R^1 = \text{Me, Ph, 4-FC}_6\text{H}_4, 4\text{-MeOC}_6\text{H}_4, 2,6\text{-Me}_2\text{C}_6\text{H}_3, 1\text{-naphthyl, 2-naphthyl}$) in the presence of a chiral Lewis acid (derived from MgI_2 and ligand **144**) to afford acetate aldol products **145** in high yield and enantiomeric purity (Scheme 123) (see also



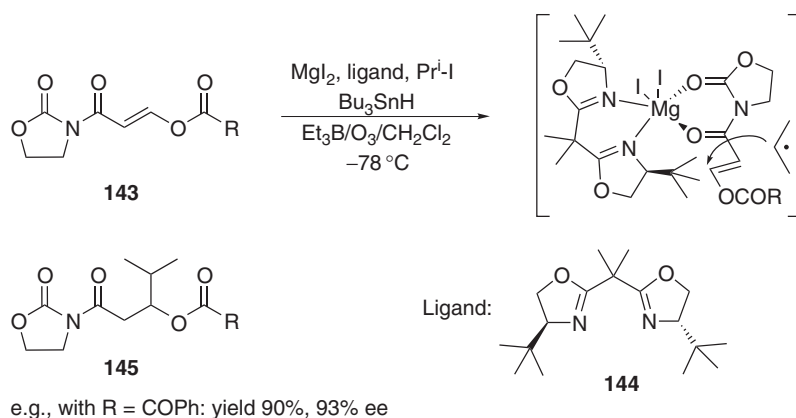
Scheme 121



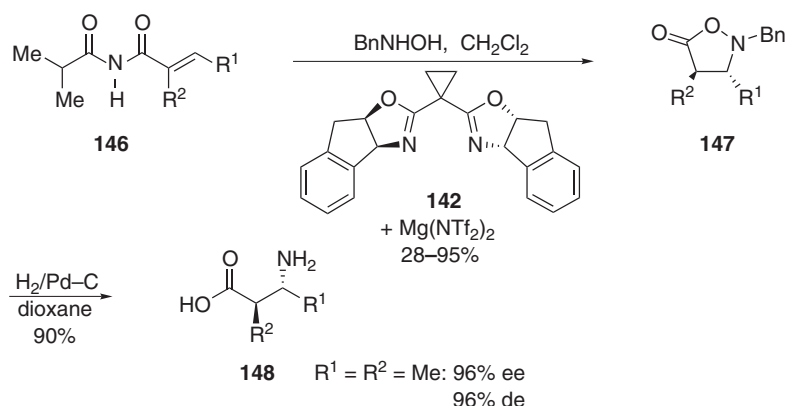
Scheme 122

<2003TA2879>, for reviews on enantioselective radical processes, see <2003CRV3263, 2003CEJ28, 2003CSR251>.

Enantioselective synthesis of α,β -disubstituted- β -amino acid **148** (R^1 = Me, Et, Prⁿ, Prⁱ, *n*-hept, Ph; R^2 = Me, Et, Br, Ph) have been realized by this approach as illustrated in Scheme 124 <2003JA11796>.



Scheme 123

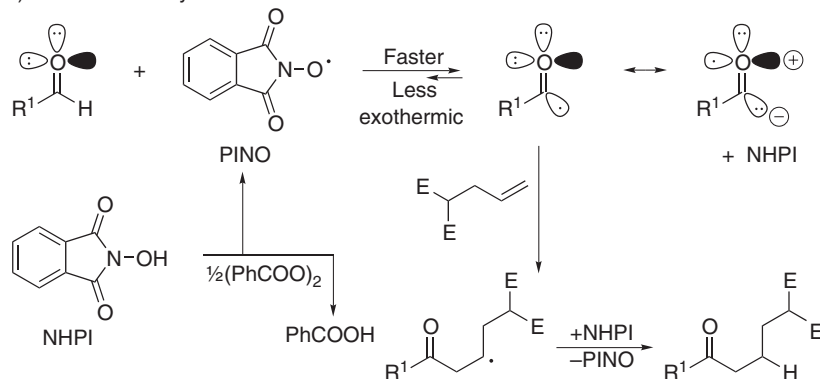


Scheme 124

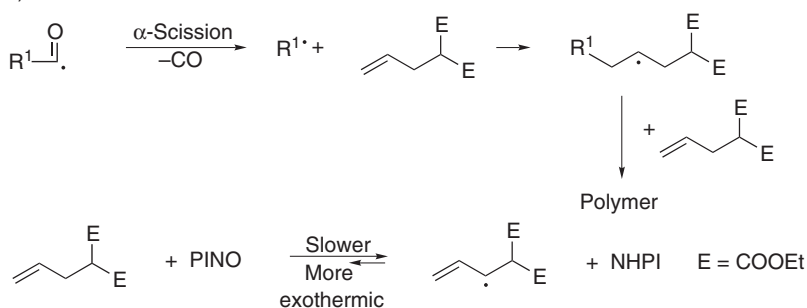
1.19.13.3.4 Abstraction of hydrogen from aldehydes: the hydroacylation of alkenes

The hydroacylation of alkenes with aldehydes via a radical-chain process involves the following sequence: (1) hydrogen abstraction from the aldehyde ($\text{RCHO} \rightarrow \text{RCO}^\bullet + \text{H}^\bullet$), (2) addition of the acyl radical (RCO^\bullet) to the alkene leading to a β -oxocarbon radical, and (3) abstraction of the aldehydic hydrogen atom from another aldehyde by the β -oxocarbon radical intermediate. As the bond dissociation enthalpies $\text{DH}^\circ(\text{MeCO}^\bullet/\text{H}^\bullet) = 361 \text{ kJ mol}^{-1}$ is higher than that forming a secondary allyl radical from the reacting alkene ($\text{DH}^\circ(\text{MeC}^\bullet\text{HCH} = \text{CH}_2/\text{H}^\bullet) = 351 \text{ kJ mol}^{-1}$), for the radical initiator to select the aldehyde rather than the alkene to generate the initial RCO^\bullet radical must be due to a favorable polarity factor. As the acyl radical is electron-rich because of the nonbonding electrons of the carbonyl oxygen center, an electron-poor radical initiator should be used preferentially. This is realized by phthalimide *N*-oxyl radical (PINO) generated by oxidation of *N*-hydroxyphthalimide (NHPI) with dibenzoyl peroxide (BPO) as shown in Scheme 125 <2001CC2352>.

a) Formation of acyl radicals and their additions to an alkene



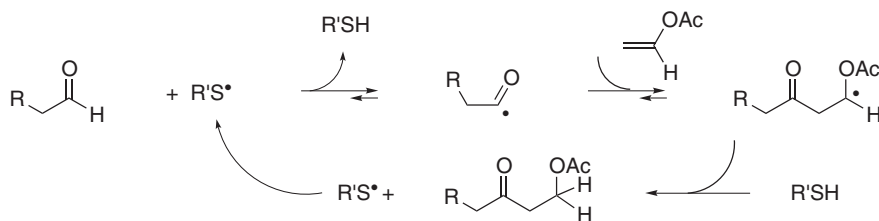
b) Concurrent reactions



Scheme 125

As fragmentation $\text{EtCO}^\bullet \rightarrow \text{Et}^\bullet + \text{CO}$ is exothermic by $-35.1 \text{ kJ mol}^{-1}$ ($\Delta H_f^\circ(\text{EtCO}^\bullet) = +4.2$, $\Delta H_f^\circ(\text{Et}^\bullet) = 117$, $\Delta H_f^\circ(\text{CO}) = -110.5 \text{ kJ mol}^{-1}$), acyl radical addition to the alkene must be faster than this fragmentation. A high concentration is required to limit the formation of secondary products resulting from the addition of radical $\text{R}^{1\bullet}$ to the alkene.

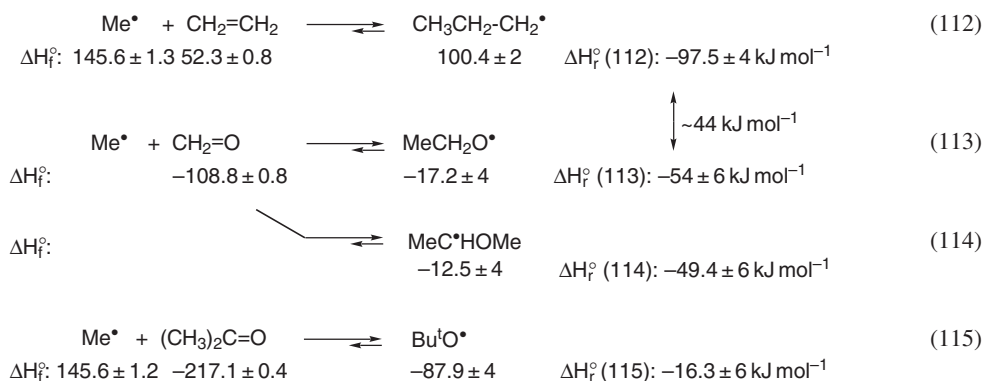
Dang and Roberts have described a radical version of the aldol reaction <1996CC2201>. Thiols can be used as catalysts to abstract the acyl hydrogen efficiently and thence to act as hydrogen atom donors to the adduct radical as shown in Scheme 126.



Scheme 126

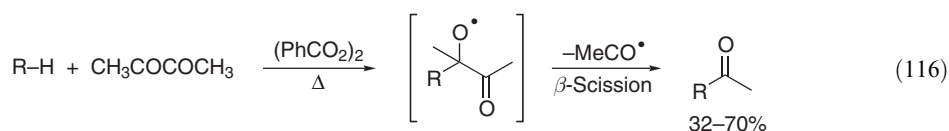
1.19.13.3.5 Intermolecular radical additions to hetero double bonds

The additions of alkyl radicals to alkenes are much more exothermic than to aldehydes and ketones. For instance (Equation (112)), $\Delta H_r^\circ = -97.5 \pm 4 \text{ kJ mol}^{-1}$ has been calculated for the addition of methyl radical to ethylene whereas $\Delta H_r^\circ = -54 \pm 6 \text{ kJ mol}^{-1}$ is estimated for the addition of a methyl radical to formaldehyde giving an ethoxy radical (Equation (113)). The addition (Equation (114)) giving methoxymethyl radical is slightly less exothermic as $\Delta H_r^\circ = -49.4 \pm 6 \text{ kJ mol}^{-1}$. Because of the negative entropies of condensation, radical additions to carbonyl compounds will have to be carried out at relatively low temperature if a suitable concentration of the corresponding adduct is to be formed. Otherwise, a fast-reacting partner for the radical intermediate has to be present in the solution, which gives a more stable adduct. Using more stable alkyl radicals than Me^\bullet and ketones their additions will be even less exothermic (see e.g., Equation (115)) (Scheme 127).

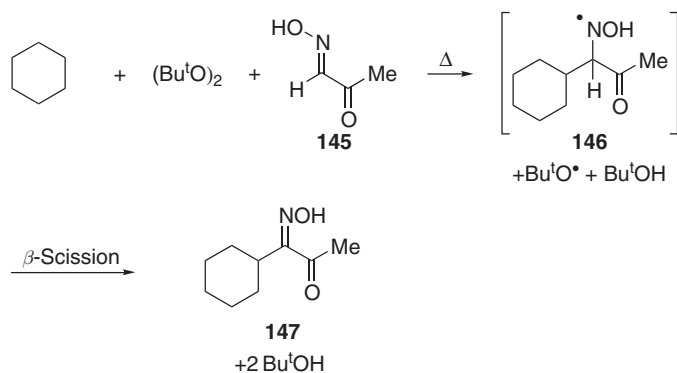


Scheme 127

These thermodynamic data demonstrate that only highly unstable carbonyl functions will add to alkyl radicals in intermolecular reactions. Kharasch and Brown reported the successful acylation of primary alkyl radicals using phosgene as a radical trap <1942JA329, 1942JA333>. The addition of an alkyl radical to biacetyl gives the corresponding methylketone and acetyl radical (Equation (116)) <1968JA3588>.

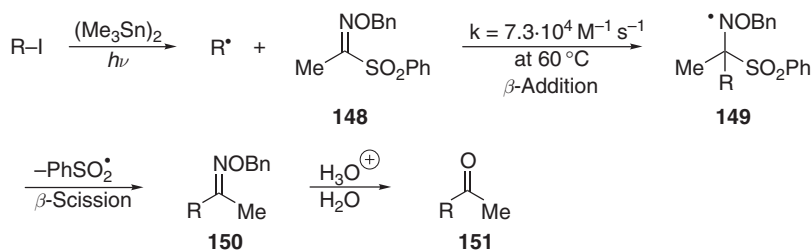


The intermolecular reaction of an aldoxime as a radical trap was first reported by Citterio in 1986 <1986S473>. The thermal decomposition of di-*t*-butyl peroxide generates Bu^tO• radical that abstracts a hydrogen atom from cyclohexane giving a cyclohexyl radical that add to the C=N double bond of aldoxime **145**, forming a nitrogen-centered radical **146** that is oxidized by Bu^tO• furnishing the corresponding ketoxime **147** (Scheme 128).



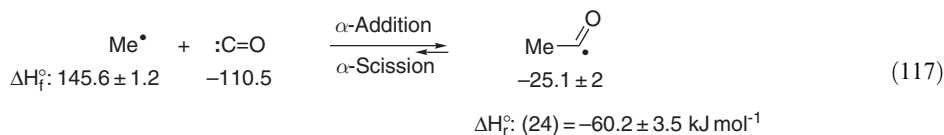
Scheme 128

Another example is the radical acylation reaction shown in Scheme 129, which involves the addition of alkyl radicals to the C=N bond of a sulfonyl oxime ether **148** giving a radical **149** that undergoes irreversible β-scission with exclusion of the phenylsulfonyl radical. Hydrolysis of the *O*-benzyloximes **150** so obtained furnishes the corresponding ketones **151** <1996JA5138, 1998TL1587, 1997JA5982>.

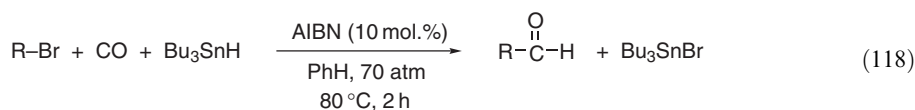


Scheme 129

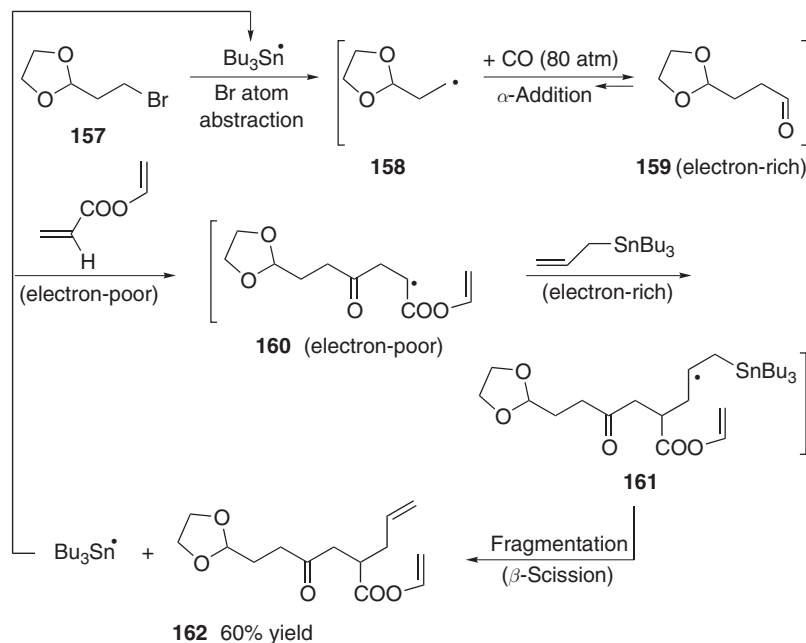
In 1939, Faltings observed the formation of acetone when a mixture of ethane and carbon monoxide was irradiated with UV light <1939CB1207>. The results imply the formation of alkyl radicals adding to CO. The heat of addition of methyl radical to CO giving the acetyl radical (Equation (117)) amounts to ΔH_r[°] = -60.2 ± 12 kJ mol⁻¹. The exothermicity of this addition is lower with other alkyl radicals <1999CRV1991>.



In 1990 Ryu and co-workers (Equation (118)) reported the first efficient trapping of alkyl radicals by CO leading to the synthesis of aldehydes, where alkyl bromides were used as substrates and tributyltin hydride as mediator for trapping the acyl radicals <1990JA1295>.



The intermediate acyl radicals can be trapped by agents other than Bu_3SnH . As acyl radicals are electron-rich radicals due to the conjugation of the unshared electron of the radical with the $n(\text{CO})$ electron pair of the carbonyl group, they react more rapidly with electron-poor alkenes (Figure 7) than with electron-rich alkenes. For instance, in the presence of vinylacrylate and allyl(tributyl)stannane the intermediate acyl radical **159** (resulting from the addition **158** + CO) adds first to the electron-poorest double bond of the vinylacrylic ester, giving an electron-rich α -oxo radical **160**, which then prefers to add to the electron-rich allylstannane (electron-richer than a vinyl ester) giving radical **161** that fragments into product **162** and the radical-chain carrier $\text{Bu}_3\text{Sn}^\bullet$ (Scheme 130) <1993JA1187, 1996CRV177>.

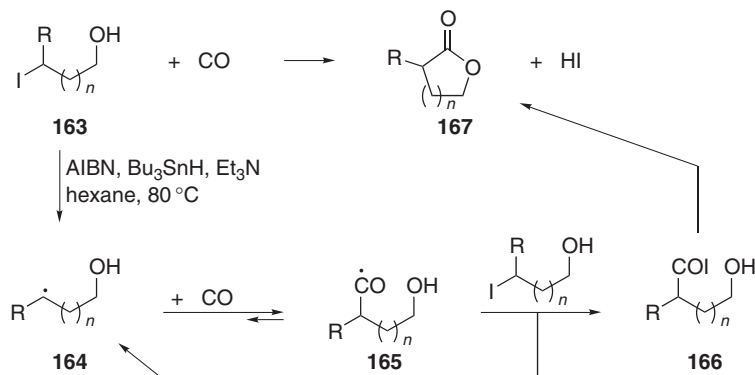


Scheme 130

A new method for the synthesis of carboxylic acid esters from the combination of alkyl iodides, alcohols, and CO has been proposed (Equation (119)). It is carried out under photoirradiation (Xe-lamp, pyrex vessel) in the absence of a metal catalyst <1997JA5465>.



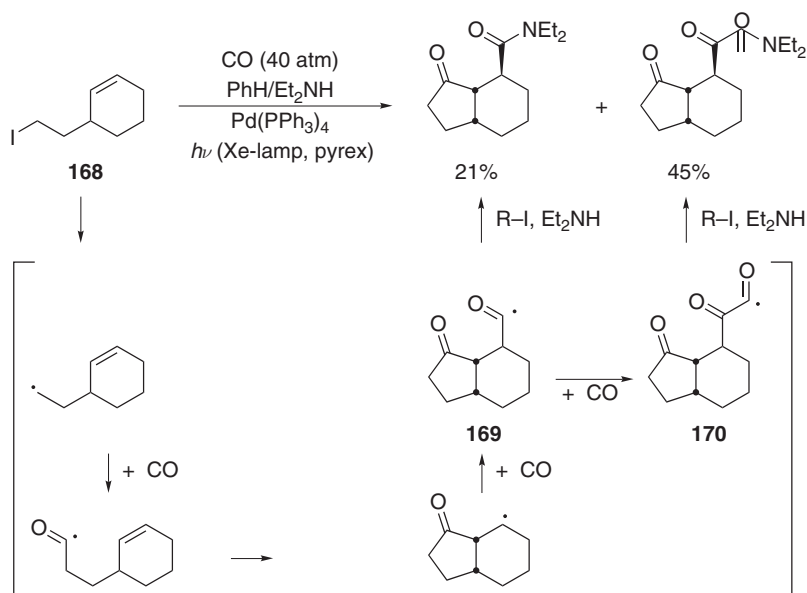
Five- to seven-membered lactones **167** have been obtained from ω -hydroxyalkyl iodides **163** and CO by atom transfer carbonylation without the need for transition metal catalysts (Scheme 131). The process implies the intermediacy of ω -hydroxyalkyl radicals **164** that add to CO, giving acyl



Scheme 131

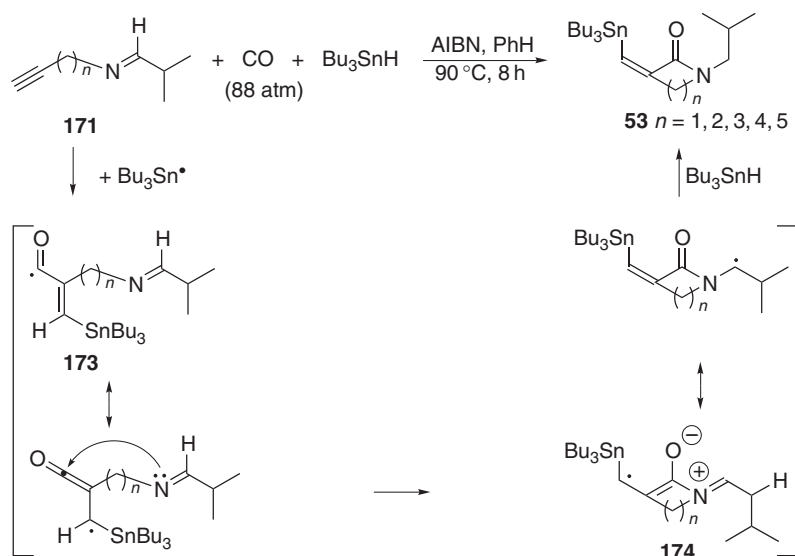
radical intermediates **165** that carry to chain reaction by reaction with the ω -hydroxyalkyl iodides **163**. This gives rise to the corresponding acyl iodides **166** that immediately generate lactones **167** <2000OL389>.

Similar carbonylative cyclizations are reported in Scheme 132. They involve 4-alkenyl iodides such as **168** (Scheme 132). Under 40 atm of carbon monoxide significant dicarbonylation (e.g., **169** + CO \rightarrow **170**) is observed <2002JA3812, 1996JA10670, 2003CC1190>.



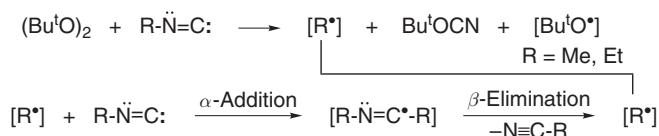
Scheme 132

A carbonylative access to α -stannylmethylene lactams **172** from azaenynes **171** and CO has been uncovered (Scheme 133). It involves an α,β -unsaturated acyl radical **173** as the attacking radical and an imino group as the acceptor giving intermediate **174**. Cyclizations occur with high regioselectivity favoring the *N*-philic mode for the synthesis of 4-, 5-, 6-, 7-, and 8-membered rings <2003JA5632>.



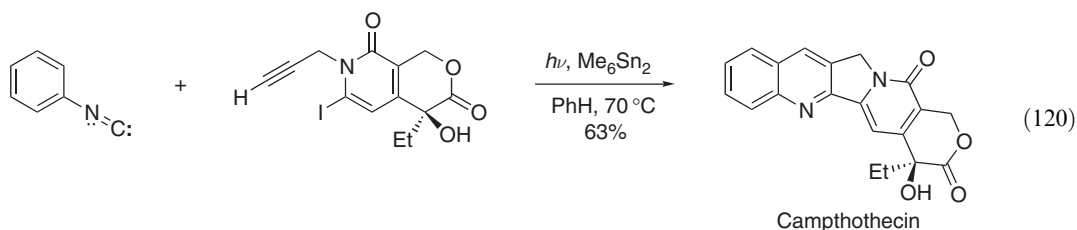
Scheme 133

Shaw and Pritchard <1968CJC2721> observed isonitrile–nitrile isomerization of methyl and ethyl isonitrile when they were heated in the presence of a catalytic amount of di-*t*-butyl peroxide ((Bu^tO)₂). A mechanism implying the addition of methyl and ethyl radical to the isonitrile was invoked (Scheme 134) <1964BCJ635, 1983TL4671>.

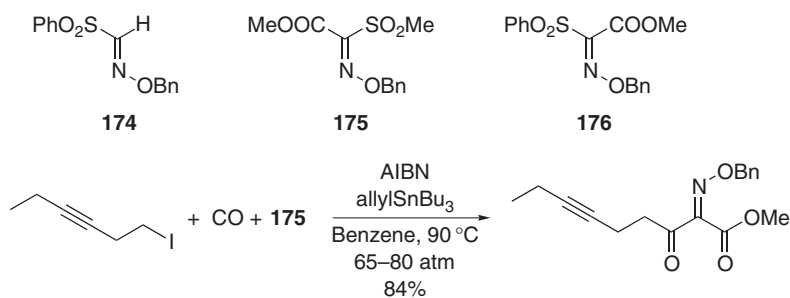


Scheme 134

The intermolecular radical addition to isonitriles has been used to construct nitrogen-containing heterocyclic compounds as illustrated by Curran's synthesis of Camphothecin derivatives (Equation (120)) <1991JA2127-2132, 1995AG(E)2683, 1996CRV177>.

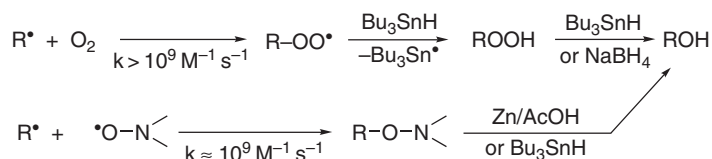


Kim and co-workers <1996JA5138, 1997SL475, 1997JA5982, 1998TL1587> have reported that sulfonyloxime ethers such as **174**–**176** can serve as viable C1 radical acceptor synthons, which serve as latent carbonyl groups, providing novel free-radical methods for acylation. When reacted with alkyl iodides and CO, the latter synthons can generate vicinal singly and doubly acylated oxime ethers <1999JA12190> as exemplified with a reaction that uses oxime derivative **176** (Scheme 135).



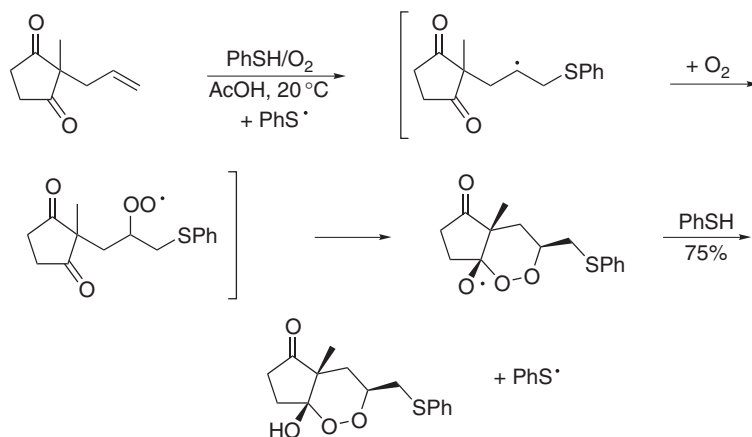
Scheme 135

Molecular oxygen and nitroxides react rapidly with alkyl radicals. The products so-obtained can then be reduced to generate the corresponding alcohols (Scheme 136) <B-2001MI93>.



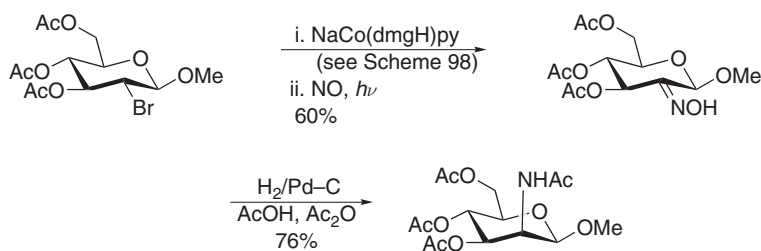
Scheme 136

Resonance-stabilized alkyl radicals react with dioxygen (a triplet diradical) with second-order rate constants $\geq 10^9 \text{ M}^{-1} \text{ s}^{-1}$ <1983JA5095>. Thus oxygen and nitroxides (e.g., TEMPO: 2,2,6,6-tetramethylpiperidine *N*-oxide) are efficient radical scavenging agents and can be used as inhibitors of reactions occurring via radical intermediates <1988JOC1629, 1992JA4992, 1995JPC8182>. With unsaturated carbon-centered radicals, O_2 generates peroxide radicals that can undergo intramolecular additions to the unsaturated moieties giving endoperoxides. One example is given in Scheme 137 <1998JOC4697>.



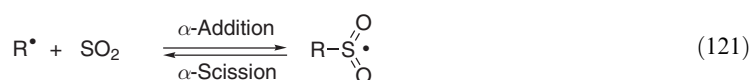
Scheme 137

Because of its free-radical character, nitric oxide ($\text{N}=\text{O}$) can act as an efficient radical trap <1984CC289, 1987TL1451>. As an example of application of this reaction, the conversion of methyl 3,4,6-*O*-triacetyl-2-bromo-2-deoxy- β -D-glucopyranoside into an *N*-acetyl mannosamine derivative is presented in Scheme 138 <1998CB1807, 1990SL166>.

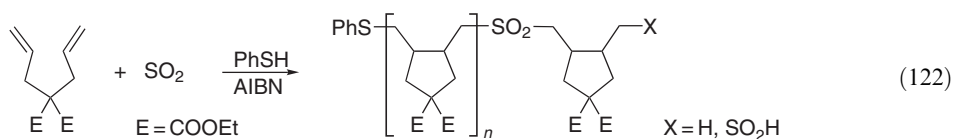


Scheme 138

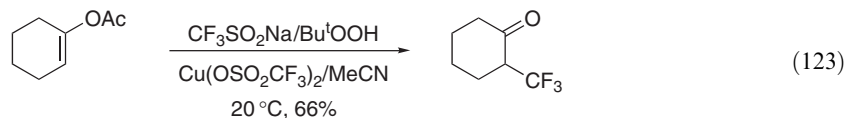
The addition of alkyl radicals to sulfur dioxide is reversible <1983JOC3588, 1986JOC2871> (Equation (121)). The rate of the reversal α -scission depends on the relative stability of the alkyl radical. In the case of $\text{PhCH}_2\text{SO}_2^{\bullet}$, the rate of loss of SO_2 exceeds $2 \cdot 10^8 \text{ s}^{-1}$ at 295 K.



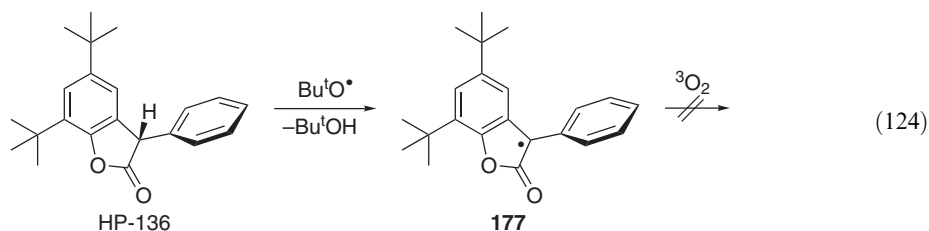
The sulfonylation of alkyl radicals plays an important role in the copolymerization of alkenes with SO_2 . Shevlin has shown that the cyclooligomerization of diallyl malonate can be controlled by the addition of a chain transfer agent such as thiophenol (PhSH) (Equation (122)) <1998JOC3230>.



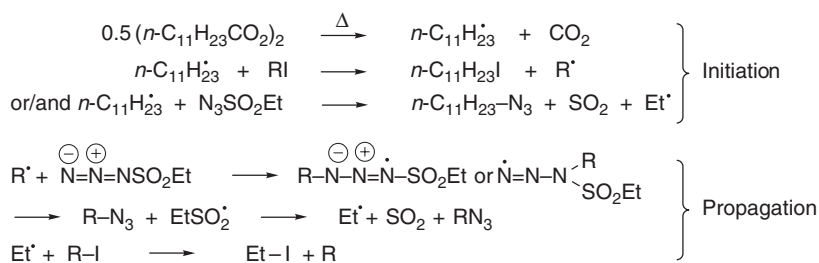
Conversely α -scissions of alkanesulfonyl radicals have been used to generate fluorinated alkyl radicals. For instance the Cu(II)-mediated addition of trifluoromethanesulfinate to enol esters affords α -trifluoromethyl ketones (Equation (123)) <1993JOC2599>.



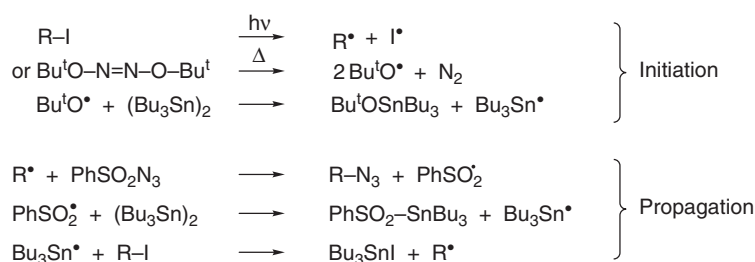
Carbon-centered radicals add to dioxygen ($^3\text{O}_2$) readily <1983JA5095>, leading to peroxy radicals (see Schemes 133 and 134). CIBAs antioxidant HP-136 reacts with $(\text{Bu}^t\text{O})_2$ to give the corresponding diphenylmethyl-like radical 177, which is estimated to react with O_2 about 10,000 times more slowly than the diphenylmethyl radical. Thus HP-136 is an antioxidant because it is not quenched rapidly with O_2 but reacts with other radicals such as alkyl and peroxy radicals (Equation (124)) <2000OL899>.



A novel approach for the formation of C—N bonds by azidation of alkyl radicals with sulfonyl azides has been proposed by Ollivier and Renaud <2001JA4717>. The alkyl radical generated by reaction of allyl iodide either with dilauryl peroxide or with $\text{Bu}_3\text{Sn}^\bullet$ was reacted with ethanesulfonyl azide (Scheme 139) or with benzenesulfonyl azide (Scheme 140).

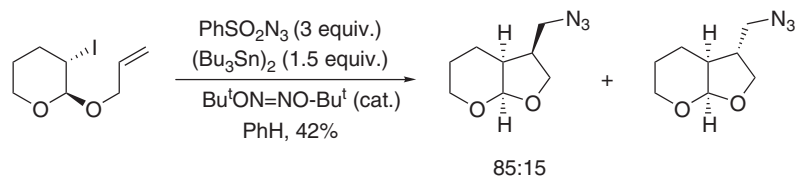


Scheme 139



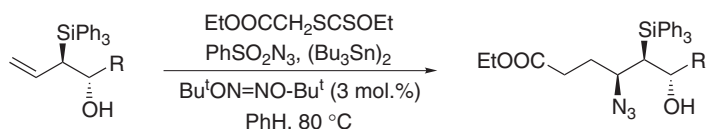
Scheme 140

The method can be coupled with a radical isomerization (cyclization) process as shown in Scheme 141.



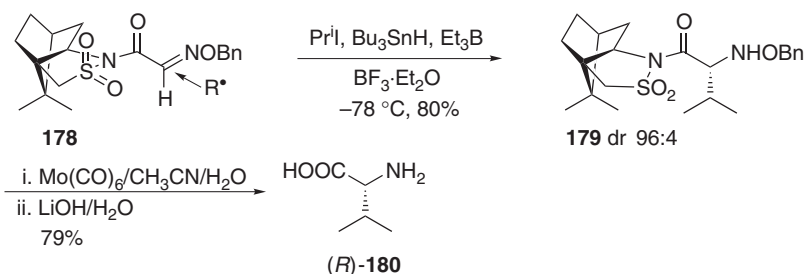
Scheme 141

Easily available chiral allyl silanes have been used as substrates for carboazidation as shown in Scheme 142 <2002OL4257>.



Scheme 142

The first asymmetric syntheses of α -amino acids based on the diastereoselective carbon radical addition to glyoxylic imine derivatives has been reported <2000JOC176>. The addition of an isopropyl radical to Oppolzer's camphorsultam derivatives **178** of the glyoxylic oxime ether afforded **179** with a diastereomeric ratio 96:4 in 80% yield (Scheme 143). The reductive removal of the benzyloxy group of the major diastereomer (*R*)-**179**, by treatment with $\text{Mo}(\text{CO})_6$ and subsequent removal of the sultam auxiliary by standard hydrolysis, gave the enantiomerically pure D-valine *R*-**180** without any loss of stereochemical purity.



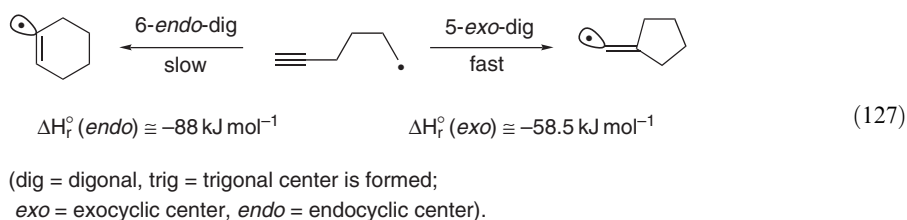
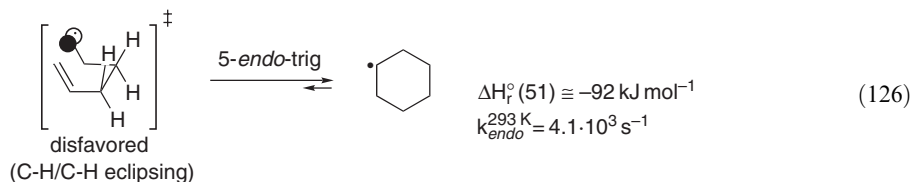
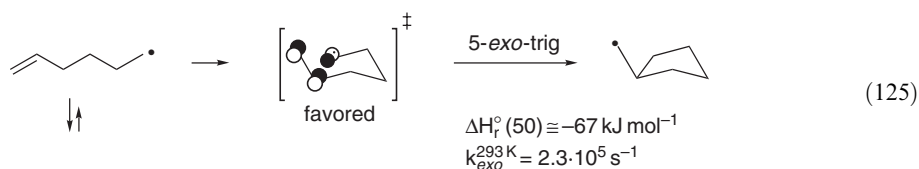
Scheme 143

1.19.13.4 Radical Isomerizations

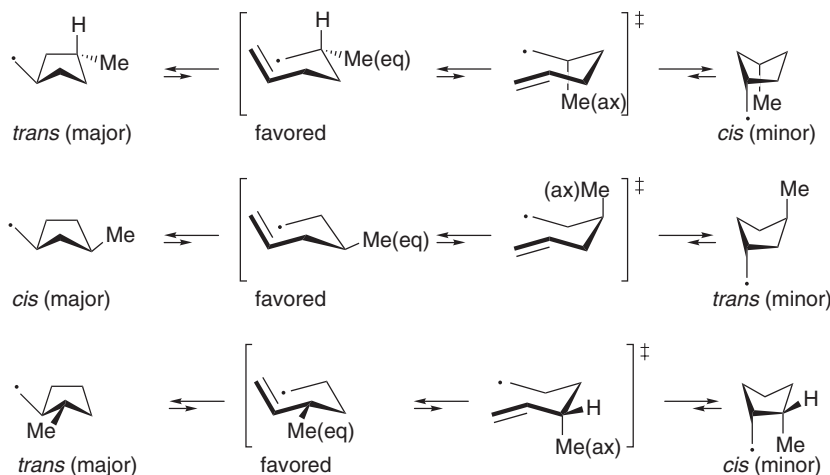
Intramolecular additions of carbon-centered radicals to a double or triple bond leading to cyclic compounds, i.e., radical cyclization reactions, have been used extensively in the synthesis of complicated organic molecules. The reverse reaction, i.e., ring opening adjacent to radical centers occurs readily with three- and four-membered rings, including oxiranylalkyl and oxetanylalkyl radicals <2003AG(E)5556>.

1.19.13.4.1 Five-membered versus six-membered ring formation

The most frequently used reactions are the 5-*exo*-trig (Equations (125), (126)) and 5-*exo*-dig isomerization (Equation (127)) of hex-5-en-1-yl and hex-5-yn-1-yl radicals, respectively. These isomerizations are favored kinetically (Baldwin rules <1976CC734, 1993ACR476>) over the more exothermic 6-*exo*-trig and 6-*endo*-dig ring closures, respectively.

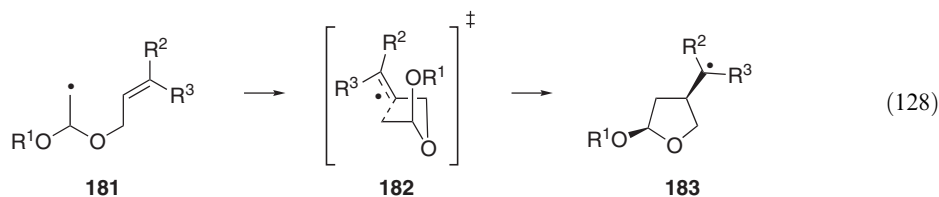


The origin of these kinetic effects arises from the preferred trajectories followed by the radical addition to the alkene and alkyne moieties [<2002JOC2982>](#). The *exo* modes imply conformations that are less strained than for the *endo* modes of cyclization. In the former nearly unstrained zig-zag conformers of the starting radical reach the transition states, whereas in the latter, the transition states imply conformations that resemble that of six-membered boat conformers that are strained because of C—H/C—H eclipsing interactions. This theory (Beckwith–Houk model [<1987JOC959, 1980CC482, 1980CC484>](#)) is supported by the observations reported in [Scheme 144](#), which show that the major cyclopentylmethyl radicals formed arise from transition structures resembling six-membered chair rings with the methyl substituents residing in equatorial rather than axial positions (optimization of the gauche interactions).

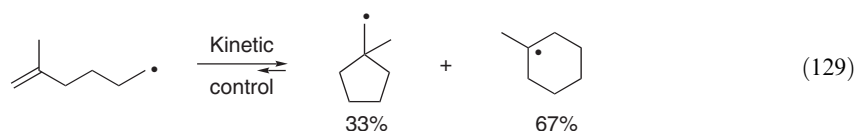


Scheme 144

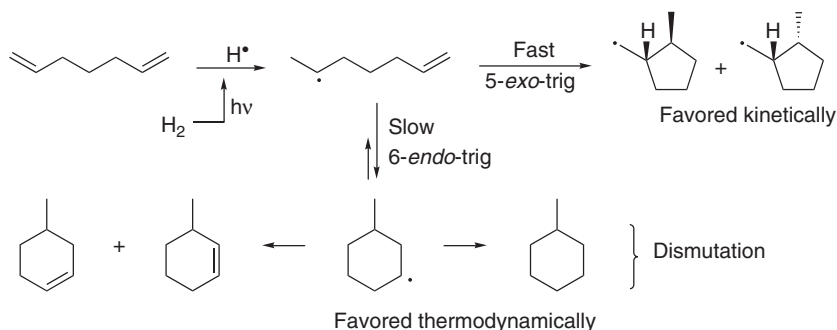
In the case of acetal-derived radicals **181** ([Equation \(128\)](#)), the *exo*-trig cyclization generates preferentially the *cis*-intermediates **183** as the transition states **182** of the cyclization can enjoy conformational anomeric effects that stabilize the pseudoaxial OR' group [<1998JOC5144>](#).



The kinetic chemoselectivity k_{exo}/k_{endo} for the isomerization of the hex-5-en-2-yl radical amounts to ca. 50 at 300 K (compare Equations (125) and (126)). If substitution increases, the reaction enthalpy difference between these two competing ring closures decreases and products of *endo*-trig isomerization are formed to a significant extent. For instance, in the case of the isomerization of 5-methylhex-5-en-1-yl radical the *endo*-trig mode generates a tertiary alkyl radical whereas the *exo*-trig mode gives a primary alkyl radical (Equation (129)). The greater driving force for the formation of 1-methylcyclohexyl radical (ca. 42 kJ mol⁻¹) makes it a preferred product of cyclization.



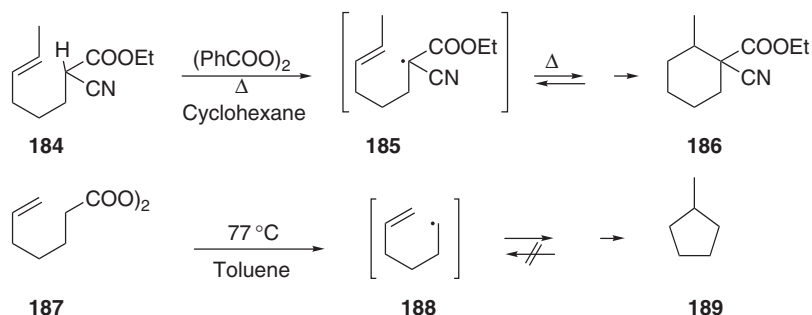
The addition of a hydrogen radical engendered by pulsed radiolysis of H₂ at -78 °C ($[H^\bullet] \cong 10^{-14}$ M) onto hepta-1,6-diene leads to a mixture of acyclic, cyclic, and dimeric products. Among the cyclic products one finds all isomeric methylcyclohexenes and methylcyclohexane and these are more abundant than cyclopentanes. Radical H[•] adds regioselectively to hepta-1,6-diene giving the hept-6-en-2-yl radical that is expected to undergo fast *exo*-trig cyclization (Baldwin's rules) generating (2-methylcyclopentyl)methyl radicals under conditions of kinetic control. In the absence of radical scavenging agents such as Bu₃SnH, these radicals have the time to rearrange into the more stable 3-methylcyclohexyl radical, which then eliminates H[•] to give methylcyclohexenes, or reacts with H[•] to furnish methylcyclohexane (dismutation) (Scheme 145) <1994JA6683>.



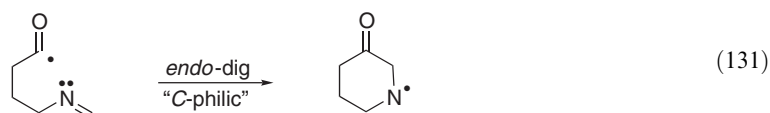
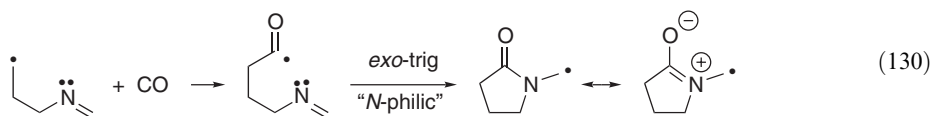
Scheme 145

In 1960, Julia <1960CR(C)1030> found that heating cyanoester **184** with benzoyl peroxide afforded the cyclohexane derivative **186** (Scheme 146). By contrast Lamb and co-workers <1963JA3483> observed that heating peroxide **187** gave methylcyclopentane **189** as the major product. The former reaction implies a reversible intramolecular radical addition to the alkene moiety, whereas in the latter reaction an irreversible *exo*-trig cyclization occurs.

Ryu and co-workers <1998JA5838> have shown that acyl radicals add selectively on the nitrogen (nucleophilic) rather than at the carbon (electrophilic) center of an imine group. Quantum calculations on the *exo*-“N-phile” cyclization (Equation (130)) and *endo*-“C-phile” cyclization (Equation (131)) predicted energy barriers of 36.1 and 46.9 kJ mol⁻¹, respectively <2002CC2338>. An aminoketone being about 80 kJ mol⁻¹ less stable than the corresponding amide, and considering the fact that the *exo*-trig mode gives a carbon-centered radical stabilized by the amido substituent, the *exo*-trig cyclization is much more exothermic than the *endo*-trig

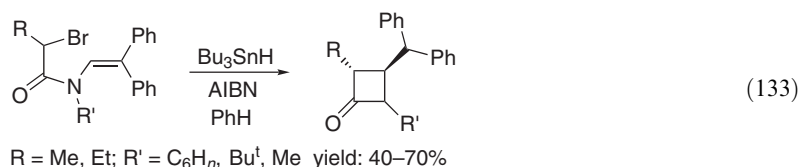
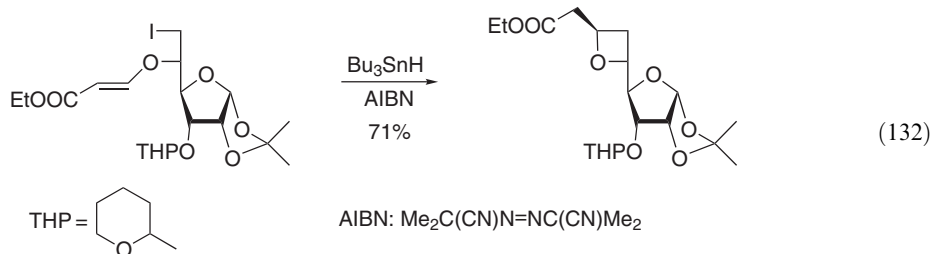


cyclization. Although the acyl radical is an electron-rich radical it prefers to add onto the nitrogen center rather than on the carbon center of the imine because the former cyclization (a carboxamide is about 85 kJ mol^{-1} more stable than an amino ketone) is much more exothermic than the latter (Dimroth principle).



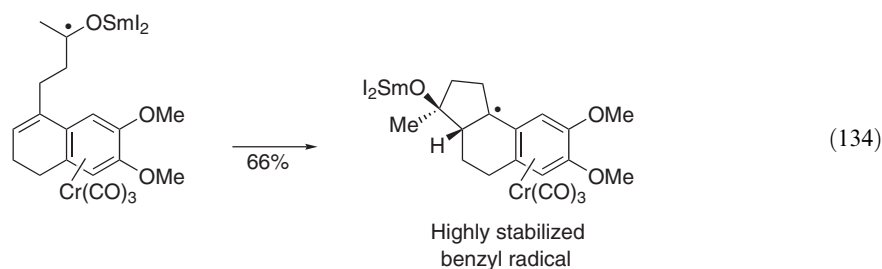
1.19.13.4.2 4-*exo* and 5-*endo* cyclizations

The 4-*exo* cyclizations of pent-4-en-1-yl radicals to give cyclobutylmethyl radicals are difficult because of the strain build up in the cyclobutylmethyl radical. But, if the latter can be trapped rapidly, four-membered ring systems can be isolated [<1990TL2975, 1992CL1487, 1992TL6719, 1997TL6521, 1999TL2661, 1999SL843>](#). The first example of a 4-*exo*-trig radical cyclization was reported by Araki and co-workers in 1989 (Equation (132)) [<1989TL2829>](#). Belletire and co-workers [<1991TL2335>](#) reported the efficient formation of β -lactams via the 4-*exo*-trig cyclization of bromo enamides (Equation (133)). In this case, the 4-*exo*-trig cyclization is facilitated by the formation of a stable benzhydryl radical intermediate.

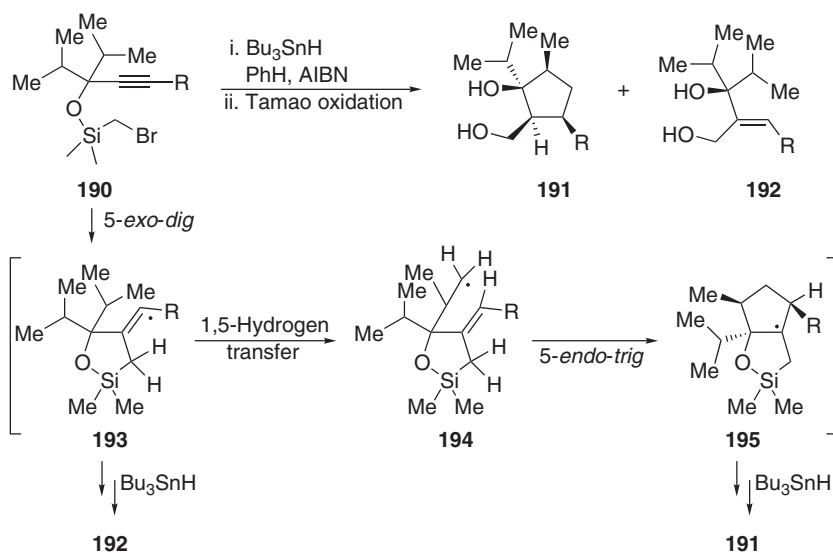


The groups of Parsons [<1998TL2815>](#), Ikeda and Ishibashi [<1998JCS\(P1\)1763>](#) have found an efficient 5-*endo*-trig radical cyclization of *N*-ethenyl- α -haloamides to form pyrrolidinones and substituted pyroglutamates. The 5-*endo* closure of the 2-formylbenzoyl radical has also been shown to be a particularly facile process [<1994JA1718>](#). Moreover, 5-*endo*-trig cyclizations

include heteroatomic-centered radicals such as Si [<1998JCS\(P1\)467>](#) or S-centered radicals [<1997JOC8630>](#). In comparison, the all-carbon pentenyl system has not led to high-yielding 5-*endo*-trig cyclizations [<1965BSF1550, 1966JOC2255, 1966JOC3018, 1973JCS\(P1\)1655>](#) except for the special case of [Equation \(134\)](#) reported by Schmalz and co-workers in 1995 [<1995AG\(E\)2385>](#).



An efficient radical sequence involving a 5-*exo*-dig cyclization, a diastereoselective 1,5-H transfer, and an all carbon 5-*endo*-trig cyclization has been discovered by Malacria and co-workers ([Scheme 147](#)) [<1999JOC4920>](#). It allows the construction of cyclopentenyl derivatives **191** bearing four controlled stereogenic centers from diisopropyl precursors **190**. Alkenes **192** were also isolated as minor side products. These reactions probably involve the radical intermediates **193–195**.

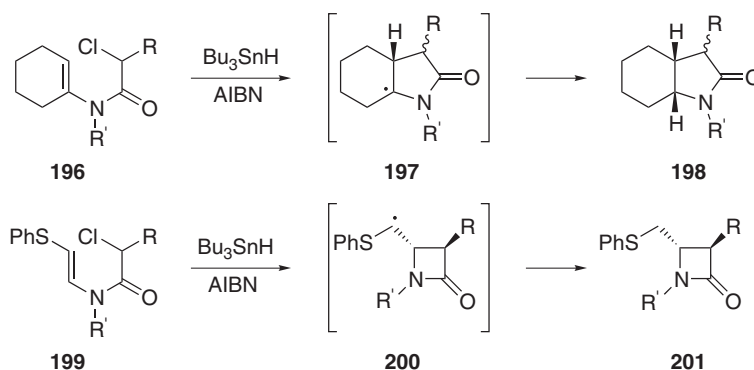


Scheme 147

Upon treatment of the α -chloro amides **196** with Bu_3SnH and AIBN the intermediate radicals undergo 5-*endo*-trig cyclization giving radicals **197** that are reduced into γ -lactams **198** ([Scheme 146](#)). Alternatively, α -haloamides **199** having a phenylthio substituent at the terminus of their *N*-vinyl bond, cyclize in a 4-*exo*-trig manner giving β -lactams **201** via radicals **200** ([Scheme 148](#)). In this latter case, the highly radical stabilizing effect of the phenylthio substituent makes the formation of the strained intermediates **200** possible [<2001T7629>](#).

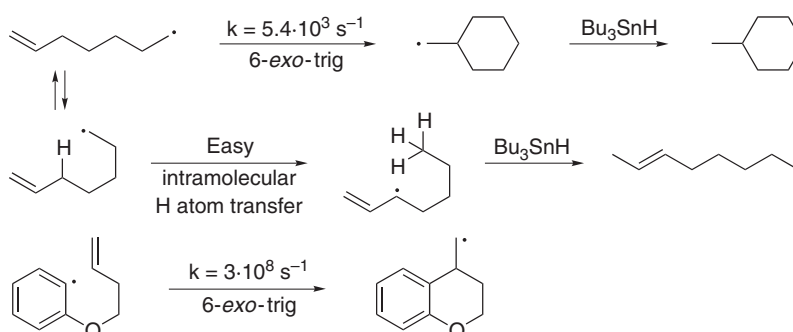
1.19.13.4.3 *n*-*exo* and *endo* cyclizations

Hept-6-en-1-yl radicals undergo preferential 6-*exo*-trig cyclizations giving cyclohexylmethyl radicals, under kinetic (Baldwin's rules) and thermodynamically controlled conditions. In some cases ([Scheme 149](#)), the 6-*exo*-trig cyclization is a relatively slow process due to an entropy factor (blockage of the free rotation of 5 $\sigma(\text{C}—\text{C})$ bonds), and a concurrent reaction intervenes which



Scheme 148

transfers an hydrogen atom intermolecularly with formation of a stable allyl radical. If substitution of the hept-6-en-1-yl system blocks a number of freely rotating σ bonds, the rate of 6-*exo*-trig cyclization increases significantly as shown below <1980CC484, 1974JA1613>.



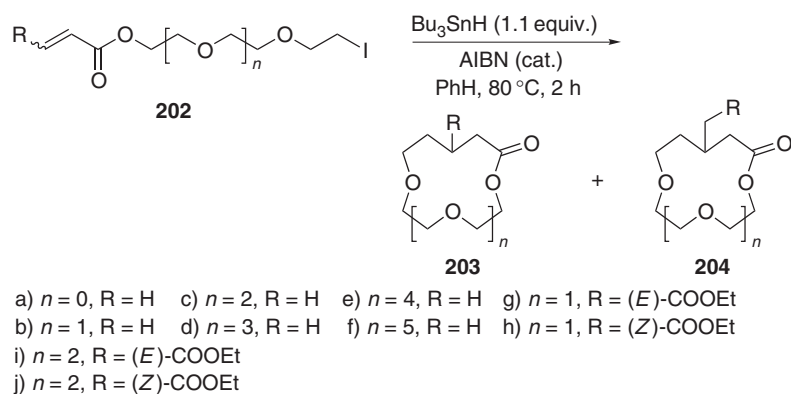
Scheme 149

Medium rings (7–12) as well as large rings have been formed by intramolecular radical additions to π -systems (alkenes, alkynes, and *O*-alkyl oximes) <B-2001MI151, B-2001MI538>.

3-Oxahex-5-enyl radicals ($\text{CH}_2=\text{CHCH}_2\text{OCH}_2\text{CH}_2^\bullet$) undergo *exo* cyclization about 25 times as fast as the hex-5-enyl radical at 80 °C <1987AJC157, 1988JOC1632>. The effect of an oxygen atom in the chain on the rates of cyclization of these alkenyl radicals has been attributed to the decrease in the strain energy of the cyclization transition structures resulting from the replacement of a carbon atom by oxygen <1985T3925>. The favorable oxygen atom effect has been exploited to prepare substituted macrocyclic polyethers by radical cyclization <1997CC499, 1998JOC6814> (Scheme 150). Iodides **202b–202j** were all cyclized into cyclic polyethers **203b–203j** (and some cases **204g–204j**), but no cyclized product could be obtained from **202a**. Uncyclized products formed by direct hydrogen transfer to the initially formed radicals were also detected.

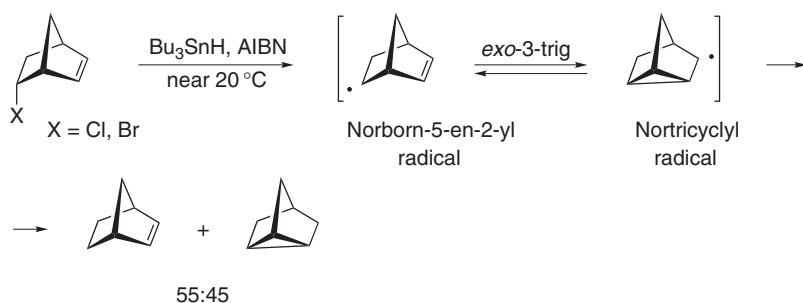
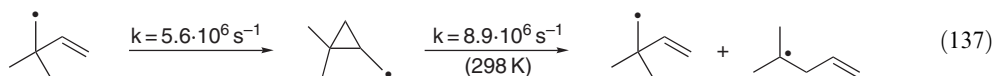
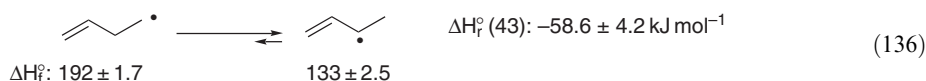
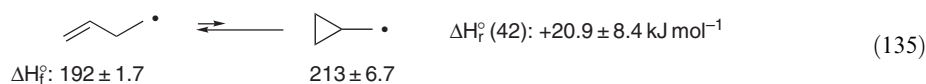
1.19.13.4.4 3-*exo*-Cyclization: Homoallyl/cyclopropylmethyl Isomerization

The isomerization of the but-3-enyl (homoallyl) radical into the cyclopropylmethyl radical is an endothermic reaction as shown in Equation (135). For the dimethyl-substituted derivative (Equation (137)) first-order rate constants for the 3-*exo*-trig ring closure is less than 100 times smaller than for the reverse reaction giving a mixture of primary and tertiary homoallyl radicals <1980JCS(P2)1473, 1993CSR347>. Unless substituents prohibit it, but-3-enyl radicals will isomerize irreversibly into but-3-en-2-yl radicals (Equation (136)). In the case of



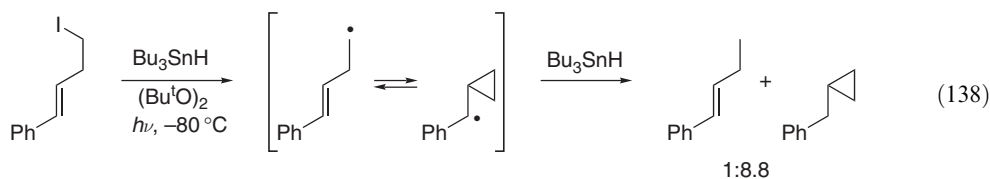
Scheme 150

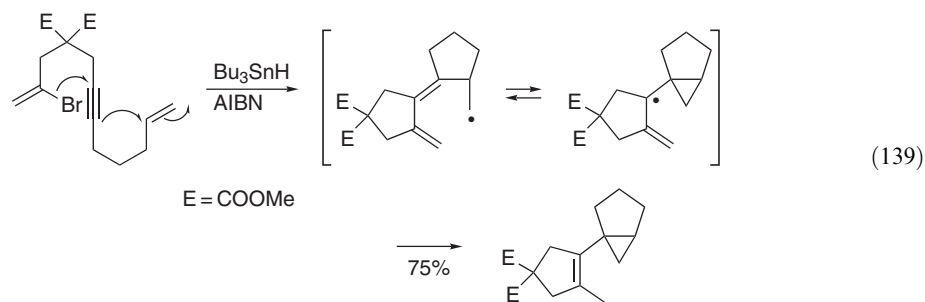
bicyclo[2.2.1]hept-5-en-2-yl chloride and bromide, Kuivila and co-workers [<1966JOC3381>](#) have reported that their reduction under radical conditions (Scheme 151) gives a 1:1 mixture of product of reduction of the bicyclo[2.2.1]hept-5-en-2-yl radical intermediate (norborn-5-en-2-yl) and of its isomeric nortricyclyl radical arising from the intermolecular 3-*exo*-trig cyclization.



Scheme 151

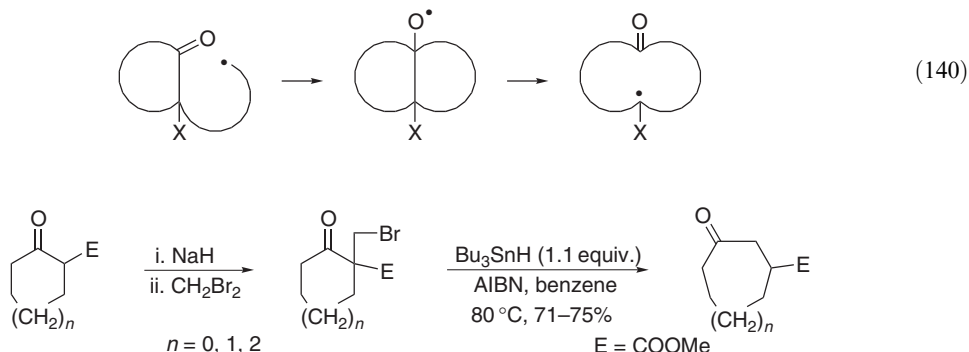
If the cyclopropylmethyl radical intermediate can be stabilized by appropriate substitution, the 3-*exo*-trig cyclization will occur more readily as shown in Equations (138) [<1990CC923>](#) and (139) [<1994JOC718>](#).





1.19.13.4.5 Ring expansions

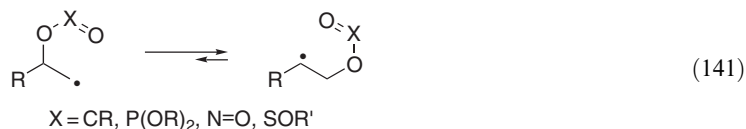
The one-carbon ring expansion according to Equation (140) was first observed by Barton [<1961JA4481>](#) and then its synthetic potential was explored by Dowd [<1993CRV2091, 1999T9349>](#) and Beckwith and co-workers [<1988JA2565>](#). Radical precursors are prepared by alkylation of β -ketoesters derived from Dieckmann condensations as shown with the examples reported in Scheme 152. One of the best examples of three-carbon ring expansion is the total synthesis of (*R*)-(-)-muscone starting from a cyclododecanone derivative [<1992T4773>](#).



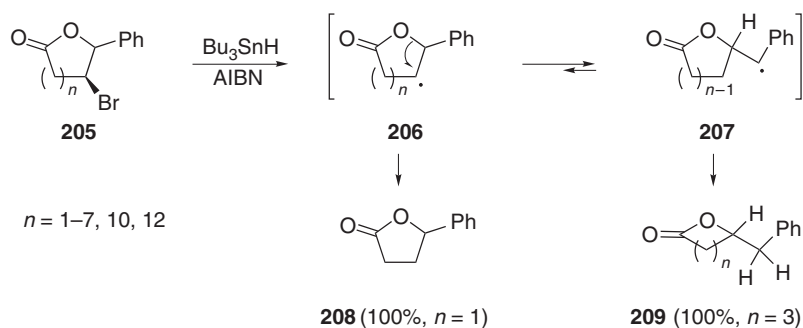
Scheme 152

1.19.13.4.6 Ring contractions

The β -(acyloxy)alkyl, or Surzur–Tanner [<1967CR\(C\)1981, 1970BSF3060, 1969JA7535>](#), rearrangement is the archetypical radical ester migration [<1993JCS\(P2\)1673>](#). These rearrangements (1,2-acyloxy shifts) can be accelerated by Lewis acids such as $\text{Sc}(\text{OTf})_3$ [<1998AG\(E\)2259>](#). Other groups such β -phosphate, β -(nitroxy)alkyl, and β -sulfate can also migrate according to Equation (141) [<1996JA7422>](#).



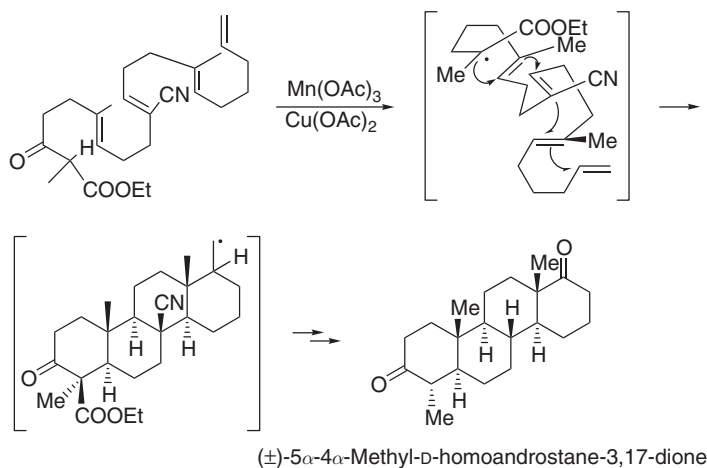
This type of rearrangement can occur with lactone-derived radicals. When bromolactones **205** were reacted with Bu_3SnH and AIBN, all lactones **205** with $n = 2$ –12 underwent ring contraction giving **209**, although with varying efficiency. In the case of **205** with $n = 1$, no products of ring contraction was observed. In all the other reactions it is the high stability of the benzyl radicals **207** arising from the 1,2- or 3,2-shift of the COO group in **206** that drives the ring contraction (Scheme 153) [<1996JA7422>](#). Using ^{17}O -monolabeled bromolactones and ^{17}O -NMR spectroscopy, it has been demonstrated that the free-radical ring contraction of six-, seven-, and eight-membered lactones occur by 1,2-shift of the carboxylic moiety, and not by 3,2-shifts [<1999JOC1762>](#).



Scheme 153

1.19.13.4.7 Cascade radical cyclizations

Cascade (tandem) radical reactions are among the most powerful methods to generate polycyclic ring systems in one step from unsaturated acyclic precursors. Landmarks in this concept include the total syntheses of (\pm)-hirsutene by Curran and Rakiewicz [<1985T3943>](#), and a more elaborate version relying on the use of SmI_2 and leading to an advanced precursor of hyptnophilin and coriolin [<1998JA5064>](#). Polycyclizations involving successive radical 6-*endo*-trig cyclizations have been used to generate poly-*trans*-decalin systems including a precursor of (\pm)-5 α , 4 α -methyl-D-homoandrostane-3,17 α -dione (Scheme 154) [<1996JOC1806, 1998JOC1162>](#).



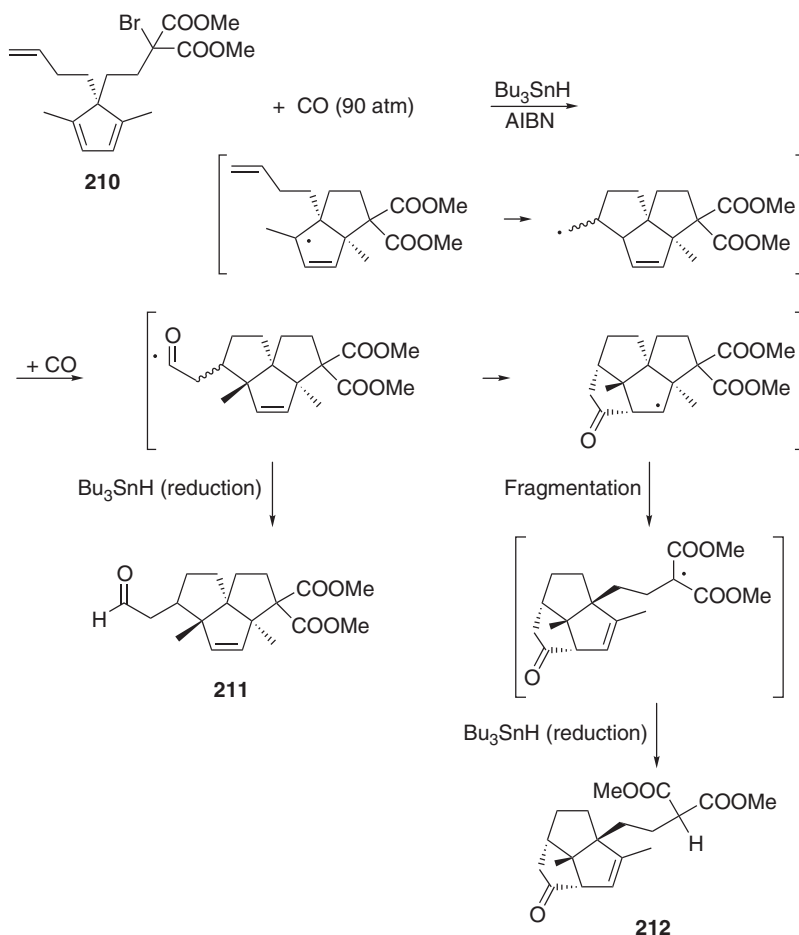
Scheme 154

Tandem radical cyclizations and carbonylative tandem cyclization of 5,5-disubstituted cyclopentadiene **210** provide angular triquinanes **211** and **212** (Scheme 155) [<1998JCS\(P1\)1591>](#).

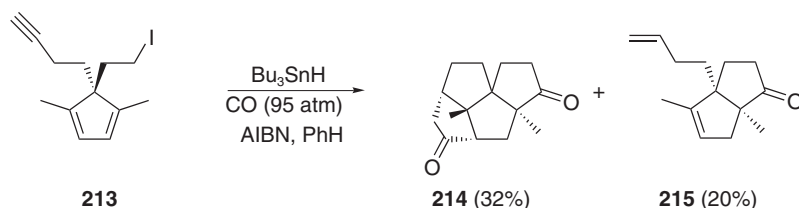
Double carbonylation of **213** (Scheme 156) occurs with triple cyclization and no fragmentation giving tetracyclic compound **214** (32%) as major product. The second product is **215** (20%).

Since the first examples reported by Beckwith and Schiesser in 1985 [<1985T3925>](#), many polycyclic skeletons including steroids [<1994TL2593, 1999JA4894>](#), diterpenes [<1998JOC7945>](#), and also triquinanes [<1994TL7845>](#) have been obtained. Among them, a linear triquinane framework **218** has been constructed from the acyclic enediyne **216** by a cascade involving intra and intermolecular radical additions and also H-transfer and β -elimination (Scheme 157) [<1998JOC6764>](#).

Pattenden illustrated the potential of the cyclopropylmethyl/homoallyl radical rearrangement associated with 6-*endo* tandem, 9-*endo* macrocyclization, and transannular processes to form a steroidal skeleton **222** starting from the acyl selenide **220** (Scheme 158) [<1998CC311>](#).



Scheme 155

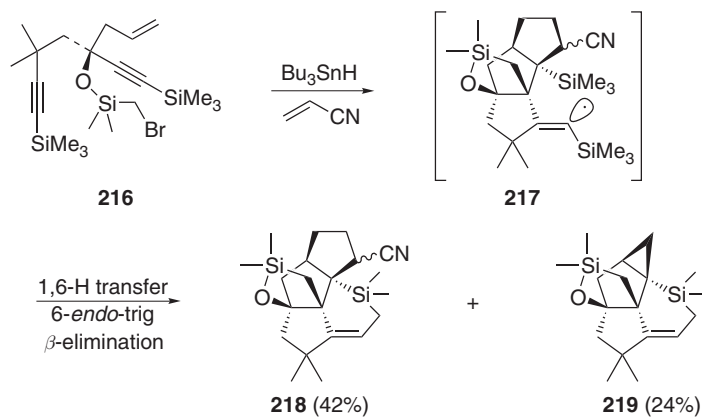


Scheme 156

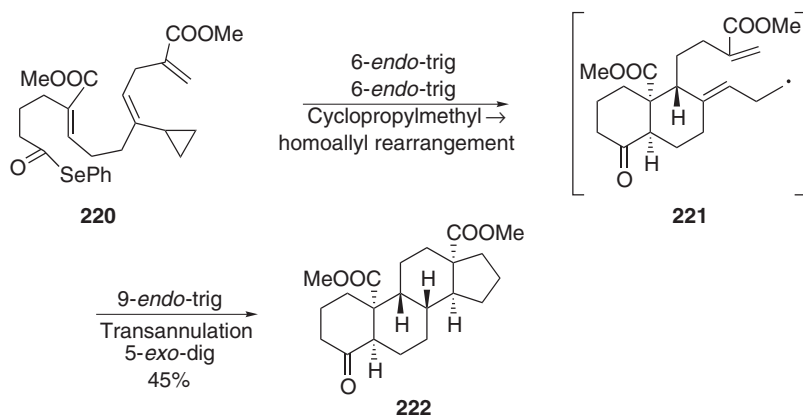
Biomimetic synthesis of *epi*-illudol **223** <1997JA3427> and of the linear triquinane framework **224** <2002AG(E)3284> have been proposed by Malacria and co-workers (Scheme 159).

Zard and co-workers have built the tetracyclic skeleton of 13-deoxyserratine **227** via radical polycyclization involving the intramolecular addition of amidyl radical **226** derived from **225** (Scheme 160) <2002AG(E)1783>. See also the synthesis of the precursor of (±)-vindoline <2002OL443>.

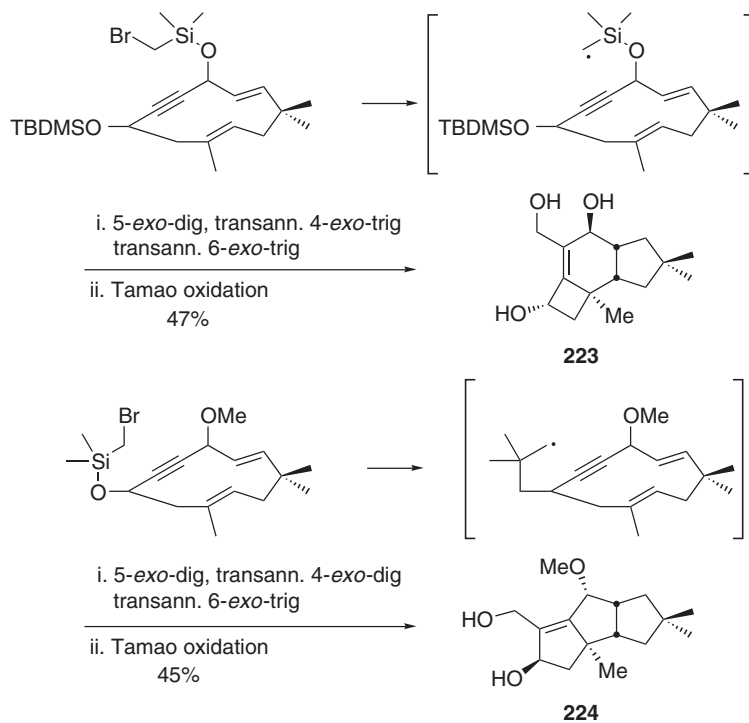
The “round trip” radical reaction of 11-iodo-2,7-dimethyldodeca-1,6,10-trien-5-one **228** is a sequence of 5-*exo*, 6-*endo*, and 5-*exo* cyclizations in which the last radical cyclization occurs at the same carbon atom as the initial generation, giving isogymnomitrene ketone **234** as major product (31%). Gymnomitrene ketone **233** was obtained also together with **230–232** (Scheme 161) <2000JOC2007>.



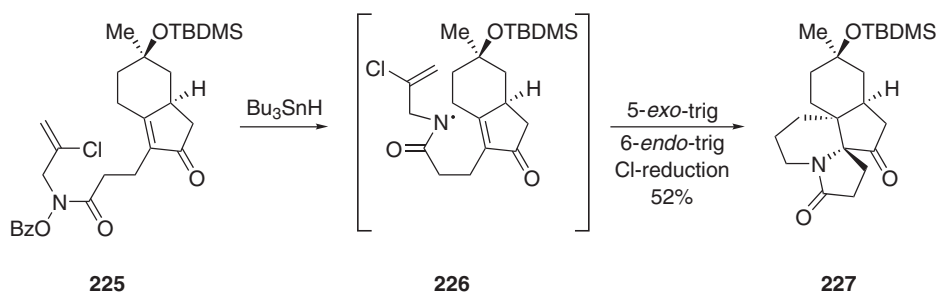
Scheme 157



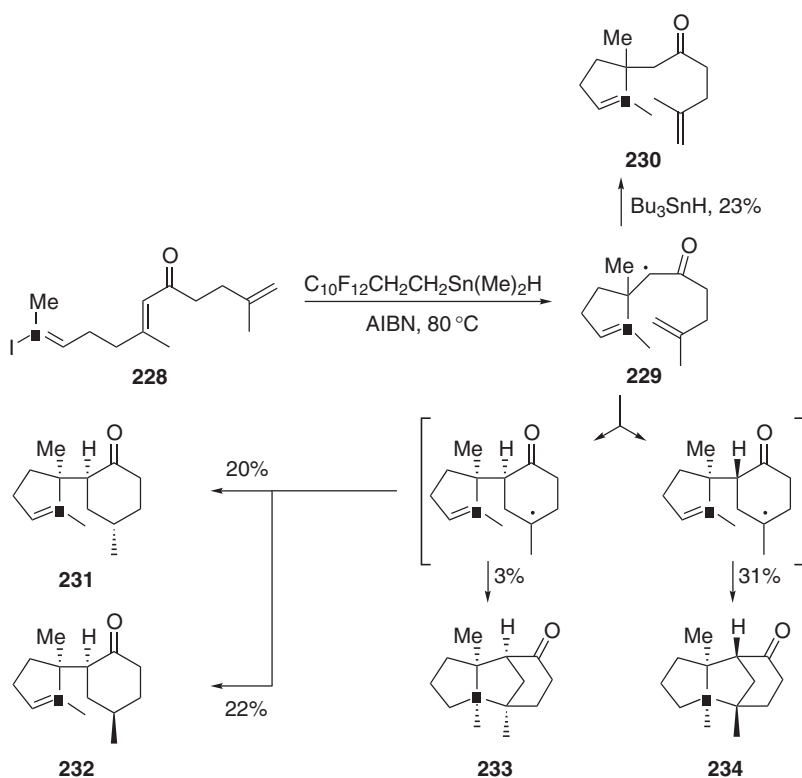
Scheme 158



Scheme 159



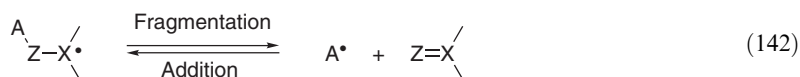
Scheme 160



Scheme 161

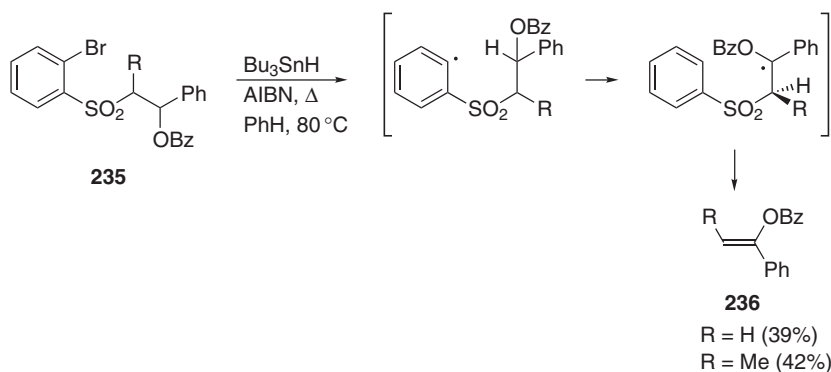
1.19.13.4.8 Radical fragmentation

Any radical can undergo a β -elimination (Equation (142)) with the formation of another radical and an unsaturated system. It is the reverse reaction of radical addition to an unsaturated moiety. Fragmentation is favored by dilution (law of mass action), by temperature (entropy effect), and by low endothermicities.

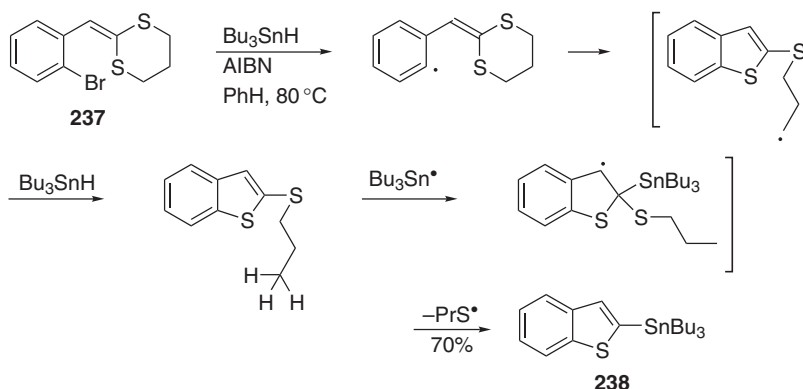


Simpkins and co-workers [<1995SL943>](#) have proposed a radical alkene synthesis (**235** \rightarrow **236**) involving a radical abstraction by β -scission as illustrated in Scheme 162.

In an efficient example of a tandem process Harrowven and Browne [<1995TL2861>](#) have proposed an approach to tributylstannyl-substituted benzothiophene **238** starting from aryl bromide **237** (Scheme 163).

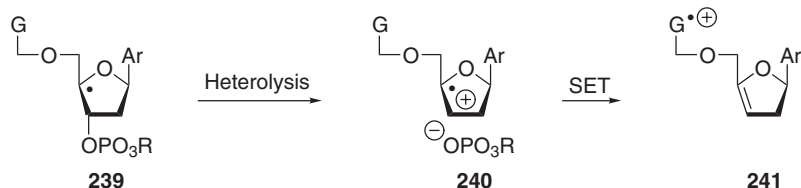


Scheme 162



Scheme 163

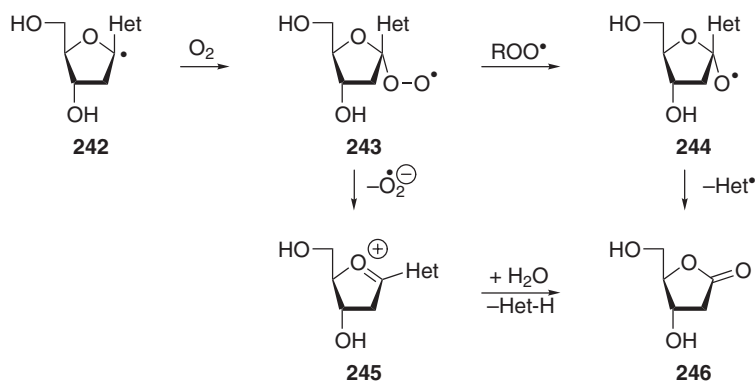
Giese and co-workers [<1998AG\(E\)460>](#) have extended their studies on the dissociation of β -phosphatoxy radicals (e.g., **239**) by examining the subsequent electron transfer reactions of the resulting cation radicals (Scheme 164). In rigid double-stranded DNA it was found that cation radical **240** could abstract electrons from neighboring guanine bases provided they were $<7 \text{ \AA}$ distant.



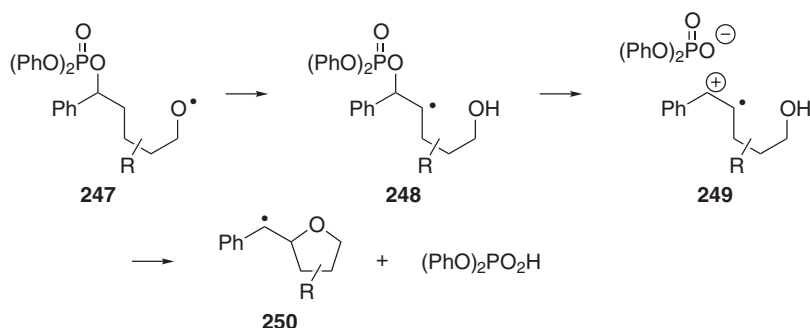
Scheme 164

Chatgililoglu and Gimisis [<1998CC1249>](#) have shown on the basis of ^{18}O labeling experiments that the peroxy radical **243** partitions between heterolytic scission to give the 2'-cation **245** which in turn is hydrolyzed to give the 2'-ribolactone **246**, and reaction with another peroxide radical to give the 2'-alkoxy radical **244**. The latter eliminates an uracil-1-yl radical also giving the ribolactone **246** (Scheme 165).

Crich and co-workers [<1999OL225>](#) (Scheme 166) reported the synthesis of tetrahydrofurans via a radical nucleophilic displacement from β -(phosphatoxy)alkyl radicals **248** following a 1,5-hydrogen atom abstraction by the initially formed alkoxy radical **247**. The mechanism probably involves a stepwise fragmentation of the β -(phosphatoxy)alkyl radical **248** to give a styrene-type radical cation/phosphate anion pair **249** which then ring closes to produce the more stable benzylic radical **250**.

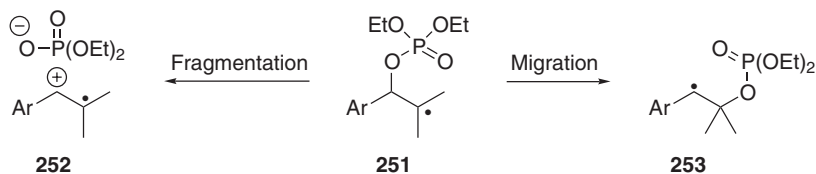


Scheme 165



Scheme 166

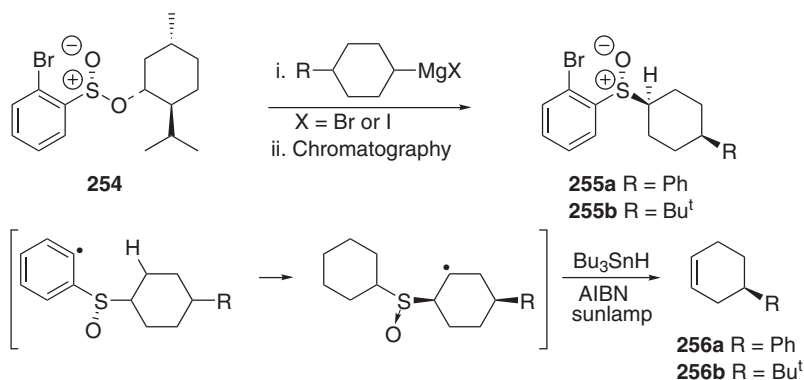
β -(Phosphatoxy)alkyl radical reactions are involved in the cleavage of DNA by anticancer agents. Solvent effect studies and measured entropies of activation indicate that radicals of type **251** react via initial heterolysis to **252** (Scheme 167). This then either collapses to products **253** (net migration) or yields free radical cation **252** <1999OL153, 1999JA10685>.



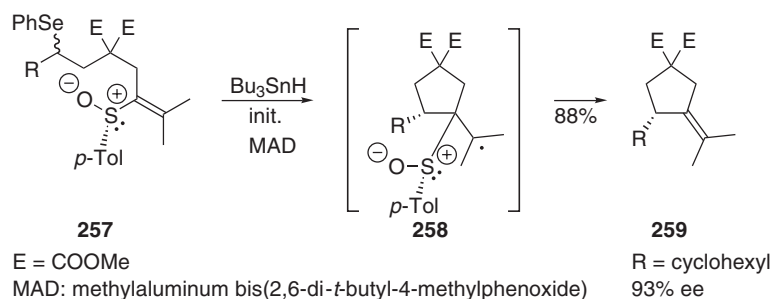
Scheme 167

An enantioselective preparation of 4-substituted cyclohexenes by radical fragmentation has been proposed by Renaud and co-workers (Scheme 168) <1999OL873>. Treatment of *cis*-**255a** and *cis*-**255b** with Bu_3SnH /AIBN/benzene (sun lamp, 10 °C) gave **256a** and **256b** with ee values of 70% and 80%, respectively.

Malacria and co-workers <1999JA11395> reported an asymmetric intramolecular radical vinylation using enantiopure sulfoxides **257** as temporary auxiliaries (Scheme 169). The intermediate radicals of type **258** undergo β -elimination producing enantiomerically enriched methylenecyclopentanes **259**.



Scheme 168

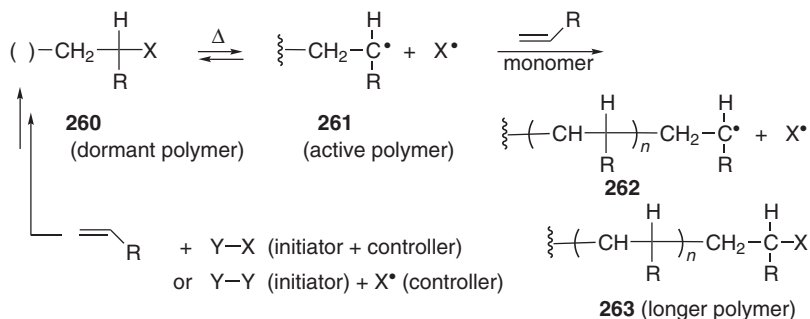


Scheme 169

1.19.13.4.9 Radical polymerization

(i) Living radical polymerization

In 1982, Otsu and Yoshida <1982MI127, 1982MI133> using phenylazotriphenylmethane as initiator to polymerize methyl methacrylate at 60°C found that molecular weight increased linearly with the conversion. The “living” character of the polymerization was demonstrated by observing that the polymer so-obtained continued to grow on heating to 80°C in the presence of the monomer, generating a high molecular weight polymer. Detailed studies on the initial step in free radical polymerization of α -(substituted methyl) acrylates have used ESR spectroscopy (Scheme 170) <2003MI2883>.

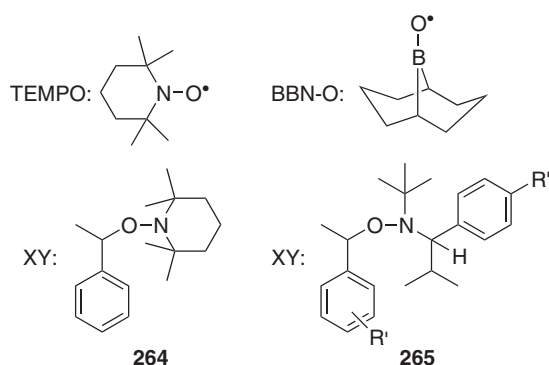


Scheme 170

Since this pioneering work, a large number of solutions have been proposed for the living radical polymerization. The strategy for controlling radical polymerization lowers the (instantaneous) concentration of a growing radical species by introducing a covalent dormant species **260**.

that exists in fast equilibrium with a small amount of **261**, the growth-active radical species. Such a dynamic and rapid equilibrium not only minimizes the extent or probability of the radical bimolecular termination but also gives an equal opportunity of propagation to all polymers (or dormant) terminals via the frequent interconversion between the active and the dormant species. These features thus lead to nearly uniform chain length (molecular weight) determined by the molar ratio of monomers to the dormant species (or the initiator). Another factor for consideration is the so-called “persistent radical,” a relatively stable radical that does not react with its own kind but does combine with the growing end (e.g., $\text{Ph}_3\text{C}^\bullet$, TEMPO). Its importance has been pointed out as it is necessary for the control [<2001CRV3581>](#).

The covalent bonds of the dormant species include C–C ($\text{X} = \text{Ph}_3\text{C}$), C–S ($\text{X} = \text{Et}_2\text{NCS}_2^\bullet$, PhCS_2^\bullet), C–Se ($\text{X} = \text{PhSe}$), C–O ($\text{X} = \text{TEMPO}$, BBN–O), C–Hal ($\text{X} = \text{I}$), and C–Metal [<2001CRV3689>](#) (Scheme 171).



Scheme 171

The initial work of Hawker [<1994JA11185, 1997MI373>](#) on the use of alkoxyamines as unimolecular initiators demonstrated that the molecular weight of polystyrene could be accurately controlled up to M_n values of ca. 75,000 using the assumption that one molecule of the TEMPO-based alkoxyamine **264** initiates the growth of one polymer chain and the length, or degree of polymerization, of the chain is governed by the molar ratio of styrene to **264**. Subsequently, the second-generation alkoxyamines, such as **265**, have conclusively proved this ability and, especially in the case of **264**, the upper molecular weight limit (M_n) for controlled molecular weights has been increased to between 150,000 and 200,000. For typical monomers and polymerization conditions, values of ca. 200,000 may represent an upper limit for nitroxide-mediated living free-radical systems [<1999JA3904>](#).

(ii) Metal-catalyzed living radical polymerization

As already mentioned earlier (Scheme 106), the Kharasch addition of alkyl halides to alkenes can be catalyzed by the nickel complex $\text{Ni}(\text{NCN})\text{Cl}$. The transition metal complex (catalyst) induces reversible activation of the carbon–halogen bond of the halide that generates an alkyl radical, which on its turn initiates the polymerization of the alkene (Scheme 172).

Organic halides such as CCl_4 , CCl_3Br , PhCH_2Cl , $\text{Ph}(\text{Me})\text{CHCl}$, $\text{PhCOC}(\text{Me})_2\text{Br}$, $\text{CH}_3\text{CH}(\text{CN})\text{Cl}$, or arenesulfonyl chlorides have been used for the radical polymerization initiated by transition metal complexes such as $\text{RuCl}_2(\text{PPh}_3)_3$, $\text{Cp}_2\text{Fe}_2(\text{CO})_4$, $\text{CpFe}(\text{CO})_2\text{Br}$, copper complex **266**, $(\text{Ph}_3\text{P})_2\text{NiBr}_2$, $(\text{Ph}_3\text{P})_2\text{ReO}_2\text{I}$, and many others [<2001CRV3689>](#) such as those shown below (Scheme 173).

One of the most important applications of living polymerization is block copolymerization. Block copolymers have interesting properties and are sought more and more in material sciences (nanotechnology). Block copolymers are usually obtained via sequential living polymerization of a monomer followed by that of another. The metal-catalyzed living radical polymerization permits a wide variety of block copolymers to be prepared, starting with a large variety of alkenes such as styrenes, acrylates, and methacrylates [<1994SCI1710>](#). Organotellurium-mediated living radical polymerization has been found suitable for the synthesis of di- and triblock copolymers (Scheme 174) [<2002JA13666>](#).

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Biographical sketch



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Professor Vogel is widely travelled and has taught in several universities of France and USA.

Professor Vogel is a member of several professional associations, Swiss, American, and French chemical societies, and was awarded the Swiss Chemical Society Werner medal in 1976.

Professor Vogel is also a member of editorial board of several journals, *Helvetica Chimica Acta*, *Chimia*, *Journal of Carbohydrate Chemistry*, *Carbohydrate letters*, *Current organic synthesis*, etc.

Professor Vogel is author of 3 books and more than 390 publications.

Professor Vogel has broad research interests in, synthetic, physical organic and Carbohydrate chemistry. His research interests also include new reaction of SO₂, new Organic Chemistry based on SO₂, new catalysts adaptive Chemistry and dynamic libraries of ligands for biopolymers.

1.20

Allenes and Cumulenes

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1.20.1 INTRODUCTION

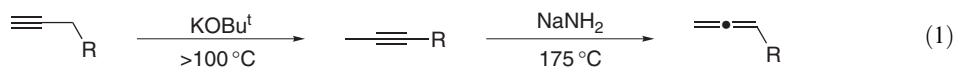
The preparation and reactivity of allenes and cumulenes have received special attention in several reviews. After the first reviews on allenes <1964RCR1, B-1969MI120-01> and cumulenes <1961BSF2176>, methods for preparation were described by Taylor <1967CR317>, Murray <1977HOU(5)963>, Hopf <B-1980MI779>, Landor, <B-1982MI120-01>, and Brandsma <B-1984MI120-01>. More specialized reviews have appeared dealing with propargylic rearrangements <B-1969MI(7)365>, allenic ketones <1980T331>, strained cumulenes <1989CRV1111>, and reactivity of allenes <1984T2805, B-1984MI120-02, 2003ACR773>. Recent synthetic methods and applications published during the 1990s has been reviewed here since the publication of <1995COFGT(1)953>.

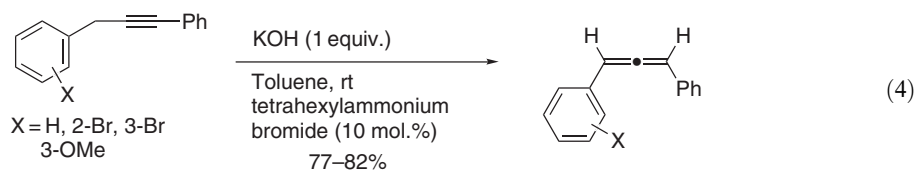
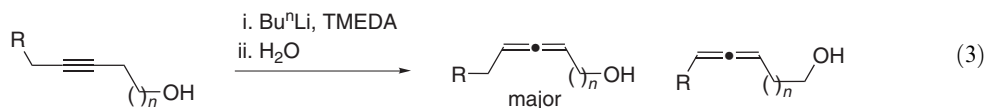
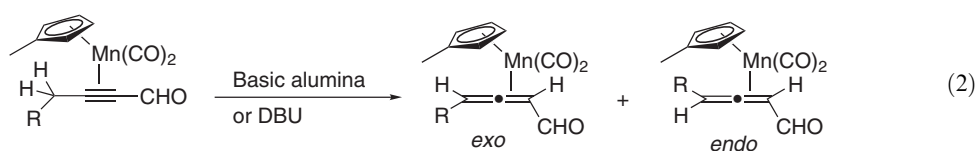
1.20.2 BY C—H BOND FORMATION

1.20.2.1 Isomerization of Alkynic Compounds

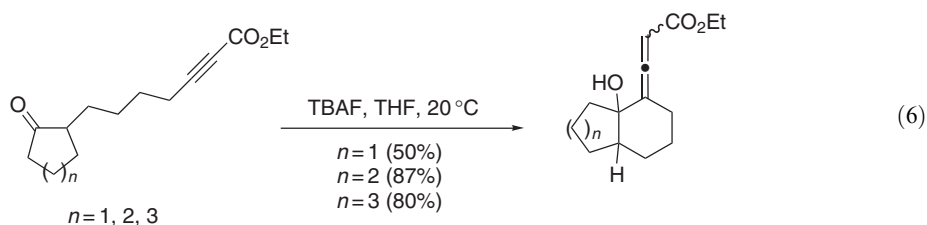
1.20.2.1.1 Isomerization of alkynes and diynes

Allenes were initially prepared by isomerization of the $\text{RCH}_2\text{—C}\equiv\text{C—}$ moiety in the presence of a strong base such as an alkali metal amide (NaNH_2) at high temperature (Equation (1)) <B-1969MI120-01>, or when the α -hydrogen is more acidic, with a tertiary amine <1965CB2611> or basic alumina <1964T2177, 1990JA2402>. Activation of the triple bond via coordination to a manganese moiety can facilitate the isomerization with Al_2O_3 <1979AG(E)688> and has been used to prepare chiral allene derivatives of high enantiomeric purity from alkynic aldehydes <1998TA697> after the separation of the allene metal complex enantiomers (Equation (2)). Internal acetylenes containing a hydroxy group can be regioselectively isomerized to allenic alcohols with BuLi/TMEDA (Equation (3)) <1986TL4599>. Recently, it has been shown that potassium hydroxide could be used as a base when the reaction was performed under phase-transfer conditions in the presence of an ammonium salt (Equation (4)) <2000SL493>. From diynes, the prototropic rearrangement leads to bisallenyl derivatives in the presence of KOBU^t <1973TL3181> (Equation (5)), and from 1,4-diynes milder conditions can be used (NaOH/EtOH) for the preparation of alkynyl allenes <1958JA1376>.



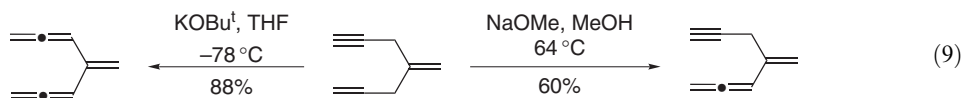
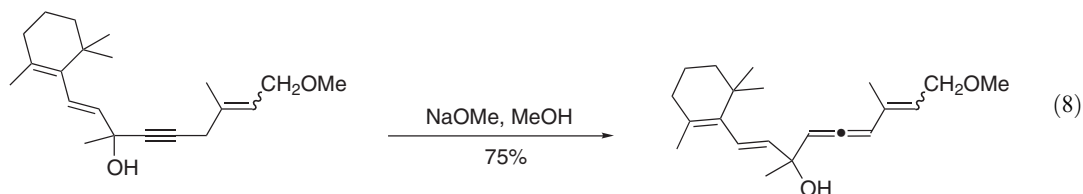
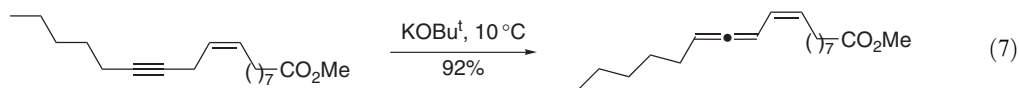


From alkynic ω -keto esters bearing a cyclic ketone in their skeleton, a cascade reaction involving successive C—C and C—H bond formation was observed in the presence of tetrabutylammonium fluoride, which led to exocyclic allenes (Equation (6)) [<2001OL2689, 2003TL4483>](#).



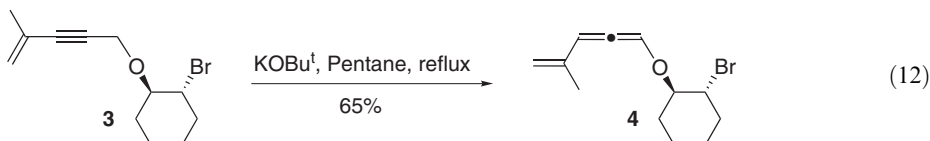
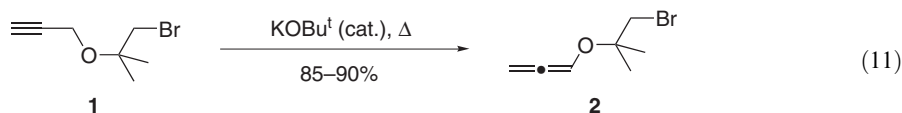
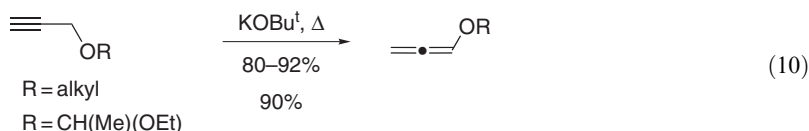
1.20.2.1.2 Isomerization of enynes

1,4-Enynes have been isomerized using KOBU^t to produce conjugated ene-allenes (Equation (7)) [<1965JOC2983>](#). 1,4-Enynes containing a hydroxy group have been transformed into conjugated vinyl allenyl alcohol derivatives in the presence of 5% methanolic sodium hydroxide (Equation (8)) [<1953JA1050>](#). Cross-conjugated ene-allenes and ene-diallenes have been produced by prototropic shift from a 1,4-enediynes under selected conditions (Equation (9)) [<1987TL2697>](#).

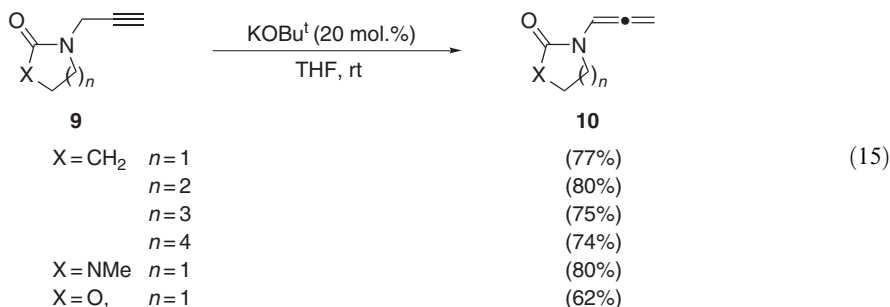
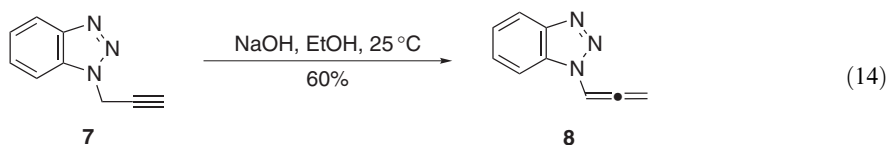
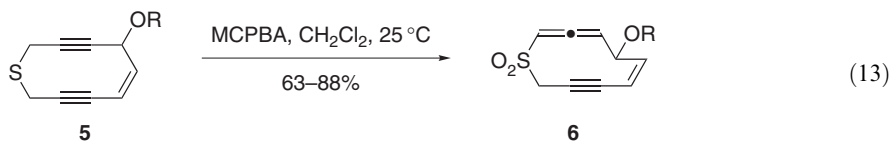


1.20.2.1.3 Propargylic rearrangement

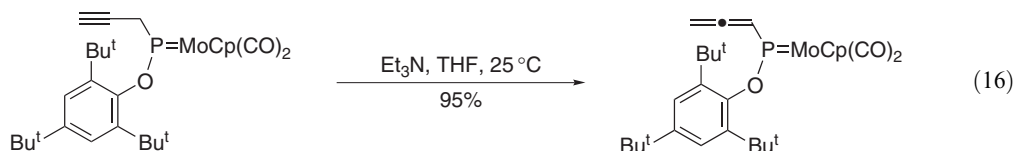
Propargyl derivatives with a heteroatom X attached to the sp^3 -C(—C≡C—CHR¹—X—R) easily undergo a base-catalyzed rearrangement leading to stable allenenes —CH=C=CR¹—X—R. Allenyl ethers, efficient building blocks in organic synthesis <1993S165, 1993SL105, 1993JOC5709, 1992AG(E)1033>, are generally obtained in 80–100% yield by reaction of propargyl ethers with KOBu^t (Equation (10)) <1968RTC916, 1993JOC5702>. Catalytic amounts of KOBu^t are used for the selective transformation of 2-alkynyl ethers **1** containing a bromine into allenyl ethers **2** (Equation (11)) <1988JCS(CC)237>. This reaction can also be applied for the generation of alkenyl allenenes **4**, precursors for Diels–Alder cycloadditions, from **3** (Equation (12)) <1993JCS(CC)270>.



Cyclic enyne allene sulfones **6** have been prepared by oxidation of cyclic enediyne sulfides **5** with MCPBA (Equation (13)) <1993JCS(CC)1406>. Propynyl sulfones <1992JCS(CC)735> and alkynyl amines can be converted into allenyl derivatives by treatment with potassium amide or alumina <1968JCS(C)228, 1968JCS(C)606>. The allenyl benzotriazole **8** has been prepared in satisfactory yield by treatment of propargyl benzotriazole **7** with NaOH (Equation (14)) <1993JOC3038>. Similarly, a variety of allenamides **10** have been obtained upon treatment of the propargylic derivatives **9** with Bu^tOK (20 mol.%) in THF at room temperature (Equation (15)) <2003ACR773, 2002OL2417, 2001T459, 1999TL6903>.

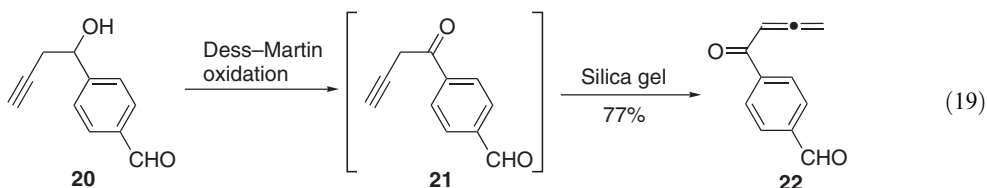
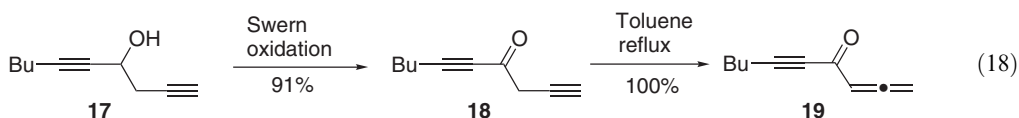
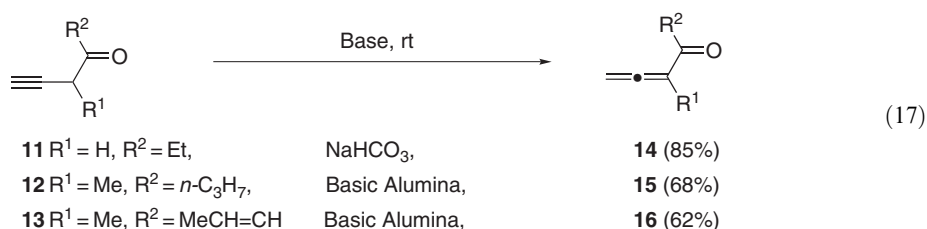


The mild isomerization of the prop-2-ynyl into the allenyl group can also be achieved from phosphine derivative ligands coordinated to metal complexes (Equation (16)) <1993CB1077>.



1.20.2.1.4 Rearrangement into α -allenic ketones

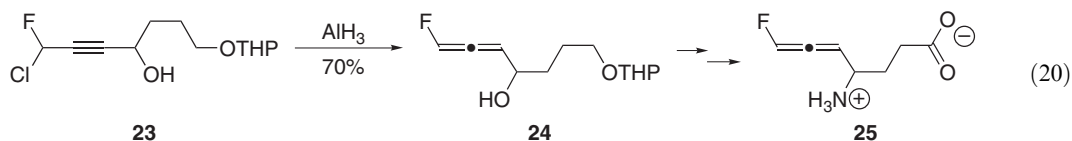
The rearrangement of β -alkynic ketones into α -allenic ketones can be achieved by using NaHCO_3 in water, e.g., **11** to **14** <B-1984MI120-01>, basic alumina, e.g., **12–15** and **13–16**, <1986JOC2623> (Equation (17)), or silica gel <1998TL7491, 1986JOC2623, 1996JA8949>. A good method to produce the allenynone **19** from the alkynyl homopropargylic alcohol **17** involves first, the Swern oxidation into **18** followed by thermal <1993TL449> or basic <1994JOC7169> rearrangement (Equation (18)). The oxidation of homopropargylic alcohols by the Dess–Martin periodinane reagent also affords allenones in good yield after work-up over alumina or silica gel <1990JOC3450, 1994JOC7169> as illustrated by the transformation of **20** into **22** via the ketone **21** (Equation (19)) <1998TL7491>.



1.20.2.2 Reduction of C—C Triple Bonds

1.20.2.2.1 Dehalogenation of alkynic halides

Dehalogenation of α -alkynic halides by reducing agents such as Zn-Cu/ROH or LAH constitute a general access to allenic derivatives. Since the direct reduction of propargylic alcohols is not possible under these conditions, α -allenyl alcohols can be prepared from α -halo- α' -hydroxy alkynic compounds <1955JOC1337>. For example, in the synthesis of the first fluoroallenyl amino acid **25**, the fluoroallenyl group is formed by reduction of the chlorofluoropropargyl synthon **23** into the fluoroallenic alcohol **24** (Equation (20)) <1987JA3491>.



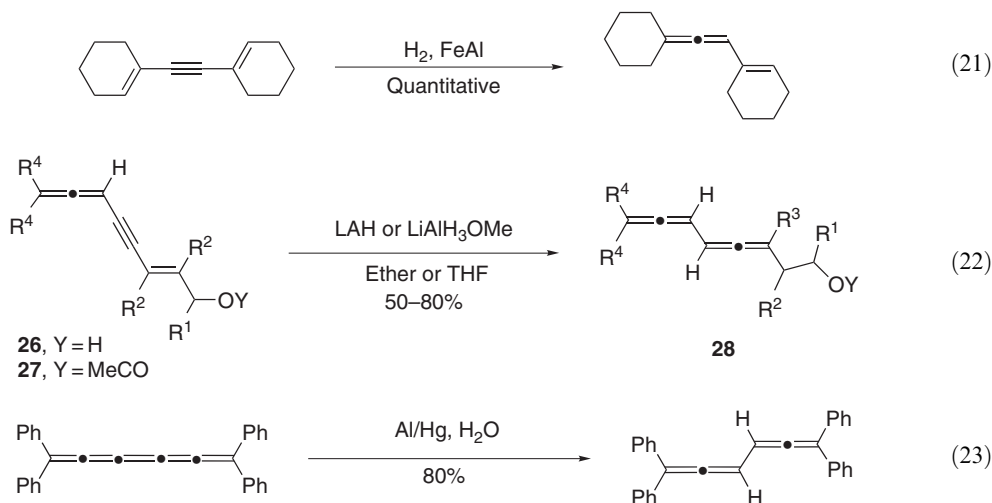
The Hiyama reagent, CrCl_2 generated from CrCl_3 and LAH , or CrCl_2 in the presence of AcOH <1983T2185> are also useful reducing systems that led to allenes and vinyl allenes from propargylic halides <1978TL3801> and 1-bromo-4-ene-2-yne <1979NJC321>. The use of a chiral

protonating agent such as (–)-menthol or (–)-borneol for the reduction of 1-bromo-2-alkynes leads to the formation of enantiomerically enriched allenenes <1981TL103>.

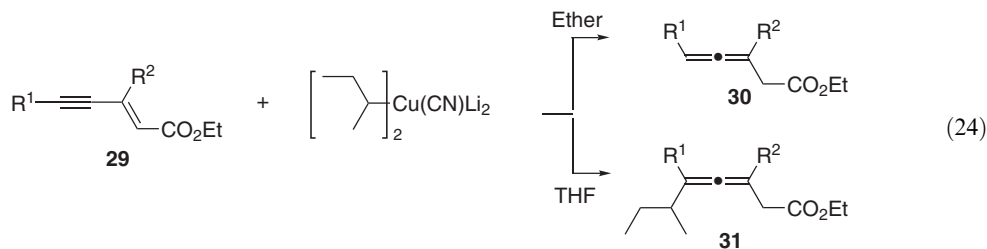
Alkynic halides of different structures, with the halogen separated from the triple bond by an unsaturated conjugated chain, have been reduced by generation of vinylallenyl metal intermediates, which release the allene on hydrolysis <1972TL4465, 1972JCS(CC)866, 1974BSF1119, 1976S755>.

1.20.2.2.2 Reduction of polyunsaturated hydrocarbons

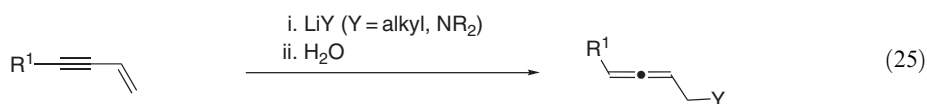
The formal 1,4-addition of hydrogen to conjugated enynes affords allenenes as illustrated by the reduction of dicyclohexen-1-yl acetylene with hydrogen in the presence of an iron/aluminum catalyst (Equation (21)) <1942AS363>. Conjugated 2-en-4-yn-1-ols are reduced to 3,4-dien-1-ols by LAH in refluxing diethyl ether <1975BSF1407>. Enynes containing an allenyl group and either a hydroxy **26** or an acetate **27** group have been reduced into diallenenes **28** with LAH (for **26**) or with LiAlH_3OMe (for **26–27**) (Equation (22)). With this latter reagent, less competing hydroxy substitution by the hydride takes place. This reduction corresponds to a 1,4-addition of H^-/H^+ and the presence of a hydroxy group in **26** probably facilitates the hydride transfer via an alkoxyhydrido aluminate- OAlH_3 intermediate <1974TL1593>. The reduction of 1,1,6,6-tetraphenylhexapentaene with aluminum amalgam in THF containing water gives 1,1,6,6-tetraphenyl-1,2,4,5-hexatetraene in 80% yield (Equation (23)) <1961CB3060>, but this strategy has been scarcely used for allene preparation.



A specific reduction of the enyne **29**, with the double bond linked to an ester group, has been achieved by treatment with cyanocuprate in ether. After protonation with pivalic acid, the allene **30** is obtained, whereas the carbocupration product **31** is formed when the reaction is performed in THF (Equation (24)) <1991TL7229>. It has also been shown that low temperature favors C–H rather than C–C bond formation in the reaction of propargylic acetates with organocuprates and LAH <1976JCS(CC)183>.

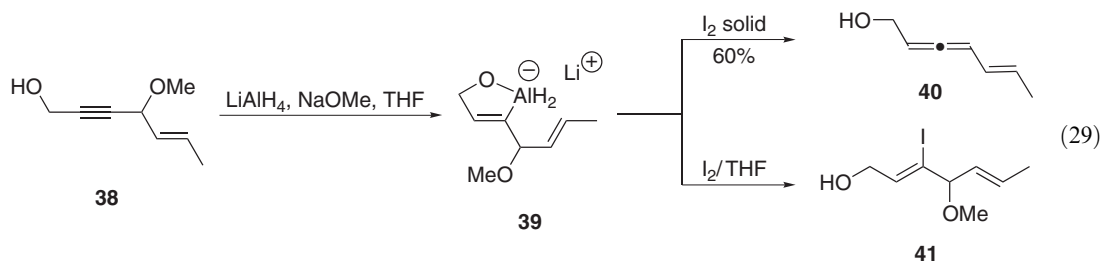
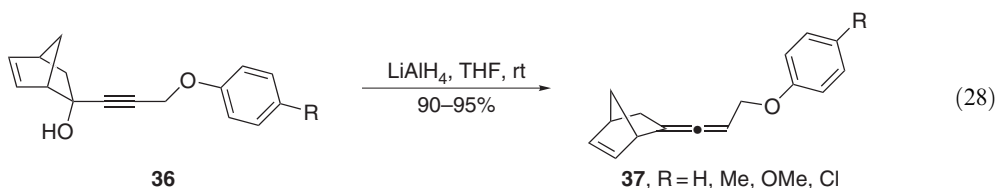
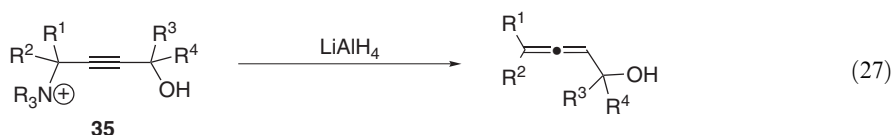
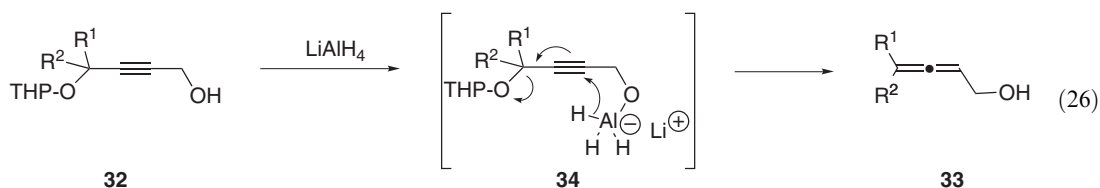


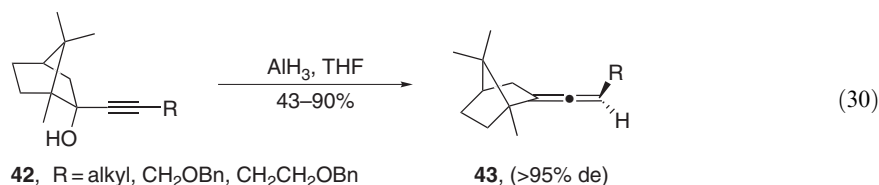
A reduction sequence, formally with R^- and H^+ , is exemplified by the addition of an organolithium <1977HOU(5)963> or a Grignard reagent <1974BSF1119> to enynes followed by hydrolysis (Equation (25)). A similar strategy was applied to the formation of aminomethyl allenenes by addition of amines to 1,3-enynes or by reaction with lithium amides followed by protonation (Equation (25)) <1977HOU(5)963>.



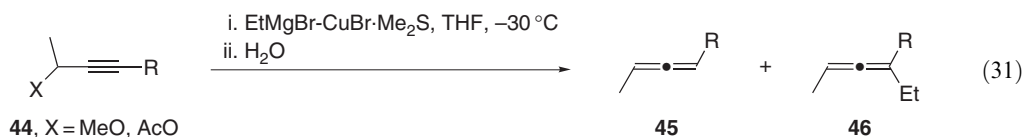
1.20.2.2.3 Reduction of propargylic derivatives

α -Allenyl alcohols **33** are obtained in good yields from the mono-*O*-tetrahydropyranyl ethers of but-2-yn-1,4-diols **32** by reduction with LAH under mild conditions (Equation (26)). This reaction is expected to produce first a $\text{C}\equiv\text{CH}_2\text{—O—AlH}_3^-$ intermediate **34** able to intramolecularly and stereoselectively substitute the leaving group O-THP by transfer of the hydride <1973JCS(P1)720>. α -Allenyl ethers and tertiary amines have been respectively prepared by reduction of 1,4-dialkoxybut-2-ynes and 4-dialkylamino-1-methoxybut-2-ynes with LAH and a Lewis acid (MgBr_2 or AlCl_3) <1985S768>. An analogous transformation can be achieved from **35**, which bears a quaternary ammonium group as the leaving group at the α' -position of the internal triple bond (Equation (27)) <1974S344>. The regioselective reduction of aryloxymethyl ethynyl carbinols **36** into aryloxymethyl allenes **37** can be achieved using only LAH in THF and in this case the regioselectivity observed is thought to result from the coordination of both oxygen atoms to the aluminum center (Equation (28)) <1986TL3777>. This reaction has been used to prepare liquid-crystalline allene derivatives with ferroelectric properties <1996LA1375>. A versatile method to produce a variety of hydroxymethyl allenes of type **40** has been shown to result from hydroxymethyl alkynes **38** by reduction with LAH in THF followed by treatment with solid iodine at -78°C . The reaction proceeds via the alanate **39**, whereas iodine in THF affords allylic iodo alcohols **41** (Equation (29)) <1982TL3051>. A one-pot protocol has been used successfully to reduce γ -methoxy- α -ynones into α -allenols with high enantioselectivities in the presence of Darvon alcohol and LAH <1994JA8526, 1993JOC5037>. It is however possible to transform propargylic alcohols with no leaving groups such as steroids into the corresponding allenes in the presence of LAH/ AlCl_3 (3/1) in THF <1975JCS(CC)362>. Propargylic alcohols **42** resulting from treatment of (*1R*)-(+)-camphor with alkynyllithiums are reduced by AlH_3 in THF at 90°C to produce chiral allenes **43** in high diastereoselectivity (Equation (30)) <2002JOC1308>.

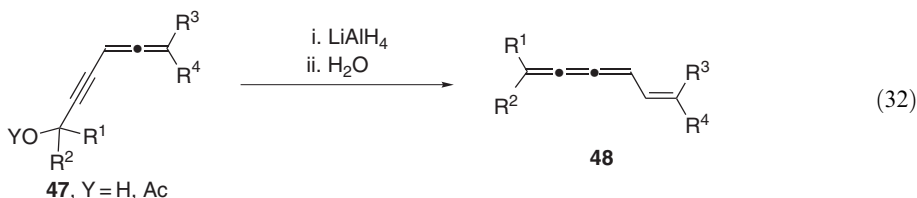




The reaction of propargylic ether or acetate **44** with ethylcuprate generated from excess EtMgBr and CuBr·Me₂S in THF actually gives a reaction mixture containing the allenes **45** and **46** resulting from reduction and alkylation, together with the alkynic isomers (Equation (31)) <1984JOC4120>.

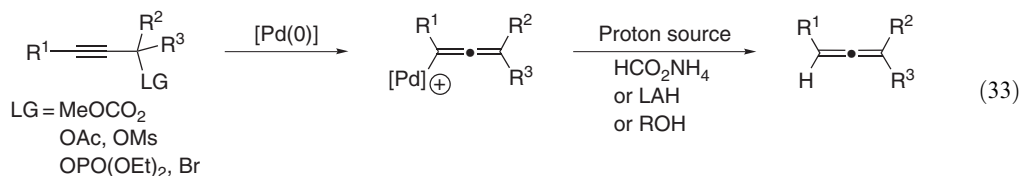


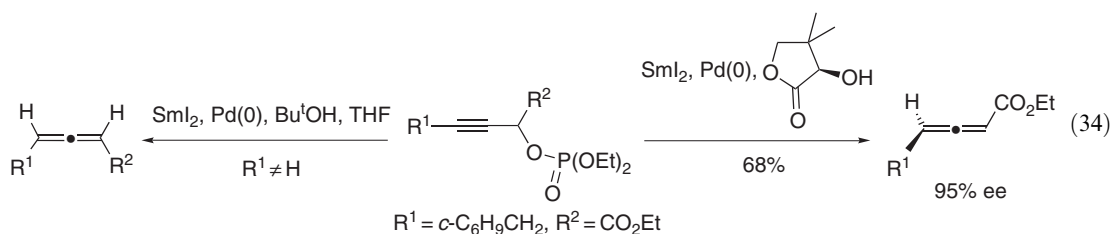
Cumulenes have been obtained from 4,5-dien-2-yn-1-ols **47** (or acetates), by reduction with LAH. The addition of the hydride to the central allenyl carbon with elimination of the hydroxy (or acetate) leads to the formation of cumulenes **48** (Equation (32)) <1975BSF2159>.



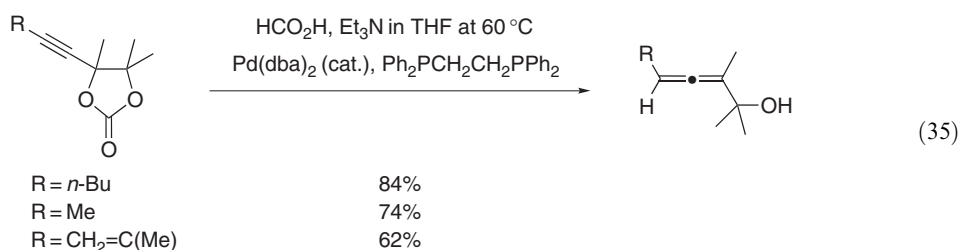
1.20.2.2.4 Palladium-catalyzed reduction of propargylic derivatives

Propargylic derivatives bearing a good leaving group (ester, carbonate, mesylate, phosphate, or halide) are known to be transformed by palladium(0) complexes to afford allenyl palladium intermediates. Their hydrogenolysis by an alcohol <1986TL5237>, or various sources of hydride like metal hydride <1984TL845> or ammonium formate <1987S603, 1986JCS(CC)922, 1996TL3417> leads to the formation of allenes (Equation (33)). The reduction of propargylic phosphates and acetates in the presence of palladium(0) catalyst and SmI₂, which proceeds via an allenyl samarium intermediate, has been shown to be highly dependent on the nature of the substrate and the proton source <1986TL5237, 1995TL907>. This method was applied to the synthesis of an isocarbacyclin analog <1996TL8515>. By tuning the proton source, regio-divergent synthesis of allenes/acetylenes from secondary propargylic phosphates was made possible (Equation (34)) <1997SL1375>. Asymmetric synthesis of allenes by reduction through a dynamic kinetic protonation of anionic allenyl samarium species was performed successfully by using a chiral proton source such as pantolactone or hydrobenzoin (Equation (34)) <1997AG(E)858, 2001T889>.



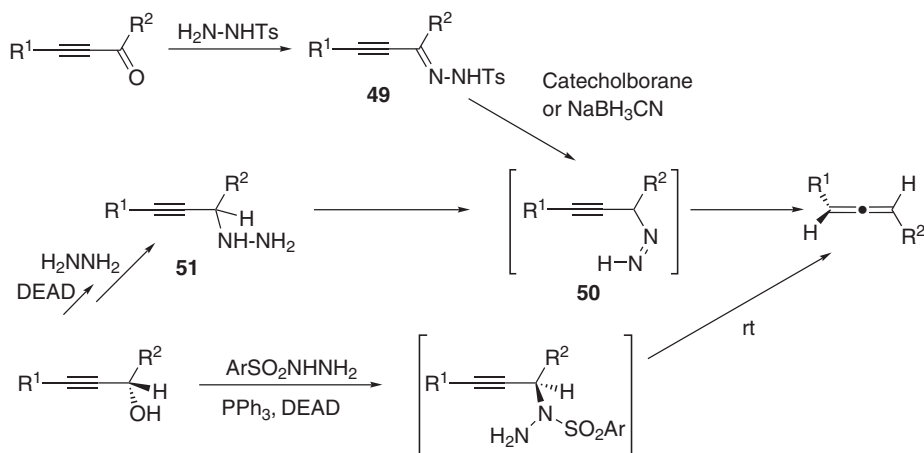


α -Hydroxy allenes have been obtained by a similar strategy, by reduction of alkynyl epoxides with triethylammonium formate in the presence of $\text{Pd}_2(\text{dba})_3 \cdot \text{CHCl}_3$ as catalyst precursor, but the selectivity was not good and homopropargylic alcohols were also formed [<1986JCS\(CC\)922>](#). α -Hydroxy allenes are more selectively formed starting from alkynyl cyclic carbonates in the presence of $\text{Pd}(\text{dba})_2/1,2\text{-bis}(\text{diphenylphosphino})\text{ethane}$ (Equation (35)) [<1994SL457>](#). Palladium-catalyzed decarboxylation-hydrogenolysis of propargylic formates having a terminal triple bond cleanly gives allenes at room temperature [<1993TL2161>](#).



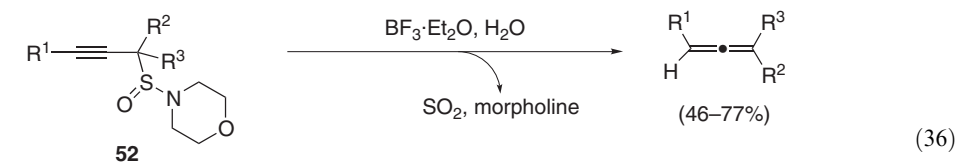
1.20.2.2.5 Elimination involving H-migration

The reduction of the tosylhydrazone derivatives **49** with catecholborane [<1978JCS\(CC\)726>](#)- or NaBH_3CN [<1980JOC3925>](#) produces allenes with loss of nitrogen and H-migration from a diazene intermediate **50** (Scheme 1). The same type of elimination reaction, which generates allenes with high stereospecificity from optically active propargylic alcohols [<1989TL5747, 1994JA6622, 1996LA1375>](#), is involved in the direct oxidation of propargylic hydrazines **51** by diethyl azodicarboxylate (DEAD) at 0°C . An improved straightforward stereoselective transformation is obtained by treatment of optically active propargylic alcohols with arenesulfonylhydrazines under mild Mitsunobu conditions (Scheme 1) [<1996JA4492, 1997JA2597, 2003JOC3739>](#).

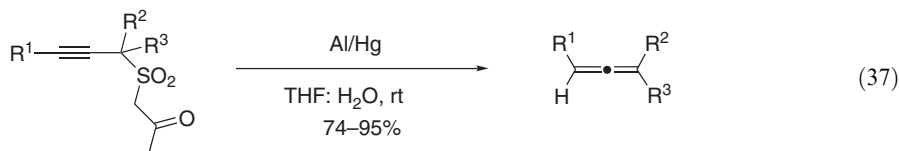


Scheme 1

Another example of elimination-rearrangement involving a sigmatropic 1,5-migration is illustrated by the formation of allenenes with loss of SO₂ via sulfinic acids generated from the hydrolytic treatment of propargylic sulfinamides **52** (Equation (36)) <1990TL213>. The reduction of alkynyl β -ketosulfones with the aluminum amalgam in THF provides an efficient method to synthesize trisubstituted allenenes via H-migration (Equation (37)) <1995TL7925>. The thermolysis of propargyl ketal at high temperature (390 °C) also affords allene and formate <1997T2049>.

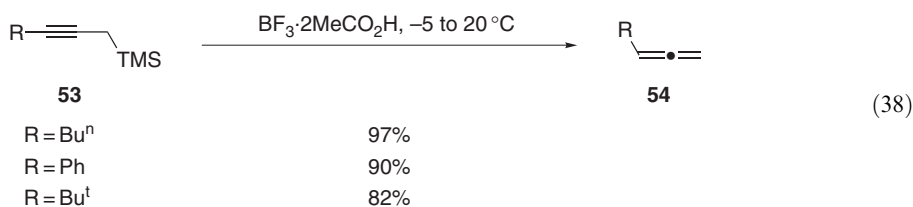


R¹ = alkyl
 R² = H, Me
 R³ = Me, allyl, *p*-tolyl-CH₂

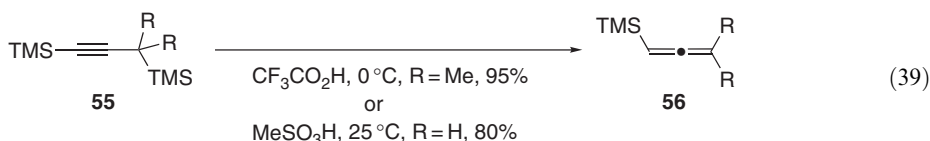


1.20.2.2.6 Hydrolysis of alkynic silanes

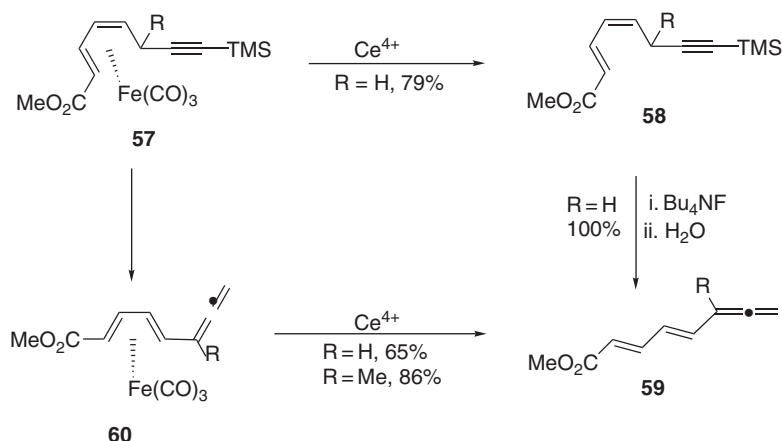
Electrophilic desilylation of propargylic silanes TMS-CH₂C≡CR **53**, in the presence of carboxylic acids such as CF₃CO₂H <1980JOC5006> or BF₃·2CH₃CO₂H <1987JOM(319)333>, provides a regioselective synthesis of monosubstituted allenenes **54** under mild conditions (Equation (38)). Selective cleavage of the propargylic trimethylsilyl group from TMS-C(Me)₂C≡C-TMS **55** leads to the substituted allenyl silanes **56** on treatment with CF₃CO₂H at 0 °C <1981JCS(CC)1094, 1981TL3401> or MeSO₃H at 25 °C <1972JOM(39)C44> (Equation (39)). 1-Trimethylsilylpropargyl alcohols are converted into trimethylsilyloxy allenenes in 63–96% yield by reaction of BuⁿLi, via migration of the trimethylsilyl group and protonation <1980TL623>.



R = Buⁿ 97%
 R = Ph 90%
 R = Bu^t 82%



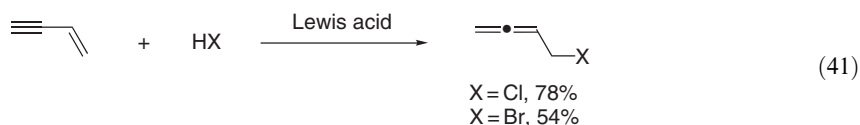
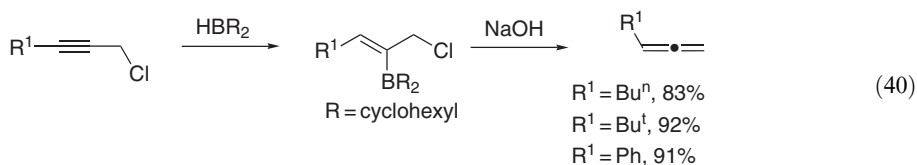
The cleavage of a ≡C–Si bond leads to a terminal allene via a propargylic proton transfer and protonolysis. This method has been used to access 1,2,4,6-tetraenes **59** and **60** from a free **58** or coordinated **57** trimethylsilyldienyne respectively, by cleavage with fluoride (Scheme 2) <1992BSF151>.



Scheme 2

1.20.2.2.7 Allenes via hydroboration, hydrohalogenation, and hydrosilylation

Hydroboration of 1-chloro-2-alkynes with diisooamyl or dicyclohexylborane in THF at 0°C gives α -chloromethylvinyl boranes, which undergo an easy elimination on treatment with sodium hydroxide to produce terminal allenes in good yield (Equation (40)) <1970JA1427>. 1,4-Addition of HX to conjugated enyne derivatives leads to allenes in satisfactory yields in the presence of Lewis acids, e.g., AlCl_3 or ZnCl_2 (X = Cl, Br) (Equation (41)), <1966JCS(C)1223> or palladium catalysts (X = $\text{B}(\text{OR})_2$) <1989TL3789, 1992OM2732>.



H_2PtCl_6 and $\text{RuHCl}(\text{CO})(\text{PPh}_3)_2$ are excellent catalysts for the hydrosilylation of conjugated *cis*-1,4-bis(trimethylsilyl)-1-buten-3-yne to produce silylated allenes <2000JOM(609)130, 1998JA1421>, whereas the rhodium- and nickel-catalyzed hydrosilylation of butadiynes leads to optically enriched silylated allenes in the presence of optically pure ligands <2000JOM(603)116>.

1.20.3 BY C—C BOND FORMATION

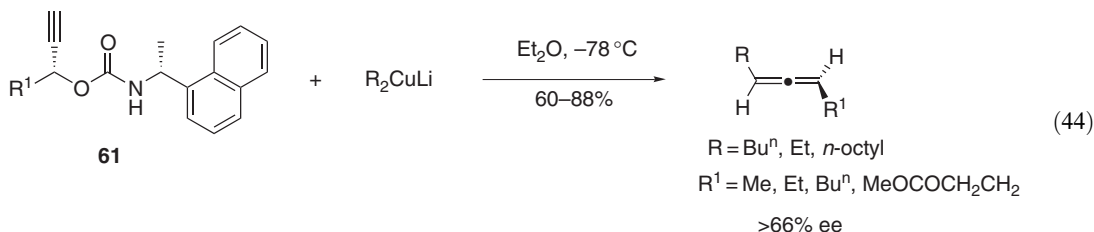
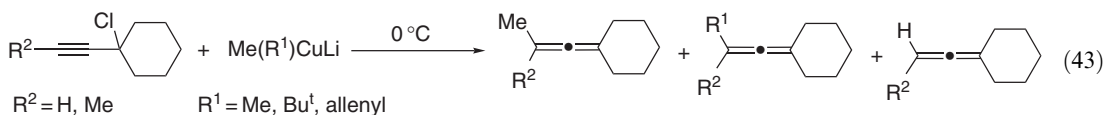
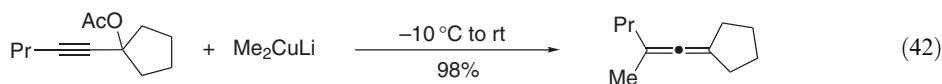
1.20.3.1 Nucleophilic Substitution with Organocopper Compounds from Propynyl Derivatives

1.20.3.1.1 Alkylcuprates as nucleophiles

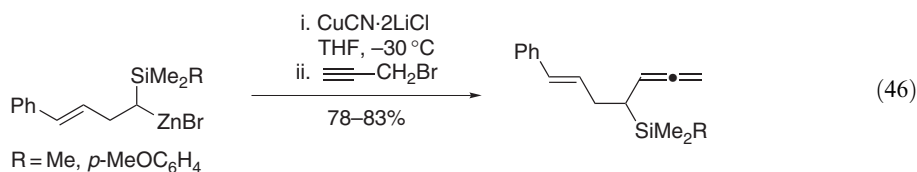
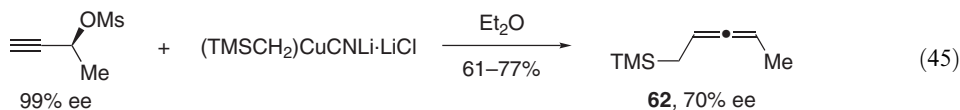
Since the first use of organocopper reagents to synthesize allenes from propargylic derivatives via selective $\text{S}_{\text{N}}2'$, displacement of a leaving group <1968JA4733>, many examples of this strategy have been reported involving a variety of labile groups and copper derivatives <1995JA6345, 1998T9373>.

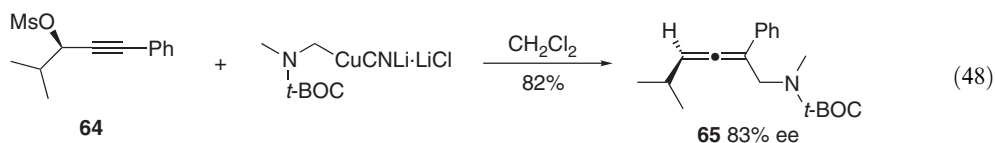
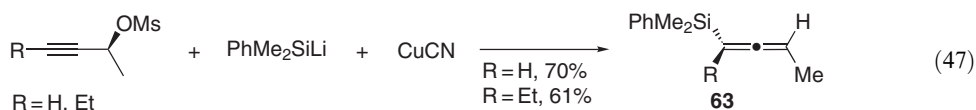
Diorganocuprates (Gilman's cuprates) are the most reactive copper reagents and the easiest to prepare. Thus, lithium cuprates allow the selective formation of allenes from propargylic acetates, mesylates, carbonates and halides, etc. Spirocycloalkyl allenes were prepared by addition of a dialkylcuprate to a propargylic acetate (Equation (42)) <1975TL4615>.

Pasto and co-workers [<1978JOC1389>](#) have observed the preferred formation of alkyl allenenes from mixed methyl alkyl cuprates and alkyl allenyl cuprates, and pointed out the competition between reduction and substitution in the case of terminal chloropropargylic derivatives ([Equation \(43\)](#)). Chiral allenenes, precursors of natural pheromones, have been obtained with lithium dialkylcuprates starting from optically active propargylic carbamates **61** ([Equation \(44\)](#)) [<1978JOC1950, 1978JOC2091>](#). Chiral allenenes, precursors of enantiomerically enriched tricyclic derivatives via a cobalt-mediated [2 + 2 + 2]-cycloaddition, were obtained with a similar methodology [<2000S985>](#).

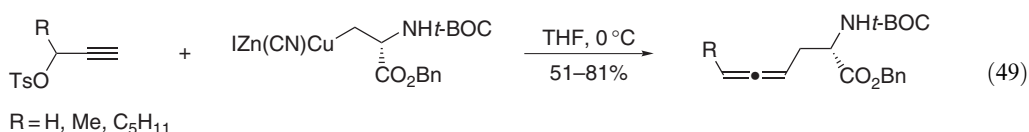


As 2 equiv. of nucleophile are required for the formation of dialkylcuprate, a more convenient procedure for functionalized nucleophiles was developed via heterocuprate chemistry. Thus, the use of alkyl cyanocuprates circumvents some of these problems; they are still reactive species and allow the synthesis of allenenes bearing nucleophilic functionalities such as nitrogen moieties [<1993SL499, 1995JOC2210, 2001JOC4904, 2001JCS\(P1\)1349>](#) or hydroxy functionality [<2003EJOC2043>](#). Allenyl methylsilanes **62** have been produced by treatment of propargyl tosylate with (trimethylsilylmethyl) cyanocuprate in ether ([Equation \(45\)](#)) [<2002OL3497>](#). By this method, a chiral allenene was synthesized in 70% ee starting from commercially available enantiopure (*S*)-but-3-yn-2-ol. α -Allenyl silanes have been produced by a $\text{S}_{\text{N}}2'$ substitution reaction of propargyl bromide with a cuprate species formed from silyl-substituted organozinc reagent and $\text{CuCN}\cdot 2\text{LiCl}$ ([Equation \(46\)](#)) [<1998SL1315>](#). Chiral allenenes **63**, precursors of the stereotriad subunits of polyketide natural products, have been prepared by a silylcuprate $\text{S}_{\text{N}}2'$ displacement method ([Equation \(47\)](#)) [<2000JOC630>](#). α -Aminoalkylcuprates, prepared from carbonates via sequential deprotonation and treatment with $\text{CuCN}\cdot 2\text{LiCl}$, react with propargyl bromides, mesylates **64**, tosylates, and acetates to afford aminoallenenes [<1999TL4293>](#). The reaction of a scalemic propargyl mesylate with the α -(*N*-carbamoyl)alkylcuprate afforded the *N*-*t*-BOC-aminoallene **65** in 82% yield and 83% ee ([Equation \(48\)](#)) [<2001OL3855>](#).

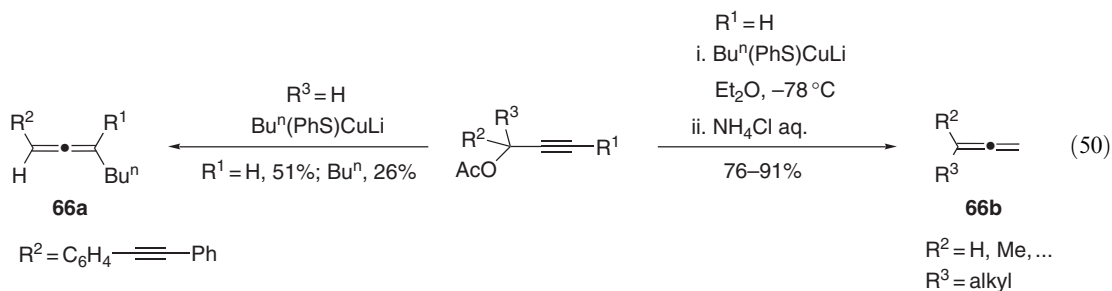




Another route, based on the use of propargyl chloride and alkylcopper reagents arising from optically active amino acids, has allowed the formation of enantiomerically pure protected amino acids containing an allenyl group [<1993SL219>](#). The same authors have described similar syntheses of allenic amino acids based on the use of zinc-copper reagents (Equation (49)) [<1993SL499, 1992JCS\(CC\)319>](#).



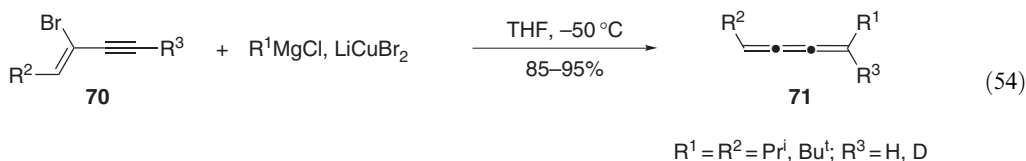
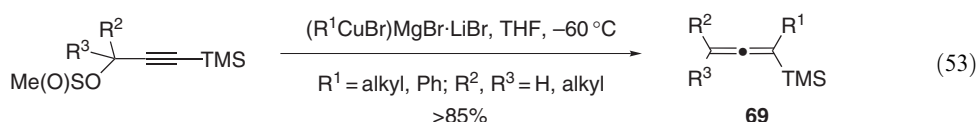
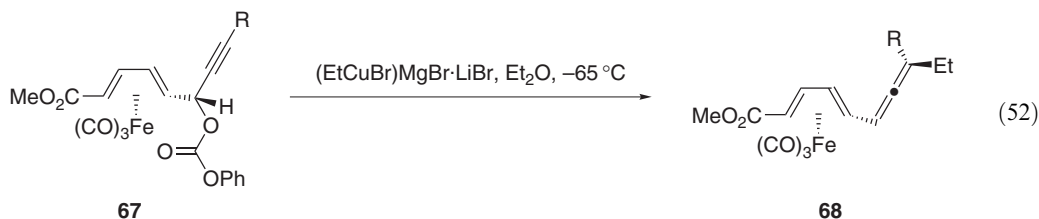
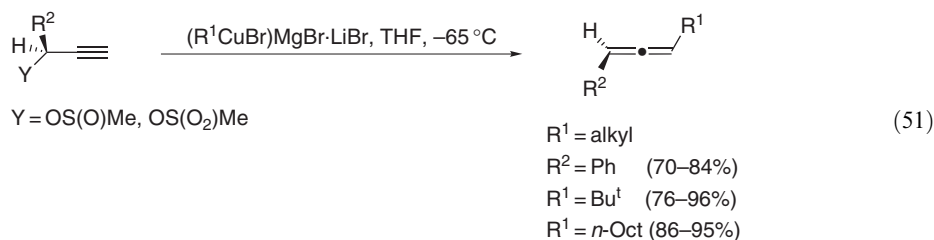
An alternative to the alkyl cyanocuprate is the lithium alkyl(phenylthio)cuprate. Depending on the reaction temperature and the stability of the intermediate copper species, the transfer of an alkyl ligand from copper to the proximal allenic carbon is possible. Thus, from propargyl acetates, substituted **66a** [<1997SL165>](#) or terminal **66b** [<1993S577>](#) allenes are readily prepared (Equation (50)).



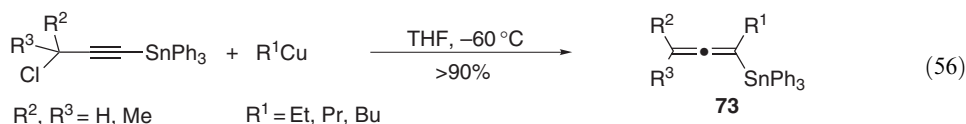
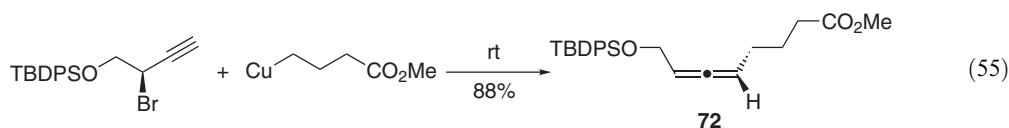
For the synthesis of the bromoallene, (–)-isolaurallene, the allenic moiety has been formed in a related copper-mediated $\text{S}_{\text{N}}2'$ -substitution reaction by using triisopropylbenzenesulfonate as the leaving group and LiCuBr_2 as the bromide reagent [<2001JA1533>](#).

1.20.3.1.2 Stoichiometric organocopper reagents as nucleophiles

As diorganocuprates are known to racemize optically active allenes, other organocopper derivatives have been used for the synthesis of optically active allenes from chiral propargylic derivatives. Chiral 1-phenyl-3-alkyl and 1,3-dialkyl allenes have been obtained from propargylic sulfinates or sulfonates and $(\text{RCuBr})\text{MgBr} \cdot \text{LiBr}$ at -65°C (Equation (51)) [<1989JOC3726>](#). Dienyllallene tricarbonyl iron complexes **68** have been obtained from dienylpropargylic carbonate **67** or mesylate complexes and $(\text{RCuBr})\text{MgBr} \cdot \text{LiBr}$ ($\text{R} = \text{Et, Bu}^t$) with very high diastereoselectivity (Equation (52)) [<1992AG\(E\)224, 1993T9775>](#). These organocopper derivatives are also suitable reagents for the synthesis of silylated allenes **69** from trimethylsilyl propargylic sulfinates, mesylates, or tosylates (Equation (53)) [<1979S390>](#). Pure butatrienes **71** have been obtained from 3-bromo-alk-3-en-1-ynes **70**, as a result of *anti*-1,3-substitution, on treatment with a copper(I) species in THF at -50°C (Equation (54)) [<1982JOM\(240\)329>](#).

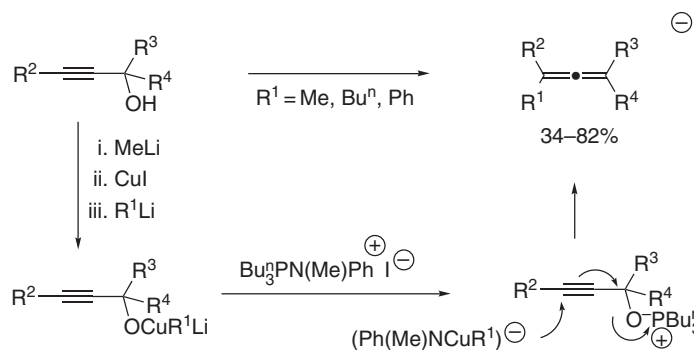


Other organocopper(I) reagents have been prepared by using Grignard or zinc reagents in the presence of stoichiometric amounts of Cu(I) halides in order to prepare liquid-crystalline allene derivatives [<1996CC977>](#). Fluorinated allenenes and bisallenenes have been prepared safely from propargylic halides or tosylates and perfluoroalkyl copper(I) compounds [<1990TL3703, 1990TL3699>](#). In a similar manner, stannylallenenes were obtained by adding the stannylcopper reagent to a suitable propargyl compound [<1994SC789>](#). The synthesis of the protected α -allenic alcohols **72**, of high optical purity, has been carried out starting from the appropriate chiral propargylic bromide or tosylate and functional Cu(I) derivatives ([Equation \(55\)](#)) [<1991JOC1083>](#). Stannyl alkynes react with alkylcopper(I) species at -60°C to give stannyl allenenes **73** in high yield, but quantitative transmetalation of the alkyne takes place with MeCu, $\text{CH}_2=\text{CH}-\text{Cu}$, $\text{Ph}-\text{Cu}$, and $\text{Me}_3\text{Si}-\text{C}\equiv\text{C}-\text{Cu}$ ([Equation \(56\)](#)) [<1984TL3019>](#). The copper(I) enolate generated from the lithium enolate of acetylacetone and CuI at -78°C substitutes propargylic esters to produce β -allenyl esters [<1978JOC555>](#).

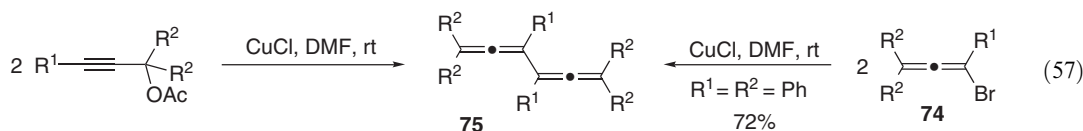


The direct 1,3-substitution of the hydroxy group of propargylic alcohols has been performed successfully by an organocopper derivative formed *in situ* from CuI, RLi, and (methyl-phenyl-amino)tributylphosphonium iodide ([Scheme 3](#)) [<1980JOC4536>](#).

Coupling either two propargylic acetate or two allenyl bromide **74** molecules in the presence of CuCl in DMF at room temperature furnishes symmetrical diallenenes **75** via allenyl radical intermediates ([Equation \(57\)](#)) [<1975JCS\(CC\)174>](#).

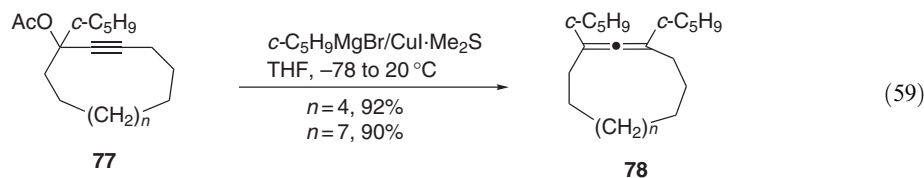
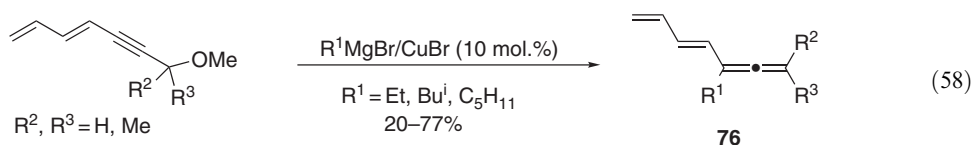


Scheme 3

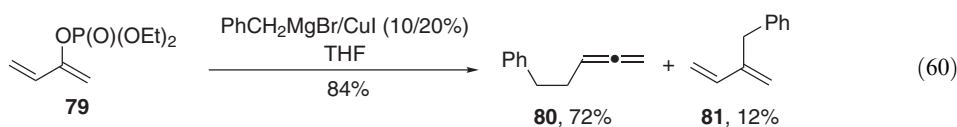


1.20.3.1.3 Copper(I)-catalyzed nucleophilic substitution

The use of Grignard reagents in the presence of a catalytic amount of copper(I) salt avoids the parallel formation of acetylenic derivatives resulting from simple nucleophilic substitution. Propargylic derivatives bearing an alkoxy leaving group have been used for access to polyalkylpropa-1,2-dienes <1976JOM(108)159>, 1,2,4,6-tetraenes **76** (Equation (58)) <1979TL7> and α -allenyl amines <1987TL2207>. Chiral functional allenes are obtained with high stereoselectivity from optically active propargylic ethers <1986TL5499, 1990JA8042> by using RMgBr , CuBr (5%), and $\text{P}(\text{OEt})_3$ to inhibit racemization. Cyclic allenes **78** can be obtained from cyclic propargylic esters **77** (Equation (59)) <1986TL4845>.



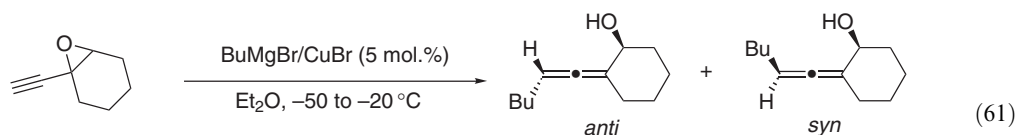
Starting from nonpropargylic conjugated 1,3-alkadien-2-yl diethylphosphate **79**, the substitution reaction with an organocopper reagent formed *in situ* from RMgX and CuX affords allene **80** in moderate yield, but suitable conditions have to be found to avoid the $\text{S}_{\text{N}}2'$ nucleophilic substitution giving the 1,3-diene **81** (Equation (60)) <1983TL1297>.



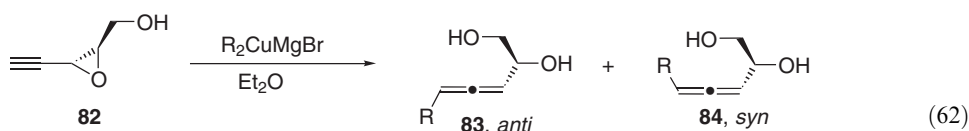
1.20.3.1.4 Organocopper-mediated ring-opening reactions

The organocopper-mediated ring-opening reaction of propargylic epoxides affords the corresponding hydroxyallenenes in high regio- and *anti*-diastereoselectivity. Thus, addition of α -amidoalkylcuprates to epoxides has led to the synthesis of amino-allenol <1999TL4293>.

The use of CuX catalysts also allows the diastereoselective synthesis of α -allenols from epoxides (Equation (61)) <1991T1677> and cyclic carbonate or sulfate derivatives in the presence of a Lewis acid <1992TA1509>. α -Allenyl alcohols, precursors of dihydrofurans, have been prepared by treatment of epoxy propargylic alcohols with methylcuprate <1993JOC7180>. The reaction of the chiral epoxy alcohol **82** with organocuprates leads to a mixture of *anti*- and *syn*-diols **83** and **84** at 35 °C, whereas the presence of dimethyl sulphide at -60 °C selectively orientates the nucleophilic substitution toward the formation of the *anti*-isomer **83** (Equation (62)) <1983TL5587>. 5-Trimethylsilyl-2-methylpenta-2,3-dien-1-ol has been produced by epoxide opening with a trimethylsilylmethylcopper(I) species formed from trimethylsilylmethyl magnesium chloride and LiCuBr₂ <1985JOC5143>.

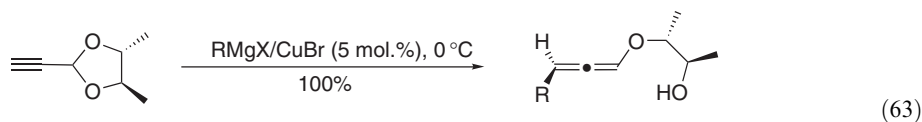


Additive: PBu₃, 74%; *anti* 100%
 TMSCl, 100%; *anti* 12%; *syn* 88%

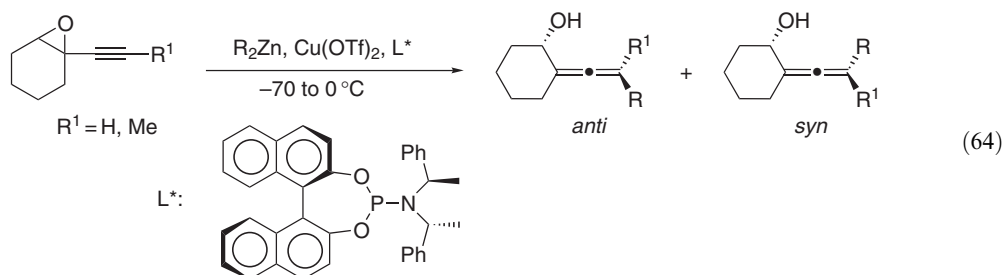


35 °C, 50%: **83/84** 40/60
 DMS, -60 °C, 57%: **83/84** 98/2

Chiral functional allenenes are obtained with high stereoselectivity either from optically active cyclic acetals <1985TL4197> by using RMgBr, CuBr (5 mol.%), and P(OEt)₃ in order to inhibit racemization (Equation (63)) or from racemic alkynyloxiranes (via kinetic resolution) by using dialkylzinc reagents in the presence of copper(II) triflate and a chiral ligand (Equation (64)) <1999TL4893>. Tetrasubstituted chiral vinylallenenes are formed from the enantioselective epoxidation of an enyne followed by an S_N2' addition of a cuprate <2000TL8033>.

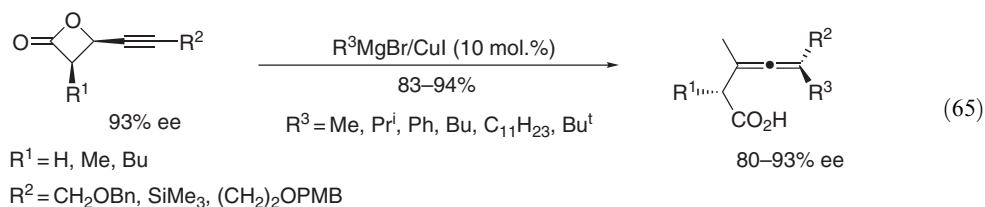


R = Me, 56% de
 R = Buⁿ, 70% de
 R = Bu^t, 100% de

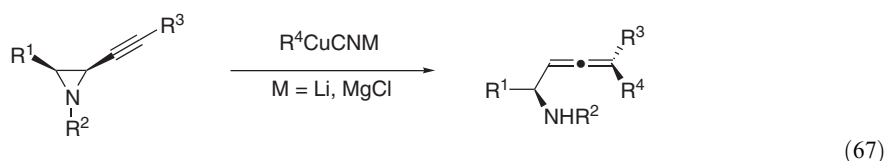
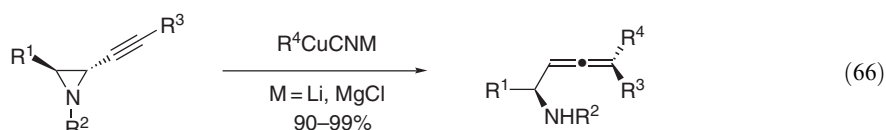


Wan and Nelson have reported the use of optically active alkynyl-substituted β -lactones as highly reactive precursors of allenenes through an S_N2' reaction with Grignard reagents in the presence of catalytic amounts of copper(I). Since the reaction occurs only via an *anti*-stereoselective addition

with complete chirality transfer from the stereogenic center of the lactone to the chirality axis of the allene, the latter was isolated in high ee (Equation (65)) <2000JA10470>.



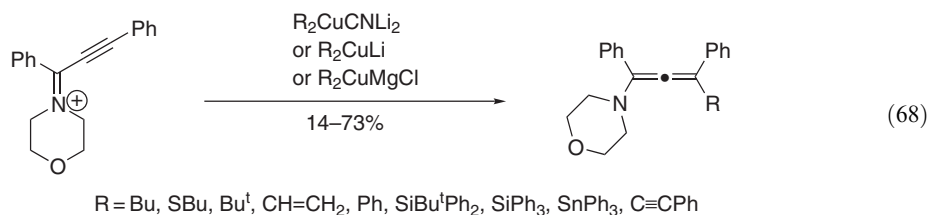
The aza-analogs of hydroxyallenes can be readily prepared by ring opening of the corresponding alkynylaziridines with diastereoselectivity from cyanocuprate reagents. Starting from chiral 2,3-*trans*- or 2,3-*cis*-ethynylaziridine, the addition of alkylcyanocuprate affords the (*S,S*)- and (*R,R*)-aminoallenes (Equations (66–67)) <1999TL7393>. With substituted alkynes, considerable differences were observed between the reaction of 2,3-*cis*- and 2,3-*trans*-aziridines with methylcyanocuprate. Moderate selectivities were reported with the *cis*-derivative whereas complete stereocontrol was obtained with the *trans*-isomer <2000T2811>.



$\text{R}^1 = \text{Pr}^i, \text{Bn, CH}_2\text{OTBDMS}$
 $\text{R}^2 = 2,4,6\text{-trimethylbenzenesulfonyl}$
 $\text{R}^3 = \text{H, CO}_2\text{Me, SiMe}_3$
 $\text{R}^4 = \text{Me, Et, Bu, Pr}^i, \text{Bu}_3\text{Sn}$

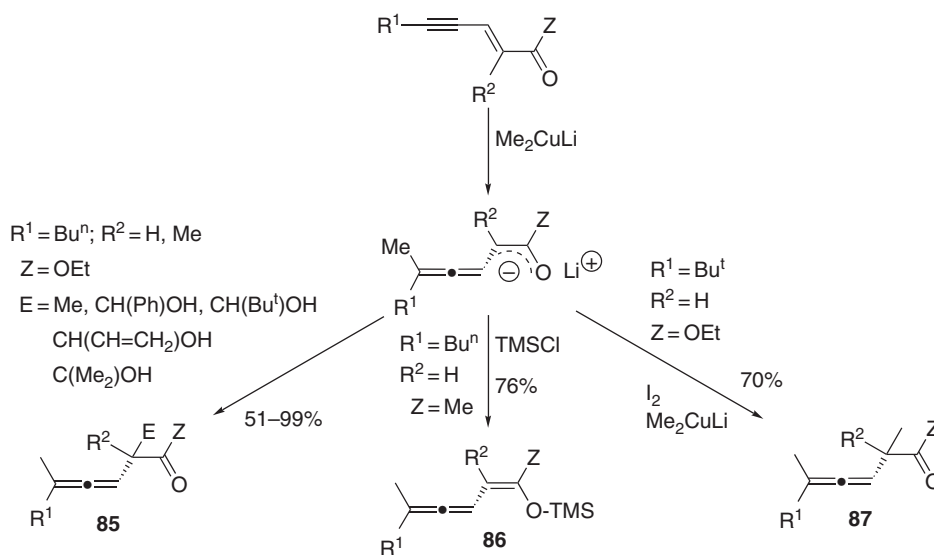
1.20.3.1.5 Copper-mediated 1,*n*-addition reactions

The copper-mediated conjugate addition of carbon, organosilyl, and organostannyl nucleophiles to propyne iminium salts allows the synthesis of aminoallenes (Equation (68)) <1990SL399, 1991S1209, 1995S957>.



3,3-Dimethylindoline-derived allenes are prepared by organocuprate addition to 2-(phenylethynyl)-3,3-dimethyl-1-methylindolium triflate <1997JOC7744>.

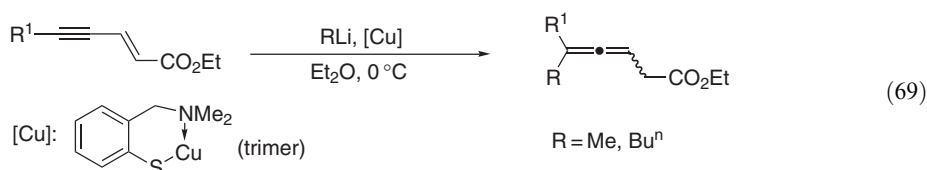
The generation of allenyl enolates by 1,6-addition of lithium dialkylcuprate to conjugated functional enynes makes possible the access to allenyl esters **85** by C–C bond formation <1995CB851, 1997AG(E)186, 1999ICA(296)1>, and to allenyl enol ethers **86** by C–O bond formation, on addition of electrophiles (Scheme 4) <1993CB251, 1993LA521>. When the starting alkyne is substituted by a bulky group such as a *t*-butyl group, these allenyl enolates can be trapped in the presence of iodine to selectively afford allene derivatives **87** (Scheme 4) <1993CB261>.



Scheme 4

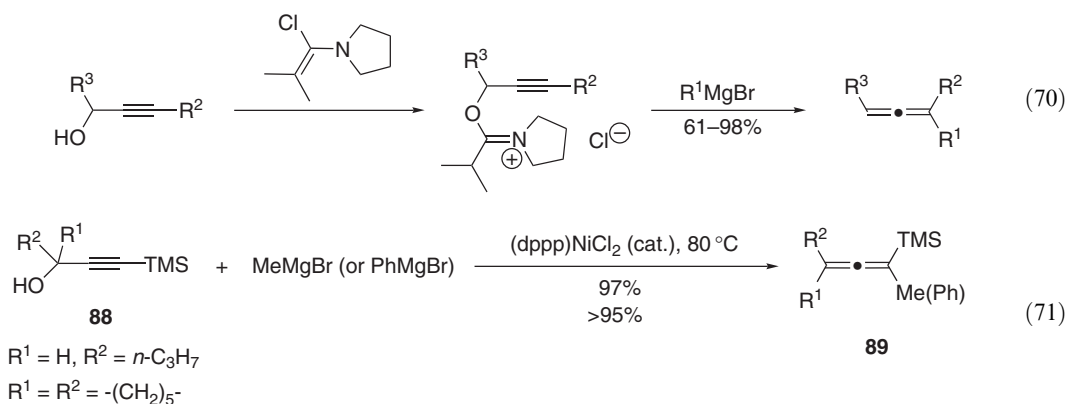
The Michael addition can be extended to 1,8-, 1,10-, and 1,12-addition with different dialkylcuprates [<1996LA1487>](#). A direct access to enantiomerically enriched and pure vinylallenes was described by Krause through 1,5-substitution reaction of chiral enyne acetate with organocuprates or organolithium reagents in the presence of a catalytic amount of copper salt [<2000AG\(E\)4355>](#). The presence of tri-*n*-butylphosphine or triethylphosphite as an additional ligand was necessary to avoid racemization of the product by reactive copper species.

Copper(I) arenethiolate with a tertiary amino substituent can also be used in catalytic amounts in 1,6-addition reactions of lithium reagents to ynenates to afford with excellent chemo- and regioselectivities the corresponding allenes ([Equation \(69\)](#)) [<1993JOC5849>](#).

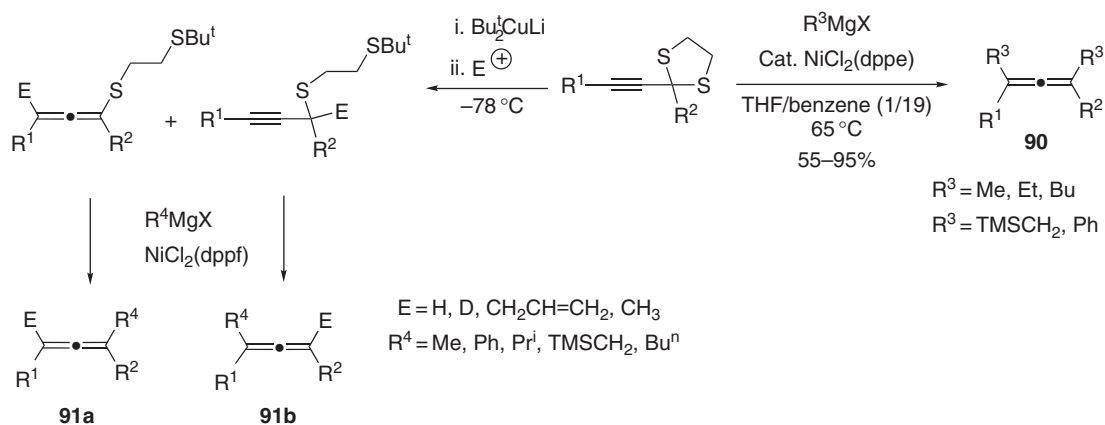


1.20.3.2 Nucleophilic Substitution with Organomagnesium Reagents

The reaction of propargyl derivatives with Grignard reagents is well documented but the competition between alkyne and allene formation has brought some restriction to its use. However, the selectivity of the 1,3-substitution has been improved by the use of specific leaving groups or catalytic systems involving transition metals. Thus, propargylic alcohols, *in situ* protected by 1-chloro-2-methyl-*N,N*-tetramethylenepropenyl amine, lead to the selective formation of allenes at 0 °C with alkyl, phenyl, vinyl, and allyl Grignard reagents in very good yield ([Equation \(70\)](#)) [<1984TL4007>](#). Pasto and co-workers [<1976JOC3496, 1978JOC1382, 1978JOC1385>](#) have shown that iron (especially $FeCl_3$) and cobalt derivatives were good catalysts for the production of allenes from propargylic halides and Grignard reagents. From optically enriched propargylic epoxides, the $Fe(acac)_3$ -catalyzed nucleophilic substitution with organomagnesium reagents leads to 2,3-allenols derivatives with high stereoselectivity [<2003AG\(E\)5355>](#). Palladium(0) is also an efficient catalyst for the cross-coupling of propargylic and allenic halides with Grignard reagents to selectively produce alkyl and aryl allenes [<1980TL5019>](#). The nickel-catalyzed reaction of propargylic alcohols **88** with organomagnesium bromides selectively gives silyl allenes **89** ([Equation \(71\)](#)) [<1985JOC1122>](#).



More recently, it has been shown that nickel-catalyzed cross-coupling reactions of propargylic dithioacetals with Grignard reagents RMgX led to substituted allenes **90** via an allenyl thioether intermediate (Scheme 5) <1996JOC8685>. Extension of this procedure, by first treating the dithioacetal with lithium *t*-butylcuprate followed by the cross-coupling reaction, allows the introduction of two different substituents on the allenes **91a** and **91b** formed (Scheme 5) <1997JOC4568, 1999JOC8582>.

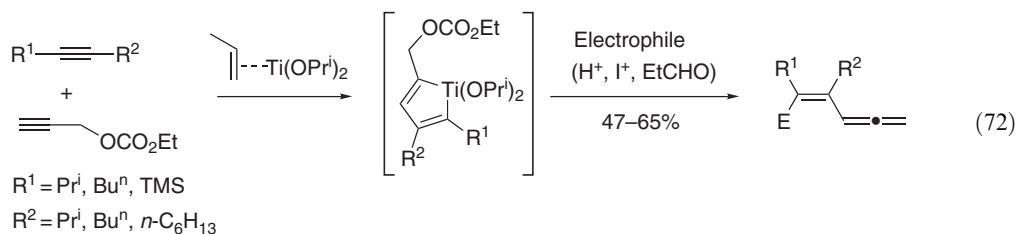


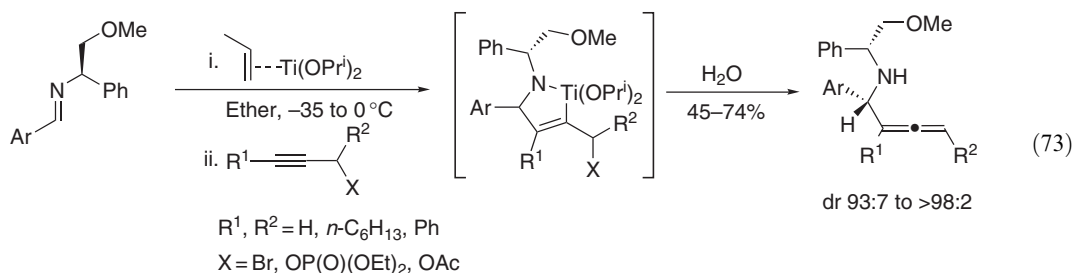
Scheme 5

1.20.3.3 Miscellaneous Nucleophilic Substitutions

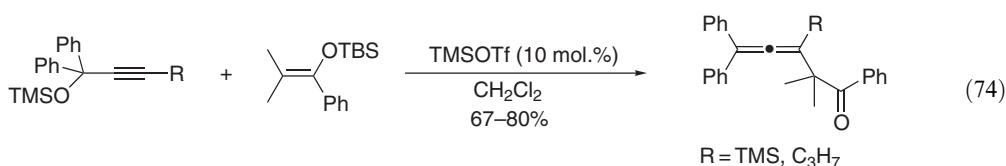
To avoid a mixture of metals such as lithium or magnesium in the presence of copper or nickel complexes, nucleophilic reactions without metal or coupling reactions with only one metal are useful alternatives.

For the synthesis of vinyl allenes, $(\eta^2\text{-propene})\text{Ti}(\text{OPr}^i)_2$, prepared *in situ* from $\text{Ti}(\text{OPr}^i)_4$ and Pr^iMgCl , appears to be a reagent of choice since it is able to mediate the coupling of an internal alkyne with a propargyl carbonate at $-50\text{ }^\circ\text{C}$ via a five-membered metallacycle (Equation (72)) <2000S975, 2001JA7937>. The same divalent titanium reagent reacts with arylaldimines and propargyl halides to afford α -allenylamines through a β -elimination reaction of the azatitanacyclopentene intermediate (Equation (73)). Starting from optically active imines, the synthesis of chiral allenes are possible <2003OL2145>.





Nucleophilic reaction of a silyl enol ether with a propargylic cation, produced by treatment of a substituted propargyl silyl ether with trimethylsilyl triflate (TMSOTf), leads to a substituted allenene [<2001JOC4635, 2003OL51>](#). It is noteworthy that two phenyl substituents and the tetrasubstituted enol ether are necessary to exclusively afford the allenene ([Equation \(74\)](#)).



Neutral phosphorus(III) nucleophiles, such as $\text{Me}_3\text{SiPPh}_2$, $\text{Me}_3\text{SiP}(\text{Ph})(\text{C}_5\text{H}_{11})$, or $\text{Me}_3\text{SiOPPh}_2$, react with propyne morpholinium salt to afford (3-morpholinoallenyl)phosphines or (3-morpholinoallenyl)phosphine oxides [<2003EJOC2071>](#). Interestingly, electron-rich phosphines (such as $\text{Me}_3\text{SiPEt}_2$) or phosphites ($\text{Me}_3\text{SiOP}(\text{OEt})_2$) delivered exclusively the propargyl derivatives.

Finally, addition of cyanide to substituted propargyl tosylate provides the opportunity to prepare substituted cyanoallenenes containing oxygen, nitrogen, or sulfur functionalities [<1994SL717>](#).

1.20.3.4 Reaction of Electrophiles with Propargyl and Allenyl Organometallics

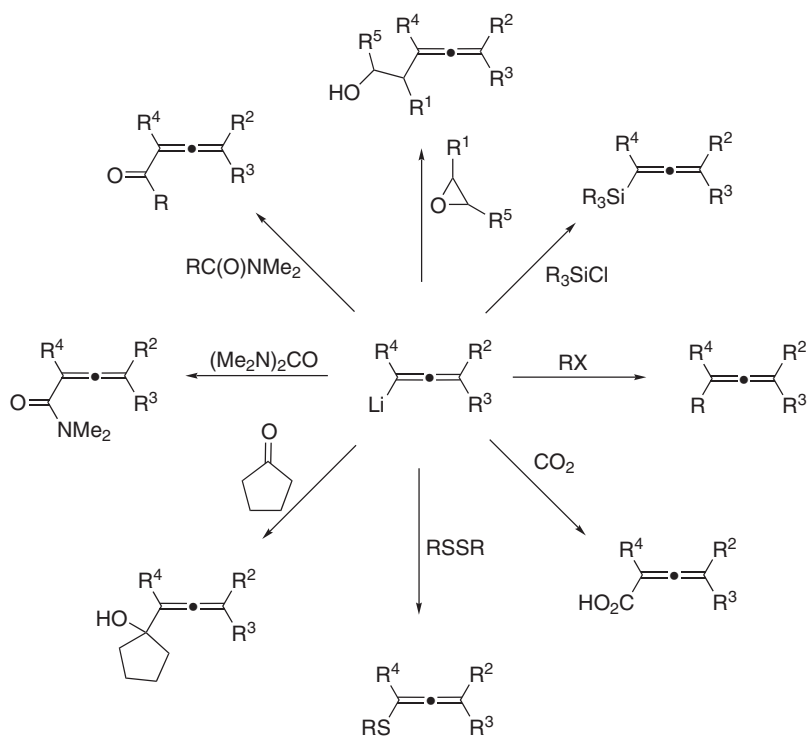
1.20.3.4.1 Lithium derivatives

Propargylic and allenic organometallics are usually prepared by reaction of a metal or an alkyllithium with either the corresponding halide or the hydrocarbon. Metallation of allenic hydrocarbons or halogen–lithium exchange from haloallenenes with butyllithium at -78°C generates carbanions able to react with electrophiles to produce allenyl derivatives via C–C bond formation [<1991COS\(2\)81>](#). Various electrophiles have been used leading to the synthesis of a number of functional allenenes [<1999TL5491>](#).

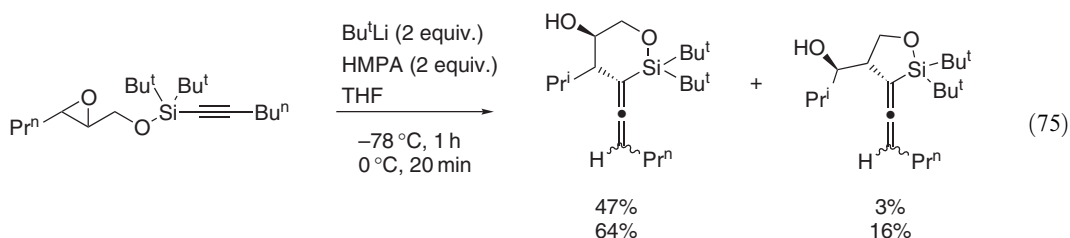
The selective formation of mono-, di-, tri-, and tetraalkyl allenenes (84–94%) is possible from alkyl halides ([Scheme 6](#)) [<1975JCS\(CC\)561, 1982SC739>](#). The cross-coupling between allenyl-lithium compounds and aryl or vinyl halides, catalyzed by $\text{Pd}(\text{PPh}_3)_4$, makes possible the preparation of vinyl and aryl allenenes [<1982S738>](#).

The reaction of allenyllithium with ketones and epoxides, respectively, leads to α -allenic and β -allenic alcohols ([Scheme 6](#)) [<1981S875, 1983JCS\(CC\)1133>](#), the selective formation of the latter being improved in the presence of hexamethylphosphoramide. When CO_2 is used as the electrophile, allenic carboxylic acids are formed in good yields ([Scheme 6](#)) [<1981S875, 1985JA6046, 1977JA7632>](#). Whereas the reaction with amides gives allenic ketones [<1977NJC373>](#), the cross-coupling reaction with ureas [<1981S875>](#) or isocyanates [<1997ZOR615, 2002TL1569>](#) provides an efficient route to allenic amides in satisfactory yields ([Scheme 6](#)).

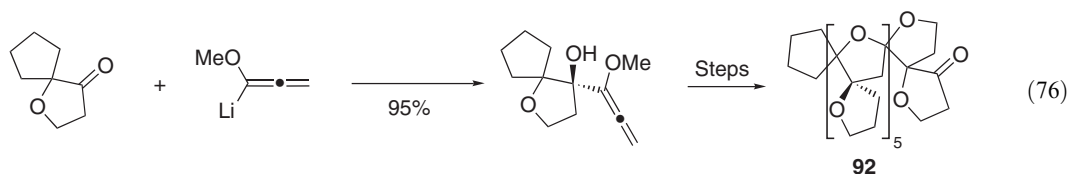
In the presence of *t*-butyllithium, cyclic allenyl silanes were obtained from 1-(alkynylsilyloxy)-2,3-epoxyalkanes ([Equation \(75\)](#)) [<2000TL9281>](#). The regioselectivity was dependent on the configuration of the epoxy moiety. *cis*-Epoxides selectively provide the five-membered silyl allenenes, whereas *trans*-epoxides lead to a mixture of five- and six-membered silyl allenenes. Addition of lithiated methoxyallene to chiral cyclic nitrones provided *N*-hydroxy allenepyrrolidines diastereoselectively [<2003EJOC1153>](#).



Scheme 6

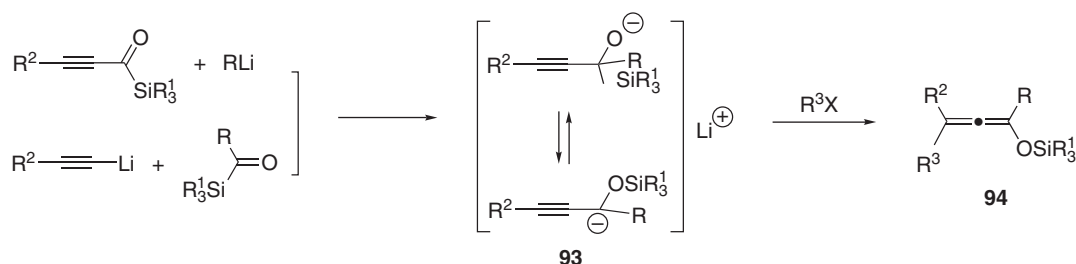


Functional allenic compounds have been prepared from α -lithio- α -alkoxyallenes <1968RTC1179>, silyl allenes <1980TL3987>, γ -methoxy- γ -alkyl allenes <1978TL1137>, and the synthesis of the first primary helicoidal molecule **92** was based on the reaction of lithio- α -methoxy- α -allene with tetrahydrofuranone moieties (Equation (76)) <1980JA2134>. The use of enantiopure alkoxy allenes has allowed the preparation of enantiomerically enriched allenols by reaction with aldehydes <1993SL105>. Silyloxypropargyl lithium reagents **93**, generated either by alkylation of silylated ketones or alkynylation of silyl ketones, react with electrophiles to produce allenol silyl ethers **94** (Scheme 7) <1980JA1423, 1986JA7791>.



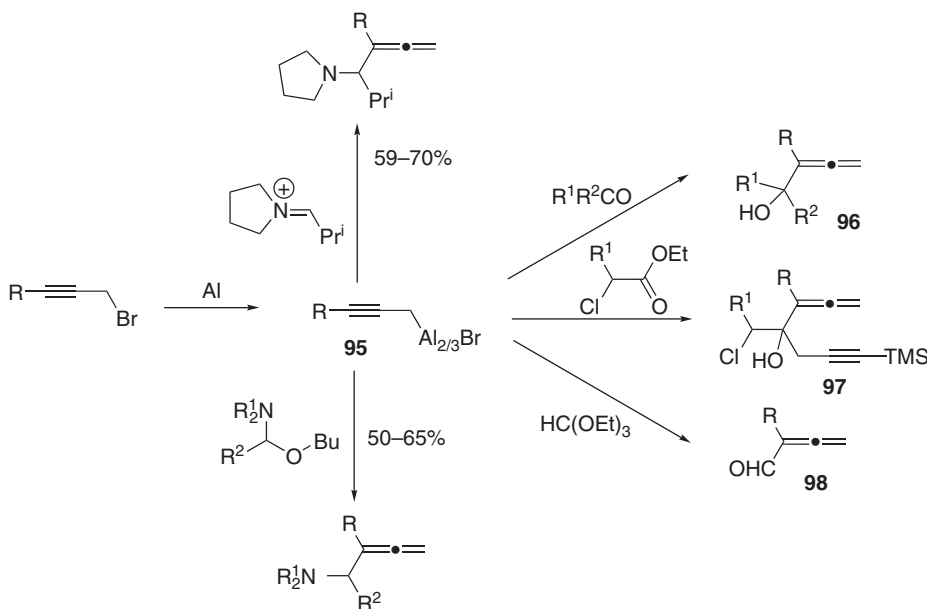
1.20.3.4.2 Magnesium, aluminum, and manganese derivatives

Allenyl Grignard reagents have not been used extensively because of their lack of selectivity. However, γ -allenyl ketones have been produced from allenyl magnesium bromide and esters <1969BSF898>.



Scheme 7

The organoaluminum derivative **95**, generated by reaction of aluminum with trimethylsilylpropargyl bromide selectively affords allenyl alcohols **96** and **97**, on reaction with carbonyl compounds (Scheme 8), whereas magnesium or zinc propargyl derivatives selectively give homopropargylic alcohols <1981TL1579, 1991JOM(403)299>. Propargylic lithium alanates generated from methylacetylenes, selectively afford allenenes, α -allenic alcohols, and acids by reaction with allyl halides, carbonyl compounds and carbon dioxide, respectively. Reaction of **95** with triethyl orthoformate affords the allenyl aldehyde **98**, a useful intermediate for access to functionalized allenic alcohols on reaction with organomagnesium, zinc, or aluminum reagents (Scheme 8) <1992JOM(440)277>. With organoaluminum derivatives arising from substituted propargyl bromides, α -allenic tertiary amines have been produced with high selectivity (>90%) when the electrophile is an iminium salt <1981JOM(218)1> or a *gem*-aminoether (Scheme 8) <1980JOM(198)1>.

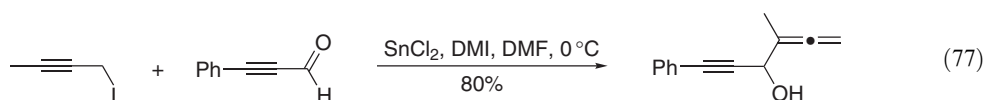


Scheme 8

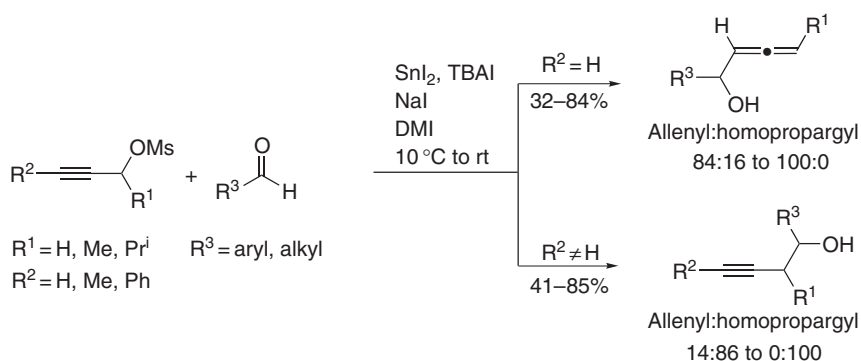
The reduction of 3-substituted prop-2-ynyl bromides by tetrabutylmanganate, followed by the addition of an aldehyde or even a ketone, produces the corresponding γ -allenyl alcohols. The allene/alkyne selectivity mainly depends on the nature of the electrophile and on the substitution of the starting bromide. From prop-2-ynyl bromide, only the prop-2-ynyl adduct was obtained <1997CC2077>.

1.20.3.4.3 Tin-mediated allenylation reactions

Stable organotin compounds react with activated aldehydes to produce γ -allenyl alcohols in good yields. The *in situ* formation of organotin derivatives by stirring stannous chloride with propargylic halides leads to allenic alcohols on reaction with aldehydes at 0 °C (Equation (77)) <1981CL621, 1993TL449>.



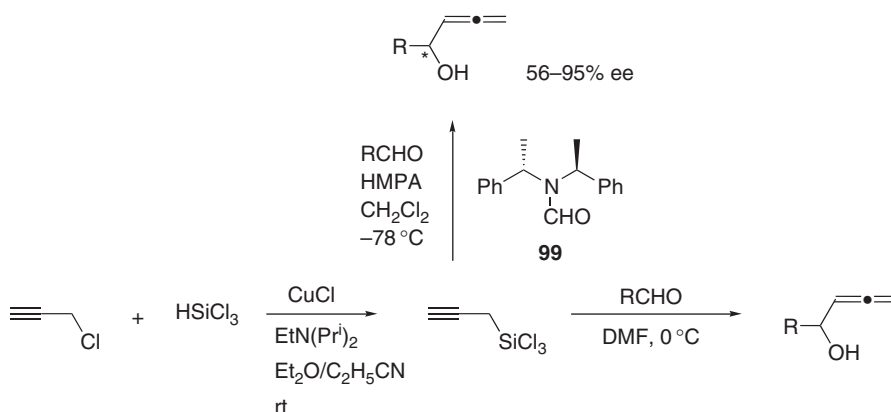
The best selectivity in allenols is obtained when γ -substituted propargyl iodides are used. The same result was obtained with tetrapropargylic stannanes in methanol. By contrast, starting from tetra-allenic stannanes (prepared from the nonsubstituted propargyl halide by a Grignard reaction and an exchange with SnCl_4), the addition to an aldehyde selectively led to the homopropargylic alcohol <1998SL909>. It is worth noting that the use of these stannane derivatives in trifluoroacetic acid in the presence of a dimethylacetal, instead of an aldehyde, provides the allenic or homopropargylic alcohol with higher selectivities. Depending on the reaction conditions (tin species, additive, solvent, and temperature), allenols or homopropargylic alcohols were accessible from propargyl halide and an aldehyde <1998CC2025>. Even mesylates can be used with tin derivatives to produce allenic alcohols <2000CC2009, 2003TL2845>. However, the carbonyl allenylation dramatically depends on the bulkiness of 1- or 3-substituents of 2-propynyl mesylates (Scheme 9) <2003SL1713>.



Scheme 9

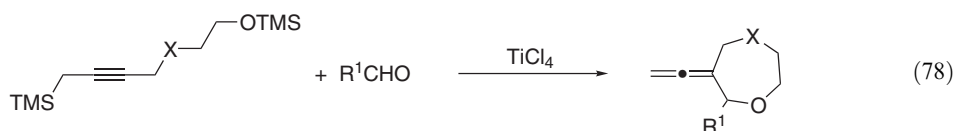
1.20.3.4.4 Reactivity of propargyl silanes

An alternative to toxic tin compounds is the use of silane derivatives. In the presence of copper(I) chloride and a sterically hindered amine, trichlorosilane reacts with propargyl halides to selectively afford propargyl silanes. Subsequent addition of an aldehyde delivers the allenic alcohol in high selectivities (Scheme 10) <1995JA6392, 1997JOC8976>. The first catalytic enantioselective allenylation of aldehyde was disclosed by Iseki using the chiral formamide **99** (Scheme 10) <1998TA2889>. Enantiomeric excesses up to 95% were obtained with aliphatic aldehydes, but no selectivity was observed from an aromatic aldehyde.



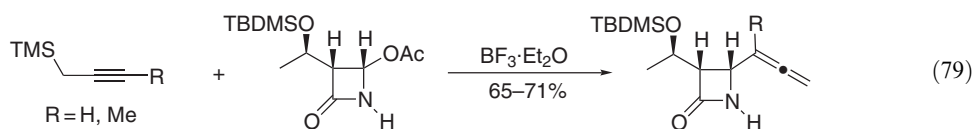
Scheme 10

In the presence of a Lewis acid catalyst, propargyl trialkylsilanes regioselectively react with electrophiles to afford allenic derivatives via stabilized vinylic carbocations. This strategy has allowed the preparation of a variety of allenenes using electrophiles such as acyl chlorides <1980JOC5006, 1981TL3401>, acetals <1981TL3609, 1985OM333>, aldehydes <1981TL455, 1984TL651, 1981TL1327, 1975JOM(93)43>, and ketones <1981TL455>. From propargyl trimethylsilanes containing a silyl ether or a hydroxy group, the reaction with aldehydes leads to cyclic vinylidene compounds (Equation (78)) <1988JOM(349)43, 1986T2501, 1986T2017, 1984TL651>.

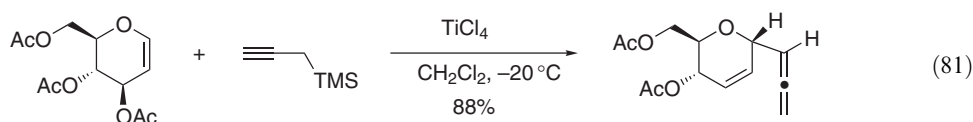
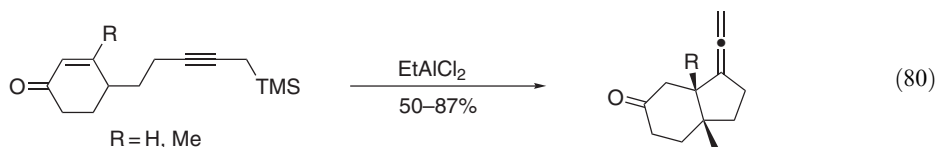


Iminium salts, generated from formaldehyde and secondary amines in the presence of $\text{CF}_3\text{CO}_2\text{H}$, react with propargyl silanes to afford tertiary allenyl amines <1990JOM(396)289>. Similarly, cyclic vinylidene amines have been prepared from amino propargyl trimethylsilanes via regioselective intramolecular reaction <1987TL4689>.

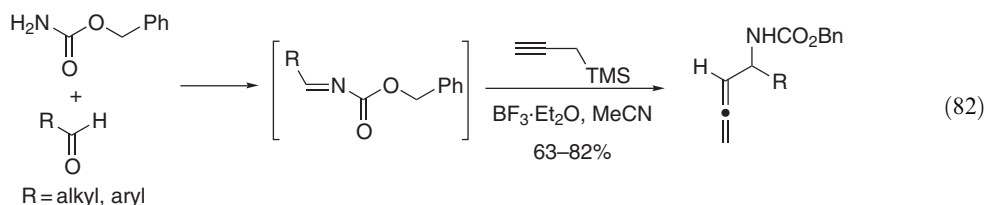
Allenyl lactams have been produced by reaction of propargyl silanes with acyl iminium cations used as electrophiles (Equation (79)) <1992T3445, 1983TL1407, 1984TL3115, 1984JOC1149, 1986TL1411, 1988TL4253>. Under similar conditions, allenyl ethers have been obtained from oxonium derivatives, formed *in situ* with $\text{BF}_3 \cdot \text{Et}_2\text{O}$ <1987JOC1370, 1988JOC2450>. The acetolysis of 8-(trimethylsilyl)-6-octyn-2-ol tosylate led to an exocyclic allene via an electrophilic intramolecular reaction <1980JA5120>.



Propargyl silanes smoothly react with the activated double bond of alkylidene malonates in the presence of TiCl_4 at 20°C to produce allenenes in moderate to good yield <1982JOM(236)177>. Allenyl acyl cyanides are obtained in good yield from α -unsaturated acylcyanides and 3-trimethylsilylprop-1-yne <1986JOC1199>. Intramolecular addition of propargyl silanes to conjugated enones, in the presence of TiCl_4 or EtAlCl_2 at very low temperature (-70°C) gives rise to annelation compounds containing an exocyclic allenic structure via C—C bond formation (Equation (80)) <1988S263, 1986JCS(CC)829, 1985TL1831>. Recent examples of acid-catalyzed or Lewis acid-promoted cyclizations from trimethylsilyl propargyl derivatives, leading to the exocyclic terminal allenyl group, have been reported <1991CB247, 1992TL8017, 1993TL7849>. This methodology was applied to the synthesis of disaccharides <2001SL82> and several glycals (Equation (81)) <2001T10241>.

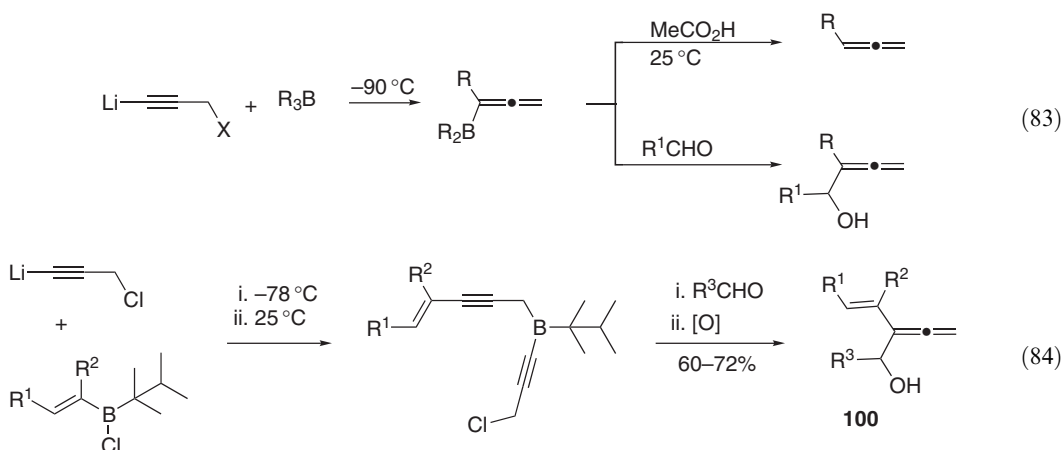


The three-component reaction, involving an aldehyde, a carbamate, and propargyl trimethylsilane, in the presence of $\text{BF}_3 \cdot \text{OEt}_2$ allows the formation of an α -allenyl amine in moderate-to-good yield (Equation (82)) <2002TL1453>.

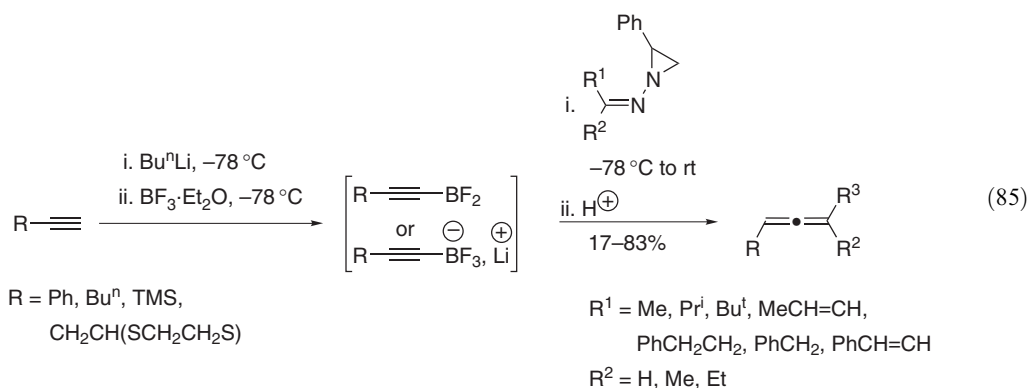


1.20.3.4.5 Boron chemistry for allene synthesis

Organoboranes react with lithium chloro- or acetato-propargylides to produce allenyl boranes at low temperature. Their treatment with acetic acid gives allenes (>70% yield), corresponding to the migration of an alkyl group from the boron atom to the terminal carbon of the initial alkyne (Equation (83)) <1974JA5620, 1977JOC2650>. Propargylic organoborane intermediates react with carbonyl compounds to produce allenic alcohols in good yield <1978JA5561, 1982JOC3364, 1983JOC5376>, with CO₂ to give allenic acids and with allylic halides to form 1,2,5-trienes <1982JOC3364>. 4-Alkenylpropargylic boranes react at -78 °C with aldehydes to afford conjugated 1,2,4-trienols in more than 60% yield (Equation (84)) <1981JOC829>. Enantioselective syntheses of chiral α-allenols via reaction of aldehydes with enantiopure propargyl boranes have been described by using a chiral auxiliary on the boron atom. The boron reagents can act as chiral catalyst <1990JA878> or as chiral mediator <1995JOC8130>.

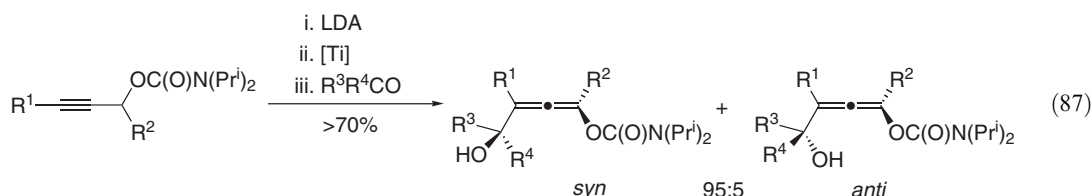
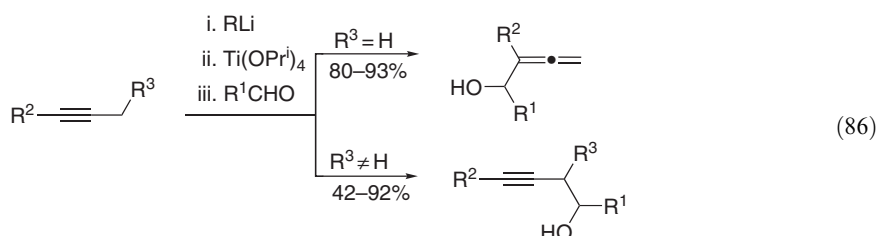


The reaction of *N*-azidinylimines with alkynyl borane reagents offers a new route to allenes from aldehydes and ketones <1996JOC6018>. After addition of the borane to the imine, the corresponding *N*-azidinyamine decomposes to deliver a propargylic anion, which equilibrates to an allenyl anion finally quenched by a proton (Equation (85)). Alkynyl Grignard reagents, alkynyllithium, alkynylcuprate, or alkynylcerium reagents do not react at all with imines.

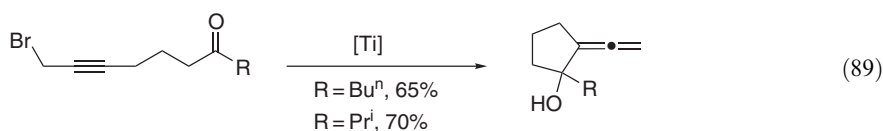
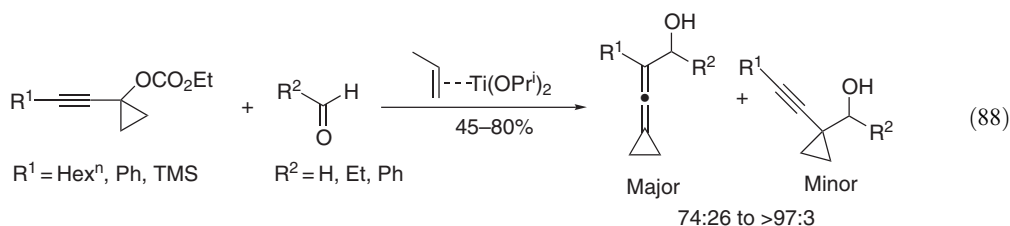


1.20.3.4.6 Allene synthesis via titanium derivatives

Transmetalation of 1-trimethylsilyl or 1-methylpropynyl lithium with titanium isopropoxide at -78°C gives access to a titanium reagent which reacts with carbonyl compounds at -78°C to afford allenic alcohols, whereas similar reactions from 1-trimethylsilyl-3-substituted propynyl lithium lead to alkynic alcohols (Equation (86)) <1982JOC2225>. Highly regio- and diastereoselective syntheses of 4-hydroxy-1,2-alkadienyl carbamates have been obtained from propargylic carbamates by using the corresponding titanium derivative, whereas no selectivity was observed with the lithium reagent <1987T2457> (Equation (87)). Extension of this work to the synthesis of enantiomerically enriched allenenes was made possible by the use of (–)-sparteine. A dynamic resolution of the lithium-(–)-sparteine complex by selective crystallization, followed by transmetalation with $\text{ClTi}(\text{OPr}^i)_3$ and subsequent addition of an aldehyde or an acid, results in the formation of allenyl carbinols or allenenes with enantioselective excesses up to 95% <2001OL1221, 2003SL1969>. Seebach demonstrated that titanated chiral allenamides could be useful in stereoselective addition to aldehydes and ketones <2002HCA963>. γ,γ -Disubstituted allenamides were thus isolated in good yields and high diastereoselectivities.



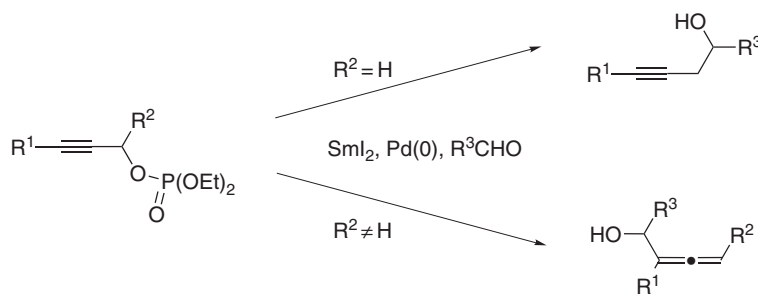
However, the previous method (Li–Ti exchange) suffers from the limited number of allenyl- and/or propargyl titanium reagents available. An extension of this protocol was made by using divalent titanium reagent $(\eta^3\text{-propene})\text{Ti}(\text{OPr}^i)_2$ which can provide functional propargyl alcohol derivatives from a wide range of propargyl- or allenyltitanium complexes, which react with carbonyl compounds. Thus, vinylcyclopropylcarbonate, in the presence of $(\eta^3\text{-propene})\text{Ti}(\text{OPr}^i)_2$, reacts with aldehydes at the less substituted carbon atom to afford the corresponding α -allenyl alcohol (Equation (88)) <1996AG(E)2848>. Propargyl halides react onto keto groups through an inter- or intramolecular addition pathway to provide allenyl alcohols (Equation (89)) <1996SL437, 1995TL3207>.



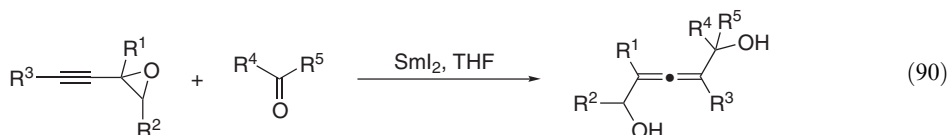
1.20.3.4.7 *SmI₂-mediated allene synthesis*

Nucleophilic organosamarium derivatives, formed by electron transfer from SmI₂ to allenyl palladium species, react with carbonyl compounds to afford homopropargylic and allenic alcohols, the proportions of which depend on the substitution pattern of the starting prop-2-yn-1-yl acetate <1986TL5237, 1987CL2275>.

High regioselectivities were obtained by reacting propargylic phosphates with carbonyl derivatives in the presence of SmI₂ and palladium(0) (Scheme 11) <1995TL907>. It is noteworthy that, with this procedure, secondary propargylic phosphates led to allenes, whereas primary propargylic phosphates gave acetylenic derivatives (Scheme 11). SmI₂ was also able to promote the reductive coupling reaction between alkynyl oxiranes and ketones, which provided 2,3-pentadiene-1,5-diols (Equation (90)) <1995TL2501>. The observed *anti*-selectivity of the reaction complements that observed with the cuprate methodology.



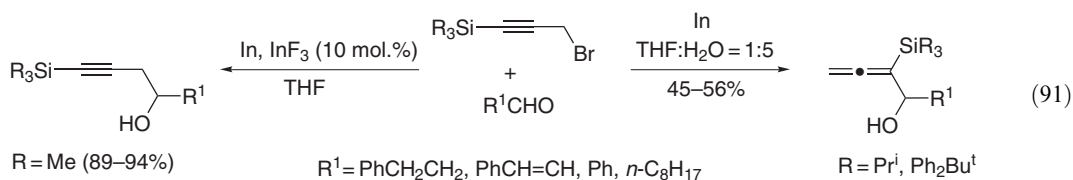
Scheme 11



(90)

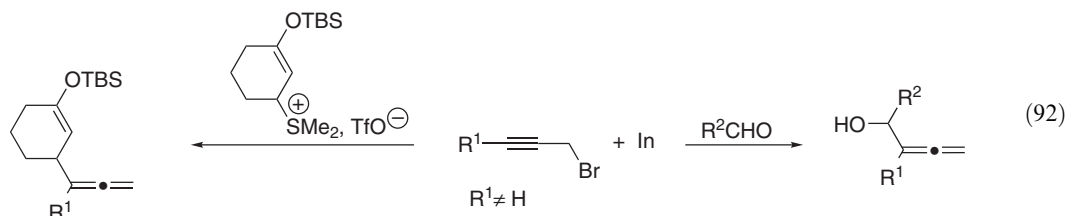
1.20.3.4.8 *Indium-mediated allene synthesis*

Metal-mediated reactions in aqueous media have found considerable applications in organic synthesis and indium appears to be the metal of choice in this area. Thus, indium-mediated coupling of aliphatic or aromatic aldehydes with γ -substituted prop-2-ynyl bromide gives α -allenols with high regioselectivities <1995CC1003, 1998JOC7472>. The intramolecular version of this reaction has been applied to the synthesis of allenyl chromane derivatives <2004SL45>. Highly regioselective synthesis of allenic or homopropargylic alcohols can be obtained from various aldehydes and trialkylsilylpropargylic bromides in the presence of indium by changing the silicon group and the reaction conditions <2003JA13042>. The use of a bulky silicon group (TIPS or TBDPS) in THF/water mixture favored the formation of allenic alcohols, whereas the use of the trimethylsilyl group in refluxing THF exclusively led to the homopropargylic alcohols (Equation (91)).



(91)

3-*t*-Butyldimethylsilyloxyalk-2-enylsulfonium triflates, generated by addition of dimethyl sulfide to α,β -enones in the presence of TBSOTf, undergo nucleophilic substitution with the organoindium reagent derived from γ -substituted propargyl bromide (Equation (92)) <2003JA9682, 2003OL1725>.

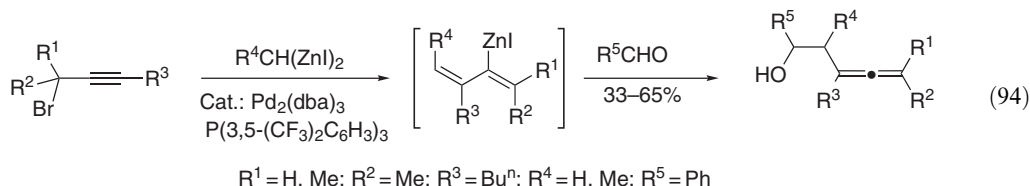
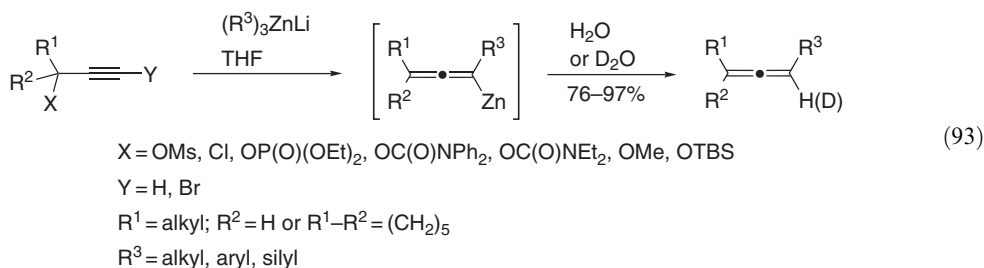


1.20.3.4.9 Miscellaneous

By reaction of aldehydes or ketones in the presence of HMPA, a very selective formation of allenols has been observed when chromium(II) derivatives were used to generate the allenyl organometallic intermediate from propargylic bromides <1981T1359>. This system allows the use of propargylic halides containing various functionalities such as ester, halide, and nitrile <1992JOC4070>.

Allenic ketones have been synthesized by reaction of propargyl mercury iodide with acyl chlorides in the presence of AlCl_3 at -40°C <1986JOC2623>.

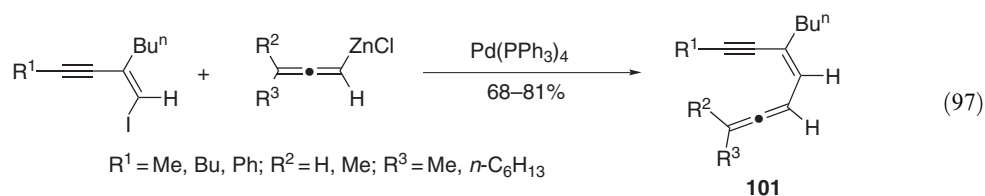
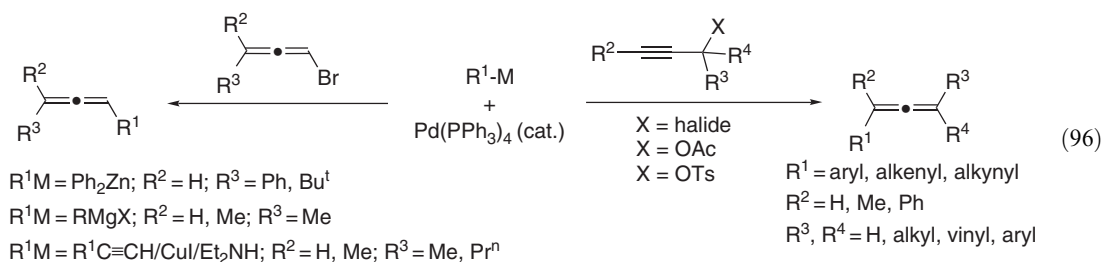
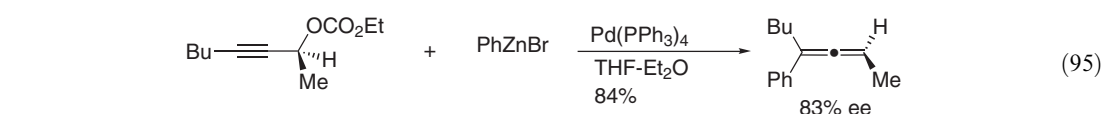
Organozinc compounds prepared from propargylic halides usually give no selectivity on reaction with carbonyl electrophiles, but after treatment with zinc, γ -substituted α -acetylenic bromides react with *N*-chloromethyl-*N*-methylformamide to afford allenic methyl formamides, which are easy to convert into secondary allenyl amines with Bu^nLi <1986BSF449>. Upon hydrolysis with D_2O , allenic zinc reagents, generated from propargylic mesylates or chlorides and triorganozincates, give allenenes in high yields via C—C and C—D bond formation (Equation (93)) <1993JOC6166, 1995TL723, 1996JA11377>. Synthesis of β -allenols is achieved either by reaction of allenyllithium with epoxides as described previously (see Section 1.20.3.4.1) or via reaction of a 2-iodozincio-1,3-alkadiene, generated from a propargyl halide and a *gem*-dizinc compound in the presence of a catalytic amount of palladium(0), and a carbonyl derivative (Equation (94)) <2000SL995>.



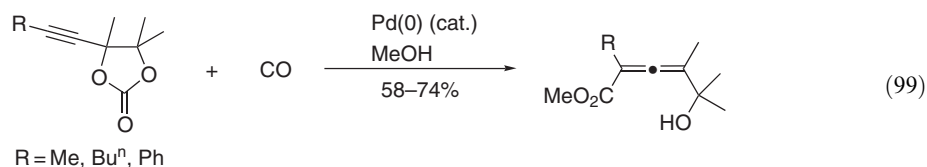
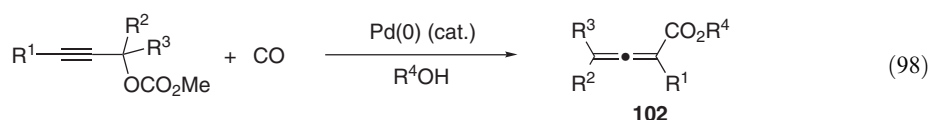
1.20.3.5 Palladium-mediated Coupling Reactions

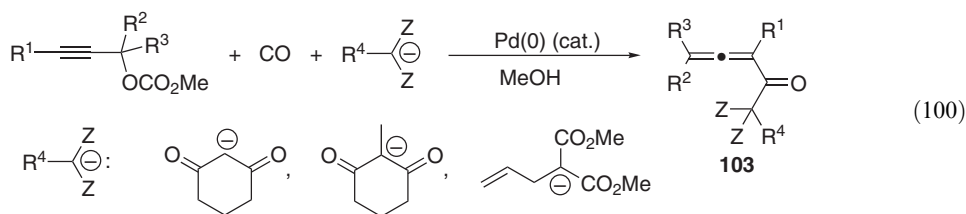
The reaction with palladium catalysts likely proceeds via oxidative addition of a propargylic ester, halide, or carbonate to produce an allenyl organopalladium(II) moiety. Subsequent reaction with nucleophiles gives rise to 1,2-diene derivatives <1997MI197>.

Starting from propargylic halides or esters and nucleophiles such as R-ZnCl, in the presence of catalytic amounts of Pd(PPh₃)₄, functionalized allenes and bisallenes have been obtained with high regio- <1981TL1451> and stereoselectivity <1983JOC1103> except in the case of 1-alkynylcyclopropyl derivatives which led to alkynic cyclopropanes as major compounds <1992JA4051>. Preparation of highly substituted allenes of good-to-excellent optical purity was thus accomplished by a cross-coupling reaction between chiral propargyl carbonates and organozinc reagents (Equation (95)) <1997CC2083>. Conjugated *p*-allenyl styrenes and vinyl allenes have been obtained from various nucleophiles including zinc, aluminum, and tin organometallics (Equation (96)) <1986JOC4006>. The cross-coupling is also possible from allenyl halides and organozinc <1984TL5571>, magnesium <1980TL5019> or copper species <1983S32> as nucleophiles, catalyzed by palladium(0) complexes (Equation (96)). Sterically hindered 1,1-diaryl-1,2-dienes were formed by treatment of 1-phenyl-1-propyne with butyllithium and zinc bromide in the presence of 1.5 mol.% of HgCl₂ in THF followed by coupling with aryl iodides in the presence of a catalytic amount of palladium(0) <1998JOC9601>. Ene-allenes are accessible either by coupling propargylic acetates and pentynoates, based on the efficient activation of both substrates by palladium complexes <1993TL3129>, or by cross-coupling reaction of vinyl iodides and allenyl zinc reagents as exemplified by the preparation of **101** (Equation (97)) <1994TL1829>.



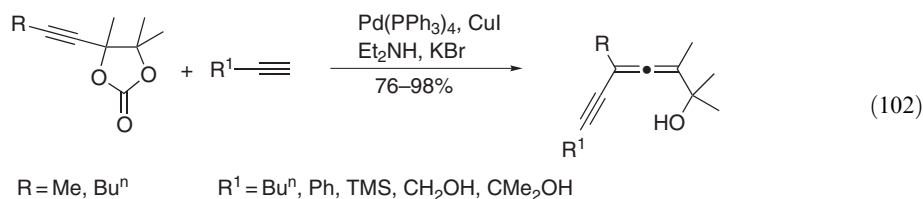
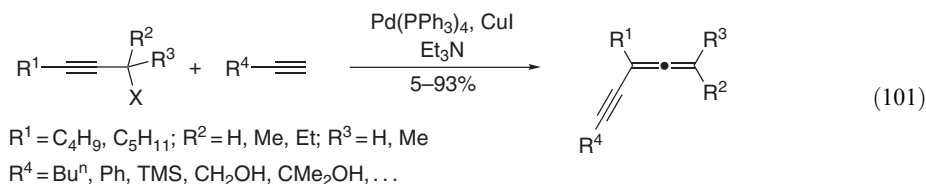
In alcohol, under CO atmosphere, propargylic carbonates are easily converted into allenic esters **102** (Equation (98)) <1993JOM(451)15, 1993JA5865, 1986TL731>. 5-Hydroxyalka-2,3-dienoates were prepared from cyclic alkynyl carbonates via a carbonylation reaction in the presence of palladium(0) (Equation (99)) <1996SL218>. Cationic palladium(II) precursors were also able to catalyze the conversion of α,γ -substituted propargyl alcohols into 2,3-dienoic acids under CO pressure <1994TL5889>. Mono- and dicarbonylation of propargyl halides are also possible under phase transfer conditions, with Ni(CN)₂·4H₂O as catalyst precursor, to produce allenyl mono- and dicarboxylic acids <1992OM493, 1993OM1871>. The carbonylation in the presence of carbanions generated from active methylene compounds with NaH gives allenyl ketones **103** (Equation (100)) <1991SL697>.



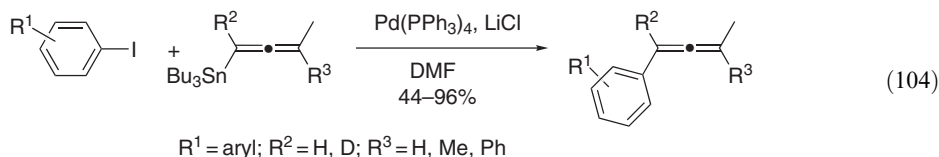
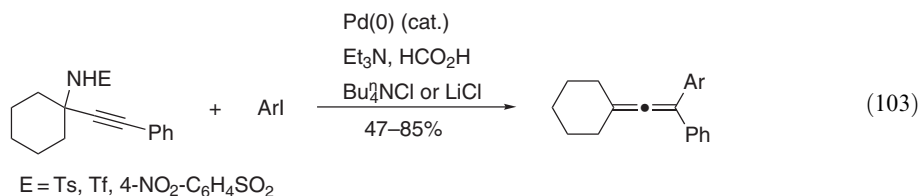


From 4-amino-2-alkynyl carbonates, the carbonylation directly leads to allenic β -lactams via subsequent intramolecular C—N bond formation <1991TL7683>.

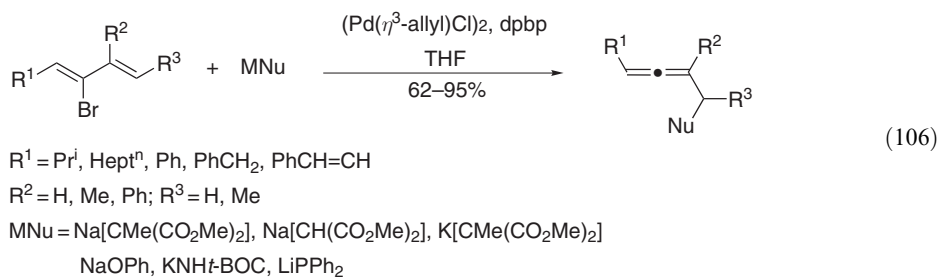
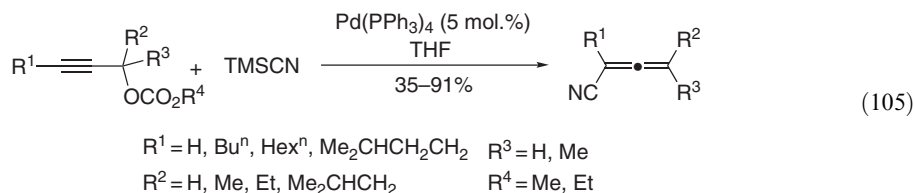
Based on the easy formation of alkynyl copper derivatives from terminal alkynes, CuI and a base, 1,2-dien-4-ynes, 1,2-dien-4-yn-6-ols, or their tetrahydropyranyl ethers have been obtained in good yields in the presence of palladium catalyst precursors with KBr or LiCl <1991JOM(417)305, 1990TL7179>. A large variety of substituted allenynes have also been synthesized in one step from propargylic halides, tosylates or acetates, and terminal alkynes in the presence of tetrakis(triphenylphosphine)palladium or palladium(II) and triphenylphosphine, copper iodide, and a base (Equation (101)) <1993TL3853, 2000T1851>. Alkynyl cyclic carbonates allow the formation of allenynols and unsaturated diols via a Sonogashira-type reaction (Equation (102)) <1994CC1845>.



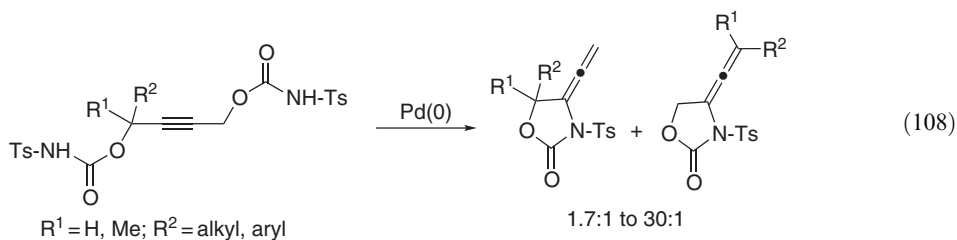
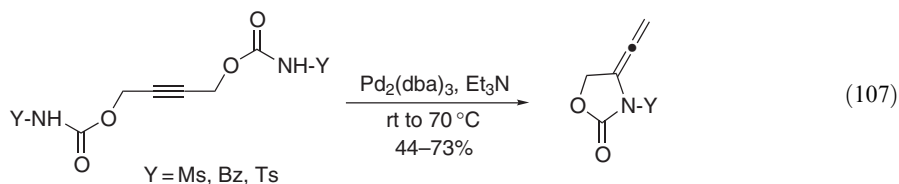
Alkenyl allenenes have been synthesized in one step from propargylic carbonates and activated olefins via the Heck reaction, in the presence of Pd(OAc)₂, PPh₃, and KBr in DMF at 70 °C <1991TL3397>. Palladium-catalyzed reaction of aryl iodides with tertiary propargylic amides affords highly substituted allenenes (Equation (103)) <2003JOM(687)562>. This reaction proceeds via a regioselective carbopalladation (which is controlled by the strong directing effect of the amide)/ β -N-Pd-elimination reaction. Stille reaction of allenylstannanes and aryl or vinyl iodides provides an efficient access to monosubstituted aryl allenenes, disubstituted allenenes, and alkenyl allenenes in good yields (Equation (104)) <2003T3635>.

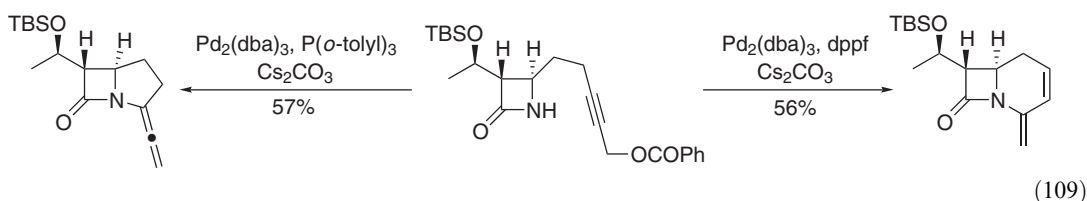


The nucleophilic substitution of allylic esters catalyzed by palladium complexes is a well-established reaction in organic synthesis. The corresponding reaction using propargylic esters as substrates and mild nucleophiles such as trimethylsilyl cyanide affords cyanoallenes (Equation (105)) <2000OL2635>. (Z)-1-Substituted-2-bromo-1,3-butadienes or chloroprenes, through a π -allylpalladium intermediate, are also efficient precursors to substituted allenes (Equation (106)) <2000AG(E)1042, 2001OL2615>.



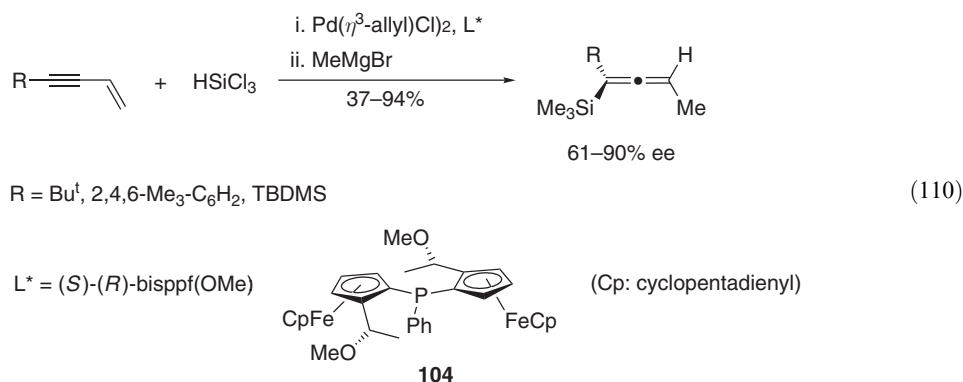
A large variety of soft nucleophiles, such as malonate derivatives, amine or phosphorus nucleophiles, can be added to the π -allyl intermediate. The enantiomerically enriched axially chiral allenes have been prepared by using a palladium-BINAP chiral catalyst <2001JA2089>. In the same manner, chiral (allenylmethyl)silanes were prepared from (3-bromopenta-2,4-dienyl)-trimethylsilane with soft nucleophiles in the presence of an optically pure palladium catalyst <2003OL217>. Allenamides can also be produced by an intramolecular cyclization of propargyl bis-urethanes through an allenyl palladium intermediate (Equation (107)) <1997TL3963, 1990TL4887>. For nonsymmetrical propargyl carbamates, the oxidative addition to Pd(0) was found to be in favor of the less hindered propargyl carbon, mainly leading to α,α -disubstituted allenes (Equation (108)). During the synthesis of carbacepham skeleton, Mori has shown that the phosphine ligand orientated the aminocyclization of the propargyl carbamate. Whereas the bidentate ligand dppf forced the attack of the nitrogen atom to the central carbon of the allenyl palladium intermediate, leading to a conjugated diene, the monodentate ligand P(*o*-tolyl)₃ orientates the amination to the formation of the allenamide (Equation (109)) <2001TL4869, 2002TL1499, 2003JOC8068>.





A similar observation was made by Ma for the cross-coupling reaction of a propargyl mesylate with (*Z*)-(2)-ethoxycarbonyl ethenyl zinc iodide or phenylzinc bromide <2003AG(E)4215>. The use of bidentate ligands with one neutral coordination atom (such as a phosphine) and a negatively charged coordination center is necessary to favor the allene synthesis.

In the presence of a catalytic amount of palladium complex, cyano-based pronucleophiles can be added to conjugated enynes to give the corresponding allenes in good-to-excellent yield <1996CC17>. It has to be pointed out that the scope of this addition is limited by the structure of the enyne. Thus, the addition of pronucleophiles to enynes, bearing an internal triple bond or substituted at the terminal olefinic position is either sluggish or may fail <1997T9097>. Axially chiral allenyl silanes, which are useful intermediates in organic synthesis, as they react with a variety of electrophiles in a regioselective manner, can be prepared by asymmetric hydrosilylation of 4-substituted enynes <2001JA12915>. Enantiomeric excesses superior to 90% were obtained by using a palladium(II) precatalyst and ((*S*)-(*R*)-bisppfOMe) **104** as chiral monophosphine (Equation (110)).



Allenylindium reagents, generated *in situ* by reaction of indium and propargyl bromides, are efficient partners in palladium-catalyzed cross-coupling reactions with a variety of organic electrophiles to produce 1,3-dienes in high yield, with complete regio- and chemoselectivity <2002AG(E)3901>. It is emphasized here that even functionalized electrophiles can be used. Thus, imidoyl bromide, cyclohexenyl triflate, and vinyl halides provide allenes in more than 86% yield.

An unusual reductive homocoupling reaction of 3-silylpropargyl carbonates opens a new entry into allenyne derivatives via a propargylpalladium intermediate <1995JOC4650>.

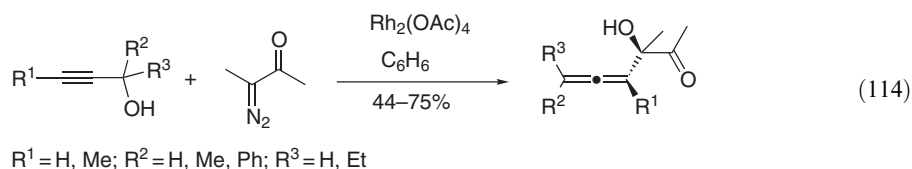
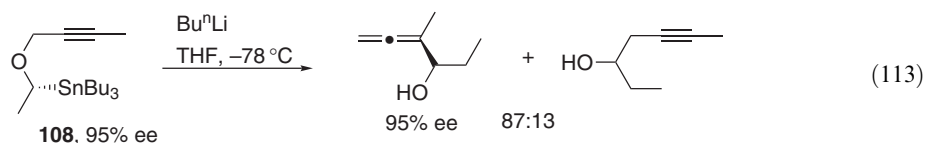
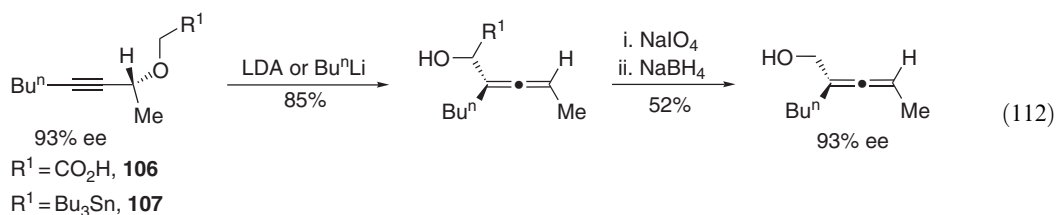
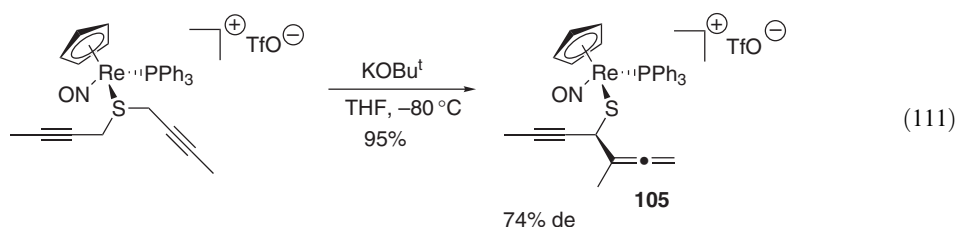
1.20.3.6 C—C Bond Formation via Sigmatropic Rearrangements

Sigmatropic rearrangements are powerful methods in organic chemistry to create new C—C bonds. In a general manner, starting from propargylic ethers, the preparation of allene derivatives through such a rearrangement might be envisaged.

1.20.3.6.1 [2,3]-Wittig rearrangement

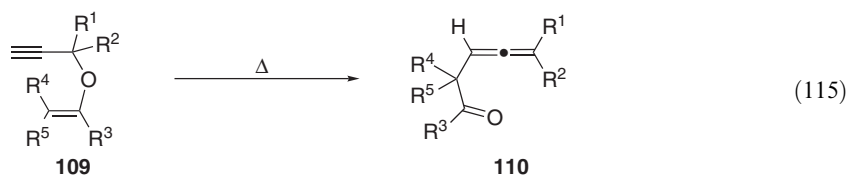
The [2,3]-Wittig rearrangement of propargylic ethers leads to allenic alcohols via a rigid five-center transition state. Asymmetric [2,3]-sigmatropic rearrangement of acyclic bis-propargylic ethers was demonstrated by Manabe <1997CC737>. Up to 62% ee was obtained by using a modified ephedrine ligand. The use of chiral metal complexes in the asymmetric propargyl ylide [2,3]- σ -rearrangement was achieved by Gladysz <1995JA11730>.

The chiral allene **105** was obtained in 95% yield and 74% ee through a sigmatropic rearrangement in the metal coordination sphere (Equation (111)). Enantiomerically enriched allenes have been produced either by treatment of optically pure (propargyloxy)acetic ester **106** with LDA or optically pure (stannylmethyl)propargyl ether **107** with *n*-butyllithium (Equation (112)) <1989JOC5854, 1991JOC4913>, or by treatment of an enantiopure stannyl ether **108** (prepared by S_N2 reaction of potassium propargyl alcoholate on pure stannyl mesylate) with BuⁿLi (Equation (113)) <1997SL1045, 1993JOC3233>. A total transfer of chirality, with complete inversion of configuration, was observed during the previous example. Lewis acids such as TMSOTf, TESOTf, in the presence of Et₃N, promote the Wittig rearrangement <1990JOC6246>. It is worth noting that, the major diastereomer produced in this reaction is different from that obtained in the base-promoted rearrangements. Treatment of primary, secondary, and tertiary propargylic alcohols with 3-diazo-2-butanone and a catalytic amount of dirhodium tetraacetate in benzene gives the allenic hydroxyketones in moderate-to-good diastereoselectivity (Equation (114)) <1999OL367> (see also Chapter 1.09).

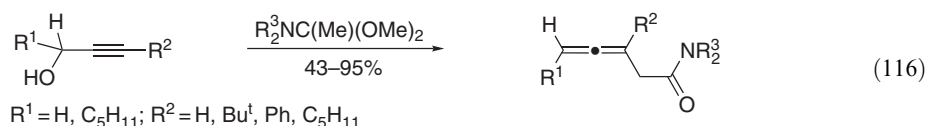


1.20.3.6.2 [3,3]-Claisen–Cope rearrangement

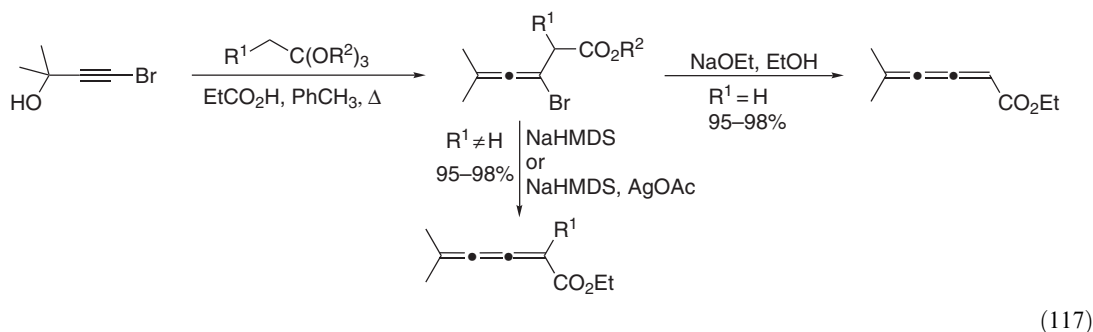
The Claisen–Cope rearrangement is the second process to prepare allenes via sigmatropic rearrangement. This is a method of choice for access to β -allenic aldehydes, ketones, esters, and amides starting from propargyl vinyl ethers **109**, according to the general (Equation (115)).



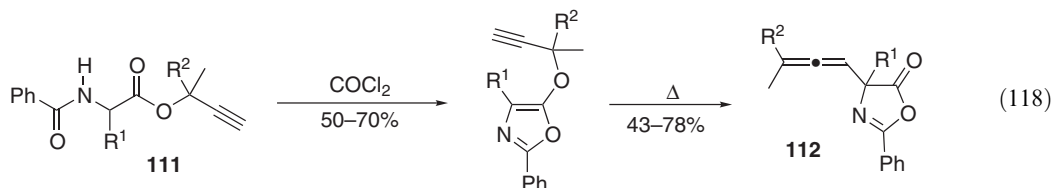
A classical route for access to intermediates of type **109** is the condensation under acidic conditions of prop-2-yn-1-ols with enol ethers <1967HCA1158> or orthoesters <1977JOC353, 1982JOC4478, 1992TL1057>. The good diastereoselectivity of this reaction has been used for the preparation of chiral methylmalonaldehyde derivatives <1988JOC4736>. The reaction of amide acetals with prop-2-yn-1-ols in refluxing benzene has made possible the preparation of allenic pyrrolidine and piperidine amides in more than 54% yield <1982JOC389, 1984JOC1204> or other tertiary allenic amides (Equation (116)) <2001JA12466>. The Claisen rearrangement can also be extended to propargyl allyl ethers <1980JOC2080> and 2-propargyloxy imines <1992TL4447>. Allenic acids have been obtained in 47–88% yield starting from propargyl glycolates via enolates generated by treatment with $(\text{Me}_3\text{Si})_2\text{NLi}$ <1985CL1457>. Furans undergo ring opening in the presence of Bu^nLi and the subsequent rearranged intermediates can be trapped by electrophiles to give allenyl ketones <1979JA2208>. Preparation of non-natural α -allenic- α -amino acids <1996S1489> and α -fluorinated allenenes <2003T4641> were also described via the propargyl-allene Claisen rearrangement. Other examples of sigma-tropic rearrangements involving C—C bond formation have been described, among them the aza-Cope rearrangement from 2-(*N*-succinimidyl)-4-pentyne derivatives <1984JA1877>, or the formation of the allenic thioether from the allylic sulfide and 3-chloro-3-methylbut-2-yn-1-yl lithium <1974JCS(CC)10>. Allenyl sulfones have been obtained by nucleophilic substitution of a phenyl sulfonyl group from 2,3-bis(phenylsulfonyl)-1,3-butadiene by soft carbanions <1993JA3776>.



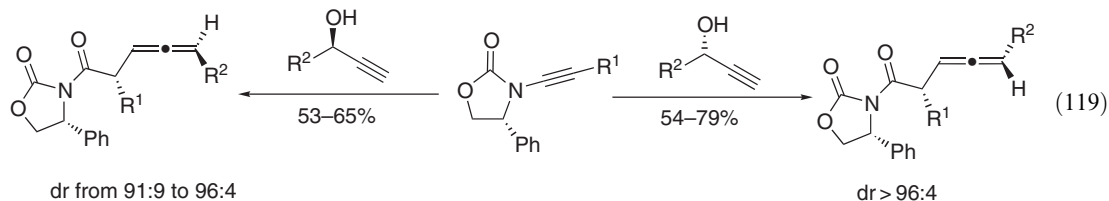
Butatrienes have been easily prepared from propynols via a two step procedure: a [3,3]-sigmatropic rearrangement, to afford the corresponding bromoallene, followed by an elimination reaction (Equation (117)) <1995AG(E)2709>. Starting from an enantiomerically enriched propargylic alcohol, using the same procedure, Tschierske synthesized the first axial chiral allenyl-acetates as novel ferroelectric liquid crystal <1997JMAC1713>.



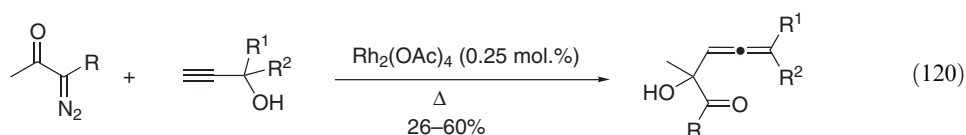
The hetero-Cope rearrangement involved in the reaction of the propargyl esters of *N*-acyl amino acids **111** with phosgene leads to allenyl oxazolinones **112** after elimination of water and prolonged heating at 50–70 °C (Equation (118)) <1975AG(E)58>.



Highly substituted chiral homoallenyl alcohols can be obtained by a stereoselective Saucy–Marbet rearrangement using chiral ynamides and propargyl alcohols (Equation (119)) <2003OL2663>.



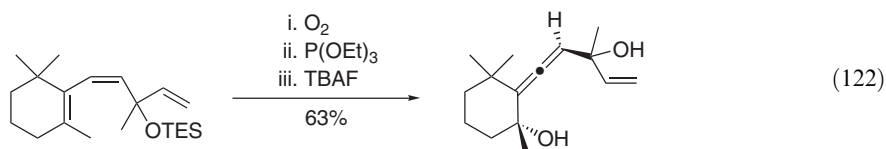
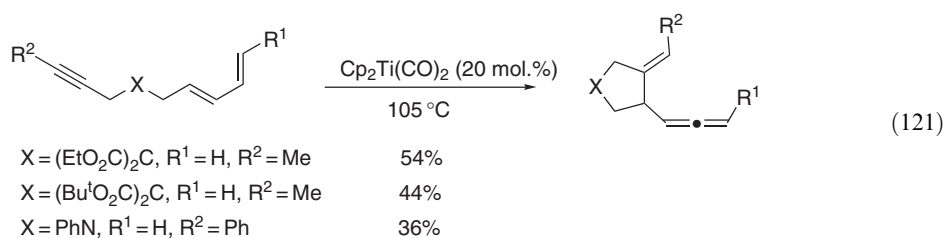
All these reactions require relatively high temperatures. Improvement of these methods was done by using organometallic complexes. Thus, α -diazoketones react with propargylic alcohols in the presence of the rhodium(III) catalyst $\text{Rh}_2(\text{OAc})_4$ to give intermediate enols, which undergo Claisen rearrangement to α -hydroxyketones (Equation (120)) <1999OL371> (see also Chapter 1.18 for other examples).



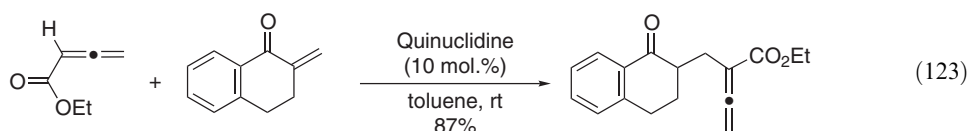
1.20.3.7 Miscellaneous

The thermal ene-reaction between terminal alkynes and indane-1,2,3-trione involving C—C bond formation and H-migration gives rise to 2-allenyl-2-hydroxy indane-1,3-diones <1992JCS(P1)2355>.

A titanocene system is able to provide an access to allene via a formal ene reaction of a ynediene compound under mild conditions (Equation (121)) <1999JA1976>. The regioselective ene-reaction of the vinyl hydrogen, rather than the allyl hydrogen of a twisted 1,3-diene, furnished a novel synthesis of allenols via the photosensitized oxygenation of the 1,3-diene (Equation (122)) <1996TL7771, 1997CC2243, 1998JOC8704, 2001TL7307>.



Conjugate addition of allenolate esters to α,β -unsaturated carbonyl compounds catalyzed by quinuclidine opens a new route to functionalized allenes under very mild conditions (Equation (123)) <2003JA12394>.



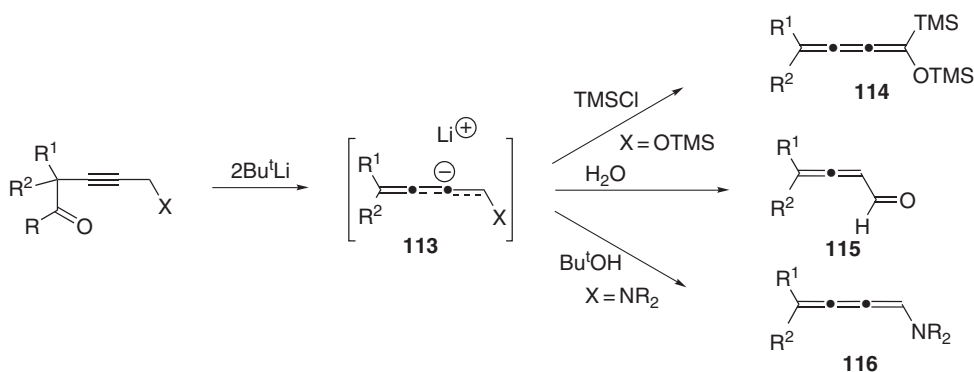
1.20.4 BY C=C BOND FORMATION

1.20.4.1 Elimination Reactions

1,2-Elimination from an unsaturated molecule or 1,4-elimination on both sides of a triple bond, provide a simple route to allenenes and cumulenes.

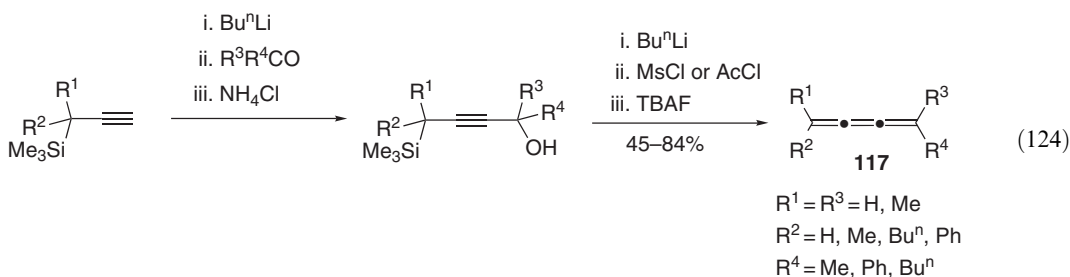
1.20.4.1.1 1,4-Elimination

1,2,3-Butatriene derivatives have been formed by treatment of propargylic methyl ether with 2 equiv. of Bu^tLi by 1,4-elimination of methanol. The intermediate lithio butatriene **113** allowed access to α -silyl α -silyloxy butatrienes **114** on reaction with Me_3SiCl , to allenyl ketones and aldehydes **115** upon hydrolysis [\[1981TL2827\]](#), and to allenyl amines **116** starting from 1-dialkylamino-4-methoxy-4-methylpent-2-yne ([Scheme 12](#)) [\[1982JOM\(233\)C25\]](#).



Scheme 12

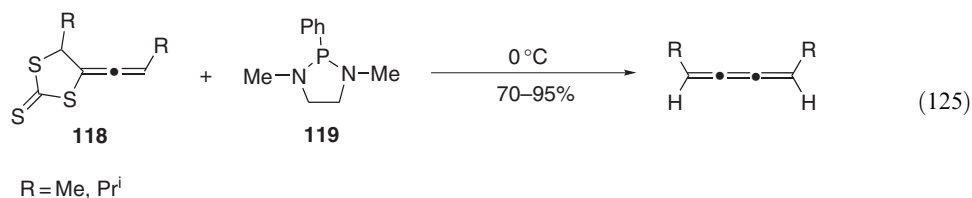
Butatrienyl ethers have been obtained from a reaction of 1-trimethylsilyloxy-4-alkoxy but-2-yne with ethyllithium by 1,4-elimination of Me_3SiOH [\[1981RTC34\]](#). [3]-Cumulenes **117** can be easily prepared after condensation of aldehydes or ketones to propargylic trimethylsilanes and subsequent TBAF-mediated 1,4-elimination reaction from the trimethylsilylmethane sulfonate [\[1995TL3785, 1995JOC1885\]](#) or trimethylsilyl acetate derivatives ([Equation \(124\)](#)) [\[1994CC2121\]](#).



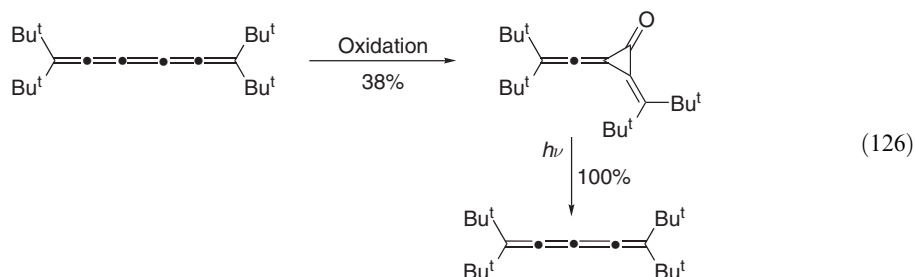
1.20.4.1.2 Desulfurization, decarboxylation, and related reactions

The elimination of sulfur compounds provides an original route to cumulenes. Thus, desulfurization of 4-vinylidene-1,3-dithiolane-2-thione **118** by 1,3-dimethyl-2-phenyl-1,3,2-diazaphospholidine **119** gives butatriene derivatives under very mild conditions ([Equation \(125\)](#)) [\[1991S1151, 1992AG\(E\)1611\]](#). Treatment of episulfides with PBU_3 at 130°C or with dimethyl diazomalonate in the presence of a rhodium catalyst leads to desulfurization and affords cumulenes [\[1986T1989\]](#). 1,2,3,4-Pentatetraenes have been obtained in fair yields (>50%) by thermolytic

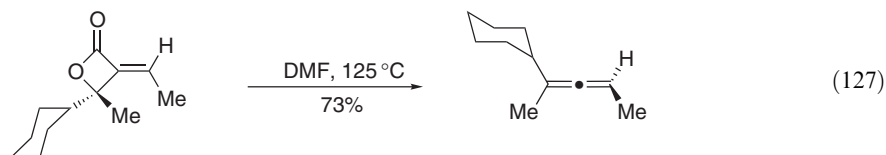
or photolytic desulfurization of episulfides [<1989TL4271, 1987TL1803>](#). The thermal elimination of sulfur dioxide from alkylidene sulfones at 650 °C affords vinyl allenes with good purity and high yield [<1983TL4691>](#).



Oxidation of cumulenes by MCPBA leads to alkylidene cyclopropanones, which photochemically release carbon monoxide to produce new cumulenes containing one double bond less ([Equation \(126\)](#)) [<1987JA4338, 1992JA5998>](#).



Upon heating in dimethylformamide at 110–125 °C, unsaturated β -lactones undergo decarboxylation to produce allenes in good-to-excellent yield ([Equation \(127\)](#)) [<1993JOC322>](#).



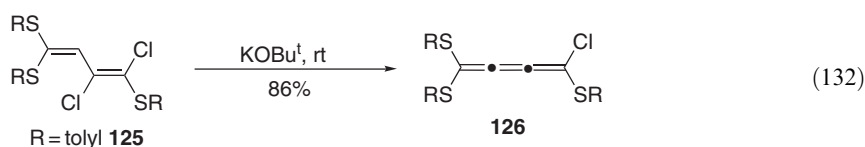
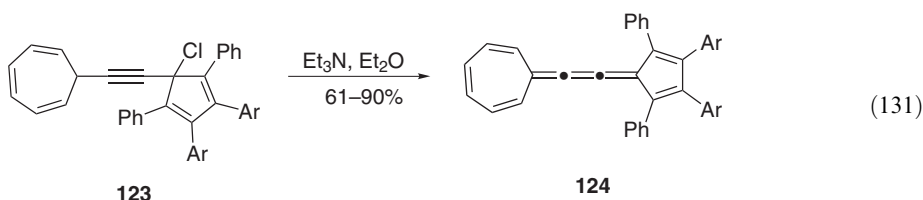
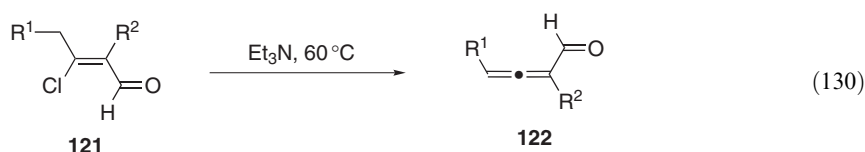
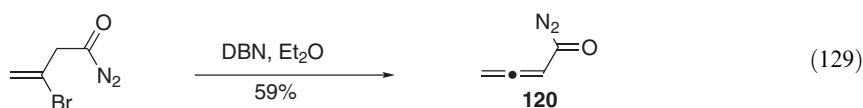
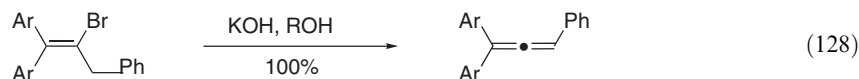
1.20.4.1.3 1,2-Elimination

The highly sterically hindered tetra-*t*-butyl allene has been obtained by elimination of water under acid catalysis from 1,1,3,3-tetra-*t*-butylprop-2-en-1-ol [<1982AG\(E\)924>](#). However, there are only a few examples of direct elimination of water from alcohols. In most cases, ester derivatives like trifluorosulfonates [<1975JOC657>](#), trifluoroacetates [<1978JOC1526, 1988TL1355>](#), or sulfonates [<1985AG\(E\)851>](#) facilitate the elimination of either a molecule of HX (X = leaving group) or XY can be produced.

1.20.4.1.4 Elimination of HX

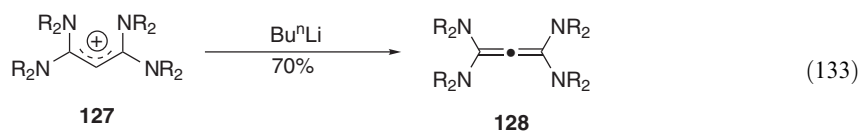
Dehydrohalogenation by strong bases has been widely used to prepare allenes in good yield from unsaturated halopropenes with release of HX ([Equation \(128\)](#)) [<1961JCS2687>](#). The reactive allenyl diazomethyl ketone **120** has been obtained at –20 °C in the presence of 1,5-diazabicyclo[4.3.0]non-5-ene (DBN) from a bromo derivative ([Equation \(129\)](#)) [<1976JOC3326>](#). Elimination of HCl by triethylamine at 60 °C from the β -chlorovinyl aldehyde **121** gave allenyl aldehydes **122** ([Equation \(130\)](#)) [<1970TL4315>](#), whereas elimination of HCl from **123** by pyridine led to a “push–pull” type cumulene **124** containing the fulvene and heptafulvene units linked by a cumulative double bond ([Equation \(131\)](#)) [<1987AG\(E\)335>](#). Similarly, 1,3-di-*t*-butyl-5-vinylidene cyclopentadiene was obtained at low temperature by elimination of HCl from 6-chloro-6-methylpentafulvene with 2,2,6,6-tetramethylpiperidine lithium as a base [<1986AG\(E\)466>](#). γ -Ketoallenes have been prepared in 34–40% yield by reaction of dialkyl ketones with 1,4-dibromobut-2-ene in the presence of NaH in dimethylsulfoxide (DMSO) at room temperature by elimination of HBr [<1991JCS\(CC\)294>](#).

Tris(arylthio) butatrienes **126** have been obtained by elimination of HCl from 1,2-dichlorobuta-1,3-dienes **125** (Equation (132)), but they rearranged at room temperature into enyne derivatives <1984LA1873>. The elimination of HX (X = Cl, ClO₄) from 1,1,3,3-tetrakis(dialkylamino) allylic chloride or perchlorate **127** with BuⁿLi yields 1,1,3,3-tetrakis(dialkylamino) allenes **128** in good yields (Equation (133)) <1973AG(E)566>. Allenoyltrimethylsilane, a precursor of substituted furans, is accessible in two steps from 3,3-dichloropropenoylsilane via a Michael addition followed by a smooth dehydrochlorination in the presence of DBU (Equation (134)) <1995SC503>.



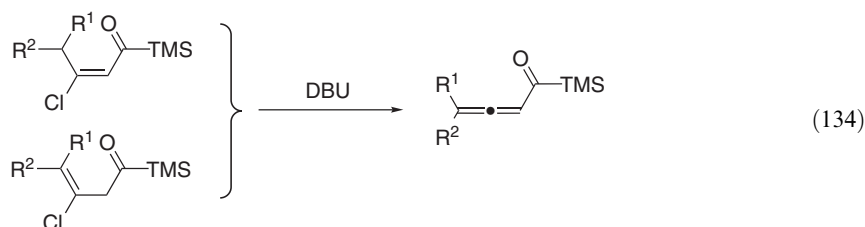
R = tolyl **125**

126

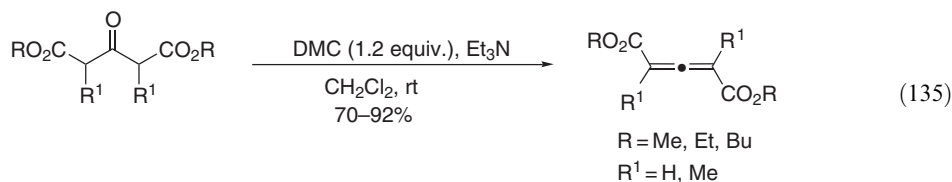


127

128

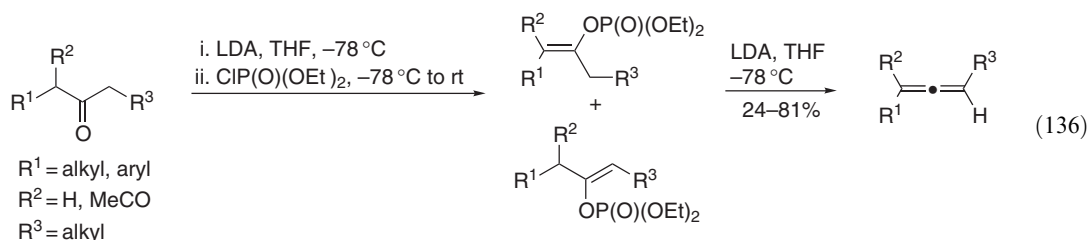


Allene-1,3-dicarboxylates are readily prepared from acetone-1,3-dicarboxylates either in a two step procedure (treatment of the ketone with PCl₅ followed by elimination in the presence of triethylamine) <1996JOC2031> or in a one step synthesis by using 2-chloro-1,3-dimethylimidazolium chloride (DMC) as a dehydrating reagent (Equation (135)) <1998TL6331>. This latter strategy was used to prepare an optically active dimethyl allene-1,3-dicarboxylate for the synthesis of (–)-epibatidine <1998CC2363>.

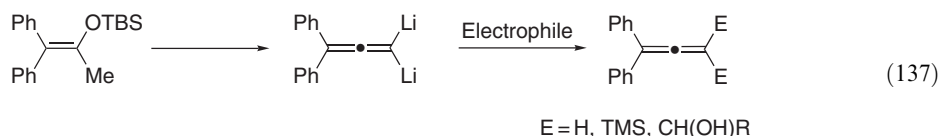


R = Me, Et, Bu
R¹ = H, Me

Dehydrohalogenation is a very useful procedure to produce allenes, but vinyl chloride compounds are not always easily available. An efficient protocol for the preparation of allenes from ketones was developed by Brummond and co-workers [<1996JOC6096>](#) through enol phosphates ([Equation \(136\)](#)).



Addition of a ketone or a diketone to dibromotriphenylphosphine gives access to a bromide salt; treatment with Et_3N leads to elimination of triphenylphosphine oxide and formation of terminal allenes and allenyl ketones [<1972TL3257>](#). In the same way, silyl enol ethers can be eliminated to produce functionalized allenes ([Equation \(137\)](#)) [<2001CEJ573>](#). Even though this methodology allows the direct formation of functionalized allenes (by trapping the polyolithiated intermediate allene with different hard electrophiles), it presents two main limitations. Only bulky silicon groups (such as TBDMS or TIPS) allow the formation of allenes and the transformations are actually limited to the use of aryl-substituted substrates.



The thermal elimination of ArSeOH from vinyl selenoxides leads to allenes when the *syn*-elimination to form a C—C triple bond is not possible [<1980JA5967>](#). Based on the same principle, the asymmetric oxidation of vinyl selenides by Davis oxidants, or Bu^tOOH in the presence of Sharpless catalysts, leads to chiral allenic sulfones [<1992JCS\(CC\)46, 1993JOC3697>](#).

1.20.4.1.5 Elimination of XY

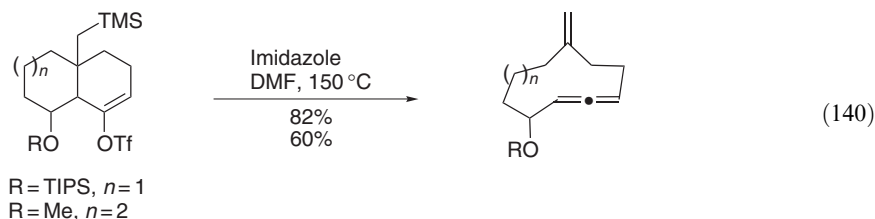
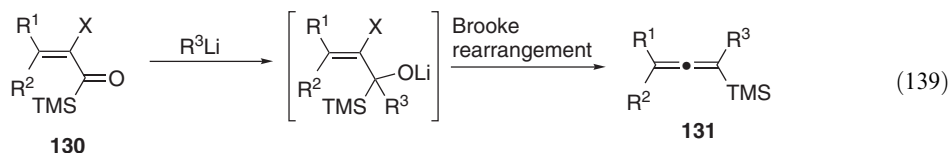
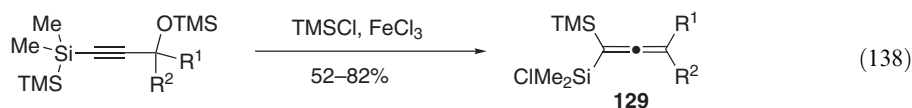
An alternative to the elimination of a molecule of HX is to remove two leaving groups, one in a vinylic and the other in an allylic position, in the presence of a base or an acid.

Cyclic allenic esters have been produced by oxidation of 3,4-polymethylene-2-pyrazolin-5-ones by thallium nitrate followed by ring opening with MeOH [<1980JOC3522>](#).

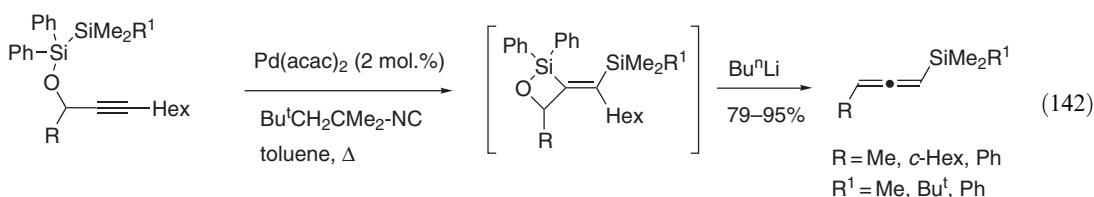
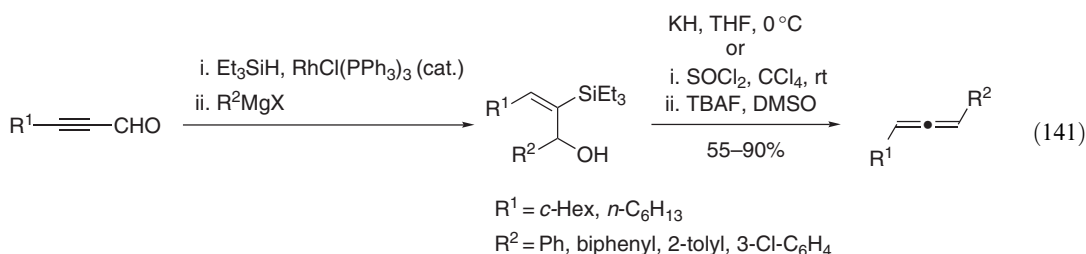
Butatrienes have been stereoselectively obtained in two steps by $\text{C}=\text{C}$ formation via intermediate divinyl boranes generated from 1-iodohex-1-yne and *t*-hexylborane on reaction with MeONa [<1991T343>](#).

Unsaturated β -chlorosilanes can eliminate one molecule of chlorosilane in the presence of fluoride (KF or Et_4NF) to afford allenes [<1974TL171, 1984S384>](#).

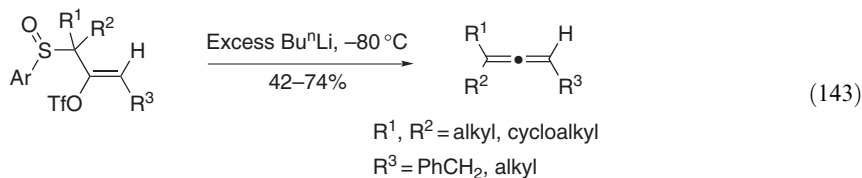
The rearrangement of acetylenic disilanes initiated by FeCl_3 or TiCl_4 leads to 1,1-bis(silyl) allenes **129** with elimination of $\text{Me}_3\text{SiOSiMe}_3$ ([Equation \(138\)](#)) [<1990TL5607>](#). The treatment of 2-halo-2-alkenoyl silanes **130** with organolithium reagent gives trimethylsilyloxy allenes **131** after migration of the silyl group to the oxygen and elimination of LiX ([Equation \(139\)](#)) [<1986JA7791>](#). A similar base-induced Brook rearrangement and elimination of an ether group is observed in the formation of 4-[(benzyloxy)(*t*-butyl)(methyl)silyloxy]penta-1,2,3-triene by reaction of the corresponding acyl silane with lithium or bromomagnesium 3-tetrahydropyranyloxy prop-1-yne [<1994TL1161>](#). Medium-sized cyclic allenes have been prepared from the enol triflate of 6-(silylmethyl)-10-substituted bicyclo[4.4.0]decan-2-one via a C—C bond cleavage directed by the silyl group ([Equation \(140\)](#)) [<1997SL461>](#) and 10-membered allenes were thus isolated in good yields.



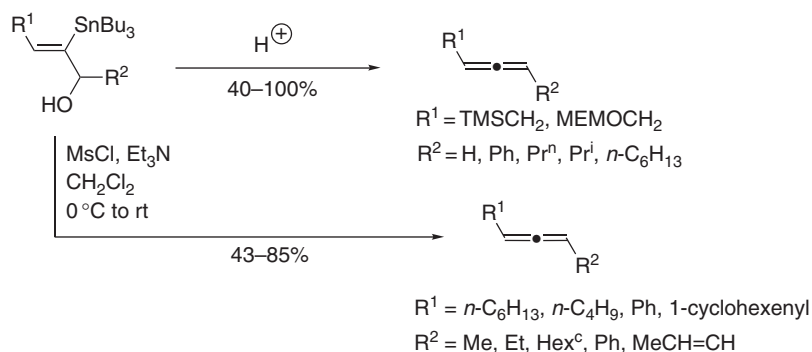
Addition of aryl Grignard reagents to α -triethylsilyl enals gave rise to secondary allylic alcohols, which can be converted into 1,3-disubstituted allenes either in the presence of KH, or after transformation into allylic chlorides followed by elimination (Equation (141)) <2001TL2605>. The intramolecular version of this β -elimination was described by Ito <1996JOC4884>. Highly enantiomerically enriched allenylsilanes were then obtained by an intramolecular bis-silylation reaction of optically active propargylic alcohols, catalyzed by palladium catalysts, followed by treatment with Bu^nLi (Equation (142)).



In the presence of Bu^nLi , alkenyl triflates having a sulfoxy group on the C_β (allylic position) lead to trisubstituted allenes, and even to macrocyclic allenes (Equation (143)) <1995T9327>. Acetylenic alkylolithium derivatives bearing a methoxy group at the distal propargylic position cyclize to give four-, five-, and six-membered alkenylidene cycloalkanes in good-to-excellent yields <1995JOC754>.

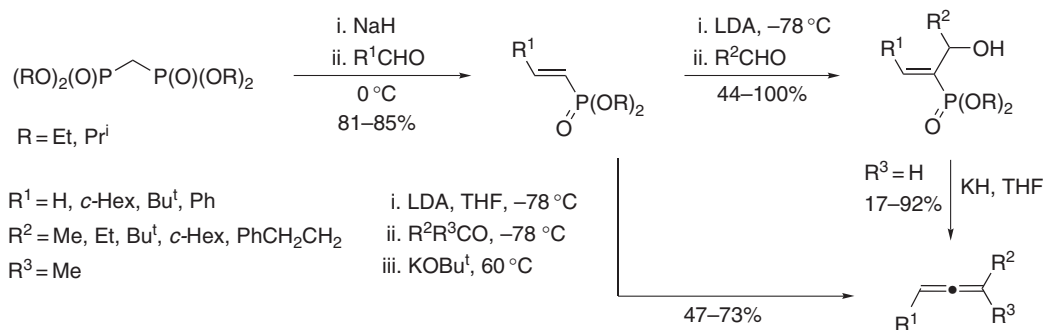


1,2-Dienes have been obtained from stannyl allylic alcohols by β -elimination either under basic conditions <1992TL5093> or acidic conditions (Scheme 13) <1987TL2751, 1994TL3797>. Chiral allenes of high enantiomeric purity can be prepared in a similar way starting from the corresponding chiral alcohols <1994TL3797>.



Scheme 13

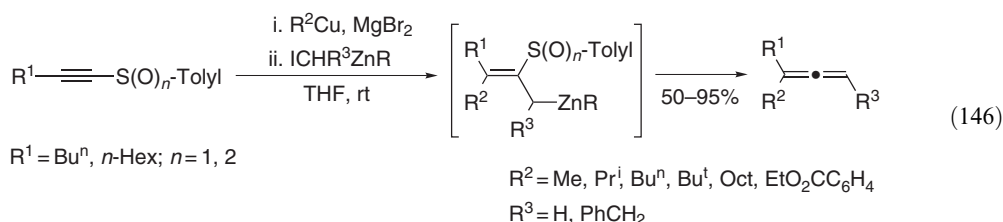
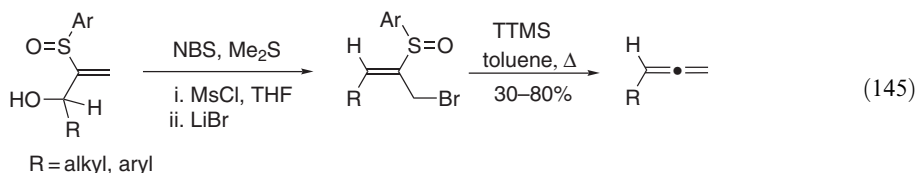
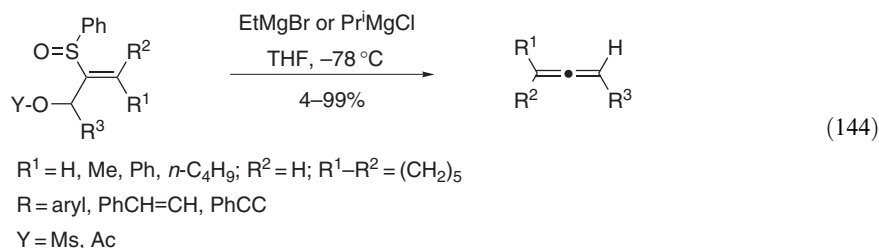
Baylis–Hillman type reaction of vinyl phosphine oxide [<2001JCS\(P1\)2240>](#) or vinyl phosphonate [<1998JOC6428, 2002T83>](#) and an aldehyde in the presence of a base afforded the hydroxyphosphine oxide or the hydroxyphosphonate. Subsequent elimination provided the allene in good yield (Scheme 14).



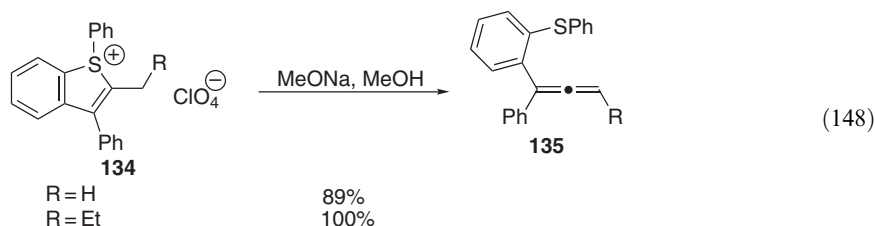
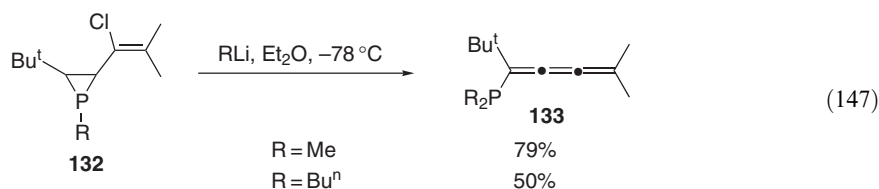
Scheme 14

Ethylene and styrene derivatives have been reacted with propargylic ethers in the presence of zirconocene to afford allenic products [<1997TL8723>](#). The reaction proceeds via initial formation of a zirconacyclopentene, followed by β -elimination of the ether and hydrolysis to liberate the allene.

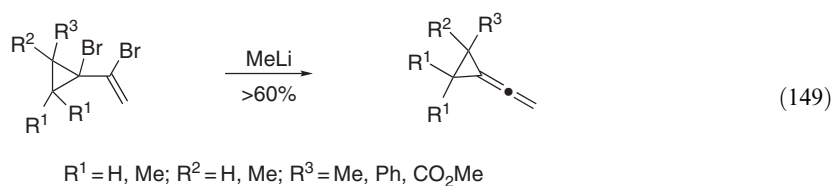
β -Elimination of a sulfinyl group is also a versatile method to obtain allenes. Thus, the sulfoxide metal-exchange reaction of a β -acetoxy sulfoxide or a β -mesyloxy sulfoxide (which was derived from alkenyl aryl sulfoxides and aldehydes in two steps) with a Grignard or alkyllithium reagent at low temperature gave allenes in good yield (Equation (144)) [<1999TL8815, 2002T2533>](#). Optically active allenes were prepared from optically active 2-substituted ethenyl *p*-tolylsulfoxide. Thus, starting from the pure (+)-(*E*)-(*Ss,IR*)-1-acetoxy-1-(2-naphthyl)-3-phenyl-2-(*p*-tolylsulfinyl)-2-propene, in the presence of 4 equiv. of EtMgBr, (–)-(*R*)-1-(2-naphthyl)-3-phenyl-1,2-propadiene was obtained in 74% ee. Treatment of allylic mesylates activated by a chiral sulfoxide group with Me₂CuLi·LiI in THF at –78 °C gave allenes corresponding to the formal elimination of MsOS(O)*p*-Tol [<1992TL4985>](#). A radical approach to this β -elimination was described by Malacria (Equation (145)) [<1999TL3565, 2002EJOC1776>](#). It is to be noted here that this reaction does not take place with sulfur groups other than sulfoxide and sulfimide. Moreover, due to the high energy of activation, disappointing results were observed for the synthesis of enantiomerically enriched 1,3-disubstituted allenes. Finally, another methodology involving vinyl sulfoxides is based on consecutive carbocupration-homologation- β -elimination reactions to afford polysubstituted propadienes in good yield (Equation (146)) [<2000OL2849, 2002EJOC4151>](#). Using a chiral ethynyl *p*-tolylsulfoxide, a thermodynamic equilibration of secondary organometallic derivatives is brought about before the *syn*- β -elimination and this opens a new access to chiral allenes.



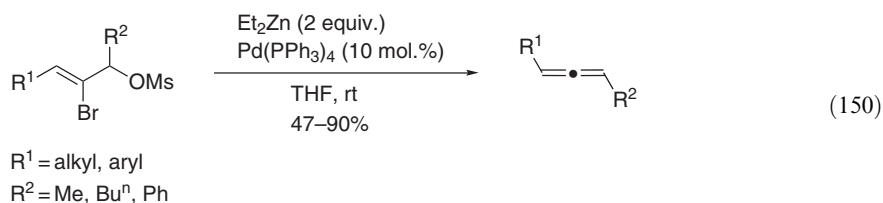
Treatment of chlorinated vinylic phosphirenes **132** with Bu^nLi at -78°C gives phosphino-butatrienes **133** via C—P bond formation, rearrangement and elimination of LiCl in good yield (Equation (147)) <1992SL635>. Deprotonation of the benzothiophenium perchlorate **134** by MeONa leads to ring opening and formation of the allene **135** (Equation (148)) <1992CL1357>.



1-Halogeno-1-(1-haloalkenyl)cyclopropanes undergo elimination of halogen and form allenenes (alkenylidenecyclopropanes) when treated with methyllithium at a temperature between -30 and 20°C (Equation (149)) <1995TL3393>.



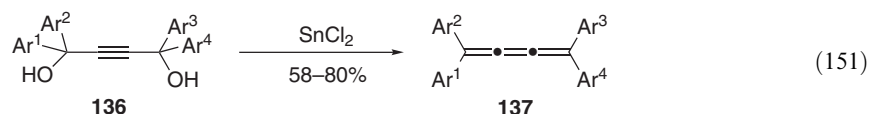
The palladium/diethylzinc system was found to be efficient for the synthesis of terminal or internal allenenes, bearing aminoalkyl, alkyl, or aryl groups (Equation (150)) <2000TL5131, 2002JOC1359>.



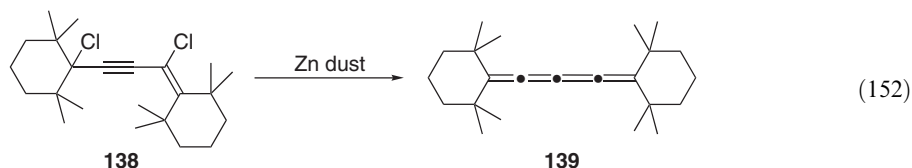
Oxidative addition of 2-bromoalk-2-en-1-yl mesylates or 3-aryl-2-bromoalk-2-en-1-yl-trichloroacetates to palladium(0) affords 2-bromo- π -allylpalladium(II) intermediates, which produce allenes by β -elimination. Both (*E*)- and (*Z*)-bromomesylate or bromoacetate can be used. It is noteworthy that there is no chirality transfer from the chirality center of the substrates to the axial chirality of the resulting allenes.

1.20.4.2 Reduction of Unsaturated Alcohols and Halides

Reduction of 1,4-dihydroxy-2-butyne **136** by various reducing reagents, such as PBr_3 , SnCl_2/HCl , has been used for the preparation of tetrasubstituted butatrienes **137** (Equation (151)) <1966BSF2885>. The extension of this reaction to 1,6-dihydroxy-2,4-hexadiynes <1966BSF2885> has been used to produce hexapentaenes and bis-hexapentaene compounds as potential molecular materials for nonlinear optics <1993CM357> or as host molecules <1991BCJ659>.



Reductive dehalogenation of 1,4-dihalo-2-butyne by zinc dust provides a simple route to cumulenes. From a 2,5-dihalo pent-1-en-3-yne like **138**, the reductive cleavage of chlorine with zinc dust leads to pentatetraenes **139** (Equation (152)) <1986AG(E)340>.



It is also possible to generate butatrienes in good yield and high stereoselectivity by reduction of 2,3-diiodobuta-1,3-dienes by Bu^nLi at -70°C <1984CL131>.

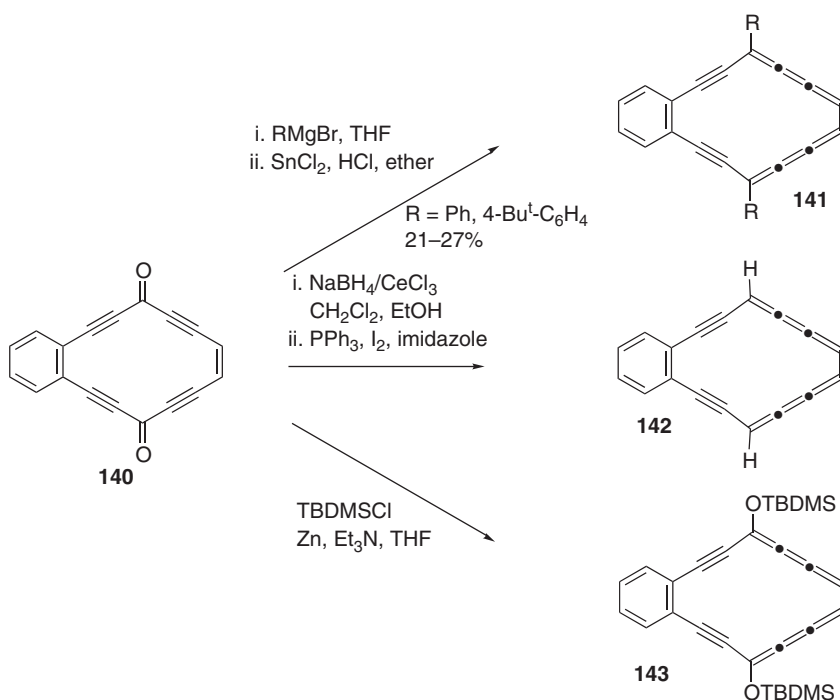
Depending on the substituents, the annulene dione **140** was transformed into the corresponding dehydroannulenes **141–143**, by three different methods: reduction by SnCl_2/HCl , dehydroxylation of the diol by treatment with PPh_3/I_2 or electron transfer reaction (Scheme 15) <1995AG(E)1892>.

1.20.4.3 Wittig and Related Reactions

The formation of allenes from phosphorus ylides and carbonyl compounds can be considered either starting from an alkylidene phosphorane and a ketene <1963CB1535> or from a vinylidene phosphorane and a carbonyl compound. Both these strategies have been used for the access to a variety of functionalized allenes.

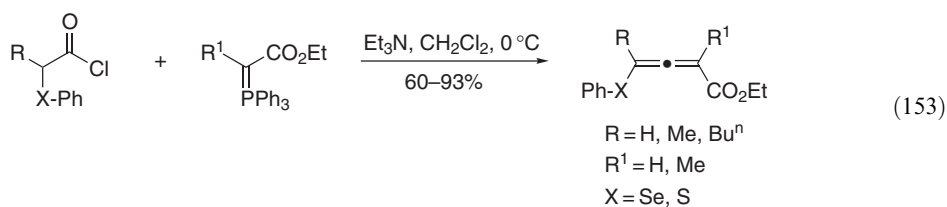
1.20.4.3.1 Reaction of a ketene and an alkylidene phosphorane

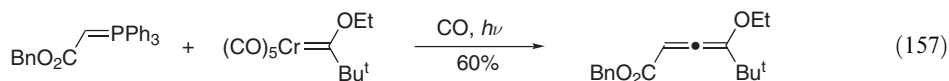
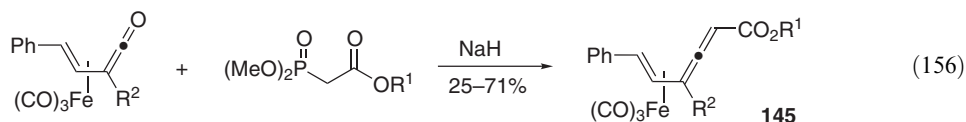
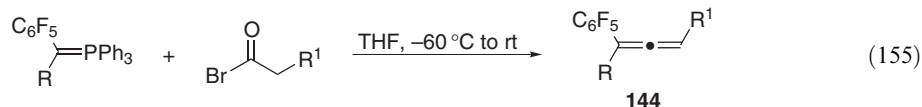
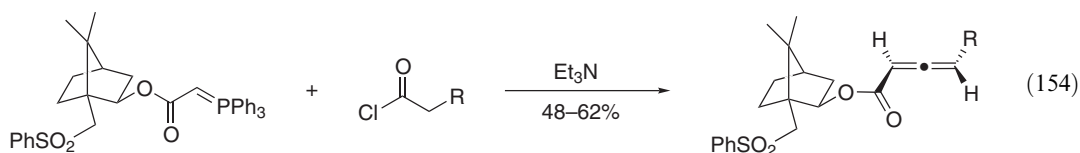
Terminal allenes have been obtained in 59–80% yield by reaction of stable phosphorus ylides with $\text{CH}_2=\text{C}=\text{O}$ at $0\text{--}5^\circ\text{C}$ <1970S543>. Electron deficient allenes such as 1,1,3,3-(tetraalkoxycarbonyl) allenes have been prepared in more than 60% yield by treatment of alkylidene phosphoranes with ketenes in refluxing benzene <1979LA1388>. A process based on the use



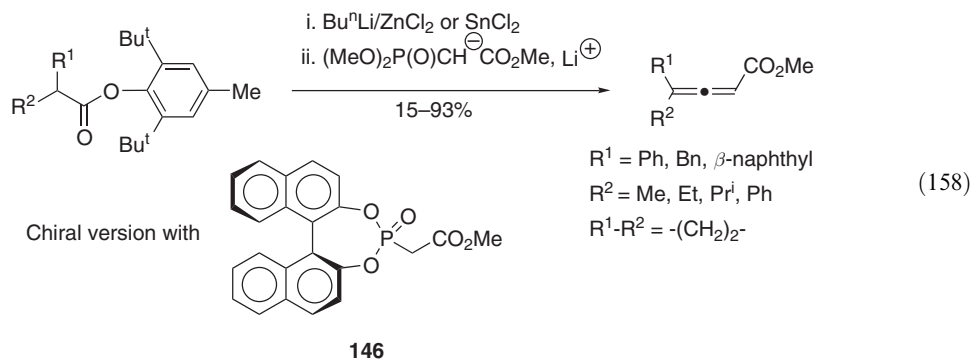
Scheme 15

of carboxylic acids or acyl chlorides which can undergo α,β -elimination reaction, can be used to prepare allenenes which is similar to the formation of ketenes. Thus, ethyl allenyl carboxylates have been obtained from [(ethoxycarbonyl)methylidene] phosphoranes and acids, in the presence of Bu₃N and 2-chloro-1-methylpyridinium iodide [<1985HCA2244>](#). In dichloromethane, at room temperature, acyl halides react with [(alkoxycarbonyl)methylidene] phosphoranes in the presence of Et₃N to provide allenenes [<1992CPLI243>](#) and alkenyl allenenes from α,β -unsaturated acyl chlorides [<1985HCA2249>](#). 4-Phenylchalcogeno allenic esters have been synthesised from α -(phenylchalcogeno)acyl chlorides and ethyl 2-(triphenylphosphoranylidene) acetate or propionate in the presence of triethylamine (Equation (153)). The corresponding allenic esters were isolated in 60 to 93% yield [<2000TL1867>](#). When a phosphorane bearing a chiral auxiliary is engaged in the Wittig–Horner–Emmons reaction, the diastereomerically pure allene is obtained in fair-to-good yield (Equation (154)) [<2003TL6409>](#). Pentafluorophenyl allenenes **144** have been prepared from corresponding phosphoranes and acyl bromide at -20°C in THF (Equation (155)) [<1998JCR\(S\)602>](#). Unsymmetrical pentatetraenes have been prepared in good yields (50–75%) on reaction of a phosphorus ylide with an allenyl acyl chloride in the presence of Et₃N at room temperature [<1986CB1208>](#). The coordination of vinyl ketenes to a Fe(CO)₃ moiety makes possible the direct synthesis of coordinated vinyl allenenes **145** [<1992JCS\(P1\)259, 1991JCS\(CC\)1290>](#) on reaction with phosphonoacetate via a Wadsworth–Emmons-type reaction (Equation (156)). Photolysis of stabilized phosphorane ylides with alkoxycarbene chromium complexes under a carbon monoxide atmosphere leads to allenenes via formation of a ketene, by classical coupling of the carbene ligand with CO (Equation (157)) [<1992JA4079>](#). On reaction with phosphonium ylides, carbon dioxide allows the formal coupling of two carbenic moieties with the carbon atom of CO₂ [<1974TL1275>](#).





Various allene carboxylates can be efficiently prepared from the corresponding 2,6-di-*t*-butyl-4-methylphenyl (BHT) esters in a one-pot procedure via *in situ* ketene generation and subsequent Horner–Wadsworth–Emmons reaction with a phosphonoacetate anion (Equation (158)) <1995SL933, 1995TL9513>. On the basis of the one-pot procedure, Tanaka and Fuji developed an asymmetric version of the Wittig-type reaction <1996TL3735, 2001TA669>. *In situ* generated ketenes react with the anion of the chiral phosphonate **146** to form optically active allenes in good yields and up to 91% ee (Equation (158)). It has to be pointed out that aryl carboxylates are required for the generation of the ketene. The high enantioselectivity can be understood by a favorable chelation of zinc to the phosphate to produce a conformationally locked anion.

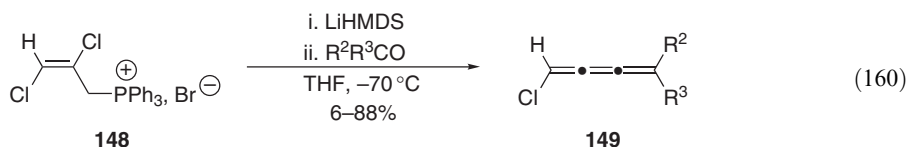
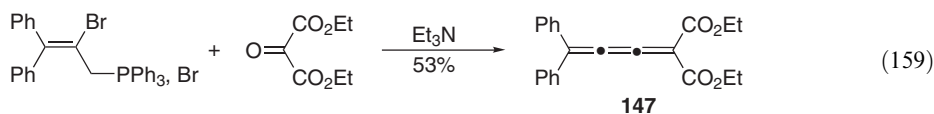


A new allene synthesis involving a boron–Wittig reaction of aldehydes with boron stabilized carbanions at -78°C has also been reported <1992JCS(P1)747>.

1.20.4.3.2 Reaction of a ketone and a vinylidene phosphorane

The other strategy based on the use of vinylidene triphenylphosphoranes can be exemplified by the synthesis of push–pull allenes from cyclic 1,2-diketones and 2,2-diethoxyvinylidene phosphorane <1973TL3985, 1975TL4405>.

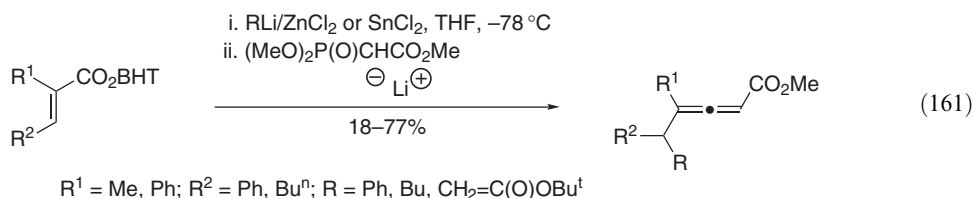
Regioselective halide displacement from halogenated phosphonium salts gives rise to phosphacumulenes, which react with ketones to afford butatriene derivatives <1969JA6112>. The bromoalkenylphosphonium bromide gave 53% yield of the cumulene diester **147** (Equation (159)) <1987AJC1675>, whereas on reaction with ketones in the presence of $(\text{Me}_3\text{Si})_2\text{NLi}$ at low temperature dibromo- or dichlorophosphonium salts **148** led to halogenated butatrienes **149** (Equation (160)) <1990JOC2983, 1988TL411, 1987JOC443, 1984JCS(CC)152>.



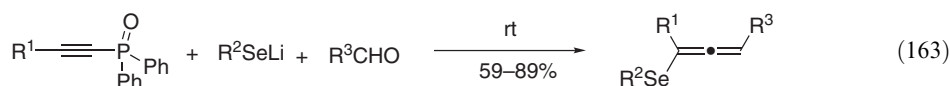
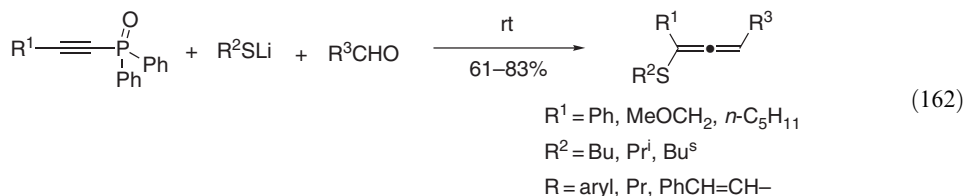
A symmetrical butatriene has been obtained in 71% yield by reaction of fluorenone with a propylidene phosphorane produced from methyldiene triphenylphosphorane and *gem*-dihaloalkenes <1975TL4025>. The Horner–Emmons-type reaction starting from allenyl diphenylphosphine oxide <1990TL7469> or allenyl phosphonates <1985IJ136, 1986JA343> and aldehydes or ketones makes possible the synthesis of butatriene derivatives, and bicyclic cumulenes via intramolecular reaction. Another strategy based on the intermediate formation of a cumulenyl diylide is exemplified by the synthesis of 1,4-diphenylbutatriene from benzaldehyde and a diphosphonium bistriflate <1991T4539>. Higher symmetrical cumulenes have been obtained by Wittig reaction of carbon suboxide with 2 equiv. of phosphorus ylide at room temperature <1986AG(E)93, 1987G625>.

1.20.4.3.3 Three-component reaction for allene synthesis

Branched allene carboxylates can also be conveniently prepared by a tandem Michael–Horner–Wadsworth–Emmons reaction of α,β -unsaturated BHT esters, a carbon nucleophile, and a phosphonoacetate derivative (Equation (161)) <1995TL9513>.



A three-component reaction between an aldehyde, a 1-alkynylphosphine oxide, and a lithium alkylthiolate (Equation (162)) or a lithium alkylselenolate (Equation (163)) allows the formation of sulfur- or selenium-substituted allenes through a Michael/aldol/Horner–Wadsworth–Emmons tandem reaction <2003TL5913, 2003CC1714>.



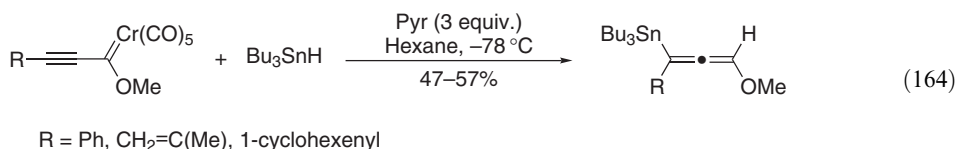
1.20.4.3.4 Addition of carbene moieties to double bonds

Unsaturated carbenes generated *in situ* by treatment of propargylic halides or esters with KOBU^t react with alkenes to produce alkenylidene cyclopropanes in moderate yield (10–52%) <1971JA4527>. Extended unsaturated carbenes like alkadienylidene, alkatrienylidene, and alkatetraenylidene carbenes have been generated starting respectively from 1-ethynylvinyl triflates <1979JA4772, 1982ACR348>, (1,3-diynyl)alkyl mesylates or halides <1981JA4638,

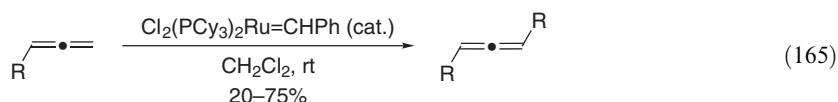
1988JOC3122>, and (1-butadiynyl)vinyl triflates <1981JA6437, 1982ACR348>. These unsaturated carbenes provide access to a variety of cyclopropyl cumulenes and dimerized cumulenenic compounds <1987JA782>. Silicon-, germanium-, and tin-functionalized cumulenes have been prepared (26–88%) on interaction of alkadienyldiene <1981JA5429> and alkatetraenyldiene <1981JA6437> carbenes with group 4 hydrides.

cis-Cumulenes have also been prepared in 20–50% yields via homocoupling of two carbenes generated from (α -methylthiovinyl)copper reagents and CH_3I at 0°C in THF <1975TL2923>.

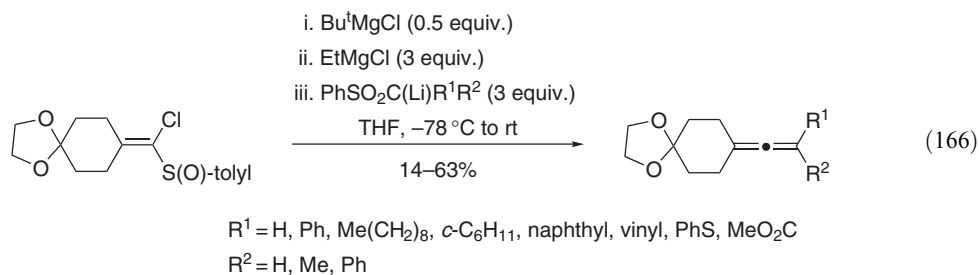
Hydrostannylation of alkynyl-chromium carbene has led to the synthesis of γ -methoxyallenylstannane, a useful reagent in organic chemistry which cannot be readily prepared by the $\text{S}_{\text{N}}2'$ substitution reactions of propargylic halides or sulfonates (Equation (164)) <1995TL1011>. Interestingly, the regiochemistry of the hydrostannylation (allenyl versus propargyl derivative) is very sensitive to the steric bulk of both the alkynyl carbene complex and the tin hydride source.



The olefin metathesis reaction catalyzed by well-defined transition metal alkylidene complexes has been known for more than a decade and has been extensively explored. This is now an efficient process for the creation of new double C–C bonds. The Grubbs catalyst, $\text{Cl}_2(\text{Cy}_3\text{P})_2\text{Ru}=\text{CHPh}$, was found to catalyze the cross-metathesis of monosubstituted allenes to 1,3-disubstituted allenes in low-to-good yield (Equation (165)) <2000OL551>.



Carbenoids can also be generated from 1-chlorovinyl *p*-tolyl sulfoxides with a Grignard reagent by sulfoxide–magnesium exchange. Treatment of magnesium alkylidene carbenoids with lithium α -sulfonyl carbanions gives allenes in moderate-to-good yield (Equation (166)) <2002TL2043>.

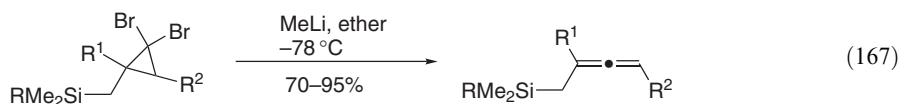


1.20.4.4 Dehalogenation

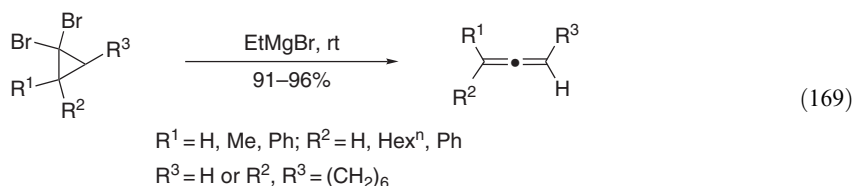
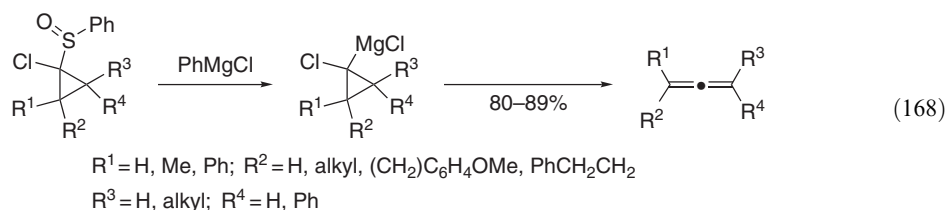
1.20.4.4.1 Dehalogenation of halocyclopropanes

Treatment of *gem*-dihalocyclopropanes by alkyllithium reagents at low temperature (-30°C to room temperature), namely the Doering–Moore–Skatteböl reaction, gives allenes in good yield <1962JOC4179, 1984TL2887, 1984CJC1558, 1985JCS(CC)1812, 1995SL880>. Butatrienes have also been prepared in approximately 75% yield by reaction of Bu^nLi with *gem*-dibromo methylene cyclopropanes <1967JCS(C)194>. This strategy has been used for the synthesis of cyclic allenes <1973JOC864, 1986TL4679> and bisallenes <1990TL1841>, bicyclic allenes <1982JOC1435> and cyclopropyl allenes <1997T11069>, and small ring cyclic cumulenes such as cyclonona-1,2,3-triene <1984JOC2880>.

Allenyl silanes have been prepared in good yield from allyl silanes by successive dibromocarbene addition and rearrangement of a cyclopropylidene (Equation (167)) <1996TL579, 1997TL3395>.



An alternative to the Doering–Moore–Skattebøl reaction suggested by Satoh is based on sulfide–metal exchange, followed by rearrangement of a magnesium carbenoid (Equation (168)) <2001T5369>. Band and co-workers reexamined the ring-opening reaction mediated by Grignard reagents <2002T1581> and found that, at room temperature, the magnesium carbenoid rearranged to produce the allene and that EtMgBr was the preferred reagent (Equation (169)). This method may offer benefits in allene synthesis as ethylmagnesium bromide is more stable and easier to prepare than alkyllithium reagents.

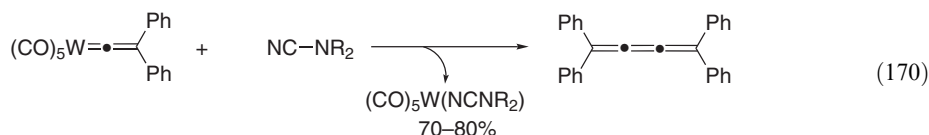


1.20.4.4.2 Dehalogenation of gem-dihaloalkenes

Dimerization of *gem*-dihaloalkenes on treatment with alkyllithium reagents leads to butatrienes via 1-halo-1-lithium alkene intermediates. Thus, cumulenenic thioesters <1983CPB3306> and tetra-(2-thienyl)butatrienes were prepared <1992JCS(CC)778>. From these intermediates, lithium can be exchanged with copper <1986JA5371> to produce functionalized alkoxy <1988JA5567>, alkynyl <1993AG(E)1187>, and fluorinated <1991JCS(CC)566> butatrienes. 1-Halo-1-lithio alkene intermediates have also been generated by treatment of a terminal monohalogenated alkenes by BuⁿLi <1984JOM(264)135, 1984JOM(271)181>. Aryl-substituted butatrienes have been conveniently prepared from 1,1-dibromoethenes using a nickel(0) catalyst at 50 °C <1984CL2005, 1989JCS(CC)1690>.

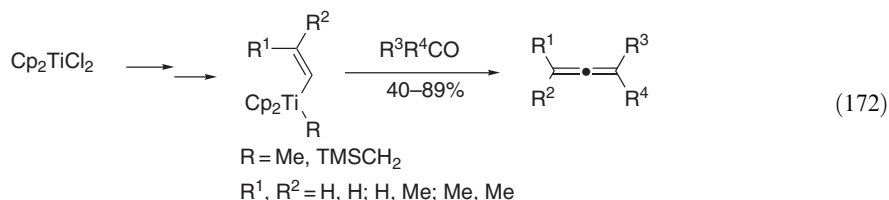
1.20.4.5 Reactions Involving Coordinated Organometallic Species

Coordinated cumulenes can be stoichiometrically generated by reaction of suitable substrates with organometallic complexes. The cumylene moiety can be eliminated from the metal center by ligand exchange <1989CB1237>, oxidation with Me₃NO <1993OM3971>, or protonation <1993AG(E)1315>. Cumulenenic systems can also be formed from metal-vinylidene intermediates by dimerization of the vinylidene ligand on thermal treatment <1985IJ131, 1990JOC1874, 1987JCS(CC)981> or ligand exchange (Equation (170)) <1992CB2667>.

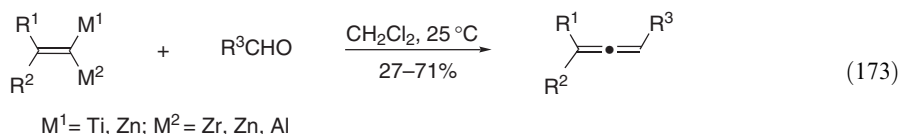


Titanium complexes react with aldehydes or ketones to afford allenes (Equation (171)) <1983JA5490, 1993JOC1298, 1993AG(E)554, 1997JOC2574>. With the development of a step-wise coupling procedure, the synthesis of unsymmetrical allenes was proposed <1997JOC2564>. Using the same reagent, a highly efficient cyclization of alkyl- and polyether-tethered aromatic

dialdehydes was described, which afforded macrocyclic allenes in good yields [<1997JA3429>](#). A carbonyl allenation process mediated by other titanium reagents such as Cp_2TiCl_2 offers a direct and versatile approach to highly functionalized allenes ([Equation \(172\)](#)) [<1997JOC782>](#).



Geminal organobimetallic derivatives became very attractive as they can create *in situ* several carbon–carbon bonds. Thus, mixed titanium–aluminum complexes react with carbonyl compounds to produce allenes [<1981JA1276>](#). Under similar conditions, 1,1-zinc, zirconium alkene reagents, generated by reaction of zinc acetylides with $\text{Zr}(\text{H})(\text{Cl})(\text{cyclopentadienyl})_2$, react with aldehydes to smoothly produce allenes in dichloromethane at 25 °C ([Equation \(173\)](#)) [<1991JA9888, 1994OM94>](#). 1,1-Dizincioalkene reagents, prepared from lithium acetylide and allyl Grignard reagent in the presence of zinc bromide, also react with aldehydes in ether to produce allenes [<1995TL7451, 1996S1499>](#).



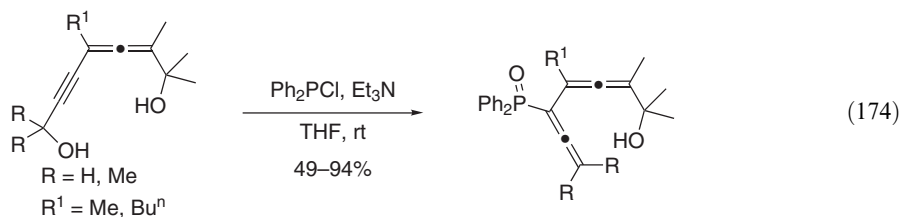
1.20.4.6 Metal-catalyzed Homocoupling of Alkynes or Cumulenes

Activation of terminal alkynes by metal complexes, via a vinylidene intermediate, makes possible the catalytic synthesis of cumulenes. Ruthenium complexes, such as $\text{H}_2\text{Ru}(\text{CO})(\text{PPh}_3)_3$ [<1976JCS\(CC\)841>](#) or $\text{Ru}(\text{cyclooctadiene})(\text{cyclooctatetraene})$, [<1991JA9604>](#) catalyze the dimerization of bulky terminal alkynes such as *t*-butylacetylene or trimethylsilylacetylene into the corresponding 1,4-disubstituted butatrienes.

Iyoda and co-workers have shown that the nickel(0)-catalyzed cyclodimerization of tetraarylhexasilanes led to new cumulenes, head-to-head dimers [<1989JA3761>](#), whereas hexasilanes bearing bulky alkyl substituents in refluxing benzene mainly gave head-to-tail dimers in good yield [<1990CL2149>](#).

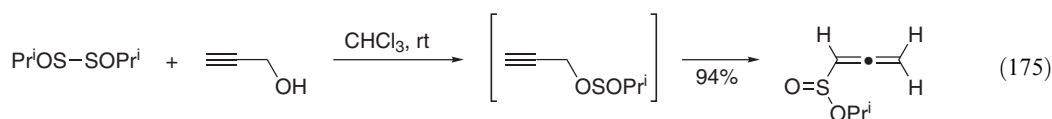
1.20.4.7 Intramolecular Rearrangement with Formation of Heteroatom–Carbon Bond

Intramolecular rearrangement involving heteroatom–C and C–C double bond formation can take place from various functional propargyl derivatives. Thus, the condensation of Ph_2PCl with prop-2-yn-1-ol derivatives leads to intermediate alkynyl phosphinites, which undergo rearrangement into allenes via intramolecular addition of the phosphorus atom to the triple bond [<1962JOC1828, 1989JA1770, 1989TL4995>](#). Similarly, allenyl dihalophosphine oxides obtained at room temperature from propargylic alcohols and phosphorus trihalide via dihalo propargyl phosphites [<1976JOC3191>](#) and are useful intermediates to access allenyl phosphonic derivatives and oxaphosphenes. This method was extensively used for the preparation of functionalized dihydrofurans [<1999S463>](#), oxaphosphenes [<1998S710>](#) or during the study of the Myers rearrangement [<1995TL4975, 1997TL7941>](#). Similarly, a selective monophosphorylation of the propargylic hydroxy group of diols, containing both propargylic and α -allenic alcohol functionalities, gives access to diallenylphosphine oxides in high yield after sigmatropic rearrangement ([Equation \(174\)](#)) [<1996S711>](#). Allenyl dialkyl phosphates have been prepared in 43–62% yields on rearrangement of stable propargylic phosphates with AgClO_4 as catalyst [<1977JOC1804>](#).



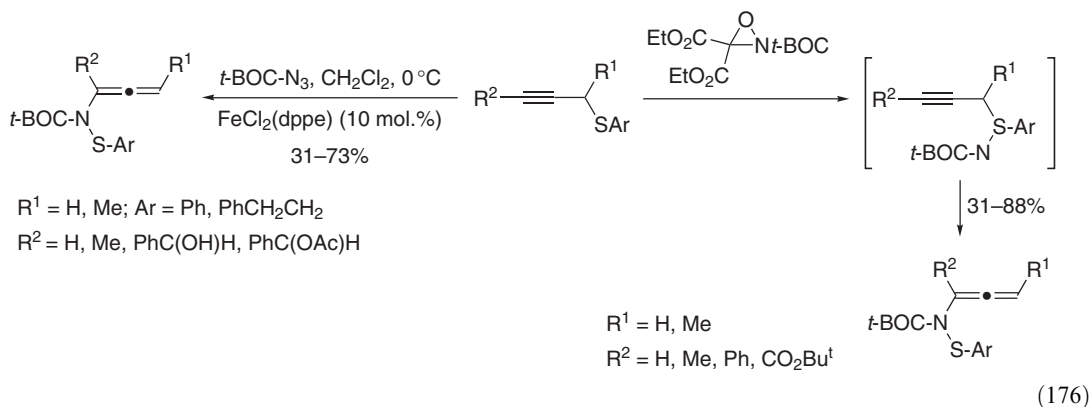
The reaction of propargylic alcohols with sulfinyl chloride at low temperature in the presence of a base leads to allenyl sulfoxides via unstable propargyl sulfenates [<1971JCS\(C\)1530, 1988JA4062, 1990JA4072, 1993SL931, 1997T12651>](#). The use of a sulfinyl chloride allows the preparation of allenyl sulfones via a similar intramolecular rearrangement [<1987JOC4031>](#). Treatment of propargylic diol monothionocarbonates with $(\text{TMS})_2\text{NLi}$ has been used to produce heterocyclic allenenes [<1994TL1255>](#).

Other sulfur reagents can be used to promote the propargylic rearrangement into allenenes. Allenyl trifluoromethyl sulfoxes and allenic trichloromethyl sulfoxide are readily prepared from propargyl alcohols and sulfinyl chloride or trichloromethanesulfinyl chloride [<1998TL5413, 2001TL1391>](#). A practical synthesis of allenyl sulfinates was also described via a one-pot/two-step procedure: treatment of a symmetrical dialkoxy disulfide with propargyl alcohol followed by spontaneous [2,3]-sigmatropic rearrangement (Equation (175)) [<2003S2079>](#). The reaction of propargyl alcohol with SOBr_2 affords an example of intramolecular nucleophilic substitution with formation of a C—C double bond. Bromoallenenes are thus preferentially formed when the reaction is carried out in the presence of propylene oxide [<1984TL3055>](#). Similarly, acyl allenenes have been obtained by reaction of SOCl_2 with acyl propargylic alcohols [<1985TL631>](#).

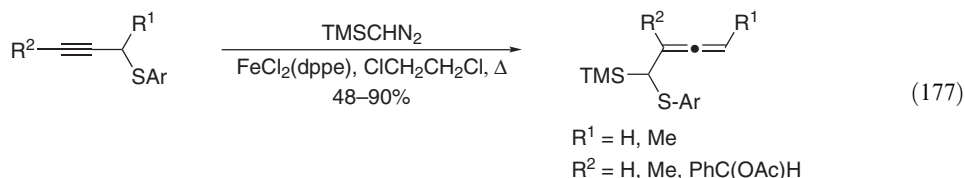


Allenyl trichloroacetamides are formed by thermal interconversion of propargylic trichloroacetimidates, which isomerize into trichloroacetamido dienes on prolonged heating [<1980ACR218>](#). Propadienyl isothiocyanates have been prepared by thermolysis of propynyl thiocyanates via a sigmatropic rearrangement in 7–20% yield in dilute solution at 60–100 °C, or better in 95–100% yield in the gas phase at 400 °C [<1992AG\(E\)90>](#).

Allenamides have demonstrated a widespread synthetic potential. Two complementary procedures dealing with this topic have appeared in 2003. The first one is the amination of propargylic sulfides with a ketomalonate-derived oxaziridine under metal free conditions, which led to the *N*-*t*-BOC-*N*-allenylsulfenimides in modest-to-good yield (Equation (176)) [<2003OBC3142>](#). The second one is an iron(II)-catalyzed Bach reaction of *t*-butoxycarbonyl azide and propargyl sulfides. Using $\text{FeCl}_2(\text{dppe})$ as catalyst, the reaction proceeds at low temperature in good yield [<2003JOC4955>](#). In contrast to the previous method with oxaziridine, the reaction is limited by the product tolerance toward the catalyst and the closure of the catalytic cycle by excess *t*-BOCN₃.



Iron(II) is also able to catalyze the reaction of propargyl sulfides with trimethylsilyldiazomethane or ethyl diazoacetate to give allenyl α -silyl- α -sulfides in 48–90% yield (Equation (177)) <2001JOC5256>. It was noted that larger substituents on the alkyne gave higher yields, presumably because of an impossible second addition/rearrangement.

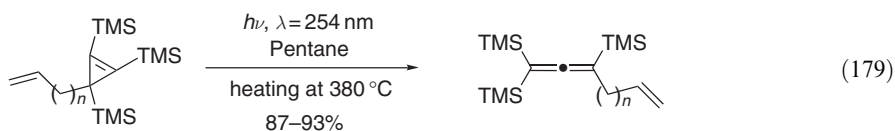
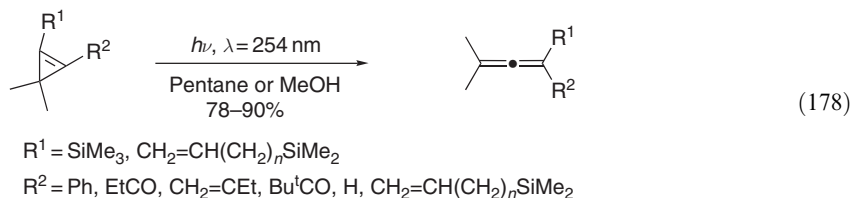


α -Hydroxyallenes have been prepared from 3-phenylselenobuta-1,3-dienes by oxidation with H_2O_2 followed by sigmatropic rearrangement and elimination <1984TL1987>.

1.20.4.8 Cyclopropane Ring Opening

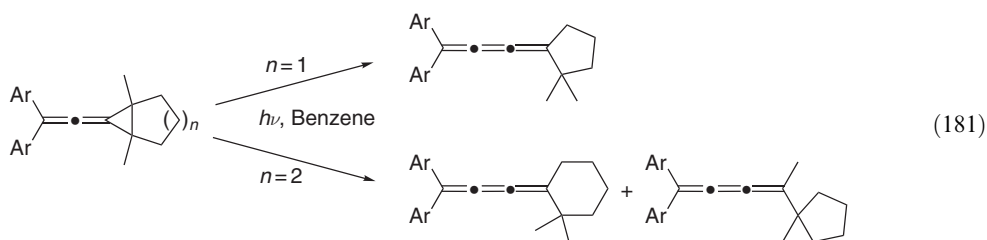
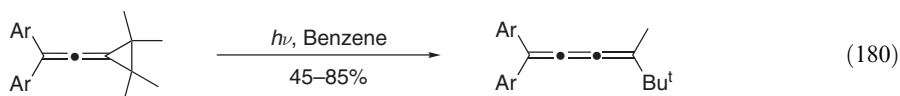
1.20.4.8.1 Photolysis of cyclopropenes

Under irradiation, substituted cyclopropenes rearrange to allenes in high yield (Equations (178)–(179)) <1995TL7979, 2000CEJ1963, 2001EJOC663>. It was demonstrated that cyclopropenes were converted into allenes via a noncarbenoid pathway.



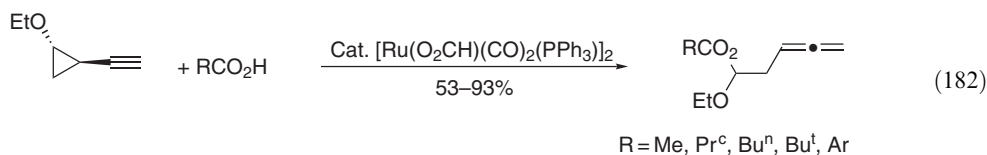
1.20.4.8.2 Photorearrangement of vinylidenecyclopropanes

Irradiation of some 1-(2',2'-diarylethenylidene)cyclopropanes allows the formation of 1,1-diaryl-1,2,3-hexatrienes (Equations (180–181)) <2001OL581>. 2,2,3,3-Tetrasubstituted cyclopropanes reacted faster than less substituted cyclopropanes and it was shown that the mechanism of this reaction proceeded through an alkyl migration, due to the generation of a 1,3-biradical intermediate.

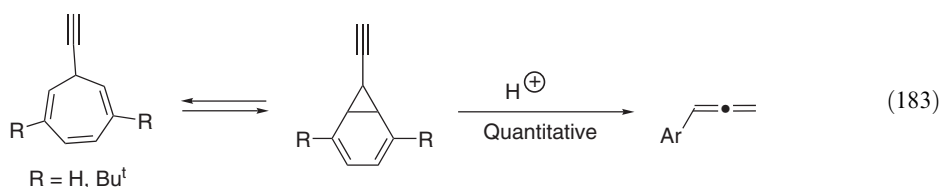


1.20.4.8.3 Ethynylcyclopropane rearrangement

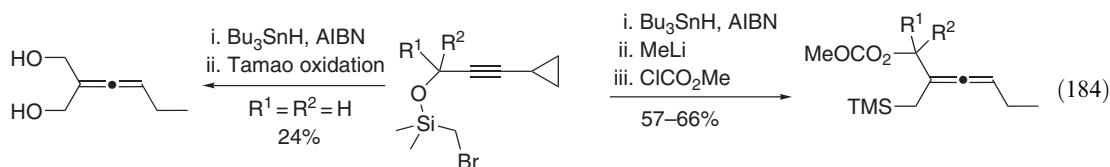
When ethynylcyclopropane and a carboxylic acid are treated in refluxing benzene with a ruthenium catalyst, a regioselective ring opening of the cyclopropane takes place to furnish 1-acyloxy-1-ethoxypenta-3,4-diene, a protected form of the corresponding aldehyde (Equation (182)) <2000SL1315>. It was shown that the yield of allene increased when the steric bulk of the acid decreased.



In acidic medium, ethynyl norcoradiene, the ethynyl cycloheptatriene tautomer, undergoes a ring cleavage into phenylallene in quantitative yield (Equation (183)) <2000OL3011>.



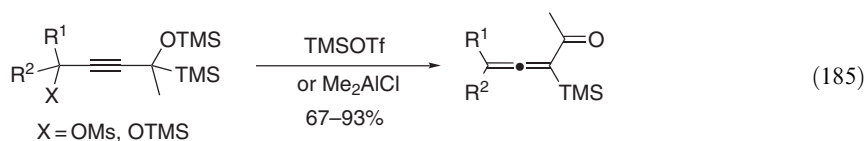
α -Cyclopropyl alkynes can lead, via ring opening under radical conditions, to allenenes, but synthesis of allenenes takes place only in the absence of another unsaturated C—C bond in the starting molecule (Equation (184)) <2002SL923>.



1.20.4.9 Miscellaneous Reactions

Push–pull butatrienes such as 1,1-bis(dimethylamino)-4,4-dicyanobutatriene <1993TL1779> and 1,1-bis(dimethylamino)-4,4-bis(methoxycarbonyl)butatriene <1978TL4263> have been synthesized by coupling 1,1-dimethylaminoethylene with 1,1-dichloroethylene compounds. Homologation of acetylenic compounds to allenenes has been performed with formaldehyde and diisopropylamine in the presence of CuBr as catalyst in refluxing dioxane <1979JCS(CC)859>. Enantiomerically enriched 2,3-allenols have been prepared by this CuBr-mediated homologation of optically active terminal propargylic alcohols <2002S1643>. On bromination, divinylacetylene derivatives containing naphthyl substituents lead to 1,6-dibromocumulatrienes via 1,6-addition of bromine <1990PJC123>. Deprotonation of the bisallene by 2,2,6,6-tetramethylpiperidine lithium (LTMP) followed by oxidation with CuCl₂ at –80 °C gives the hexapentaene <1990PAC531>.

5,5-Disubstituted-3-trimethylsilyl allenones are readily accessible from 1,4-trimethylsilyloxybut-2-yne via an elimination-trimethylsilyl group migration within the propargylic framework (Equation (185)) <1994TL2291, 1997TL25, 1999JOC9307>.



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 1964T2177
 1965CB2611
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 1966BSF2885
 1966JCS(C)1223
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 1968JCS(C)228
 1968JCS(C)606
 1968RTC916
 1968RTC1179
 B-1969MI(7)365
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1.21

Alkynes

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1.21.1 INTRODUCTION

Traditionally alkynes have been of considerable value to the organic chemist by virtue of the fact that they may be readily transformed into a variety of other functional groups. In recent years,

however, their importance has intensified as novel applications of alkynes have been described including those with antitumor activity <2000JNP1511>, cytotoxic activity <2003BMCL877>, carbon-rich materials <1996T4925>, and solid-state materials possessing technologically useful properties <1997CRV637, B-1995MI001>. Concomitant with this has been an increase in innovative methods for the introduction of the alkynyl moiety into organic molecules and these are discussed when appropriate.

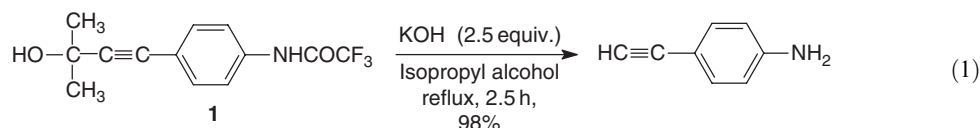
The aim of this chapter is to provide the reader with an up-to-date review of current methods for the formation of alkynes. This will be undertaken by adopting the format used in COFGT (1995) <1995COFGT997> and focusing upon the preparation of alkynes via C—H bond formation (Section 1.21.1), C—C single bond formation (Section 1.21.2), and triple bond formation (Section 1.21.3).

1.21.2 ALKYNES BY C—H BOND FORMATION

As a rule, the synthetic organic chemist is more concerned with the application of terminal alkynes for the formation of carbon—carbon bonds to provide alkynyl derivatives. Historically, a number of early papers have described methods for the reduction of alkynyl-heteroatoms to terminal alkynes and these have been discussed previously <1995COFGT997>. Most recent efforts have been directed toward the development and removal of terminal alkyne protecting groups and deuterium quenching experiments.

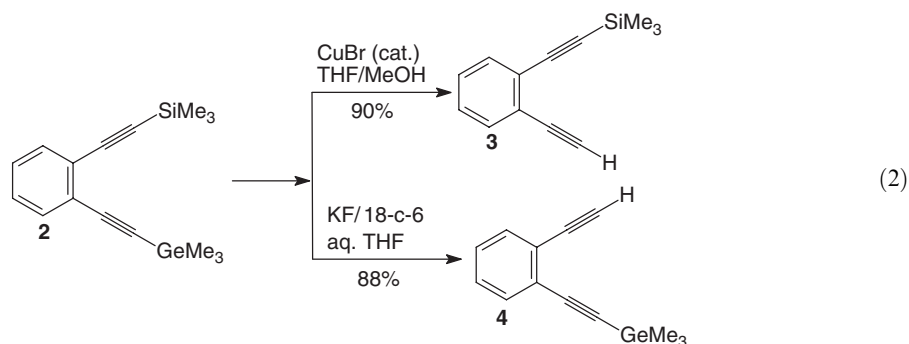
1.21.2.1 Reduction of Alkynylcarbon Functions

As an improvement to existing methods for the synthesis of *p*-ethynylaniline, 2-propanol was employed as a protecting group in 4-(*N*-(trifluoroacetyl)anilin-4-yl)-2-methyl-3-butyn-2-ol **1**. The trifluoroacetamido linkage was found to be a very effective blocking group for *p*-iodoaniline during the coupling reaction. In addition, both the hydrolysis reaction and the deprotection of the 2-hydroxypropyl protecting group occurred simultaneously to afford the desired product in excellent yield and with high levels of purity (Equation (1)) <1994JOC5818>.



1.21.2.2 Reduction of Alkynyl-metalloid Functions

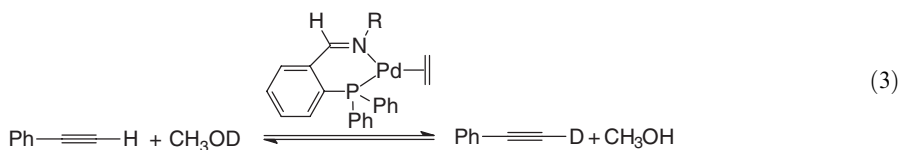
Alkynyl silanes have proved to be versatile reagents in organic synthesis by virtue of their stability and have been widely employed to protect terminal alkynes from organometallic reagents <B-1983MI002>. As a consequence of this, a variety of reagents to effect the corresponding protodesilylation reaction have been discovered. Cleavage of the alkynyl—silicon bond is an important reaction in organic synthesis and provides access to a methodology for selectively functionalizing terminal alkynes. Tetrabutylammonium fluoride, in diethyl ether, has been used to effect the protodesilylation of alkynyl-TMS and alkynyl-TIPS moieties <2000T4951>, in tetrahydrofuran (THF) to deprotect an alkynyl-TIPS group <2000TL2339>, and in ethane-1,2-diol for an alkynyl-TMS moiety <2000JA939>. A regioselective protodegermylation of the diprotected alkyne **2** was achieved using catalytic cuprous bromide in THF/MeOH to afford **3** <1996TL7959>. Alternatively, the corresponding protodesilylation reaction was achieved to afford **4** using potassium fluoride in THF and 18-crown-6 (Equation (2)).



Other protodesilylating reagents that have been employed in recent years include potassium hydroxide in methanol <2001JOM19>, sodium hydroxide in aqueous methanol <1995TL5167>, ammonium fluoride <1995TL5167>, potassium carbonate <2002T10197, 1999TL3347, 2001TL3057, 2002T10387, 2003JOM17>, caesium fluoride in dimethylformamide (DMF)/MeOH <1997HCA2215>, and the silver nitrate/sodium iodide couple <2000T2183>. This particular set of reaction conditions has been observed to effect the regioselective protodesilylation of a triple bond in the presence of a silyl enol ether <1987TL3923>. The cleavage of alkynylgermanium bonds has been accomplished under acidic conditions <1997HCA2215>.

1.21.2.3 Reduction of Alkynyl-metal Functions

During recent studies in the generation and reactions of alkynylsamarium reagents, THF was found to be the solvent of choice <2000T9927> and that these organometallic reagents coupled with ketones in good yield using either Barbier or Grignard methodologies <1999CRV745>. The samarium Grignard reaction (SGR) produced superior results and quenching of alkynylsamarium reagents with D₂O led to a 60% incorporation of deuterium at the terminal *sp*-carbon atom. Analogous deuterium quenching experiments of alkynylsamarium species have been reported <1995TL3707>. A Pd(0)-olefin complex that catalyses the alkoxy carbonylation of terminal alkynes has been developed. Exposure of a terminal alkyne to CH₃OD in the presence of this catalyst led to a hydrogen/deuterium exchange (Equation (3)) <2001JMOC51, 1998OM630>.



1.21.3 ALKYNES BY C—C BOND FORMATION

A variety of methods have been described for the preparation of alkynes that involve the chemistry of substitution reactions, addition reactions, and addition/elimination reactions. A number of noteworthy reviews have been published on acetylenic coupling reactions <2000AG(E)2632>, alkylation reactions of alkynes <2002CCR171>, palladium-copper-catalyzed cross-coupling reactions <2002JOM46, 1995OPP127>, palladium-catalyzed reactions on a solid phase <2003T885>, the chemistry of the carbon-transition metal double and triple bond <2002CCR1>, the 1,1-organoboration of alkynylsilicon, -germanium, -tin, and -lead compounds <1995CCR125>, organozinc-mediated reactions <1998T8275>, luminescent polynuclear metal acetylides <1999JOM3>, and the chemistry of platinum-alkyne complexes <2000JOM37>.

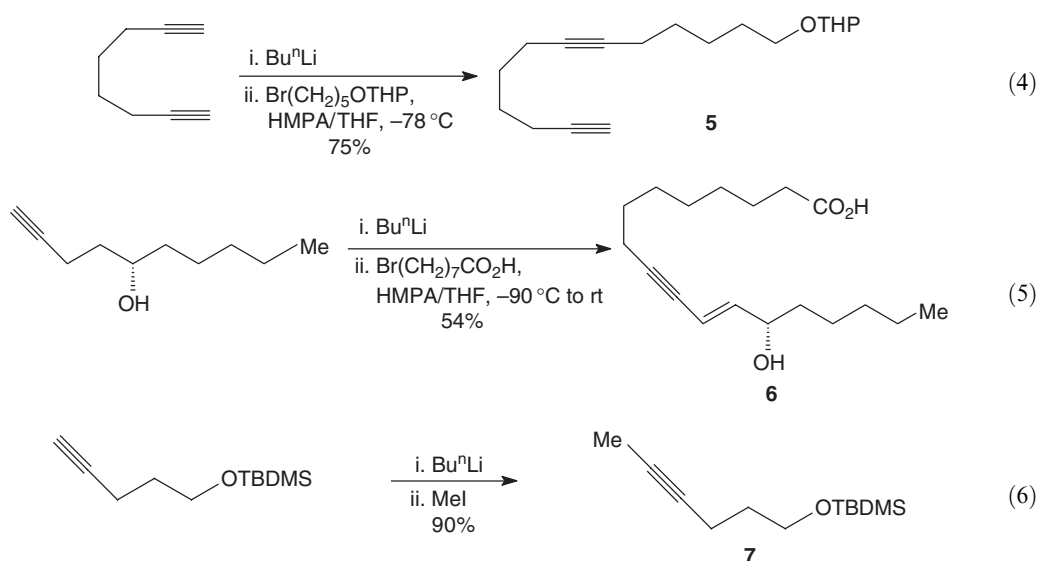
1.21.3.1 Substitution Reactions of Alkynyl Carbanions

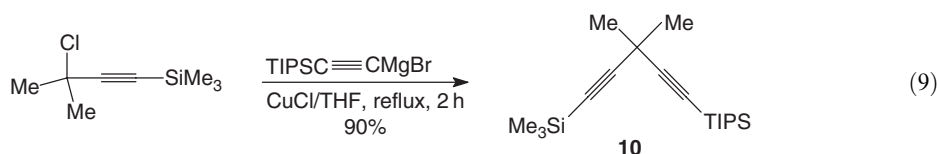
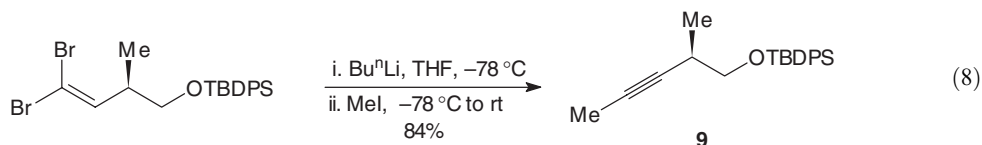
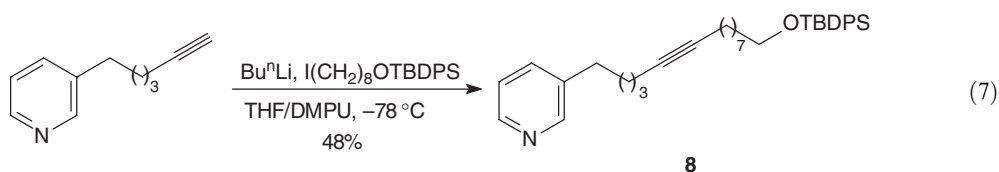
The synthesis of alkynes may be accomplished by the reaction of an alkynyl carbanion with an alkyl halide (Section 1.21.2.1.1.(i)), by the reaction of a terminal alkyne or an alkynyl organometallic reagent with an alkenyl, aryl, or allenyl halide (Section 1.21.2.1.1.(ii)) and from the formal substitution reaction of an alkynyl halide (Section 1.21.2.1.1.(iii)).

1.21.3.1.1 Substitution of halogens

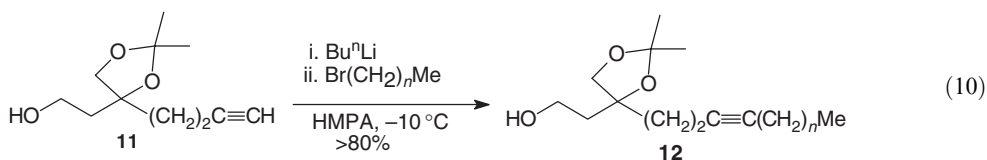
(i) The reaction of alkynyl carbanions with alkyl halides

The formation of $Csp-Csp^3$ -bonds tends to follow traditional ionic methodologies [<1991COS3, 1997MI129>](#) and may be readily accomplished by deprotonation of a terminal alkyne followed by the reaction of the resulting alkynyl carbanion with a suitable alkyl halide. This method tends to be limited to the alkylation of primary unhindered alkyl halides. Attempted alkylation reactions with secondary, tertiary, or sterically hindered primary alkyl halides have a propensity to afford elimination products. The traditional methods for the formation of alkynyl metals derived from lithium, sodium, potassium, and magnesium have been described [<1995COFGT1000>](#). In general, these methods are still in common practice and have been reviewed [<B-1988MI003, B-1978MI004, B-1983MI005, 2003JOM151>](#). Methods of avoiding undesired side-reactions associated with the high reactivity and strong basicity of these reagents have been revealed [<B-1981MI006>](#). Considerable interest has been directed at finding alternative reagents and solvents for overcoming the problems associated with the low solubility of the alkynyl carbanions, in liquid ammonia, as well as the variable yields that result when this solvent is used [<B-1955MI007>](#). The use of hexamethylphosphoramide (HMPA) as a dipolar aprotic co-solvent, for facilitating the reaction between alkynyl anions and the alkylating reagent, fell in popularity when the dangers associated with its use were highlighted. Alternative reagents to HMPA, such as *N,N*-dimethylpropyleneurea (DMPU) in DMSO [<1988S250>](#), have been revealed but its use is limited to applications involving acid-stable alkynes [<1986TL5445>](#). Recent reports have highlighted the use of Grignard reagents [<1995S299>](#), weak bases such as morpholine [<1997HCA2215>](#), as well as continued interest in alkyllithium reagents [<2001TL5825, 1999JOM223>](#), in THF for deprotonation of terminal alkynes. Despite the hazards associated with the use of HMPA in the generation of alkynyl carbanions, this reagent has recently regained its popularity in syntheses [<2000SC1895, 1999EJO2167, 1999OL845, 2000TL4801, 1996T157, 1997JOC3332, 1999JOC5732>](#). When the alkylating reagent is particularly reactive, the need for a co-solvent has been reported to be unnecessary and exposure of alkyllithium reagents with iodomethane [<1999JOM223>](#) or with an allylic halide [<2000T7123>](#) in THF affords the alkylation product. Some recent representative examples are shown (Equations (4)–(9)).



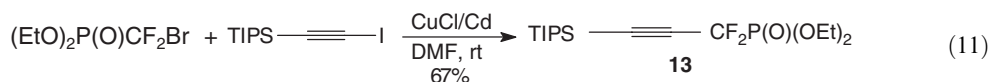


The synthesis of **5**, a substrate in the synthesis of linear enediynes for cobalt-mediated [2+2+2]-cycloadditions, was achieved by the monoalkylation of 1,7-octadiyne (Equation (4)) <1999TL707> using a lithiation reaction in THF, as solvent, with HMPA as a co-solvent. The ether **5** was formed in 75% yield and 12% of the product arising from dialkylation. Analogous reaction conditions have been employed in other syntheses including a stereocontrolled synthesis of (+)-lycoperdic acid, a novel neurotoxin <2000TL4801>, as well as a recent approach to the alcohol **6**, a key intermediate in a novel synthesis of (*S*)-coriolic acid (Equation (5)) <2000T327>. The methylation reaction of the ether (Equation (6)) <2002TL2725> was carried out in the absence of HMPA to provide **7** in 90% yield. The synthesis of compound **8** (Equation (7)) <2003T1719> serves to emphasize the use of DMPU as a co-solvent in conjunction with THF. The authors noted that the best yield (48%) was only obtained by modification of the known procedure <1988S250>. This involved the addition of DMPU to the reaction mixture prior to the addition of BuⁿLi. The yield was only optimized by varying the quantities of the iodide, DMPU, and BuⁿLi used during the reaction. Using a method developed by Corey <1972TL3769> for the *in situ* synthesis of terminal alkynes by the exposure of the vinyl dibromide with BuⁿLi, the ether **9** was prepared (Equation (8)) <2001TL3649>. Although this transformation was conducted at -78 °C, the use of a co-solvent was not necessary. The pentadiyne **10** (Equation (9)) <2000T9581> served as a precursor in the synthesis of one of several macrocyclic enediynes that were used as probes in Bergman–Miles cyclization reactions. Noteworthy was the deprotonation reaction of triisopropylsilylacetylene with a Grignard reagent, the addition of CuCl prior to reaction of the alkynyl carbanion with the chloride and that the substitution reaction was conducted at reflux. An investigation into the synthesis of analogs for topostin B, an DNA topoisomerase 1 inhibitor, serves as a good example of solvent dependency during the alkylation of lithiated alkynes (Equation (10)) <1998T551,1998T565>. Attempts at the alkylation of the lithiated derivative of **11** were thwarted using THF–HMPA as the solvent. When the reaction was repeated having evaporated hexane from the reaction mixture, originating from the butyllithium, a low yield of **12** resulted. The yield of this reaction was optimized, however, by using a diethylether–HMPA solvent system. Addition of the alkyl halide to the lithiated alkyne derivative of **11** was followed by removal of the volatiles by evaporation. Normal work-up then provided **12** in an acceptable yield.

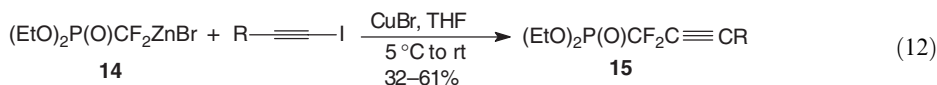


α -Fluoroalkylphosphonates have aroused considerable interest as selective fluorinating agents <B-1996MI006, 1996T8619, 1996CC1447> and for their use in the study of biological phosphate mimics <2000JBC4783, 1999BJP1419, 1997BP255>. In a recent study on the suitability of

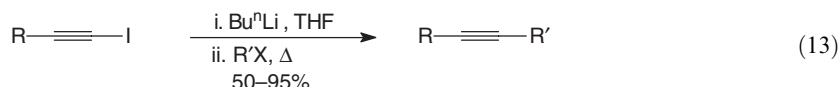
candidate molecules for the formation of β,γ -unsaturated α -fluorinated phosphonates, the difluoroalkyne **13** was revealed (Equation (11)) <2001JFC127>. The optimized method involved a CuCl/Cd-promoted coupling reaction, pioneered by Burton <1996TL2745>, between a readily available diethylbromodifluoromethylphosphonate with 1-iodo-3-TIPS ethyne. This compound was generated, *in situ*, by the lithiation of triisopropylsilylacetylene in THF at -78°C .



Burton's own attempt at the synthesis of α,α -difluorophosphonates focused upon the generation of stable organometallic reagents based upon $(\text{EtO})_2\text{P}(\text{O})\text{CF}_2\text{M}$ ($\text{M} = \text{Zn}$ **14**, Cd , and Cu) followed by reaction with electrophiles including alkynes (Equation (12)) <2002JFC15>. The direct coupling of the zinc organometallic reagent **14** with alkynyl halides to afford **15** takes place rather slowly; however, significant rate enhancements have been observed when stoichiometric amounts of $\text{Cu}(\text{I})\text{Br}$ were added with the haloalkyne. This presumably facilitates the coupling reaction by formation of the $(\text{EtO})_2\text{P}(\text{O})\text{CF}_2\text{Cu}$ reagent *in situ*. The choice of solvent was important for the success of the coupling reaction; thus, although DMF and dimethyl aluminum chloride (DMAC) stabilize the $(\text{EtO})_2\text{P}(\text{O})\text{CF}_2\text{Cu}$ reagent, the presence of accompanying side-reactions complicated the reaction. Optimum, but variable, yields were obtained in THF as the solvent. The authors noted that bromoalkynes provided higher yields of propargyl phosphonates than the corresponding iodoalkynes as a result of a reduction in the amount of metal/halogen exchange.

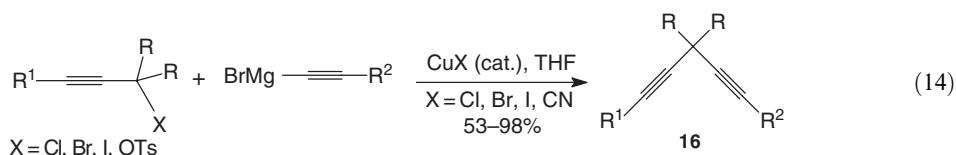


The reactions of lithiated alkynes with primary alkyl halides tends to be viewed as low-temperature reactions; however, studies on the alkylation of 1-alkynes in THF at elevated temperatures have recently been reported (Equation (13)) <2001TL5825>.

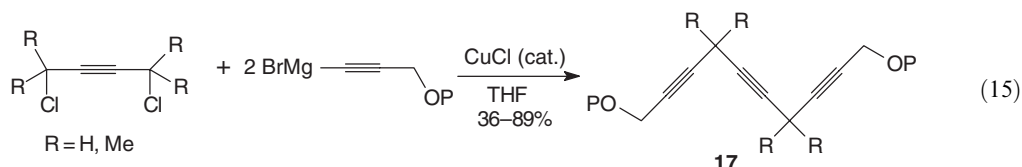


When conducted at ambient temperatures, coupling reactions were slow, although heating the reaction mixture to a reflux temperature led to complete reaction in 8 h. Reactions involving bromoalkanes were slower than with the corresponding iodides and in some examples the reactions did not continue to completion, although the addition of catalytic amounts of tetra-*n*-butylammonium iodide or NaI significantly increased the rate of reaction. The formation of iodide from bromide, *in situ*, is expected to promote the $\text{S}_{\text{N}}2$ reaction; however, this had no effect when carried out with primary alkyl chlorides.

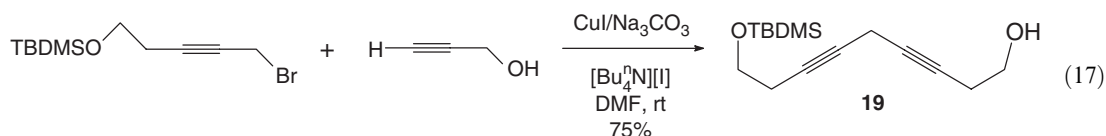
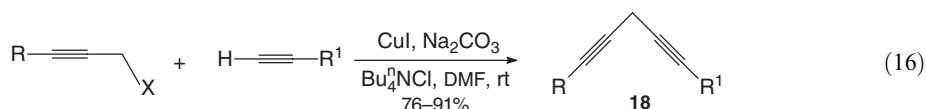
Skipped 1,4-diyne, such as **16**, serve a useful role as precursors in the synthesis of materials, fatty acids, and as hydrocarbon equivalents of 1,2,4,5-pentatetraols. Of the numerous methods devised for their synthesis, the reaction between metal alkynyl reagents and propargylic electrophiles receives the most attention <2003JOM151>. As a general observation lithiated and magnesium alkynyl reagents couple with propargyl halides in low-to-moderate yielding reactions <1995JOC218>. The corresponding bimetallic derivatives based upon a magnesium/copper system have, however, been shown to couple with primary propargyl halides to afford 1,4-pentadiynes using either stoichiometric or catalytic conditions <1995AG(E)805, 1995TL147>. Using stoichiometric quantities of copper requires the use of HMPA as co-solvent in order to dissolve the copper salts that otherwise precipitate from the solution. Under catalytic conditions optimum yields are obtained using THF as solvent. Work-up procedures must avoid acidic and basic media in order to circumvent potential isomerization of the skipped diyne to an allenyne. The coupling reaction has been successfully accomplished with various CuX species. With regard to the propargyl halides the leaving groups employed have been iodide <1995JOC218>, bromide <1995T4359, 1997JOM211, 1998JOC337, 2001JOM94> and chloride <2000T9581> (Equation (14)).



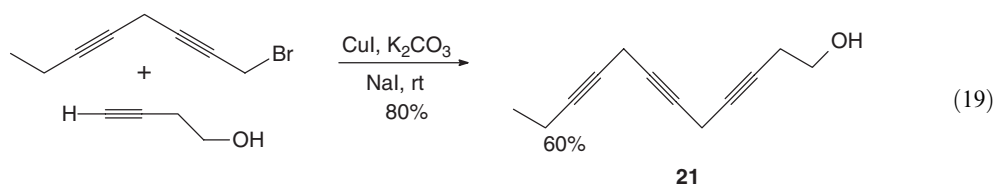
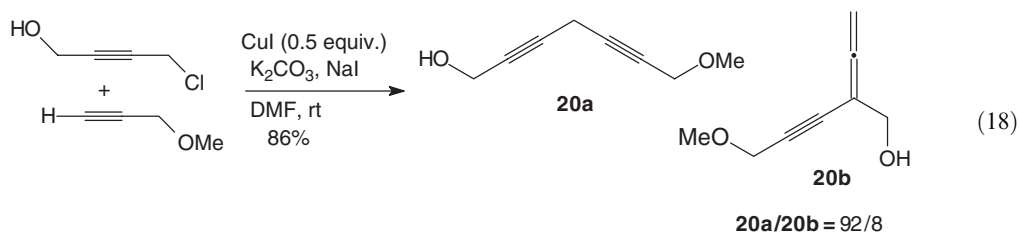
In most syntheses of skipped diynes, the propargyl halide partners are primary halides ($\text{R} = \text{H}$); however, couplings involving tertiary propargyl chlorides ($\text{R} = \text{Me}$) have been demonstrated as shown for the one-pot synthesis of the diyne **17** involving the substitution of the bispropargylic dichloride with alkynyl Grignard reagents (Equation (15)) <1994JA10275>.



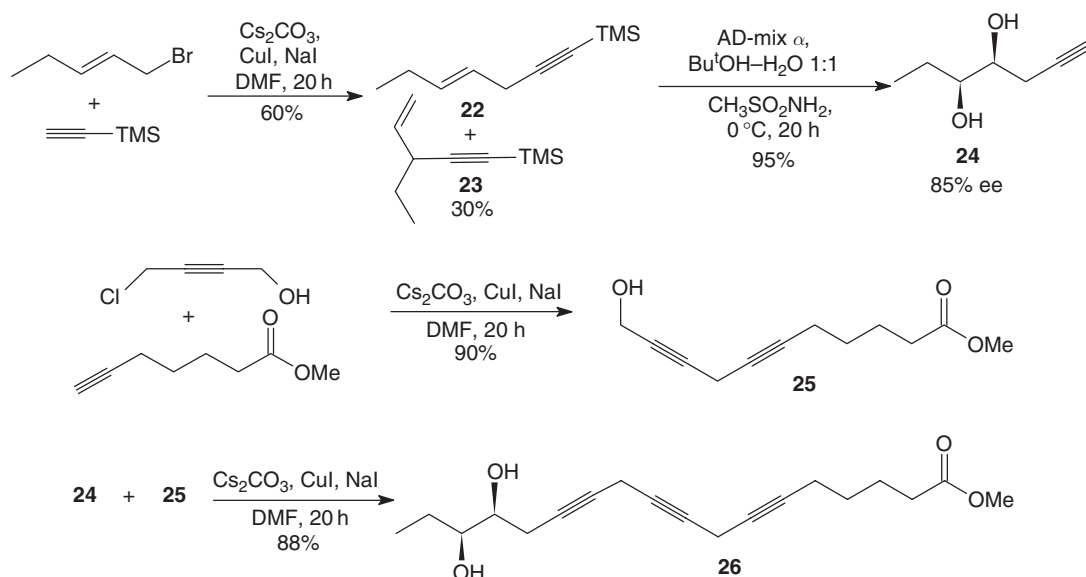
As long ago as 1992, the feasibility of coupling terminal alkynes directly, to afford diynes such as **18** (Equation (16)), in the absence of a strong metal-alkyl base was first highlighted <1992T5757>. Reversible deprotonation is facilitated by the presence, *in situ*, of sodium carboxylate. Improvements in the yield of the reaction have been demonstrated by using tetrabutylammonium chloride <1996T6635>. The exact role that it serves has yet to be elucidated; however, the use of TBAF appears as efficacious affording the diyne **19**, an arachidonic acid analog (Equation (17)) <1998TL771>, in 75% yield.



A comprehensive study, carried out in 1998 (Equation (18)) <1998S1015>, concluded that regioselectivity, in terms of the propargylic-allenic coupling ratios, (**20a:20b**), depends upon a range of criteria. These include the nature of the copper salt, the temperature of the reaction mixture, the nature of the leaving group, and the necessity for DMF as solvent. Although the reaction may be conducted in water, using stoichiometric copper, in acceptable yields the work-up is arduous. The mild reaction conditions are compatible with a comprehensive range of substrate substituents. Using NaI, as an alternative to TBAI <1993S65>, provided the triyne **21** (Equation (19)) <1998TL621, 2000T8083> with no loss in yield for the coupling reaction.

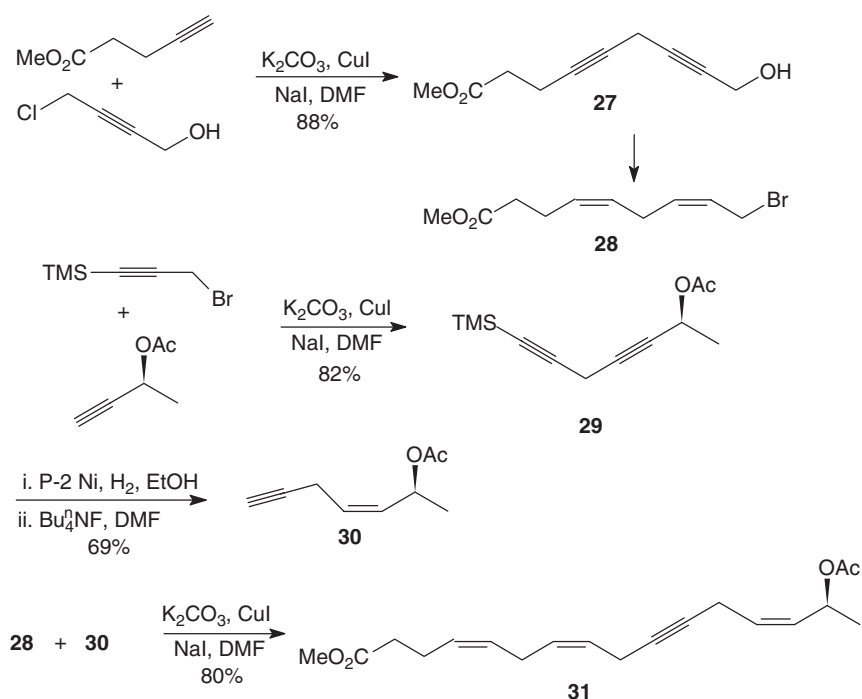


Recent examples report the use of a high-yielding caesium–copper system for alkynyl–propargyl couplings, in the presence of NaI (Scheme 1) <2002TL1681, 2002TA2071>. The enyne **22** was obtained from the coupling of trimethylsilylacetylene and *trans*-1-bromo-2-pentene in 60% along with the isomeric product **23**. Sharpless enantioselective dihydroxylation of **22** <1992JOC2768> provided the diol **24** in an impressive 95% yield and an enantiomeric excess of 85%. The diol **24** was then efficiently coupled to the bromo-derivative diyne **25**, using the same experimental reaction conditions for the coupling reactions, to afford triyne **26**, a key precursor in the first total synthesis of natural aplyolides C and E.



Scheme 1

Other workers have reported the first total synthesis of (–)-aplyolide A (Scheme 2) <2001TA1407>. The partial reduction of the diyne, **27**, and bromination provided diene **28** containing two of the skipped double bonds found in the natural product. The authors used

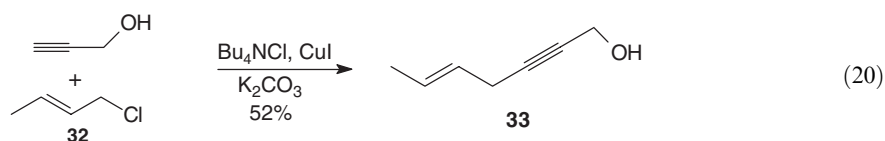


Scheme 2

analogous coupling conditions to provide the diyne **29** in good yield. This then underwent stereo- and regiospecific reduction of the internal alkyne to afford the enyne, **30**. Coupling between the diene **28** and the enyne **30** was accomplished efficiently again exploiting the same experimental methodology.

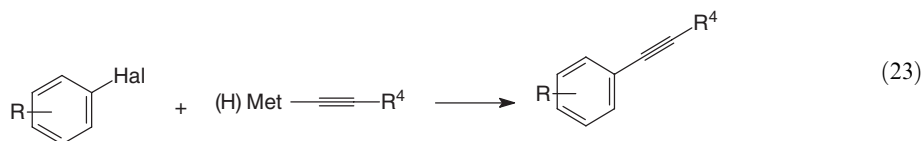
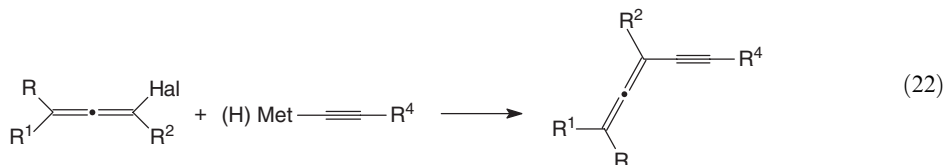
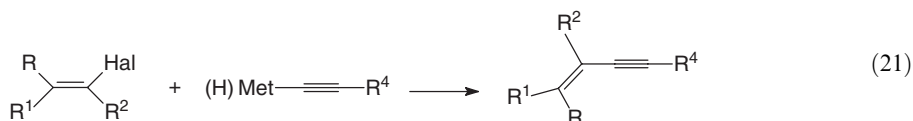
One of the few examples of a coupling reaction between crotyl chloride **32** and a terminal alkyne was used in a reported total synthesis of (\pm)-kumausyne (Equation (20)) <1997T2835>.

The Jeffery coupling reaction is a Cu(I)-catalyzed allylic substitution of (un)substituted allyl halides by 1-alkynes <1989TL2225>. The propargyl alcohol and the allylic chloride **32** coupled to afford the enyne **33** (Equation (20)). This was subsequently transformed either to an (*E*),(*E*)-dienol using LAH or to an (*E*),(*Z*)-dienol using a Lindlar catalyst. The reported yields for both coupling reaction and the reductions were 52%; however, the authors failed to comment whether the isomeric product, analogous to **23**, was formed. To conclude this section on coupling reactions, the reader is directed to the following review on enediynes, enyne, and related compounds <1996T6453>.



(ii) *Substitution reactions of alkenyl, allenyl, or aryl halides*

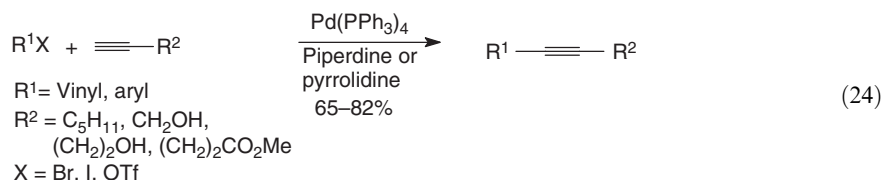
The palladium-catalyzed coupling reaction between an aryl halide/tosylate and a 1-alkyne has become an established method for the synthesis of alkynes and has been the subject of several recent books and reviews <B-1998MI008, B-1995MI009, B-1998MI010, B-2002MI012, 2001YKG607, 2000CCR199, 1999JOM305>. Couplings are traditionally achieved by the reaction of an alkenyl (Equation (21)), allenyl (Equation (22)), or aryl halide (Equation (23)) with a terminal alkyne or with the corresponding alkynyl organometallic reagent.



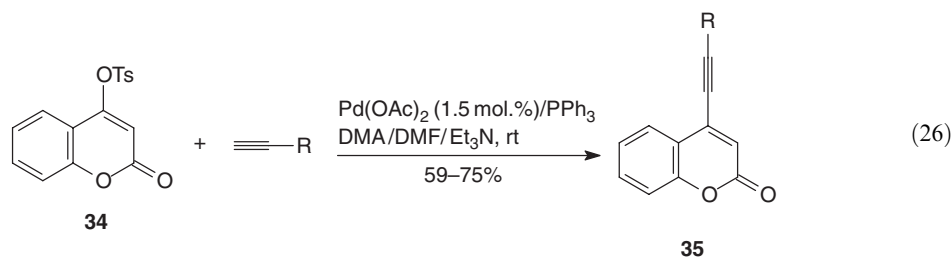
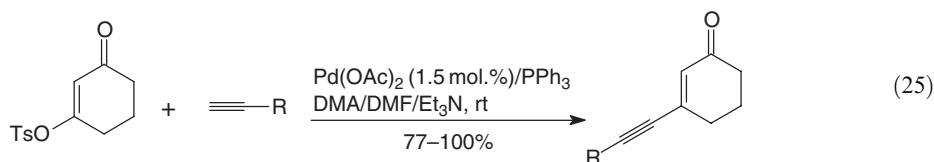
The need for a bimetallic palladium–copper-catalyzed couple for these cross-coupling reactions can impose limitations in their use especially with regard to industrial scale-up where the need for 1–5 mol.% of palladium has warranted the development of costly recycling processes. Furthermore, the development of solid support cross-coupling reactions has highlighted the incompatibility of copper which, in examples using heteroatom linkers, has been shown to contaminate the final products <1999TL6201, 2002BMC2415>. The development of copper-free cross-coupling reaction conditions has been an ongoing process in an effort to reduce “Glaser” type homocoupling reactions between copper alkynides in the presence of oxygen <2000AG(E)2632>.

(a) *Reaction of terminal alkynes with aryl, alkenyl, and allenyl halides/triflates in the presence of catalytic palladium(II) or palladium(0) compounds in the absence of a copper co-catalyst.* The first to report the use of copper-free cross-coupling reaction conditions under palladium catalysis was Linstrumelle (Equation (24)) <1993TL6403>, who was able to effect the synthesis of conjugated

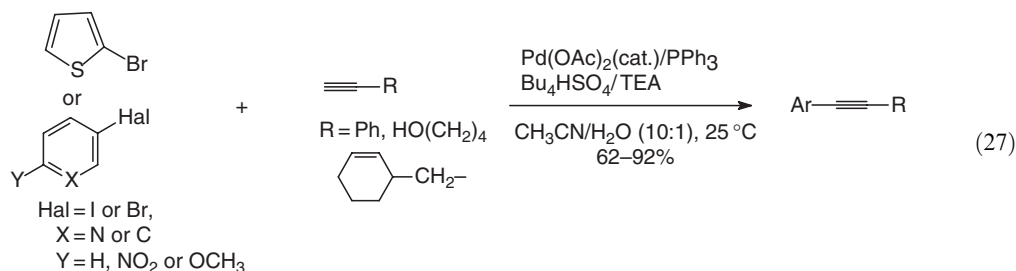
enynes and aryl alkynes in high yield by the reaction of terminal alkynes with vinyl and aryl halides/triflates in piperidine or pyrrolidine, as solvent, in the presence of tetrakis(triphenylphosphine)palladium.



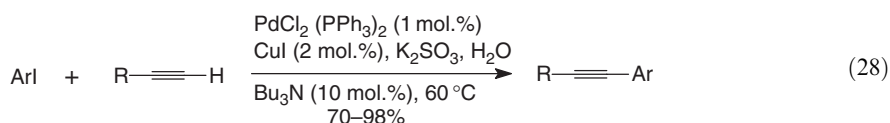
Although the palladium-catalyzed cross-coupling reaction of aryl/vinyl triflates with terminal alkynes provides an alternative to the use of the corresponding halides [<2000OL2291, 1996TL605>](#) vinyl tosylates are generally regarded as too inactive [<2000TL2741>](#). The successful copper-free coupling of vinyl tosylates with terminal alkynes has, however, recently been highlighted (Equation (25)) [<2002TL6673>](#). Excellent conversions were recorded which took place readily at ambient temperatures. The authors extended their investigations to successfully couple the tosylate **34** with a range of terminal alkynes to afford derivatized coumarins **35** in good-to-excellent yields (Equation (26)).



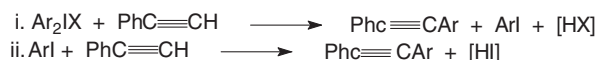
Cross-coupling reactions, under copper-free conditions, are often conducted at elevated temperatures [<1975JOM253, 1975JOM259>](#) using either piperidine or pyrrolidine as base and $\text{Pd(PPh}_3)_4$ as the catalyst [<1993TL6403>](#). The presence of water-soluble ligands, however, permits the reaction to take place in water or an aqueous solvent mixture. A copper-free Jeffery reaction [<1985TL2667, 1994TL3051, 1994TL4103>](#) involving the catalytic Pd(OAc)_2 coupling of terminal alkynes with aryl halides under phase-transfer conditions was reported (Equation (27)) [<1996TL5527>](#). When the coupling reaction was conducted using halides with electron-donating substituents, a slight reduction in yield and extended reaction times were observed. Heterocyclic bromides such as bromopyridine and bromothiophene coupled efficiently using lower amounts of catalyst (2.5 mol.%) without poisoning or deactivating the catalyst although slightly longer reaction times were reported.



Palladium-catalyzed coupling of alkynes with iodoarenes or iodothiophenes, in the presence of diaryliodonium salts in water, was reported (Equation (28)) <1996TL897>. Although the coupling reactions described were conducted using 2 mol.% of cuprous iodide, the coupling of *p*-iodonitrobenzene with phenyl acetylene occurred in a yield of 93% without CuI although the reaction took longer to complete.



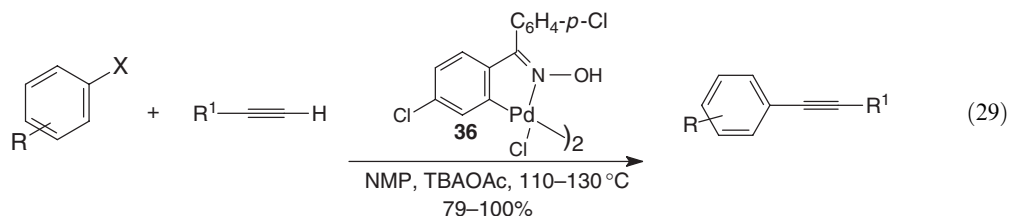
It was suggested that the reaction proceeds in two steps (Scheme 3).



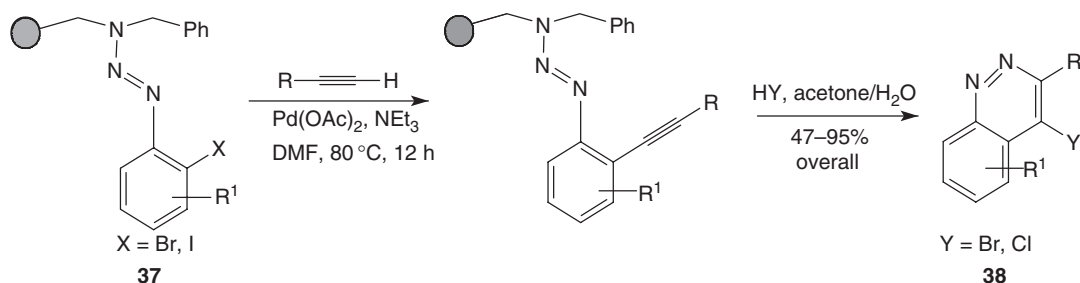
Scheme 3

For insoluble reagents aqueous DMF may be used which also facilitates the rate of reaction; however, in most examples the reaction took place in water in the presence of K_2CO_3 and 10 mol.% Bu_3N .

The use of an air- and moisture-stable phosphapalladacycle catalyst for the facile coupling of aryl bromides with alkynes has been reported <1996JMOC51, 1999JOM23, 2000EJO3679>. Although the catalyst was found to be very durable, without forming palladium black, the coupling reaction itself was solvent dependent for triethylamine and optimum yields were only obtained using phenyl acetylene as the *sp*-coupling partner. However, a copper- and amine-free coupling procedure has been developed that uses an oxime-based palladacycle shown to be an effective air- and water-stable precatalyst in a wide range of cross-coupling processes in organic solvents <2000OL1729, 2000OL1823, 2002JOC5588> as well as in aqueous solvents <2002AG(E)179, 2002JOM46>. The palladacycle **36** (Equation (29)), derived from 4,4'-dichlorobenzophenone, effectively catalyzes the cross-coupling reaction between a range of aryl and naphthyl halides and terminal alkynes in very high yields and with a high catalyst turnover number <2002TL9365>. Optimized reaction conditions identified tetra-*n*-butylammonium acetate (TBAOAc) as the best additive, with catalyst loadings as low as 0.1 mol.%, providing excellent couplings using reagent-grade chemicals. *N*-Methyl-2-pyrrolidone (NMP) and NMP/water mixtures serve equally well as solvent with organic solvents such as THF requiring longer time for the reaction to go to completion and affording lower yields of coupled products.

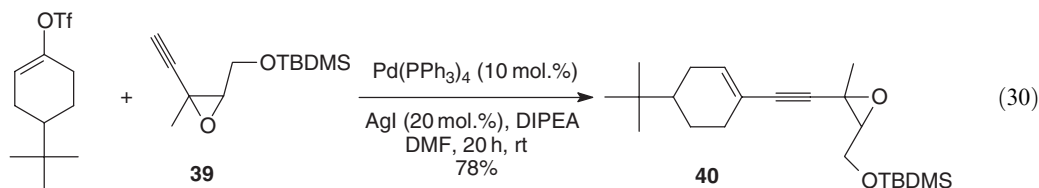


Reactions, conducted on a polymer support, have come into prominence in recent times for the synthesis of molecules for high throughput screening using combinatorial techniques <1996AG2436, 1996AG(E)2289, 1996T4527>. The benzylaminomethylpolystyrene-supported triazene **37** (Scheme 4) underwent a palladium-catalyzed cross-coupling reaction with four different alkynes to afford *o*-alkynyl aryl resins. Previously it was shown that the diazonium group, formed upon cleavage from the resin, was lost as dinitrogen. In solution, however, in the presence of a suitable nucleophilic *o*-substituent cyclization occurs to afford heterocyclic compounds <B-1994MI011>. Thus, cleavage <1995LA775> using aqueous hydrogen chloride or hydrogen bromide in acetone provided the cinnolines **38** in good-to-excellent yields <1999TL6201, 2002BMC2415>. The absence of copper, from the coupling reaction, was crucial in order to prevent coordination to the triazene moiety. This coordination tended to afford contaminants in the final product.



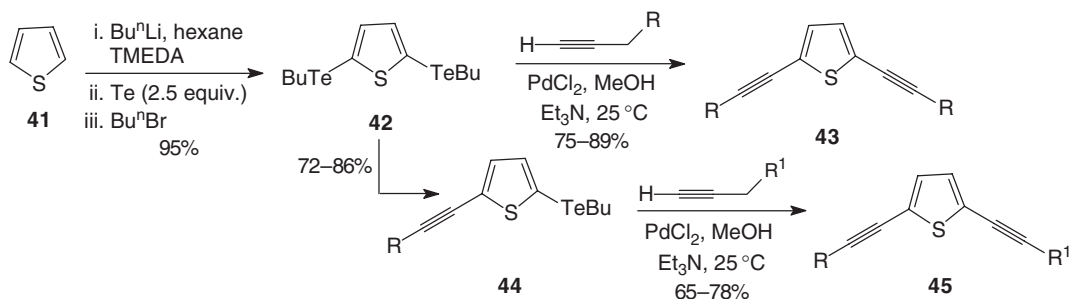
Scheme 4

One of the first reports to describe the successful cross-coupling reaction between an ethynyloxirane **39** and alkenyl triflates involved treatment of the substrates with tetrakis(triphenylphosphine)palladium in the presence of silver salts (Equation (30)) <1996TL2019>. Attempts to effect the cross-coupling reaction using either copper as a co-catalyst or $[\text{Pd}(\text{OAc})_2(\text{PPh}_3)_2]$ as the catalyst <1986S320> proved to be a very inefficient method providing the epoxyenyne **40** in yields of 25% and 45%, respectively, accompanied by considerable decomposition of compound **39**.



Although silver iodide was shown to be the most effective co-catalyst for these coupling reactions, silver nitrate, silver carbonate, and silver triflate were also effective but less efficient.

The use of vinylic tellurides in the copper-free cross-coupling reaction with terminal alkynes has been highlighted as a method for the synthesis of alkynyl furans <2001TL8927, 1995SL1145> and symmetrical/unsymmetrical alkynyl thiophene derivatives (Scheme 5) <2001TL7921, 2003TL685>. A range of catalysts, co-catalysts, and solvents were examined for their suitability in the cross-coupling reactions involving these heterocycles with palladium(II) chloride (20 mol.%) proving to be the best. Copper salts were shown to have little effect and triethylamine as base and methanol as solvent provided optimal yields. Metallation of thiophene **41** and treatment of the dilithio-derivative with elemental tellurium and *n*-bromobutane gave **42** in excellent yield. Exposure of 2,5-bis-(butyltelluro)thiophene **42** with an excess of alkyne and catalyst provided the symmetrical alkynyl derivative **43**. Alternatively, by using 1 equiv. of both **42** and a terminal alkyne gave **44** in good yield. This compound could then furnish the unsymmetrical alkynylthiophene derivative **45** upon exposure to the appropriate experimental conditions. For an additional contribution in this area, see <2001OL4295>.

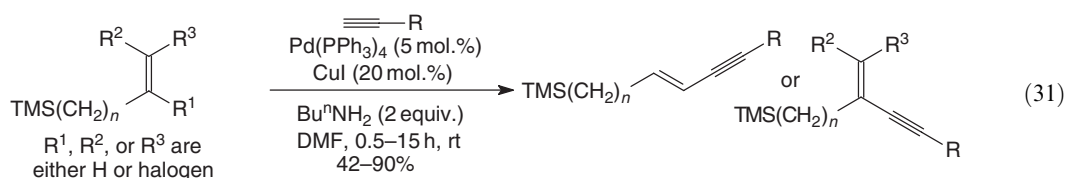


Scheme 5

(b) Reaction of terminal alkynes with aryl, alkenyl, and allenyl halides in the presence of a copper co-catalyst. The Castro–Stephens reaction provides a method for coupling unactivated aryl iodides with, in some examples, stoichiometric copper(I) alkynides without a palladium complex

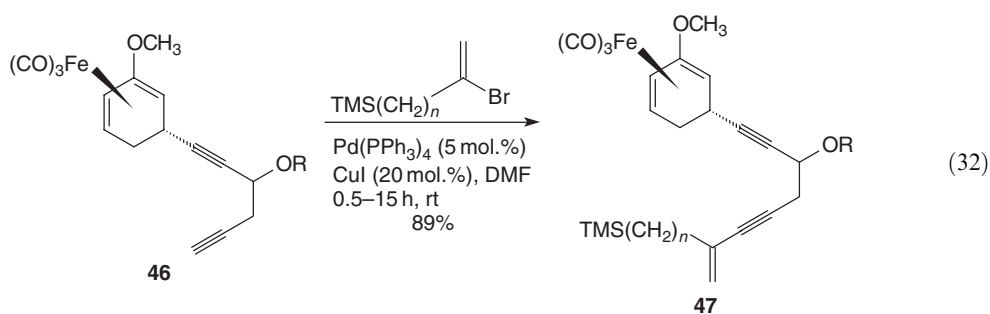
catalyst <1963JOC2163, 1963JOC3313>. The early developments in this area have been comprehensively discussed <1995COFGT1000>. Other examples of this chemistry reveal the use of potassium carbonate as a base with catalytic copper and triphenylphosphine <1993JOC4716>, catalytic copper with Aliquat-336 and 30% NaOH <1992JOC2188>, and the use of a CuI:NaI:K₂CO₃ mixture (1:2:2) <1993S65>. It should be noted, however, that in the alkali media required to effect these palladium-free coupling reactions, isomeric enynes and allenes are observed. As a result, a variety of modifications, to the original experimental procedures, have been developed with the aim of improving the compatibility of this reaction for molecules that contain other diverse and sensitive functionality <1975TL4467, 1985TL3811>.

A catalytic tetrakis(triphenylphosphine)-palladium(0) and substoichiometric CuI to effect the Castro–Stephens coupling between vinylic/allylic silanes and propargylic/homopropargylic alcohols has been used to provide access to polyunsaturated silanes <1995S299> (Equation (31)).

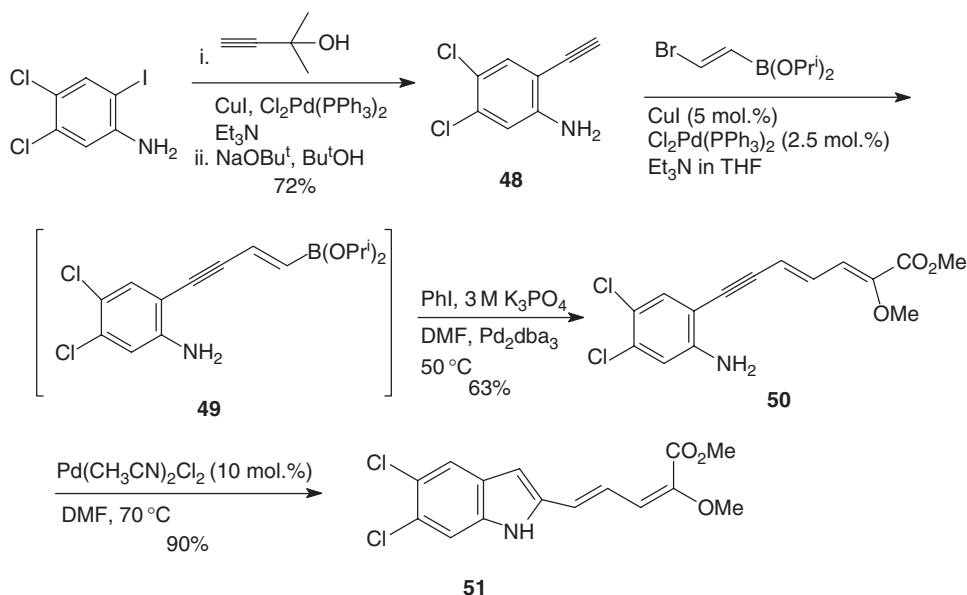


The copper alkynide was generated, *in situ*, by reaction of the terminal alkyne with a mixture of copper(I) iodide in DMF in the presence of the palladium catalyst and base. Although vinyl bromides gave good results, vinyl iodides exhibited higher reactivity. Interestingly, the coupling reaction proved very efficient for the reaction between bromovinyl silane (R² = R³ = H) and the alkyne (R = H) (86%) compared to reaction with the ethoxyethyl-derivatized alkyne (63%). Unprotected propargyl and homopropargyl alcohols appear to facilitate the coupling reaction with vinyl halides.

The reagents used in this reaction were compatible with the cross-coupling of *n*⁴-tricarbonyliron complexes. Thus, exposure of the *n*⁴-tricarbonyliron complex **46** (Equation (32)) with various vinyl halides provided the coupled enediyne **47** in good yields. The coupling reaction was found to be base sensitive; thus, for example where R = benzyl, the coupling took place efficiently using *n*-butylamine, but for more base-sensitive protecting groups, such as the acetate moiety, 1,8-bis-(dimethylaminonaphthalene), “proton sponge,” was needed to successfully produce the coupled product in 89% yield.

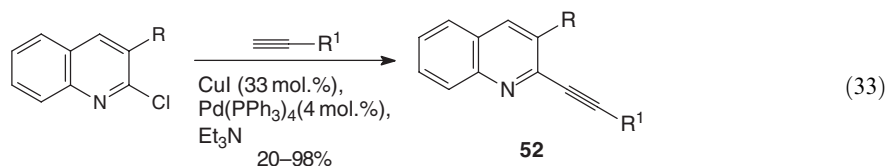


A novel one-pot tandem Castro–Stephens–Suzuki reaction was employed for the synthesis of the 2-dienylindole **51**, a key compound developed for the treatment of osteoporosis <1998TL9347>. The initial alkynylaniline **48** was synthesized via a Castro–Stephens coupling reaction followed by a subsequent alkyne deprotection <1994JOC5818> (Scheme 6). Proton NMR studies conducted upon the product obtained from the Castro–Stephens coupling between **48** and the bromoboronate ester indicated chemoselective coupling to afford **49**. Using a modification to a Suzuki coupling procedure, described by Wright <1994JOC6095>, the boronate ester **49** underwent transformation to the dienyne **50** in a tandem sequence in a recorded yield of 63% overall yield. Compound **50** readily underwent a palladium-catalyzed cyclization reaction to afford indole, **51**, in an excellent 90% yield.



Scheme 6

In general Castro–Stephens coupling reactions succeed only with aryl bromides, iodides, and triflates as the sp^2 -partner, with aryl chlorides proving to be relatively unreactive toward oxidative insertion of Pd(0) into the C–Cl bond. Exploiting the known mobility of 2-halogens in quinolines, however, allowed successful couplings to occur with a range of 2-chloroquinolines (Equation (33)) <1996TL8281>.



The efficiency in the substitution of chloride, by Cu(I) acetylide, was found to dependent upon C-3 alkyl substituents. Thus, when R = H, the couplings, to provide **52**, were quoted as 50% (R^1 = Buⁿ) but only 20% when R^1 = Ph. In contrast to these results for cases when R = Me, the yields were 98% and 88%, respectively. This enhancement in yield was attributed to a steric acceleration process during the reductive elimination step from a Pd(II) complex to Pd(0).

(c) *Reaction of terminal alkynes with aryl, alkenyl, and allenyl halides/triflates in the presence of catalytic palladium(II) or palladium(0) compounds, a copper co-catalyst and a base.* The palladium-catalyzed cross-coupling reaction between sp^2 -C halides and terminal alkynes was first reported concomitantly by Sonogashira <1975TL4467>, Heck <1975JOM259>, and Cassar <1975JOM253>. Coupling utilizing copper(I) halides, as co-catalysts, in the presence of a base is commonly known as the Sonogashira reaction. This reaction, which may be formally considered as an application of palladium catalysts to the Castro–Stephens reaction, has been put to good use in a wide variety of natural product and heterocyclic syntheses. These have been the subjects of review articles by the discoverer <2002JOM46> and others <1995OPP127, 1996T6453, 2000CCR199, 1999JOM305> in homogeneous media as well as on polymer supports <2003T885>.

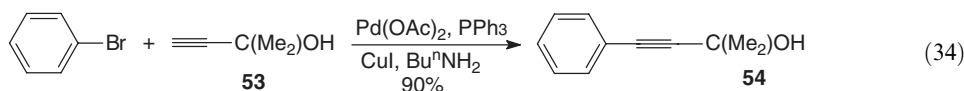
The development of a palladium–copper bimetallic catalyst facilitates the coupling reaction to occur under very mild reaction conditions. For instance, in his original studies, Sonogashira identified the optimal molar ratio between CuI and the palladium catalyst to be at least 2:1 respectively using triethylamine as both the base and solvent. Under these conditions, the coupling of aryl and vinyl halides with terminal alkynes was recorded to be very high at ambient temperatures.

From a mechanistic point of view the coupling reaction follows the accepted oxidative addition–reductive elimination process exemplified by most palladium catalysts. The precise details of the mechanism, however, are still largely unknown particularly with regard to the structure of the

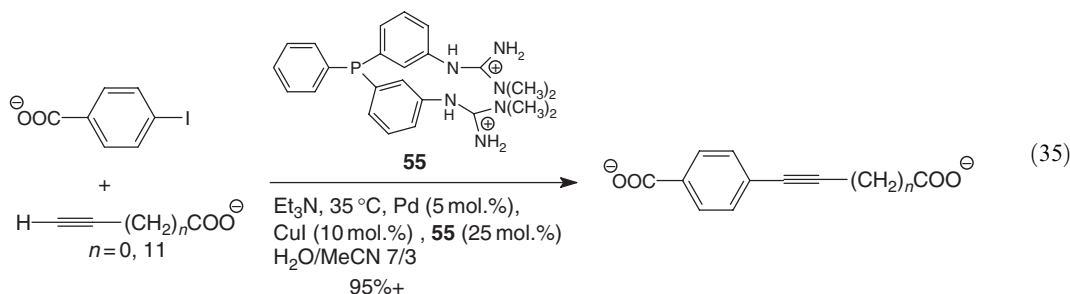
catalytically active species and the precise role played by the copper co-catalyst. The most frequently used palladium species is $(\text{PPh}_3)_2\text{PdCl}_2$, although both $\text{Pd}(\text{OAc})_2$ and $(\text{CH}_3\text{CN})_2\text{PdCl}_2$ in the presence of phosphine ligands have also been employed where appropriate. For coupling reactions involving less reactive aryl and alkenyl halides, attempts have been made to identify conditions to minimize the side-reactions that often accompany attempted couplings at elevated temperatures <2000OL1729>.

For the purpose of this review, the effects of the type of catalyst, substrate, base, and solvents <2000CCR199> on the reaction outcome will be summarized. Representative examples will be used to emphasize and couplings that generate carbocyclic and heterocyclic alkynyl derivatives in both solution phase and syntheses conducted upon polymer supports. Developments in the use of microwave synthesis will be highlighted.

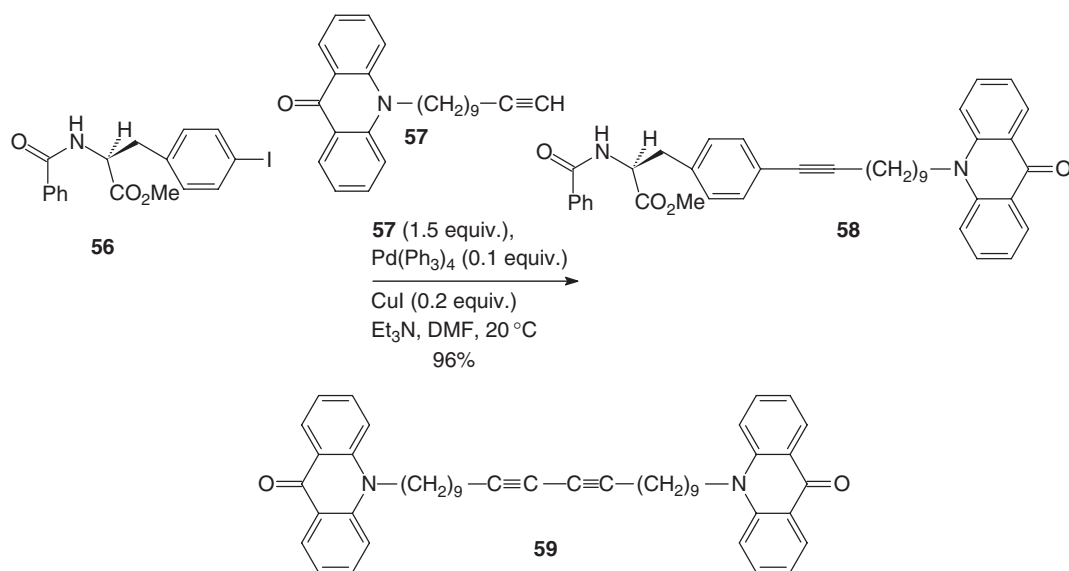
Attempts have been made to improve and optimize the formation of the enyne **54** obtained from the coupling reaction between an aryl bromide and the protected alkyne 2-methylbut-3-yn-2-ol **53** (Equation (34)) <2000JMOC77>. The reagents shown were those that provided optimal results from these investigations and included the choice of the palladium catalyst in combination with triphenylphosphine. Copper salts were essential for high reaction rates, but interestingly neither the oxidation state, the counter-ion, nor the presence or absence of water of crystallization had any effect upon the rate. The choice of amine, which acts as both a solvent and a scavenger of HBr , was critical as the reaction rate was very solvent dependent. A sum of both electronic and steric factors appeared to be operating in this system with basic primary aliphatic amine providing the highest yields in 1 h. With regard to the stoichiometry of reagents, these were optimized as follows: both aryl halide and alkyne (5 mmol.), the ratio of catalyst ($\text{Pd}:\text{PPh}_3:\text{Cu}$ 90.025:0.075:0.05 mmol, respectively) in 10 ml of amine at 55°C for 1 h.



The synthesis of the cationic guanidinophosphine ligand **55** facilitated the quantitative and rapid biocompatible cross-coupling reaction of water-soluble iodoarenes, with terminal alkynes, in aqueous solution at low temperatures (Equation (35)) <1998TL525>. Interestingly, when the coupling reaction was repeated in the presence of the enzyme RNAase, the authors not only observed an enhancement in the kinetics of the reaction, which were accelerated due to hydrophobic interactions, but the protein itself was recovered, intact, from the reaction mixture.



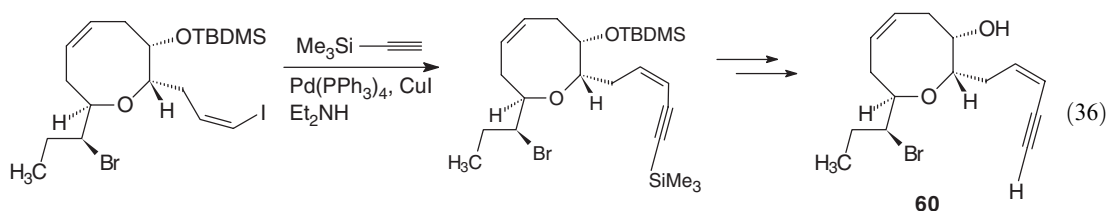
Palladium-catalyzed coupling reactions have been used to attach fluorescent and enzymic labels, containing terminal alkynyl moieties, with a range of biological electrophiles including amino acids, nucleosides, and steroids (Scheme 7) <1997T1523>. Coupling of suitable fluorescent labels, such as **57**, with iodo-derivatized biomolecule such as the L-tyrosine derivative **56**, gave an excellent yield of **58** with the synthesis of the homocoupled product **59** being almost entirely suppressed under the standard reaction conditions shown. Higher reaction temperatures, or increasing the amounts of catalyst used, led to a predomination in the synthesis of the homo-coupled product **59**.



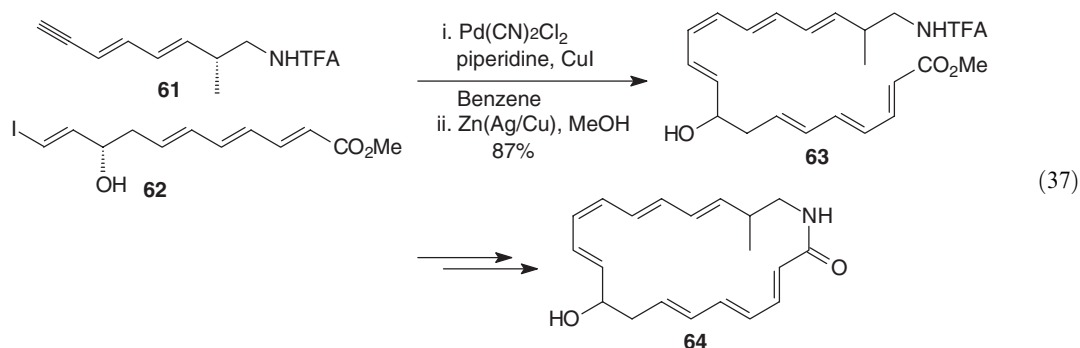
Scheme 7

Problems such as these, related to issues, e.g., the compatibility of functional groups, homo-coupling reactions, and reagent stability, serve to emphasize the care that must be taken in the choice of substrates for coupling reactions as well as the careful selection of the reaction conditions themselves.

Standard Sonogashira cross-coupling reactions have been put to good use in the synthesis of biologically active compounds and natural products [<1995OPP127>](#). Representative examples include the taxane skeleton [<1995TL5891>](#), enediynes [<1996CC749, 1996T6453, 1999T2737>](#), and other candidates for Bergman cyclization reactions [<2000JA939>](#), antitumor compounds [<2003T1719, 2002TL2725, 2003T1627, 2000JOC7977, 2000JOC2479, 2000AG\(E\)3622>](#), hormone analogs [<2000JOC5647>](#), fatty acid metabolites [<2000T327>](#), and toxins [<2000OL2479, 2000T10209>](#). The first total synthesis of the eight-membered ring ether (+)-prelaureatin **60**, a potent larvacidal agent against mosquitos, utilized the Sonogashira cross-coupling reaction between a vinyl iodide and trimethylsilylacetylene in order to install the C-6 enyne motif ([Equation \(36\)](#)) [<2000JA5473>](#).

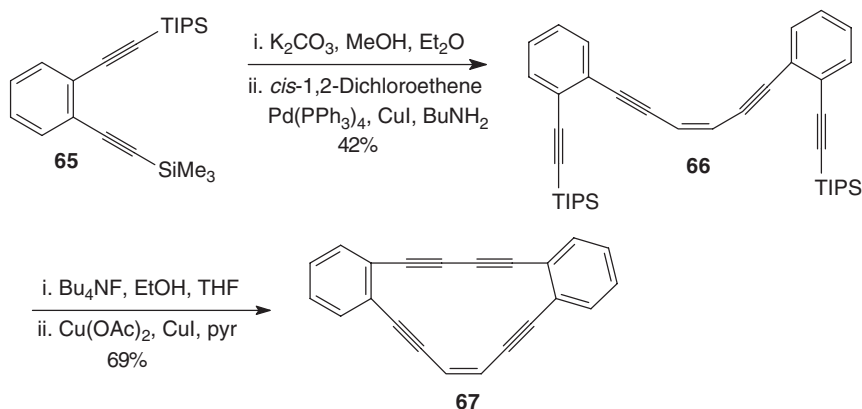


Using analogous chemistry provided access to (+)-laurallene, another member of the laurenan class of metabolite derived from the red algae *Laurencia nipponica*. The macrocyclic polyene lactam cyclamenol, **64**, derived from *Streptomyces spec.* MHW 846, is an inhibitor of leukocyte adhesion to endothelial cells an important event initiated by inflammation, tissue trauma, and infections. The cyclization precursor **63** was accessed via the stereoselective cross-coupling reaction between the C-12-C-19 alkynyl fragment **61** and vinyl iodide **62**. This step provided the entire carbon backbone of **64**, which upon stereoselective reduction of the alkynyl moiety furnished **63** in good yield ([Equation \(37\)](#)) [<2000TL625>](#).

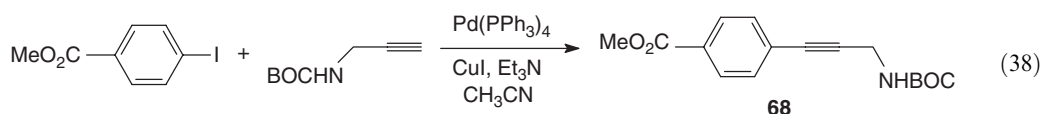


Selective desilylation [<1997JA2956>](#) of diyne, **65**, and exposure to standard cross-coupling reaction conditions with 1,2-dichloroethene provided the monoene **66**. Further desilylation and intramolecular coupling with copper salts gave the macrocycle **67** in modest yield (Scheme 8) [<2000T9581>](#). A range of compounds based upon the bis(enediyne) **67** were synthesized with the aim of evaluating their potential as Bergman cyclization “warheads”. The use of cross-coupling reactions in related syntheses of enyne macrocycles has been highlighted during the period of this review [<2000JA6917, 2000TL6775, 2000OL1757, 2000OL3849>](#).

Another recent application of the Sonagashira coupling reaction includes its use in the synthesis of rigid spacers based upon aminopropynylbenzoic acid derivatives such as **68**. These were used as spacers to separate divalent phosphopeptide ligands, which possess high affinity for cellular signal transduction protein (Syk tandem SH2) domains (Equation (38)) [<2003BMC1241>](#).

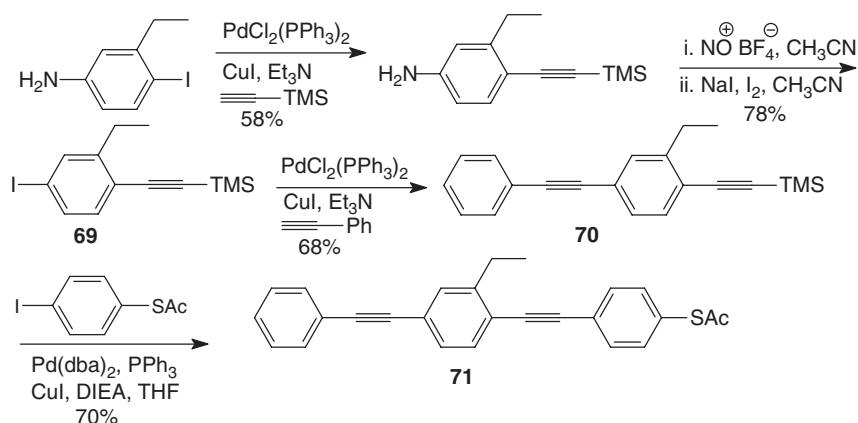


Scheme 8



Conjugated oligomers, based upon polyazulenes, are of commercial interest due to their electrical, optical, and nonlinear properties [<1996CRV537, 1999AC1440>](#). Cross-coupling reactions have played an important role in the synthesis and development of these and other novel materials [<2000TL8343, 2000TL4079, 2000TL2855>](#).

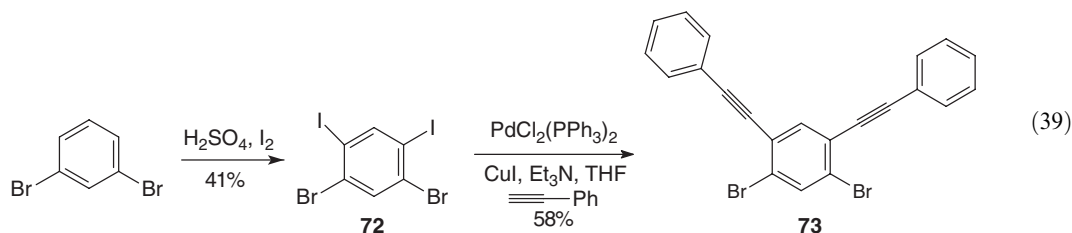
The synthesis of oligo(phenylene ethynylene)s (OPEs), which may serve as potential molecular electronic devices, emphasizes the importance of palladium-catalyzed coupling reactions in obtaining suitable candidate structures for evaluation (Scheme 9) [<2003T2497>](#).



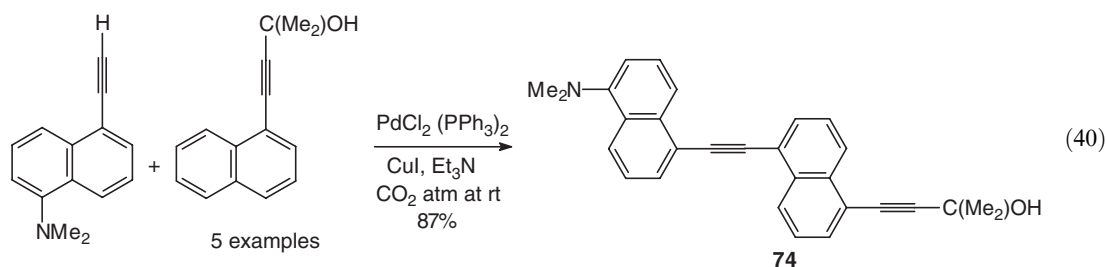
Scheme 9

The cross-coupling reaction between the 1,4-disubstituted aryl halide **69** and phenyl acetylene provided **70**. This was deprotected and coupled with 4-(thioacetyl)iodobenzene in the presence of *N,N*-diisopropylamine (DIEA) in good yield to afford the molecular wire **71**.

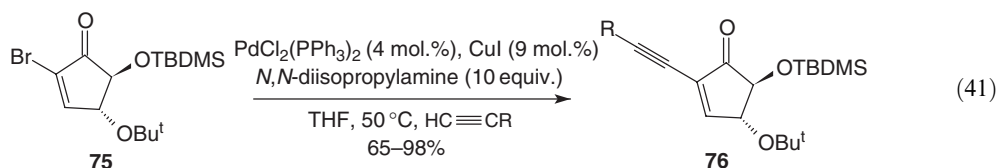
Heteroatom containing OPEs were accessed using analogous chemistry (Equation (39)). Applying these cross-couplings with the diiododibromobenzene **72** followed by selective alkynylations provided **73**, a precursor to U-shaped OPEs. It was reported that these novel structures may provide further insight into the relationship between conformation and electronic properties of molecular electronic devices.



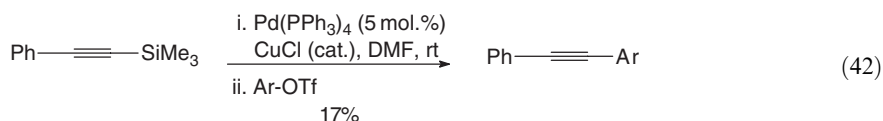
By conducting cross-coupling reactions in a high-density carbon dioxide atmosphere, 1,5-naphthylethynyl nanostructure networks based upon **74** (Equation (40)) <2003TL2691> were readily accessed. The associated Eglington–Glaser homocoupling reaction was suppressed under these experimental conditions.



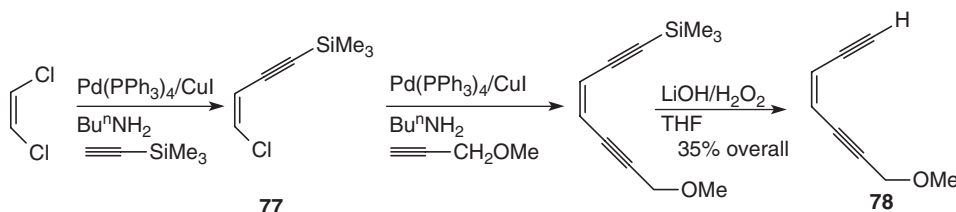
The cross-coupling reaction involving cyclopentenyl vinyl bromides has been reported to take place rather inefficiently <1997JOC1582> using Sonogashira conditions. Cyclopenten-2-one **75**, however, underwent smooth coupling to afford **76** in high yield and in the presence of multifunctionality (Equation (41)) <2001T6295>.



The reaction of 1-phenyl-2-trimethylsilylthyne with CuCl in DMF forms the alkynylcopper species $[\text{Cu}_2\text{Cl}(\text{CCPh})]_n$ *in situ* via the transfer of the alkynyl group from silicon to copper. This reagent then undergoes a palladium-catalyzed coupling reaction, in modest yields, with aryl triflates. The corresponding homocoupled adduct forms the major by-product from this reaction (Equation (42)) <2001JOM282>.

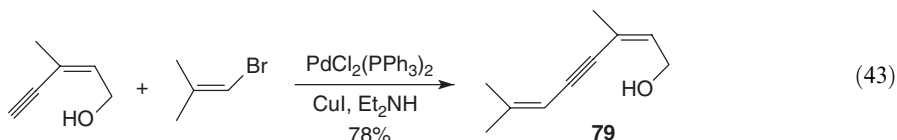


The (Z)-ene-yne **77** (Scheme 10) <2002JOM342> was obtained from the coupling of silyl acetylene with (Z)-dichloroethylene. The coupled adduct was further coupled with a propargylic ether, using analogous catalytic conditions, followed by desilylation, to afford **78**.

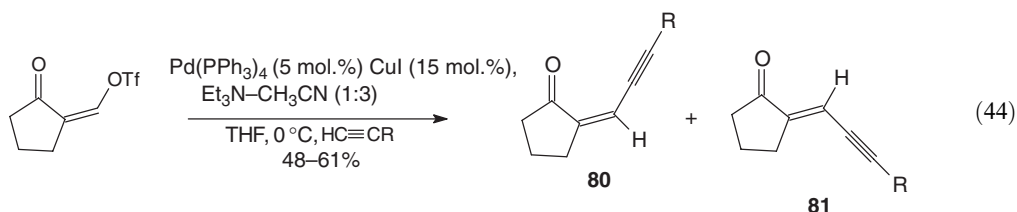


Scheme 10

(Z)-3,7-Dimethylocta-2,6-dien-4-yn-1-ol **79**, obtained in 78% yield from the coupling reaction between commercially available (Z)-3-methylpent-2-en-4-yn-1-ol and 1-bromo-2-methylpropene (Equation (43)) <1997CC1083>, readily cycloaromatized to afford the fragrant oil rosefuran.



The Sonogashira cross-coupling reaction has been used extensively in the synthesis of enediyne antitumor antibiotics <1996COS41, 1996COS93, 1996T6453>. In an attempt to obtain stereoselective cross-coupling conditions for the synthesis of the (Z)-ketoeneyne **80**, both the base and alkynyl-R group were investigated. Optimum stereoselectivity, in favor of **80**, was established using Et_3N in CH_3CN at 0°C with R other than hydrogen (e.g., when $\text{R} = (\text{CH}_2)_4\text{OMe}$ **80/81** 100%/0%, for $\text{R} = \text{Ph}$ **80/81** 91/9). (Equation (44)) <1997T9107>.



Recently the coupling of terminal alkynes with aryl iodides in the presence of a nickel catalyst and CuI was reported <2003TL5011>. Due to coordination of the nickel to the triple bond, low yields were reported using solvents such as anhydrous THF, dioxane, and MeCN but the reaction proceeded smoothly in aqueous dioxane. Yields were found to be critically dependant upon the nickel catalyst used with mono- and bidentate ligands as well as simple nickel salts proving to be unsuccessful. Potassium carbonate was shown to be the best base in place of the usual amine base used in the palladium-catalyzed reaction. The stoichiometry of reagents that provided optimum yields are shown (Equation (45)).

Table 1 Palladium-catalyzed formation of heteroarylalkynes


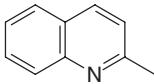
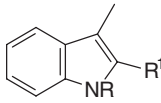

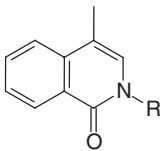
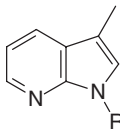
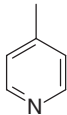
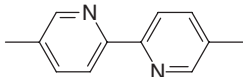
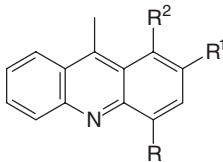
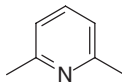
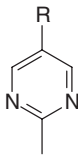
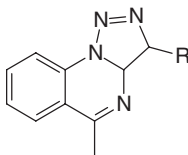
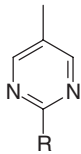
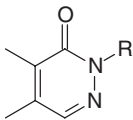
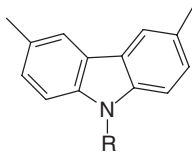
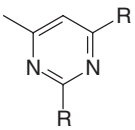
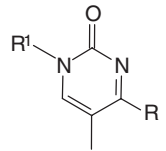
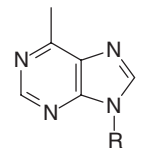
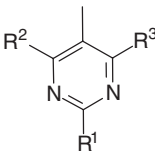
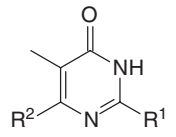
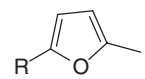
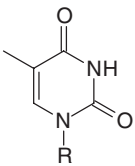
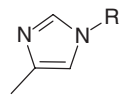
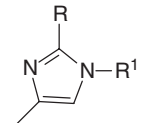
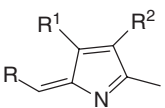
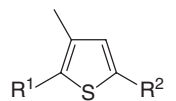
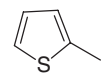
$\text{Het-X} + \text{C}\equiv\text{C-R} \xrightarrow{\text{Pd}^{\text{II}} \text{ or } \text{Pd}^0, \text{CuI, amine}} \text{Het-C}\equiv\text{C-R}$					
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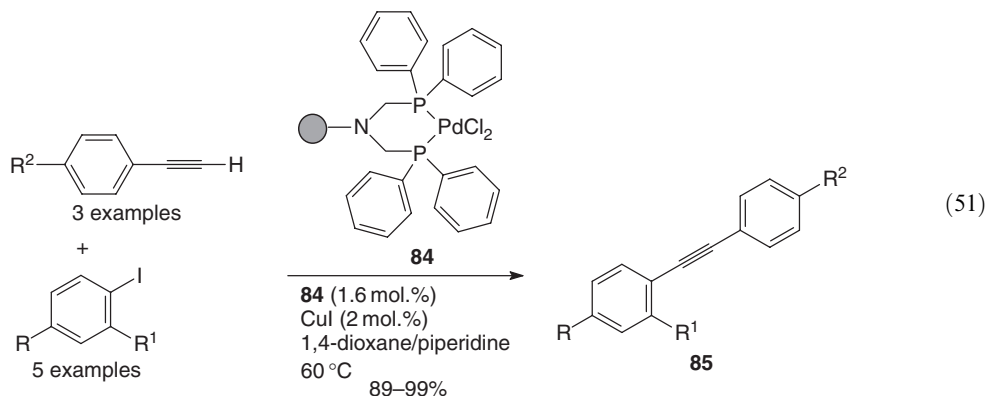
Table 1 (continued)

	<2000JOC5668>		<2003T5595>		<1999T211, 2002BMC1581>
	<2000BMC739>		<2000BMC739>		<1997TA1791>
	<1996TL3959, 2000TL8741, 2000TL7529, 2000JOC3571, 2000T6501, 2002TL1381>		<2000JOC2806>		<2003TL3667>
	<2000JOC205, 1995TL1197>		<1998EJO525>		<2002T10197, 2000JOC616, 1999JOM305, 2001T7871, 2000AGE3481, 2000JA974>

yield upon microwave irradiation for 3 min (Equation (50)). This was compared with the use of KOH or K₂CO₃, which required longer reaction times and gave a lower yield. The same microwave conditions have been used to access indoles and benzo[*b*]furans in good-to-excellent yields.

A recent study compared the use of microwave radiation to conventional wall-heat transfer to effect the Sonogashira coupling reaction between a range of iodoanilines and trimethylsilylacetylene. The conclusion reached was that at elevated temperatures these two heating methods operate under identical thermal and pressure effects compared to the analogous experiments conducted at ambient temperatures <2001JOC4165>.

The application of palladium-catalyzed reactions to solid-phase organic synthesis (SPOS) is advantageous as tedious work-up procedures are minimized and soluble reagents such as palladium catalysts, as well as by-products such as those derived from homocouplings, may be removed from the supported reagents by simply washing with an appropriate solvent <1996CRV555>. It is not surprising therefore that palladium-catalyzed cross-coupling reactions have featured significantly in the SPOS literature and have been the subject of a number of reviews <2002BMC2415, 2003T885, B-2002M1014>. One of the few examples of SPOS in which the tethered reagent is actually the palladium catalyst was recently revealed (Equation (51)) <2003SL1049>. The tethered catalyst **84** was accessed in a one-pot synthesis using readily available aminomethyl-polystyrene beads. The optimized reaction conditions shown required 1.4 equiv. of the alkyne and provided complete conversion into compounds **85**, in excellent yields within 2 h. The stability and durability of **84** to act as a catalyst in cross-coupling reactions of this kind was confirmed from the results of additional experiments in which the recovered tethered palladium moiety catalyzed the complete conversion of substrates to products in four experimental runs.



Palladium-catalyzed cross-coupling reactions are shown in which either the alkynyl moiety (Table 2) or the aryl halide (Table 3) are tethered to a polymer support.

Besides using reagents tethered to polymer supports in combinatorial chemistry, the same principles can be applied to the complementary solution-phase, homogeneous reactions. The synthesis of libraries of compounds in solution phase offers advantages over solid-phase techniques in that standard reagents can be used during key bond-forming steps and compounds made may be screened directly, *in situ*, with cellular isolates such as enzymes or receptors.

In a recent study, aimed at the synthesis and evaluation of a library of polyenes based upon (–)-stipiamide for reversal of P-glycoprotein-mediated multidrug resistance, individual vinyl iodides were coupled with a mixture of seven alkynes to produce 42 compounds based upon amide **86**. Analogous syntheses were conducted with the individual alkynes and mixtures of the alkenes (Equation (52)) <2000JOC4973>.

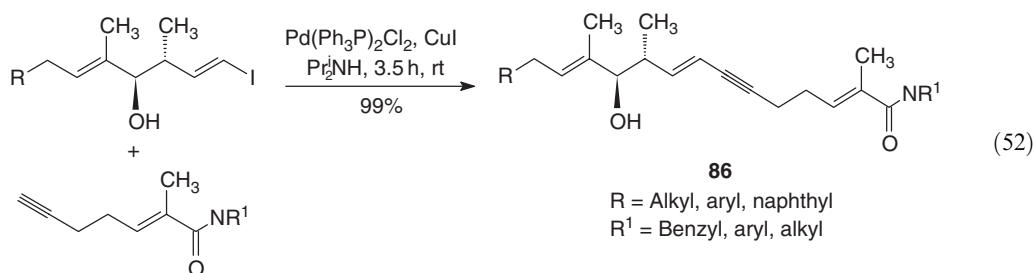


Table 2 Arylation and alkenylation of alkynes: immobilization of alkynes

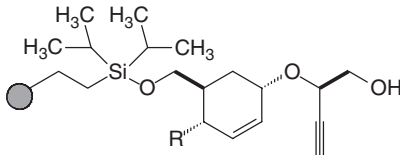
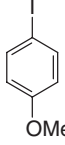
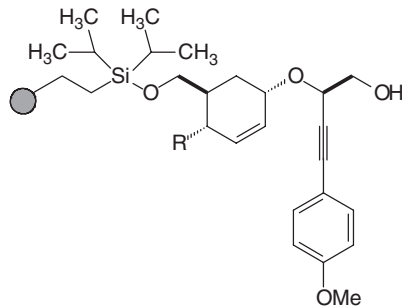
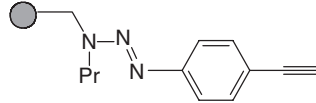
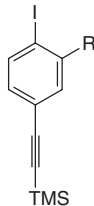
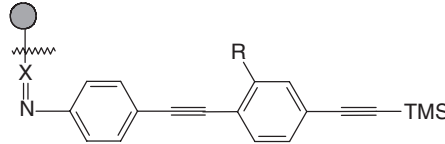
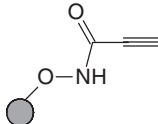
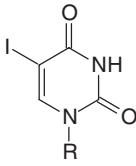
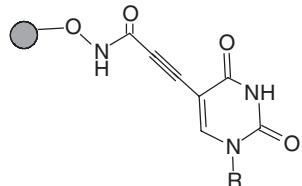
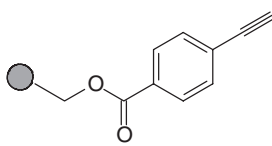
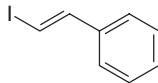
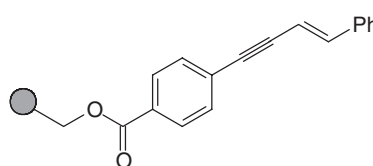
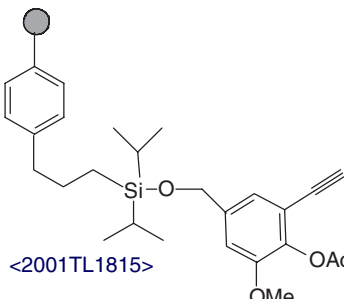

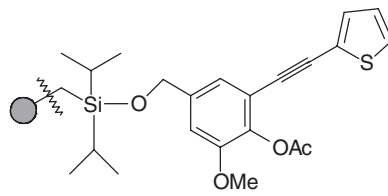
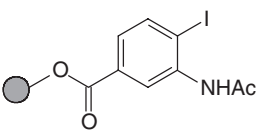
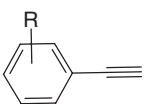
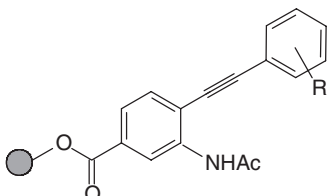
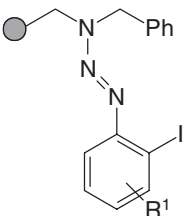

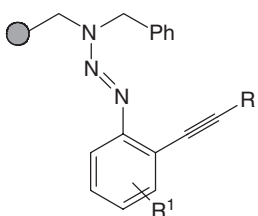
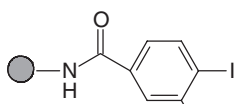

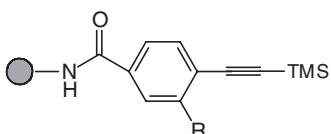
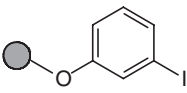

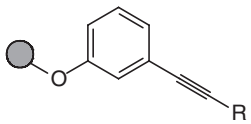
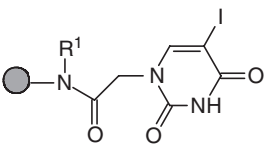

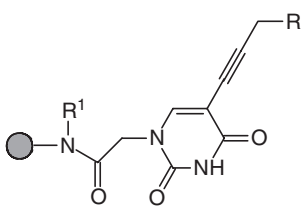
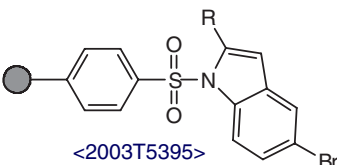

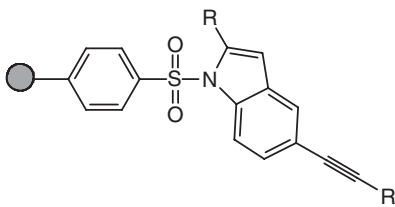
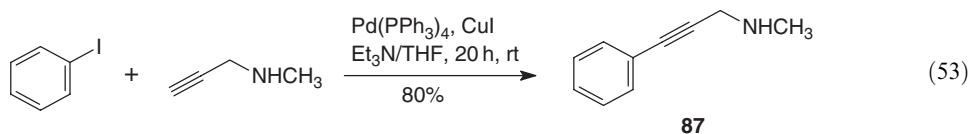
Starting material	Aryl halide/catalysts	Product
 <p><2002C&B265></p>	 DIPEA, $(\text{Ph}_3)_2\text{PdCl}_2$ Cul, DMF	
 <p><2002T10387> for similar couplings <1996JOC8160> <1997JOC1388> <2001EJO4706></p>	 TMS Pd(dba) ₂ , Cul, Et ₃ N 5 examples 82%	
 <p><1998TL8031></p>	 Pd(PPh ₃) ₄ , Cul, Et ₃ N, DMF, 25 °C > 90%	
 <p><1998SC3645></p>	 Pd(PPh ₃) ₄ , Cul, NaHCO ₃ , DMF, 40 °C, 20 h 55–75%	
 <p><2001TL1815></p>	 Pd(PPh ₃) ₄ , Cul, DIPEA, THF/DMF, 25 °C, 24 h 85–95% + homodimer 16 examples hetero and nonheterocyclic	

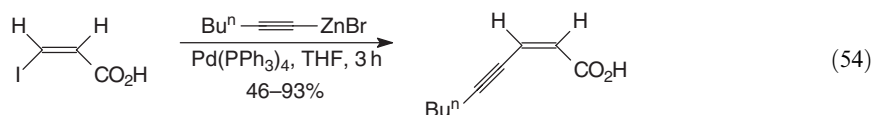
Table 3 Arylation and alkenylation of alkynes: immobilization of the aryl halide

Starting material	Alkyne/catalysts	Product
 <p><1997TL2307> similar couplings <1997TL7963></p>	 <p>$\text{Pd}(\text{PPh}_3)_2\text{Cl}_2$, CuI, tetramethylguanidine (TMG), dioxane, 90 °C, 18 h, 7 examples 48–95%</p>	
 <p><1999TL6201> similar couplings <1997JA3391, 2001MM3812></p>	 <p>$\text{Pd}(\text{OAc})_2$, NEt_3, DMF, 80 °C, 12 h, 4 examples</p>	
 <p><1998TL3647> similar couplings <1998TL4449, 1998SL1085 1999AG(E)1073, 2000AG(E)1629 2003T1571></p>	 <p>$\text{Pd}(\text{PPh}_3)_4$, CuI NEt_3/THF, rt, 4 h several examples >90%</p>	
 <p><1998SL676></p>	 <p>$\text{Pd}(\text{OAc})_2$, NaOAc Bu_4NCl, DMA, 100 °C 24 h, 7 examples 77–96%</p>	
 <p><2002TL1381></p>	 <p>$\text{Pd}(\text{PPh}_3)_4$, CuI, DMF rt, 3–16 h several examples</p>	
 <p><2003T5395></p>	 <p>$\text{Pd}(\text{PPh}_3)_2\text{Cl}_2$, CuI, DMF, Et_3N >75%</p>	

Solution-phase combinatorial Sonogashira coupling reactions were also used for an investigation into the structure–activity relationship of semicarbazide-sensitive amine oxidase inhibitors such as **87** (Equation (53)) <2001BMCL2565>. Although coupling reactions involving propargylamines have not featured in the literature, it was observed that they coupled successfully without the need for protection.



(d) *Reaction of terminal metallated alkynes with aryl, alkenyl, and allenyl halides in the presence of catalytic palladium(II) or palladium(0) compounds and a base.* Besides the use of copper as a co-catalyst in cross-coupling reactions between terminal alkynes and aryl/vinyl halides, a number of other metals have been successfully applied to effect this transformation and a number of relevant reviews have been forthcoming <2002CCR1, 2001OR417, 1998T8275>. The organometallic species may be preformed, as, for instance, organotin or organozinc reagents, or may be generated *in situ*, as is the case with copper co-catalysts. The use of metals of intermediate electronegativity, compared with sodium or lithium, are most preferred as these reduce the tendency for tetraalkynylpalladate formation prior to the cross-coupling reaction. Organozinc compounds have recently come to prominence partly due to the diverse range of functionality that may be accommodated using mild experimental conditions (Equation (54)) <2002TL5673>.



These features often remove the need for protection/deprotection steps. The ease with which zinc reagents undergo transmetalations with transition metals, including palladium, has led to an increase in their use in efficient cross-coupling reactions including couplings between alkynylzinc reagents with alkenyl and aryl halides <1998T135, 1999JOM179>. Coupling reactions with alkenyl halides occur stereospecifically with zinc reagents and may often be accompanied by enhanced yields, compared to the use of corresponding copper co-catalyst (Table 4).

With regard to organotin reagents such as trimethylalkynyltins or tributylalkynyltins, the rate of transfer of the alkyl group compared to the alkynyl moiety is significantly slower, thus affording exclusive transfer of the alkynyl motif. These reagents have been used in a range of efficient and selective cross-coupling reactions including the synthesis of 6-alkynylpurines (Equation (55)) <2003BMCL877> and 3-propynylindoles (Equation (56)) <2000H1877>.

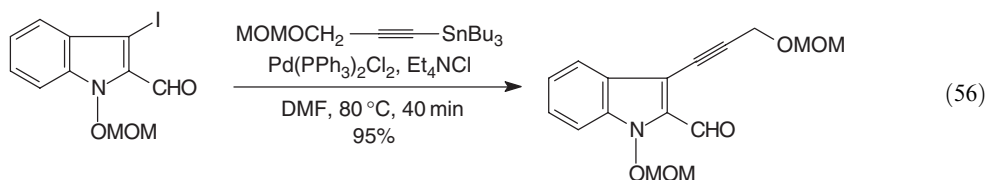
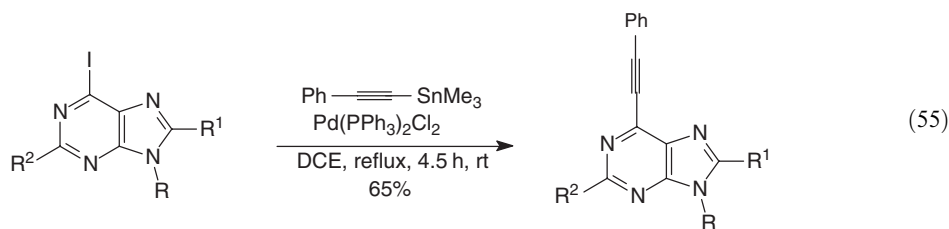
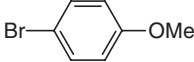

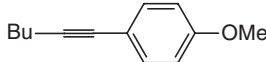
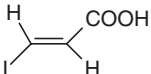

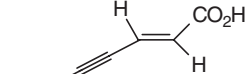
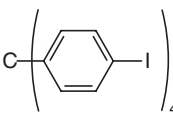
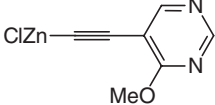
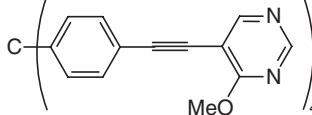
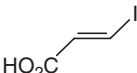
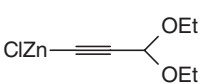
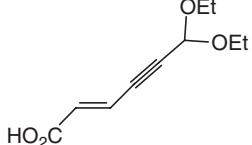
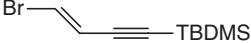
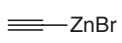
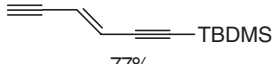
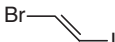
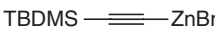
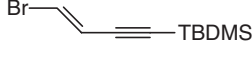
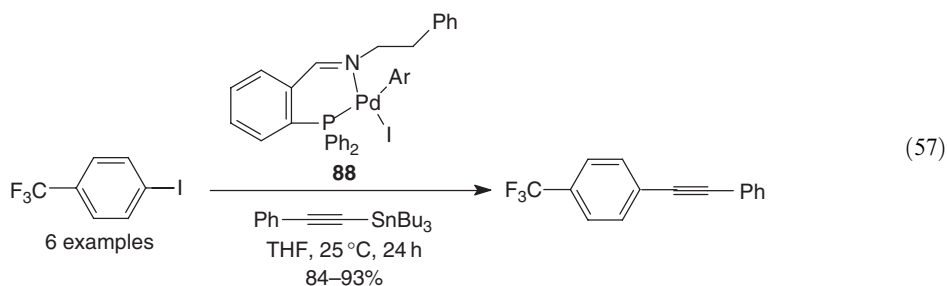


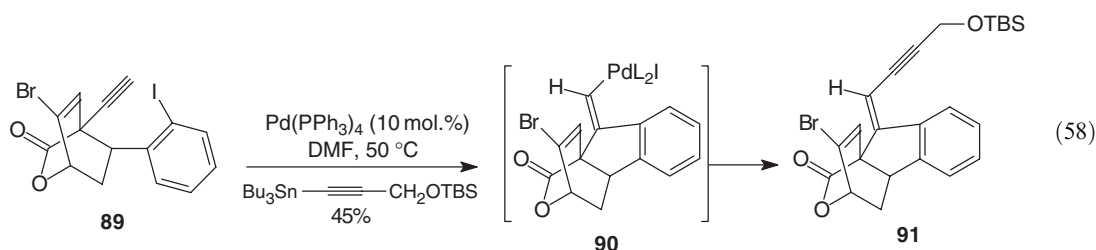
Table 4 Arylation and alkenylation of alkynylzinc reagents

Starting material	Alkyne/catalysts	Product
 <1998JOM219> related reactions <2000T407, 1997JOC8957>	 ZnCl_2/NaI , $\text{Pd}(\text{PPh}_3)_4$ piperidine, 60 °C 4–8 h	 86%
 <1996S82>	 $\text{Pd}(\text{MeCN})_2\text{Cl}_2$ DMF, Et_2O , 25 °C, 3 h	 87–88%
 <1998JOC9746>	 $\text{Pd}(\text{PPh}_3)_2\text{Cl}_2$ THF, 65 °C, 12 h	 34%
 <1998JOC9746> related reaction <1996S82>	 $\text{Pd}(\text{PPh}_3)_2\text{Cl}_2$ THF, 65 °C, 20 h	 71%
 <2000OL65>	 2% $\text{Pd}(\text{PPh}_3)_4$	 77%
 <2000OL65>	 2% $\text{Pd}(\text{PPh}_3)_4$	 70%

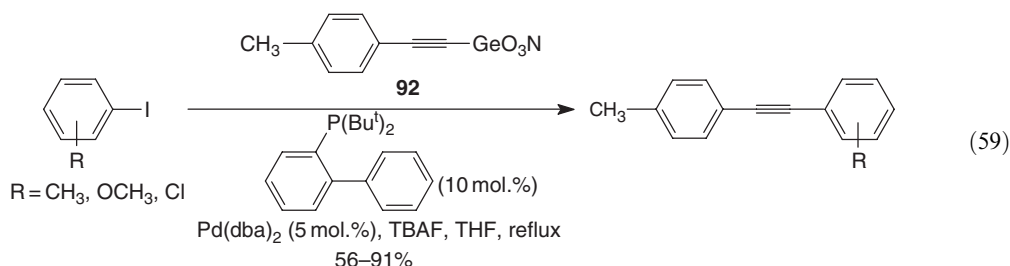
The novel iminophosphine–palladium complex **88** was shown to be an effective catalyst for the cross-coupling of aryl halides with organostannanes (Equation (57)) <1997TL3759>. Compared to traditional catalysts, this particular catalyst was reported to provide high reaction rates, to exhibit wide applications and versatility in its use and to provide appropriate metal-supporting ability.



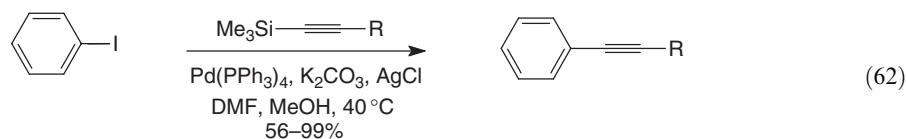
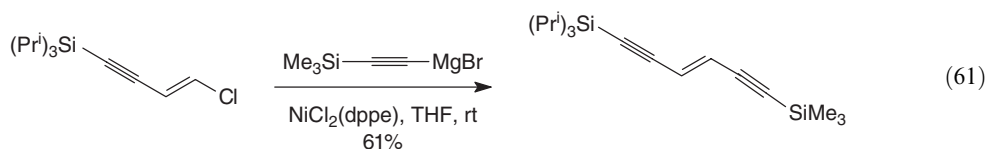
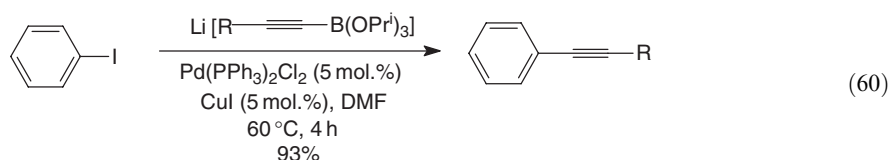
In a recent report, the synthesis of tetrahydrofluorenes was achieved by treatment of **89** with an excess of organotin reagent (Equation (58)) <2003TL4439>. In a tandem sequence of reactions, the initial arylpalladium species adds across the triple bond in **89** in a *syn*-fashion to afford the (*E*)-vinyl palladium adduct **90**. Further reaction with the stannane delivers the alkynyl motif to provide **91** in a modest 45% yield.



In general, organogermanes are less reactive than the corresponding organotin reagents in cross-coupling reactions; furthermore, the chemistry of these reagents is obscure. A recent study aimed at redressing this imbalance has shown that the palladium cross-coupling reaction of organogermanes with aryl iodides occurs in good yield under fluoride-induced activation (Equation (59)) [<2002OM5911>](#). The alkynyl germane **92** was readily accessible from germanium trichloride. In the presence of TBAF, transfer of phenylethynyl group took place rapidly with minimal homocoupling. It is thought that the role of fluoride, in the catalytic step, involves the formation of a hypervalent and thus more reactive germanium complex.



Examples of other alkynyl metal reagents used in cross-coupling reactions include lithium alkynyl(triisopropoxyborates) either with or without copper as a co-catalyst (Equation (60)) [<2000TL8513>](#), organomagnesium reagents where coupling using a nickel catalyst proved more efficient than palladium (Equation (61)) [<2001T10213>](#), and the use of silver ions as a co-catalyst and promoter in coupling reactions (Equation (62)) [<2000OL2935, 2000TL2377, 2002TL2039>](#).



From a mechanistic point of view, it has been suggested that the electropositive silver ion can displace the silicate that is formed by the addition of methylate to the 1-trimethylsilylalkyne shown in (Figure 1). This step favored as volatile methoxytrimethylsilane is liberated during the process. The silver acetylide formed in this step may then enter the palladium catalytic cycle so releasing the silver ion that can then enter another catalytic cycle. In contrast to the use of a copper co-catalyst, in palladium-catalyzed cross-coupling reactions, the oxidative homocoupling reaction between alkynyl silane was significantly suppressed under the prevailing reaction conditions.

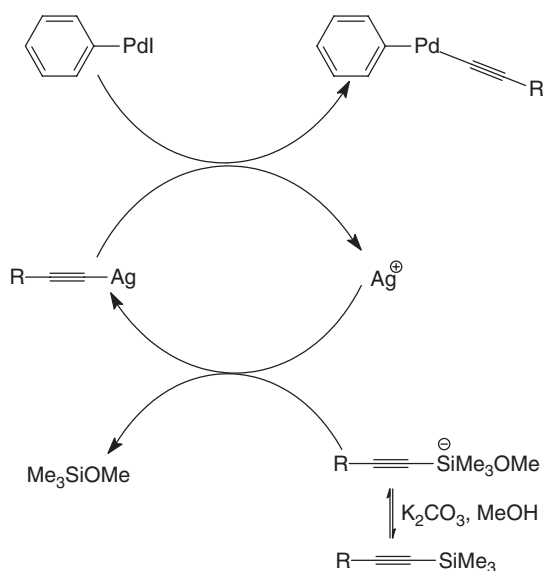


Figure 1

(iii) Substitution reactions of alkynyl halides

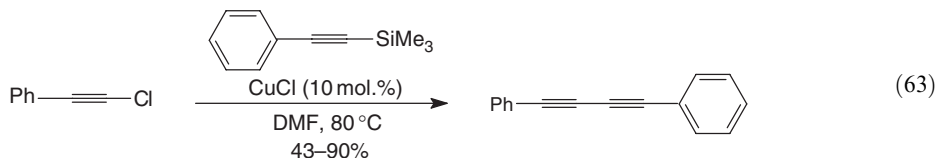
An alternative approach to the formation of a bond between an sp -center and an sp^3 -, sp^2 -, or an sp -hybridized carbon atom may be achieved by the reaction of an alkynyl halide with a suitable alkyl, alkenyl, allenyl, aryl, or alkynyl organometallic derivative.

A number of methods have been described for the synthesis of alkynyl halides. These include the halodecarboxylation of α,β -acetylenic acids <1999TL1495>, the treatment of alkynyl selenonium salts with tetrabutylammonium halides <1999TL931>, and the exposure of a 1-lithioalkyne to either 2,2,2-trifluoro-1-iodoethane <1999TL6671> or molecular iodine <1996TL7661>.

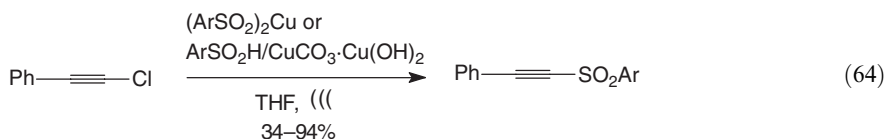
The presence of a diyne, oligoalkynyl, or a dienyl motif in compounds is often associated with a wide range of physical, electronic, and/or biological properties. The synthesis of novel compounds bearing such moieties has therefore spawned a range of new methodologies, some of which have been the subject of reviews <2000AG(E)2632, 2001OR417, 1998T8275, 2003JOM151>.

Alkynyl halides are generally inert toward most nucleophiles; however, successful substitution reactions have been reported using a variety of organometallic species that include organosamarium, organocopper(I) and (II), alkylcopper/zinc reagents of the type $\text{RCu}(\text{CN})\text{ZnX}$, organozinc, and organozirconium reagents.

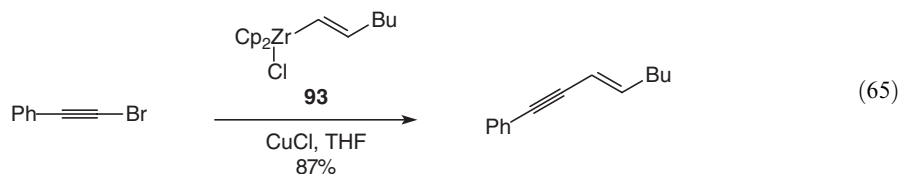
The copper(I)-catalyzed cross-coupling reaction between alkynyl silanes and 1-chloroalkynes, to afford unsymmetrical conjugated diynes, has been reported via the transmetalation of an alkynyl group, derived from the silane, to the copper(I) catalyst (Equation (63)) <1998TL4075>. Homocoupling of the alkynyl halide was largely suppressed under the prevailing experimental conditions; however, the requirement for a polar aprotic solvent at 80°C may limit the usefulness of this procedure.



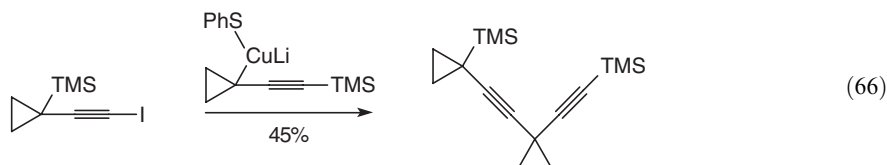
The sulfonyl group is an activator of triple bonds as well as a useful protecting group. Alkynyl iodides have been efficiently converted to the corresponding alkynyl sulfones by reaction with copper sulfinate in a THF suspension under sonication conditions (Equation (64)) <1996TL3717>.



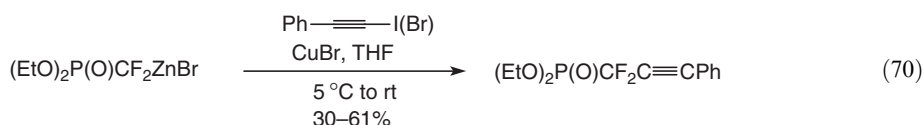
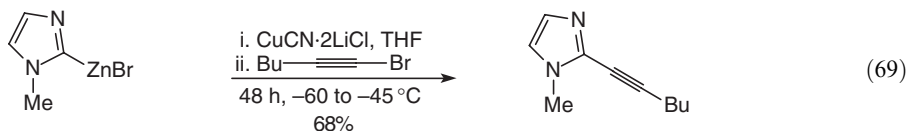
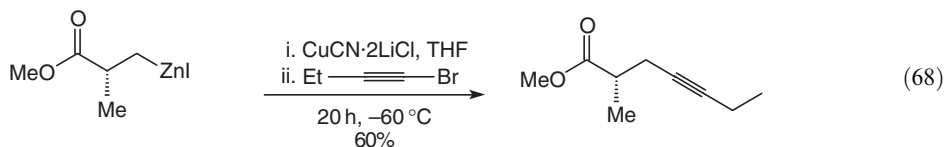
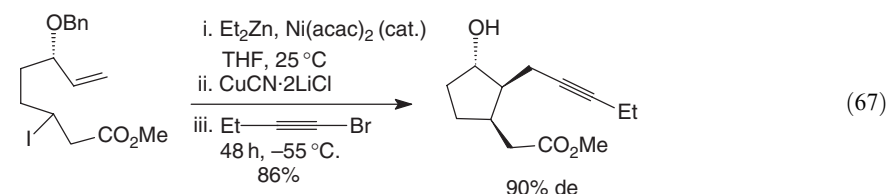
The stereoselective synthesis of 1,3-enynes from the coupling of highly substituted alkenyl moieties was achieved using alkenylzirconium reagent **93** (Equation (65)) <1997TL4103>. Compound **93** was prepared by hydrosilyrconation of 1-hexyne using $\text{Cp}_2\text{Zn}(\text{H})\text{Cl}$ (87%). More highly substituted alkenylzirconium compounds were obtained from the carbosilyrconation of alkynes, carbocupration, or carboalumination reactions of terminal alkynes. These were then reacted with alkynyl halides, in the presence of CuCl , to provide a convenient one-pot methodology for the synthesis of highly substituted 1,3-enynes.



An alternative approach for the synthesis of 1,4-diynes that involved the umpolung of a “natural” alkynyl–propargyl coupling reaction (Equation (66)) <1991JA3935>. This regioselective head-to-tail coupling involved attack between a metallated propargylic carbon atom, in this example a propargyl(phenylthio)lithium cuprate, to an electrophilic iodoalkyne.

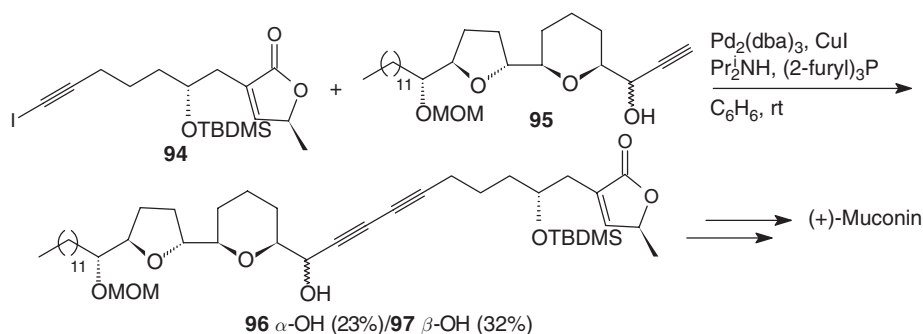


Organozinc reagents are tolerant to most functional groups resulting in their use in a wide variety of chemical transformations including coupling reactions with alkynyl halides <1998AG(E)2460, 1997T16711, 1997SL327>. With highly reactive alkynyl iodides and bromides, the coupling reaction takes place efficiently at low temperatures <1995SL463, 1997TL7511, 1997T7237, 2002JFC15> (Equations (67)–(70)). Performing the reaction at elevated temperatures leads to the preferential formation of copper acetylides via an iodine–copper exchange reaction.



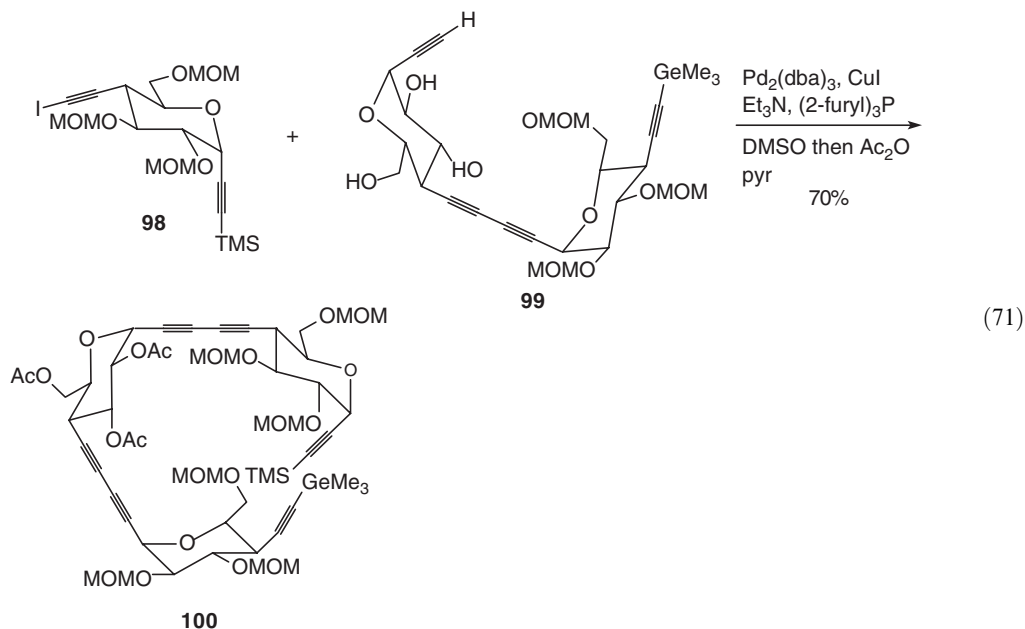
The use of palladium in conjunction with either zinc (Negishi conditions <1980JA3298>) or copper have been reported for cross-coupling reactions of alkynyl halides. In a recently reported total synthesis of (+)-muconin, a potent biologically active compound, the coupling between the iodoalkyne **94** and propargyl alcohol **95** was achieved under palladium catalysis (Scheme 11)

<2000T1451> to provide a separable mixture of diynes **96** and **97** (1:1.4). Conversion to the natural product, itself, was accomplished via hydrogenation of the diyne, in **96** and **97**, followed by an oxidation/reduction sequence of the β -isomer and deprotection of the MOM and TBDMS groups using $\text{BF}_3 \cdot \text{Et}_2\text{O}$.

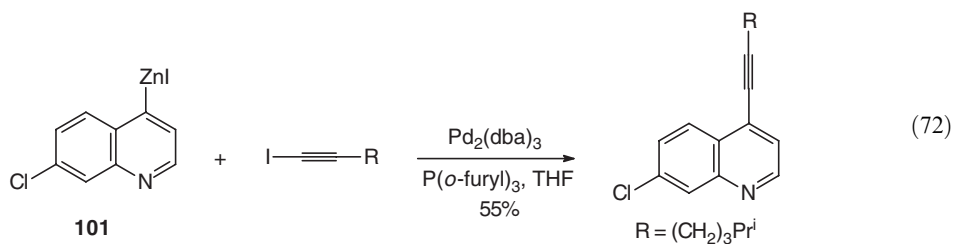


Scheme 11

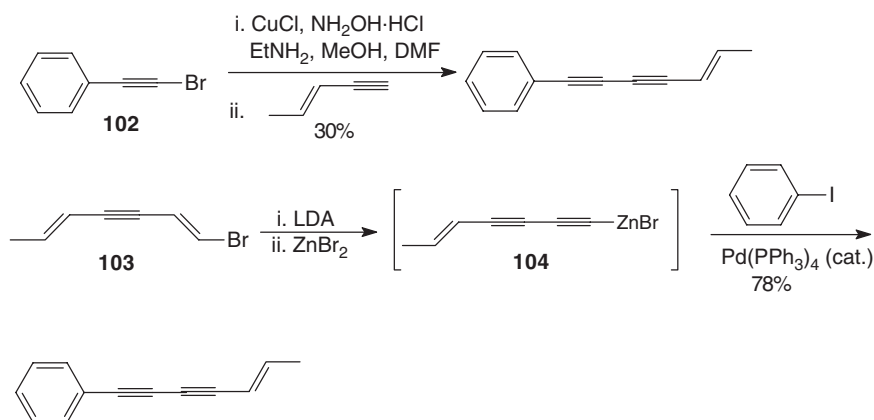
Analogous copper-assisted reaction conditions were employed to effect the synthesis of the trimer **100** by the heterocoupling reaction between dimer **99** and the iodoalkyne **98** (Equation (71)) <1997HCA2215>. These studies were aimed at the synthesis of cyclodextrin analogs possessing modified cavities to accommodate specific host molecules.



With regard to the analogous zinc couplings, an efficient palladium-catalyzed cross-coupling was reported involving the zincated quinoline **101** and an iodoalkyne (Equation (72)) <1997T7237>. For less reactive iodides higher temperatures and longer reaction times were reported without significant reduction in the corresponding yield.



An alternative method for optimizing the selectivity in the synthesis of conjugated diynes is shown (Scheme 12) <2000OL3687>. The outcome of this approach, which makes use of a palladium-assisted cross-coupling reaction between (*E*)-5-hepten-1,3-diynylzinc bromide **104**, generated *in situ* from the LDA treatment of dienyne **103**, with iodobenzene, was compared to the corresponding Cadiot–Chodkiewicz methodology involving the coupling of (*E*)-3-penten-1-yne and 2-bromo-1-phenylethyne **102**.



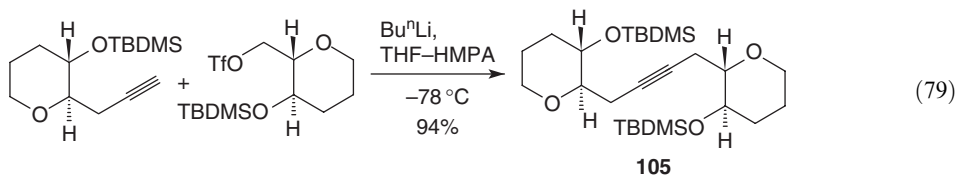
Scheme 12

The generality of this palladium-catalyzed approach was studied further and was shown to be just as efficient with *p*-substituted aryl iodides as well as heterocyclic iodides. Of equal importance was the absence of any by-products from the reaction. In contrast the coupling reaction conducted under Cadiot–Chodkiewicz conditions was noted for lower yields (34–48%) and the formation of at least one of the two possible symmetrical diynes (20–25%).

1.21.3.1.2 Substitution of oxygen functions

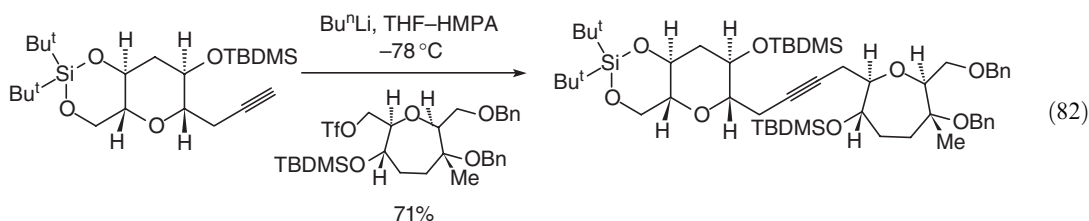
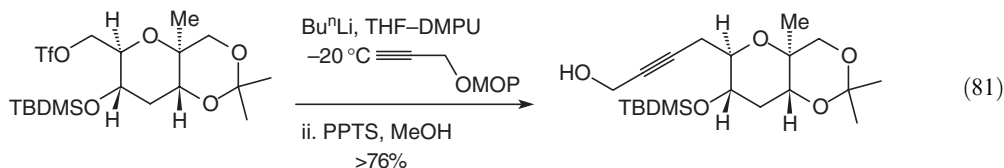
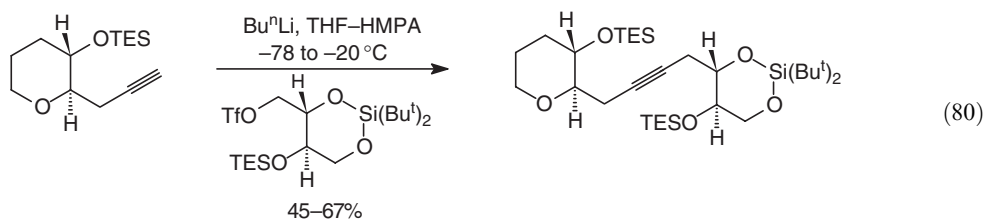
(i) Substitution of alkyl-oxygen functions

The substitution of tosylates or triflates by alkynyl metal reagents is an extremely important method for forming carbon to carbon bonds. Acetylide–triflate coupling reactions have been widely utilized in recent years in reported syntheses of marine polycyclic ethers such as brevetoxin, maitotoxin, and yessotoxin <1993CRV1897, 1993CRV1685, 1996JA1565, 1999SL1037>. In several of these approaches the resulting alkyne, such as **105**, is oxidized to afford an α -diketone, which is subsequently converted into a tetracyclic diacetal via a double intramolecular acetalization step (Equation (79)) <2000TL903>. The symmetrical alkyne was formed in 94% yield using a procedure first described by Kotsuki <1990TL4609>. This involved the use of a strongly coordinating co-solvent, such as HMPA in THF or DMPU in THF, to enhance the nucleophilicity of the alkynide anion and thus improve the efficiency of the substitution reaction.



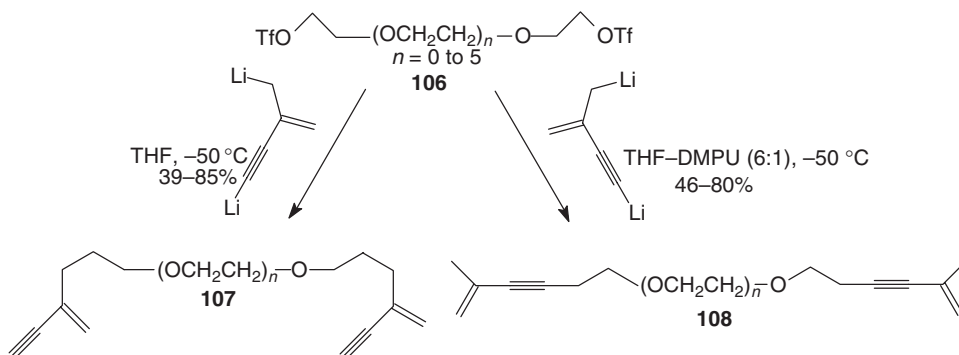
A similar convergent strategy was employed to gain access to a *trans*-fused tetracyclic oxane via a triflate–acetylide displacement to afford **105** <2000TL507>.

Further examples of coupling reactions between cyclic triflates and terminal alkynes providing access to marine natural products such as brevetoxin-B (Equation (80)) <2000TL7681>, maitotoxin (Equation (81)) <2000TL4161>, and yessotoxin (Equation (82)) <2002T1789> are illustrated.



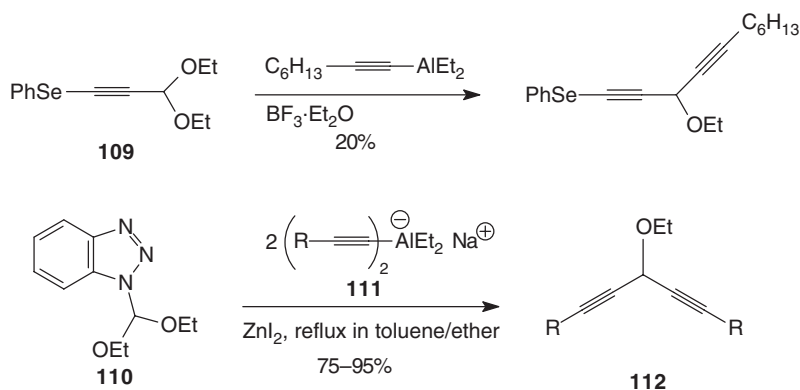
The synthesis of enynes, as candidates for palladium-catalyzed [4 + 2]-benzannulation reactions to afford novel polysubstituted benzenes, has been reported [<1999JOM232>](#). It was observed that alkylation of polyethylene glycol derivatives that contain an alkoxy group in the β -position to the leaving group proved difficult to accomplish due to the electron-withdrawing effect of the β -oxygen atom. The triflate moiety **106** was found to be an acceptable leaving group for displacement reactions.

The addition of DMPU as a co-solvent prior to the addition of the nucleophile dramatically enhanced the nucleophilicity of the acetylide anion to favor the formation of the bis-enyne **108** rather than the isomeric compound **107** that predominates in the absence of DMPU (Scheme 13).



Scheme 13

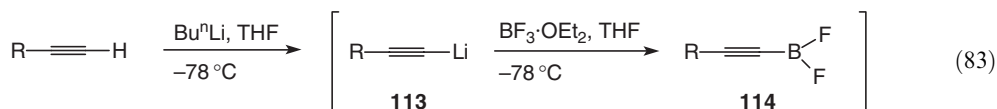
Although alkynyl alanes are rather soft nucleophiles, they do react with propargylic cations under S_N1 conditions. Using an appropriate Lewis acid, both benzensulfonyl and benzeneselenenylpropynyl diethyl acetal **109** (Scheme 14) have been reported to undergo substitution reaction with alkynyl alanes albeit in a modest yield [<1995CC149>](#). The anionic aluminum alkynyl **111** underwent substitution of the benzotriazole moiety in **110** to afford the skipped pentadiyne **112** in excellent yield [<1999JOC488>](#). As a general observation, dialkynylaluminates conferred better chemoselectivity than the corresponding lithium alkynyls. Depending upon the reaction conditions, two different selectivities are thus possible in the presence of 1 equiv. of aluminate and 2 equiv. of Lewis acid, at low temperatures monosubstitution of the benzotriazole moiety occurs to afford propynal diethyl acetal derivatives in quantitative yield.



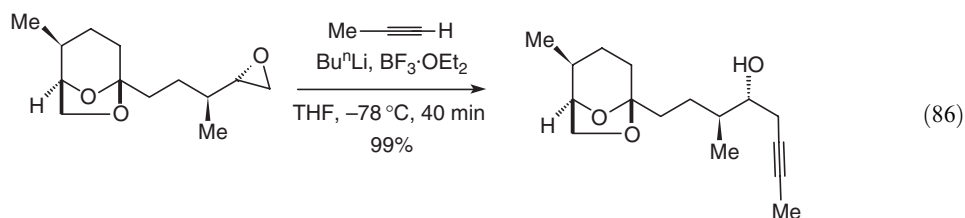
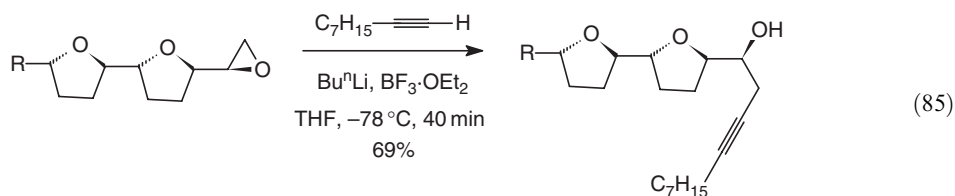
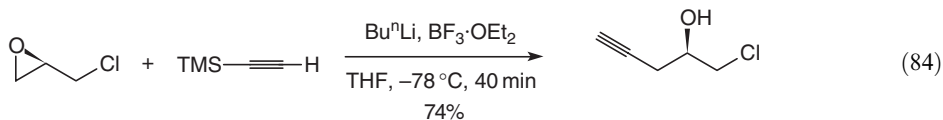
Scheme 14

Oxiranes also undergo substitution reactions with alkynyl metal reagents to afford β -hydroxyalkynes. Ring opening of unsymmetrical epoxides, using lithio-acetylides, tends to occur at the less substituted carbon atom; however, the relatively poor electrophilic nature of epoxides often requires the use of Lewis acid to trigger the reaction.

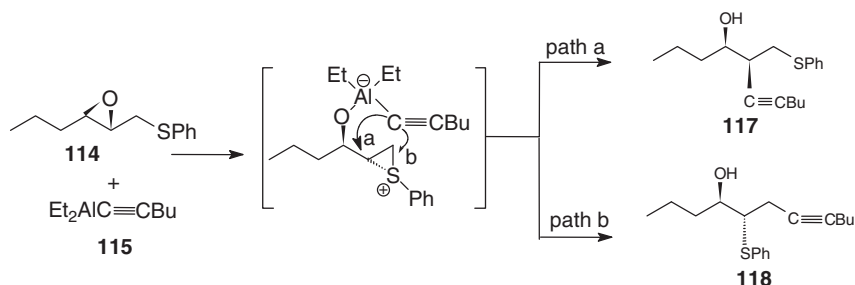
In the Yamaguchi–Hirao reaction <1983TL391>, boron trifluoride etherate is used for this purpose (Equation (83)) and is thought to involve the rapid formation of a difluoroborane species **114** from the reaction of the lithio-acetylide **113** in THF with $\text{BF}_3 \cdot \text{OEt}_2$.



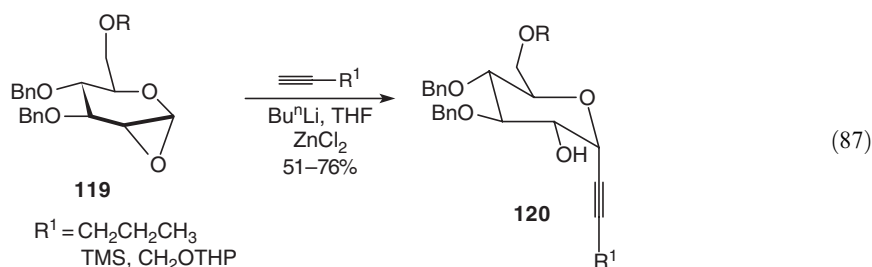
In a modification to the Lewis acid used in this reaction, it has been reported that $\text{BF}_3 \cdot \text{THF}$ delivered virtually quantitative yields of homopropargylic alcohols <2001TL6947>. The enhanced yields, obtained by using this Lewis acid, have been explained in terms of the extra stability imparted upon complexes such as **114** from the THF ring compared to diethyl ether. These reaction conditions have been shown to effect the rapid opening of oxiranes even at -78°C in the presence of a wide variety of functional groups including ketals, halogens, and esters as well as a range of protecting groups which remain unscathed by the reaction conditions (Equation (84)) <2002T9859>, (Equation (85)) <2003BMCL2385> and <2002BMCL2089>, and (Equation (86)) <2003TL4965>; also see <1996BMCL467, 1997TL2057, 2001TL4907, 2002TL2725, 2002T4955, 2002TA261, 2003TL3175, 2001TL1543, 2000TL7697, 2001TL65>.



Methods to effect stereoselective alkynylations from epoxide ring-opening reactions that proceed with retention in configuration (i.e., double inversion of configuration at the stereogenic center) have been reported [<1999TL9267>](#). The stereoselective alkynylation of *trans*-2,3-epoxy sulfide **114** (Scheme 15) was accomplished, with double inversion of configuration, using the alkynylaluminum reagent **115**. The regioselectivity of the alkynylation reaction was found to be highly solvent dependent. Thus, reaction in hexane at 0 °C provided a 10:90 mixture of **117**, via double inversion, and **118**, via a sulfenyl shift, in 78% yield overall [<1996BCJ2095>](#). In contrast, conducting the reaction in toluene at –78 °C, provided a 30:70 mixture in 66% yield, whereas the use of CH₂Cl₂ at –78 °C reversed the selectivity to favor the production of **117** in 62%.



The ring opening of an α -1,2-epoxide moiety in sugars, with lithium alkynyl derivatives in the presence of an activator, such as the weak Lewis acid zinc chloride, has been reported (Equation (87)) [<1997TL6251, 1997SL1263, 1999T8253, 1998T9913>](#). Thus, treatment of a cooled solution of **119** with an alkynyl anion provided **120** as a single diastereoisomer with the pentynyl group axially orientated.



The outcome, from this series of α -C-glycosidation reactions, was explained in terms of the formation of an alkynyl-zinc complex such as complex **A** (Figure 2), which is in equilibrium with the ion pair **B**. Intramolecular α -directed delivery of the alkynyl group in ion-pair **B** affords the α -C-glycoside.

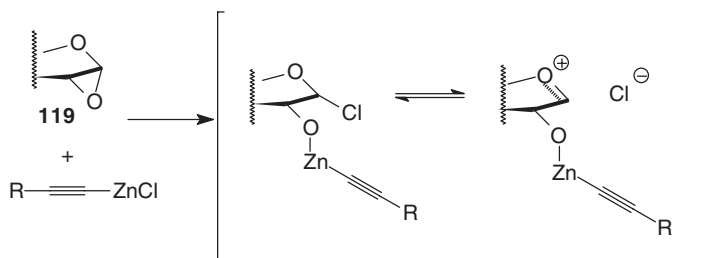
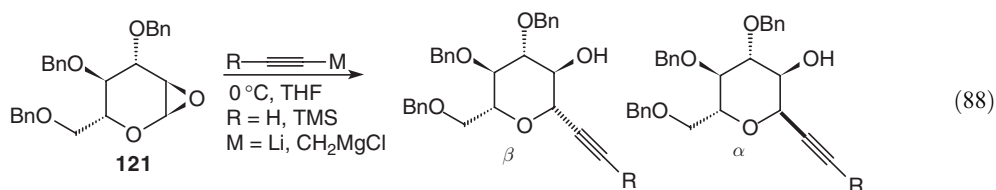


Figure 2

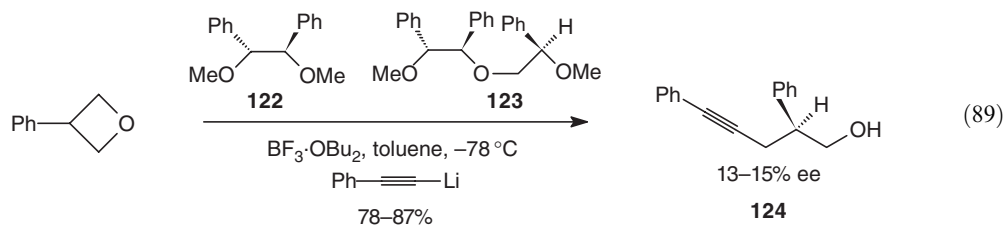
The formation of β -glycosides, from the ring opening of oxirane **121** (Equation (88)), has also been reported [<2002T1997>](#). The formation of either the α - or the β -adduct was found to be very dependent upon the nature of the counter ion and upon the temperature of the reaction mixture.

For example, whilst treatment with a Grignard reagent ($R = H$) stereoselectively provided the β -*C*-glycoside in 78%, the corresponding lithium reagent ($R = TMS$) delivered the α -*C*-glycoside in a comparable yield.

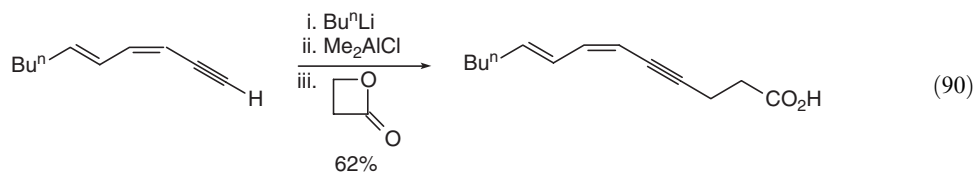


Interestingly, the analogous reaction performed at -95°C with dimethylaluminum acetylene ($R = TMS$) provided the α -*C*-glycoside in 80% yield with no observable competitive methyl transfer.

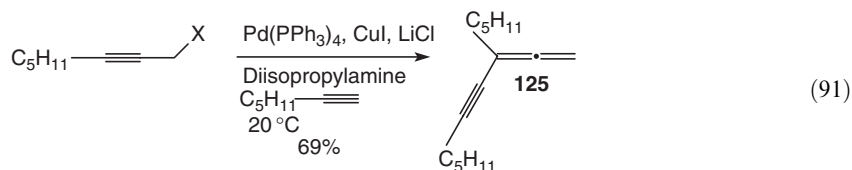
Oxetane and substituted oxetanes undergo substitution reactions with alkynyllithium reagents in the presence of Lewis acids to afford γ -hydroxyalkynes [<1984T4261>](#). An attempted enantioselective ring-opening reaction of 3-phenyloxetane, by treatment with a combination of the external chiral ligands **122** and **123**, and lithium phenylacetylide provided the alcohol **124** in good yield but with rather low enantiomeric excesses ([Equation \(89\)](#)) [<1994SL199, 1997T10699>](#).



Besides oxetanes, β -propiolactones also undergo analogous substitution reactions with dimethylalkynylaluminum reagents to afford β -alkynylpropionic acids [<1986TL87>](#). In general, the dimethylalkynylaluminum is generated via a lithium–aluminum exchange reaction as shown ([Equation \(90\)](#)) [<1996TL1913>](#). This coupling was used to provide access to an alkyne-propionic homologation reaction in a synthesis of the marine metabolite carduusyne A.



Both allylic and propargylic oxygen derivatives undergo 1,1- and 1,3-substitution reactions with terminal alkynes and alkynyl metal reagents [<B-1998MI013>](#). The regiochemistry of the substitution reaction depends upon a number of criteria, particularly those related to substituents and the metal associated with the alkynyl anion. In recent years, most attention has focused upon the use of palladium catalysis in the reaction of propargylic acetates, tosylates, and carbonates with terminal alkynes to afford allenes via 1,3-substitution reactions [<1993TL3853, 1994JOM343>](#). In a recent investigation, a systematic study into the effects of reaction conditions was conducted in the synthesis of enynes from the reaction of propargyl halides/triflates with alkynes under palladium catalysis [<2000T1851>](#) ([Equation \(91\)](#)). The nature of the leaving group was critical and the displacement of chloride was found to be superior to either bromide or tosyl groups. However, by conducting the reaction in diisopropylamine in the presence of lithium chloride, the formation of allenyne **125** was accomplished in 69% ($X = \text{tosyl}$).



Propargyl acetates were similarly unreactive, although activation was readily achieved by the addition of either zinc chloride or lithium chloride. Optimum results were achieved using zinc chloride in refluxing THF, where secondary and tertiary propargyl acetates gave good yields of allenyne (42–75%), although primary acetates proved less reactive. As a further observation, the reaction could be accomplished in the absence of copper presumably via a zinc acetylide. The reaction has been proposed to proceed via an organopalladium complex originating from the oxidative addition of the propargyl moiety to the palladium catalyst (Figure 3). Reaction of the complex with a terminal alkyne and subsequent reductive elimination of palladium provides the corresponding allenyne.

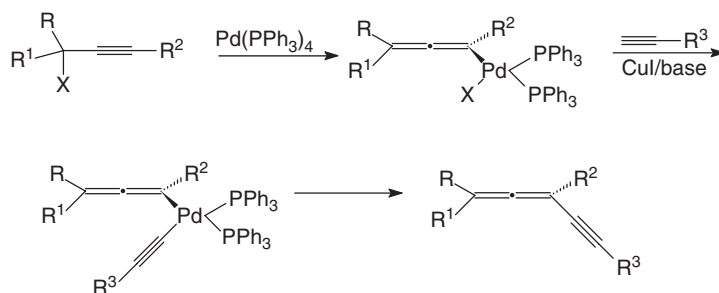
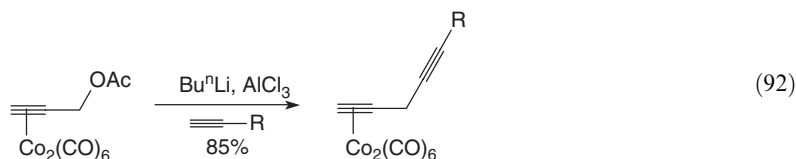


Figure 3

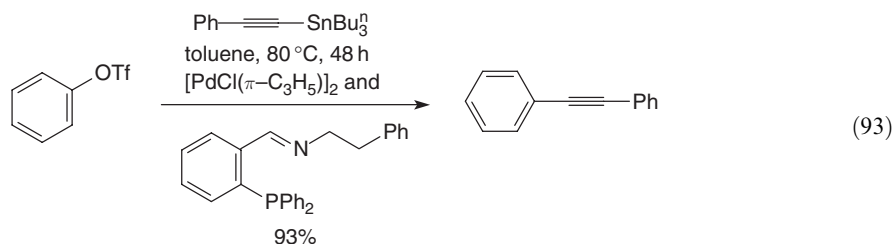
Propargyl acetates, in which the alkynyl carbon–carbon bond has been protected as a hexacarbonyldicobalt complex, undergo substitution reactions with alkynyl alanes to afford 1,4-diynes (Equation (92)) <2001JOM118>. The cobalt complex serves an additional role of activating the propargylic position to afford a monocomplexed diyne in good yield under rather mild conditions.

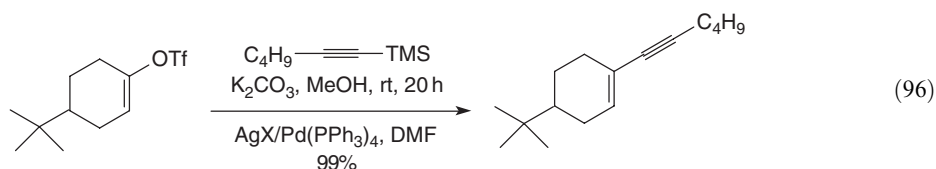
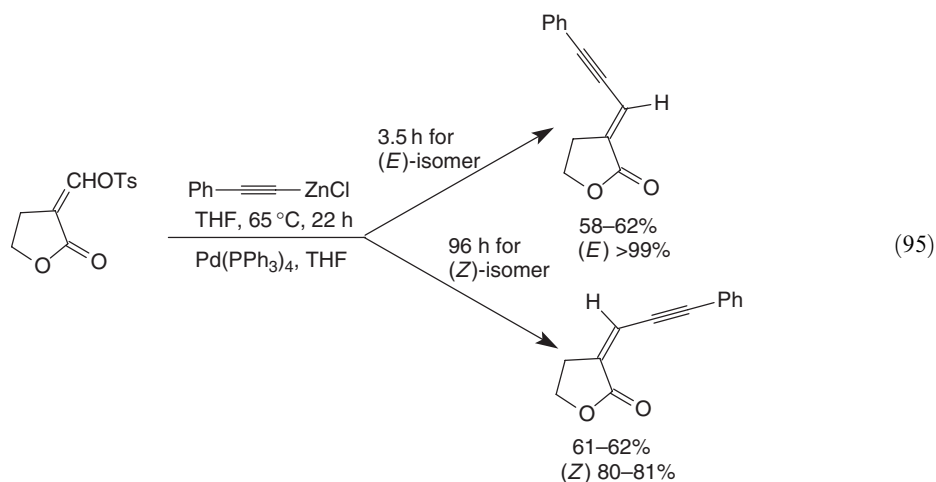
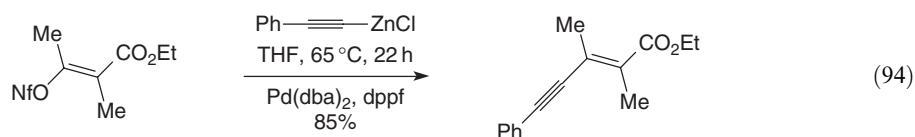


(ii) Substitution of alkenyl-, allenyl-, and aryloxygen functions

The substitution of alkenyl-, allenyl-, or aryloxygen functionality by a terminal alkyne may be readily achieved under palladium catalysis, either with or without a copper co-catalyst, to provide a useful methodology for the synthesis of enynes, allenynes, or arynes, respectively.

(a) The reaction of metallated alkenyl sulfonates in the presence of catalytic quantities of Pd(II) or Pd(0) compounds. The coupling reaction of alkenyl and aryl sulfonates with alkynes has been reported to take place very efficiently under mild conditions using metals of intermediate electronegativity such as tin (Equation (93)) <1997TL3759>, zinc (Equations (94) and (95)) <1999T2103, 2000TL2741>, and silver (Equation (96)) <2002TL2039>. The low reactivity of organostannanes in coupling reactions such as these often require rather drastic reaction conditions. To overcome this the *N*-(2-diphenylphosphinobenzylidene)-2-phenylethylamine ligand (Equation (93)) was developed and reported to act as an effective preformed catalyst, in conjunction with a stoichiometric amount of palladium, in coupling reactions of this type. The catalyst exhibited high turnover rates, wide applications, and adequate metal-supporting qualities in its use. This ligand provided optimum results in either THF or toluene as solvent, whereas other phosphine heterocycles affording significantly reduced yields.



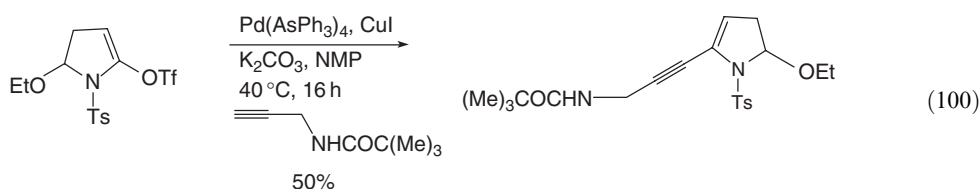
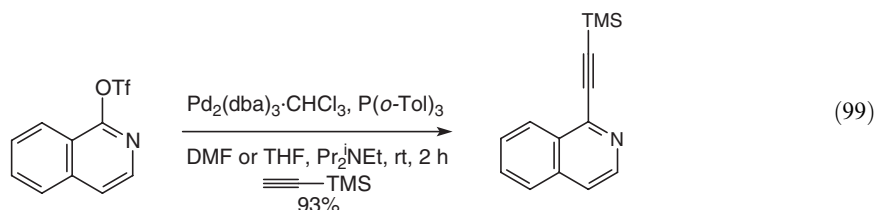
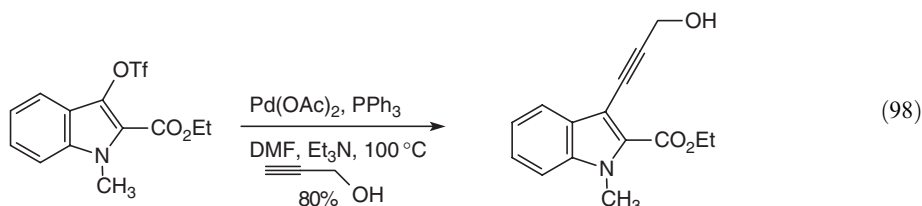
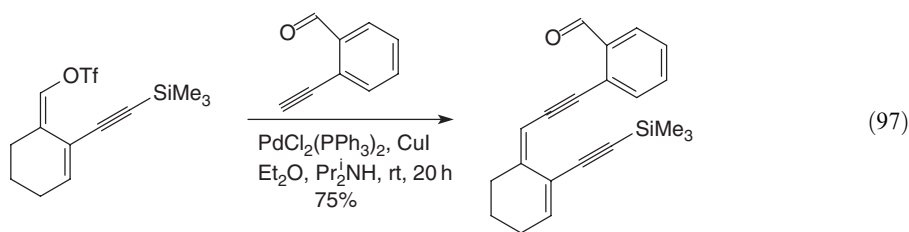


The use of nonaflates (Nf), in coupling reactions with alkynylzinc reagents, can offer a cheaper alternative to the use of alkenyl triflates (Equation (94)). They undergo efficient cross-coupling reactions, with alkynylzinc chloride, to allow the preparation of tetrasubstituted α,β -unsaturated esters in stereoisomerically pure form.

Analogous coupling procedures were used in the reaction of (E) - and (Z) -tosylates with α -hydroxymethylene- γ -butyrolactone (Equation (95)) to provide a stereoselective method for preparing substituted α -alkylidene- γ -lactones. Optimum stereoselectivity in the coupling reaction was achieved by conducting the reaction at 0 – 5°C . The amount of (E) -products arising from (Z) -substrates, however, increased with longer reaction time in the order aryl < heteroaryl < alkyl < alkynyl. The highest stereochemical conversion, (Z) -substrate to (E) -product, was observed in the reaction of alkynylzinc chloride with (Z) -lactone where the amount of (Z) -product obtained was reduced to 80%.

Functionalized enynes were also obtained from the coupling of trimethylsilylacetylenes with vinyl triflates in the presence of a silver co-catalyst (Equation (96)). Optimum yields were reported from the use of 4 equiv. of potassium carbonate and methanol in a single step without the need to carry out a preliminary deprotection step.

(b) *The reaction of terminal alkynes with alkenyl and sulfonates in the presence of catalytic quantities of $\text{Pd}(\text{II})$ or $\text{Pd}(0)$ compounds and a base.* Terminal alkynes undergo efficient coupling with alkenyl and aryl sulfonates in the presence of a palladium catalyst and a base (often an amine). The synthesis of a comprehensive range of enynes has been reviewed <1995OPP127>; these include the use of a $\text{Pd}(\text{OAc})_2(\text{PPh}_3)_2$ catalyst in DMF and Bu_3N with or without CuI , $\text{Pd}(\text{PPh}_3)_4$ in either DMF or DMSO with Et_2NH or piperidine, and $\text{PdCl}_2(\text{PPh}_3)_2$ with CuI . In general, reactions that use copper as a co-catalyst are conducted at an ambient temperature, whereas higher temperatures ($>60^\circ\text{C}$) are needed in its absence. The palladium-catalyzed cross-coupling reactions of alkenyl triflates with terminal alkynes, as well as between heteroaryl triflates and terminal alkynes, have been extensively utilized in synthesis. Some of these syntheses have focused upon applications toward natural product synthesis, such as the dienediynyl core of the neocarzinostatin chromophore (Equation (97)) <1995TL5167>, indole carboxylate derivatives (Equation (98)) <1998T11079>, analogs for dynemycin A intermediates (Equation (99)) <1995T3737>, and an N -tosylpyrrolidinone-derived enamine triflate (Equation (100)) <1996TL3561>.

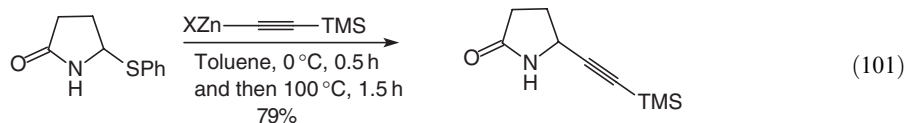


Additional examples of analogous cross-coupling reactions have involved the use of terminal alkynes with a (Z)-vinyl carbamate <1995SL435>, a tosylate derived from 1,3-cyclohexanedione <2002TL6673>, and a labile (Z)-keto enol triflate <1997T9107>.

(c) *Substitution of alkynyloxy functions.* Applications of alkynyl ethers as electrophilic partners in substitution reactions with suitable nucleophiles have a limited application and the reader is referred to <1995COFGT1030> for previous references to this transformation.

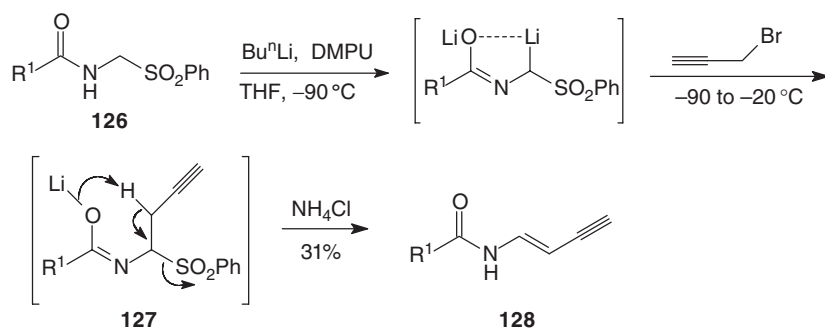
1.21.3.1.3 Substitution of sulfur, selenium, or tellurium functions

The substitution of sulfur, selenium, and tellurium functionalities by either 1-alkynes or by a corresponding alkynyl metal reagent is generally more difficult to carry out compared to the analogous oxygen derivative. The basis of this difference is attributed to the weaker inductive effect of these moieties compared to the carbon–oxygen bond coupled with a propensity for substitution to occur at the heteroatom rather than at carbon. However, an unusual example was reported during the synthesis of 5-ethynyl-2-pyrrolidinone that involved the use of an alkynylzinc reagent (Equation (101)) <1993TL915>.



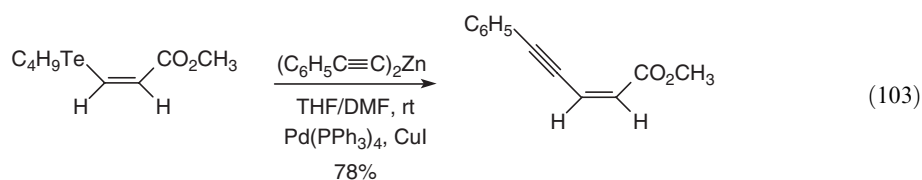
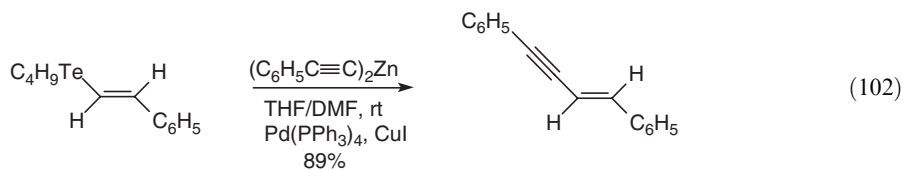
Successive treatment of α -amidomethylsulfone **126**, with *n*-butyllithium and propargyl bromide, provided the enamide **128** upon hydrolysis (Scheme 16) <1997T4835>.

The dilithiated species proved unstable and alkylation with reactive bromides, including propargyl bromide, gave enamide **128** in a modest yield as a mixture of diastereoisomers. This outcome is thought to arise from an intramolecular dehydrosulfinylation of the alkylated product **127**.

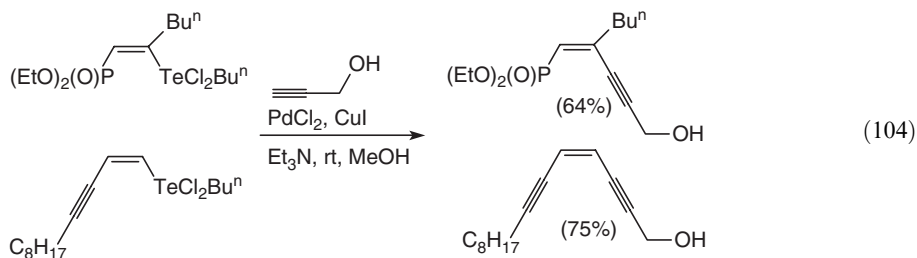


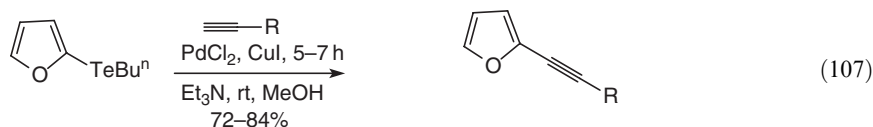
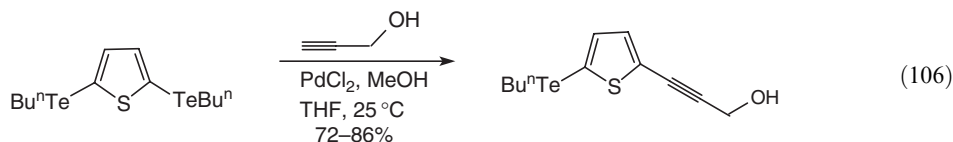
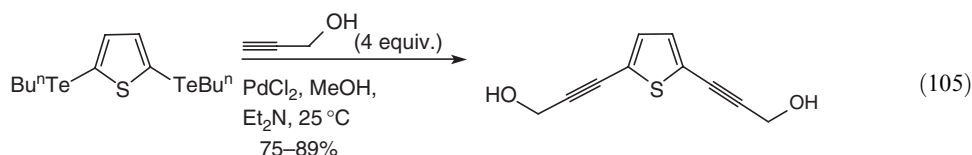
Scheme 16

Examples of direct substitution reactions between 2-benzenesulphonyl cyclic ethers and alkynylzinc reagents have been reported to occur in high yield [<1989T4293>](#). Alkynyl sulfones undergo substitution reactions with Grignard and organolithium reagents via mechanisms that are thought to involve electron-transfer processes and radical intermediates [<1984TL4851>](#). 2-Lithiated phospholes have been reported to react with alkynyl sulfones, via the substitution of the sulfone moiety, to provide access to a variety of unsymmetrically disubstituted alkynes [<1996BSF33>](#). The chemistry of alkynyl and allenyl sulfones has been reviewed [<2001T5263>](#). Interest in the chemistry of organotellurium compounds has recently increased and has been reviewed [<2000ACA66>](#). The use of vinylic tellurides, of well-defined geometry, in cross-coupling reactions with terminal and monosubstituted alkynes has recently come to prominence [<1995SL1145, 1999TL265, 2001JOM43>](#) and provides access to enynes in good yield [<2001SL1473>](#). Alkynylzinc compounds may be readily formed, by a Te/Zn exchange reaction, employing diethylzinc under halide-free conditions in THF at room temperature. These readily undergo cross-coupling with vinyl and aryl tellurides ([Equations \(102\) and \(103\)](#)) [<2000TL437>](#).



Further representative examples illustrate couplings of alkynes with phosphonates and enynes ([Equation \(104\)](#)) [<2003TL1779, 1999TL4619, 2001TL8563>](#), 2,5-bis-(butyltelluro)thiophenes ([Equation \(105\)](#) and (106)) [<2003TL685, 2001TL7921>](#), and 2-(alkyltelluro)furans ([Equation \(107\)](#)) [<2001TL8927>](#).

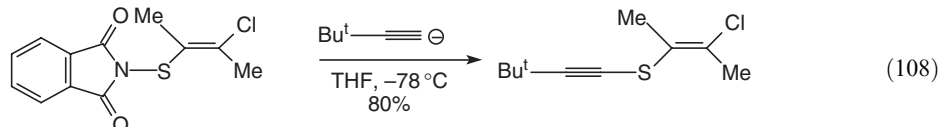




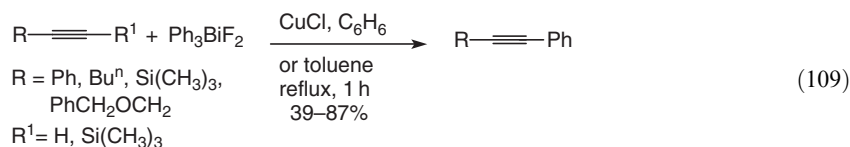
As a general observation, cross-coupling reactions using vinylic tellurides occur at ambient temperatures using very mild conditions which offer a distinct advantage when substrates contain sensitive functionality such as alcohols, esters, and silanes.

1.21.3.1.4 Substitution of nitrogen, phosphorus, arsenic, antimony, or bismuth functions

The direct substitution reaction of an amino group by an alkynide anion remains an elusive transformation, although the substitution of a phthalimido group, from the corresponding N—S bond, has been reported (Equation (108)) <1990TL6213>. The alkynyl alkenyl sulfide formed represents a member of an almost unknown class of compounds.



Organobismuth(V) reagents are known to be useful acylating reagents but a recent report confirms that they react directly with terminal alkynes in the presence of CuI to afford phenylated alkynes in modest-to-good yields (Equation (109)) <1996TL4051>. Optimum yields were obtained using CuCl as a co-catalyst and Ph₃BiF₂, whilst other bismuth reagents such as Ph₃BiCO₃ or Ph₃BiCl₂ provided considerably poorer yields.



The proposed mechanism invokes the initial formation of a cuprous alkynide species, formed from the reaction of CuCl and the terminal alkyne, which is a well-known transformation <1963JOC3313>. This then reacts with Ph₃BiF₂ to afford the pentavalent bismuth compound **129** (Figure 4) and regenerating the copper catalyst. This intermediate then collapses to afford the products of reductive coupling at the bismuth atom.

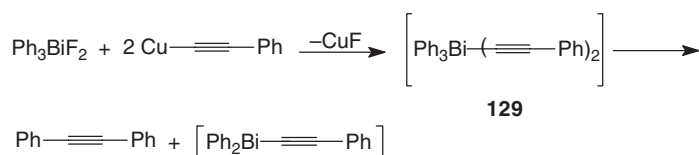


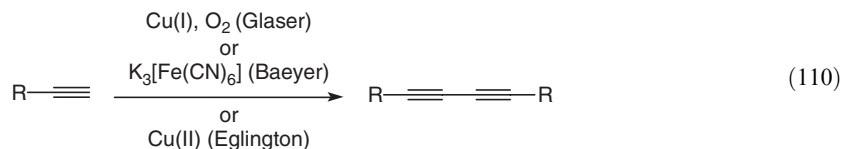
Figure 4

1.21.3.1.5 Substitution of boron, silicon, or germanium functions

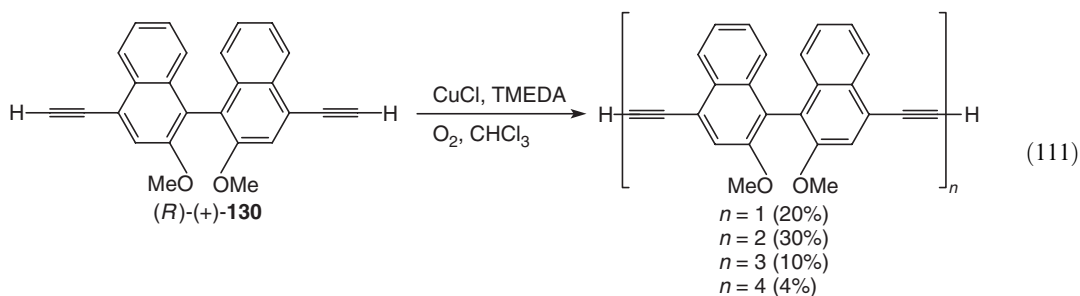
The synthesis of alkynes from substitution reactions at silicon or germanium moieties has little precedent. However, the organoboration of alkynylsilicon, alkynylgermanium, and other group 14 alkynides is a useful transformation and the reactions of these modified species have been reviewed <1995CCR125>. Lithium(1-alkynyl)organoborates, readily obtained from the reaction of organoborane or $\text{BF}_3 \cdot \text{OEt}_2$ <2003SL937> with an alkynyllithium, react with electrophiles such as iodine resulting in the migration of an alkyl, alkenyl, or aryl group from boron to an adjacent alkynyl α -carbon to form an intermediate iodovinylborane. The migration process has been modelled <2001JMS(T)213, 2001JMS(T)1>. One fate of the iodovinylborane is to undergo a β -elimination to afford a disubstituted alkyne although no recent examples of the β -elimination sequence have been reported <1991T343>.

1.21.3.1.6 Oxidative homocoupling reactions of terminal alkynes and their derivatives

The oxidative coupling of terminal alkynes has been extensively investigated as a result of the considerable utility of this reaction for the synthesis of 1,3-diynes <2000AG(E)2632>. The first reported coupling reaction of alkynes was revealed in 1869 by Glaser using copper(I) chloride in an atmosphere of air (Glaser reaction). Baeyer was able to obtain an analogous homocoupling using potassium ferricyanide as the oxidant and confirmed that the presence of dioxygen was not a prerequisite for a successful coupling reaction to occur. Eglington made further contributions in this area with the introduction of copper(II) salts as the oxidant (Equation (110)).

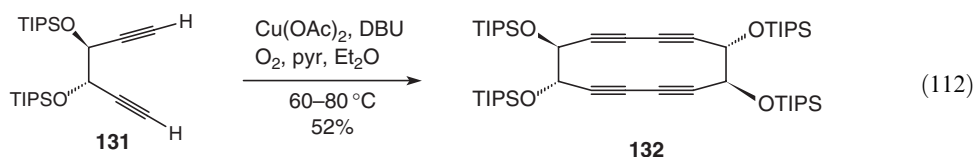


The Hay coupling procedure invariably requires an excess of the alkyne in chlorinated solvents such as CH_2Cl_2 , chloroform, or chlorobenzene. The use of a complexing agent such as TMEDA has been reported to enhance the yield of reaction and is now a common additive used for these coupling reactions. The oxidative coupling of the optically pure monomer **130** provided access to higher oligomers (dimers and trimers) that were reported to exhibit moderate optical rotations (Equation (111)) <1996TA2251>.

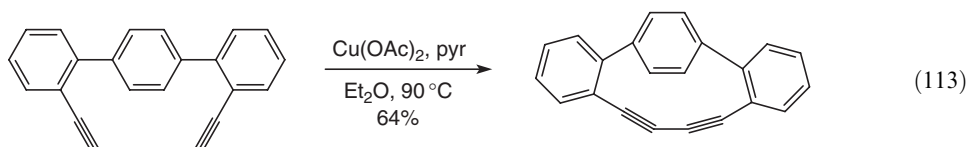


Analogous Hay coupling procedures were used to afford an extensive array of novel fullerene-alkyne derivatives <1996T4925>, axially chiral binaphthol-based oligomers <1996TL2979>, enyne macrocycles <2000JA6917>, covalent analogs of DNA base pairs <2002BMCL1055>, and novel carbonaceous materials <2002CARBON345>.

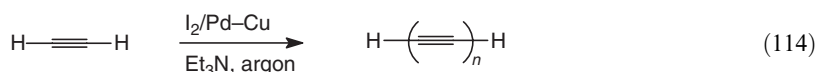
The Eglington method of effecting coupling between two terminal alkynes has recently experienced an increase in use as a result of the interesting array of molecular structures generated, many of which possess intriguing chemical, physicochemical, and biological properties. Particular applications include cyclophanes <2002TL7695>, alkyne-bridged diazulenenes <2002TL711>, dehydrobenzoannulenes <2001T3507>, and butadiyne-bridged pyridinophane derivatives <2000OL3265>. In general, the coupling reactions are conducted at elevated temperatures in solvents such as pyridine or in a CH_3CN /pyridine or water/pyridine using stoichiometric copper(II) acetate. Yields vary, but are typically 40–60%, although optimum yields have been recorded under high dilution conditions <2000OL3265>. Other applications include a concise synthesis of the bicyclic core of the chromoprotein antibiotic kedaricin. The tetrayne **132** was produced from the coupling of diyne **131** under Eglington conditions (Equation (112)) <1998TL9633>.



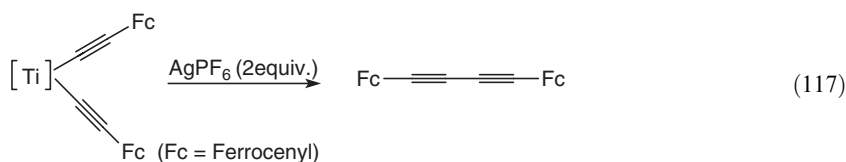
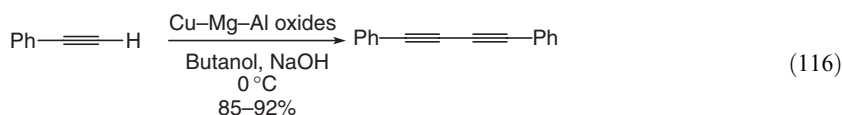
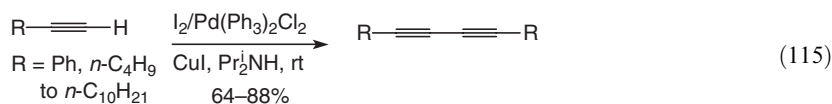
The intramolecular coupling of alkynes may be applied to the synthesis of cyclic diynes and polynes (Equation (113)) <2000OL3265>.



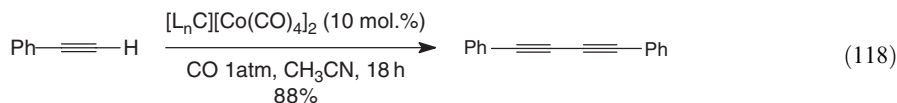
In recent years, a number of alternative methodologies have been reported for effecting couplings between terminal alkynes that serve to complement the more established procedures described above. Examples include the novel use of molecular iodine in the presence of palladium/copper catalysts (Equation (114)) <1997SM357>. This system effectively provided disubstituted butadiynes under mild anaerobic reaction conditions, which prevent oxygen from reacting with the π -conjugated system.



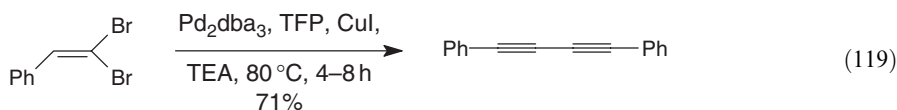
Others have used analogous conditions in the presence of an amine base (Equation (115)) <1997TL4371>. An unusual Cu—Mg—Al mixed oxide in a basic media was reported to efficiently catalyze coupling reactions (Equation (116)) <1997JCat1> as was the oxidation of a titanium complex using silver ions (Equation (117)) <2002JOM41>.



Although dicobalt octacarbonyl is known to act as an efficient catalyst for the Pauson–Khand reaction, a recent report has shown that amine-ligated cobalt complexes (L = phenanthroline, $n = 3$) afford 1,3-diynes in good yield (Equation (118)) <2001TL7733>.



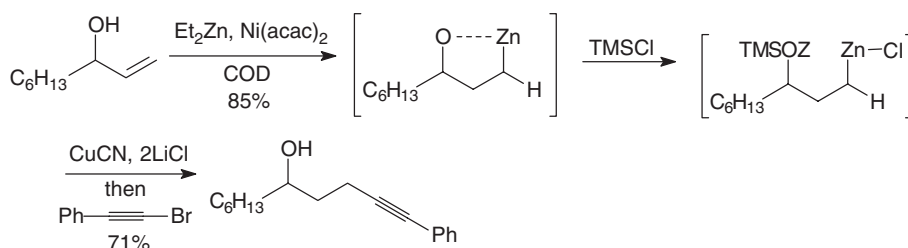
Finally, a palladium-catalyzed reaction of 1,1-dibromo-1-alkenes is included that provides symmetric 1,3-diynes using a weak ligand, tris(2-furyl)phosphine (TFP) in the presence of CuI, an important accelerator for the reaction (Equation (119)) <2000OL2857>.



1.21.3.2 Addition Reactions of Alkynyl Carbanions

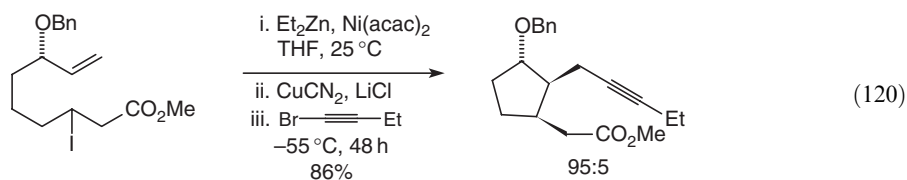
1.21.3.2.1 Addition to carbon–carbon multiple-bonded functions

Functionalized allylic and homoallylic alcohols react with organozinc and 1,5-cyclooctadiene in the presence of catalytic $\text{Ni}(\text{acac})_2$ to afford the corresponding hydrozincate. Treatment with TMSCl forms an alkylzinc halide that, upon transmetalation with copper and exposure to electrophiles, including alkynyl halides, affords the addition product in good yield (Scheme 17) <1995TL1023>.

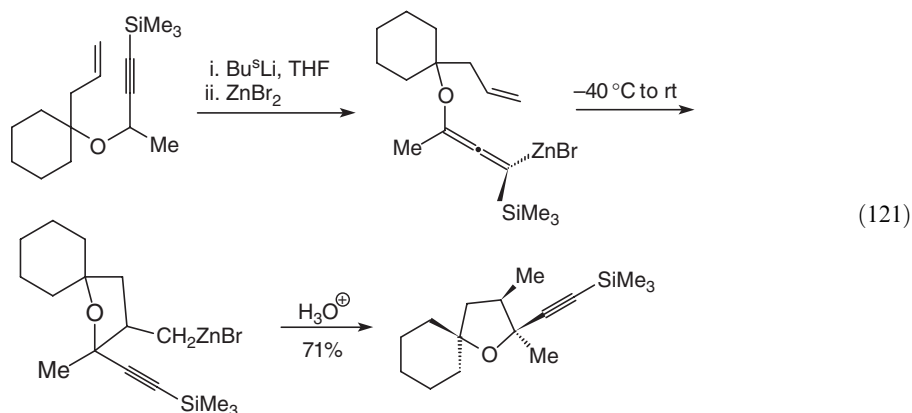


Scheme 17

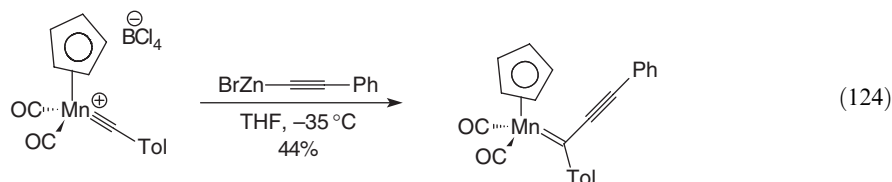
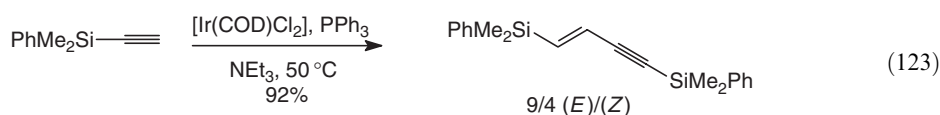
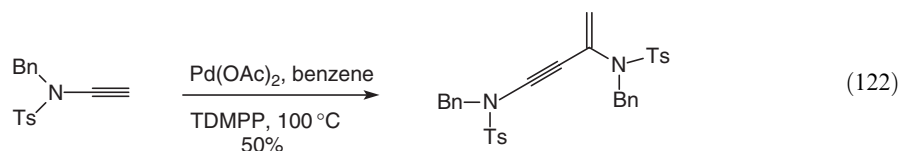
The reaction appears quite general, and intramolecular examples have been reported for the preparation of natural products such as *cis*-methyljasmonate (Equation (120)) <1995SL463>.



Substituted THFs were accessed via a novel metallo-ene-allene reaction (Equation (121)) <1995TL1263>. Treatment of alkynyl silane with base in the presence of ZnBr_2 affords the corresponding allenylorganozinc bromide which was reported to undergo a rapid, highly diastereoselective cyclization reaction to afford the tetrahydropyran in 71% yield as a single isomer.



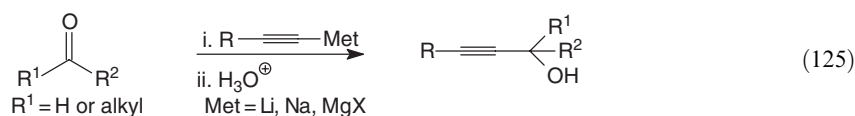
The palladium-catalyzed homocoupling of aminoynes in the presence of tris(2,6-dimethoxyphenyl)phosphine (TDMPP) (Equation (122)) <2000JOC4338>, an iridium-catalyzed dimerization of terminal alkynes (Equation (123)) <2000OM366>, and the cross-coupling of alkynyl carbenes (Equation (124)) <2003ICA320> to afford the corresponding 1,3-enynes have also been reported.



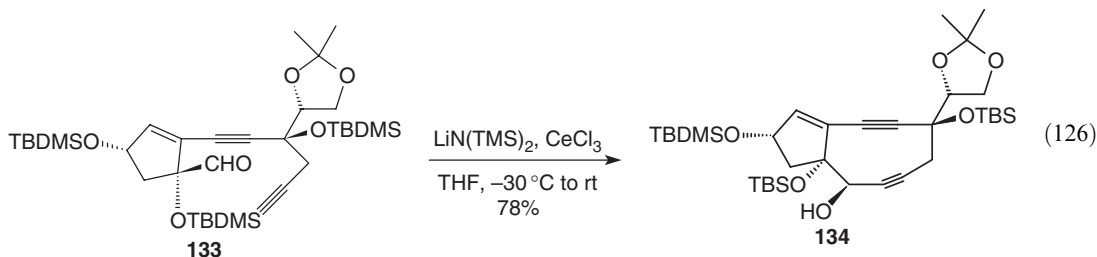
The yield of the manganese enyne carbene complex was found to depend on the purity of the initial manganese alkynylcarbene complex, with higher yields obtained when it was freshly prepared [<2001CC1690>](#). Mild heating of the manganese alkynylcarbene complex led to a dimerization reaction to afford mixtures of (*E*)- and (*Z*)-enediynes manganese complexes, which were readily released to afford the free enediyne by thermolysis at 100 °C. Reviews of heteroatom-substituted alkynylcarbene complexes are available [<2000CRV3591, 2000CCR237, 2000T1257>](#).

1.21.3.2.2 1,2-Addition to carbon–oxygen double-bonded functions

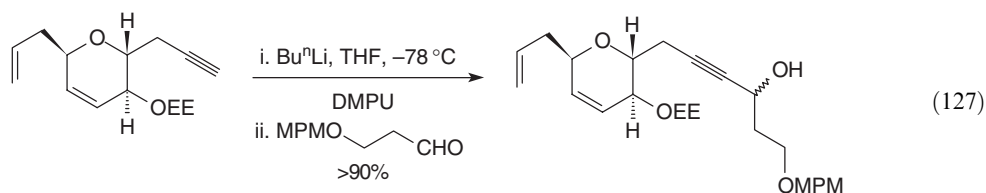
The addition of alkynyl metal reagents to carbonyl compounds including aldehydes and ketones affords α -hydroxyalkynes ([Equation \(125\)](#)). These are most frequently obtained by the action of an alkali metal alkynide or an alkynyl Grignard derivative [<1995JOC585, 1995TL401>](#) with the carbonyl compound in an appropriate organic solvent such as THF or liquid ammonia [<B-1977MI015>](#). A survey of laboratory methods for the preparation of α -hydroxyalkynes has been made [<B-2003MI016>](#).



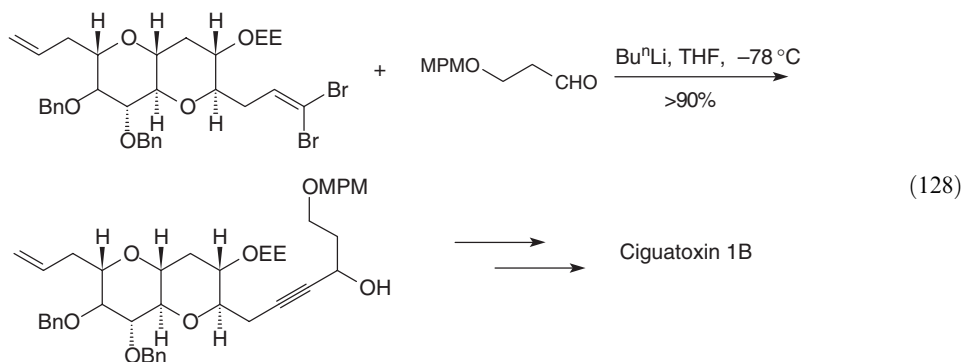
Throughout the 1990s, interest in the development of methods for cyclizing nonrigid precursors such as **133** to afford highly strained nine-membered cyclic diynes such as **134** ([Equation \(126\)](#)) [<1996TL5135>](#) emerged. The use of cerium ions in conjunction with LiN(TMS)_2 was considered to be an essential requirement for a successful cyclization reaction to take place. For optimum yields the reactions of aldehydes with alkynyllithium reagents are usually conducted at low temperatures, typically at -78°C in solvents such as THF [<2000T2203, 2002TL2725, 2002T2755>](#).



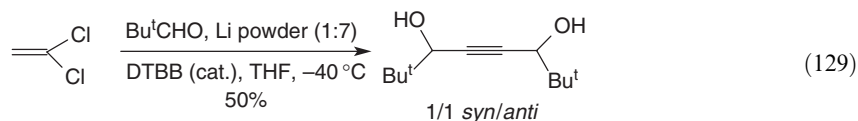
Yield enhancements have also been observed in the presence of additives such as DMPU [<1998T649>](#) ([Equation \(127\)](#)) [<2000TL5951>](#).



For some applications, the terminal alkyne may be generated *in situ* from the corresponding dibromoolefin acting as an acetylene equivalent [<1972TL3769>](#). Lithiation of the dibromoolefin, by treatment with 2.2 equiv. of butyllithium, followed by exposure of the lithium alkynide to an aldehyde affords the coupled product. This procedure was used in a highly stereoselective synthesis of the tricyclic BCD ring system of ciguatoxin 1B (Equation (128)) [<2002T1875>](#) as well as other applications [<2002T6485>](#).

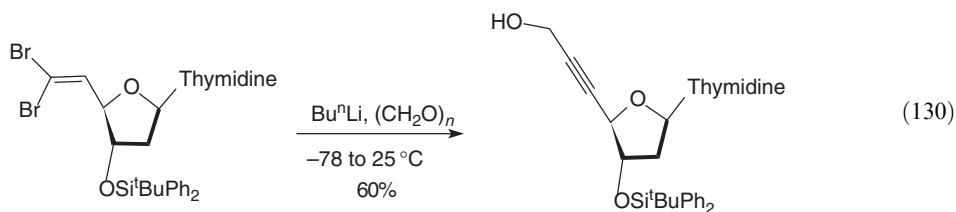


This methodology has been applied to the reaction of *gem*-dichloroolefins with lithium powder and catalytic 4,4'-di-*t*-butylbiphenyl (DTBB) in THF at -40°C . In this example (Equation (129)) [<1996T1797>](#) a 1:1 mixture of diastereoisomers were obtained upon exposure of the dianion with pivaldehyde.

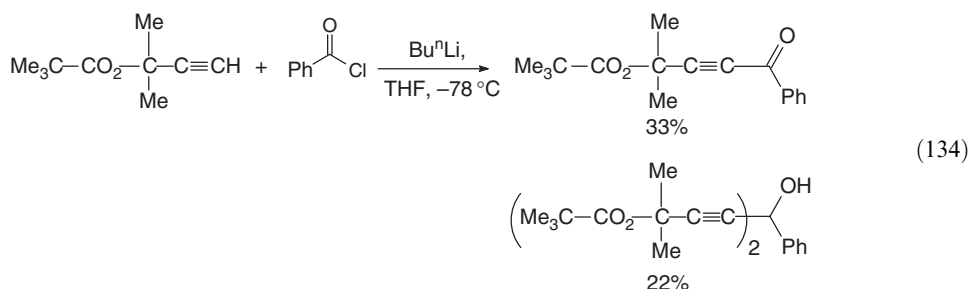
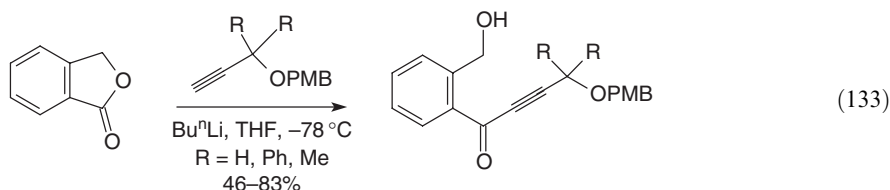
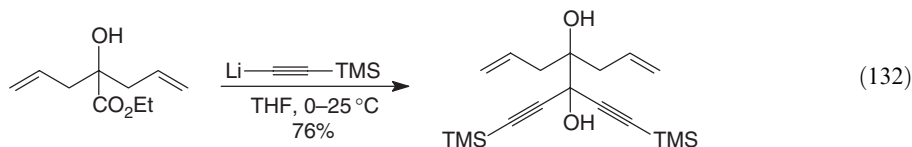
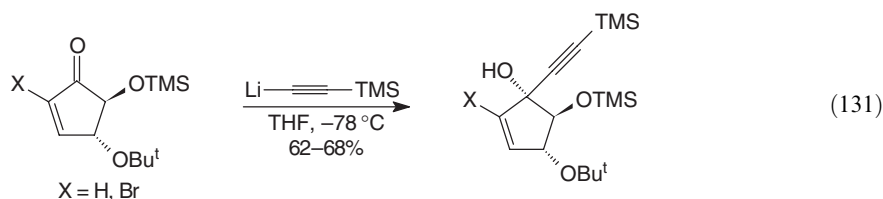


The mechanism proposed for this sequence of reactions involved the formation of a vinyl anion as a result of the first lithiation. This undergoes an α -elimination of chloride to form a carbene that then undergoes a 1,2-hydrogen shift to give an acetylene. The lithium-promoted dideprotonation of this material [<1992JOC5805>](#) followed by nucleophilic addition to the aldehyde account for the final product.

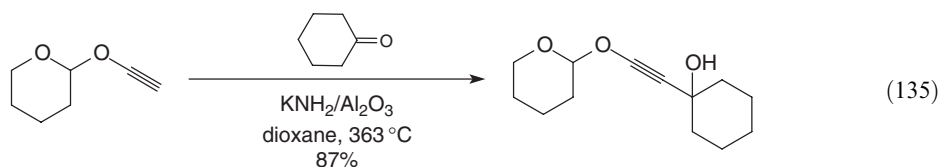
The hydroxymethylation of alkynyllithium reagents can be accomplished by employing paraformaldehyde in THF at -78°C [<1997TL7353>](#). In a recent example, the 1,2-addition reaction between paraformaldehyde and a vinylic dibromide was reported in which both the alkyne as well as the depolymerization of paraformaldehyde occurred *in situ* (Equation (130)) [<1996TL5511>](#).



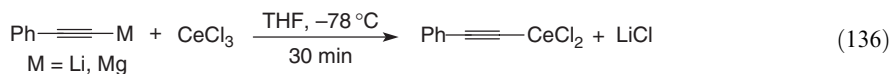
Besides regioselectively adding to aldehydes, metal alkynides also react with ketones (Equation (131)) [<2001T6295, 1995TL7391>](#), esters (Equation (132)) [<1996TL7185, 2001OL1741, 2000JA2742>](#), lactones (Equation (133)) [<1995TL897>](#), and acyl chlorides (Equation (134)) [<1993ZOB1810, 1995JCS\(D\)1686>](#).



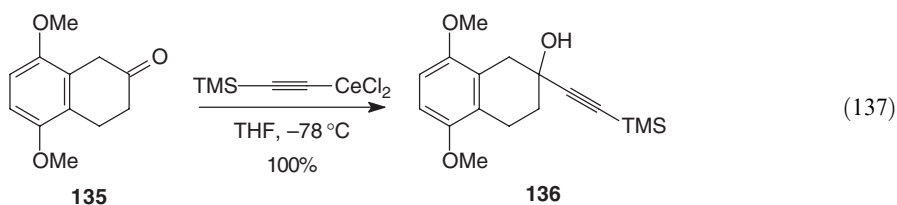
A novel approach to the 1,2-addition of alkynes to ketones employed a variety of strong solid bases to promote the synthesis of 1-alkynyl alcohols (Equation (135)) <2000AC203>. The reaction proceeds through the formation of an alkynyl anion that forms in the basic sites of the catalyst. Optimum results were obtained using the catalyst indicated with lower yields being obtained with the use of CsOH/Al₂O₃, KNO₃/Al₂O₃, KFAI₂O₃, or CaO.



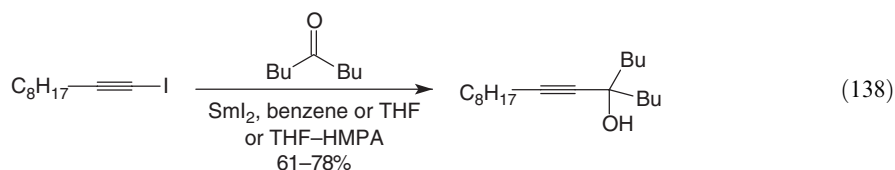
In spite of the synthetic utility of alkynyllithium and alkynylmagnesium-mediated 1,2-addition reactions to carbonyl compounds, these reactions are frequently accompanied by competing reactions such as enolization, 1,4-addition reactions in the case of α - β -unsaturated carbonyl compounds, reduction, and condensation reactions. These side-reactions are associated with the high basicity and oxidation potential of alkynyl metallic reagents. As a consequence, methods to allow normal addition reactions have been investigated. Organolanthanide reagents based upon cerium <1999T3803> and samarium <1995TL3707> have recently become popular alternatives for effecting transformations of this kind. Organocerium reagents may be formed *in situ* from the transmetallation reaction with the organomagnesium (Equation (136)) <1989JA4392> or organolithium reagent <1982CC1042> as well as from the corresponding lithium enolate <1991CJC2008>.



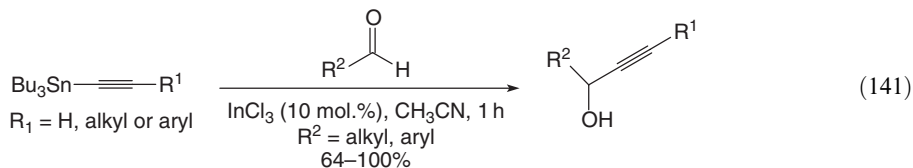
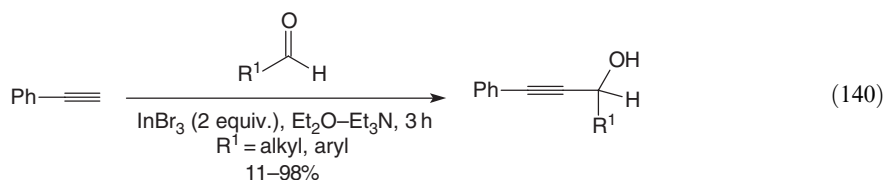
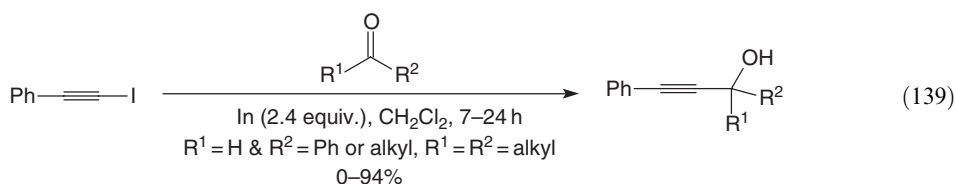
The use of organocerium reagents is known to suppress undesirable self-aldol condensation reactions of ketones. For example, the reaction of ketone **135** (Equation (137)) <1995AG(E)2046> with the alkynyl cerium reagent provided the derivative **136** in a quantitative yield. The low-temperature reaction conditions reflect the rather unstable nature of the alkynyl-cerium reagent.



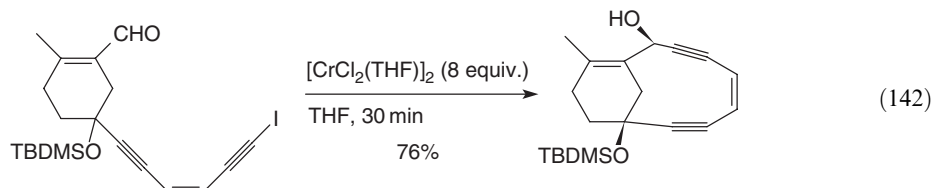
The development and use of organosamarium reagents for use under Barbier or Grignard style reaction conditions in order to effect carbon–carbon bonds have been reviewed <1999CRV745>. Methods for the generation and reactions of alkynylsamarium reagents in solvent such as THF or in a THF–HMPA couple have also been extensively reviewed <2000T9927>. The advantage in their use lies in their rapid, mild, and chemoselective reduction of organohalides and carbonyl compounds <1995TL3707> (Equation (138)).



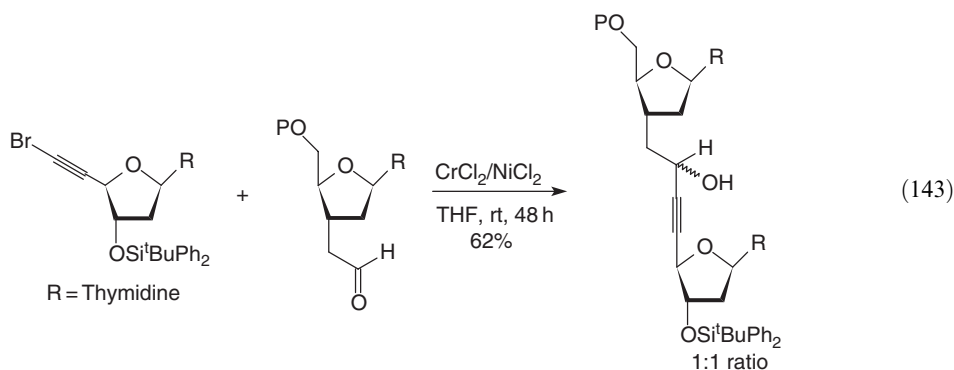
Analogous Barbier-type indium-mediated carbonyl alkynylation reactions have also been developed using solvents such as CH_2Cl_2 (Equation (139)) <2002TL5255> or diethyl ether in the presence of triethylamine (Equation (140)) <2003TL4171>. In addition, the use of catalytic indium trichloride is to catalyze the addition of alkynyl tin reagents to aldehydes (Equation (141)) <1995TL9497>. The transmetallation reaction between indium trichloride and the alkynyltin reagent was optimized in acetonitrile with the reaction appearing sluggish in solvents such as toluene or dichloromethane.



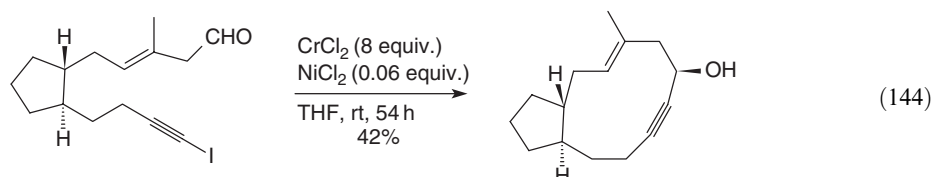
Alkynylchromium reagents also undergo chemoselective reactions with aldehydes to furnish propargyl alcohols <1997JOC7902>. The use of the preformed $[\text{CrCl}_2(\text{THF})_2]$ complex in THF <1974CI(L)164> was found to provide an enhanced yield (76%) compared to commercially available anhydrous chromous chloride (60–70%) in an intramolecular coupling reaction in a taxamycin synthesis (Equation (142)) <1998TL6139>.



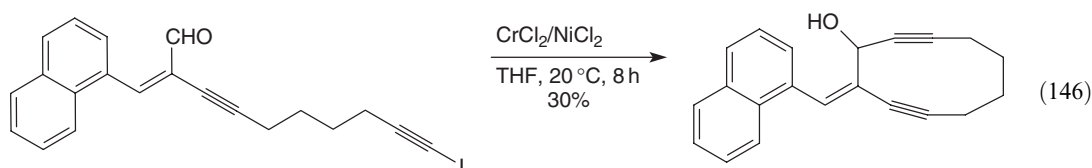
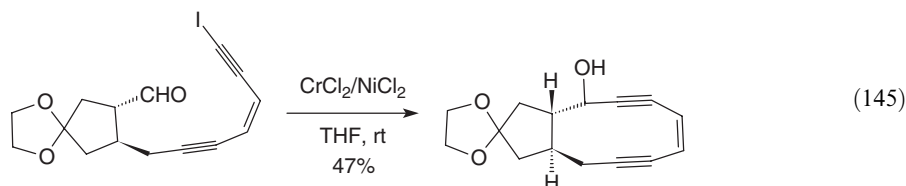
Catalytic quantities of nickel(II) chloride are often used in conjunction with chromous chloride to improve selectivity, particularly during intramolecular cyclization reactions. This modification, the Nozaki–Hiyama reaction [<1983TL5281>](#), has been applied with particular effect in the synthesis of alkynyl dimers for incorporation into oligonucleotides ([Equation \(143\)](#)) [<1996TL5511>](#).



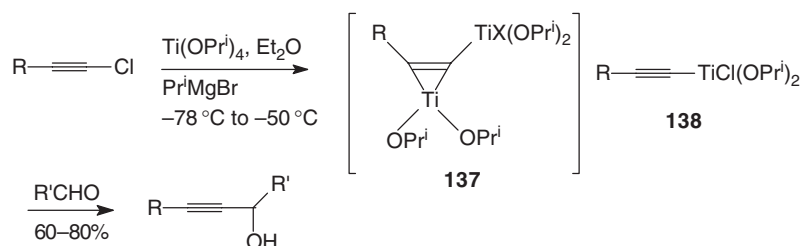
A ring-closure step to afford a bicyclo[9.3.0]tetradecane ([Equation \(144\)](#)) [<1996TL7661>](#) was reported to occur with a significantly enhanced yield when conducted by slow addition (over 54 h) of a dilute suspension of the $\text{NiCl}_2/\text{CrCl}_2$ couple that had undergone prior sonication.



Alkynylchromium reagents have also been described to effect intramolecular cyclization reactions via addition to enolizable aldehydes to effect efficient syntheses of eight-membered ([Equation \(145\)](#)) [<2002TL4947>](#) and 10-membered ([Equation \(146\)](#)) [<2001TL4211, 2002TL6521, 1997TL5583, 1997TL5507>](#) enediyne ring systems.

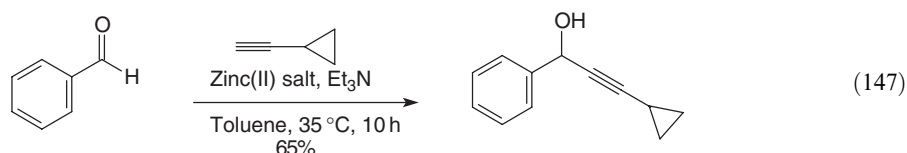


The synthesis of functionalized metallated alkynes has been described that were synthesized via the use of low-valent titanium derivatives ([Scheme 18](#)) [<2000POL563>](#). An alkynyltitanium derivative **138** was suggested that itself was derived from the chlorotitanacyclopropene **137**. The metallated alkyne **138** exhibited remarkable functional group tolerance including groups such as esters, sulfones, and halides. Exposure of the metallated alkyne to an aldehyde provided access to propargyl alcohols in good yield.

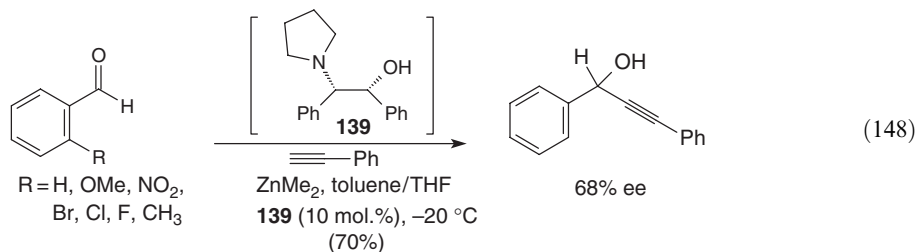


Scheme 18

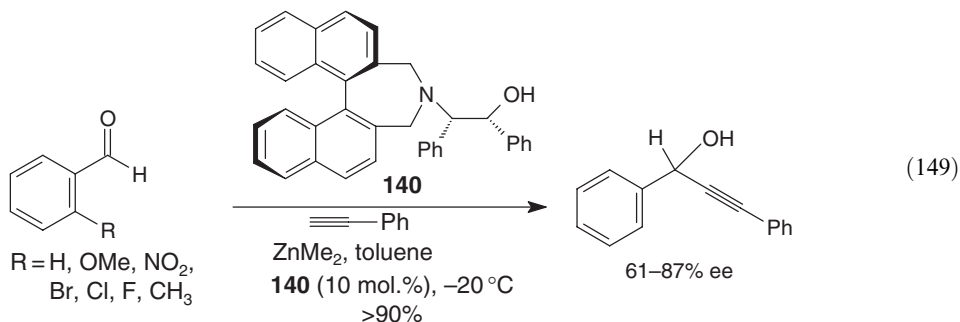
As a general method to attenuate the reactivity associated with the use of basic alkynyl metals, such as alkynyllithium, alkynylpotassium, and alkynylmagnesium reagents, alkynylation of aldehydes using a Lewis acid in combination with a base has proved useful. Examples include $SnCl_4$ <1992CL2479>, GaI_3 <1995TL7277>, and $Zn(OTf)_2$ <2001JA9687>. However, recent studies suggest that the use of either zinc dust <2000TL2339> or zinc chloride <1999TL723> provides an inexpensive as well as an efficacious alternative reagent. In methods that use $ZnCl_2$ as a promotor (Equation (147)) <2002TL8323>, triethylamine is often added to the reaction mixture as a co-promotor. Under these mild reaction conditions, alkyl ketones were also observed to undergo the alkynylation reaction in high yields. However, for activated substrates, prone to enolization, the alkynylation reaction was inhibited, and thus reaction with phenyl acetone occurred in only 10% yield although with trifluoroacetylbenzene the reaction took place in 60% yield.

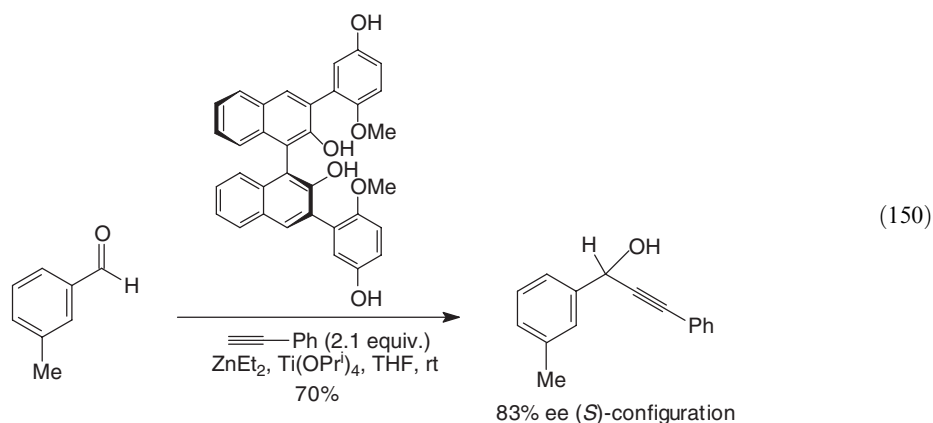


Enantioselective alkynylation reactions to aromatic aldehydes have been reported. These reactions have been catalyzed by a variety of moieties that include chiral amino-alcohol-based ligands such as **139** Equation (148) <1999S1453>.

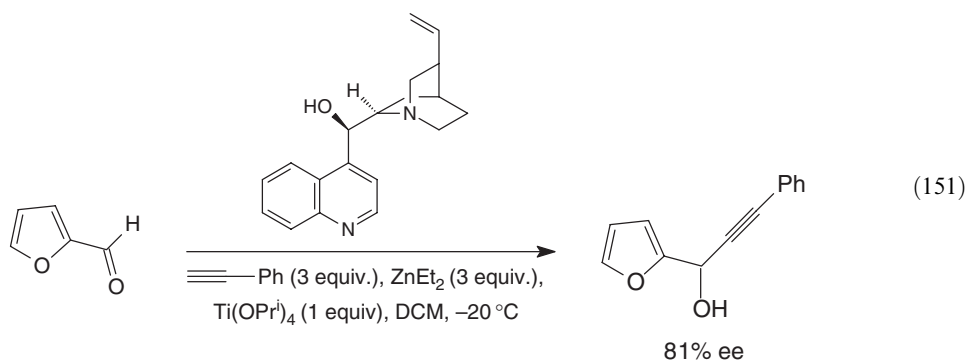


A corresponding binaphthylamino alcohol **140** provided good levels of selectivity (Equation (149)) <2001TA2147> as did a 1,1'-binaphthyl-catalyzed alkynylzinc (Equation (150)) <2002TL8831>. A chiral BINOL/ $Ti(OPr^i)_4$ catalyst, in the presence of phenolic additives, was used in analogous transformations to provide propargyl alcohols with levels of enantioselectivity up to 99% <2003TA449>.





A 1,2-addition of phenyl acetylene to aldehydes in the presence of cinchona alkaloids such as cinchonidine reported modest-to-good enantiomeric excesses (Equation (151)) <2003TL5347>.



Three types of catalysts, based upon palladium complexes such as $\text{PdCl}_2\text{--CuCl}_2$, have been employed in syntheses of esters of 2-alkynoic acids via an oxidative carbonylation process <1998ICA202>. It is speculated that the alkynylpalladium species plays a key role although the pathways to this intermediate are dependent upon the catalyst and co-catalyst used and the way they activate the C—H bond in the alkyne.

1.21.3.2.3 1,2-Addition to carbon—chalcogen double-bonded functions

Thiocarbonyl compounds such as thioketones, thioaldehydes, and thioesters normally add carbon nucleophiles at the heteroatom of the C=S bond (thiophilic attack) <1988ZC269>. In a recent study investigating stereoselective addition reactions to ruthenium thioaldehyde complexes (Figure 5) <2002JOM129>, access to the sulfur atom was blocked by the ruthenium complex, thus directing any attacking nucleophile to the adjacent carbon atom. Anionic carbon nucleophiles such as deprotonated β -dicarbonyls as well as vinyl, allyl, and benzyl Grignard reagents added smoothly to afford neutral ruthenium complexes of secondary thiolates (for other examples to this transformation the reader is directed to <1995COFGT1058>).

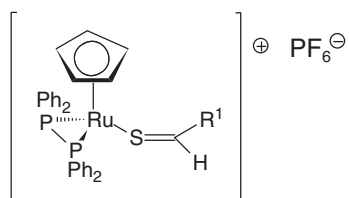
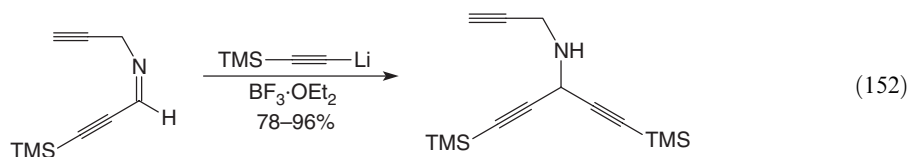


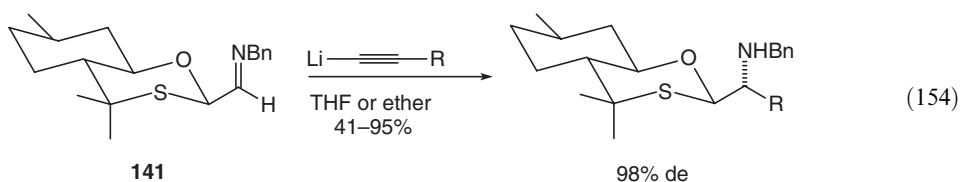
Figure 5

1.21.3.2.4 1,2-Addition to carbon—nitrogen multiple-bonded functions

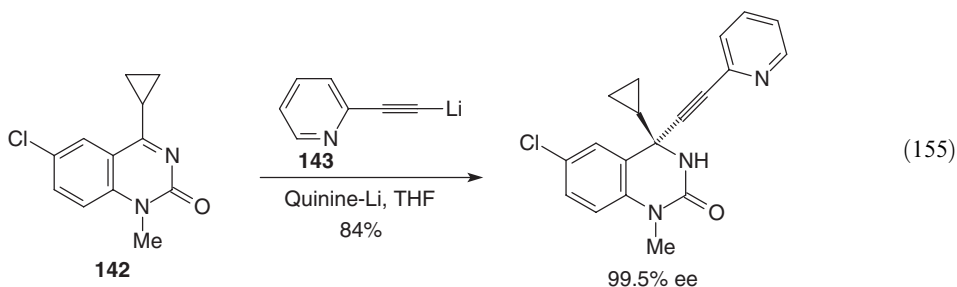
Alkynes and alkynylmetallic reagents undergo addition reactions with a range of carbon—nitrogen multiple-bonded moieties, although in this section the focus will be upon their reactions with aldimines, nitrones, oximes, pyridinium salts, and quinolines. As a general observation, imines exhibit low reactivity in nucleophilic addition reactions with ethynides due to the low electrophilicity of imine carbon atom and, where applicable, competing deprotonation reactions. However, activation toward nucleophilic addition may be accomplished by the addition of a suitable coordinating Lewis acid such as $\text{BF}_3 \cdot \text{OEt}_2$. The use of this coordinating group (Equation (152)) <1994JOC6133> as well as stoichiometric $\text{ZnCl}_2/\text{Et}_3\text{N}$ in the presence of 1.5 equiv. TMSCl (Equation (153)) <2003TL6767> has been successfully utilized.



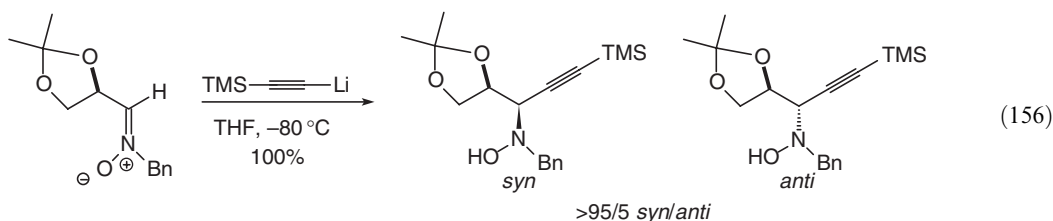
Other examples include the use of enantiopure imines where outstanding diastereoselectivities (>98%) were reported using the 1,3-oxathiane **141**, irrespective of the nucleophile used and in the absence of any activating additives (Equation (154)) <1994CL831>.



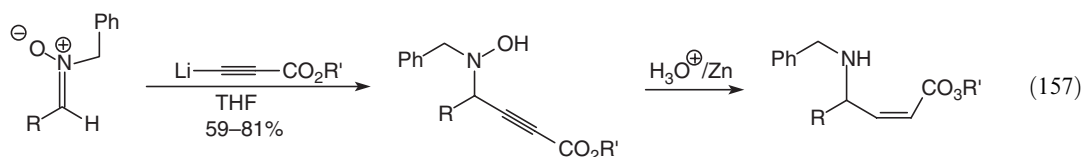
Ligand-induced enantioselective additions, using the lithium alkoxide of quinine, have been used effectively to ensure high levels of selectivity in the addition of the lithium alkynyl **143** to the cyclic *N*-acylketimine **142** (Equation (155)) <1995JOC1590>.



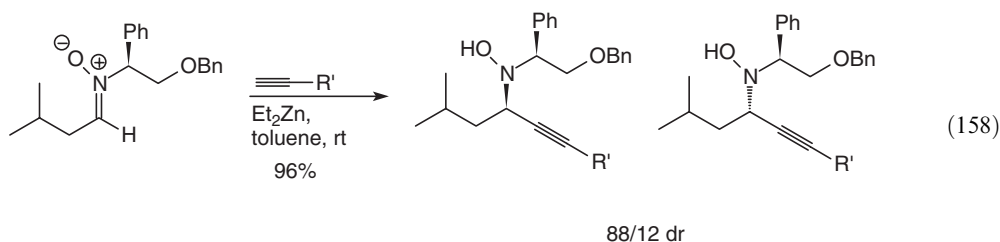
The 1,2-addition reaction of terminal alkynes to nitrones is a useful method to access propargylic *N*-hydroxylamines which, themselves, represent versatile intermediates for the synthesis of natural and biologically active compounds. The first totally stereocontrolled addition of ethynyl organometallics to a nitrone derived from D-glyceraldehyde, has been reported in a stereoconvergent synthesis of propargylamines (Equation (156)) <1996TA1887, 1997TA3489>. In the absence of any Lewis acid, a quantitative yield of the *syn*-isomer was obtained. In contrast, pretreatment of the nitrone with a Lewis acid such as Et_2AlCl reversed this selectivity to favor the *anti*-hydroxylamine as the major product in a slightly reduced yield. The hydroxylamines were readily desilylated and deoxygenated to afford enantiomerically pure propargylamines.



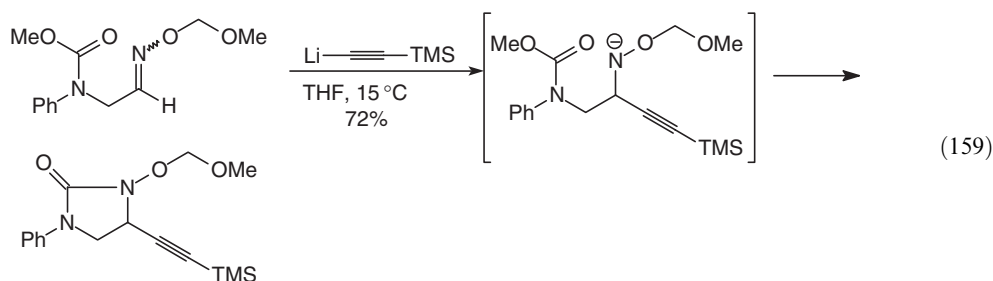
Nitron cyclization reactions involving lithium propiolates were used to access γ -*N*-hydroxyl-amino- α,β -acetylenic esters (Equation (157)) <1999SL602, 1997TL5503>. Treatment of the resulting hydroxylamine with zinc in MeOH—CH₃COOH was not only effective in cleaving the N—O bond but also effected the hydrogenation of the triple bond to afford the corresponding (*Z*)- γ -amino- α,β -ethylenic ester exclusively.



The diastereoselectivity in the addition of terminal alkynes to nitrones (bearing a chiral auxiliary) is facilitated by addition of diethylzinc (Equation (158)) <2003TA525>. The diastereoselectivity depends upon the substituent R' and upon the nature of the auxiliary. Optimum diastereoselectivity was obtained when R' was butyl (88:12); however, enhancement in the selectivity was observed when an *N*-glycosynitron was employed (>95:5). The major diastereoisomer of the propargyl *N*-hydroxylamine was found to be (*R*)- in all cases. It was suggested that this occurs via a chelated transition state involving the coordination of zinc to the heteroatom of the chiral auxiliary which directs a preferred attack onto the Si-face of the nitron.

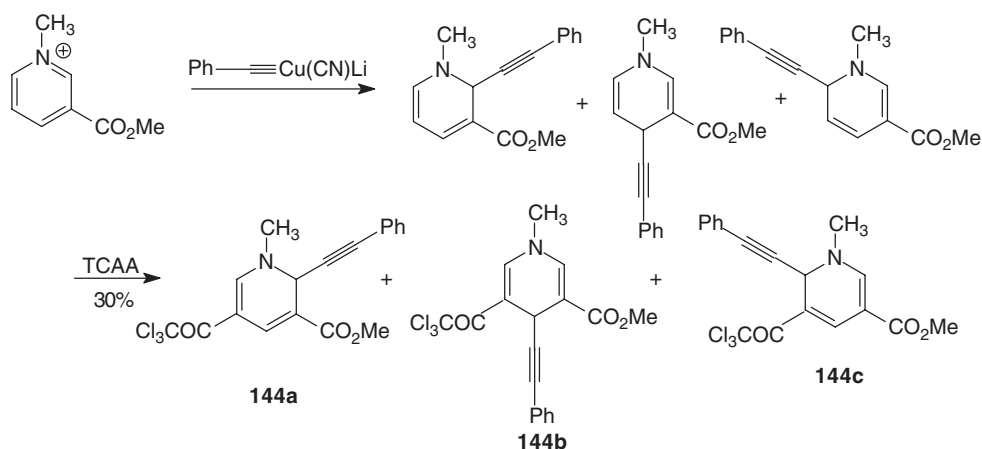


In general, oximes and hydrazones exhibit low reactivity toward addition reactions with alkynyl organometallics. However, pretreatment with Lewis acids activates the carbon—nitrogen bond sufficiently to facilitate attack. It was recently reported that the addition of nucleophilic lithium salt derived from (trimethylsilyl)ethyne was accomplished in the absence of any added precomplexing agent (Equation (159)) <2000T3697>. Addition of the lithium alkynyl salt to oxime affords an *N*-anion, which undergoes an intramolecular cyclization reaction via attack onto the carbamic ester to afford ethynyl-substituted cyclic ureas in modest-to-good yields.



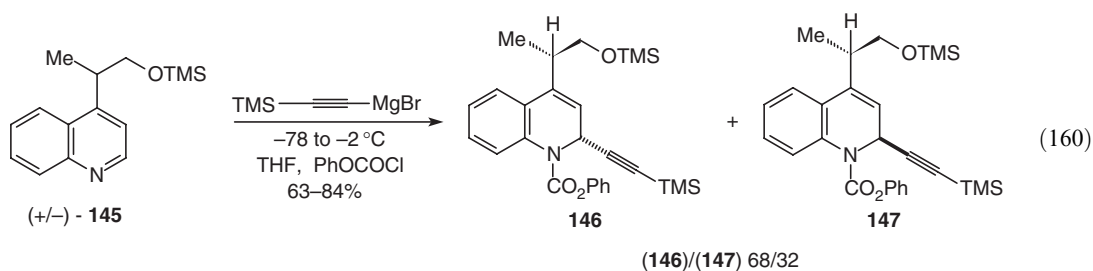
Pyridine and other heterocyclic nitrogen-containing compounds, possessing an azomethine motif, have been reported to undergo addition reactions with alkynyl organometallic reagents via the corresponding iminium ion. The addition of an alkynylcopper reagent was reported to

react chemoselectively at the α -position in a range of *N*-methylpyridinium salts to provide access to polysubstituted dihydropyridines (Scheme 19) <2001TL585>. In contrast to the selectivity observed with alkyl cuprates, reaction with phenylethynyl copper reagents reacted preferentially at the α -position to provide mixtures of the C-2 and C-6 adducts, **144a** and **144c**, upon acylation with trichloroacetic anhydride (TCAA). The ratio **144a**:**144c** varied markedly upon the nature of the cuprate. Thus, zinc cyanocuprate provided isomer **144c** exclusively in very low yield, whereas reaction with lower-order cyanocuprates provided equimolar mixture of **144a** and **144c** in yields of 68%.

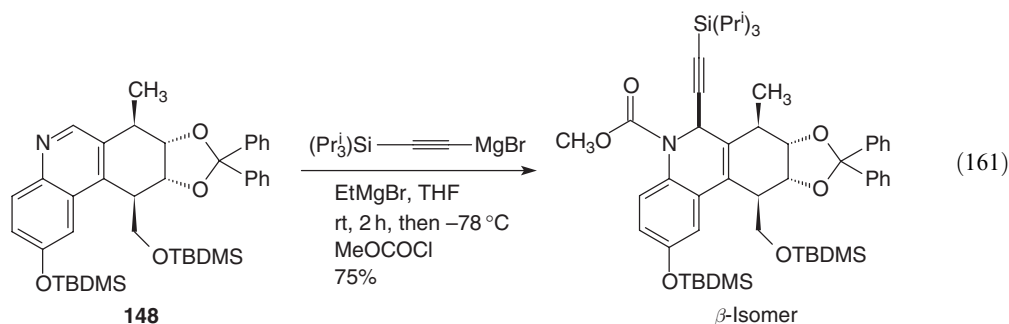


Scheme 19

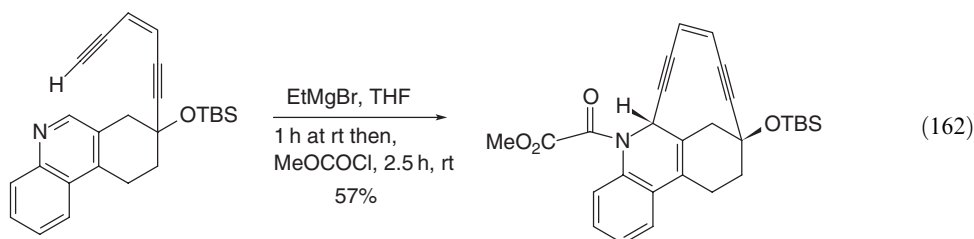
Magnesium alkynyl reagents have been reported to undergo exclusive regioselective attack at the C-2 position of 4-substituted quinolines such as **145** (Equation (160)) <2002TA2703>. The low electrophilicity associated with the heterocycle was enhanced and optimized by preforming the reaction in the presence of phenyl chloroformate. The reaction was found to be very regioselective for C-2, although attack at C-(4) was observed when the corresponding cerous alkynide was used. In all examples, the diastereoselectivity was moderate favoring the formation of **146** over **147**.



The propensity for quinolines, pyridines, and isoquinolines to undergo nucleophilic addition reactions with organometallic species at C-2/C-4 is well known. This observation has become increasingly significant since the discovery of enediynes, such as dynemycin A, which contain the quinoline motif as a key structural feature. An analogous diastereoselective addition to the quinoline **148** was also achieved via activation of the $\text{C}=\text{N}$ bond using methyl chloroformate (Equation (161)) <1994JOC3752>. X-ray analysis, performed upon the major product, confirmed that the magnesio(triisopropylsilyl)alkynide attacked from the β -face of **148**, consistent with the natural product.

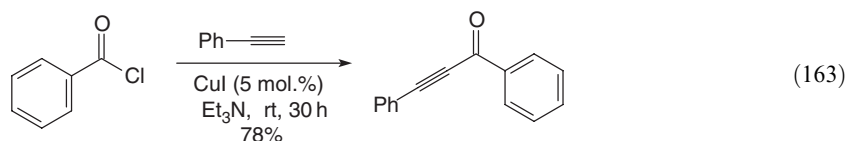


The extension of this chemistry to include intramolecular cyclization reactions is referred to as the Reissert reaction and this was used in order to gain access to the enediyne core structure of dynemicin (Equation (162)) <1996TL8687>. The key step involved the intramolecular addition of the anion of (*Z*)-1,3-diyne-2-ene to an *N*-acyltetrahydrophenanthridinium intermediate. The key Reissert-type cyclization reaction was conducted under high dilution in THF. The metallation itself was carried out, with EtMgBr, whereupon methyl chloroformate was added to afford complete cyclization within 3 h at room temperature. Reversal of these addition steps led to the formation of significant quantities of by-products.

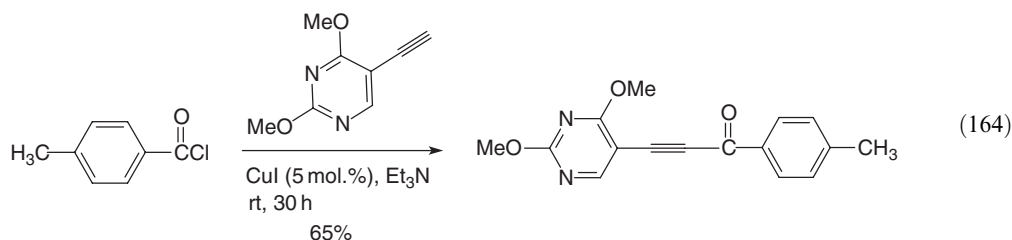


1.21.3.2.5 1,2-Addition–elimination reactions

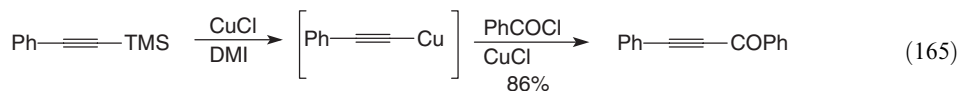
The reaction of carboxylic acid derivatives, such as acyl chlorides, with alkynyl organometallic reagents provides a facile, direct, and convenient route for the synthesis of conjugated alkynones <1999T4177>. As a general observation, the high basicity and reactivity of the group 1 and group 2 alkynyl metal reagents often results in low yields as a result of enolization and further reaction of the ketone. Copper(I) salts have been reported to act as useful catalysts for the synthesis of α,β -unsaturated alkynyl ketones via reaction of 1-alkynes with acyl halides (Equation (63)) <1996TL7323>.



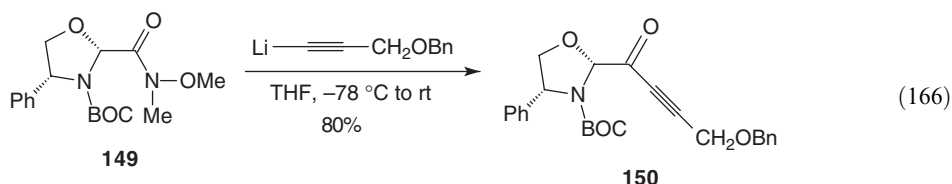
The same group of researchers have extended these studies to include uracil derivatives. The advantage of the mild methodology (Equation (164)) <1999T7011> was the uses of Et₃N as both a base and solvent at an ambient temperature. These conditions, using terminal alkynes, proved more efficient than other more traditional metallated alkynides <1984TL2411>, silylated <1963CB3280> or stannyl derivatives <1982JOC2549>.



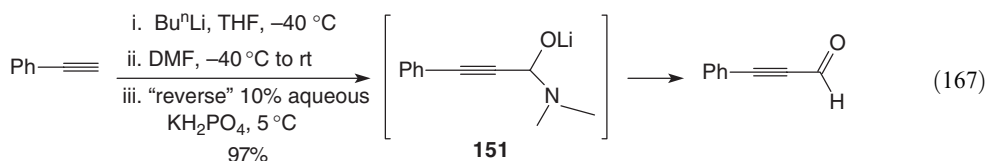
Mechanistically, the alkynylcopper salt, formed from the reaction of the terminal alkyne with cuprous iodide and Et_3N , reacts with the acyl chloride to form an alkynyl ketone liberating copper(I) chloride in the process that can then perpetuate the reaction. Furthermore, the reaction was found to proceed without the formation of alkynyl dimers that can be formed in the analogous palladium-catalyzed reaction of terminal alkynes <1997JCS(P1)2815>. Complementary investigations reported the direct alkynyl transfer from silicon to copper <2001JOM282> and the application of the copper species formed to the synthesis of alkynyl ketones catalyzed by CuCl (Equation (165)) <1997TL3977>. Addition of 1-phenyl-2-(trimethylsilyl)ethyne, to a suspension of CuCl in dry 1,3-dimethyl-2-imidazolidinone (DMI), precipitated the corresponding alkynylcopper reagent as a yellow powder in the absence of fluoride ions. Exposure of the alkynylcopper reagent to acid halides, in the presence of CuCl , gave the corresponding alkynyl ketones in good yield.



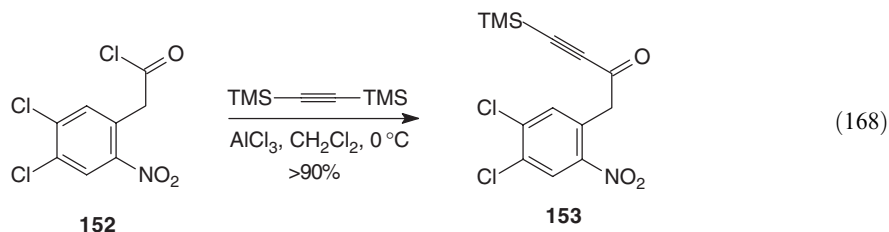
Lithium alkynides have been shown to react with the Weinreb amide **149** to provide the corresponding 2-acyloxazolidine **150** in good-to-excellent yields (Equation (166)) <2000T367>. Optimum yields of the alkynone **150** were obtained by application of a reverse quench of the reaction mixture with a phosphate buffer. Diminished yields and considerable by-products result if this step was omitted.



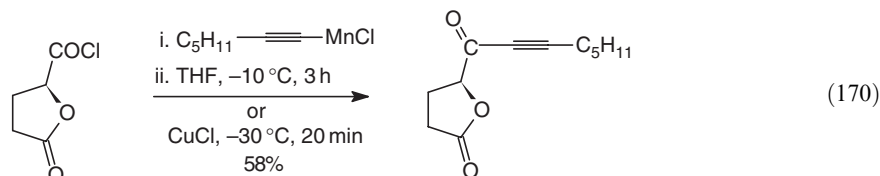
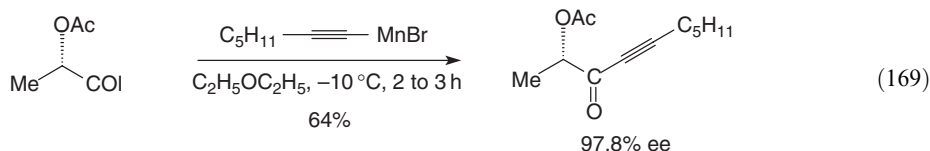
The first reported use of this phosphate reverse quenching procedure occurred in a highly efficient synthesis of α,β -alkynyl aldehydes from terminal alkynes using N,N -dimethylformamide as the source of a formyl group (Equation (167)) <1998TL6427>. The distribution of products obtained was found to be very dependent upon the reaction conditions used for the hydrolysis step. This step was optimized for the aldehyde by the efficient trapping of the strongly nucleophilic dimethylamine intermediate, obtained from the collapse of **151**, via a reverse addition of the reaction mixture into a phosphate buffer solution. This modification provided the alkynals in virtually quantitative yield.



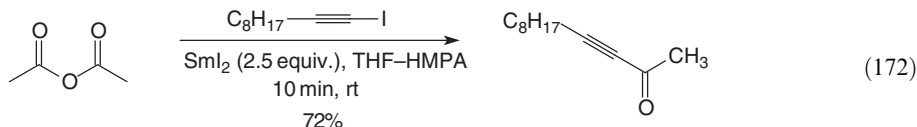
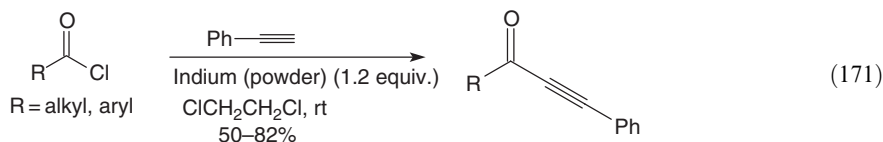
In a recent approach toward the synthesis of osteoclast inhibitor SB-242784, the acyl chloride **152** was efficiently transformed into alkynone **153** with bis-trimethylsilylacetylene in the presence of stoichiometric quantities of aluminum chloride (Equation (168)) <2003TL3081>. The product from this step was sufficiently pure to be used crude in the next step.



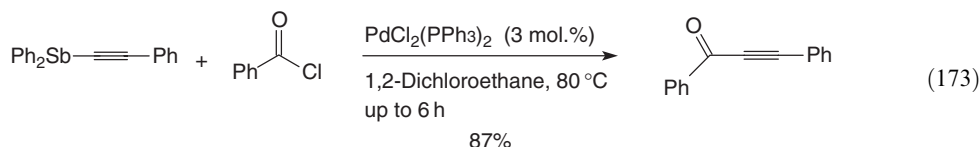
Besides the alkynylaluminum organometallics, the asymmetric reaction of organomanganese reagents with acyl chlorides has also been used for the preparation of α -acyloxy ketones from α -hydroxy amino acids (Equation (169)) <1995TL6449> as well as the enantioselective synthesis of δ -ketobutanolides from (L)-glutamic acid (Equation (170)) <1997TA1373>.



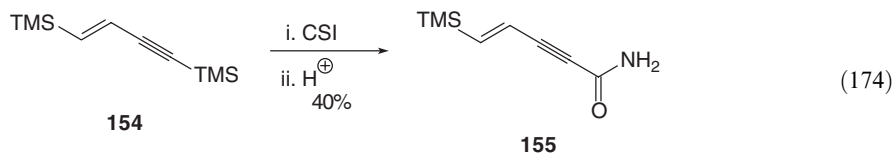
Other transition metals have also played an important role in the development of methods for the synthesis of alkynones including the recent report into the synthesis of propargyl ketones from aldehydes via an indium-mediated alkylation reaction <2002TL5255> followed by an indium-mediated Oppenauer oxidation (Equation (171)) <2003TL819>. Alkynylsamarium reagents have also been reported to afford alkynyl ketones from their reaction with acid anhydrides in THF–HMPA (Equation (172)) <2000T9927>.



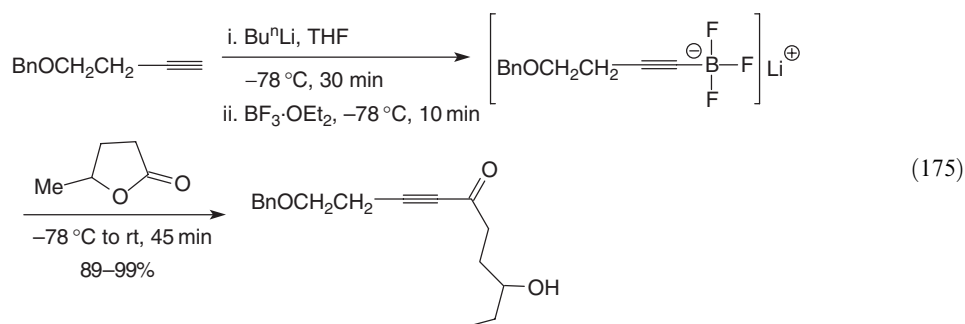
In contrast, the reaction with acid chlorides and activated esters was unsuccessful, affording the corresponding bis-decynylated tertiary alcohol instead. The first reported coupling of trivalent organoantimony alkynides with acid halides using palladium catalysis has been revealed (Equation (173)) <2000TL4143>. These studies confirmed that alkynyl ketones resulted even in the absence of the palladium catalyst, although the yields were substantially diminished. Reaction rates were enhanced in polar solvents such as acetonitrile and HMPA and the coupling was sensitive to the palladium species used, with optimum yields being obtained with $\text{Pd}(\text{PPh}_3)_4$ and $\text{PhCH}_2\text{PdCl}(\text{PPh}_3)_2$. Complete substituent selectivity was observed in the cross-coupling reaction resulting in only the alkynyl moiety being transferred from the antimony reagent.



Exposure of the bis-silylated enyne **154** with chlorosulphonylisocyanate (CSI), followed by an acidic work-up, has proved to be a useful method for the synthesis of monosilylated amides such as **155** (Equation (174)) <1998T12399, 2002T9547>.



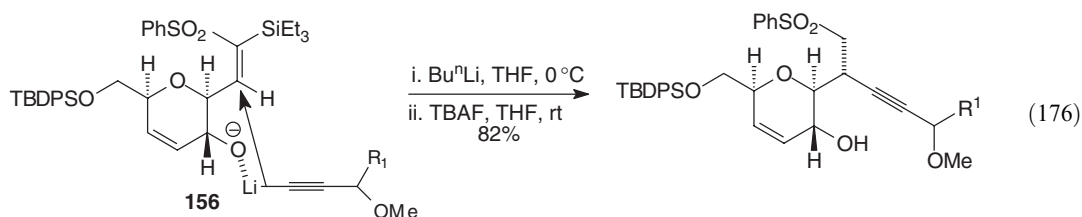
The ring opening of lactones, with alkynyltrifluoroborates, has recently been revealed as a new, highly efficient, route to functionalized α -alkynones (Equation (175)) <2003SL937>. Using this reaction with the alkynyllithium failed to deliver any of the desired products, but the corresponding borate effectively and regioselectively ring-opened five- to seven-membered lactones in quantitative yields.



In a mechanistic investigation into terminal alkyne activation processes, the precise role of catalytic palladium complexes has been studied. The complexes used in these studies were involved in the synthesis of alkynylcarboxylic acids from monosubstituted alkynes via oxidative carbonylation reactions <1998ICA202>.

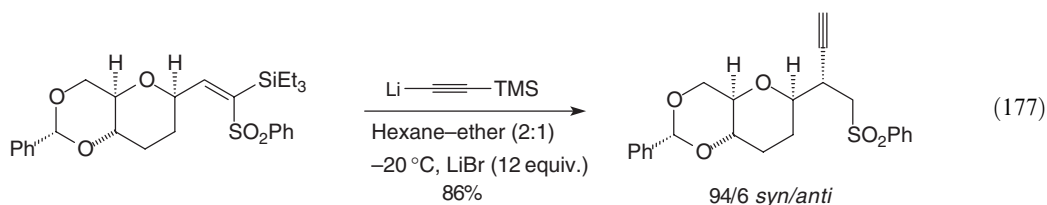
1.21.3.2.6 1,4-Addition reactions

There are a limited number of methods for securing the conjugate addition of terminal alkynes, or the corresponding alkynyl metal derivatives, to α,β -unsaturated carbonyls and sulfones. As a general observation group I and II metal alkynides do not undergo 1,4-addition reactions very successfully however, exceptions to the rule have been reported that involve the heteroconjugate addition of lithium alkynides to α -silyl- α,β -unsaturated sulfones (Equation (176)) <2000T5391, 2000SL587>. It was anticipated that the lithium alkynide would undergo 1,4-addition to the α -silyl- α,β -unsaturated sulfone **156** via β -chelation. Thus, 1,4-addition of the lithium alkynide salt to a THF solution of **156** took place in 82% yield to afford the desired product as a single adduct.

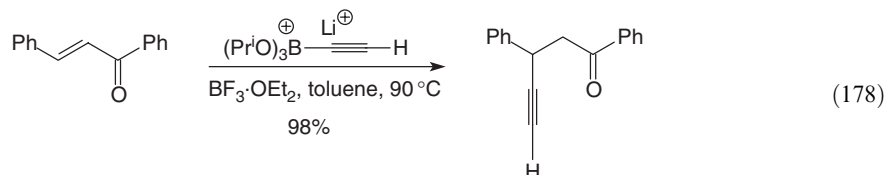


The optimized experimental conditions developed during these studies were recently utilized in a synthesis of a ring fragment of ciguatoxin <2003T6851>.

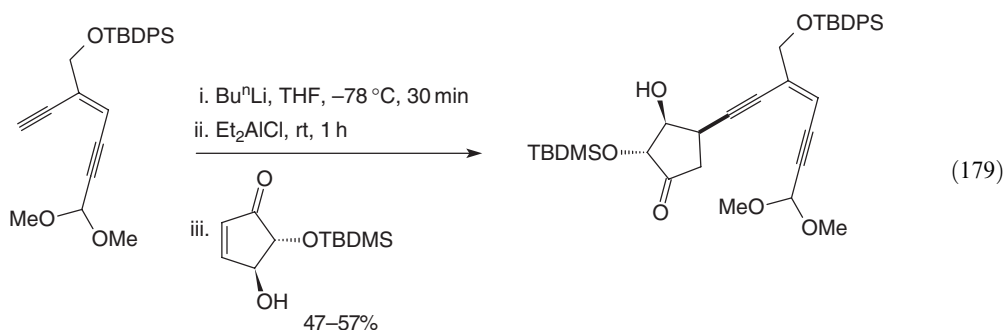
Previous results obtained from the synthesis of the spiro-component of tautomycin established the dependence of the heteroconjugate addition reaction upon the solvent/co-solvent and the types of salt additives (Equation (177)) <1996T2877>. Thus, the use of HMPA as a co-solvent, essential for some syntheses, was unnecessary and using ether gave only 20% of the desired adduct with low selectivity. However, the mixed solvent of choice provided better *syn/anti*-selectivity. The addition of LiBr to the reaction mixture facilitated the reaction suggesting the formation of a cluster complex between the substrate, reagents, salt, and the solvent system.



Alkynylboronates have also been reported to undergo 1,4-addition reactions to conjugated enones. The exposure of a stable borate, prepared from the reaction of lithium alkynide and triisopropylborate, with $\text{BF}_3 \cdot \text{OEt}_2$, provides the corresponding boronate. In the presence of an enone the transfer of the alkynyl moiety, from the boronate, to the enone occurred to afford γ -alkynones (Equation (178)) <1999T14233>. Optimum yields were obtained by conducting the experiments in toluene, as solvent, at 90 °C.

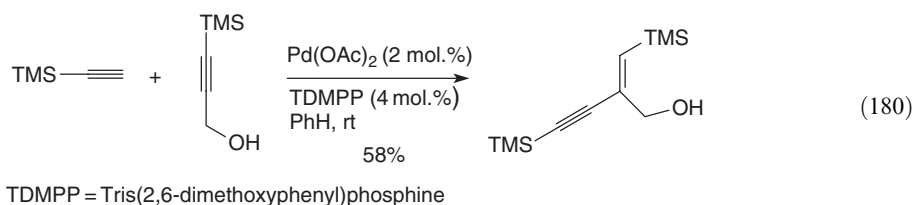


Diethylalkynylalanes react with conjugated enones to provide access to 1,4-addition products (Equation (179)) <1997TL2355, 1999T2737>. In general, the method is limited to enones that can assume a *cisoid*-geometry. For substrates, such as cyclic enones, in which the geometry is fixed in a *transoid*-array, 1,2-addition rather than 1,4-addition is observed.

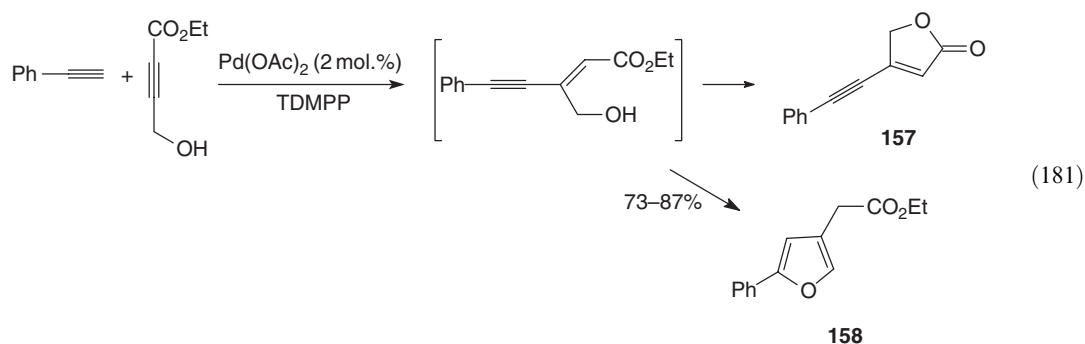


For enones such as this, bearing a C-4 hydroxyl-directing group, alkynylalanes have been observed to be delivered to the same face as the hydroxyl group to provide an intramolecular stereoselective bias to the addition. Further studies on the topic, using functionalized enones, serve to emphasize the generality of this protocol <2001T6295>.

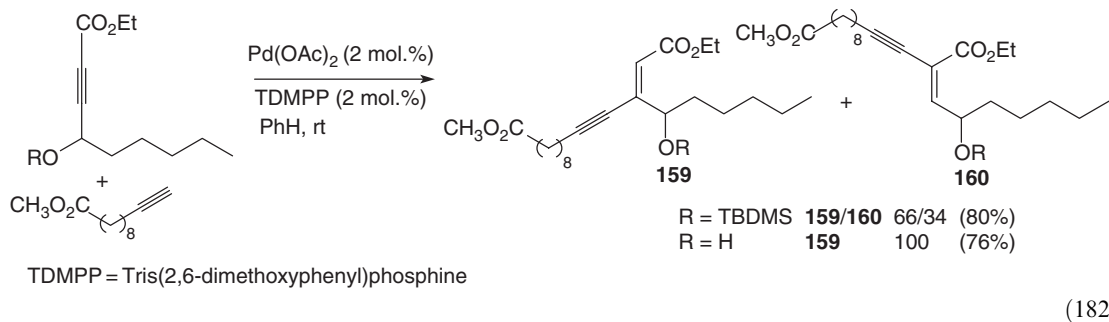
The combination of a palladium-catalyzed addition of a terminal alkyne to an internal alkyne has been revealed as a method for accessing enediynes even in the absence of conjugating substituent (Equation (180)) <1997TL3207>.



The same conditions were employed for analogous additions to γ -hydroxyalkynoates as a means to access 2,4-disubstituted furans. For these particular substrates the ratio of the palladium salt to the ligand, tris(2,6-dimethoxyphenyl)phosphine (TDMPP), was crucial to the outcome of the reaction (Equation (181)) <1995JA7255>. Thus, when equimolar amounts of both catalyst and cocatalyst were used (2 mol.%), the major product was the butenolide **157**, although in the presence of excess palladium catalyst (5 mol.%), followed by DBU high yields of 2,4-disubstituted furans **158** were obtained.



As a result of ongoing investigations [<1998TL6445>](#) into palladium-catalyzed addition reactions between terminal alkynes and alkynoates, contra-Michael-type processes that occur alongside 1,4-addition reactions have been highlighted ([Equation \(182\)](#)) [<2001TL3775>](#). Several hypotheses are proposed to explain this outcome; these are based upon electronic and steric factors. Thus, it would appear that if the alkynoate bears bulky substituents, the migratory step directs the insertion reaction α - to the ester to afford **160** as well as **159**. In the absence of such bulky groups, smooth insertion into the carbon atom β - to the ester occurs to afford **159** regioselectively.

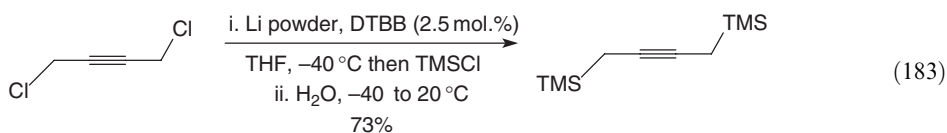


1.21.3.3 Substitution Reactions of Propargyl/Allenyl Carbanions

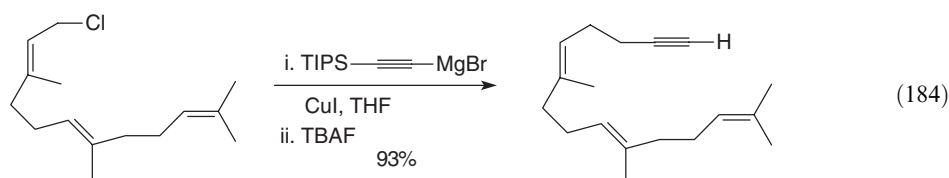
Substitution reactions of propargyl/allenyl organometallic species serve to complement other traditional methods for introducing carbon—carbon triple bonds into molecules and for homologation reactions in general. Most examples of substitution reactions involve the displacement of either a halogen or an oxygen functionality from either alkyl, allyl, propargyl and benzyl electrophiles.

1.21.3.3.1 Substitution of halogen

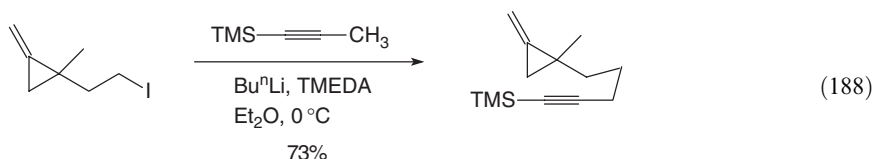
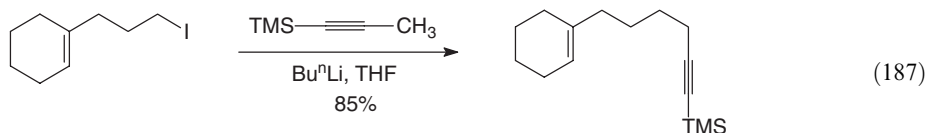
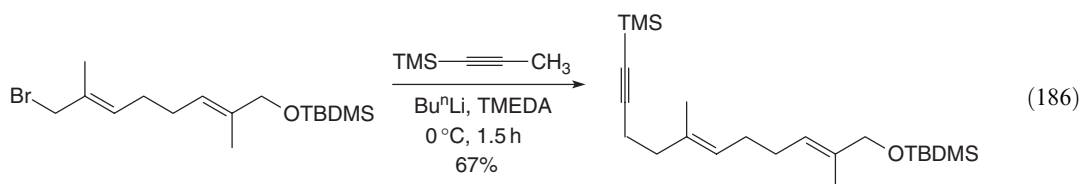
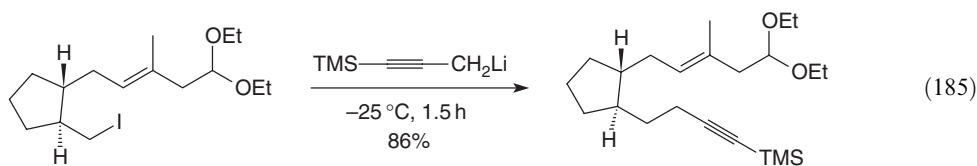
Organometallic reagents derived from propargyl/allenyl derivatives readily act as nucleophiles in substitution reactions, although the balance between allenic and propargylic products can be problematic. Attempts have been made to modulate this isomerization process by the application of catalytic additives such as 4,4'-di-*t*-butyldiphenyl (DTBB) ([Equation \(183\)](#)) [<1995T231, 1997T17201>](#).



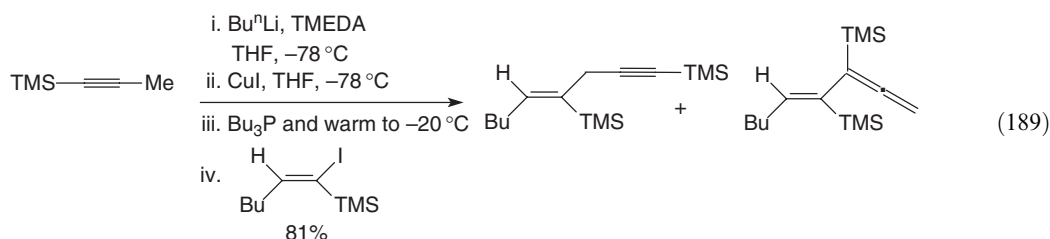
The magnesium derivative of 1-(triisopropylsilyl)propyne has been used in the synthesis of cembrane derivatives. The substrate, which was readily obtained from farnesol, underwent an efficient copper(I)-assisted allylic substitution reaction to afford the corresponding alkynyl derivative in virtually quantitative yield upon desilylation with TBAF ([Equation \(184\)](#)) [<1993JOC3912>](#).



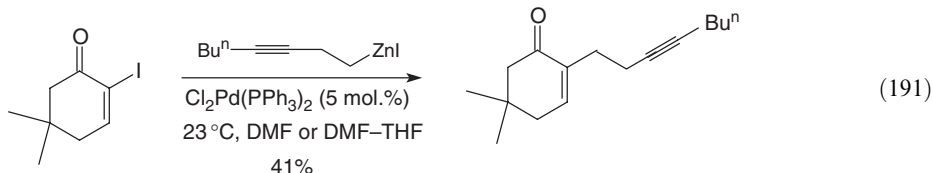
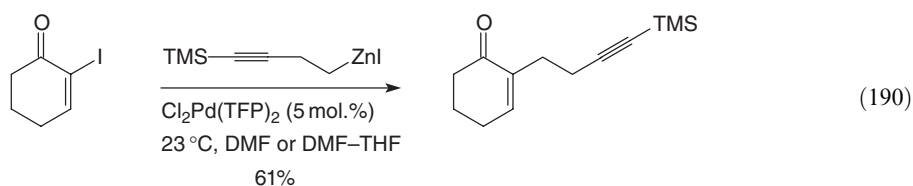
The lithium derivative of 1-(trimethylsilyl)propyne, prepared using the Corey procedure for position-specific alkynylations [<1968TL5041, 1970JA6314>](#), has been used extensively in chain lengthening and homologation sequences. Representative examples of its use include the synthesis of dolabellane (Equation (185)) [<1996TL7661>](#), of polyene probes of active sites (Equation (186)) [<2002BMC1249>](#), of angular triquinanes (Equation (187)) [<2001T2729>](#), and of methyl-enecyclopropanes with associated alkynyl acceptors (Equation (188)) [<1995T3303>](#).



In a recent report, the use of 4-DMAP as an additive during a propargyl-copper-alkenyl iodide coupling process provided a skipped enyne as well as the corresponding allenyl-coupled product in a selectivity of 85/15 [<2003OL2339>](#). The addition of an electron-rich phosphine, to replace DMAP, has been reported to favor the propargyl skipped enyne with a selectivity in excess of 95/5 (Equation (189)) [<2003T8913>](#).



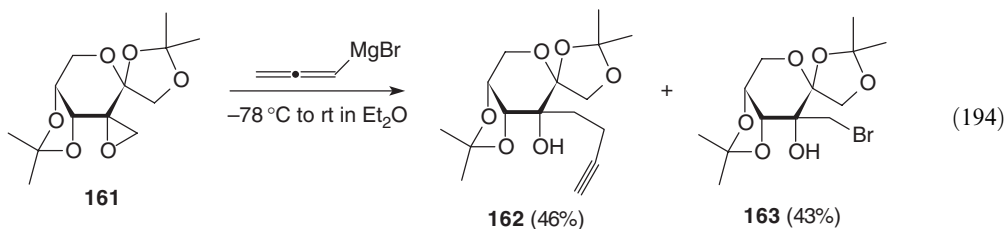
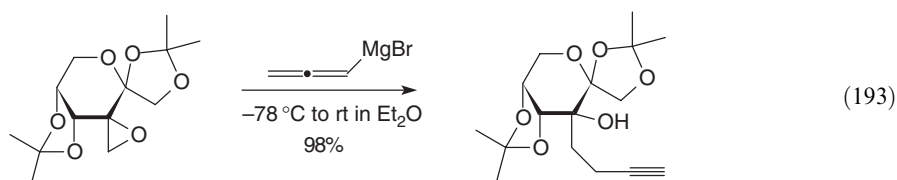
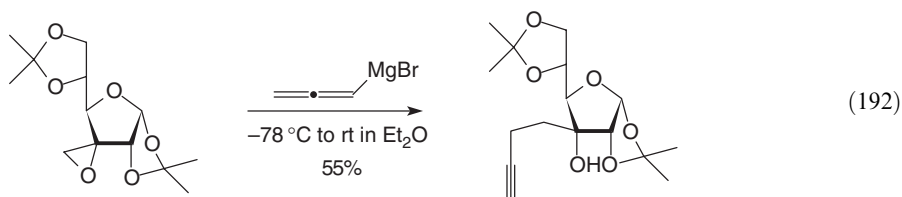
This improvement in the selectivity was explained in terms of the enhanced solubility and/or thermal stability of the organocopper species in the presence of tributylphosphine, changes in the aggregation state, and/or accelerated oxidative addition into the carbon-iodine bond. An analogous homopropargyl coupling reaction has been reported from the systematic studies of palladium-catalyzed cross-coupling reaction of α -iodoenones with alkylzinc and dialkylzinc reagents (Equation (190) and (191)) [<1999JOM179, 2000T10197>](#).



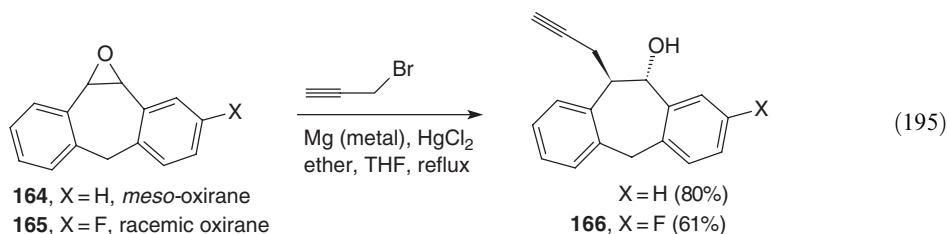
The α -substitution reaction was reported to proceed rather sluggishly, which was attributed to chelation of the homopropargyl group. The corresponding reaction involving substitutions with propargylzinc derivatives was reported to proceed via a 1,2-addition at the carbonyl rather than the coupling reaction required.

1.21.3.3.2 Substitution of oxygen functions

Allenylmagnesium bromide has been reported to react with spirocyclic oxirane precursors to afford carbohydrate-derived 4-pentynyl-1-ols (Equations (192)–(194)) <2000JOM37>. In general, the reaction affords the ring-opened products selectively, but the exception is the outcome of the reaction of allenylmagnesium bromide with spirocyclic oxirane **161**. This provided a 1/1 separable mixture of the pentynol **162** and the 3-C-bromomethyl- β -psicopyranose **163**. The formation of this compound was rationalized on the basis of oxirane ring opening by a bromide anion; however, no explanation was offered for the lack of selectivity with this substrate.



Propargylmagnesium bromide was also used in a nucleophilic opening of the *meso*-oxirane **164** and the racemic analog **165** (Equation (195)) <2002TL3011>.



Ring opening of the fluoro-oxirane **165** occurred with some level of regioselectivity to afford **166** in a ratio of 7/3. The preferred attack of the alkynyl organometallic at the less electron-deficient benzylic position in **165** was rationalized by invoking an S_N1 -type of mechanism as a result of coordination of magnesium to the oxirane *O*-atom.

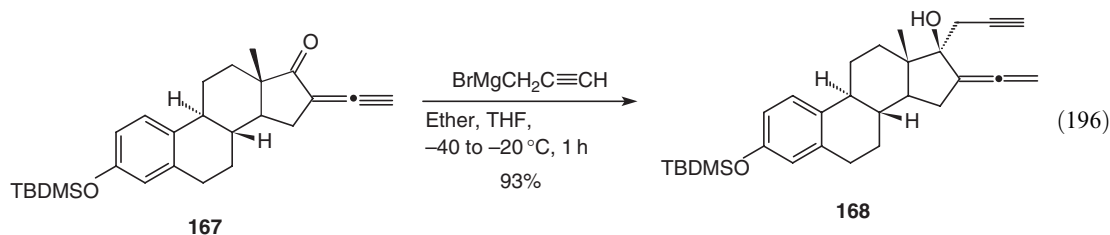
1.21.3.4 1,2-Addition Reactions of Propargyl/Allenyl Carbanions

The 1,2-addition reaction of organometallic reagents, derived from propargyl halides, to a $C=X$ bond provides an additional methodology for the introduction of the carbon—carbon triple bond into organic compounds. Depending on the nature of the metal employed, the outcome of the addition reaction may be complicated by the propensity of a propargyl organometallic reagent to equilibrate to the corresponding isomeric allenyl derivative to afford a mixture of propargylic and allenic products.

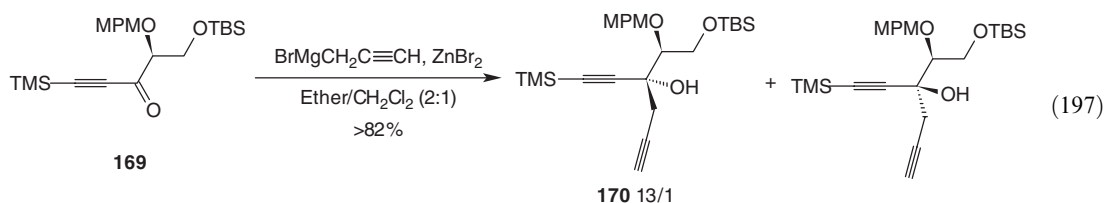
The factors that favor the preponderance of one isomer over the other are discussed below.

1.21.3.4.1 1,2-Addition to carbon—oxygen double-bonded functions

Propargyl/allenyl organometallic reagents readily undergo 1,2-addition reactions with aldehydes and ketones to afford homopropargyl alcohols. Extensive studies on the regio- and stereochemical outcomes from these reactions have been reported [<1991COS2>](#). Propargylmagnesium bromide in diethyl ether underwent 1,2-addition with the conjugated ketone **167** to afford the allene-alcohol **168** in very good yield (Equation (196)) [<1996TL3395>](#). It was anticipated that dehydration of the propargyl alcohol, in **168**, would lead to a cycloaromatization via Myers cyclization [<1989JA8057>](#); however, this elimination step was found to be slow and decomposition of the substrate was reported.

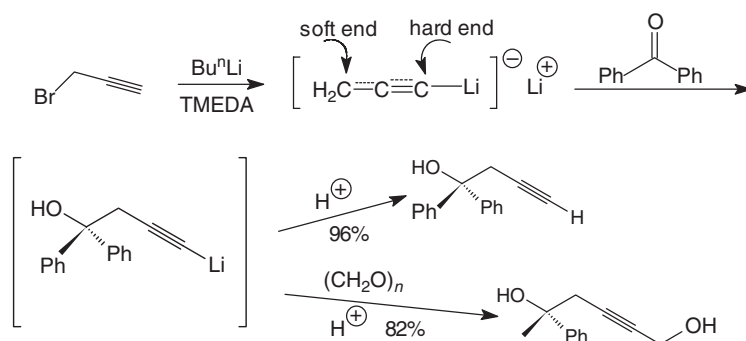


1,2-Chelation control, in the addition of the same Grignard reagent, was accomplished with good effect using $ZnBr_2$ in order to favor the diastereoselective synthesis of **170** from **169** (Equation (197)) [<1996TL5135>](#). The addition reaction was found to be highly solvent dependent providing a 1/1 mixture of diastereoisomers in ether, regardless of the presence or absence of $MgBr_2 \cdot OEt_2$. This ratio improved to 2.5/1, in favor of the desired isomer **170** in CH_2Cl_2 /diethyl ether (4/1) and optimized by the addition of zinc bromide.



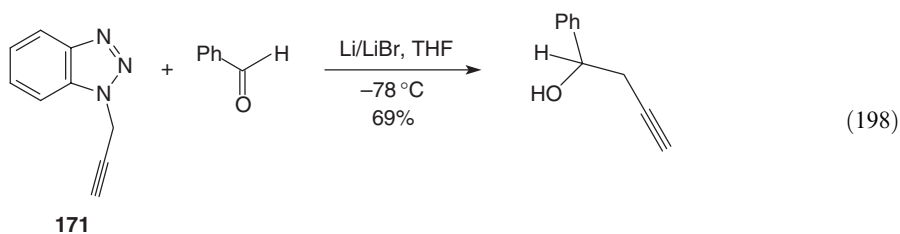
A quantitative yield was reported for the reaction of propargylmagnesium bromide with a range of oxoketene dithioacetals <1996TL2817>.

In general, allenyllithium reagents react with aliphatic ketones to afford allenic alcohols <1981S875>, whereas with aromatic carbonyls they provide homopropargyl alcohols albeit in low yields <1989SC1705>. Propargyl dianions, obtained from the reaction of propargyl bromide with an alkyllithium in the presence of TMEDA, however, react with aldehydes and ketones to afford the corresponding homopropargyl alcohols regioselectively and in good yield. Sequential reaction of the “soft” propargylic center with benzophenone followed by reaction at the “hard” alkynyl center with alternative electrophiles provided the corresponding homopropargyl alcohols (Scheme 20) <1998TL3935, 2001TL6819> in excellent yields.

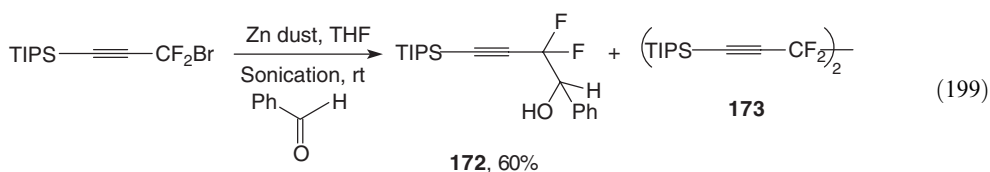


Scheme 20

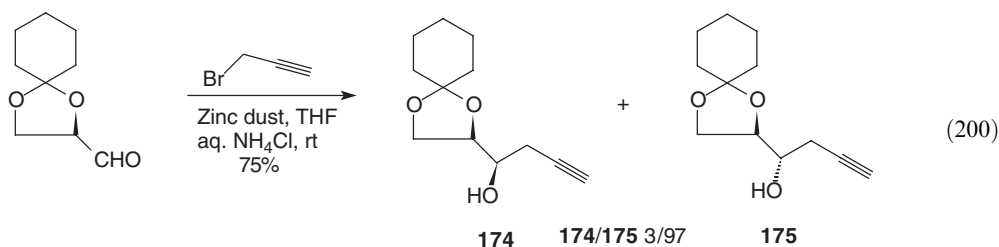
The reactions of functionalized propargyllithium reagents have been forthcoming from other laboratories <1997T17201, 1995T231>. Using a procedure to generate lithium carbanions from the reductive lithiation of a C-benzotriazole bond-scission reaction <1998TL363, 1998TL2289>, 1-propargylbenzotriazole **171** was lithiated by treatment with lithium/lithium bromide (Equation (198)) <1999TL253>. Subsequent condensation of the lithiated dianion with a range of carbonyl compounds provided homopropargyl alcohols in acceptable yields.



In recent years, Barbier-type propargylation reactions have been reported using a variety of transition metals including zinc <1999TL5015, 1996JOC2731>, tin <1998JOC7472, 1998SC2999>, copper <1999SC3083>, and gallium <1999SC1287>. A zinc-mediated propargylation of aldehydes and ketones was reported as an efficient method for accessing α,α-difluorohomopropargylic alcohols **172** as a means of introducing a CF₂ moiety into organic molecules (Equation (199)) <2000TL2339>. In all of the examples the desired compound was accompanied by formation of the isolable dimer **173** in ratio of **172**:**173** 3/1 to 5/1. Analogous reaction conditions were employed, without the need for sonication, in a highly efficient synthesis of acyclic conjugated enediynes <1995TL897>.

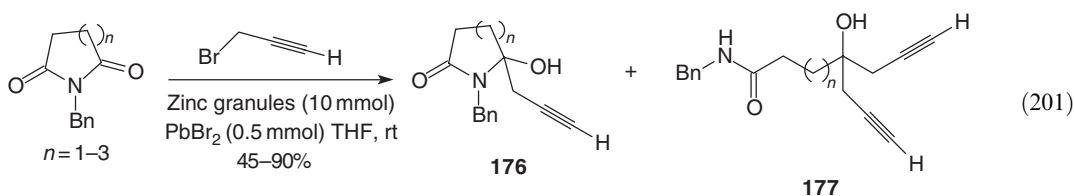


A highly stereoselective zinc-mediated propargylation reaction to afford *anti*-homopropargyl alcohol **175** in aqueous media has been reported (Equation (200)) <1996JOC6104>.

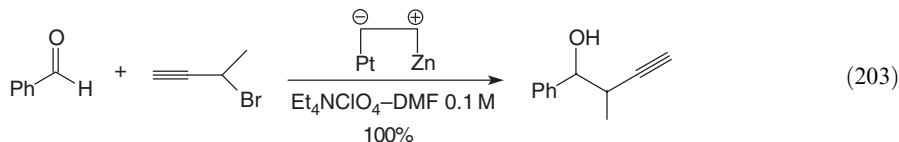
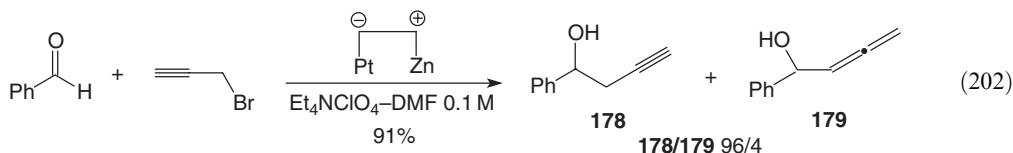


The propargylation reaction occurred with a high level of regioselectivity as only 1% of the corresponding allene was detectable by ^1H NMR spectroscopic studies of the product mixture. The high levels of diastereoselectivity reported, that favor the formation of the *anti*-isomer **175** over the *syn*-isomer **174**, was in marked contrast to the corresponding Grignard reaction under anhydrous conditions <1995JOC585>. The preference for the formation of the *anti*-isomer was explained by invoking a Felkin–Anh model on the basis of solvation by water rather than chelation control. An analogous zinc-mediated propargylation reaction of 6-oxomethylenepenam has been reported to occur with high diastereoselectivity in an aqueous media <1999TL1725>.

One of the first examples of a zinc-mediated Barbier-style propargylation reaction of cyclic imides has been revealed (Equation (201)) <2000TL6479>. The requirement for catalytic lead bromide additive was essential for the *in situ* generation of propargyllead. For propargylation reactions of five-membered imide rings the reaction favored only the formation of **176**, although for larger ring systems ($n = 2, 3$) the ring-opened disubstituted alcohol **177** predominated.

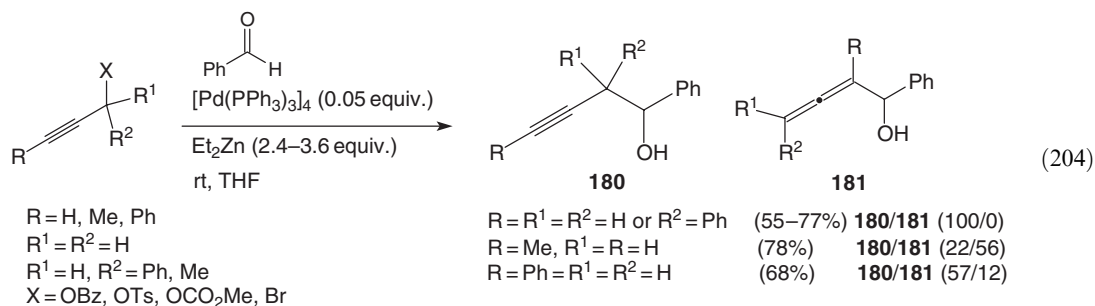


A novel regioselective propargylation of aldehydes and ketones has been reported with unsubstituted (Equation (202)) and α -substituted propargylic bromides (Equation (203)) using an electrochemical process involving a platinum cathode with either a zinc or aluminum anode <2000T847>. The reactions were conducted in DMF as solvent containing Et_4NClO_4 . Electrochemical propargylation reactions of aldehydes and ketones using unsubstituted or α -substituted propargyl bromides gave the homopropargyl alcohol **178** along with the associated homoallenyl alcohol **179**.

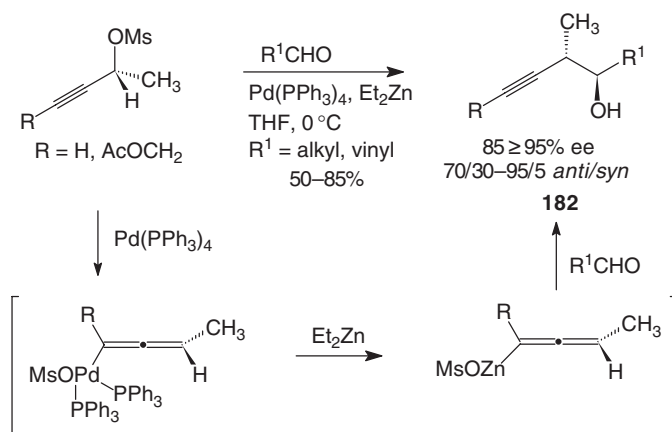


The propargylation of carbonyl compounds has been reported to take place via an unpolung derived from a propargylpalladium complex and diethylzinc (Equation (204)) <1996AG(E)878>. In general, reactions involving propargylpalladium complexes with “hard” carbon nucleophiles, derived from zinc or magnesium, afford allenyl products. In contrast, applications of the reaction with “soft” carbon nucleophiles and with carbonyl compounds remain relatively uninvestigated. For comparatively unhindered complexes, the formation of the corresponding homopropargyl

alcohols **180** takes place unambiguously, although as the substituent R is changed from H to Me or Ph the formation of the allene derivative **181** is observed. Furthermore, the ratio of **181** to **180** depends extensively upon the nature of the substituent R.

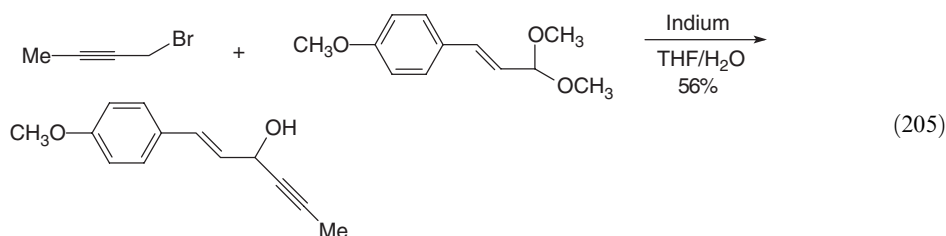


An analogous use of allenylzinc reagents, derived from nonracemic propargyl mesylates, in conjunction with a Pd(0)–phosphine catalyst, provides access to highly enriched homopropargyl alcohols **182** (Scheme 21) <1998JOC3812, 1999JOC5201>. The palladation of propargylic mesylates is known to take place with inversion of configuration <1997JOC367> and thus the predominance of the *anti*-adduct strongly suggests that a *syn*-addition process operates via a cyclic transition state. The zincation step is thought to proceed with retention of configuration. The authors concluded that configurationally stable chiral allenylzinc reagents may be readily synthesized from the corresponding propargyl mesylates. The chiral organozinc reagent readily adds to a variety of aldehydes to afford *anti*-adducts almost exclusively. The high levels of enantioenriched propargyl alcohols formed, the apparent lack of allenyl by-products, coupled with the ease and reproducibility of the palladation–zincation reaction make this a very appealing methodology.

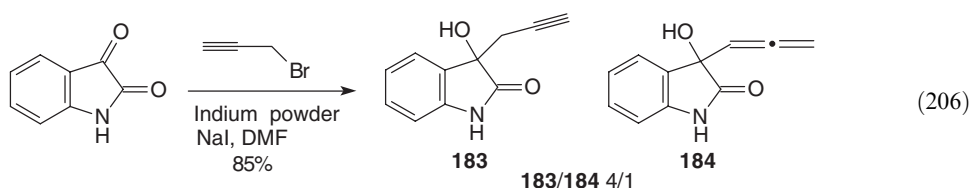


Scheme 21

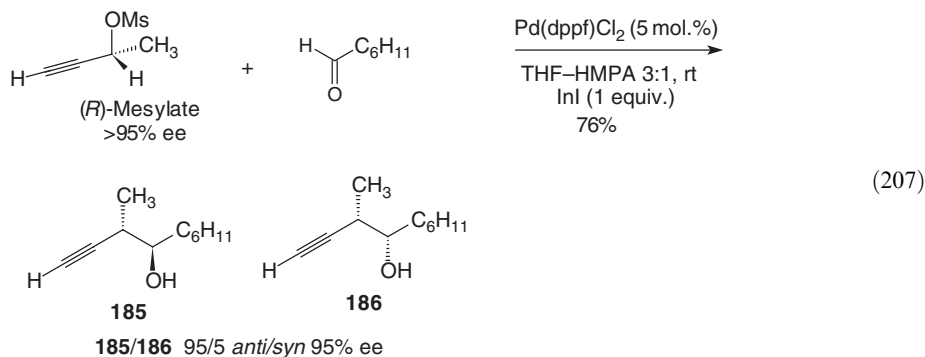
Besides zinc reagents, other transition metals such as indium have found an application in propargylation reactions. One novel approach involved the propargylation of acetals and ketals in which a one-pot deprotection–propargylation reaction takes place (Equation (205)) <2001TL1957>. Reaction with 1-bromo-2-butyne provided only the α -addition product in contrast to the reaction with propargyl bromide, which yielded a mixture of products resulting from α - and γ -additions. The ratio of propargyl allenyl was 100/0 (R = H, n = 0) to 2/1 (R = OMe, n = 0 and R = H, n = 1). A similar selectivity was observed during indium-mediated propargylation of cyclohexanone dimethyl ketals (50–58%) in which a 3/2 mixture of propargyl/allenyl products arose from the reaction with propargyl bromide. The lower yields observed with these substrates reflect the reduced reactivity of aliphatic ketals. Indium-mediated propargylation reactions have also been reported to take place in water as solvent <1995CC1003> and in a water/THF mixture <1999TL1725>.



A very useful application of indium-mediated propargylations involved reactions with 1,2-diones to afford α -hydroxy carbonyls (Equation (206)) <2001T9453>. The reaction was found to be facile affording separable propargylic/allenic products in very high yield. Thus, propargylation of istatin occurred in good yield to afford **183** and **184** in 75% yield as a 4/1 mixture. In general, however, the reaction was not quite so regioselective, and exposure of benzyl and phenanthrenequinone to propargyl bromide and indium led to a rapid and highly efficient addition reaction to afford 1/1 mixtures of the corresponding homopropargyl alcohol and allene.

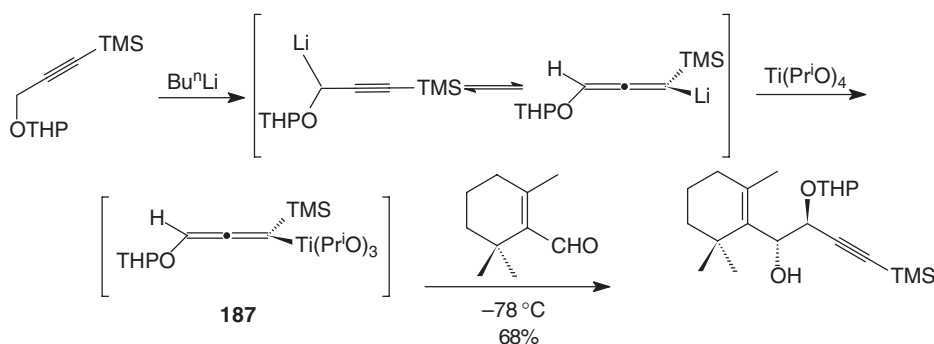


The formation of a transient chiral allenylindium reagent, derived from the corresponding enantioenriched propargyl mesylate, and subsequent exposure to carbonyl compounds has been reported to afford enantioenriched homopropargylic alcohols **185** and **186** (Equation (207)) <1999JOC696>. For the reaction between the propargyl mesylate and cyclohexanecarboxaldehyde, in the absence of a palladium catalyst, a good conversion was observed in 66% yield to afford a 95:5 mixture of *anti/syn*-isomers but the adducts were racemic. Furthermore, no additions were reported in the absence of InI.



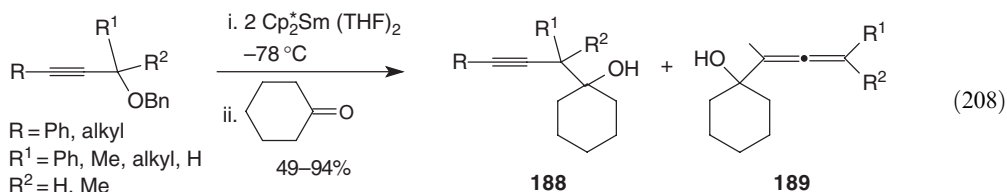
Reports from the same laboratories reveal analogous diastereoselective and enantioselective synthesis of homopropargyl alcohols from nonracemic propargyl mesylates via the corresponding allenyl and propargyl trichlorosilane derivatives <1997JOC8976>.

Yamamoto <1984BCJ2768> first reported a synthesis of propargyl and allenyltitanium intermediates for the preparation of allenyl and homopropargyl alcohols. Low-valent titanium, derived from Cp_2TiCl_2 and magnesium <2001TL2839>, as well as $\text{Ti}(\text{O}^i\text{Pr})_4$ <1995TL3207>, reacts under Yamamoto conditions with propargyl acetates and alcohols to form allenyltitanium intermediates, which then undergo nucleophilic addition reactions with aldehydes and ketones to afford homopropargyl alcohols in good-to-excellent yield. Lithiated α -alkoxypropargyl and γ -alkoxyallenyl derivatives undergo transmetalation, with titanium tetra-*iso*-propoxide, to afford the corresponding allenyltitanium intermediate **187** (Scheme 22) <1996TL5519>. Exposure of the allenyltitanium reagent **187** to either propynal or α,β -unsaturated aldehydes provided the corresponding adducts in modest-to-good yield. In all examples the *anti*-adduct predominated.

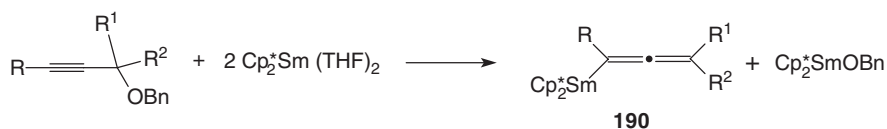


Scheme 22

Allenylsamarium complexes <1995TL1505>, derived from both secondary and tertiary propargylic ethers, have been trapped with electrophiles such as cyclohexanone to afford propargylic products selectively (Equation (208)) <1995TL6283>. In contrast, reactions involving a complex derived from the corresponding primary ether tend to afford a higher proportion of the allenyl adduct. Optimum selectivity in favor of **188** was observed when $R = n\text{-Bu}$, $R^1 = \text{Ph}$, and $R^2 = \text{H}$ (**188/189** 92/8), this result was reversed when $R = \text{Ph}$, $R^1 = R^2 = \text{H}$.



The authors invoked the intermediacy of allenic complex **190** which is formed, *in situ*, from a reaction between $\text{Cp}_2^*\text{Sm}(\text{THF})_2$ and the propargylic benzylether.



1.21.3.4.2 1,2-Addition to other carbon—chalcogen double-bonded functions

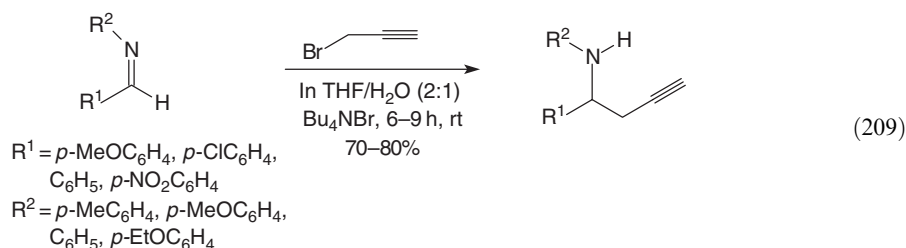
Developments in the area of 1,2-addition reactions to the carbon—chalcogen double-bonded functionality have been insignificant since the 1980s, and the reader is directed to prior investigations in this relatively unexploited area <1995COFGT1058>.

1.21.3.4.3 1,2-Additions to carbon—nitrogen multiple-bonded functions

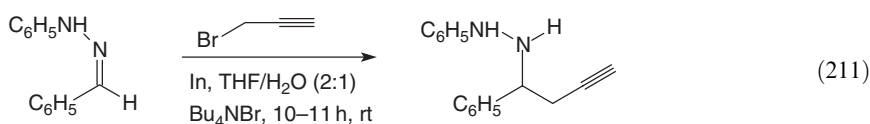
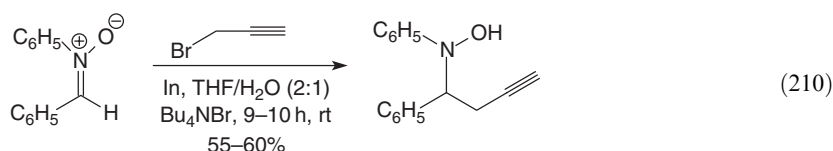
The development in methods to effect the addition of organometallic reagents to the $\text{C}=\text{N}$ double bond of imines/imine oxides has been hampered by both the low electrophilic character of the azomethine carbon atom coupled with the tendency for enolizable substrates to undergo deprotonation rather than addition <1998CRV1407>. Most 1,2-additions are limited to reactions involving aldimines and their iminium salts and most recently with *N*-heterosubstituted imines. In contrast to this, little information is available for analogous reactions between propargyl/allenyl organometallics with ketimines and their salts or nitriles.

An indium-mediated propargylation of imines derived from aromatic aldehydes, in aqueous media, has been reported (Equation (209)) <2003TL6755>. The 1,2-addition reactions took place very efficiently at ambient temperatures with little or no side-reactions, such as aqueous hydrolysis of the imine, occurring <1996T6453>. Similar results were observed with the use of

propargyl chloride affording the coupled derivative in good yield after 9 h. Attempts to carry out the reaction with a ketimine, derived from acetophenone and aniline, failed and afforded only the products of decomposition. The outcome of the addition reaction was dependent upon the use of Bu^nNBr with alkynylation failing to take place with indium alone. The authors suggest that Bu^nNBr may be involved in the formation of an active organoindium reagent.



Homoalkynyl products were also obtained in good yield from the indium-catalyzed coupling of propargyl bromide with imine oxides and hydrazones (Equations (210) and (211)). The extended reaction times and lower yields reflect the reduced reactivity of these derivatives.

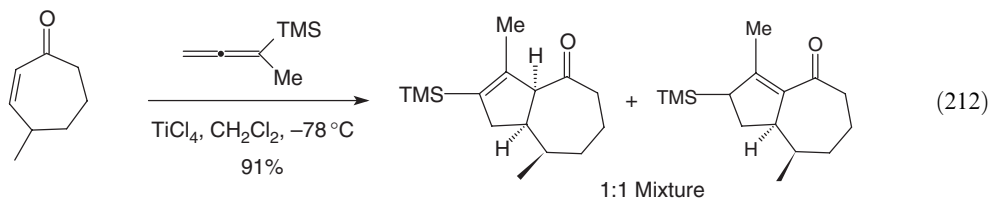


1.21.3.4.4 1,2-Addition–elimination reactions

Developments in the area of 1,2-addition–elimination reactions of propargyl/allenyl organometallics to appropriate substrates have not been forthcoming since the 1980s, and the reader is therefore directed to <1995COGT1060>.

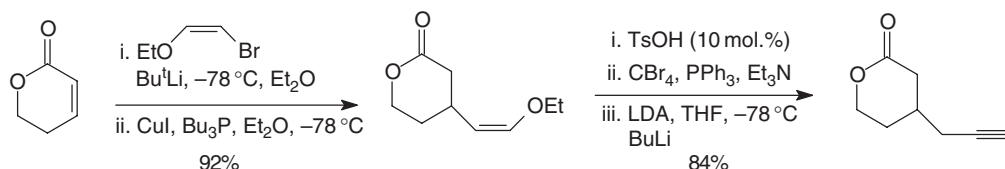
1.21.3.4.5 1,4-Addition reactions

The relatively few examples of 1,4-additions of propargyl/allenyl organometallic reagents to enones are a consequence of the difficulty associated with this transformation in terms of controlling the site selectivity of the addition reaction. Despite this obstacle, propargyl-selective conjugate additions to enones have been reported <1974TL4467, 1982TL719>. Reactions involving silyllallenes, in the presence of TiCl_4 , have been shown to undergo 1,4-addition reactions with enones. The “Danheiser” reaction <1981JA1604, 1983T935>, the reaction of trimethylsilyllallene with methylcycloheptenone, was used in the synthesis of a cyclopentene derivative (Equation (212)) <2002TL2683>. This provided a 1:1 mixture of separable diastereoisomers in excellent yield.



Despite the availability of methods to effect a conjugate propargylation to enones <1990JOC4853>, the corresponding transformation with α,β -unsaturated lactones has yet to be recorded. In an effort to access compounds of this type, an alternative procedure was developed that involved the conjugate addition of (*Z*)-2-ethoxyvinyl anion to a range of

α,β -unsaturated lactones. This step was accomplished using Noyori-type organocopper reagents (Scheme 23) <2000TL8873>. The resulting vinyl ethers were then transformed, in high yield, to the corresponding β -alkynyllactones via hydrolysis to the aldehyde followed by a Corey–Fuchs alkylation reaction <1972TL3769>.



Scheme 23

1.21.4 ALKYNES BY $\text{C}\equiv\text{C}$ BOND FORMATION

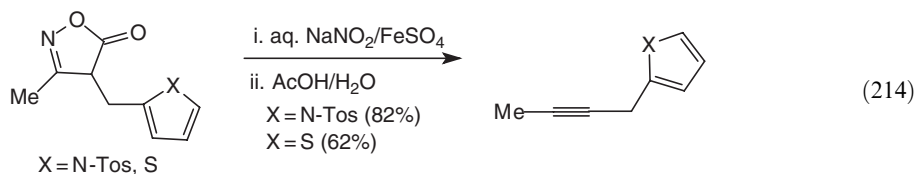
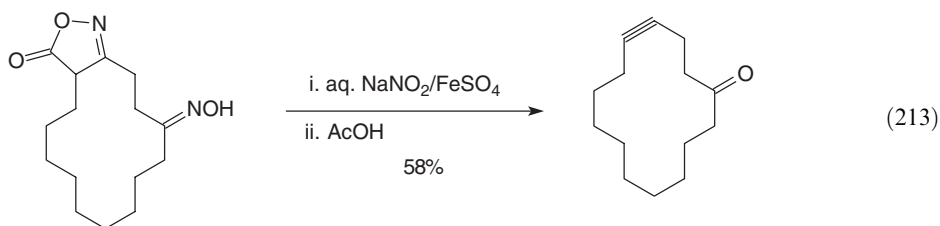
The vast majority of methods for the formation of carbon–carbon triple bonds tend to be focused upon elimination reactions. Other methods, such as fragmentation or electrocyclic reactions, have been previously reported <1995COFGT(1)997>.

1.21.4.1 Elimination Reactions

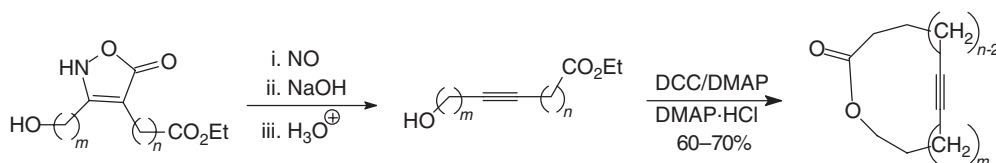
The most frequently encountered elimination reaction involves the loss of groups from adjacent centers (1,2-elimination reactions), although the alkyne motif has also been obtained via 1,1-eliminations and less commonly from 1,4- and 1,6-elimination reactions.

1.21.4.1.1 Elimination of carbon functions

The conversion of a terminal isopropylidene moiety into an alkynyl derivative has been known for sometime <1986TL267>, and the precise mechanism for effecting this transformation has generated some conjecture <1987TL4921, 1995TL3333>. Recent developments in this area include the synthesis of large-ring acetylenes from the nitrosation of an isoxazolinone in the presence of ferrous sulfate (Equation (213)) <1995TL5737> and functionalized alkynes using an analogous methodology (Equation (214)) <1996TL8735>.



Alkynolides possessing olfactory properties were obtained from the heterocycle via the corresponding *N*-nitroso derivative (Scheme 24) <1999T2639>.



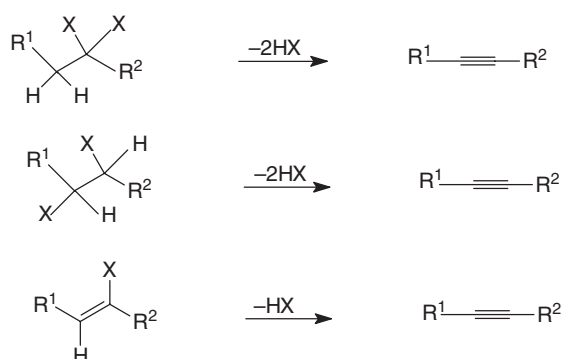
Scheme 24

1.21.4.1.2 Elimination of halogen

(i) Dehydrohalogenation

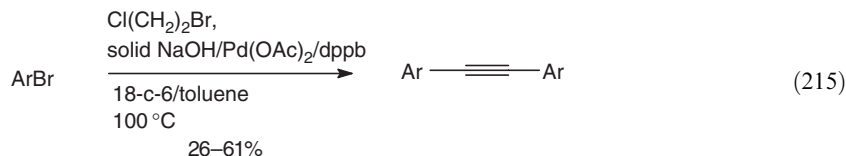
Although alkynes have frequently been prepared from alkyl/alkenyl halides via 1,1-, 1,2-, 1,4-, and 1,6-elimination reactions of hydrogen halides, the most frequently used method involves the elimination from adjacent atoms via a 1,2-dehydrohalogenation reaction.

The most frequently employed method for effecting the 1,2-elimination of HX from a corresponding alkyl/alkenyl halide involves elimination from either a 1,1- or a 1,2-dihaloalkanes or from haloalkenes (Scheme 25). Representative methods for generating these functional motifs will be included where relevant.

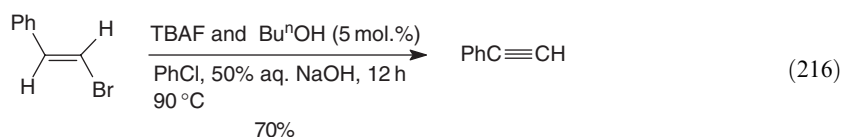


Scheme 25

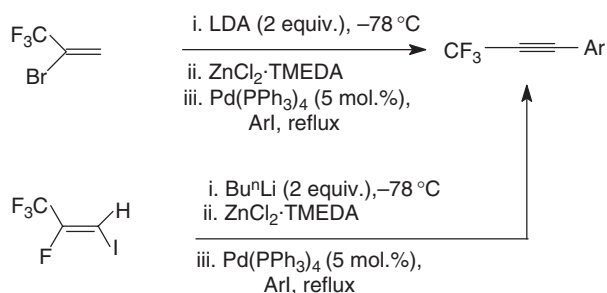
A new method for the synthesis of diarylalkynes involved the coupling of aryl bromides with 1-bromo-2-chloroethane using a palladium catalyst under phase transfer conditions (Equation (215)) <2003TL3911>. 1-Bromo-2-chloroethane acts as a source of “acetylene” that is formed *in situ* from the dehalogenation reaction. The alkali metal hydroxide, solid KOH, in association with 18-Crown-6 was found to be essential for effecting this transformation. It is proposed that the aryl bromide forms an adduct with the palladium catalyst followed by a Heck reaction of vinyl chloride, formed *in situ*, to afford ArCH=CHCl . This then eliminates HCl, in the presence of base, to give an aryl acetylene, which subsequently couples with further aryl bromide to provide the desired diaryl alkyne.



An analogous β -elimination of HBr from *trans*- β -styrene, known to be resistant to this reaction, has been reported to occur in the presence of a phase transfer catalyst (TBAF) and aqueous NaOH (Equation (216)) <2002T7295>. The dehydrobromination reaction proceeds efficiently by utilizing this “ion-pair extraction” technique with a slight increase in conversion observed when Bu^nOH was added as a co-catalyst. In contrast, the use of more acidic co-catalysts, such as PhCH_2OH or mesitol, actually impedes the reaction.

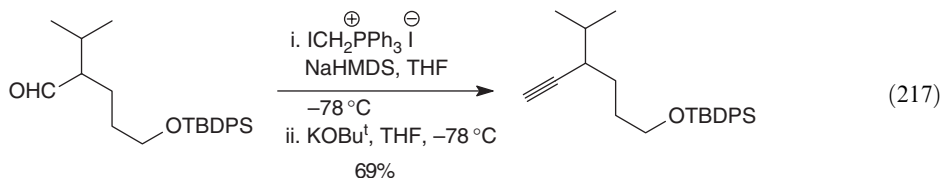


As a general observation, exposure of either bromo- or fluoroalkenes to organolithium reagents leads to lithium–halogen exchange rather than alkyne formation. However, several fluorinated alkynyl derivatives were accessed via a palladium-catalyzed coupling reaction of zinc alkynes with a range of aryl iodides (Scheme 26) <2003JFC185>. The alkynes themselves were generated via dehydrohalogenation using LDA or BuⁿLi.

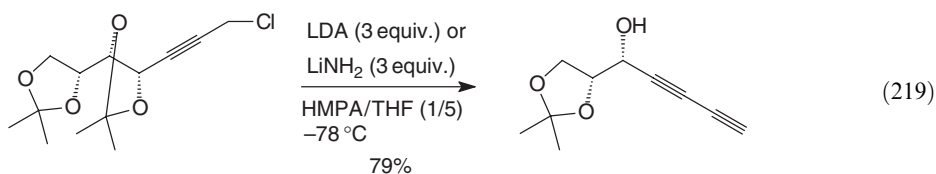
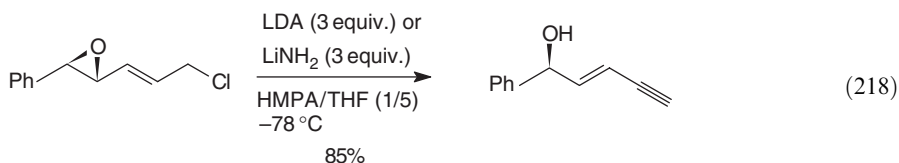


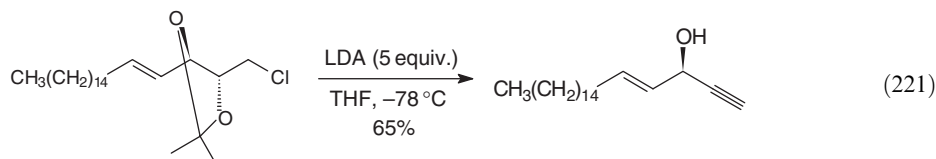
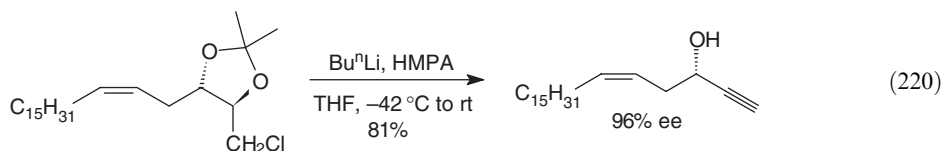
Scheme 26

The use of *t*-butoxide, in combination with a Wittig reaction of aldehydes with iodomethylene-triphenylphosphorane, has been reported to provide access to terminal alkynes (Equation (217)) <1996T4769>. This low-temperature Stork methodology <1989TL2173> provided the (*Z*)-iodoalkene exclusively. This then underwent *trans*-elimination of HI to provide the terminal alkyne.



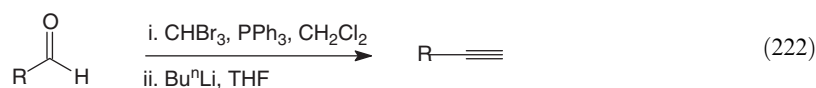
Alkali metal amide bases have been used extensively in elimination reactions and in the preparation of optically active hydroxyenynes from 4,5-epoxy *trans*-allyl chlorides and 4,5-*O*-isopropylidene allyl chlorides (Equation (218)) <1997TL4479>, chiral polyhydroxydialkynyl alcohols (Equation (219)) <2001TL3909>, chiral alkynyl alcohols (Equation (220)) <2002TL8043>, and chiral eicos-(4*E*)-en-1-yn-3-ols (Equation (221)) <1999T4649>.



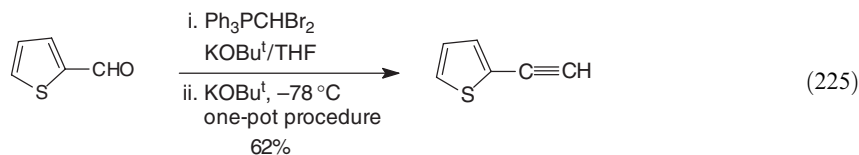
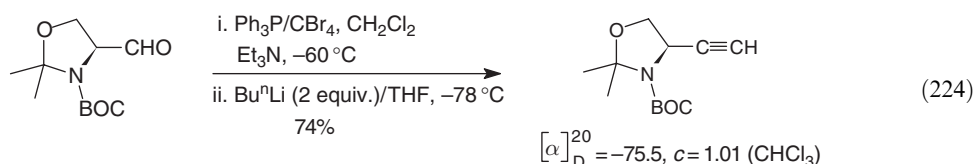
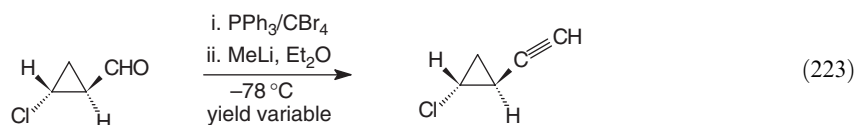


The mechanism of these elimination reactions appears to follow similar pathways. Thus, deprotonation, alpha to the halogen atom, provides an alkenyl halide from the elimination of the ether oxygen. Subsequent exposure of the *in situ* generated alkenyl halide to further base effects the dehydrohalogenation reaction to provide the alkyne.

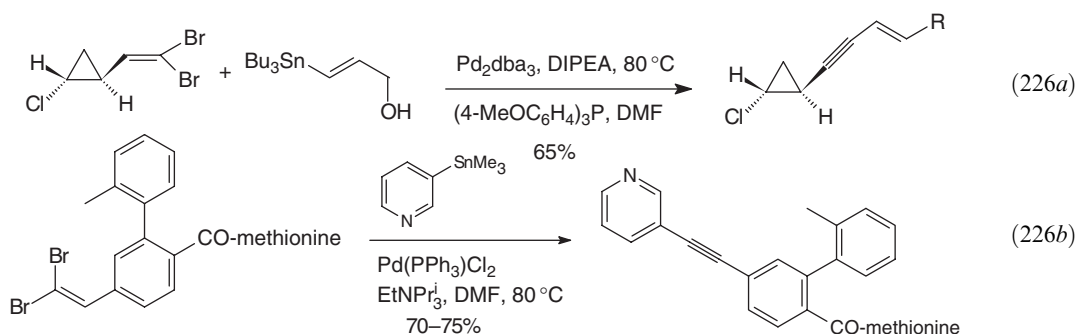
The transformation of an aldehyde to an alkenyl moiety by reaction of $\text{CHBr}_3/\text{CHI}_3$ with triphenylphosphine, followed by an organolithium-induced dehydrohalogenation reaction of the corresponding 1,1-dihalogenated alkene provides an alkyne; the Corey–Fuchs reaction (Equation (222)) <1972TL3769>. It is generally considered that the conversion proceeds in two steps. First ylide is formed in dichloromethane to afford an isolable dihaloalkene, and in the second step, often conducted in THF, the elimination of HX occurs to provide the alkyne.



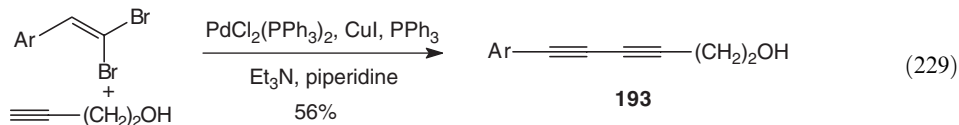
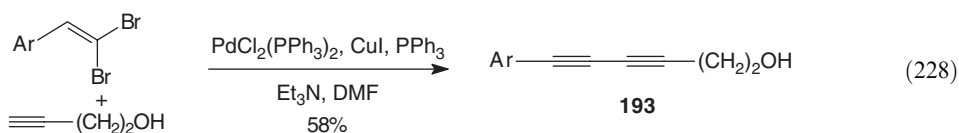
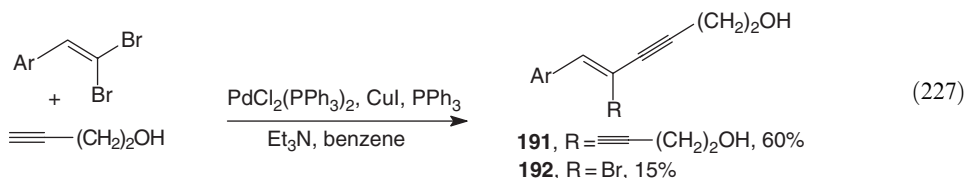
Modifications to this procedure have reportedly produced alkynes from aldehydes using a one-pot process <1999TL8575, 1999TL8579>. Representative examples of this useful transformation are shown (Equations (223)–(225)) <2000OL4055, 1995TL8275, 1999TL8575, 1999TL8579>, which illustrate the generality of this reaction and its functional group compatibility. Other examples may be obtained from the following sources <1999T1607, 2003T155, 2002TL1847, 2001TL6195, 2002T1799, 2002T6485>.



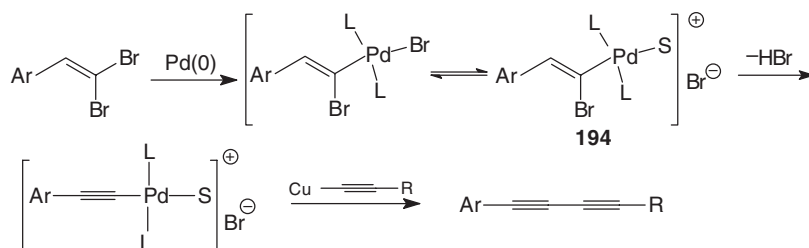
A palladium-catalyzed variant of this reaction <1994JOMC6>, a novel Stille reaction, has been employed to effect the coupling between dihaloalkenyl intermediates, derived from the corresponding aldehyde, with an organotin reagent. This has been put to good use as a means to access enynes <2000OL4055> and aryl alkynes <1999BMCL703> from the *in situ* tin-mediated generation of the terminal alkyne (Equations (226a) and (226b)).



In an alternative palladium-assisted coupling, requiring CuI as a co-catalyst, the traditional Sonogashira coupling between a 1,2-dihaloalkene and a terminal alkynes to afford **191** may be suppressed entirely to afford a 1,3-diyne **193** instead. The solvent dependency of this transformation has been investigated and optimized in order to provide diynes as the major product <2001T8283>. In solvents such as toluene or benzene, no 1,3-diyne resulted (Equation (227)) however, in DMF or DMSO the diyne **193** predominated in a yield of 58% (Equation (228)). In amine solvents such as piperidine, the diyne could be obtained as the sole product (56%), whereas in di-*iso*-propylamine its formation was entirely suppressed in favor of **191** (20%) and **192** (68%) with 2.2 equiv. of the amine. In the presence of 4.4 equiv. the outcome was reversed in favor of **191** (65%) and **192** (5%).

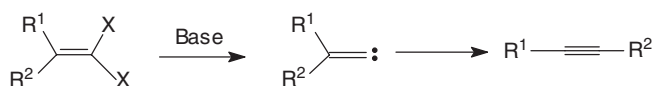


A reaction pathway has been suggested in which highly polar solvents such DMF or DMSO favor the formation of a solvated ionic complex, **194** (Scheme 27), and this is then converted into the alkynyl palladium intermediate via the elimination of HBr. Small optimally coordinating amines would thus favor the formation of **194**, which then leads to the synthesis of the diyne **193**.



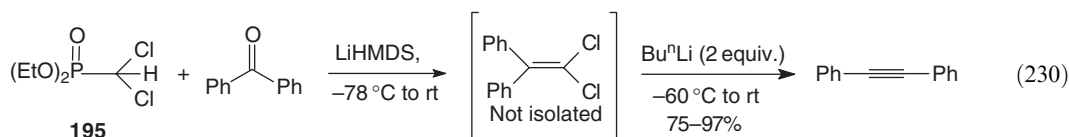
Scheme 27

The Fritsch–Buttenberg–Wiechell (FBW) rearrangement reaction (Scheme 28) is a well-documented technique for the formation of alkynes from 1,1-dibromoalkenes and has recently been reviewed <1997AG(E)1164, 2000OL419>.

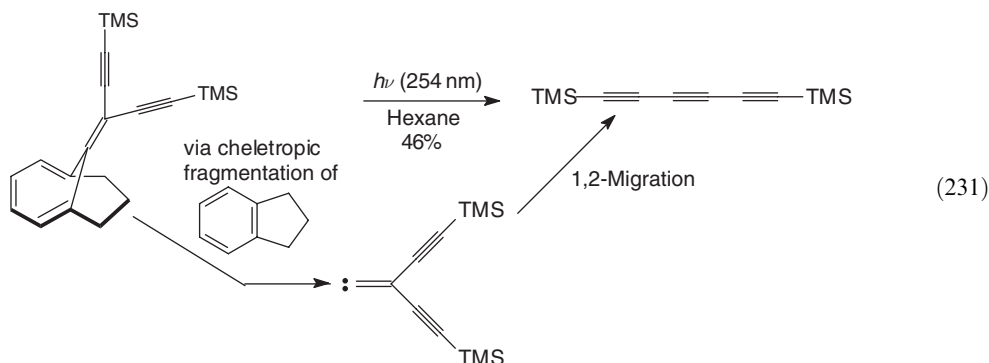


Scheme 28

The rearrangement itself is highly stereoselective with the R group (aryl/alkynyl) migrating in a *trans*-arrangement to an α -elimination from the 1,1-dihaloalkene that generates an alkylidene carbene intermediate. Several applications of this reaction for the synthesis of symmetrical and unsymmetrical diynes have been reported [<2000JA10736, 1996T8143, 2001TL8575>](#). A recent one-pot synthesis of symmetrical and unsymmetrical diynes has been published that uses the reaction of diethyldichloromethylphosphonate **195** with carbonyl compounds to afford the dichloroalkene rearrangement precursor ([Equation \(230\)](#)) [<1998S271>](#).



A vinylidene to alkyne rearrangement has been reported in which the resulting polyynes are accessed via a photolytically initiated cheletropic fragmentation of dialkynylmethylenebicyclo[4.3.1]decatriene derivatives, followed by a 1,2-migration reaction ([Equation \(231\)](#)) [<2001TL5485>](#). The photolysis reaction provides a route to linear polyynes as the major products together with isomerization products.

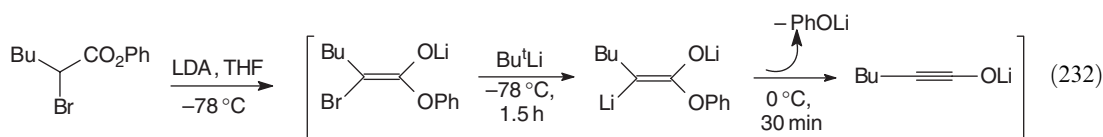


(ii) Dehalogenation

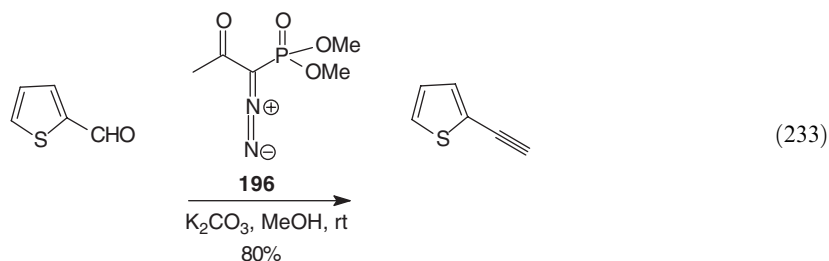
Developments in the area of dehalogenation reactions of 1,2-dihaloalkenes and 1,1,2,2-tetrahaloalkanes have been insignificant over the past two decades, and the reader is directed to prior investigations in this relatively unexploited area [<1995COFGT\(1\)997>](#).

1.21.4.1.3 Elimination of oxygen functions

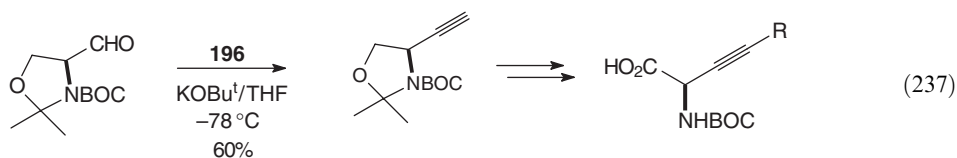
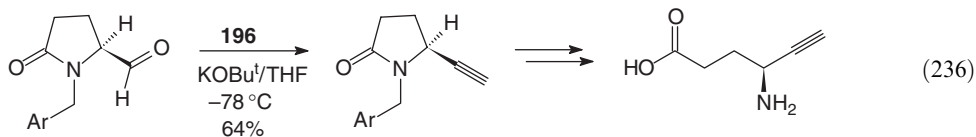
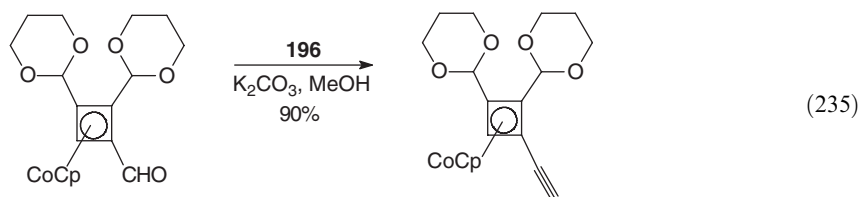
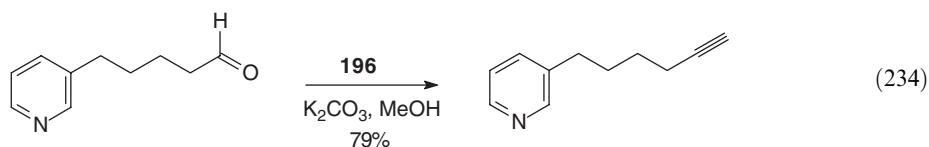
The elimination of an oxygen function, from the thermally induced cleavage of an ester dianion, has been reported to provide access to ynolates ([Equation \(232\)](#)) [<1998T2411, 2002TL5039>](#). The resulting ynolates were then trapped by reaction with aldehydes to afford β -lactones (69–85%) or with benzophenone to afford olefins (72–99%) [<2001TL8357>](#).



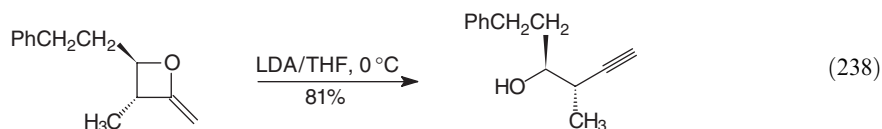
The transformation of aldehydes to terminal alkynes may be readily achieved, in a one-pot procedure, by the addition of dimethyl 1-diazo-2-oxopropylphosphonate **196** to a methanolic solution of potassium carbonate at an ambient temperature (Equation (233)) <1996SL521>. The advantage of this procedure over traditional Wittig protocols is the avoidance in the use of a strong base in low-temperature conditions.



This and other related procedures have been applied to a variety of different aldehydic substrates including heterocycles (Equation (234)) <2003T1719>, cyclopentadienylcobalt-stabilized butadienes (Equation (235)) <2002JOM21>, optically active amino acids (Equation (236)) <1995TA239>, and glycine derivatives obtained from L-serinal (Equation (237)) <1995TL877, 1996T11215>.

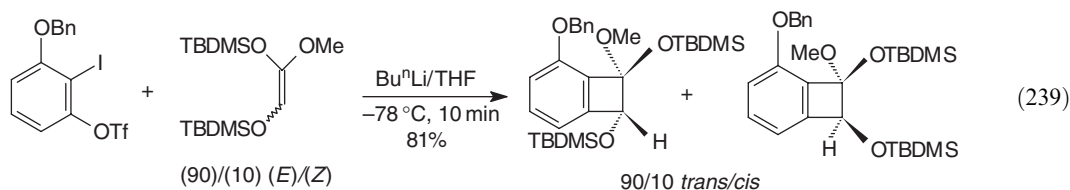


An unexpected ring opening of 2-methylenoxetanes has been reported to provide a novel method to access homopropargylic alcohols (Equation (238)) <1998JOC6782, 2002T7101>. Although LDA alone efficiently effected oxetane ring opening, alternative bases such as butyllithium or phenyllithium were unsuccessful, and ring opening could only be achieved by the additional use of trimethylaluminum.

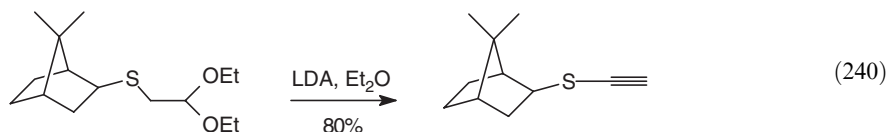


The elimination reaction of *o*-haloaryl triflates, by exposure to *n*-butyllithium, has proved to be a useful method for synthesizing aryne intermediates. Due to their extreme reactivity, these are usually generated and reacted *in situ*, where they readily undergo thermal [2 + 2]-cycloaddition

reactions with olefins (Equation (239)) <1995TL3377>. Applications into the synthesis and uses of arynes have been the topic of a recent review <2003T701>.



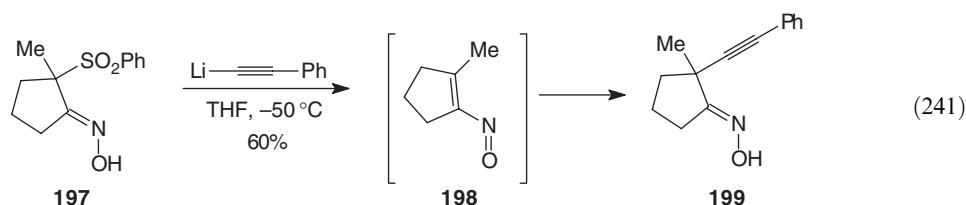
Chiral alkynyl thioethers have been prepared in excellent yield via an LDA-directed double-elimination reaction of the corresponding acetal derivative (Equation (240)) <1997T8651>.



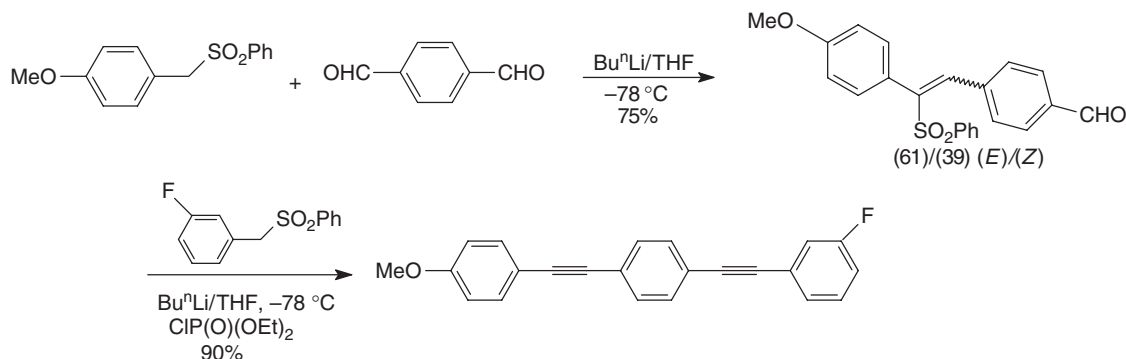
1.21.4.1.4 Elimination of sulfur, selenium, or tellurium functions

Possibly as a result of recent applications that provide access to alkynes from the elimination of alternative functional groups, developments in this area have not been significant, and the reader is directed to earlier reports <1995COFGT(1997)>.

Treatment of the cyclopentyl β -ketoxime sulfone **197** with the lithium anion derived from phenyl acetylene gave the alkynylated product **199** in good yield (Equation (241)) <1996T6903>. The intermediacy of the vinylnitroso species **198** was invoked as a possible precursor to **199**.

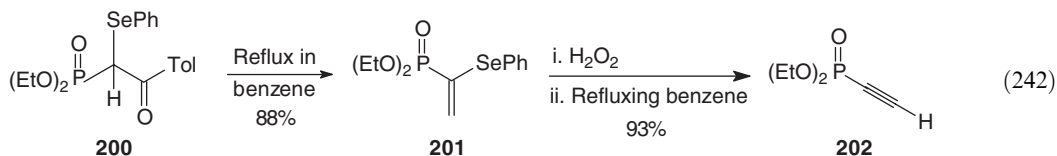


A double-elimination reaction of β -substituted sulfones, with the use of butyllithium, has been established in order to access unsymmetrically substituted aromatic polyynes (Scheme 29) <2003T5635>. The process is compatible with a number of different aryl substituents, including F, Br, CF₃, and MeO, to provide a useful method for synthesizing various aromatic polyynes.

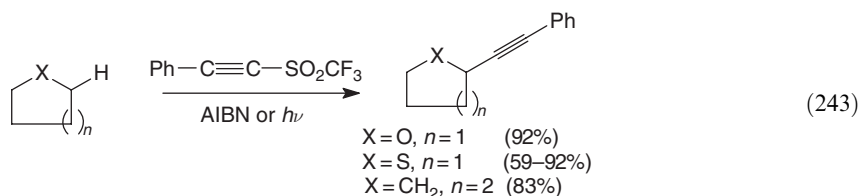


Scheme 29

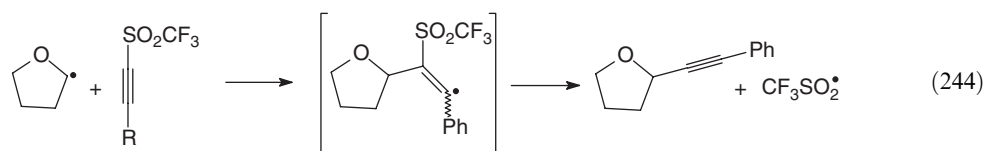
The first synthesis of α -phosphoryl vinyl selenides and selenoxides, which are derived from the corresponding sulfoxides, has been reported to provide access to alkynylphosphonates via a thermolysis reaction (Equation (242)) <1995TL2871>. Thus heating a benzene solution of the α -phosphorylsulfoxide **200** eliminates sulfenic acid to afford the corresponding α -phosphoryl-vinylselenide **201** in high yield. Quantitative oxidation followed by a thermal *syn*-elimination of selenoxide affords the corresponding α -phosphorylalkynes arrays **202** in high yield.



Ethers, sulfides, and hydrocarbons have been reported to react with alkynyl triflones under radical conditions, to afford substituted alkynes (Equation (243)) <1996TL5269, 1997TL6635, 1998TL8597, 2001T5263, 2001C.R.Acad Sci547>. The reaction may be initiated by light or peroxides.



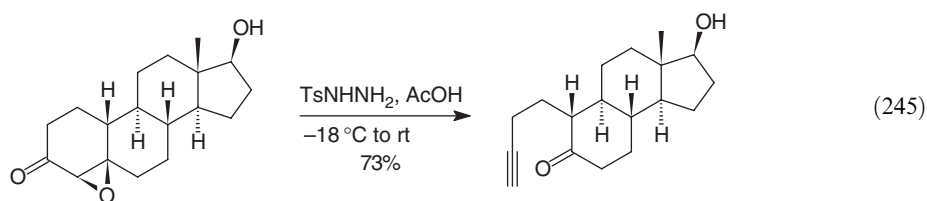
A mechanism has been suggested (Equation (244)) that proceeds via a vinyl radical, which eliminates the SO_2CF_3 radical to afford the corresponding alkyne. An alternative mechanism involving a carbene rearrangement reaction has been discounted on the basis of extensive isotope labeling experiments.

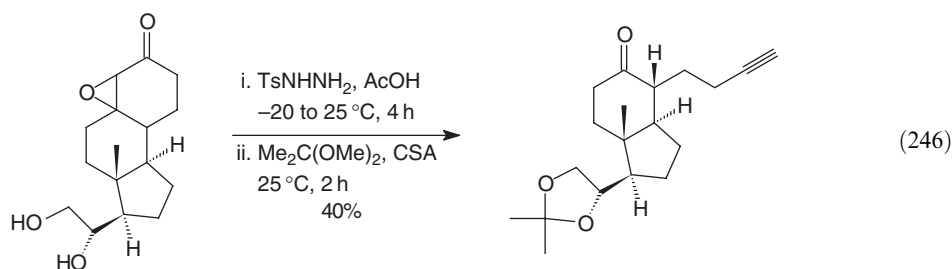


1.21.4.1.5 Elimination of nitrogen functions

One of the most widely used methods for the preparation of alkynes involves the elimination of molecular nitrogen from functional motifs that possess two adjacent nitrogen atoms. Examples include hydrazones and 1,2-dihydrazones as well as a variety of other nitrogen-containing heterocycles.

Fragmentation of α,β -epoxy hydrazones by base cleavage, the Eschenmoser–Tanabe ring-fragmentation reaction, has been used to access alkynylcarbonyls <1998T12071>. The reaction is of most use, synthetically, with epoxy ketones derived from α,β -unsaturated cyclic ketones as the resulting alkyne and carbonyl groups are linked. Recent applications have been directed to syntheses of *ent*-19-nortestosterone (Equation (245)) <2001TL1869> and second-generation steroids (Equation (246)) <1998T5425>.





The suggested mechanism invokes an epoxide ring opening and subsequent formation of the carbonyl followed by alkyne formation from the loss of nitrogen and a toluenesulfonate ion (Figure 6).

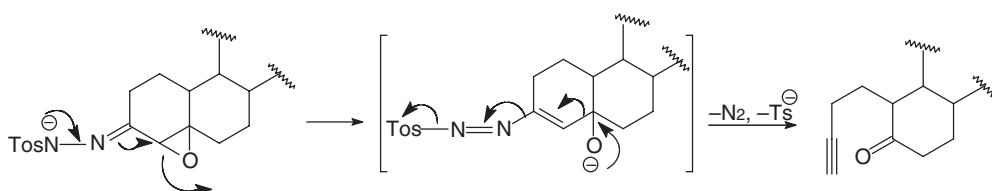
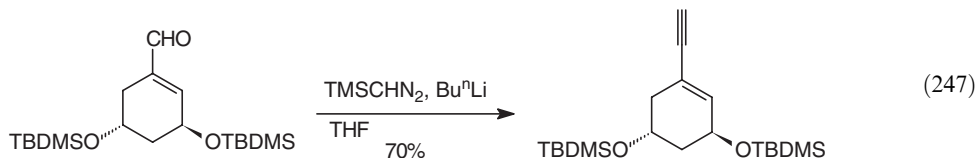


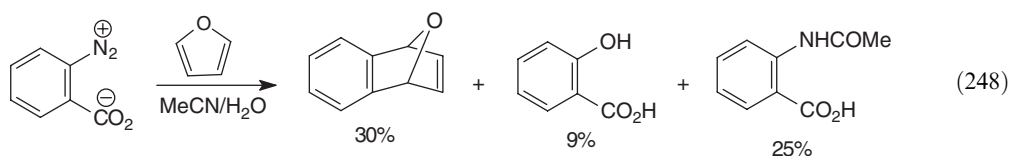
Figure 6

Compounds that contain a diazo functional group adjacent to a leaving group such as trimethylsilyldiazomethane have been used as a means to access alkynes *in situ*.

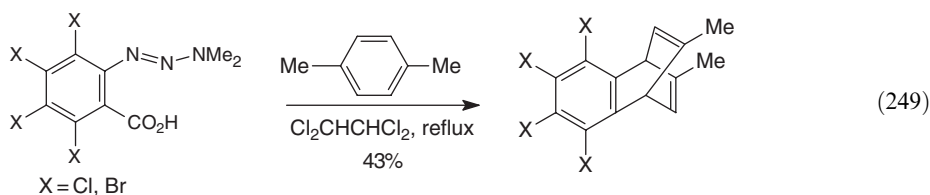
This chemistry has been applied to the synthesis of steroid A-ring precursors. These were then coupled to the corresponding C/D fragment to afford previtamin D₃ analogs (Equation (247)) <2000JOC5647, 2000TL775>. The complete array of diastereoisomeric enynes were available, via multistep syntheses, from the use of both enantiomeric forms of carvone <2002JOMC21>.



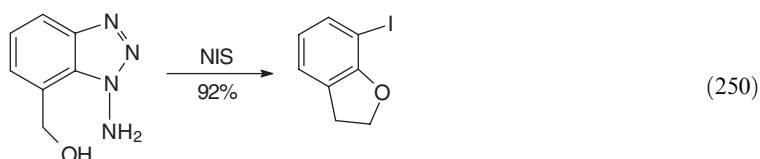
The diazotization of anthranilic acid and its derivatives has become a standard method for the formation of benzyne by the concomitant loss of nitrogen and carbon dioxide from the diazonium salt. The decomposition of the corresponding benzenediazonium-2-carboxylate also provides arynes from a similar process under appropriate conditions (Equation (248)) <1995T2959>. Although the results from these studies suggest that the diazonium salt decomposes by a number of different chemical processes, the total benzyne formed was optimized at (91%) at 60 °C in the presence trimethylamine hydrochloride.



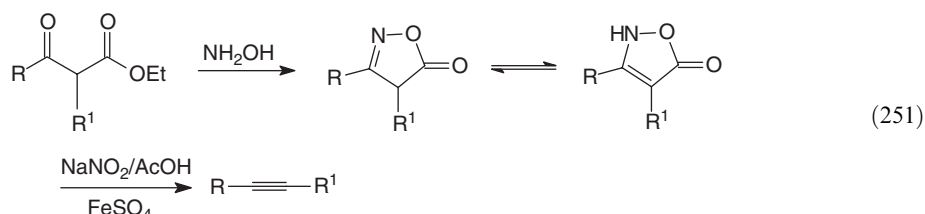
Further investigations established a method for generating arynes from the decomposition of 1-(2'-carboxyaryl)-3,3-dimethyltriazenes (Equation (249)) <1995T3929>.



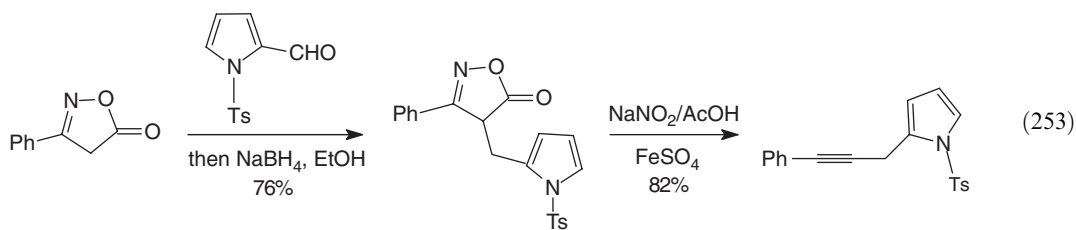
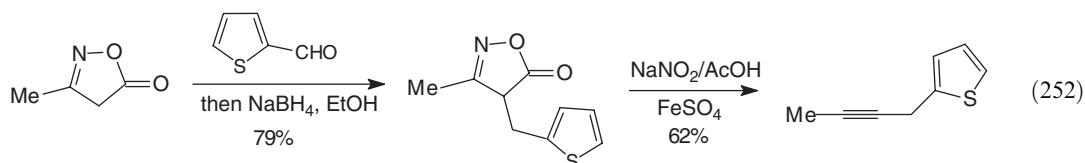
The generation of benzyne from other heterocycles such as 1-aminobenzotriazoles, that contain a strategically positioned *o*-hydroxyethyl motif, has been reported (Equation (250) <1994SL253>). The intramolecular trapping process provided access a range of iododihydrobenzofurans. Other applications of arynes in organic synthesis have been reviewed <2003T701>.



A new method for converting β -keto esters into alkynes via nitrosation of the corresponding isoxazolino-5-one derivative in the presence of ferrous sulfate was first described in 1991 (Equation (251))<1991TL5321>

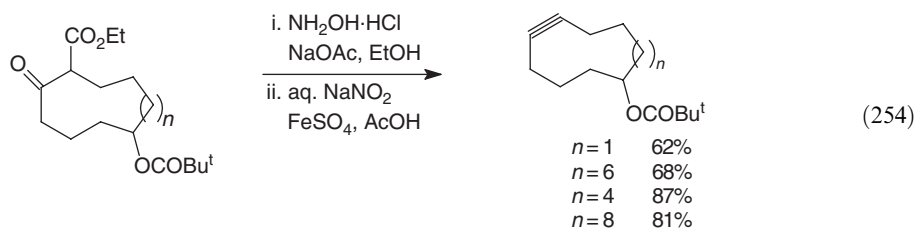


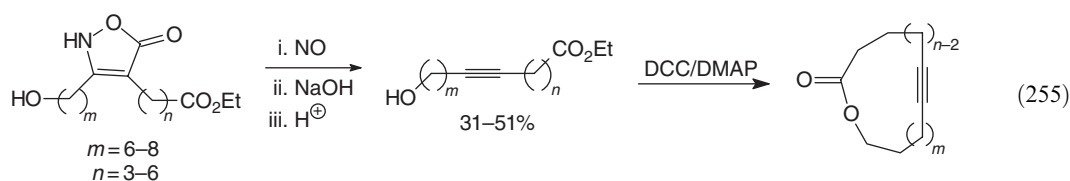
Applications of this chemistry in the synthesis of functionalized alkynes have since been developed from the condensation reaction of derivatized isoxazolinones with various carboxaldehydes (Equations (252) and (253)) <1996TL8735>.



Using ketones, instead of aldehydes in the condensation step, provides a means to access branched alkynes. A further, very useful application of the conversion of isoxazolinones into alkynes, has been in the synthesis of large-ring alkynes, where typically the alkyne moiety is installed prior to the ring-closure step.

The following examples serve to illustrate this transformation for the synthesis of cycloalkynones (Equation (254)) <1995TL5737> and alkynolides (Equation (255)) <1999T2639>.





1.21.4.1.6 Elimination of phosphorus, arsenic, antimony, or bismuth functions

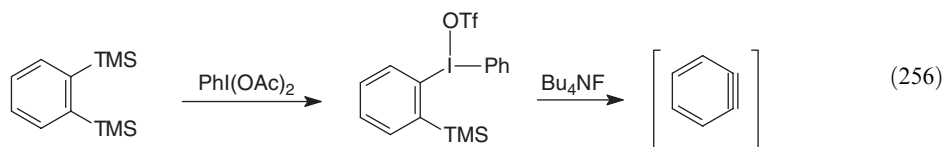
Wittig-type reactions between phosphorus-based ylides, with either ketones or aldehydes, have been reported as a method for the preparation of alkynes. Unlike the use of Wittig reagents in alkene synthesis, however, their use for preparing alkynes usually precedes other heteroatom elimination steps. As a result, examples that illustrate the elimination of phosphorus moieties for the synthesis of alkynes are somewhat limited and frequently require forcing experimental conditions associated with flash vacuum pyrolysis (FVP) or from heat treatment to facilitate thermal extrusions of triphenylphosphine oxide.

These techniques have tended to be replaced by the myriad of other milder and readily accessible methods for the synthesis of alkynes that have been reported in the literature in recent years. For examples in the use of FVP for the synthesis of alkynes, the reader is directed to prior investigations in this relatively unexploited area <1995COFGT(1)997>.

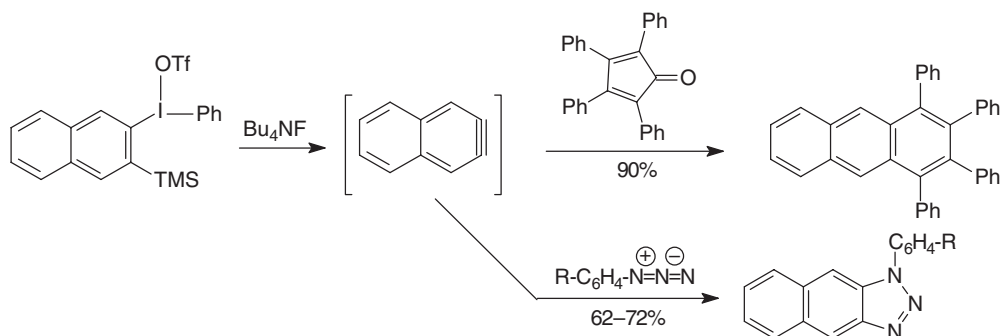
1.21.4.1.7 Elimination of boron, silicon, or germanium functions

Methods to access alkynes from the elimination of boron, silicon, or germanium, from a suitable 1,2-disubstituted alkene or aryl derivative, via the nucleophilic displacement of the heteroatom followed by a subsequent β -elimination reaction of a halogen or other suitable leaving group have been limited.

Exposure of *o*-bis-(trimethyl)benzene to $\text{PhI}(\text{OAc})_2$ affords phenyl{*o*-(trimethylsilyl)phenyl}-iodonium triflate. This reagent has been reported to serve as a new and highly efficient precursor of benzene from an elimination reaction in the presence of fluoride ions (Equation (256)) <1995CC983>.

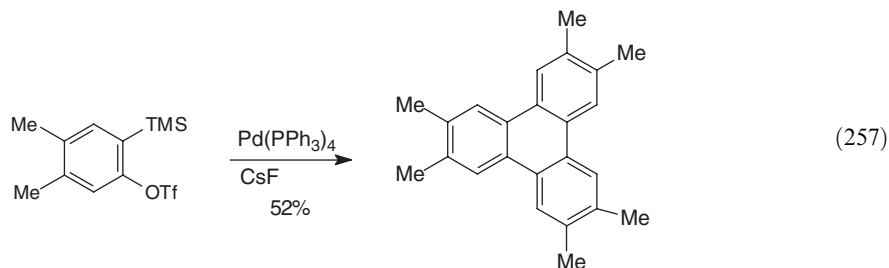


Exposure of the aryne to a range of typical trapping agents provides quantitative yields of the adduct under extremely mild and neutral reaction conditions. The same group has extended the scope of the reaction in order to access 1,2,3,4-tetraphenylantracene and a triazole (Scheme 30) <1998JOC8579>.



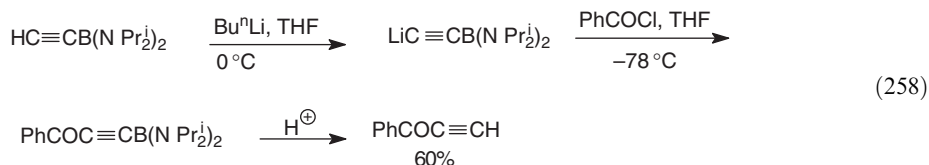
Scheme 30

An efficient palladium-catalyzed trimerization of arynes has been reported as a method for the synthesis of triphenylenes. These are core components of many discotic liquid crystals. The formation of the aryne is initiated via a fluoride-induced silicon fragmentation process (Equation (257)) <1998AG(E)2659, 1997S1007>.



More recent developments in this chemistry have focused upon the regioselectivity of the reaction <1997CC1615, 1998AG(E)2659>, the synthesis of strained polycyclic compounds <1999OL1555>, catalyst ligands <1999TL7533>, naphthalene/phenanthrene formation <1999JA5827>, synthetic applications using more complex arynes <1999TL7533, 1999JA5827, 2000JOC6944, 2000SL1061>, arynes as partners in carbopalladation reactions with π -allylpalladium chloride <2000AG(E)173> and bis- π -allylpalladium complexes <2000TL729>, and conversion to *o*-substituted arylstannanes <2001CC1880>.

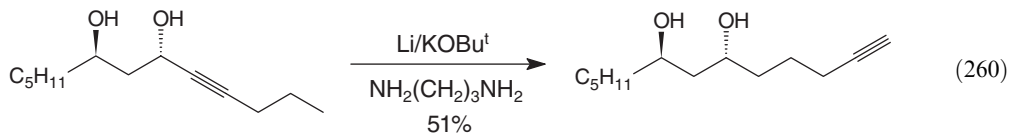
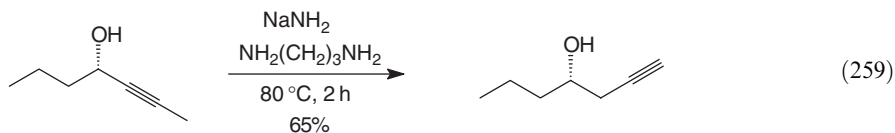
Lithium bis-(di-*iso*-propylamino)boracetylide has been shown to be a novel reagent for the synthesis of terminal alkynes <1996S45>. Its use as a synthetic equivalent for lithium acetylide and the corresponding reactions with electrophiles has also been reported (Equation (258)) <1997TL8863>. The boracetylide reagent is reported to be air-sensitive but keeps indefinitely under an inert atmosphere at ambient temperatures.



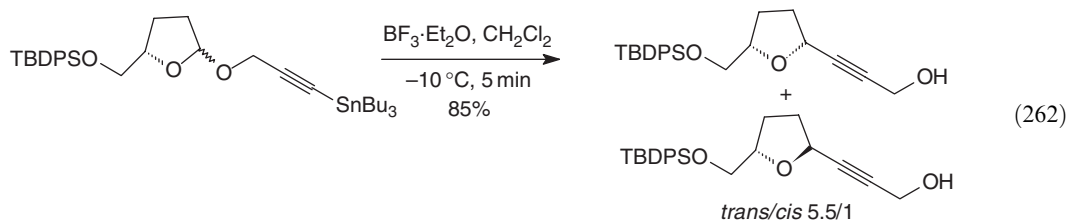
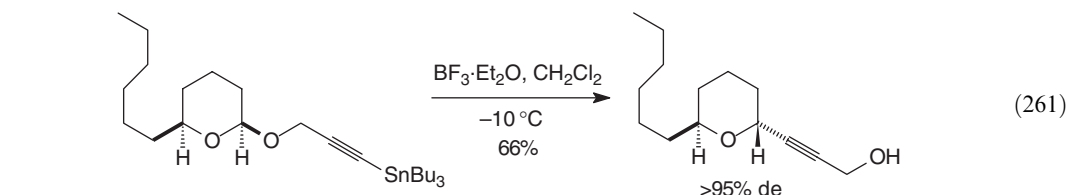
Electrophiles consisted of acyl halides, aldehydes, alkyl, allyl, and benzyl halides—of which the alkyl halides proved to be unreactive upon exposure to the boracetylide, whereas in contrast reaction with acyl chlorides provided optimum yields of terminal alkynes.

1.21.4.1.8 Formation by isomerization reactions

Exposure of a methine or methylene carbon atom, alpha to a carbon—carbon triple bond, with a strong base facilitates an isomerization reaction of the triple bond. For linear alkynes, equilibrium tends to favor internal alkynes; however, isomerization of the more thermodynamically stable internal alkyne to a terminal alkyne may be achieved with the use of a strong base such as sodamide in an amine solvent (Equation (259)) <1996TL8613>. The acetylene Zipper reaction <1981TL4171>, the base-assisted multipositional isomerization of internal alkynes has become a useful method for accessing terminal alkynes. Applications of this transformation to the synthesis of optically active *anti*-1,3-diols have been reported (Equation (260)) <1998TL3103>.



Treatment of tributylstannylalkynyl tetrahydropyranyl ether derivatives (Equation (261)) <1998SL1091> or the corresponding tetrahydrofuranyl ether derivatives (Equation (262)) <2000AG(E)3622> with $\text{BF}_3 \cdot \text{Et}_2\text{O}$ affords an oxygen to carbon rearrangement reaction at the anomeric center in good yield and with an excellent diastereoselectivity.



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1.22

Ions, Radicals, Carbenes, and Other Monocoordinated Systems

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1.22.1 DICOORDINATE CARBANIONS (i.e., VINYLIC CARBANIONS)

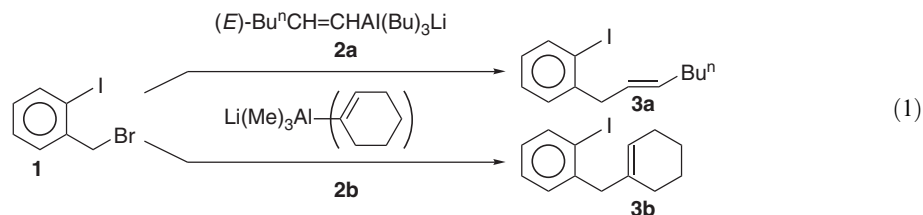
1.22.1.1 General Introduction

The general aspects of vinyl carbanion formation were highlighted in chapter 1.22 of COFGT (1995, pp. 1087–1145). The synthesis and uses of vinyl metal reagents have recently been reviewed <2000CRV1891>. Of interest is the emergence of allyl zincation of substituted vinyl metals, which allows efficient access to *gem*-1,1'-dimetallic species <2001ACR640, 1996CRV3241>. Palladium-mediated cross-coupling reactions of various vinyl organometallics are increasingly employed in target-directed synthesis and in catalyst discovery/design and have been extensively reviewed <2000CRV3009, 2003CC1787, 2002AG(E)4176, 2000CRV3257>. The following sections, which detail generation and uses of vinyl anion reagents, are separated according to individual elements.

The selection of material taken from the literature reflects the general interest in the different areas since 1995. Given the large amount of attention that has been focused on the generation, use, and application of dicoordinate carbanions (vinylic carbanions), this chapter contains the largest number of references to literature examples. Each section contains lead references to reviews or important highlight publications, which should aid the reader.

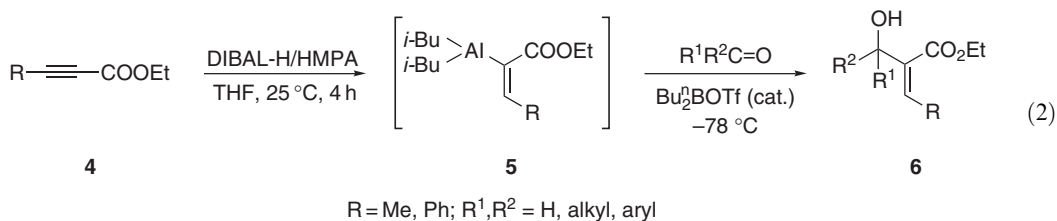
1.22.1.2 Vinylaluminum Reagents

The reaction of *o*-iodobenzyl bromide **1** with aluminates **2a** and **2b** provided **3a** and **3b**, respectively, in good yield (Equation (1)) <1996JA5904>. The resultant products have been employed to probe the Pd-catalyzed carbonylation of ω -vinyl-substituted *o*-iodoalkenylbenzenes <1996JACS5904>.



1.22.1.2.1 Formation by addition to alkynes and allenes

Vinylaluminum reagents **5** are formed as intermediates on reacting β -substituted propiolates **4** with DIBAL-H (Equation (2)) <1998TL4607>. Further reactions of **5** with aldehydes and ketones in the presence of catalytic amounts of Lewis acids affords β -substituted α -(hydroxy-alkyl)acrylates **6**. The reaction proceeds stereospecifically to give only the (*Z*)-isomers in good yields. Activated ketones, such as α -keto esters, α -acyl cyanides, and α -acetylenic ketones, undergo the same reaction in the absence of a Lewis acid <1999TL627>.



Functionalized allyl alcohols may be accessed by reaction of [α -(ethoxycarbonyl)vinyl]diisobutylaluminum, or the β -methyl or β -phenyl derivatives, with aldehydes and ketones <2003JOC9310>.

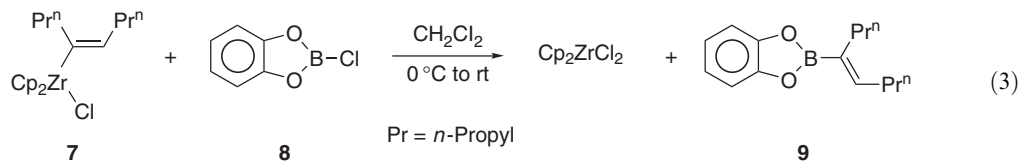
1.22.1.3 Vinylboron Reagents

The palladium-catalyzed cross-coupling reactions of various vinylboron compounds have been reviewed <1995CRV2457>. Hydroboration catalyzed by transition metal complexes, including the addition of boranes across acetylenic bonds to give vinylboranes, has also been the subject of a review <1997T4957>.

1.22.1.3.1 Formation of vinylic carbanions by deprotonation, metal-halogen exchange, and transmetallation

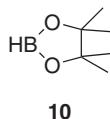
To overcome the limitations of the steric hindrance to the production of boron stabilized carbanions, various alkylbis(2,6-dimethyl-4-methoxyphenyl)boranes ((DMP)₂BR) have been synthesized <1994T13775>. Alkylations and condensations with aldehydes from the anions of (DMP)₂BR were studied. Although the isolation of (DMP)₂BH was not successful, the borane was readily trapped with alkynes to yield alkenylboranes <1994T13775>.


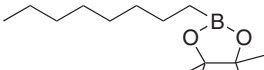
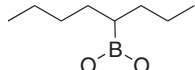
The reaction of alkenylzirconium compounds with a boron halide results in exchange of the halogen and organic group to give an alkenylborane. The migration process to a variety of boron halides is facile, yielding a series of alkenylboranes in good yields <1995T4297>. For example, 4-octenylzirconocene chloride **7** was transmetalated with 1 equiv. of *B*-chlorocatecholborane **8** in 80% yield (Equation (3)). Transmetalation of this same alkenylzirconocene with 1 equiv. of boron trichloride, followed by methanolysis, gave the expected 4-octenyldimethoxyborane **9** in 75% yield.



1.22.1.3.2 Formation by addition to alkynes and allenes

Pinacolborane (PBH) **10** is an excellent stoichiometric hydroboration reagent for alkenes and alkynes in the presence of catalytic amounts of transition metals <1996TL3283>. Whilst Wilkinson's catalyst $[(\text{Ph}_3\text{P})_3\text{RhCl}]$ gives the terminal alkylpinacol boronates such as **12a** from alkene **11**, $\text{Rh}(\text{CO})(\text{PPh}_3)_2\text{Cl}$ gives the internal alkyl pinacolboronates **12b** in excellent regioselectivity. Rhodium and nickel are also extremely effective catalysts for the hydroboration of alkynes with PBH (Equation (4)).



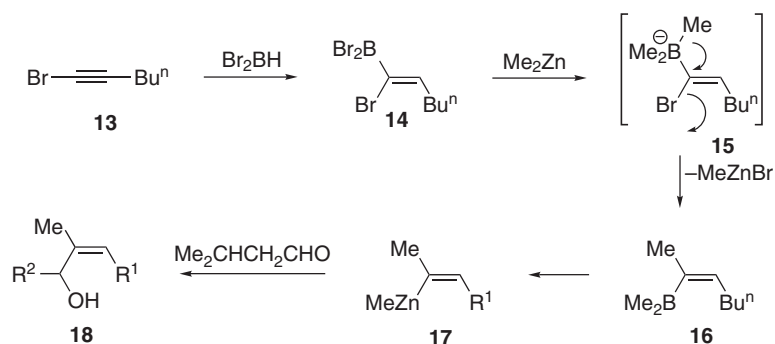
Entry	Alkene	Catalyst	Product ratio		Yield (%)
1	<div>Trans-4-octene</div> <div></div> <div>11</div>	RhP(Ph ₃) ₃ Cl	<div></div> <div>12a</div> <div>100</div>	<div></div> <div>12b</div> <div>0</div>	92
		Rh(CO)(PPh ₃) ₂ Cl	3	97	94

(4)

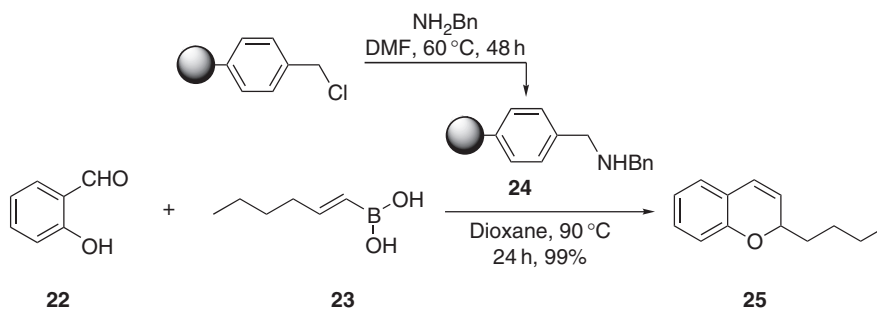
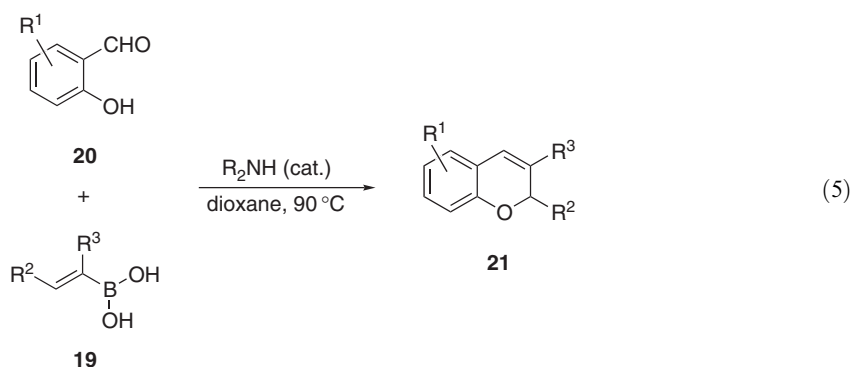
A one-pot, multicomponent-coupling reaction that allows facile access into (*Z*)-trisubstituted allylic alcohols in a stereocontrolled manner has been developed <2004JA3702>. Hydroboration of 1-bromoalkynes **13** with a dialkylborane, followed by addition of dimethylzinc to the resultant 1-bromo-1-alkenylborane **14**, occurs with concurrent migration of a methyl group from boron to the alkene terminus, through **15** to give **16** (Scheme 1). This key migration occurs with inversion at the vinylic centre. *In situ* transmetalation of the newly formed (*Z*)-vinylborane **16** with dimethylzinc then generates a stereodefined (*Z*)-vinylzinc species **17** that reacts with aldehydes to give isomerically pure (*Z*)-allylic alcohols **18**.

1.22.1.3.3 Applications in synthesis

Vinylboronic acids **19** undergo condensation reactions with salicyl aldehydes **20** to give 2*H*-chromene compounds **21** (Equation (5)) with ejection of an amine upon heating. A catalytic preparation of 2*H*-chromenes **25** using resin-bound amine **24** was further reported, which allowed for the convenient incorporation of a variety of components (**22** + **23** → **25**) (Scheme 2) <2000OL4063>.

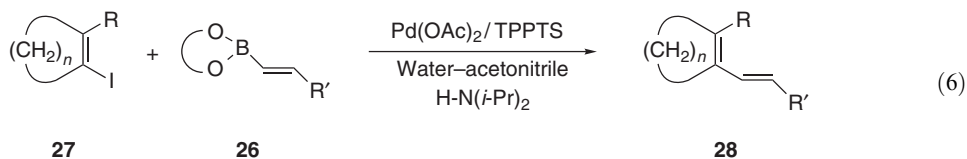


Scheme 1

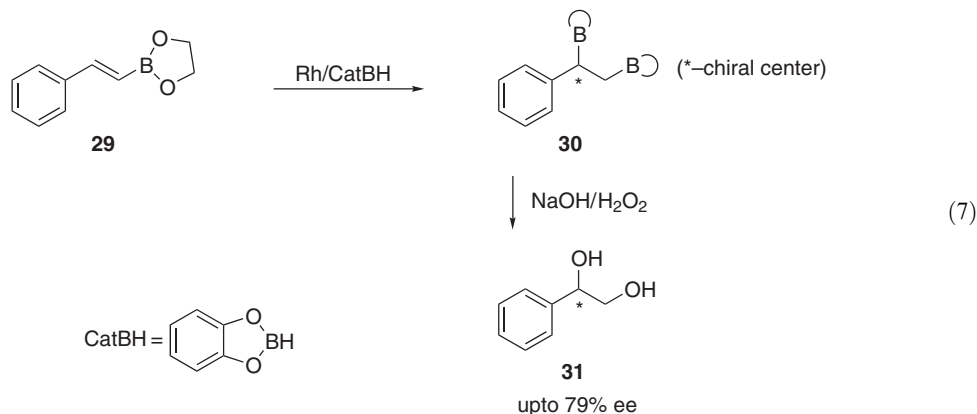


Scheme 2

Vinylboronic acids and vinylboronates undergo Suzuki-type cross-coupling reactions [<1995TL1443, 1996SL893, 1998JA657>](#). For example, vinylboronic esters **26** couple with methyl (*Z*)-3-iodoacrylate **27** to give the corresponding dienes **28** in good yield (Equation (6)). The watersoluble catalyst system was generated *in situ* from palladium(II) acetate and *m*-sulfonated triphenylphosphine (TPPTS).



Alkenylboronic esters such as (*E*)-2-(2-phenylethenyl)-1,3,2-dioxaborolane **29** undergo a second hydroboration reaction with catecholborane (CatBH), in the presence of neutral and cationic rhodium complexes modified by various diphosphine ligands, to give 1,2-diboryl compound **30** <1996TA5>. The resulting 1,2-diboryl intermediate **30** was oxidized with alkaline hydrogen peroxide to give the corresponding 1,2-diol **31**, with enantioselectivities up to 79% ee (Equation (7)).



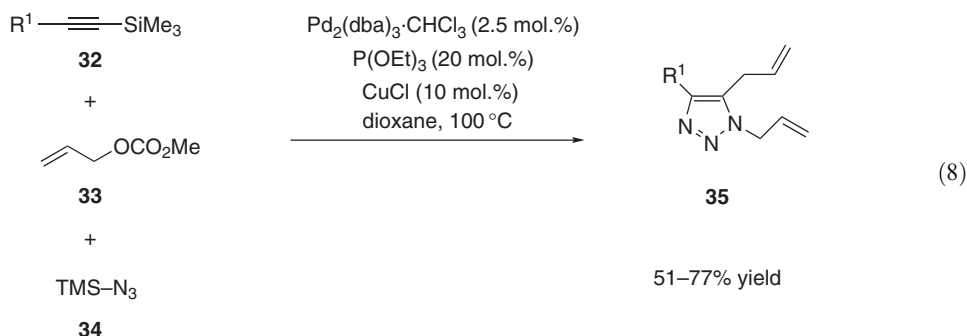
1.22.1.4 Vinylcopper Reagents

1.22.1.4.1 Formation of vinylic carbanions by deprotonation, metal–halogen exchange, and transmetalation

Enynes and enediyne systems have been obtained on transmetalation of vinyl tellurides with cyanocuprates <1999TL265, 1995SL1145, 1995T9839>.

A practical and versatile difluorovinylcopper reagent has been synthesized through transmetalation of an α -lithio- β,β -difluoroenol carbamate with Li_2CuX_3 <1996TL5975>. The resultant vinylcopper reagent is thermally stable and reacts with activated haloalkanes and acid chlorides to give products in moderate-to-high yields. The sequence expands the scope of building block chemistry available from trifluoroethanol.

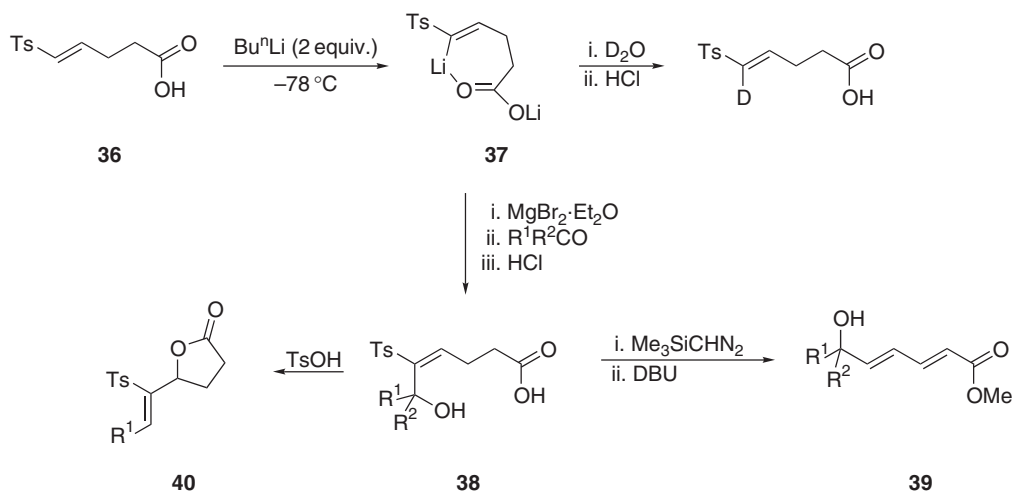
Trisubstituted 1,2,3-triazoles **35** may be obtained by reaction of unactivated silylacetylenes **32**, 2equiv. of allyl carbonates **33** and trimethylsilyl azide **34**, in the presence of a palladium(0)–copper(I) bimetallic catalyst system (Equation (8)) <2004TL689>. The reaction is proposed to proceed via a [3 + 2]-cycloaddition process between an alkynylcopper species and azide, followed by the reaction between the vinylcopper intermediate and a π -allyl-palladium(II) complex.



1.22.1.5 Vinyl lithium Reagents

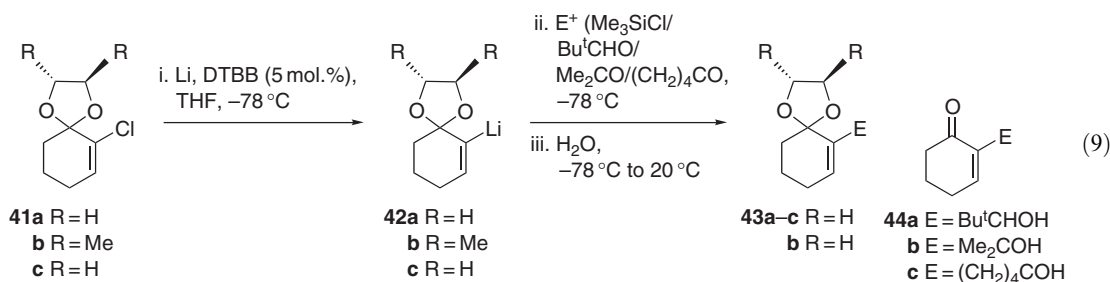
1.22.1.5.1 Formation of vinylic carbanions by deprotonation, metal–halogen exchange, and transmetalation

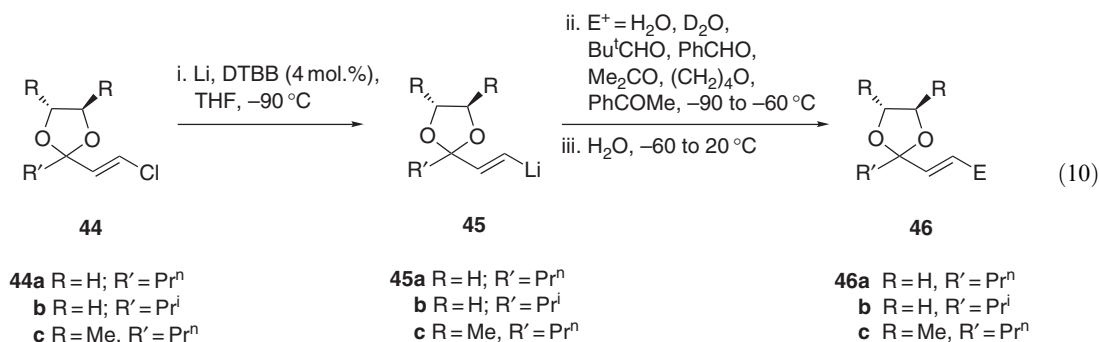
(*E*)-5-(*p*-Toluenesulfonyl)pent-4-enoic acid **36** undergoes lithiation at the vinylic position to give **37** (Scheme 3) <1999TL5957>. Reaction of **37** with carbonyl compounds gives carboxylic acids **38** in good yields. Esterification of **38** with trimethylsilyldiazomethane, followed by dehydro-sulfinylation with DBU, affords esters of the type **39**. Lactonization of **38** affords **40** in good yield.



Scheme 3

α -Lithiated α,β -unsaturated cyclic ketones, such as the protected ketal **42**, can be prepared by halogen–lithium exchange of the corresponding chlorinated precursor **41** with excess lithium powder and a catalytic amount of 4,4'-di-*t*-butylbiphenyl (DTBB) in THF at low temperature (Equation (9)) <1997T4921>. Species such as **42** may be quenched by appropriate electrophiles to give compounds **43**, and the enone derivatives, after hydrolysis. Acyclic compounds **44** undergo a similar reaction via vinyl lithium species **45** (Equation (10)). Further treatment of **45** with electrophiles such as aldehydes or ketones, affords **46**, and the enone derivatives after hydrolysis.

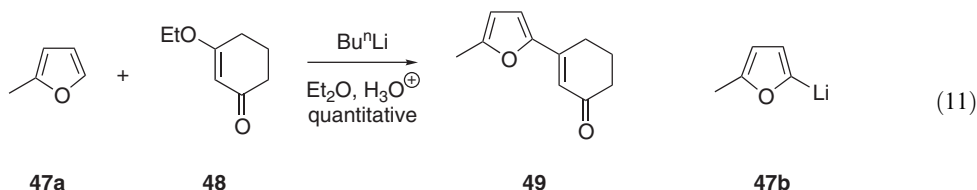




Vinyl lithium reagents, obtained from bromine/lithium exchange with *t*-butyllithium, react with diisopropyl squarate, followed by 2-lithiopropene, to give tricyclic enones <1998EJOC1709, 1997JOC1723>.

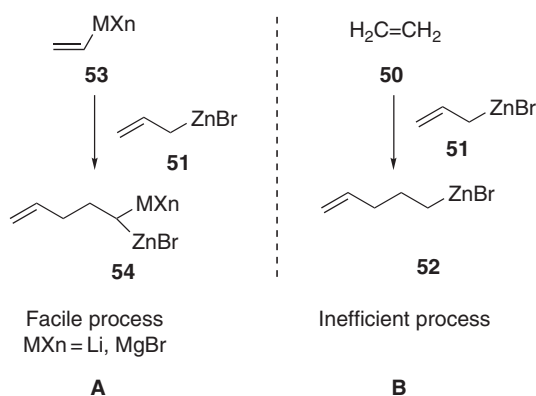
1.22.1.5.2 Applications in synthesis

Lithiated 2-methylfuran **47b** (available by lithiation of **47a**) reacts with 3-ethoxycyclohexenone **48** to give the corresponding α,β -unsaturated ketone **49** in excellent yield (Equation (11)). The reaction was the first step in the synthesis of sesquiterpenolide (\pm)-decipienin A <1999T6997>. Vinyl lithium chemistry is commonly employed in target directed synthesis and the total synthesis of taxol represents a lead example <1995AG(E)1723, 1995AG(E)452>.



The introduction of two vicinal methyl groups, either *syn* or *anti*, on a nonfunctionalized linear chain, starting from (*E*)- or (*Z*)-1-metalla-1-alkenes and crotylzinc bromide has been reviewed <2001ACR640>. It has been demonstrated that this addition requires the presence of zinc salts, and that good regio- and diastereoselectivities can be obtained if a low polarity solvent is used. The vinyl metal partner can bear heteroatoms (O, N, S) on allylic or homoallylic positions, and the crotylzinc reagent can be replaced by a silylallyl or an alkoxyallylzinc reagent. In all cases, the di-, tri-, or tetrasubstituted linear skeletons are formed diastereoselectively. The influence of Lewis acid additives, e.g., MgBr₂, is important, and the C—Zn bond, in the clusters involved in the various transition states, has a tremendous importance in promoting the observed high stereoselectivities <2000JA11791>.

A high diastereoselection may be obtained during addition of a crotylzinc reagent to a (*Z*)- or an (*E*)-vinyl lithium reagent to give *gem*-1,1'-dimetallic species <1999MI001>. The key point is the use of ether as a solvent. Ether is less basic than THF, which allows coordination of zinc with the electron-rich C=C bond. The reaction is faster and occurs at $\sim -50^\circ\text{C}$. However, zinc metal insertion in the allyl—Br bond is not efficient in ether. The problem is solved by using allyl Grignards (made in ether) via a transmetalation with zinc bromide. In this case, MgBr₂ is formed, which may have a role in accelerating the addition step as well as in further reactions of the *gem*-dimetallics (*vide infra*). Preformed vinylzinc bromide reacts directly with an allyl Grignard reagent, as do other vinyl metals (Li, B, MgX, Al, Cu), but only if zinc (or cadmium) salts are added in the latter case: the requirement of zinc is crucial. The efficiency of this reaction as compared to the addition of allyl metals to nonmetallated olefins is markedly different. For example, ethylene **50** reacts under pressure (20–80 °C at 40–70 atm in 2–100 h) with allylzinc compounds **51** in ether to give the corresponding unsaturated organometallics **52** (Scheme 4, process B). The key question is why is the metallated alkene **53** much more reactive toward

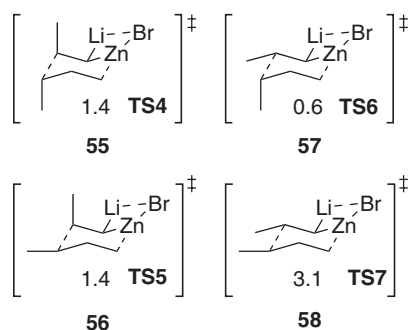


Scheme 4

addition of an allylmethyl reagent **51** (Scheme 4, process A)—they react readily at -40°C to give **54**—rather than a nonmetallated alkene as in process B, which requires more forcing conditions (temperature and pressure) [\[1999OL929\]](#).

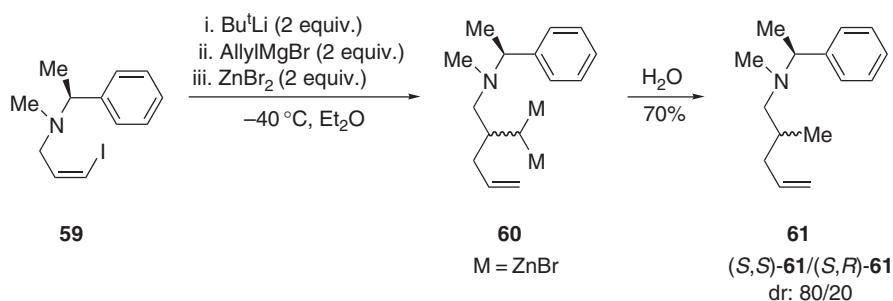
Theoretical calculations show that the allylzinc bromide and the vinyl lithium reagent first form a very stable complex, due to a square planar arrangement of the Li-C-Zn-Br [\[1999OL929\]](#). The transition state leads to an energetic lithio-zinc adduct, which gives the trimeric or tetrameric form of a di-zinc compound [\[1999JA8665\]](#).

It was initially postulated that a “metalla-Claisen rearrangement” wherein a zinc atom, in a preformed vinylallyl zinc, would play a role similar to that of oxygen in Claisen sigmatropy. The driving force for the reaction is the complexation to the LiBr-vinyl-allyl-Zn species. Furthermore, the product-forming step is endothermic. To account for this, the authors proposed the involvement of aggregation, which drives the reaction [\[1999OL929\]](#). Also of interest is the fact that the crotylzinc reagent, which is prone to metallopropanol, reacts preferentially in a cisoid-form (Scheme 5 [\[1999OL929\]](#)). This accounts for the observed *syn*- or *anti*-products, depending on the geometry (*E* or *Z*) of the starting vinyl lithium used [\[1999OL929, 1999JA8665\]](#)—with (*Z*)-propenyllithium, the (*Z*)-configuration of the crotyl reagent leads to a transition **55** state that is 1.4 kcal mol^{-1} lower in relative energy than that starting from the (*E*)-isomer **56**. Alternatively, when (*E*)-propenyllithium is employed, the same holds true, with an even larger energy difference of 2.5 kcal mol^{-1} more (**57** versus **58**).



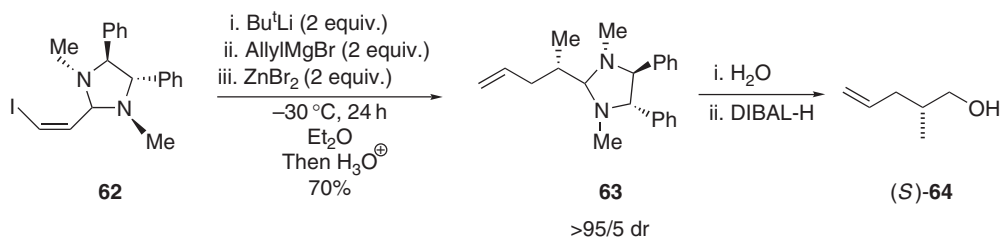
Scheme 5

When the allylic carbon of the (*Z*)-vinyl metal partner is primary, it is possible to induce face selection via the introduction of a chiral appendage on vinyl iodide **59** (Scheme 6). Thus, a 1-phenylethyl substituent on N, derived from (*S*)-*N*-methyl methylbenzylamine, promotes a facial choice, which is also attributed to π -stacking between the phenyl group and the vinyl metal in **60**, so that an 80:20 dr is obtained on quenching to give **61**. If the phenyl moiety is replaced by a 1-naphthyl, the dr is enhanced to 96:4 [\[1998TL4821\]](#).



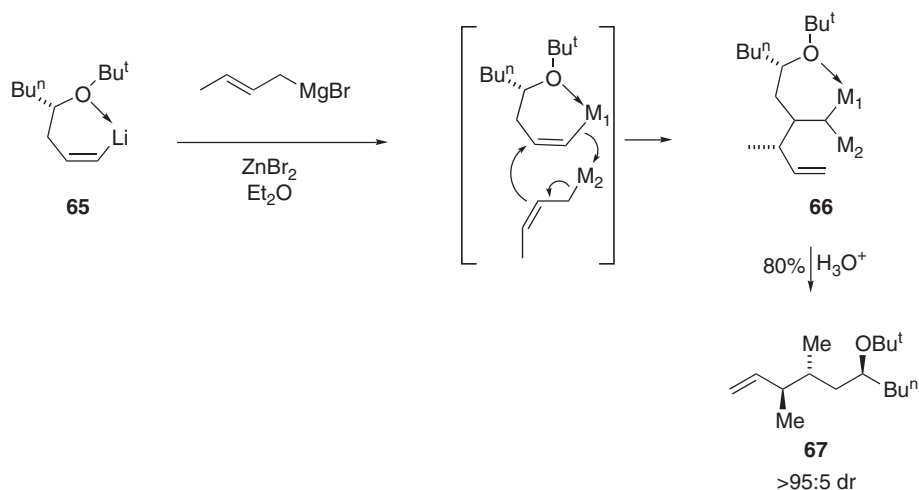
Scheme 6

Z- β -Iodoacrolein can be derivatized to a C_2 -symmetric aiminal **62** and submitted to an iodine/lithium exchange, followed by allyl zincation, which forms the major diastereoisomer **63**, easily hydrolyzed to the parent aldehyde however, the alcohol **64** was isolated after reduction of the aldehyde with DIBAL-H (Scheme 7) <1998TL4821>.



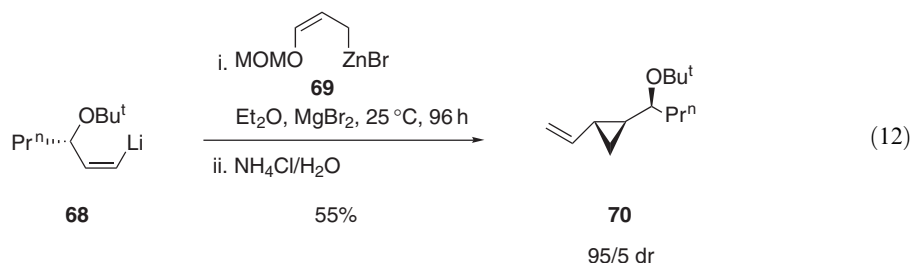
Scheme 7

In vinylolithiums derived from homoallylic ethers **65**, the chiral center is more remote in **66** (γ to the metal). Nevertheless, excellent induction occurs, delivering a 3,4,6-trisubstituted 1-alkene **67** (Scheme 8) <1996TL5873>. *O*-Coordination to the metal centre is proposed to account for the remote stereinduction.



Scheme 8

A mono-addition product **70** arises from the reaction of the vinyl lithium **68** with allylzinc reagent **69**, which immediately undergoes γ -elimination of the OMOM moiety. Magnesium bromide is added to accelerate the addition process. The process allows direct access to 2-vinyl-substituted *trans*-cyclopropyl *syn*-secondary carbinols **70**, with three defined stereocentres (Equation (12)) <2000TL1733>.



1.22.1.6 Vinylmagnesium Reagents

The synthesis of highly functionalized organomagnesium reagents, prepared through halogen–metal exchange, has been reviewed <2003AG(E)4302>. The synthesis and applications of *gem*-1,1'-dimetallic compounds containing magnesium has been highlighted <2001ACR640>.

1.22.1.6.1 Formation of vinylic carbanions by deprotonation, metal–halogen exchange, and transmetallation

A general stereoselective approach to functionalized vinylmagnesium reagents via an iodine–magnesium exchange reaction is available <1999JOC1080, 2000TL3319>. 3-Iodoenoates are easily converted into highly functionalized (*Z*)-3-magnesiated enoates by an iodine–magnesium exchange reaction, which proceeds with complete retention of configuration of the double bond. The direct reaction of these reagents, and the copper(I)-mediated reactions, with various electrophiles give polyfunctional enoates <2001CC2068>. Halogen–magnesium exchange can be achieved using trialkylmagnesesates, facilitating the synthesis of vinylmagnesium reagents in good yield <2000AG(E)2481>.

A general preparation for vinylmagnesium reagents containing electron-withdrawing substituents in the α -position, such as CN, CO₂R, CONR₂, SO₂Ph, is possible by employing a low temperature (–40 to –30 °C) bromine–magnesium exchange process with *iso*-propylmagnesium bromide in THF <2001TL6847, 2002T4787>. The reaction may be used to prepare 5-magnesiated-1,3-dioxin-4-one compounds, bearing an alkoxy substituent in the β -position to the C–Mg bond.

Vinylmagnesium species have been prepared by reaction of allenes with allylmagnesium chloride in the presence of a catalytic amount of manganese(II) chloride. The resulting vinylmagnesium species react with a range of electrophiles <2003OL4623>.

The reaction of β,β -dibromo- or diiodo-unsaturated esters with 1 equiv. of *iso*-propylmagnesium bromide, in diethyl ether as the solvent, facilitate alkenylmagnesium carbenoid generation, which react with retention of configuration with electrophiles, providing highly functionalized unsaturated esters and lactones. Use of 2 equiv. of *iso*-propylmagnesium bromide results in a 1,2-migration, with retention of configuration, provides a useful route to tetrasubstituted esters and lactones <2003SI797>.

1.22.1.6.2 Applications in synthesis

Various vinylgallium dichlorides may be prepared by reaction of gallium trichloride with vinylmagnesium bromides <2002SL1137>. The former reagents undergo cross-coupling with aryl halides in the presence of a palladium catalyst <2002SL1137>.

The diastereoselective addition of vinylmagnesium bromide to the *N*-benzylimine, derived from 2,3-*O*-isopropylidene-D-glyceraldehyde, provides easy access to L- α -vinylglycine <1997S747>.

The conjugated addition of vinylmagnesium bromide to chiral α,β -unsaturated *N*-acyl oxazolidinones is promoted by Lewis acids, facilitating access to a series of enantiomerically pure β -branched 4-pentenoic acid derivatives in high diastereomeric excess <1997TL7317, 1998TL8561>.

1.22.1.7 Vinylpalladium Reagents

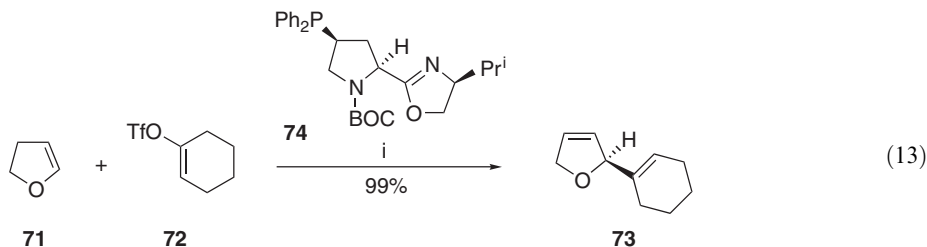
Palladium-catalyzed coupling reactions continue to expand in terms of both catalyst development and applications in target-directed synthesis (natural products, medicinal agents and materials). There have been several recent reviews of general interest <2000CRV3009, 2003CC1787, 2002AG(E)4176>.

1.22.1.7.1 Formation by metal–halogen exchange

The Heck reaction remains one of the most widely used Pd-catalyzed methodologies in synthesis and catalyst discovery and optimization <2000CRV3009, 2001T7449>. One of the major limitations for the Heck reaction is the precipitation of Pd metal, which results in catalyst deactivation. To combat this problem, more highly active palladium catalysts/precatalysts have been developed which offer enhanced thermal stability, higher turnover numbers and turnover frequencies <2003CC1787, 2002AG(E)4176, 2003JOM229>. Interestingly, it has been shown that palladium concentration is key to the successful coupling of iodobenzene with *n*-butyl acrylate <2003OL3285>. Essentially, negligible coupling is seen at a catalyst loading of 1.28 mol.% Pd(OAc)₂, but reducing the loading to 0.08 mol.% results in near complete conversion (>98%) to products. It has been proposed that higher palladium concentrations lead to aggregation and precipitation of palladium black, at a very early stage in the reaction. There is a key message here – if a Heck reaction fails to turnover, adding more catalyst to the reaction may not facilitate the coupling process!

Recycling precipitated palladium from ligandless Heck reactions has been an area of great interest for the production of fine chemicals <2001CJC1086, 2002TC101>. In general, the catalyst activity of precipitated palladium is poor. However, treatment with molecular iodine completely restores the activity of the catalyst, allowing palladium to be recycled many times <2002ASC996>.

There has been recent interest in the development of new ligand-catalyst systems for the intermolecular asymmetric Heck reaction (IAH) <2001OL161, 2001TA263>. For example, a series of proline-based phosphine-oxazoline ligands **74** may be used in combination with Pd₂dba₃ (dba = dibenzylideneacetone) to catalyze the IAH reaction of 2,3-dihydrofuran **71** with triflate **72** to give **73**, quantitatively in 86% ee (Equation (13)) <2001JOC7240, 2001TL365>. The specific choice of base and solvent is crucial to inducing high enantioselectivity.

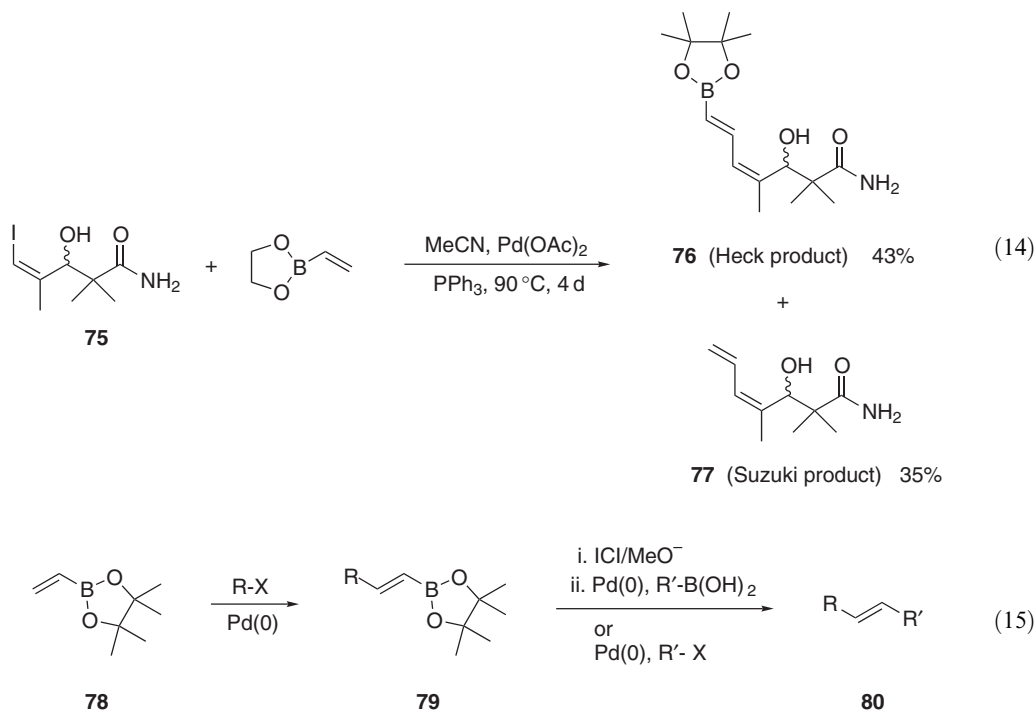


i. Pd₂(dba)₃ (1.5 mol.%), ligand **74** (3 mol.%), Et₃N (3 equiv.), alkene **71** (5 equiv.), benzene, rt, 36 h

Computational and mechanistic studies on the IAH reaction have been conducted <2001HCA3043>. There is a review detailing recent studies into the asymmetric intramolecular Heck reaction <2003CRV2945>. Studies on microwave assisted Heck reactions, including other general coupling processes, have also been highlighted <2002ACR717>.

1.22.1.7.2 Applications in synthesis

The first total synthesis of racemic phthoxazolin A included a partially selective Heck coupling of vinylboronate pinacol ester **78**, as a vinyl dianion equivalent, with vinyl iodide **75** to give **76** as the major product, with retention of the boronate ester functionality accompanied with Suzuki coupling product **77** (Equation (14)) <2000T5193>. Generally, **78** may be used for successive Heck and Suzuki reactions (**78** → **79** → **80**, Equation (15)) <1995TL3925>. Careful deoxygenation of the reaction mixture is important for successful Heck coupling <2000T5193>.



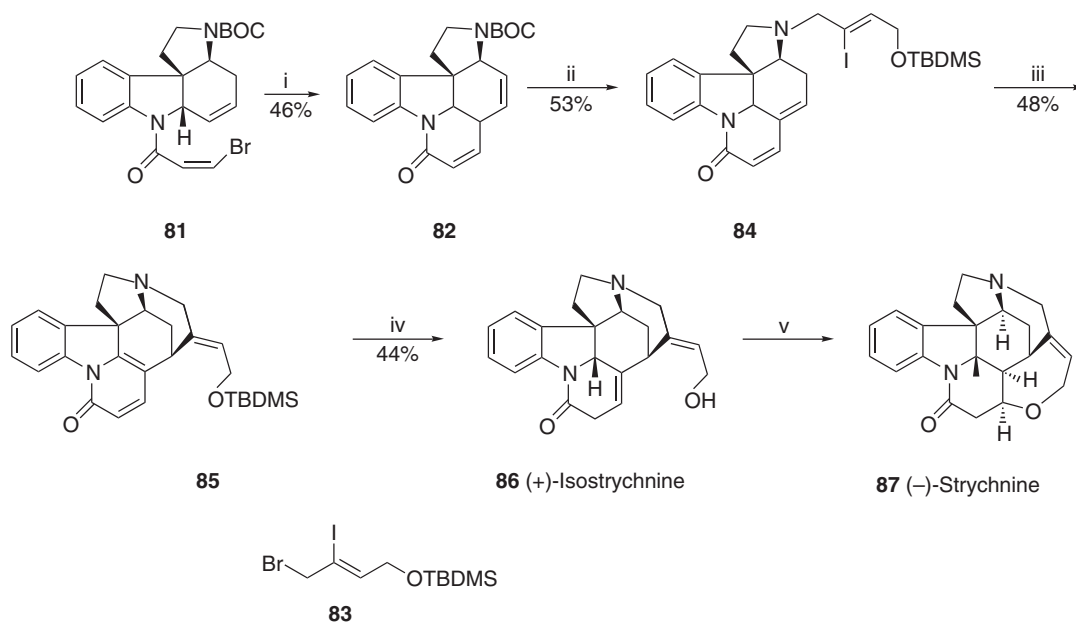
Heck coupling, as well as other coupling processes, played an important role in an elegant total synthesis of (–)-strychnine **87** <2002AG(E)1934>. Intramolecular Heck cyclization of vinyl bromide **81** gave **82**, with migration of the double bond in the cyclohexyl ring (Scheme 9). The addition of a second vinyl fragment **83** to **82** gives **84**, which facilitates a second intramolecular Heck cyclization to give pyridinone **85**, which proceeds with migration of the double bond into conjugation. Silyl deprotection to give **86** and then an intramolecular 1,4-conjugate addition reaction affords **87**.

A selective Stille–Heck coupling sequence of bromide **88** with alkenylstannanes **89** and alkyl acrylates **90** has been utilized for the synthesis of steroid and steroid analogs (Scheme 10) <2004AG(E)895>.

In the first step, **88** was selectively coupled (Stille) at the position bearing the triflate substituent (**89** → **91**). Of the reaction conditions investigated, the protocol developed by Farina and co-workers with triphenylarsine as a ligand, and a copper(I) co-catalyst proved to be best and gave yields in the range of 70–86%, although in this particular case, triphenylarsine need not be added <1993JOC5434>. This protocol has been used many times in the total synthesis of natural products, particularly where other coupling protocols have failed <1997OR1>. The subsequent Heck coupling of **91** with *t*-butyl acrylate using palladacycle **93** <1995AG(E)1844, 1997CEJ1357> in the presence of tetrabutylammonium acetate, gave the unsymmetrically substituted tricyclic 1,3,5-hexatriene *cis*-**92** in ~75% yield.

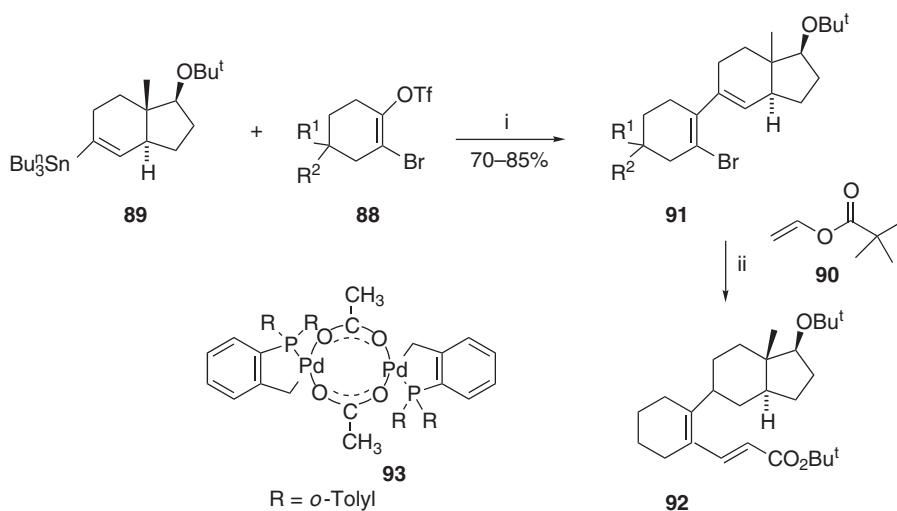
1.22.1.8 Vinylphosphorus Reagents

The formation of P–C bonds by the metal-catalyzed addition of P–H bonds present in P(III) reagents (hydrophosphination) and P(V) reagents (hydrophosphinylation and hydrophosphorylation) to alkynes has been reviewed <2004CRV3079>. The synthesis of phosphorus-heterocycles from vinylphosphines has also been reviewed <1994AHC59>. The application of phosphaaalkenes in organophosphorus chemistry has been highlighted <1999PS97>.



i. $\text{Pd}(\text{OAc})_2$ (10 mol.%), PPh_3 (20 mol.%), Pr_2NEt , DMSO, 80 °C, 1.5 h; ii. (a) NaOPr^i , (b) $\text{CF}_3\text{CO}_2\text{H}$, (c) **83**, Li_2CO_3 , DMF, 40 °C; iii. $\text{Pd}(\text{OAc})_2$, Bu_4NCl , K_2CO_3 , DMF, 70 °C, 0.5 h; iv. 1. LiAlH_4 , 2. HCl ; v. KOH , EtOH .

Scheme 9



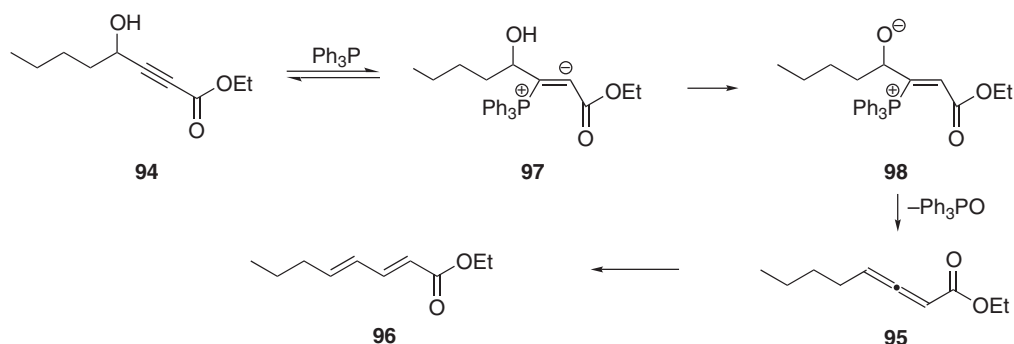
i. $\text{Pd}_2(\text{dba})_3 \cdot \text{CHCl}_3$ (10 mol.%), AsPh_3 (8 mol.%), CuI (5 mol.%), LiCl (3 equiv.), NMP, 65 °C, 5 h; ii. **93** (8 mol.%), Bu_4OAc (2 equiv.), *t*-butyl acrylate **90** (5 equiv.), DMF, MeCN, H_2O (5:5:1), 105 °C, 4 h

Scheme 10

1.22.1.8.1 Formation by addition to alkynes and allenes

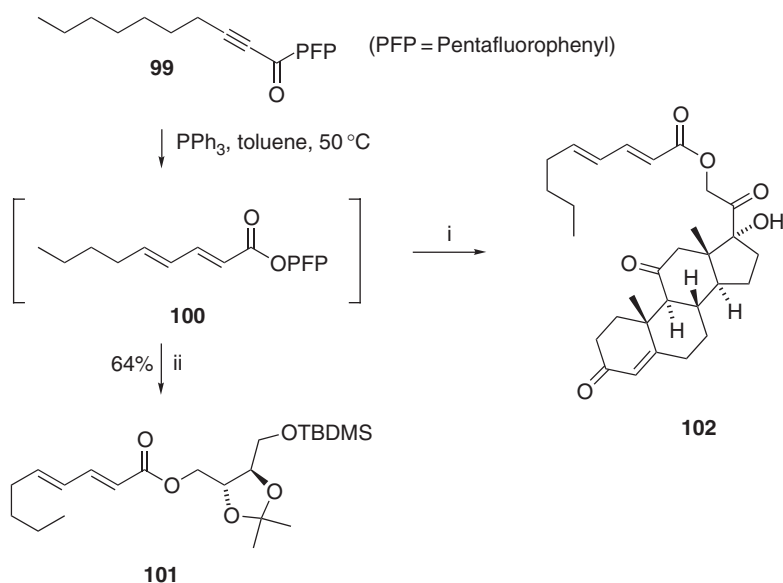
Nucleophilic tertiary phosphines such as Ph_3P , add to electron-deficient alkynes **94** and then eliminate from the reaction product, after a series of transformations [<2001ACR535>](#). The tertiary phosphine plays the role of a catalyst, and the reaction is proposed to proceed via a

vinyllic anion **97** formed β to the phosphorus group, followed by a hydrogen migration to give **98** (Scheme 11). The final products include allenes **95** or dienes **96**. These phosphine-catalyzed reactions are illustrated by the examples that follow.



Scheme 11

A simple and highly stereoselective isomerization reaction catalyzed by a phosphine such as that shown in Scheme 12 (**99** \rightarrow **100**), provides a practical method for the synthesis of useful polyenyl carbonyl compounds **101** and **102** <1997CC2305, 1998T1491, 1996CJC419>.

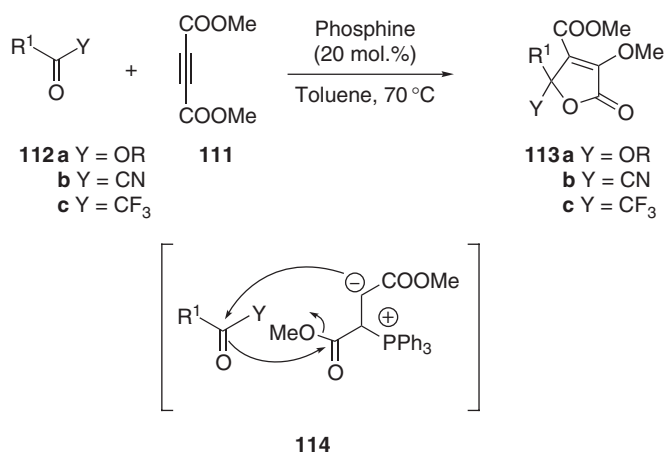


- i. R^*OH , DBU, LiBr, toluene, THF, 80°C , 10 h;
 ii. Cortisone, DBU, LiBr, DMF, toluene, 80°C , 14 h

Scheme 12

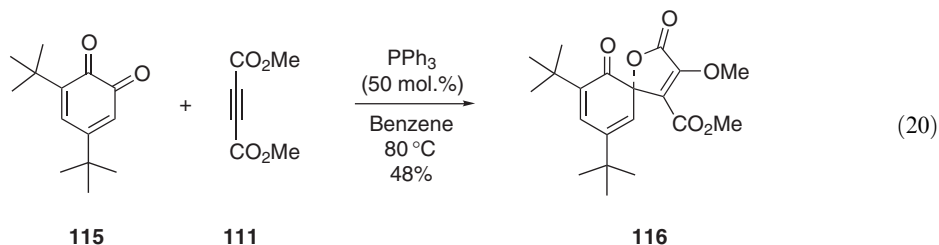
The phosphine-catalyzed γ -addition of nucleophiles (including **105**) to 2-alkynoates **103** to give substituted alkenoates **104** and **106** has been reported (Equations (16) and (17)) <1997JOC5670, 2000JOC3544>. Interestingly, demethoxylation of **106**, through cleavage of the N—O bond, is accomplished using TiCl_3 in wet THF at room temperature to give the demethoxylated products **107** in excellent yield (Equation 18). Oxygen and carbon nucleophiles add to allenates in a similar manner <1995SL645>.

A number of organic transformations of a zwitterionic intermediate **114**, generated from the reaction of triphenylphosphine with dimethyl acetylenedicarboxylate **111**, were reported in the literature, but use of this reaction in a catalytic cycle has been limited <2000TL567, 1997TL3529, 1997TL4259, 1998TL1051>. However, the triphenylphosphine-catalyzed cyclization of α -keto esters **112a**, α -ketonitriles **112b**, or α,α,α -trifluoroacetophenone **112c** with **111**, provides highly functionalized α,β -unsaturated γ -butyrolactones (**113a–113c**) in moderate yields, has been reported (Scheme 13) <1996JOC4516>.



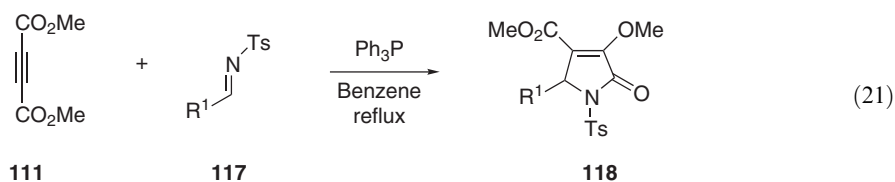
Scheme 13

Similarly, the reaction of **111** with *o*-quinones **115** under catalysis with triphenylphosphine was reported to give highly functionalized γ -spiro lactones **116** (Equation (20)) <1997JCS(P1)3129>.



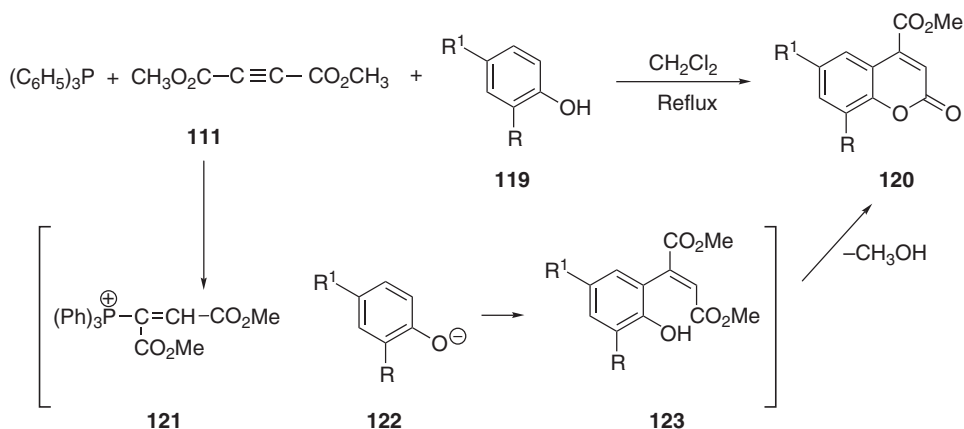
(20)

In these reactions, an electron-withdrawing group attached to the carbonyl group was essential. *N*-Sulfonylimines also undergo the cyclization reaction in place of the electron-deficient carbonyl compounds as trapping reagents. Treatment of **111** with *N*-tosylimines **117**, in the presence of 20 mol.% of triphenylphosphine in dry benzene under reflux, gave pyrrolin-2-ones **118** in high yields (Equation (21)) <1998JOC5031>.



(21)

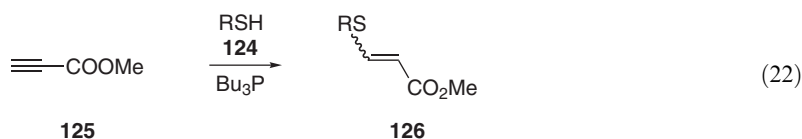
An efficient approach to 4-carboxymethylcoumarins **120** via triphenylphosphine-mediated reaction of phenols **119** with **111** has been reported <1998TL2391>. The mechanism of this reaction was envisaged as proceeding via the vinyltriphenylphosphonium salt **121**, generated from protonation of the zwitterionic intermediate by phenols. The cation **121** undergoes aromatic electrophilic substitution reaction with the phenolate conjugate base **122**, followed by intramolecular lactonization of the resultant intermediate **123**, to produce coumarins **120** (Scheme 14).



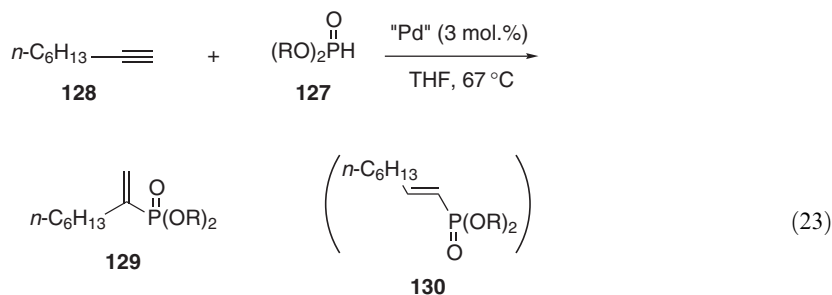
Scheme 14

Interestingly, dimethyl halomalonates undergo a complex reaction with various dialkyl acetylenedicarboxylates and triphenylphosphine to produce tetra-alkoxycarbonylallylidene-triphenylphosphoranes in good yields [<1998TL1051>](#).

There are many reports of the addition of thiols [124](#) [<1996SC1539>](#), and other nucleophiles, to propynoates [125](#) to give the substituted acrylates [126](#) (Equation (22)).



The oxidative addition of $HP(O)(OR)_2$ [127](#) to either a $Pt(0)$ or $Pd(0)$ complex generates a $H-M-P(O)(OR)_2$ species which is able to add to alkynes [128](#) under mild conditions to afford various alkenylphosphonates [129](#) (major) and [130](#) (minor) in excellent yields (Equation (23)) [<1996JA1571>](#). The oxidative addition of $Ph_2P(O)H$ to $M(PEt_3)_3$ (where $M = Pd$ or Pt) readily takes place at room temperature in benzene to afford *cis*- $MH[P(O)Ph_2][PPh_2(OH)](PEt_3)$ complexes, with the structure of the platinum complex being determined by X-ray crystallography [<1996OM3259>](#).



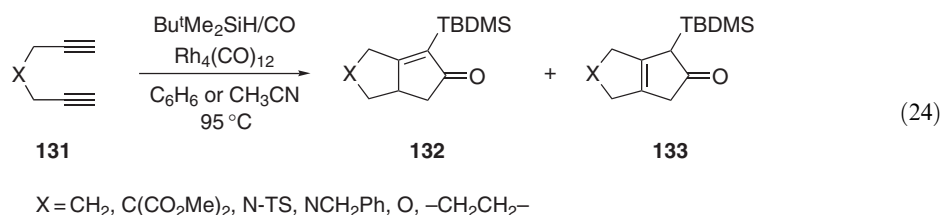
R = Me 91% (2/2 = 96/4)
R = Et 93% (2/3 = 90/10)

"Pd" = *cis*- $PdMe_2(PPh_2Me)_2$

1.22.1.9 Vinylrhodium Reagents

1.22.1.9.1 Formation by addition to alkynes and allenes

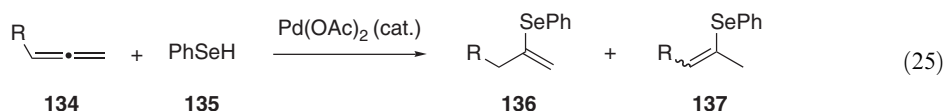
A rhodium-catalyzed cyclopentenone annulation occurs in the reaction of two moles of phenylacetylene and *t*-BuMe₂SiH under CO pressure, possibly proceeding via a vinylrhodium intermediate <1995TL241>. This type of CO incorporation has been applied to the construction of bicyclo[3.3.0]octenone frameworks (**132** and **133**), from 1,6-diynes **131** (Equation (24)). Switching the catalyst from Rh to Ru changes the product to catechol derivatives in an identical reaction system containing 1,6-diynes, *t*-BuMe₂SiH, and CO.



1.22.1.10 Vinylselenium Reagents

1.22.1.10.1 Formation by addition to alkynes and allenes

Palladium(II) acetate (Pd(OAc)₂) catalyzes the addition of benzeneselenol **135** to allenes **134**, providing the corresponding vinylic selenides **136** and **137** in good yields (Equation (25)). In contrast to the oxygen-induced radical addition of PhSeH to terminal allenes, which occurred at the terminal double bond preferentially **136**, the palladium-catalyzed hydroselenation to terminal allenes affords the internal adduct **137** preferentially; thus, these two reactions are complementary to each other for the synthesis of vinylic selenides <1998TL5213>.

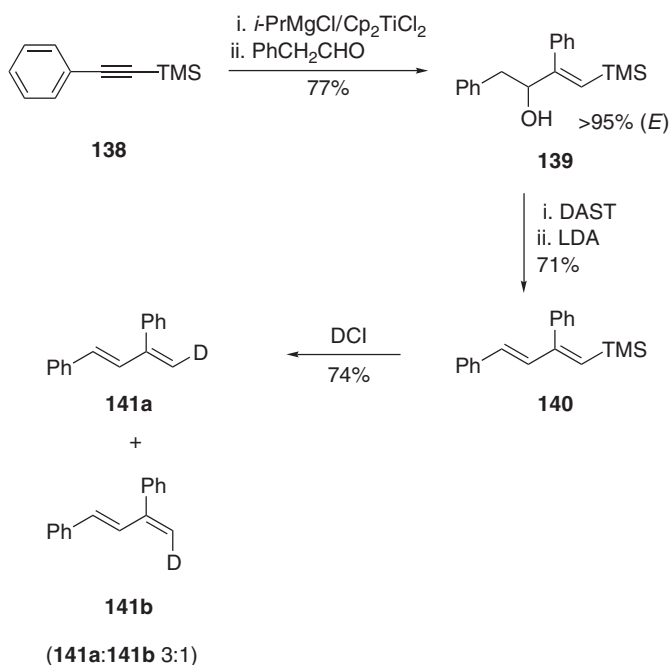


1.22.1.11 Vinylsilicon Reagents

Hyperconjugative stabilization of the β-silyl cation restricts rotation about the C—C bond well enough for it to maintain its configuration <1995AG(E)895>. This explains why most vinylsilanes react with electrophiles with retention of configuration. The stereospecificity is maintained even with highly stabilized cations as intermediates, as in the preparation of the deuterated butadienes **141a** and **141b** from acetylene **138**, used in a mechanistic study of the Diels-Alder reaction (Scheme 15).

A silyl group, typically trimethylsilyl, is a large electropositive substituent. As such it exerts a substantial effect on the stereochemistry of reactions taking place in its immediate neighborhood. It is also attached to the organic framework by a relatively long bond, and so it does not always hinder reactions in its neighborhood as one might at first expect. In some cases, it is tempting to ascribe some of the effects to electronic factors, and it is still a matter of some debate whether the electronic component is of any importance in determining the stereochemistry of reactions taking place near or involving a silyl group. Whatever the cause, it is certainly becoming clear that the silyl group is a powerful force in controlling stereochemistry in organic synthesis. The silyl group has a striking advantage over many other possibilities for the role of a stereochemistry determining group: the Si—C bond is relatively robust toward many of the reagents used in organic synthesis, but, after the silyl group has exerted whatever influence it has, it can often be removed quite easily from the product, typically by protodesilylation or oxidation <1997CRV2063>.

Vinyl silanes undergo electrophilic substitution with either retention or inversion of configuration of the double-bond geometry. Stereochemical consequences elsewhere in the molecule are rare, because vinyl silanes are not as powerfully nucleophilic as silyl enol ethers, allyl silanes, or silyl cyanides, and

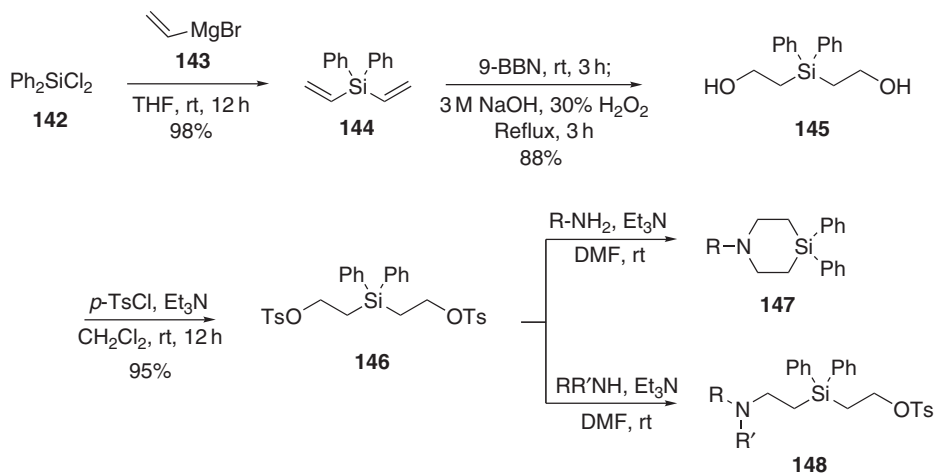


Scheme 15

they are used less often as carbon nucleophiles in C—C bond formation. However, there are several reactions of vinyl silanes, in which reaction takes place on a double bond to which a silyl group is attached, and the presence of the silyl group has stereochemical consequences <1997CRV2063>.

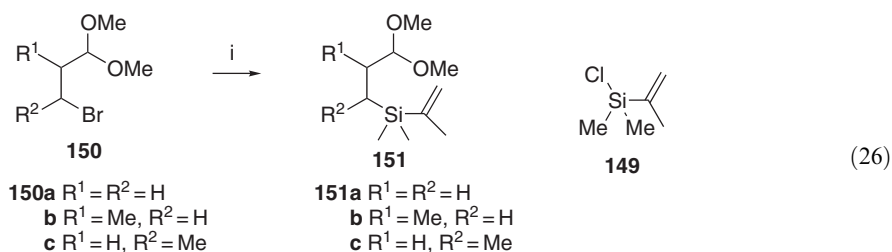
1.22.1.11.1 Formation of vinylic carbanions by deprotonation, metal–halogen exchange, and transmetalation

A vinyl silane **144**, prepared by transmetalation of vinylmagnesium bromide **143**, has been used in the synthesis of bis(2-tosyloxyethyl)diphenylsilane **146** (**142** → **146**) was developed as a protecting group for primary amines (Scheme 16) <1999TL5333>. Protection of primary amines leads to the formation of 4-diphenylsilapiperidines **147** or monoprotected amines **148**, which can be cleaved by exposure to CsF or Bu₄NF in THF or DMF.



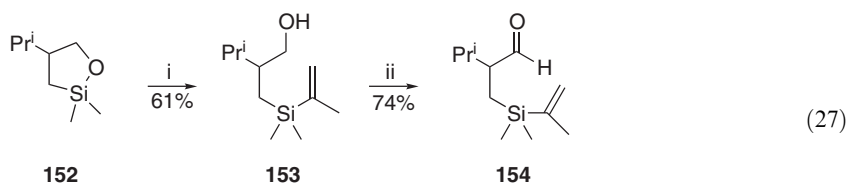
Scheme 16

Vinyl silanes **149** have been prepared through the displacement of chloride ion from chlorodimethyl(dimethylamino)silane with 2-propenyllithium <2000T8309>. The vinyl silane **149** can be elaborated into more complex vinyl silanes **151a–151c** by reaction with the Grignard reagents derived from known bromides **150a–150c** (Equation (26)).



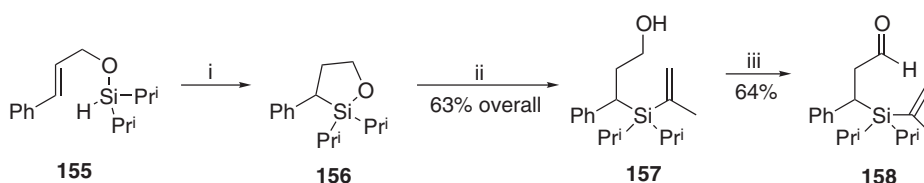
i. Mg, THF then dimethyl(2-propenyl)silyl chloride **149**

Oxasilacyclopentanes **152** are readily opened with 2-propenyllithium to generate alcohols **153**. PDC oxidation gave the synthetically useful silyl aldehydes **154** (Equation (27)) <2000T8309>.



i. 2-Propenyllithium, THF; ii. PDC, MS 4 Å, CH₂Cl₂

A diisopropyl silane derivative **155** cyclized in the presence of Wilkinson's catalyst [Rh(PPh₃)₃Cl(0.2 mol.%)] in THF at reflux (3.5 h) to give a siloxane **156** in essentially quantitative yield <H2000T8309>. This, in turn, was opened (66%) with 2-propenyllithium to provide the vinyl silane **157**, which was oxidized to give a vinylsilylaldehyde **158** in 64% yield (Scheme 17).

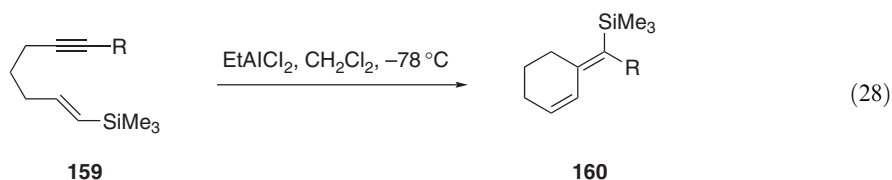


i. (Ph₃P)₃RhCl (0.2 mol.%), MS4 Å, THF; ii. 2-Propenyllithium, THF; iii. PDC, MS 4 Å, CH₂Cl₂

Scheme 17

1.22.1.11.2 Formation by addition to alkynes and allenes

Intramolecular vinylsilylation of 1,6-enynes **159** proceeds stereoselectively when treated with ethylaluminum dichloride to give silylcyclohexadienes **160** (Equation (28)) <1999JA3797>.

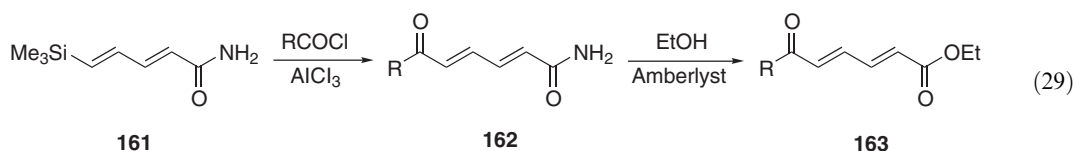


The activation of the Si—Si bond in disilanes by transition metal complexes and their subsequent use in synthesis has been the subject of a review <1995CRV1351>. The methodology developed has been exploited in the preparation of bissilylated alkenes.

The reaction of pentamethyl disilane with phenylacetylene in the presence of an $\text{NiCl}_2(\text{PEt}_3)_2$ catalyst underwent an α -elimination to extrude dimethylsilylene, which was trapped by phenylacetylene to produce a substituted 1,4-disilacyclohexadiene in excellent yields. In the presence of a variety of Pd catalysts, 1,3-dichlorohexamethyltrisilane did not undergo bissilylation, but generated a silylene species thermally, which was trapped by 2 equiv. of acetylene to produce 1,4-disilacyclohexa-2,5-diene derivatives in 20–82% yields, accompanied by Me_2SiCl_2 .

1.22.1.11.3 Applications in synthesis

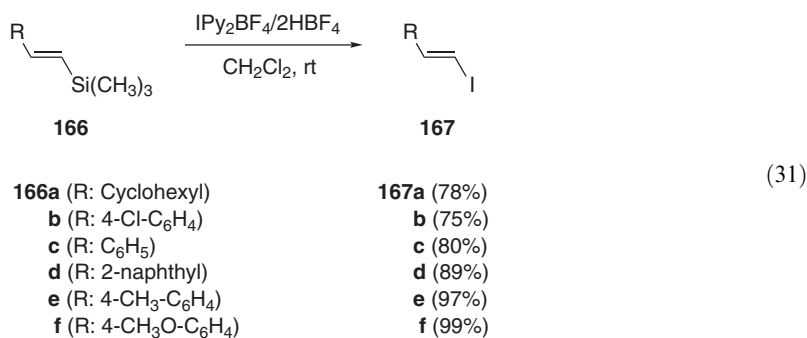
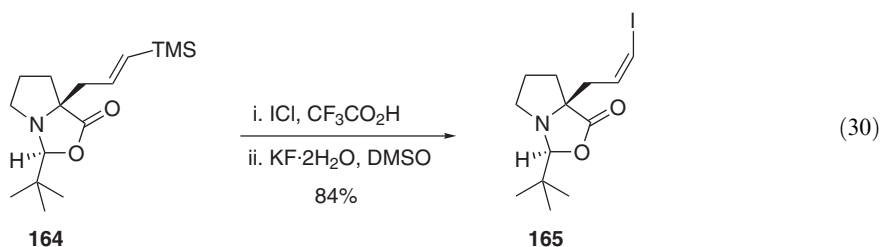
Bis(trimethylsilyl)buta-1,3-diene **161** reacts with acyl chlorides in the presence of aluminum chloride to give 1,6-dicarbonyl compounds **162** (Equation (29)) <1998T12399>. This methodology has been applied to the synthesis of various polyenes of the type **163** <1997JOC3291>.



Vinyl silanes, in the presence of ruthenium catalysts, have been used as silylating reagents in the formation of aryl and heteroaryl silanes <2000CL750>. For example, reaction of 2-acetylthiophene with trimethylvinylsilane was carried out, using $\text{Ru}_3(\text{CO})_{12}$ as the catalyst, resulted in the efficient silylation of C—H bonds. Furans could be silylated in a similar manner.

The stereochemistry for the iododesilylation of vinyl silanes is dependent upon the iodinating agent and on the substitution pattern. Retention is normal when the vinyl silane is β,β -disubstituted, where it has been used in syntheses of rapamycin <1995CEJ318, 1996TL755>.

Terminal vinyl silanes give mainly inversion of configuration during iododesilylation, especially when iodine chloride is used to encourage the addition–elimination pathway, as in the synthesis of cephalotaxine by way of **164** to **165** (Equation (30)) <1995JOC115>. In contrast, retention of configuration (for both (*E*)- and (*Z*)-terminal vinyl silanes), can be cleanly achieved with terminal vinylsilanes by using *N,N*-dipyridyliodonium tetrafluoroborate as the iodinating agent, to give vinyl iodides **167a–167f** (Equation (31)) <1995TL2153>.



1.22.1.12 Vinyltellurium Reagents

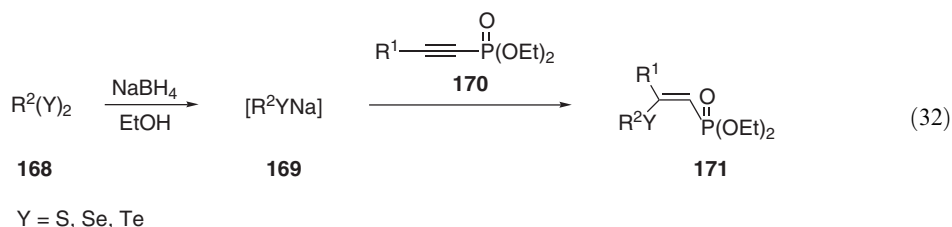
Vinyltellurium agents are generally useful intermediates in organic synthesis <2000MI001, 1997S373, 2003ACR731>. It should be noted that (*Z*)-vinyltellurium reagents have been used more frequently in synthesis than their (*E*)-counterparts, because of their better availability.

Transmetalation of vinyltellurium reagents is one of the more important reactions of these reagents <1995SL671, 2002JA1664>, rather than their generation by deprotonation, metal-halogen exchange or transmetalation.

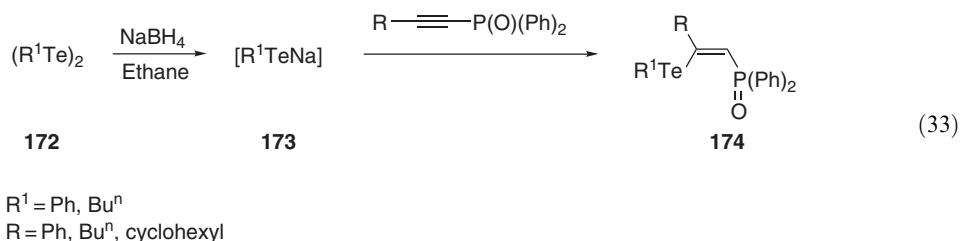
1.22.1.12.1 Formation by addition to alkynes and allenes

(*Z*)-Vinyltellurium reagents have been obtained by hydrotelluration of alkynes by lithium tellurolate ($\text{Te}^0/\text{Bu}^n\text{Li}/\text{THF}$) <2000TL1311>. (*E*)-Vinyltellurium reagents have been obtained by stereospecific *cis*-hydrometallation of alkynes, followed by transmetalation of the (*E*)-vinylorgano-metallic complexes formed with organotellurenyl halides <1995T12971>.

Organotellurolate anions **169**, available by reduction of organotellurium reagent **168**, react with alkynylphosphonates **170** to give vinyltellurium reagents **171** in good yields. The reaction is stereoselective, producing the (*Z*)-stereoisomer of **171** (Equation (32)) <2000TL161>.



β -Organotelluro vinylphosphine oxides **174** have been prepared by addition of sodium alkyl tellurolates **173** to alkynylphosphine oxides **170** (Equation (33)) <2002TL4399>. The sodium tellurolates **173** were prepared by reduction of ditellurides **172** with sodium borohydride in ethanol at rt.



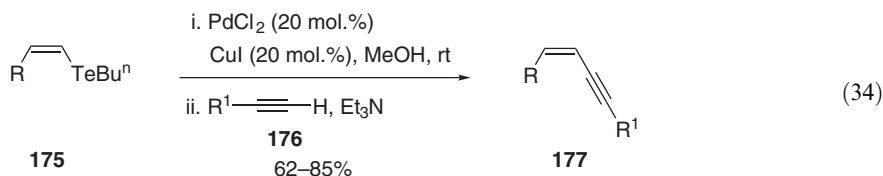
1.22.1.12.2 Applications in synthesis

Vinyltellurium reagents react in a similar manner to vinyl halides or triflates in palladium-catalyzed cross-coupling reactions <2002JOM1>. The easy access to vinyltellurides, the lack of isomerization at the double bond, and the enhanced stability of these reagents, along with the tolerance of many sensitive functional groups and the mild reaction conditions employed during the coupling reaction, makes these reagents invaluable. Coupling reactions of vinyltellurium reagents have been utilized in the synthesis of polyacetylenic acids isolated from *Heisteria acuinata* <2001OL819>.

The (*Z*)- and (*E*)-phenylstyryltellurides, and (*Z*),(*Z*)- and (*E*),(*E*)-bisvinyllic tellurides undergo palladium-catalyzed cross-coupling reactions with *p*-methylstyrene to give dienes in reasonable yields and high stereoselectivity <1996JOM197>. The reactions were carried out in methanol at 25°C in the presence of PdCl_2 catalyst using Et_3N as base and AgOAc as the oxidant. Use of $\text{Pd}(\text{OAc})_2$ also afforded isomeric homocoupling butadiene products ((*E*),(*E*); (*E*),(*Z*); and (*Z*),(*Z*)) in good-to-moderate yields <1996JOM335>. The presence of the reoxidant was crucial to the success of the reaction as was the nature of the solvent. The best results were obtained with

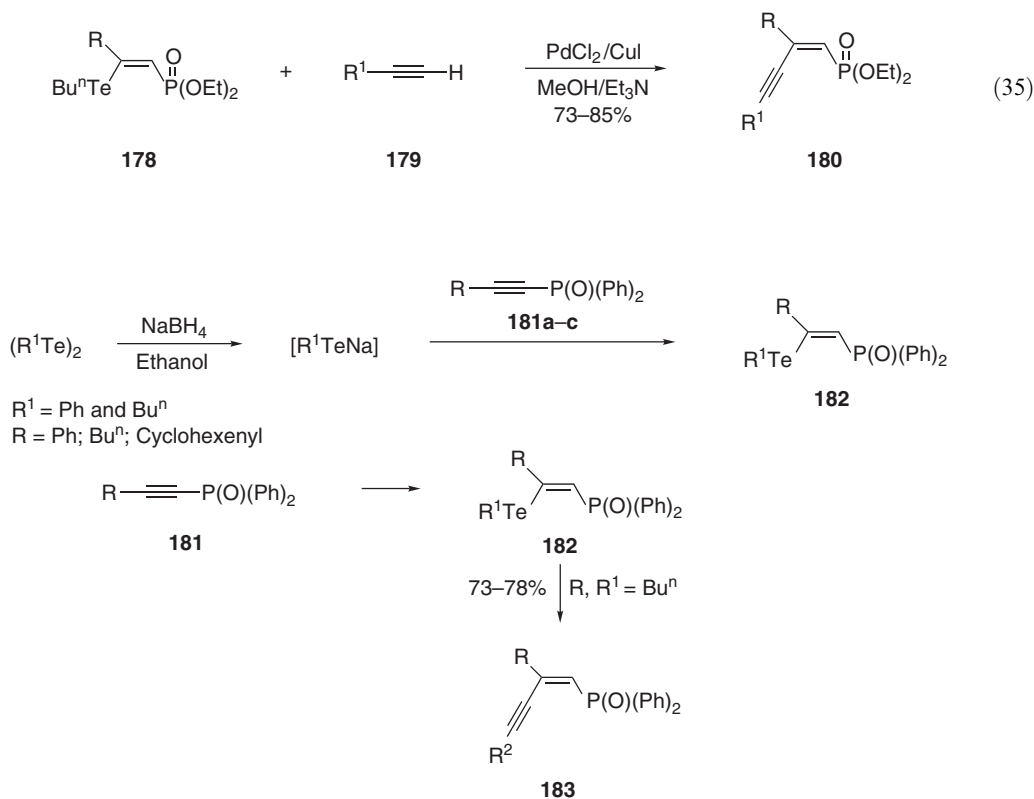
methanol and acetonitrile, whereas benzene and THF gave lower yields of the products. The optimum conditions were found to be the use of the vinylic tellurides (0.5 mmol.), Pd(OAc)₂ (0.05 mmol), AgOAc (1 mmol.), and acetonitrile (10 ml) at 25 °C for 20 h.

Palladium-catalyzed cross-coupling reactions of (*Z*)-vinylic tellurides **175** with terminal alkynes **176** proceeds stereospecifically to give (*Z*)-enyne **177**, in good yields and under mild conditions (Equation (34)) <1999TL4619, 1996JOC4975>. The methodology developed avoids the preparation of other vinyl metal reagents and haloalkynes.



(*Z*)-Bisvinylic tellurides react with terminal alkynes under Pd-catalyzed cross-coupling reactions to give (*Z*)-enyne systems <2001SL1473>. The choice of catalyst (PdCl₂/CuI) and amine base (Et₃N) were crucial to the outcome of the reaction which then proceeded in excellent yields and stereospecifically.

β-Organotelluro vinylphosphonates **178** undergo palladium-catalyzed cross-coupling reactions with alkynes **179** to give enynephosphonates **180** in good yields and with complete retention of configuration about the vinyl group (Equation (35)) <2001TL8563>. Similarly, β-organotelluro vinylphosphine oxides **182**, available from alkynylphosphine oxide **181**, give β-alkynyl vinylphosphine oxides **183** in good yields (Scheme 18) <2002TL4399>.



Scheme 18

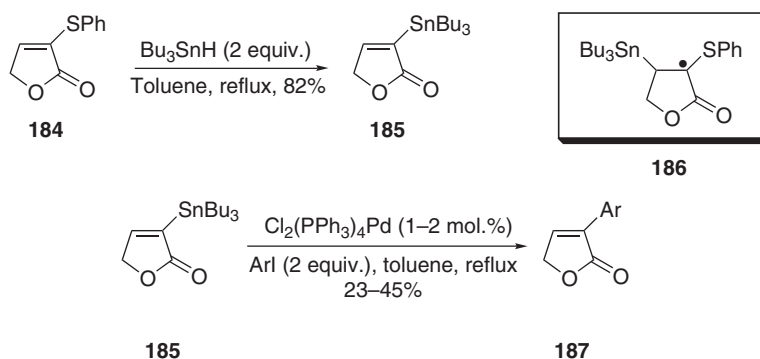
Palladium-catalyzed coupling of terminal alkynes with ketene telluroacetals (vinylic tellurides) to give conjugated enediynes has been studied <2002SL975>. (*Z*)-β-Trifluorovinyltellurides have been found to react with zinc cuprates to give α,β-unsaturated trifluoromethyl ketones with (*E*)-configuration <1995SL180>.

1.22.1.13 Vinyltin Reagents

Vinyltin reagents continue to be one of the most popular organometallic components for many types of reactions. Generally, metal-catalyzed hydrostannylation reactions have been the subject of a review <2000CRV3257>.

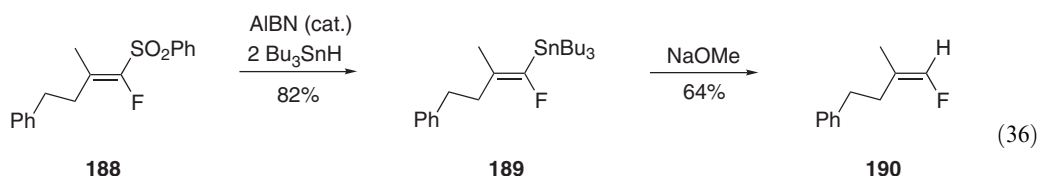
1.22.1.13.1 Formation of vinylic carbanions by deprotonation, metal–halogen exchange, and transmetalation

Stannylfuranone **185** is prepared from the corresponding phenylsulfanylfuranone **184** by *ipso*-radical desulfurative stannylation via **186**. Subsequent palladium-catalyzed cross-coupling of **185** with aryl iodides gives 3-arylfuranones **187** in modest yields (Scheme 19) <1996JCS(P1)1913>.



Scheme 19

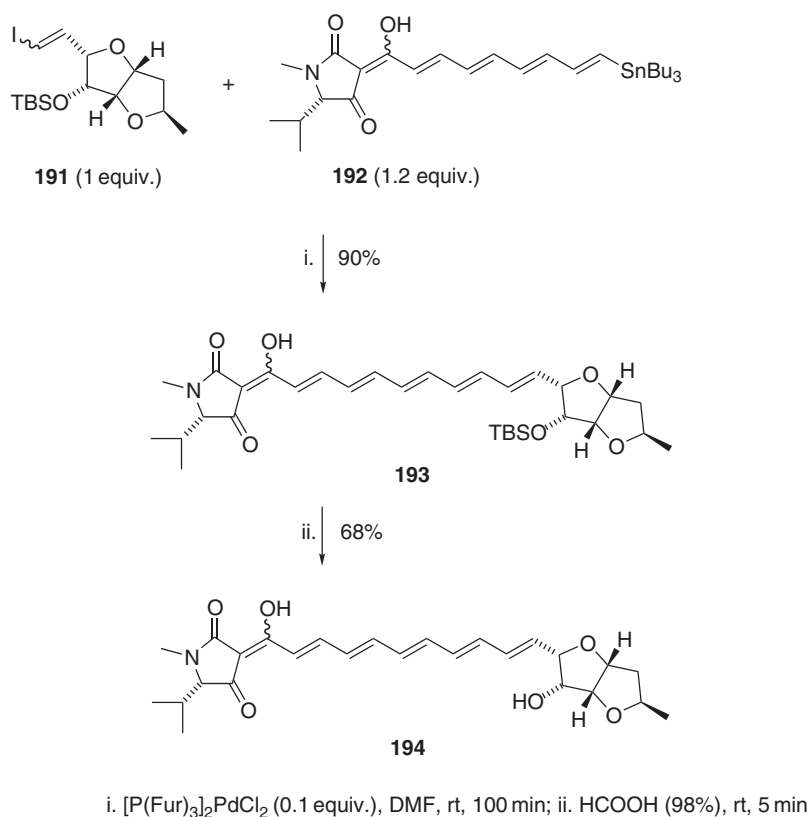
Fluorovinylsulfones ((*E*) and (*Z*)) **188** form (fluorovinyl)stannanes **189** on treatment with 2 equiv. of tributyltin hydride and a catalytic amount of AIBN; the free-radical-catalyzed reaction proceeds with retention of configuration for 2,2-disubstituted fluorovinyl sulfones <1996T45>. Conversion of **189** to 1-fluoroalkene **190** is a stereospecific reaction and provides a general method to (*E*)- and (*Z*)-fluoroalkenes (Equation (36)). The utility of this method was exemplified by the synthesis of fluorinated nucleosides and amino acids.



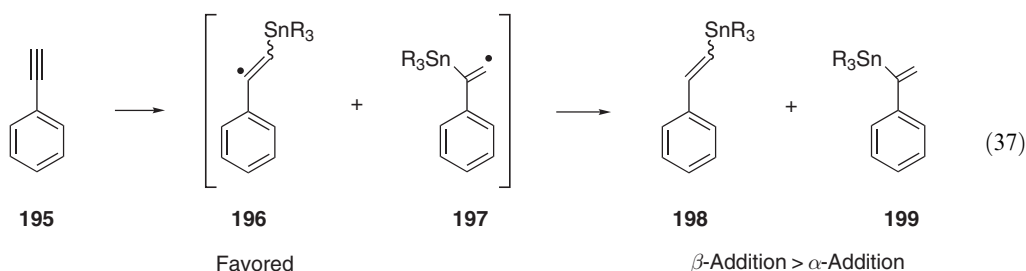
Vinylic polyene tributylstannyl derivative **192** undergoes coupling reactions under Stille conditions with iodoalkene **191** to give, after deprotection via **193**, polienoyltetramic acid erythrokyrine **194**, a mycotoxin which exhibits antibiotic action against some *Staphylococcus* species (Scheme 20) <1996JCS(P1)1913>. A similar vinylic polyenoyl stannyl derivative has been employed in a Stille coupling reaction towards the synthesis of the plasmodial pigment physarorubinic acid <1999JCS(P1)839>.

1.22.1.13.2 Formation by addition to alkynes and allenes

The hydrostannylation of alkynes **195**, alkenes, and allenes under free-radical conditions has been widely studied and gives, in general, a mixture of stereoisomers (**198** and **199**) with the regiochemistry controlled by the relative stability of the two possible intermediate β -stannyl radicals **196** and **197** (Equation (37)) <2000CRV3257>.



Scheme 20



Despite the high regioselectivity of radical hydrostannylation, stereoselectivity is often a significant problem since the initially formed kinetic product is equilibrated by further addition–elimination processes under the reaction conditions. Good stereoselectivities may be obtained if this equilibration process leads to a thermodynamic product favored by other factors (often steric). Radical stannylation of unsaturated bonds is not applicable to all substrate types as discrimination between other sites of unsaturation (i.e., alkyne versus alkene) or reduction (alkyne versus halogen) in the molecule can lead to undesired side reactions.

In most cases, radical hydrostannylation reactions were found to proceed in fair-to-poor yields when applied to propargyl derivatives or enynols **200** (especially in the case of substituted alkyne functions), and regio- and stereoselectivities were generally mediocre (Equation (38)) <1997JOC7768>. Treatment of **200** by Bu_3SnH (1.2 equiv.)/AIBN (0.1 equiv.) in toluene at 80°C for 4 h led to a 80:20 mixture of dienylstannanes **201** and **203** in 75% yield. Under these conditions, partial isomerization of the double bond of **201** into **203** is observed.

Entry	Method conditions ^a	Enynol	Yield (%) ^b	Product	Dienylstannanes and ratio		
		200		201	202	203	204
1	A		75	80			
2	B		>99	60		20	
3	C C ₁	−30 °C, 1.5 h	92	100			40
4	C ₃	−78 °C, 1.5 h	92	89	11		
5	C ₄	−78 °C, 1.5 h	78	67	33		

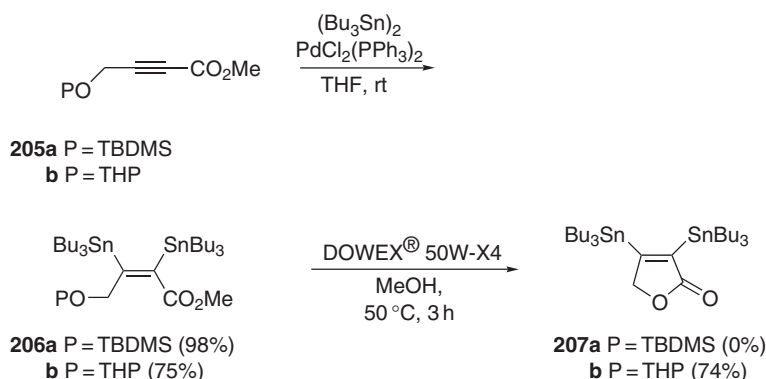
^a Method A: 1.2 equiv. Bu₃SnH/0.1 equiv. AIBN, toluene, 80 °C. Method B: 1.2 equiv. Bu₃SnH/0.02 equiv. PdCl₂(PPh₃)₂, THF, 20 °C. Method C: Conditions C₁) 2 equiv. Bu₃Sn(Bu)CuCNLi₂, THF. Conditions C₂) 4 equiv. Bu₃Sn(Me)CuCNLi₂, THF. Conditions C₃) 2 equiv. (Bu₃Sn)₂CuCNLi₂, THF. Conditions C₄) 2 equiv. (Bu₃Sn)₂CuCNLi₂, THF, MeOH (110 equiv.). ^b Yields are given after purification on basic silica gel. ^c This reaction was not reproducible.

(38)

Pd(0)-catalyzed hydrostannylation of **200** using Bu₃SnH (1.2 equiv.)/PdCl₂(PPh₃)₂ (0.02 equiv.) in THF at 20 °C for 10 min gave the distal dienylstannane **201** and the diene derivative **204** in quantitative yield and in a 60:40 ratio. Regio- and stereoselectivities are strongly dependent on the substitution of the α-position for alkynes, and dependent on the substitution of the double bond in the case of enynes <1997JOC7768>.

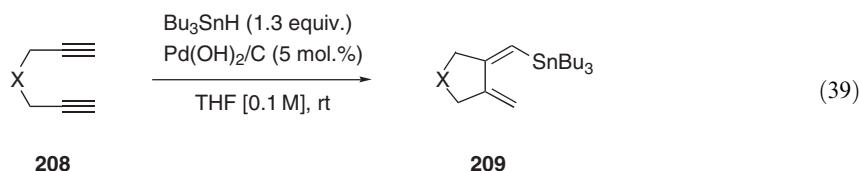
Stannylcupration of **200** using 2 equiv. of the mixed cyanocuprate, Bu₃Sn(Bu)CuCNLi₂, in THF/Et₂O at −30 °C for 1 h, afforded the *E,E*-dienylstannane **201** as a single isomer in excellent yield. When stannylcupration of **200** was performed in THF at −78 °C, reaction of the same homocuprate took place in 92% yield to furnish the two regioisomeric dienylstannanes **201** and **202** in a 89:11 ratio. Addition of methanol to the cuprate solution under the previous conditions (−78 °C) resulted in a 67:33 mixture of the *distal* and *proximal* stannanes **201** and **202**. These experiments infer that the *proximal* isomer **202** is the kinetic product in this stannylcupration reaction <1997JOC7768>.

Butynoate **205a** reacted with hexabutylditin in the presence of PdCl₂(PPh₃)₂ to give the 2,3-bis(tributylstannyl)acrylate **206a** in 98% yield. The analogous THP-protected bis(stannane) **206b** was prepared using the same reaction conditions in 75% yield from propynoate **205b** (Scheme 21) <1999JOC328>. Reaction of 2,3-bis(tributylstannyl)acrylate **206b** with acidic ion-exchange resin in methanolic solution unmasks the hydroxyl group allowing cyclization to occur, thus furnishing 3,4-bis(tributylstannyl)-2(5*H*)-furanone **207** as a colourless liquid in 74% yield. This compound is stable indefinitely when stored at −30 °C. Regioselective Stille reaction of bis(stannane) **207** allows the preparation of 4-substituted 3-stannyl-2(5*H*)furanones.

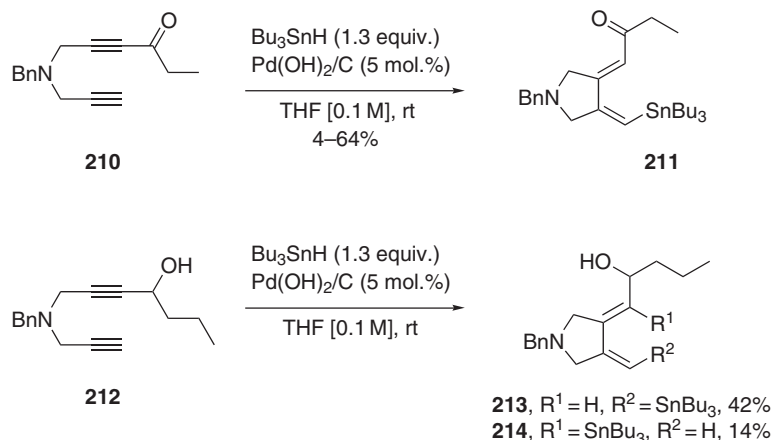


Scheme 21

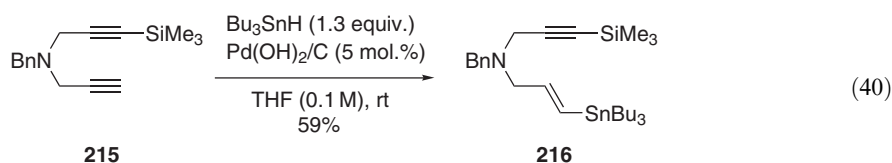
Terminally substituted 1,6-diynes **208** were shown to undergo stannylative cyclization to give cyclic 1,3-dienes **209**, although the nature of the substituent had a dramatic effect on the course of the reaction, which is presumably attributable to the Thorpe–Ingold, reactive rotamer effects and related phenomena (Equation (39)) <1997JOC8970>.



Thus, alkynone **210** undergoes stannylation to furnish the α,β -unsaturated ketone **211** in 64% yield. In contrast, alkynol **212** gives a mixture of regioisomers **213** and **214** in 42% and 14% yield, respectively, pointing to electronic effects influencing the reaction pathway (Scheme 22). Monosilylacetylene **215** undergoes regioselective hydrostannylation, as the major reaction pathway, to give terminal vinylstannane **216** in 59% yield (as opposed to a stannylation cyclization) while the disilane gave mostly recovered starting material (Equation (40)) <1997JOC8970>. A possible catalytic cycle for these reactions was discussed.

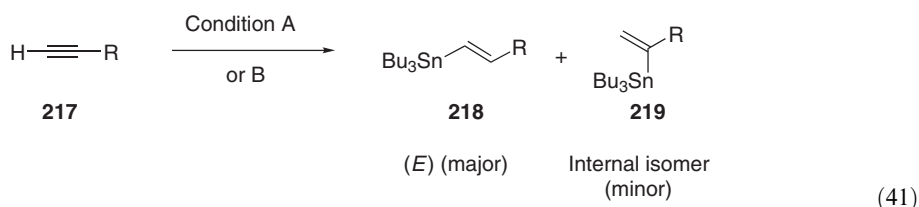


Scheme 22



$\text{Mo(CO)}_3(\text{CN-}i\text{-Bu})_3$ is a suitable catalyst for the regioselective hydrostannylation of several types of alkynes, giving rise preferentially to the α -stannylated products <1999OL1017>. These products are not available under radical reaction conditions or by using other metal catalysts. This protocol can also be applied to sensitive substrates, which cannot be hydrometallated with the commonly used palladium catalysts. For example, $\text{PrC}\equiv\text{CCO}_2\text{CH}_2\text{CH}=\text{CH}_2$, gave 80% hydrostannylation products, 91% of which were (*E*)- $\text{PrCH}=\text{C}(\text{SnBu}_3)\text{-CO}_2\text{CH}_2\text{CH}=\text{CH}_2$.

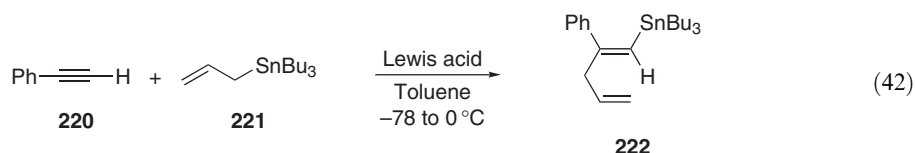
Either $\text{Bu}_3\text{SnCl}/\text{PMHS}/\text{KF}_{(\text{aq.})}$ or a combination of tributyltin fluoride, polymethyl hydrosiloxane (PMHS), and catalytic quantities of tetrabutylammonium fluoride (TBAF) can serve as *in situ* sources of tributyltin hydride for both free radical and palladium-catalyzed hydrostannylation reactions (**217** \rightarrow **218** + **219**) (Equation (41)) <1999JOC5958>.



Condition A	Condition B
Bu_3SnCl , PMHS, aq. KF, Bu_4NF (cat.) (or Bu_4NI), $(\text{Ph}_3\text{P})_2\text{PdCl}_2$ (cat.), Et_2O	Bu_3SnF , PMHS, Bu_4NF (cat.) $(\text{Ph}_3\text{P})_2\text{PdCl}_2$ (cat.), Et_2O

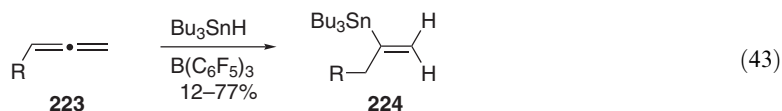
Furthermore, other trialkyltin halides such as trimethyltin chloride, as well as alternative reductants such as Red-Sil, appear to be amenable to the method. These methods are tolerant of a variety of functional groups, including silyl ethers. These methods were applied to the hydrostannylation of alkynes to produce vinylstannanes in good yields and with standard regio-chemical outcomes. The vinylstannanes are accompanied by little if any hexabutylditin by-product, which can be of particular practical advantage when vinyltins are desired in quantities that dissuade their distillation, and when they are also sufficiently nonpolar so as to make the chromatographic separation from the ditin difficult.

The addition of allyltributylstannane **221** to unactivated aromatic alkynes **220** in the presence of catalytic amounts of ZrCl_4 or EtAlCl_2 , produced the stannylated 1,4-dienes **222** with very high regio- and stereoselectivities in good-to-high yields (Equation (42)) <1999T3779>.



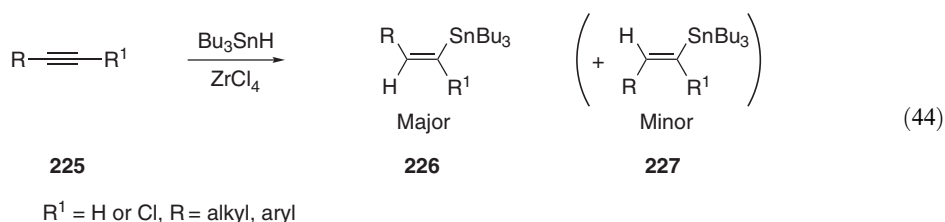
The exclusive *trans*-mode of addition was confirmed by ^1H NMR spectroscopic analysis of the crude reaction mixtures. However, the stereochemistries of the addition products produced from the reactions using aliphatic acetylenes depended on the reaction conditions and the type of Lewis acid employed. The mechanisms for the ZrCl_4 - and EtAlCl_2 -catalyzed allylstannylation of alkynes are proposed.

The hydrostannylation of allenes **223** with tributylstannyl hydride in the presence of 20 mol. % of $\text{B}(\text{C}_6\text{F}_5)_3$ catalyst produced vinylstannanes **224**, regioselectively <1997JOC2963>. A plausible mechanism for this Lewis acid-catalyzed hydrostannylation was reported (Equation (43)).

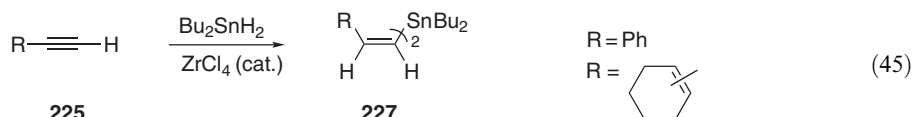


A Lewis acid such as ZrCl_4 or HfCl_4 has been shown to catalyze the hydrostannylation of acetylenes, e.g., $\text{Me}(\text{CH}_2)_5\text{C}\equiv\text{CH}$, to produce (*E*)-hydrostannylation products, e.g., (*E*)- $\text{Me}(\text{CH}_2)_5\text{CH}=\text{CHSnBu}_3$, regio- and stereoselectively <1995CC2405>.

Using these Lewis acids, *cis*-vinylstannanes **226** are available from disubstituted acetylenes **225**. The products form regio- and stereoselectively through an *anti*-hydrostannylation reaction (Equation (44)) <1996JOC4568>.

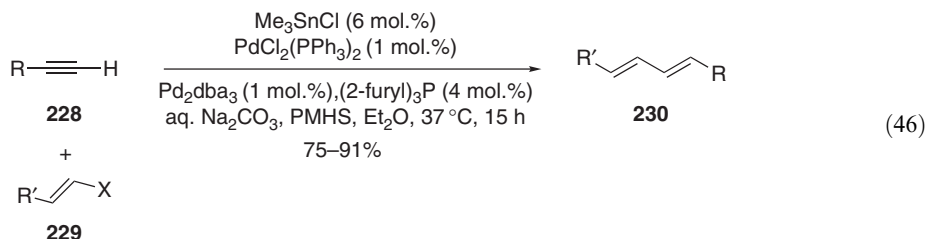


The hydrostannylation reaction of terminal acetylenes **225** using dibutyltin dihydride was also catalyzed by ZrCl_4 , to give the stereodefined (*Z*)-divinyltin derivatives **226**, by an *anti*-hydrostannylation pathway (Equation (45)).

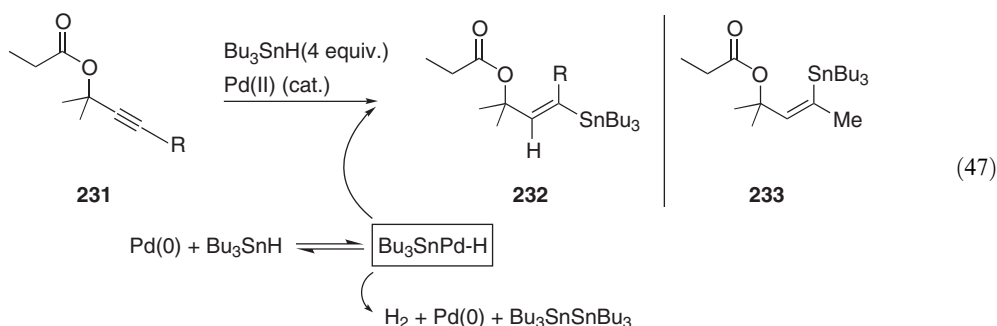


The use of nonpolar solvents, such as toluene or hexane, was essential for obtaining high stereoselectivity and chemical yield. Since ZrCl_4 and HfCl_4 are not soluble in such solvents, the hydrostannylations were carried out in a heterogeneous system. The reactions of internal acetylenes with Bu_3SnH proceeded smoothly, although the use of stoichiometric amounts of ZrCl_4 gave better results. The ZrCl_4 -catalyzed hydrostannylation at 0°C gave better yields and stereoselectivities than the reaction at rt. To help clarify this observation, the reaction of Bu_3SnH with ZrCl_4 was monitored by ^1H and ^{119}Sn NMR spectroscopy, and it was found that Bu_3SnH reacted with ZrCl_4 at room temperature to afford a mixture of tributyltin hydride, dibutyltin dihydride, and tetrabutyltin.

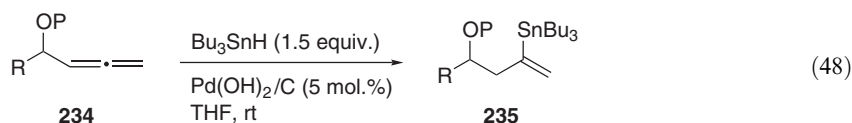
Stille cross-couplings involving the palladium-catalyzed reaction of vinyl halides **229** with vinylstannanes (formed *in situ* from hydrostannylation of the corresponding alkyne **228**) to form 1,3-dienes **230** have been investigated with a view to making the reaction catalytic in tin <2000JA384>. Syringe pump addition of 1.5 equiv. of various Stille electrophiles to a 37°C ethereal mixture of alkyne, aqueous Na_2CO_3 , PMHS, Pd_2dba_3 , trifurylphosphine, $\text{PdCl}_2(\text{PPh}_3)_2$, and 0.06 equiv. of Me_3SnCl over a period of 15 h, afforded the corresponding cross-coupled products in 75–91% yield, and reduced the traditional tin requirement by 94% (Equation (46)).



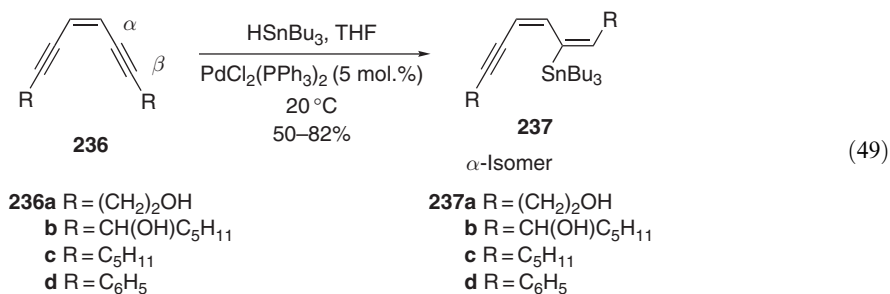
Hexane has been found to be particularly favorable as a solvent for palladium-catalyzed hydrostannylation of hindered internal alkynes **231** to give either **232** or **233** by minimizing the competing formation of H_2 and $\text{Bu}_3\text{SnSnBu}_3$. The optimum conditions involve $\text{Pd}(\text{OAc})_2$ and a sterically bulky, strong σ -donor monophosphine (PCy_3) in hexane at 23°C (Equation (47)) <2003TL5737>.



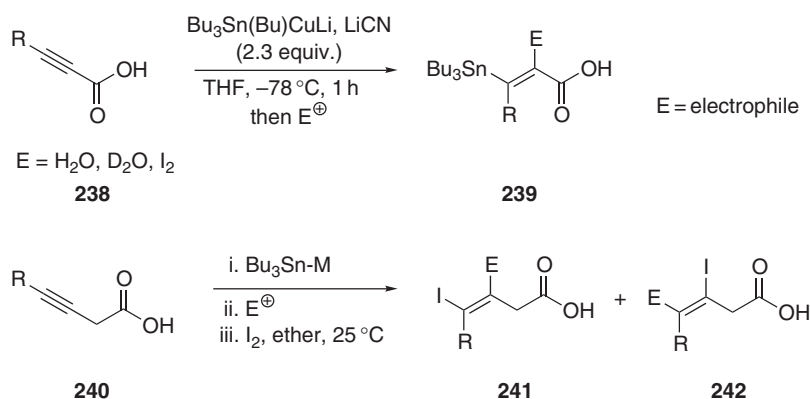
A series of mono-substituted allenes **234** have been shown to undergo regioselective hydrostannylation when treated with Bu_3SnH in the presence of $\text{Pd}(\text{OH})_2/\text{C}$ (Pearlman's catalyst) in THF to give the vinylstannanes **235** in good yields (Equation (48)) <1997TL6343>. The reaction conditions employed were tolerant of a range of functional groups. The use of $\text{Pd}(\text{PPh}_3)_4$ led to regioisomeric mixtures of allyl stannanes.



Hydrostannylation of readily available (*Z*)- or (*E*)-enediynes **236** allows the stereo- and regio-selective construction of stannylated dienyne derivatives **237** (Equation (49)) <1996TL7971>.

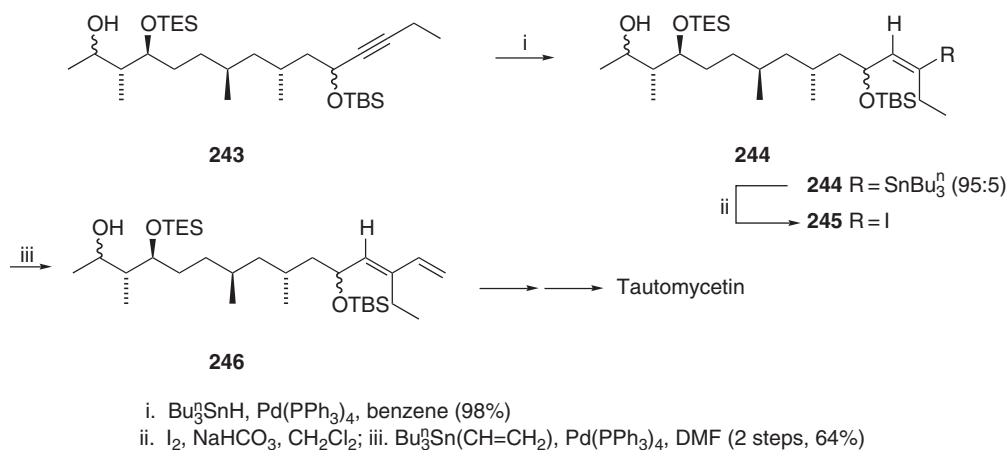


The stereoselective synthesis of vinylstannanes bearing a carboxylic acid function **239** was achieved from acetylenic acids **238** via stannylcupration reaction (Scheme 23) <1998TL4277>. In the formation of the homoallylic series, regioselectivities are highly dependent on the nature of stannyl anion counter-metal and on the protection of the carboxylic acid function (**240** → **241** + **242**).



Scheme 23

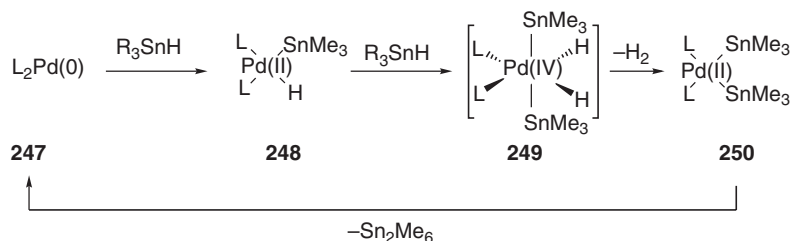
The efficient construction of a dienone moiety **246** for the synthesis of tautomycetin has been achieved by regioselective hydrostannylation of an internal alkyne **243**, and subsequent Stille coupling of vinyl iodide **245** with vinylstannane, to give **246** (Scheme 24) <1997TL7897>.



Scheme 24

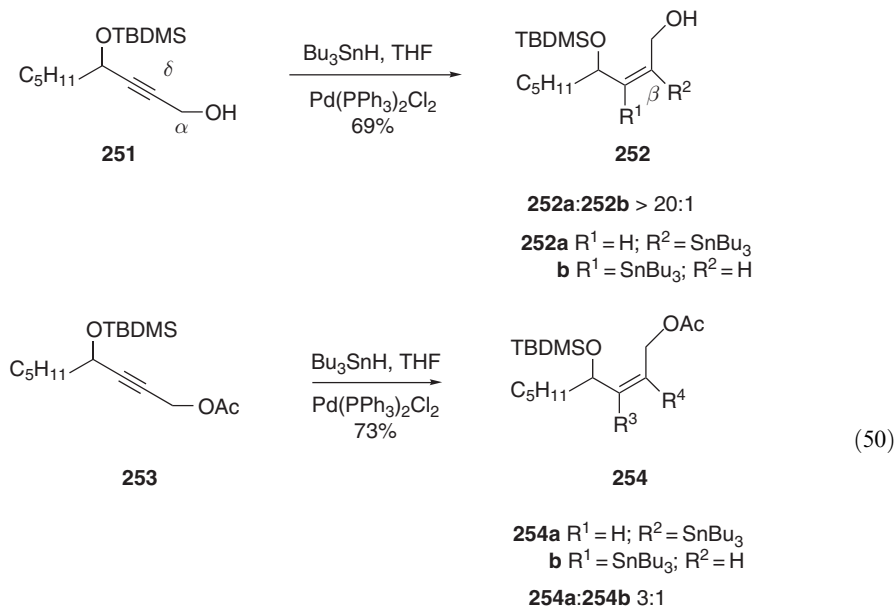
Whereas the spontaneous hydrostannylation of alkynes affords (*Z*)-vinylstannanes, the $\text{L}_2\text{Pd}(0)$ -catalyzed reaction leads regio- and stereospecifically to the (*E*)-vinylstannanes, the exact course of the reaction being dependent on the nature of the phosphane ligands in PdL_2 **247**

<2000OM521>. Monodentate phosphane complexes, such as $\text{Pd}(\text{PPh}_3)_4$, which is in equilibrium with $\text{Pd}(\text{PPh}_3)_3$, $\text{Pd}(\text{PPh}_3)_2$, $\text{Pd}(\text{PPh}_3)$, and free phosphine, are effective catalysts, whereas the chelating phosphane derivative $\text{Pd}(\text{Ph}_2\text{PC}_2\text{H}_4\text{PPh}_2)_2$ [$\text{Pd}(\text{dppe})_2$] is not (dppe = diphenylphosphinoethane). Chelating phosphane-containing fragments [$(\text{R}'_2\text{PC}_2\text{H}_4\text{PR}'_2)\text{Pd}$] ($\text{R}' = i\text{-Pr}, t\text{-Bu}$) were found to be best suited to stabilizing intermediates such as the $\text{Pd}(\text{II})$ hydrido stannyls, since the use of a chelating phosphane retards loss of one phosphane ligand. It was also found that the intermediates are the same for both the Pd -catalyzed degradation of R_3SnH into Sn_2R_6 and H_2 and the Pd -catalyzed hydrostannylation of alkynes. The presence of the $\text{Pd}(\text{II})$ hydrido stannyl intermediates **248**, formed by the oxidative addition of R_3SnH to **247**, in both reactions seems to imply a $\text{Pd}(0) \leftrightarrow \text{Pd}(\text{II}) \leftrightarrow \text{Pd}(\text{IV})$ (**248** \leftrightarrow **249** \leftrightarrow **250**) change in oxidation states and hence the existence of the additional octahedral $\text{Pd}(\text{IV})$ intermediate **249** (Scheme 25).



Scheme 25

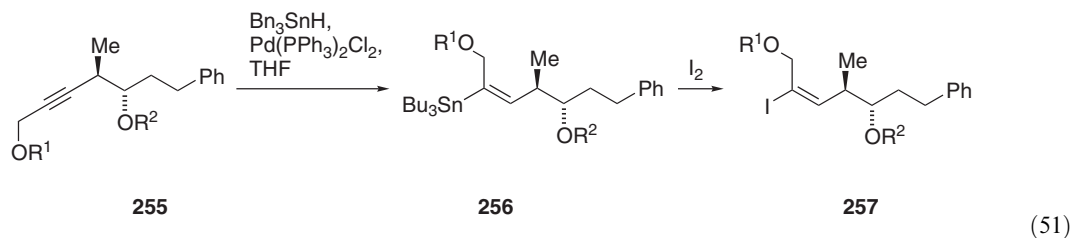
Hydrostannations of primary propargylic alcohols **251** with Bu_3SnH catalyzed by $\text{Pd}(\text{PPh}_3)_2$ yield (*E*)-allylic alcohols **252**, in which the Bu_3Sn group is affixed to the carbon proximal to the CH_2OH substituent <2003TL1087>. This observation suggested that the OH group was exerting a directing effect. Hydrostannations of the related propargylic acetates **253** to give **254** show no such effect (Equation (50)).



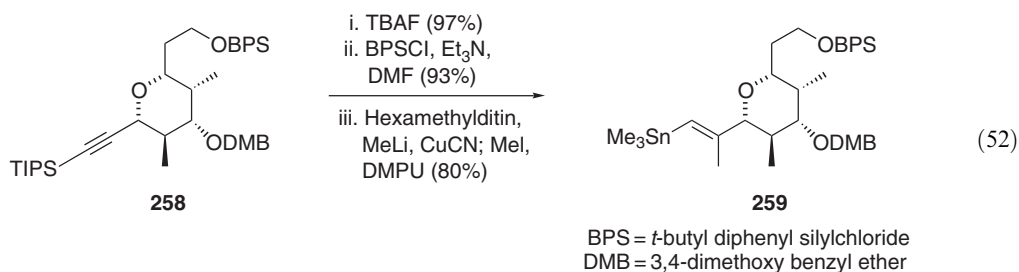
Series	R^1	R^2	Yield (%)	Ratio 252a:252b
a	C_5H_{11}	OTBDMS	69	>20:1
b	C_5H_{11}	OBOM	70	>20:1
c	C_5H_{11}	OMe	66	6.3:1
d	C_5H_{11}	OH	71	2.9:1
e	C_2H_5	CH_3	75	>20:1
f	C_3H_7	H	73	7:1
g	H	H	80	3:1

Series	R^1	R^2	Yield (%)	Ratio 254a:254b
a	C_5H_{11}	OTBDMS	73	3:1
b	C_5H_{11}	OBOM	63	3.2:1
c	C_5H_{11}	OMe	73	6.3:1
d	C_5H_{11}	OH	62	4:1
e	C_2H_5	CH_3	79	>20:1
f	CH_3	H	73	7:1

An improved route to the polypropionate segment of callistatin A **256** is described in which the efficient directed hydrostannylation of an internal alkyne **255** and subsequent iodinolysis provides a key vinylic iodide intermediate **257** (Equation (51)) <2002OL3931>. Hydrozirconation methodology was less successful.

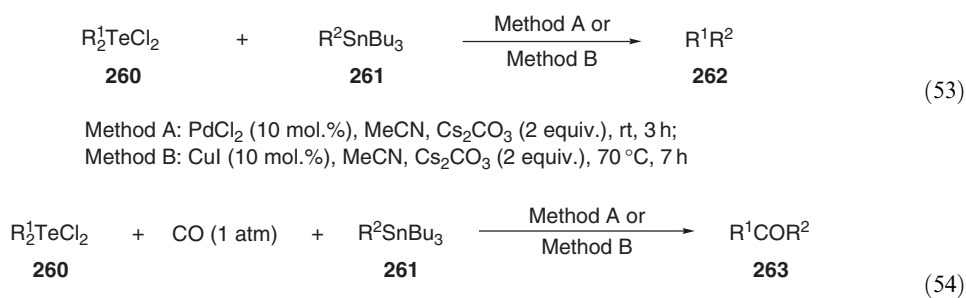


Deprotection of the terminal alkyne (+)-**258**, followed by addition of trimethylstannyl cuprate (Me_6Sn_2 , MeLi , CuCN), led to the formation of an intermediate vinyl anion which could be captured with methyl iodide (DMPU) to furnish trisubstituted olefin (+)-**259** (Equation (52)) <2001JA10942>.



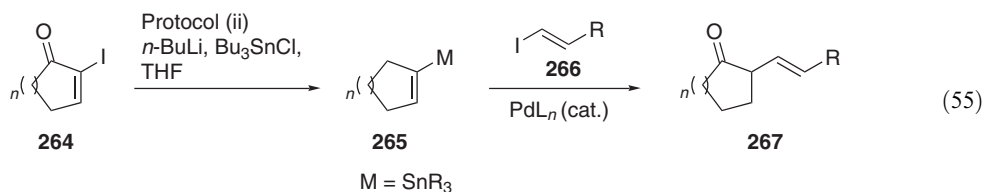
1.22.1.13.3 Applications in synthesis

Vinylstannanes **261** undergo coupling with organotellurium dichlorides **260**, in the presence of PdCl_2 with Cs_2CO_3 as the base and acetonitrile as the solvent, to give the cross-coupling products **262**, in good yields (Equation (53)) <1999CC2117>. Other catalysts such as $\text{Pd(PPh}_3)_4$, $\text{Pd}_2(\text{dba})_3\text{CHCl}_3$, and $\text{PdCl}_2(\text{PPh}_3)_2$ have been employed, although the yields are not as good. Cs_2CO_3 was also more effective than K_2CO_3 , Na_2CO_3 , or MeONa as base. Copper(I) salts may also be employed as an effective catalyst for this process. In the presence of carbon monoxide, vinyl ketones **263** were also obtained (Equation (54)) <1999CC2117>.

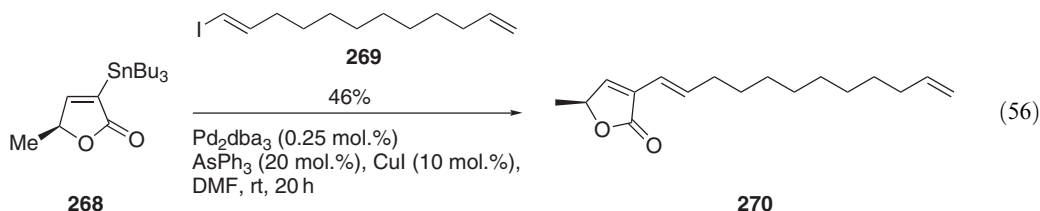


Stille coupling of tri-*n*-butylstannyl isopropyl squarate has been carried out using solid-supported aryl halides <1997JA7607>. Silica-supported palladium catalysts have also been used for the alkenylation of 5-iodouracil <1999JOC1077>.

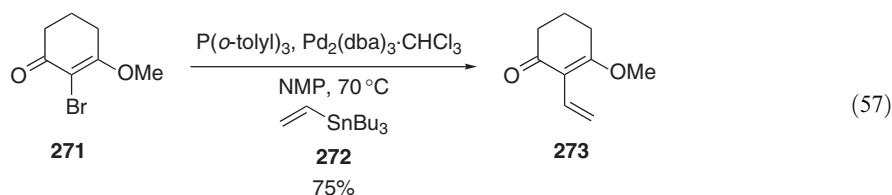
Cyclopent-2-enone **264** undergoes palladium-catalyzed cross-coupling with vinyl iodide **266** to give α -alkenylated enones **267** in good yields (Equation (55)) <1998T7057>. The reaction proceeds via vinyltin intermediate **265**. Vinylstannanes also undergo Stille coupling with iodoenones; this methodology has been used for the synthesis of a series of fungicides <1998T7595>.



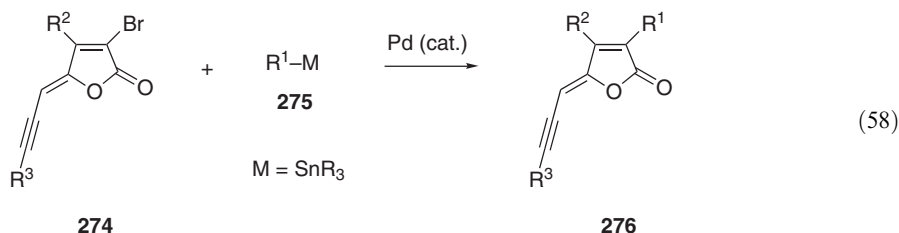
Chiral (*S*)-5-methyl-3-tri-*n*-butylstannylfuran-2-(5*H*)-one **268** undergoes catalyzed-catalyzed Stille cross-coupling with (*E*)-1-iodododeca-1,11-diene **269** to give (+)-hamabiwalactone B **270** in reasonable yield (Equation (56)) <1998TL8901>.



Vinylstannane **272** undergoes Stille palladium-catalyzed cross-coupling with 2-bromo-3-methoxycyclohex-2-enone **271** to give the corresponding vinyl derivative **273** (Equation (57)) in good yields <1999TL459>.

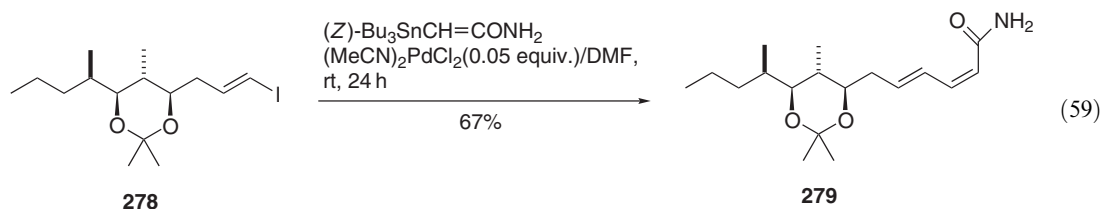


Bromobutenolides **274** undergo palladium-catalyzed cross-coupling reactions with alkenylstannanes **275** to give the corresponding 3-substituted (*Z*)-5-ylidene-(5*H*)-furan-2-ones **276** in good-to-excellent yields (Equation (58)) <1998TL3017>.

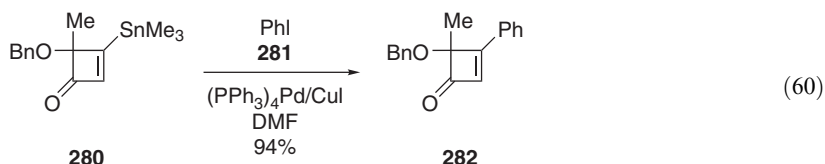


Vinylstannanes may be used in the Cu(I)-mediated coupling with an iodoalkene in the synthesis of the hypocholesterolemic agent 1233A <1998S1655>.

An amidovinylstannane **277** has been coupled with a vinyl iodide **278** to give a dienamide **279** (Equation (59)) <1996TL6711>. The latter is a key intermediate in the total synthesis of the enantiomer of naturally occurring antifungal antibiotic, YM-47522.

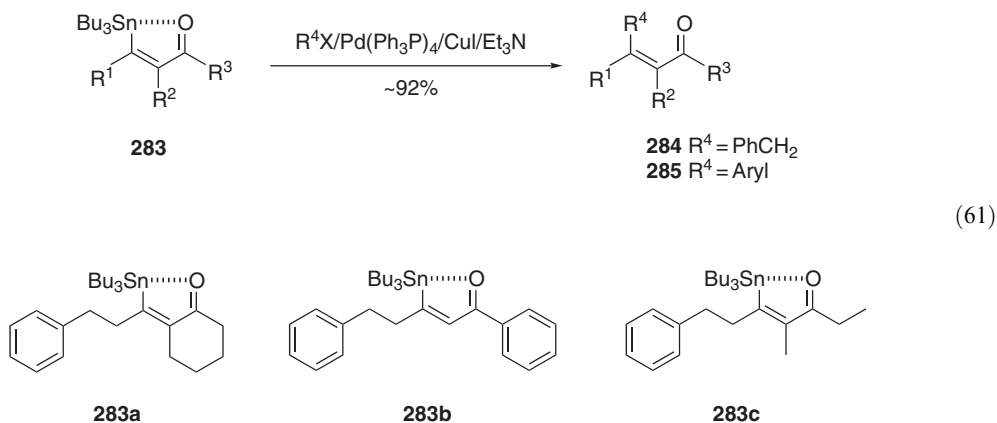


β -Trimethylstannylcyclobutenones **280** undergo facile coupling with iodobenzene **281** to give 4-substituted cyclobutenones **282** (Equation (60)) <1998JOC4691>.

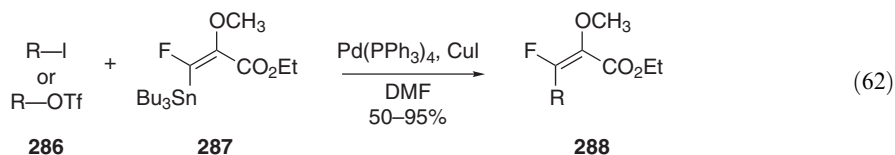


3,4-Bis(tributylstannyl)-5(*H*)-furanones undergo Stille coupling reactions with aryl halides to give 3-(tributylstannyl)-4-aryl-(5*H*)-furan-2-ones, with excellent regioselectivity and good yields <1999JOC328>.

Palladium(0)/copper(I) co-catalyzed cross-coupling of vinylstannyl ester derivatives (**283a–283c**) with benzyl or aryl halides gives tri- and tetra-substituted enones **284** and **285** in good yields and with high stereoselectivity (Equation (61)) <1995T2515>. Coordination of the oxygen lone pair electrons to the Bu_3Sn group supposedly deactivates the vinylstannane and reduces the nucleophilicity of the α -carbon to Sn.



Vinylstannyl derivatives **287** undergo palladium(0)/copper(I) co-catalyzed cross-coupling with aryl iodides or triflates **286** to give *Z*- β -substituted β -fluoro- α -methoxyacrylates **288** in good-to-excellent yields (Equation (62)) <1995JOC6608>. Coupling with vinyl triflates occurs under the same conditions.

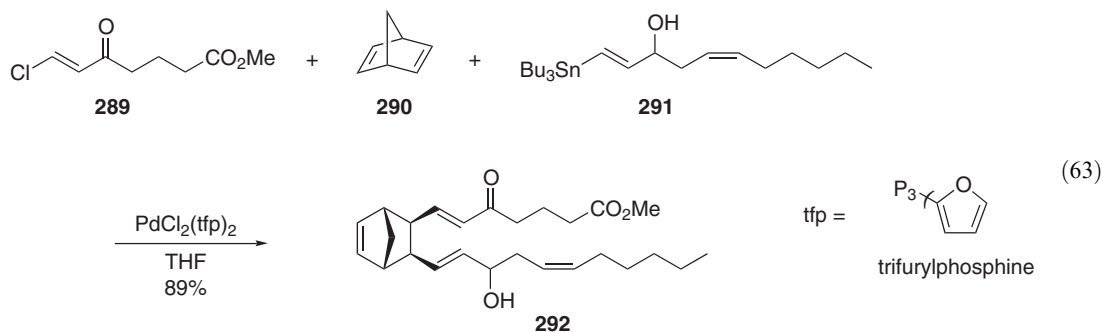


Vinylstannane reagents undergo palladium-catalyzed Stille-type coupling with (*E*)- or (*Z*)-3-iodoprop-2-enoic acids to give dienoid acids with good stereoselectivity <1995TL2469, 1997SL771, 1996S82, 1998SC239>. They have been further employed in the synthesis of some naturally occurring dienamides <1996S82, 1998SC239>, amide bond-anchored polyethyleneglycol derivatives

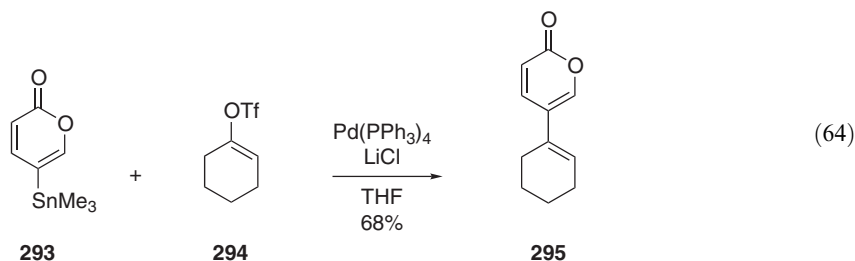
<1998JOC1119>, or intramolecularly for the synthesis of polyene macrolides such as macrolactin A <1996TL3501>. A vinylic furanostannane has also been shown to undergo palladium-catalyzed coupling with β -bromobutenolide to give furanones in good yields <1996S155, 1996S164>.

Tri-*n*-butylvinylstannane participates in a Stille-type palladium-catalyzed coupling with a protected β -bromo- γ -hydroxybutenolide to give a furanone in excellent yields <1998S1367>. This reaction contributed towards the total synthesis of the nonsteroidal anti-inflammatory sesquiterpene, manolide.

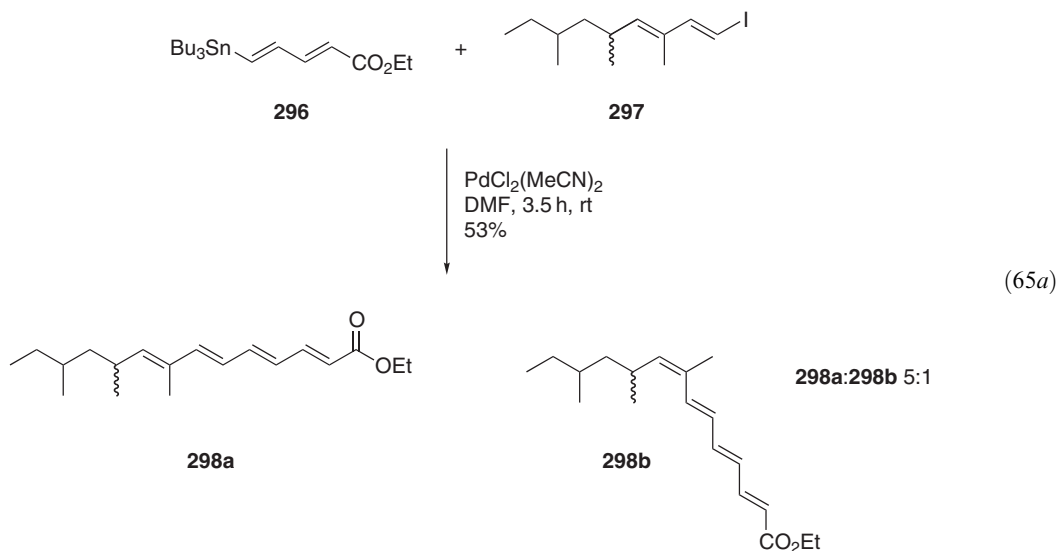
Palladium-catalyzed ternary coupling between β -chloroenone **289**, norbornadiene **290**, and a vinylstannane **291** gives racemic 5,12-diHETE-8,9-cyclopentadiene Diels–Alder adduct **292**, a potential precursor of a member of the leukotriene families, in good yields (Equation (63)) <1995T695>.



Vinylic pyran-2-one stannane **293** reacts with the enol triflate **294**, derived from cyclohexanone, in a Stille-coupling-type process to give the substituted pyran-2-one **295** (Equation (64)) <1996JOC6693>. The methodology was extended to the synthesis of cardiotoxic agents lucibufagins and bufadienolides.



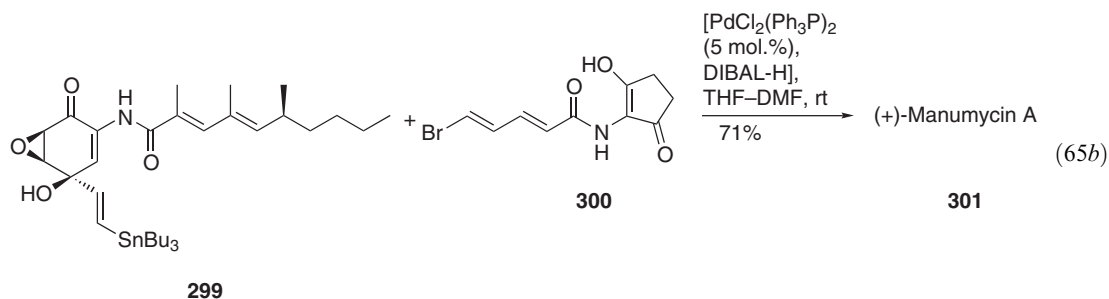
Dienylstannanes, **298a** and **298b**, can be prepared from reaction of (*E*)- β -stannylacrylate **296** with vinyl iodide **297** in reasonable yields (Equation (65a)).



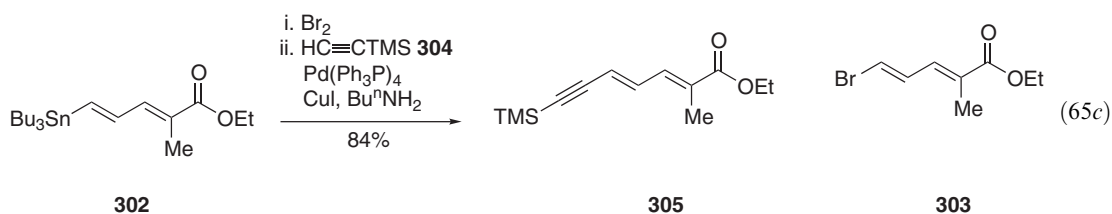
Related Stille palladium-catalyzed cross-couplings with vinyl iodides <1998TL6033> or bromides <1999JOC5053, 1998TL6033> have proven synthetically useful. For example, carbonyl-protected dienylstannanes have been employed in palladium-catalyzed coupling reactions <1998SL879>. 5-Trimethylstannyl-substituted dienic esters have been reported to undergo Cu(I) chloride-mediated oxidative homocouplings with concomitant lowering of yields of the expected products from Stille cross-coupling <1998T10609>.

The Stille coupling reaction between δ -iododienoic acids and vinylstannanes has been used for the preparation of retinoic acids with an all-*trans* stereochemistry <1999SL141>. Vinylic stannanes have also been used for the synthesis of a number of naturally occurring polyenamides <1996TL6619, 1996CC2647>.

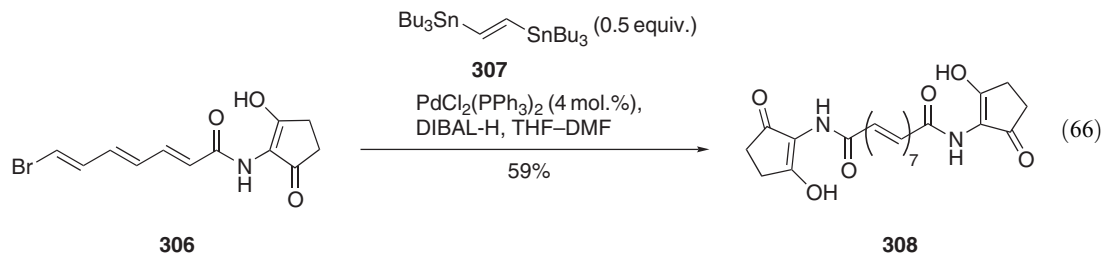
Vinylstannane **299** undergoes coupling with bromide **300**, in the presence of a pre-reduced palladium catalyst, to give the (+)-enantiomer of the antibiotic manumycin A **301** (Equation (65b)) <1998JOC3526, 1999T3707>. This methodology has also been applied to the analog of manumycin A <1998S775, 1999CC421, 1999JCS(P1)1143> and to the *Streptomyces*-produced biosynthetic precursor of the antibiotic triamide asuka-*m*ABA <1998T9823, 1996CC2647>.



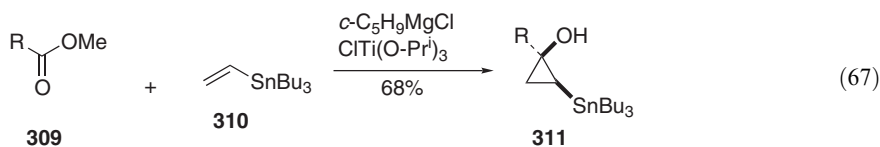
Vinylstannane **302** was converted to bromoester **303** by stereospecific bromine tin exchange, which then undergoes Sonogashira palladium-catalyzed cross-coupling with trimethylsilylacetylene **304** to give dienic ester **305** in excellent yield (Equation (65c)) <1997JA12159>. This reaction has been utilized in the total synthesis of the polyene 6,7-dehydrostipiamide, which reverses the multidrug resistance of human breast cancer cells.



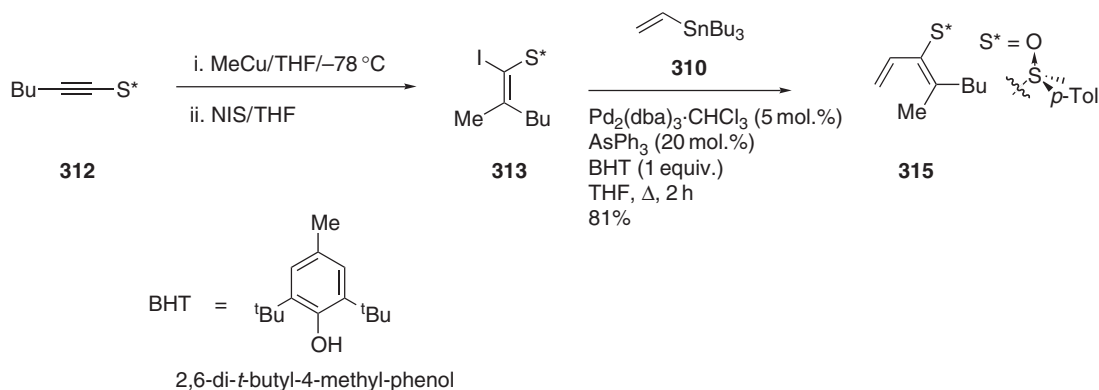
Bis-stannylated ethene **307** undergoes cross-coupling with 2 equiv. of bromotrienamide **306**, in the presence of a pre-reduced palladium catalyst, to give the antiviral diamide limocrocine **308** (Equation (66)) <1996CC2647>.



Vinylstannanes **310** undergo dialkylcyclopropanation with various esters **309** to give stannyl cyclopropanes **311** in moderate-to-good yields (Equation (67)) <1998JOC9135>.

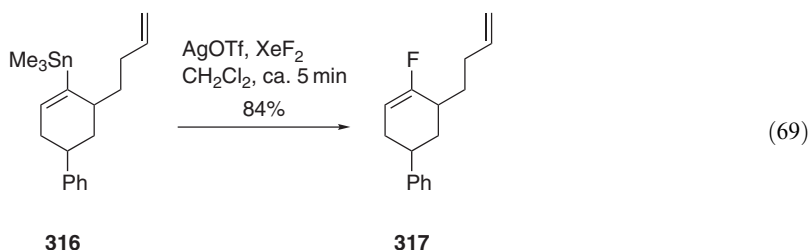


Enantiopure 2-sulfinyl dienes **315** can be prepared via regio- and stereoselective hydrostannylation of alkynylsulfoxides **312**; after conversion to the corresponding vinyl iodides **313**, these substrates may be coupled with vinylstannanes **310**, via Stille methodology, in the presence of the radical initiator BHT (Equation (68)) <1995TL3605>.

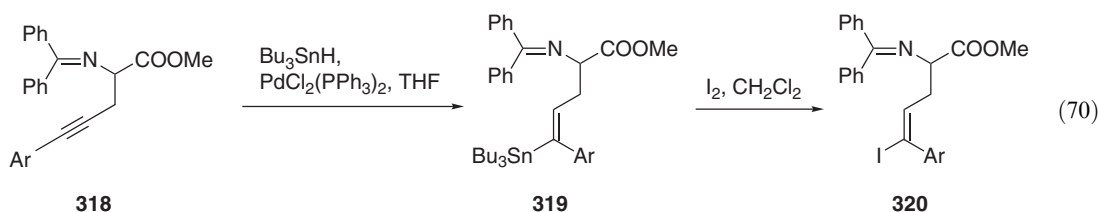


(68)

The combination of a vinylstannane **316** with xenon difluoride in the presence of silver(I) triflate results in a very rapid process leading to the corresponding vinyl fluoride **317** (Equation (69)) <1995T3997>. The reaction is regio- and stereospecific and does not require stoichiometric Ag(I). No evidence could be obtained of radical intermediates on the reaction pathway leading to the vinyl fluorides. A symmetrical dimer derived from the vinylstannane was obtained as a reaction by-product and was shown to arise from oxidative coupling by the silver salt. The results are consistent with an electrophilic mechanism following an initial interaction of the vinylstannane with Ag(I).



The palladium-catalyzed stereoselective hydrostannylation of **318** provided **319** in 55% yield, which was subsequently treated with iodine to effect a stereospecific iodine–tin exchange to afford **320** (Equation (70)) <2001TL2957>.

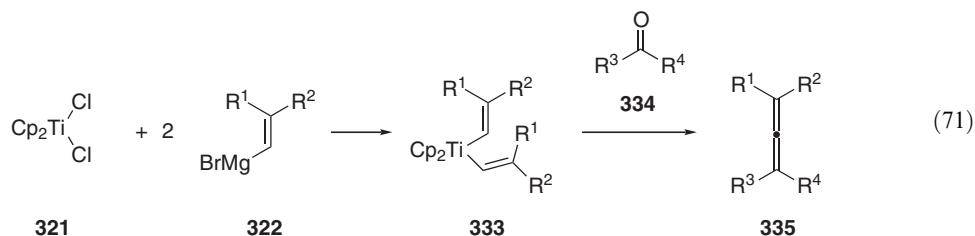


1.22.1.14 Vinyltitanium Reagents

A review on the synthesis of vinyltitanium complexes, formed by addition to alkenes, and synthetic applications is available <2000CRV2835>.

1.22.1.14.1 Formation of vinylic carbanions by deprotonation, metal–halogen exchange, and transmetallation

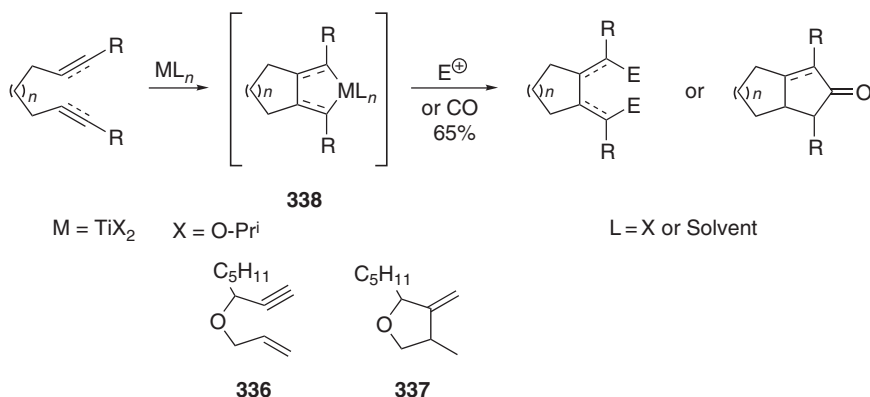
Bis(alkenyl)titanocene precursors **333**, formed by reaction of **321** with vinylmagnesium reagent **322**, are efficient allenating agents for ketones **334**, and provide a versatile route into substituted allenes **335** (Equation (71)) <1997JOC782>.



1.22.1.14.2 Formation by addition to alkynes and allenes

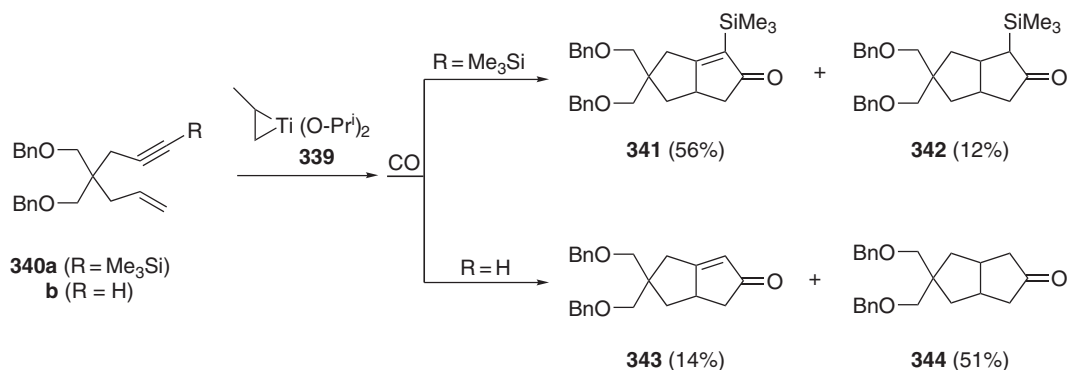
Chirally modified titanacyclopropenes generated from chlorotris[(–)-menthyloxy]titanium, *iso*-propylmagnesium bromide, and disubstituted acetylenes add to carbonyl compounds with moderate enantiofacial selectivity <1996CC1725>.

Is-propylmagnesium halide and titanium tetraisopropoxide [Ti(O*i*-Pr)₄] have been recommended as a convenient reagent system in a practical sense for the generation of vinylic titanacyclopentanes by intramolecular cycloaddition of a titanacyclopentane intermediate **339** to a multiple bond <1996JA8729, 1996CC197, 1997JA10014, 1995TL4261, 1996TL1253, 1996JOC6756>. The reactions are conducted by adding *iso*-propylmagnesium bromide (2 equiv. with respect to Ti(O*i*-Pr)₄) to a mixture of the bis-unsaturated substrate and a slight excess of Ti(O*i*-Pr)₄ in ether at –78 °C, then keeping the reaction mixture at –50 °C for a few hours. This *i*-PrMgBr/Ti(O*i*-Pr)₄ reagent system was successfully applied to the cyclization of enynes with unprotected terminal triple bonds. For example, the substituted allyl propargyl ether **336** could be smoothly transformed into the corresponding 3-methylenetetrahydrofuran **337**, by subsequent acidic quench of intermediate **338** (Scheme 26) <1995TL4261>.



Scheme 26

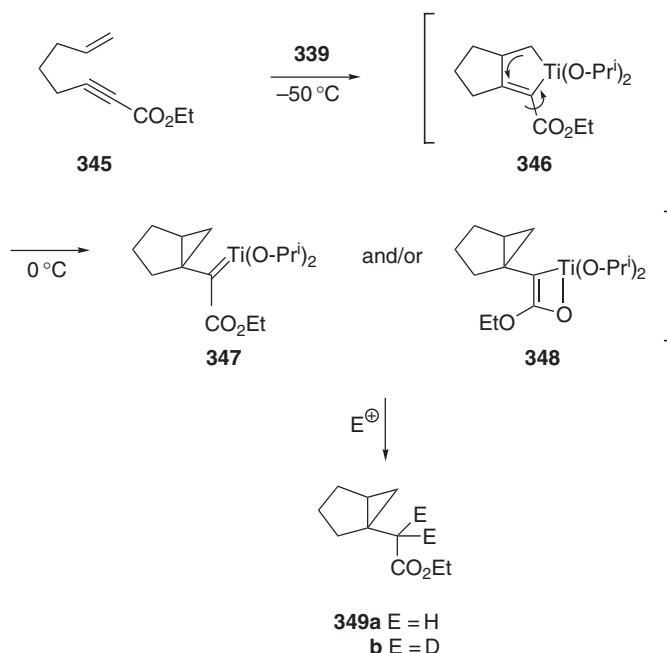
Vinylic titanacyclopentadienes with a 1,4-dicarbocationic reactivity pattern have been quenched with deuterium oxide <1996JA8729, 1997JA10014, 1995TL4261>, iodine <1997JA10014, 1996TL1253>, aldehydes <1996JA8729, 1997JA10014, 1995TL4261, 1996JOC6756>, ketones <1996JA8729, 1997JA10014>, carbon monoxide, and carbon dioxide <1995TL4261>. For example, the substituted bicyclo[3.3.0]oct-1-en-3-ones, **341** and **344**, are prepared by reaction of the intermediate titanacyclopentenes, formed by reaction of **339** with either **340a** or **340b**, with carbon monoxide (Scheme 27) <1995TL4261>. Here, the free terminal acetylene **340b** leads to the predominant formation of the reduced product **344**, whereas the silyl-protected derivative **340a** gives the enone **341** as the major product.



Scheme 27

A modification of this method for the construction of bicyclic skeletons uses bis-unsaturated substrates containing an α,β -unsaturated ester moiety [<1996JA8729, 1997JA10014>](#). The second ring closure in this case occurs by intramolecular attack of one of the carbanionic centers on the vinylic titanium intermediate at the ester group, which leads to a titanium enolate that can be trapped with an added external electrophile. This methodology circumvents the uses of carbon monoxide for the preparation of bicyclic ketones.

1,6-Enynes with a terminal propargylic moiety underwent reductive cyclization to a vinylic titanacyclopentene intermediate **346**, but this subsequently underwent ring contraction to a cyclopropylmethylidenetitanium complex, **347** or **348**, which was diprotodemetalated. For example, ethyl oct-7-en-2-ynoate **345**, upon treatment with PrⁱMgCl and Ti(O-Prⁱ)₄ at -50°C to form **339**, afforded, after acidic hydrolysis, ethyl 2-(1'-bicyclo[3.1.0]hexyl)acetate **349a** (Scheme 28) [<1997JA10014>](#).



Scheme 28

The formation of the cyclopropane ring in this reaction has been rationalized as an intramolecular Michael-type addition of the alkyl-carbon-titanium bond onto the α,β -unsaturated ester moiety of the intermediate titanabicyclo[3.3.0]octenecarboxylate. The intermediacy of the titaniumcarbene complex **347** (or the corresponding biscyclopentadienyl species, **348**) has been confirmed by deuteriolysis with DCl to yield the ester, which was completely deuterated in the two α -positions as well as by reaction with diethyl ketone to give the α -(diethylmethylene)carboxylate. This original transformation

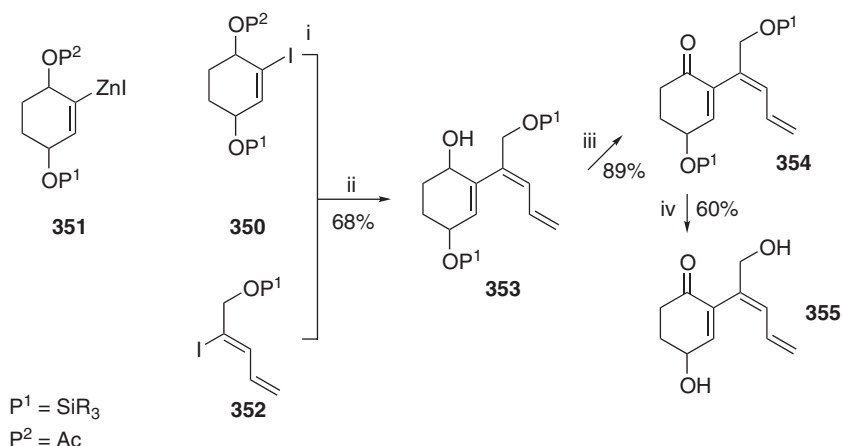
of a 1,4-dicarbanoionic organotitanium intermediate has successfully been applied toward the construction of the bicyclo[3.3.0]octane skeletons of terpenic hydrocarbons <1997JA10014>.

1.22.1.15 Vinylzinc Reagents

The uses of vinylzinc reagents in palladium-catalyzed coupling processes have been highlighted <2002JOM34>.

1.22.1.15.1 Formation of vinylic carbanions by deprotonation, metal–halogen exchange, and transmetallation

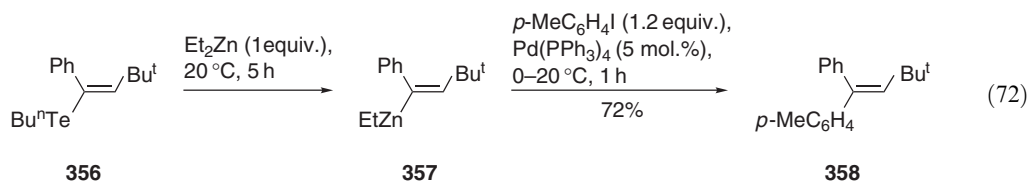
Vinyl iodide **350** undergoes lithiation with Bu^nLi , and then exchange with zinc bromide, to give vinylzinc reagent **351**. Subsequent Negishi cross-coupling of **351** with vinyl iodide **352**, then oxidation and removal of the protecting groups (**353** \rightarrow **354**), gives nakienone B **355** (Scheme 29) <1996TL4679>.



- i. (a) Bu^nLi , THF-Et₂O-pentane, -110°C , 15 min, (b) ZnBr_2 (0.5 equiv.), THF, -110 to 25°C .
 ii. (a) 5% $\text{Pd}(\text{PPh}_3)_4$, DMF, 25°C , 6 h, (b) K_2CO_3 , MeOH, 25°C , 1 h. iii. (a) $(\text{COCl}_2)_2$, DMSO (4 equiv.), 450°C , 2 h. (b) Et_3N (10 equiv.), -60 to 25°C . iv. Bu_4NF (4 equiv.), THF, 45 min.

Scheme 29

Alkenyl tellurides **356** were converted to the corresponding alkenylzinc compounds **357** by reaction with diethylzinc (Equation (72)) <1996TL4741>. The exchange reaction proceeds efficiently in THF at rt with retention of the stereochemistry of the starting tellurides. The successive reaction of the formed alkenylzinc with 4-iodotoluene in the presence of $\text{Pd}(\text{PPh}_3)_4$ afforded a cross-coupling product as a single stereoisomer.



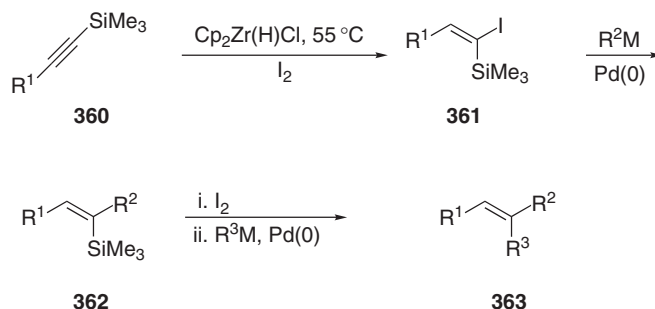
1.22.1.15.2 Formation by addition to alkynes and allenes

Vinylzinc reagents can be obtained by treatment of terminal alkynes with Cp_2ZrHCl followed by Zr–Zn exchange with Me_2Zn <1996OS205>.

1.22.1.16 Vinylzirconium Reagents

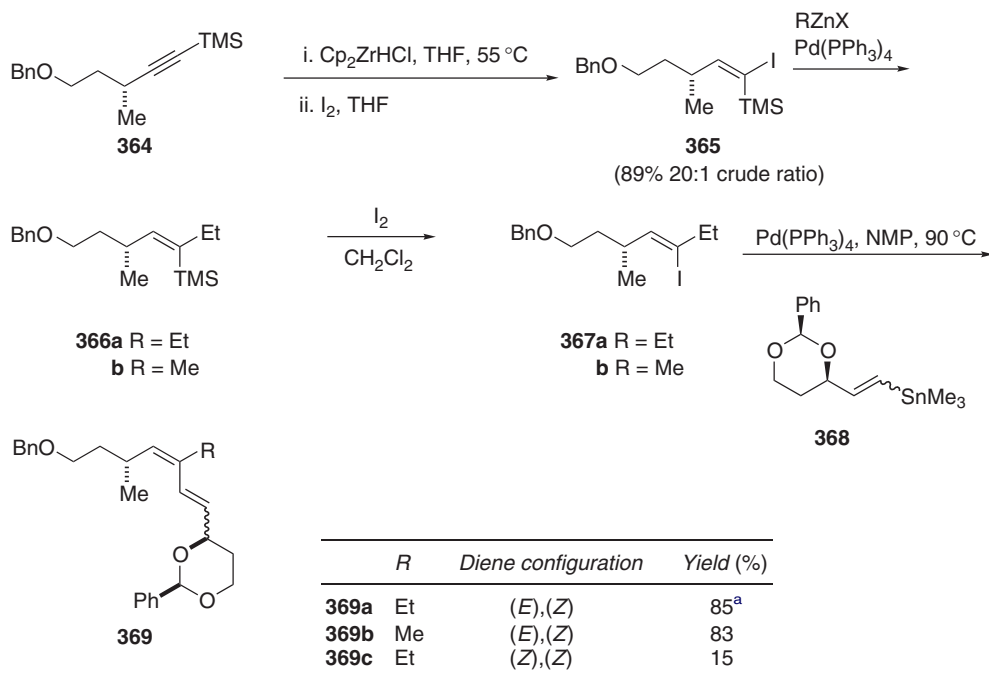
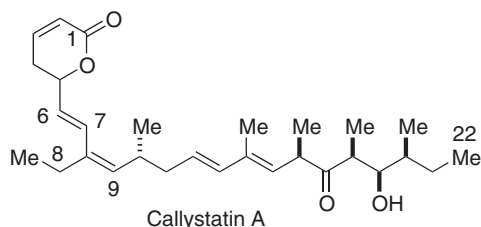
1.22.1.16.1 Formation by addition to alkynes and allenes

A highly flexible and stereoselective protocol for the synthesis of branched (*E*)- and (*Z*)-trisubstituted alkenes **363** has been developed [<2001OL3281>](#). The key steps are hydrozirconation-iodination of (1-alkynyl)trimethylsilane **360**, to give **361**, followed by Negishi-type cross-coupling. The resultant (*Z*)-vinylsilane **362** is iododesilylated and subjected to a second cross-coupling reaction to give the trisubstituted olefin **363** (Equation (73)).



(73)

This methodology was applied to the construction of the C14–C15 (*Z*)-trisubstituted olefin of discodermolide and the C8–C9 (*Z*)-trisubstituted olefin of callistatin A. The latter synthetic sequence is shown in Scheme 30 (**364** → **369**).

^a Callistatin A fragment.

Scheme 30

1.22.2 DICOORDINATE CARBOCATIONS (i.e., VINYLIC CATIONS)

1.22.2.1 General Introduction

Vinyl carbocation chemistry has been explored mainly through solvolysis of an appropriate intermediate, although photolytic and thermolytic techniques have been utilized. Developments in this area were reviewed in a monograph *Vinyl Cations* published in 1979 <B-1979MI001>, and more recently updated in a book *Dicoordinated Carbocations* published in 1997 <B-1997MI001>. Major advances in this field were accelerated by the introduction of the triflate group, classified as a “super” leaving group, in the 1970s <1970ACR209, 1978ACR107>. More recently, the introduction of vinyl iodonium salts and their increased availability has opened up the whole area of carbocation research <1985TL2351, 1988T4095, 1993JA11626, 1994S313, 1997TL6709, 1996CRV1123>. The greatly enhanced nucleofugality <1983PAC1281> of the iodonio group, as compared to the triflate, has allowed the study of simpler, more labile cations not previously accessible.

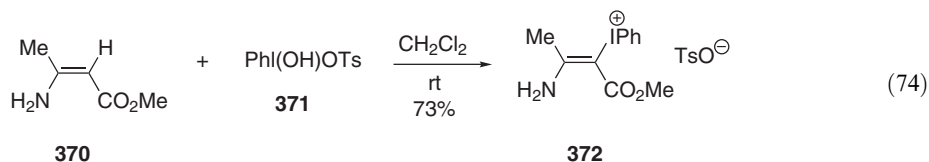
Parent and primary vinyl cations are both thermodynamically and kinetically unstable and can usually only be thermally generated under forced conditions in solution. Gas-phase spectroscopic studies <1995JPC15611> have shown that the smallest vinylic cation has the structure of a protonated acetylene rather than that of the classical vinyl cation. A number of theoretical studies including an *ab initio* study on the thermochemistry of the vinyl cation <1996Science179, 1998CPL51>, rotational spectroscopy using a negative glow discharge <1996JMS59>, and hollow-cathode spectroscopy <1995JPC15611> have lent further support to the nonclassical form of the vinyl cation.

1.22.2.2 Formation of Primary Vinylic Cations from Iodonium Salts

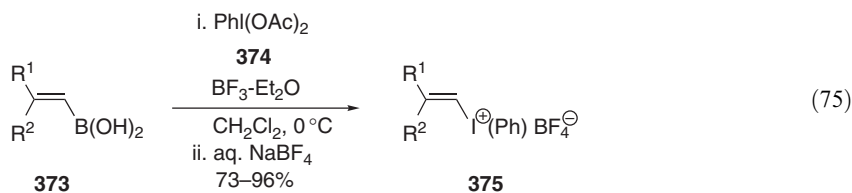
Secondary vinyl carbocations are readily generated from the corresponding iodonium salts (Section 1.22.1.3); however, primary vinyl carbocations have proven more elusive. Mechanistic aspects of the reaction of vinylic iodonium salts with nucleophiles have been reviewed <2002ACR12, 1999MI001, 2000JOM494>. Whenever possible, rearrangements occur through participation of the β -substituent to generate a secondary carbocation; alternatively vinylic S_N2 substitution followed by elimination occurs. The electron-withdrawing ability of the iodonium group and the acidity of the α -hydrogen easily leads to α -elimination reactions, and also allows Michael addition of a nucleophile under certain conditions. Intramolecular reactions and ligand coupling lead to substitution with retention as well as β -elimination. Regardless of the mechanism involved, vinylodonium salts can be considered as synthons of the corresponding vinyl cation.

1.22.2.2.1 Preparation of vinylodonium salts

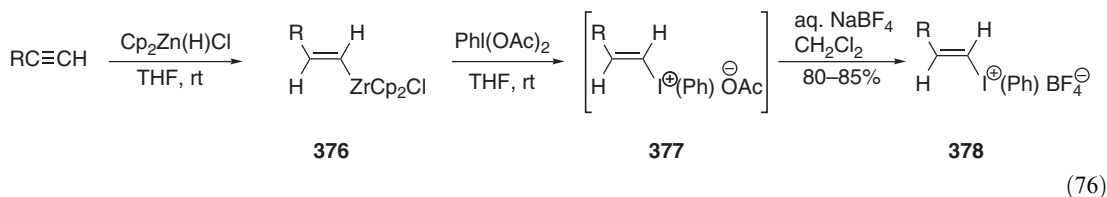
Methyl 3-aminocrotonate **370** reacts with $\text{PhI}(\text{OH})\text{OTs}$ **371** to give vinyl(phenyl)iodonium tosylate **372** in good yield (Equation (74)) <1998T1005>.



Vinylboronic acids **373** or esters react under mild conditions with (diacetoxyiodo)benzene **374** and catalytic $\text{BF}_3 \cdot \text{Et}_2\text{O}$ to give the vinyl(phenyl)iodonium tetrafluoroborates **375** in excellent yields. The reaction proceeds stereoselectively, with retention of configuration at the alkene (Equation (75)) <1997TL6709>.

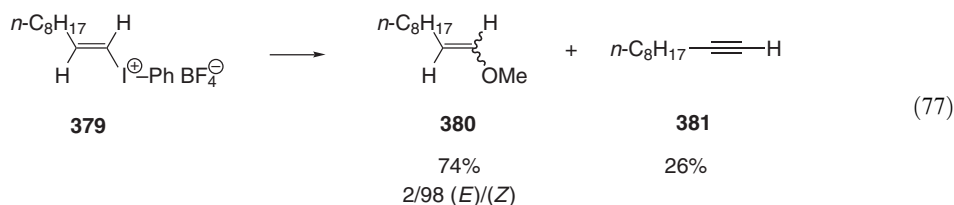


Vinylzirconium derivatives **376** react with **374**, followed by anion exchange of **377** with NaBF₄, to give vinyl(phenyl)iodonium salts **378** in good-to-excellent yields. The reaction again proceeds stereoselectively, with retention of configuration at the alkene (Equation (76)) <1998JCS(P1)3321>.

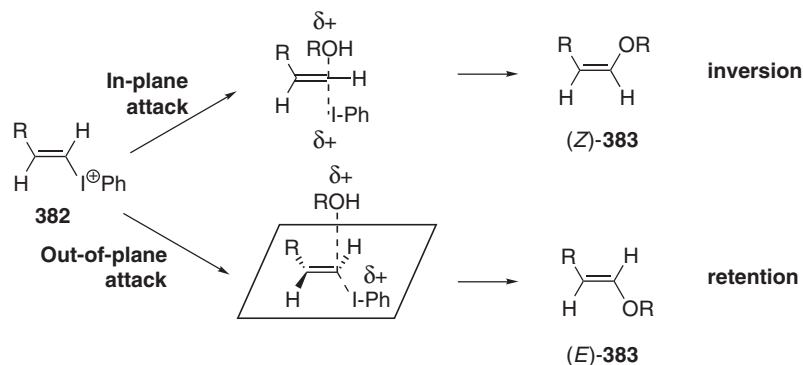


1.22.2.2.2 Vinylic S_N2 mechanism

Particular attention has been paid to the mechanism of formation of a vinyl cation from solvolysis of **379** <1998BCJ243, 1998JA2275, 2002ACR12>. In spite of the fact that a primary vinyl cation was expected as an intermediate, the solvolysis in alcoholic and aqueous solvents proceeded fairly rapidly to give both substitution **380** and elimination **381** products (Equation (77)). The rate of solvolysis was dependent on the nucleophilicity of the solvent rather than on the ionizing power, whereas the product ratio was dependent on the basicity of the medium.

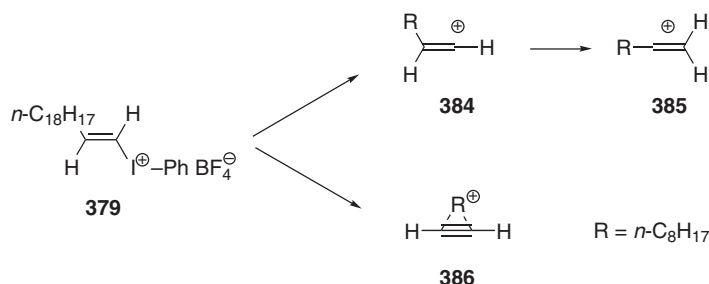


Formation of substitution products proceeds predominantly with inversion of configuration and so it was concluded that they were derived from a vinylic S_N2 reaction. The feasibility of both an in-plane σ* S_N2 pathway leading to inversion of configuration, and an out-of-plane π* S_N2 pathway leading to retention of configuration in the product has been established theoretically <1995JA2297, 2000JA2294> (Scheme 31). Iodonium salt **382** therefore reacts via the former route to give *Z*-**383**, with a small amount of the minor isomer, *E*-**383**, accounted for by the latter route <1998BCJ243, 1998JA2275>.



Scheme 31

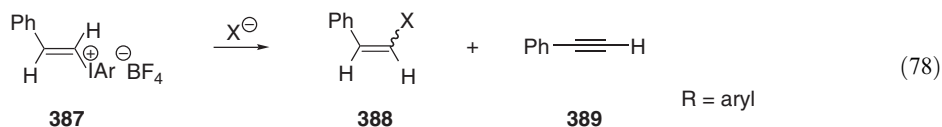
The formation of a primary vinyl cation **384** was ruled out on the basis that no rearranged products, e.g., **385** (as a result of rearrangement to the more stable secondary vinyl cation via 1,2-hydride shift), were observed. The formation of a nonclassical vinyl cation **386** was excluded, as no isotope scrambling was observed in the product from the deuterium-labeled substrate (Scheme 32) <1997JA4785, 1999BCJ163>.



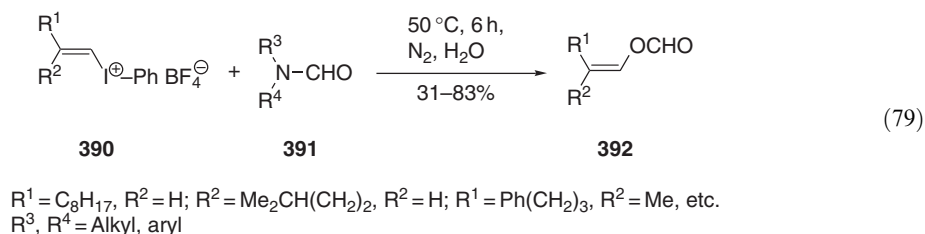
Scheme 32

The elimination product **381** can be formed by either an α - or β -elimination pathway, the preferred route being dependent on the reaction conditions. In neutral methanol, for example, iodonium salt **379** was evaluated to undergo an α,β elimination in a ratio of about 3:1.

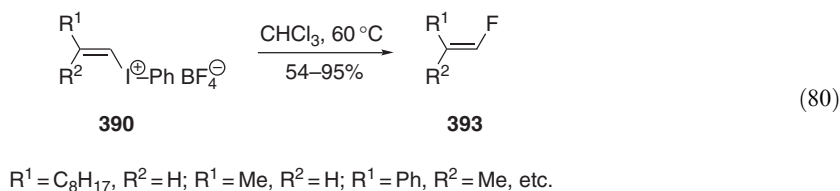
(*E*)-Phenyl(styryl)iodonium tetrafluoroborate **387** reacts with halide ions to give (*Z*)-1-halo-2-phenylethene **388**, and phenylacetylene **389**, as the major products (Equation (78)). The isomer (*E*)-**388** was also formed, albeit in minor amounts <1998BCJ1915>. The yields and isomeric ratios were dependent on solvents and concentrations. Kinetic studies and UV absorption spectroscopy established that the reaction proceeded via an in-plane vinylic $\text{S}_{\text{N}}2$ mechanism to give the (*Z*)-isomer. It was concluded that the (*E*)-isomer was formed through a vinylenebenzenium ion or through ligand coupling within the λ^3 -iodane intermediate depending on which solvent was used.



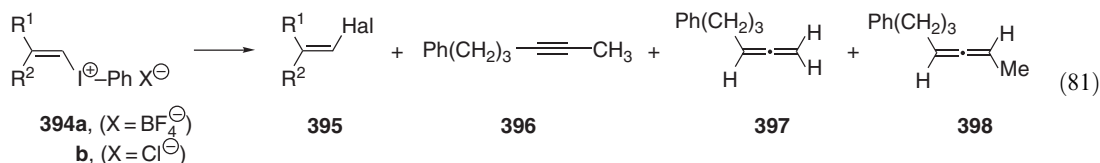
Reaction of alkenyl(phenyl)iodonium tetrafluoroborates **390** with formamides **391** affords vinyl formates **392** (Equation (79)) <1999CC1363>. The reaction proceeds stereoselectively to give predominantly inversion of configuration via an in-plane vinylic $\text{S}_{\text{N}}2$ mechanism.



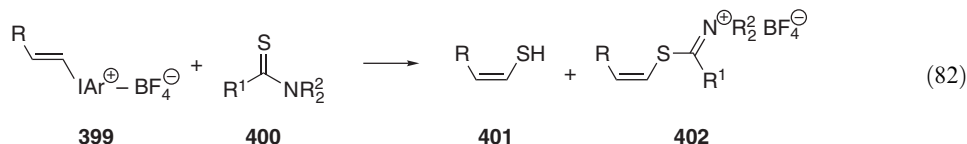
Thermolysis of alkenyl(phenyl)iodonium tetrafluoroborates **390** at 60 °C in chloroform, or in the solid-state, provides 1-fluoroalkenes **393** via an $\text{S}_{\text{N}}2$ -type reaction (Equation (80)) <2000TL5125>. The reaction is stereospecific occurring exclusively by inversion of configuration.



(*E*)-2-Methyl- and (*Z*)-2-methyl-5-phenylpent-1-enyl(phenyl)iodonium tetrafluoroborate **394a** and chloride **394b** react with halide ions in various solvents at 50 or 60 °C to give mainly substitution products such as 1-halo-2-methyl-5-phenylpent-1-ene **395**, with inversion of configuration (Equation (81)) <2000BCJ2341>. The yields are dependent on the solvent and concentrations used. Minor substitution products with retention of configuration, rearranged and elimination products were also observed (**396–398**). A study of the kinetics of the reaction suggested that the major product (inversion of configuration) proceeded via a vinylic in-plane $\text{S}_{\text{N}}2$; products formed from via retention of configuration were proposed to proceed via an out-of-plane $\text{S}_{\text{N}}2$ and/or ligand coupling mechanism. Rearrangement reactions appeared to occur via β -alkyl participation.

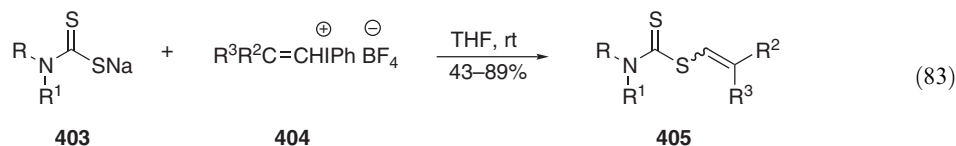


Alkenyl(phenyl)iodonium tetrafluoroborates **399** react as alkenylating reagents with thioamides **400** to give (*Z*)-vinylthiols **401** and/or (*Z*)-*S*-vinylthioimidonium salts **402** (Equation (82)) <2001OL2753>. The mechanism of the reaction is discussed, and is proposed to proceed via a vinylic $\text{S}_{\text{N}}2$ process rather than a primary vinyl carbocation.

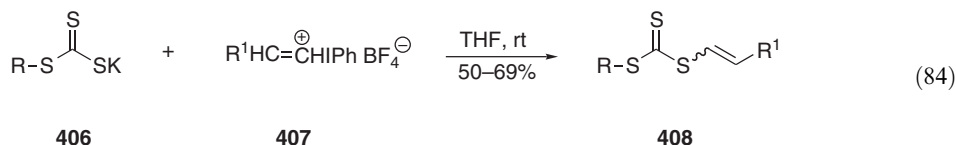


Other sulfur nucleophiles also react stereospecifically at the vinylic centre of alkenyl(phenyl)iodonium salts **399**.

Sodium dithiocarbamates **403** addition to **404** gives vinyl esters of dithiocarbamic acids **405**. When $\text{R} = \text{Bu}^n$ the reaction proceeds with inversion of configuration, whereas when $\text{R} = \text{Ph}$ retention of configuration is observed (Equation (83)) <1999SC2867>.

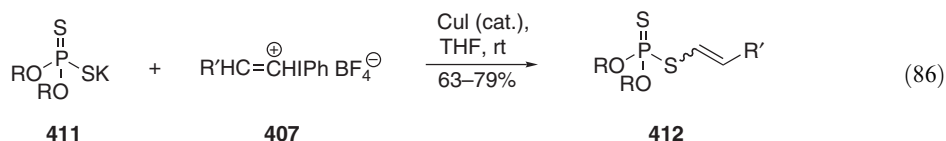
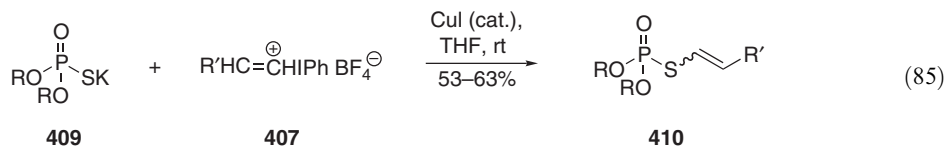


Likewise, iodonium salts **407** react with potassium carbonotrithioates **406** to give vinyl esters of carbonotrithioic acids **408** (Equation (84)) <2000SC3897>.

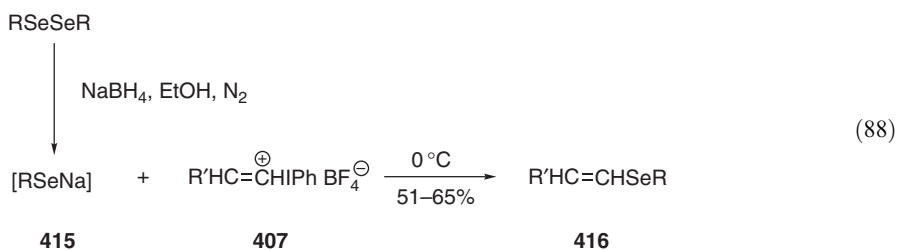
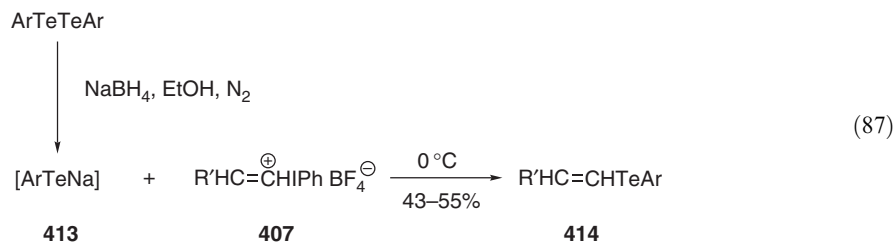


The reaction proceeds under mild conditions and in good yields. The stereochemistry is dependent on the nature of the vinyl substituent.

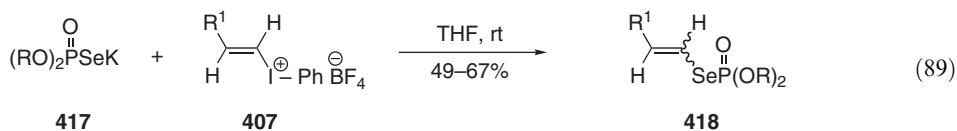
Potassium *O,O*-dialkylphosphorothioates **409** react with **407**, in the presence of Cu(I) catalysts, to give *S*-vinyl *O,O*-dialkylphosphorothioates **410** (Equation (85)) <1999SC3605>. Likewise, potassium *O,O*-dialkylphosphorodithioates **411** react with **407**, in the presence of Cu(I) catalysts, to give *S*-vinyl *O,O*-dialkylphosphorodithioates **412** (Equation (86)) <1999SC3275>.



Similarly, selenium and tellurium nucleophiles react at the vinylic centre of alkenyl(phenyl)-iodonium salts **407**; the vinylic S_N2 mechanism has also been implicated in these reactions. As with sulfur nucleophiles the observed stereochemistry is dependent on the nature of the vinylic substituent. Sodium tellurolates **413** react to give vinylic tellurides **414** in good yields (Equation (87)) <2000SC2359>. Sodium selenolates **415** give vinyl selenides **416** on reaction with **407** (Equation (88)) <2000SC1009>.

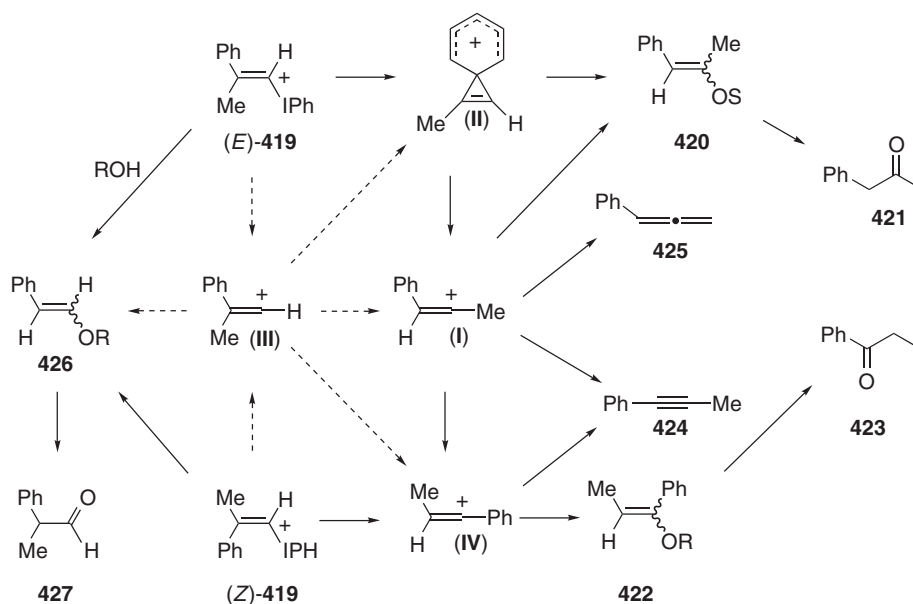


Potassium *O,O*-dialkyl phosphoroselenoates **417** react with **407** to give *Se*-vinyl-*O,O*-dialkyl phosphoroselenoates **418** (Equation (89)) <1999TL5757>.



1.22.2.2.3 Rearrangements

The primary vinyl cation derived from a β -phenylvinylidonium salt has been predicted to be unstable <1996JOC5274>. However, solvolysis of (*E*)-styryl(phenyl)iodonium tetrafluoroborate took place at a reasonable rate, suggesting that the reaction proceeded via another intermediate <1997JA4785, 1999BCSJ163>. Indeed, solvolysis of (*E*)-2-phenylprop-1-enyl(phenyl)iodonium tetrafluoroborate (*E*)-**419** occurred at a much faster rate than that observed for the (*Z*)-isomer, (*Z*)-**419**, in trifluoroethanol at 60 °C, and the product distribution was also different (Scheme 33) <2001JA8760>. The (*E*)-isomer (*E*)-**419** gives mainly the rearranged product **420**, as well as two



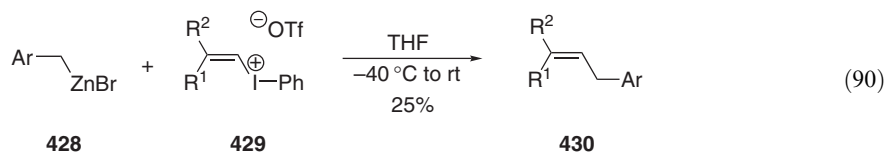
Scheme 33

elimination products **424** and **425**, derived from the cation (I) and/or (II). In less nucleophilic solvents, the rearranged product **422** was also obtained. The (Z)-isomer, (Z)-**419**, gave products **422** and **424**, as well as the unrearranged product **426**. The results obtained were consistent with the substituent *trans* to the iodobenzene leaving group participating in the reaction. There was no evidence for the formation of the primary vinyl cation (III) during solvolysis of either isomer.

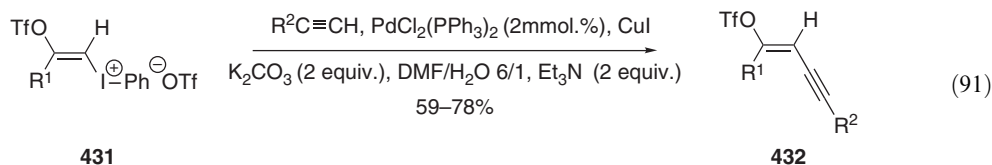
Photosolvolysis of (Z)-**419** and (E)-**419** was found to give a similar distribution of products in both cases, although these were quite different to those observed from thermal solvolysis [\[2001JA8760\]](#). The formation of the heterolysis products **426**, **420**, **422**, and **424**, derived from cleavage of the vinyl-iodine bond, strongly supports the photochemical generation of the primary vinyl cation (III).

1.22.2.2.4 Primary vinylic cations in synthesis

The cross-coupling of vinyl(phenyl)iodonium triflates **429** with benzylic organozinc reagents **428** gives single stereoisomers of trisubstituted alkenes **430**, under mild conditions (Equation (90)) [\[2000OL1521\]](#).

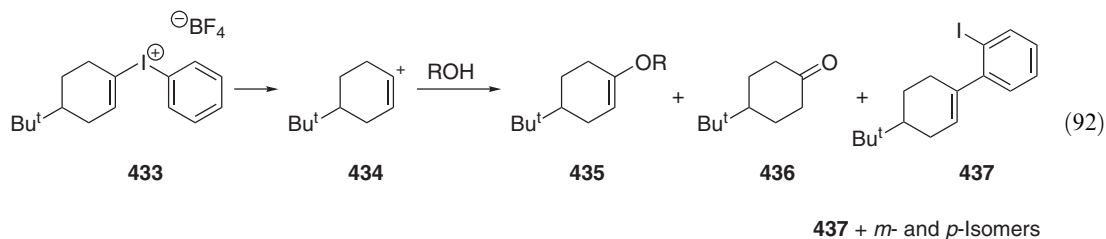


Palladium-catalyzed coupling of vinyl(phenyl)iodonium triflates **431** with terminal alkynes, and catalytic amounts of CuI, gives conjugated enynes **432** in good yields (Equation (91)) [\[E1999T12377\]](#).

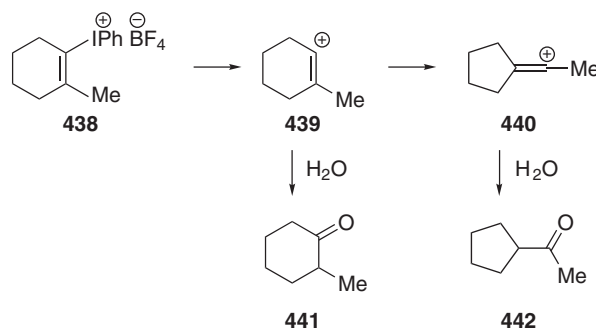


1.22.2.3 Formation of Secondary and Tertiary Vinylic Cations from Iodonium Salts

The cyclohex-1-enyliodonium salt **433** undergoes solvolysis in various alcoholic and aqueous solutions [<1995JA3360>](#). The main products observed are those expected for a cyclohexenyl secondary cation intermediate **434**, the enol ether **435**, and/or the cyclohexanone **436** (Equation (92)). Besides the expected solvolysis products, (4-*t*-butylcyclohex-1-enyl)iodobenzenes were also obtained, the yields being dependent on the nature of the solvent. The *ortho*-product **437** was the predominant isomer, presumably from the internal return of the contact ion molecule pair of cyclohexenyl cation **434** and iodobenzene. The rate of solvolysis is independent of the nature of the solvent.

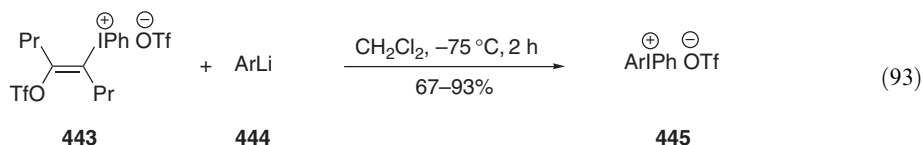


Rearrangement of 2-methylcyclohexen-1-yl(phenyl)iodonium tetrafluoroborate **438** provided further evidence for the formation of a secondary vinyl cation intermediate (Scheme 34) [<1995JA3360>](#). The strained bent vinyl cation **439** (addition of H₂O gives **441**) rearranges to give the more stable linear secondary vinyl cation **440** (addition of H₂O gives **442**). The rate of solvolysis is enhanced by the presence of the 2-methyl group, as compared to the unsubstituted iodonium salt **433**, as expected for methyl group stabilization of vinyl cations [<B-1997MI001>](#).



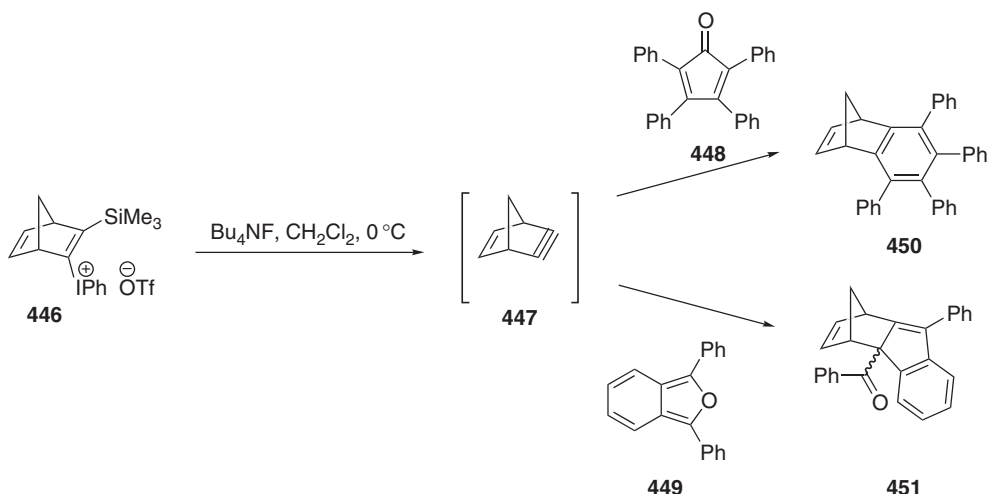
Scheme 34

Vinyliodonium salt **443** is reported to undergo a ligand transfer reaction with aryllithium reagents **444** to generate aryl and heteroaryl(phenyl)iodonium triflates **445** in good-to-excellent yields (Equation (93)) [<1996TL3721>](#).

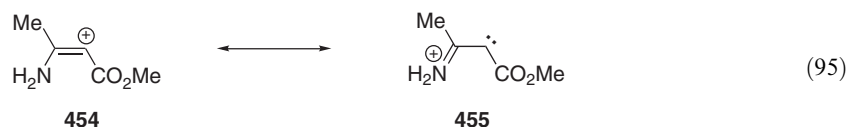
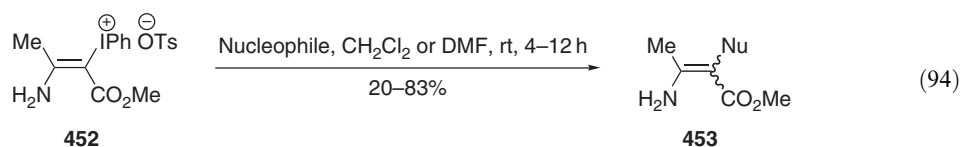


Vinyliodonium salt **446** generates a highly strained cyclic alkyne **447** which acts as a dienophile in reactions with tetraphenylcyclopentadienones **448** or 1,3-diphenylisobenzofuran **449** to give the cycloadducts **450** and **451**, respectively (Scheme 35) [<1999JOC680>](#).

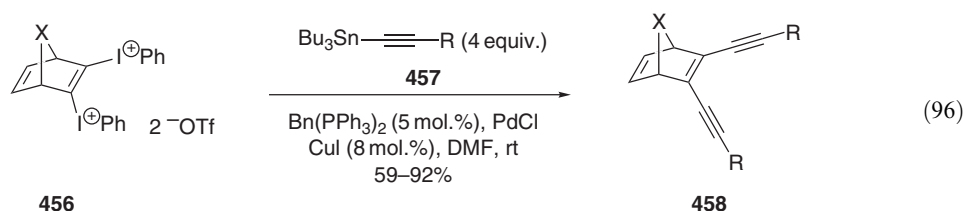
Soft nucleophiles react readily with the vinyliodonium salt **452**, derived from methyl 3-amino-crotonate, under mild conditions to give substituted enamine derivatives of crotonic acid **453** (Equation (94)) [<1998T1005>](#). With the exception of the nitrite ion, which required Cu(II), all the reactions proceeded without any catalyst. The stereochemistry of the reaction was dependent on



the reaction conditions and the nature of the product. These vinylic substitutions were proposed to proceed with elimination of iodobenzene from the salt to give a vinylic cation **454**, stabilized through electron donation from the amino group (as in **455**) (Equation (95)) <1998T1005>.



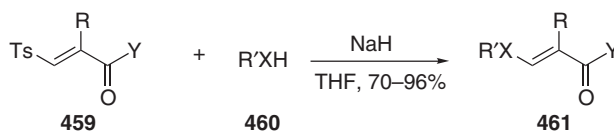
Palladium(II)/copper(I) co-catalyzed cross-coupling of bis-iodonium salts **456** with alkynylstannanes **457** gives enediynes **458** (Equation (96)) <1996JOC6162>.



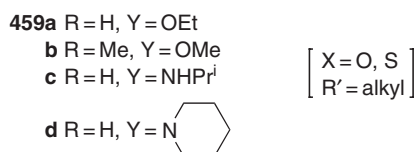
1.22.2.4 Formation of Vinylic Cations by Bond Scission

Vinylsulfones have frequently been used as sulfur-leaving groups in addition-elimination reactions with nucleophiles, thus acting as vinyl cation equivalents. The high stability of the sulfones makes them easy-to-handle starting materials <1999T10547>.

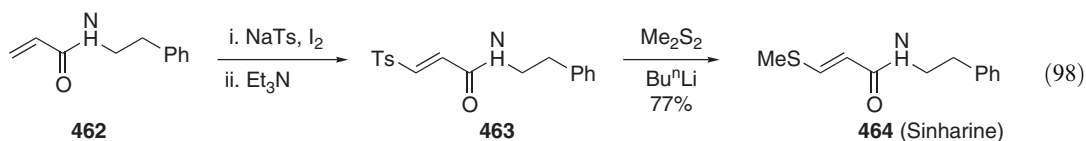
β -(*p*-Toluenesulfonyl)- α,β -unsaturated esters and amides **459** react regio- and stereoselectively with organomagnesium compounds, sodium alkoxides, or sodium thiolates **460**, to yield β -substituted α,β -enoates (**416a-461b**) or enamides (**461c-461d**) (Equation (97)) <1995T3617>.



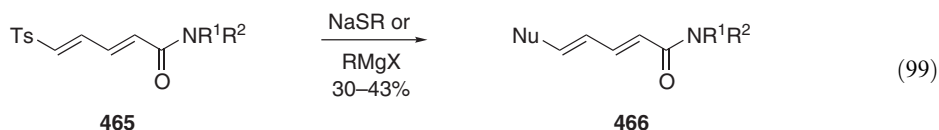
(97)



Vinylsulfone **463**, easily available from **462**, may act as a vinyl cation equivalent, has been utilized in the synthesis of natural antifungal sinharine **464** (Equation (98)) <1995T3617>.



A sulfonyl group in dienamides such as **465** also functions as a vinyl cation equivalent, acting as a leaving group in the addition–elimination vinylic substitution reactions. Sulfonyldienamides **465** react in a regio- and stereoselective manner to give *2E,4E*-dienamides **466** on treatment with sodium thiolates or Grignard reagents (Equation (99)) <1995TL3901>. This methodology has been extended to the total synthesis of sarmentine and an *Achillea* amide.



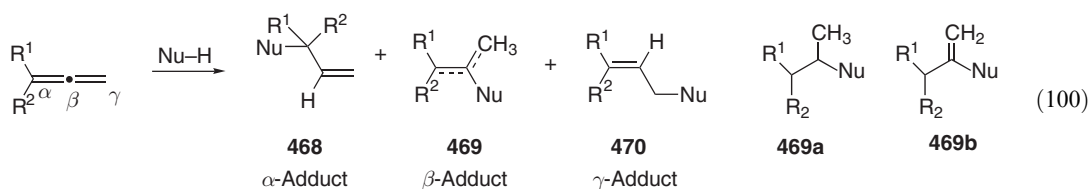
1.22.2.5 Formation of Vinylic Cations by Addition to Alkynes and Alkenes

General aspects of the chemistry of allenes, including their reactions to generate vinyl cations, anions, and radicals, have been the subject of a number of reviews <1998PAC1047, 1998PAC1059>.

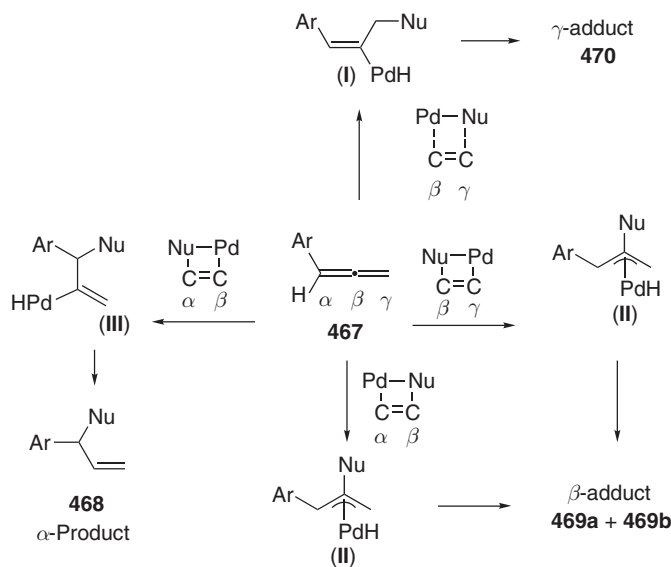
Palladium-catalyzed reactions of allenes have gained considerable attention in recent years. Over the last few decades, palladium-catalyzed reactions have been most widely investigated and proven extremely useful and advantageous in organic synthesis because they exhibit a high level of chemo-, regio-, and stereoselectivity in numerous transformations <1996T9289, 1998CRV675>.

Palladium-catalyzed reactions of allenes with carbon and heteroatom nucleophiles, leading to the formation of C–C and C–heteroatom bonds, generally proceed with the involvement of a π -allylpalladium intermediate, which plays an ever increasing role in organic synthesis <1999CSR199>. This intermediate acts in some cases as a vinylic cation synthon. The reactivity of allene-derived π -allylpalladium species with a wide variety of carbon and heteroatom nucleophiles leading to new bond-forming processes, and the synthesis of a number of interesting intermediates and natural products, have been reviewed <2000CRV3067>.

A nucleophilic addition on allene **467** can occur on all three carbons depending on the terminal substituents. All three possible regioisomers (**468–470**) can be selectively produced by appropriate substitution on the allene at its terminal carbon (Equation (100)).



Mechanistically, three pathways can be predicted for this reaction to proceed via a carbopalladation process: (a) addition of Pd–Nu to the coordinated allene (β – γ C=C addition) giving intermediate (I), followed by reductive elimination to give the γ -adduct **470**; (b) involving the π -allyl complex (II) (β – γ and α – β C=C addition to Pd–Nu are possible) to give the β -adduct **469**; (c) via complex (III) by (α – β C=C addition to Pd–Nu) to give the α -adduct **468** (Scheme 36). Recent studies on similar systems support the involvement of the π -allyl complex (II) [<1995TL2811>](#). However, it should be noted that the more stable η^3 -coordination can, due to the orthogonal orbitals of the allene, never be formed directly. Examples of these reactions, and a mechanistic account, have been covered in the review [<2000CRV3067>](#).

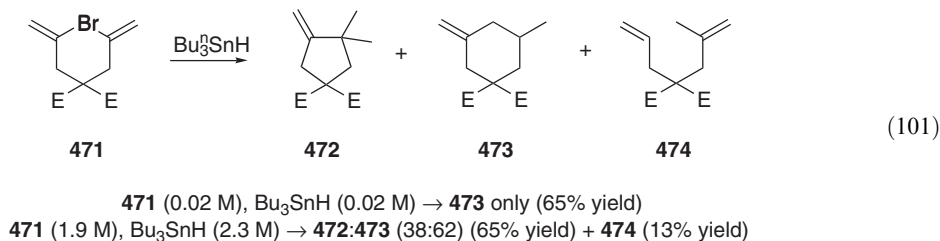


Scheme 36

1.22.3 DICOORDINATE RADICALS (i.e., VINYLIC RADICALS)

1.22.3.1 General Introduction

In the vinyl radical ring closure of 5-methyl hexenyl radicals **471**, it has been shown that, unlike vinyl radical cyclization of 5-unsubstituted substrates, a direct 6-*endo-trig* ring closure is responsible, to a considerable extent, for the regiochemical outcome of the reaction (three products are possible, **472–474**) (Equation (101)) [<2002TL4997>](#). The regioselective control does not rely exclusively on the presence of the methyl group, as the tin hydride concentration plays an essential role in the observed regiochemistry. Thus, substituted cyclohexanes can be efficiently prepared by cyclization of 5-alkyl-vinyl radicals.

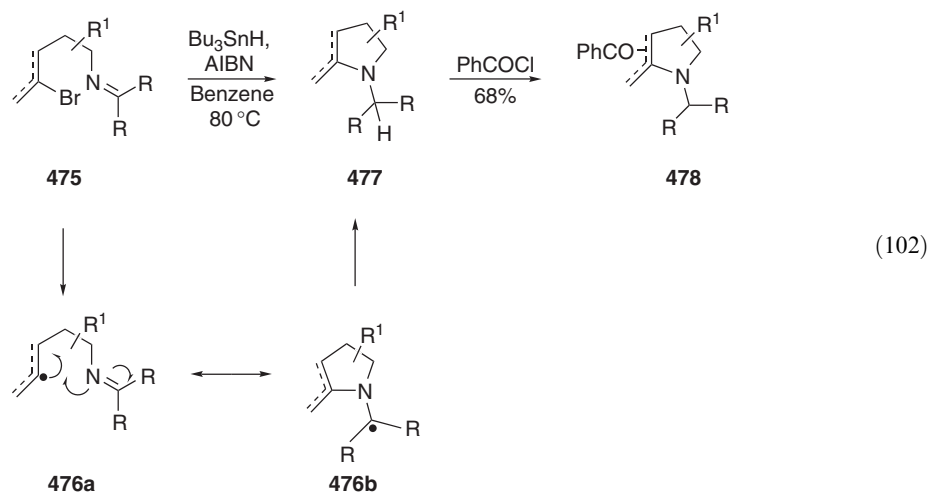


Reviews on the intermolecular addition of heteroatom radicals to an alkene or alkyne, which can initiate a cyclization event when a second radical acceptor moiety is appropriately situated, have been reported.

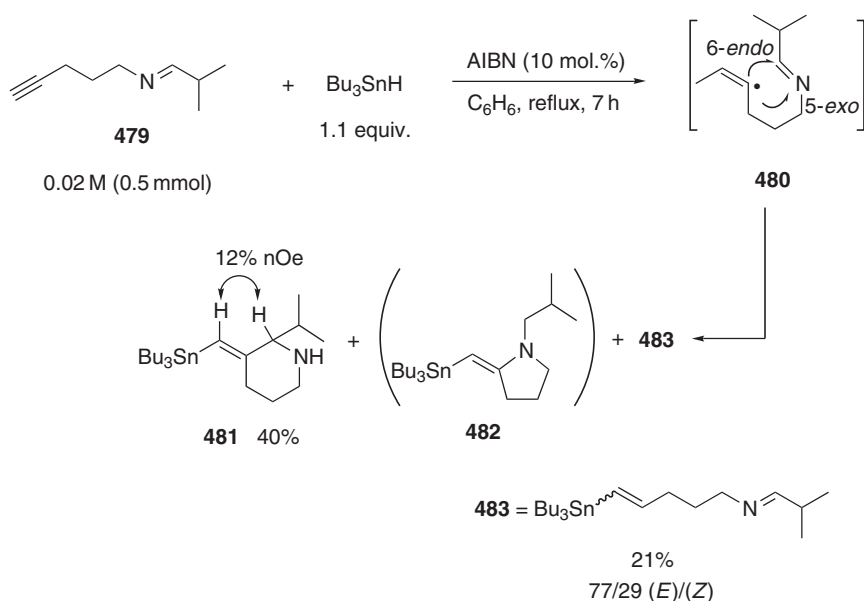
1.22.3.2 Formation of Vinylic Radicals by Bond Scission

1.22.3.2.1 Bromides

The 5-*exo-trig* cyclizations of vinyl radicals, generated from vinyl bromide (**475**), to azomethine nitrogen have been reported to provide a strategically innovative approach to the synthesis of highly nucleophilic *N,N*-dialkyl enamines (**477** and **478**) (Equation (102)) <2003T8877>. With only two exceptions, the expected kinetic enamine product was formed selectively and under mild, nondehydrative conditions. The vinyl radical **476a** was produced from the corresponding bromide **475** on treatment with Bu₃SnH/AIBN (cat.) in benzene at 85 °C. The cyclizations were limited to the formation of pyrrolidine derivatives, and demonstrated the efficiency with which carbon radicals can be added regioselectively to the nitrogen of an azomethine.

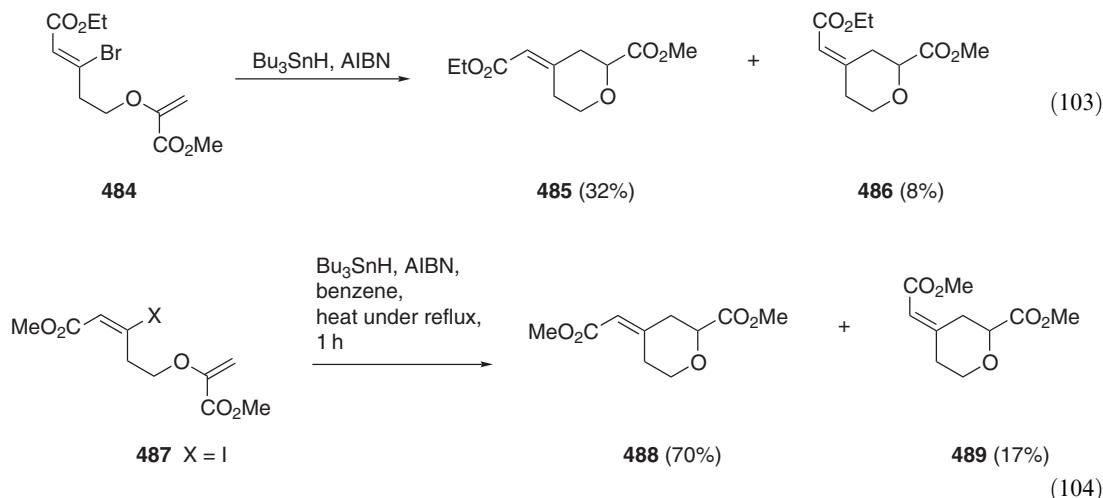


The complementary regioselective 6-*endo-trig* cyclization of a vinyl radical **480** to azomethine carbon through the deployment of an aldimine **479**, instead of a ketimine, has also been reported to give **481** as the major product (Scheme 37) <1999TL1515>. The turnover in regioselection highlights the importance of steric effects in the control of regioselectivity. In this instance, the vinyl radical **480** was prepared by hydrostannylation of an alkyne.

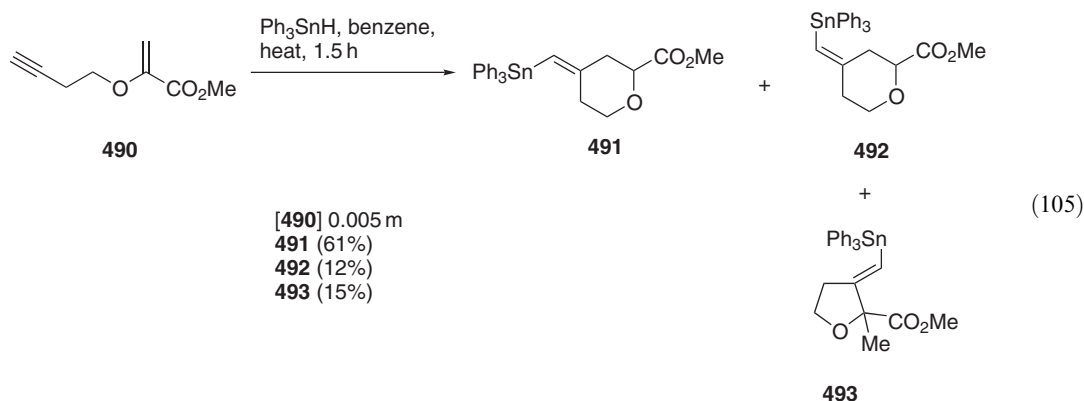


Scheme 37

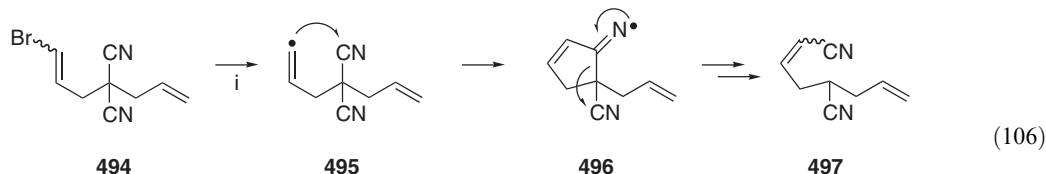
On treatment with tributyltin hydride, the vinyl bromide **484** and the vinyl iodide **487** cyclize to give mixtures of the (*E*)- and (*Z*)-4-(alkoxycarbonylmethylene)tetrahydropyrans, (*E*)-**485** and (*Z*)-**486**, and (*E*)-**488** and (*Z*)-**489**, in which the (*E*)-isomers (*E*)-**485** and (*E*)-**488** are the major components, accounting for 80% of the products (Equations (103) and (104)) <1998JCS(P1)2853>.



Addition of triphenyltin hydride to the alkyne **490** initiates cyclization giving a mixture of products (**491–493**), the composition of the mixture depending upon the concentration of the tin hydride (Equation (105)) <1998JCS(P1)2853>. These results are consistent with faster cyclization of the (*Z*)-vinyl radical with kinetic formation of five-membered ring containing products, which are either trapped by hydrogen transfer from the tin hydride, or which rearrange to form a 4-methylenetetrahydropyran.

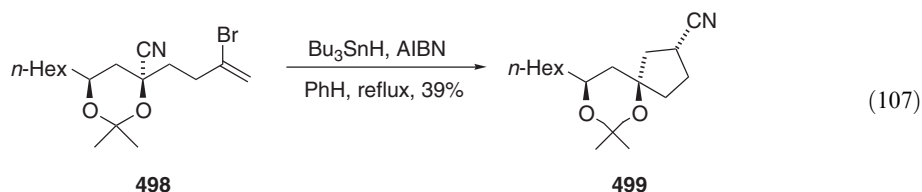


Radical cyclization onto nitriles has been the subject of a review <1997T17543>. The vinyl radical **495**, derived from vinyl bromide **494**, undergoes cyclization onto a nitrile group to give an iminyl radical **496**, which rearranges to give nitrile **497** in 23% yield (Equation (106)) <2000TL8989> AMBN required as AIBN is insoluble in cyclohexane (AMBN = azobismethylisobutyronitrile). The rate of cyclization onto the nitrile is faster than 6-*exo* cyclization of the vinyl radical onto the alkene; the rate of translocation is also faster than 5-*exo* cyclization of the iminyl radical onto the alkene.

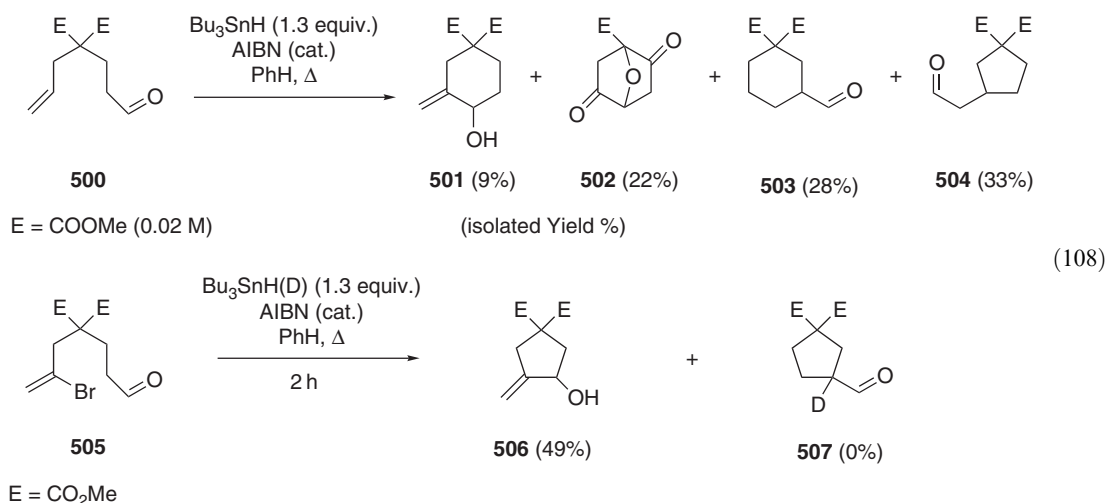


i. Bu₃SnH (1.3 equiv., syringe pump addition over 3 h),
 (6 h reflux, azobismethylisobutyronitrile(AMBN), cyclohexane)

The slow addition of a solution of Bu_3SnH and AIBN in benzene to a solution of **498** gives the spirocyclic compound **499** as a mixture of diastereomers at the nitrile centre in 39% yield (Equation (107)) <1997T16489>. A 5-*endo-trig* cyclization like this is disfavored according to Baldwin's rules. However, the alternative "favored" 4-*exo-trig* cyclization faces significant ring strain in the transition state and product. The complementary electronic distributions of the α -alkoxy radical and β -cyano alkene undoubtedly favor the cyclization, and thus transfer of the nitrile group not only produces the α -alkoxy radical, but in this case serves to activate the alkene for cyclization.



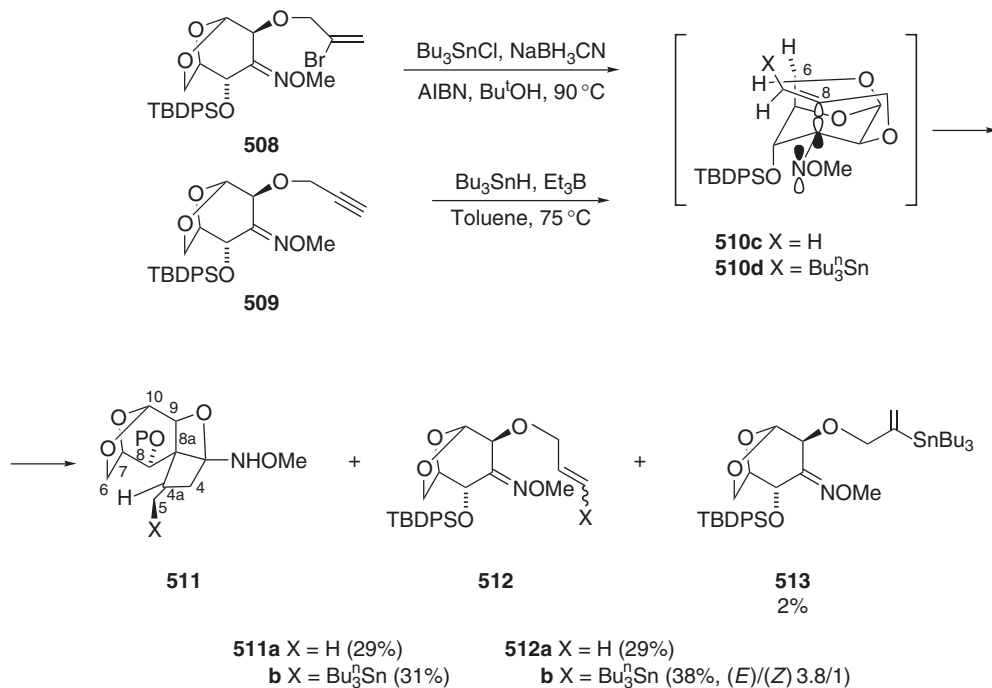
The reaction of aldehydes **500** and **505** with vinyl radicals generated from the vinylic bromide moiety has proven to be totally chemoselective in favor of the 6-*exo-trig* and 5-*exo-trig* cyclization processes, respectively (Equation (108)) <1998TL833>. Under thermal conditions, the resulting alkoxy radicals fragment to afford various rearrangement products (**501–507** and **506–507**). Low-temperature conditions and an $\text{Et}_3\text{B}/\text{O}_2$ system appear to be the method of choice to trap the intermediate alkoxy radicals and provides an efficient synthetic route to α -methylene cyclopentanol and cyclohexanol.



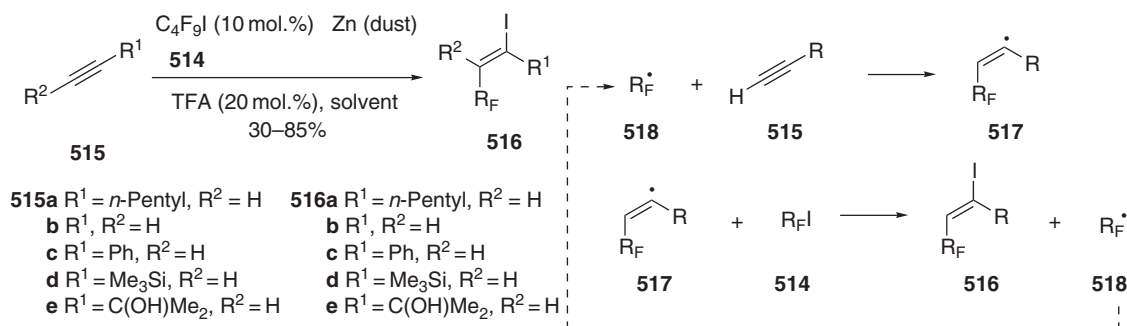
Vinyl σ -radicals derived from **508** and **509** underwent 1,5-*exo* cyclization, via vinyl radical **510**, affording advanced precursors of (–)-tetrodotoxin **511a** (Scheme 38). This type of transformation was reported to be useful for the formation of sterically crowded N-bearing carbon centres in carbohydrate-derived substrates <1997TL2745>.

1.22.3.2.2 Iodides

Catalytic amounts of zinc, as low as 10 mol.%, in the presence of trifluoroacetic acid (TFA), initiate the radical addition of perfluoroalkyl iodides **514** to terminal alkynes **515** with high regio- and stereoselectivities to give (*E*)-perfluoroalkyl vinyl iodides **516** (Scheme 39) <2000JOC8763>. The reaction proceeds via formation of a vinyl radical **517**, which participates in a chain propagation sequence by abstracting an iodine from another molecule of **514**. Palladium-mediated cross-coupling of **516** provides a useful route into fluoroorganic intermediates.

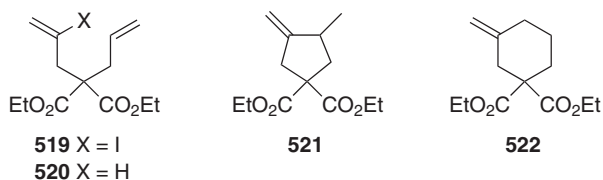


Scheme 38



Scheme 39

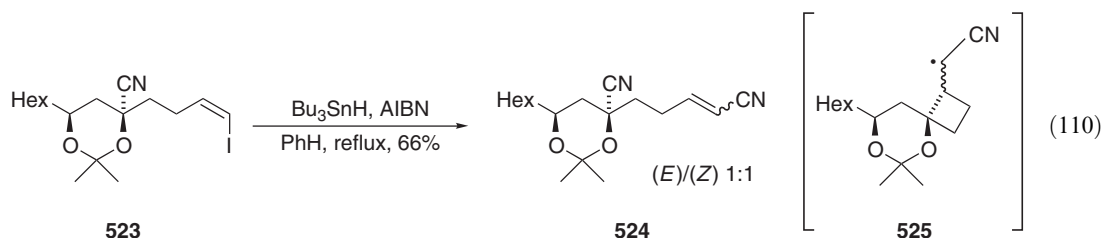
The 5-*exo*/6-*exo* product ratio (**521/522**) in the stannane-mediated cyclizations of vinyl iodide **519** is significantly improved by operating in the presence of catalytic PhSeSePh, with no loss in overall cyclization yield to give **521** as the major product (Equation (109)) <1996TL3105>. A small amount of the reduction product **520** was also obtained.



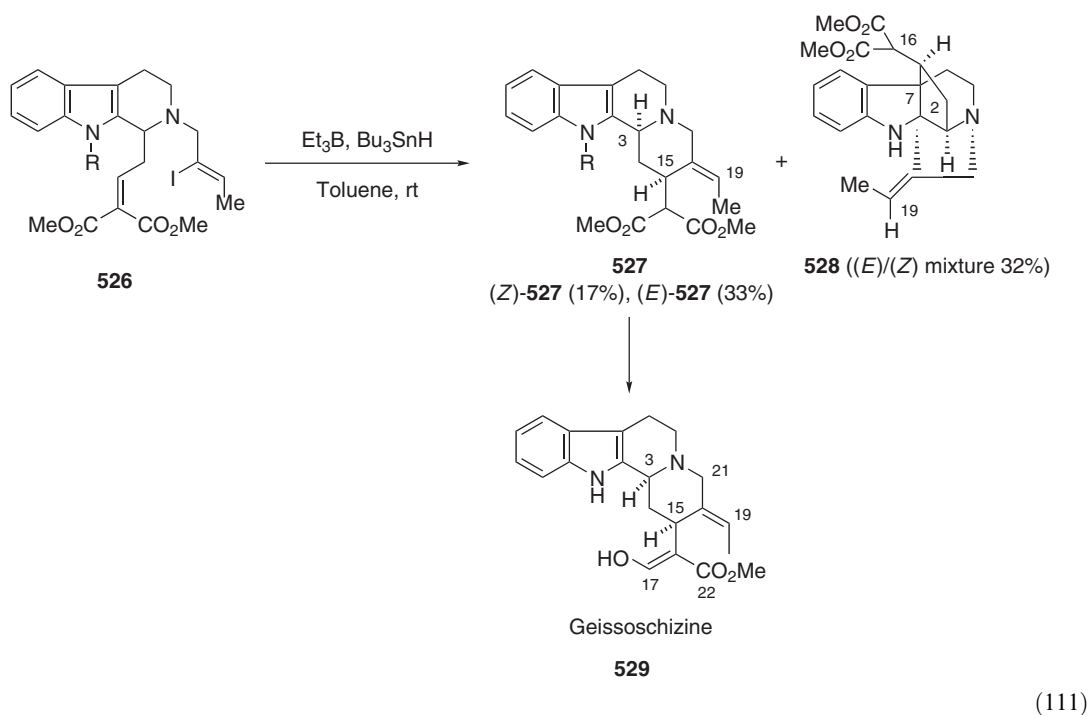
(109)

Substrate (Conc. M)	Bu ₃ SnH (mol.%, conc.[M])	PhSeSePh (mol.%, conc.[M])	Acyclic Product ^a	5- <i>exo</i> :6- <i>endo</i> ratio ^a
5 (9 × 10 ⁻²)	120, 1.2 × 10 ⁻¹	20, 1.8 × 10 ⁻²	6(5%)	7:8 => 95:5

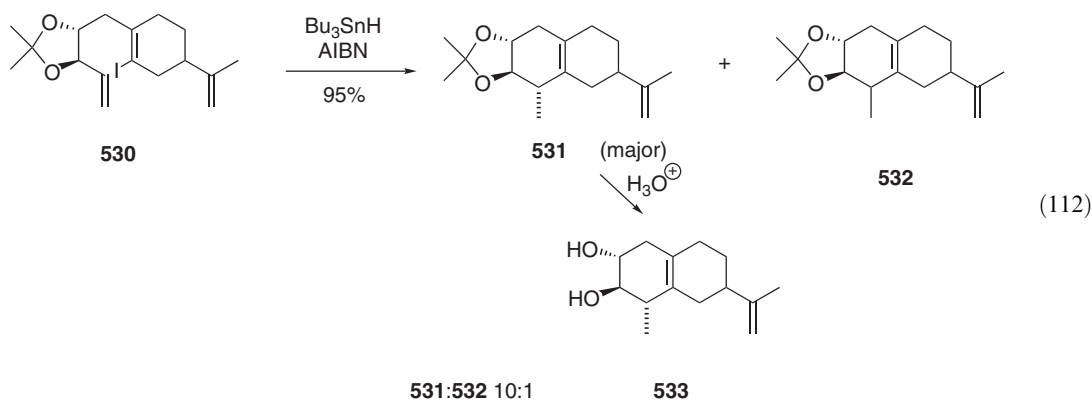
Treatment of iodide **523** with *n*-Bu₃SnH provided the transfer product **524** in 66% yield as a 1:1 mixture of (*E*)- and (*Z*)-alkenes (Equation (110)) <1997T16489>. The 1,5-nitrile transfer was quite efficient under high-dilution conditions. The isolation of **524** as a mixture of alkene isomers was surprising, as in an intramolecular radical transfer process, only the (*Z*)-vinyl radical can potentially cyclize onto the nitrile, yet both (*E*)- and (*Z*)-alkenes in the product **524** were observed. The alkene geometry could have been scrambled by reversible addition of an external radical, or by reversible cyclization to cyclobutane **525** prior to reduction by Bu₃SnH.



A short synthetic route to (±)-geissoschizine **529** was developed for which the key step in the construction of a corynanthe-skeleton was via radical cyclization of the vinyl radical generated from the vinyl iodide **526** to give (*E*)-**527** as the major product (Equation (111)) <1997TL5307>.

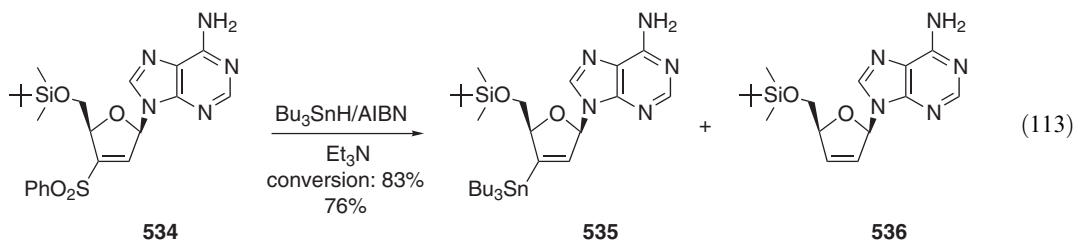


The key step in a new convergent synthesis of (–)-rishitin **533**, a phytoalexin from diseased potato tubers, is the vinyl radical cyclization of **530** to **531**, which proceeds stereoselectively in favor of **531** (10:1, **531**:**532**) (Equation (112)) <1997TL1889>.



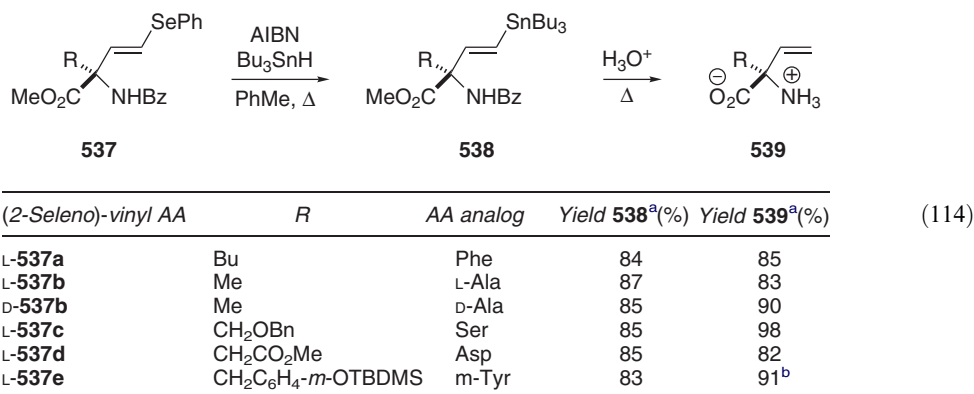
1.22.3.2.3 Sulfur

Radical-mediated desulfonylative stannylation of **534** proceeded efficiently by reaction with Bu_3SnH (3 equiv.)/AIBN in refluxing benzene for 5.5 h to give vinylstannane **535** (Equation (113)) <2002T2497>. The addition of 4 equiv. of Et_3N to the crude product **535** was essential in obtaining useful isolated yields after column chromatography. No appreciable amount of the reduced product **536** was formed in this reaction.



1.22.3.2.4 Selenium

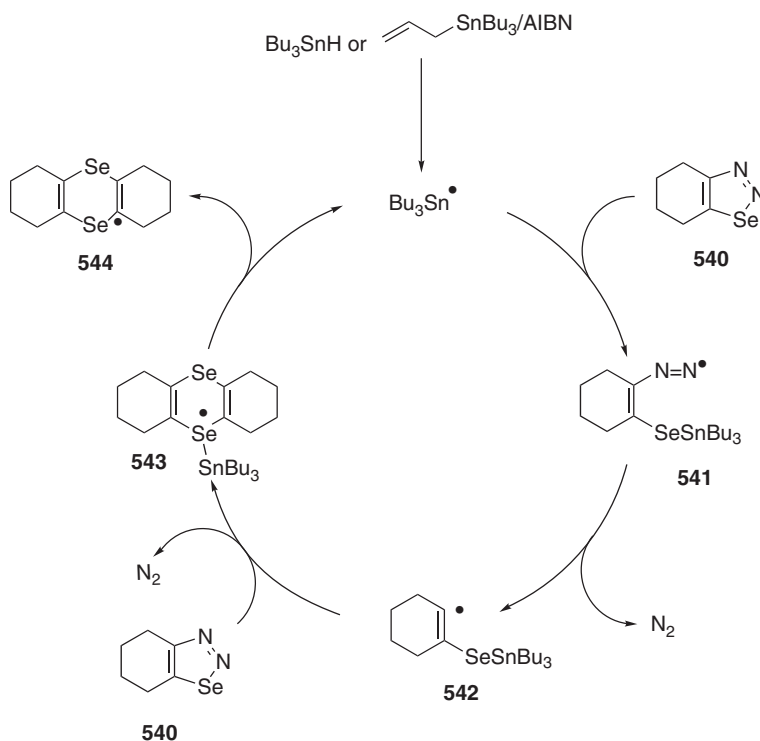
Upon heating with $n\text{-Bu}_3\text{SnH}$ and AIBN in toluene, the α -(2-phenylseleno)vinyl branch of **537** is smoothly converted to an α -(2-tributylstannyl)vinyl branch **538**. This substitution reaction of the vinyl selenide in **537** was shown to be highly stereoselective and proceeded to give excellent yields (Equation (114)) <2000JA11031>. These quaternary amino acids served as either vinyl stannane or vinyl halide Stille-coupling partners, or underwent protodestannylation to provide the free vinyl amino acids **539**, with stereospecific deuterium incorporation also a possibility.



^a Yields are of isolated, purified compounds. ^b Isolated as the HCl salt.

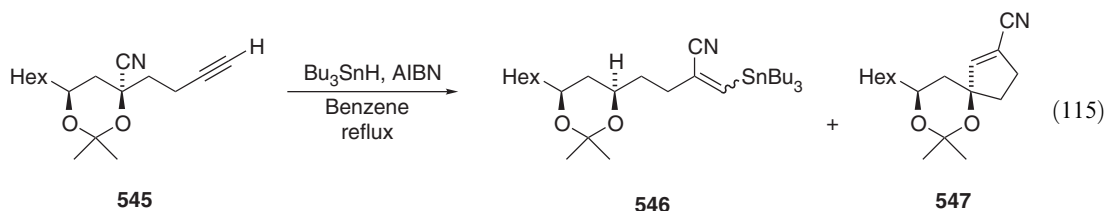
1.22.3.2.5 Fragmentation

When 1,2,3-selenadiazoles **540** were treated with excess amounts of olefins in the presence of a catalytic quantity of Bu_3SnH and AIBN, the addition of a vinyl radical **542**, which was generated *in situ* by the denitrogenation of 1,2,3-selenadiazoles, to the C—C double bond followed by intramolecular cyclization (**543** \rightarrow **544**), proceeded efficiently to afford the corresponding dihydroselenophenes **544** in moderate to good yields <1999TL6293>. The reaction pathway shown in Scheme 40 was proposed to account for the catalytic nature of the reactions.

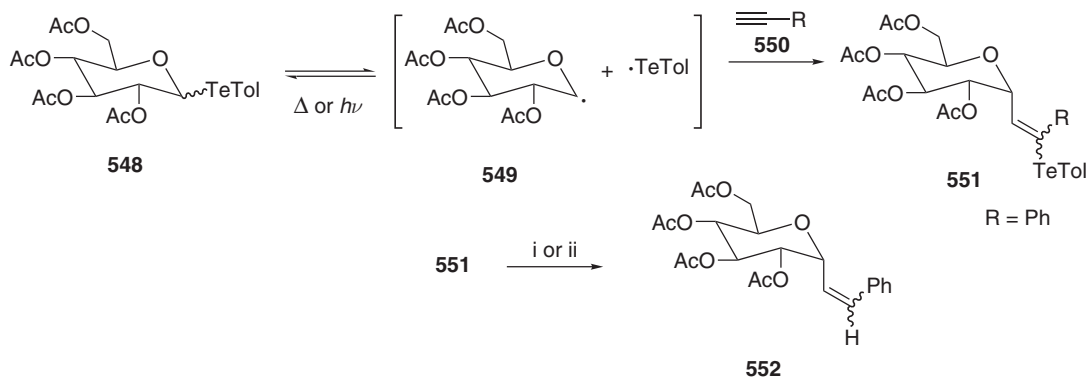


1.22.3.3 Formation of Vinylic Radicals by Addition to Alkynes and Allenes

Slow addition of Bu_3SnH and AIBN to a solution of **545** in refluxing benzene gave a mixture of the nitrile-transfer adduct **546** and the cyclized product **547** in 95% and 5% yield, respectively (Equation (115)) <1997T16489>. The tributyltin addition and nitrile transfer were very efficient, but the final cyclization of a vinyl radical proceeded poorly. At higher temperatures, the cyclization was more efficient, generating up to 33% of the cyclized product **547** in xylenes at 140 °C, although the reaction was accompanied by significant decomposition.



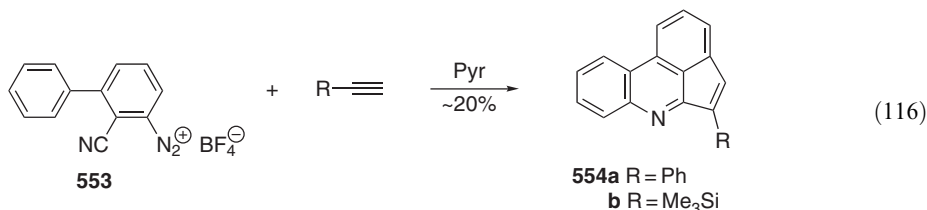
Glycosyl radicals **549**, generated from telluroglycosides **548**, react with a variety of alkynes **550** to give the corresponding vinylic C-glycosides **552** in good to excellent yields (Scheme 41) <1999TL2343>. The reaction takes place in an atom transfer manner to form a vinyl telluride **551**, and the resulting C—Te bond transmetalates with Et_2Zn to give a C—Zn bond which may be quenched by dilute acid, or reduced directly to the C—H bond by Bu_3SnH to give **552**.



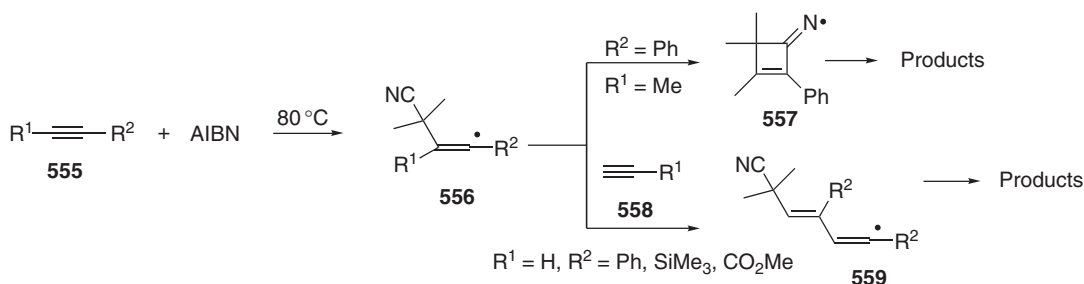
i. Et₂Zn (3.0 equiv.), DME, rt 6 h, then H₃O⁺ (57%);
 ii. Bu₃SnH (1.2 equiv.), AIBN (0.1 equiv.), C₆H₆, reflux, 21 h (66%)

Scheme 41

New radical annulation reactions have been described involving addition of *ortho*-cyano-substituted aryl radicals to alkynes (Equation (116)) <1998TL2441>. Addition of the aryl radical, generated from 553, to the C—C triple bond gives rise to a vinyl radical, whose cyclization onto the carbon atom of the nitrile moiety produces an iminyl radical. The final reaction products 554a–554b derive from the iminyl by hydrogen abstraction, followed by hydrolysis, dimerization, or cyclization onto another aromatic ring.



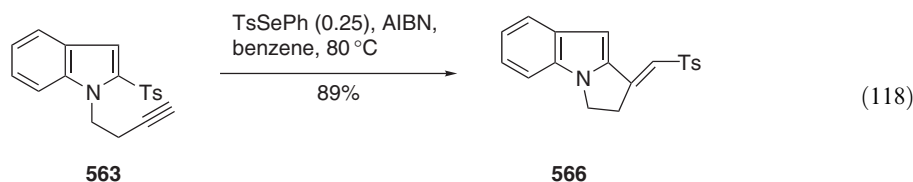
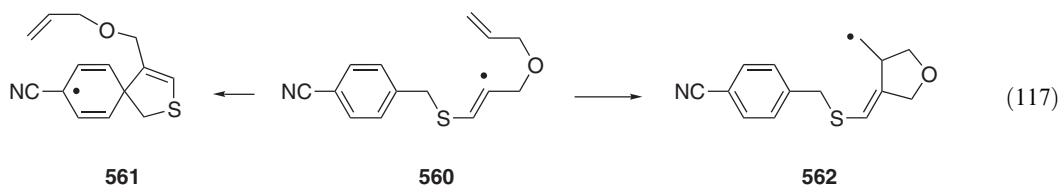
The thermolysis of azobisisobutyronitrile (AIBN) in benzene in the presence of various mono- and di-substituted acetylenes (555 or 558) has been investigated in order to ascertain the chemical reactivity of transient 2-cyano-*isopropyl* radical towards C—C triple bonds (Scheme 42) <1997T7929>. Results show that this rather sluggish and bulky carbon centered radical successfully adds in a regioselective fashion to alkynes bearing an electron acceptor phenyl, methoxycarbonyl and trimethylsilyl substituent, but fails with alkyl-substituted and sterically hindered acetylenes. The vinyl radicals produced 556 undergo H-abstraction, alkyne addition to give 559, aromatic addition and intramolecular cyclization to give 557, the relative proportions being strongly dependent upon the nature of the substituents. Examples of 4-*exo* and 6-*exo* vinyl radical cyclization onto a cyano triple bond were reported.



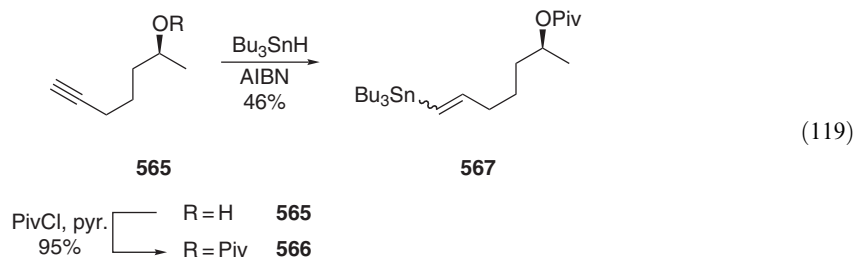
Scheme 42

Vinyl radicals **560**, generated by addition of a thiol radical to the corresponding alkyne, undergo *exo* cyclization onto an aromatic ring to give **561**, and to an alkene double bond to give **562**, in competition with a 1,4-hydrogen migration process (Scheme 117) <1996TL6583>.

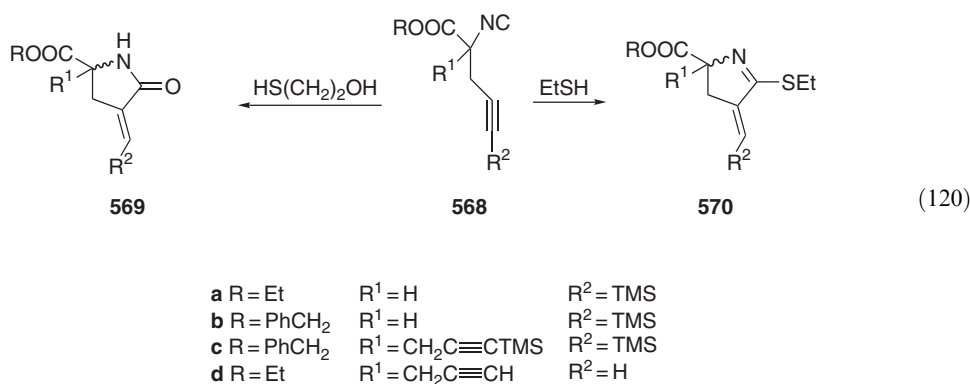
The radical cyclization of a β -toluenesulfonylvinyl radical or β -toluenesulfonyl-alkyl radical, generated from the corresponding alkynes **563**, onto a sulfone-substituted indole is catalyzed with phenyl-*p*-toluene-selenosulfonate (TsSePh). The resulting fused indoles **566** are produced in excellent yields (Equation (118)) <1997TL6249>.



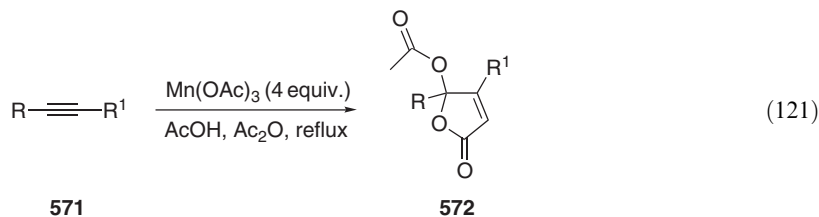
Vinylstannane **567** was prepared in two steps from the acetylenic alcohol (+)-**565** via protection of the secondary hydroxyl, as pivaloate **566**, followed by radical-induced hydrostannylation of the alkyne. The vinylstannane **567** was obtained as an inseparable mixture of (*E*)- and (*Z*)-isomers ($\sim 4.1:1$) (Equation (119)) <1998JA3935>.



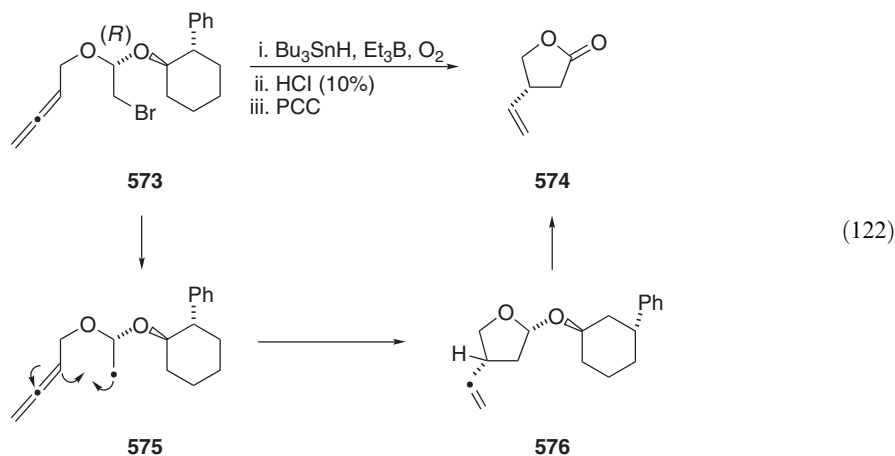
Alkynyl isocyanides **568** were synthesized and then reacted, using microwave flash-heating technology, with thiophenol, 2-mercaptoethanol and ethanethiol, in the presence of a radical initiator, to give highly functionalized pyrrolines **569** and pyroglutamates **570** (Equation (120)) <2003TL1347>. A thiyl radical ($\text{RS}\cdot$) adds to an alkenyl isocyanide, generating a thioimidoyl radical which cyclizes in a 5-*exo* manner. The vinyl radical formed undergoes subsequent hydrogen atom abstraction to afford *cis*- and *trans*-pyroglutamates **570**. Direct comparison with results obtained using traditional heating techniques showed that the microwave technology led to faster reactions and much improved yields.



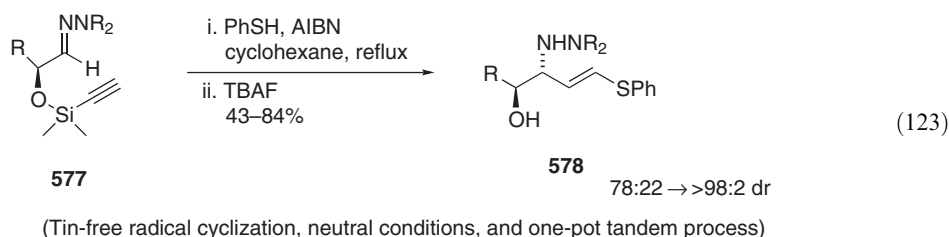
Mn(III)-promoted oxidative functionalization of acetylenes **571** can lead to the corresponding 5-acetoxypyrans **572**, through initial carboxymethyl radical addition to the alkyne triple bond, followed by an oxidative cyclization of the ensuing vinyl radical (Equation (121)) <2000T9339>.



Radical cyclization of a bromo-substituted allenyl acetal **573** provided a route into 4-vinyl-substituted tetrahydrofurans **574**, via intermediate radicals **575** and **576**, in good-to-excellent yields (Equation (122)) <2003TA3005>.

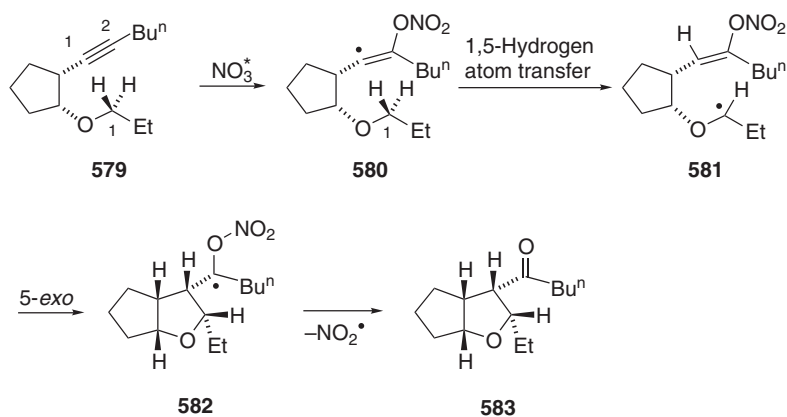


A diastereoselective method for addition of an (*E*)-2-(phenylthio)vinyl radical to α -hydroxy hydrazones has been reported <2003TA2853>. An ethynyl group, tethered to α -hydroxy hydrazones via a silicon tether **577**, undergoes thiyl radical addition to generate a vinyl radical which then cyclizes under neutral tin-free conditions. In the same pot, desilylation with potassium fluoride or tetrabutylammonium fluoride affords (*E*)-vinyl sulfides **578** (Equation (123)).

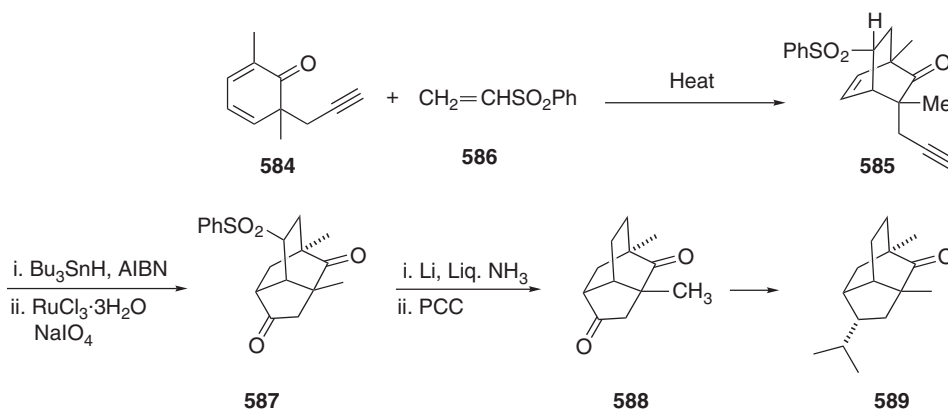


The addition of electrogenerated nitrate radicals to triple bonds in the alkynyl ether *cis*-**579** affords anellated tetrahydrofurans **583** with high diastereoselectivity through a new type of oxidative, self-terminating radical cyclization cascade (**580** \rightarrow **582** \rightarrow **583**) <1999T10119>. The reaction is proposed to proceed via an intramolecular, rate-determining hydrogen atom transfer (HAT) in the vinyl radical of type **580**, and a subsequent diastereoselective 5-*exo* radical cyclization to give **582**. Elimination of NO_2 terminates the reaction sequence to give the product **583** (Scheme 43).

Addition of $Bu_3Sn\cdot$ radical to a 5-(prop-2-ynyl)bicyclo[2.2.2]oct-2-ene **585**, generated by Diels–Alder reaction of alkene sulfone **586** with diene **584**, and subsequent 5-*exo-trig* cyclization of the resulting vinyl radical, furnishes an isotwistane **587**, providing a short route to the sesquiterpene, 2-pupukeanane **589** (Scheme 44) <1997TL2003>.

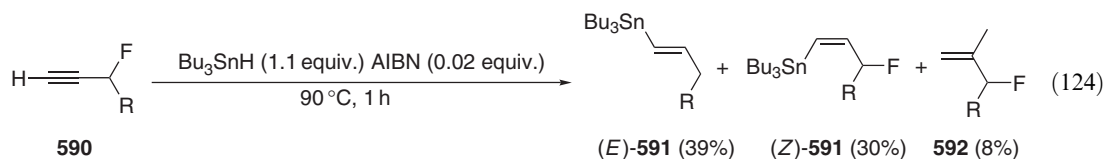


Scheme 43



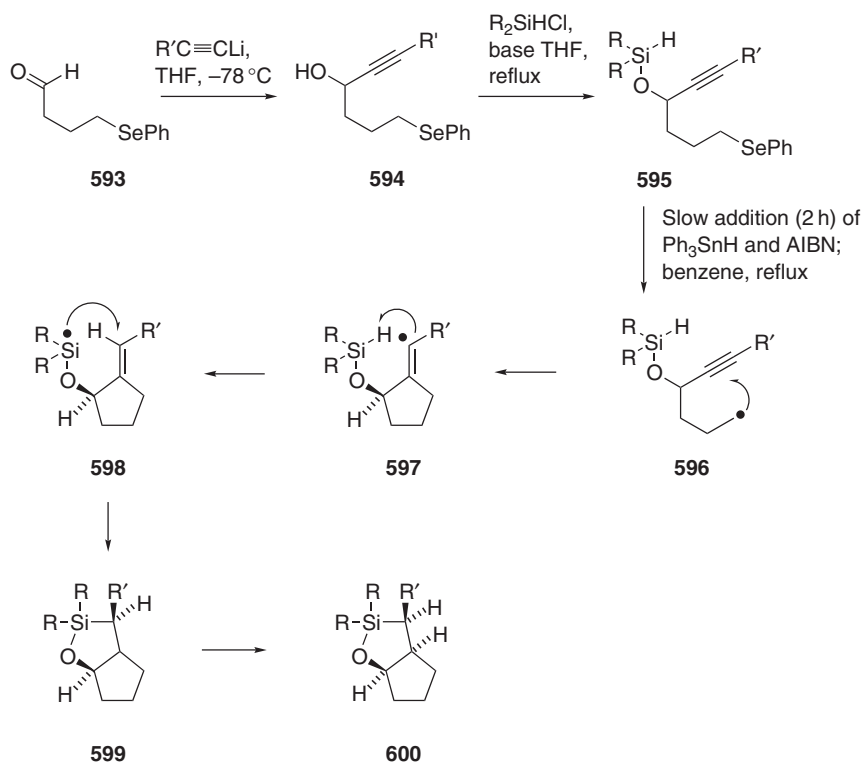
Scheme 44

The hydrostannylation of **590**, under classical radical type reaction conditions, occurs smoothly giving (77% overall yield) a 5:4:1 mixture of the (*E*)- and (*Z*)-isomers of vinylstannane **591**, together with the regioisomer **592**; these compounds can be separated by chromatography (Equation (124)) <1999TL6403>.

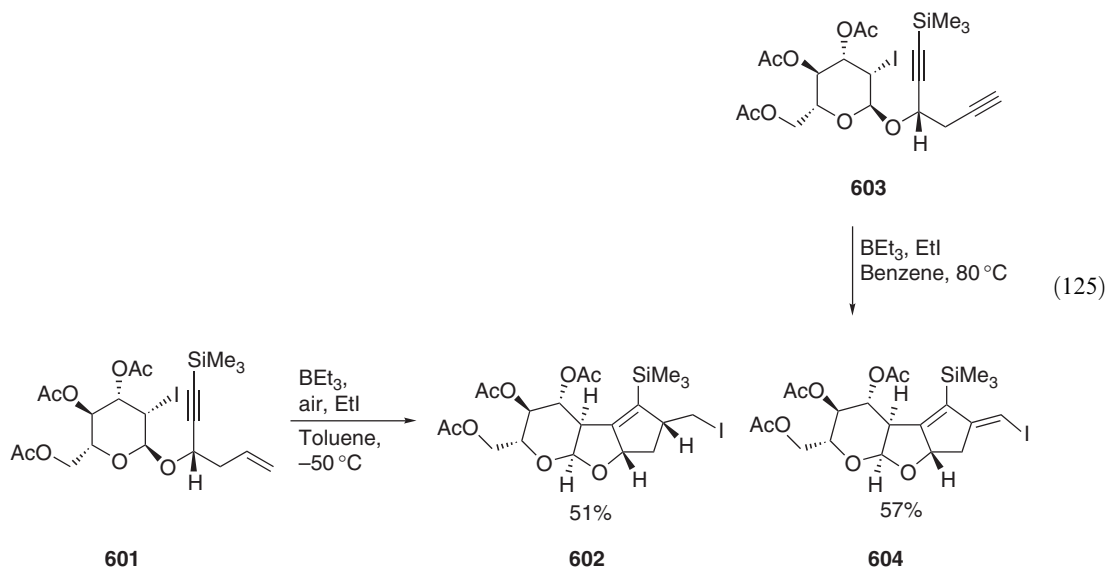


The radical **596**, formed through homolytic cleavage of the C—Se bond in **595**, attacks the alkyne to generate a vinyl radical **597** (Scheme 45). This abstracts a hydrogen atom from the neighbouring silyloxy group to give a silyl radical **598**, which can participate in cyclization reactions (such as in **598** → **599**), culminating in the formation of the silyl ether **600** <1995CC319>.

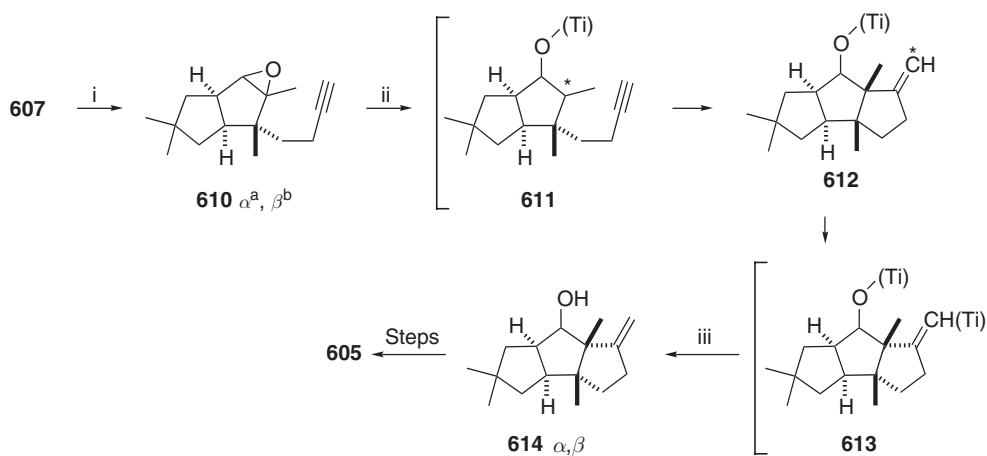
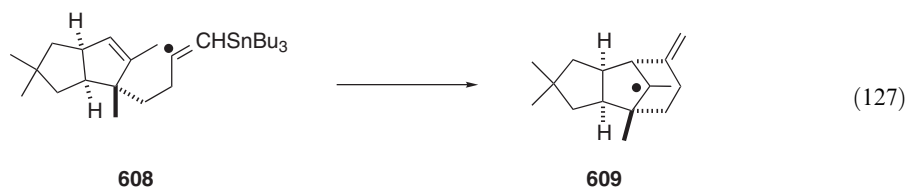
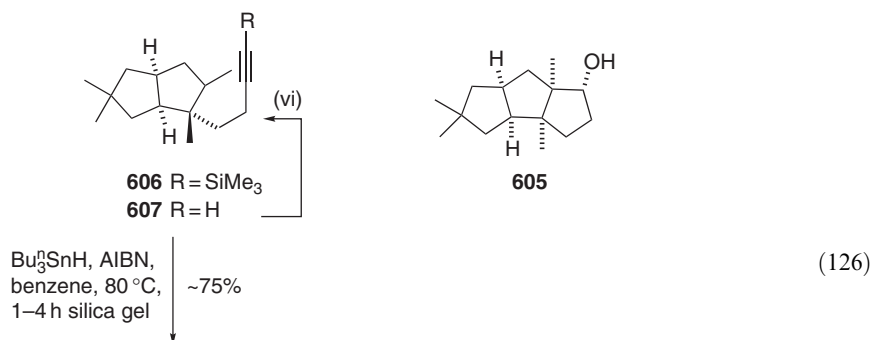
Et_3B -Induced iodine atom transfer radical cascade reactions with 1,5-enynes (**601** → **602**) and 1,5-diynes (**603** → **604**), proceed with vinyl radical formation and have been applied to the synthesis of dioxatriquinanes and tricyclic glycoconjugates (Equation (125)) <1995T7389>. Some of these cascade cyclizations were also performed at temperatures as low as -50°C .



Scheme 45



A key step in the synthesis of ceratopicanol **605** involved a radical cyclization in which acetylene **607** was expected to undergo 5-*exo* closure to give radical **608** (Equation (126)) <1995TL15>. However, treatment of **607** in refluxing benzene with Bu_3SnH in the presence of AIBN gave **609**, the formal result of a 6-*endo-trig* ring closure (Equation (127)). Epoxidation of acetylene **607** gave epoxide **610** (Scheme 46). Treatment of **610** with bis(cyclopentadienyl)titanium(III) chloride in THF gave an intermediate vinyl radical **612**, which upon cyclization gave **614** via **613**. Further synthetic elaboration gave (+)-**605**.



^a Oxygen *syn* to acetylenic chain. ^b Oxygen *anti* to acetylenic chain.

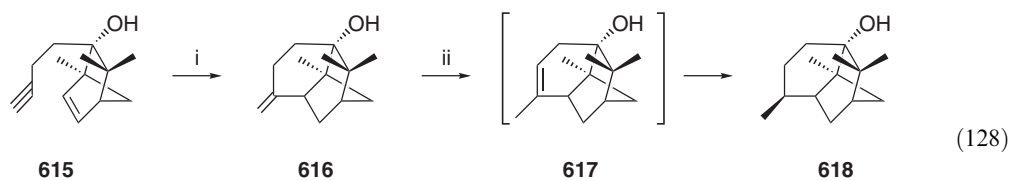
i. MCPBA, CH_2Cl_2 , 0°C , 2 h (16α 75%; 16β ca 25%);

ii. Cp_2TiCl , THF, rt, 7 h for 17α , 2 h for 17β ;

iii. 10 % H_2SO_4 workup (17α ; 82% from 16α ; 17β ; 81% from 16β).

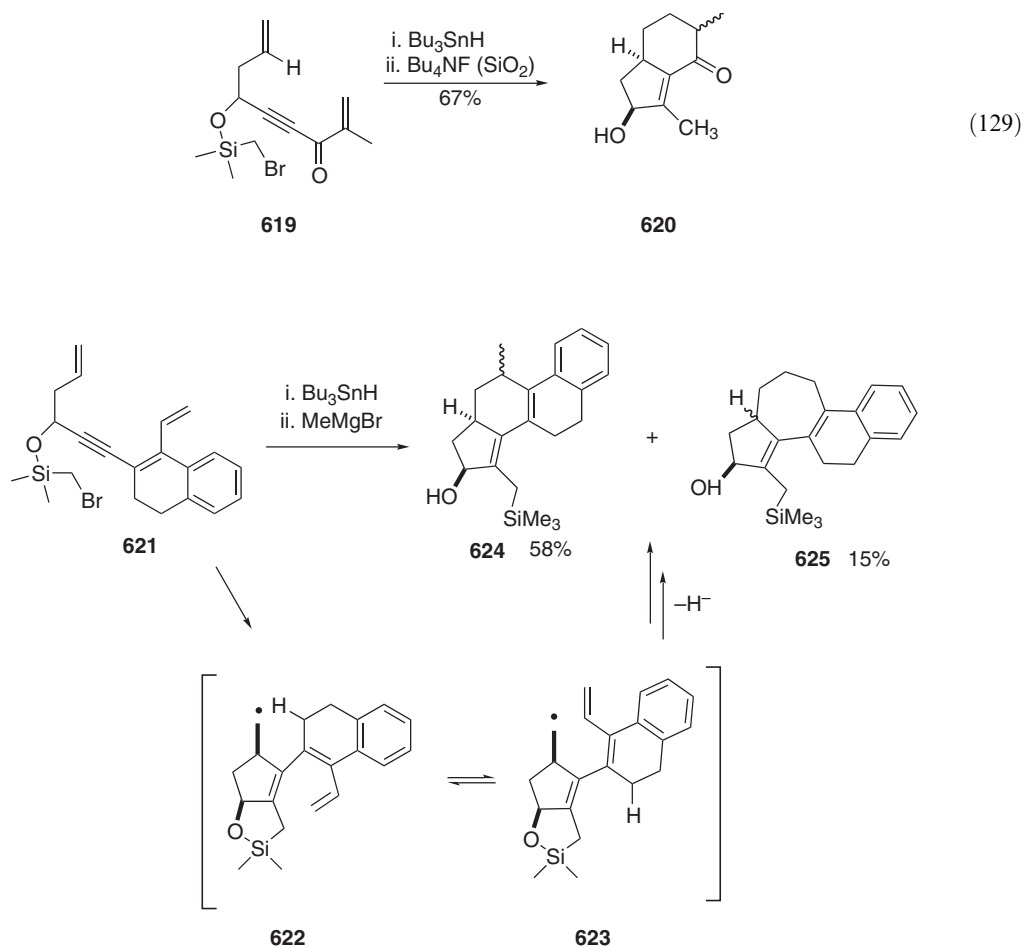
Scheme 46

The total synthesis of patchouli alcohol **618** has been reported in which a 6-*exo-trig* vinyl radical cyclization strategy to effect 6-membered ring closure to the desired tricyclic skeleton was employed as the key step (Equation (128)). The vinyl radical was generated through treatment of the corresponding alkyne **615** with Bu^nSnH in the presence of AIBN, which cyclized to give **616** <1995TL7607>.



i. $\text{Bu}_3\text{SnH/AIBN/0.01 M}$ in refluxing PhH ; ii. SiO_2 ; 80% H_2 /10% Pd-C in EtOAc ; 85%

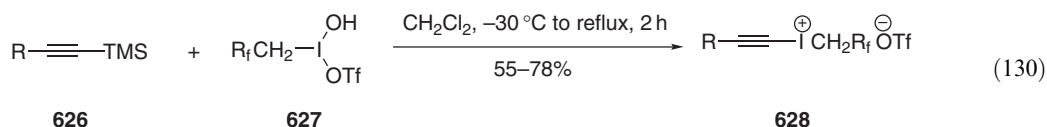
Vinyl radicals generated from bromomethyldimethylsilyl propargyl ethers (**619** and **621**) have been efficiently engaged in cascades of radical cyclizations such as 5-*exo-dig*-5-(π -*endo*)-*exo-trig*-6-*endo-trig* (to give bicyclic compound **620** from **619**) (Equation (129)) or 5-*exo-dig*-5-(π -*endo*)-*exo-trig*-6-*exo-trig* (to give **624** and **625** from **621**) radical intermediates (via **622** \rightarrow **623**) (Scheme 47), allowing the assembly of hydrindene and a steroid skeleton <1996T11405>.



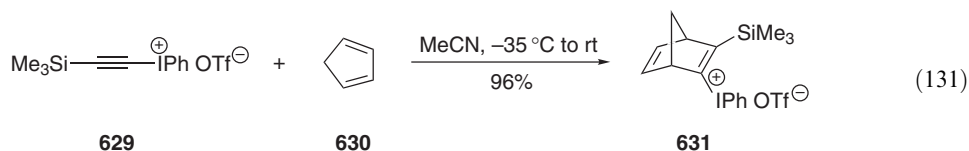
1.22.4 MONOCOORDINATE CARBOCATIONS AND RADICALS

Alkynic cations continue to be rare. For general reviews and lead references, see COFGT (1995, pp. 1141–1142).

Fluoroalkyl(alkynyl)iodonium triflates **628** can be prepared by the reaction of the corresponding (trimethylsilyl)acetylenes **626** with triflate **627** (Equation (130)) <1996JOC8272>. The reaction proceeds under mild conditions and in good yields.



Alkynyliodonium salts undergo Diels–Alder reactions; for example, alkynyliodonium salt **629** reacts with cyclopentadiene **630** to give the vinylic norbornadienyl iodonium salt **631** in excellent yield (Equation (131)) <1999JOC680>.



1.22.4.1 General Introduction

The use of alkynyl metal complexes as building blocks for molecular wires and polymeric organo-metallic materials has been reviewed <2003AG(E)2586>. Such materials possess a number of interesting electronic and structural properties including nonlinear optical effects <1997CRV637, 1998MI291>, luminescence and photoconductivity <1998MI722, 1999JOM(578)3, 2002ACR555, 1997OM3541> and crystallinity <B-1996MI001>.

Acetylide anions derived from alkali or alkaline earth metals have great synthetic utility undergoing additions to a wide range of electrophiles such as aldehydes, imines, epoxides, and acid chlorides <B-1995MI002>. The most-utilized acetylides are those prepared from a terminal alkyne and strong bases such as EtMgBr and Me₂Zn <B-1995MI003>, metallated amides such as KHMDS, LDA, and Et₂NLi, alkoxides such as potassium *t*-butoxide, and hydroxides such as KOH and CsOH <1996JOC416, 1999AG(E)1463>.

Alkynes react with transition metals to yield stable complexes in several ways (Figure 1) <2002ACR218>: (i) reactions of internal alkynes mostly yield π -alkyne complexes **632**; (ii) those of terminal alkynes frequently yield alkynyl complexes **633**; (iii) metallacyclopentadienes **634** are obtained from the reactions of internal and terminal alkynes, depending on the metals and the alkyne substituents; and (iv) alkynes are inserted into the M=L (L: C=C=CR'₂ <1999OM5426>, C≡C-R' <1998JA2975>, H <2000OM3455>, Cl <1998JA12365>, SiR'₃ <1998OM2567, 1997OM4327> NR'₃ <1999OM4810, 1998JA1757, 1997OM816, 2001BKCS739>, PR'₃ <2001BKCS739, 1995CC1495, 2000OM1572> and AsR'₃ <2001BKCS739, 1995CC1495> bonds to produce alkenyl complexes **635**. It is well known that

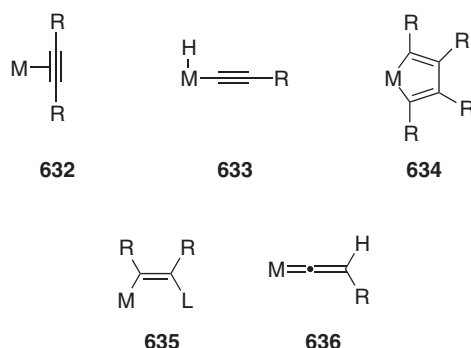


Figure 1

hydridoalkynyl complexes **633** readily undergo hydride transfer reactions to yield metal vinylidenes **636**, which are also obtained directly from the rearrangement of π -coordinated terminal alkynes <1999ACR311>. The metal complexes, **632–636**, are key intermediates in the C–C bond-forming reactions mediated by metals that react initially with alkynes.

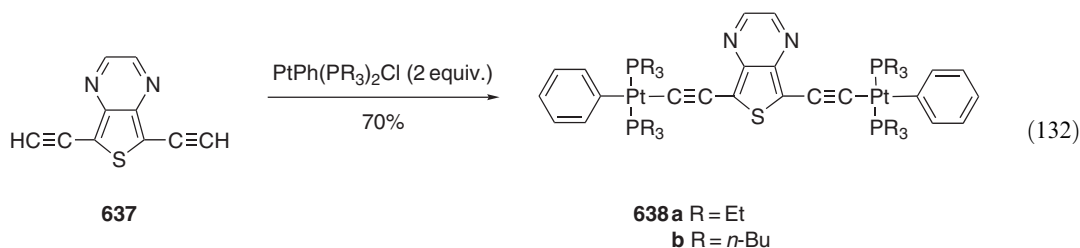
Metal alkynyls **633** are in general obtained by oxidative addition of terminal alkynes to metals ($M + H-C\equiv C-R \rightarrow H-M-C\equiv C-R$) and by ligand (L) substitution reactions with alkynyl groups in the presence of terminal alkynes and base, (B) ($[M-L]^+ + H-C\equiv C-R + (B) \rightarrow M-C\equiv C-R + BH^+ + L$) <1999OM2210, 1999OM4810, 1997OM4816, 1997OM5589, 1997JA698>.

1.22.4.2 Alkynylcopper, Alkynylgold, and Alkynylsilver Reagents

The complexation of terminal acetylenes with Cu(I) or Ag(I) is generally accepted to yield π -complexes in which the terminal C(sp)–H is sufficiently labile as to be deprotonated by weakly basic amines with concomitant generation of the corresponding metal acetylide. Copper acetylides formed in this way have been used in palladium-mediated coupling processes such as Sonoga–shira, Eglington, Glaser and Cadiot–Chodkiewicz reactions <B-1999MI001>.

Alkynyl Au(I) complexes exhibit short Au...Au contacts and produce a wide range of molecular structures <B-1995MI001>. A series of mixed-metal Au–Cu alkynyl complexes have been prepared and it has been established that the alkynyl ligands are σ -bonded to the Au(I) center and π -bonded to the Cu(I) center <2001OM1968>.

Diyne **637** reacts with 2 equiv. of *trans*-[PtCl(PEt₃)₂(Ph)] and *trans*-[Pt(PBu₃)₂Cl(Ph)], in which one coordination site is protected by a phenyl group, in CH₂Cl₂/Et₂NH in the presence of catalytic Cu(I) at 20°C to afford the pure platinum alkynyl complexes **638a** and **638b** in ca. 70% yield (Equation (132)) <1998AG(E)3036>.

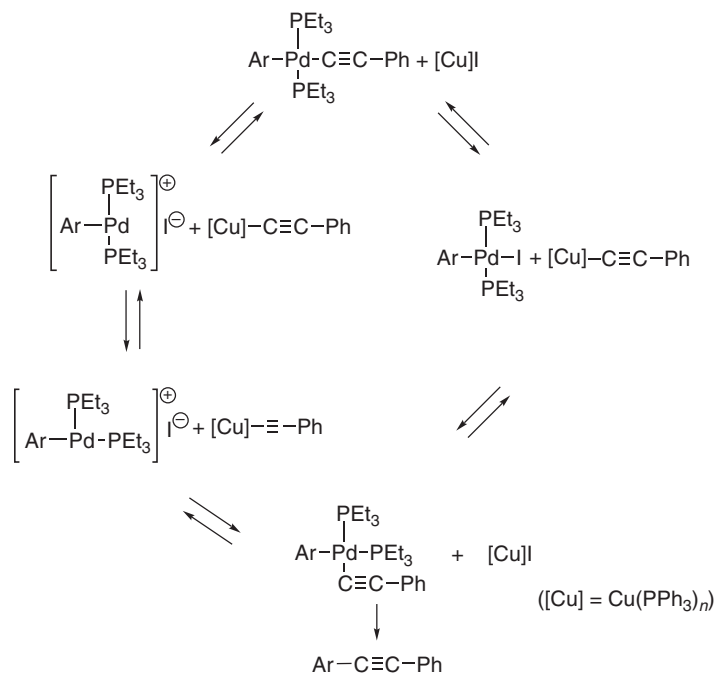


It has been shown that alkynyl ligands migrate from Cu(I) to Pd centers in a process that appears to be reversible. Possible mechanisms have been proposed including that shown in Scheme 48 <1997OM5354>. A similar process for Pt alkynyl complexes is more difficult because of the high stability of the complexes, but is facilitated by addition of CuI. Crucially, the addition of CuI in the catalytic process serves to make cross-coupling efficient by promoting selective and reversible transfer of the alkynyl ligand between the metal centers.

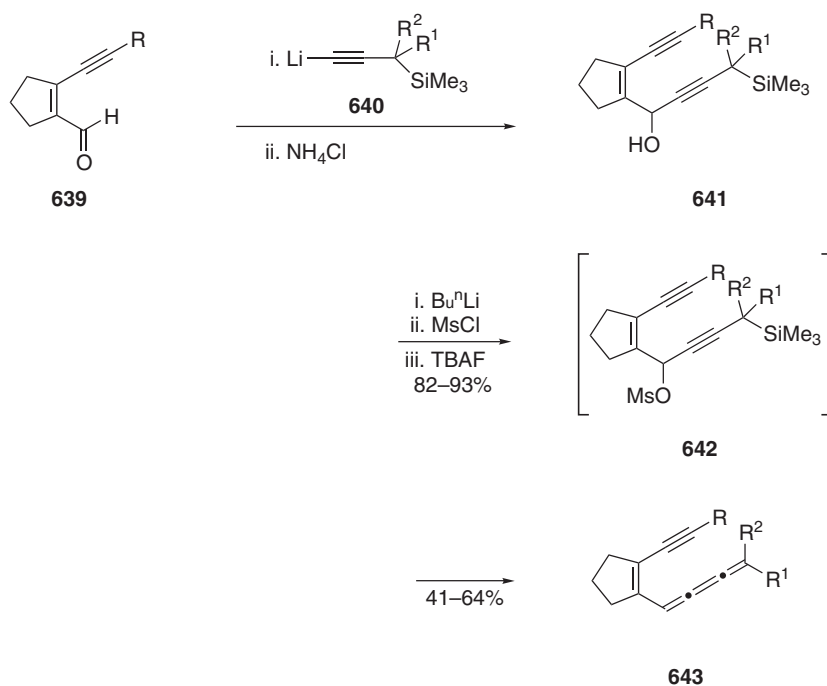
1.22.4.3 Alkynyllithium Reagents

Lithium acetylides have been shown to be useful building blocks in the synthesis of the enediyne class of antitumor antibiotics <1995SL13>.

The synthesis of the enyne[3]cumulenes **643** via 1,4-elimination of hydroxytrimethylsilane from 4-(trimethylsilyl)-2-butyne-1-ols **641**, obtained from condensation of lithium acetylides **640** with conjugated enynyl aldehydes **639**, has been reported (Scheme 49) <1995TL3785>. These cumulenes have been used in an investigation into the mechanism of the DNA cleavage process mediated by neocarzinostatin.



Scheme 48

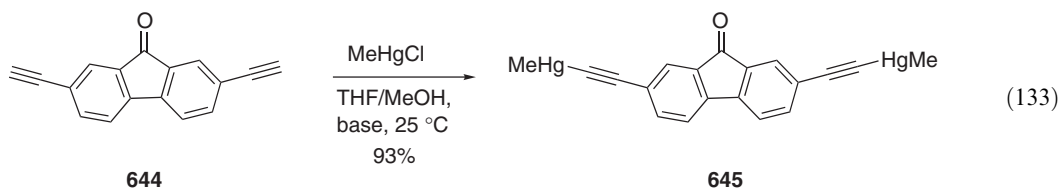


Scheme 49

1.22.4.4 Alkynylmercury Reagents

Phenylalkynyl mercury complexes have been synthesized by the deprotonation of phenylalkynes by mercury(II) acetate. The complexes react with $[\text{Pt}(\text{dppm})_2\text{Cl}_2]$ to give the corresponding dinuclear platinum(II) alkynyl complexes, which show interesting luminescence properties <1998OM2590>.

The reactions of a diyne **644** and methylmercury(II) chloride, in the presence of base, gives a dimercury-dialkynyl complex **645** (Equation (133)); the X-ray crystal structure of **645** was reported <2001OM5446>.

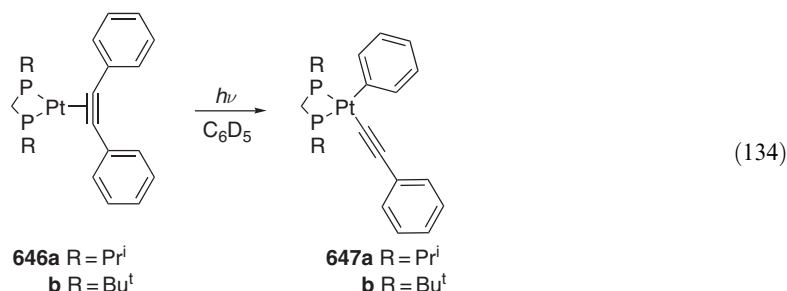


1.22.4.5 Alkynylmolybdenum Reagents

Alkynylmolybdenum complexes have been utilized as alkynyl-transfer reagents <2002CC384>. Long Mo—C(*sp*) bond lengths have been observed in [Mo(C≡CR)(η^3 -allyl)(CO)₂(phen)], and these bonds can be easily cleaved. Thus, reaction of Mo alkynyl species with trimethyltin chloride gives Me₃SnC≡CPh.

1.22.4.6 Alkynylpalladium and Alkynylplatinum Reagents

Under photolytic conditions, diphenylacetylene-Pt(0) complexes **646a–646b**, bonded via π -coordination, undergo cleavage of the C(*sp*)—C(*sp*²) bond in the alkyne to give the platinum(II) complexes **647a–647b**. The reverse reaction can be carried out by thermal activation (Equation (134)) <2001JA9718>.



Monosubstituted alkynes undergo Sonogashira cross-coupling reactions with vinyl bromides, iodides, chlorides, and triflates in the presence of a Pd(0) or Pd(II)/CuI catalyst system to give enynes <2000S1499, 2001JOM114>.

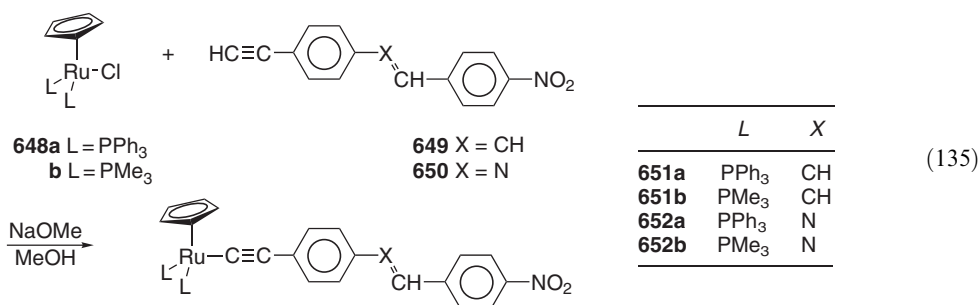
Alkynyl ligand transfer from Pd and Pt complexes has been observed. Here, the substituent on the alkynyl ligand and the co-catalyst employed are crucial <2000OM458>.

1.22.4.7 Alkynylrhodium Reagents

Alkynylrhodium complexes can be formed by coordination of a terminal alkyne to the metal center, as in [RhCl(PPrⁱ)₃]₂, followed by an intramolecular oxidative addition <1996OM2806>.

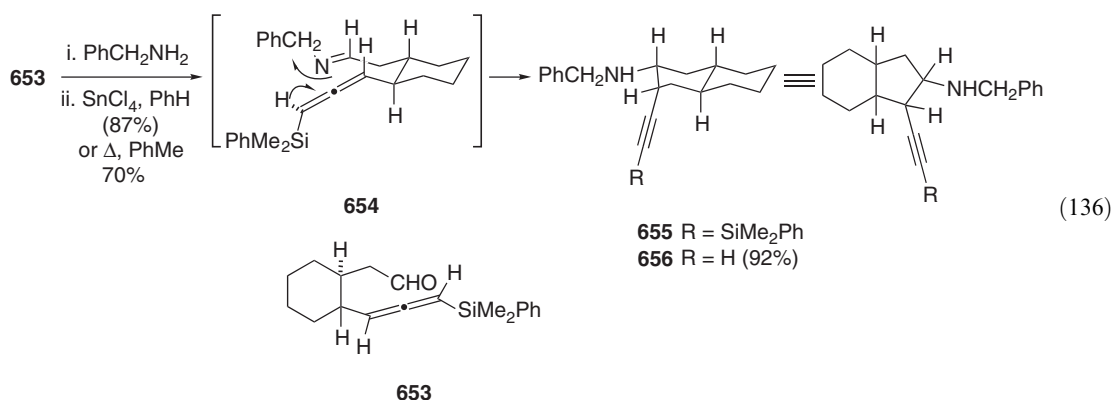
1.22.4.8 Alkynylruthenium Reagents

Treatment of terminal alkynes, **649** and **650**, with sodium methoxide in methanol, in the presence of Ru—Cl complexes, gives ruthenium-alkynyl complexes, (**651a–b**) and (**652a–b**), which were investigated for their nonlinear optic properties (Equation (135)) <1995OM3970, 1996OM1935>.



1.22.4.9 Alkynylsilicon Reagents

Allenylsilanes containing an imino-substituent **654**, easily available from aldehyde **653**, undergo an intramolecular reaction to generate an alkynyl silane **655** <1995JA10905>. The stereospecificity was expected for the *anti* attack to the silyl group, but the proton transfer of an ene reaction, **654** → **655**, took place, rather than loss of the silyl group. The removal of the silyl group from the acetylene to give **656** was facile. The intermediate **655** was used in a synthesis of (–)-papuamine (Equation (136)).



Alkynyl silanes are known to react with transition metal complexes in various ways, which include a C–H oxidative addition, vinylidene complex formation, the formation of metallacyclopentadiene, and cyclotrimerization <2002ACR826>. The competition between these and C–H/acetylene coupling has been explored <1998CRV2599>.

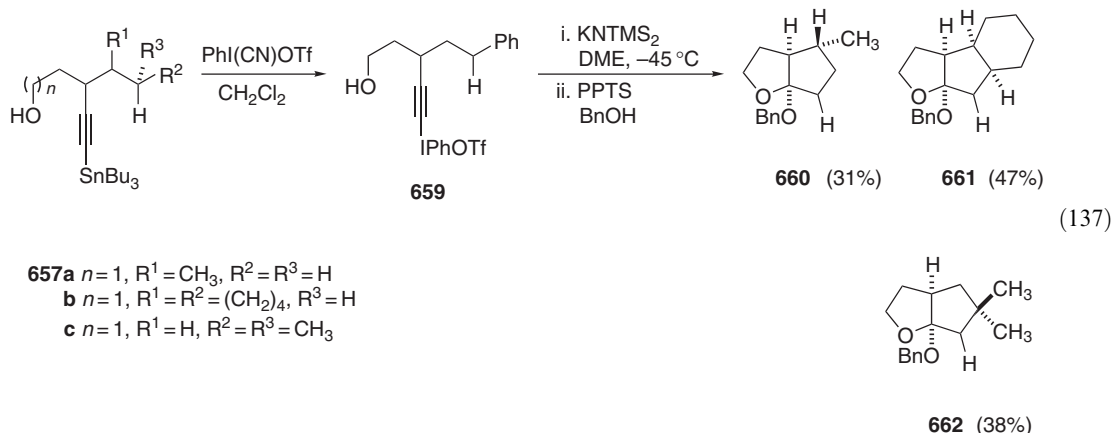
1.22.4.10 Alkynylsodium Reagents

Generally, treatment of terminal alkynes and metal dihalides in sodium methoxide solution gives compounds with alkynyl ligands via the sodium acetylide <1996OM1935, 1997JOM189, 1997JCS(D)4146>. These sodium acetylides can be quenched by a large number of electrophiles.

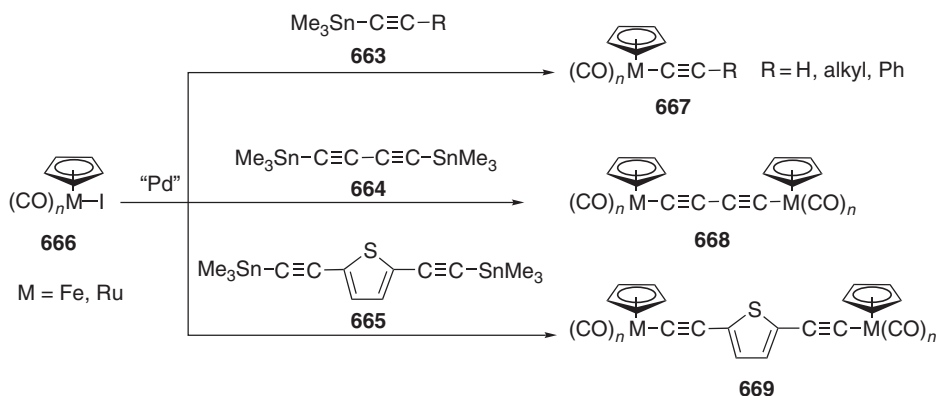
1.22.4.11 Alkynyltin Reagents

Generally, the formation of alkynylstannanes from alkynylmolybdenum compounds has been reported <2002CC384>.

Treatment of alkynylstannanes **657** with phenyl(cyano)iodonium triflate **658**, under mild conditions, is a general method for the preparation of alkynyliodonium salts **659**, through a ligand exchange process <1998TL2911>. The resultant iodonium salt **659** can be bicyclized with KHMDS to provide cyclopentannelated tetrahydrofuran derivatives such as **660**, **661** and **662**, in modest-to-good yields (Equation (137)).

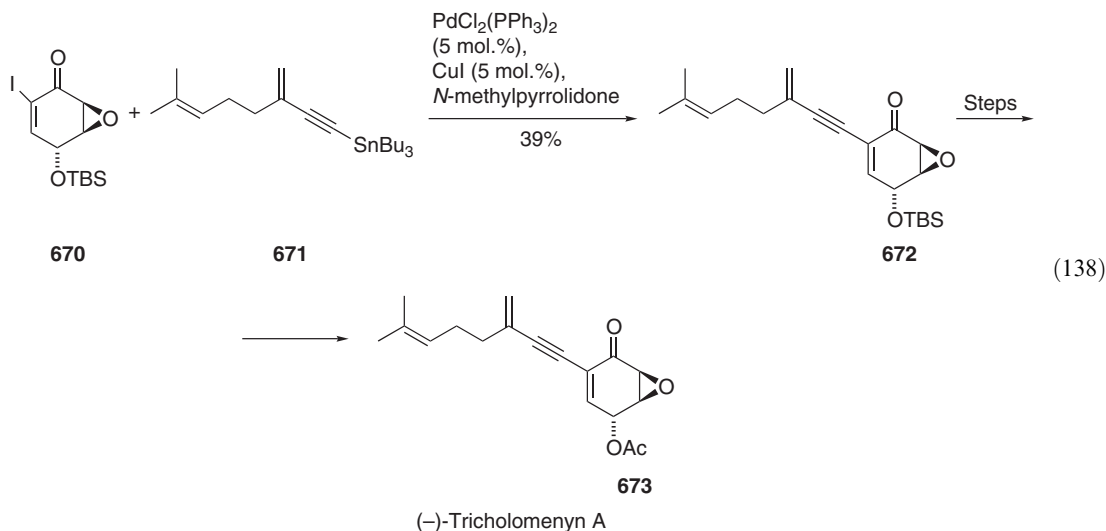


Trimethylstannylalkynes (**663–665**) have been utilized in the synthesis of Fe and Ru complexes having half-sandwich cyclopentadienyl metal centers (**667–669**). It was shown that metal–C bond formation was dependent on the presence of Pd(0) catalysts in a reaction that is reminiscent of the Stille reaction (Scheme 50) <1995JOM55, 1996OM4352>.



Scheme 50

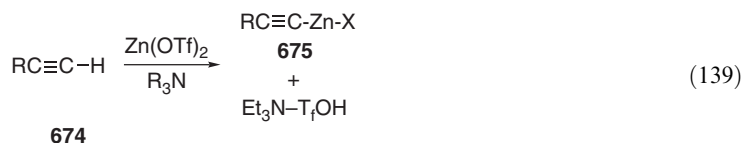
Alkynylstannanes **671** have been used in Stille-type coupling reactions with iodoenone **670** to give **672**, has been employed in the synthesis of the enynylcyclohexenone antimetabolic (–)-tricholomenyn A **673** (Equation (138)) <1996CC1679>. Other similar antimetabolic enynylcyclohexenones such as harveynone and *epi*-harveynone, have been prepared following the same methodology <1996TL7445>.



Tributylstannylalkynes couple with *n*-tributylstannyl 3-iodopropenoate derivatives to give (*E*)- γ -*n*-tributylstannylmethylidene butenolides <1999OL701>.

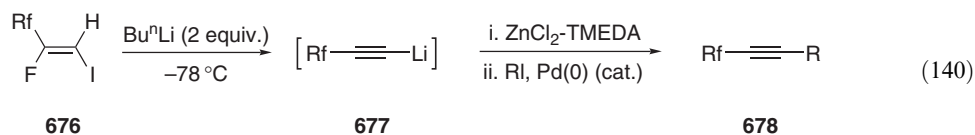
1.22.4.12 Alkynylzinc Reagents

Treatment of terminal alkynes **674** with Et₃N and Zn(OTf)₂ generates zinc acetylides **675** (Equation (139)), which are useful for a number of reactions <2000ACR373>.

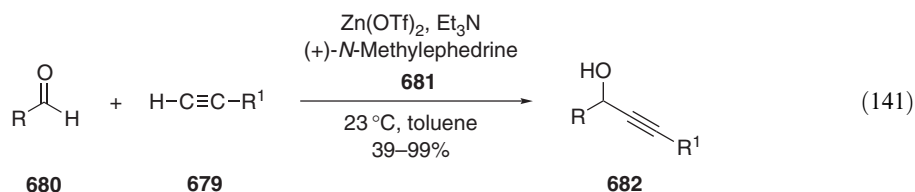


Lithiation of terminal alkynes followed by addition of zinc bromide gives alkynylzinc derivatives <1997S121>. These have been utilized in coupling reactions in the synthesis of γ -alkylidenebutenolides such as rubrolides A, C, D and E.

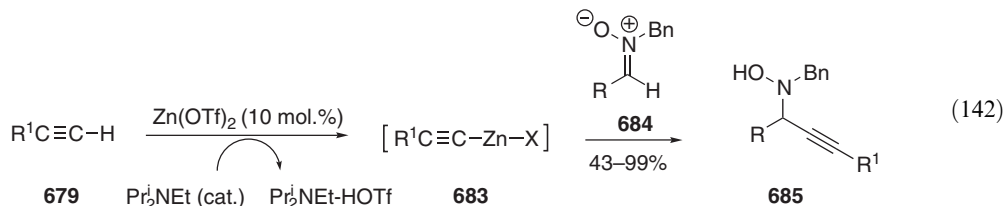
Treatment of per- or polyfluoroalkylated vinyl iodides **676** with 2 equiv. of *n*-BuLi in THF produced the corresponding lithium acetylides **677** *in situ*, which were transformed into zinc acetylides by the addition of ZnCl₂·TMEDA complex into the reaction mixture. The *in situ* generated zinc acetylides were exposed to palladium-catalyzed cross-coupling conditions giving rise to the desired per- or polyfluoroalkylated acetylenes **678** in high yields (Equation (140)) <2003T7571>.



Terminal acetylenes **679** react with Zn(OTf)₂, in the presence of amine bases, to give zinc acetylides, which react further with aldehydes **680** and (+)-*N*-methylephedrine **681** to give propargyl alcohols **682** in up to 99% ee and good yields (Equation (141)) <2000JA1806>. The reaction is tolerant of moisture, solvent, air, and substrate concentration.



Zinc acetylide **683**, generated in a similar fashion from **679**, reacts with *N*-benzyl nitrones **684** at room temperature to give propargylamines **685** (Equation (142)) <1999JA11245>. The reaction is facilitated by catalytic quantities of Zn(OTf)₂ in good yields (up to 99%).



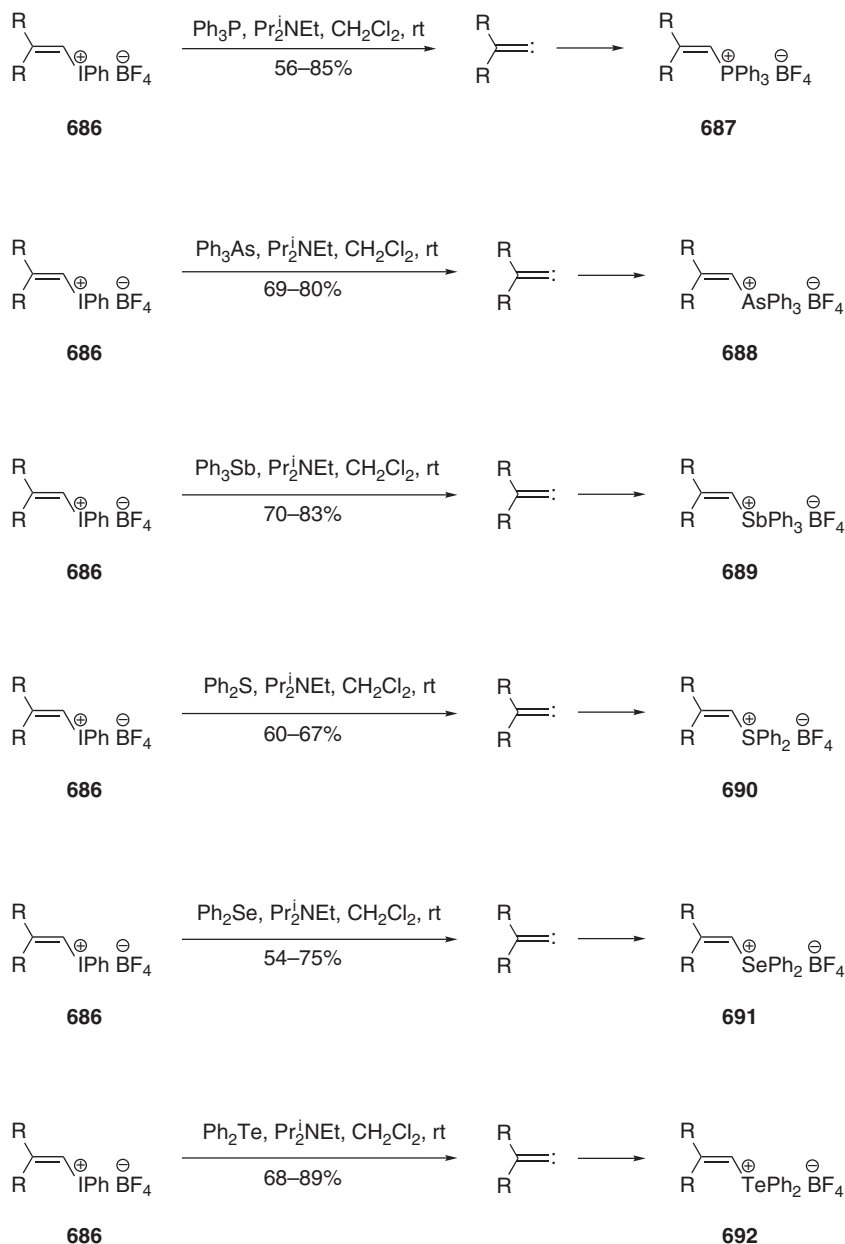
1.22.5 VINYLIDENE CARBENES

1.22.5.1 General Introduction

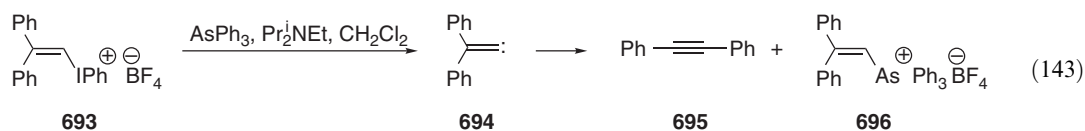
The simplest unsaturated carbene is vinylidene, H₂C=C:, which is tautomeric with ethyne. Reviews concerning this and related species are of general interest <2002ACR695, 2002ACR826, 2003CRV1271, 2004CRV1317, 2002CRV1731, 2002ACR218, 2001CRV2067>.

1.22.5.2 Formation of Primary Vinylidene Carbenes from Iodonium Salts

It has been found that treatment of alkenyl(phenyl)iodonium tetrafluoroborates **686** with base leads to a reductive α -elimination of the iodonium salt. The resulting free alkylidene carbene may then be trapped by triphenylphosphine to give alkenyl(triphenyl)phosphonium tetrafluoroborates **687** in good yields (Scheme 51) <1999JOC8563>. Likewise, trapping with triphenylarsine gives alkenyl(triphenyl)arsonium tetrafluoroborates **688** <1999JOC8563>. Various other salts may be trapped out in a similar manner such as the alkenyl(triphenyl)stibonium salts **689**, alkenyl(diphenyl)sulfonium salts **690**, alkenyl(diphenyl)selenonium salts **691** and alkenyl(diphenyl)telluronium salts **692** were prepared in a similar manner <1999JOC8563>. 1,2-Migration of α -aryl groups of alkylidene carbenes proceeds rapidly. Thus, when vinylidonium salt **693** was treated with base in the presence of triphenylarsine, the alkylidene carbene **694** rearranged to give diphenylacetylene **695** as the only product. There was no evidence for formation of the arsonium transfer product **696** (Equation (143)) <1999JOC8563>.



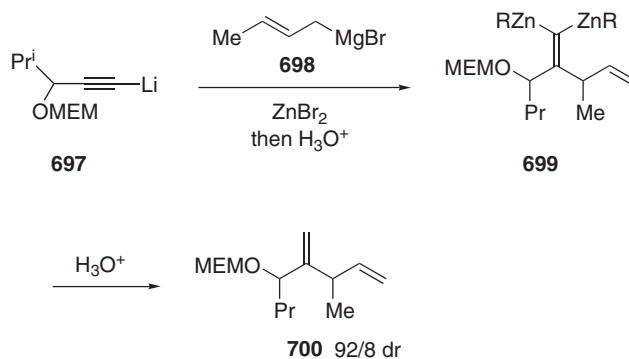
Scheme 51



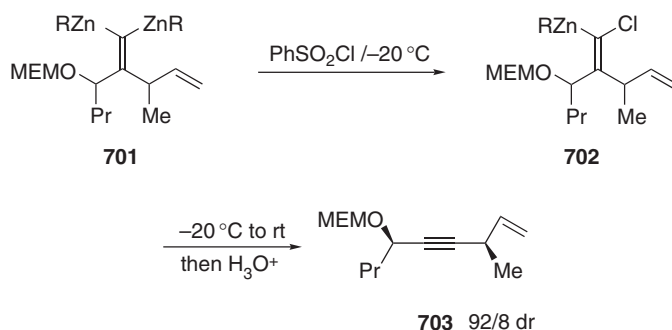
When the reaction was repeated in the absence of base with acetonitrile as the solvent, 2,2-diphenylvinylarsonium tetrafluoroborate **696** was produced in 67% yield. This was explained by either a direct in-plane vinylic $\text{S}_{\text{N}}2$ substitution [<1998JA2275, 1998BCJ243>](#), an ionic mechanism through a vinylbenzenium ion intermediate [<1997JA4785>](#), or ligand coupling on hypervalent iodine(III) [<1997CL955, 1998BCJ1915>](#).

1.22.5.3 Formation of Vinylidene Carbenes via Other Routes

1,1-Dizinca-reagents (**699** or **701**), of the vinylidene type [<2000CRV2887, 1998CRV911>](#), can be prepared and further reacted to give interesting 1,3- or 1,4-diastereoselectivities (**700** or **703**, respectively). For example, crotyl zincation of a lithiated propargylic ether **697**, metallated on the acetylenic position, can give highly diastereoselective reactions ([Schemes 52](#) and [53](#)).



Scheme 52



Scheme 53

The intramolecular chelation of one metal (M_1), as in **707**, lowers its nucleophilicity and allows the selective replacement of M_2 by chlorine (using PhSO_2Cl). The resultant vinylidene zinc carbenoid **708** thus formed is prone to undergo a Fritsch–Buttenberg–Wiechell rearrangement to give **709** [<1999TL1899>](#) (the analogous lithio-carbenoid would not do so), whereby the alkoxyalkyl moiety migrates exclusively (**708** \rightarrow **709**) [<2000OL419>](#) (confirmed by ^{13}C labeling), and with retention of configuration of the migrating carbon ([Scheme 54](#)).

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