

# COMPREHENSIVE ORGANIC FUNCTIONAL GROUP TRANSFORMATIONS II

Editors-in-Chief

Alan R. Katritzky, Richard L.K. Taylor

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Volume

4

Carbon with Two Heteroatoms, Each Attached by  
a Single Bond

Volume Editor

Gary Molander



ÔUT ÚÜÒÐÒÐÙÒÀÁÜÕÐÐÔÁ  
 ÔMPÔNÐÐÔŠÕÜUWÁ  
 VÜÐÙØÜT ÆVÐÐÙÁ



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  
 <UfXVci bXž`G6B. `!\$ , !\$ ( ( & ) \*! \$ž`\* + , , `dU[ Ygž  
 `di V`V]h]cb`XUHY. ` &\$\$(  
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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`hYfUhi fY`žcf`U`gVYbh]ghg`  
 ]bhYfghYX`]b`VX`Ya ]W`HfUbgžcfa Uh]cbg`DfYgYbh]b[ `hY`j Ughgi V`VW`cZ  
 cf[ Ub]Wgnb`hYg]g]b`hYfa g`cZ`hY`]bhfcXi V]cb`UbX`]bhYfV`bj 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 YhlcXg`cZYZZVYbhmidYfžcfa ]b[ `U`  
 dUf]hV`Uf`HfUbgžcfa Uh]cb`Cf[ Ub]gYX`Vmi`hY`ž bV]cbU`[ fci d`  
 žcfa YXž`7C: ; H!=k`j`V`b]g]ghicZ%( `gdYV]U`]ghfYj ]Yk gž`k f]hYb`Vmi  
 `YUX]b[ `gVYbh]ghg`k`c`k`j`Yj U`i UhY`UbX`gi a`a Uf]gY`hY`a YhlcXg`  
 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`5HJWYX`<YhYfcUha`g`

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

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

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

J c`i a Y`). 7UfVcb`k ]h`Hk`c`5HJWYX`<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`5HJWYX`<YhYfcUha`g`

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

**Editors-in-Chief**

**Professor Alan R. Katritzky, FRS**

*University of Florida, Gainesville, FL, USA*

**Professor Richard J. K. Taylor**

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# 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](http://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 4

The original *Comprehensive Organic Functional Group Transformations*, published in 1995, was a landmark publication, outlining in detail the most highly effective synthetic routes to virtually all imaginable organic functional groups. In a discipline over 100 years old and as “mature” as synthetic organic chemistry, one might have thought that the vast majority of the best synthetic methods for all of these useful functional groups would have been thoroughly explored. However, the past ten years have witnessed enormous advances. Thus, the imagination, creativity, and experimental skills of organic synthesis chemists continue to provide astounding new entries to these important structures.

These are superbly analyzed and highlighted by a very talented group of authors in Volume 4 of the present edition of *Comprehensive Organic Functional Group Transformations*. The outline and overall content of this volume have been retained from the previous, successful work. In this updated compendium, highly efficient and creative new approaches to carbons with two heteroatoms, each attached by a single bond, are highlighted. The authors have performed a marvelous job in their individual contributions. I congratulate them and thank them for their hard work and dedication.

Gary Molander  
Philadelphia, USA  
July 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 &amp; 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)
$\Delta$	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 <sub>N</sub> 1	first-order nucleophilic substitution
S <sub>N</sub> 2	second-order nucleophilic substitution
S <sub>N</sub> i	internal nucleophilic substitution
STM	scanning tunneling microscopy
TLC	thin-layer chromatography
UV	ultraviolet
vol.	volume
wt.	weight

## REAGENTS, SOLVENTS, ETC.

Ac	acetyl CH <sub>3</sub> 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 <sub>6</sub> H <sub>5</sub> CH <sub>2</sub> - (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 <sub>6</sub> H <sub>5</sub> CO- (NB avoid confusion with Bn)
Bzac	benzoylacetone
CAN	ceric ammonium nitrate
Cbz	carbobenzoxyl
chalcogens	oxygen, sulfur, selenium, tellurium
CH <sub>2</sub> Cl <sub>2</sub>	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
DMTSF	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 <sup>+</sup>	electrophile
EADC	ethylaluminum dichloride
EDG	electron-donating group
EDTA	ethylenediaminetetraacetate
EEDQ	<i>N</i> -ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline
Et	ethyl
Et <sub>2</sub> O	diethyl ether
EtOH	ethanol
EtOAc	ethyl acetate
EWG	electron-withdrawing group
HMPA	hexamethyl phosphoramide
HMPT	hexamethylphosphoric triamide
IpcBH <sub>2</sub>	isopinocampheylborane
Ipc <sub>2</sub> 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 <sup>−</sup>	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 <sub>2</sub> 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 <sub>6</sub> H <sub>4</sub> (CH <sub>3</sub> )–
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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# 4.01

## Dihaloalkanes, $R^1R^2C(Hal)_2$

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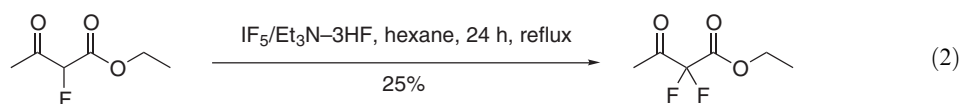
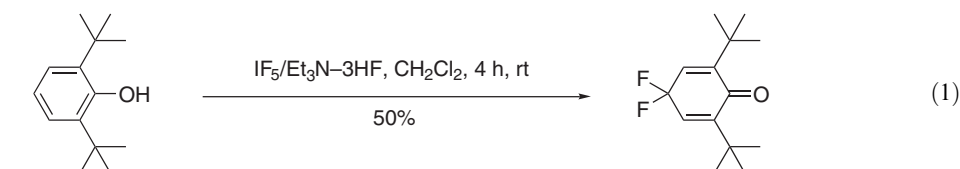
### 4.01.1 GENERAL METHODS

The review by Hill (COFGT (1995)) should be consulted for general methods for the preparation of aliphatic halogenated compounds and for the synthesis of difluoro- and dichloroalkanes from alkanes.

### 4.01.2 DIFLUOROALKANES— $R^1R^2CF_2$

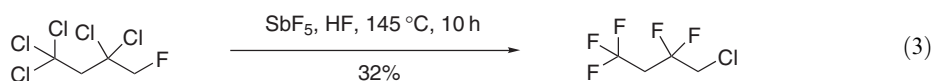
#### 4.01.2.1 Difluoroalkanes from Alkanes

Pentafluoridide–triethylamine–hydrogen fluoride complex ( $IF_5-NEt_3-3HF$ ) is a novel fluorination reagent <2001CL222>.  $IF_5-NEt_3-3HF$  is a stable, nonhazardous, and inexpensive reagent that allows selective fluorination of alkanes to produce *gem*-difluoro compounds under mild conditions. Reported results indicate that the reagent is very effective for the difluorination of thioether substrates (see Chapter 6.02). Difluorination products are obtained in poor-to-moderate yield when fluorinating a variety of alkanes (Equations (1) and (2)).

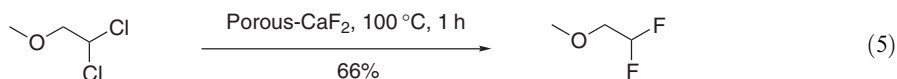
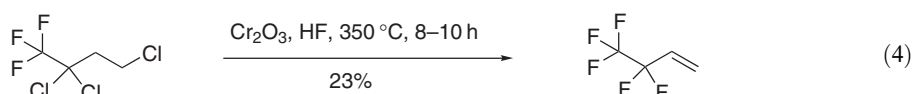


#### 4.01.2.2 Difluoroalkanes from Dihaloalkanes

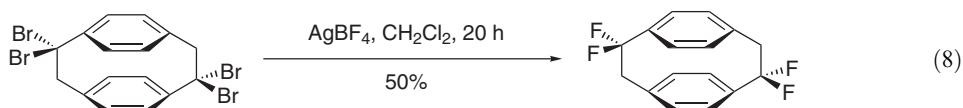
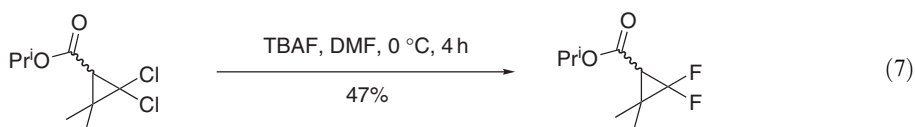
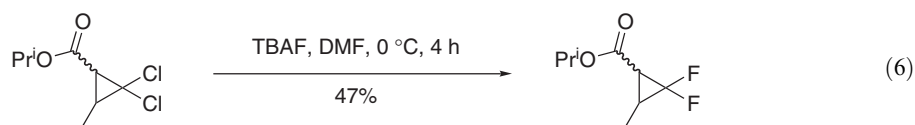
The substitution of *gem*-dihalides by fluoride is still mostly accomplished by employing potassium, mercury, and antimony fluoride salts. Antimony(V) halides and chromium(III) oxide have been used to catalyze challenging and unpredictable HF-fluorinations of highly halogenated hydrocarbons <1996JFC(76)49>. 4-Chloro-1,1,1,3,3-pentafluorobutane is the main product of the antimony(V) fluoride-promoted fluorination reaction of 4-fluoro-1,1,1,3,3-pentachlorobutane (Equation (3)). Interestingly, during this halogen-exchange process, all chlorines are replaced by fluorine and vice versa. These halogen-exchange reactions have proved to be very difficult to accomplish whenever adjacent carbons are halogenated. These challenging transformations have been effected by employing a chromium(III) oxide-catalyst in the vapor phase (Equation (4)). Porous calcium fluoride (PCF) is a novel material that has found application as a solid-phase fluorinating material (Equation (5)) and as a support for catalysts in hydrogenation reactions. PCF is prepared by treating commercial soda lime with anhydrous hydrogen fluoride <2002JFC(116)65>.





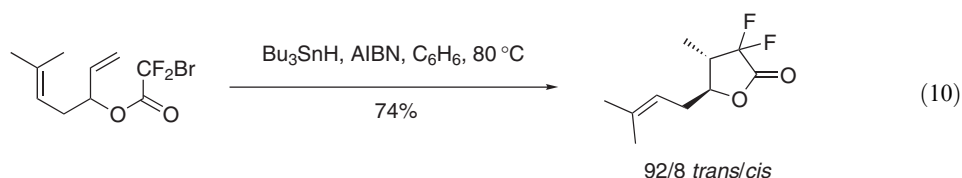
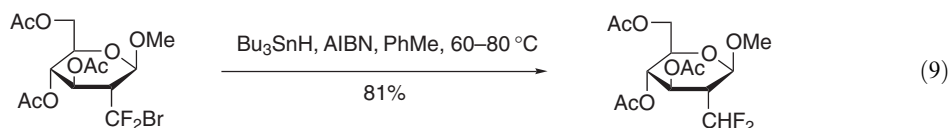


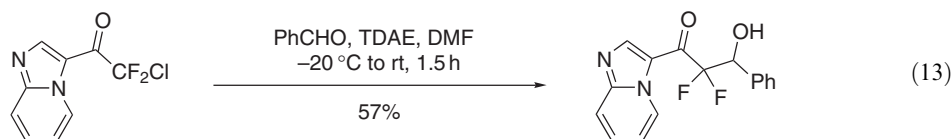
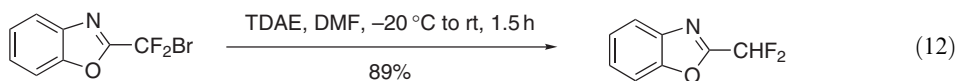
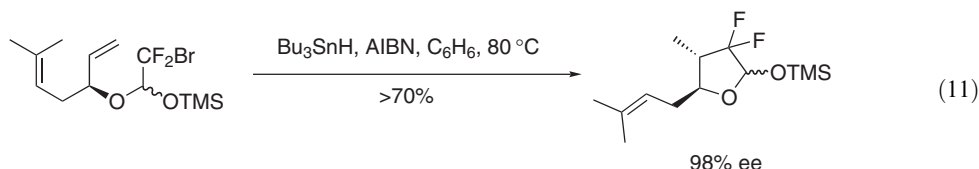
Geminal difluorocyclopropanes having an electron-withdrawing group are accessible by treatment of the corresponding dichlorocyclopropanes with tetra-*n*-butylammonium fluoride (TBAF) under mild conditions (Equations (6) and (7)) <1996TL4085>. This synthetic pathway seems more efficient than the sluggish reaction between an electron-deficient alkene and the weakly electrophile difluorocarbene, whose generation is troublesome. Bromide–fluoride exchange is expected to be an easier reaction compared to the chloride–fluoride exchange. This could be noticed in the halogen-exchange reaction of *gem*-dibromides with silver tetrafluoroborate ( $\text{AgBF}_4$ ) under mild conditions <2001TL3555>. This convenient synthetic protocol has been employed in the synthesis of fluorinated [2,2]-paracyclophanes (Equation (8)).



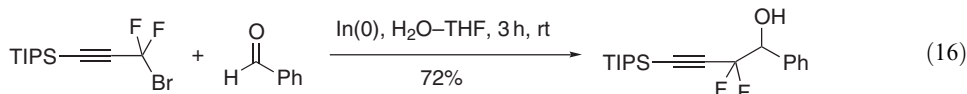
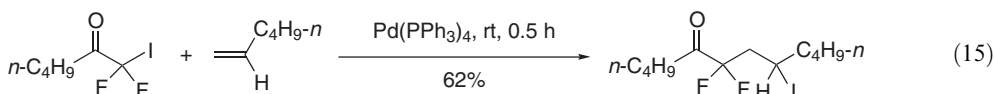
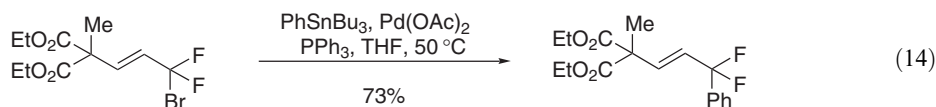
#### 4.01.2.3 Difluoroalkanes from Trihaloalkanes

Monosaccharides containing the difluoromethyl functionality have been prepared by reduction of the bromodifluoromethyl group with tri-*n*-butyltin hydride (Equation (9)) <1998EJO919>. Under similar reaction conditions,  $\alpha,\alpha$ -difluoro- $\gamma$ -lactones have been synthesized from bromodifluoromethyl substrates via an intramolecular radical cyclization <1999JOC252>. This intramolecular radical cyclization proved to be highly diastereoselective and suitable for the production of optically active  $\alpha,\alpha$ -difluoro- $\gamma$ -lactones with the proper choice of appropriate substrates (Equations (10) and (11)). The bromodifluoromethyl group can also be reduced electrochemically using tetrakis(dimethylamino)ethylene (TDAE) as reductant (Equation (12)) <2001JFC(109)39>. In addition, the generated difluoromethyl heterocyclic anion can be trapped with aromatic and heterocyclic aldehydes and ketones to produce the corresponding  $\beta,\beta$ -difluoro- $\alpha$ -hetero-arylated alcohols in moderate yields (Equation (13)).





$\alpha$ -Bromo- $\alpha,\alpha$ -difluoroallyl derivatives undergo nucleophilic substitution reactions in the presence of palladium catalysts to afford 1,3-disubstituted 3,3-difluoroalkenes (Equation (14)) <2000CFB885>. Also in the presence of palladium catalysts, iodo-fluoromethyl alkyl ketones react with alkenes to give the corresponding  $\alpha,\alpha$ -difluoro- $\gamma$ -iodoketone in moderate-to-good yields (Equation (15)) <1995JOC5570>. Activation of the bromodifluoromethyl group by indium metal has found application in the synthesis of homopropargylic *gem*-difluoroalcohols in aqueous media (Equation (16)) <2000JOC6547>.



The fluoride ion-promoted alkylation of 2,2-difluoro-2-trimethylsilylacetates with a variety of electrophiles such as aldehydes, ketones, imines, acyl halides, and alkyl halides produces *gem*-difluoroacetates in good yields (Table 1) <1999JOC6717>. The reaction between this Reformatsky-type reagent and an  $\alpha,\beta$ -unsaturated aldehyde selectively produces the corresponding 1,2-adducts. This  $\alpha$ -alkylation process is efficient when allyl and benzyl halides are employed, but has not led to satisfactory results with other alkyl halides.

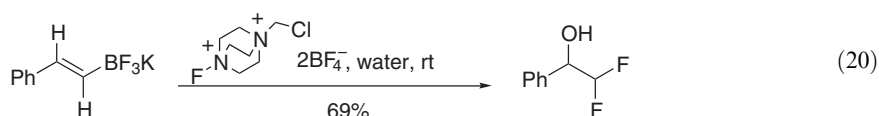
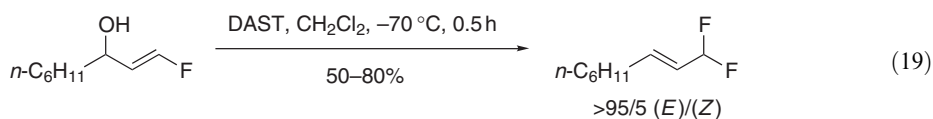
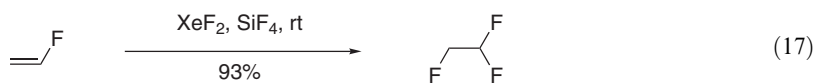
#### 4.01.2.4 Difluoroalkanes from Alkenes

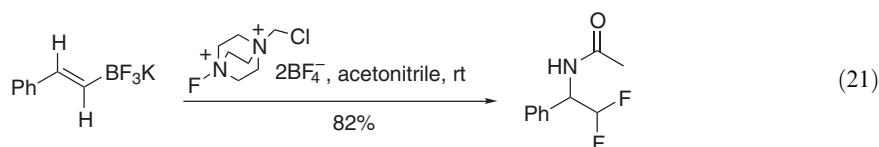
Alkenes and fluoroalkenes commonly serve as precursors to *gem*-difluoro compounds. Difluoromethyl groups can be generated from a *vic*-fluorination reaction involving fluoroalkenes and xenon difluoride ( $XeF_2$ ) in the presence of silicon tetrafluoride ( $SiF_4$ ) <1999EJO3151>. The products are obtained in high yield, and common side reactions, such as rearrangements and polymerization, are not observed (Equations (17) and (18)). 1-Fluoro-1-alken-3-ols react with diethylaminosulfur trifluoride (DAST) in an  $S_N2'$  process to afford the corresponding 1,1-difluoro-methyl-3-alkene products with high stereoselectivity (Equation (19)) <1995TL4223>. Difluoromethyl-substituted alcohols or amides can be prepared by treating alkenyl trifluoroborates with 2 equiv. of Selectfluor<sup>TM</sup>, a commercially available electrophilic fluorinating agent <1997SL606>. This practical method led to alcohol derivatives in aqueous media, while producing amides in nitrile solvents (Equations (20) and (21)).

**Table 1** Reaction of *n*-hexyl 2-trimethylsilyl-2,2-difluoroacetate with various electrophiles

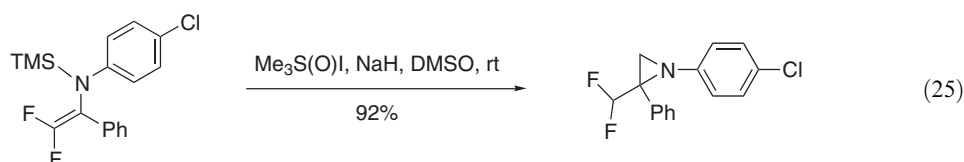
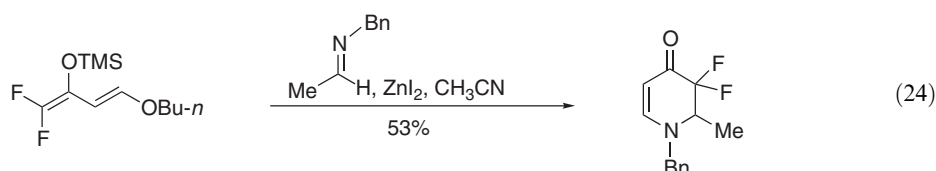
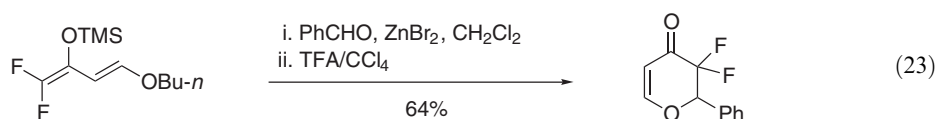
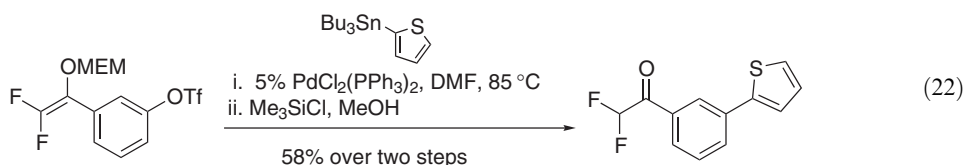
$\text{TMS}-\text{C}(\text{F})_2-\text{C}(=\text{O})\text{OC}_6\text{H}_{13-n} \xrightarrow[\text{TBAF or KF-CuI}]{\text{Electrophile}} \text{E}-\text{C}(\text{F})_2-\text{C}(=\text{O})\text{OC}_6\text{H}_{13-n}$				
Entry	Substrate	Method	Product	Yield (%)
1	PhCHO	A		82
2		A		76
3		B		92
4		B		83
5		B		60
6		A		45
7		B		85

Reproduced by permission of American Chemical Society from *J. Org. Chem.*, **1999**, 64 (18), 6720; © American Chemical Society (<1999JOC6717>). Method A: TBAF. Method B: KF-CuI.



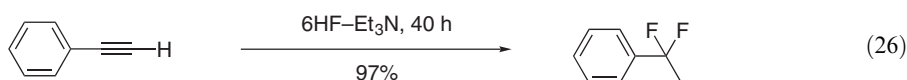


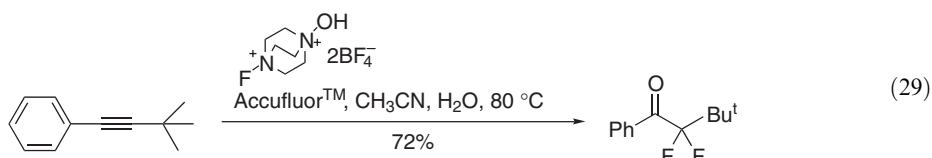
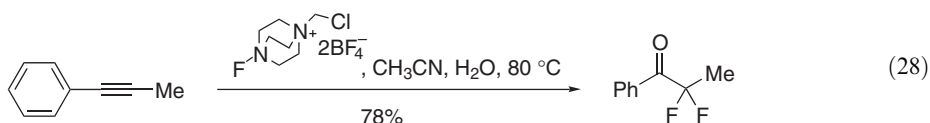
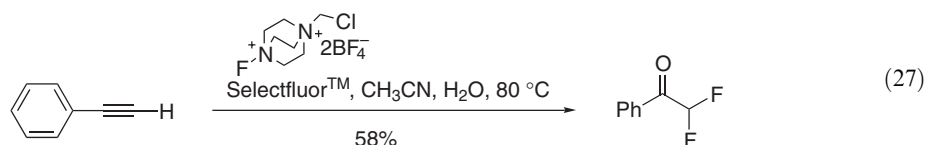
Difluoroenol derivatives are suitable materials for the synthesis of a range of difluoromethyl ketone derivatives <2001OL2859>. Some difluoroenols are readily available and have been employed in a variety of synthetic sequences in which the latent difluoroketone is released in the final step under mild conditions (Equation (22)). Similarly, a difluorinated version of Danishefsky's diene undergoes hetero-Diels-Alder reactions with aldehydes and imines to produce *gem*-difluorinated six-membered heterocycles (Equations (23) and (24)) <2001OL3103>. Difluoroenamines, which are easily prepared from trifluoromethylimines, are also precursors to difluoromethyl-containing compounds <2002TL2069>. For example, trifluoromethylimines react with dimethylsulfonium methylide to yield difluoromethylaziridines in excellent yields (Equation (25)).



#### 4.01.2.5 Difluoroalkanes from Alkynes

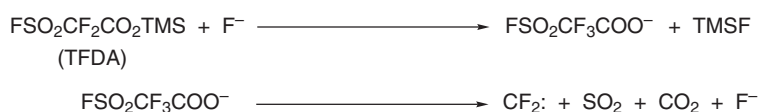
The addition of HF across an alkyne represents a general method for the preparation of difluoroalkanes (COFGT (1995)). Mild and selective reagents are desirable for the introduction of fluorine into functionalized molecules. 6HF-NEt<sub>3</sub> complex has proven to be a very mild reagent for hydrofluorination reactions <1996SL529>. Treatment of ethynylbenzene with 6HF-NEt<sub>3</sub> complex promotes difluorination at the internal alkynyl carbon producing (1,1-difluoroethyl)benzene in excellent yield (Equation (26)). Complementarily, treatment of ethynylbenzene with Selectfluor<sup>TM</sup> promotes difluorination at the terminal alkynyl carbon to produce  $\alpha,\alpha$ -difluoroketones in good yields (Equations (27) and (28)) <1995JOC259>. Accufluor<sup>TM</sup> is a commercially available fluorinating agent that under similar conditions promotes the difluorination of alkynes and phenols to produce  $\alpha,\alpha$ -difluoroketones in good-to-excellent yields (Equation (29)) <1996SL693>.





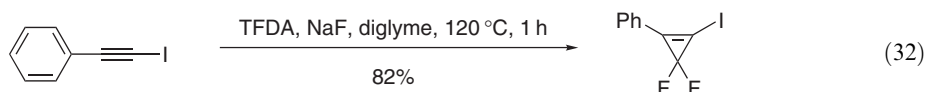
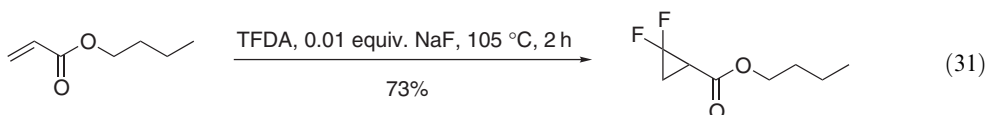
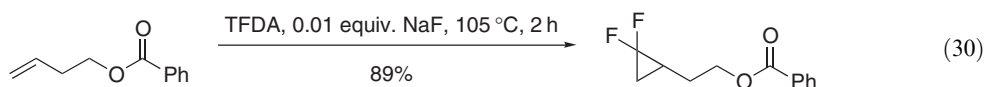
#### 4.01.2.6 Difluoroalkanes from Difluorocarbene

Practical methods for difluorocarbene generation are limited, and this process continues to challenge the organic chemist. The generation and reactivity of difluorocarbene has been extensively reviewed in the past (COFGT (1995) and references within). Trimethylsilylfluorosulfonyl-difluoroacetate (TFDA) has been identified as a convenient source of difluorocarbene at moderate temperatures [Scheme 1](#) [<2000OL563>](#).

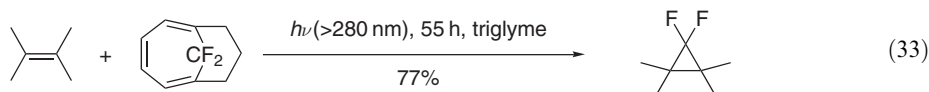


**Scheme 1**

Difluorocarbene formation is catalyzed by fluoride under nitrogen atmosphere. This method allows the addition of difluorocarbene to alkenes as well as electron-deficient alkenes ([Equations \(30\) and \(31\)](#)), which has not been efficiently achieved by previous methods. Due to the mild reaction conditions, TFDA has effectively been applied to the preparation of highly reactive cyclopropenes ([Equation \(32\)](#)) [<2002JOC9421>](#).



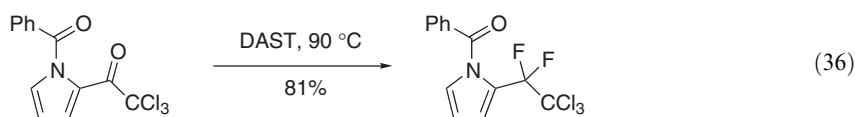
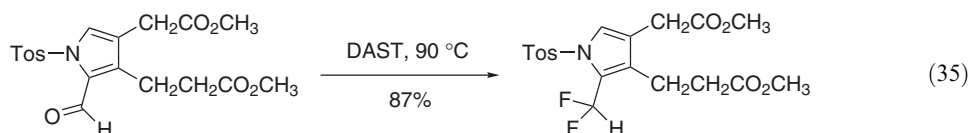
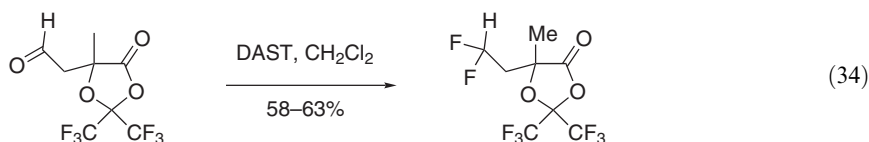
An alternative difluorocarbene source is 10,10-difluorobicyclo[4.3.1]deca-1,3,5-triene, which has been prepared from indane in four synthetic steps and in 55% overall yield [<2003JFC\(119\)75>](#). This triene differs from other difluorocarbene precursors because it is an effective photochemical source of difluorocarbene ([Equation \(33\)](#)).



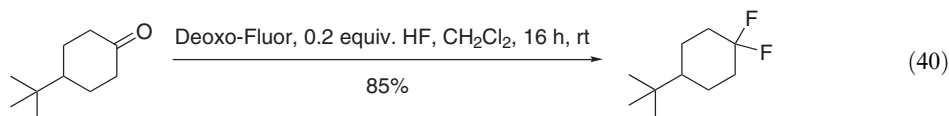
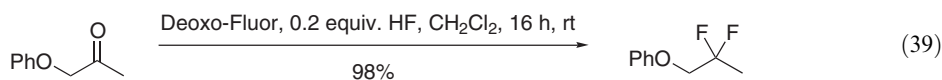
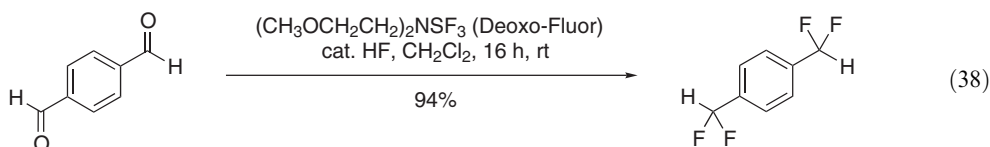
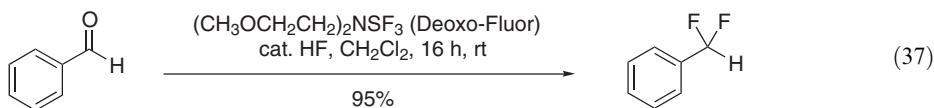
#### 4.01.2.7 Difluoroalkanes from Aldehydes and Ketones

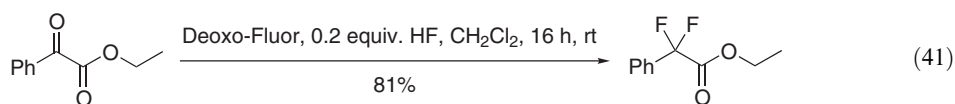
The conversion of carbonyl groups to *gem*-difluoro compounds is an important transformation that continues to find applications in organic synthesis. Many methods and reagents to achieve this functional group transformation have been reviewed in the literature. Hill (COFGT (1995)) should be consulted for general methods and procedures for the conversion of carbonyls to *gem*-difluoroalkanes.

DAST continues to find applications for the generation of the difluoromethyl functionality <1995TL2389, 2000JFC(102)317>. DAST reacts under mild conditions that are tolerated by many functional groups, including carboxylic acid derivatives (Equations (34)–(36)). In addition, DAST is easy to handle and practical for most laboratory procedures. However, utilization of DAST in large-scale industrial settings is limited by its thermal instability.



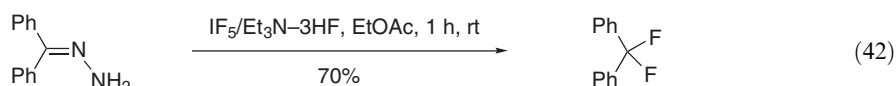
Bis(2-methoxyethyl)aminosulfur trifluoride (Deoxo-Fluor<sup>TM</sup>) is an alternative reagent having greater thermal stability and good performance in fluorination reactions of carbonyl compounds at lower temperatures <1999CC215, 1999JOC7048, 2001OL2713>. Similar to DAST, Deoxo-Fluor<sup>TM</sup> reacts with alcohols but does not react with carboxylic acid derivatives. In contrast, Deoxo-Fluor<sup>TM</sup> reacts with carboxylic acids to produce acid fluorides in good yields (Equations (37)–(41)). In addition, Deoxo-Fluor<sup>TM</sup> has found significant application in the preparation of *gem*-difluoro compounds from thiocarbonyl derivatives (see Chapter 6.02) <2000JOC4830>.





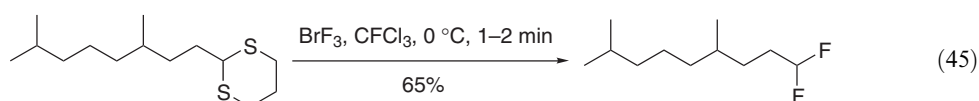
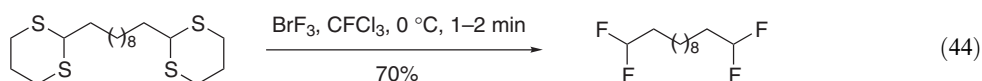
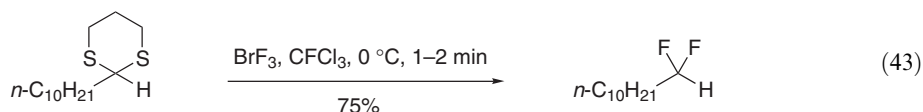
#### 4.01.2.8 Difluoroalkanes from Imines

The treatment of aziridines with hydrogen fluoride—pyridine complex continues to be a common method for the preparation of *gem*-difluoroalkanes with adjacent amino groups (COFGT (1995), <1995JFC(73)165>). Pentafluoroiodide—triethylamine—hydrogen fluoride complex ( $\text{IF}_5\text{—NEt}_3\text{—3HF}$ ) reacts with hydrazones to yield the corresponding *gem*-difluoro compound in modest-to-good yields (Equations (42)) <2001CL222>.



#### 4.01.2.9 Difluoroalkanes from Dithianes

1,1-Difluoromethyl alkanes can be prepared from the corresponding 2-alkyl-1,3-dithiane by treatment with bromine trifluoride as a fluorinating agent <2003OL769>. Moderate yields of the desired products are obtained under mild conditions (Equations (43)–(45)). The main limitation of this methodology is that the use of bromine trifluoride in the presence of unsaturated systems can lead to undesired products resulting from electrophilic bromination reactions.



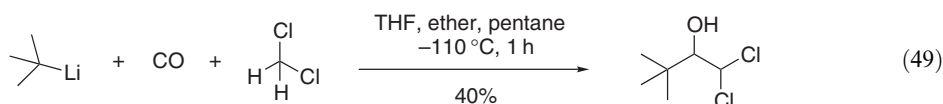
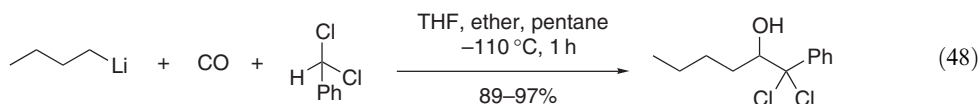
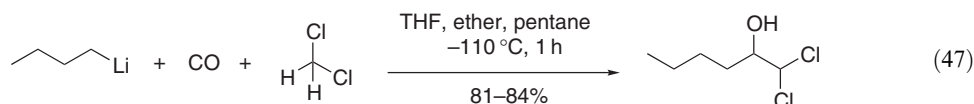
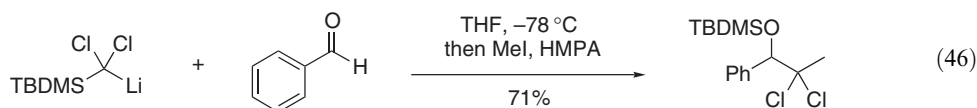
### 4.01.3 DICHLOROALKANES— $R^1R^2\text{CCl}_2$

#### 4.01.3.1 Dichloroalkanes from Alkanes

The review by Hill (COFGT (1995)) should be consulted for the preparation of aliphatic *gem*-dichloro compounds and the synthesis of dichloroalkanes from alkanes.

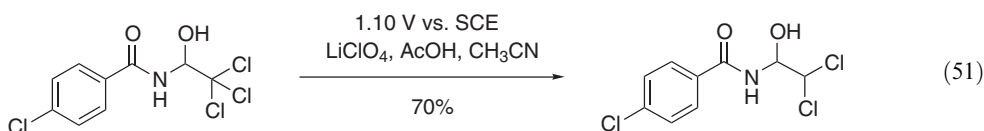
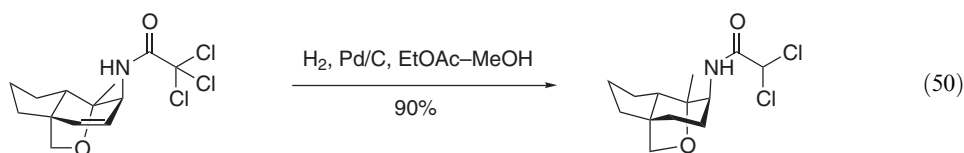
#### 4.01.3.2 Dichloroalkanes from Dihaloalkanes

$\alpha,\alpha$ -Dichloroalcohols are prepared simply by the addition of lithium (*t*-butyldimethylsilyl)dichloromethane to carbonyl compounds <1999JOM(572)31>. In addition, these types of *gem*-dichloro compounds are obtained from the protonation of acyllithium reagents generated *in situ* from alkylolithiums and carbon monoxide in the presence of dichloromethane (Equations (46)–(49)).

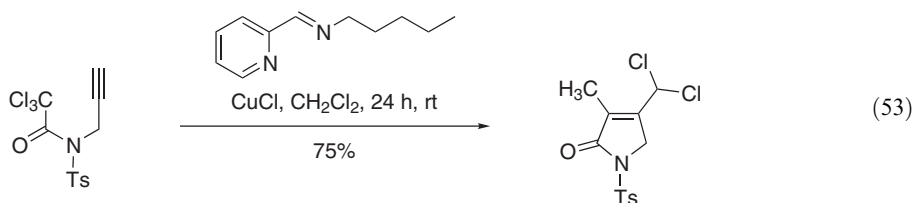
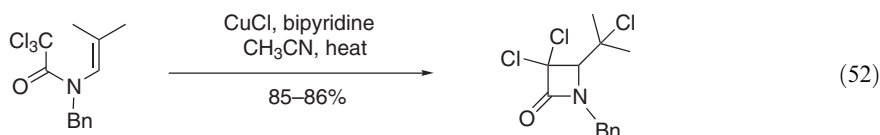


#### 4.01.3.3 Dichloroalkanes from Trihaloalkanes

The reduction of the trichloromethyl group to dichloromethane has widely been reported in the literature (Hill, COFGT (1995)). This transformation usually involves the use of tin or iron salts, as well as zinc or copper metals. In some cases, standard catalytic hydrogenolysis conditions are suitable to achieve the reduction (Equation (50)) <2000TL9357>. Alternatively, electrochemical methods can be effectively employed for the production of *gem*-dichloro compounds from the corresponding trichloromethane-containing substrate (Equation (51)) <2001T4925>.

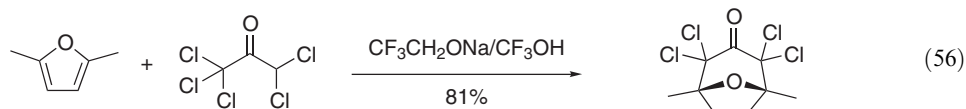
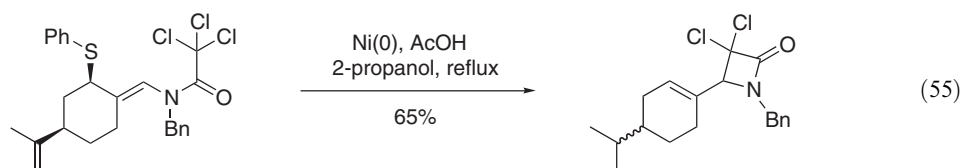
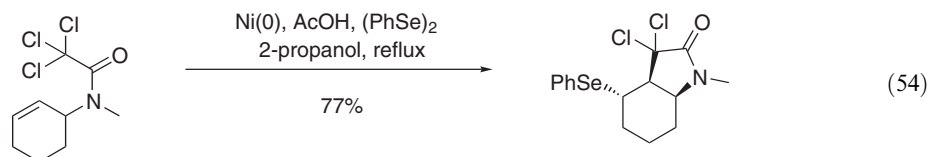


Highly functionalized *gem*-dichloro  $\beta$ - and  $\gamma$ -lactams are prepared from trichloromethane substrates via a radical cyclization reaction. These reactions are mediated by multidentate amine-derived copper(I) complexes, and the generated dichloro radical reacts with alkene and alkyne functionalities (Equations (52) and (53)) <2001TL1999, 2001TL2901>. The regiochemical outcome of the reactions can be controlled by changes in multidentate amine–metal complex.



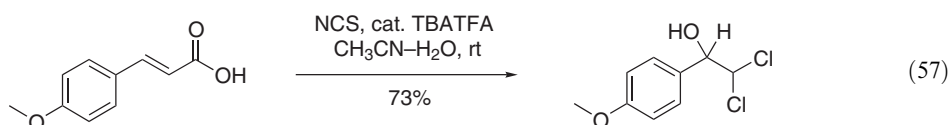


In addition, *gem*-dichloro  $\beta$ - and  $\gamma$ -lactams can be prepared via a similar nickel-catalyzed radical cyclization (Equations (54) and (55)) <1998T1029, 2001JOM(624)316>. Pentachloroacetone undergoes [4+3]-cycloadditions to furans to produce a variety of 2,2,3,3-tetrachloro-8-oxabicyclo[3.2.1]oct-6-en-3-ones in moderate-to-good yields (Equation (56)) <1999JOC3398>.

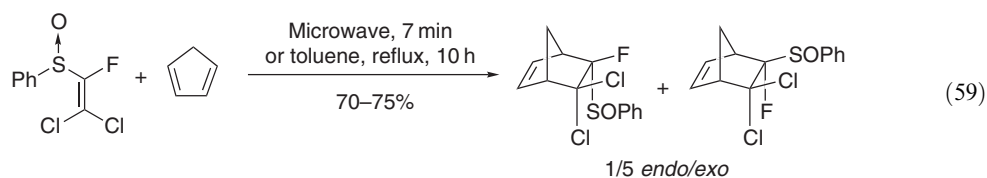
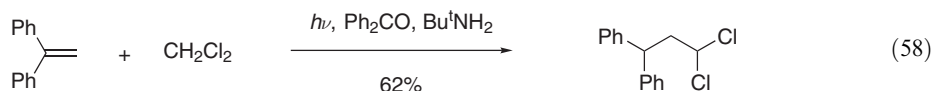


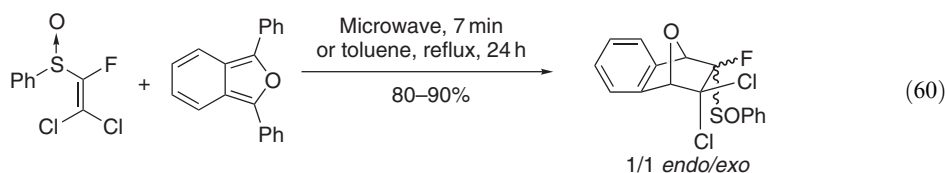
#### 4.01.3.4 Dichloroalkanes from Alkenes

The reaction of  $\alpha,\beta$ -unsaturated aromatic carboxylic acids with 2 equiv. of *N*-chlorosuccinimide (NCS) affords the corresponding  $\alpha,\alpha$ -dichloromethylbenzyl alcohols <2000T1369>. This Hunsdiecker-type halodecarboxylation reaction is catalyzed by tetrabutylammonium trifluoroacetate (TBATFA) under mild aqueous conditions (Equation (57)). This practical method is suitable for the preparation of  $\alpha,\alpha$ -dibromo- and  $\alpha,\alpha$ -iodomethylbenzyl alcohols when the corresponding *N*-halosuccinimide is employed (see Sections 4.01.3.4 and 4.01.5.3). Interestingly, the corresponding (*E*)-haloalkenes are obtained under anhydrous conditions.



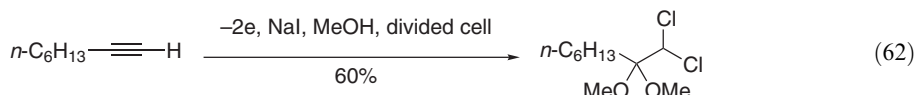
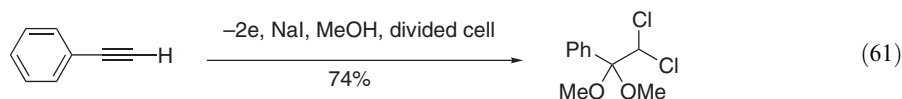
The dichloromethylation of diarylethenes with dichloromethane by benzophenone photosensitization in the presence of *t*-butylamine affords the corresponding alkylation products in moderate yields (Equation (58)). A dichloromethylene radical ( $\cdot\text{CHCl}_2$ ) is believed to be the reactive species in this photo-induced alkylation reaction <1996JOC6438>. The cycloaddition reactions of halo-substituted vinyl sulfoxides provide access to some specific *gem*-dichloro compounds. The Diels–Alder reaction of (2,2-dichloro-1-fluoro-ethenesulfinyl)benzene with cyclopentadiene and 1,3-diphenylisobenzofuran under conventional heating as well as under microwave irradiation produce the corresponding cycloadducts in good yield (Equations (59) and (60)) <2000T3539>.



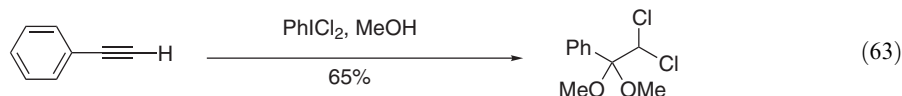


#### 4.01.3.5 Dichloroalkanes from Alkynes

Terminal alkynes continue to be important substrates for the preparation of dichloromethyl ketones. Terminal alkynes submitted to electrochemical oxidation conditions in a divided cell and in the presence of lithium chloride resulted in the exclusive formation of the corresponding 1,1-dichloro-2,2-methoxy compound in good yields (Equations (61) and (62)) <2000SL89>.

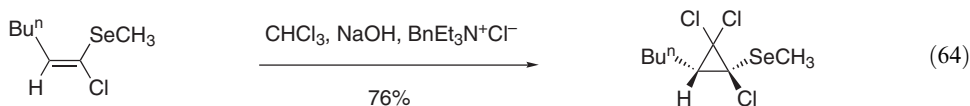


The same alkyne chloromethoxylation reaction can be easily achieved by employing iodosobenzene dichloride in methanol (Equation (63)) <2002ZOR(E)902>. The corresponding dichloromethyl ketones are obtained after hydrolysis of the ketal product.

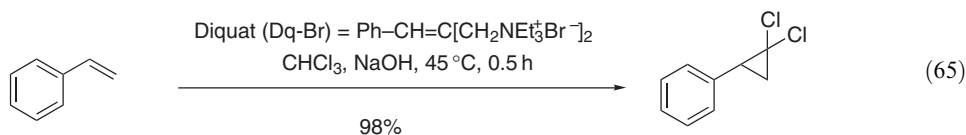


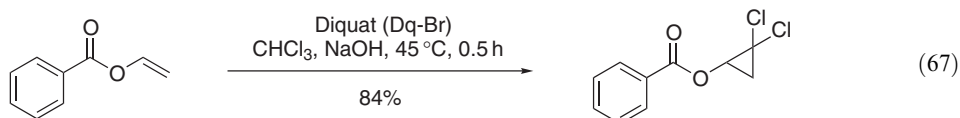
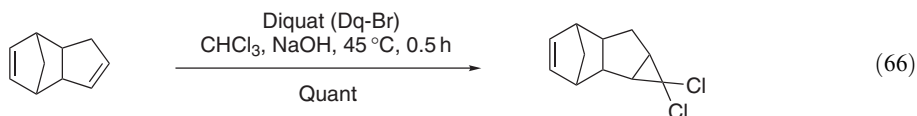
#### 4.01.3.6 Dichloroalkanes from Dichlorocarbene

Dichlorocarbene can be generated by several methods under a variety of reaction conditions. Phase-transfer conditions are the most widely used to generate dichlorocarbene as one of many synthetic protocols leading to novel organic molecules. The most common phase-transfer conditions for the preparation of dichlorocarbene still involves chloroform, aqueous sodium or potassium hydroxide, and a phase-transfer reagent such as benzyltriethylammonium chloride (TEBA), which continues to be a widely used reagent for this purpose. These methods have found application in the synthesis of highly functionalized *gem*-dichlorocyclopropanes. For example, vinylic selenides are reacted with dichlorocarbene to produce the corresponding 2,2-dichloro-1-selenopropanes with retention of configuration in good yields (Equation (64)) <1998SC1667>.

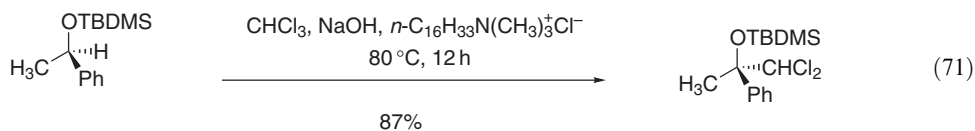
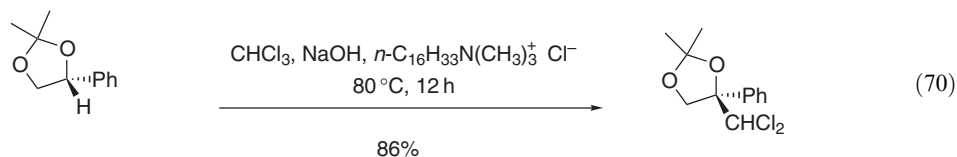
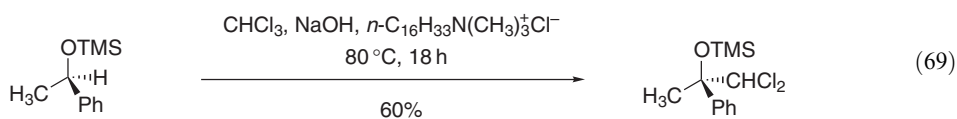
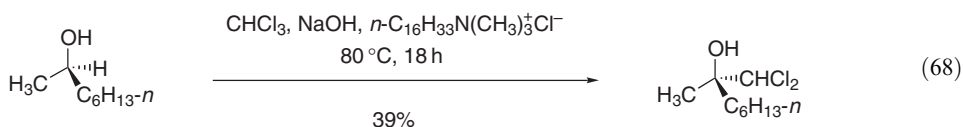


A new phase-transfer reagent, 2-benzylidene-*N,N,N',N',N',N'*-hexaethylpropane-1,2-diammonium dibromide (Diquat), has been reported to be ideal for the generation of dichlorocarbene and its subsequent reactions <1999SC4101, 2001AC(206)19>. The use of Diquat in selective dichlorocyclopropanation reactions comes along with advantages such as faster reaction times, lower base concentrations, and higher yields than standard TEBA reaction conditions (Equations (65)–(67)).





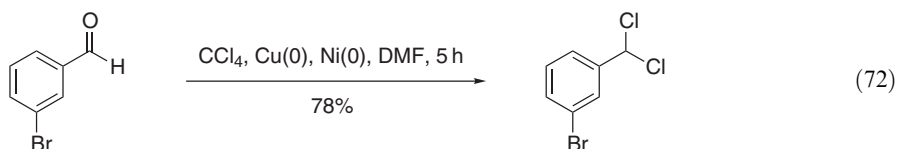
Cetyltrimethylammonium chloride (CTAC) is a phase-transfer reagent that has found application in stereospecific C—H insertion reactions of dichlorocarbene. The synthesis of optically active  $\alpha,\alpha$ -dichloromethylated tertiary alcohols has been accomplished by generating dichlorocarbene from a chloroform–sodium hydroxide–CTAC phase-transfer system [\(<2000CL1180, 2003CL4>\)](#). The C—H insertion reaction of dichlorocarbene and protected chiral secondary alcohols is stereospecific and proceeds with retention of configuration (Equations (68)–(71)).

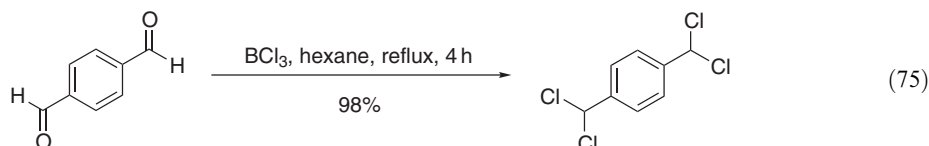
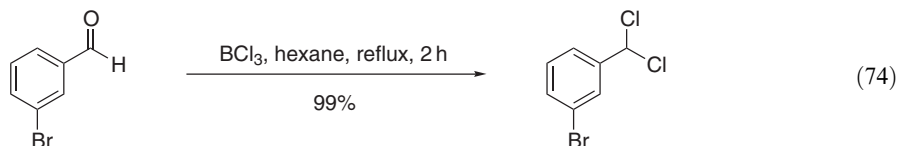
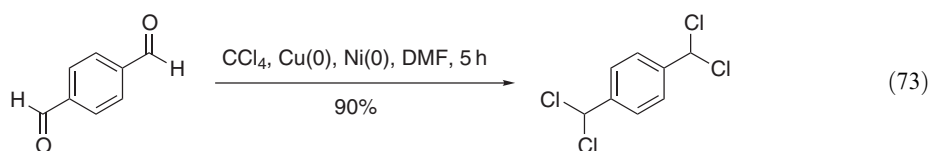


#### 4.01.3.7 Dichloroalkanes from Aldehydes and Ketones

The conversion of aldehydes and ketones to dichloroalkanes by phosphorus pentachloride is still a widely used synthetic protocol. Similar reagents such as  $\text{PCl}_3$ ,  $\text{SOCl}_2$ , and  $\text{SO}_2\text{Cl}_2$  are also employed for the same purpose. Most of these reagents are toxic and/or moisture sensitive. New general methods involving more stable reagents and mild reaction conditions are still not available.

Benzyl dichlorides can be prepared by reaction of the aryl aldehyde with a Vilsmeier-type reagent formed *in situ* by reduction of carbon tetrachloride [\(<1999SC4015>\)](#). The reduction is promoted by a combination of copper(0) and nickel(0) in DMF solvent at 60 °C. The protocol works efficiently in 100 mmol scale, and the desired dichloro compound is obtained in good-to-excellent yields (Equations (72) and (73)). The limitations of this protocol are that it is exclusive to benzaldehydes and that it uses excess amounts of  $\text{Cu}(0)/\text{Ni}(0)$ . Another dichlorination protocol limited to benzaldehydes involves the use of boron trichloride in hexanes under reflux conditions [\(<2000TL579>\)](#). This method is notable because the desired dichlorination products are obtained in excellent yields (Equations (74) and (75)).

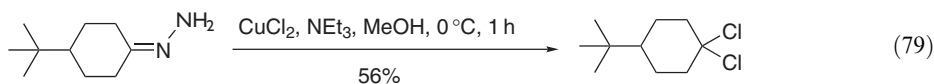
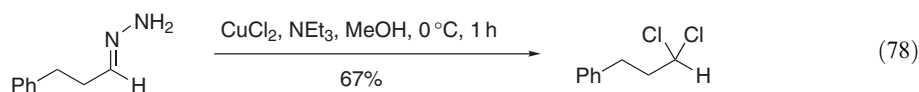
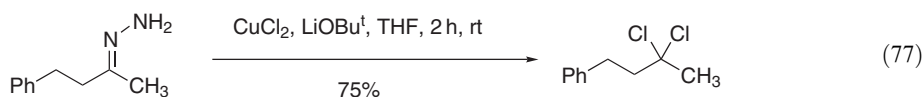
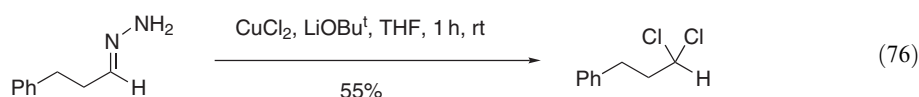




#### 4.01.3.8 Dichloroalkanes from Imines

Aliphatic *gem*-dichloride compounds can be produced from a copper(II) chloride-promoted oxidation of hydrazones [<1997T557>](#). The hydrazones are easily prepared from the corresponding aldehyde or ketone with hydrazine hydrate in the presence of 4 Å molecular sieves.

Treatment of hydrazones with copper(II) chloride–lithium *t*-butoxide in THF produces *gem*-dichlorides in moderate yields ([Equations \(76\) and \(77\)](#)). A variation of this method simply consists of using copper(II) chloride–triethylamine in methanol ([Equations \(78\) and \(79\)](#)). This procedure proved to be practical and more efficient than the copper(II) chloride–lithium *t*-butoxide oxidative system. Analogously, the use of copper(II) bromide leads to *gem*-dibromo compounds (see [Section 4.01.4.8](#)).



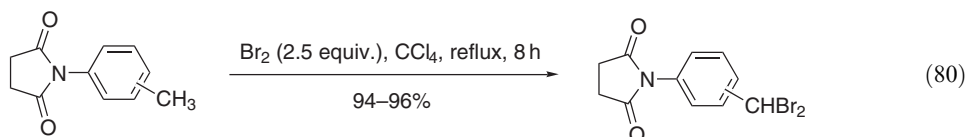
#### 4.01.4 DIBROMOALKANES— $R^1R^2CBr_2$

##### 4.01.4.1 Dibromoalkanes from Alkanes

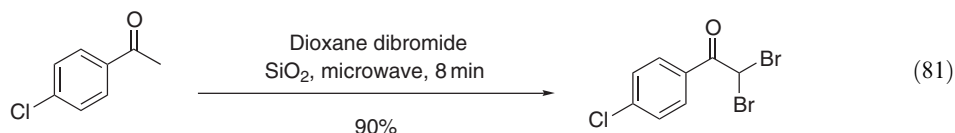
The review by Hill (COFGT (1995)) should be consulted for the preparation of aliphatic *gem*-dibromo compounds and the synthesis of dichloroalkanes from alkanes.

Tolylamines undergo electrophilic aromatic substitution when treated with electrophilic halogenating reagents. Methods for direct benzylic halogenation of tollyamines are unknown. Nevertheless, benzylic *gem*-dibrominations have been achieved by preparing the succinimide derivative of the corresponding tollyamine followed by treatment with molecular bromine [<2002S221>](#).

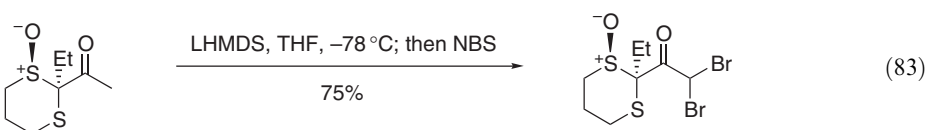
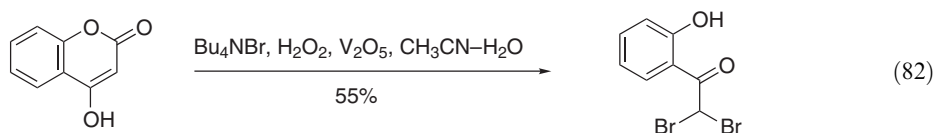
The synthetic sequence produces the desired *gem*-dibromo compound in excellent yield (Equation (80)). In addition, simple changes to the reaction conditions lead to benzylic monobromination product exclusively.



Complex mixtures of mono-, di-, and tribrominated products are not uncommon when preparing  $\alpha,\alpha$ -dibromoketones from the corresponding alkyl ketone. The selective synthesis of  $\alpha,\alpha$ -dibromomethyl aryl ketones is possible by employing dioxane dibromide and silica gel under microwave irradiation and solvent-free conditions (Equation (81)) <2003TL439>. Exclusive monobromination can be obtained by limiting the amount of dioxane dibromide and reducing the irradiation time. This method is not suitable for the preparation of  $\alpha,\alpha$ -dibromomethyl alkyl ketones.



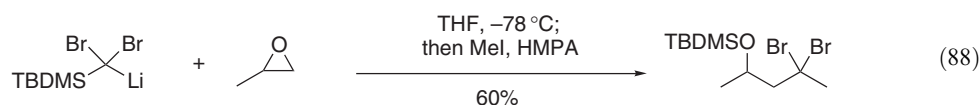
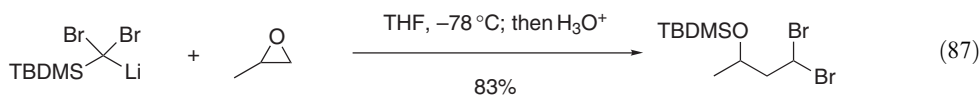
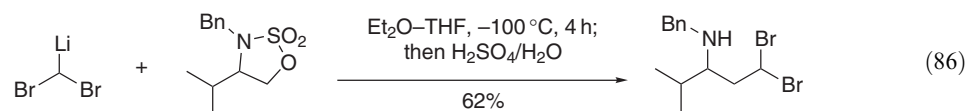
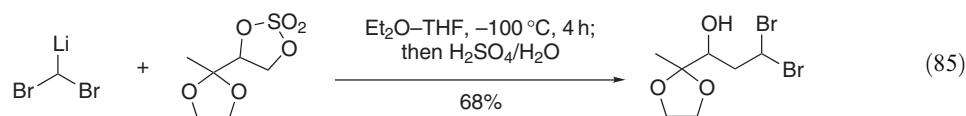
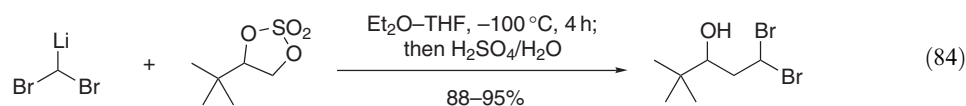
$\alpha,\alpha$ -Dibromomethyl-*o*-hydroxyacetophenone can be obtained from 4-hydroxycoumarin derivatives in a vanadium pentoxide-promoted bromination reaction (Equation (82)) <2000OL247>. Dibromomethyl ketones have efficiently been prepared from 2-ethyl-2-acetyl-1,3-dithiane-1-oxide by deprotonation followed by the addition of *N*-bromosuccinimide (NBS) <1995T1285>. The reaction leads exclusively to the dibromination product, and good yields are obtained separately for both *anti* and *syn* isomers (Equation (83)).



#### 4.01.4.2 Dibromoalkanes from Dihaloalkanes

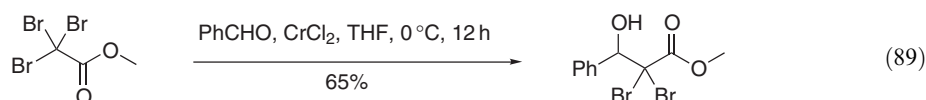
Reactions of dibromomethyl lithium with carbonyl compounds and carboxylic acid derivatives are still widely used transformations for the preparation of *gem*-dibromo compounds (Hill COFGT (1995)). These methods have found applications in natural product synthesis. For example, the total syntheses of (+)-13-carbaartemisinin and (–)-cylindrocyclophane A both employ a dibromomethyl lithium reaction to generate an  $\alpha,\alpha$ -dibromoalcohol and  $\alpha,\alpha$ -dibromoketone, respectively <1996JMC1885, 2001JACS5925>. All of these methods are suitable for most laboratory preparations, but the required low temperatures (–100 °C to –78 °C) for the generation of dibromomethyl lithium could represent a challenge for some industrial settings.

Reaction of dibromomethyl lithium with cyclic sulfates produces 1,1-dibromo-3-hydroxyalkanes. The cyclic sulfates are easily prepared from 1,2-diols, and the alkylation reactions proceed in good yields (Equations (84) and (85)) <1996S259>. In addition, the method applies to cyclic sulfamates to produce the corresponding 1,1-dibromo-3-aminoalkanes (Equation (86)). Another synthetic strategy into 1,1-dibromo-3-hydroxyalkanes involves the reaction of *t*-butyldimethylsilyldibromomethyl lithium with oxiranes followed by 1,4-rearrangement of the silyl group <1996T503>. This silyl group migration from carbon to oxygen produces a carbon-centered lithium anion that can further react with electrophiles such as alkyl halides or simple aldehydes (Equations (87) and (88)).

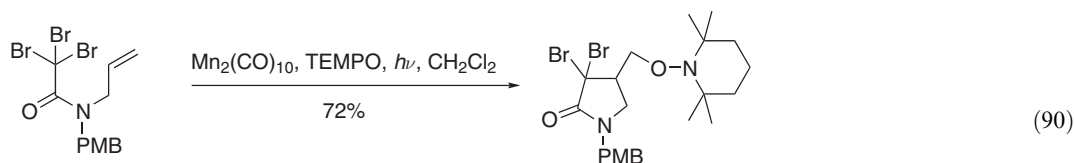


#### 4.01.4.3 Dibromoalkanes from Trihaloalkanes

2,2-Dibromo-3-hydroxy-alkyl acid esters can be prepared via Cr(II)-mediated alkylation of aldehydes with tribromoacetates. These Reformatsky-type synthetic intermediates can be prepared in good yields under relatively mild conditions using either stoichiometric or catalytic amounts of chromium(II) salts (Equation (89)) <2003JACS3218>. The catalytic system requires the use of manganese(0) and TMSCl. These synthetic intermediates can be further reacted to produce (Z)- $\alpha$ -bromoacrylates in excellent yields.



*gem*-Dibromo- $\gamma$ -lactams can be prepared from tribromomethane substrates via a radical cyclization reaction. These reactions are mediated by manganese decacarbonyl under irradiation conditions, and the generated dibromo radical reacts with an alkene to produce the corresponding *gem*-dibromo- $\gamma$ -lactam (Equation (90)). The product is obtained in good yields and the by-products are easily removed by a simple DBU work-up <2000JSC(P1)1187>.

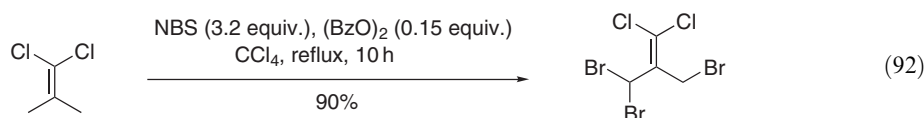
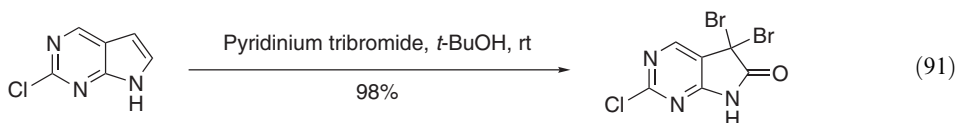


TEMPO = 2,2,6,6-tetramethyl-1-piperidinyloxy, free radical  
PMB = *p*-methoxybenzyl

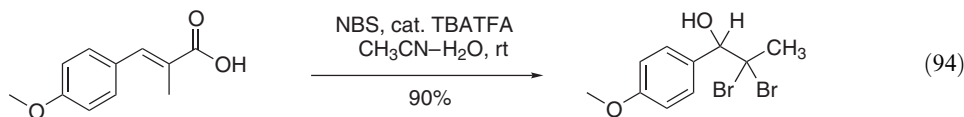
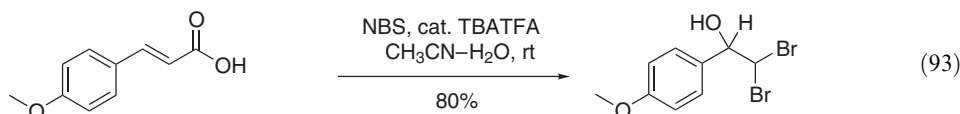
#### 4.01.4.4 Dibromoalkanes from Alkenes

Addition of hydrogen bromide or bromine to bromoalkenes is still the most common method to produce *gem*-dibromo compounds. Valuable examples of these methods have been presented by Hill (COFGT (1995)).

Dibromodiazaoxindoles can be prepared from pyrimidines by treatment with pyridinium tribromide in *t*-butanol (Equation (91)) <2001TL999>. Radical allylic bromination of 1,1-dibromo-2-methylpropene with NBS produces exclusively 3,3-dibromo-2-(bromomethyl)-1,1-dichloroprop-1-ene (Equation (92)) <2000S139>. It is interesting that treatment with an excess of brominating reagent did not produce the expected bis(*gem*-dibromo) compound.

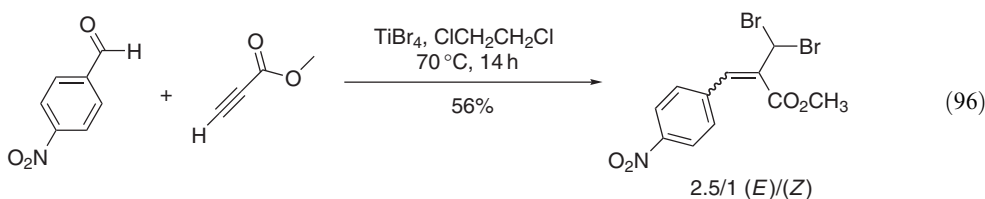
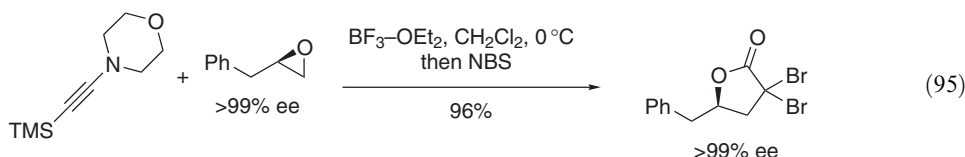


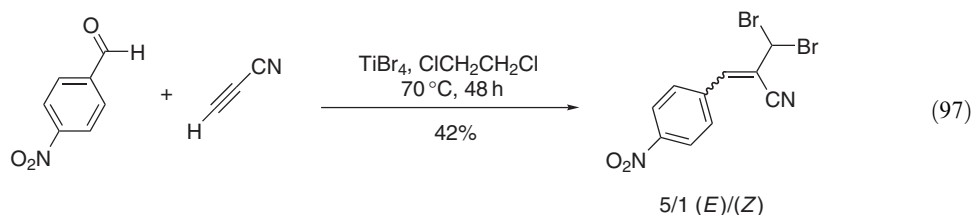
The reaction of  $\alpha,\beta$ -unsaturated aromatic carboxylic acids with 2 equiv. of NBS affords the corresponding  $\alpha,\alpha$ -dibromomethylbenzyl alcohols <2000T1396>. This Hunsdiecker-type halodecarboxylation reaction is catalyzed by TBATFA under mild aqueous conditions (Equations (93) and (94)). This practical method is suitable for the preparation of  $\alpha,\alpha$ -difluoro- and  $\alpha,\alpha$ -iodomethylbenzyl alcohols when the corresponding *N*-halosuccinimide is employed (see Sections 4.01.2.4 and 4.01.5.3). Interestingly, the corresponding (*E*)-haloalkenes are obtained under anhydrous conditions.



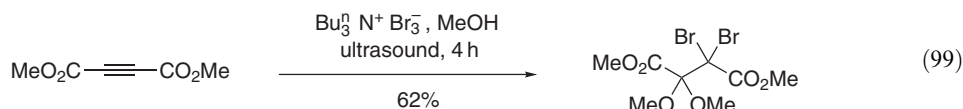
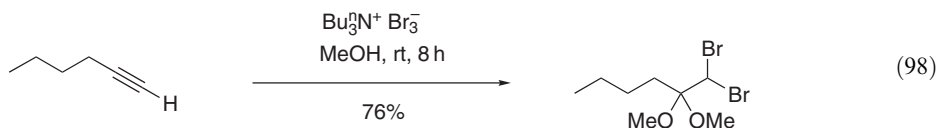
#### 4.01.4.5 Dibromoalkanes from Alkynes

Enantiomerically enriched  $\alpha,\alpha$ -dibromo- $\gamma$ -butanolides can be prepared from an electron-rich alkyne and the corresponding terminal epoxides. The Lewis acid-catalyzed reaction between an enantiomerically enriched terminal epoxide and 1-morpholino-2-trimethylsilyl acetylene produces a cyclic ketene aminal <2002JACS2456>. Sequential treatment with NBS leads to the efficient synthesis of the corresponding enantiopure  $\alpha,\alpha$ -dibromo- $\gamma$ -butanolides in excellent yields (Equation (95)). The titanium tetrabromide-promoted reaction between electron-deficient alkynes and aryl aldehydes leads to the corresponding  $\beta,\beta$ -dibromo compounds in moderate yields (Equations (96) and (97)) <2002T9063>.



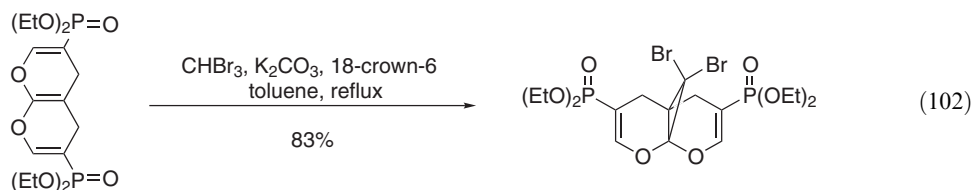
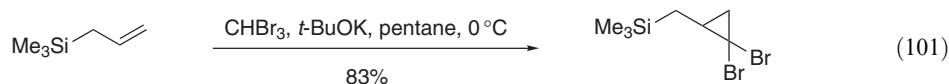
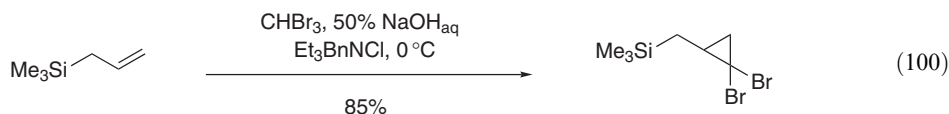


The regioselective methoxybromination of alkynes can be accomplished by employing tetrabutylammonium tribromide, which is a stable, nontoxic, and nonhygroscopic solid [<1997SC2865>](#). This method allows easy preparation of the corresponding *gem*-dibromo compounds under mild reaction conditions in moderate-to-good yields ([Equations \(98\) and \(99\)](#)).

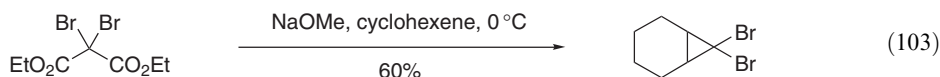


#### 4.01.4.6 Dibromoalkanes from Dibromocarbene

Bromoform is still the main source of dibromocarbene. Carbene generation and reactions can occur under anhydrous or phase-transfer conditions (COFGT (1995), [<1997TL3395>](#)). Strong bases such as potassium *t*-butoxide or potassium carbonate promote these reactions under anhydrous conditions. The most common phase-transfer conditions for the preparation of dibromocarbene use bromoform, aqueous sodium or potassium hydroxide, and a phase-transfer reagent such as TEBA ([Equations \(100\) and \(101\)](#)). These methods continue to find application in the synthesis of novel *gem*-dibromo compounds ([Equation \(102\)](#)) [<2002JOC7303>](#).



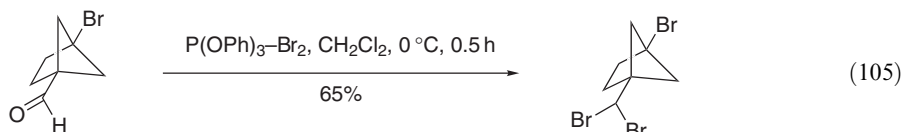
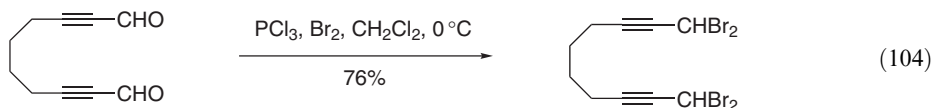
It is possible to generate dibromocarbene from ethyl tribromoacetate via a bromophilic attack of the carboethoxydibromomethyl anion to diethyl dibromomalonate (Mebane and co-workers [<1999TL1459>](#)). For example, 7,7-dibromo-bicyclo[4.1.0]heptane is the main product in the reaction of dibromomalonate and sodium methoxide in cyclohexene ([Equation \(103\)](#)).



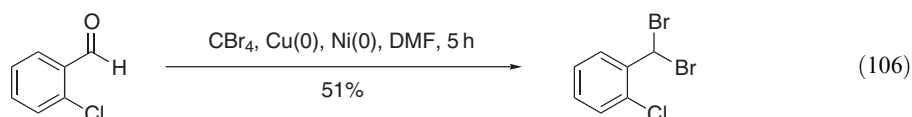


#### 4.01.4.7 Dibromoalkanes from Aldehydes and Ketones

The conversion of aldehydes and ketones to dibromoalkanes by phosphorus pentabromide is still a widely used synthetic protocol. Similar reagents such as  $PBr_3$  and  $PCl_3Br_2$  are also employed for the same purpose (Equation (104)) <2002JOC5369>. Most of these reagents are toxic and/or moisture sensitive. A variation to these protocols involves the use of triphenyl phosphite—bromine reagent (Equation (105)) <2002CEJ4506>.



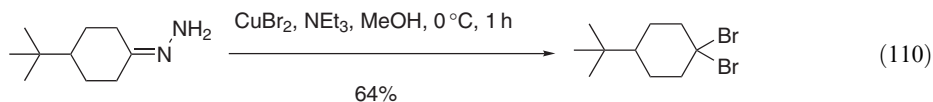
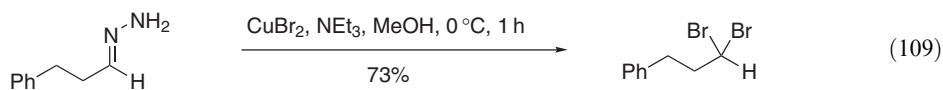
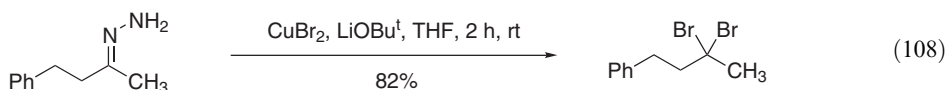
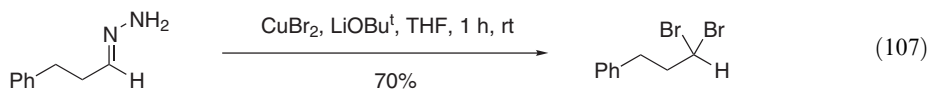
Benzyl dibromides can be prepared by reaction of the aryl aldehyde with a Vilsmeier-type reagent formed *in situ* by reduction of carbon tetrachloride (Equation (106)). The reduction is promoted by a combination of copper(0) and nickel(0) in DMF solvent at 60 °C. The limitations of this protocol are that it is exclusive to benzaldehydes and that it uses excess amounts of Cu(0)/Ni(0).



#### 4.01.4.8 Dibromoalkanes from Imines

Aliphatic *gem*-dibromide compounds can be produced from a copper(II) bromide-promoted oxidation of hydrazones <1997T557>. The hydrazones are easily prepared from the corresponding aldehyde or ketone with hydrazine hydrate in the presence of 4 Å molecular sieves.

Treatment of hydrazones with copper(II) bromide—lithium *t*-butoxide in THF produces *gem*-dibromides in moderate yields (Equations (107) and (108)). A variation of this method simply consists of using copper(II) bromide—triethylamine in methanol (Equations (109) and (110)). This procedure proved to be practical and more efficient than the copper(II) bromide—lithium *t*-butoxide oxidative system. Analogously, the use of copper(II) chloride leads to *gem*-dichloro compounds (see Section 4.01.3.8).



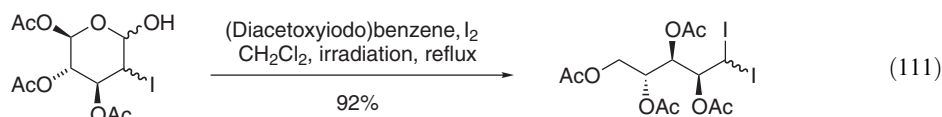
### 4.01.5 DIIDOALKANES— $R^1R^2Cl_2$

Methods for the preparation and isolation of *gem*-diiodo compounds are limited mostly due to the relative instability of the *gem*-diiodo functional group compared to the other *gem*-dihalo species. Hill (COFGT (1995)) should be consulted for common methods for the preparation of *gem*-diiodo compounds.

#### 4.01.5.1 Diiodoalkanes from Alkanes

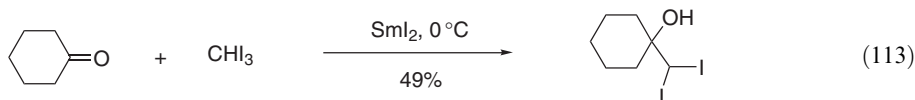
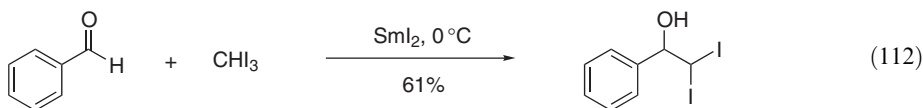
Chiral 1,1-diiodo compounds can be prepared from 2-deoxy-2-iodo-sugars via an alkoxy radical fragmentation reaction. This reaction is promoted by (diacetoxyiodo)benzene and iodine under irradiation with two 80 W tungsten filament lamps <2001AG(E)2326>.

The corresponding *gem*-diiodo compounds are produced in high yields under mild conditions that are compatible with most common protecting groups. This method allows the preparation of 1-iodo-1-halo compounds from the corresponding 2-deoxy-2-halo-sugar (Equation (111)).



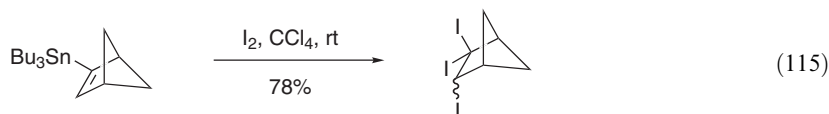
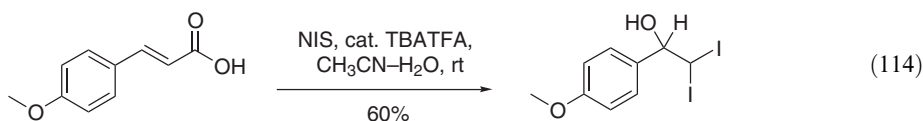
#### 4.01.5.2 Diiodoalkanes from Trihaloalkanes

Diiodomethylation of carbonyl compounds provides an entry into  $\beta,\beta$ -diiodoalkanol. This transformation can be easily carried out by using diiodomethylsamarium (Equations (112) and (113)), which is prepared *in situ* from iodoform and samarium diiodide <1998TL1409>.



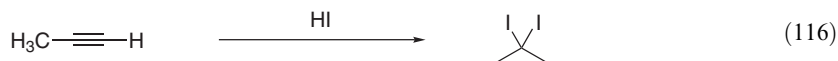
#### 4.01.5.3 Diiodoalkanes from Alkenes

The reaction of  $\alpha,\beta$ -unsaturated aromatic carboxylic acids with 2 equiv. of *N*-iodosuccinimide (NIS) affords the corresponding  $\alpha,\alpha$ -diiodomethylbenzyl alcohols <2000T1396>. This Hunsdiecker-type halodecarboxylation reaction is catalyzed by TBATFA under mild aqueous conditions (Equation (114)). This practical method is suitable for the preparation of  $\alpha,\alpha$ -difluoro- and  $\alpha,\alpha$ -chloromethylbenzyl alcohols when the corresponding *N*-halosuccinimide is employed (see Sections 4.01.2.4 and 4.01.3.4). Interestingly, the corresponding (*E*)-haloalkenes are obtained under anhydrous conditions. Simple 1,1,2-triiodo compounds can be prepared by treatment of the corresponding vinylstannane with iodine in carbon tetrachloride (Equation (115)) <2001JACS1768>.

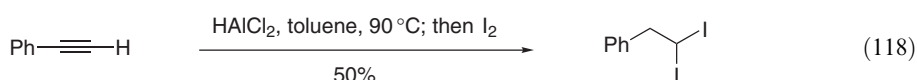
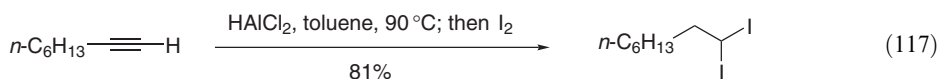


#### 4.01.5.4 Diiodoalkanes from Alkynes

As is well documented in the literature, 2 equiv. of hydrogen iodide adds to terminal alkynes to produce diiodoalkanes (see Hill (COFGT 1995)). In this case, diiodination occurs at the internal alkynyl carbon (Equation (116)). In order to achieve diiodination at the terminal alkynyl carbon, Marek and co-workers have developed a practical method for the synthesis of 1,1-diiodoalkanes from the corresponding alkynes <1999CC2207>.



Treatment of the alkynes with diisobutylaluminum hydride leads to corresponding 1,1-bis(diisobutylalumino)alkanes, which upon reaction with iodine produces the desired *gem*-diiodo compounds in good yields (Equations (117) and (118)).

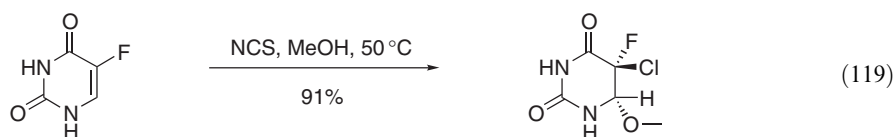


#### 4.01.6 FLUOROHALOALKANES— $R^1R^2CFHal$

##### 4.01.6.1 Chlorofluoroalkanes— $R^1R^2CFCI$

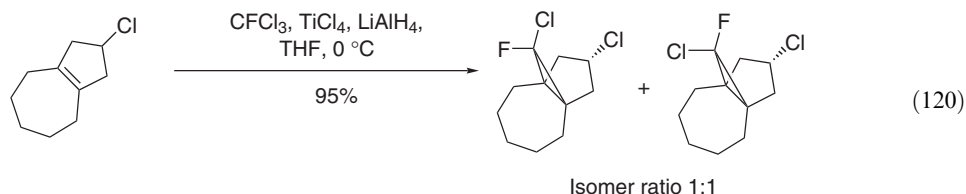
###### 4.01.6.1.1 Chlorofluoroalkanes from alkenes

The reaction of 5-fluorouracil with NCS produces highly functionalized 5-chloro-5-fluoro-5,6-dihydrouracils in high yields <1998JCS(P1)3145>. When the reaction is carried out in methanol, 5-chloro-5-fluoro-6-methoxy-5,6-dihydrouracil is obtained as a single stereoisomer (Equation (119)).



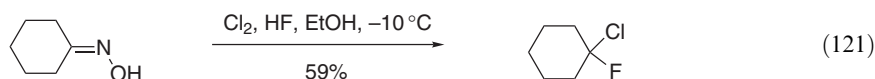
###### 4.01.6.1.2 Fluorochloroalkanes from chlorofluorocarbene

Chlorofluorocarbene has been generated from trichlorofluoromethane by reduction with low-valent titanium (Ti[0]) <2001JOC1216>. Addition of chlorofluorocarbene to alkenes yields the corresponding chlorofluoromethyl compound (Equation (120)).



###### 4.01.6.1.3 Fluorochloroalkanes from imines

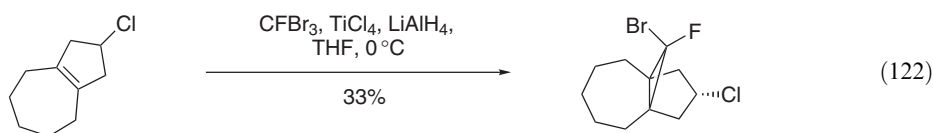
Oximes have been transformed into chlorofluoromethyl groups by treatment with chlorine in hydrogen fluoride as a medium. Complex mixtures of *gem*-dihalo compounds are usually obtained from these reactions, but their solvent-dependent product distribution can be controlled to produce the desired product (Equation (121)) <1995JFC(70)207>.



#### 4.01.6.2 Bromofluoroalkanes— $R^1R^2CFBr$

##### 4.01.6.2.1 Bromofluoroalkanes from bromofluorocarbene

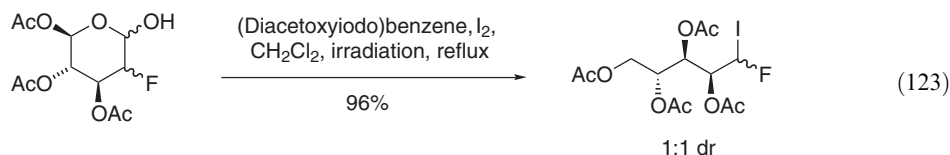
Bromofluorocarbene has been generated from tribromofluoromethane by reduction with low-valent titanium ( $Ti[0]$ ) [<2001JOC1216>](#). Addition of bromofluorocarbene to alkenes yields the corresponding bromofluoromethyl compound ([Equation \(122\)](#)).



#### 4.01.6.3 Fluoroiodoalkanes— $R^1R^2CFI$

##### 4.01.6.3.1 Fluoroiodoalkanes from alkanes

Chiral 1-fluoro-1-iodo compounds can be prepared from 2-deoxy-2-fluoro-sugars via an alkoxy radical fragmentation reaction. This reaction is promoted by (diacetoxyiodo)benzene and iodine under irradiation with two 80 W tungsten filament lamps ([Equation \(123\)](#)) [<2001AG\(E\)2326>](#).

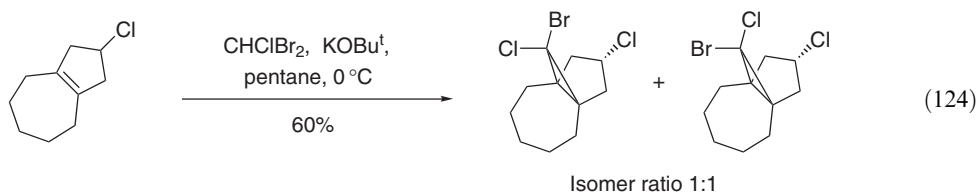


#### 4.01.7 CHLOROHALOALKANES— $R^1R^2CClHal$

##### 4.01.7.1 Chlorobromoalkanes— $R^1R^2CClBr$

##### 4.01.7.1.1 Chlorobromoalkanes from bromochlorocarbene

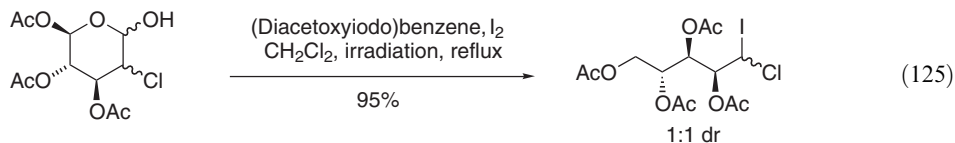
Bromochlorocarbene has been generated from dibromochloromethane by deprotonation with potassium *t*-butoxide in anhydrous solvent [<2001JOC1216>](#). Addition of bromochlorocarbene to alkenes yields the corresponding bromochloromethyl compound ([Equation \(124\)](#)).



#### 4.01.7.2 Chloroiodoalkanes— $R^1R^2CClI$

##### 4.01.7.2.1 Chloroiodoalkanes from alkanes

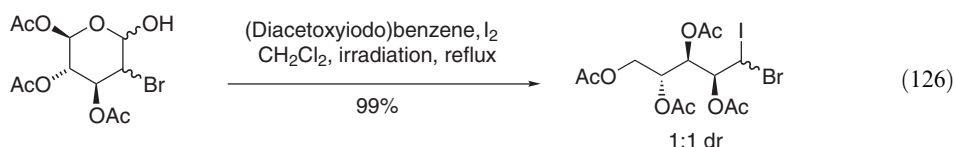
Chiral 1-chloro-1-iodo compounds can be prepared from 2-deoxy-2-chloro-sugars via an alkoxy radical fragmentation reaction (Equation (125)). This reaction is promoted by (diacetoxyiodo)benzene and iodine under irradiation with two 80 W tungsten filament lamps <2001AG(E)2326>.



#### 4.01.8 BROMOiodoALKANES— $R^1R^2CBrI$

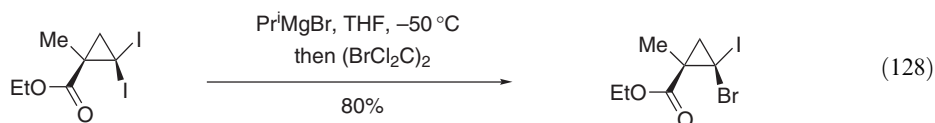
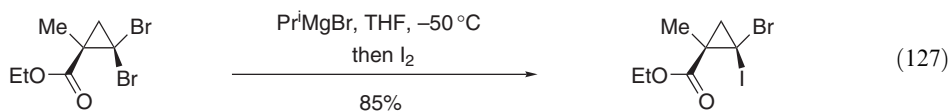
##### 4.01.8.1 Bromoiodoalkanes from Alkanes

Chiral 1-bromo-1-iodo compounds can be prepared from 2-deoxy-2-bromo-sugars via an alkoxy radical fragmentation reaction (Equation (126)). This reaction is promoted by (diacetoxyiodo)benzene and iodine under irradiation with two 80 W tungsten filament lamps <2001AG(E)2326>.



##### 4.01.8.2 Bromoiodoalkanes from Dihaloalkanes

Iodobromocyclopropanes have been stereoselectively synthesized in good yields by trapping a magnesium carbenoid prepared from ethyl 2,2-dihalo-1-methyl-cyclopropanecarboxylate (Equations (127) and (128)) <2002AG(E)351>.



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**Biographical sketch**

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## 4.02

# Functions Incorporating a Halogen and a Chalcogen

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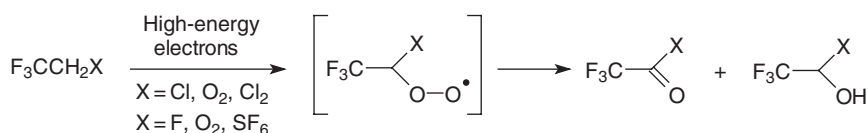
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### 4.02.1 HALOGEN AND OXYGEN DERIVATIVES— $R_2^1CHal(OR^2)$

#### 4.02.1.1 $\alpha$ -Haloalcohols (Geminal Halohydrins)— $R_2CHal(OH)$

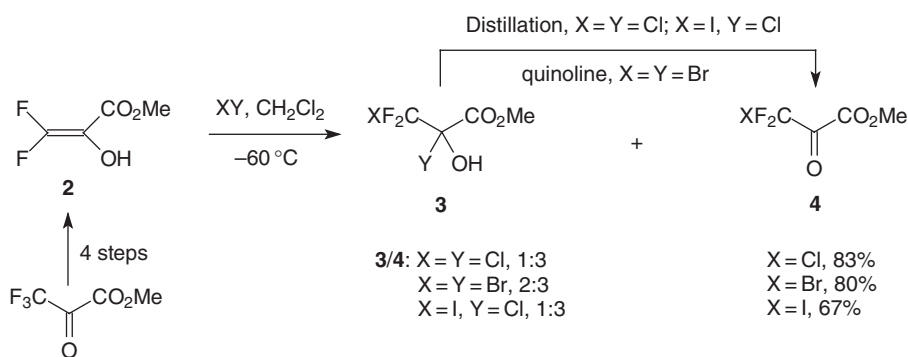
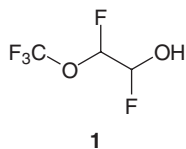
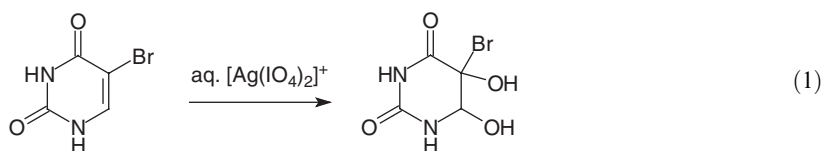
The chemistry of this functional group is dominated by the fact that it is inherently unstable relative to the corresponding ketone and hydrogen halide, and so claims in respect of the synthesis of molecules containing it should be viewed with scepticism unless supported by

appropriate spectroscopic evidence. Much of the work relating to the preparation of simple  $\alpha$ -haloalcohols has been carried out in the gas phase. Under these conditions it is claimed that the reaction of hydrogen fluoride with formaldehyde in the presence of formic acid produces fluoromethanol <1998MI2146>, and that the near UV laser photolysis of a mixture of dichloromethane, methane, and oxygen at 298 °C results in the formation of a range of products including chloromethanol <1996JPC14372>. This  $\alpha$ -chloroalcohol has also been prepared by the UV irradiation of gaseous mixtures of methanol, chlorine, and nitrogen at room temperature, and in this case it has been characterized using IR spectroscopy and the kinetics of its decay to HCl and formaldehyde have been studied <1999MI776>. A number of more highly halogenated  $\alpha$ -haloalcohols have also been prepared. The photocatalytic oxidation of trichloroethene on the surface of BaY zeolite coated optical fibres using visible light gives a range of products which includes 1,2,2-trichloroethanol <2000JA404>. The  $\alpha$ -haloalcohol was found to be “unstable on storage.” The use of high-energy electrons to produce radicals has found application in the gas phase synthesis of some  $\alpha$ -haloalcohols (Scheme 1). Thus irradiation of a gaseous mixture of 2-chloro-1,1,1-trifluoroethane,  $\text{Cl}_2$ , and  $\text{O}_2$  produces a peroxy radical which in turn forms a product mixture containing 1-chloro-2,2,2-trifluoroethanol <1995JPC13437> (Scheme 1,  $\text{X} = \text{Cl}$ ). In the same way irradiation of a mixture of 1,1,1,2-tetrafluoroethane, oxygen, and sulfur hexafluoride gives 1,2,2,2-tetrafluoroethanol <1997MI673> (Scheme 1,  $\text{X} = \text{F}$ ).

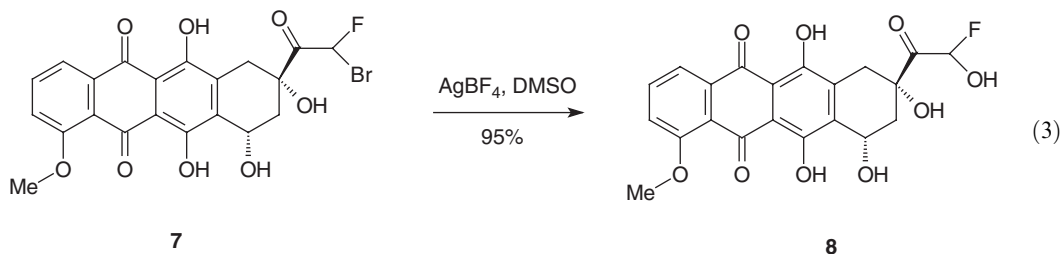
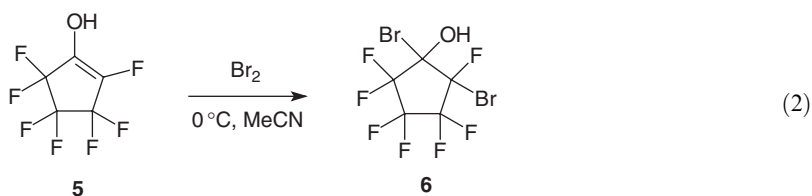


Scheme 1

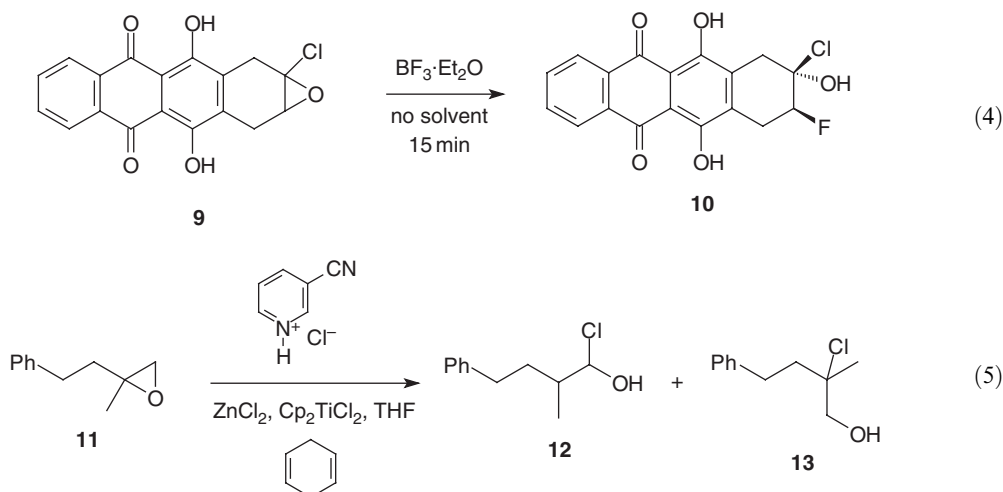
The synthesis of a number of more highly functionalized  $\alpha$ -haloalcohols has been reported. The ultrasonically mediated oxidation of vinyl bromide with potassium permanganate was found to give an 88% yield of 1-bromoethane-1,2-diol in 15 min, but spectroscopic data for the product were not provided <1998TL7463>. In a similar fashion the oxidation of the vinyl bromide component of 5-bromouracil with aqueous diperiodoargentate(III) leads to the formation of a geminal bromohydrin <1998IJC(A)1106> (Equation (1)). The synthesis of the highly fluorinated compound **1** has been claimed but again no physical data (other than boiling point), and in this case no experimental details either, were given <2001MI897>. It has been suggested <1961JA4670> that perfluorination and ring strain can contribute to make  $\alpha$ -haloalcohols more stable relative to the corresponding ketone and hydrogen halide. An  $\alpha$ -carbonyl group may also play a stabilizing role, as cyclic 2-chloro-2-hydroxy-1,3-diketones are among the best characterized representatives <1981CB1951> of this particular functional group. One or more of these structural features are present in many of the more satisfactorily characterized  $\alpha$ -haloalcohols which have been synthesized recently. For example, the addition of a halogen to the metastable fluorinated enol **2**, which can be prepared from readily available methyl 3,3,3-trifluoropyruvate, gives a mixture of the  $\alpha$ -haloalcohol **3** and the trihalopyruvate **4** (Scheme 2) <1996JOC7521>. In this case complete conversion of **3** to **4** requires distillation where the halogen used is  $\text{Cl}_2$  or  $\text{ICl}$ , and treatment with quinoline where  $\text{Br}_2$  is involved. The NMR data provided for the product mixture unambiguously confirm the formation of the  $\alpha$ -haloalcohol in this case. The addition of bromine to the stable perfluorinated enol **5** leads to the formation of the  $\alpha$ -bromo alcohol **6** (Equation (2)) <1996JOC5109>. Although it could not be isolated, reverting to the enol and bromine,  $^{19}\text{F}$ -NMR data provide convincing evidence for its formation. The silver tetrafluoroborate promoted solvolysis of the bromofluoromethyl ketone **7**, giving the geminal fluorohydrin **8** which is unstable in even dilute base, is a key step in the synthesis of the anthracycline antibiotic 14-fluorodoxorubicin (Equation (3)) <2002TL2867>.



Scheme 2



Two groups have reported that the ring opening of epoxides can lead to the formation of  $\alpha$ -haloalcohols. Thus the  $\text{BF}_3$ -mediated ring opening of the chloroepoxide **9** leads to the formation of the anthracyclinone **10** in which perhaps significantly the  $\alpha$ -haloalcohol again has an adjacent fluorine atom (Equation (4)) <1996G771>. However, although it has been claimed that ring opening of the epoxide **11** in a similar fashion gives a mixture of the  $\alpha$ - and  $\beta$ -haloalcohols **12** and **13**, the  $^1\text{H}$ -NMR data provided are not consistent with the structure of the former (Equation (5)) <1998JA12849>.



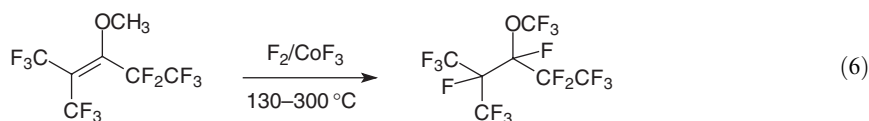
#### 4.02.1.2 $\alpha$ -Haloethers— $R_2^1CHal(OR^2)$

As would be expected on the basis of their reactivity, many  $\alpha$ -haloethers (geminal halohydrin ethers) possess limited thermal stability and are susceptible to hydrolysis. A number of low molecular weight  $\alpha$ -haloethers are lachrymatory and linked to the fact that they are strong alkylating agents, concerns have been expressed about the carcinogenic character of others [\[1969MI481\]](#).

##### 4.02.1.2.1 $\alpha$ -Fluoroethers— $R_2^1CF(OR^2)$

There has been an extremely high level of activity over the last few years in areas relating to the synthesis of  $\alpha$ -fluoroethers. This activity is due in the first instance to the importance of H or OH replacement by F as a strategy for the enhancement of biological activity. It is also due to the fact that perfluorinated ethers are materials of considerable industrial importance, finding use, for example, as lubricants, inert fluids, and in the biomedical area [\[B-1994MI463\]](#), and that partially fluorinated ethers have been considered as CFC replacements [\[1996CT44\]](#). As a result of these interests, a very large amount of work relating to the synthesis of fluoroethers, using a wide range of techniques, has been carried out. A relatively large number of the compounds prepared contain the  $\alpha$ -fluoroether functional group.

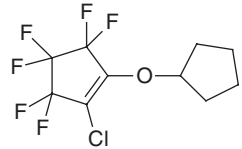
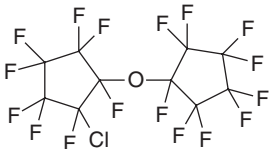
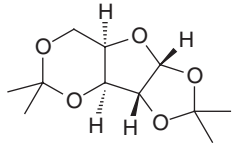
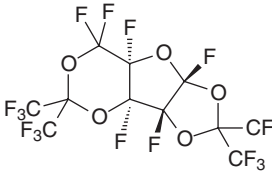
Although electrochemical fluorination in anhydrous hydrogen fluoride (see below) and reaction with higher transition metal fluorides such as  $CoF_3$  (Equation (6)) [\[1996JFC\(80\)86\]](#) are the principal methods used in industry for the production of perfluoro organic compounds, interest in the use of elemental fluorine as a reagent for this purpose has increased in recent years (Table 1). The safety problems associated with the use of fluorine however, which include the extremely exothermic nature of its reaction with C—H bonds, present problems in relation to scale up. The use of microreactors for elemental fluorine (Table 1, entry 1) has been described and this may encourage further developments in the area. Liquid phase reactions (Table 1, entries 2 and 3) and the use of UV light to promote fluorination (Table 1, entries 4 and 5) have also been reported. The first synthesis of a perfluorinated carbohydrate has been carried out using the so-called LaMar direct fluorination procedure (Table 1, entry 6). This method was also used to prepare a range of perfluoro crown ethers including the 24-crown-8 **14**, which was obtained as a mixture of stereoisomers (Equation (7)) [\[1994JA5172\]](#).

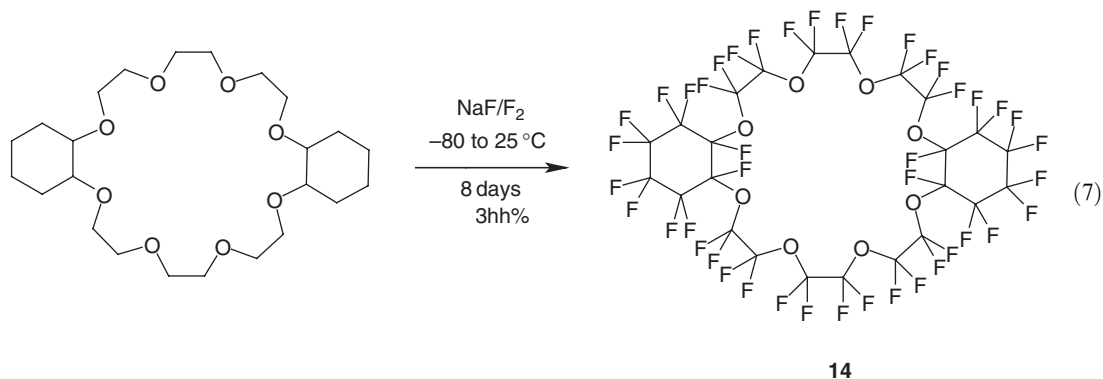


**Table 1** Direct fluorination route to  $\alpha$ -fluoroethers

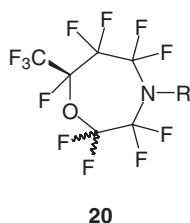
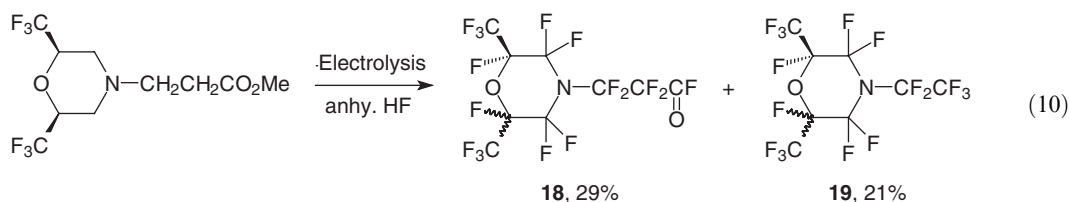
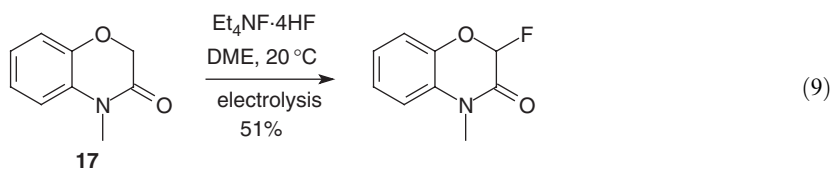
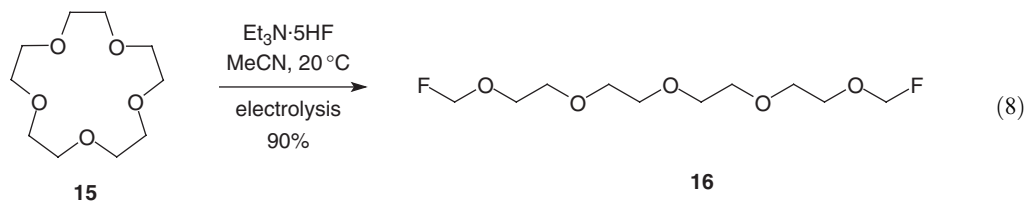
Entry	Reactant	Product	Conditions	Yield (%)	References
1			F <sub>2</sub> /N <sub>2</sub> (i) rt; (ii) 280 °C	91	<1999CC883>
2			F <sub>2</sub> -30 to 80 °C 14 h	93	<1999JFC(94)157>
3			20% F <sub>2</sub> /N <sub>2</sub> F <sub>2</sub> ClCCCl <sub>2</sub> F 20–40 °C 0.2 MPa	78	<2001JFC(112)109>
4			20% F <sub>2</sub> /N <sub>2</sub> hν 120 h	73	<2000JFC(101)97>

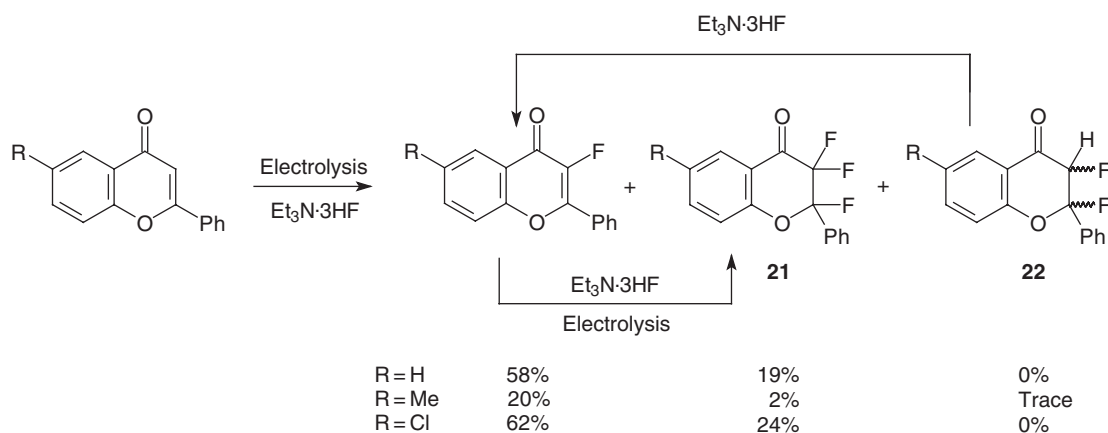
**Table 1** (continued)

<i>Entry</i>	<i>Reactant</i>	<i>Product</i>	<i>Conditions</i>	<i>Yield (%)</i>	<i>References</i>
5			F <sub>2</sub> , <i>hν</i> CFC solvent −40 to −28 °C 12 h	29	<a href="#">&lt;1995JFC(75)197&gt;</a>
6			F <sub>2</sub> /N <sub>2</sub> NaF 15 days −90 to 40 °C	20	<a href="#">&lt;1999JOC8127&gt;</a>



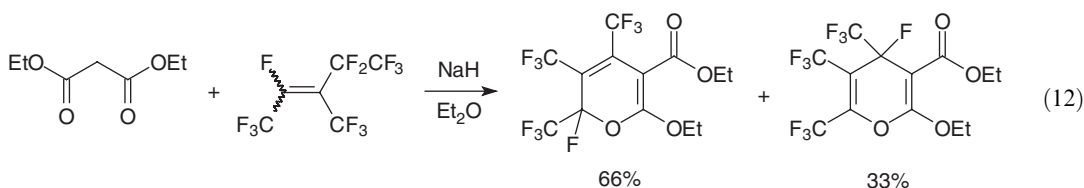
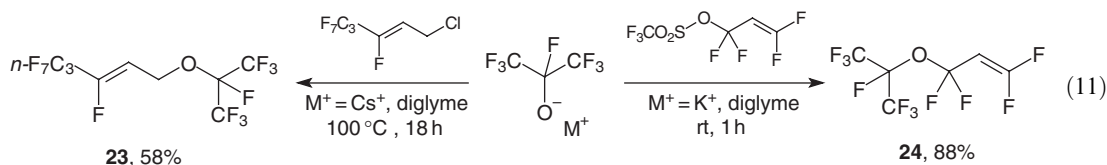
Electrochemical fluorination is an attractive alternative to the use of elemental fluorine for the replacement of hydrogen in molecules which are sufficiently polar to be soluble in anhydrous hydrogen fluoride. The method does not involve the production of fluorine, the organic solute being fluorinated at the anode, and it has been used to prepare primary, secondary, and tertiary  $\alpha$ -fluoroethers. The crown ether **15** reacts under these conditions to give bis- $\alpha$ -fluoromethyl ether **16** (Equation (8)) <2000T8877> and the benzoxazinone **17** undergoes fluorination in the 2-position (Equation (9)) <2001SL1644>. The electrochemical fluorination of a number of esters carrying morpholine substituents leads to the formation of mixtures of products, which include a number of  $\alpha$ -fluoroethers <1998JFC(87)193, 2001JFC(111)115>. Thus, methyl *cis*-dimethylmorpholinopropionate gives a product mixture which contains the  $\alpha$ -fluoroethers **18** and **19** (Equation (10)), and methyl *cis*-dimethylmorpholinoacetate, in addition to the corresponding acid fluoride (47%) and *N*-perfluoroalkyl derivative (2%), gives a small amount of the oxazepan **20**. The electrochemical fluorination of a number of biologically interesting flavones (Scheme 3) resulted in the formation of significant amounts of  $\alpha$ -fluoroether **21**, together with traces of a second, **22**, which was unstable under the reaction conditions <1999JOC3346>.





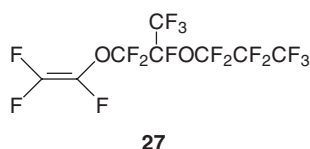
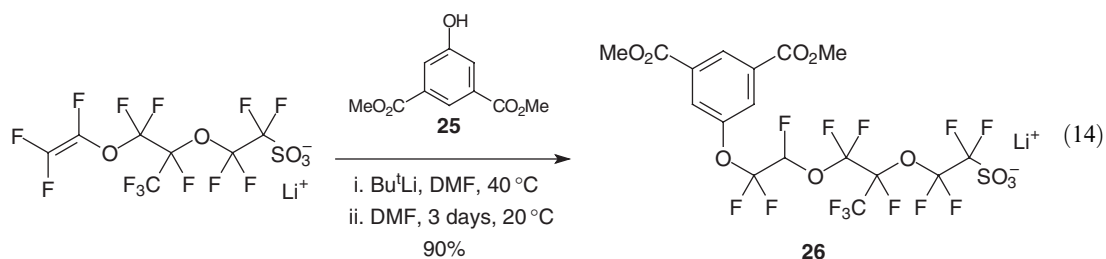
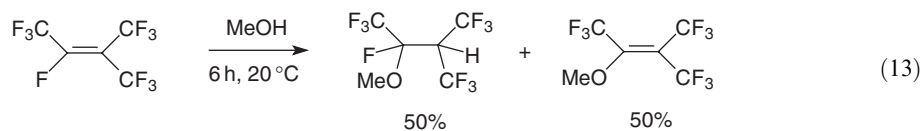
Scheme 3

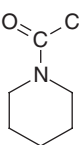
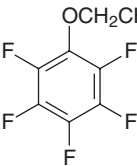
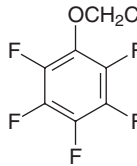
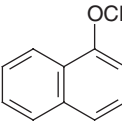
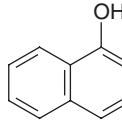
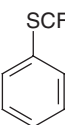
A number of substitution reactions have been used to assemble the  $\alpha$ -fluoroether functional group. Thus, perfluoroisopropoxide displaces chloride and triflate anions (Equation (11)) to give the ethers **23** <1995JOC3423> and **24** <1995JFC(73)17>, respectively. The nucleophilic displacement of fluorine from  $\text{CF}_2$  groups by ethoxide <1994JFC(66)39, 1998JFC(91)221>, *t*-butoxide <1996JOC5109>, and malonate anions (Equation (12)) <1998JFC(88)169> has also been used synthetically.



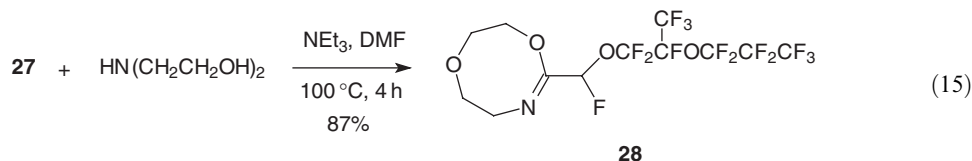
A wide variety of addition reactions have been used to produce  $\alpha$ -fluoroethers of equally diverse structural types. The fluoroalkenes which are often involved are strongly electron deficient and so the nucleophilic addition of  $\text{X}-\text{H}$  bonds ( $\text{X} = \text{N}, \text{O}, \text{S}$ ) occurs readily. Although the uncatalyzed addition of methanol to such alkenes has been reported (Equation (13)) <2000JFC(104)239>, these reactions usually involve the prior generation of the appropriate anion. In this way the phenoxide anion derived from **25** (Equation (14)) affords the  $\alpha$ -fluoroether **26** <2000JFC(105)129>. The regiochemistry of the addition to trifluorovinyl ethers is controlled not only by the inductive effect of the fluorine substituents but also by the stabilization of the intermediate carbanion by negative hyperconjugation <B-1995MI729>. The perfluoroalkyl vinyl ether **27** is easily synthesized <2000JFC(106)13> and is also commercially available, and so has been used as a model compound in a number of studies of this type of addition reaction (Table 2). Primary and secondary amines react directly with **27**, forming imines, amine adducts, or the corresponding amides according to the reaction conditions or separation technique employed (Table 2, entry 1). In one case the use of a polyfunctional amine, diethanolamine, results in the formation of the novel cyclized product **28** (Equation (15)) <2000JFC(106)13>. Alcohols, phenols, and thiols must first be converted to their anions (Table 2, entries 2–7) and although a range of solvents can be employed for the addition reaction, alternatively the use of THF or dioxane is reported to lead to the formation of  $\alpha$ -substituted tetrahydrofurans (THFs) and dioxanes <1999MI125>.



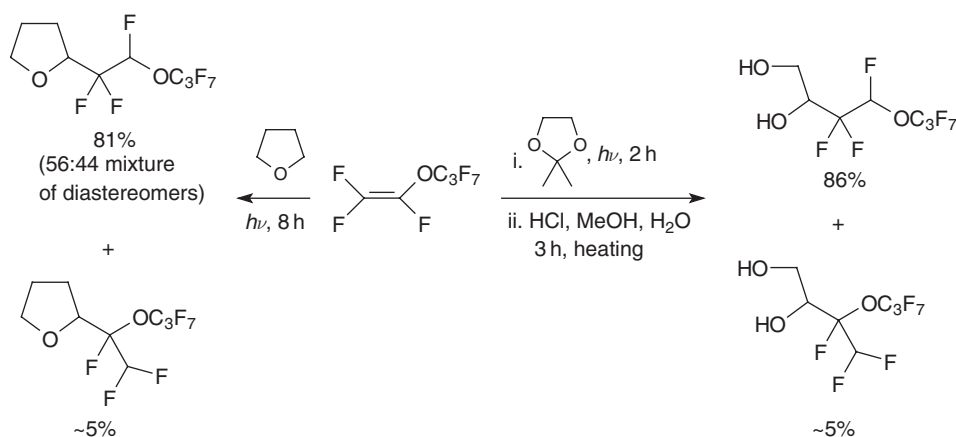

 Table 2 Nucleophilic addition reactions of **27**

Entry	Product	Conditions	Yield (%)	References
1		i. Piperidine, THF, 0–20 °C ii. H <sub>2</sub> O	63	<1999ZPK1345>
2	MeOCF <sub>2</sub> CHFOR <sub>f</sub>	MeONa, 20 °C	54	<2000JFC(106)13>
3	Me(CH <sub>2</sub> ) <sub>15</sub> OCF <sub>2</sub> CHFOR <sub>f</sub>	Me(CH <sub>2</sub> ) <sub>15</sub> OH, Bu <sup>n</sup> Li, THF/hexane, 5 days, 20 °C	41	<2002JFC(117)149>
4	N(CH <sub>2</sub> CH <sub>2</sub> OCF <sub>2</sub> CHFOR <sub>f</sub> ) <sub>3</sub>	N(CH <sub>2</sub> CH <sub>2</sub> OH) <sub>3</sub> , KOH, DMSO	80	<2000JFC(106)13>
5		 , KOH, DMSO	67	<2000JFC(106)13>
6		 , Bu <sup>n</sup> Li, THF/hexane, 5 days, 20 °C	61	<2002JFC(117)149>
7		i. PhSH, Bu <sup>n</sup> Li, THF/hexane, 10 min, –70 °C ii. THF, 122 h, –75 to 20 °C	55	<2002JFC(117)149>

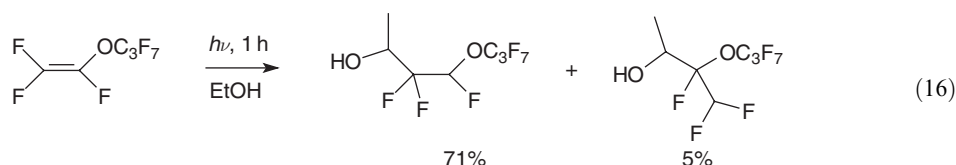
<sup>a</sup> R<sub>f</sub> = F<sub>3</sub>CCF<sub>2</sub>CF<sub>2</sub>OCF(CF<sub>3</sub>)CF<sub>2</sub>.



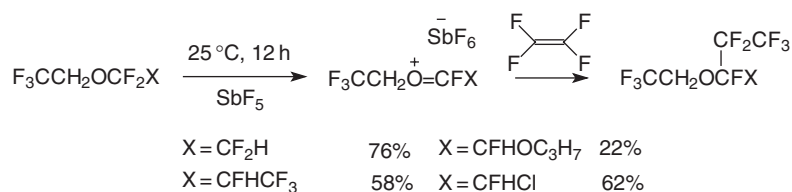
$\alpha$ -Substituted THFs, which again are  $\alpha$ -fluoroethers, can also be formed by the highly regio-selective addition of radicals generated photochemically or using dibenzoyl peroxide from THFs and dioxolanes (Scheme 4) <1996JFC(80)125, 1999JFC(94)141>. Hydrolysis of the initially formed dioxolanes gives the corresponding diols (Scheme 4).  $\alpha$ -Fluoroethers have also been produced by the photochemical addition of methanol, and primary and secondary alcohols to perfluorovinyl ethers (Equation (16)) <1996JFC(80)135>.



Scheme 4

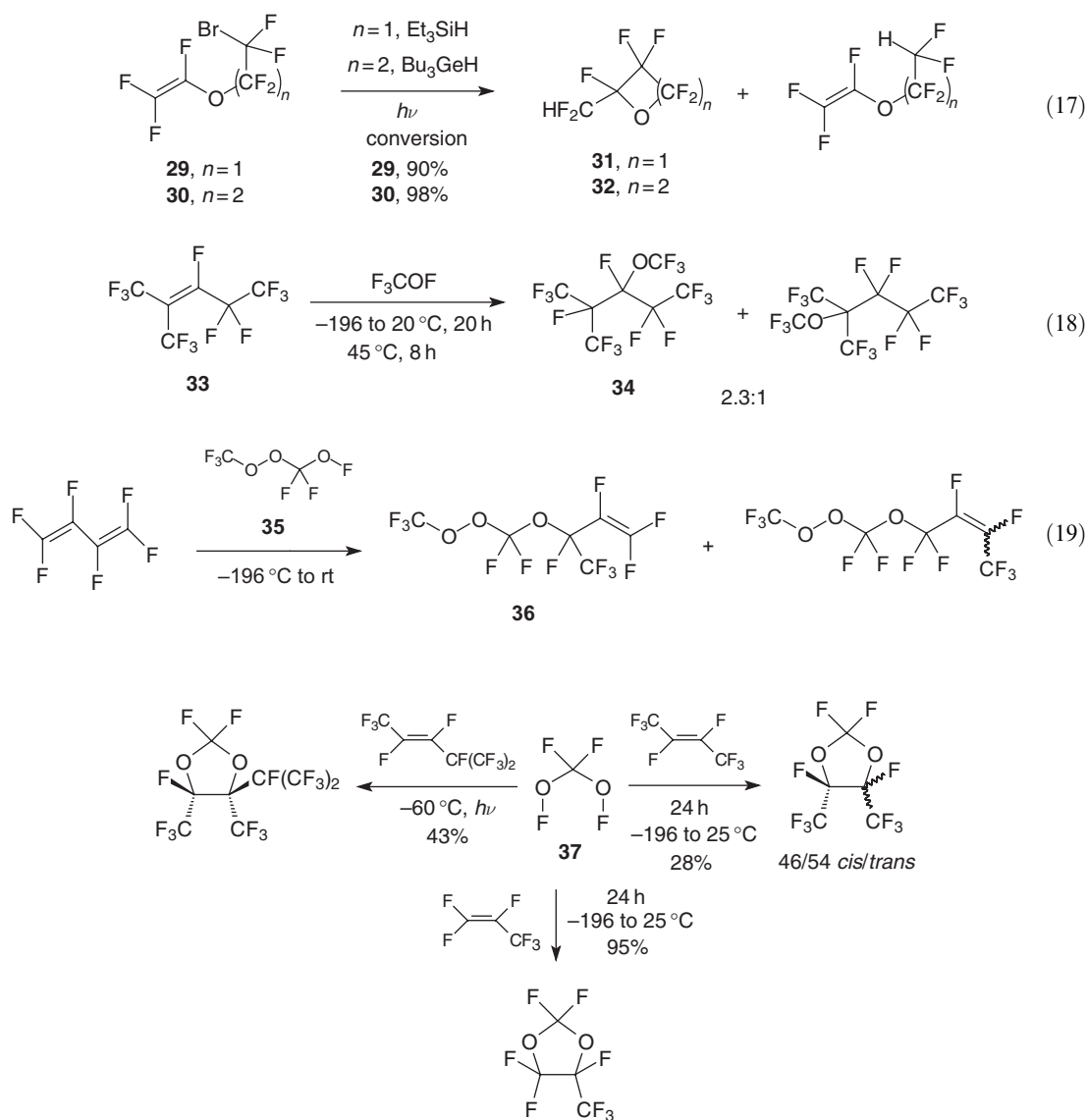


The stability of polyfluorinated ethers in the presence of Lewis acids is critically dependent on their structure. Perfluorinated ethers are stable up to quite high temperatures whereas partially fluorinated ethers react at room temperature, sometimes undergoing a cleavage-based decomposition reaction. Ethers of the type  $\text{R}_f\text{CH}_2\text{OCF}_2\text{R}_f$  are more stable and in the presence of  $\text{SbF}_5$  participate in an addition reaction with tetrafluoroethene or 1,2-difluoro-1,2-dichloroethene resulting in the replacement of one of the fluorine atoms on the  $\alpha$ -carbon and the generation of  $\alpha$ -fluoroethers (Scheme 5) <2001JFC(112)117>.



Scheme 5

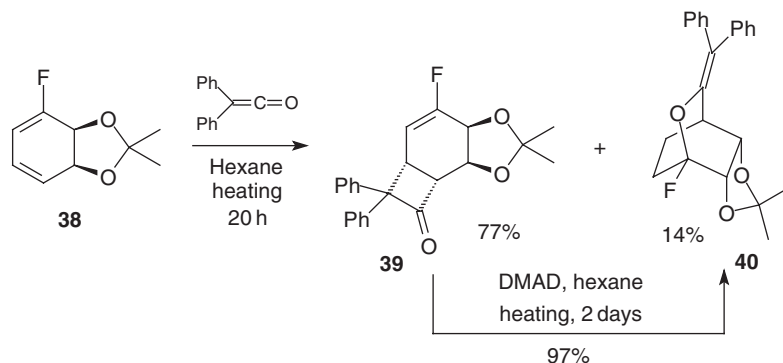
A number of  $\alpha$ -fluoroether-forming reactions which involve the addition of radicals to alkenes have been reported. Photochemically generated radicals are involved in the cyclization of the  $\omega$ -bromo vinyl ethers **29** <1994JA4521> and **30** <1996JOC4824>, which give the cyclic  $\alpha$ -fluoroethers **31** and **32**, respectively (Equation (17)). In both cases a significant amount of reduction also occurs, the cyclization/reduction ratio being, for example, 1:2.71 in the case of **30**. The reaction of **29** was remarkable in that no five-membered ring product was obtained, a result which is in contrast to those reported previously <1971JCS(C)3959>. The homolytic cleavage of the O—F bond in hypofluorites has also been used as a source of radicals. Thus, trifluoromethylhypofluorite reacts with the perfluoroalkene **33** to give a mixture of regioisomers which includes the  $\alpha$ -fluoroether **34** (Equation (18)) <1995TL3543>. The reaction of the peroxy hypofluorite **35** with perfluorobutadiene gives the  $\alpha$ -fluoroether **36**, the result of a regioselective 1,2-addition, together with a mixture of 1,4-addition products (Equation (19)) <1995JFC(74)83>. The bis-hypofluorite **37** behaves in an analogous fashion reacting with fluoroalkenes to give dioxolanes which contain the  $\alpha$ -fluoroether functional group (Scheme 6) <1995JFC(71)111>.



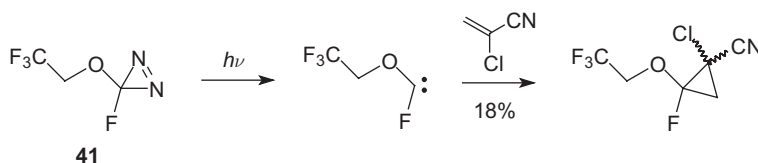
Scheme 6

Two cycloaddition reactions have been reported which allow structurally complex  $\alpha$ -fluoroethers to be prepared. The major product of the reaction of diphenyl ketene with the diene **38**

is the [2+2]-adduct **39**, with only small amounts of the  $\alpha$ -fluoroether containing [4+2]-product **40** being formed (Scheme 7). However, prolonged heating of **39** in hexane containing dimethyl acetylenedicarboxylate (DMAD) results in its essentially quantitative conversion to **40** <1996JCS(P1)1157>. The fact that irradiation of the diazirene **41** (Scheme 8) generates fluoro(trifluoroethoxy)carbene has considerably greater synthetic potential in terms of a general route for the preparation of  $\alpha$ -fluoro- $\alpha$ -cyclopropyl ethers. The carbene is nucleophilic in character and although it does not react with acrylonitrile, it does add to the more electrophilic  $\alpha$ -chloroacrylonitrile to give a 2:1 mixture of diastereomeric cyclopropanes <1993TL7549>.



Scheme 7

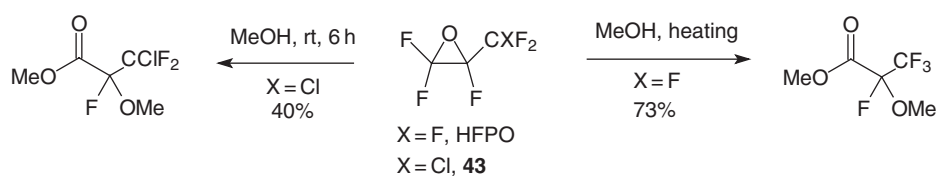


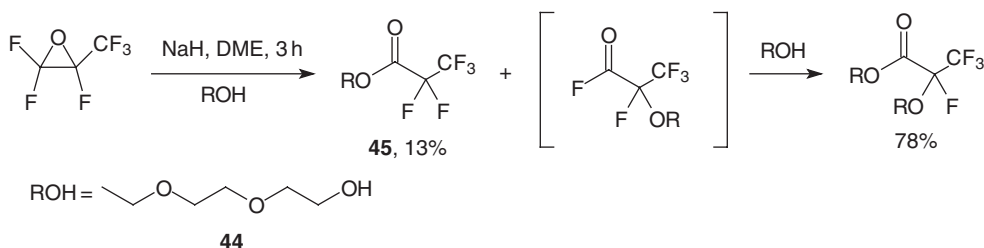
Scheme 8

Fluorocarbon epoxides are important intermediates in the preparation of fluorinated compounds for the pharmaceutical and agricultural industries, with hexafluoropropylene oxide (HFPO) being by far the most widely used. The addition of acyl fluorides to this compound or its oligomerization, both promoted by fluoride ion, have been a rich source of  $\alpha$ -fluoroethers (Table 3). In addition to the usual sources of fluoride, the ammoniumperfluorocyclobutane ylide **42** (Table 3) has also been used for this purpose to good effect <1996T9755>. The key step in these reactions is regiospecific attack by the nucleophile at the more sterically hindered ring carbon of HFPO, a process which is controlled by the electron withdrawing effect of the CF<sub>3</sub> group. A similar regiospecificity is observed in the reaction of methanol with HFPO <2002JFC(115)67> and with **43** (Scheme 9), and in the reaction of the alkoxide derived from the alcohol **44** with HFPO (Scheme 10) <1997JOC7844>, all of which give  $\alpha$ -fluoroethers. The formation of the minor product **45** (Scheme 10) is probably the result of an initial ring-opening due to regiospecific attack of fluoride in the standard way, followed by reaction of the acyl fluoride thus formed with the alkoxide. On heating to temperatures close to 200 °C, HFPO exhibits another useful property in that it fragments producing difluorocarbene. This behavior has been exploited in the formation of the  $\alpha$ -fluoroether **46** (Equation (20)) <1995JA5397>.

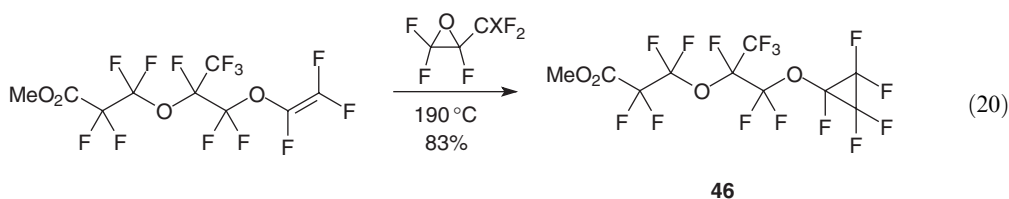
**Table 3**  $\alpha$ -Fluoroethers from hexafluoropropylene oxide

Entry	Co-reactant	Product	Conditions	References
1			KF, diglyme	<1999JFC(94)65>
2			KF, tetraglyme, 0°C, 16 h	<1995JFC(75)163>
3			CsF, tetraglyme	<2002JFC(114)51>
4			 NEt <sub>3</sub> <sup>+</sup> , MeCN, 2 h <b>42</b>	<1996T9755>
5			CsF, diglyme	<1998ZOR1786>
6			KF, MeCN	<1995MI151>
7			KF, diglyme, 30 h, 43 °C	<1995ZOR1145>

**Scheme 9**



Scheme 10



The regioselective and stereoselective introduction of a fluorine atom into a molecule continues to present a formidable synthetic challenge. A range of reagents have been developed for this purpose and of these diethylaminosulfur trifluoride (DAST) continues to be the most widely used for primary, secondary, and tertiary  $\alpha$ -fluoroethers. Its recent use has been reviewed [\[2002S2561\]](#). The selective introduction of fluorine is of particular importance in synthetic carbohydrate chemistry where glycosyl fluorides are important synthetic intermediates ([Table 4](#)). In this context using DAST generally involves the direct replacement of an anomeric OH group with a fluorine atom, a process that can occur with either inversion or retention ([Table 4](#), entry 1) of configuration, and results in the formation of what is an  $\alpha$ -fluoroether. In some cases a competing elimination reaction can be involved ([Table 4](#), entry 3). The behavior of 2-uloses is different in that reaction with DAST gives rise to difluoro derivatives. In many cases *gem*-difluoro compounds are obtained, but in others fluorination is accompanied by a 1,2-transposition leading to the formation of 1,2-difluoro compounds which also contain the  $\alpha$ -fluoroether group ([Table 4](#), entry 4). Ring contraction, again resulting in the formation of an  $\alpha$ -fluoroether, can also occur ([Table 4](#), entry 6). The conversion of a glycosyl chloride to the corresponding fluoride, with inversion of configuration, has been achieved using a combination of DAST and AgOTf [\[1996CL337, 1996MI857\]](#).

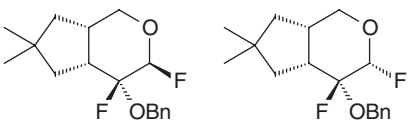
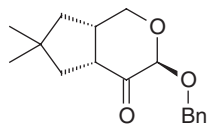
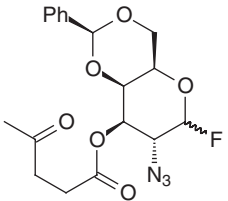
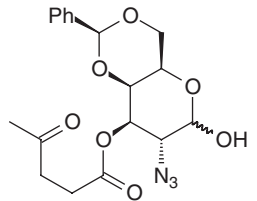
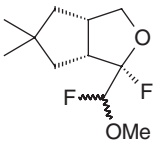
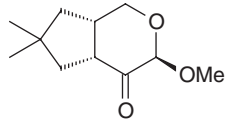
DAST has also been used with noncarbohydrate systems with, for example, the epoxy alcohol **47** undergoing exclusive C—C bond cleavage to give an  $\alpha$ -fluorovinyl ether ([Equation \(21\)](#)) [\[2001JFC\(107\)271\]](#). This reaction was subsequently developed in the context of cyclic epoxy alcohols so that it now constitutes a reasonably general method for the synthesis of cyclic  $\alpha$ -fluoroethers although they are generally formed together with an  $\alpha$ -fluoro epoxide ([Equation \(22\)](#)) [\[2002OL451\]](#). The outcome of the reaction is sensitive to the relative stereochemistry of the alcohol and the epoxide, and to the nature of the alcohol with the hydroxy cyclododecene oxide **48** giving selectively an  $\alpha$ -fluorovinyl ether **49** ([Equation \(23\)](#)). DAST has also been used in a Pummerer-type process to produce primary  $\alpha$ -fluoroethers ([Equation \(24\)](#)) [\[1999ACS41\]](#). Deoxo-Fluor ([bis(2-methoxyethyl)amino]sulfur trifluoride) is similar to DAST in that it is a source of nucleophilic fluorine, however it does have a somewhat different reactivity profile. It has been used to convert the bisindandione hydrate **50** into the cyclic polyfluoroether **51** ([Equation \(25\)](#)) [\[2002JOC1918\]](#). Hypervalent iodoarene difluorides are yet another source of nucleophilic fluorine and once again they have been used in the preparation of glycosyl fluorides [\[1996T149\]](#).

**Table 4** Preparation of  $\alpha$ -fluoroethers by the selective fluorination of carbohydrates using DAST

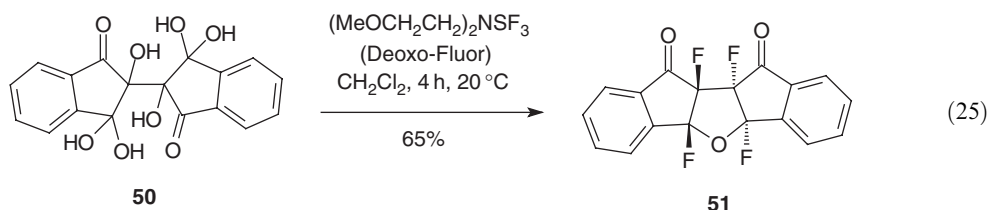
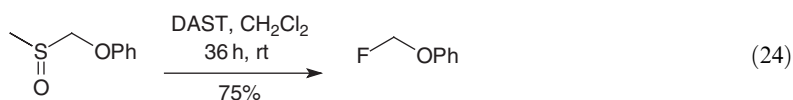
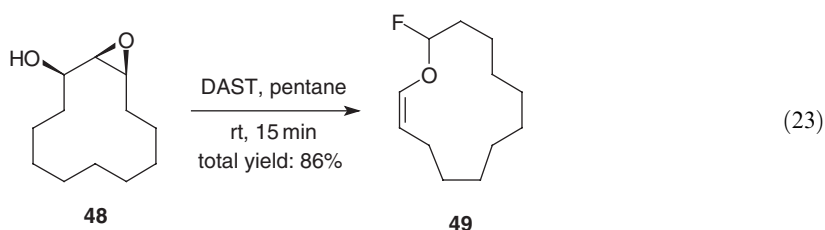
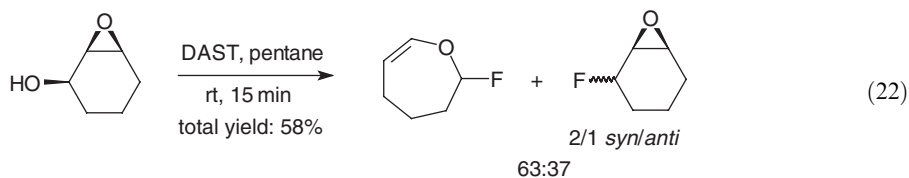
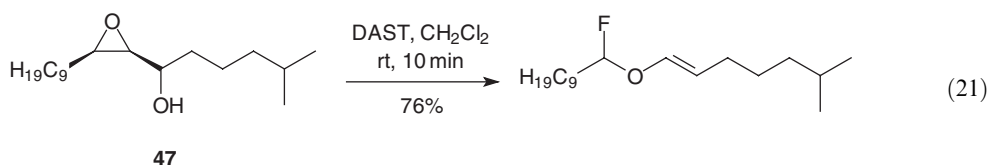
Entry	Product	Reactant	Conditions	Yield (%)	References
1			THF, 45 min, -20 °C	88	<1995T5657>
2			CH <sub>2</sub> Cl <sub>2</sub> , 2 h, -60 to 0 °C	75 ( $\alpha$ ) 25 ( $\beta$ )	<1998BCJ2893>
3			CH <sub>2</sub> Cl <sub>2</sub> , 4A molecular sieves, 30 min, -78 to 25 °C	88 mixture	<2001AG(E)1475>

3:1

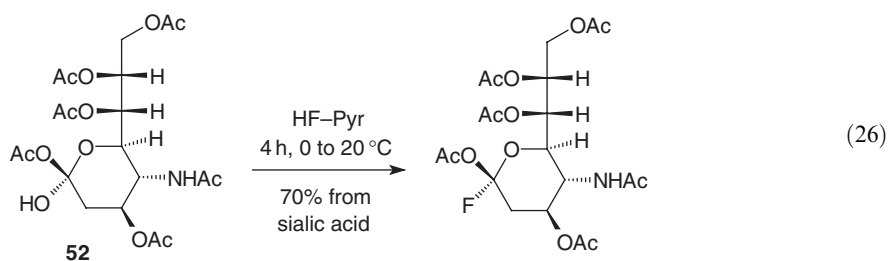
**Table 4** (continued)

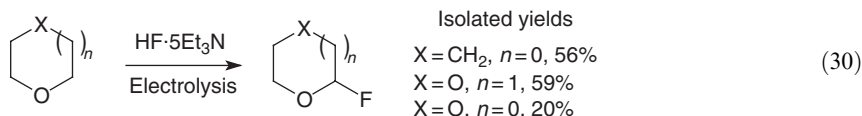
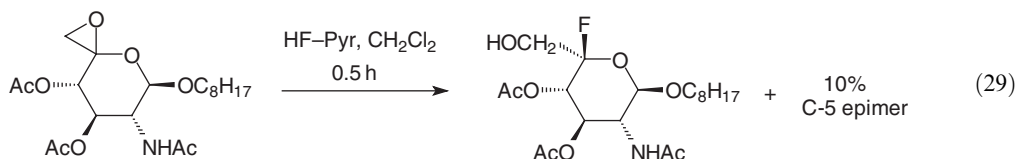
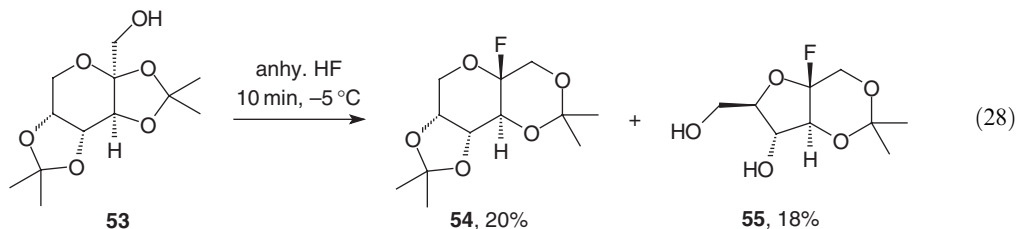
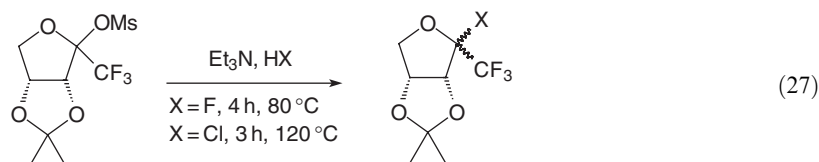
Entry	Product	Reactant	Conditions	Yield (%)	References
4			C <sub>6</sub> H <sub>6</sub> , 24 h, rt	78 mixture	<1994T9125>
5			CH <sub>2</sub> Cl <sub>2</sub> , 30 min	53 ( $\alpha$ ) 47 ( $\beta$ )	<1995CAR(269)227>
6			CH <sub>2</sub> Cl <sub>2</sub> , 8 h, 20 °C	72	<2001T6733>



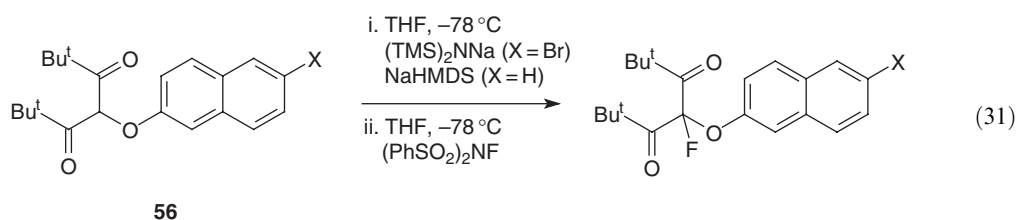


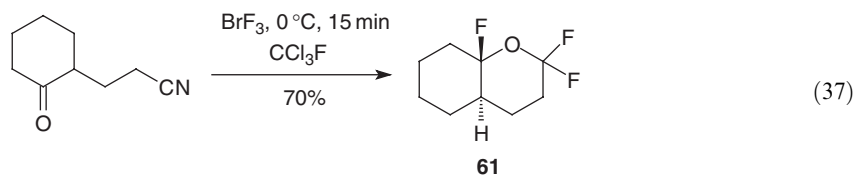
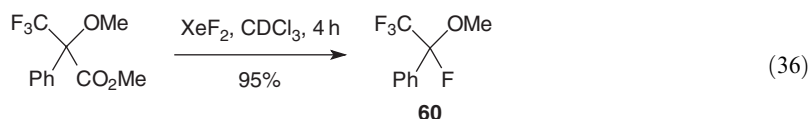
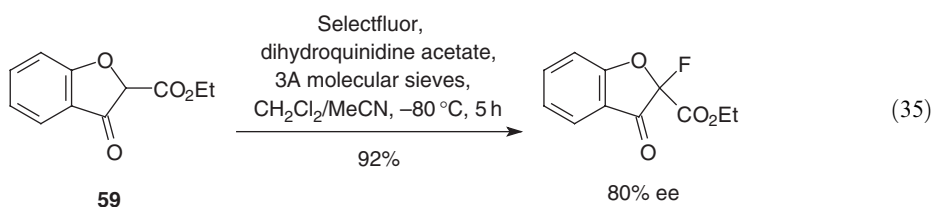
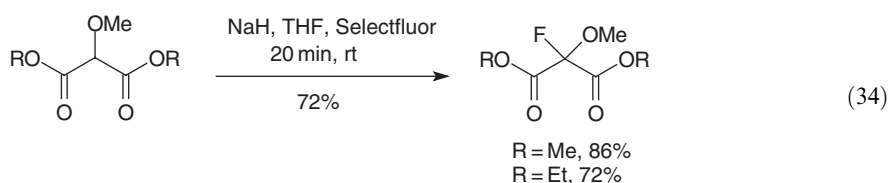
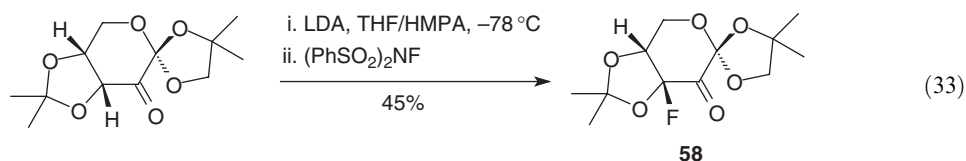
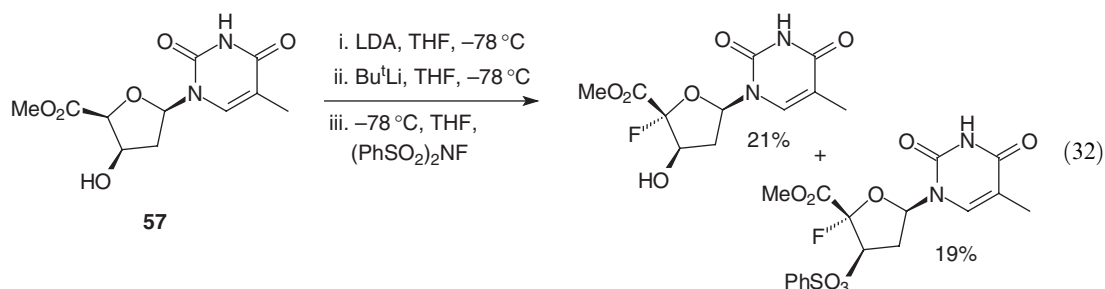
HF, most frequently used in pyridine solution, has also been extensively used for the selective introduction of fluorine into complex polyfunctional molecules through the replacement of an hydroxy group, an example being the formation of a glycosyl fluoride from peracetylated sialic acid **52** (Equation (26)) <2000JOC6145>. In keeping with the general pattern for these reactions this conversion proceeds with retention of configuration. In an analogous manner, HF/NEt<sub>3</sub> has been used in the replacement of a mesityl group (Equation (27)) <1994MI1225> whereas the reaction of the primary alcohol **53** in anhydrous HF results in rearrangement and the formation of the  $\alpha$ -fluoroethers **54** and **55** (Equation (28)) <1995TA307>. An alternative method of using HF–pyridine to introduce a fluorine atom into a carbohydrate molecule involves epoxide fluoridolysis (Equation (29)) <2002JA10036>. In the noncarbohydrate area, the electrochemical fluorination of cyclic ethers has been developed as a general method of producing cyclic  $\alpha$ -fluoroethers (Equation (30)) <2002TL1503>. The electrolysis takes place in the absence of solvent, using 5HF·Et<sub>3</sub>NF as the supporting electrolyte, and the product is isolated by simple distillation from the electrolysis solution.



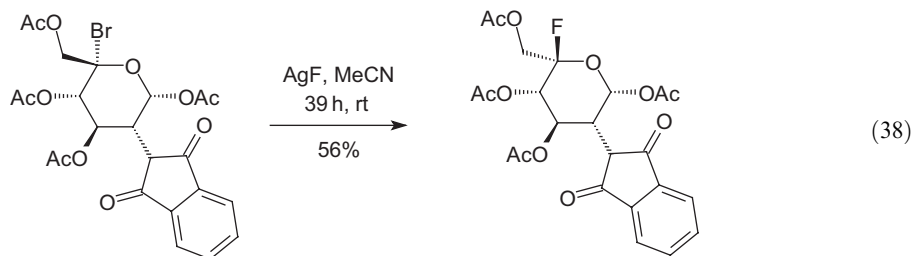


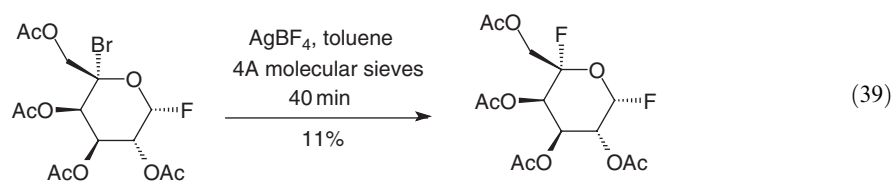
The most frequently used source of electrophilic fluorine is *N*-fluorobenzenesulfonimide, ((PhSO<sub>2</sub>)<sub>2</sub>NF) and this has been used with a range of bases to produce  $\alpha$ -fluoroethers through the selective introduction of fluorine into molecules containing an acidic hydrogen. It has been used together with sodium bis(trimethylsilyl)amide [<1996JMC1021>](#) or sodium hexamethyldisilazane [<1998BMCL3275>](#) to fluorinate the malonate derivatives **56** (Equation (31)), the products being used in the synthesis of fluorinated heterocyclic systems and phosphate mimics. A combination of this fluorinating agent, LDA and Bu<sup>t</sup>Li, has been employed to fluorinate the trianion of the thymine derivative **57** (Equation (32)) [<2001JOC2624>](#). An alteration in the reaction conditions allows the  $\beta$ -fluoro-3'-sulfonate to be obtained as a single product in 48% yield. The reagent has also found application in the carbohydrate area, producing the  $\alpha$ -fluoroether **58** from a protected diulose (Equation (33)) [<1998JOC8475>](#). An alternative source of electrophilic fluorine is Selectfluor (1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate)), which has, for example, been used to fluorinate 2-alkoxymalonates, forming  $\alpha$ -fluoroethers (Equation (34)) [<1999TA1223>](#). Interestingly, dimethyl 2-fluoro-2-methoxymalonate has also been prepared by direct fluorination using NaH/F<sub>2</sub> at -15 °C (51%) [<1996JFC\(78\)165>](#). More impressively Selectfluor, together with a chiral base, has been used in an asymmetric fluorination of the benzofuran **59** (Equation (35)) [<2001JA7001>](#). Although not commonly used, an XeF<sub>2</sub> promoted fluorodecarboxylation of a chiral substrate giving an optically inactive  $\alpha$ -fluoroether **60** (Equation (36)) has been reported [<1993JOC705>](#). The stereochemical outcome of the reaction has been used to argue for the involvement of radicals in the reaction. XeF<sub>2</sub> has also been used to convert hemithioacetals to primary  $\alpha$ -fluoroethers [<1996ACS850>](#). BrF<sub>3</sub>, described as “under-utilized,” has been used to convert 2-(2-cyanoethyl)-cyclohexanone to the oxadecaline **61** (Equation (37)) [<2001JFC\(111\)161>](#). The reaction is made possible by the presence of both the ketone and nitrile groups in the starting material, as neither cyclohexanone or 2-(cyanoethyl)cyclohexane reacts with BrF<sub>3</sub>.



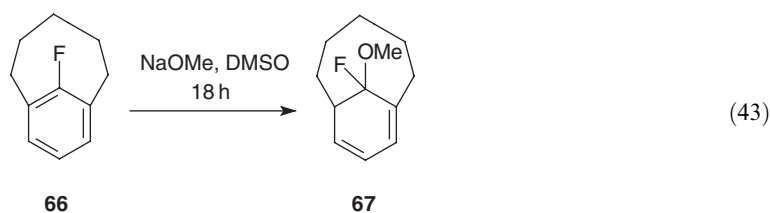
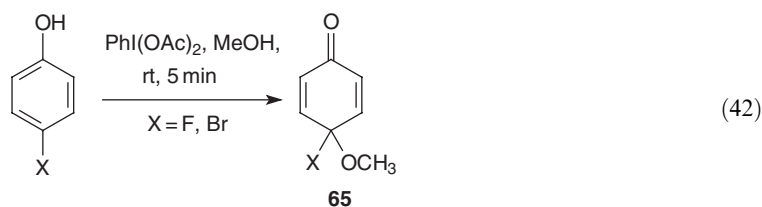
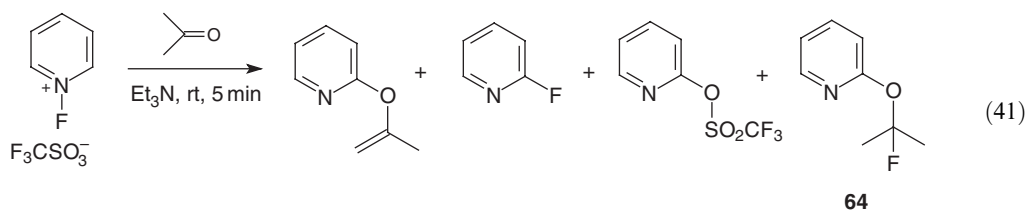
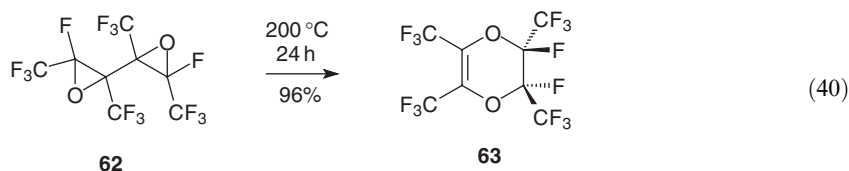


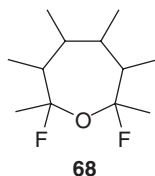
The replacement of a bromine atom with a fluorine atom forms part of a selective fluorination method in synthetic carbohydrate chemistry which involves a preliminary photochemical bromination, a process which is often highly regio- and stereoselective. Replacement of the bromine involves either  $\text{AgF}$  (Equation (38)) <2002JA10036, 1998T13267>, in which case the reaction generally proceeds with inversion and can sometimes involve competitive elimination of  $\text{HBr}$  <1998T13267>, or  $\text{AgBF}_4$  which results in retention (Equation (39)) <2000CAR(329)539, 1996JA241>. The replacement of a bromine atom with a fluorine atom is also possible using  $\text{CF}_3\text{ZnBr}$  <1997S159>.





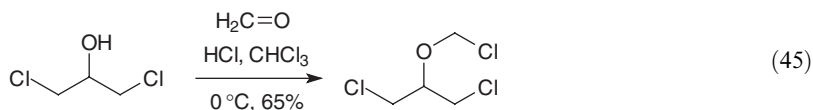
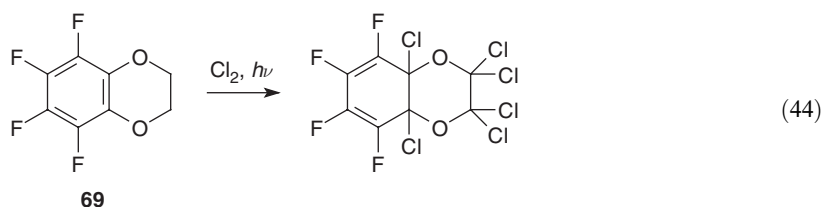
In addition to these reasonably general methods of preparing  $\alpha$ -fluoroethers, a number have been synthesized by methods which only apply to a particular compound. Thus the perfluorinated bisepoxide **62** undergoes an unusual rearrangement to give the 1,4-dioxine **63** (Equation (40)) <1995CC629, 1995JFC(72)231>, the product containing an  $\alpha$ -fluoroether grouping. The reaction of *N*-fluoropyridinium triflate with a base in acetone, proceeding via a carbene intermediate, gives a mixture of products which includes the  $\alpha$ -fluoroether **64** (Equation (41)) <1996JFC(77)161>. The cyclohexa-2,5-dienone **65** is formed by the oxidation of 4-fluorophenol with phenyliodonium acetate (Equation (42)) <1997T4387> and a further unstable cyclohexa-2,4-dienone **67**, which could only be characterized spectroscopically by the reaction of methoxide with **66** (Equation (43)) <2002EJO614>. Finally, it has been reported that a fluorofullerene with the formula  $C_{60}F_{18}O$ , formed by the reaction of [60]-fullerene with  $K_2PtF_6$ , probably contains an  $\alpha$ -fluoroether subunit **68** <2000JCS(P1)2212>.





#### 4.02.1.2.2 $\alpha$ -Chloroethers— $R^1CCI(OR^2)$

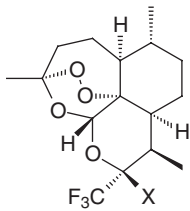
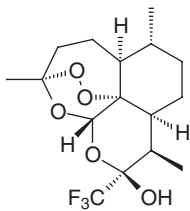
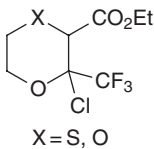
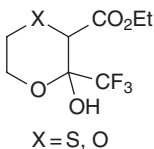
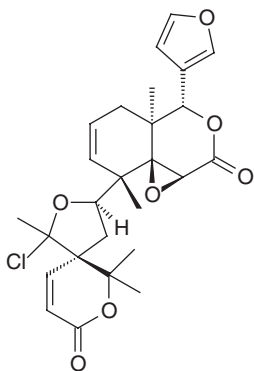
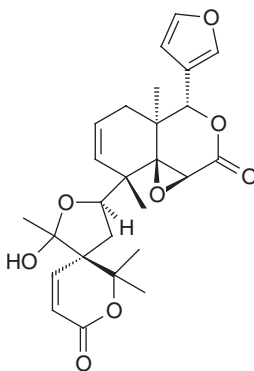
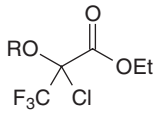
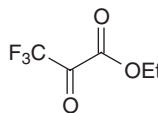
The traditional methods of preparing  $\alpha$ -chloroethers include the direct  $\alpha$ -chlorination of ethers, the reaction of acetals with acetyl chloride, and the chloroalkylation of ketones and aldehydes. There are only two recent examples of the preparation of  $\alpha$ -chloroethers by the direct  $\alpha$ -chlorination of ethers. These are the low temperature chlorination of chloromethyl ethyl ether to give chloromethyl 1-chloroethyl ether <1996TL9241>, and the chlorination of **69** (Equation (44)) <1994JFC(68)287> which actually involves the formal addition of chlorine to the aromatic double bond. The chloroalkylation of formaldehyde (Equation (45)) <1998JOC3694, 2002TL6317> and other aldehydes <1995AP531> continues to be used for the preparation of primary and secondary  $\alpha$ -chloroethers, respectively. The reaction of hemiacetals with thionyl chloride, essentially one half of the chloroalkylation procedure, has been successfully used for the preparation of tertiary  $\alpha$ -chloroethers in molecules containing a wide variety of other functional groups (Table 5). The outcome of this reaction can depend on the precise manner in which it is carried out. Thus in the synthesis of the  $\alpha$ -chloroether **70a** (Table 5, entry 1) if thionyl chloride and pyridine are added together to the corresponding alcohol, a mixture of **70a** and an alkene is obtained. If, however, the thionyl chloride is added first on its own, followed by pyridine, no elimination occurs. Unlike most  $\alpha$ -chloroethers, the  $\alpha$ -chlorinated lactyl esters **71** obtained from ethyl trifluoropyruvate (Table 5, entry 4) were found to be quite stable to hydrolysis because of the strongly electron-withdrawing trifluoromethyl group and could be easily purified by aqueous work up followed by distillation. Secondary allylic alcohols also gave hemiacetals with ethyl trifluoropyruvate but on treatment with thionyl chloride these gave a mixture of hydrated ethyl trifluoropyruvate and allylic chlorides.



The addition of  $Cl_2$ , or the regioselective Markovnikov addition of  $HCl$ , to enol ethers has been found to be a convenient way of preparing  $\alpha$ -chloroethers (Table 6). *N*-Chlorosuccinimide (NCS) in the presence of acetic acid has also been used to chlorinate an enol ether, the reaction giving a mixture of all the possible stereoisomeric products (Equation (46)) <1996MI701>. Although the nature of the chlorinating agent is not clear, a radical mechanism has been suggested for the reaction in dichloromethane between the electron deficient olefin **72** and MCPBA which results in its chlorination (Scheme 11) <1998TL6453>. If the reaction is carried out in the presence of a radical scavenger and methanol, then an  $\alpha$ -chloromethyl ester is obtained <1998TL4659, 2002CAR(337)2077>. The mechanism suggested for this process <1998TL4659> involves the initial slow epoxidation of the electron-deficient olefin, with the hydroquinone protecting the peracid from decomposition (Scheme 11).

Subsequent rearrangement of the dichloroepoxide gives an acid chloride, which reacts with methanol to give the methyl ester. The chlorination of compounds related to **72** has also been carried out in the standard way using  $\text{Cl}_2$  (Table 6, entry 6). The regiochemistry of the addition of benzenesulfonyl chlorides to carbohydrate enol ethers is also such as to produce  $\alpha$ -chloroethers <1995JOC3378>. The reaction can be highly stereoselective as is the case for the addition of 2,4-dimethylphenylsulfenyl chloride to the sialyl glycal **73** (Equation (47)), which gives only 4% of the minor *trans*-isomer <1996JA8187>. The reaction with benzenesulfonyl chloride is less stereoselective and it was found that the anomeric ratio of the products is a function of the solvent used <1996CAR(284)207>.

**Table 5** Preparation of  $\alpha$ -chloroethers by reaction of hemiacetals with thionyl chloride

Entry	Product	Reactant	Conditions	Yield (%)	References
1	 <b>70a</b> , X = Cl; <b>70b</b> , X = Br		i. $\text{SOX}_2$ , $-30^\circ\text{C}$ X = Cl, 74 ii. Pyr X = Br, 86		<2002OL757>
2	 X = S, O	 X = S, O	$\text{SOCl}_2$ Pyr/ $\text{C}_6\text{H}_6$ $20^\circ\text{C}$		X = S <1998H2253> X = O <2000JHC1003>
3			$\text{SOCl}_2$ , Pyr 2 h, $0^\circ\text{C}$	75	<1994T9343>
4	 R = Me, allyl, alkynyl, benzyl <b>71</b>	 R = Me, allyl, alkynyl, benzyl	i. ROH, $\text{C}_6\text{H}_6$ ii. $\text{SOCl}_2$ Pyr/ $\text{C}_6\text{H}_6$ 30 min, $0^\circ\text{C}$	65–80	<1995JOC6289, 1995CC1969>

**Table 6** Preparation of  $\alpha$ -chloroethers by the addition of  $\text{Cl}_2$  or  $\text{HCl}$  to enol ethers

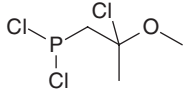
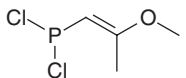
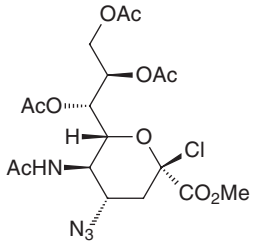
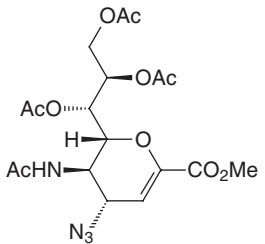
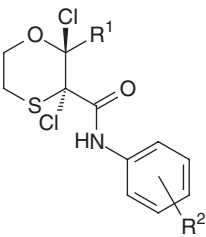
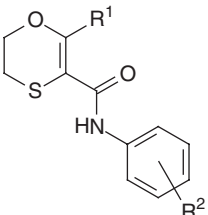
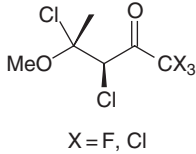
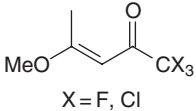
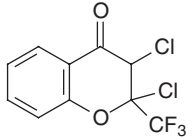
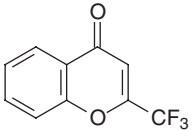
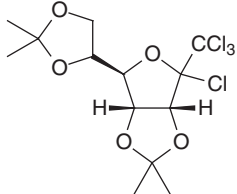
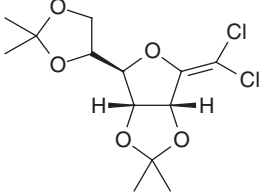
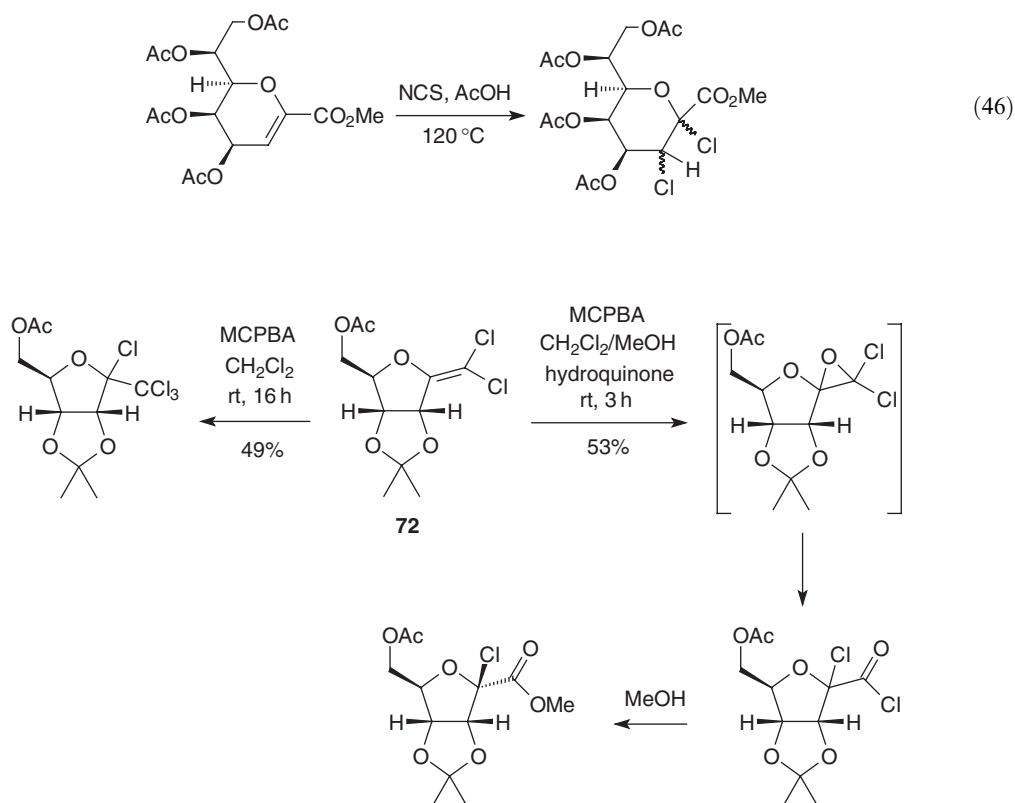
Entry	Product	Reactant	Conditions	Yield (%)	References
1			$\text{HCl}$ gas, $\text{CH}_2\text{Cl}_2$ $-40^\circ\text{C}$ , 35 min		<1996ZOR1657>
2			$\text{HCl}$ gas, MeCN, 4A molecular sieves, LiCl 6 days, rt, $20^\circ\text{C}$	85	<1995CAR(267)239>
3	 $\text{R}^1 = \text{Me}; \text{R}^2 = 4\text{-Me}, 2,4,6\text{-Me}, 2\text{-OMe},$ $4\text{-OMe}, 4\text{-Cl}, 2\text{-NO}_2$ $\text{R}^1 = \text{Ph}; \text{R}^2 = \text{H}$	 $\text{R}^1 = \text{Me}; \text{R}^2 = 4\text{-Me}, 2,4,6\text{-Me}, 2\text{-OMe},$ $4\text{-OMe}, 4\text{-Cl}, 2\text{-NO}_2$ $\text{R}^1 = \text{Ph}; \text{R}^2 = \text{H}$	$\text{Cl}_2$ , THF/ $\text{CH}_2\text{Cl}_2$ , rt		<1999H(50)713>

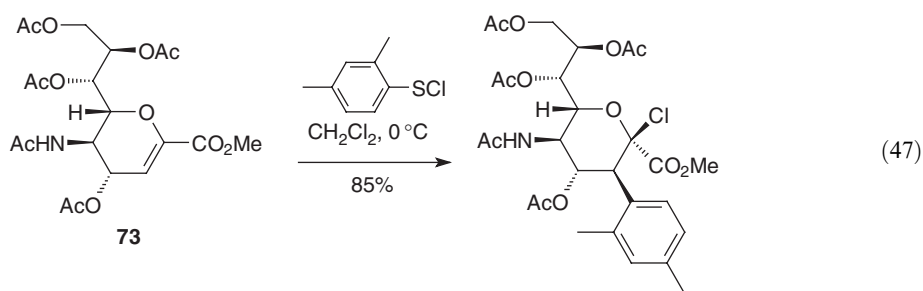
Table 6 (continued)

Entry	Product	Reactant	Conditions	Yield (%)	References
4	 X = F, Cl	 X = F, Cl	Cl <sub>2</sub> , CCl <sub>4</sub> , 0 °C	90	<2001S431>
5			Cl <sub>2</sub> , CCl <sub>4</sub> , 1 h, 60 °C		<2000IZV2109>
6			A: Cl <sub>2</sub> , CH <sub>2</sub> Cl <sub>2</sub> , 5 min, rt B: Et <sub>4</sub> N <sup>+</sup> Cl <sub>3</sub> <sup>-</sup> , CH <sub>2</sub> Cl <sub>2</sub> , 0 °C, 15 min	A: 88 B: 77	<1998TL6453>



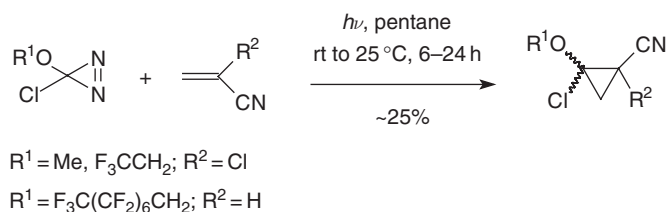


Scheme 11

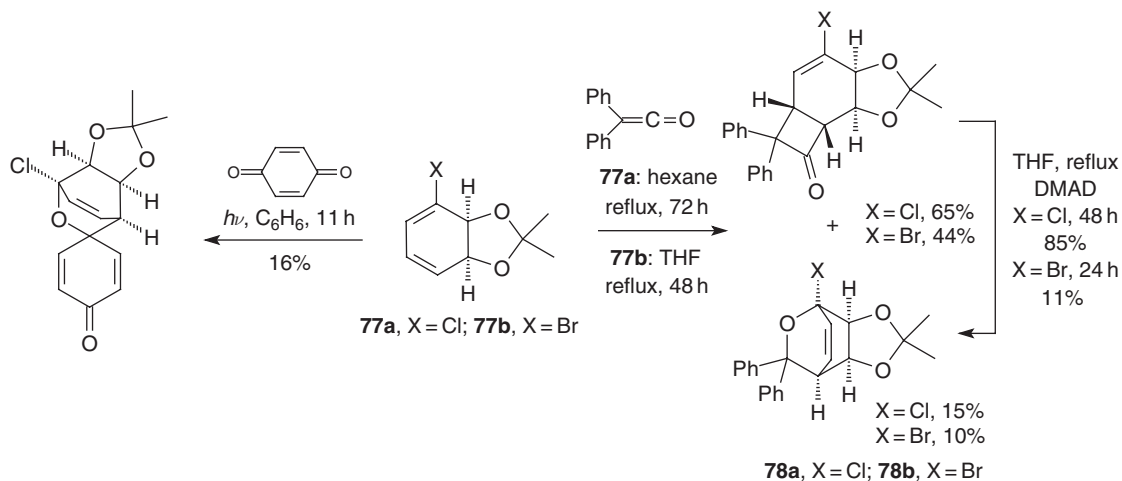
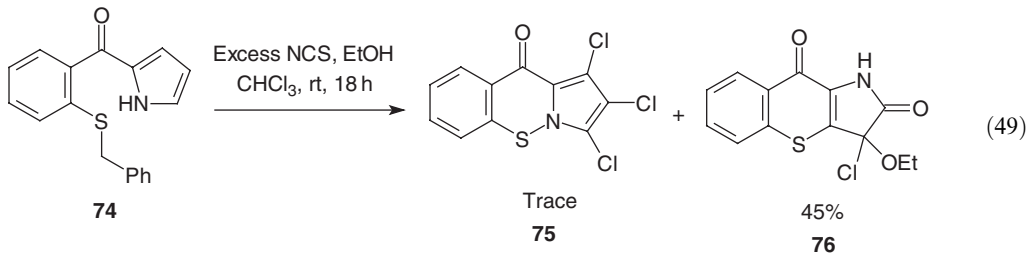
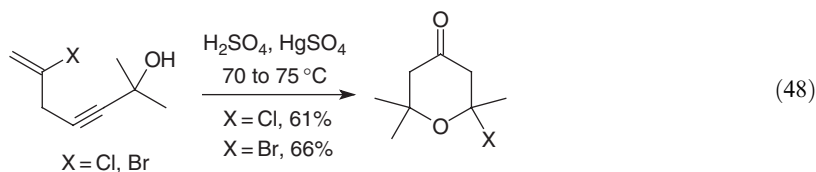


Addition reactions involving chloroalkenes have also been used to assemble  $\alpha$ -chloroethers. The Michael-type addition of alcohols to  $\beta$ -chloroenones [<2000JFC\(102\)147>](#) and the addition of chloro(alkoxy)carbenes to  $\alpha$ -chloroacrylonitrile ([Scheme 12](#)) [<1995TL3083, 1995JFC\(73\)101>](#) are both reactions of this type, as is the intramolecular addition of an alcohol to a chloroalkene which has been used as the key ring-closing step in the synthesis of a cyclic  $\alpha$ -chloroether ([Equation \(48\)](#)) [<1995ZOR58>](#). The mechanism for the novel cyclization of the pyrrole derivative **74**, which occurs in the presence of a large excess of NCS and gives **75** and the  $\alpha$ -chloroether **76**, is not understood ([Equation \(49\)](#)) [<1996JOC9289>](#). A number of  $\alpha$ -chloroethers have also been produced via cycloaddition reactions. These include the photochemical oxa-Diels–Alder reaction between the carbonyl group of quinone and the chlorodiene **77a** [<1994JA5108>](#) ([Scheme 13](#)). The diene **77a** also undergoes a thermal reaction with diphenyl ketene to give the  $\alpha$ -chloroether **78a**, a [4+2]-adduct, as the minor product; the major product, a [2+2]-adduct can however be thermally converted to **78a** ([Scheme 13](#)) [<1995JCS\(P1\)1499>](#). The chlorofuran **79** undergoes a microwave-assisted indium triflate catalyzed intramolecular Diels–Alder reaction to give another  $\alpha$ -chloroether **80** ([Equation \(50\)](#)) [<2000TL8639>](#). Addition reactions involving epoxides have also been used to

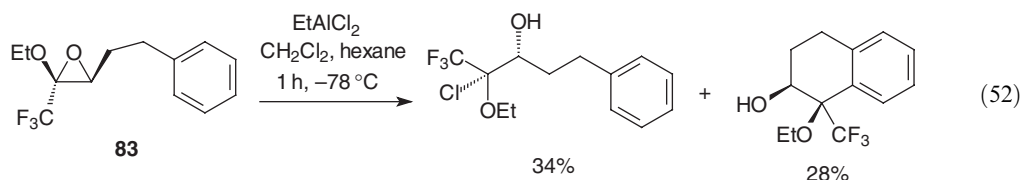
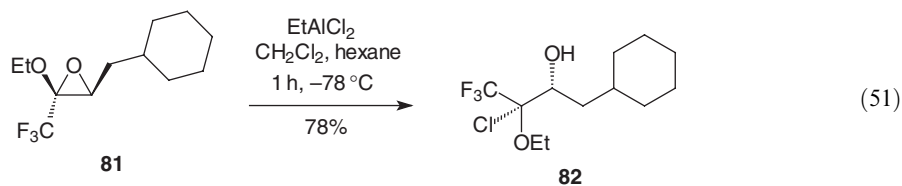
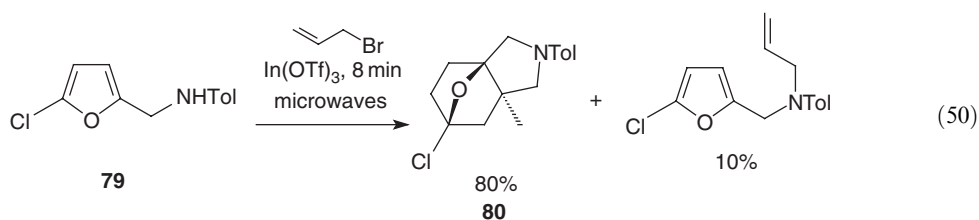
construct  $\alpha$ -chloroethers. The  $\text{EtAlCl}_2$  induced ring-opening of the epoxide **81** at  $-78^\circ\text{C}$  produces the  $\alpha$ -chloroether **82** as a single diastereomer (Equation (51)) [<1995JOC5029>](#). The reaction is not as stereoselective at higher temperatures, giving a 1:1 mixture of diastereomers at  $0^\circ\text{C}$ . Its outcome also depends on the nature of the Lewis acid and epoxide used. The epoxide **83**, for example, in the presence of  $\text{EtAlCl}_2$  gives a mixture of  $\alpha$ -chloroether and tetraol at  $-78^\circ\text{C}$  (Equation (52)), whereas with  $\text{TiCl}_4$  at  $0^\circ\text{C}$  the tetraol is the only product formed.



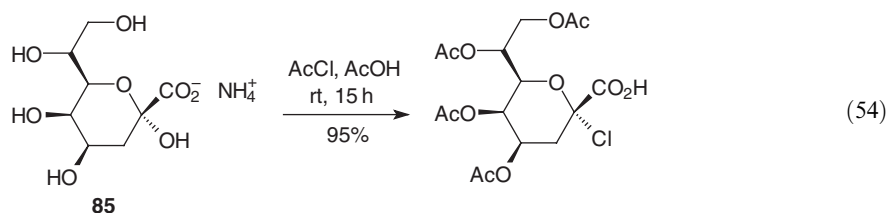
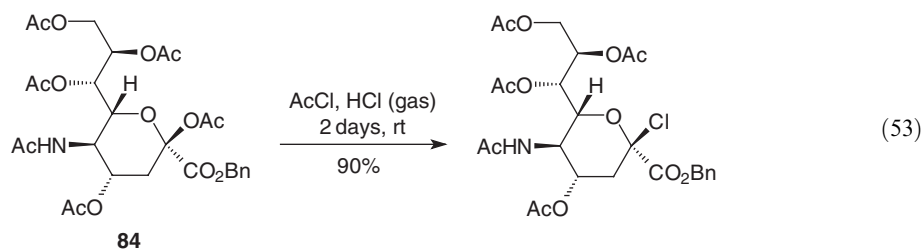
### Scheme 12

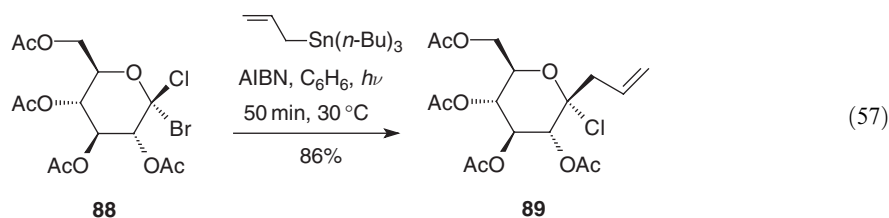
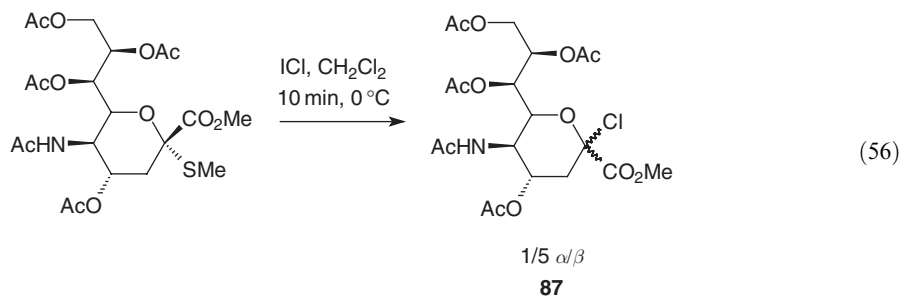
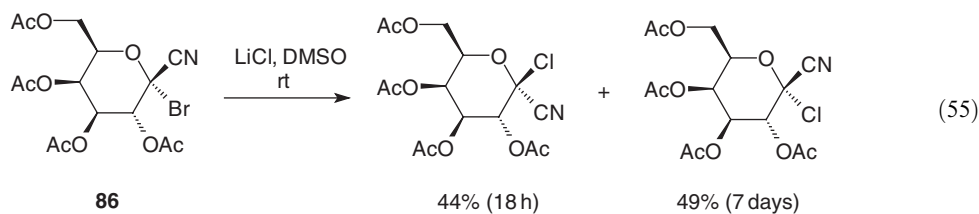


### Scheme 13

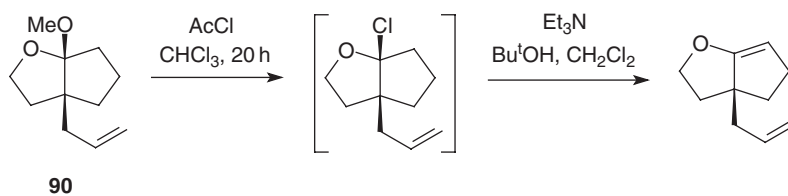
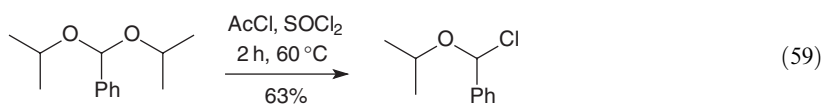
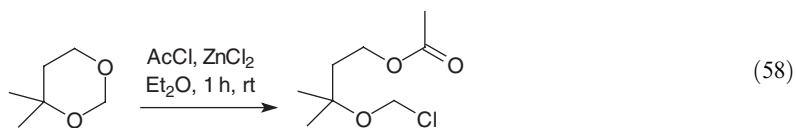


A wide range of substitution reactions involving chloride, oxygen, and carbon nucleophiles have been used to prepare  $\alpha$ -chloroethers. The importance of glycosyl chlorides, formally  $\alpha$ -chloroethers, in synthetic carbohydrate chemistry means that a lot of the work in this area relates to their synthesis. The use of traditional reagents such as  $\text{AcCl}/\text{HCl}$  <1995MI227, 1995CPB1844, 1995OPP637, 1997T11109, 1999CAR(317)198, 2001BMCL141, 2002JOC7565, 2002S1959>, or  $\text{AcCl}$  on its own <1994JMC3419, 1997MI139, 1997SL650, 2000CAR(323)1, 2000EJO2643, 2001JCS(P1)1098, 2001AG(E)366, 2001MI227, 2002OL3067, 2002SL1487>, to replace an acetate group on the anomeric carbon with chlorine continues to be the most widely used method of carrying out this functional group transformation. The conversion of the acetate **84** (Equation (53)) <2002CAR(337)755> and the alcohol **85** (Equation (54)) <2000OL3361> to their corresponding chlorides are representative examples of this type of reaction.  $\text{HCl}$  <1998ACS141> and  $\text{TiCl}_4$  <1994TL3179>, both in dichloromethane, are other reagents that have been used for this purpose. Glycosyl chlorides have also been prepared by procedures that involve the nucleophilic displacement of leaving groups other than acetate. Thus the reaction of the bromogalactose derivative **86** with  $\text{LiCl}$  in DMSO gives a mixture of anomers from which each can be isolated by fractional crystallization after different reaction times (Equation (55)) <1996T9121>.  $\text{ICl}$  has been used to prepare the glycosyl chloride **87** presumably through chloride ion displacement of a sulfonyl iodide from the thioglycoside (Equation (56)) <1997TL8233>. A radical-based replacement of bromine in the bromoglycosyl chloride **88** with an allyl group gives a high yield of the glycosyl chloride **89** as a single diastereomer (Equation (57)) <1997TL8185, 2001EJO2939>. The corresponding D-galacto and D-manno derivatives gave yields of 51% and 34%, respectively.

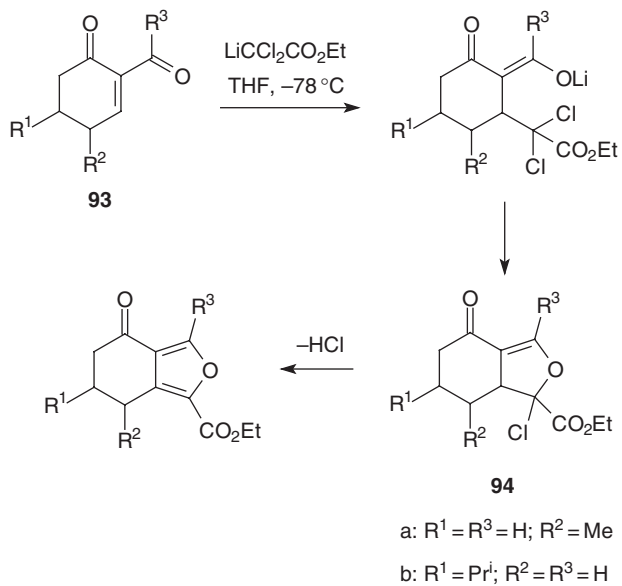
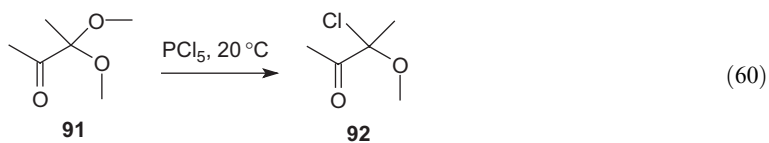




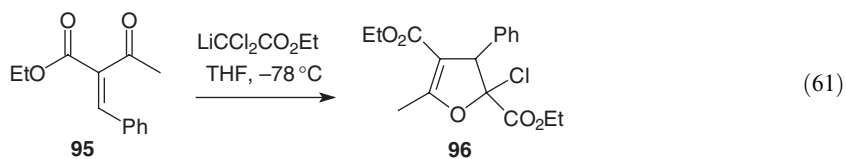
Substitution reactions have also been used in the synthesis of noncarbohydrate  $\alpha$ -chloroethers with, for example, the  $\text{ZnCl}_2$  reaction of  $\text{AcCl}$  with acetals being widely used to convert cyclic and acyclic 1,3-dialkoxymethanes to primary  $\alpha$ -chloroethers (Equation (58)) <1995JOC2532> and 2-alkyl-1,3-dialkoxymethanes to the corresponding secondary compounds (Equation (59)) <1998BCJ915>.  $\text{AcCl}$  has also been used in the conversion of the acetal **90** to a relatively unstable  $\alpha$ -chloroether, which was dehydrohalogenated directly (Scheme 14) <1994TL7785>. The displacement of mesylate by chloride ion, for example, has been used in the preparation of a chlorotetrahydrofurodioxole (Equation (27)) <1994MI1225> and it has been reported that treating the acetal **91** with  $\text{PCl}_5$  produces the  $\alpha$ -chloroether **92** (Equation (60)) <2000CEJ684>. The reaction between the lithium enolate of ethyl dichloroacetate and the acylcyclohexenone derivatives **93** has been used in a synthesis of highly functionalized furans (Scheme 15) <1997SL1259>. A key element in the synthesis is the fact that in general the  $\alpha$ -chloroethers **94** undergo spontaneous dehydrohalogenation. The  $\alpha$ -chloroethers **94a** and **94b** are quite stable however and treatment with DBU is required to complete the synthesis. The stability of these  $\alpha$ -chloroethers was attributed to “a conformation effect due to the alkyl group on the ring.” The issue is, however, complicated by the fact that the  $\beta$ -keto ester **95** gives an  $\alpha$ -chloroether **96** (Equation (61)) which is also stable, whereas the 1,3-diketones corresponding to **95** gave a furan directly, with no  $\alpha$ -chloroether being isolated. Nucleophilic displacement of chloride from a dichloromethane by methoxide has been used in the preparation of the  $\alpha$ -chloroether **97** (Scheme 16) <1995JOC5931>. Although the product is obtained in very low yield and as an inseparable mixture with **98**, it has been used to prepare an extensive range of bicyclo[2.2.1]heptane adducts **99** in 15–55% yields through Diels–Alder reactions with monosubstituted alkenes (Scheme 16), 1,4-naphthaquinone, diethyl acetylenedicarboxylate, 4-phenyl-[1,2,4]triazole-3,5-dione, *N*-phenylmaleimide, and 1,3-dioxol-2-one. Each of the adducts contains the  $\alpha$ -chloroether group and the cycloaddition is completely face selective.

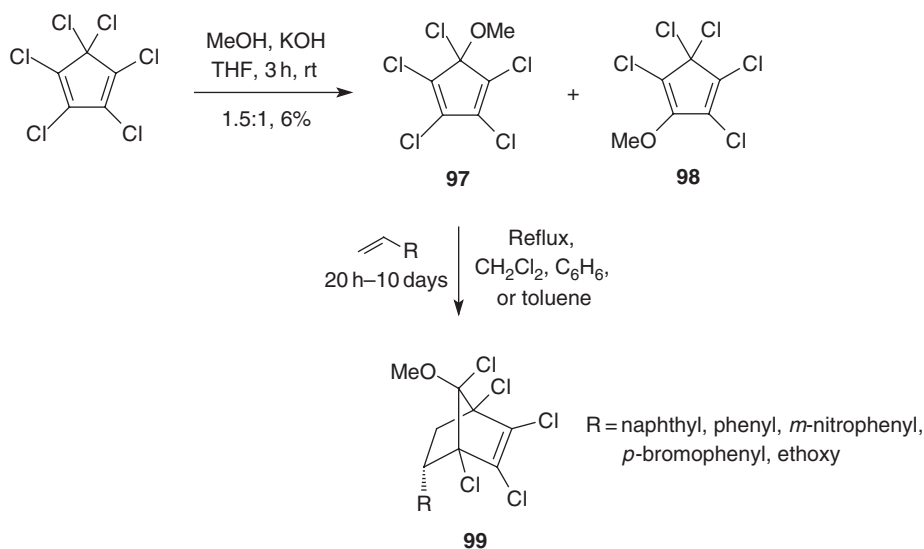


Scheme 14



Scheme 15

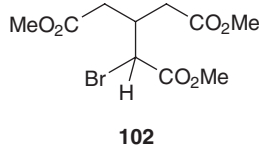




Scheme 16

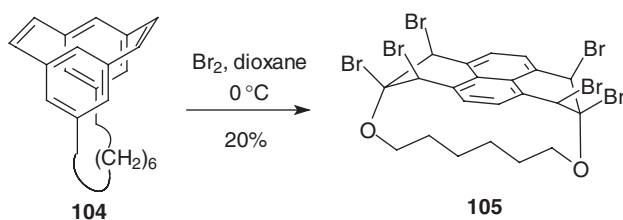
#### 4.02.1.2.3 $\alpha$ -Bromoethers— $R^1CBr(OR^2)$

$\alpha$ -Bromoethers are less stable and thus more reactive than the corresponding chloro compounds. In synthetic terms the main difference between  $\alpha$ -bromo- and  $\alpha$ -chloro ethers is the much greater involvement of radical reactions in the synthesis of the former due to the facility with which bromine atoms can be produced. However, many standard reactions can be applied successfully to both classes of compound. Thus, for example, the addition of bromine to vinyl ethers has been used to prepare a wide range of  $\alpha$ -bromoethers (Table 7). These reactions generally proceed in high yield although the stability of the products appears to vary greatly. The dibromo adduct **100** (Table 7, entry 1) was reported to be too sensitive for long-term storage and the dibromocyclobutane **101** (Table 7, entry 2) underwent hydrolysis on chromatography to give the ring opened product **102**. However, it is reported that the bromoether **103** (Table 7, entry 3) and related compounds prepared by the same method, are particularly stable and indeed are formed with high diastereoselectivity (90:10). Bromination of dienes can result in the formation of 1,4-adducts (Table 7, entry 4) and in polyfunctional molecules there is the possibility of intercepting an intermediate bromonium ion (Table 7, entry 7). The attempted bromination of the cyclophane **104** results, remarkably, in the formation of a product to which the structure **105**, containing an  $\alpha$ -bromoether, has been tentatively assigned (Equation (62)) <2000JOC5360>. Pyridinium tribromide, a commercially available reagent which is useful for small scale brominations, has been used to brominate the 2-styryl-4-chroman-4-one **106**, resulting in the formation of a mixture which contains the  $\alpha$ -bromoether **107** (Equation (63)) <1999H(51)481>.

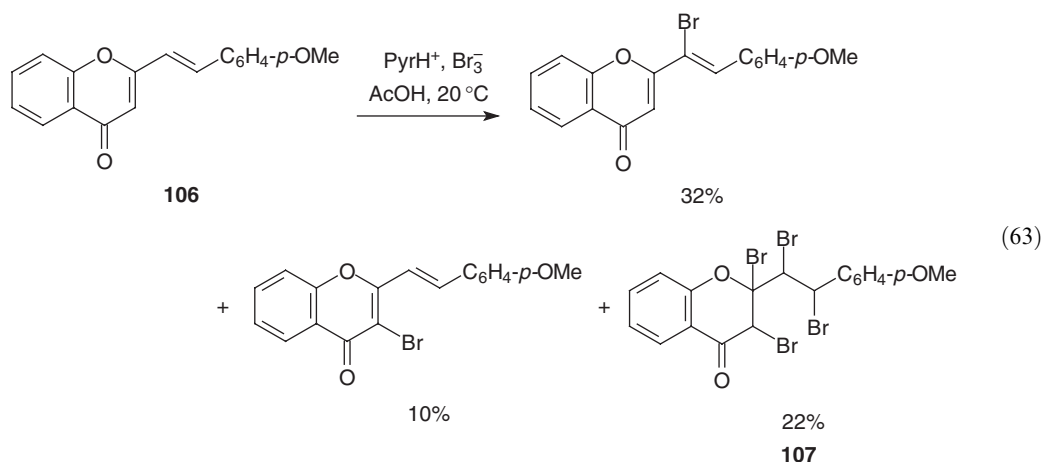


**Table 7** Preparation of  $\alpha$ -bromoethers by the addition of  $\text{Br}_2$  to enol ethers

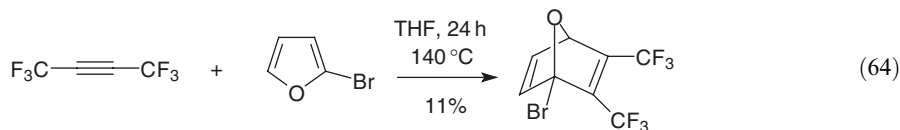
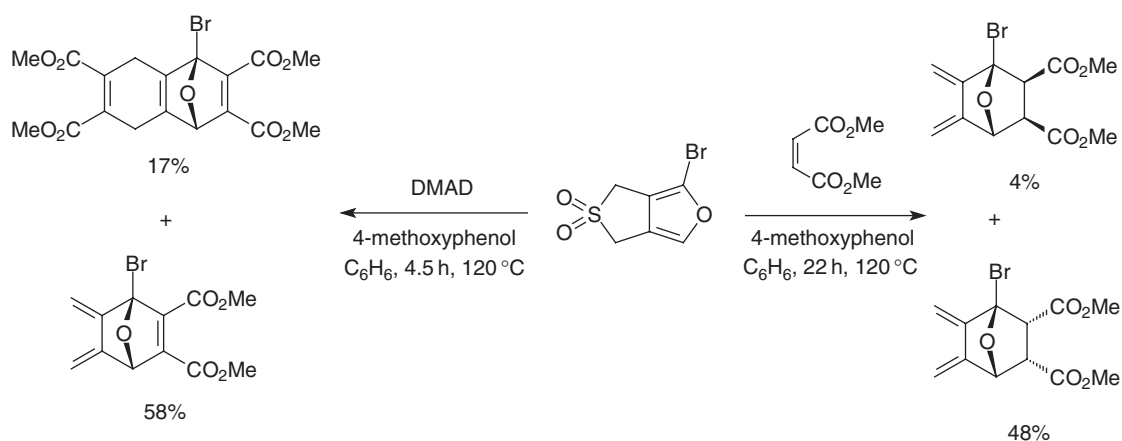
Entry	Product	Reactant	Conditions	Yield (%)	References
1			$\text{Br}_2$ , $\text{CH}_2\text{Cl}_2$	99%	<2000SL1419>
2			$\text{Br}_2$ , $\text{CH}_2\text{Cl}_2$ , rt, 15 min	>35%	<1997JCS(P1)2155>
3			$\text{Br}_2$ , $\text{CH}_2\text{Cl}_2$ , 12 h, rt	92	<1998S288>
4			$\text{MeOH}$ , $\text{Br}_2$ , $\text{Et}_2\text{O}$	96%	<1997TL4811>
5			$\text{Br}_2$ , $h\nu$	53	<1994IZV174>
6			$\text{NaBr}$ , $\text{CH}_2\text{Cl}_2$ , $\text{H}_2\text{O}$ electrolysis	84	<2001H825>
7			$\text{Br}_2$		<2000TL6709>



(62)



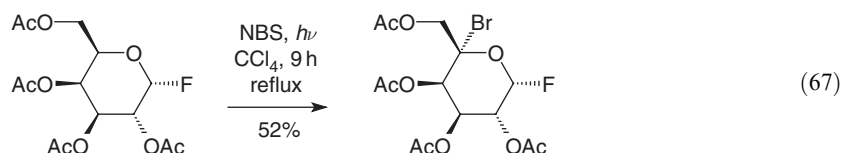
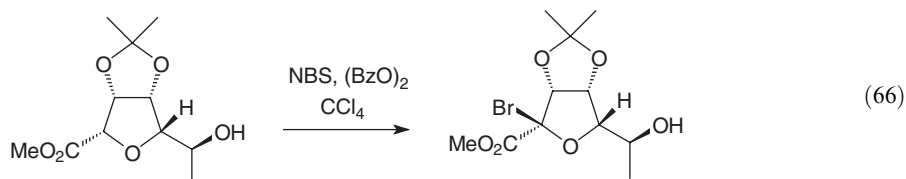
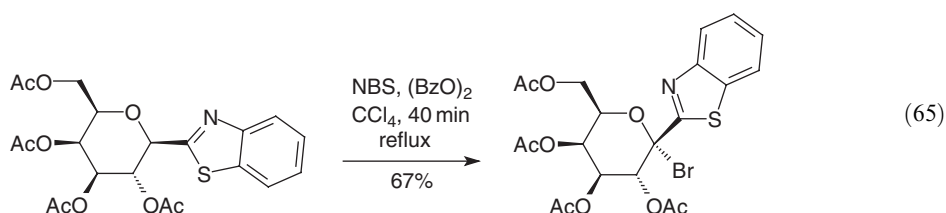
2-Bromofurans have three of the four components of  $\alpha$ -bromoethers already in place and C—C bond formation at the 2-position completes the assembly of this functional group. This has been achieved through cycloaddition reactions with dimethyl maleate, DMAD (Scheme 17), <1996JCS(P1)2699> and hexafluoro-2-butyne (Equation (64)) <1996JCS(P1)1095>. In the same way addition reactions which create a C—O bond at the 1-position of bromoalkenes also produce  $\alpha$ -bromoethers. The bromodiene **77b** undergoes an oxa-Diels–Alder reaction with the carbonyl group of diphenyl ketene to give the  $\alpha$ -bromoether **78b** (Scheme 13) <1996JCS(P1)1157>, and as was the case for the chloro analog, the major product in the reaction can be converted thermally to this compound <1995JCS(P1)1499>. The intramolecular insertion of an alcohol into a bromoalkene has also been reported (Equation (48)) <1995ZOR58>.



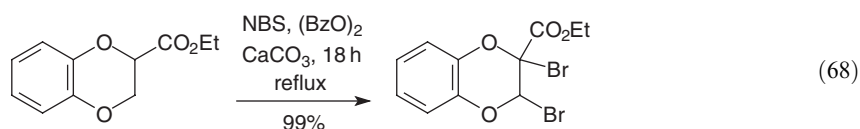
In terms of substitution reactions, the most widely used reagent for the introduction of bromine is *N*-bromosuccinimide (NBS). It has been used to prepare all classes of  $\alpha$ -bromoethers. The reactions are generally radical in character and are promoted by the use of peroxides, AIBN, or irradiation, NBS thus effectively providing a source of bromine atoms. In synthetic carbohydrate chemistry, NBS has been used to produce  $\alpha$ -bromoethers through the introduction of Br at anomeric and nonanomeric carbons. The relative merits of various radical-mediated brominations

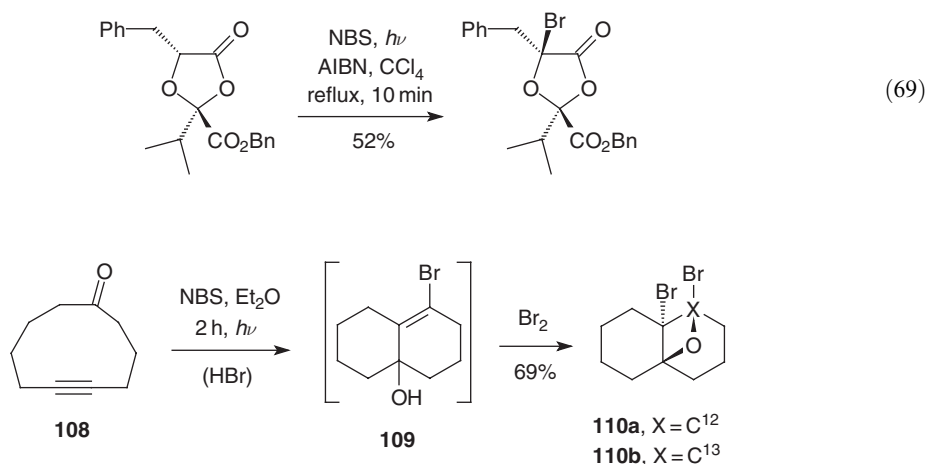


in synthetic carbohydrate chemistry, including the use of NBS, have been reviewed <2002TL8849>. The standard procedure for the bromination of anomeric carbons involves the use of benzoyl peroxide as an initiator <1995MI1307, 1995MI1295, 1995TL2149, 1999SL1151, 2001OL2415>. This approach has been used for both pyranoses <2002TL8849> (Equation (65)) and furanoses <1996TA383> (Equation (66)) and usually proceeds with retention of configuration. There is one instance of a furanose being brominated photochemically at the anomeric position <1996SC75>. The captodative effect has been adduced to account for the regioselectivity of these brominations <1996TA157>. Selective bromination at C-5 in pyranosides is also possible using NBS and again produces an  $\alpha$ -bromoether (Equation (67)) <2000CAR(329)539>. In this case photochemical promotion of the reaction is usually involved <1996JA241, 2001CJC510, 2002JA9756, 2002JOC4505> although benzoyl peroxide has occasionally been used <2002TL8849>. The regioselectivity of this radical bromination has been attributed to the well-established preference of such reactions to occur at tertiary carbons <2000CAR(329)539> and to the captodative effect <1995JOC1880>. Although primary and secondary amides are not compatible with photochemical bromination using NBS, the use of phthaloyl protecting groups has proved successful <2002JA10036>. Bromination at C-5 generally proceeds with retention of configuration.

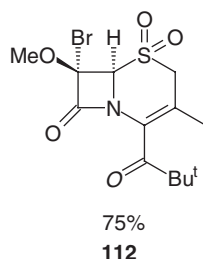
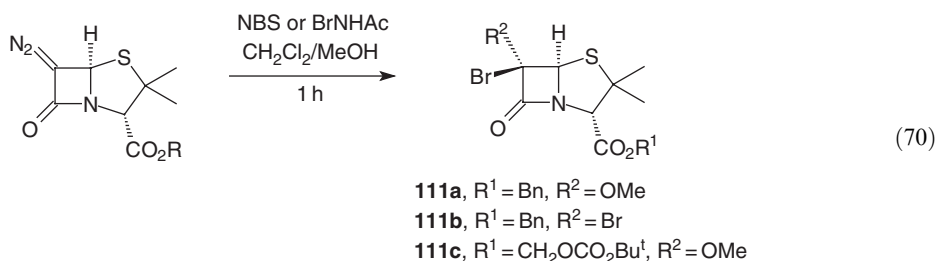


NBS has also been used widely to generate  $\alpha$ -bromoethers in noncarbohydrate systems. This includes the bromination of 1,4-dioxines using AIBN <2002T1533> or benzoyl peroxide (Equation (68)) <1996AJC533> as initiator, as well as that of the functionally related 4-oxodioxolanes (Equation (69)) <2001HCA3766, 1995JOC1880>. NBS reactions can involve the formation of HBr and in the case of 5-cyclodecyn-1-one **108** this leads to the formation of intermediate **109**, bromination of which gives the  $\alpha$ -bromoether **110a** (Scheme 18) <1995JOC2714>. In keeping with the proposed involvement of **109**, reaction of **108** with a  $^{13}\text{C}$  label in the 5-position leads to the formation of **110b**. NBS has also been used to create an  $\alpha$ -bromoether at the 6-position of a penicillin derivative through the displacement of a diazo group (Equation (70)). The reaction is carried out in methanol and leads to the formation of **111a** (64%) <1995T10723>. An occasionally used alternative to NBS, *N*-bromoacetamide is less selective in this case leading to the formation of mixture of **111a** (10%) and a dibromo derivative **111b** (15%). It has been reported however that *N*-bromoacetamide gives **111c** selectively, although in modest yield (37%) <1994JHC909>. Formation of the  $\alpha$ -bromoether **112** from the corresponding diazo compound using NBS is equally chemoselective although the stereochemistry of the bromine atom is reversed <1998SL322>.

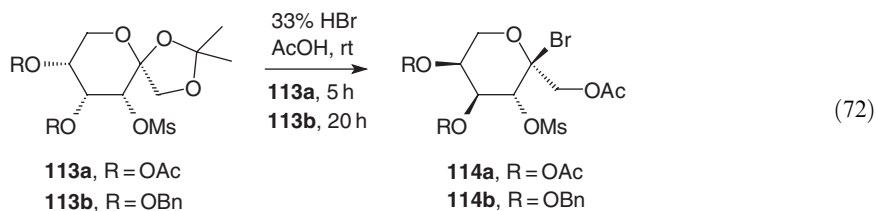
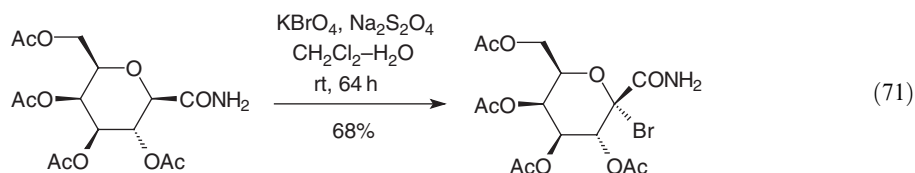




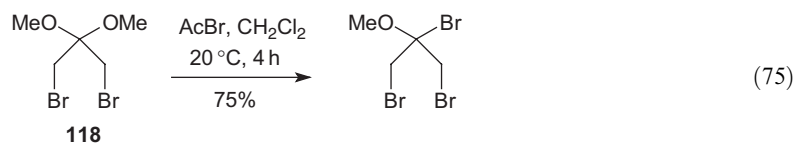
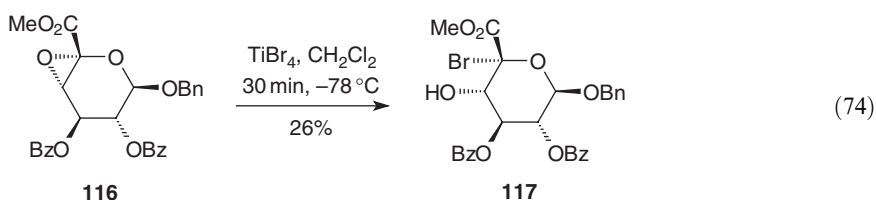
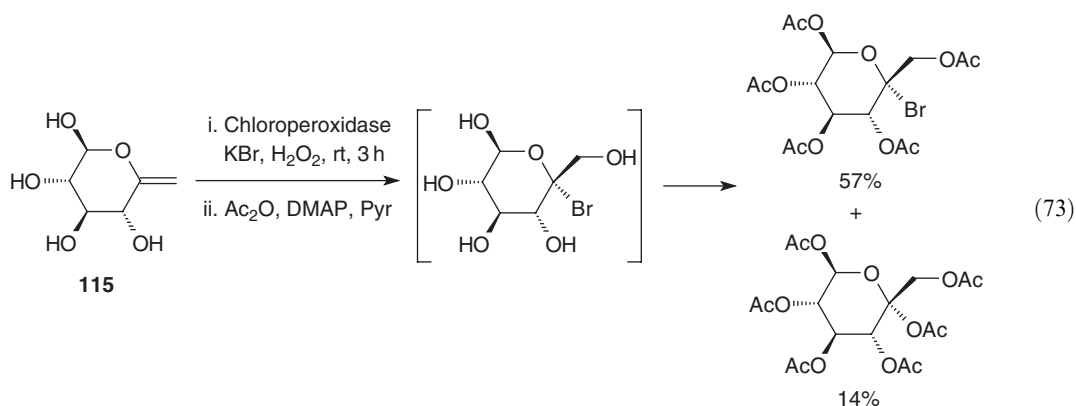
Scheme 18



Pyranose brominations, again resulting in the formation of  $\alpha$ -bromoethers, have also been carried out using a variety of other reagents. A particularly useful assessment of various methods for radical bromination has been carried out in an attempt to identify a suitable replacement for methods that involve the use of the undesirable carbon tetrachloride [<2002TL8849>](#). This concluded that a biphasic system based on  $\text{KBrO}_3\text{--Na}_2\text{S}_2\text{O}_4$  had considerable potential in this regard for both anomeric and nonanomeric centers [<2002TL8849>](#) (Equation (71)). Other methods for anomeric bromination include  $\text{Br}_2/\text{CHCl}_3$  [<2000TA405>](#), [2000TA1719](#), [2002TL8849](#), and  $\text{Br}_2/\text{BaCO}_3/\text{CCl}_4$  [<2000TA1719>](#), both of which involve irradiation,  $(\text{TMS})_2\text{NLi}/\text{CBr}_4$  [<1995TL2145>](#) and  $\text{HBr}/\text{AcOH}$  [<1999TL57>](#).  $\text{Br}_2/\text{CCl}_4$ , again under irradiation, has also been used to brominate C-5 in a pyranoside [<2002TL8849>](#). The introduction of bromine at the anomeric carbon through acid-assisted nucleophilic displacement of OH and OAc is also a standard approach for the synthesis of glycosyl bromides. Thus HBr and  $\text{HBr}/\text{AcOH}$  have been used to convert hemiacetals to the corresponding bromide [<1995LA2081>](#); AcOH can co-crystallize with the product given by the latter, a problem that is avoided by using HBr. The substitution of OAc has been achieved using  $\text{HBr}/\text{Ac}_2\text{O}/\text{AcOH}$  [<1995LA2081>](#), [2002JOC7407](#),  $\text{HBr}/\text{AcOH}$  [<1999CAR\(316\)85>](#), and  $\text{PBr}_3$  [<1999CAR\(316\)85>](#). The displacement of *p*-nitrobenzoate [<2000CAR\(329\)549>](#) and chloroacetate [<1997JCS\(P1\)1973>](#) using  $\text{TiBr}_4$ , and the direct one-pot conversion of isopropylidene acetals **113** to glycosyl bromides **114** (Equation (72)) [<1995LA2081>](#), have also been reported.

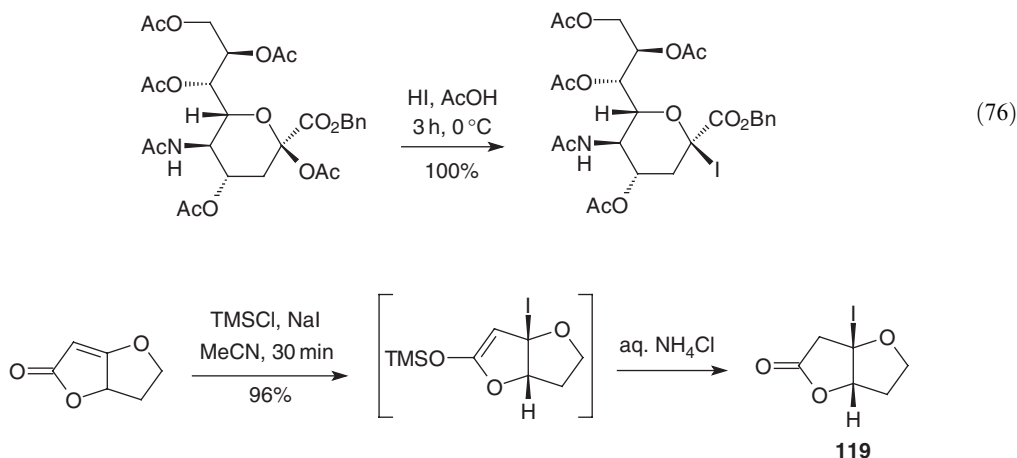


A number of nonstandard approaches have been used to produce  $\alpha$ -bromoethers. A completely different approach to anomeric bromination involves chloroperoxidase catalyzed bromohydration of the vinyl ether **115** in the presence of KBr and  $\text{H}_2\text{O}_2$  (Equation (73)) <1995JCS(P1)967>. In the same way, the bromination of the epoxide **116** is an unusual method of introducing a bromine atom at C-5 (Equation (74)) <1999JOC144>. The low yield of isolated product in this case is due in large measure to the decomposition of the  $\alpha$ -bromoether **117** during chromatography on  $\text{SiO}_2$ . Although the use of acetyl chloride is a standard synthetic carbohydrate chemistry method of replacing acetate with chloride, and in so doing creating an  $\alpha$ -chloroether, acetyl bromide is in general much less widely used. The only recent example of the corresponding use of acetyl bromide involves the displacement of methoxide from the acetal **118** (Equation (75)) <2000JOC3085>. In the same way thionyl bromide is rarely used to prepare  $\alpha$ -bromoethers despite the fact that the reaction of thionyl chloride with acetals is a standard method of producing  $\alpha$ -chloro ethers. The only example of the use of thionyl bromide in this respect is the stereoselective preparation of the halogenoartemisinin derivative **70b** from the corresponding hemiacetal (Table 5, entry 1) <2002OL757>.

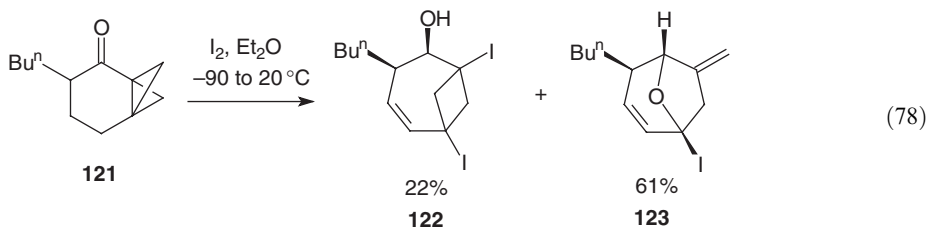
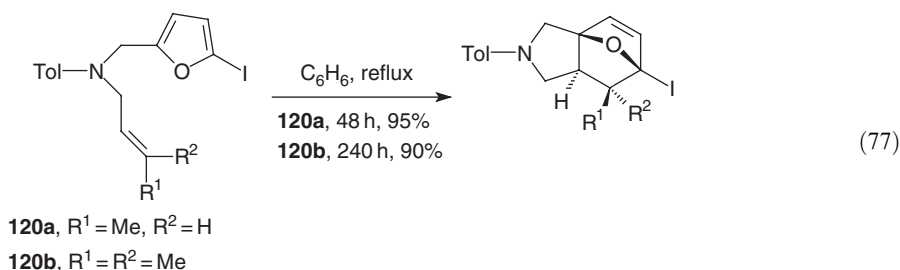


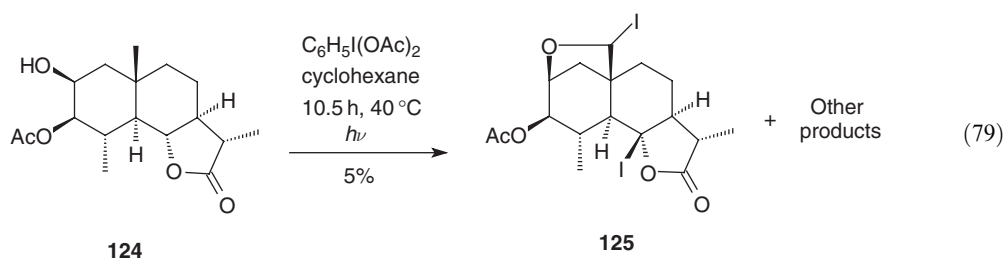
4.02.1.2.4  $\alpha$ -Iodoethers— $R_2^1CI(OR^2)$ 

Although  $\alpha$ -iodoethers are relatively unstable, they are increasingly finding application as intermediates in synthetic carbohydrate chemistry where a variety of nucleophilic substitutions have been used to prepare glycosyl iodides. Acetate displacement has been achieved using a variety of reagents including HI/AcOH (Equation (76)) <1997TL5921>,  $I_2$ /thioacetic acid <2000OL369>,  $I_2$ /Et<sub>3</sub>SiH <2002SL269>, TMSI <1999CAR(316)47, 2002OL2039>, NaI/TMSCl/molecular sieves <1995H(41)937>, and BiI<sub>3</sub>/TMSCl <1997CAR(297)175>. The displacement of hydroxyl from the anomeric center has been carried out using a polymer-bound triarylphosphane–iodine complex and imidazole <1999EJO3147>. TMSI has been used to introduce iodine in place of an OTMS group <1998MI1181, 2001OL2081> and  $I_2$ /HMDS to displace a pivalate group <2003CC1266>. Nucleophilic attack by iodide is again effectively involved in the formation of the cyclic  $\alpha$ -iodoether **119** through 1,4-addition of TMSI followed by hydrolysis (Scheme 19) <1994T8237>. The potential of a 2-iodofuran as an  $\alpha$ -iodoether precursor has been exploited in the intramolecular Diels–Alder reaction of **120** (Equation (77)) <1997JHC1315>. The strained nature of the propellane **121** is responsible for its ring-opening reactions with  $I_2$ , which gives the diiodo compound **122** through addition to the bicyclobutane bridge bond, and the  $\alpha$ -iodoether **123** through the rearrangement of an intermediate formed during the addition process (Equation (78)) <2000T1115>. Finally, the remote oxidation of the angular methyl group in the eudesmanolide **124** results in the formation of a range of products including the  $\alpha$ -iodoether **125** (Equation (79)) <1994JOC6395>.



Scheme 19



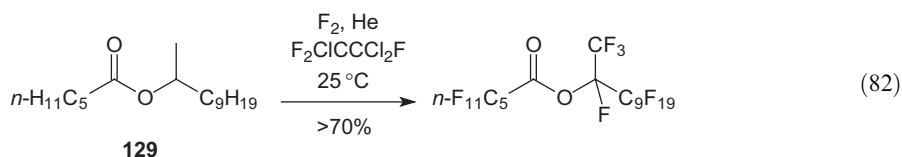
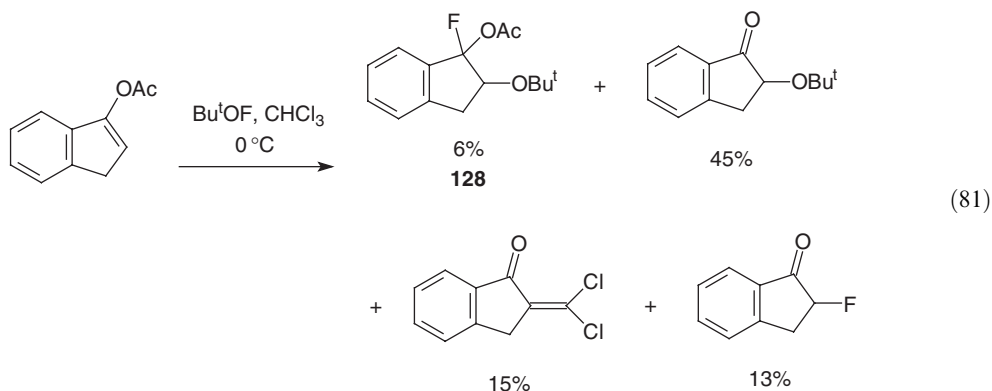
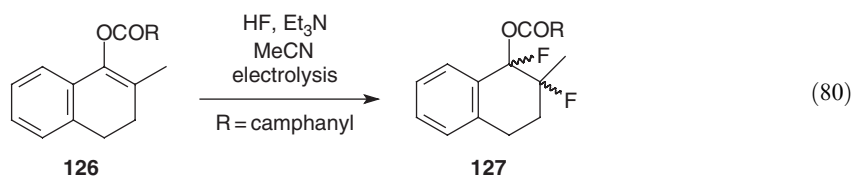


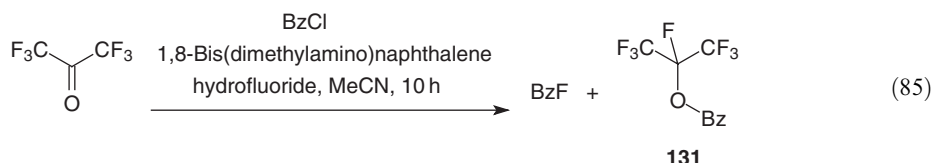
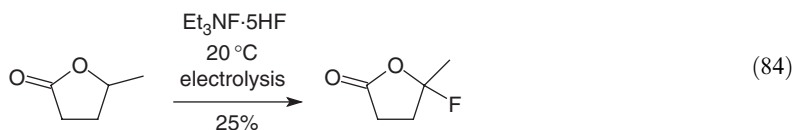
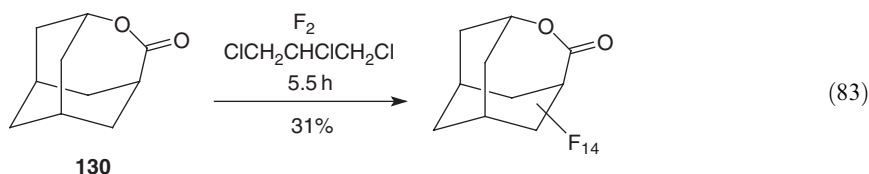
#### 4.02.1.3 Other Derivatives of $\alpha$ -Halo Alcohols— $\text{R}_2^1\text{CHal}(\text{OR}^2)$ and $\text{R}_2^1\text{CHal}(\text{OX})$

##### 4.02.1.3.1 $\alpha$ -Haloalkyl esters— $\text{R}_2^1\text{CHal}(\text{OCOR}^2)$

###### (i) $\alpha$ -Fluoroalkyl esters— $\text{R}_2^1\text{CF}(\text{OCOR}^2)$

The reaction of acyl fluorides with formaldehyde gives fluoromethylcarboxylates [<1995T5807>](#). The  $\alpha$ -fluoroalkyl ester functional group can also be constructed by the addition of fluorine or fluorine-containing reagents to enol esters. Thus, the anodic fluorination of the camphanyl enol ester **126** results in a mixture of diastereomeric  $\alpha$ -fluoroalkyl esters **127** (Equation (80)) [<1994TA1909>](#). Similarly the reaction of *t*-butyl hypofluorite, a source of electrophilic *t*-butoxylum ion ( $\text{Bu}^t\text{O}^+$ ), with indenyl acetate results in the formation of a product mixture from which the unstable  $\alpha$ -fluoroalkyl ester **128** was isolated in low yield (Equation (81)) [<1998JOC4632>](#). The perfluorination of the secondary alkyl esters **129** (Equation (82)) [<1998JA7117>](#) and **130** (Equation (83)) [<1994JOC5883>](#), and the selective introduction of fluorine at the secondary  $\gamma$ -carbon of  $\gamma$ -valerolactone (Equation (84)) [<2002TL1503>](#) are the only recent examples of an obvious route to  $\alpha$ -fluoroalkyl esters. The substitution reaction of  $\text{BzCl}$  with perfluoroisopropoxide, generated by the reaction of hexafluoroacetone with fluoride anion, gives the  $\alpha$ -fluoroalkyl ester **131** (Equation (85)) [<1994JFC\(69\)103>](#).





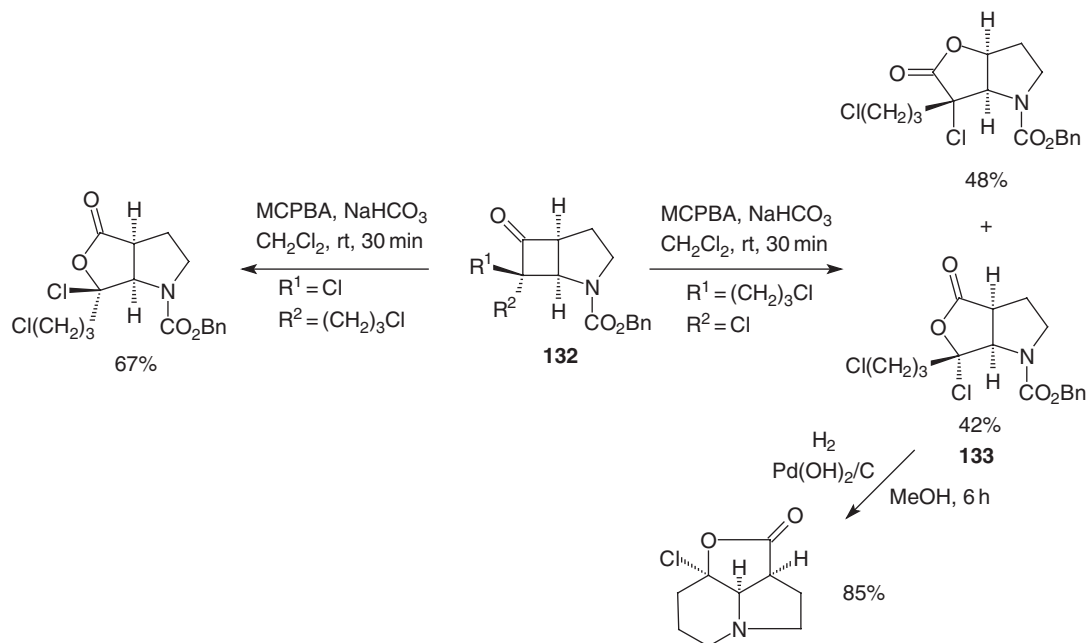
(ii)  $\alpha$ -Chloroalkyl esters,  $R_1^2\text{CCl}(\text{OCOR}^2)$

The thionyl chloride-mediated halolactonization of  $\gamma$ -keto carboxylic acids allows cyclic  $\alpha$ -chloroalkyl esters to be prepared in high yield. The standard reagent used for this transformation is  $\text{SOCl}_2$  (Table 8, entries 1–3 and 6–7), although  $(\text{COCl})_2$  (Table 8, entry 4),  $\text{PCl}_3$  (Table 8, entry 5), and  $\text{PCl}_5$  (Table 8, entry 8) have also been successfully used. Another route to  $\alpha$ -chloroalkyl

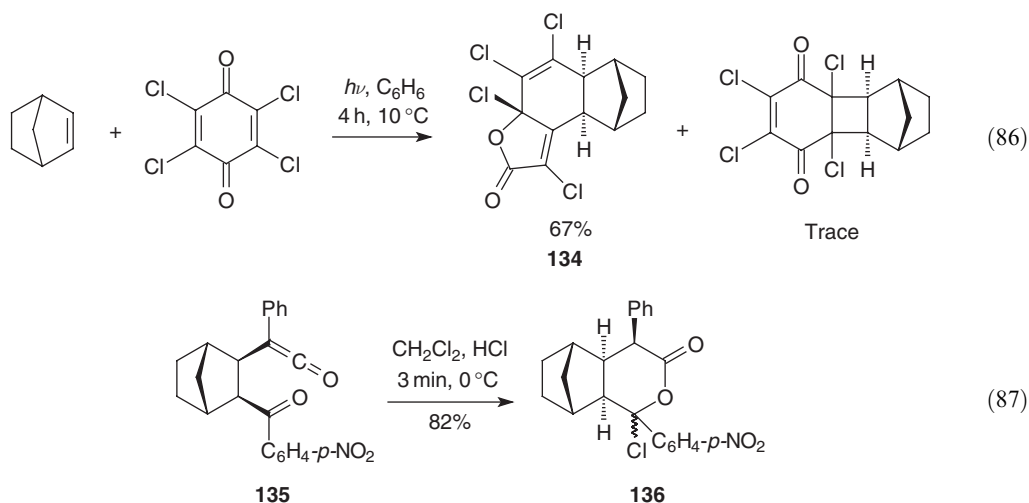
**Table 8** Preparation of  $\alpha$ -chloroalkyl esters from  $\gamma$ -keto carboxylic acids

Entry	Product	Reactant	Conditions	Yield (%)	References
1	R = Ph		$\text{SOCl}_2$ , DMF, 17 h, rt	100	<1999SL997>
2	R = 2,5-Me <sub>2</sub> C <sub>6</sub> H <sub>3</sub>		$\text{SOCl}_2$ , DMF, 20 h, rt	87	<1993HCA1821>
3	2-Quinoliny		$\text{SOCl}_2$ , rt, 0.5 h, reflux		<1995KGS938>
4	R = Me, X = OMe		$(\text{COCl})_2$ , C <sub>6</sub> H <sub>6</sub> , 20 min, 70 °C		<1995JCR(M)526>
5	R = Ph, X = NO <sub>2</sub>		$\text{PCl}_3$ , 48 h, rt	91	<1998ZPK2029>
6	R = H, n = 2, X = CH <sub>2</sub>		$\text{SOCl}_2$ , 2 h, 0 °C	100	<1995LA797>
7	R = Me, n = 1, X = CO		$\text{SOCl}_2$ , 15 min, reflux	85	<1998SC3041>
8	R = Me, n = 2, X = CH <sub>2</sub>		$\text{PCl}_5$ , 30 min, 60 °C	56	<1995LA797>

esters, which could be generally useful, involves the Baeyer–Villiger oxidation of the  $\alpha$ -chloro-cyclobutanone **132** (Scheme 20) <2002JOC3651>. However, as is often the case, the regiochemistry of this Baeyer–Villiger reaction is crucially dependent on the stereochemistry of the reactant. The Baeyer–Villiger product **133** was converted to another  $\alpha$ -chloroalkyl ester via hydrogenolysis of the C–N bond. The photochemical reaction of chloranil and norbornene gives a complex  $\alpha$ -chloroalkyl ester **134** (Equation (86)), which is the end result of a series of rearrangements that occurs following an initial [4+2]-cycloaddition <1999JCS(P1)2813>. The addition of HCl to the ketene **135** results in the formation of the  $\alpha$ -chloroalkyl ester **136** (Equation (87)) <1995JPR659>, presumably the result of intramolecular trapping of the intermediate carbocation.



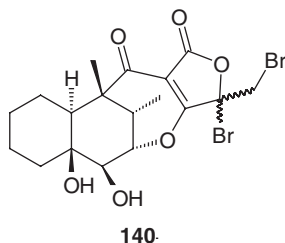
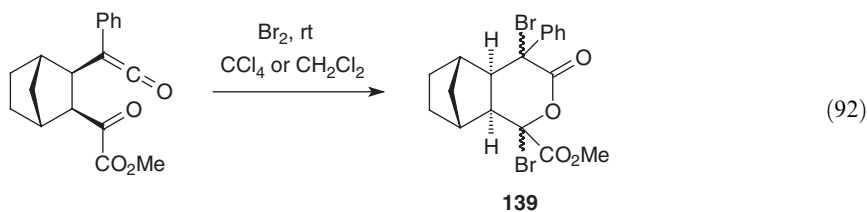
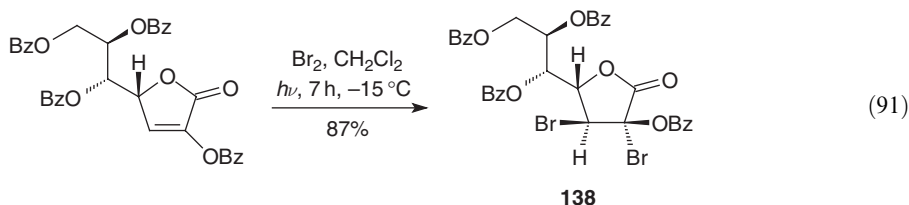
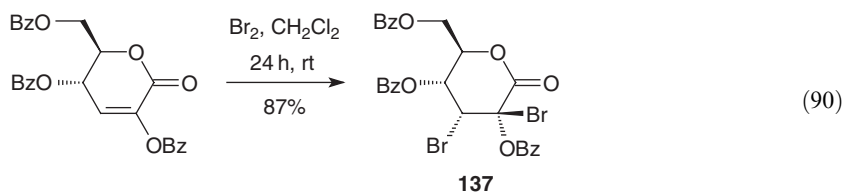
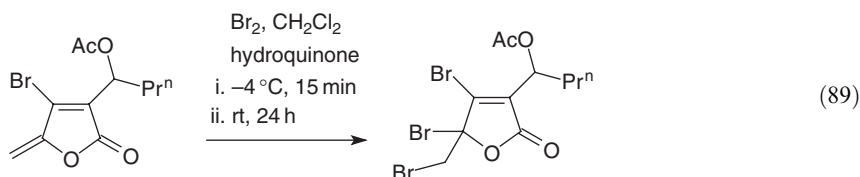
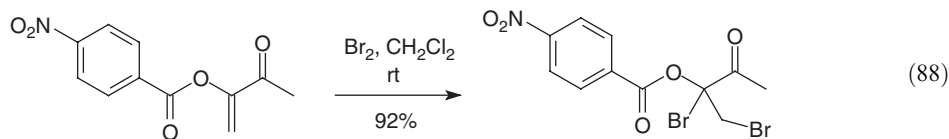
Scheme 20



(iii)  $\alpha$ -Bromoalkyl esters— $R_2^1\text{CBr}(\text{OCOR}^2)$

The ionic addition of bromine to enol esters has also been used extensively to produce  $\alpha$ -bromoalkyl esters (Equation (88)) <1995T3979>. In one case hydroquinone has been used to ensure that radical allylic bromination does not compete (Equation (89)) <1995JOC1814>. The

*trans*-stereochemistry of the  $\alpha$ -bromoalkyl benzoate **137** (Equation (90)) has been attributed to steric control by the C-4 substituent and charge stabilization in the intermediate bromonium ion due to the benzyloxy substituent <1995CAR(269)99>. Interestingly, the same product is obtained when the reaction is irradiated and, as is the case with furanose **138** (Equation (91)), allylic bromination does not appear to be a problem. The possibility of intramolecular interception of intermediate bromonium ions is demonstrated by the formation of the dibromolactone **139** (Equation (92)) <1998JOC6000, 1998JCS(P1)2031>. The enol ester to  $\alpha$ -bromoalkyl ester transformation is also involved in the formation of the dibromotetradecamycin **140** <1995JAN1330>.



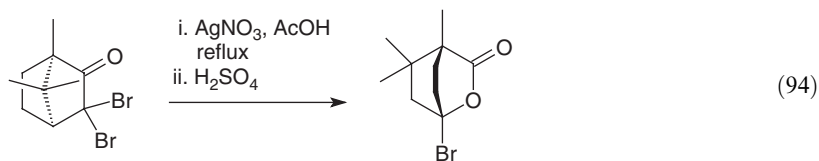
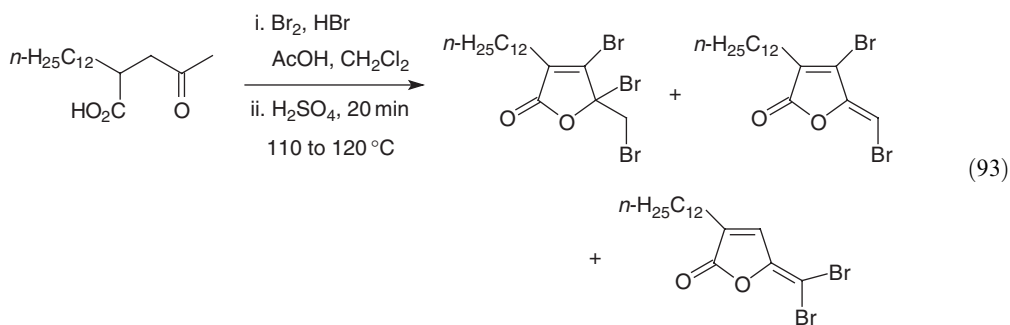
The allylic bromination of furanones has been used in the preparation of  $\alpha$ -bromoalkyl esters, which are useful in the synthesis of metabolites of marine algae and sponges (Table 9, entries 1–3), with use being made of all the standard initiators: AIBN, (BzO)<sub>2</sub>, and light. The formation of the dibromoadducts **141** (Table 9, entry 2) and **142** (Table 9, entry 4) results from initial allylic bromination, followed by dehydrobromination and bromination of the alkene thus formed. Brominated furanones containing



the  $\alpha$ -bromoalkyl ester group have also been prepared from  $\gamma$ -keto carboxylic acids by  $\alpha$ -bromination of the ketone followed by acid promoted cyclization (Equation (93)) <1997T15813>.  $\alpha$ -Bromoalkyl esters have also been produced by bromination of a pagodane bis-lactone <1997LA2069> and through the rearrangement of 3,3-dibromocamphor (Equation (94)) <1998AJC97>

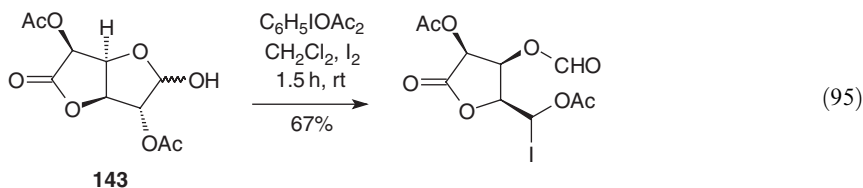
**Table 9** Preparation of  $\alpha$ -bromoalkyl esters by allylic bromination

Entry	Product	Reactant	Conditions	Yield (%)	References
1			NBS, CCl <sub>4</sub> 55, -60 °C, 2.5 h, <i>hν</i>	88	<1995JOC1814>
2			NBS, AIBN, CCl <sub>4</sub> , 72 h, reflux	63	<1994T12457>
3			NBS, AIBN, CCl <sub>4</sub> , 15 min reflux	> 46	<1995JCS(P1)1483>
4			NBS, (BzO) <sub>2</sub> , CHCl <sub>3</sub> , 3 h, reflux		<2002CPB1479>



(iv)  $\alpha$ -Iodoalkyl esters— $R_2^1CI(OCOR^2)$ 

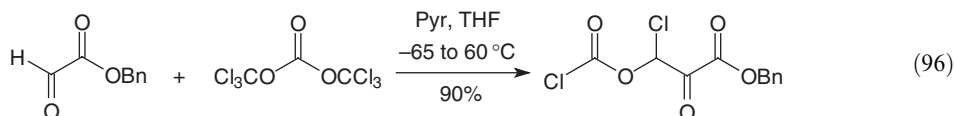
The Finkelstein reaction continues to be the most important method of preparing  $\alpha$ -iodoalkyl esters <1999BMCL1921, 1995TL655>. The tandem oxidative cleavage–iodination of the hemiacetal **143** (Equation (95)) also results in the formation of an  $\alpha$ -iodoalkyl ester <1998JOC8092, 1998JOC2099>. Only one tertiary  $\alpha$ -iodoalkyl ester has been reported since 1995: the remote oxidation of the angular methyl group in the eudesmanolide **124** with iodobenzene diacetate results in the formation of a range of products including the  $\alpha$ -iodoalkyl ester **125** (Equation (79)) <1994JOC6395>.



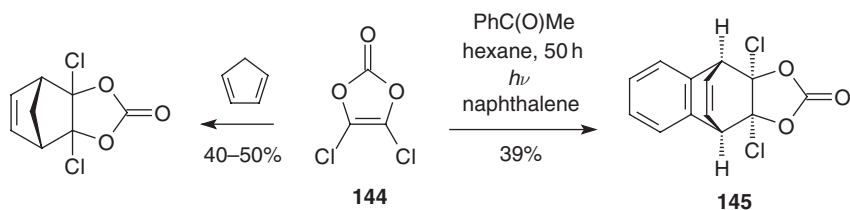
#### 4.02.1.3.2 $\alpha$ -Haloalkyl haloformates— $R_2^1CHalOCOHal$ and carbonate derivatives— $R_2^1CHalOCOOR^2$ , etc.

(i)  $\alpha$ -Haloalkyl haloformates— $R_2^1CHal(OCOHal)$ 

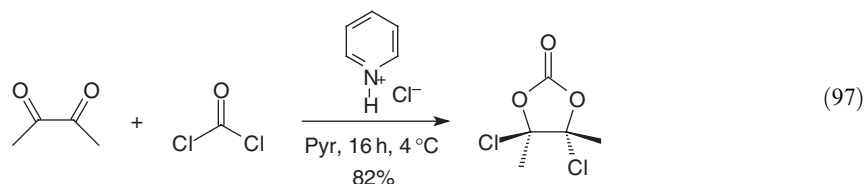
The preparation of fluoromethyl fluoroformate by the reaction of the commercially available chloromethyl chloroformate with KF in the presence of a crown ether has been reported <1995T5807>. The reaction of aldehydes with trichloromethyl carbonate, from which phosgene is formed *in situ*, continues to be used to prepare  $\alpha$ -chloroalkyl chloroformates (Equation (96)) <2001TL7751, 2002S365>.

(ii)  $\alpha$ -Haloalkyl alkyl and aryl carbonate derivatives— $R_2^1CHalOCOOR^2$ , etc.

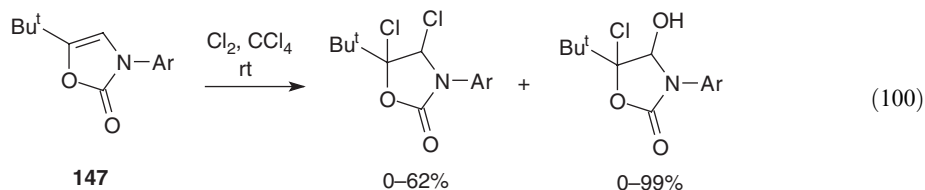
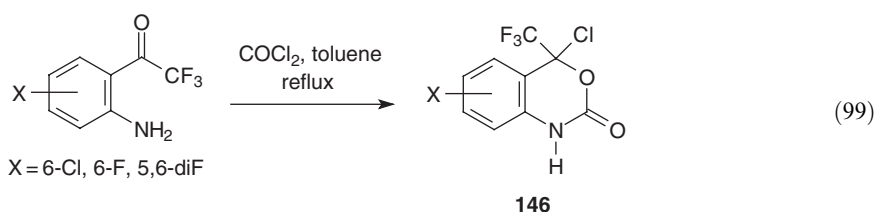
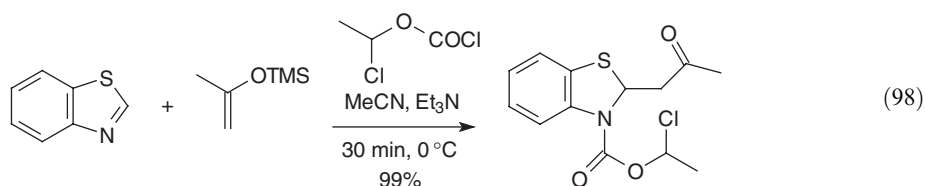
The reaction of alcohols and phenols with chloromethyl chloroformate is a convenient way to prepare  $\alpha$ -chloroalkyl carbonates <1995JMC3983>. The photosensitized cycloaddition reaction of dichlorovinylene carbonate **144** with naphthalene (Scheme 21) <1996LA303> produces a fused bis( $\alpha$ -chloroalkyl) carbonate **145** which is quite stable and can be purified by sublimation. Dichlorovinylene carbonate also undergoes a Diels–Alder reaction with cyclopentadiene to give another bis( $\alpha$ -chloroalkyl) carbonate (Scheme 21) <2000MI1062>. The same functional group is again created when phosgene reacts with butane-2,3-dione in the presence of pyridinium hydrochloride (Equation (97)) <1993SC847>.



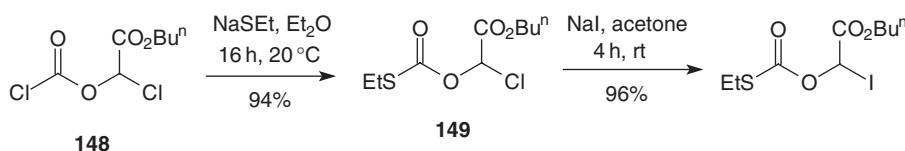
Scheme 21



The reaction of fluoromethyl fluoroformate with amines has been used to prepare *O*-fluoromethyl carbamates <1995T5807>.  $\alpha$ -Chloroalkyl carbamates are available through the reaction of amines with chloromethyl chloroformate <1997JA7230, 1995JOC4549, 2003BMCL65>. The addition reaction of imidazoles and thiazoles with silyl enol ethers in the presence of chloromethyl chloroformate also results in the formation of carbamates via an unstable *N*-acylated quaternary azole salt (Equation (98)) <2000T4383>. Six-membered cyclic  $\alpha$ -chloroalkyl carbamates **146** have been prepared in high yield by the reaction between phosgene and a range of substituted 2-aminotrifluoroacetophenones (Equation (99)) <2001BMCL1177>. Chlorination of oxazol-2-ones **147** gives a mixture of two five-membered cyclic  $\alpha$ -chloroalkyl carbamates, the composition of the product mixture depending on the nature of the *N*-aryl group (Equation (100)) <1998MI5305>.



The reaction of the  $\alpha$ -chloroalkyl chloroformate **148** with sodium ethanethiolate gives the  $\alpha$ -chloroalkyl thiocarbonate **149** which can be converted to the corresponding iodo compound using a Finkelstein reaction (Scheme 22) <2002S365>. Chloromethyl chloroformate undergoes a similar reaction with ethanethiolate <1999ACS594>.



Scheme 22

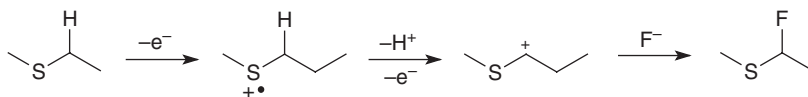
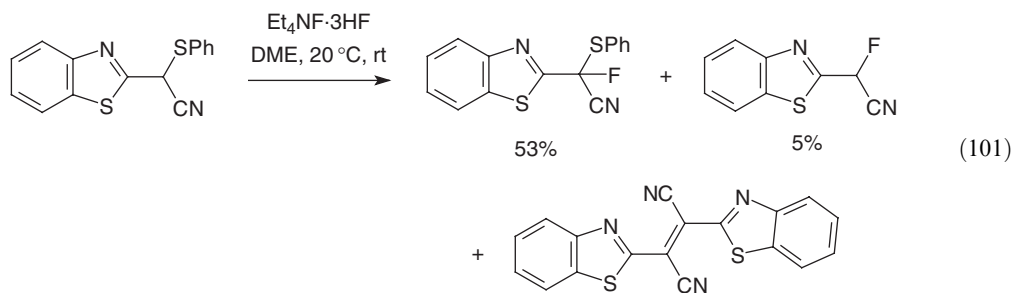
## 4.02.2 HALOGEN AND SULFUR DERIVATIVES— $R_2^1\text{CHal}(\text{SR}^2)$ , etc.

### 4.02.2.1 Dicoordinate $\alpha$ -Halosulfur Derivatives— $R_2^1\text{CHal}(\text{SR}^2)$

#### 4.02.2.1.1 $\alpha$ -Halosulfides— $R_2^1\text{CF}(\text{SR}^2)$

##### (i) $\alpha$ -Fluorosulfides— $R_2^1\text{CF}(\text{SR}^2)$

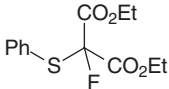
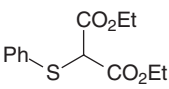
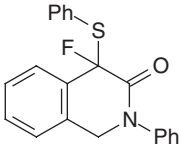
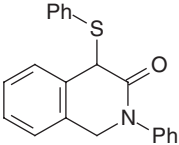
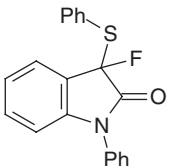
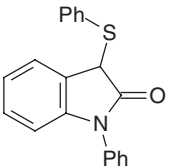
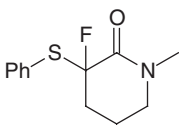
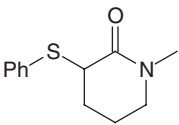
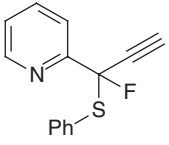
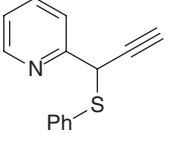
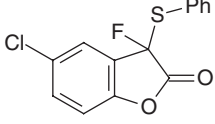
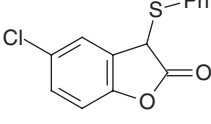
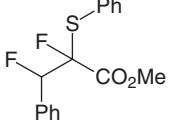
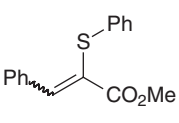
$\alpha$ -Fluorosulfides are important intermediates in the preparation of fluorine containing  $\beta$ -lactams, amino acids, and other substances of importance in human and veterinary medicine. Many, however, are not stable to standard purification and full characterization must take place at the level of the sulfoxide or sulfone. The selective introduction of a fluorine atom into a molecule can be achieved electrochemically or using one of a range of reagents of which the best known is DAST. In its original form electrochemical fluorination suffered from a lack of selectivity and from the fact that fluoride ions are poor nucleophiles. Recent developments have led to significant improvements and the method now provides an alternative to the use of DAST and other chemical fluorinating agents (Table 10) <1998JFC(87)215>. The use of additives has occasionally proved beneficial in providing a clean reaction (Table 10, entry 5) and the formation of dimers and desulfurized products has been observed (Equation (101)) <1999JFC(99)189>. The fluorination reaction involves initial oxidation of the S atom at the anode giving a radical cation (Scheme 23). The subsequent loss of an  $\alpha$ -proton and of another electron gives an  $\alpha$ -carbocation which reacts with fluoride ion.



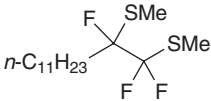
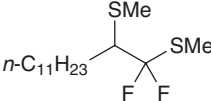
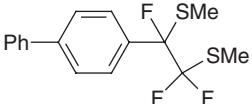
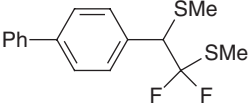
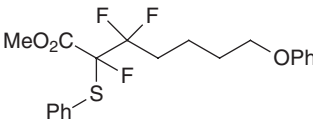
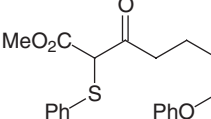
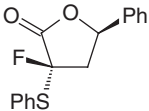
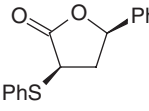
Scheme 23

A very extensive range of chemical reagents is also available for the preparation of mono- $\alpha$ -fluorosulfides, most of which are commercially available (Table 11). In addition to DAST <1995TL5007, 1996TL8759> and DAST/NBS <1994TL85>, they include HF/pyridine/NBS or NIS (Table 11, entry 1) <1994TL85>,  $\text{Bu}_4\text{NH}_2\text{F}_3/1,3$ -dibromodimethyl-5,5-hydantoin (Table 11, entry 2), MeDAST (Table 11, entry 3) <1995TL5007>,  $\text{F}_2\text{IC}_6\text{H}_4\text{Me}$  (Table 11, entry 4) <2001TL8523, 2002JCS(P1)2816>, and  $\text{IF}_5/\text{Et}_3\text{N}/\text{HF}$  (Table 11, entry 5). The recent use of DAST for the fluorination of sulfides has been reviewed <2002S2561>. These reagents have somewhat different selectivity/reactivity profiles but all are considered to proceed via a fluoropummer-type mechanism. Reagents such as DAST, which are based on the N-SF<sub>3</sub> group, have limited thermal stability and this restricts the usefulness of these reagents if the reaction requires forcing conditions. The use of *N*-fluoropyridinium triflates (Table 11, entry 6), and Selectfluor (Table 11, entry 7b), sources of electrophilic fluorine, for the fluorination of sulfides has been reviewed <1996CR1737>. Selectfluor is usually employed to  $\alpha$ -fluorinate a sulfide attached to an active methylene group <1995TL5007>, but it has also been used to fluorinate an unactivated sulfide in the presence of  $\text{Et}_3\text{N}$  (Table 11, entry 7a). There has been only one recent example of the generation of  $\alpha$ -fluorosulfides through the deoxyfluorination of a sulfoxide, a previously

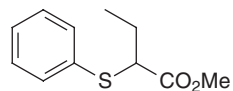
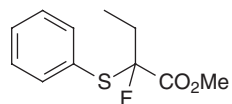
**Table 10** Electrochemical preparation of  $\alpha$ -fluorosulfides

Entry	Product	Reactant	Conditions	Yield (%)	References
1			0.37 M $\text{Et}_3\text{N}\cdot 3\text{HF}$ , MeCN, rt	77	<1995JOC3459>
2			$\text{Et}_4\text{NF}\cdot 3\text{HF}$ , rt, MeCN	71	<1997JOC8773>
3			$\text{Me}_4\text{NF}\cdot 4\text{HF}$ , rt, MeCN	64	<1997SL655>
4			$\text{Et}_3\text{N}\cdot 3\text{HF}$ , rt, MeCN	69	<1999ACS887>
5			0.33 M $\text{Et}_4\text{NF}\cdot 3\text{HF}$ , DME, $\text{Ph}_2\text{S}$	55	<1998JFC(87)203>
6			$\text{Et}_4\text{NF}\cdot 4\text{HF}$ , DME, rt	42	<1999JFC(99)189>
7			$\text{Et}_3\text{N}\cdot 3\text{HF}$ , MeCN, 13 °C	75	<1995T2605>

**Table 11** Preparation of  $\alpha$ -fluorosulfides by selective monofluorination

Entry	Product	Reactant	Conditions	Yield (%)	References
1			HF-pyridine, NIS, CH <sub>2</sub> Cl <sub>2</sub> , 0 °C	55	<1995TL8243>
2			Bu <sub>4</sub> NH <sub>2</sub> F <sub>3</sub> , 1,3-dibromo- 5,5-dimethyl hydantoin, CH <sub>2</sub> Cl <sub>2</sub> , 20 min, rt	58	<1998BCJ2687>
3			MeDAST, CH <sub>2</sub> Cl <sub>2</sub> , rt, 48 h	75	<1996TL4941>
4			Difluoroiodotoluene, CH <sub>2</sub> Cl <sub>2</sub> , 0 °C, 7 h	62	<2002JCS(P1)2809>

5

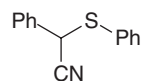
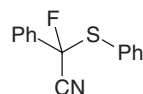


IF<sub>5</sub>-Et<sub>3</sub>N-3HF,  
hexane, 36 h, 40 °C

82

&lt;2002BCJ1597&gt;

6

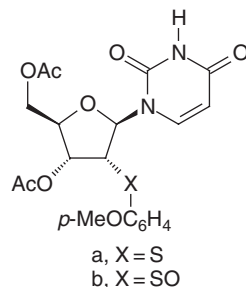
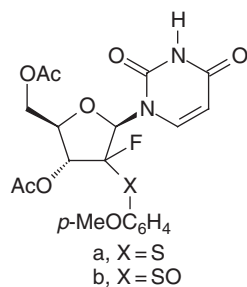


1-Fluoropyridinium  
triflate,  
ClCH<sub>2</sub>CH<sub>2</sub>Cl,  
3.5 h, reflux

77

&lt;1999S676&gt;

7



a: i. Selectfluor,  
MeCN, rt,  
15 min  
ii. Et<sub>3</sub>N, MeCN,  
10 min  
b: (2-methoxy-ethyl)-  
aminosulfur tri-  
fluoride, SbCl<sub>3</sub>,  
CH<sub>2</sub>Cl<sub>2</sub>, 16 h, rt

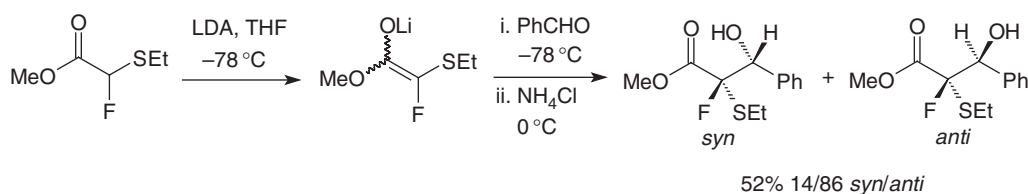
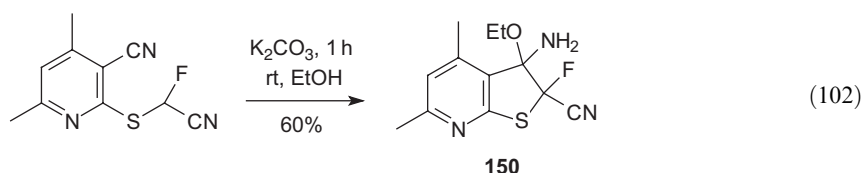
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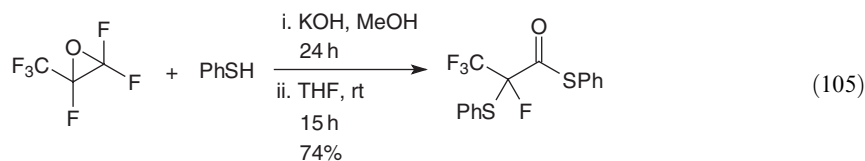
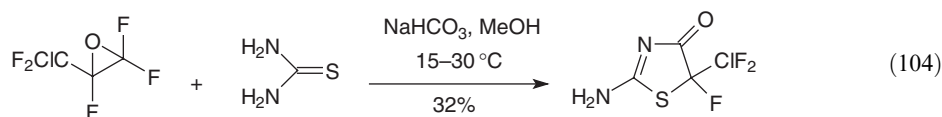
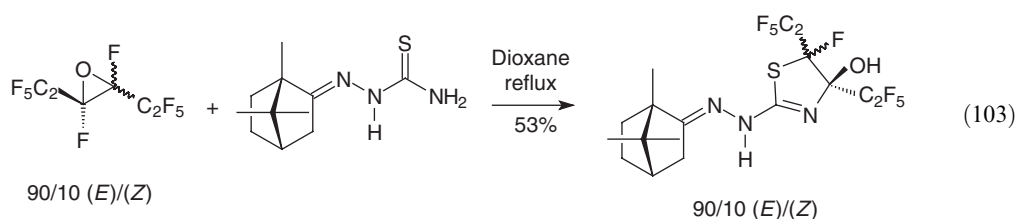
&lt;1995SC725&gt;

commonly used synthetic method. This involved the use of bis(2-methoxyethyl)aminosulfur trifluoride (Table 11, entry 7b), which is reported to have enhanced reactivity and thermal stability relative to DAST. Its use has been reviewed <2002S2561>.

An extensive range of tertiary  $\alpha$ -fluorosulfides has been prepared through the addition of  $\alpha$ -fluoro- $\alpha$ -thioester enolate ions to aldehydes and ketones (Scheme 24) <1996TL8759, 1998T10801, 2002T4759>.  $\alpha,\beta$ -Unsaturated aldehydes are reported to undergo exclusive 1,2-addition <1998T10801>. An intramolecular variation of this reaction involves the addition of anions from  $\alpha$ -fluoro- $\beta$ -thionitriles and esters to a cyano group (Equation (102)) <1995JOC7654, 1998BCJ2387>, the product **150** being obtained as a single diastereomer whose stereochemistry was not determined. The addition of sulfur nucleophiles to fluorinated epoxides also leads to the formation of compounds with an  $\alpha$ -fluorosulfide functional group. Thus, the addition of thiosemicarbazones (Equation (103)) <2003JFC(120)41> and thiosemicarbazides <2000JFC(104)155> to a range of fluorinated epoxides gives 4-hydroxy-5-fluoro-1,3-thiazoliny derivatives. In a similar fashion thiourea affords a 5-fluorothiazol-4-one (Equation (104)) <2001JFC(108)1>. Ring opening of hexafluoropropylene oxide with phenyl sulfide anion also gives on  $\alpha$ -fluorosulfide (Equation (105)) <1999JCS(P1)569>.

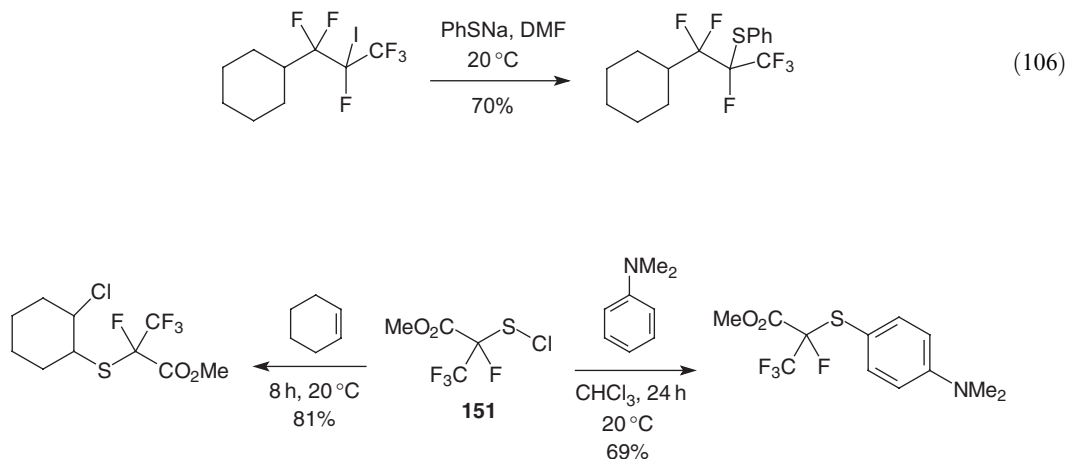


Scheme 24





A number of substitution reactions have also been used to prepare  $\alpha$ -fluorosulfides. Thus the nucleophilic displacement of iodide from a fluoriodomethylene by thiolate has been reported (Equation (106)) <2001CC2428>. The  $\alpha$ -fluorosulfonyl chloride **151** undergoes an extensive range of substitution reactions, generating  $\alpha$ -fluorosulfides with substrates which include ketones, 1,3-diketones, pyrrole, and DMAP (Scheme 25); it also generates  $\alpha$ -fluorosulfides through addition to alkenes (Scheme 25) <1996IZV1745>.

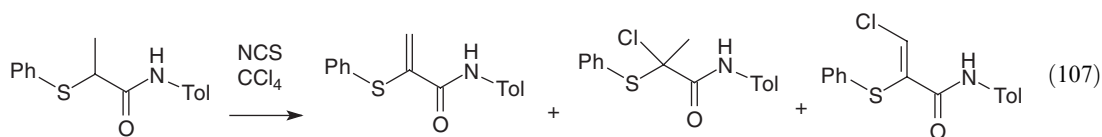


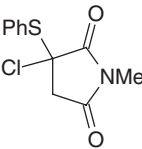
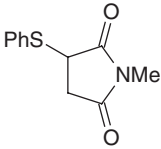
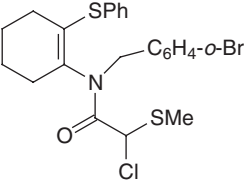
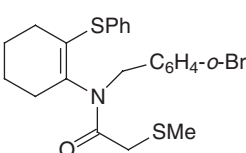
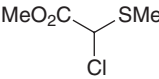
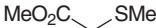
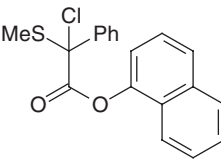
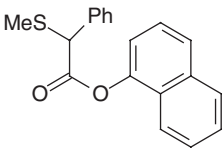
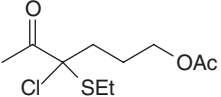
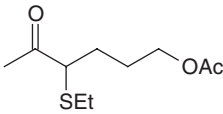
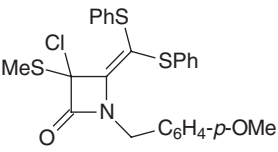
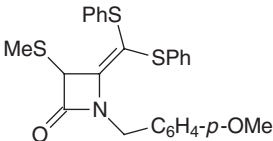
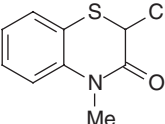
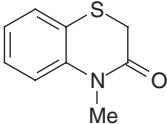
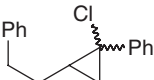

Scheme 25

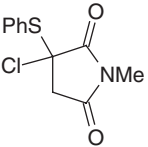
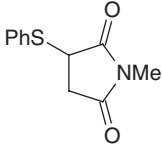
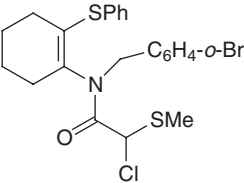
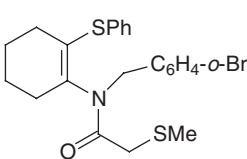
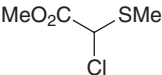
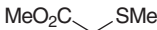
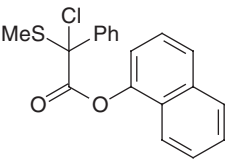
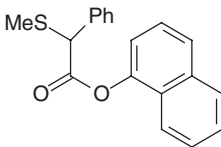
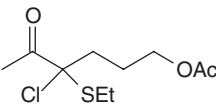
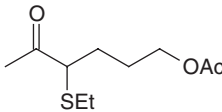
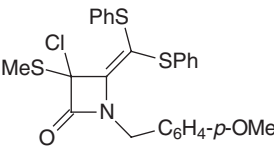
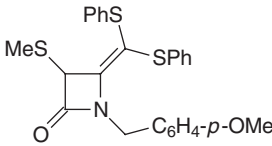
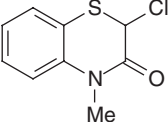
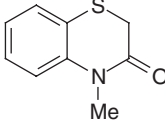
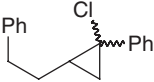

(ii)  $\alpha$ -Chlorosulfides,  $R_2^1CCl(SR^2)$

$\alpha$ -Chlorosulfides are important synthetic intermediates as they are easily prepared in high yield by chlorination of the readily available sulfides, and as the presence of a good leaving group on the  $\alpha$ -carbon facilitates reaction at this center particularly in terms of C—C bond formation. They have limited thermal stability and can decompose on chromatography, and so if required for synthetic purposes they are generally used immediately without purification. The standard method for preparing  $\alpha$ -chlorosulfides continues to be the direct chlorination of the appropriate sulfide using NCS or sulfonyl chloride ( $SO_2Cl_2$ ). The former has the advantage that it is a solid, easily handled, reagent that is compatible with a wider range of functional groups as it does not produce HCl when it reacts with the sulfide. However  $SO_2Cl_2$  is more reactive and should be considered if NCS does not produce satisfactory results.

In the preparation of  $\alpha$ -chlorosulfides, NCS is almost always used in  $CCl_4$  as the reaction by-product, succinimide, is insoluble in this solvent and can thus be removed after the reaction by simple filtration. NCS has been used for chlorinating secondary and tertiary alkyl sulfides containing a very wide range of functional groups (Table 12); there are relatively few examples of its use with primary sulfides <2001T5369, 1996IJC(B)1331>. The reaction is usually carried out at 0–20 °C but occasionally refluxing is required (Table 12, entry 1). In general the reaction results in clean monochlorination but there are examples where a mixture is obtained as a result of the product reacting further with the reagent (Equation (107)) <1995TL467>. The reaction of NCS with unsymmetrical sulfides is regiospecific with the product being that which results from reaction at the center having the more acidic hydrogen (Table 12, entries 2–6).

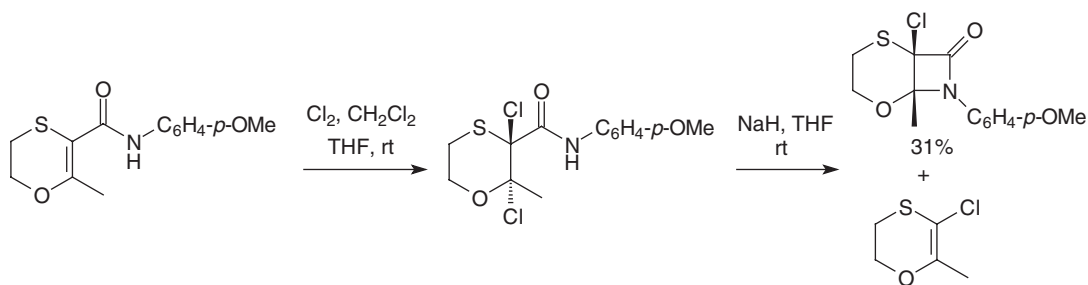


Entry	Product	Reactant	Conditions	Yield (%)	References
1			CCl <sub>4</sub> , 48 h, reflux	93	<1995T12797>
2			CCl <sub>4</sub> , rt		<1997H37>
3			CCl <sub>4</sub> , 2 h, rt	> 78	<1997JCS(P1)835>
4			CCl <sub>4</sub> , 1.5 h, 25 °C	> 77	<1999TL451>
5			CCl <sub>4</sub> , 1 h, 0 °C	100	<1996S1131>
6			CCl <sub>4</sub> , 15 h, rt	> 59	<1995T2929>
7			CH <sub>2</sub> Cl <sub>2</sub> , 5 h, rt	> 82	<1997JCS(P1)309>
8			CCl <sub>4</sub> , 20 h, rt	> 90	<2001T5369>

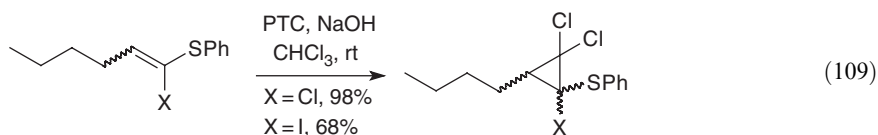
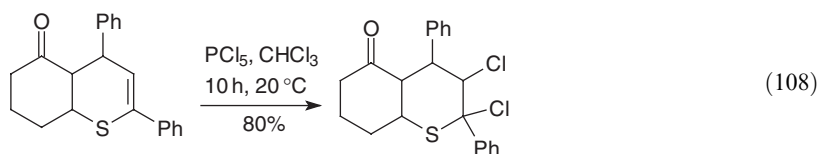
Entry	Product	Reactant	Conditions	Yield (%)	References
1			CCl <sub>4</sub> , 48 h, reflux	93	<1995T12797>
2			CCl <sub>4</sub> , rt		<1997H37>
3			CCl <sub>4</sub> , 2 h, rt	> 78	<1997JCS(P1)835>
4			CCl <sub>4</sub> , 1.5 h, 25 °C	> 77	<1999TL451>
5			CCl <sub>4</sub> , 1 h, 0 °C	100	<1996S1131>
6			CCl <sub>4</sub> , 15 h, rt	> 59	<1995T2929>
7			CH <sub>2</sub> Cl <sub>2</sub> , 5 h, rt	> 82	<1997JCS(P1)309>
8			CCl <sub>4</sub> , 20 h, rt	> 90	<2001T5369>

The main alternative to NCS in terms of chlorinating sulfides is  $\text{SO}_2\text{Cl}_2$ . Although a much wider range of solvents has been used with this reagent, including benzene,  $\text{CCl}_4$ , hexane, pyridine, and  $\text{CHCl}_3$ , the usual reaction conditions involve  $\text{CH}_2\text{Cl}_2$  at  $0$ – $25^\circ\text{C}$ . The general features of the reactions (Table 13) involving this reagent are similar to those involving NCS with the reagent being used with secondary and tertiary alkyl sulfides containing a wide range of functional groups. Chlorination of the furanone **152** (Table 13, entry 1) occurs readily with  $\text{SO}_2\text{Cl}_2$  but has been reported to be problematic with NCS. The reactions are again regiospecific with chlorination occurring on the  $\alpha$ -carbon carrying the most acidic hydrogen (Table 13, entry 2). Many of the reactions of this type do not involve stereogenic centers, and even where there is the possibility of diastereomers being produced, the stereochemistry of the products may not have been determined as both isomers are subsequently converted to a common product. However, the results for a number of reactions show that chlorination can be highly stereoselective (Table 13, entries 1, 3, and 4), the process resulting in an inversion at the  $\alpha$ -carbon. These reactions again involve a Pummerer-type mechanism and the migration of  $\text{Cl}^+$  from the sulfur is generally to the less hindered side. Chlorination of the dithiolodithiine **153** (Table 13, entry 5) is reported to be stereospecific, the migration of  $\text{Cl}^+$  following chlorination of the second sulfur again occurring to the less hindered side.

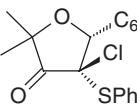
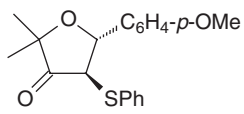
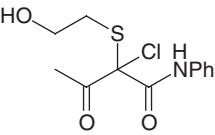
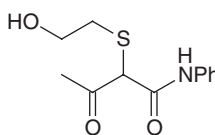
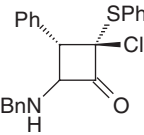
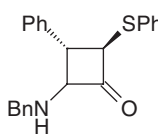
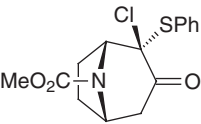
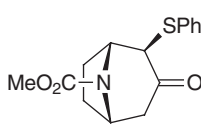
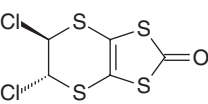
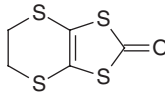
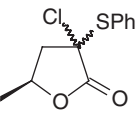
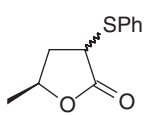
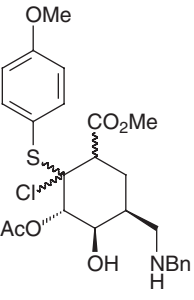
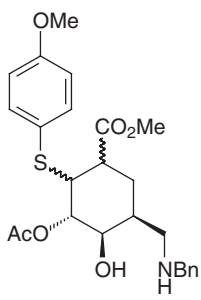
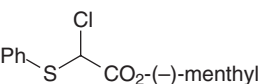
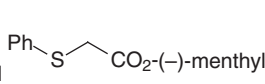
A range of varied addition reactions has been employed in preparing  $\alpha$ -chlorosulfides. This includes the addition of  $\text{Cl}_2$  to amido-5,6-dihydrooxathiines giving  $\alpha$ -chlorosulfides which can in turn be cyclized using base to give bicyclic azetidinones containing the same functional group (Scheme 26) <1999H(50)713>. A similar transformation has been achieved using  $\text{PCl}_5$  (Equation (108)) <1999KGS836>. The addition reactions of chloro- and sulfanylalkenes can also produce  $\alpha$ -chlorosulfides. The addition of dichlorocarbene to a 1-chlorovinyl thioether (Equation (109)) <1998SCI667>, the regioselective addition of an alkyl/thio radical pair to 2-chloroacrylonitrile (Equation (110)) <1995T1867>, and the addition of benzenesulfonyl chloride to the vinyl sulfide **154** (Equation (111)) <2002EJO4024> are examples of such reactions. The classical addition of a thiol to an aldehyde in the presence of  $\text{HCl}$  has been used to prepare a secondary  $\alpha$ -chlorosulfide (Equation (112)) <1998JOC3706>. In this case it was found that  $\text{SOCl}_2$  was required to drive the equilibrium involving the initially formed hemithioacetal to completion. A modified version of this reaction involving  $\text{TMSCl}$  instead of  $\text{HCl}$  has also been used to prepare primary  $\alpha$ -chlorosulfides <1996BMCL2053, 1998ZOR1305>.

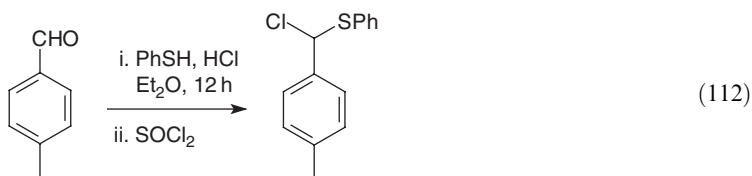
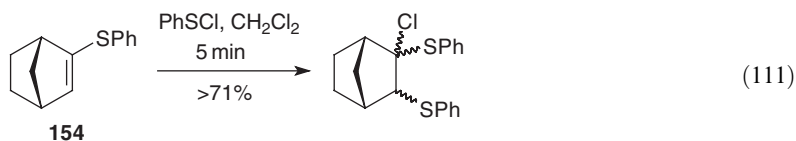
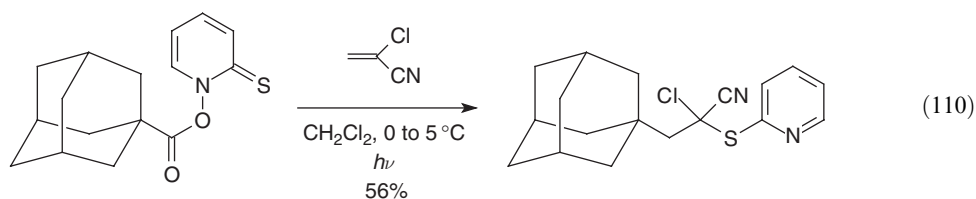


Scheme 26

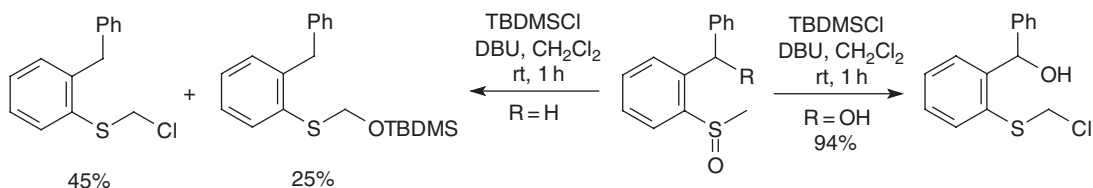
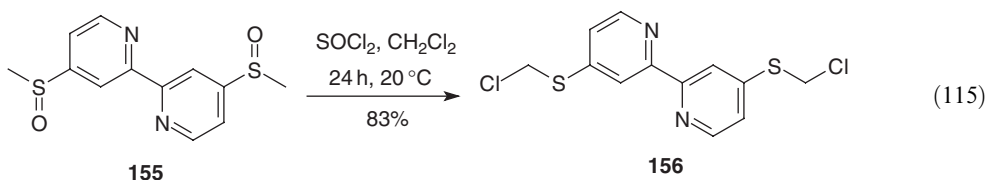
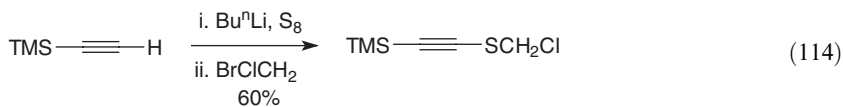
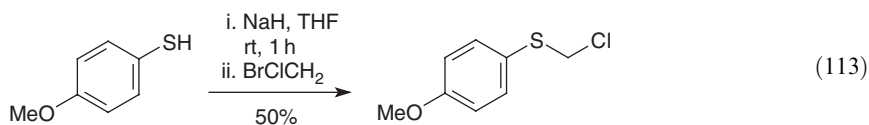


**Table 13** Preparation of  $\alpha$ -chlorosulfides by chlorination using sulfuryl chloride ( $\text{SO}_2\text{Cl}_2$ )

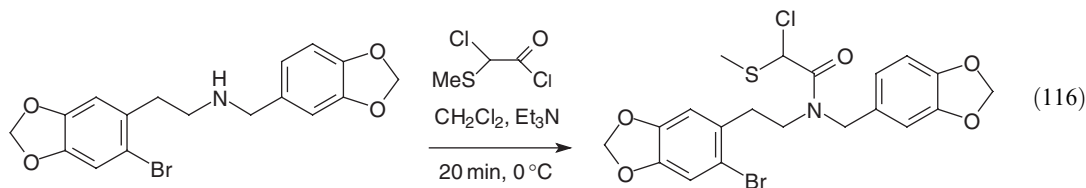
Entry	Product	Reactant	Conditions	Yield (%)	References
1		 <b>152</b>	$\text{CH}_2\text{Cl}_2$ , 3 h, $20^\circ\text{C}$	82	<1999JCS(P1)3667>
2			$\text{C}_6\text{H}_6$ , 2 h, rt,	94	<1995H(41)921>
3			$\text{CH}_2\text{Cl}_2$ , $0^\circ\text{C}$		<2000TL5577>
4			$\text{CCl}_4$ , 30 min, rt	97	<1998JCS(P1)3689>
5		 <b>153</b>	$\text{CCl}_4$ , 24 h, reflux	60	<2000CC1117>
6			$\text{CCl}_4$ , 2 h, $0^\circ\text{C}$	97	<2000T389>
7			$\text{CH}_2\text{Cl}_2$ , 20 min, $0^\circ\text{C}$	48	<1997T5195>
8			$\text{CH}_2\text{Cl}_2$ , $0^\circ\text{C}$	100	<2000TA2267>



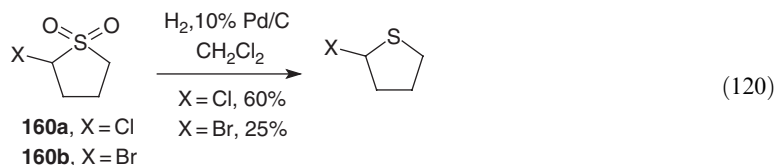
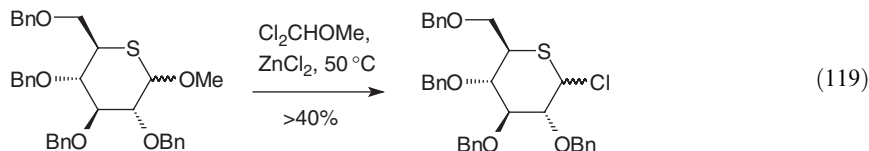
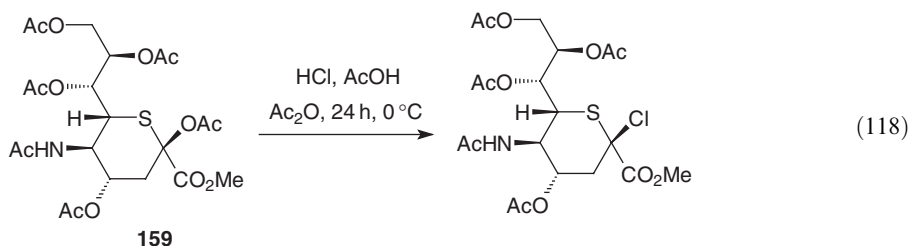
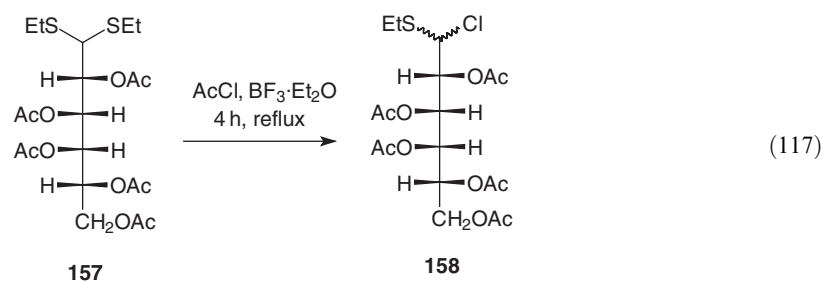
Substitution reactions involving bromochloromethane have been widely used to alkylate thiols producing chloromethyl sulfides (Equation (113)) <1996IJC(B)1331, 1995CC307, 1996JCS(P1)359, 1999SC1003>. This reagent has also been employed in constructing an alkynyl chloromethyl sulfide using  $S_8$  as the source of sulfur (Equation (114)) <2000JA7012>. Pummerer rearrangements are an important way of transforming  $\alpha$ -halosulfoxides into  $\alpha$ -halosulfides <1995T6819> and the use of  $SOCl_2$  to convert the sulfoxide **155** to the chloromethyl sulfide **156** (Equation (115)) <2001JCR(S)110> is typical of the standard approach adopted. An alternative approach involves treating an arylmethyl sulfoxide with a trialkylsilyl halide and a base to give a mixture of an  $\alpha$ -siloxy and an  $\alpha$ -chlorosulfide (Scheme 27) <1995TL2299, 1995T6819>. The reaction gives only the  $\alpha$ -chlorosulfide if an *o*-hydroxymethyl group is present. The use of  $SOCl_2$  to convert an  $\alpha$ -hydroxy sulfide to an  $\alpha$ -chlorosulfide has also been reported <1995JMC4393> and *N*-acylation with (chloromethylsulfanyl)acetyl chloride is a versatile method of introducing an  $\alpha$ -chlorosulfide group (Equation (116)) <2000CPB399>.



Scheme 27



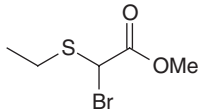
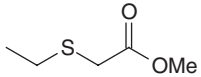
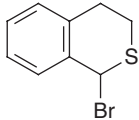
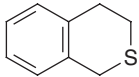
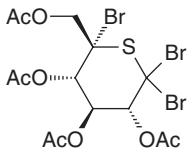
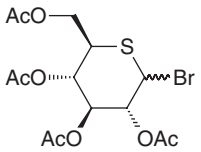
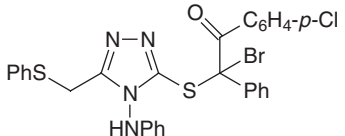
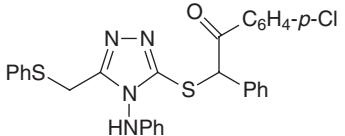
Carbohydrate chemistry also provides a number of examples of substitution reactions being used to construct  $\alpha$ -chlorosulfides. Thus, treating the dithioacetal **157** with AcCl gives the  $\alpha$ -chlorosulfide **158** as a 1:1 mixture of diastereomers (Equation (117)) <1997JOC1234>. Other examples include the displacement of acetate from the thiopyranose **159** using chloride (Equation (118)) <1998T4521> and the use of dichloromethyl methyl ether to convert a thiopyranoside to the corresponding thioglycosyl chloride (Equation (119)) <2001TL1197>. Finally in what is a reversal of the commonly used sulfide to sulfone oxidation, catalytic hydrogenation of the sulfone **160a** gives the corresponding  $\alpha$ -chlorosulfide (Equation (120)) <1998JOC9490>.



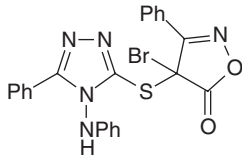
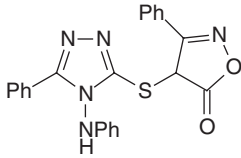
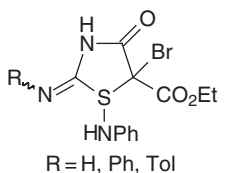
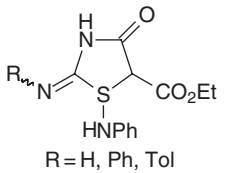
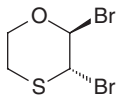
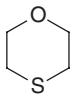
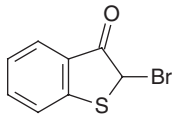
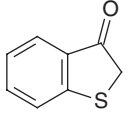
(iii)  $\alpha$ -Bromosulfides— $R_2^1CBr(SR^2)$

The greater reactivity and hence lower stability of  $\alpha$ -bromosulfides makes them less attractive than the chloro analogs as synthetic intermediates and in almost all cases necessitates their immediate use following preparation. Most of the approaches used in the synthesis of  $\alpha$ -chloro sulfides have found application in preparing the bromo compounds as well, the main difference being the involvement of radicals in the majority of the reactions used. Thus, the bromination of sulfides (Table 14) is one of the most widely used methods of preparing secondary and tertiary  $\alpha$ -bromosulfides, with NBS and Br<sub>2</sub> being the most commonly used reagents for the purpose.

**Table 14** Preparation of  $\alpha$ -bromosulfides by bromination of sulfides

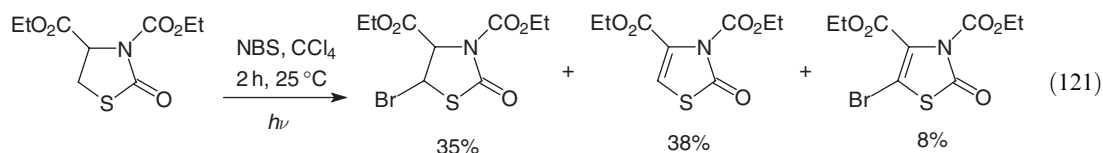
Entry	Product	Reactant	Conditions	Yield (%)	References
1			NBS, pentane, 0 °C	70	<1998T10801>
2			NBS, CCl <sub>4</sub> , 0.5 h, reflux		<1995JCS(P1)2845>
3			NBS, CCl <sub>4</sub> , 36 h, reflux, $h\nu$	30	<1996CAR(282)237>
4			Br <sub>2</sub> , AcOH, $h\nu$	70	<1995IJC(B)54>

**Table 14** (continued)

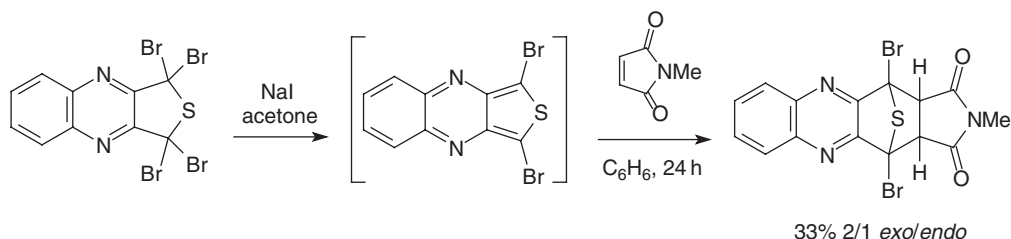
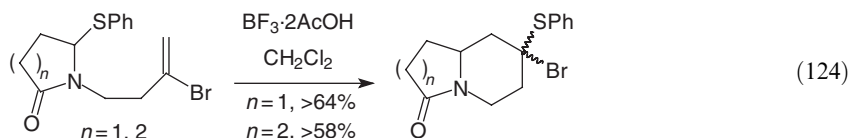
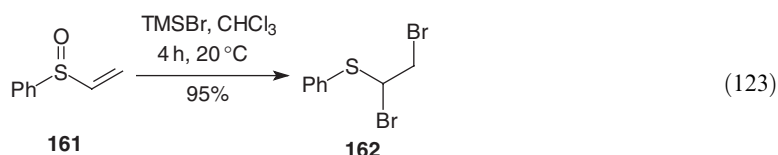
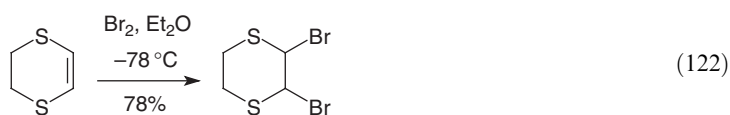
Entry	Product	Reactant	Conditions	Yield (%)	References
5			Br <sub>2</sub> , AcOH, <i>hν</i>	72	<1999IJC(B)218>
6	 R = H, Ph, Tol	 R = H, Ph, Tol	Br <sub>2</sub> , AcOH, <i>hν</i>	90	<1996IJC(B)373>
7			Br <sub>2</sub> , CH <sub>2</sub> Cl <sub>2</sub> , 4 h, reflux	100	<1996S198>
8			Br <sub>2</sub> , Et <sub>2</sub> O, 2 h, -10 °C to rt	91	<1999H(50)259>



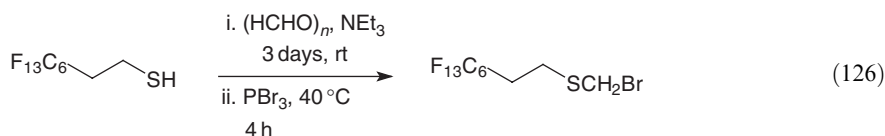
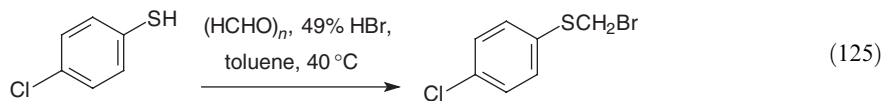
As with NCS, the reactions of NBS are generally regiospecific, giving rise to bromination at the carbon carrying the more acidic hydrogen or at that carbon which can give the more stable radical (Table 14, entries 1 and 2). Dehydrohalogenation occurs more readily for  $\alpha$ -bromo than for  $\alpha$ -chlorosulfides and this can result in the formation of product mixtures (Equation (121)) <1995H2701>. The conversion of a thiophene ring to a 2,3-dibromo-2,3-dihydrothiophene using NBS has also been reported <1997TL6501>. Bromination using  $\text{Br}_2$  usually involves irradiation, the reaction being subject to the same considerations as that involving NBS. Thus the regiochemistry is determined by the stability of possible intermediate radicals (Table 14, entry 4) and the final product can be formed by bromination of a sulfide, dehydrobromination and the addition of  $\text{Br}_2$  to the vinyl sulfide thus formed (Table 14, entry 7).



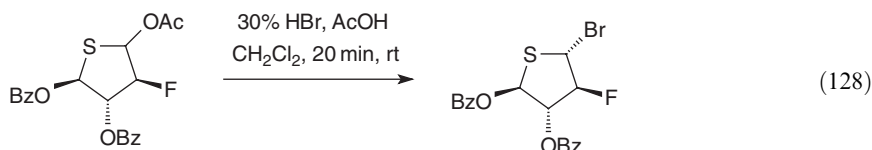
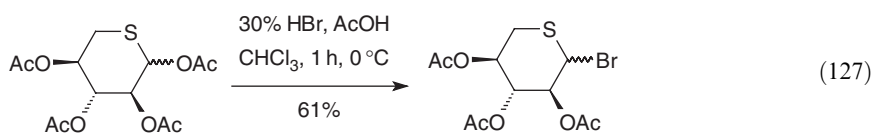
The direct addition of  $\text{Br}_2$  to vinyl sulfides (Equation (122)) <1998JOC3952, 1998ZOR1792, 1995PS(104)5> has also been used to prepare  $\alpha$ -bromosulfides. The conversion of the unsaturated sulfoxide **161** to the brominated product **162** using  $\text{TMSBr}$  is also believed to involve  $\text{Br}_2$ , (Equation (123)) <2002T10145> which is produced *in situ* as the sulfur function is reduced. Examples of the other types of addition reaction by which  $\alpha$ -bromosulfides could possibly be constructed, the addition of a sulfide to a vinyl bromide (Equation (124)) <2000T10159> and of an electrophilic carbon to a 1-bromovinyl thioether (Scheme 28) <1995JOC8283>, have also been reported. Recent preparations of primary  $\alpha$ -bromosulfides have been based exclusively on the addition of a thiol to formaldehyde in the presence of a brominating agent (Equation (125)) <1998JOC7348> (Equation (126)) <1996JFC(79)27>.



Scheme 28

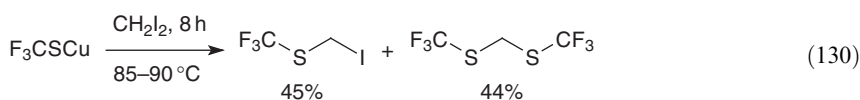
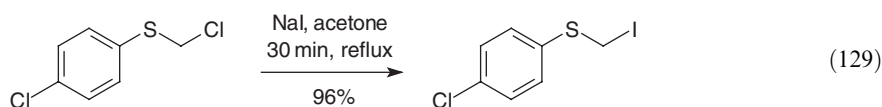


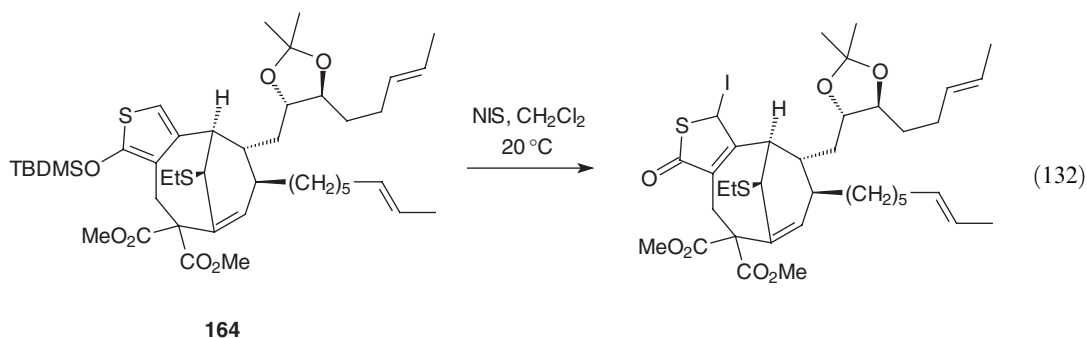
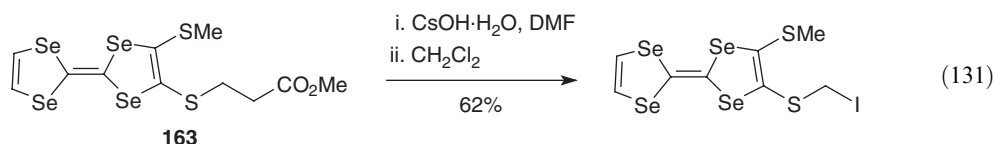
The displacement of acetate using HBr/AcOH is the standard method of producing thioglycosyl bromides. These unstable  $\alpha$ -bromosulfides are important synthetic intermediates and are generally used immediately after preparation without purification. The reaction has been used for both thiopyranoses (Equation (127)) <1997CAR(304)271, 1998HCA2043> and thiofuranoses (Equation (128)) <1999TL1937, 1999JOC7912>. The displacement of hydroxide from the anomeric carbon by bromide has also been reported <1998CAR(308)297>. Finally the reduction of the sulfone **160b** gives the corresponding  $\alpha$ -bromosulfide (Equation (120)) <1998JOC9490>. This involved a hydrogen pressure of 30 bar, in contrast to the chlorosulfone which was reduced at atmospheric pressure.



(iv)  $\alpha$ -Iodosulfides— $R_2^1\text{CI}(\text{SR}^2)$

The standard method of preparing primary  $\alpha$ -iodosulfides involves the displacement of chloride by iodide in acetone (Equation (129)) <1995T10593>. The reaction has been used to prepare simple <1998CEJ1480, 2000JOC3460>, steroidal <1997MI567>, and heterocyclic  $\alpha$ -iodosulfides <2000BMC2317> in high yield. The reaction of  $\text{F}_3\text{CSCu}$  with  $\text{CH}_2\text{I}_2$  (Equation (130)) <1996JFC(76)7>, and the CsOH promoted cleavage of the  $\beta$ -thioester **163** followed by alkylation with  $\text{CH}_2\text{I}_2$  (Equation (131)) <2001AG(E)1122>, also afford  $\alpha$ -iodosulfides. The preparation using NIS of a secondary  $\alpha$ -iodosulfide **164**, formally an  $\alpha$ -iodoalkyl thioester, has been reported (Equation (132)) <2000JA7825> and the addition of dichlorocarbene to a 1-iodovinyl thioether produces a tertiary analog (Equation (109)) <1998SC1667>.

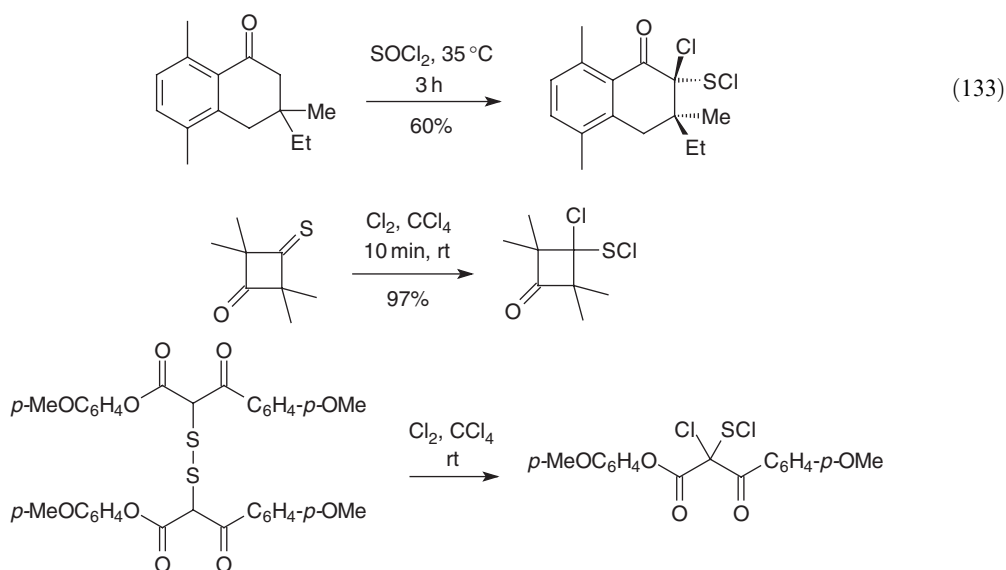




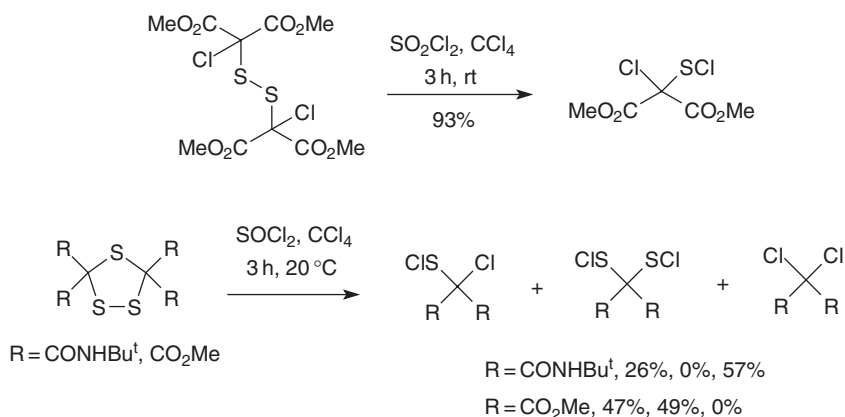
#### 4.02.2.1.2 Other dicoordinate $\alpha$ -halosulfur derivatives— $R_2CHal(SX)$ , etc.

##### (i) $\alpha$ -Chloroalkanesulfenyl chlorides— $R_2CCl(SCl)$

The reaction of active methylene compounds with  $\text{SOCl}_2$  continues to be the standard method of preparing  $\alpha$ -chloroalkanesulfenyl chlorides (Equation (133)) <1996BSF903, 1998JOC9840, 1999ACS133, 2002ZN(B)922>. The reaction is believed to involve an intermediate sulfinyl chloride and can be highly diastereoselective <1999ACS284>, although it may not be possible to separate the diastereomers. Sulfur dichloride has been used in place of  $\text{SOCl}_2$  in these reactions <2002EJO2039>.  $\alpha$ -Chloroalkanesulfenyl chlorides have also been prepared by the reaction of  $\text{Cl}_2$  with thioxocyclobutanes <1999EJO83> and 1,3-diketone disulfides <1996MI895> (Scheme 29).  $\text{PCl}_5$  reacts with thioxocyclobutanes in a similar fashion <2002JOC5690>. The reaction of  $\text{SO}_2\text{Cl}_2$  with dipropyl disulfide produces an  $\alpha$ -chloroalkanesulfenyl chloride <1997MI4414>, as does its reaction with 1,3-dicarbonyl compound derived disulfides and trithiolanes, a 2,2-dichloro- or a 2,2-di(chlorothio)-1,3-dicarbonyl compound being formed as a by-product in some cases <2002EJO2039> (Scheme 30).



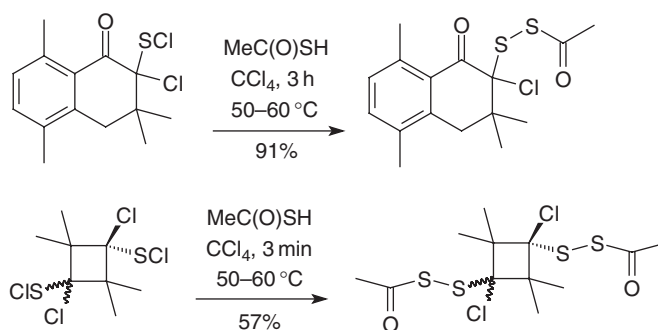
Scheme 29



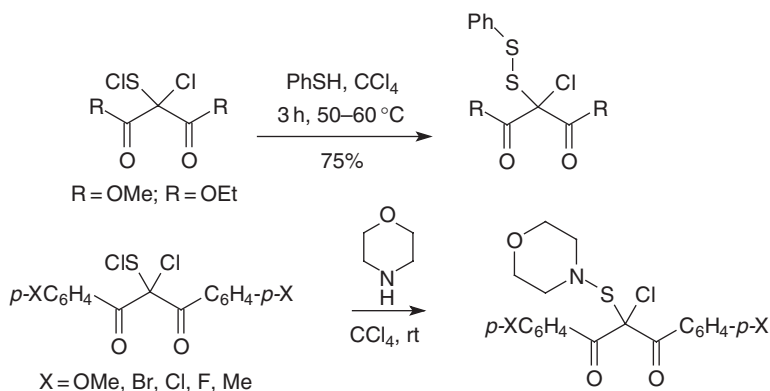
Scheme 30

(ii) Miscellaneous dicoordinate  $\alpha$ -halosulfur derivatives— $\text{R}_2\text{CHal}(\text{SX})$ 

$\alpha$ -Chloroalkanesulfonyl chlorides can be used to construct a range of other dicoordinate  $\alpha$ -halo sulfur derivatives. They would be expected to undergo easy substitution with nucleophilic reagents and thus they react, for example, with thiocarboxylic acids to give acetyl  $\alpha$ -chloroalkyl disulfides (Scheme 31) <1996MI895, 1998JOC9840, 1999EJO83, 1999ACS133, 2002EJO2039, 2002JOC5690>. In the same way reaction with thiophenols gives aryl  $\alpha$ -chloroalkyl disulfides <2002EJO2039> and with morpholine gives an  $\alpha$ -chloroalkyl sulfenamide <1996MI895> (Scheme 32). Although the reaction of the  $\alpha$ -chloroalkanesulfonyl chloride **165** with sulfinate anion affords an  $\alpha$ -chloroalkylsulfanylsulfonyl derivative **166**, the result of a simple substitution, two reduction products, a trithiolane **167** and an  $\alpha$ -chloroalkyl disulfide **168** are also obtained

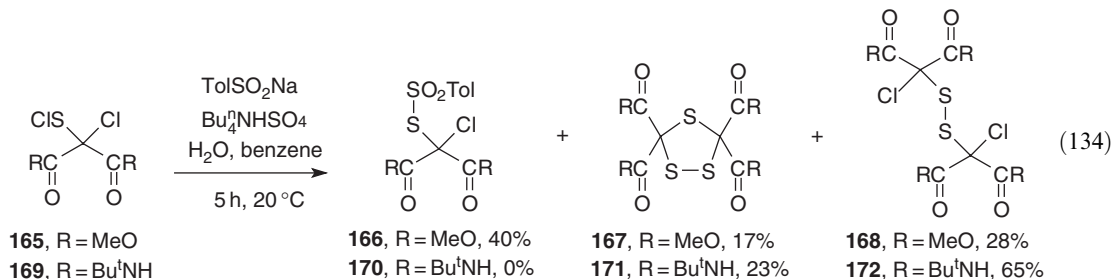


Scheme 31

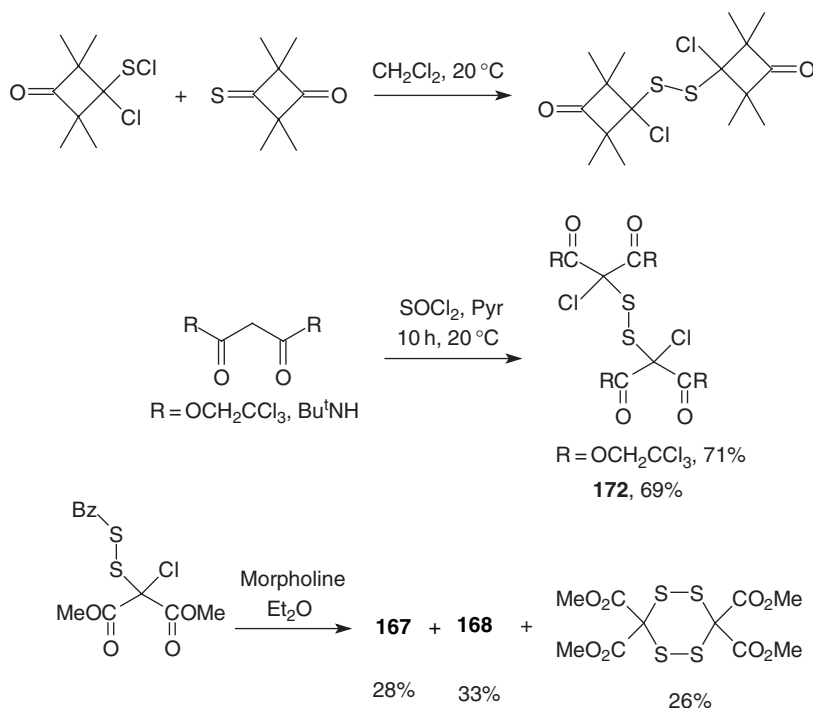


Scheme 32

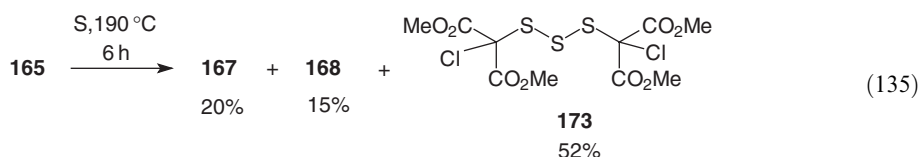
<2002EJO2039> (Equation (134)), the latter probably arising via a thione intermediate. In contrast to the behavior of **165**, the corresponding *N,N'*-di-*t*-butylmalonamide **169** gives a trithiolane **171** and an  $\alpha$ -chloroalkyl disulfide **172**, but none of the sulfanysulfonyl **170** (Equation (134)). The  $\alpha$ -chloroalkyl disulfide **168** has also been obtained by the electrochemical reduction of the  $\alpha$ -chloroalkanesulfonyl chloride **165**, in which case it is formed as the sole product in high yield (88%) and can be isolated in an analytically pure form without chromatography <2002EJO2039>.



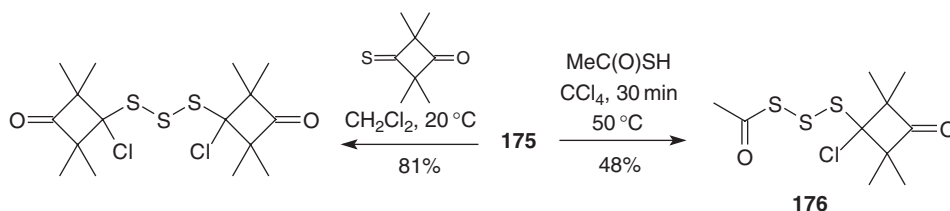
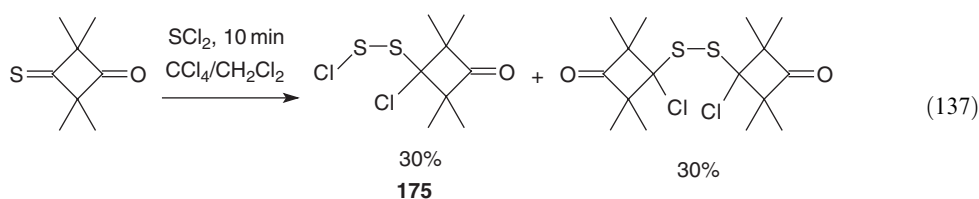
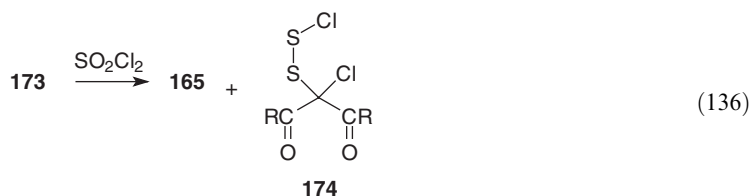
Heating **169** at 190 °C in the presence of S gives the  $\alpha$ -chloroalkyl disulfide **172** (39%), together with **171** (27%) and *N,N'*-di-*t*-butyl-2,2-dichloromalonamide (25%) <2002EJO2039>.  $\alpha$ -Chloroalkyl disulfides have also been prepared by the addition of  $\alpha$ -chloroalkanesulfonyl chlorides to thiones <2002JOC5690>, the reaction of *N,N'*-di-*t*-butylmalonamide and bis(2,2,2-trichloroethyl) malonate with thionyl chloride, and the reaction of a benzoyl  $\alpha$ -chloroalkyl disulfide with morpholine <2002EJO2039> (Scheme 33). Although when the  $\alpha$ -chloroalkanesulfonyl chloride **165** is heated at high temperature with S, it gives, like **169**, an  $\alpha$ -chloroalkyl disulfide, the major product is  $\alpha$ -chloroalkyl trisulfide **173**, another dicoordinate  $\alpha$ -halosulfur derivative (Equation (135)). It is not clear how **173** is formed in this case but it was also obtained in low yield (10%), together with **165** (58%) and **168** (25%), from the reaction of dimethyl malonate with SOCl<sub>2</sub> <2002EJO2039>.



Scheme 33

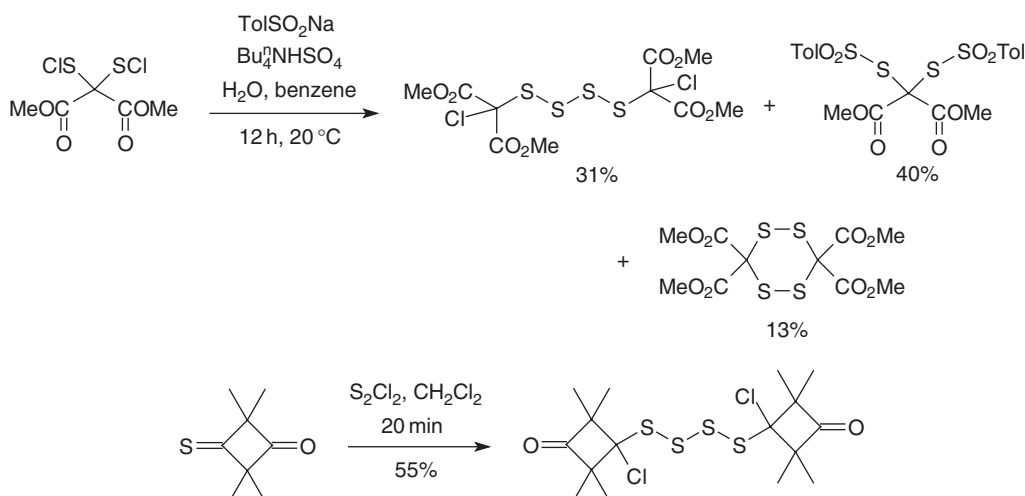


An  $\alpha$ -chloroalkyl thiosulphenyl chloride **174** is obtained when the  $\alpha$ -chloroalkyl trisulfide **173** is treated with sulfuryl chloride [<2000EJO2583>](#) (Equation (136)). The  $\alpha$ -chloroalkylthiosulphenyl chloride **175**, together with an  $\alpha$ -chloroalkyl disulfide, is formed in the reaction of thiones with sulfur dichloride,  $\text{SCl}_2$  (Equation (137)) [<2002JOC5690>](#). The reaction of these  $\alpha$ -chloroalkyl thiosulphenyl chlorides with nucleophiles facilitates the preparation of a further dicoordinate  $\alpha$ -halosulfur derivative, an acetyl  $\alpha$ -chloroalkyl trisulfide **176**, and their addition to thiones provides another route to  $\alpha$ -chloroalkyl trisulfides [<2002JOC5690>](#) (Scheme 34).  $\alpha$ -Chloroalkyl tetrasulfides have also been prepared by the reaction of a 2,2-di(chlorothio) malonate with *p*-toluenesulfonate anion [<2000EJO2583>](#) and the reaction of thiones with disulfur dichloride ( $\text{S}_2\text{Cl}_2$ ) [<2002JOC5690>](#) (Scheme 35).

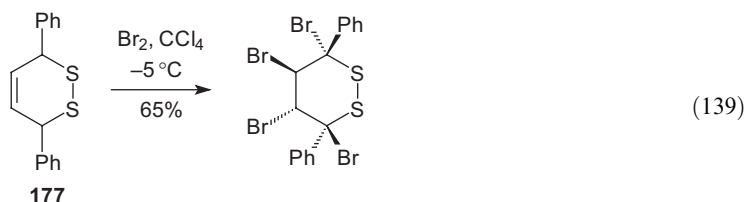
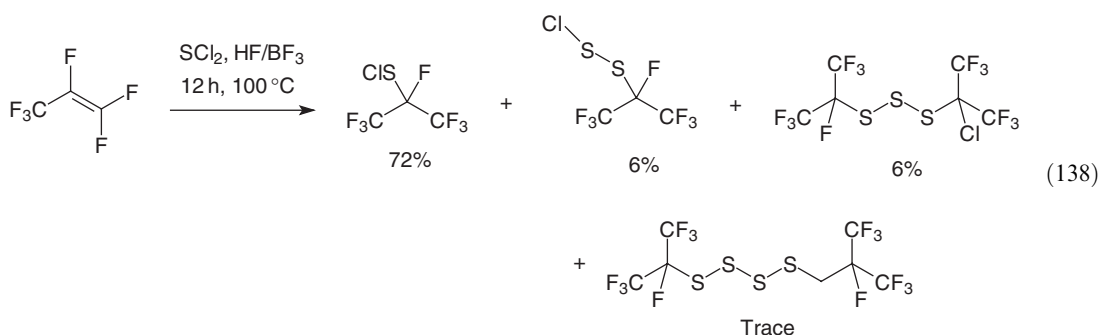


Scheme 34

There has been little work in this area that involves the other halogens. The reaction of distilled  $\text{SCl}_2$  with hexafluoropropene gives an  $\alpha$ -fluoroalkylsulphenyl chloride in an isolated yield of 65%, together with smaller amounts of an  $\alpha$ -fluoroalkylthiosulphenyl chloride, and  $\alpha$ -fluoroalkyl tri- and tetrasulfides (Equation (138)) [<2001JFC\(112\)325>](#). An  $\alpha$ -bromoalkyl disulfide, which even at  $-20^\circ\text{C}$  was only stable for 3–4 days, was obtained by brominating the 1,2-dithiin **177** (Equation (139)) [<1996T12677>](#).



Scheme 35



#### 4.02.2.2 Tricoordinate $\alpha$ -Halosulfur Derivatives— $\text{R}_2^1\text{CHaS}(\text{O})\text{R}^2$ , etc.

##### 4.02.2.2.1 $\alpha$ -Halosulfoxides— $\text{R}_2^1\text{CHaS}(\text{O})\text{R}^2$

This functional group is generally assembled from the appropriate sulfide through halogenation followed by oxidation, or the reverse. A key issue in relation to the oxidation step is preventing sulfone formation as a result of over-oxidation.

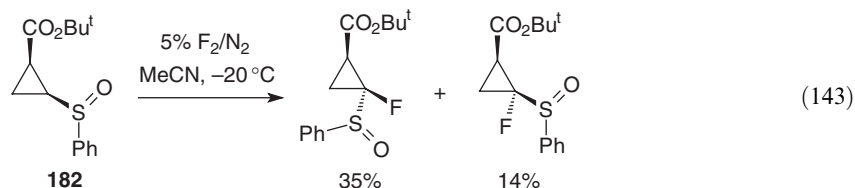
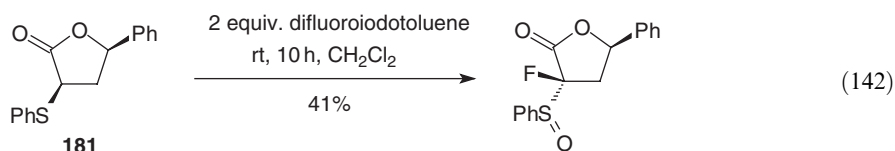
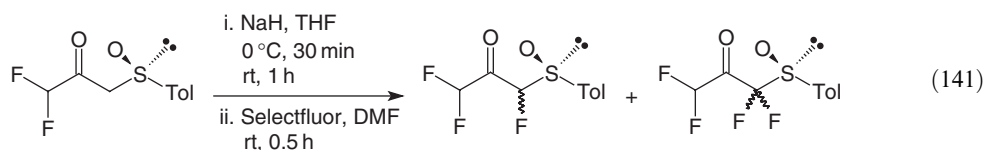
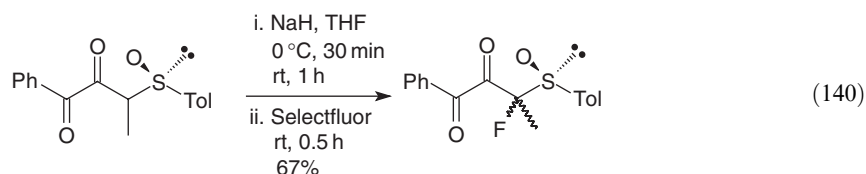
##### (i) $\alpha$ -Fluorosulfoxides— $\text{R}_2^1\text{CFS}(\text{O})\text{R}^2$

The preparation of  $\alpha$ -fluorosulfoxides has been reviewed [<1996CR1641>](#). The availability of  $\alpha$ -fluorosulfides through the chemical or electrochemical fluorination of sulfides and the ease with which they can be oxidized to the corresponding sulfoxides explains why sulfide oxidation is currently the standard route to secondary and tertiary  $\alpha$ -fluorosulfoxides. MCPBA is an almost universal choice as oxidizing agent and it can be used at temperatures as low as  $-78^\circ\text{C}$  ([Scheme 36](#)) [<1995JFC\(71\)9, 1998JOC1205, 2000BCJ1633, 2001OL593>](#). There has been one report of the





$\beta$ -keto sulfoxides (Equation (141)). Treating the  $\alpha$ -phenylsulfanyl lactone **181** with 2 equiv. of difluoroiodotoluene results in the fluorooxidation of the sulfide (Equation (142)). The stereochemistry of the product is the result of diastereospecific fluorination followed by a diastereoselective oxidation which gives a 5:2 mixture of sulfoxides <2002JCS(P1)2809>. A broadly similar transformation has been reported for  $\alpha$ -thioacids, which undergo an electrochemical fluorooxidative decarboxylation <1998JFC(87)215>. Elemental fluorine has also been used to fluorinate sulfoxides. The reaction of the cyclopropyl sulfoxide **182** with fluorine, which is believed to occur via a sulfuran derivative, is slightly stereoselective with the fluorine being introduced preferentially from the side of the phenyl sulfinyl group, resulting in inversion of configuration (Equation (143)) <1996TL8507>. The use of fluorine can result in the formation of a sulfone by-product <1996CPB703> and, with a methyl sulfoxide, in the formation of both mono- and difluorinated products <1995CL581>.

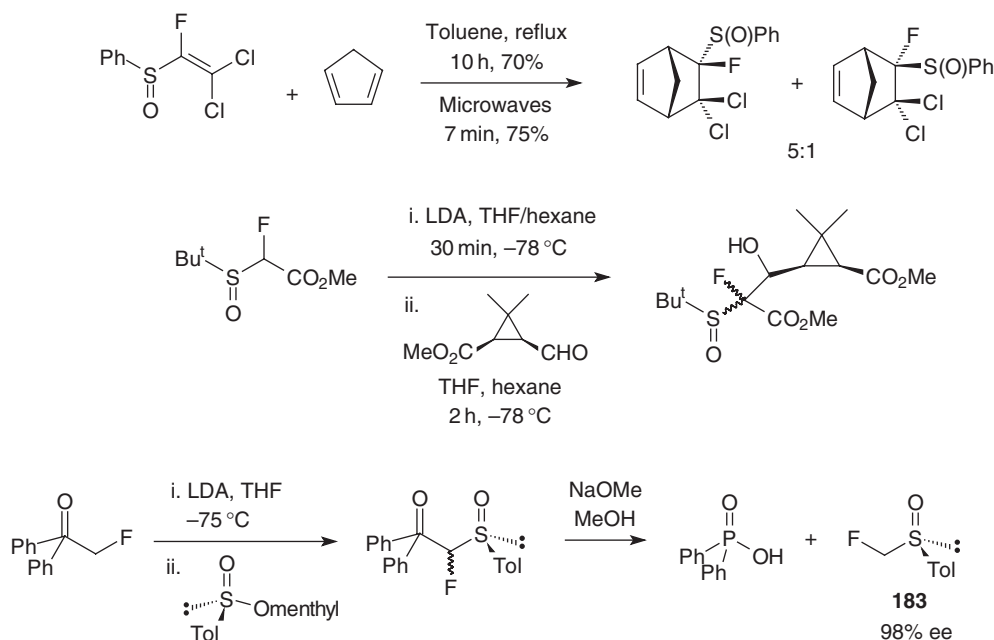


$\alpha$ -Fluorosulfoxides have been prepared recently by a small number of other methods (Scheme 38). Thus, the standard thermal- or microwave-assisted Diels–Alder reactions of 1-fluoro-1-sulfinylalkenes result in the formation of  $\alpha$ -fluorosulfoxides <2000T3539>. Standard thioenolate chemistry has been used to elaborate primary and secondary  $\alpha$ -fluorosulfoxides <1996CR1641, 1998T5557, 2002T4759> and the first enantioselective synthesis of (*S*)-1-(fluoromethyl)sulfinyl-4-methylbenzene **183** has also been reported <2001EJO911>.

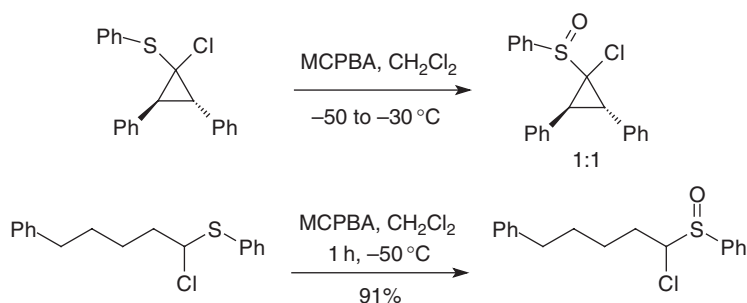
(ii)  $\alpha$ -Chlorosulfoxides— $R_2CClS(O)R^2$

In general, as with their fluoro analogs, the preparation of most  $\alpha$ -chlorosulfoxides begins with the appropriate sulfide and uses a chlorination–oxidation or oxidation–chlorination sequence to generate the required functional group. The recent literature in this area is dominated by the use of MCPBA, NCS, and the application of thioenolate chemistry to convert relatively simple  $\alpha$ -chlorosulfides to more structurally complex derivatives containing the same functional group. The only reagent now being used for the oxidation of secondary and tertiary  $\alpha$ -chlorosulfides is MCPBA, with reactions generally being carried out in  $CH_2Cl_2$  at low temperature (Scheme 39) <1996T2349, 1997T7805, 2001T493, 2001T5369, 2002T4217>. The diastereoselectivity of  $\alpha$ -chlorosulfide oxidation is generally low, and if chromatography is to be used to obtain a pure diastereomer, the stability of the  $\alpha$ -chlorosulfoxides on silica must be considered. A range of oxidizing agents have been used for primary  $\alpha$ -chlorosulfoxides, largely because chloromethylphenylsulfide has been used as a convenient and readily available standard for assessing the

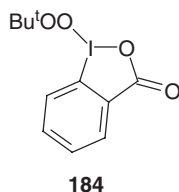
performance of new oxidizing agents. This includes two hypervalent iodine systems, periodic acid/ $\text{FeCl}_3$  <2002S2484> and the (*t*-butylperoxy)iodane **184** <1997JOC4253>. Calcium hypochlorite ( $\text{Ca}(\text{OCl})_2$ ) on moist alumina <1997S1161> is reported to be superior in terms of yield and/or reaction time to reagents used previously for the oxidation of chloromethyl phenyl sulfide and because its use avoids the S–O and C–S cleavage, and dichlorination, that can occur with some oxidants. The  $\text{Mn}(\text{acac})_3$  catalyzed oxidation of chloromethyl phenyl sulfide using sodium chlorite ( $\text{NaClO}_2$ ) <1996JCS(P1)2693>, and its oxidation with  $\text{H}_2\text{O}_2$  in the presence of methyltrioxorhenium <1996BCJ2955> have also been reported.



Scheme 38

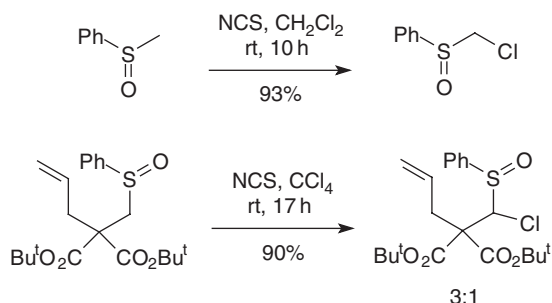


Scheme 39

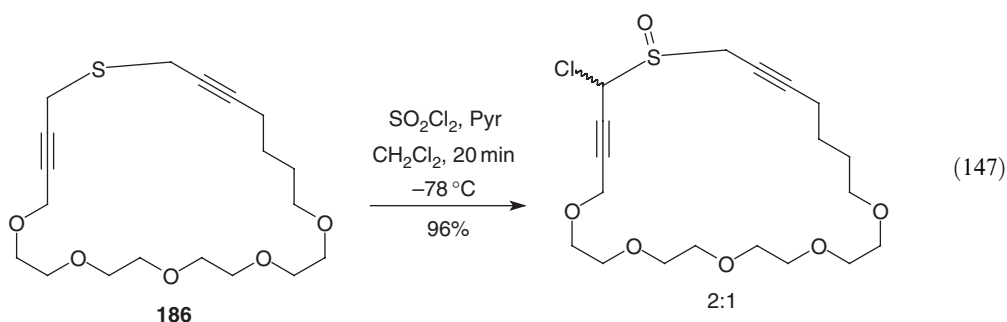
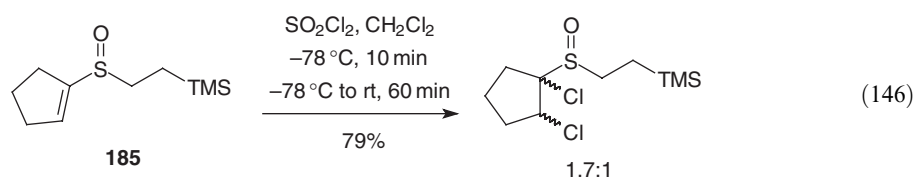
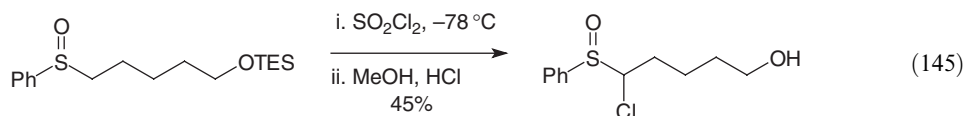
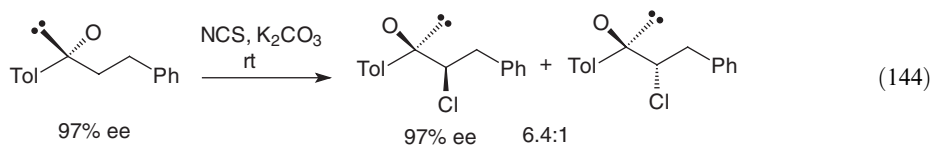


NCS is the reagent of choice for the  $\alpha$ -chlorination of all classes of sulfoxide (Scheme 40) <1995JCS(P1)1397, 1997T7805, 1998JOC4954>. The reaction occurs in high yield at room temperature with  $\text{CH}_2\text{Cl}_2$  being the usual solvent. The chlorination of secondary sulfoxides results in the creation of a second chiral center, and although the diastereoselectivity is generally not high, the

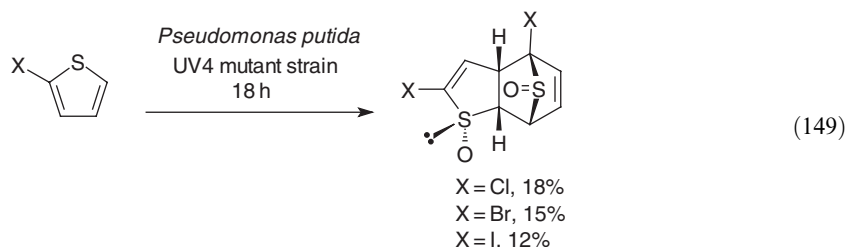
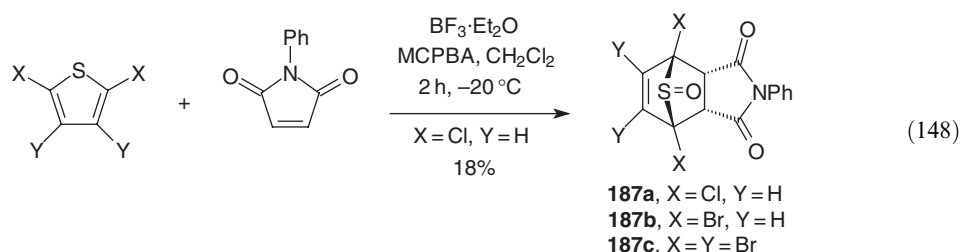
individual diastereomers can be separated, for example, by crystallization <1999AG(E)338> (Equation (144)). Chlorination with  $\text{SO}_2\text{Cl}_2$  has been used occasionally to produce  $\alpha$ -chlorosulfoxides, an example being the chlorination of a silylated 6-hydroxysulfoxide (Equation (145)) <1997TL4407>.  $\text{SO}_2\text{Cl}_2$  has been used to convert the  $\alpha,\beta$ -unsaturated sulfoxide **185** to an  $\alpha,\beta$ -dichlorosulfoxide (Equation (146)) <2001EJO1643>, and to convert the macrocyclic  $\beta,\gamma$ -acetylenic sulfide **186** to an  $\alpha$ -chlorosulfoxide in a one-pot reaction (Equation (147)) <1996JOC9385>.



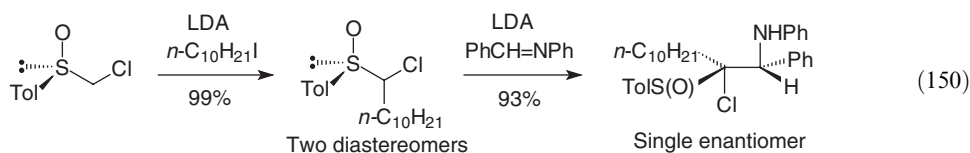
Scheme 40



Oxidative cycloadditions of 2-chloro- and 2,5-dichlorothiophene are also a source of  $\alpha$ -chlorosulfoxides. The  $\text{BF}_3$ -promoted Diels–Alder reaction of thiophene *S*-monoxide, formed from the latter *in situ* by MCPBA oxidation, with the electron-poor dienophile *N*-phenylmaleimide results in the selective formation of the *endo*-adduct **187a** (Equation (148)) with the sulfinyl lone pair directed toward the newly formed alkene bond <1997JOC7926>. It is suggested that the Lewis acid complexes with the monoxide, making it less nucleophilic and thus less susceptible to oxidation to the sulfone. However, the same reaction in the absence of  $\text{BF}_3$  gives a higher yield of adduct, albeit in a longer reaction time, and no sulfone is formed <1998JCR(S)346>. The biological oxidative dimerization of 2-chlorothiophene, which gives an  $\alpha$ -chlorosulfoxide (Equation (149)), also involves an *S*-monoxide produced in this case by the dioxygenase catalyzed sulfoxidation of the thiophene <2003OBC984>.



The addition and substitution reactions of thioenolates generated in the usual way from primary and secondary  $\alpha$ -chlorosulfoxides have been used extensively in the last few years to produce further secondary and tertiary  $\alpha$ -chlorosulfoxides, respectively (Table 15). Thus the substitution of  $\alpha$ -chlorosulfoxides with iodomethane, primary and secondary alkyl halides, and benzyl halides have all been reported (Table 15, entries 1 and 2), the product being obtained as a mixture of diastereomers in all cases.  $\alpha,\omega$ -Bis- $\alpha$ -chlorosulfinyl compounds have been alkylated in the same way, although a poor yield is obtained for those with a short connecting methylene chain (Table 15, entries 3 and 4). The addition of  $\alpha$ -chlorosulfinyl carbanions to carbonyl compounds in general has been the subject of considerable interest <1995JCS(P1)1397, 1998JOC6200>. The reaction of the anions from diastereomeric mixtures of 1-chloroalkyl phenyl sulfoxides with symmetrical carbonyl compounds such as acetone, below  $-40^\circ\text{C}$ , takes place with complete chiral induction from the sulfur chiral center and so the reaction of the bis- $\alpha$ -chlorosulfinyl compound **188** gives only two diastereomers (Table 15, entry 5). The reaction of the imine **189** with  $\alpha$ -chlorosulfoxide **190** gives a single diastereomer <2001T3891>, 1,2 and 1,3 chiral induction taking place simultaneously. The reaction of chloromethyl phenyl sulfoxide with lactones (Table 15, entry 8) and esters has also been reported <1997T7843> and again affords a range of more complex  $\alpha$ -chlorosulfoxides as diastereomeric mixtures (Table 15, entries 8). (*R*)-Chloromethyl *p*-tolylsulfoxide has been used as a starting material for these addition and substitution reactions, thus producing the respective products in chiral form (Equation (150)) <2001T3891>.



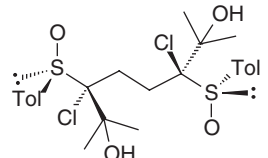
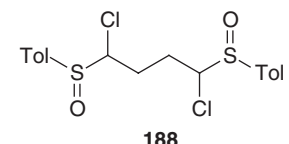
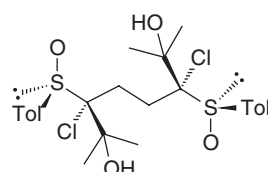
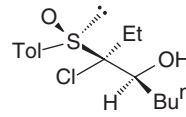
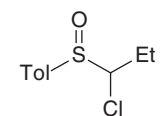
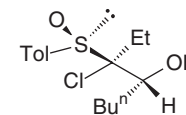
### (iii) $\alpha$ -Bromosulfoxides— $R_2CBrS(O)R^2$

Although there is currently little synthetic interest in  $\alpha$ -bromosulfoxides, a small number have been prepared by a variety of diverse methods. The addition of  $\text{Br}_2$  to a range of vinyl sulfoxides, for example, gives  $\alpha$ -bromosulfoxides, in some cases accompanied by a variety of by-products (Equation (151)) <1999ZOR1785>. Surprisingly, the  $\text{AgNO}_3$ -assisted bromination of the sulfoxide **191** (Equation (152)) is the only example of a sulfoxide to  $\alpha$ -bromosulfoxide transformation reported recently <2000CEJ3359>. In keeping with the behavior of the corresponding chloro compounds, the oxidative addition of 2,5-di- and 2,3,4,5-tetrabromothiophenes to *N*-phenylmaleimide gives the polycyclic  $\alpha$ -bromosulfoxides **187b** (42%) and **187c** (45%) (Equation (148)), respectively, no  $\text{BF}_3$  being used in these cases <1998JCR(S)346>. The biological oxidative dimerization of 1-bromothiophene (Equation (149)) <2003OBC984> also parallels that of the analogous chloro compound.  $\alpha$ -Sulfinyl carbanions feature in a number of reactions that have been used to produce  $\alpha$ -bromosulfoxides. Thus the  $\alpha$ -sulfinyl carbanion derived from bromomethyl phenyl sulfoxide has

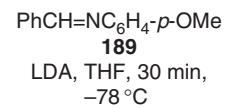
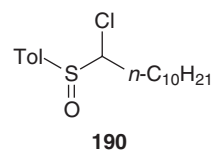
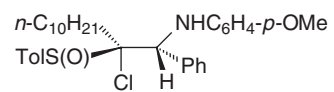
**Table 15** Preparation of primary and secondary  $\alpha$ -chlorosulfoxides using thioenolate chemistry

Entry	Product	Reactant	Conditions	Yield (%)	References
1			LDA, HMPA/THF, $n$ -C <sub>10</sub> H <sub>21</sub> I 2 h, -60 to -25 °C	95	<2001T493>
2			i. LDA, THF, -65 °C, 10 min ii. BnBr, THF, -65 to -35 °C, 2 h	100	<1996T2349>
3			LDA, HMPA/THF, Pr <sup>i</sup> I 4.7 h, -50 °C	71	<2001T493>
4			LDA, HMPA/THF, MeI 3 h, -78 to -50 °C	13	<2001T493>

Table 15 (continued)

Entry	Product	Reactant	Conditions	Yield (%)	References
5	 <b>a</b>	 <b>188</b>	LDA, THF, acetone, 10 min, -60 °C	<b>a:</b> 49 <b>b:</b> 29	<2002T4217>
	 <b>b</b>				
6	 <b>a</b>		LDA, THF, pentanal, 10 min -78 °C	<b>a:</b> 38 <b>b:</b> 45	<1998JOC4954>
	 <b>b</b>				

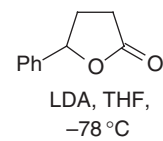
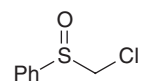
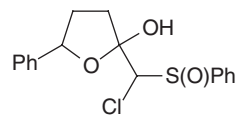
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78

&lt;2000T4415&gt;

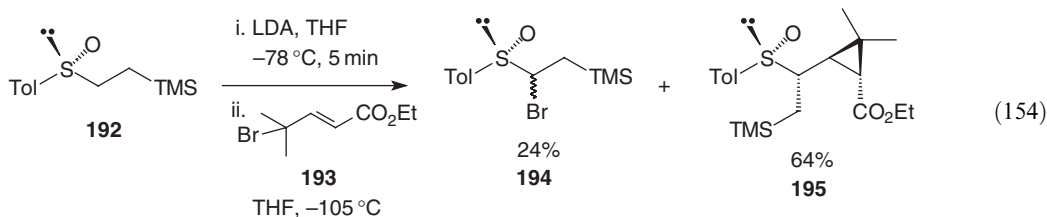
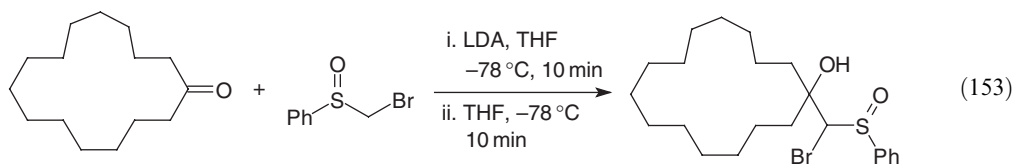
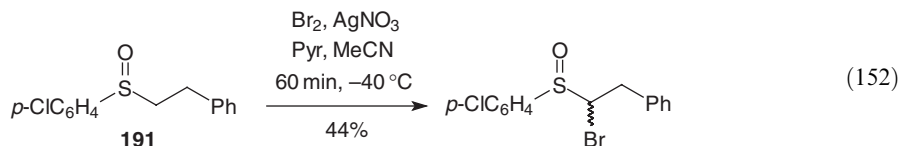
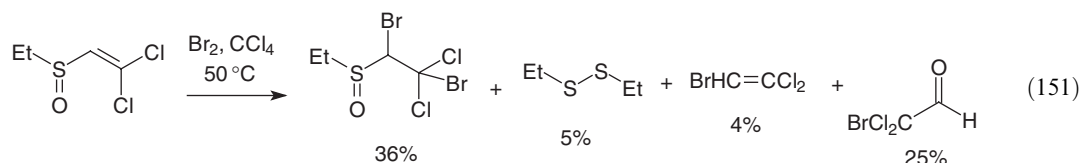
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94

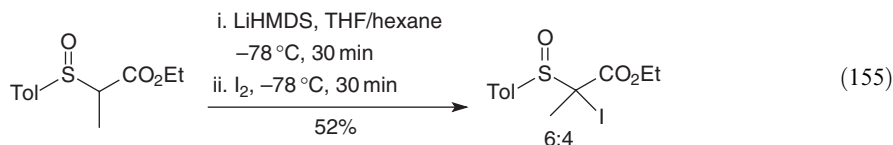
&lt;1998TL9215&gt;

been added to the carbonyl group in cyclopentadecanone to give a secondary  $\alpha$ -bromosulfoxide (Equation (153)) <1998T5557>. The  $\alpha$ -sulfinyl carbanion from sulfoxide **192** reacts in an unusual way with **193** as the formation of the  $\alpha$ -bromosulfoxide **194** is competitive with the conjugate addition that initiates the formation of the chrysanthemate precursor **195** (Equation (154)) <1999JCS(P1)3403>. The selective 1,4-addition of allylmalonate anion to  $\alpha$ -bromovinyl phenyl sulfoxide also produces a secondary  $\alpha$ -bromosulfoxide (70%) <1997T7805>.



#### (iv) $\alpha$ -Iodosulfoxides— $R_2^1\text{CIS}(O)R^2$

Only three new  $\alpha$ -iodosulfoxides have been reported in the last 9 years. They were formed by the reaction of vinyl *p*-tolyl sulfoxide with NIS in aqueous DMSO giving 2-iodo-2-(toluene-4-sulfinyl)ethanol in 96% yield as a 6:1 mixture of diastereomers which were inseparable by chromatography <1997JOC6326>, the iodination of an  $\alpha$ -sulfinyl carbanion giving an unstable  $\alpha$ -iodosulfoxide (Equation (155)) <1998HCA1048>, and the biological oxidative dimerization of 2-iodothiophene (Equation (149)) <2003OBC984>.

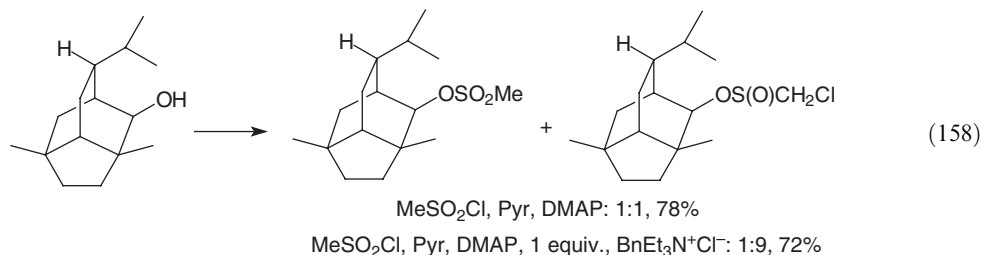
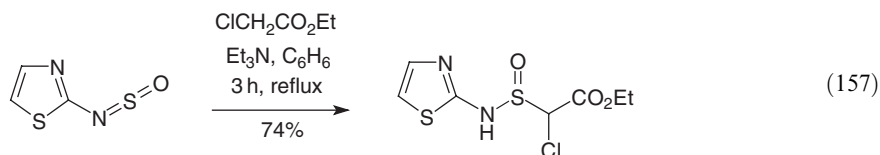
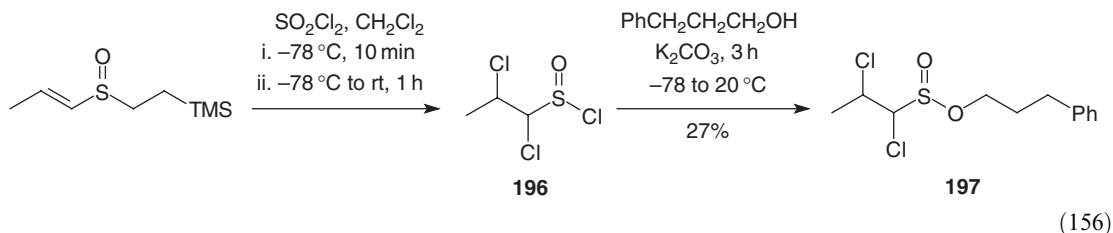


#### 4.02.2.2.2 Other tricoordinate $\alpha$ -halosulfur derivatives— $R_2^1\text{CHalS}(O)X$

The oxidative fragmentation of a  $\beta$ -silyl sulfoxide produces an unstable sulfinyl chloride **196** whose formation can be confirmed spectroscopically and which can be converted to the sulfinate **197** by reaction with 3-phenylpropanol (Equation (156)) <2001EJO1643>. The formation of an *N*-thiazolyl sulfinamide by the addition of chloroacetate to an *N*-sulphinylamine (Equation (157)) <1995JIC525> has also been reported. Surprisingly, it has been found that the reaction of certain very hindered alcohols with methanesulfonyl chloride (Equation (158)) <2000SL1354> gives not only the expected mesylate but also a chloromethanesulfinate, the latter on occasions actually



being the major product. The addition of benzyltriethylammonium chloride improves the yield of the sulfinate further. The reaction is believed to involve a sulfene intermediate formed by the elimination of HCl from methanesulfonyl chloride under the basic conditions. A similar result has been reported for chloromethanesulfonyl chloride <1998T21>.



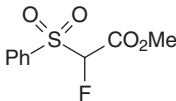
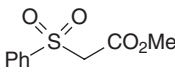
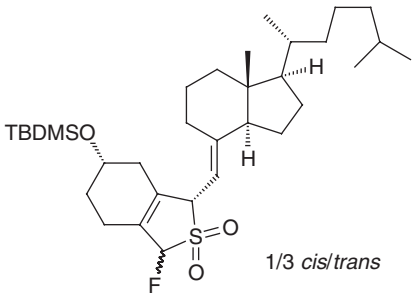
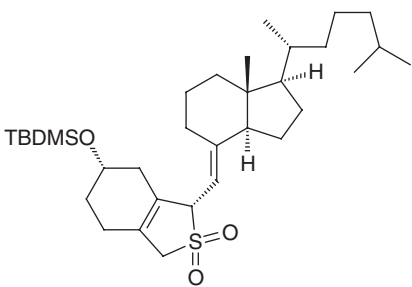
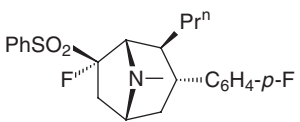
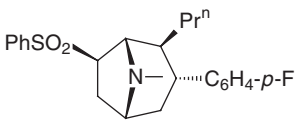
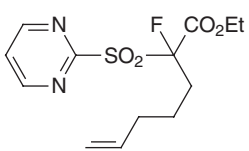
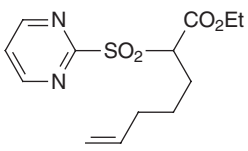
#### 4.02.2.3 Tetracoordinate $\alpha$ -Halosulfur Derivatives— $\text{R}_2^1\text{CHalS}(\text{O})_2\text{R}^2$ , etc.

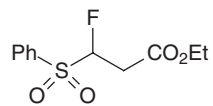
##### 4.02.2.3.1 $\alpha$ -Halosulfones— $\text{R}_2^1\text{CHalS}(\text{O})_2\text{R}^2$

###### (i) $\alpha$ -Fluorosulfones— $\text{R}_2^1\text{CFS}(\text{O})_2\text{R}^2$

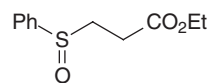
The preparation of  $\alpha$ -fluorosulfones has been reviewed <1996CR1641>. Selective mono- $\alpha$ -fluorination (Table 16) is currently the most widely used method of producing  $\alpha$ -fluorosulfones, and given the acidity of a sulfones's  $\alpha$  hydrogens it is not surprising that this is usually accomplished using electrophilic fluorinating agents such as Selectfluor <1996JA2519>, *N*-fluorobenzenesulfonimide <2000CPB1484> or *N*-fluoro-*o*-benzenesulfonimide <1995JOC4730>. The yields obtained are generally good (Table 16, entries 1–4). The regiochemistry of the process is determined at the deprotonation step with bases such as NaHMDS delivering the kinetically controlled product (Table 16, entry 2). The stereochemistry of the process, in the few reported examples where it is relevant, is dependent on the structure of the substrate (Table 16, entries 2 and 3). Elemental fluorine has been used to convert both sulfoxides and sulfones to  $\alpha$ -fluorosulfones (Table 16, entries 5 and 6). The fluorination of  $\alpha$ -sulfonyl esters is catalyzed by metal salts (Table 16, entry 6), an effect that has been attributed to the ability of the cation to accelerate enolate formation <1998JF(92)45>. The yields obtained are modest with  $\alpha,\alpha$ -difluorinated sulfones, and in the case of sulfoxides some unfluorinated sulfones being obtained in varying amounts as by-products. The product distribution obtained on fluorooxidation of the sulfoxide 198 indicates that fluorination occurs preferentially with inversion of configuration (Equation (159)) <1998TL4687>. The oxidation of  $\alpha$ -fluorosulfides <2001JOC7030, 2001TL4861> and sulfoxides <2002JCS(P1)2816> with MCPBA, and of  $\alpha$ -fluoro-sulfides with  $\text{CrO}_3$  <2001CC2428>, have also been used to prepare  $\alpha$ -fluorosulfones (Scheme 41). The yields with simple substrates are generally good but the use of  $\text{CrO}_3$  would clearly not be compatible with many functional groups. Treating the  $\alpha$ -fluoro- $\beta$ -hydroxy sulfoxide 199 with  $\text{SO}_2\text{Cl}_2$  resulted in the oxidation of the sulfoxide as well as the chlorination of the alcohol (Equation (160)) <2002T4759>.

**Table 16** Preparation of  $\alpha$ -fluorosulfones by selective fluorination

Entry	Product	Reactant	Conditions	Yield (%)	References
1			i. NaHMDS, THF 10 min, $-78^{\circ}\text{C}$ ; 30 min, $-78$ to $0^{\circ}\text{C}$ ii. <i>N</i> -fluoro- <i>o</i> -benzenesulfonimide $0^{\circ}\text{C}$ , 2 h	88	<1995JOC4730>
2	 1/3 <i>cis/trans</i>		i. NaHMDS, THF, HMPA, $-78^{\circ}\text{C}$ ii. $(\text{PhSO}_2)_2\text{NF}$	51	<1996TL6753>
3			i. $\text{Bu}^n\text{Li}$ , THF ii. <i>N</i> -fluoro-benzenesulfonimide, $-78$ to $20^{\circ}\text{C}$	70	<2000BMCL1443>
4			KH, Selectfluor, THF $0-20^{\circ}\text{C}$	88	<2000JOC4169>



**a**

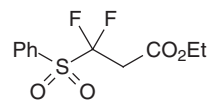


F<sub>2</sub>, MeCN, -20 °C

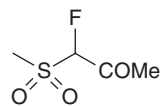
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**b:** 19

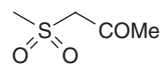
<1995CL581>



**b**



**a**

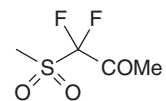


- i. NaH, MeCN, 1 h, 5 °C,
- ii. F<sub>2</sub>, 4 h, 5 °C  
Cu(NO<sub>3</sub>)<sub>2</sub>·2.5H<sub>2</sub>O, 4 h, 5 °C

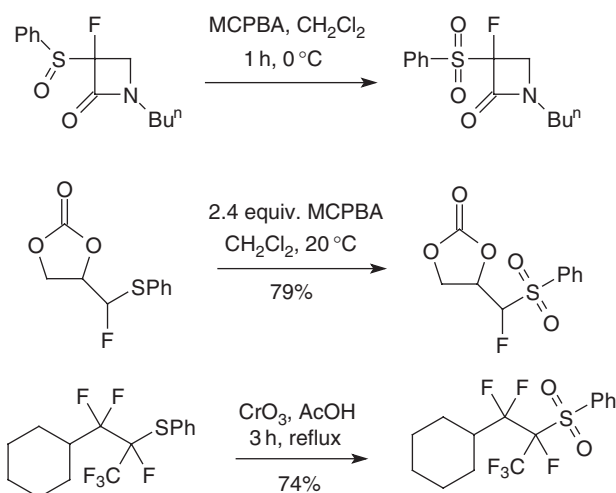
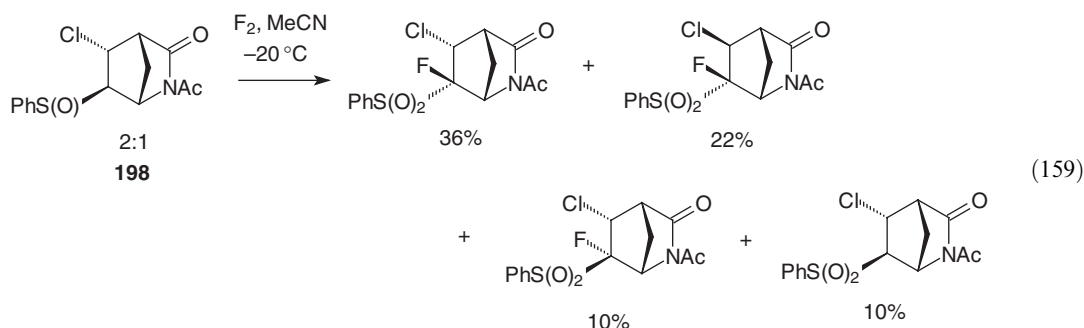
**a:** 45

**b:** 5

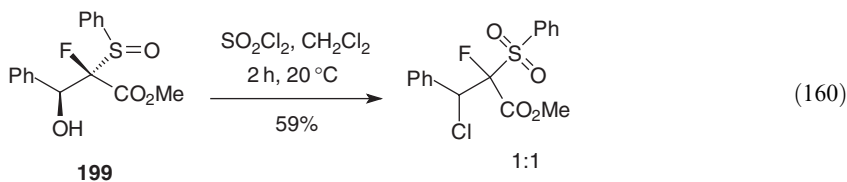
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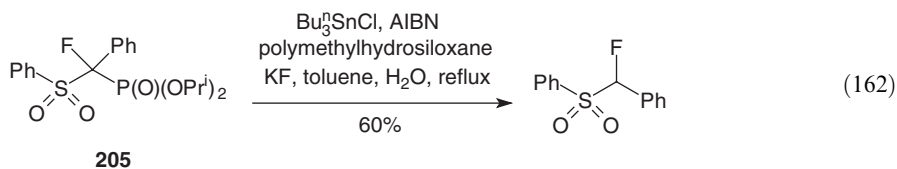
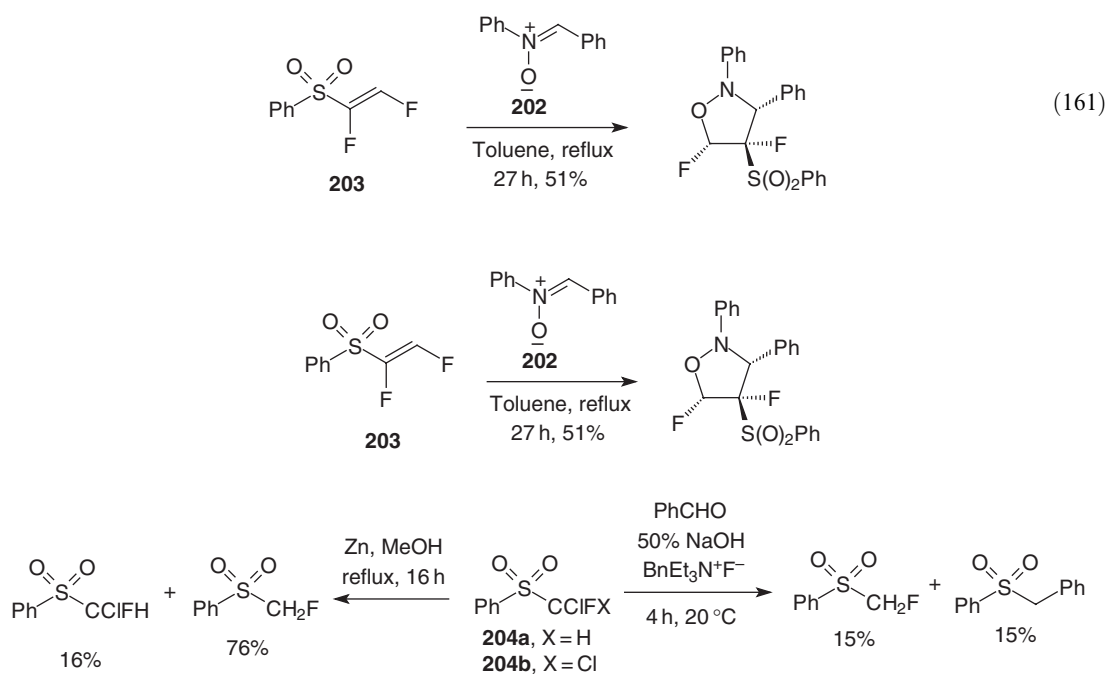
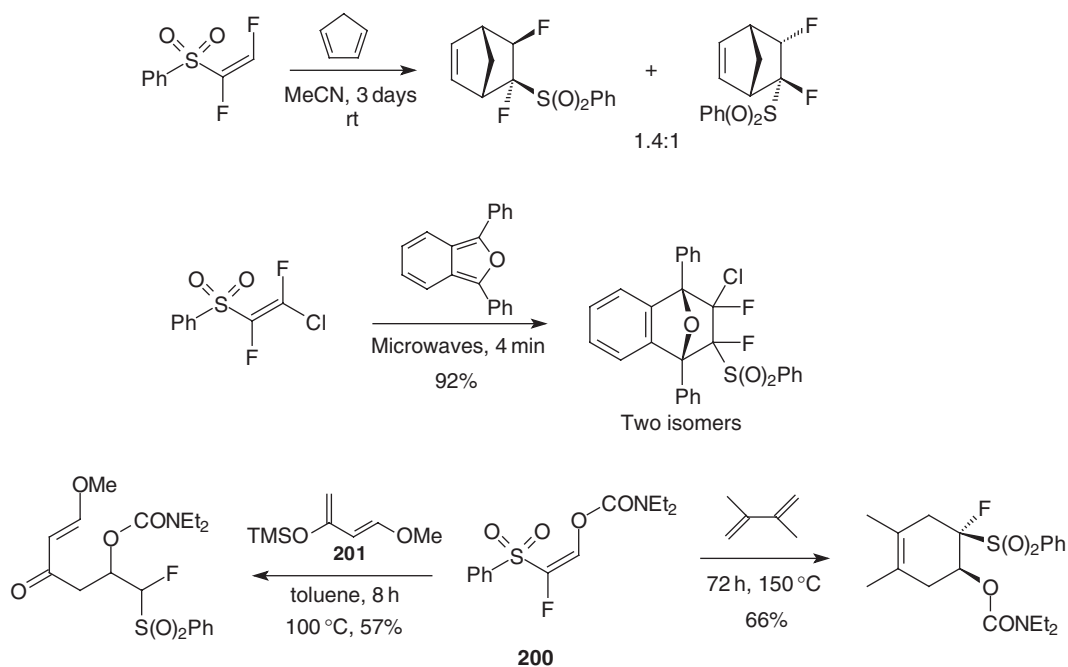
**b**



Scheme 41



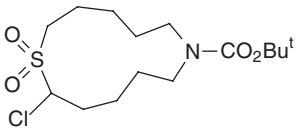
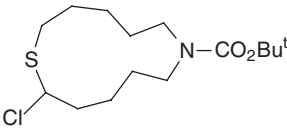
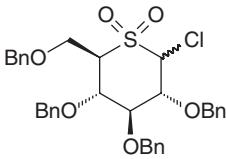
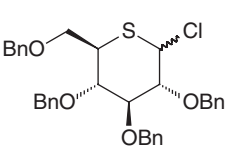
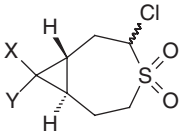
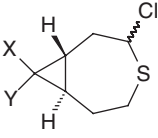
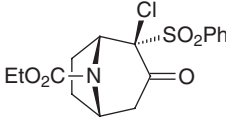
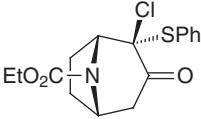
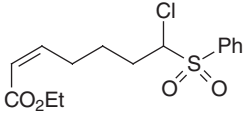
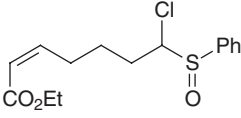
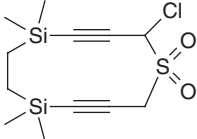
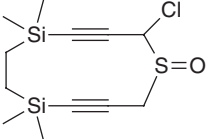
Fluorovinyl sulfones can be transformed into cyclic  $\alpha$ -fluorosulfones through thermal-[\[1996TL8237, 1997T17127\]](#) and microwave-assisted [\[1998TL6529\]](#) Diels–Alder reactions, although the vinyl sulfone **200** gives an  $\alpha$ -fluoro sulfone with Danishefsky's diene **201** which is the result of conjugate addition rather than [4 + 2]-cycloaddition ([Scheme 42](#)). The 1,3-dipolar cycloaddition of fluorovinyl sulfones with *N*-oxides [\[1997BSB677\]](#) also generates cyclic  $\alpha$ -fluorosulfones, and although the reaction of *N*-oxide **202** with fluorovinyl sulfone **203** is regioselective, a mixture of regioisomers is generally obtained ([Equation \(161\)](#)). Fluoromethyl phenyl sulfone, an important reagent for the introduction of a fluoromethyl group, has been prepared by the Darzens condensation of benzaldehyde with **204a** under PTC conditions and by reduction of **204b** with Zn ([Scheme 43](#)) [\[2001JOC643\]](#). The chemistry of the anions derived from  $\alpha$ -fluorosulfones has been reviewed [\[1996CR1641\]](#). More complicated  $\alpha$ -fluoro-sulfones have been built up by adding the fluoromethyl sulfinyl carbanion derived from fluoromethyl phenyl sulfone to ketones [\[2001CPB312\]](#). The radical dephosphonylation of the  $\alpha$ -(phenylsulfonyl)phosphonate **205** gives  $\alpha$ -fluorobenzyl phenyl sulfone ([Equation \(162\)](#)) [\[2002JOC3065\]](#).



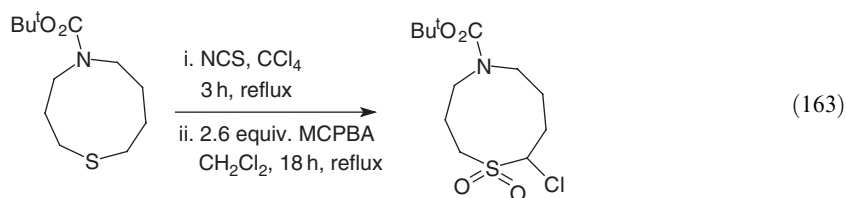
(ii)  $\alpha$ -Chlorosulfones— $R^1CCLSO_2R^2$ 

The preparation of  $\alpha$ -chlorosulfones from the appropriate sulfide using NCS followed by MCPBA remains the most widely used method of preparing this functional group. The oxidation step simply involves stirring the  $\alpha$ -chlorosulfide with 2–3 equiv. of MCPBA in  $CH_2Cl_2$  at room temperature (Table 17, entries 1–4). In many cases this sulfide to  $\alpha$ -chlorosulfone transformation is carried out as an effective one-pot procedure with no attempt being made to characterize the intermediate  $\alpha$ -chlorosulfide (Equation (163)) <2000JOC8367, 2002OL3047>. It has been reported that 10/11-membered ring sulfides give low yields with by-products that are possibly unsaturated sulfones being formed <2000JOC8367>.  $\alpha$ -Chlorosulfones have also been prepared from  $\alpha$ -chlorosulfoxides using MCPBA (Table 17, entry 5 and 6) and an extensive range of other oxidants which includes  $KHSO_5$  <1997T7805>,  $KMnO_4$  <1997T7805>, peracetic acid

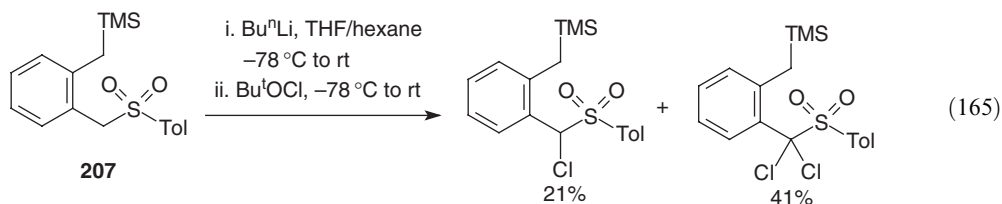
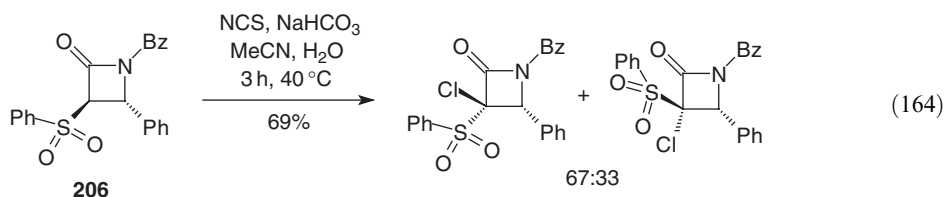
**Table 17** Preparation of  $\alpha$ -chlorosulfones by oxidation of  $\alpha$ -chlorosulfides and  $\alpha$ -chlorosulfoxides using MCPBA

Entry	Product	Reactant	Conditions	Yield (%)	References
1			MCPBA, $CH_2Cl_2$ , 18 h, 20 °C	58	<2000CJC1060>
2			MCPBA		<2001TL1197>
3		 X = Y = Cl X = Y = Br X = Br, Y = Cl	MCPBA, $CH_2Cl_2$	64 84	<1998TL5459>
4			2.2 equiv. MCPBA, $CH_2Cl_2$ , 18 h, rt	85	<1998JCS(P1)3689>
5			1 equiv. MCPBA, $CH_2Cl_2$ , rt	85	<1997T7805>
6			MCPBA, $CH_2Cl_2$ , 0 °C, 10 h	>90	<1998S665>

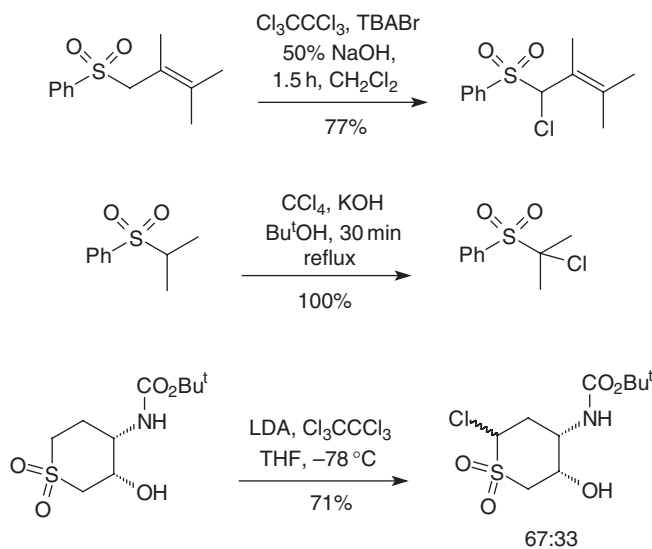
<1996JOC9385>,  $\text{H}_2\text{O}_2/\text{Ac}_2\text{O}$  <1996ZOR1709>,  $\text{CrO}_3$  <1997AJC683>,  $\text{F}_2$  <1996CPB703>,  $\text{H}_2\text{O}_2/\text{MeReO}_3$  <1996BCJ2955>, and  $\text{H}_5\text{IO}_6/[\text{Mn(IV)-Mn(IV)}(\mu\text{-O})_3(1,4,7\text{-trimethyl-1,4,7-triazacyclononane})_2](\text{PF}_6)_2$  <1998TL7055> which is claimed to give selective oxidation in the presence of other easily oxidizable groups.



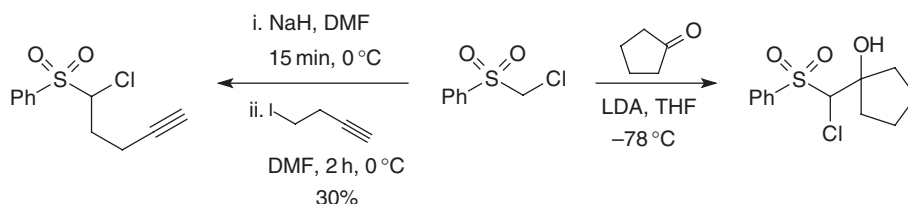
The various combinations by which  $\alpha$ -chlorosulfones can be produced from sulfides by the alternative oxidation–chlorination sequence are less convenient than the NCS/MCPBA approach and so this route is less frequently used. The  $\alpha$ -chlorination of sulfones involves the initial generation of an  $\alpha$ -sulfonyl anion which then interacts with the chlorinating agent. NCS/ $\text{NaHCO}_3$  is one of the most frequently used combinations for achieving this transformation (Equation (164)) <2000JOC7203>. The stereochemistry of the reaction of **206** is subject to steric control, with chlorination occurring preferentially from the less hindered side of the azetidinone ring, *trans* to the Ph group. Radical chlorination of sulfones using NCS/AIBN is also possible <1996T6903>. The use of  $\text{Bu}^t\text{OCl}$  with the sulfone **207** results in the formation of a dichlorosulfone as the major product (Equation (165)) <1998JOC2086>. Carbon tetrachloride and other perchlorinated hydrocarbons have also been used as chlorinating agents under basic conditions. The reaction involves a single electron transfer (SET) from the  $\alpha$ -sulfonyl carbanion to the chloroalkane giving a radical anion/radical pair, with transfer of a chlorine atom completing the formation of the  $\alpha$ -chlorosulfone (Scheme 44) <1995PJC1422, 1996TL7457, 2003JOC500>.



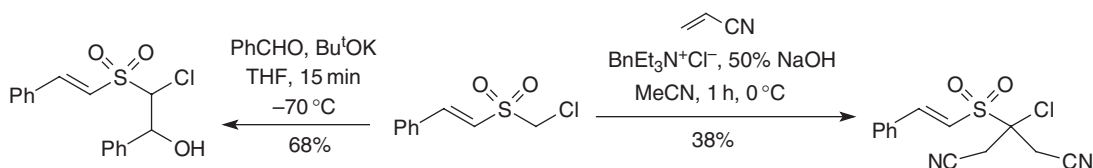
Carbanions from aryl  $\alpha$ -chloroalkyl and any other sulfones that cannot undergo the Ramberg–Backlund reaction react with the usual range of electrophilic partners. Thus the carbanion from chloromethyl phenyl sulfone reacts with alkyl halides <2002CPB463>, ketones <2002TL2285> (Scheme 45), and iminium salts <2001IZV2136>, and that from chloromethyl styryl sulfone with acrylonitrile and benzaldehyde <1997LA2337> (Scheme 46). Interestingly, it has now been reported that chloromethyl methyl sulfone can be efficiently (98%) added to benzaldehyde at  $-78^\circ\text{C}$ , the addition occurring faster than the Ramberg–Backlund reaction <2003TL1473>. The reaction of dichloromethyl phenyl sulfone with ketones under SET conditions also gives a secondary  $\alpha$ -chloroalkyl sulfone (Equation (166)) <2001SC47>.



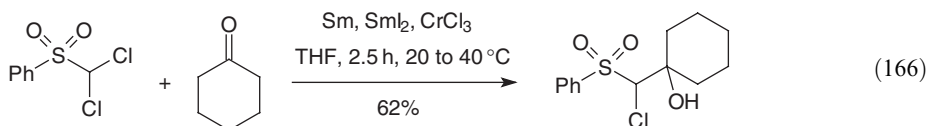
Scheme 44



Scheme 45

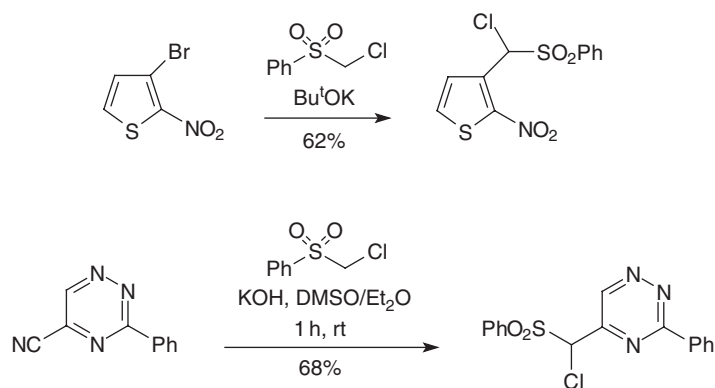


Scheme 46

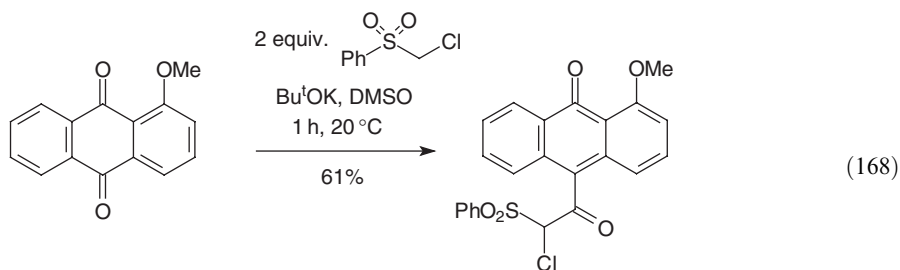
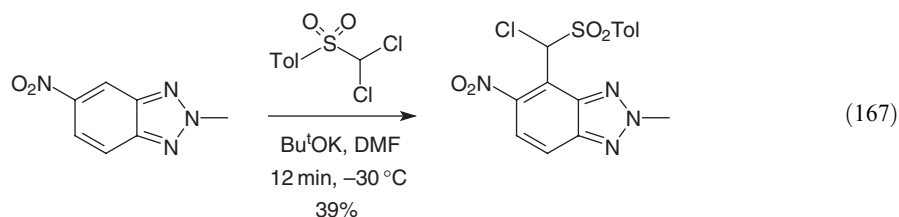


Chloromethyl phenyl and related sulfones undergo vicarious nucleophilic substitution with aromatic systems containing an electron withdrawing group, the process resulting in the loss of the  $\alpha$ -Cl. However, if the aromatic system contains an alternative leaving group (Scheme 47) <1995T7277, 1995T8339, 1996JHC1567, 2002EJO1412>, or if a dichloromethyl aryl sulfone is used (Equation (167)) <1995PJC918, 2001PJC1465>, the product of the reaction is a secondary  $\alpha$ -chloroalkyl sulfone. Chloromethyl tolyl sulfone reacts with pyridazinium methylides to give mixtures of secondary  $\alpha$ -chloroalkyl sulfones and the products of vicarious nucleophilic substitution as a result of its disproportionation to dichloromethyl tolyl sulfone and methyl tolyl sulfone under the reaction conditions <1998JCS(P1)1637>. The formation of the  $\alpha$ -chloroalkyl sulfone 208 involves the initial addition of an  $\alpha$ -chlorosulfonyl carbanion to the carbonyl group of 1-methoxyanthraquinone to give an oxirane, rearrangement of which to an anthracenyl ketone followed by displacement of phenylsulfonyl anion by another  $\alpha$ -chlorosulfonyl carbanion gives the observed product (Equation (168)) <1998T6147>.



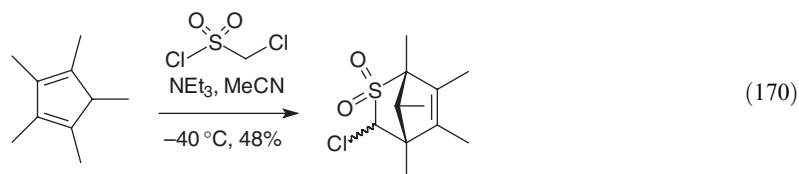
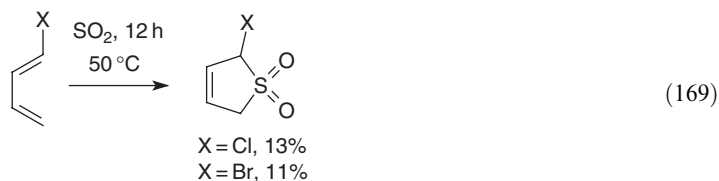


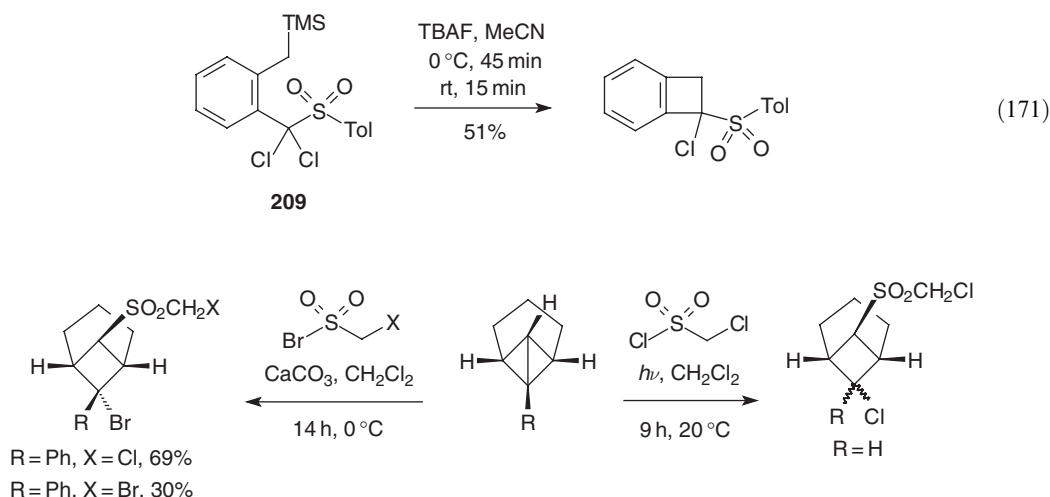
Scheme 47



208

$\alpha$ -Chloroalkyl sulfones have also been produced by a variety of cycloaddition reactions. These include the addition of  $\text{SO}_2$  to a 1-chlorodiene in a sealed tube (Equation (169)) <1998JOC9490>, the Diels–Alder reactions of sulfenes derived from  $\alpha$ -chloroalkylsulfonyl chlorides (Equation (170)) <1995LA2151> and those of tetrachlorothiophene dioxide <2000EJO743> for which monoclonal antibody catalysis has been reported <2002CJC657>. Other processes used to prepare  $\alpha$ -chloroalkyl sulfones include the fluoride-induced dechlorotrimethylsilylation of **209** via an *o*-quinodimethane intermediate (Equation (171)) <1998JOC2086>, the preparation of chloromethyl phenyl sulfone by the diphenyl selenide catalyzed reduction of chlorobromomethyl phenyl sulfone using  $\text{NaBH}_4$  <1997TL5651>, and the addition of chloromethanesulfonyl halides to strained  $\sigma$ -bonds in bicyclo[4.1.0.0<sup>2,7</sup>]heptanes <1996ZOR1701, 1999ZOR1189> (Scheme 48).

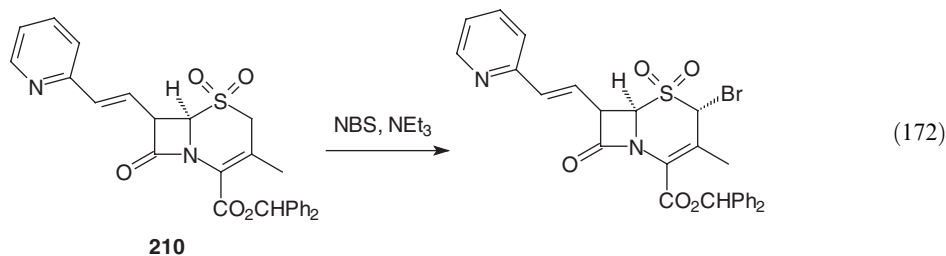


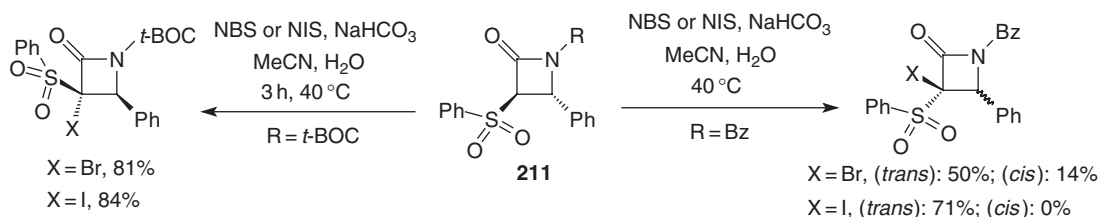


Scheme 48

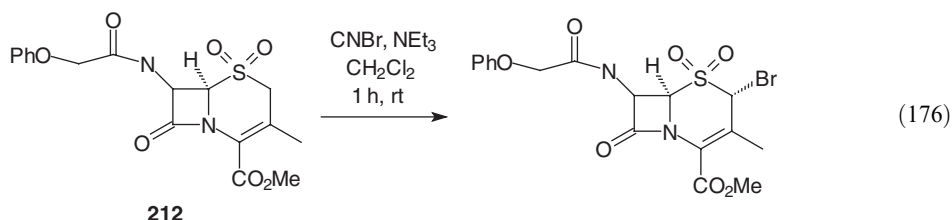
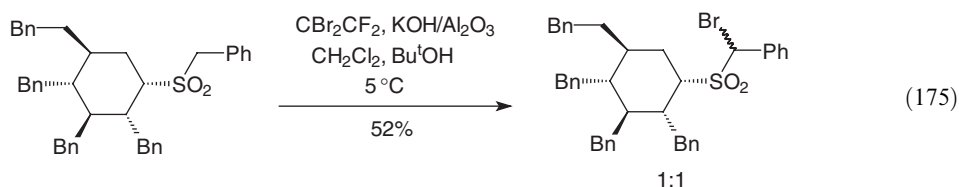
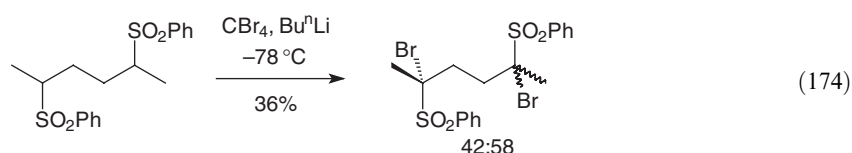
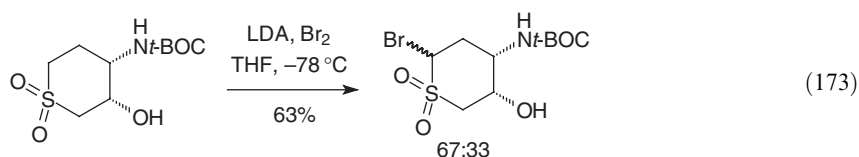
(iii)  $\alpha$ -Bromosulfones— $R_2^1\text{CBrS}(O)_2R^2$ 

Although the methods used to prepare  $\alpha$ -bromosulfones closely parallel those used to prepare  $\alpha$ -chlorosulfones, there are differences in the approach adopted. Thus the halogenation/MCPBA combination which is the method of choice of preparing  $\alpha$ -chlorosulfones has not been used at all since 1995 for constructing  $\alpha$ -bromosulfones. Instead, the standard method for the bromo compounds is the reverse oxidation/bromination procedure. However, as for  $\alpha$ -chlorosulfones, the approach employed for brominating sulfones generally involves the use of base and a source of electrophilic bromine: NBS/ $\text{Et}_3\text{N}$  <2000BMCL847> (Equation (172)), NBS/ $\text{NaHCO}_3$  (Scheme 49) <2000JOC7203, 2002MI1015>,  $\text{Br}_2/\text{Bu}^n\text{Li}$  <1998JOC2086, 2003JOC500>, and  $\text{Br}_2/\text{LDA}$  (Equation (173)) <1996TL7457>. The bromination of aryl isopropyl sulfones in the presence of  $\text{O}_2$  is complicated by the fact that oxidative cleavage of the sulfonyl carbanion competes with bromination, leading to the formation of arenesulfonyl alcohols, bromoarenes, and arenesulfonyl bromides, the composition of the product mixture depending on when the  $\text{Br}_2$  is introduced, the amount used and when the final work-up is carried out <2003JOC500>. Although in general these methods give mixtures of diastereomers (Equation (173)), the use of NBS/ $\text{Et}_3\text{N}$  results in the stereospecific bromination of the cephalosporin **210** (Equation (172)), and the stereochemical outcome for the azetidinone **211** (Scheme 39) is dependent on the nature of the *N*-substituent. A  $\beta,\gamma$ -unsaturated sulfone has been brominated using  $\text{Br}_2$  alone <2000PS(167)133>, an example of radical allylic bromination. The use of  $\text{CBr}_4$  (Equation (174)) <1997TL5651>,  $\text{CBr}_2\text{F}_2$  <2001CC81, 2002EJO1305>, and  $\text{CBrCl}_3$  <2003JOC500> as brominating agents under basic conditions has also been reported. Although the use of any of these reagents with dialkyl sulfones can occasionally result in isolable  $\alpha$ -bromosulfones (Equation (175)) <1998TL8179>, the principal product is usually that resulting from a subsequent Ramberg–Backlund reaction <2001CC81, 2002EJO1305>. Cyanogen bromide is a little used alternative to NBS but it has been employed for the regio- and stereoselective bromination of the cephalosporin **212** (Equation (176)) <1997SC3395, 1998T6565>.

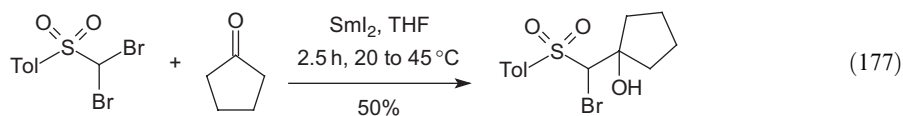


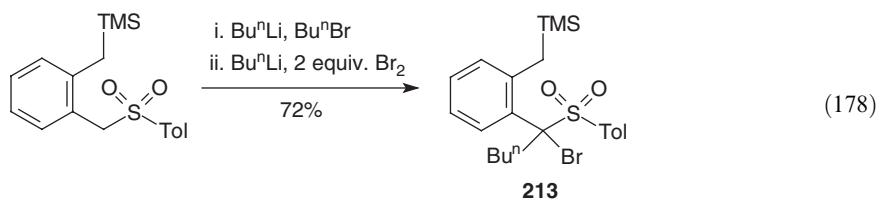


Scheme 49

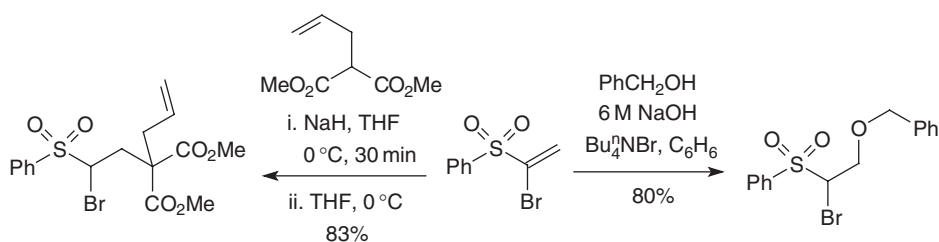


The behavior of  $\alpha$ -bromosulfonyl carbanions is entirely consistent with that of their chloro analogs. Thus primary and secondary  $\alpha$ -bromosulfones which cannot participate in the Ramberg–Backlund reaction have been converted to anions that undergo 1,2-addition to ketones [<2002TL2285>](#), aldehydes [<2002TL2285>](#) and iminium salts [<2001IZV2136>](#), and Michael addition to  $\alpha,\beta$ -unsaturated aldehydes [<2002TL2285>](#), giving mixtures of diastereomeric products with unsymmetrical substrates. 1,2-Addition products have also been obtained under radical conditions using the SmI<sub>2</sub> promoted reaction of *p*-tolyl dibromomethyl sulfone with cyclopentanone (Equation (177)) [<2001SC47>](#). These  $\alpha$ -bromosulfonyl carbanions have also been alkylated using alkyl halides [<1997TL5651>](#). A particularly convenient one-pot alkylation bromination protocol has been developed for the synthesis of tertiary  $\alpha$ -bromosulfones such as **213** (Equation (178)) [<1998JOC2086>](#). Although standard vicarious nucleophilic substitution with  $\alpha$ -bromomethyl aryl sulfones involves the loss of Br, the presence of an alternative leaving group in the electrophilic partner allows the Br to be retained and results in the formation of secondary  $\alpha$ -bromosulfones [<2002EJO1412>](#).

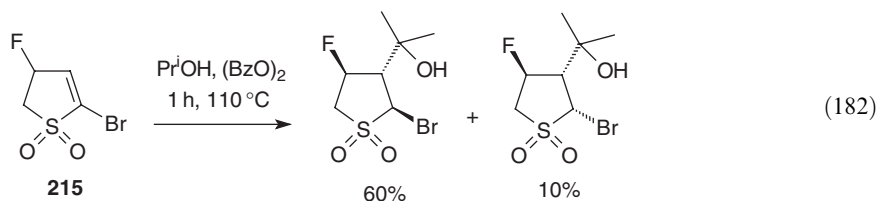
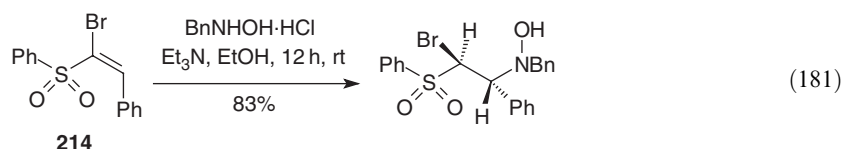
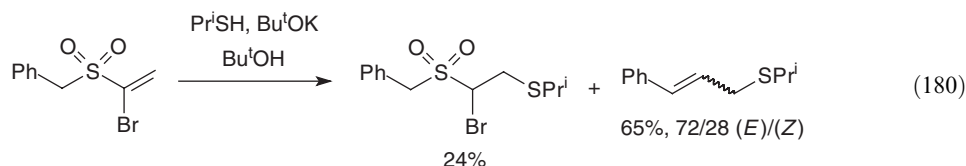
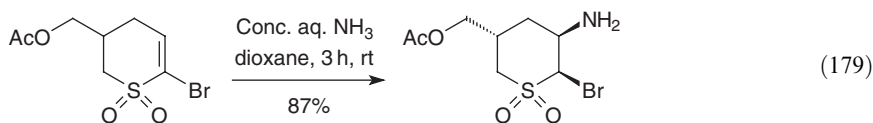




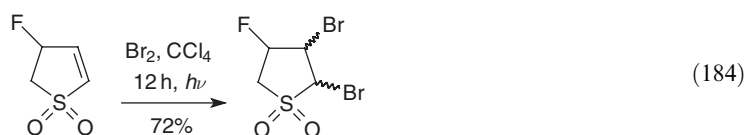
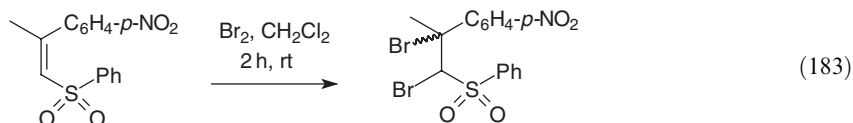
$\alpha$ -Bromovinyl sulfones are efficient Michael acceptors and the addition of C- (Scheme 50) <1997T7805>, N- (Equation (179)) <1995TL7767, 1997SL1043>, O- (Scheme 50) <1997TL1995>, and S-nucleophiles (Equation (180)) <1997SL1043> results in the formation of a diverse range of  $\alpha$ -bromosulfones. A mixture of products may be obtained if the initially formed  $\alpha$ -bromosulfone can undergo the Ramberg–Backlund reaction <1997SL1043>. Interestingly, this approach has not been used to prepare  $\alpha$ -chlorosulfones in the period covered by this review. A number of stereogenic reactions of this type are diastereospecific (Equation (179)) <1995TL7767> including the stereospecific *syn* addition of hydroxylamines to **214**, a result that is consistent with a concerted mechanism (Equation (181)) <2001TL8251>. A very modest de value is obtained in the reaction of (*S*)-1-phenylethylamine with benzyl  $\alpha$ -bromovinyl sulfone <1997SL1043>. The Michael-type addition of oxyradicals to the  $\alpha$ -bromovinyl sulfone **215** also gives an  $\alpha$ -bromosulfone, the addition being stereospecific with respect to the  $\gamma$ -substituent (Equation (182)) <1999JFC(99)73>.



Scheme 50

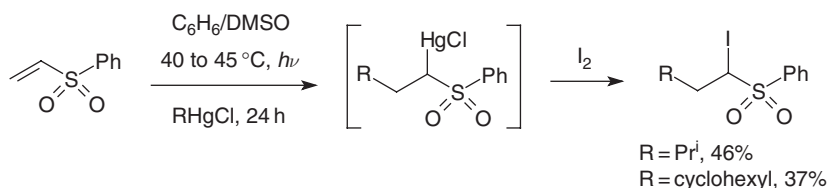
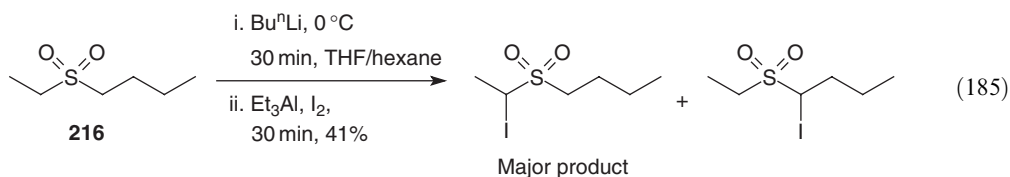


The addition of  $\text{Br}_2$  to  $\alpha,\beta$ -unsaturated sulfones has also been a source of  $\alpha$ -bromosulfones. The reaction can be carried out thermally (Equation (183)) <1995JPR363, 1995TL7767, 1998ZOR1792, 2001KGS840> or photochemically (Equation (184)) <1999JFC(99)73>. In many cases the stereochemistry of the product has not been determined as it is used immediately in processes which involve the loss of any stereochemical elements. Secondary dehydrobromination products may be formed <1995JPR363>. The addition of bromomethanesulfonyl bromide to strained  $\sigma$ -bonds in bicyclo[4.1.0.0<sup>2,7</sup>]heptanes (Scheme 48) <1999ZOR1189> and related reactions <1996ZOR1709, 1998ZOR1190> also produce  $\alpha$ -bromosulfones, as does the addition of  $\text{SO}_2$  to 1-bromo-1,4-butadiene (Equation (169)) <1998JOC9490>. The reductive monodebromination of  $\alpha,\alpha$ -dibromosulfones using  $\text{NaOH}/\text{CHCl}_3$  <2003JOC500> and  $\text{NaBH}_4/(\text{PhSe})_2$  <1997TL5651> has also been reported.



(iv)  $\alpha$ -Iodosulfones— $\text{R}_2^1\text{CIS}(\text{O})_2\text{R}^2$

The methods described previously for  $\alpha$ -chloro- and  $\alpha$ -bromosulfones can, in general, be used in the preparation of  $\alpha$ -iodosulfones. Thus  $\text{NIS}/\text{NaHCO}_3$  has been used in the kinetically controlled, highly stereoselective, iodination of the azetidinone **211** (Scheme 49) <2000JOC7203> and the  $\alpha$ -iodosulfonyl carbanion derived from phenyl iodomethyl sulfone has been alkylated with alkyl halides <1997TL879> and added to ketones <2002TL2285>.  $\text{I}_2/\text{Bu}^n\text{Li}$  can also be used to introduce iodine, with the sulfone **216** undergoing iodination via an alanate to give predominantly the iodoethyl product (Equation (185)) <1997JCS(P1)323>. Alkyl mercuric halides add to vinyl sulfones to give an  $\alpha$ -mercuric halide from which the mercury can be displaced using  $\text{I}_2$  (Scheme 51) <1995JA3952>. The addition of  $\text{NaI}$  is reported to result in the faster initiation of the reaction.

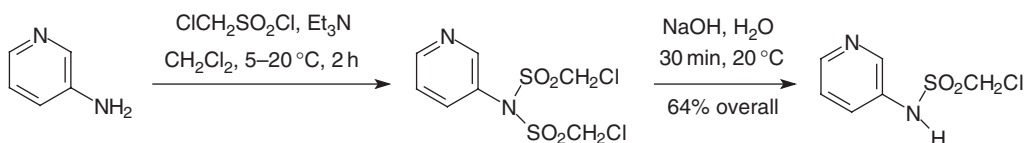
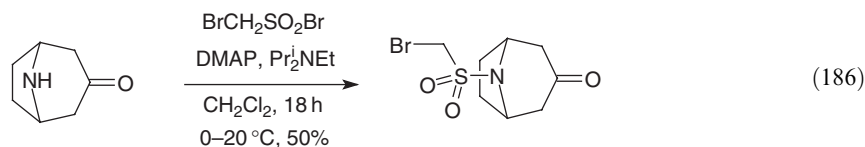


Scheme 51

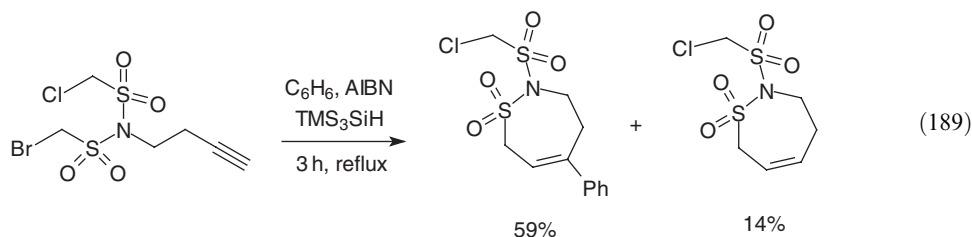
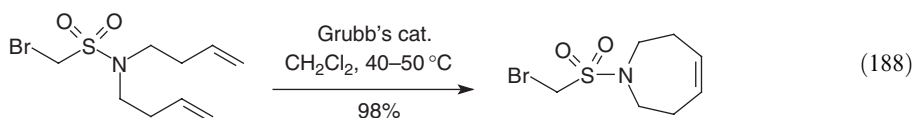
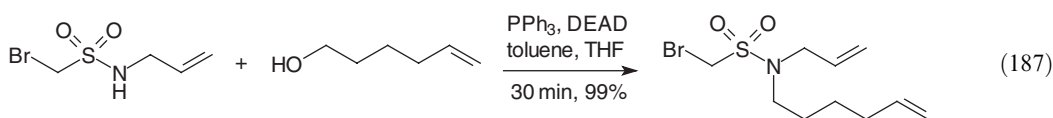
4.02.2.3.2 Other tetracoordinate  $\alpha$ -halosulfur derivatives— $\text{R}_2^1\text{CHaIS}(\text{O})_2\text{R}^2$

A very wide variety of  $\alpha$ -halomethanesulfonamides and methanesulfonates have been prepared using chloromethanesulfonyl chloride, whose preparation from 1,3,5-trithiane using  $\text{KOCl}$  in aqueous  $\text{HCl}$  has been reported <1997AJC1027>, and bromomethanesulfonyl bromide. Primary and secondary  $\alpha$ -halomethanesulfonamides have been prepared from the corresponding amines

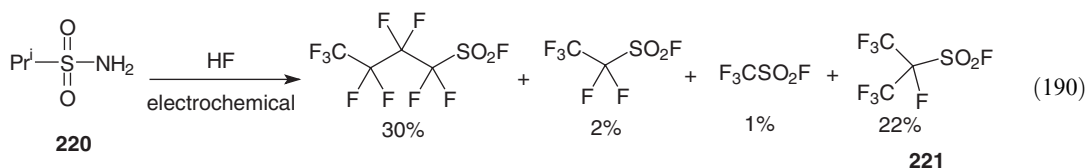
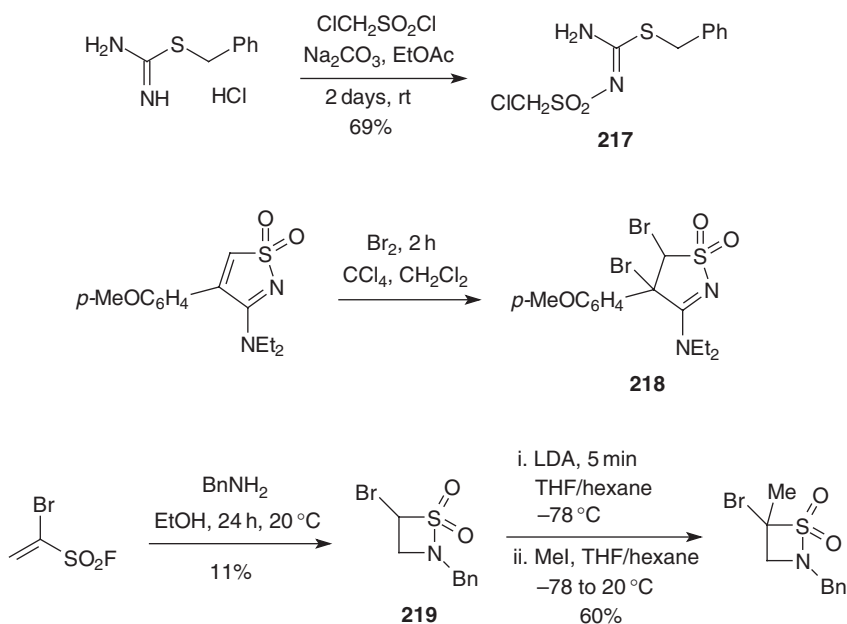
using DMAP in the presence of  $\text{Pr}_2^i\text{EtN}$  (Equation (186)) <1999JOC9225, 2000JOC7119>. Preventing bis-sulfonylation can be a problem with some primary amines and it is reported that bis-sulfonylation followed by monodesulfonylation is a convenient method of obtaining the monosulfonylated product in such cases <2001T5009> (Scheme 52). Monosulfonylated amines have been converted to the bis-product using DMAP/ $\text{Pr}_2^i\text{EtN}$  <2001JOC3564>. These  $\alpha$ -halo-methanesulfonamides can be *N*-alkylated under solid-liquid PTC <2001T5009> or Mitsunobu conditions (Equation (187)) <1999JOC9225, 2001JOC3564>, and protection and deprotection based on the *t*-BOC group occurs in high yield <2001JOC3564>. More structurally complex  $\alpha$ -halomethanesulfonamides are available through ring-closing metathesis reactions of bis-*N*-alkenylated sulfonamides (Equation (188)) <2001JOC3564> and the intramolecular cyclization of  $\alpha$ -sulfonyl radicals, generated in the standard way using AIBN/ $\text{TMS}_3\text{SiH}$  (Equation (189)) <2001JOC3564>.



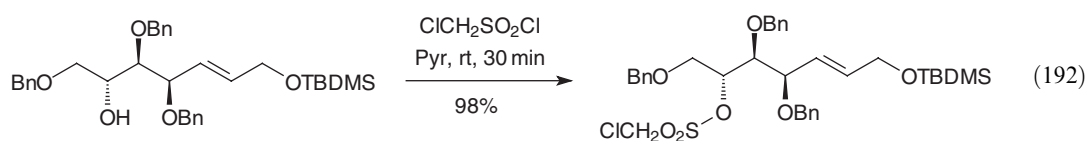
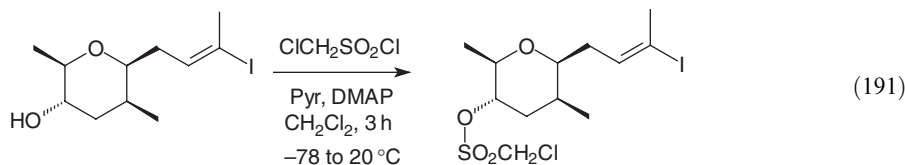
Scheme 52

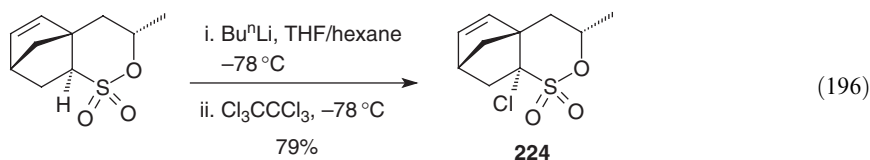
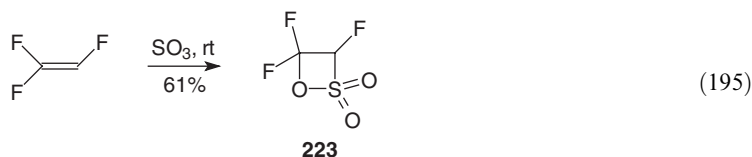
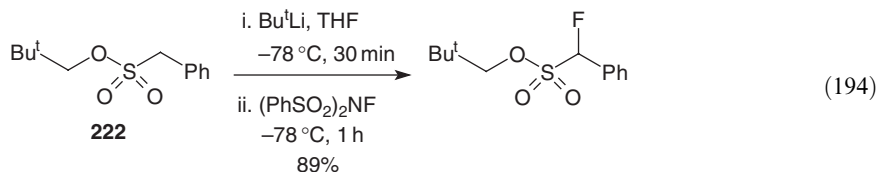
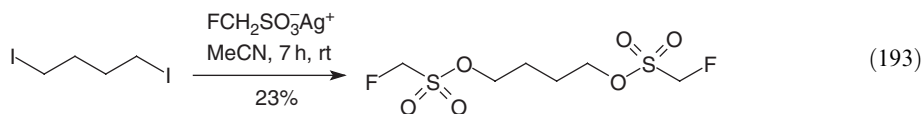


The *N*-sulfonylthioiourea **217** <1997AJC1027>, the isothiazole **218** <1996JFC(79)71>, and the thiazetidine **219** <2000JA3375>, which has been alkylated under standard conditions, are further examples of tetracoordinate  $\alpha$ -halosulfur derivatives that are structurally related to sulfonamides (Scheme 53). The electrochemical fluorination of the sulfonamide **220** gives a mixture containing the  $\alpha$ -fluorosulfonyl fluoride **221** <1996JFC(79)71> (Equation (190)).



A very large number of  $\alpha$ -chloromethanesulfonates have been prepared using chloromethanesulfonyl chloride. Chloromethanesulfonate is an extremely efficient leaving group that has been found to be superior to methanesulfonate in terms of reactivity and to trifluoromethanesulfonate in terms of stability [\[1999S1373\]](#). Chloromethanesulfonates are generally prepared by stirring an alcohol at 0 °C in  $\text{CH}_2\text{Cl}_2$  containing a base such as pyridine [\[2000T7123\]](#), lutidine [\[2003CEJ389\]](#), or DMAP/pyridine (Equation (191)) [\[2000JA10482\]](#). Pyridine has also been used as the solvent for these reactions (Equation (192)) [\[1999JOC5280, 2003BMCL937\]](#).  $\alpha$ -Fluoromethanesulfonates have been prepared by the reaction of the silver salts of fluoromethanesulfonic acid with alkyl iodides (Equation (193)) [\[1998ACS42\]](#), the parent acid being prepared by heating fluoromethanesulfonyl chloride in refluxing methanol. The electrophilic fluorinating agent *N*-fluorobenzenesulfonimide has been successfully used to monofluorinate the neopentyl sulfonate **222** (Equation (194)) [\[1998JOC8052\]](#), but the corresponding methyl, ethyl, and isopropyl esters afforded only decomposition products. The cycloaddition of  $\text{SO}_3$  to trifluoroethene gives the cyclic  $\alpha$ -fluoromethanesulfonate **223** (Equation (195)) [\[2000JFC\(105\)137\]](#). The  $\alpha$ -chloromethanesulfonate **224** has been obtained by the stereoselective halogenation of an  $\alpha$ -sulfonyl carbanion using hexachloroethane (Equation (196)) [\[1995TL711\]](#).



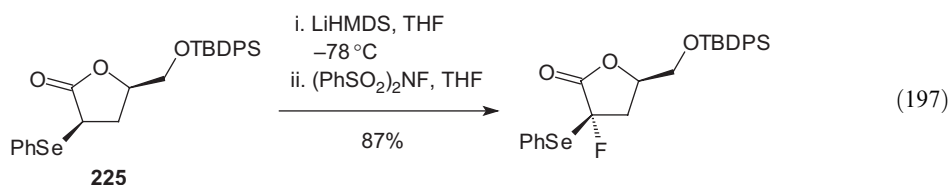


#### 4.02.3 HALOGEN AND SELENIUM OR TELLURIUM DERIVATIVES— $\text{R}_2\text{CHal}(\text{SeR}')$ , $\text{R}_2^1\text{CHal}(\text{TeR}^2)$ , etc.

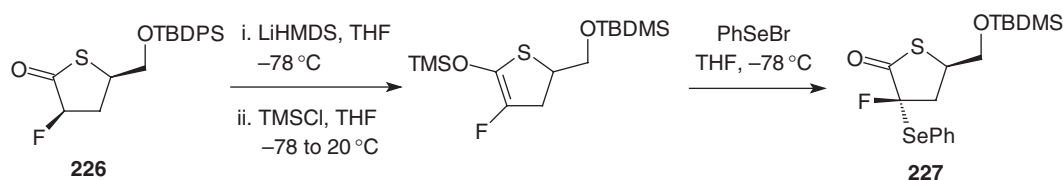
##### 4.02.3.1 $\alpha$ -Haloselenium Derivatives— $\text{R}_2^1\text{CHal}(\text{SeR}^2)$ , etc.

##### 4.02.3.1.1 Dicoordinate $\alpha$ -haloselenium derivatives— $\text{R}_2^1\text{CHal}(\text{SeR}^2)$

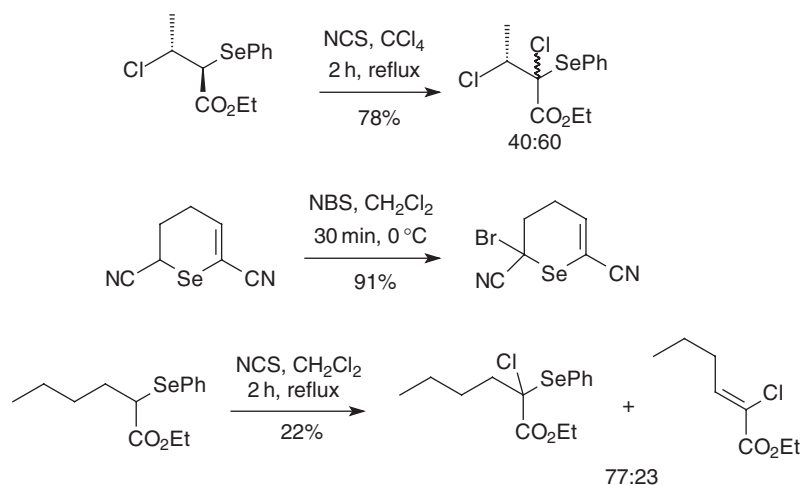
In keeping with the behavior of the lighter chalcogens, the electrophilic fluorinating agent  $(\text{PhSO}_2)_2\text{NF}$  has been used to monofluorinate the  $\alpha$ -selenolactone **225** stereoselectively (Equation (197)) <1998BMCL1589>. The alternative approach of adding benzeneselenenyl bromide to the silyl enol ether derived from the  $\alpha$ -fluoroketone **226** has been used to prepare, again stereoselectively, the related  $\alpha$ -selenothiolactone **227** (Scheme 54) with the opposite stereochemistry <2002OL305, 2002JMC4888, 2003JMC389>. The  $\alpha$ -fluoroselenide **227** is stable to the diisobutylaluminum hydride (DIBAL-H) reduction, acetylation and reaction with the lithium amides obtained from purine and pyrimidine derivatives which precede the oxidative elimination that completes the synthesis of a synthetic nucleoside. The reaction of benzeneselenenyl fluoride with 2-diazo-3-phenylpropionate to give the corresponding 2-fluoro-2-phenylselenenyl compound <2000JOM(611)158> is a recent extension of an established method of preparing  $\alpha$ -chloro- and  $\alpha$ -bromo- $\alpha$ -benzeneselenenyl ketones. NCS <2000T7495> and NBS <2001H465> continue to be used to produce  $\alpha$ -haloselenides, although the formation of by-products as a result of the elimination of benzeneselenol has been reported <2000T7495> (Scheme 55).





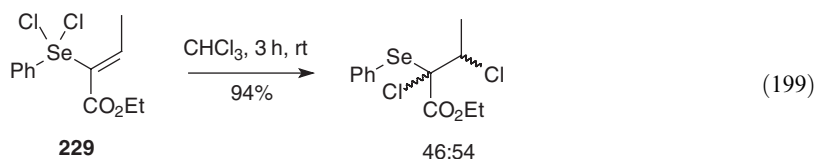
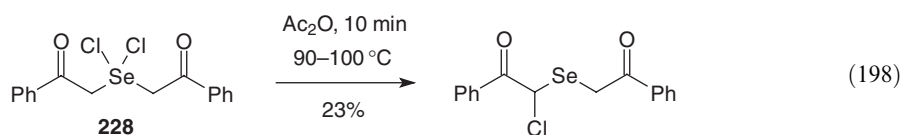


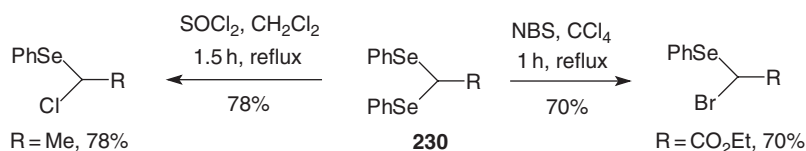
Scheme 54



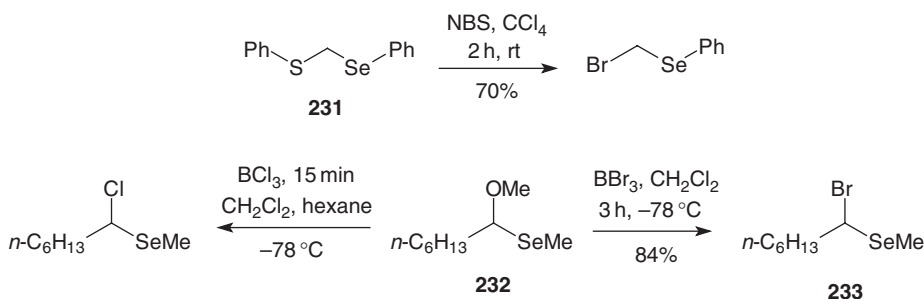
Scheme 55

The NCS/NBS reactions involve a Pummerer-type process as does the rearrangement of selenium(IV) dichlorides which, in the case of **228** (Equation (198)), has been carried out in  $\text{Ac}_2\text{O}$  <1995ZOR1548> although it is generally effected thermally or in the presence of pyridine. Rearrangement of the alkenylselenium(IV) dichloride **229** (Equation (199)) leads to the formation of a dichloro adduct (2000T7495) in high yield. The conversion of the bis-selenoacetals **230** to  $\alpha$ -haloselenides using NBS and  $\text{SOCl}_2$  (Scheme 56) <1995SC117> is yet another example of how Pummerer-type processes play an important role in functional group transformations involving chalcogen ethers. Surprisingly, tris-(phenylseleno)-methane under these conditions is reported to give chloromethyl phenyl selenide in good yield (67%) <1995SC117>. The mixed acetals **231** <1995SC117> and **232** <1995JOC6141> (Scheme 57) demonstrate an interesting chemospecificity in that in each case it is the lower chalcogen which acts as the leaving group. The  $\alpha$ -bromo-selenide **233** is described as being very labile.



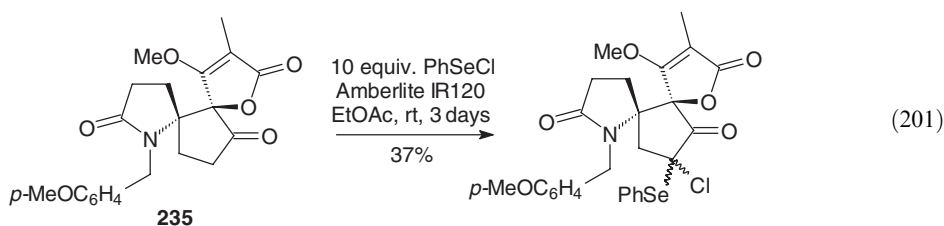
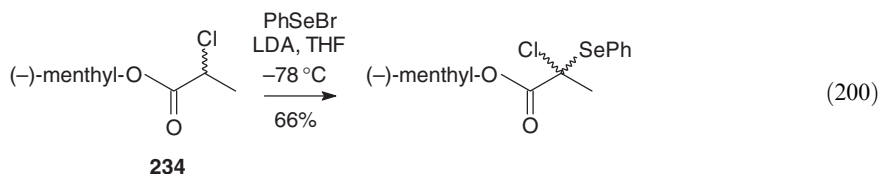


Scheme 56



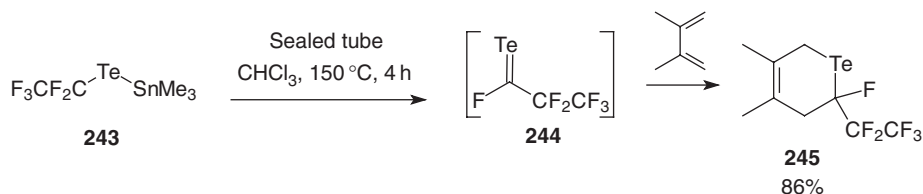
Scheme 57

$\alpha$ -Haloselenides have also been prepared by a variety of substitution reactions, a typical example being the selenenylation of the anion derived from the  $\alpha$ -chloro ester **234** (Equation (200)) <1999TL4969>. The reaction of the lactone **235** with a large excess (10 equiv.) of PhSeCl and in the presence of an ion-exchange resin gives an  $\alpha$ -chloro- $\alpha$ -seleno derivative (Equation (201)) <2002T61>, the production of which involves the reaction of the initially formed selenyl derivative with a second molecule of PhSeCl in which the chlorine acts as an electrophile. The reaction of aryl diselenides with Zn and  $\text{CH}_2\text{Cl}_2$  <2001TL4597>, or  $\text{KBH}_4$  and  $\text{CH}_2\text{Cl}_2$  <1998SL1191>, gives aryl selenomethyl chlorides. It has been suggested that these reactions involve an initial SET to the halide to give a radical anion that either attacks the diselenide directly, or is converted to a radical which could also interact with the diselenide producing the arylselenomethyl chloride. The standard NaI in acetone procedure has been used to convert phenylselenomethyl chloride to the iodide <2001JOC1966>, and the selenomethyl chloride grouping is sufficiently stable to permit the acid catalyzed addition of water to the ethynyl bond in **236** (Equation (202)) <2001T3297>. At high temperature and in the presence of a mixture of Se and Cu, perfluoroalkyl iodides undergo a substitution process resulting in the formation of  $\alpha$ -fluoro selenides (Equation (203)) <2000JFC(102)301>. The Cu acts as a catalyst and as an iodine scavenger. Finally the addition, under PTC conditions, of dibromo- and dichlorocarbene to  $\alpha$ -halovinyl selenides **237** gives  $\alpha$ -halocyclopropyl selenides (Scheme 58) <1998SC1667>.





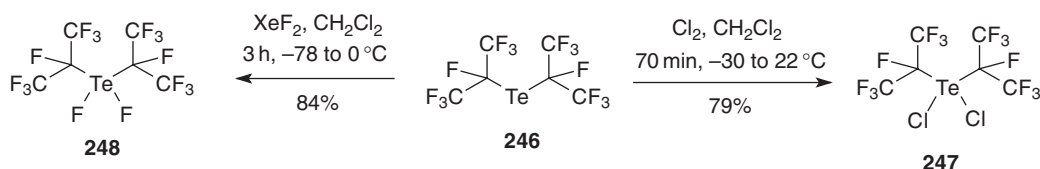
(Equation (203)), the Cu acts as an iodine scavenger and a catalyst. The telluride **238** can be converted photochemically to the ditelluride **239**, reaction of which with  $I_2$  gives the  $\alpha$ -fluoro-tellurenyl iodide **240** that is only stable in solution (Scheme 48) (2000JCS(D)11). The ditelluride **239** has also been converted to the air-stable perfluorocyanotellurium compound **241** (Scheme 59) <2000JCS(D)11>. The reaction of **238** with  $SnMe_3H$  gives a light-sensitive perfluoroalkyl trimethylstannyl telluride **242**. The pyrolysis of the corresponding perfluoroethyl compound **243** results in the formation of a perfluoroalkyltellurocarbonyl fluoride **244** that can be trapped by a diene to give a volatile  $\alpha$ -fluoro dihydrotelluropyran **245** that is extremely air-sensitive and decomposes at room temperature with separation of tellurium (Scheme 60) <1996JCS(D)4463>. Perfluoro-*n*-propyltrimethylstannyl fluoride gives the same reaction <2000JCS(D)11>.



Scheme 60

#### 4.02.3.2.2 Tri- and tetracoordinate $\alpha$ -halotellurium derivatives— $R_2^1CHaTe(O)R^2$ , $R_2^1CHaTe(O)_2R^2$ , etc.

The reaction of the telluride **246** with  $XeF_2$  and  $Cl_2$  gives the tetracoordinated  $\alpha$ -fluorodihalo-tellurium(IV) compounds **247** and **248**, respectively (Scheme 61) <2000JFC(102)301>. Attempts to make the corresponding dibromotellurium compound failed.



Scheme 61

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## 4.03

# Functions Incorporating a Halogen and Another Heteroatom Group Other Than a Chalcogen

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4.03.1	HALOGEN AND NITROGEN DERIVATIVES— $R_2^1CHal(NR_2^2)$ , $R_2^1CHal(NR^2X)$ , $R_2CHal(NX_2)$ , $R_2CHal(NY)$	130
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This chapter aims to present the synthesis of molecules incorporating a halogen and another group other than a chalcogen (N, P, As, Sb, Bi, Si, Ge, B, Li, Mg, Cr, Mo, W, Mn, Fe, Co, Ru, Rh, Pd, Re, Os, Ir, Pt, Cu, Ag, Au, Zn, Cd, Hg, Al, Ga, In, Th, Sn, and Pb) bonded to the same carbon atom. This implies that nearly half of the stable elements of the periodic table are involved in the reactions that are described in this chapter.

#### 4.03.1 HALOGEN AND NITROGEN DERIVATIVES— $R^1CHa(NR^2_2)$ , $R^1CHa(NR^2X)$ , $R_2CHa(NX_2)$ , $R_2CHa(NY)$

This section covers the synthesis of compounds bearing the *N*-( $\alpha$ -haloalkyl) unit, which is present in a wide range of compounds. The most important structural motifs included in this broad definition are, in the order of appearance in the section, *N*-haloalkyl amines, *N*-haloalkyl ammonium salts,  $\alpha$ -halo amides,  $\alpha$ -halo carbamates, *N*-thio  $\alpha$ -halo amides,  $\alpha$ -halo nitroso derivatives,  $\alpha$ -halo nitro derivatives,  $\alpha$ -halo azo alkanes,  $\alpha$ -halo heteroarylium salts,  $\alpha$ -halo isocyanates, and 2-halo azirines (Figure 1).

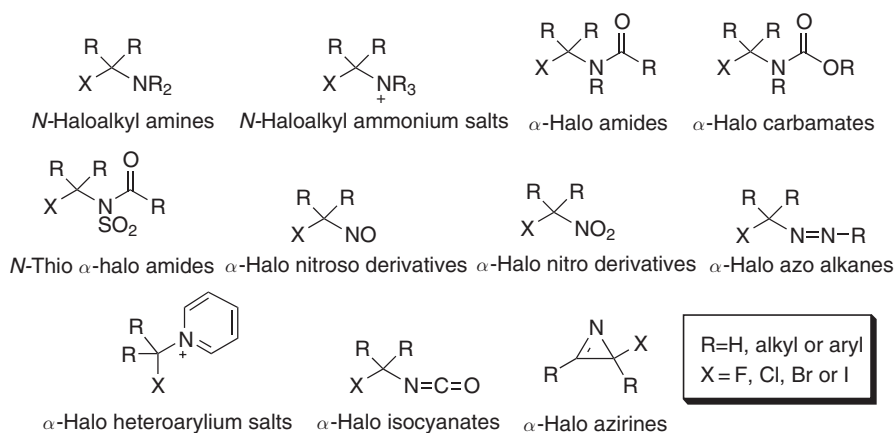


Figure 1 Examples of  $\alpha$ -halo nitrogen derivatives.

##### 4.03.1.1 $\alpha$ -Halo Amines— $R^1CHaNR^2_2$ and $[R^1CHaNR^2_3]^+X^-$ (Where $R^1, R^2 = H$ , Alkyl or Aryl)

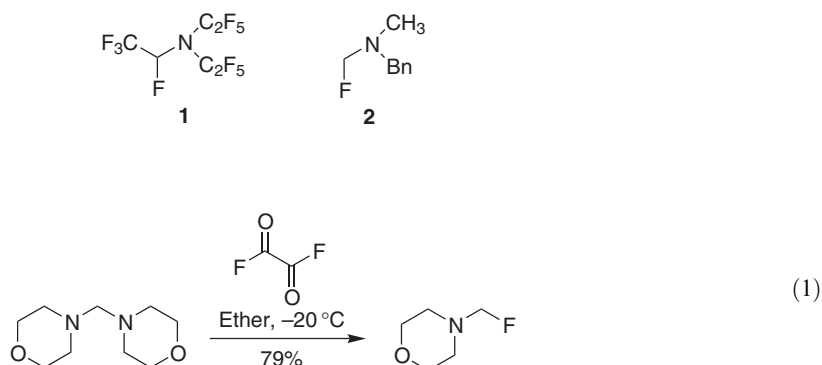
This section describes the synthesis of *N*-haloalkyl amine derivatives and of *N*-haloalkyl ammonium derivatives.

###### 4.03.1.1.1 *N*-Haloalkyl amines— $R^1CHaNR^2_2$ (where $R^1, R^2 = H$ , alkyl, or aryl)

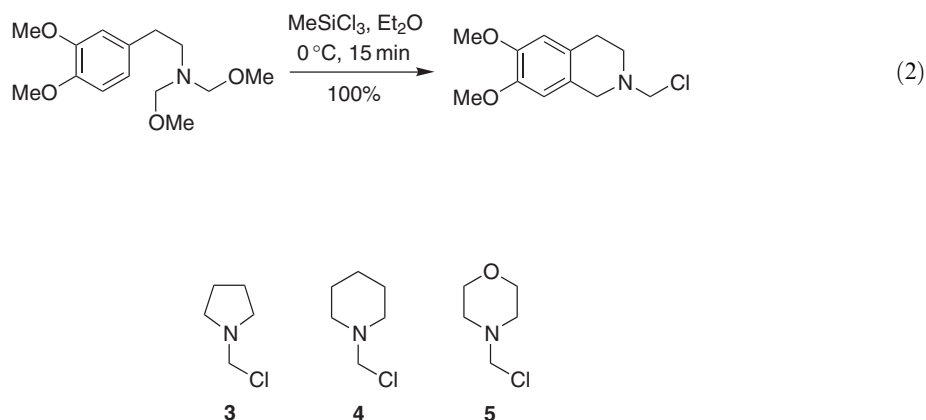
The preparation of *N*-haloalkyl amines has been described in several articles. In the following paragraphs, several examples of the synthesis of *N*-haloalkylamines are discussed.



The electrochemical fluorination of trialkylamines affords compounds such as **1** <1997JFC143>, although in low yields. The *N*-fluoromethylamine **2** has also been prepared <1988JA1964>. The cleavage of aminals led to haloalkylamines <1957CB2003, 1960CB1305, 1996JA3720>, as exemplified for the preparation of *N*-fluoromethylmorpholine utilizing oxalyl fluoride (Equation (1)) <1970CB104>.



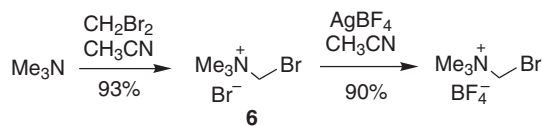
Treatment of an *N,N*-di(methoxymethyl)amine or an *N*-methoxymethylamine with trichloromethylsilane led to the corresponding chloride derivative (Equation (2)) <1990SL617, 1995T10737>. Tris(chloromethyl)amine has been obtained by treatment of hexamethylenetetramine with phosphorus pentachloride <1971AG(E)653, 1973CB69>. The reaction of secondary amines with  $\text{CH}_2\text{ClBr}$  <1983JFC371> gave the corresponding chloromethylamines **3**, **4**, and **5**, albeit the ionic form—an iminium chloride—may contribute significantly in compounds with this structure <1987JOC1857, 1990JOC2254>.



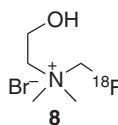
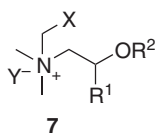
#### 4.03.1.1.2 *N*-Haloalkyl ammonium salts— $[\text{R}_2^1\text{CHalNR}_2^2]^+ \text{X}^-$ (where $\text{R}^1, \text{R}^2 = \text{H}$ , alkyl, or aryl)

The general method for preparing halomethylammonium salts is the treatment of a trialkylamine with a dihalomethane, which is a particular case of the Menshutkin reaction. A detailed study of the quaternization reaction of tertiary amines has been performed by Isaacs and co-workers <1986T601>. The reaction of dichloromethane with brucine <1998MI573, 1999MI778>, with zacopride **1** <1994BMCL945>, with DABCO <1973IC102>, with galanthamine <1994HCA1611>, and with ferrocenylmethyldimethylamine <1998JOM(570)201> gave the corresponding *N*-chloromethylammonium salts. Similarly, treatment of trimethylamine with  $\text{CH}_2\text{Br}_2$  yielded the bromo derivative **6** <1971JCS(C)3471>, which can be transformed into the corresponding tetrafluoroborate salt by an anion exchange reaction (Scheme 1) <1999JCS(P2)1187>. This anion exchange reaction can be similarly performed using the iodides <1996JA11313, 1999JCS(P2)1187> or chlorides <1999JCS(P2)1187>, as starting material. The Menshutkin reaction has also been utilized for the synthesis of a variety of iodomethyl compounds, from diiodomethane <1971AG(E)330, 1996CC1637, 1996JA11313, 1997TL7041, 1999JCS(P2)1187,

1999JOC1798>. Alkyl iodine(III) dichlorides can be prepared by oxidation of iodomethyl ammonium salts with chlorine (Equation (3)) <1999TL1839>. Reaction of trialkylamines with mixed dihalomethanes generated a number of different halides <2000MI55>, such as **7** <1991JMC2031> and **8** <2002MI347>. An ammonium salt bearing an *N*-fluoromethyl group has been obtained from the corresponding amine <1986ZAAC(537)63>.



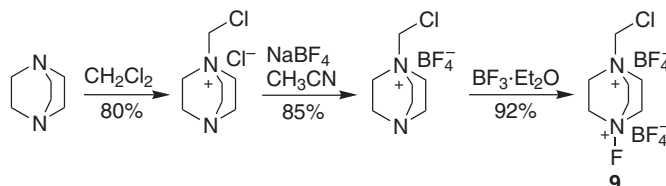
Scheme 1



X = Cl, Br or I; Y = Br or I

R<sup>1</sup> = H or Me; R<sup>2</sup> = H or COMe

Selectfluor<sup>TM</sup> **9**, whose chemistry has been reviewed <1998JFC1, 1999JFC157>, is a powerful electrophilic fluorination agent that is produced on a large scale. This useful compound for the pharmaceutical companies can be prepared by the sequence of steps shown in Scheme 2 <1992CC595, 1996JCS(P1)2069, 1996JFC43>.



Scheme 2

#### 4.03.1.2 *N*-Substituted $\alpha$ -Halo Amines— $\text{R}_1^1\text{CHal}(\text{NR}^2\text{X})$ , $\text{R}_2\text{CHal}(\text{NX}_2)$ , $\text{R}_2\text{CHal}(\text{NY})$

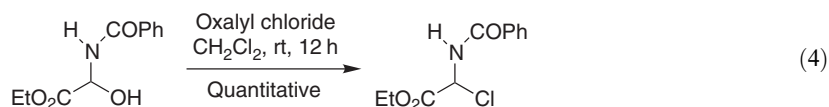
*N*-Substituted haloamines can be classified into two different groups. The first are those having a nitrogen singly bonded, which include compounds such as  $\alpha$ -halo amides,  $\alpha$ -halo carbamates and *N*-thio  $\alpha$ -halo amides. The second group contains molecules such as  $\alpha$ -halo nitroso derivatives,  $\alpha$ -halo nitro derivatives,  $\alpha$ -halo nitro compounds,  $\alpha$ -halo azo alkanes,  $\alpha$ -halo heteroarylium salts,  $\alpha$ -halo isocyanates, and 2-halo azirines, which have a doubly bonded nitrogen. In the following paragraphs, the synthesis of these compounds is presented according to this classification.

##### 4.03.1.2.1 $\alpha$ -Halo amine derivatives— $\text{R}_1^1\text{CHal}(\text{NR}^2\text{X})$ , $\text{R}_2\text{CHal}(\text{NX}_2)$ (singly bonded nitrogen)

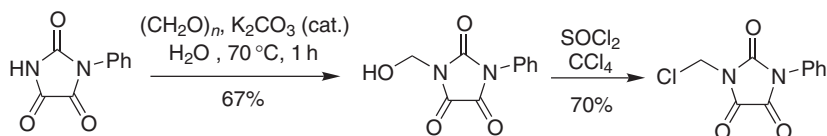
###### (i) $\alpha$ -Halo amides and imides

(a) *By replacement of an  $\alpha$ -hydroxy group.* The most widely used method for the synthesis of *N*-chloroalkyl amides is the replacement of a hydroxyl group by a halogen. This protocol is useful to obtain either  $\alpha$ -chloroamides or  $\alpha$ -chlorolactams. The most commonly used reagent to promote

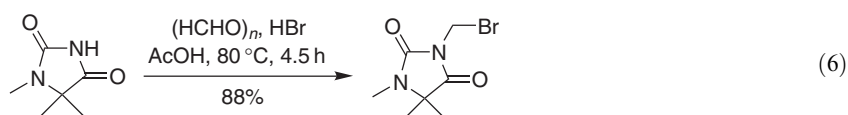
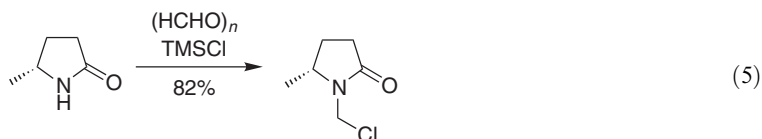
such a functional group transformation is thionyl chloride, which has been used in the synthesis of a wide range of chloro amides <1980JOC1577, 1981TL2689, 1987JHC1381, 1991ZOB2679, 1994ZOB1048, 1995SL97>. Another reagent employed is oxalyl chloride (Equation (4)) <2002OL387, 2003JOC5819>. For the preparation of *N*-bromomethylamides from the corresponding hydroxy derivative, HBr <1971JOC1379> and PBr<sub>3</sub> <1972BCJ2531> have been used.



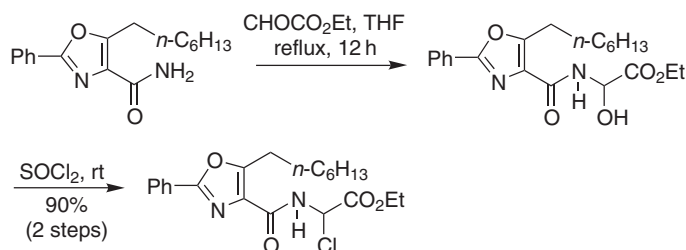
The transformation of an amide into the corresponding *N*-halomethyl amide can also be performed by a two-step procedure called halomethylation, through an *N*-hydroxyalkyl intermediate. This hydroxy derivative is obtained by reaction of an amide with paraformaldehyde. For the second step, thionyl chloride (Scheme 3) <1995T9551, 1994JOC1719, 1995JCS(P1)1317> or trimethylsilyl chloride (Equation (5)) <1994JOC1719, 1984ZOB2645, 1991ZOB2024, 1992SC2381, 1995TL2483> can be utilized. The halomethylation process can be directed toward the synthesis of  $\alpha$ -bromo amides using HBr (Equation (6)) <2001T7675, 1994SL933>.



Scheme 3

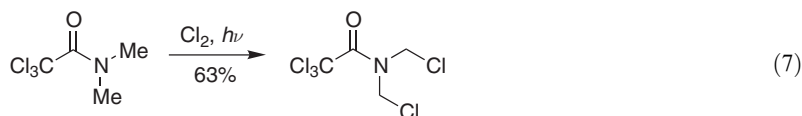


A variation of the halomethylation process has been used by Ciufolini and co-workers, for the introduction of an  $\alpha$ -chloroacetate moiety, in their studies toward the total synthesis of (–)-muscoride A (Scheme 4) <2003AG(E)1411>.

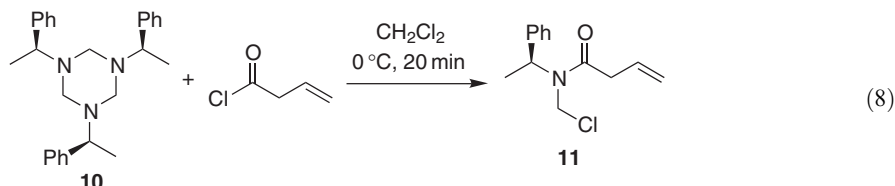


Scheme 4

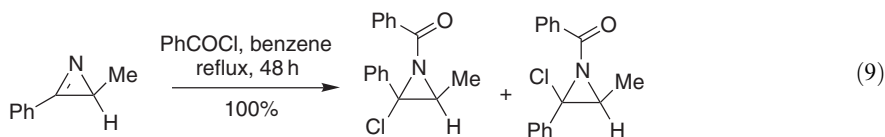
(b) *By direct halogenation.* There are examples in the literature describing the preparation of haloalkyl amides by direct halogenation using chlorine (Equation (7)) <1979LA1447>. Bromomethylamides are intermediates in the succinimidation of *N,N*-dimethylamides by NBS <1984JCS(P1)281>.



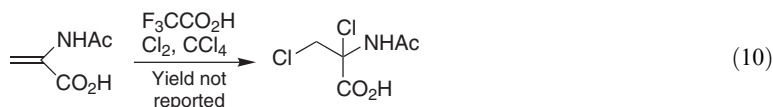
(c) *By cleavage of gem-diheteroatomic compounds.* The cleavage of the triazine **10** promoted by 3-butenoyl chloride gave the chiral nonracemic amide **11** (Equation (8)) <1992H349>. The reaction of triazines with oxalyl chloride gives imidazolidinediones, through an *N*-chloromethyl amide intermediate <1993T10609>. Halomethyl amides are also intermediates in the reaction of tris(trimethylsilylmethyl)hexahydro-1,3,5-triazine with acyl chlorides <1985CPB4596>.



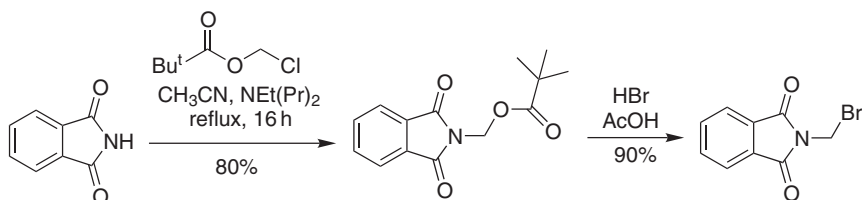
(d) *By addition of electrophiles to imines and enamines.* The addition of acyl chlorides to imines is an efficient method for the preparation of *N*-chloroalkyl amides (Equation (9)) <1968JA2875, 1963CB600, 1963JOC2592, 1974JOC3745, 1975CB2917>. The reaction also occurs with acyl bromides instead of chlorides <1969JOC1192>.



The addition of chlorine to enamines is also an effective approach for the synthesis of chloro amides (Equation (10)) <1973JOC126, 1991ZOB1910>. An analogous reaction can also be performed using bromine, as well as hydrogen chloride <1973JOC126>.



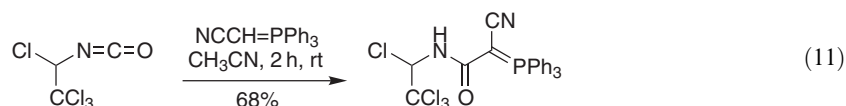
(e) *By miscellaneous methods.* The cleavage of a protected *N*-hydroxymethyl group followed by halogenation is an efficient method to prepare  $\alpha$ -halo amides. This approach can be an alternative to the traditional halogenation of a hydroxy derivative. Thus, a two-step protocol, in which a pivalate ester is the intermediate, has been developed for the *N*-bromomethylation of amides (Scheme 5) <1995SL423>. The action of HCl, HBr, or SOCl<sub>2</sub> on alkoxy methyl compounds led to the corresponding halides <1982JOC3169>. Similarly, treatment of *N*-[(trimethylsiloxy)methyl]amines with TMSCl, TMSBr, or TMSI gave the corresponding *N*-halomethylamides <1984ZOB1437>.



Scheme 5

Reaction of 6-phthalimidopenicillanate with chlorine or with sulfonyl chloride afforded chloroalkyl amides by opening of the thiazolidine ring <1971JA6267>. Similarly, *N*-(chloromethyl)phthalimides have been obtained in good yield from thiophthalimides, utilizing sulfonyl chloride <1979JOC1178>.

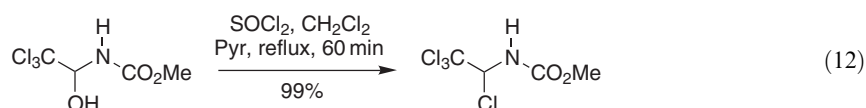
The reaction of a chloro isocyanate with a phosphorane led to a phosphorus amide, in good yield (Equation (11)) <1997ZOB391>.



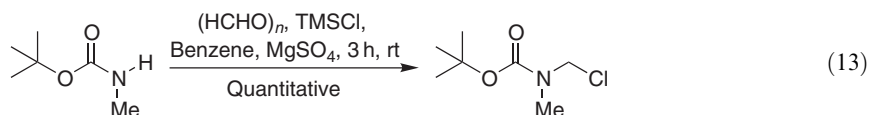
(ii)  $\alpha$ -Halo carbamoyl derivatives

The strategies used so far for the synthesis of  $\alpha$ -halo carbamoyl derivatives are quite similar to those mentioned for  $\alpha$ -halo amides, whose section may be consulted for additional insights concerning the synthesis of the halo carbamoyl derivatives. For this reason, this section is organized in a similar manner as the previous one.

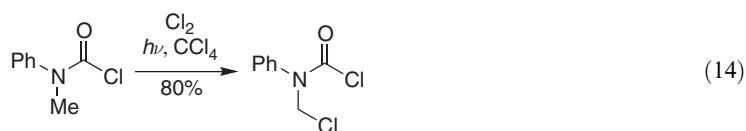
(a) *By replacement of an  $\alpha$ -hydroxy group.* Thionyl chloride can efficiently promote the transformation of the hydroxy group of an  $\alpha$ -hydroxy carbamoyl derivative into the corresponding chloride (Equation (12)) <1968JOC2887, 1998TL8845, 1985JHC1479, 1986LA1133, 1993PS(85)183>. This type of functional group transformation can also be performed using phosphorus pentachloride <1991TL3123, 1992JCS(P2)857>.



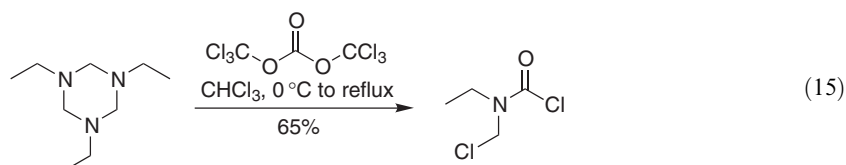
Treatment of a carbamate with paraformaldehyde led to an *N*-hydroxymethyl intermediate, which reacted *in situ* with trimethylsilyl chloride, giving the desired chloromethyl carbamate (Equation (13)) <1996TL5597, 1999T4831>.



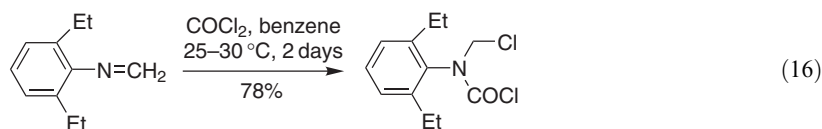
(b) *By direct halogenation.* The reaction of an alkyl amide with chlorine can afford the corresponding chloroalkyl carbamoyl compound, in good yield (Equation (14)) <1974JOC2897>. The utilization of sulfonyl chloride has also been reported for the chlorination of *N*-methylformanilide, leading to *N*-chloromethyl-*N*-phenylcarbamoyl chloride, in 64% yield <2000JFC111>. There are several reports describing the preparation of  $\alpha$ -bromo carbamates by bromination using either bromine <1982AG(E)203, 1983LA599, 1985T1693> or NBS <1983LA599, 1984JCS(P1)281, 1985T1693>.



(c) *By cleavage of gem-diheteroatomic compounds.* Bis(trichloromethyl)carbonate can mediate the cleavage of the triazines leading to a chloromethyl carbamoyl chloride (Equation (15)) <2000JFC111>. This kind of transformation is also promoted by phosgene <1974JOC2897>, as well as acyl halides <1962BEP621378, 1981CPB1747, 2000M953>. The preparation of compounds such as *N*-chloromethyl-*N*-methylformamide by the cleavage of *gem*-diamines has been reported <1981CB3421, 1986BSF449>.



(d) *By addition of electrophiles to imines and enamines.* The addition of phosgene to an imine led to a halo carbamoyl chloride (Equation (16)) <1987JHC945, 1974JOC3745>.

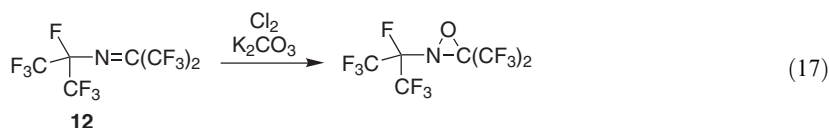


(iii) *N,N-Difluoro  $\alpha$ -halo amines*

No further advances have occurred in this area since the publication of chapter 4.03 in <1995COFGT(4)95>.

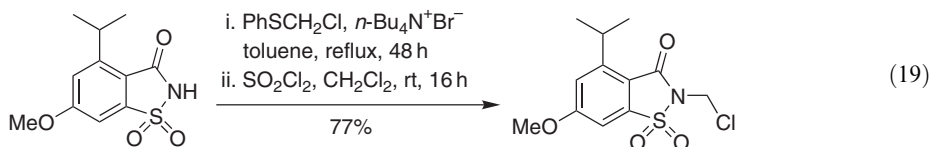
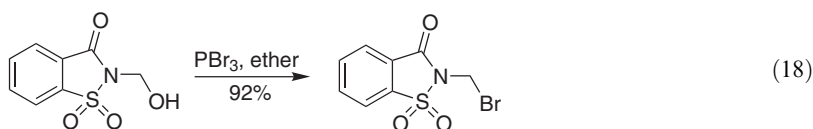
(iv) *N-Oxy  $\alpha$ -halo amines*

In studies toward the synthesis of polyfluorinated oxaziridines <1996CRV1809>, the reaction of the imine **12** with chlorine has been carried out, leading to the desired heterocyclic compound (Equation (17)) <1981USP4287128>.

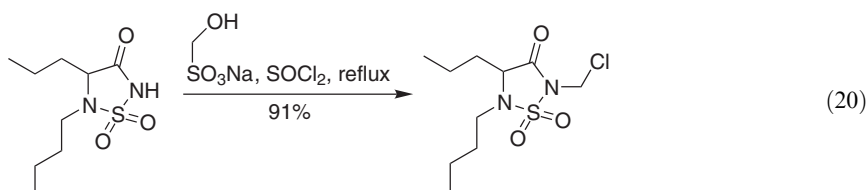


(v) *N-Thio  $\alpha$ -halo amines*

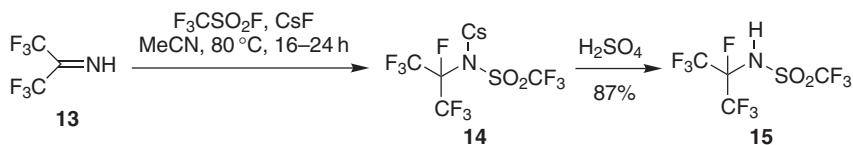
The approaches utilized for the synthesis of *N*-thio-*N*-halomethyl amides are similar to that used in the preparation of *N*-halomethyl amides and carbamates, which are described above. Thus, reaction of *N*-thio-*N*-hydroxymethyl amide with  $\text{PBr}_3$  gave the desired bromide, in excellent yield (Equation (18)) <1994JMC2623>. Similarly, chloromethyl derivatives were synthesized from the corresponding alcohol, after treatment with thionyl chloride <1992PS(70)99, 1996JHC615>. Treatment of a thioamide with chloromethyl phenyl sulfide, followed by reaction with sulfonyl chloride led to chloro *N*-thioamides in good overall yield (Equation (19)) <1995JMC739, 1995JMC4687, 1998BMC661>.



The bromomethylation procedures mentioned earlier (see Equation (6) and Scheme 5) were also suitable for the synthesis of *N*-thioamides in an efficient manner <1994SL933, 1995JMC4687, 1995SL423>. Groutas and co-workers reported the chloromethylation reaction of *N*-thioamides using formaldehyde sodium bisulfite adduct, instead of paraformaldehyde (Equation (20)) <1999JA8128, 2001SC3055>. *N*-Thio-*N*-iodomethyl amides have been obtained by reaction of the corresponding chlorides with NaI in anhydrous acetone <1998BMCL539, 1999BMCL2199>.



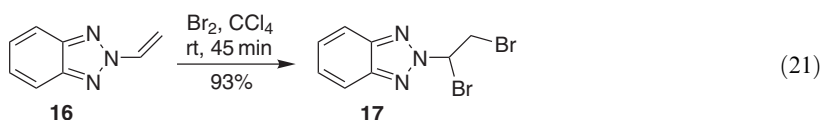
Treatment of the imine **13** with alkylsulfonyl fluorides and caesium fluoride led to the sulfo-  
namide **15**, after quenching the caesium salt intermediate **14** with sulfuric acid (Scheme 6)  
<1994JFC277>.



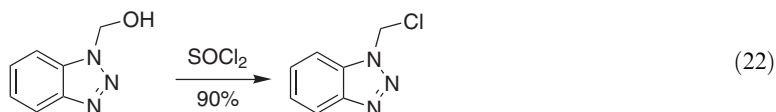
Scheme 6

(vi) *N*-Amino  $\alpha$ -halo amines

The addition of bromine into the enamine derivative **16** led to the *N*-bromoalkyl compound **17** in  
excellent yield (Equation (21)) <1999JOC346>. *N*-Amino  $\alpha$ -halo amines have also been obtained  
from the reaction of bis-trialkylhydrazinomethane with trichloroacetyl fluoride <1970CB3930>.

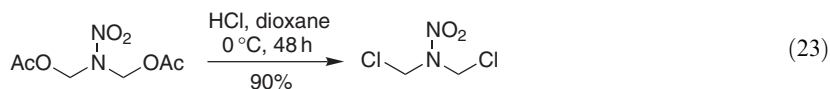


Reaction of the *N*-hydroxymethyl group of a triazole with thionyl chloride gives the corre-  
sponding chloride in 90% yield (Equation (22)) <1952JA3868, 1987JCS(P1)781>. Reaction of  
this chloride with sodium bromide (or iodide) yielded the corresponding 1-bromo- (or 1-iodo)-  
methylbenzotriazole <1993ACS167>.



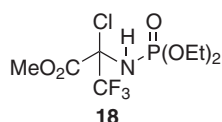
(vii) *N*-Nitro  $\alpha$ -halo amines

The seminal work concerning the synthesis of *N*-nitro-*N*-haloalkyl amines has been performed by  
Majer and Denkstein <1966CCC2547>. Treatment of *N,N*-bis(acetoxymethyl)-*N*-nitroamine  
with HCl led to the corresponding chloride in good yield (Equation (23)). A similar procedure  
was used in the preparation of *N*-(chloromethyl)-*N*-nitro-methylamine. The latter compound was  
also obtained from the cleavage of *N*-(piperidinomethyl)methylnitroamine promoted by acetyl  
chloride. The above-mentioned approaches were used in the synthesis of other *N*-nitro haloamines  
<2002WOP60881>.



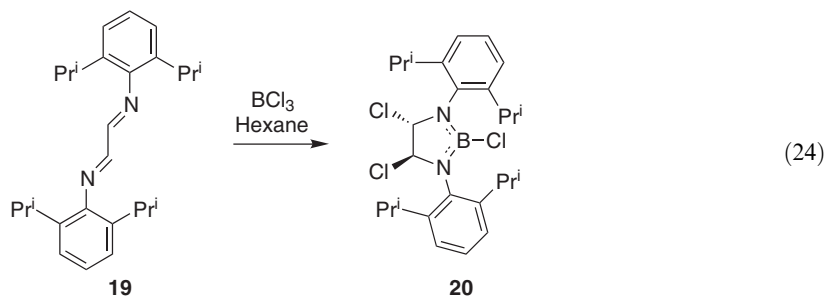
(viii) *N*-Phosphoryl  $\alpha$ -halo amines

The chloro derivative **18** has been synthesized from the corresponding alcohol, utilizing thionyl  
chloride in benzene <2002ZOB1802>.



(ix) Miscellaneous  $\alpha$ -halo amides

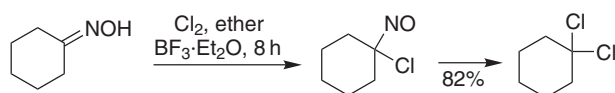
The chloroboration of the diazadiene **19** with boron trichloride afforded the unusual and crystalline diazaborolidine **20** (Equation (24)) <2001CC1136>.

4.03.1.2.2 Other  $\alpha$ -halo amines— $R_2CHal(NY)$  (doubly bonded nitrogen)

In this section, synthetic methods developed toward the synthesis of  $\alpha$ -halo amines with a nitrogen doubly bonded will be described. In this class of compounds are included  $\alpha$ -halo nitroso derivatives,  $\alpha$ -halo nitro derivatives,  $\alpha$ -halo azo alkanes,  $\alpha$ -halo heteroarylium salts,  $\alpha$ -halo isocyanates and 2-halo azirines.

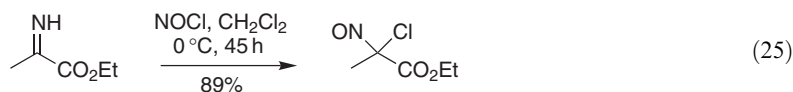
(i)  $\alpha$ -Halo nitroso derivatives

The preparation of  $\alpha$ -halo nitroso compounds has been restricted to *gem*-chloronitroso compounds, which are formed when chlorine gas is passed through a solution of an oxime in anhydrous diethyl ether. Such a reaction, known for several decades <1953JCS3483, 1954CB1449, 1954JCS4215>, constitutes the most used method for the preparation of this class of compounds <1971RTC(90)866, 1995JCS(P2)1381, 1995JFC207>. In the presence of either Lewis or Bronsted acids, oximes are transformed into the corresponding *gem*-dichloro compounds through a chloro nitroso intermediate (Scheme 7) <1993JOC1939>.



Scheme 7

Other reagents, namely *t*-BuCOCl <1992JA5900> and nitrosyl chloride (Equation (25)) <1958JOC1517, 1982MM894>, are also effective to transform an oxime moiety into the *gem*-chloro nitroso functionality.



The oxidation of oximes to chloro nitro compounds occurs through chloro nitroso intermediates. Thus, the following section might be consulted for insights concerning the synthesis of  $\alpha$ -halo nitroso derivatives.

(ii)  $\alpha$ -Halo nitro derivatives

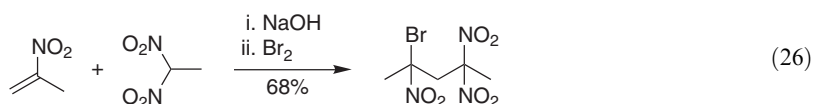
Based on the starting material, the approaches to the synthesis of *gem*-halo nitro compounds can be classified into three different categories. The first constitutes the halogenation of nitro



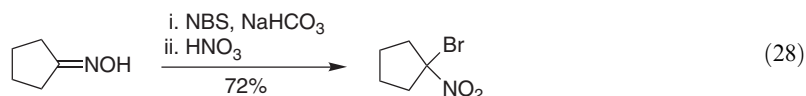
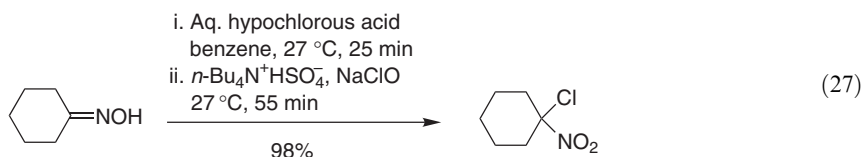
compounds, whereas the second is the halogenation/oxidation of oximes. Finally, in the third a molecule that already bears the *gem*-halo nitro moiety is transformed into a relatively more complex halo nitro derivative.

(a) *Halogenation of nitro compounds.* The typical protocol for the synthesis of halo nitro compounds is the treatment of a nitro derivative with a source of halogen under basic conditions <1940JOC100, 1960JCS2976, 1977JOC3764>. Using this standard protocol all halogens have been introduced into a number of nitro compounds utilizing several slightly different variations of the general procedure (Table 1).

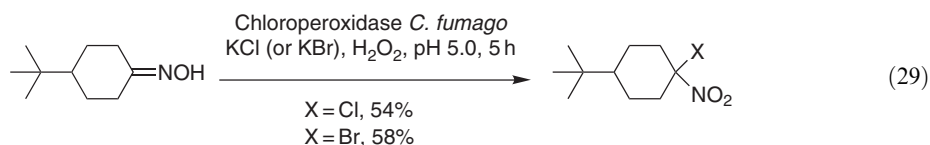
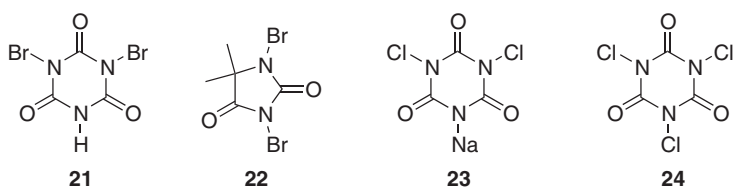
In addition to the above-mentioned protocols, the preparation of a *gem*-halo nitro compound has also been achieved by trapping with bromine a nitro enolate, obtained from a conjugate addition (Equation (26)) <1969JOC2049>.



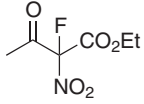
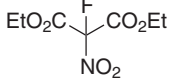
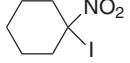
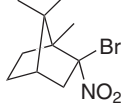
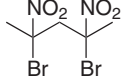
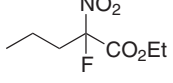
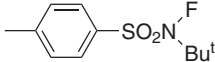
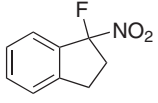
(b) *Halogenation–oxidation of oximes.* The oxidation of oximes into *gem*-halo nitro compounds can be performed under a variety of conditions, although only the preparation of bromides and chlorides has been reported. This transformation occurs in two steps, through a halo nitroso intermediate, which is oxidized *in situ*. The  $\alpha$ -chloro nitro derivatives are usually obtained by treating the oxime with  $\text{Cl}_2$ , followed by oxidation with  $\text{NaClO}$  (Equation (27)) <1980TL1117, 1989JOC2869> or ozone <1976JOC733, 1985JOC2498>. The *gem*-bromonitro derivatives are obtained in an analogous fashion using bromine <1953JA4044, 1984JOC2041, 1984JOC4078, 1988JOC443, 1988JOC4969> or NBS (Equation (28)) <1953JA4047, 1988JOC443, 1988JOC4645>.

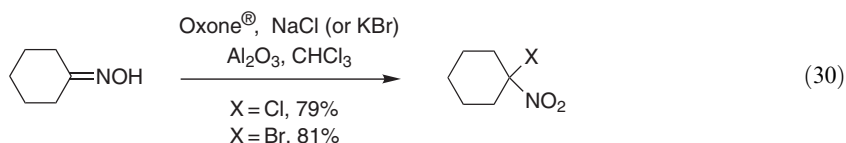


A few alternatives to the standard protocol have also been reported. Some new halogenating agents, namely **21**, **22**, **23**, and **24**, have been developed to convert an oxime into the corresponding halo nitro compound <1991JOC316>. A biocatalytic version of this functional group transformation has been reported for the synthesis of either chlorides or bromides (Equation (29)) <1996JOC8692>. Oxone in the presence of sodium chloride or potassium bromide is effective to obtain nitro compounds, in good yield (Equation (30)) <1998TL4385, 1999T6211>.

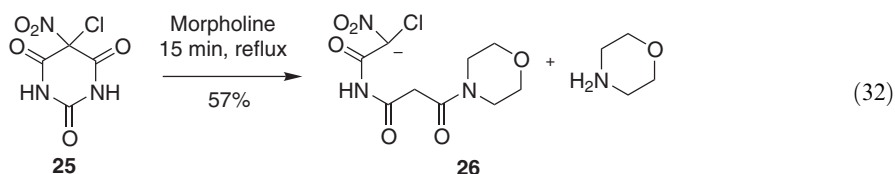
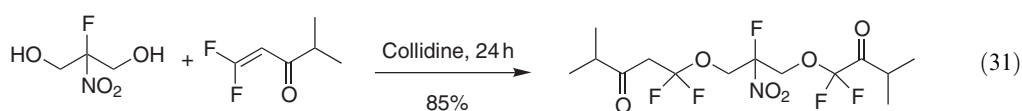


**Table 1** Reagents and conditions for the conversion of nitro compounds into *gem*-halo nitro compounds

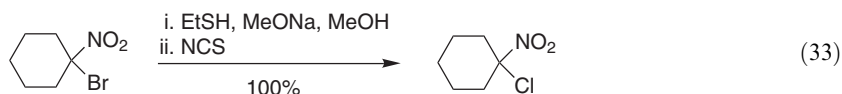
Entry	Reagents and conditions	Product (yield, %)	References
1	(i) NaH, THF, rt, 2 h; (ii) FClO <sub>3</sub> , 0 °C, 2 h	 (100)	<1992JOC2196>
2	(i) NaH, THF; (ii) FClO <sub>3</sub> , 0 °C	 (76)	<1969JOC4176>
3	(i) NaOH, H <sub>2</sub> O, 50 °C; (ii) I <sub>2</sub> , KI, rt, 10 min	 (64)	<1969JOC2049>
4	(i) <i>t</i> -BuOK, <i>t</i> -BuOH, 30 min; (ii) Br <sub>2</sub> , H <sub>2</sub> O	 (66)	<1978T3129>
5	(i) <i>t</i> -BuONa, <i>t</i> -BuOH; (ii) Br <sub>2</sub> , CH <sub>2</sub> Cl <sub>2</sub> , 0 °C, 5 min	 (79)	<1987JA5452>
6	(i) NaOH, H <sub>2</sub> O; (ii) F <sub>2</sub> , 0–5 °C	 (85)	<1970JOC846>
7	(i) NaOH, H <sub>2</sub> O; (ii) Cl <sub>2</sub>	1-Chloro-1-nitropropane (95)	<1962JOC2930>
8	(i) NaOH, H <sub>2</sub> O; (ii) Br <sub>2</sub> , 0 °C, 30 min	1-Bromo-1-nitroethane (69)	<1986JCS(P1)1171>
9	 Toluene, –20 °C	2-Fluoro-2-nitropropane (83)	<1984JA452>
10	(i) KOH, CH <sub>3</sub> OH; (ii) NCS (or NBS), rt, 45 min (or 30 min).	2-Chloro-2-nitropropane (95); 2-Bromo-2-nitropropane (90)	<1986S828>
11	<i>hν</i> , TiO <sub>2</sub> , AgF	2-Fluoro-2-nitropropane (47)	<1990JA2016>
12	(i) MeONa, MeOH, 65 °C, 10 min; (ii) AcOF, 0 °C, <1 min.	 (90)	<1994JOC6800>



(c) *From  $\alpha$ -halo nitro derivatives.* A useful strategy for the synthesis of *gem*-halo nitro compounds is the manipulation of a molecule that already bears this moiety to a new one, which is usually relatively more complex. In this context, several transformations (reduction, decarboxylation followed by alkylation, etc.) of halo nitro substrates have been investigated, allowing the synthesis of different substituted *gem*-halo nitro molecules (Equation (31)) <1990JOC3562, 1987JOC5061, 1989JOC5453, 1993JOC3483>. When 5-chloro-5-nitrobarbituric acid **25** is added to morpholine, the formation of the morpholine salt **26** was observed (Equation (32)) <2002JOC7833>.



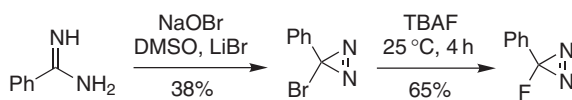
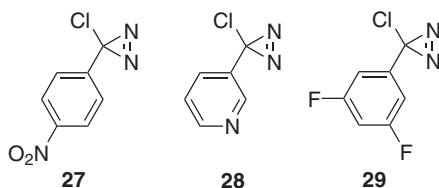
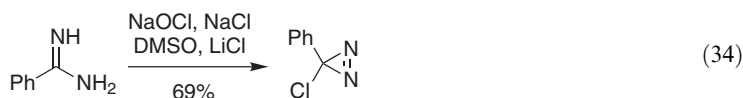
Bromonitro compounds can be transformed into the corresponding chloro derivatives, through a nitronate intermediate (Equation (33)) <1986S826>. A *gem*-bromonitro derivative is the intermediate in the alkylation of an enamine with bromonitromethane <1999JOC9653>.



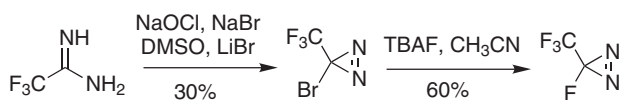
### (iii) $\alpha$ -Halo azo alkanes and $\alpha$ -halo azides

The synthesis of halo azo alkanes, which are the starting materials for a wide range of useful molecules, has often been reported in the literature. These studies are divided into three different groups in this section. As the chemistry of 3-halodiazirines has received great attention in the last decade, the synthesis of these compounds is discussed separately from that of the other halo azo derivatives. Then, the halogenation of hydrazones and the cycloaddition of halo alkenes to diazo alkanes are described.

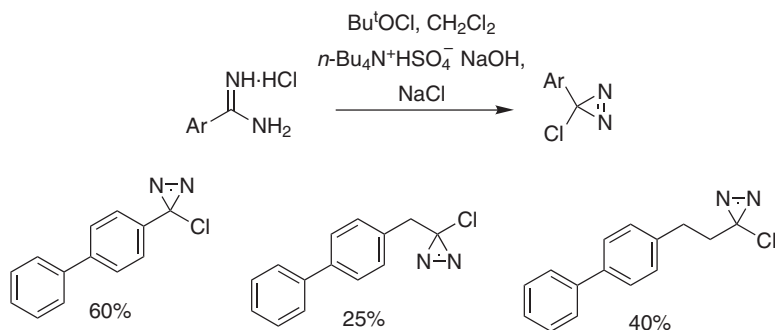
(a) *Preparation of 3-halodiazirines.* In 1965, Graham <1965JA4396, 1981JOC5048> reported that 3-halodiazirines can be obtained by oxidative cyclization of amidines promoted by sodium hypochlorite (or hypobromite) (Equation (34)) <2003JOC4819>. As halodiazirines are useful compounds for the generation of carbenes, the research concerning Graham's reaction has been intense in the 1990s <1992ACR31, 2002JMC1879>, providing straightforward access to a wide range of substituted halodiazirines <1980CB2040, 1983JA6513, 1989AG(E)225, 1990JOC2005, 1991CB1207, 1993HCA197>, such as **27** <1993JA7584>, **28** <1989JCR(S)374>, and **29** <1993JA7584>. This method can also be used in the preparation of either 3-alkyl- or 3-aryl 3-fluorodiazirines (Scheme 8, <1985JA2743> and Scheme 9, <1987TL5801>). The use of a phase-transfer catalyst led to higher yields of diazirines as compared to the traditional Graham conditions (Scheme 10) <2003MI3287>. The preparation of labeled <1990JA368, 1999TL29> and of hindered <1995TL8761> diazirines has also been reported.



Scheme 8

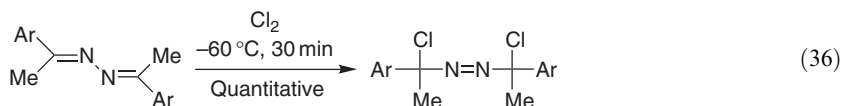
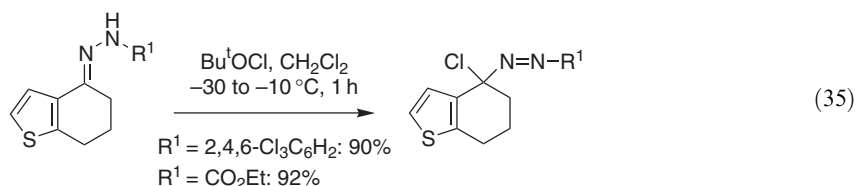


Scheme 9

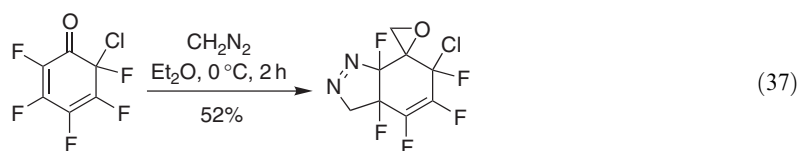


Scheme 10

(b) *Halogenation of hydrazones.* The halogenation of hydrazones has been mainly applied to the synthesis of the chloro azo molecules, although there are reports concerning the corresponding bromo [1989CJC1125](#) and fluoro derivatives [1991JOC4695](#). The chlorination of hydrazones is a general method to obtain a broad range of *gem* chloro azo compounds in good-to-excellent yields (Equation (35)) [1993T9973](#), [1995M431](#), [1996S274](#), [1998JCS\(P1\)947](#), [1998M1293](#), [1998S721](#), [1999S1313](#), [2003S1231](#). The reagent of choice for this efficient transformation is *t*-butyl hypochlorite in  $\text{CH}_2\text{Cl}_2$  or in  $\text{CHCl}_3$  [1972JOC386](#), [1992S710](#), although chlorine has also been used [1972JOC383](#). The chlorination of 2,3-diazabuta-1,3-dienes (or ketazines), which is best performed utilizing chlorine as an oxidant [1970JA4586](#), [1970JA4593](#), has been intensively used for the preparation of dichloro azo compounds (Equation (36)) [1975JOC3529](#), [1999CAR67](#), [1999T751](#), [2001MI372](#). Treatment of hydrazones with IF led to difluorides, through a fluoro azo intermediate [1991JOC4695](#).



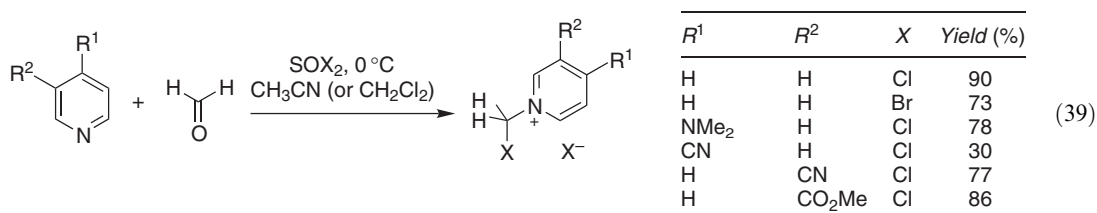
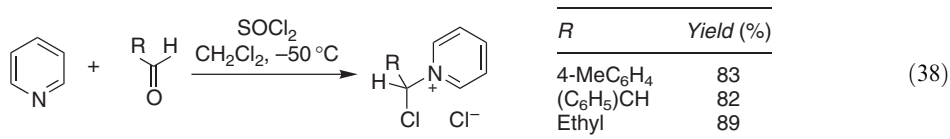
(c) *Cycloaddition of halo alkenes to diazo alkanes.* Another approach for the synthesis of halo azo compounds is the [2 + 3]-cycloaddition of halo alkenes to diazo alkanes. Thus, reaction of 6-chloro-2,3,4,5,6-pentafluorocyclohexa-2,4-dienone with diazomethane gave the corresponding halo azo derivative, as a mixture of diastereomers (Equation (37)) <2000JCS(P1)1929>.



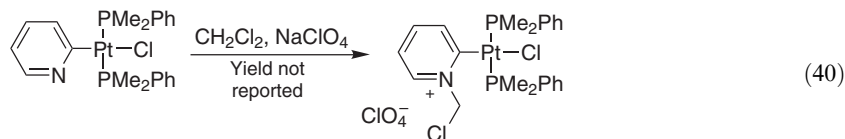
(iv)  $\alpha$ -Halo heteroarylium salts

*N*-(1-Haloalkyl)heteroarylium salts react with a broad range of nucleophiles giving rise to several interesting molecules, including a number of structurally diverse heterocyclic derivatives. Based on a three-component reaction, a general approach for the synthesis of these compounds was developed by Anders and co-workers. Prior to these studies, only a few papers reported the preparation of halo heteroarylium salts. The syntheses and applications of *N*-(1-haloalkyl)heteroarylium salts have been reviewed <2000AHC183>. In the following paragraphs an overview of their synthesis is presented.

(a) *Three-component synthesis.* The three-component reaction utilizing equimolar amounts of pyridine, an aliphatic or an aromatic aldehyde, and thionyl chloride (or bromide) led to pyridinium salts, in good-to-excellent yield (Equation (38)) <1987BSB719, 1989JOC4808>. The reaction tolerates substituted pyridines as well as other *N*-heterocycles such as isoquinoline and imidazole <1987BSB719, 1989JOC4808>. Formaldehyde can also be used as starting material under slightly different experimental conditions (Equation (39)) <1999JOC3113>. Because the pyridinium halides formed in this three-component reaction are useful starting materials, a number of new *N*-(1-haloalkyl)heteroarylium salts have been synthesized since the 1990s <1991CB2013, 1992BSB233, 1992BSB509, 1992SC3291, 1992T1263, 1993S867, 1994H815, 1997LA745, 1998JST55, 2001JOC720, 2001SI327>.

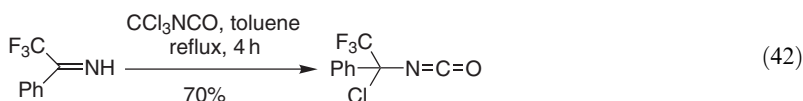
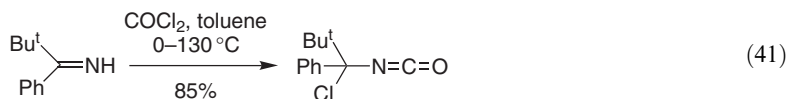


(b) *Miscellaneous methods.* The *N*-halomethyl pyridinium moiety is formed by treating pyridyl platinum complexes with  $\text{CH}_2\text{Cl}_2$  (Equation (40)) <1989JOM(361)255, 1992JCR(S)296, 1992JOM(425)155>. Reaction of trichloromethylarenes with pyridine led to pyridinium halides <1995KGS1375, 1995TL5075>.



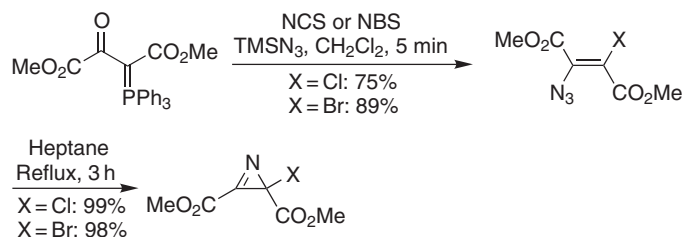
(v)  *$\alpha$ -Halo isocyanates*

There are several methods for the synthesis of  $\alpha$ -haloalkyl isocyanates which are covered in a review article <1980S85>. The most common method used for the preparation of these compounds is the treatment of imino derivatives with phosgene (Equation (41)) <1969CB2972, 1994LA1069>. However, alternative procedures have been developed to perform such an addition reaction under phosgene-free conditions (Equation (42)) <1977ZOR271, 1996ZOR1432, 1998ZOR310>.



(vi) *2-Halo-2H-azirines*

2H-Azirines have a number of applications, and are the smallest unsaturated heterocyclic compounds bearing nitrogen. An efficient two-step protocol for the synthesis of 2-halo-2H-azirines has been developed. This method is based on the reaction of oxophosphonium ylides with NCS or NBS, which, after elimination of triphenylphosphine oxide, gives haloazidoalkenes. Subsequently, these compounds are transformed into the desired halo-azirines by heating (Scheme 11) <1999TL789>. Using such a strategy, several 2-halo-2H-azirines have been obtained <2000TL7217, 2001T6203, 2002JOC66, 2003T2345, 2003TL6313>. This two-step approach appears to be a good alternative to the known methods for the synthesis of halo-azirines, namely, the thermal or the photochemical decomposition of vinyl azides <1966JCS(C)2304, 1970JCS(C)2172, 1971JA1482, 1979CC419, 1979JOC3281, 1981TL2905, 1996JOC4351>.

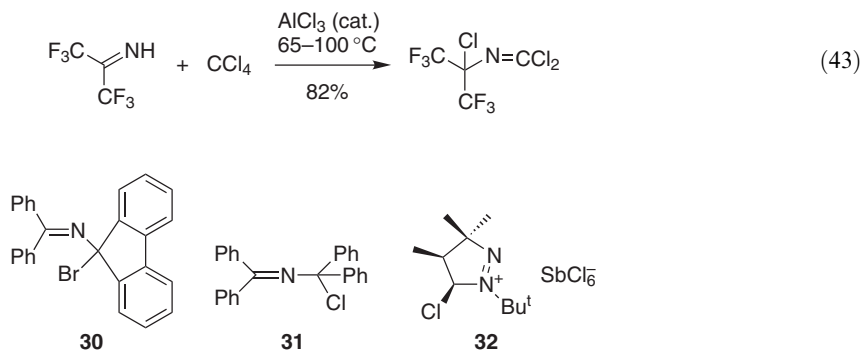


Scheme 11

(vii) *Miscellaneous  $\alpha$ -halo amines*

The complex pentacarbonyl(fluoromethyl isocyano)chromium has been prepared from pentacarbonyl(dichlorofluoromethyl isocyanide)chromium by reduction utilizing tributyltin hydride <1992JOM(436)185>. Other compounds with similar structure were also obtained <1993AG(E)1456, 1999JOM(592)41>.

Treatment of the imine of hexafluoroacetone with carbon tetrachloride, in the presence of catalytic amounts of aluminum chloride, resulted in the formation of an imidoyl chloride (Equation (43)) <2001JFC123>. The analogous compounds **30** and **31** were obtained from reaction of a dihalide with  $\text{Ph}_2\text{C}=\text{NSiMe}_3$  <1987T2945> or with  $\text{Ph}_2\text{C}=\text{NLi}$  <1969JCS(A)1742>, respectively. The preparation of pyrazolium salts, such as **32**, has been described <2000JCS(P1)4356>. Synthetic methods to obtain 1-chloroalkylcarbodiimides <1997ZOR108> and 2,4-dichloroimidazoles <1988ZOR986> are also available.



#### 4.03.2 HALOGEN AND PHOSPHORUS DERIVATIVES— $\text{R}_2^1\text{CHalPR}^2$ , $\text{R}_2^1\text{CHalPR}_2^2$ , $\text{R}_2^1\text{CHalPO}(\text{OR}^2)_2$ , etc.

The chemistry of molecules bearing a carbon bonded to both halogen and phosphorus is involved in several important applications. Thus, the syntheses of these compounds have been intensively investigated and will be described in the following sections. This section is organized according to the coordination number of the phosphorus, ranging from di- to hexacoordinate. However, the effort has been concentrated toward the synthesis of tri- and tetracoordinate phosphorus compounds, which have as the most important members, in order of presentation, the dialkyl ( $\alpha$ -haloalkyl)phosphines, the halo ( $\alpha$ -haloalkyl)phosphines, the  $\alpha$ -halophosphonium salts, the  $\alpha$ -halophosphinic acid esters, and the  $\alpha$ -halophosphonic acid esters (Figure 2).

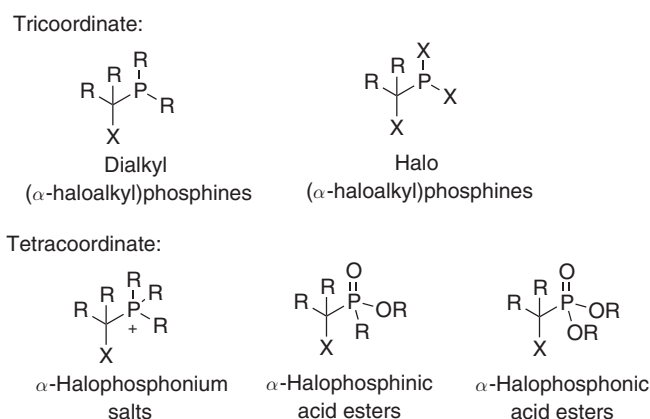
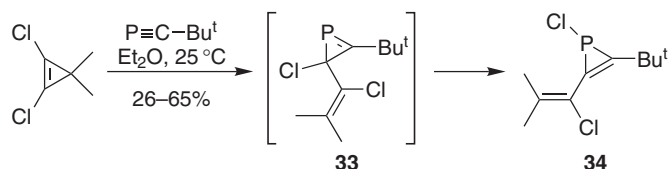


Figure 2 Examples of  $\alpha$ -halo phosphorus derivatives.

##### 4.03.2.1 Dicoordinate Phosphorus Derivatives— $\text{R}_2^1\text{CHalPR}^2$

The formation of stable dicoordinate phosphorus compounds bearing a haloalkyl moiety has not been reported. However, 2*H*-phosphirenes, such as **33**, are intermediates in the formation of the 1*H*-phosphirenes **34** from phosphalkynes and tetrachlorocyclopropene (Scheme 12) <1991SL433>. Other similar examples were also reported, as previously reviewed <1995COFGT(4)95>. A review concerning three-membered carbo-phosphorus heterocycles, including 1*H*- and 2*H*-phosphirenes, has been published <1990CRV997>.



Scheme 12

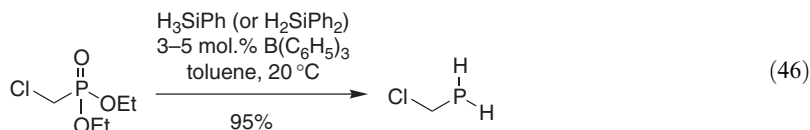
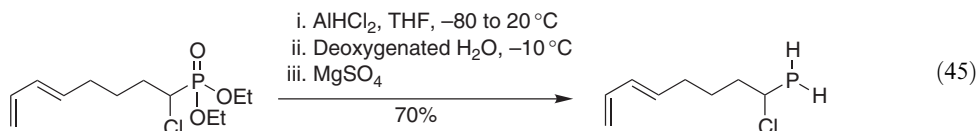
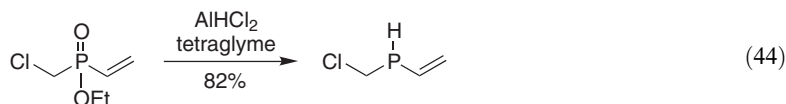
#### 4.03.2.2 Tricoordinate Phosphorus Derivatives— $R_2^1CHalPR_2^2$ , etc.

The tricoordinate phosphorus derivatives bearing a haloalkyl moiety can be divided into two different groups. The first contains primary and secondary  $\alpha$ -halophosphines, whereas the second group includes tertiary  $\alpha$ -halophosphines. This classification will be utilized in the presentation of the syntheses of these compounds in the following paragraphs. The free phosphines, whose syntheses are also described in this section, share a common feature: they are very sensitive to oxidative conditions.

##### 4.03.2.2.1 Primary and secondary $\alpha$ -halophosphines— $R_2CHalPH_2$ , $R_2^1CHalPH(R^2)$

The synthesis of primary and secondary  $\alpha$ -halophosphines has been restricted to the fluoro and chloro derivatives. Since the publication of COFGT (1995), <1995COFGT(4)95>, there have been no advances in the synthesis of fluorophosphines. However, some improvements in the known approaches for the synthesis of  $\alpha$ -chlorophosphines have been achieved, and this is discussed below.

The most general method for the synthesis of chloroalkylphosphines is the reduction of a chloroalkylphosphonate, for which several conditions have been utilized. Based on the reported results, the most efficient reducing reagent for this transformation is dichloroalane (Equation (44)) <1993IC5021, 1995JST135, 1996IC6667>. As phosphines are readily oxidized, whenever an aqueous work-up is necessary, it has to be performed utilizing only deoxygenated water (Equation (45)) <1998CC457>. Another reducing agent able to promote this reaction is aluminum hydride <1989PS(44)27>. Lithium aluminum hydride has also been used <1987TL5811>. However, in this case reduction of the C—Cl bond also occurred, leading to methylphosphine derivatives together with the desired product <1989PS(44)27>. A boron-catalyzed reduction of phosphonates has also been developed. In such a protocol the substrate is mixed with a mixture of anhydrous tris(pentafluorophenyl)borane and a silane, leading to the phosphine in excellent yield (Equation (46)) <2002TL5569>. Another approach to the synthesis of chlorophosphines is heating of the chloromethylphosphinic acid, to give chloromethylphosphine, although in low yield <1966JOC2424>.



##### 4.03.2.2.2 Tertiary $\alpha$ -halophosphines— $R_2^2CHalPR_2^1$

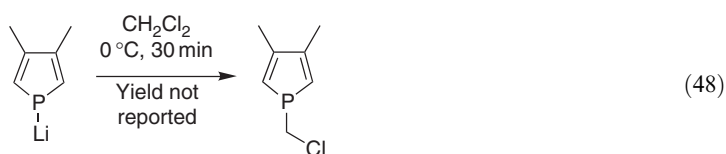
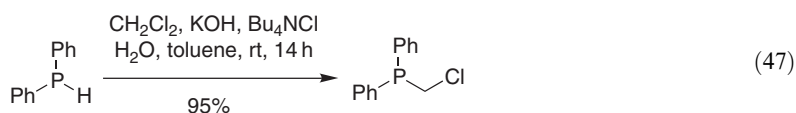
There are several methods for the synthesis of tertiary  $\alpha$ -halophosphines, which are divided in this section according to the substitution pattern on the phosphorus. Thus, in the following sections will be discussed the synthesis of, in order of presentation, dialkyl (or aryl) ( $\alpha$ -haloalkyl)phosphines,



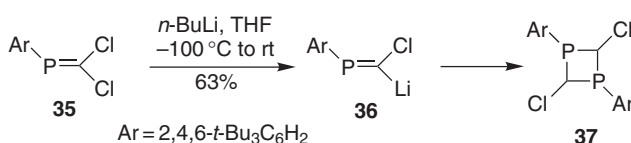
halo ( $\alpha$ -haloalkyl)phosphines, amino ( $\alpha$ -haloalkyl)phosphines, alkoxy ( $\alpha$ -haloalkyl)phosphines, and phosphoryl ( $\alpha$ -haloalkyl)phosphines. In addition to these, a number of other approaches have also been reported, as previously reviewed <1995COFGT(4)95>.

(i) *Dialkyl (or aryl) ( $\alpha$ -haloalkyl)phosphines*

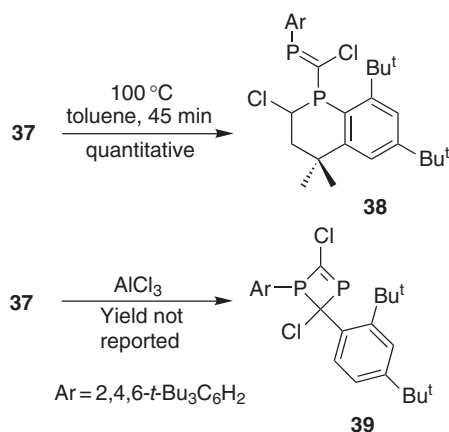
Diphenyl(chloromethyl)phosphine is the starting material of choice in several studies. Thus, its preparation has been carefully investigated. The reaction of diphenylphosphine and dichloromethane under basic conditions, developed by Stelzer <1990CB995>, has been utilized by several groups <1996OM3360, 2000MI94>. This procedure was recently optimized, leading to diphenyl(chloromethyl)phosphine in 95% yield (Equation (47)) <2001S626>. The phosphorus of a heterocyclic compound can displace a chlorine in dichloromethane, leading to the introduction of the chloromethyl unit (Equation (48)) <1985CC1010>.



Several studies toward the synthesis of phosphacycles have been performed. The synthesis of the diphosphabutadiene **37** has been achieved by dimerization of the carbenoid **36**, formed by treating the dichloromethylene compound **35** with butyllithium (Scheme 13) <1995AG(E)555>. The preparation of an analogous compound was also reported <1998JOM(553)135>. The heterocycle **37** can be transformed into the bicyclic compound **38** after heating, through a carbene intermediate <1995AG(E)555>. Alternatively, under acidic conditions the compound **37** led to a  $\beta$ -elimination product **39** <1996PS(109-110)613> (Scheme 14).

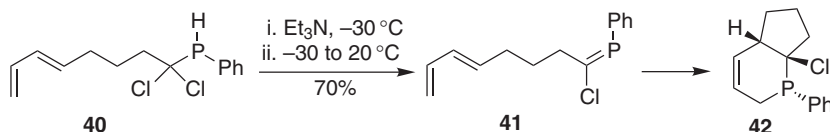


Scheme 13

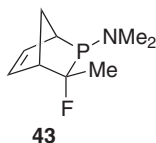


Scheme 14

Another strategy for the synthesis of heterocyclic compounds bearing a (haloalkyl)phosphine moiety is the well-known [4 + 2]-cycloaddition. Thus, treatment of the unsaturated  $\alpha,\alpha$ -dichlorophosphine **40** with base led to the phosphalkene **41**, which gave the bicyclic compound **42**, after an intramolecular Diels–Alder reaction (Scheme 15) <1998CC457>. An intermolecular version of this reaction was also reported in the synthesis of the  $\alpha$ -fluorophosphine **43** from  $\text{Me}_2\text{N}-\text{P}=\text{C}(\text{F})\text{CF}_3$  and cyclopentadiene <1992ZN(B)321>.



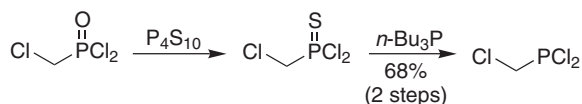
Scheme 15



### (ii) Halo ( $\alpha$ -haloalkyl)phosphines

An efficient method to obtain monochloro(chloroalkyl)phosphines is by reacting the corresponding dichloride with a Grignard reagent or with an organolithium compound. Thus, the chloro phosphines  $\text{R}(\text{Cl})\text{PCH}_2\text{Cl}$  ( $\text{R}$  = cyclohexyl,  $\text{CHMeEt}$ , 2,4,6-*t*- $\text{Bu}_3\text{C}_6\text{H}_2$  or 2,4,6-*i*- $\text{Pr}_3\text{C}_6\text{H}_2$ ) were prepared from  $\text{Cl}_2\text{PCH}_2\text{Cl}$  <1997ZN(B)883>.

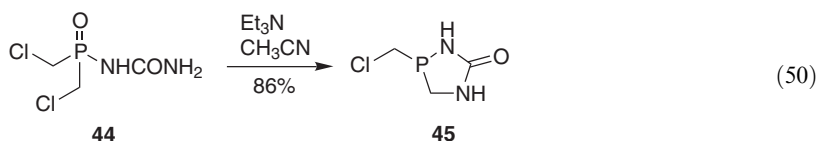
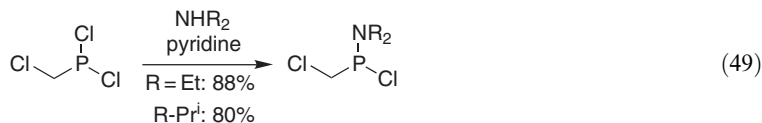
Chloromethylphosphines were also prepared in a two-step procedure from chloromethylphosphine oxide, which is transformed into the corresponding thio derivative by  $\text{P}_4\text{S}_{10}$ . Then, in the second step a sulfur exchange reaction with tributylphosphine gives dichloro(chloromethyl)phosphine (Scheme 16) <1986PS(28)289, 1961JA2299>. The halogen exchange reaction mediated by magnesium bromide allowed the conversion of  $\text{R}(\text{Cl})\text{PCH}_2\text{Cl}$  ( $\text{R}$  = cyclohexyl) to  $\text{R}(\text{Br})\text{PCH}_2\text{Cl}$  <1997ZN(B)883>.



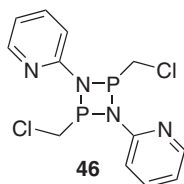
Scheme 16

### (iii) Amino ( $\alpha$ -haloalkyl)phosphines

Reaction of secondary amines with dichloro(chloromethyl)phosphine gave the corresponding chloro amino phosphine in good yield (Equation (49)) <1993JOM(462)111>. An analogous reaction also occurred using  $\text{R}_2\text{NSiMe}_3$  ( $\text{R}$  = Et or *i*-Pr) <1997ZN(B)883>. Under basic conditions, a nitrogen of the phosphorus amide **44** can promote an intramolecular displacement of the chloride, leading to the heterocyclic compound **45**, in good yield (Equation (50)) <2002ZOB1157>.

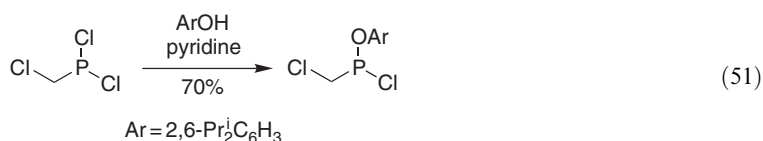


The unusual heterocyclic compound **46**, which bears an amino ( $\alpha$ -haloalkyl)phosphine moiety, was isolated from the base-catalyzed reaction of  $\text{ClCH}_2\text{PCl}_2$  with 2-aminopyridine <1986PS(28)289>. Amino (bromoalkyl)phosphines were prepared from  $\text{R}(\text{Cl})\text{PCH}_2\text{Cl}$  ( $\text{R} = \text{Ph}_2\text{N}$ ,  $\text{Et}_2\text{N}$ , and  $i\text{-Pr}_2\text{N}$ ) by a halogen exchange reaction promoted by magnesium bromide <1997ZN(B)883>.



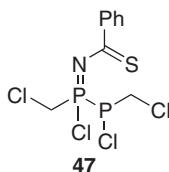
(iv) *Alkoxy ( $\alpha$ -haloalkyl)phosphines*

Reaction of a phenol with dichloro(chloromethyl)phosphine gave the chloro phenoxy (chloromethyl)phosphine, in good yield (Equation (51)) <1993JOM(462)111>.



(v) *Phosphoryl ( $\alpha$ -haloalkyl)phosphines*

The amino phosphine **47**, which possesses a  $\text{P}-\text{P}$  bond, was isolated from the base-catalyzed reaction of  $\text{ClCH}_2\text{PCl}_2$  with thiobenzamide <1986PS(28)289>.



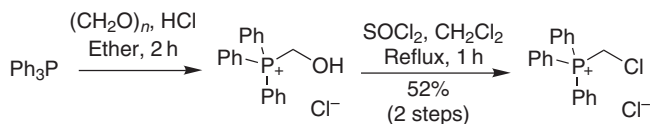
#### 4.03.2.3 Tetracoordinate Phosphorus Derivatives— $[\text{R}_2^1\text{CHalPR}_2^2]^+ \text{X}^-$ , $\text{R}_2^1\text{CHalP}(\text{O})\text{R}_2^2$ , $\text{R}_2^1\text{CHalPO}(\text{OH})\text{R}^2$ , $\text{R}_2^1\text{CHalPO}(\text{Hal})\text{R}^2$ , $\text{R}_2\text{CHalPO}(\text{OH})$ , etc.

##### 4.03.2.3.1 $\alpha$ -Halophosphonium salt— $[\text{R}_2^1\text{CHalPR}_2^2]^+ \text{X}^-$

(Haloalkyl)phosphonium salts are useful reagents in organic synthesis, whose main application is in the introduction of an unsaturated  $\text{C}-\text{C}$  moiety. Thus, several methods have been developed for their synthesis. An excellent review covering the preparation and application of these compounds, as well as other phosphorus derivatives, has been published <2000S182>. Some  $\alpha$ -halophosphonium salts, such as (chloromethyl)triphenylphosphonium chloride, are commercially available.

A straightforward approach to the synthesis of (halomethyl)trialkylphosphonium salts is the reaction of triphenylphosphine with an electrophile such as dihalomethane. Thus, when diethylphosphine was treated with carbon tetrachloride, chloro(chloromethyl)diethylphosphonium chloride was formed <1993PS(85)41>. Reaction of chloriodomethane with triphenylphosphine gave (chloromethyl)triphenylphosphonium iodide in 70% yield <1979BCJ1197>. The preparation of (bromomethyl)triphenylphosphonium bromide has been performed in an analogous manner <1965JOC2208, 2002JCS(P1)2260>.

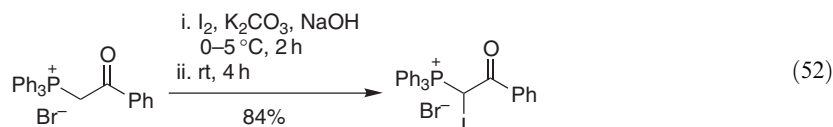
The halomethylation protocol described for the synthesis of *N*-halomethyl derivatives (see Scheme 3 and Equations (5) and (6)) can also be used with phosphorus compounds. Thus, reaction of triphenylphosphine with paraformaldehyde led to the hydroxymethyltriphenylphosphonium chloride, which gave (chloromethyl)triphenylphosphonium chloride when treated with thionyl chloride (Scheme 17) <2002JCS(P1)2260>.



Scheme 17

Reaction of triphenylphosphine with chlorocarbene, generated from dichloromethane and butyllithium, gave chloromethyltriphenylphosphonium chloride <1960JA1510, 1961JA1613, 1961JA1617>. Similarly, treatment of triphenylphosphine with tetrachloromethane in the presence of water gave the same product <1977S699>.

The direct halogenation of alkylphosphonium salts to afford (haloalkyl)phosphonium salts in good yields can be used for the preparation of iodoalkyl derivatives (Equation (52)) <1987S498, 1990S631>.

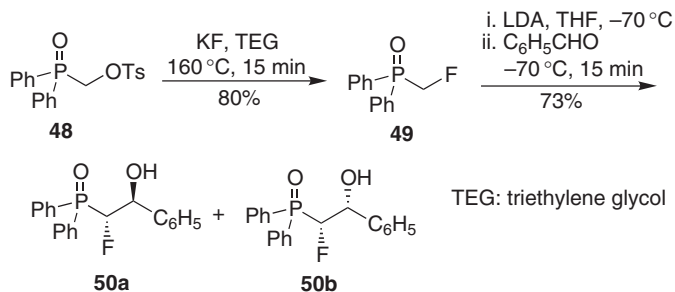


Other approaches for the synthesis of (haloalkyl)phosphonium salts have been described for all halogens in COFGT (1995) <1995COFGT(4)95>.

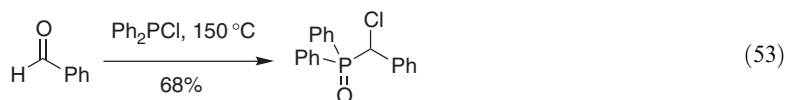
#### 4.03.2.3.2 $\alpha$ -Halophosphine oxides and sulfides— $\text{R}_2^1\text{CHalP}(Y)\text{R}_2^2$

The synthesis of  $\alpha$ -halophosphine oxides and sulfides has been the subject of several reports. These studies allowed the preparation of halo derivatives of all halogens with a variety of substitution patterns. A detailed description of these methods was previously reviewed <1995COFGT(4)95>. In the following paragraphs, some new and additional aspects are discussed.

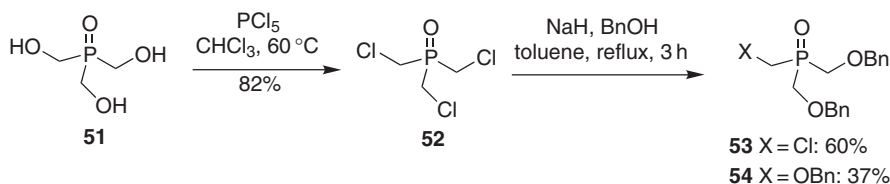
Aiming toward the synthesis of terminal monofluoro olefins, (fluoromethyl)diphenylphosphine oxide **49** has been prepared from the corresponding tosylate **48**, after treatment with anhydrous potassium fluoride. The phosphane oxide **49** can be elaborated into more complex halo derivatives by an aldol-type reaction with aldehydes, leading to compounds such as **50**, as a mixture of diastereomers (Scheme 18) <2001EJO897>. In somewhat analogous fashion, the ( $\alpha$ -chlorobenzyl)diphenylphosphine oxide can be prepared from benzaldehyde and chlorodiphenylphosphine (Equation (53)) <2002JCS(P1)2260>.



Scheme 18



Treatment of tris(hydroxymethyl)phosphine oxide **51** with  $\text{PCl}_5$  led to the corresponding chloride **52**. Other phosphines were also obtained with this reagent <1990ZOB808>. The chloride **52** can be transformed into the bis(benzyloxy)derivative **53**, although a significant amount of the tris(benzyloxy) compound **54** is also formed in the reaction (Scheme 19) <2001T9149>. Alkylphenyl(chloromethyl)phosphine oxides can be submitted to traditional nitration conditions, affording alkyl(chloromethyl)(*m*-nitrophenyl)phosphine oxides <1990ZOB1511>.



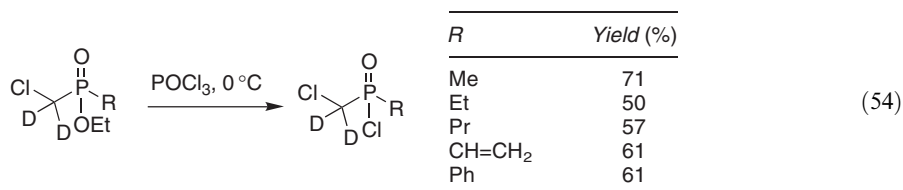
Scheme 19

#### 4.03.2.3.3 $\alpha$ -Halo oxo acids of phosphorus

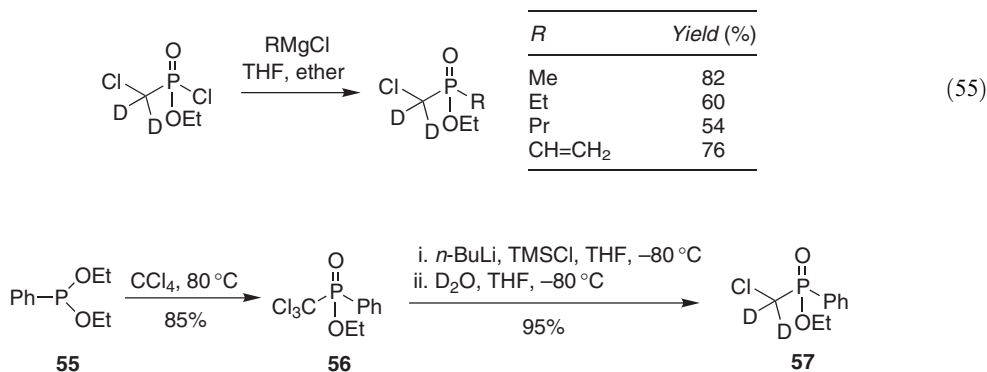
##### (i) $\alpha$ -Halophosphinic acids and derivatives

(a)  $\alpha$ -Halophosphinic acids. The alkylation (followed by hydrolysis) of dihalo(alkyl)phosphines with carbonyl compounds, the homologation of halo(alkyl)phosphines promoted by diazomethane, and the hydrolysis of halo(alkyl)phosphines appear to be the most useful methods to obtain  $\alpha$ -halophosphinic acids. These reactions, as well as others, were previously discussed <1995COFGT(4)95>.

(b)  $\alpha$ -Halophosphinic halides. When a (chloromethyl)phosphinate is mixed with phosphorus oxychloride, the (chloromethyl)phosphinic chloride is formed. This reaction tolerates the presence of several *P*-alkyl groups (Equation (54)) <1995JCS(P1)2045>. As phosphinates are readily available, this reaction constitutes a general approach to the synthesis of (chloroalkyl)phosphonic chlorides. Other useful methods for the synthesis of some chlorides, as well as other halogenides, are the halomethylation of dihalophosphines and the reaction of aldehydes with dihalophosphines <1995COFGT(4)95>.

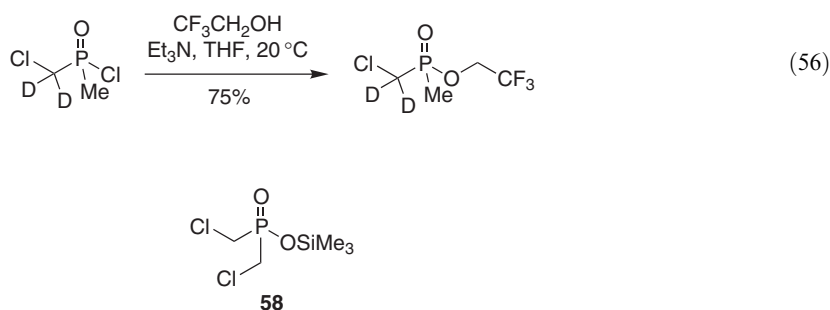


(c)  $\alpha$ -Halophosphinic acid esters. Reaction of  $\alpha$ -chlorophosphonochloridate with both saturated and unsaturated aliphatic Grignard reagents gave the corresponding phosphinates in good yields (Equation (55)) <1995JCS(P1)2045, 1993IC5021, 1996IC6667, 1996JCS(P1)2179>. Alternatively, the analogous phosphinate **57** bearing a phenyl group has been obtained from phenyl(trichloromethyl)phosphinate **56**, which was prepared by a Michaelis–Arbuzov reaction from **55** and tetrachloromethane. Subsequently, the two chlorines of the compound **56** were replaced by a deuterium (Scheme 20) <1995JCS(P1)2045, 1996JCS(P1)2179>. Thus, by selecting the reaction conditions it is possible to substitute a P–Cl bond by a P–R bond, where R may be alkyl, alkenyl, or aryl.

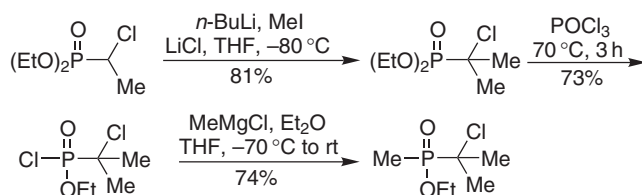


Scheme 20

Phosphinic esters are also obtained from the corresponding chloride by an ethanolysis reaction (Equation (56)) [<1995JCS\(P1\)2045, 1996JCS\(P1\)2179>](#). The preparation of trimethylsilyl bis(chloromethyl)phosphinate **58** was achieved from chloro bis(chloromethyl)phosphine oxide using a variety of different silylating reagents [<1999ZOB1788, 2001ZOB354, 2003ZOB159>](#). Analogous phosphinates have also been obtained utilizing a similar approach [<1999ZOB1788>](#).



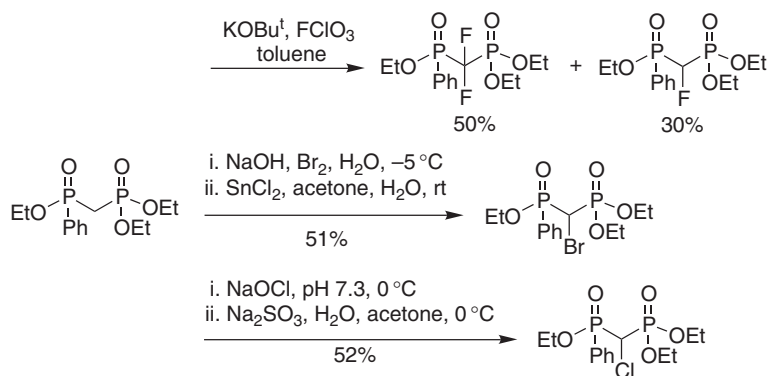
Phosphonates are also suitable starting materials for the synthesis of chloroalkylphosphinates, using a route that features two alkylation reactions utilizing organometallic reagents, as well as the selective replacement mediated by POCl<sub>3</sub> of the P—OR bond by a P—Cl bond (Scheme 21) [<1996JCS\(P1\)2179>](#).



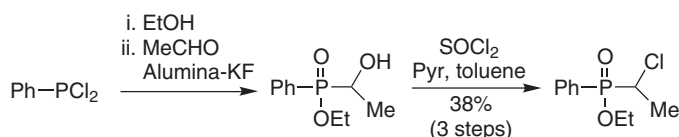
Scheme 21

The halogenation of esters constitutes another possible route to synthesize halophosphinic esters. This approach allowed preparation of the bromide and the chloride derivatives in reasonable yields. However, the fluoride counterpart was obtained together with the corresponding difluoride (Scheme 22) [<1992JMC4885>](#).

One of the most commonly used reagents for transforming a hydroxy group into the corresponding chloride, namely, a mixture of thionyl chloride and pyridine, has been explored for the preparation of chloro phosphinate derivatives, although the yields were only moderate (Scheme 23) [<1996JCS\(P1\)2179>](#).



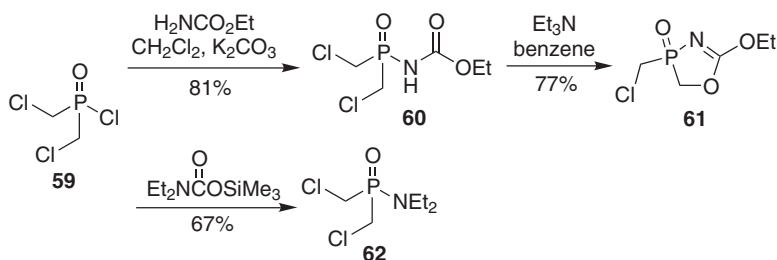
Scheme 22



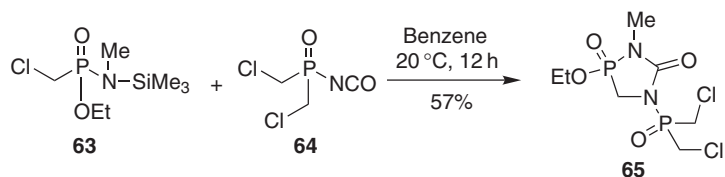
Scheme 23

(d) *α*-Halophosphinic amides and carbamoyl derivatives. The most common method for the synthesis of (haloalkyl)phosphinic amides is the reaction of a primary or secondary amine with a halo (haloalkyl)phosphine oxide <1995COFGT(4)95, 1998ZOB23>. In the past few years, efforts have been directed mainly toward the synthesis of heterocyclic compounds bearing an exocyclic *P*-chloromethyl unit.

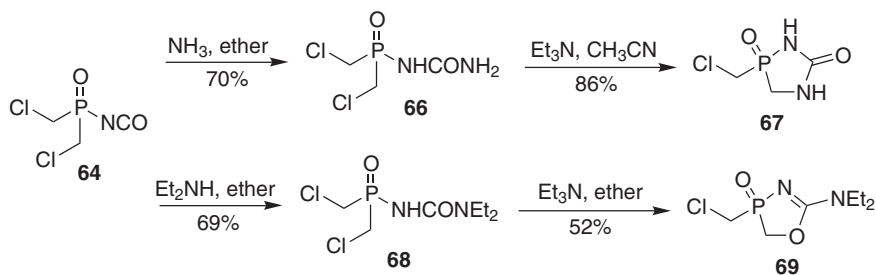
The amide **60** has been prepared by the reaction of the chloride **59** with a carbamate. The amide thus obtained was transformed into the heterocycle **61** under basic conditions <2002ZOB1157>. Similarly, the chloride **59** gave **62** (Scheme 24) <2001ZOB354>. An annulation strategy has been utilized for the preparation of heterophosphacyclanes such as **65** (Equation (57)) <1999ZOB865>. Addition of ammonia to bis(chloromethyl)phosphinic isocyanate led to the amide **66** <2002ZOB1145>, which affords the heterocyclic compound **67** by a cyclization reaction mediated by triethylamine <2000ZOB247, 2002ZOB1157>. The analogous two-step procedure, utilizing diethylamine instead of ammonia, resulted in the isolation of a different heterocyclic compound **69**, because in the latter case only the oxygen can act as an effective nucleophile (Scheme 25) <2002ZOB1145>. The *N,N*-diethyl (*α*-chlorobenzyl)phosphinic amide has been obtained by the reaction of benzyl chloride with *t*-butyl tetraethylphosphorodiamidite <2002ZOB2061>.



Scheme 24

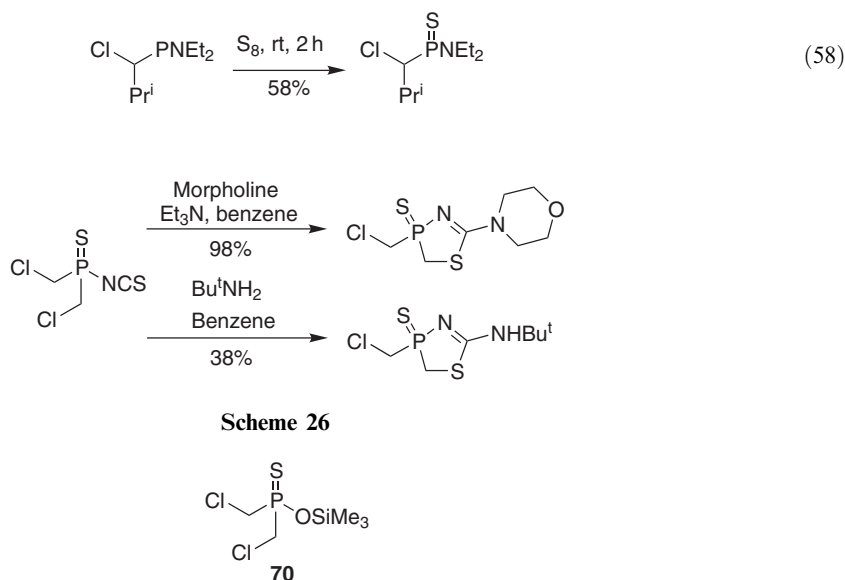


(57)



Scheme 25

(e)  $\alpha$ -Halothio- and  $\alpha$ -haloselenophosphinic acid derivatives. Sulfur can act as an oxidant, allowing the introduction of the  $\text{P}=\text{S}$  bond, in reasonable yield (Equation (58)) <1995PS(102)133>. The formation of halothiophosphinic acid derivatives can be performed from isothiocyanates (Scheme 26) <2002ZOB1145>. The preparation of the phosphinothiolate derivative **70** from the corresponding  $\text{P}-\text{Cl}$  derivative has been reported utilizing three different procedures <2001ZOB354>. The synthesis of other  $\alpha$ -halothio- and  $\alpha$ -haloselenophosphinic acid derivatives has also been reported <1995COFGT(4)95>.



Scheme 26

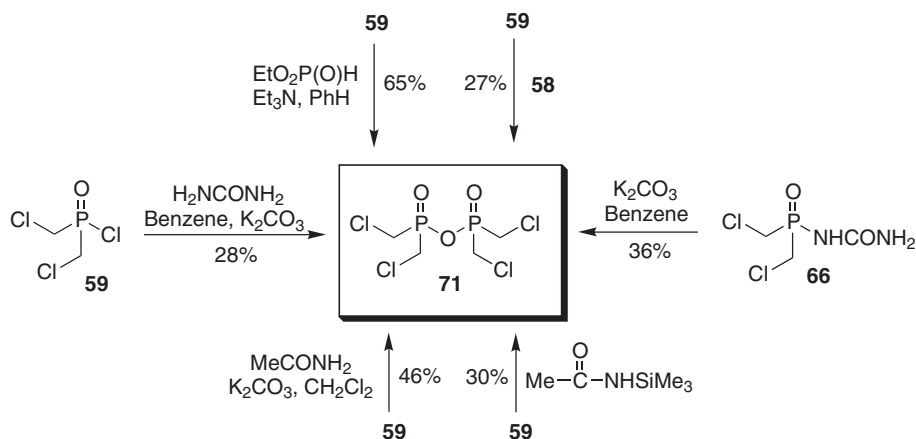
(f)  $\alpha$ -Halophosphinic anhydrides. Several routes were developed to obtain  $\alpha$ -halophosphinic anhydrides <1995COFGT(4)95>, as exemplified in the synthesis of the anhydride **71**, which has been performed by several different protocols (Scheme 27) <1999ZOB1788, 2001ZOB354, 2002ZOB1157>.

(g) Miscellaneous  $\alpha$ -halophosphinic acid derivatives. Treatment of bis(dichloromethyl)phosphinic acid with sodium <2001MI501>, with silver <2001MI501>, with lithium <2001MI1096>, with lanthanum <2001MI396>, or with copper salts <2001MI838> led to the formation of the corresponding crystalline complexes.

## (ii) $\alpha$ -Halophosphonic acids and derivatives

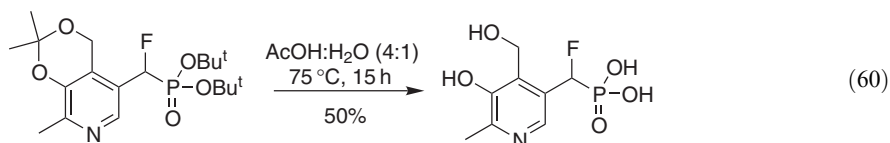
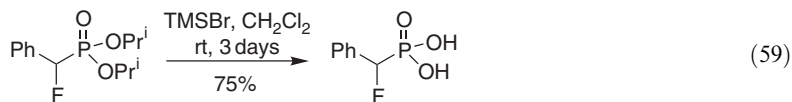
(a)  $\alpha$ -Halophosphonic acids. Several methods are known for the synthesis of  $\alpha$ -halophosphonic acids <1995COFGT(4)95>. However, in the last few years, the most commonly used method was hydrolysis of the corresponding ester, which can be prepared by several methods. The reagent of choice to mediate such a transformation is bromotrimethylsilane ( $\text{TMSBr}$ ), utilizing



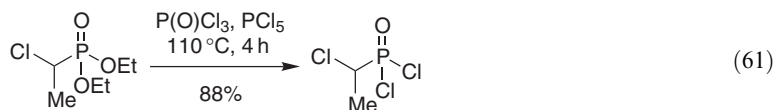


Scheme 27

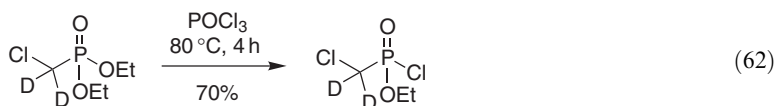
dichloromethane as solvent. Several examples of this reaction have been reported, which refer mainly to ethyl  $\alpha$ -fluorophosphonate derivatives, although isopropyl esters have also been hydrolyzed (Equation (59)) <1981JOC4573, 1998BMCL345, 1998CC1087, 1999JCS(P1)1051, 2000JCS(P1)1271, 2002JOC3065, 2003JOC5320>. The classical conditions for the hydrolysis of an ester, namely, an aqueous solution of sodium hydroxide, led to the partial hydrolysis of an ethyl  $\alpha$ -fluorophosphonate ester <1999JCS(P1)1051>. In the case of a *t*-butyl phosphonate, the hydrolysis can be performed under acidic conditions utilizing an aqueous solution of acetic acid (Equation (60)) <2003JMC3680>.

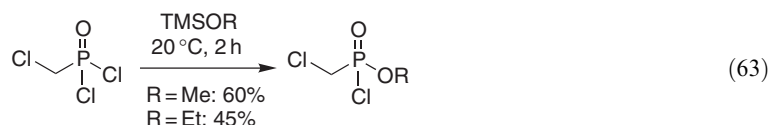


(b)  $\alpha$ -Halophosphonic dihalides. An efficient reagent to transform readily available phosphonic acid esters into alkylphosphonyl dichlorides is a mixture of phosphorus oxychloride and phosphorus pentachloride (Equation (61)) <1993BSF485>. This transformation was performed with dimethyl (bromomethyl)phosphonate using exclusively  $\text{PCl}_5$  <1998JCS(P1)211>. Bromomethylphosphonic dibromide can be prepared from  $\text{CH}_2\text{Br}_2$  and  $\text{PBr}_3/\text{AlBr}_3$  <1997JCS(P1)527, 1998JCS(P1)211>. Other methods for the preparation of  $\alpha$ -halophosphonic dihalides have been described, as previously reviewed <1995COFGT(4)95>.

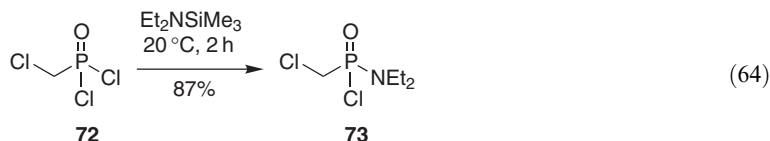


(c)  $\alpha$ -Halophosphonochloridates. Chloromethylphosphonates, which are readily available, can be selectively chlorinated utilizing  $\text{POCl}_3$ , leading to  $\alpha$ -halophosphonochloridates, in an efficient manner (Equation (62)) <1995JCS(P1)2045, 1991SC793, 1993IC5021, 1996IC6667, 1999ZOB339>. Another method to prepare phosphonochloridates is the monoesterification of a phosphorus dihalide, utilizing several different sources of an alkoxy group such as alcohol and silyl ethers (Equation (63)) <1997JCS(P1)527, 1998JCS(P1)211, 1999ZOB1788>.





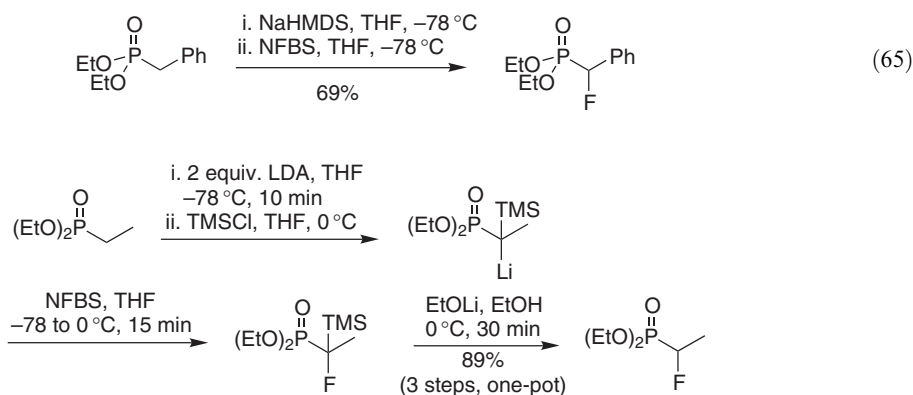
(d)  *$\alpha$ -Halophosphonamidic halides.* The formation of  $\alpha$ -halophosphonamidic halides can be efficiently achieved by a selective substitution reaction of a phosphonic dichloride and an amine. Thus, the chloromethyl phosphorus derivative **73** has been prepared in 87% yield from the dichloride **72** and trimethyl(*N,N*-diethylamino)silane (Equation (64)) <1999ZOB1788>.



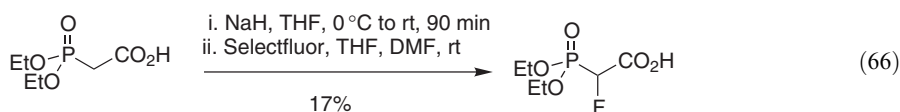
(e)  *$\alpha$ -Halophosphonic acid esters.* During the last few years, a tremendous effort has been made toward the synthesis of  $\alpha$ -halophosphonic esters, especially for the  $\alpha$ -fluoro derivatives. Some review articles related to this subject have been published <1997CRV3401, 1997S727, 2001JFC13, 2002YGK740>.

Phosphate ester derivatives have an important role in living organisms. However, it is readily cleaved under physiological conditions by phosphatase enzymes, making impractical the proposition of new drugs with such a moiety. The replacement of the P—O—C bonds by the P—CHF—C unit is an alternative to increase stability without losing high affinity for the enzymatic site, because the CHF moiety can mimic the bridging oxygen of the phosphate ester sterically and electronically <1984JCS(P1)1119>. Thus, synthetic approaches to obtain fluoro phosphonates that mimic the phosphate moiety have been thoroughly investigated <2001JFC13>.

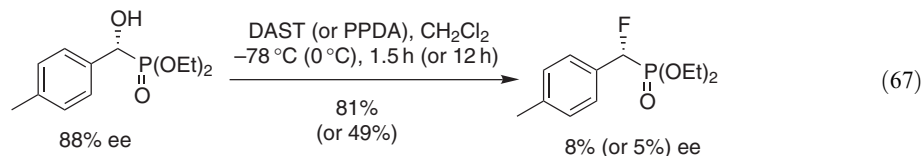
The synthesis of  $\alpha$ -fluorophosphonates can be efficiently performed utilizing fluorinating reagents. One such reagent is *N*-fluorodibenzenesulfonimide (NFBS) <1991SL395>. This reaction is usually performed by treating an anion of the phosphonate with NFBS (Equation (65)) <1996TL8089, 1998CC1087, 2000JOC227>, although variations of this protocol to increase both yield and selectivity have been reported (Scheme 28) <1998TL3693, 2000S576>. An analogous fluorinating reagent, the *N*-fluorobenzenedisulfonimide (NFOBS), has also been developed. The use of perchloryl fluoride for the fluorination of methanediphosphonate esters has been reported <1981JOC4573>. Selectfluor<sup>®</sup> (F-TEDA-BF<sub>4</sub>, Scheme 2) has been used to prepare  $\alpha$ -fluorophosphonate (Equation (66)) <1999JCS(P1)1051, 2002EJO2640>. A three-step procedure – sulfonylation, fluorination, and desulfonylation – is an alternative protocol to introduce the fluorine atom into a phosphonate ester utilizing Selectfluor<sup>®</sup> <1996JA2519, 2002JOC3065>.



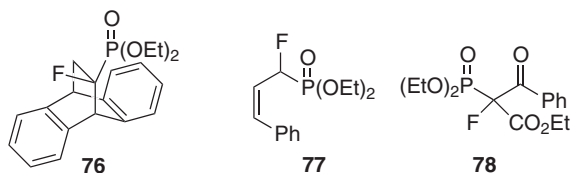
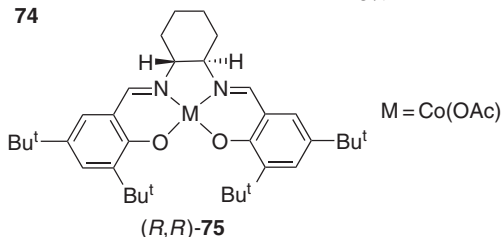
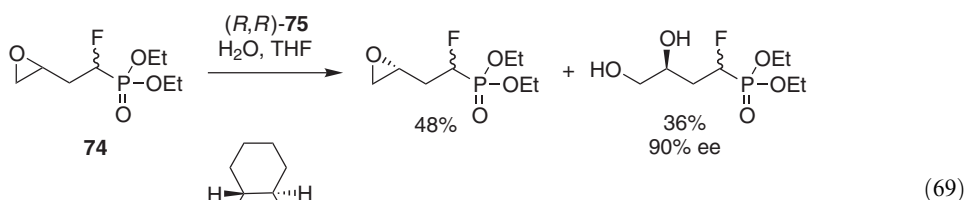
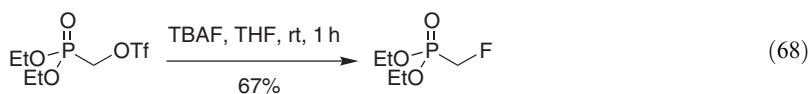
Scheme 28



The fluorination of  $\alpha$ -hydroxy phosphonates has been studied utilizing different reagents. One of the most commonly used is (diethylamino)sulfur trifluoride (DAST), which gives a good yield of the desired fluorinated molecule [<1993JOC1336, 1993JOC5598, 1996JOC5159, 2000JOC4498, 2003JMC3680, 2003JOC5320>](#). However, racemization has been observed when an enantiomerically enriched substrate was used. A similar result was obtained utilizing 1,1,2,3,3,3-hexafluoro-propyldiethylamine (PPDA) ([Equation \(67\)](#)) [<1996T11725>](#).

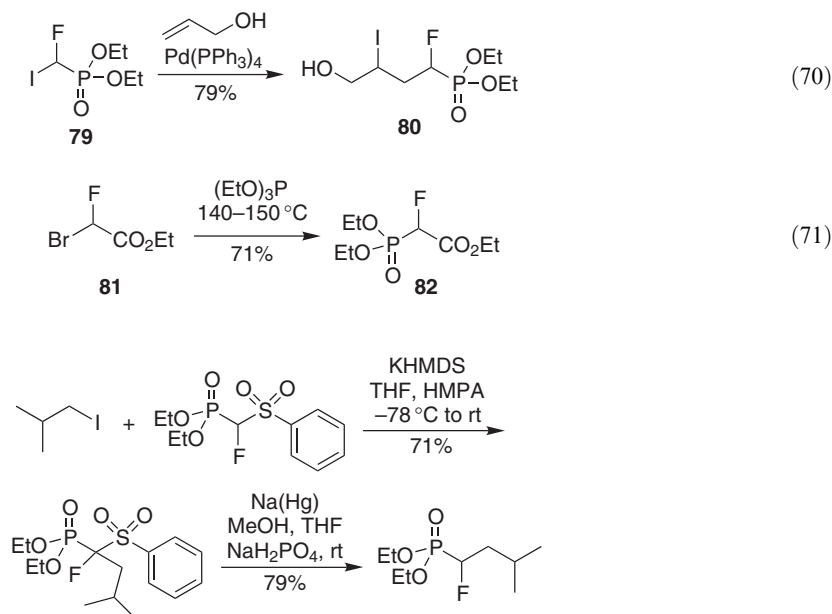


The TBAF-mediated nucleophilic displacement of a triflate has been applied to the synthesis of a fluorophosphonate ([Equation \(68\)](#)) [<1999JCS\(P1\)1051>](#). Fluorophosphonates have been accessed by a hydrolytic kinetic resolution of the racemic fluoro epoxide **74**, utilizing a cobalt salen complex ([Equation \(69\)](#)) [<2003JOC5320>](#). A Diels–Alder reaction has been used to obtain the fluoro-phosphonate **76** [<2000CC395>](#). The hydrogenation of ( $\alpha$ -fluoropropargyl) phosphonates allowed the synthesis of unsaturated fluoro derivatives, such as **77** [<1998T15541>](#). Magnesium chloride in the presence of triethylamine can promote the acylation reaction of fluorophosphonates, leading to compounds such as **78**, although in low yield [<1999T12983>](#).

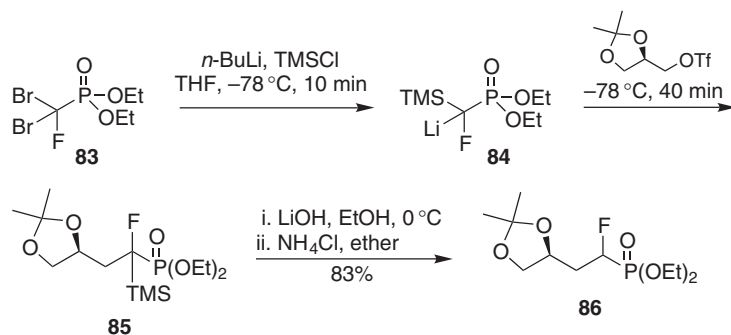


A general approach to the synthesis of functionalized  $\alpha$ -fluorophosphonates is the displacement of a leaving group from a *gem*-heteroatom-fluoro substrate to form a new C–C bond. The palladium-catalyzed addition of the *gem*-iodo-fluoride **79** to allyl alcohol giving **80** is an example of such a transformation ([Equation \(70\)](#)) [<2003JOC5320, 1998JFC39>](#). It is also possible to use the Michaelis–Arbuzov reaction between the triethyl phosphite and the bromide **81** to obtain **82** ([Equation \(71\)](#)) [<1991JOC273, 1994JOC7085>](#). Reaction of  $(\text{EtO})_2\text{P}(\text{O})\text{CFHBr}$  with zinc in THF led to the organometallic species  $(\text{EtO})_2\text{P}(\text{O})\text{CFHZnBr}$ , which can be treated with electrophiles, such as allyl halides and diethylchlorophosphate [<1999TL2681>](#), to provide functionalized fluorophosphonates [<1999TL2681>](#). A two-step approach was investigated by Berkowitz utilizing the reaction of the potassium salt of diethyl ( $\alpha$ -fluoro- $\alpha$ -phenylsulfonyl-methyl)phosphonate with triflates or iodides. The  $\alpha$ -fluoro sulfonylphosphonate, thus obtained, is desulfonated with  $\text{Na}(\text{Hg})$  ([Scheme 29](#)) [<2001OL2009>](#). In a similar fashion, the lithium derivative of the diethyl(dibromofluoromethyl) phosphonate **83** is alkylated to give the silylated

fluoro intermediate **84**, which afforded the desired compound **86**, after hydrolysis (Scheme 30) <1995CC719, 1996T165>. Several functionalized  $\alpha$ -fluorophosphonates have been synthesized using an analogous approach <1993CC1711, 1997JCS(P1)1135, 1997JOC7260, 1997T6391, 1998MI49, 1998TL4477, 2003TL3987>. This procedure has also been used for the synthesis of  $\alpha$ -chlorophosphonates <1998CC457>. The chemistry of silylphosphonates, as well as several other aspects, has been reviewed <2001SL447>.

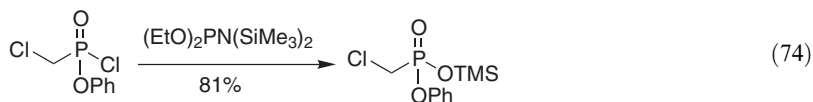
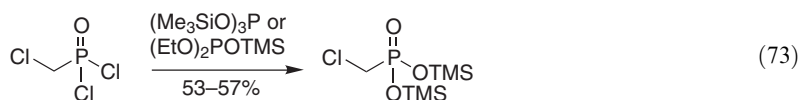
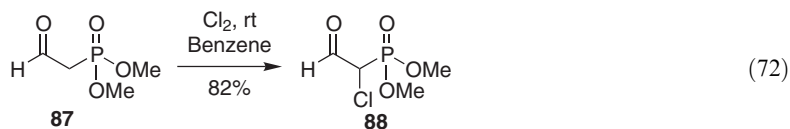


Scheme 29

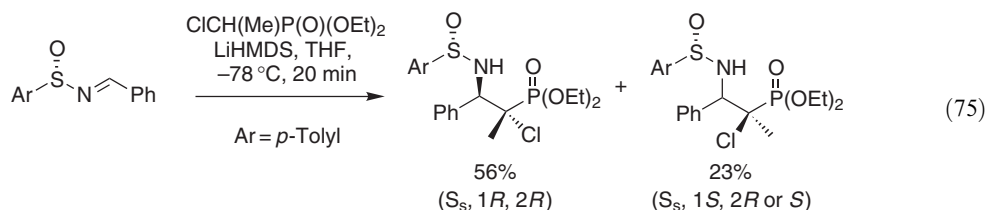


Scheme 30

Chlorophosphonates can also be prepared by a variety of different methods. The preparation of chlorophosphonates has been performed from the corresponding hydroxy compound utilizing  $\text{SOCl}_2$  in triethylamine <1989PS(44)27, 1997S207>. This functional group transformation can also be performed using a mixture of  $\text{PPh}_3$  and  $\text{CCl}_4$  <1990S717> or  $\text{P}(\text{O})\text{Cl}_3$  <1965JA2777, 1992JOC1622>. The chlorinating agent hexachloroethane mediates the transformation of alkylphosphonates into the corresponding  $\alpha$ -chloro phosphorus compounds <1998TL3693, 1999T2671, 2000JCS(P1)3311, 2001JOM(624)203> in a protocol similar to that described for the fluorination with NFBS (see Equation (65)). When chlorine was bubbled through a solution of the phosphonate **87** in benzene, the corresponding  $\alpha$ -chloro phosphonate **88** was obtained in good yield (Equation (72)) <1993ZOB93>. The ester  $\text{ClCH}_2\text{P}(\text{O})(\text{OPh})_2$  was obtained by treatment of chloromethylphosphonic dichloride with phenol in the presence of triethylamine <1995JST135>. Bis(trimethylsilyl) (chloromethyl)phosphonate has been prepared from a phosphorus dihalide derivative (Equation (73)). Mixed esters of  $\alpha$ -chloro (Equation (74)) <2003ZOB159, 2000ZOB699> and of  $\alpha$ -fluorophosphonate <1985JCS(P1)233> can also be prepared.

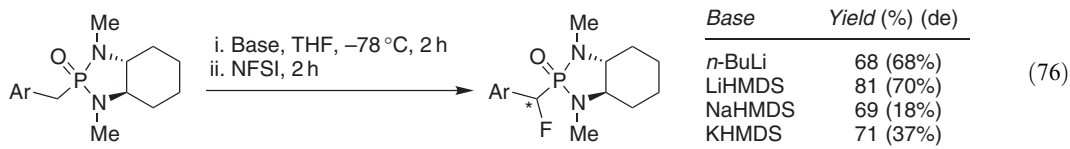


An asymmetric approach to the synthesis of  $\alpha$ -aminophosphonates has been developed through an  $\alpha$ -chlorophosphonate intermediate, formed by a Darzens-type reaction of a chiral, non-racemic sulfinimine and diethyl 1-chloroethylphosphonate (Equation (75)) <1999OL1053, 1999TL249, 2003JOC2410>. Optically active 1-chloro-2-hydroxypropanephosphonates were obtained by resolution mediated by *Candida antarctica* lipase B (CALB) <2003OBC3564>. The corresponding bromide was obtained by a dynamic kinetic resolution <1995JA2931>.



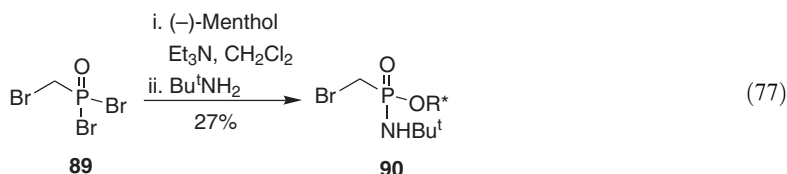
The preparation of a variety of  $\alpha$ -bromo- and  $\alpha$ -iodophosphonates has been described by a halogenation reaction. Such a transformation has been performed from  $\alpha$ -hydroxyphosphonates utilizing thionyl bromide <1997S207>, a mixture of *N,N'*-carbonyldiimidazole (CDI) and allyl bromide (or methyl iodide) <1996T10215>,  $\text{PI}_3$  <1997S207>, or  $\text{NaI}$  <1997T7291>. The direct transformation of a methylene phosphorus derivative into the corresponding  $\alpha$ -bromo or  $\alpha$ -iodophosphonate has been described using bromine <1961JOC1733>, dibromotetrachloroethene, or iodine <1999T2671, 2000JCS(P1)3311, 2001JOM(624)203>.

(f)  $\alpha$ -Halophosphonic diamides. Aiming toward the synthesis of optically active  $\alpha$ -fluoroalkylphosphonic acids, the electrophilic fluorination of a chiral phosphonamide using *N*-fluorobenzenesulfonimide (NFSI) was investigated, allowing the synthesis of the desired molecule in 70% de by careful adjustment of the effects of both base and counter-ion in the course of the reaction (Equation (76)) <2000JCS(P1)1271>. In addition, a straightforward approach to obtain  $\alpha$ -halophosphonic diamides is reaction of an  $\alpha$ -halophosphonic dihalide with an amine <1995COFGT(4)95, 1997JCS(P1)527>.

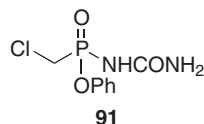


(g)  $\alpha$ -Halophosphonamides. Starting from an  $\alpha$ -halophosphonic dihalide, it is possible to form selectively the required P—O and P—N bonds. Depending on the structure of the dihalide, the order in which these bonds are formed might be crucial for the success of the route. Thus, when bromomethylphosphonic dibromide **89** is treated successively with an alcohol and an amine, the phosphonamides are obtained (Equation (77)) <1997JCS(P1)527>. However, adding the amine first led to the formation of the corresponding phosphonic diamide <1997JCS(P1)527>. Furthermore, using bromomethylphosphonic dichloride as substrate it is possible to introduce first the amine group and, then the alcohol <1998JCS(P1)211>. This different behavior is explained by the fact that the bromide is a better leaving group than the chloride <1998JCS(P1)211>. The preparation of phosphonamides has also been performed

by electrophilic fluorination using a protocol analogous to that described for the phosphonic diamides (see Equation (76)) <2000JCS(P1)1271>.

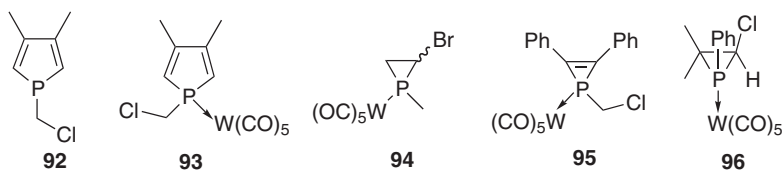


The phosphonamidate **91** can be obtained in 24% yield by treating the corresponding isocyanate with diethyl hydrogen phosphate <2000ZOB337>. A higher yield (74%) was obtained utilizing gaseous ammonia in ether instead of the phosphate <2000ZOB247, 2002ZOB1145>.



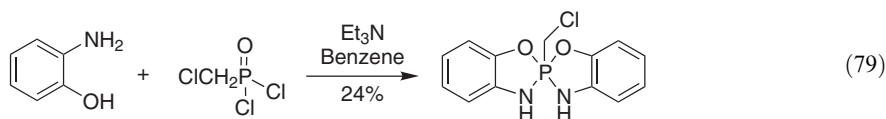
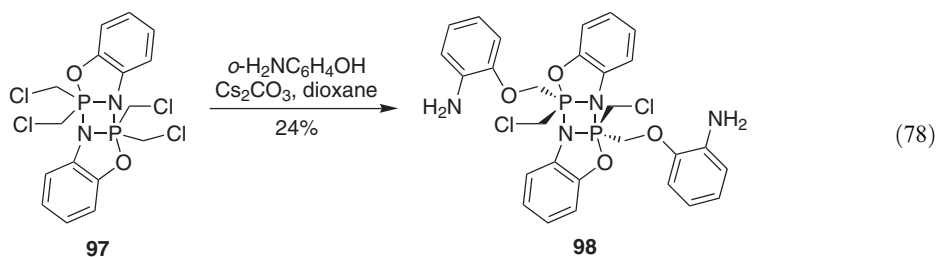
#### 4.03.2.3.4 Miscellaneous

The chloromethylphosphole **93**, prepared from **92**, can participate in cycloaddition reactions, leading to bicyclic *P*-chloromethyl derivatives <1985CC1010>. The synthesis of tungsten-phosphorus complexes bearing a haloalkyl moiety, such as **94** <1995SL353>, **95**, <1988JOM(354)83>, and **96** <2000JOC652> has also been reported.



#### 4.03.2.4 Penta- and Hexacoordinate Phosphorus Derivatives— $\text{R}_2^1\text{ChalPR}_2^2$ , $[\text{A}]^+[\text{R}_2\text{ChalPX}_5]^-$ , etc.

The synthesis of the pentacoordinate phosphorus derivative **98** bearing an unusual four-membered 1,3,2,4-diazadiphosphetidine ring was reported (Equation (78)) <1993MI285>. Another heterocyclic compound bearing a pentacoordinate phosphorus was prepared from *o*-aminophenol and chloromethylphosphonic dichloride (Equation (79)) <2001ZOB363>. Additional examples of penta- and hexacoordinate phosphorus derivatives have also been reported, as previously reviewed <1995COFGT(4)95>.



### 4.03.3 $\alpha$ -HALO ARSENIC, ANTIMONY, AND BISMUTH DERIVATIVES

Treatment of arsenic(III) oxide with dichloroacetic acid in the presence of sodium hydroxide gave arsonochloroacetic acid ( $\text{HO}_2\text{CCHCl-AsO}_3\text{H}_2$ ), in 25% yield. Decarboxylation of this acid gave chloromethylarsonic acid, in 84% yield <1995MI726>. The synthesis of other  $\alpha$ -halo arsenic compounds has also been reported, as previously reviewed <1995COFGT(4)95>.

### 4.03.4 $\alpha$ -HALO ALKYL METALLOIDS— $\text{R}_2\text{CHalMETALLOID}$

#### 4.03.4.1 $\alpha$ -Halo Silicon Derivatives— $\text{R}_2\text{CHalSiR}_3$

This section outlines the syntheses of compounds bearing a carbon bonded to both silicon and halogen. The reactions were divided according to the substitution pattern on the silicon, which led to the following groups: alkyl and aryl( $\alpha$ -haloalkyl)silanes, halo ( $\alpha$ -haloalkyl)silanes, ( $\alpha$ -haloalkyl)oxysilanes, and miscellaneous  $\alpha$ -halo silicon derivatives.

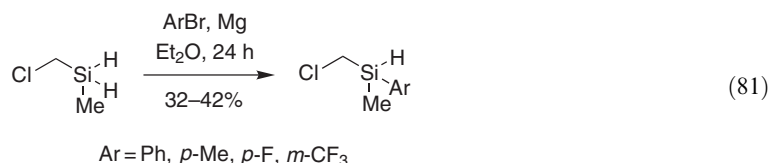
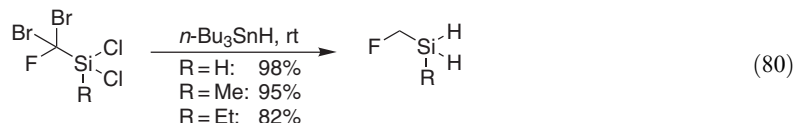
There are several silanes bearing a halomethyl unit that are commercially available, which might be used as a building block in the synthesis of relatively more complex silanes. Examples are (chloromethyl)trimethylsilane, (chloromethyl)triethoxysilane, (chloromethyl)dimethylisopropoxysilane, (chloromethyl)dimethylphenylsilane, (chloromethyl)trichlorosilane, (bromomethyl)-chlorodimethylsilane, etc.

In addition to the methods described here, others also have been reported, as previously reviewed <1995COFGT(4)95>.

#### 4.03.4.1.1 Alkyl- and aryl( $\alpha$ -haloalkyl)silanes)

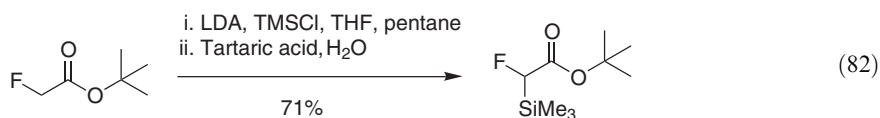
##### (i) Compounds with Si—H bonds

Several (fluoromethyl)silicon derivatives have been prepared by reduction of the Si—Cl and C—Br bonds of (fluorodibromomethyl)dichlorosilanes with excess of tributyltin hydride (Equation (80)) <1993OM4930>. Starting with a substrate such as (chloromethyl)methyldichlorosilane, it is possible to run the reaction with a Grignard reagent that replaces only one of the Si—H bonds by a Si—R bond, thus leading to a relatively more complex silane (Equation (81)) <1989OM2031>.



##### (ii) Compounds with Si—alkyl and Si—aryl bonds

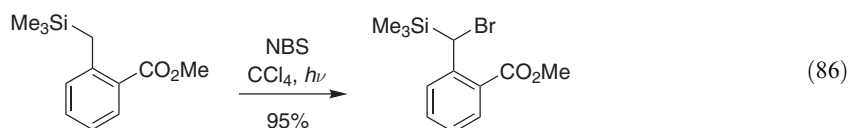
(a)  $\alpha$ -Fluorosilanes. An efficient method to obtain  $\alpha$ -fluorosilanes is the C-silylation of fluoroacetates utilizing LDA and trimethylsilyl chloride (Equation (82)) <1996T291>. An analogous result has been obtained when triisopropylsilyl triflate was used instead of TMSCl <1998TL9613>.



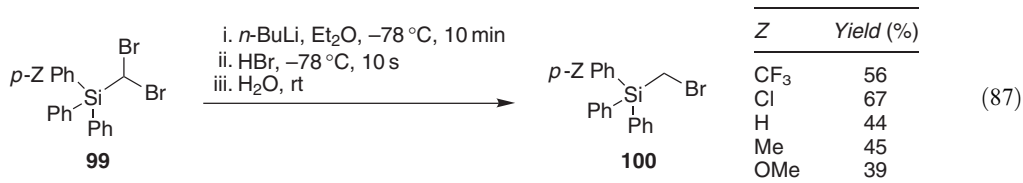




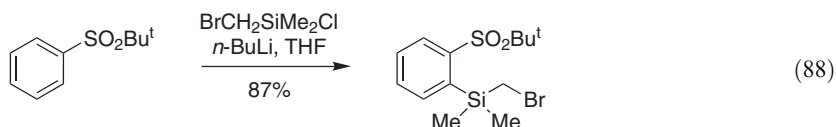




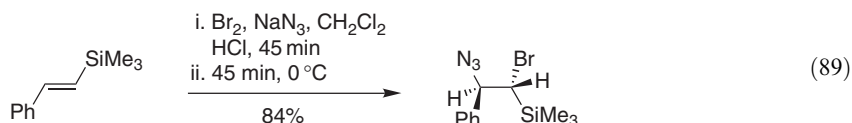
Another approach is the reduction of a silane, which has been performed under two different conditions. Treatment of the dibromide **99** with butyllithium gave the monobromo derivative **100**, after quenching with an acid (Equation (87)) <2002JOC3561>. When  $\text{Ph}_2\text{MeSiCHBr}_2$  was reacted with lithium tributylmagnesate ( $n\text{-Bu}_3\text{MgLi}$ ), a bromine–magnesium exchange reaction took place, leading to  $\text{Ph}_2\text{MeSiCH}_2\text{Br}$  in 89% yield after quenching with methanol <2001AG(E)2085>.



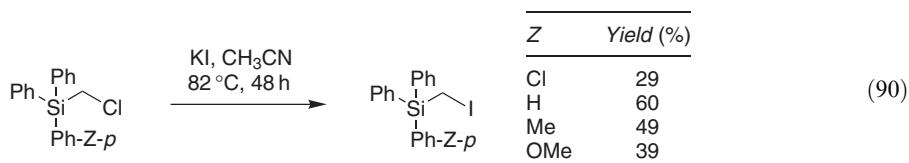
The coupling of a lithiated phenyl sulfone with (bromomethyl)chlorodimethylsilane occurs exclusively at the more reactive site—the Si–Cl bond—leading to a bromosilane, in good yield (Equation (88)) <1997JOC7142>.



Aiming toward the synthesis of silylaziridines, the electrophilic addition of bromoazides, prepared prior to use, to vinyl silanes was performed, giving the desired product in good yield and selectivity (Equation (89)) <2000JCS(P1)1173>.



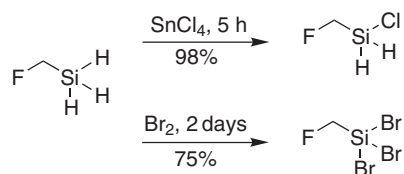
(d)  $\alpha$ -Iodosilanes. Iodoalkyl silanes are usually prepared by a halogen–iodide exchange reaction from the corresponding bromides or chlorides <1947JA1976>. The typical protocol involves refluxing the substrate with potassium iodide in anhydrous acetonitrile <1984OM1051>, although sodium iodide can also be used <1994TL2047>. Several (iodomethyl)diphenylsilanes have been prepared by this method from (chloromethyl)diphenylsilanes (Equation (90)) <2002JOC3561>. In addition, (iodomethyl)diphenyl(*p*-trifluoromethylphenyl)silane was prepared from the corresponding chloride in 65% yield after the reaction with NaI in acetonitrile. Treating (*p*-dimethylaminophenyl)(bromomethyl)diphenylsilane with KI/ $\text{CH}_3\text{CN}$  led to (*p*-dimethylaminophenyl)(iodomethyl)diphenylsilane in 55% yield <2002JOC3561>. The exchange reaction of silanes  $\text{ClCH}_2\text{SiMe}_2(\text{CH}_2)_2\text{R}$  mediated by NaI where R can be  $\text{Et}_2\text{MeSi}$ ,  $\text{Et}_3\text{Si}$ ,  $\text{Ph}_3\text{Si}$ , or  $\text{Et}_3\text{Ge}$ , gave the corresponding iodides in good yield <2001MI85>.



#### 4.03.4.1.2 Halo ( $\alpha$ -haloalkyl)silanes

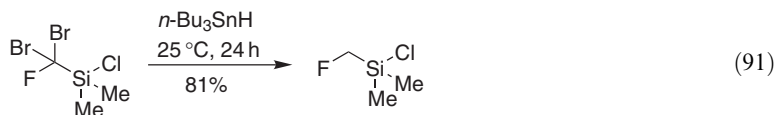
There are two approaches to the synthesis of halo ( $\alpha$ -haloalkyl)silanes based on a halogenation reaction. In the first, the hydrogen to be substituted is bonded to a silicon, whereas in the second it is bonded to a carbon. The former case has been performed with chlorides or bromides in

several (fluoromethyl)silanes. For the synthesis of chlorides, the halogenation can be performed utilizing  $\text{SnCl}_4$  <1993OM4930>, leading to (fluoromethyl)chlorosilanes. In the reaction with bromine, substitution of all hydrogens occurs, furnishing (fluoromethyl)tribromosilanes <1993OM4930, 1996JOM(511)293> (Scheme 33). Chlorination of dichlorodimethylsilane in tetrachloromethane gave a mixture of dichloro(dichloromethyl)methylsilane and dichloro(chloromethyl)methylsilane, which can be separated by distillation <2001JST137>. New processes for the production of (chloromethyl) chlorosilanes by a chlorination reaction have been developed for compounds such as  $(\text{ClCH}_2)\text{CH}_3\text{SiCl}_2$ ,  $(\text{ClCH}_2)(\text{CH}_3)_2\text{SiCl}$ ,  $(\text{ClCH}_2)\text{SiCl}_3$ ,  $(\text{ClCH}_2)_2\text{CH}_3\text{SiCl}$ , and  $(\text{ClCH}_2)\text{CH}_3\text{SiCl}_2$  <2001MIP1317488-A, 2002GEP10154943>.

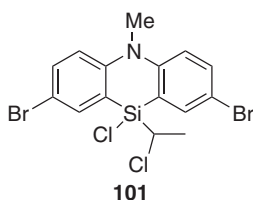


Scheme 33

The reduction of a carbon—halogen bond can lead to halo ( $\alpha$ -haloalkyl)silanes. The previously mentioned reduction of fluorodibromomethyl chlorosilanes promoted by  $n\text{-Bu}_3\text{SnH}$  (see Equation (80)) can take place exclusively at the dibromomethyl moiety by controlling the reaction time. Thus, in such a case the isolated product is a fluoromethyl chlorosilane (Equation (91)) <1993OM4930>. A transition metal-catalyzed dechlorination of (polychloromethyl)silanes with trichlorosilane, giving (chloromethyl)silanes, has been investigated. The transition metal compounds tested were, in decreasing order of reactivity,  $\text{Pd}(\text{OAc})_2$ ,  $\text{PdCl}_2$ ,  $\text{Pt-C}$ ,  $\text{H}_2\text{PtCl}_6$ ,  $\text{Ni}(\text{OAc})_2$ ,  $\text{NiCl}_2$ ,  $\text{Pd}(\text{PPh}_3)_2\text{Cl}_2$ , and  $\text{K}_2\text{PtCl}_4$  <1998OM570>.

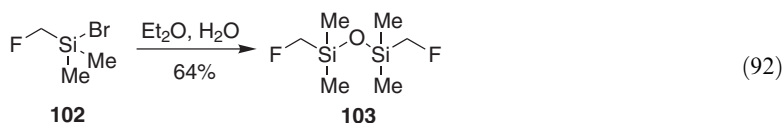


The coupling of chlorosilanes with organomagnesium and organolithium compounds discussed above is also useful for preparing highly branched chlorosilanes (Scheme 31) <2002JOC3561>. This strategy, for instance, has been used for the coupling of the organolithium  $(2,4\text{-LiBrC}_6\text{H}_4)_2\text{NMe}$  with the chloro silane  $\text{Cl}_3\text{SiCHClCH}_3$ , giving the tricyclic silicon heterocycle **101** <1984OM1051>.

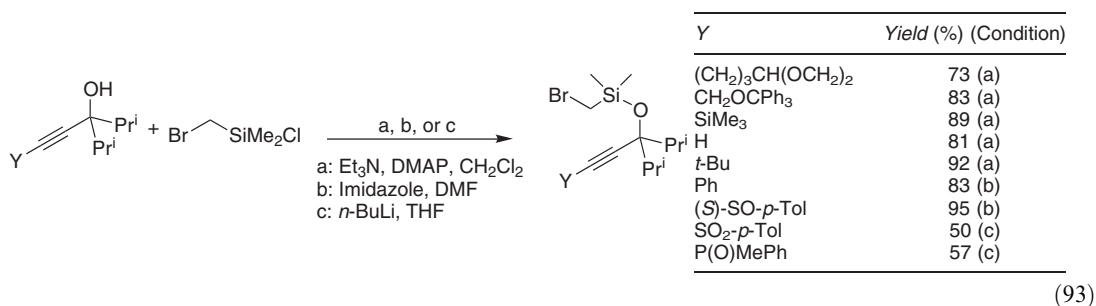


#### 4.03.4.1.3 ( $\alpha$ -Haloalkyl)oxysilanes

Hydrolysis of the bromosilane **102** led to the disiloxane **103** (Equation (92)), whereas the cyclotetrasiloxane  $(\text{CH}_2\text{FMeSiO})_4$  has been obtained from the dibromosilane  $\text{CH}_2\text{FMeSiBr}_2$ , under similar reaction conditions <1996JOM(511)293>.

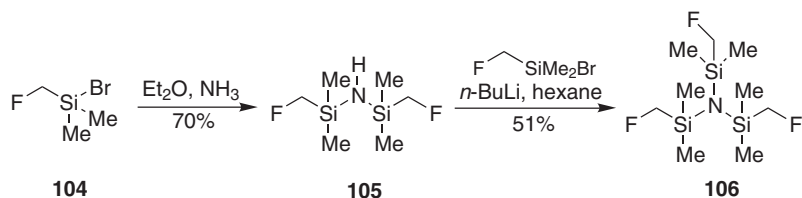


In their studies toward the synthesis of compounds bearing cyclopentyl units by radical cyclizations, Malacria and co-workers prepared a series of (bromomethyl)dimethylsilyl ethers [<1998JOC6764>](#). The approach to obtain these compounds consisted of the reaction of an unsaturated alcohol with (bromomethyl)dimethylsilyl chloride under basic conditions ([Equation \(93\)](#)) [<1999JOC4920>](#).



#### 4.03.4.1.4 Miscellaneous $\alpha$ -halo silicon derivatives

The (fluoromethyl)bromosilane **104** can be elaborated into the trisilylamine **106** in a two-step sequence. In the first reaction, two nucleophilic attacks on the nitrogen toward two different Si—Br bonds occurred, leading to **105**. In the second, the formation of the third N—Si bond took place through a lithiated intermediate (Scheme 34) <1996JOM(511)293>.



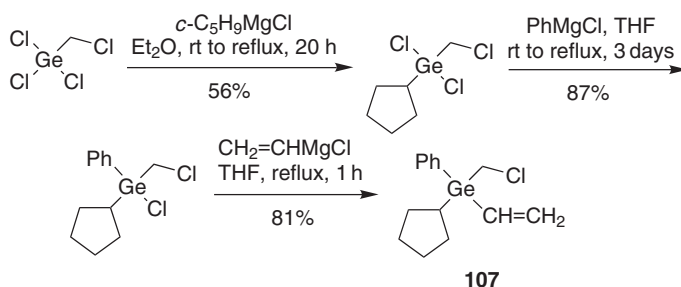
### Scheme 34

#### 4.03.4.2 $\alpha$ -Halo Germanium Derivatives— $R_1^1CHalGeR_3^2$ , etc.

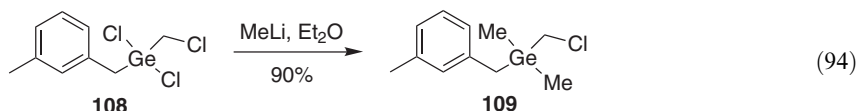
Investigations of the bioisosterism of carbon and germanium compounds have led to a continuous advance in the chemistry of germanium compounds, including the synthesis of the halo germanium derivatives described in this section <1999PS(151)69>. As the carbon—halogen bond is less reactive than the germanium—halogen bond toward carbon nucleophiles, the general approach to obtain such compounds is by reacting a halo(halomethyl)germanium derivative with an organometallic species. Other methods have also been reported, as previously reviewed <1995COFGT(4)95>.

#### 4.03.4.2.1 Alkyl- and aryl( $\alpha$ -haloalkyl)germanes

The reaction of a chlorogermane derivative with an organometallic species has been utilized for the synthesis of several (chloroalkyl)germanes. The introduction of an alkyl (or alkenyl or aryl) group into a trichlorogermane using Grignard reagents can be performed with excellent control, allowing the efficient synthesis of substituted (chloroalkyl)germanes, such as **107**, which is an alkyl alkenyl aryl germane (Scheme 35) <1996JOM(521)305, 2001JOM(640)140>. When the target germane compound bears two identical substituents, its preparation is straightforward from Grignard reagents. Thus, the dimethyl(chloromethyl)germane compound **109** has been obtained from **108**, in 90% yield (Equation (94)) <2002OM113>.



Scheme 35

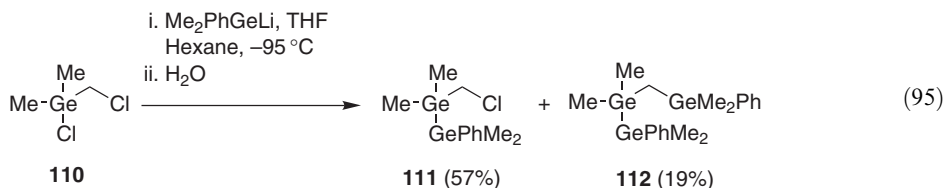


#### 4.03.4.2.2 Halo ( $\alpha$ -haloalkyl)germanes

The reaction of tri- or dichloro ( $\alpha$ -chloromethyl)germane compounds with Grignard reagents can also be used to obtain the corresponding monoaryl (or alkyl) derivatives, in an efficient manner (Scheme 35) <1996JOM(521)305, 1998OM1687, 2001JOM(640)140, 2002OM113>. Another approach is the copper-catalyzed homologation of chlorogermanes using diazomethane. By treating germanium tetrachloride with diazomethane, it was possible to obtain either trichloro(chloromethyl)germane <1955JA907, 1996JOM(510)157> or dichlorobis(chloromethyl)germane <1994CB639>.

#### 4.03.4.2.3 Miscellaneous ( $\alpha$ -haloalkyl)germanes

The chemistry of ( $\alpha$ -haloalkyl)germane derivatives bearing a Ge—Ge or Ge—Si bond was also investigated. Treating the chloro(chloromethyl)germane derivative **110** with  $\text{Me}_2\text{PhGeLi}$  led to a mixture of the compounds **111** and **112**, which bear a Ge—Ge bond (Equation (95)) <1989OM1237>. Alkyl lithium reagents also react with halogermanes, as demonstrated by reacting  $\text{ClGeMe}_2\text{SiMe}_3$  with  $\text{ClCH}_2\text{Li}$ , which lead to  $\text{ClCH}_2\text{GeMe}_2\text{SiMe}_3$  <1993OM3979>.



#### 4.03.4.3 $\alpha$ -Halo Boron Derivatives— $\text{R}_2^1\text{CHaIBR}_2^2$ , etc.

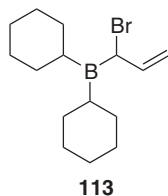
This section aims to summarize the synthetic methods for the synthesis, in order of presentation, of ( $\alpha$ -haloalkyl)boron hydrides, of alkyl- and aryl( $\alpha$ -haloalkyl)boranes, of halo ( $\alpha$ -haloalkyl)boranes, and of ( $\alpha$ -haloalkyl)oxyboranes. In the latter group are included  $\alpha$ -haloboronic esters, which are useful compounds in asymmetric synthesis and have experienced significant progress recently.

##### 4.03.4.3.1 ( $\alpha$ -Haloalkyl)boron hydrides

The reaction of vinyl halides with boron hydrides occurs with formation of ( $\alpha$ -haloalkyl)boron hydride, as previously reviewed <1995COFGT(4)95>.

#### 4.03.4.3.2 Alkyl- and aryl( $\alpha$ -haloalkyl)boranes

The synthesis of isolable alkyl ( $\alpha$ -haloalkyl)boranes has been described in a few papers which were previously discussed [<1995COFGT\(4\)95>](#). An additional example of the formation of a ( $\alpha$ -haloalkyl)borane and its use *in situ* has been reported. Treatment of dicyclohexylborane with propargyl bromide led to the  $\alpha$ -bromoallylborane **113**, which was trapped with aldehydes [<2000JOC8767>](#).



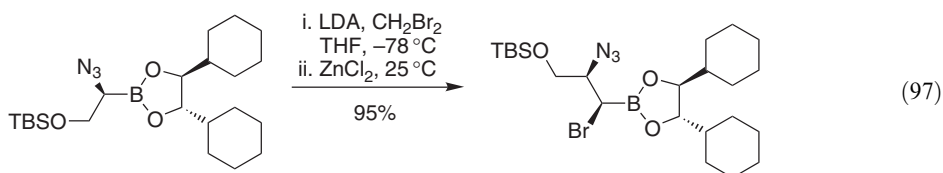
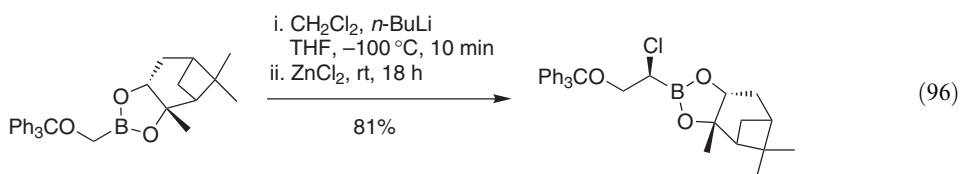
#### 4.03.4.3.3 Halo ( $\alpha$ -haloalkyl)boranes

A few examples of the synthesis of halo ( $\alpha$ -haloalkyl)boranes have been reported in the literature, as previously reviewed [<1995COFGT\(4\)95>](#).

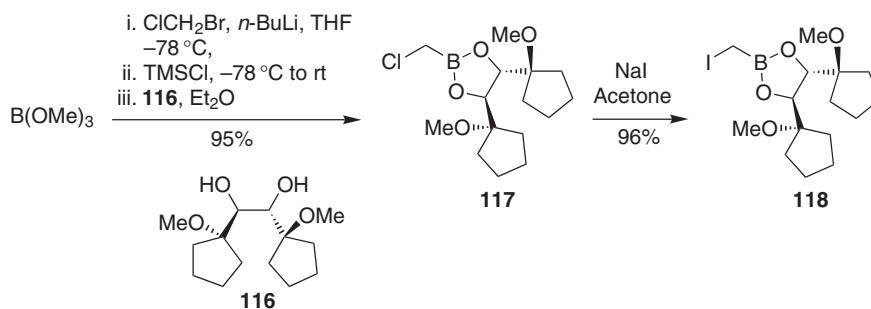
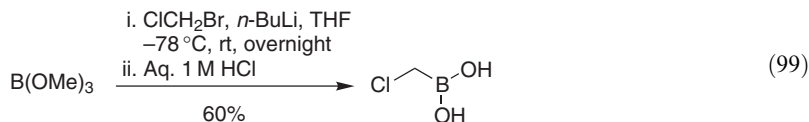
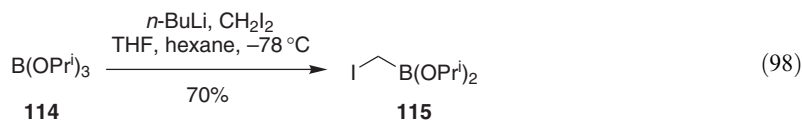
#### 4.03.4.3.4 ( $\alpha$ -Haloalkyl)oxyboranes

Since the pioneering work of D. S. Matteson, halo boronic esters are well-established reagents for asymmetric synthesis. Studies toward their preparation have been investigated by several researchers, and are summarized here. Several review articles are available for additional examples and further information [<1986S973, 1988ACR294, 1989CRV1535, 1998T10555, 1999JOM\(581\)51>](#).

The most widely used method for the synthesis of  $\alpha$ -haloalkyl boronic esters is the homologation reaction of boronic esters promoted by halomethylolithium [<1983OM1529>](#). This reaction occurs in a highly stereoselective manner and with excellent yield, constituting an efficient method for the synthesis of  $\alpha$ -chloro (Equation (96)) [<1986JOC3150, 1995OM2855, 1998SL253>](#) and  $\alpha$ -bromo (Equation (97)) [<1995OM2855, 1998SL253, 2000JOC6650>](#) boronic esters.

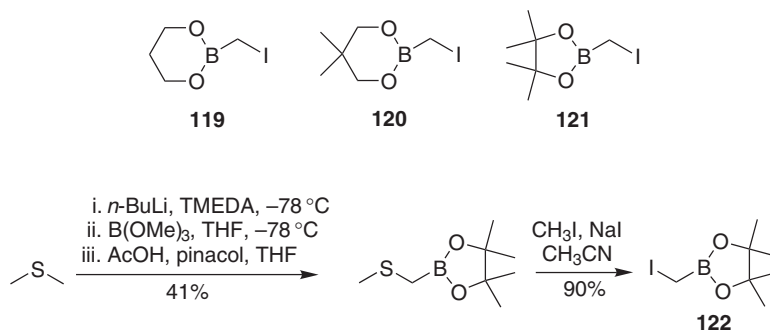


A similar homologation reaction also occurs with borates, instead of boronic esters, as substrates. Thus, treatment of the borate **114** with iodomethylithium afforded the corresponding boronate **115**, in good yield (Equation (98)) [<1985OM1687, 1996JOC100>](#). Alternatively, the  $\alpha$ -halo boronate obtained by this method might be hydrolyzed *in situ*, leading to the corresponding boronic acid (Equation (99)) [<1997BSF583>](#). The reaction of boronic acids with chiral diols can lead to optically active boronates [<1997BSF583>](#). An example of the use of the two latter reactions in the synthesis of an enantiomerically pure boronic ester is the efficient preparation of the iodide **118** (Scheme 36) [<2000JCS\(P1\)3250>](#).



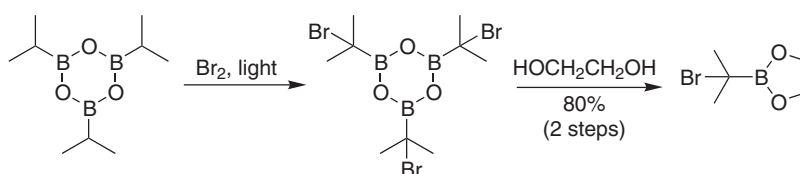
Scheme 36

Reaction of (*R*),(*R*)-2,3-butanediol dichloromethylboronate with *t*-butylmagnesium chloride in the presence of anhydrous zinc chloride led to the corresponding chiral, nonracemic boronate ester <1991JOC3286>. Some cyclic boronates, **119**, **120**, and **121**, have been obtained by transesterification of diisopropyl iodomethylboronate with the corresponding diols <1997TL765>. Diisopropyl ( $\alpha$ -iodopentyl)boronate has been synthesized from the corresponding chloride by a halogen exchange reaction <1999TL9183>. A large-scale route for the iodo boronate **122** has been developed (Scheme 37) <1986JOC1610>.



Scheme 37

The bromination of the cyclic anhydride of isopropylboronic acid occurs smoothly using bromine giving, after reaction with ethylene glycol, a boronic ester in good overall yield (Scheme 38) <2003JOM(680)100>.



Scheme 38

### 4.03.5 $\alpha$ -HALO METAL DERIVATIVES

This section outlines the synthesis of molecules bearing a halogen and a metal bonded to the same carbon and are called carbenoids. This name was first used by Closs and co-workers in the 1960s in their studies concerning  $\alpha$ -haloalkyllithium compounds <1964JA4042>, referring now to molecules bearing a metal and leaving group in the same carbon. The common name for this organometallic species is the “Köbrich reagent,” named after the pioneering researcher <1963ZN(B)1125>.

With the evolution of laboratory techniques, occurring mostly due to evolution of the laboratory techniques, carbenoids have become important synthetic intermediates. The generation of a carbene is probably the most important application, because this highly reactive intermediate plays an important role in new methods for the formation of C—C bonds. Some review articles covering several aspects of the chemistry of carbenoids have been published <1998AG(E)430, 2001CRV697>.

In this section, molecules bearing an  $\alpha$ -halo metal unit that were not isolated are also included.

#### 4.03.5.1 Group 1 and Group 2 Derivatives— $R_2CHaLi$ , etc.

This section will describe the synthesis of lithium and magnesium carbenoids. The preparation of useful  $\alpha$ -halomethylithium compounds is discussed separately from the other  $\alpha$ -haloalkyllithiums. Subsequently, the formation of  $\alpha$ -halomagnesium derivatives is discussed. A review concerning some aspects of these compounds has already been published <2003CSR225>.

##### 4.03.5.1.1 $\alpha$ -Haloalkyllithium derivatives

###### (i) $\alpha$ -Halomethylithium compounds

The preparation of  $\alpha$ -halomethylithium compounds through a lithium–halogen exchange reaction is performed by reacting a dihalomethane with an organolithium. Low temperature, usually  $-78^\circ\text{C}$ , is crucial, because these intermediates are unstable <1995COFGT(4)95>. Thus, some recent studies have been performed mainly to increase the stability of this organometallic reagent.

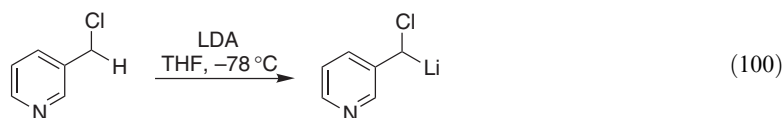
Concellón and co-workers reported the preparation of epoxides from aldehydes and ketones using  $\text{ICH}_2\text{Li}$ , describing for the first time that  $\alpha$ -halomethylithium could be formed and handled at  $0^\circ\text{C}$ . The protocol consisted of treating  $\text{CH}_2\text{I}_2$  with  $\text{MeLi}$  in THF <2001T8983>. A study concerning the preparation of dihalolithium compounds was reported, showing an aspect that might be useful in future studies toward the corresponding halolithium derivatives. The stability of  $\text{Hal}_2\text{CHLi}$ , which usually decomposes at  $-65^\circ\text{C}$  for the chloride and at  $-100^\circ\text{C}$  for the bromide and iodide, was increased significantly by complexation with transition metals, such as  $\text{Ti}(\text{O-}i\text{-Pr})_4$  <1988AG(E)943>.

###### (ii) Other $\alpha$ -haloalkyllithium compounds

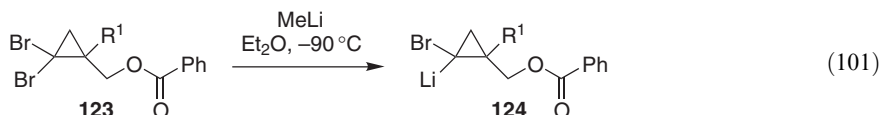
There are two general approaches to prepare lithium carbenoids. The first is the reaction of an organolithium reagent (or lithium metal) and a *gem*-dihalo derivative, leading to a lithium–halogen exchange as discussed above for  $\alpha$ -halomethylithium compounds. In this method the reactions are carried out at low temperatures, in which the carbenoids are stable. The second approach is the  $\alpha$ -metallation of an organic halide, promoting a lithium–hydrogen exchange. This reaction can be applied only for alkyl fluorides or chlorides, because for these halogens the lithium–halogen exchange does not occur at a competitive rate. An advantage of this method is that halides are usually more available than the corresponding *gem*-dihalo derivative. Examples of both approaches are described in the following paragraphs.

The preparation of (3-pyridinylchloromethyl)lithium was performed utilizing lithium diisopropylamine at low temperature (Equation (100)). In the presence of the ketones, this carbenoid furnished epoxides, whereas aziridines were obtained from Schiff's bases <1996JOC4148>. Similarly, treatment of allyl chloride with LDA led to the formation of  $\alpha$ -chloroalkyllithium, which is a versatile reagent for alkylation reactions <1981JOC1506, 1992OM1948, 1996JOC7513>.

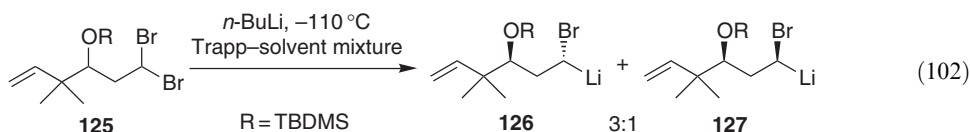




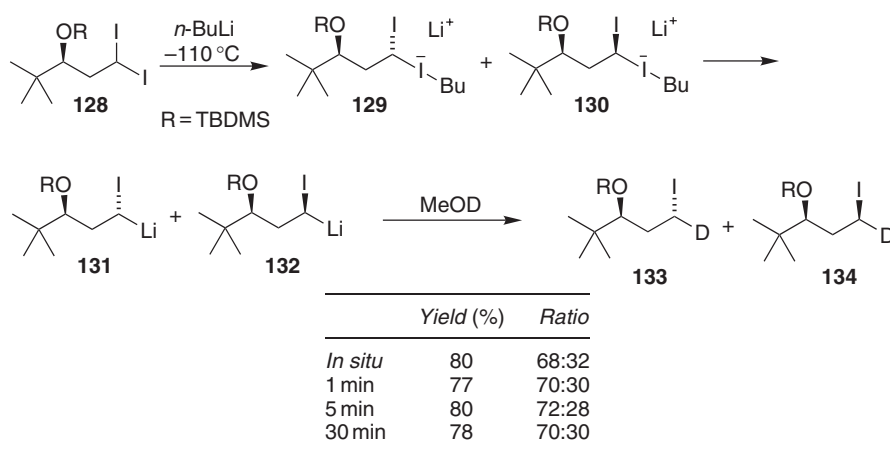
Treatment of the dibromocyclopropane **123** with MeLi gave the halolithium **124**, which provided a cyclic ether by an intramolecular nucleophilic attack of the carbenoid moiety on the ester group (Equation (101)) <1998TL9081, 2000T4799>. A similar process has also been reported utilizing amides instead of esters <2001T1593>. A similar *gem*-bromolithium cyclopropane derivative was formed from the corresponding dibromide, using *n*-butyllithium <1993JOC2958>. Under similar conditions, a fluoro carbenoid was formed from 1-fluoro-1-iodo-2,2-diphenylcyclopropane <1993JOC546>.



Hoffmann and co-workers investigated the stereoselectivity of the halogen–lithium exchange reactions of *gem*-dibromides and of *gem*-diiodides. The reaction of the *gem*-dibromo compound **125** with *n*-butyllithium, for example, led to the carbenoids **126** and **127**, in 3:1 ratio (Equation (102)) <1995TL4595, 1996T7421>.



An important aspect of  $\alpha$ -iodolithium compounds was also investigated, i.e., studying the formation of **133** and **134** from the reaction of the diiodide **129** with *n*-butyllithium. In this system, the iodine ate-complexes **129** and **130** are formed irreversibly and transformed into the corresponding organolithium compounds **131** and **132**, leading to the iodides **133** and **134** in the same ratio under different quenching conditions (Scheme 39). Therefore, the stereoselectivity of the formation of the ate complexes **129** and **130** defines the ratio in which the isomeric carbenoids are generated <1998EJO1851, 1999JCS(P2)731>.



Scheme 39

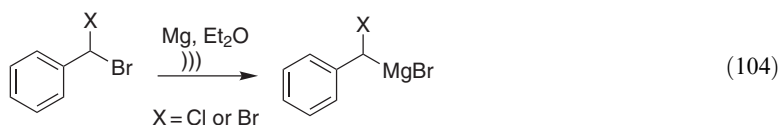
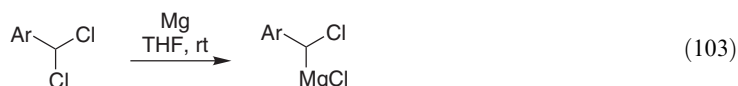
#### 4.03.5.1.2 $\alpha$ -Haloalkylmagnesium derivatives

The most commonly used method for the formation of  $\alpha$ -haloalkylmagnesium derivatives is the reaction of a *gem*-dihalo compound with magnesium or with an organomagnesium reagent. The crucial step in this general procedure is the halide–magnesium exchange reaction,

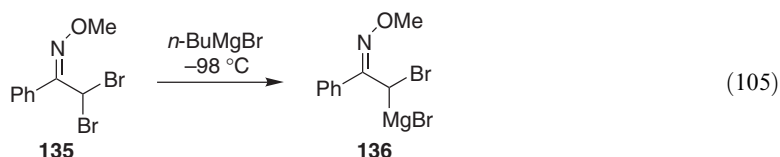


which was first reported by Villieras, who demonstrated that the reactive magnesium carbenoids  $\text{HCBBr}_2\text{MgCl}$  can be prepared from  $\text{HCBBr}_3$  using  $i\text{-PrMgCl}$  in THF at  $-78^\circ\text{C}$  <1967BSF1520>. Some advances in the preparation of  $\alpha$ -haloalkylmagnesium derivatives have been reported recently.

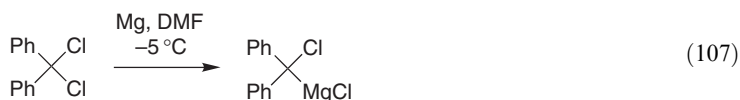
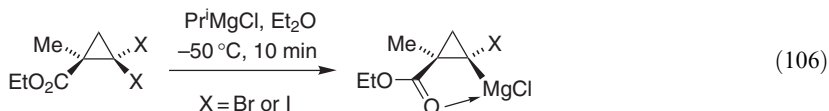
The formation of some  $\alpha$ -chlorobenzylmagnesium chlorides from the reaction of  $\alpha,\alpha$ -dichloroarylmethanes with magnesium has been reported in studies toward the synthesis of alkylarylcarbinols (Equation (103)). Lithium can also be used to promote this reaction, through a lithium carbenoid, although lower yields were observed <1997JOM(531)101>. Another protocol for the preparation of  $\alpha$ -halobenzyl carbenoids is the treatment of a *gem*-dihalide with magnesium under ultrasonic irradiation (Equation (104)). These organomagnesium compounds were reacted with imines leading to aziridines <2001TL2759>.



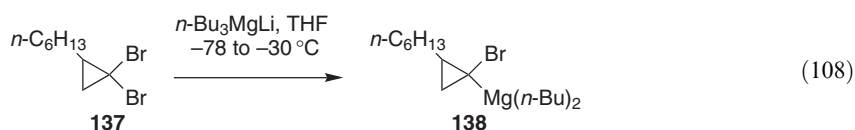
The bromine–magnesium exchange reaction of  $\alpha,\alpha$ -dibromo oxime ethers was used to prepare pyrimidines through the organomagnesium intermediate **136**, which was generated from the reaction of a Grignard reagent with **135** (Equation (105)) <2002JA9032>.



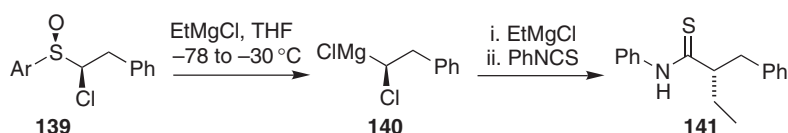
The stereoselective preparation of functionalized cyclopropylmagnesium carbenoids from a dihalocyclopropanecarboxylate has been utilized for the synthesis of cyclopropyl derivatives. The diastereoselectivity of the reaction depends on the solvent used. Thus, a stereoselective Br–Mg exchange was observed by performing the reaction in diethyl ether (*dr* > 99:1), whereas the use of THF resulted in a lower diastereoselectivity (*dr* > 65:35) (Equation (106)) <2002AG(E)351>. The formation of cyclopropanes was also achieved from a carbenoid prepared by treatment of dichlorodiphenylmethane with magnesium in DMF (Equation (107)). The formation of the dimerization product  $\text{Ph}_2\text{C}=\text{CPh}_2$  albeit in small amount indicated that the reaction might also occur by a carbene intermediate <2003SL485>. The cyclopropanation reaction promoted by carbenes, formed from magnesium carbenoids, was used in the reactions with allylic alcohols, furnishing cyclopropyl alcohols in modest yields <1997TL7349>.



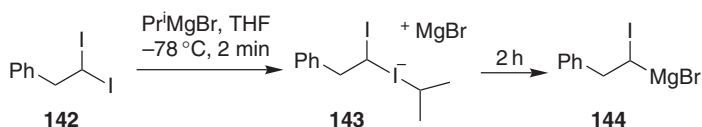
The formation of the carbenoid **138** from the reaction of a trialkylmagnesium with the *gem*-dibromocyclopropane **137** was reported. The addition of electrophiles to **138** gave double-alkylated cyclopropane derivatives as a diastereomeric mixture (Equation (108)) <2002CEJ1730>.



To obtain a better understanding of the reactions of Grignard reagents with electrophiles, several studies have been performed to elucidate the mechanism of the halogen–magnesium exchange <2003CSR225>. This addition is usually considered as a polar addition process, but there is evidence that free radicals may also be involved. An approach to decide between these two alternatives involves the use of a chiral nonracemic secondary Grignard reagent, since the loss of optical activity or the formation of rearrangement products would indicate the presence of radicals formed by a single electron transfer (SET) process. The preparation of chiral nonracemic secondary Grignard reagents is very difficult to achieve by standard protocols because an achiral radical intermediate is involved. Hoffmann and co-workers used the magnesium carbenoid chemistry to access such compounds <2000AG(E)3072, 2000CEJ3359>. Thus, the enantiomerically pure  $\alpha$ -chloroalkyl sulfoxide **139** was treated with EtMgCl, furnishing the carbenoid **140**. Subsequently, reaction of **140** with a second molecule of EtMgCl, followed by quenching with phenyl isothiocyanate, gave **141** as a single enantiomer (Scheme 40) <2000AG(E)1642>. Other contributions to elucidate the mechanism of the halogen–magnesium exchange reaction were the experiments performed to identify the intermediate in the formation of the colorless **144**. Supported by experiments such as, isotope effect, NMR spectroscopy, and kinetic studies, the deep-yellow -ate complex **143** was proposed as the intermediate (Scheme 41) <1998AG(E)824, 1999CEJ337, 2003OM2925>.



Scheme 40



Scheme 41

#### 4.03.5.2 Transition Metal Derivatives— $R_2CHaFeX_n$ , etc.

The preparation of complexes bearing an  $\alpha$ -haloalkyl unit can be performed by several methods, the most used are: (i) the reaction of a metal complex bearing a halo-metal bond with a diazo compound, usually diazomethane. This leads to an ( $\alpha$ -haloalkyl)metal derivative by an insertion-type reaction, where the halogen of the product is that of the starting material. Copper is frequently used as a catalyst in such a reaction; (ii) the oxidative addition of a transition metal to a *gem*-dihalo-alkane which gives a halo ( $\alpha$ -haloalkyl)metal complex where both halogens, as well as the alkyl chain, come from the dihalo derivative used as reagent.

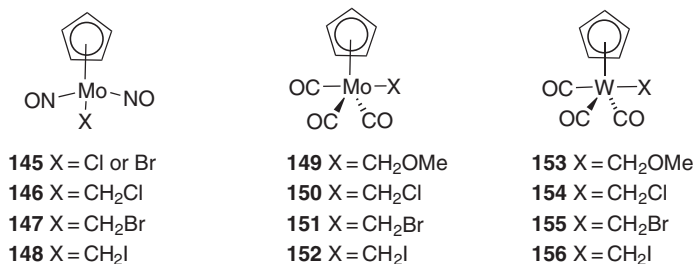
Studies concerning  $\alpha$ -halometal derivatives have been reviewed <1991AOC235>.

##### 4.03.5.2.1 Derivatives of chromium, molybdenum, and tungsten

The synthesis of the chloromethyl complex *trans*-[CrCH<sub>2</sub>Cl(acac)<sub>2</sub>L], where L is H<sub>2</sub>O, CH<sub>3</sub>OH, or pyridine, using CrCl<sub>3</sub>·6H<sub>2</sub>O as starting material, was described. The protocol consisted of the treatment of this chromium salt with amalgamated zinc, CHCl<sub>3</sub>, and HCl, giving a solution of the complex [Cr(CHCl<sub>2</sub>)(H<sub>2</sub>O)<sub>5</sub>]<sup>2+</sup>. This complex was resubmitted to the treatment with CrCl<sub>3</sub>·6H<sub>2</sub>O, amalgamated zinc and HCl, affording the complex [Cr(CH<sub>2</sub>Cl)(H<sub>2</sub>O)<sub>5</sub>]<sup>2+</sup>. Addition of acetylacetone to a buffered solution of the latter complex gave *trans*-[CrCH<sub>2</sub>Cl(acac)<sub>2</sub>(H<sub>2</sub>O)], in 15% yield, which was treated with pyridine, furnishing *trans*-[CrCH<sub>2</sub>Cl(acac)<sub>2</sub>(py)], in 73% yield <1987IC2542>.

A general approach for the introduction of the halomethyl unit is the copper-catalyzed homologation using diazomethane, used in the preparation of the following molybdenum complexes. Thus, the preparation of ( $\eta$ -C<sub>5</sub>H<sub>5</sub>)Mo(NO)<sub>2</sub>(CH<sub>2</sub>X) complexes **146–148** has been achieved by the dropwise addition of CH<sub>2</sub>N<sub>2</sub> to a slurry of Cu and the corresponding ( $\eta$ -C<sub>5</sub>H<sub>5</sub>)Mo(NO)<sub>2</sub>X complex **145**. The same procedure was used to prepare ( $\eta$ -C<sub>5</sub>Me<sub>5</sub>)Mo(NO)<sub>2</sub>(CH<sub>2</sub>Cl). The direct

formation of the iodomethyl derivatives by treatment of the  $(\eta\text{-C}_5\text{H}_5)\text{Mo}(\text{NO})_2\text{I}$  with  $\text{CH}_2\text{N}_2/\text{Cu}$  is especially sluggish. However, **148** and  $(\eta\text{-C}_5\text{Me}_5)\text{Mo}(\text{NO})_2(\text{CH}_2\text{I})$  were obtained in good yield from the corresponding chlorides under classic conditions for chloride–iodide exchange using  $\text{NaI}$  <1996OM2534>. Such a reaction was also used in the preparation of the (iodomethyl)tungsten complex **156** from the bromide derivative **155**, in 87% yield <1993JOM(453)85>.

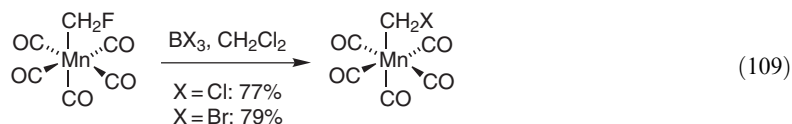


The chlorine and bromine derivatives (**150** and **151**) were prepared in 80% and 40% yield, respectively, by treating the (methoxymethyl)molybdenum complex **149** with the appropriate hydrogen halide. The same procedure was utilized to obtain the (halomethyl)tungsten complexes **154** and **155**, in 90% and 40% yield, respectively <1967JCS(A)1508>.

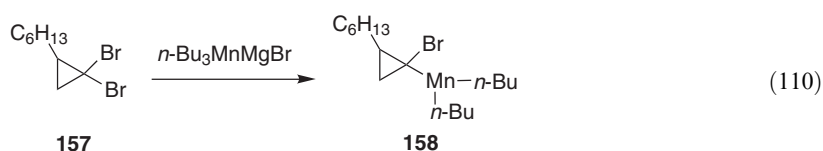
A straightforward method to obtain halomethyl complexes is the generation of an anion of the complexes followed by treatment with a dihalomethane. The (chloromethyl)molybdenum complex **150** could be prepared in 70% yield by the reaction between the sodium anion  $\text{Na}[(\eta\text{-C}_5\text{H}_5)\text{Mo}(\text{CO})_3]$  and the dihalide  $\text{ClCH}_2\text{I}$ . However, an analogous reaction with  $\text{CH}_2\text{I}_2$  furnished the complex **152**, in low yield (17%), whereas treatment with  $\text{CH}_2\text{Br}_2$  did not give the corresponding bromomethyl derivatives **151** <1973JOM(54)9>. The reaction between the tungsten sodium anion  $\text{Na}[(\eta\text{-C}_5\text{H}_5)\text{W}(\text{CO})_3]$  and  $\text{ClCH}_2\text{I}$  furnished a mixture of the derivatives **154** and **156**, in 60% and 12% yield, respectively <1973JOM(54)9>.

#### 4.03.5.2.2 Derivatives of manganese, iron, and cobalt

The preparation of the chloromethyl and (bromomethyl)manganese complexes by an electrophilic halogen exchange between boron trihalides and (fluoromethyl)manganese complex occurred in good yield (Equation (109)) <1984OM305>. The iodomethyl complex *fac*- $\text{Mn}(\text{CO})_3(\text{dppp})\text{CH}_2\text{I}$  was prepared from the corresponding methoxy ether *fac*- $\text{Mn}(\text{CO})_3(\text{dppp})\text{CH}_2\text{OCH}_3$  by reaction with trimethylsilyl iodide <1999JOM(592)61>. The (chloromethyl)manganese complex  $\text{Mn}(\text{CO})_5\text{CH}_2\text{Cl}$  was prepared from the reaction between the metal anion of  $\text{Na}[\text{Mn}(\text{CO})_5]$  and  $\text{ClCH}_2\text{I}$ , giving  $\text{Mn}(\text{CO})_5\text{CH}_2\text{Cl}$ , in 45% yield. The same procedure was utilized to prepare the complex *cis*- $[\text{Mn}(\text{CO})_4(\text{PPh}_3)\text{CH}_2\text{Cl}]$  from  $\text{Na}[\text{Mn}(\text{CO})_4(\text{PPh}_3)]$  and  $\text{ClCH}_2\text{I}$ , in 60% yield <1982JOM(236)221>.

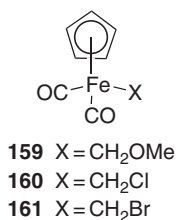


The reaction of a trialkylmanganate with the dibromocyclopropane **157** led to the  $\alpha$ -bromo-manganate **158**, formed by a bromine–manganese exchange (Equation (110)). Subsequently, the intermediate **158** was transformed into a poly-alkylated cyclopropane derivative by a double alkylation process <2000T2131, 2001T10063>.

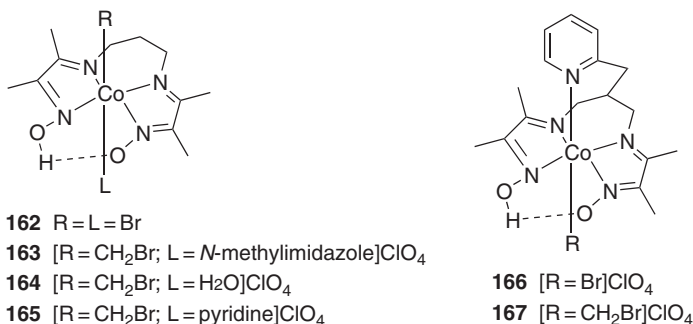


The synthesis of (halomethyl)iron complexes has been performed using a similar procedure to that employed to prepare the molybdenum and tungsten complexes **150** and **151** and **154** and **155**,

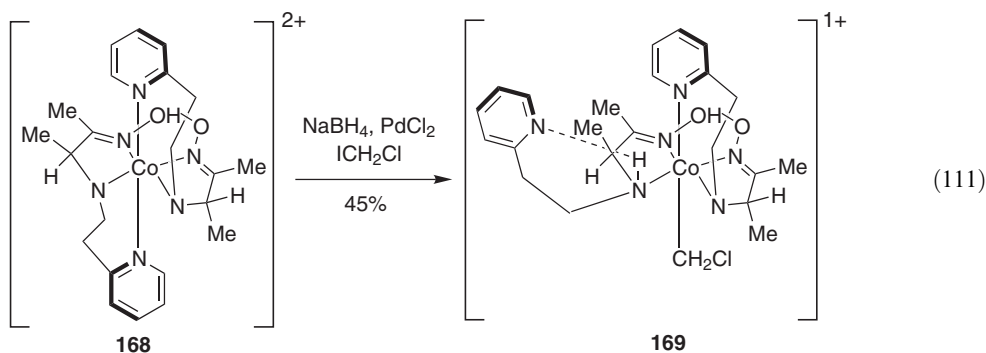
respectively. Thus, treatment of (methoxymethyl)iron complex **159** with the corresponding hydrogen halide furnished the complex **160** and **161**, in 90% and 75% yield, respectively <1967JCS(A)1508>. The preparation of the chloromethyl complex **160** using the metal anion of  $\text{Na}[(\eta\text{-C}_5\text{H}_5)\text{Fe}(\text{CO})_2]$  and  $\text{ClCH}_2\text{I}$  furnished the desired product in low yield (13%) <1973JOM(54)9>.



Several cobalt(III) complexes have been prepared in studies toward the synthesis of models of vitamin B<sub>12</sub> and its derivatives. The perchlorate salt of (bromomethyl)cobalt complex **163** was prepared in 76% yield by treating **162** with *N*-methylimidazole, followed by addition of  $\text{CH}_2\text{Br}_2$  and  $\text{NaBH}_4$  <1985IC3908>. The same procedure was employed to prepare **167** from **166**, although in low yield (20%) <1997IC3854>. Treatment of **163** with a cation-exchange resin, led to **164** in 77% yield. Reaction of **164** with pyridine furnished **165** in 31% yield. Other analogs of **164** were also prepared <1997IC3854>.



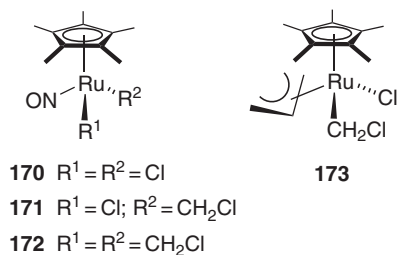
The synthesis of another class of perchlorate salts of (halomethyl)cobalt complexes has been described, where a reduction of cobalt(III) to cobalt(I) is involved. Thus, the complex **168** was reacted with  $\text{NaBH}_4$  in the presence of a catalytic amount of palladium chloride, giving a Co(I) species which displaced the iodide of  $\text{ICH}_2\text{Cl}$ , leading to the complex **169** in 45% yield (Equation (111)) <2001EJ1267>. The preparation of the corresponding bromomethyl and (iodomethyl)-cobalt derivatives was also reported <2001IC5541>.



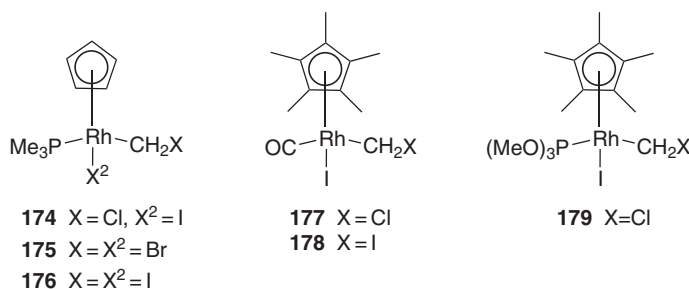
#### 4.03.5.2.3 Derivatives of ruthenium, rhodium, and palladium

The preparation of the (chloromethyl)ruthenium complexes **171** and **172** has been performed using conditions similar to those described for the preparation of the corresponding molybdenum complexes.

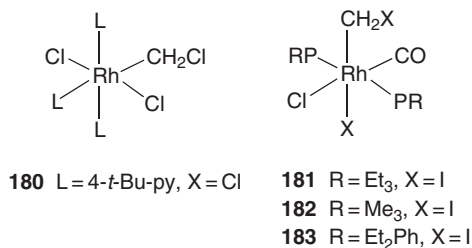
Thus, the addition of ethereal diazomethane to a solution of the complex **170** in the presence of Cu powder furnished the complex **171** in good yield, together with a minor amount of the complex **172**. Similarly, the complex **172** was prepared in 95% yield by two consecutive additions of  $\text{CH}_2\text{N}_2$ , both using fresh Cu powder <1991JA9180>. The same procedure was employed in the preparation of the allyl(chloromethyl) complex **173** from  $(\eta\text{-C}_5\text{Me}_5)\text{Ru}(\eta\text{-C}_3\text{H}_5)\text{Cl}_2$  <1995JOM(487)65>, in 52% yield. In this case no trace of  $(\eta\text{-C}_5\text{Me}_5)\text{Ru}(\eta\text{-C}_3\text{H}_5)(\text{CH}_2\text{Cl})_2$  was detectable in contrast to the synthesis of **171**. The (chloromethyl)ruthenium complex  $(\eta\text{-C}_5\text{H}_5)\text{Ru}(\text{CO})_2(\text{CH}_2\text{Cl})$  could be prepared in 15% yield from the corresponding (methoxymethyl)ruthenium complex  $(\eta\text{-C}_5\text{H}_5)\text{Ru}(\text{CO})_2(\text{CH}_2\text{OMe})$  by treatment with hydrogen chloride <1982JOM(236)221>.



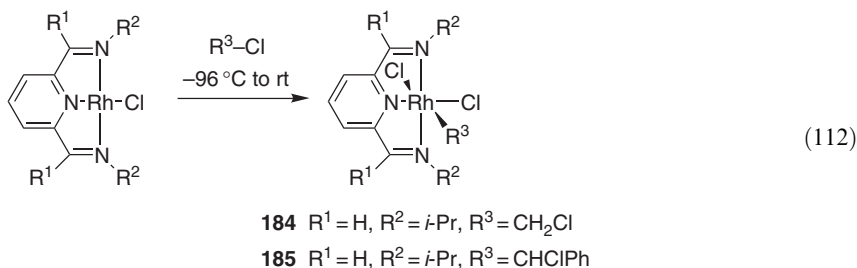
The most common method used for the formation of a C—Rh  $\sigma$ -bond is by the oxidative addition of *gem*-dihalogenoalkanes to a rhodium complex, giving the corresponding (halomethyl)rhodium complex. Depending on both substrate and reaction conditions, this reaction can occur by three different mechanisms: an oxidative insertion, a nucleophilic  $\text{S}_{\text{N}}2$  substitution <2001IC560>, or a radical pathway. The reaction of  $(\eta\text{-C}_5\text{H}_5)\text{Rh}(\text{C}_2\text{H}_4)\text{PMe}_3$  and a dihalogenoalkane ( $\text{ClCH}_2\text{I}$ ,  $\text{CH}_2\text{Br}_2$ ,  $\text{CH}_2\text{I}_2$ ) gave the corresponding (halomethyl)rhodium complexes **174–176** in 51%, 23%, and 78% yield, respectively <1985CB261>. Similarly, the complexes **177** and **178** were obtained in 43% and 65% yield, respectively, from  $(\eta\text{-C}_5\text{Me}_5)\text{Rh}(\text{CO})_2$  <1985CB3032>. Other (halomethyl)rhodium complexes containing phosphine ligands, such as **179**, were similarly prepared <1985CB3032, 1985JOM(281)317, 1998EJI1605>.



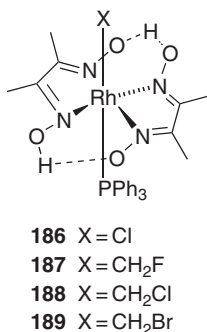
The oxidative addition of  $\text{CH}_2\text{Cl}_2$  to the rhodium(I) complex  $[\text{Rh}_2(\text{C}_8\text{H}_{14})_4(\mu\text{-Cl})_2]$ , in the presence of a monodentate nitrogen ligand furnished a (chloromethyl)rhodium(III) complex in 77% yield, whose geometry is probably as shown in **180**. Reaction of *trans*- $[\text{RhCl}(\text{CO})(\text{PEt}_3)_2]$  with  $\text{CH}_2\text{I}_2$  furnished the complex **181** in 67% yield. The reaction of the same starting material with  $\text{ClCH}_2\text{I}$  furnished  $[\text{RhCl}(\text{I})(\text{CH}_2\text{Cl})(\text{CO})(\text{PEt}_3)_2]$  in 20% yield as a mixture of isomers <1994JCS(D)1963>. The rhodium compounds **182** and **183** were obtained in analogous fashion.



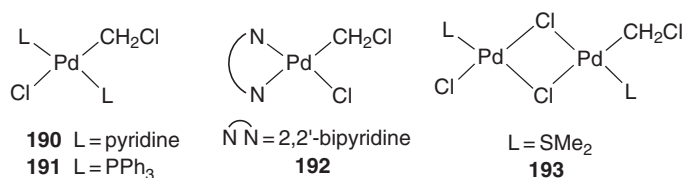
Vrieze and co-workers reported an extensive study concerning the preparation of (chloromethyl)rhodium(III) complexes containing trinitrogen ligands. Such a class of ligand can stabilize the rhodium complex by donation of electrons, facilitating reactions where nucleophilic properties are important. Thus, the rhodium(I) complexes participate in oxidative addition with alkyl chlorides furnishing (chloroalkyl)rhodium(III) complexes such as **184** and **185** in 94% and 79% yield, respectively (Equation (112)) <1997OM887>. The preparation of other (halomethyl)rhodium complexes bearing tridentate ligands has also been reported. Other interesting kinds of tridentate ligands are the hybrid ligands which contain both P and N donor atoms <1991OM2706, 1997JCS(D)1075, 1997JCS(D)3777>.



The synthesis of the (halomethyl)rhodoximes  $[\text{RhX}(\text{dmgH})_2(\text{PPh}_3)]$  **187–189**, was achieved in 37%, 74%, and 14% yield, respectively, by reduction of the rhodoxime **186** with  $\text{NaBH}_4$  in methanolic KOH, followed by reaction of the generated rhodium anion with  $\text{ClCH}_2\text{F}$ ,  $\text{CH}_2\text{Cl}_2$ , or  $\text{CH}_2\text{Br}_2$  <1993JOM(463)65, 2001JOM(622)172>.

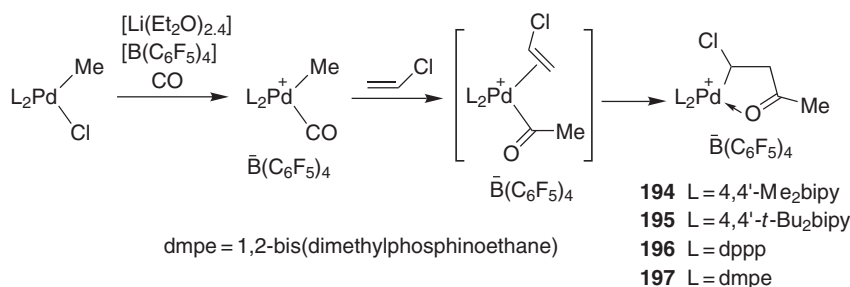


The preparation of the (chloromethyl)palladium complex *trans*- $[\text{PdCl}(\text{CH}_2\text{Cl})(\text{Pt-}t\text{-Bu}_2\text{H})_2]$  was performed in 70% yield by the oxidative addition reaction of  $\text{CH}_2\text{Cl}_2$  with the complex  $\text{Pd}(\text{PBU}^t_2\text{H})_3$  <1993OM2432>. Several (chloromethyl)palladium complexes were prepared by a ligand exchange reaction, utilizing as substrate a complex that already bears the halomethyl moiety. Thus, the introduction of ligands such as sulfides, amines, and phosphines has been performed in quantitative yield from the chloromethyl complex  $[\text{Pd}(\text{CH}_2\text{Cl})\text{Cl}(\text{COD})]$ . Examples of complexes obtained by such a strategy are **190–193** <1995OM2741>.



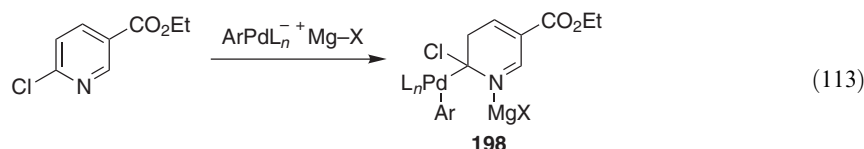
The treatment of  $\text{L}_2\text{Pd}(\text{Me})\text{Cl}$  with  $[\text{Li}(\text{Et}_2\text{O})_{2.4}][\text{B}(\text{C}_6\text{F}_5)_4]$ , CO, and vinyl chloride furnished the (chloroalkyl)palladium complexes **194–197** in good yield (83–96%). Utilizing NMR techniques, the formation of such complexes was proposed based on the formation of a cationic palladium acyl complex  $\text{L}_2\text{Pd}\{(\text{C}=\text{O})\text{Me}\}^+$ , which would react with vinyl chloride by 2,1 insertion yielding the palladium complexes **194**, **195**, **196**, and **197** (Scheme 42) <2003OM1878>.





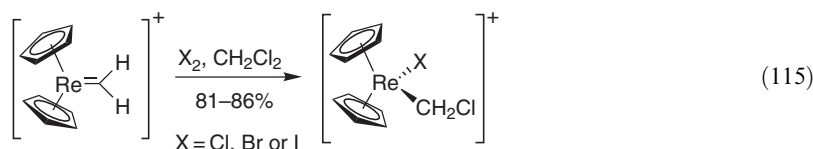
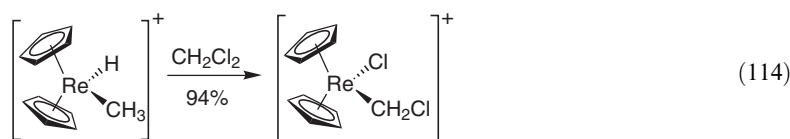
Scheme 42

The presence of the palladium carbenoid **198** was proposed in the mechanism of Pd(0)-catalyzed cross-coupling of functionalized arylmagnesium compounds with chloro- or bromopyridines to prepare polyfunctional pyridines in good yields (Equation (113)) <2001TL5717>.



#### 4.03.5.2.4 Derivatives of rhenium, osmium, iridium, and platinum

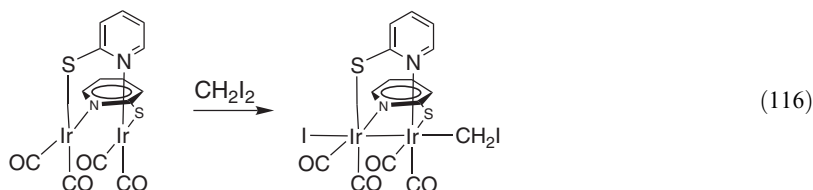
The cleavage of complexes bearing a methoxymethyl ether moiety is a general approach to obtain rhenium complexes in good yield. Thus, *cis*-[Re(CO)<sub>4</sub>(PPh<sub>3</sub>)CH<sub>2</sub>I] was prepared from the reaction of *cis*-[Re(CO)<sub>4</sub>(PPh<sub>3</sub>)CH<sub>2</sub>OCH<sub>3</sub>] and TMSI <1999JOM(592)61>. Similarly, Re(CO)<sub>5</sub>CH<sub>2</sub>OCH<sub>3</sub> furnished Re(CO)<sub>5</sub>CH<sub>2</sub>Cl, Re(CO)<sub>5</sub>CH<sub>2</sub>Br, or Re(CO)<sub>5</sub>CH<sub>2</sub>I when treated with HCl, TMSBr, or TMSI, respectively. However, an analogous approach failed for the preparation of the fluoro counterpart Re(CO)<sub>5</sub>CH<sub>2</sub>F, for which the reaction of Na[Re(CO)<sub>5</sub>] with ICH<sub>2</sub>F has been utilized <1993OM1073>. Two different strategies have been developed to access tetracoordinate rhenium complexes bearing a halomethyl unit. The first was the treatment of a methyl hydride complex with dichloromethane (Equation (114)), whereas the second was the halogen addition to a Re=C double bond (Equation (115)) <1998OM51>. On heating, the tetracoordinate rhenium complex [( $\eta$ -C<sub>5</sub>Me<sub>5</sub>)Re(NO)(PPh<sub>3</sub>)(ClCH<sub>2</sub>Cl)]<sup>+</sup> gave the oxidative addition product [( $\eta$ -C<sub>5</sub>Me<sub>5</sub>)-Re(NO)(PPh<sub>3</sub>)(Cl)CH<sub>2</sub>Cl]<sup>+</sup> in 70% yield <1988JOM(354)C33>.



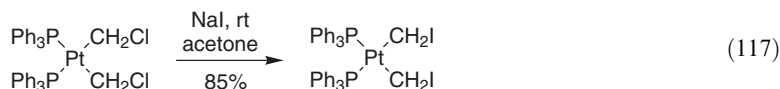
Compounds of iridium bearing an  $\alpha$ -chloromethyl unit have been prepared by standard procedures, as previously described <1995COFGT(4)95>.

The method of choice for the synthesis of iridium complexes bearing an  $\alpha$ -halomethyl unit is the treatment of an iridium complex with a dihalomethane compound. Using this approach, chloro, bromo, and iodo derivatives have been obtained. The complex [ $\eta$ -C<sub>5</sub>Me<sub>5</sub>IrCl(CH<sub>2</sub>Cl)PMe<sub>3</sub>] was prepared from the reaction of [ $\eta$ -C<sub>5</sub>Me<sub>5</sub>Ir(Ox)PMe<sub>3</sub>] (where Ox = oxalate) with CH<sub>2</sub>Cl<sub>2</sub>, under photochemical conditions <1991IC836>. Treatment of [Ir(CO)<sub>2</sub>( $\mu$ -pz)]<sub>2</sub> (where pzH = pyrazole) with CH<sub>2</sub>I<sub>2</sub> gave [Ir<sub>2</sub>(CO)<sub>4</sub>( $\mu$ -pz)<sub>2</sub>I(CH<sub>2</sub>I)], as the main product <1986CC285>. The conversion of *trans*-[IrCl(CO)(PMe<sub>3</sub>)<sub>2</sub>] into *trans*-[IrCl<sub>2</sub>(CH<sub>2</sub>Cl)(CO)(PMe<sub>3</sub>)<sub>2</sub>] and the

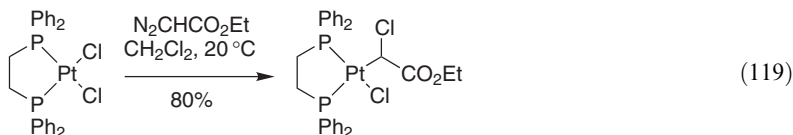
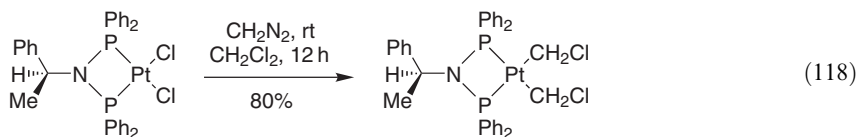
conversion of *trans*-[IrClBr(CH<sub>2</sub>Br)(CO)(PMe<sub>3</sub>)<sub>2</sub>], or *trans*-[IrClI(CH<sub>2</sub>I)(CO)(PMe<sub>3</sub>)<sub>2</sub>] was performed using CH<sub>2</sub>X<sub>2</sub>, where X = Cl, Br, or I <1980IC3236>. A binuclear (iodomethyl)iridium(II) complex could be prepared using a similar approach (Equation (116)) <1987AG(E)444>. The complex [Ir<sub>2</sub>(μ-aza)<sub>2</sub>(CH<sub>2</sub>I)(I)(CO)<sub>4</sub>], (where aza = 7-azaindolate) was similarly prepared <1993JOM(445)273>. The insertion of a methylene into the chloroiridium complex [IrCl(CO)(PPh<sub>3</sub>)<sub>2</sub>] was performed using diazomethane, yielding [Ir(CH<sub>2</sub>Cl)(CO)(PPh<sub>3</sub>)<sub>2</sub>] <1966JA1654>.



In contrast to other transition metals, there is a great diversity of methods available for the synthesis of α-halo platinum derivatives. In analogy with iridium and rhenium, treatment of a platinum complex with a dihalomethane compound affords the corresponding halomethyl derivative. Thus, for example, a mixture of *cis*- and *trans*-[PtBrMe<sub>2</sub>(CH<sub>2</sub>Br)(1,10-phenanthroline)] was obtained from [PtMe<sub>2</sub>(1,10-phenanthroline)] and CH<sub>2</sub>Br<sub>2</sub> <1985OM1406>. The chloride–iodide exchange reaction using NaI in acetone has been used to obtain a bis(iodomethyl)platinum derivative (Equation (117)) <1988OM2082>. Another approach for the synthesis of molecules bearing an α-halo platinum moiety is the transformation of a starting material that already bears such a unit to the desired compound by exchanging one of the ligands <1991JCS(D)949, 1999OM2428>. In this fashion, [Pt(CH<sub>2</sub>Cl)(dppm)(PPh<sub>3</sub>)] (where dppm = Ph<sub>2</sub>PCH<sub>2</sub>PPh<sub>2</sub>) was prepared in 56% yield from [Pt(dppm)(CH<sub>2</sub>Cl)<sub>2</sub>] and triphenylphosphine <1996JOM(517)227>.



The preparation of α-haloalkylplatinum derivatives can be efficiently achieved by the insertion reaction of a diazo compound into a halo-platinum bond <1986OM1171>. When diazomethane is used, the insertion of a methylene unit occurs, leading to the corresponding (halomethyl)platinum derivative in good yield (Equation (118)) <1998JOM(554)105, 2001JOM(617-618)671>. In the case of platinum complexes, the insertion reaction has also been performed utilizing diazo compounds other than diazomethane, allowing the synthesis of α-haloalkylplatinum compounds <1987OM28, 1993OM2445>. Using this approach, Pt(dppe)Cl<sub>2</sub> was reacted with ethyl diazoacetate, giving a platinum(II) chloro ester in 80% yield (Equation (119)) <1991OM2989, 1997OM3083>.



#### 4.03.5.2.5 Derivatives of copper, silver, and gold

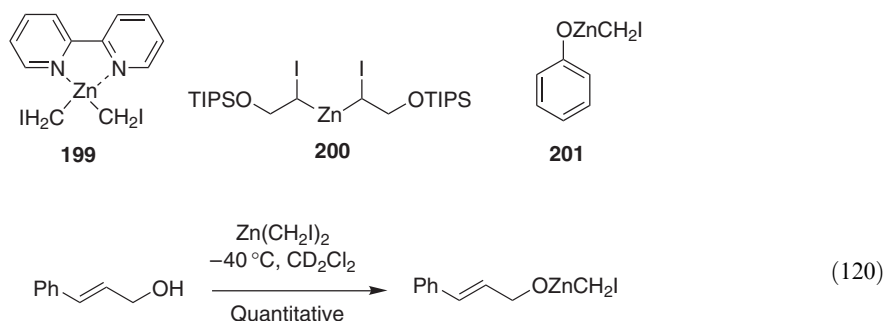
The reaction of chloro complex [AuCl(PPh<sub>3</sub>)<sub>3</sub>] with Mg(CH<sub>2</sub>Cl)Cl led to the corresponding (chloromethyl)gold complex [Au(CH<sub>2</sub>Cl)(PPh<sub>3</sub>)<sub>3</sub>], which furnished [Au(CH<sub>2</sub>I)(PPh<sub>3</sub>)<sub>3</sub>] by chloride–iodide exchange promoted by LiI in the presence of NaOMe and triphenylphosphine <1998ZAAC(624)1303>. The preparation of other α-halo metal derivatives bearing copper, silver, or gold has been previously reviewed <1995COFGT(4)95>.



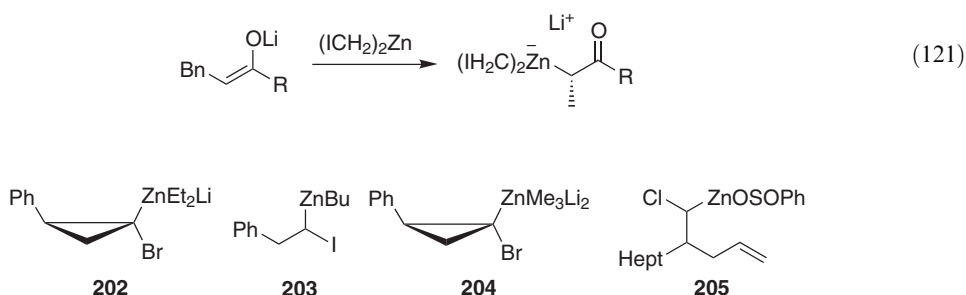
## 4.03.5.2.6 Derivatives of zinc, cadmium, and mercury

The chemistry concerning the synthesis of  $\alpha$ -halozinc derivatives has experienced a great advance in the 1990s. The main reason for this was their use in asymmetric cyclopropanation reactions, motivating the search for new halomethylzinc compounds that could improve the efficiency of the reaction. Some review articles cover several aspects of organozinc compounds, including examples of  $\alpha$ -halozinc derivatives <1993JOC588, 1995SL1197, 2002T9463>. The iodomethyl zinc  $\text{Zn}(\text{CH}_2\text{I})_2 \cdot \text{ZnI}_2$  is the classic Simmons–Smith reagent. Later,  $\text{Zn}(\text{CH}_2\text{I})_2$  was used by Denmark and co-workers in their studies toward diastereoselective cyclopropanation reactions <1992JA2592>. To expand the scope and efficiency of this transformation, Charette and his group investigated the chemistry of several new iodomethyl reagents, including a detailed study of their structure.

Treating diethylzinc with diiodomethane in dichloromethane led to  $\text{EtZnCH}_2\text{I}$  <1995JOC2966, 1996JA4539>. Similarly, the chloromethylzinc carbenoid  $\text{ZnCH}_2\text{Cl}$  was also prepared <2001JA12168>. When  $\text{EtZnCH}_2\text{I}$  was prepared in the presence of an ether such as 18-crown-6, crystals of  $\text{IZnCH}_2\text{I} \cdot 18\text{-crown-6}$  could be grown, which allowed its solid-state structure to be solved by X-ray analysis <1996JA6792>. The preparation of stable iodomethylzinc reagents, such as **199**, was achieved in good yield by treatment of bis(iodomethyl)zinc in dichloromethane with 1,1'-bipyridine <2000JA4508>. Moreover, the cyclopropanation reagent **200** was prepared from the corresponding *gem*-diiodide 1-triisopropylsilyloxy-3,3-diiodopropane and  $\text{Et}_2\text{Zn}$  <1997AG(E)1090>. Other reagents utilized in cyclopropanation reactions are iodomethyl zinc alkoxides, which can be prepared from an alcohol and  $\text{Zn}(\text{CH}_2\text{I})_2$  (Equation (120)) <1995JA11367>. The preparation and solid-state structure of several halomethylzinc alkoxides have also been investigated <2001JA12160, 2002CC466>. Similar reagents are obtained from the treatment of diethylzinc, diiodomethane, and a phenol, leading to phenoxide zinc carbenoids such as **201** <2000AG(E)4539>.



The reaction of a lithium enolate with bis(iodomethyl)zinc led to the formation of a carbon-bound zincate, bearing the iodomethyl unit (Equation (121)) <1996JA11970>. In an analogous manner, several zincate carbenoids, such as **202**, were obtained from the reaction of the corresponding organolithium with a dialkylzinc <1993JOC2958>. Alternatively, a zincate such as **203** may be generated from *gem*-dihalo compounds and dialkylzinc derivatives in the presence of lithium bromide <2000OL2849, 2001SL818>. Furthermore, the carbenoid **204** was formed in a stereoselective manner from 1,1-dibromo-2-phenylcyclopropane and dilithium tetramethylzincate in THF at room temperature <2001JOC300>. The chloride **205** originated from the corresponding *gem*-bis-zinc derivative after reaction with  $\text{PhSO}_2\text{Cl}$  <1993SL665>.

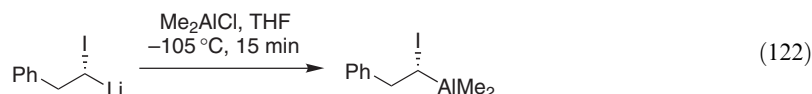


No further advances have occurred in the synthesis of cadmium and mercury derivatives since the publication of chapter 4.03 in <1995COFGT(4)95>.

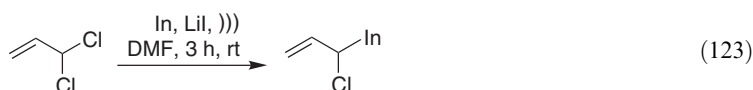
### 4.03.5.3 Group 3 and Group 4 Derivatives— $R_2CHalSnX_3$ , etc.

#### 4.03.5.3.1 Derivatives of aluminum, gallium, indium, and thallium

Treatment of a solution of tri(isobutylaluminum) in dichloromethane at  $-40^\circ\text{C}$  with diiodomethane in the presence of a catalytic amount of oxygen gave  $i\text{-Bu}_2\text{AlCH}_2\text{I}$ , which was directly used in the cyclopropanation of allylic alcohols <2001JOM(617–618)702>. Transmetalation of an  $\alpha$ -halolithium derivative to the corresponding dimethylaluminum derivative has been performed using dimethylaluminum chloride (Equation (122)) <1999CEJ337>. The formation of other  $\alpha$ -haloaluminums, as well as  $\alpha$ -halothalliums and  $\alpha$ -halogalliums, have been reported, as previously reviewed <1995COFGT(4)95>.

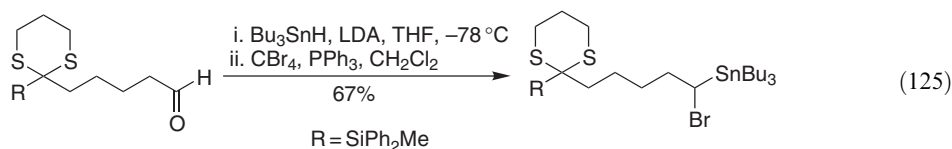
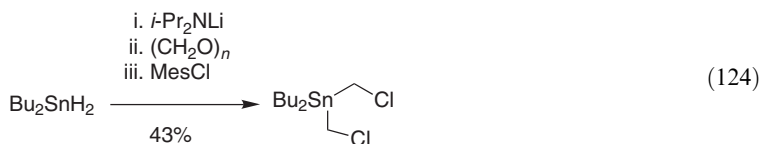


The preparation of  $\text{Br}_2\text{InCH}_2\text{Br}$  has been described by treating indium(I) bromide with an excess of dibromomethane in acetonitrile. Similarly,  $\text{Br}_2\text{In}(\text{dioxane})_2\text{CH}_2\text{Br}$  and  $\text{Br}_2\text{In}(\text{THF})_2\text{CH}_2\text{Br}$  were also obtained <1999OM99>. Reaction of  $\text{Br}_2\text{InCH}_2\text{Br}$  with  $\text{Et}_4\text{NBr}$  gave  $[(\text{Et}_4\text{N})][\text{Br}_3\text{InCH}_2\text{Br}]$ , in 95% yield <1999OM99>. The preparation of  $\text{Br}_2\text{In}[\text{OPPh}_3]_2\text{-CH}_2\text{Br}$  from  $\text{Br}_2\text{In}(\text{dioxane})_2\text{CH}_2\text{Br}$  and triphenylphosphine oxide was also described <2001JOM(626)68>. The reaction of a *gem*-dichloride with indium powder led to the formation of  $\alpha$ -haloindium, which was reacted *in situ* with carbonyl compounds (Equation (123)) <1996T2803>.



#### 4.03.5.3.2 Derivatives of tin

Several approaches can be utilized for the synthesis of  $\alpha$ -halo tin derivatives, as previously reviewed <1995COFGT(4)95>. In the 1990s, only a few new methods and/or examples have been reported. Bis(chloromethyl)dibutyltin can be prepared by metallation, followed by addition of electrophile (Equation (124)) <1994OM24>. The introduction of the bis(chloromethyl) unit has also been achieved treating tin tetrachloride with diazomethane in toluene, leading to  $\text{Cl}_2\text{Sn}(\text{CH}_2\text{Cl})_2$  in 85% yield. When the latter compound was submitted to the same conditions,  $\text{Sn}(\text{CH}_2\text{Cl})_4$  was obtained in 40% yield. Hydrolysis of the stannane  $\text{Cl}_2\text{Sn}(\text{CH}_2\text{Cl})_2$  in benzene gave  $[\text{Cl}(\text{CH}_2\text{Cl})_2\text{SnOSn}(\text{CH}_2\text{Cl})_2\text{Cl}]_2$ , in good yield <2002JOM(646)138>. The geminal dizinc derivative  $\text{CH}_2(\text{ZnI})_2$  promoted the methylenation of  $\text{Me}_3\text{SnCl}$  in THF, giving  $\text{Me}_3\text{SnCH}_2\text{I}$  in 26% yield <1994JOC2668>. The synthesis of some (1-bromoalkyl)tributyltin derivatives has been described by transformation of an  $\alpha$ -hydroxy tin intermediate into the corresponding bromide by reaction with  $\text{CBr}_4/\text{PPh}_3$  (Equation (125)) <1995CC981, 1999OL945, 2001JOC8983>. Treatment of tributyltin hydride with LDA and paraformaldehyde gave (hydroxymethyl)tributyltin, which was transformed into the bromo and iodo derivatives using  $\text{CBr}_4/\text{Ph}_3\text{P}$  and  $\text{NIS}/\text{Ph}_3\text{P}$ , respectively <1994SC1117>.



## 4.03.5.3.3 Derivatives of lead

No further advances have occurred in this area since the publication of chapter 4.03 in <1995COFGT(4)95>.

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## Biographical sketch



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## 4.04

# Functions Bearing Two Oxygens, $R_2C(OR^2)_2$

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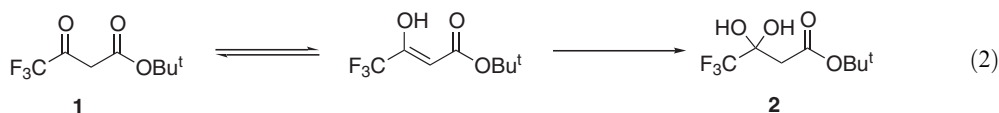
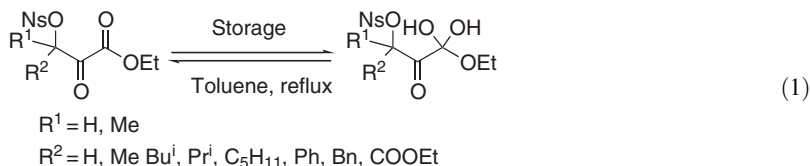
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#### 4.04.1 $\alpha$ -DIOLS— $R_2C(OH)_2$

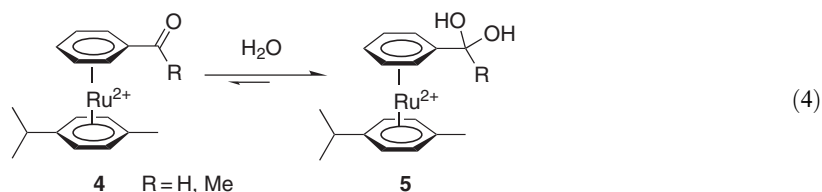
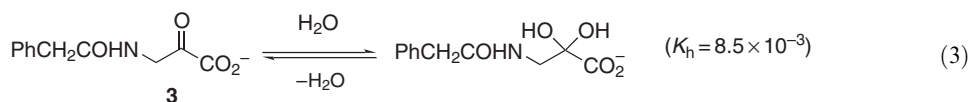
The addition of water or an alcohol to a ketone, giving, respectively, a hydrate or hemiacetal, is an equilibrium that generally favors the starting materials. The unstable tetrahedral adducts, however, can often be isolated or spectroscopically detected when one of the following criteria is met: the addition of water or alcohol relieves strain, a strong electron-withdrawing substituent, such as a polyhalogenated derivative, stabilizes the hydrate or hemiketal, or a carbonyl function is adjacent to the position to be attacked. For example, upon storage, sterically unencumbered nosylates (Ns = *p*-nitrobenzenesulfonate) are readily hydrated (Equation (1)) <1997JOC2458>, and when *t*-butyl trifluoroacetoacetate **1** was left without protection from atmospheric moisture, solid hydrate **2** was formed (Equation (2)) <1997CC359>.



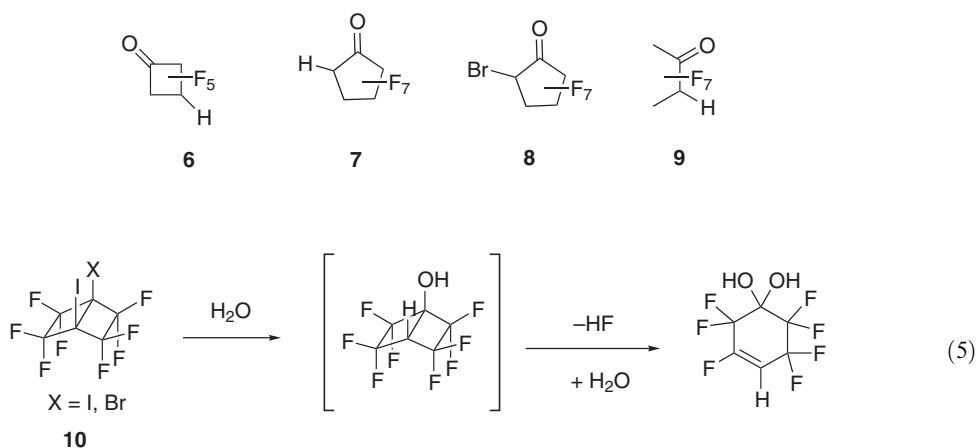
##### 4.04.1.1 $\alpha$ -Diols by Hydration of Carbonyl Compounds Bearing Electron-withdrawing Groups

Numerous studies have been conducted to determine the equilibrium constants and rates of hydration for carbonyl compounds bearing electron-withdrawing substituents. The hydration constant,  $K_h$ , of 3-(phenylacetamido)pyruvic acid **3** in organic solvents has been reported as  $8.5 \times 10^{-3} \text{ M}^{-1}$  (Equation (3)) <1997JOC4479>. Although modest, this value is larger than that of pyruvate ( $1.3 \times 10^{-3} \text{ M}^{-1}$ ), which is reasonable in view of the electron-withdrawing amido substituent present in the amido acid. The greater electron-withdrawing ability of the trifluoromethyl functionality, however, results in a hydration constant for trifluoroacetoacetic acid of  $2.90 \times 10^3 \text{ M}^{-1}$  <1999JA8345>. Remarkably, dissolving the (bis)arene ruthenium complex **4** in wet solvents also led to its clean conversion into the new hydrated (bis)areneruthenium complex **5**, as evidenced by the absence of an aldehyde resonance and the presence of a new proton nuclear magnetic resonance (NMR) at 6.16 ppm (Equation (4)) <2003JA1188>. This provides the first example of the highly electronegative character of the aromatic rings in the dicationic bis(arene)-ruthenium complexes extending to substituents attached to the arene rings. The astonishing equilibrium constant for the hydration of **4**, where  $R = \text{H}$ , was reported to be approximately  $1.1 \times 10^4 \text{ M}$ .

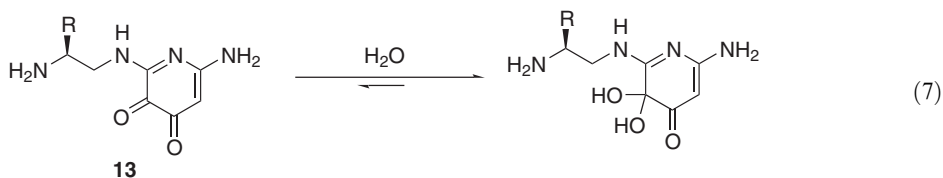
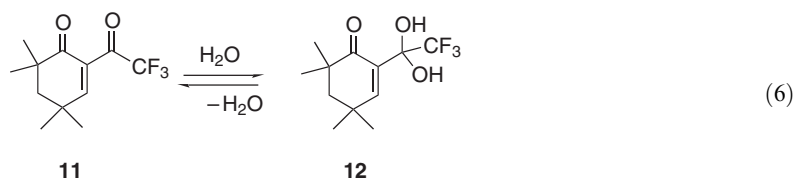




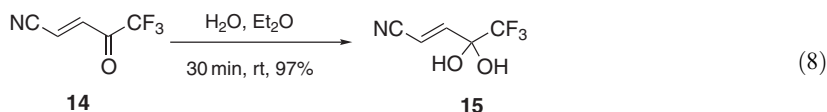
Polyfluorinated carbonyl compounds, such as **6–9**, add water readily to form hydrates. Such hydration has been found to be considerably more favorable in cyclic rather than acyclic systems with quantum mechanical calculations indicating that this difference can be attributed to the steric hindrance in the acyclic adducts <1996TL9165>. An alternative approach for the synthesis of the hydrate of ketone **8** involves bromination of an enol followed by hydrolysis <1996JOC5109>, while hydrated **6** may be synthesized by hydrolysis of the corresponding oxime <1996JA2556>. Following loss of hydrogen fluoride in the presence of  $\text{H}_2\text{O}$ , perhalogenated bicyclic compounds, such as **10**, are readily hydrated (Equation (5)) <1996JA9454>.



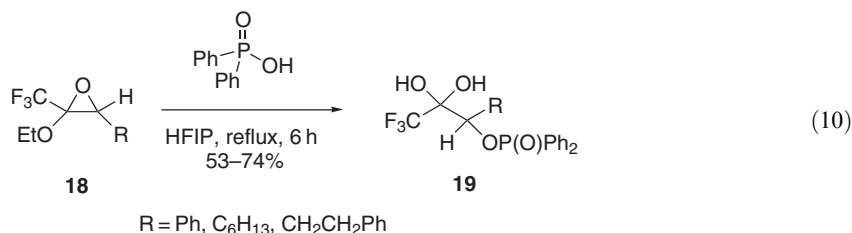
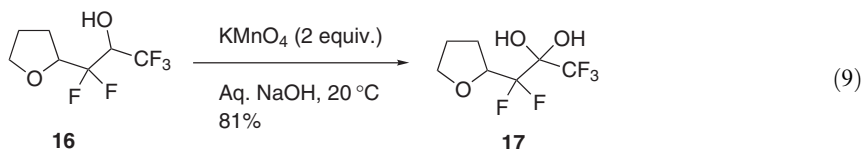
Trifluoroacetyl enone **11** also readily adds  $\text{H}_2\text{O}$ , or  $\text{MeOH}$ , to afford hydrate **12** or the hemiacetal, respectively (Equation (6)) <2001HCA3818>. The quantitative formation of these  $\text{C}=\text{O}$  addition products becomes evident from the NMR spectrum with the signal of the C-atom adjacent to the  $\text{CF}_3$  group shifting from 185 ppm ( $\text{C}=\text{O}$ ) to values of around 95 ppm. Diketone derivative **13**, formed by the hydrolysis of the corresponding imine, exists primarily in its hydrated form (Equation (7)) <1995JA10203>.



Acyclic hydrated ketones bearing perhalo groups are abundant. For example, after treatment with hydrochloric acid in water, the HCl salts of *N*-protected amino trifluoromethyl ketones are easily isolated <2000JOC3241>.  $\alpha$ -Halo pyruvamides are similarly hydrated by heating in  $H_2O$  at  $60^\circ C$  for 1 h <1997T13739>, while liquid  $\beta$ -cyanovinyl trifluoromethyl ketone **14** is readily hydrated in the presence of water to give **15** (Equation (8)) <2002S71>.

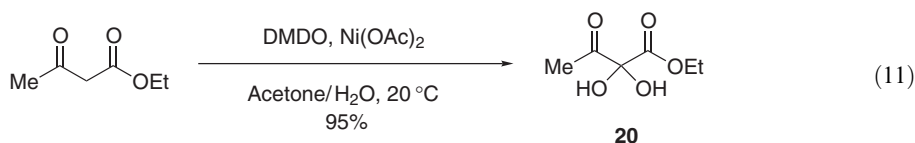


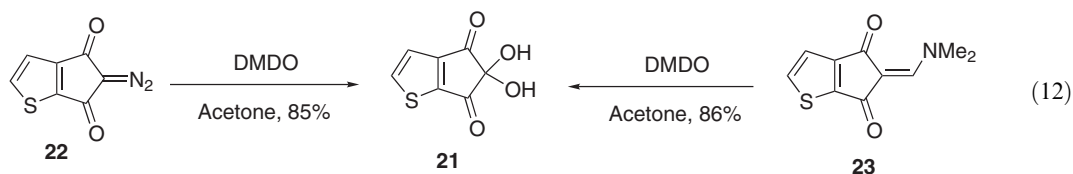
Indeed, the ease of hydrolysis of many polyhalogenated ketone derivatives is best reflected by their preferential isolation after other organic transformations. For example, the Claisen condensation of phenylpropionitriles with ethyl trifluoroacetate using lithium diisopropylamide (LDA) afforded  $\beta$ -ketonitriles in their more stable hydrated form <2002TL9233>, while treatment of *N*-methanesulfonylpiperidine with butyllithium in tetrahydrofuran (THF) at  $-78^\circ C$  to  $-30^\circ C$ , followed by addition of ethyl trifluoroacetate, yielded trifluoroacetylated methanesulfoamide in its hydrated form <1997S866>. Similarly, 4-hydroxy-1,1,1,3,3-pentafluoro-2-hexanone hydrate may be synthesized by the aldol-type reaction between lithium pentafluoropropen-2-olate and propionaldehyde <1999OS151>. Oxidation of tetrahydrofuran derivative **16** with  $KMnO_4$  also gave the hydrated ketone **17** in good yield (Equation (9)) <1995TL6091>. Ring opening of epoxide **18** with diphenylphosphoric acid in a refluxing solution of hexafluoropropan-2-ol, similarly resulted in the isolation of hydrated ketone adducts **19** in yields of 53–74% (Equation (10)). Ring opening of the epoxide with other nucleophiles, however, gave only ketone derivatives <2002EJO3402>.



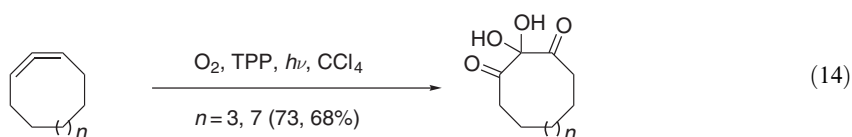
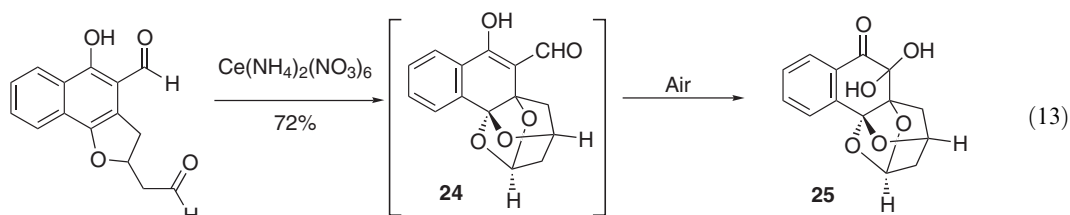
#### 4.04.1.2 $\alpha$ -Diols by Oxidation of Active Methyl or Methylene Groups

In the late 1990s and early 2000s, dimethyldioxirane (DMDO) has become an increasingly versatile oxidizing reagent. A highly efficient nickel(II)-catalyzed oxidation of 2-alkylated 1,3-dicarbonyl substances to the corresponding hydroxy derivatives by DMDO has been described <1996T5799>. This procedure may be adapted to the synthesis of *gem*-diols such as **20** (Equation (11)). Alternatively, DMDO has been used in the synthesis of thianinhydrin **21**, either by oxidation of diazodione **22** or enamine **23** (Equation (12)) <1997T4239>. Sodium periodate has also been used to oxidize enamines flanked by two carbonyl derivatives <1996JOC1872>.



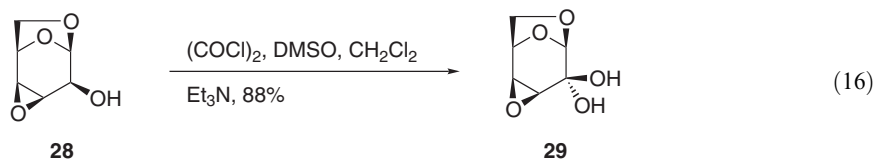
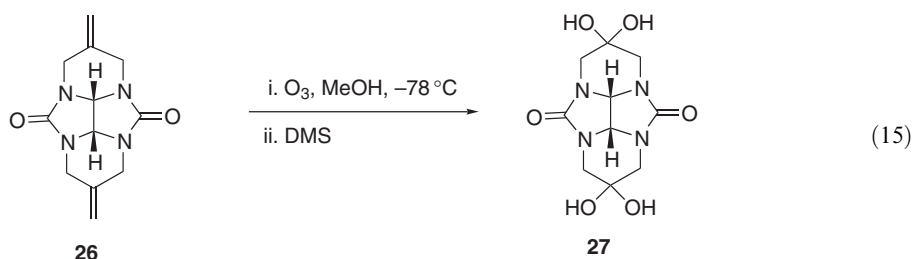


A noteworthy, but somewhat more substrate specific reaction, is the autooxidation of enol **24** to diol **25** (Equation (13)) <1998T14053>. Examples of autooxidation of simple enols have been documented in the literature, and the intermediacy of four-membered cyclic peroxy hemiacetals in the cleavage step has also been noted. Acetal **24** was itself synthesized via an intramolecular spiroacetalization, followed by intramolecular conjugate addition. The unprecedented photooxidation of cyclic allenes gives rise to cyclic 1,2,3-trione hydrates (Equation (14)) <2000OL1383>. The formation of these compounds points to a novel photooxidation mechanism involving both singlet and triplet oxygen.

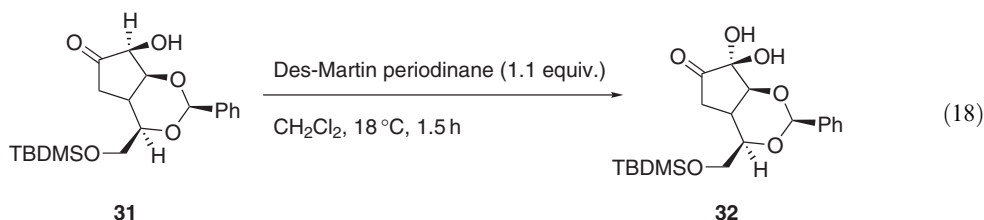
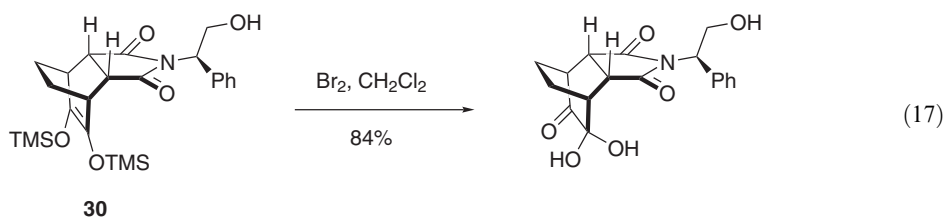


#### 4.04.1.3 $\alpha$ -Diols from Strained Cyclic Ketones

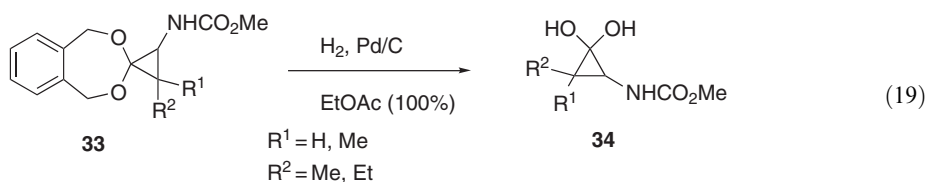
Highly strained, cyclic ketone derivatives are particularly susceptible to nucleophilic attack, as illustrated by the ozonolysis of **26** leading to the preferential isolation of hydrated adduct **27** (Equation (15)) <1999TL447>. During the synthesis of the two lactones from levoglucosenone, oxidation of the hydroxyl group of **28** under Swern conditions also gave 3,4-dianhydro- $\beta$ -D-lyxo-hexopyranos-2-ulose **29** as the hydrated adduct (Equation (16)) <1995BCJ670>.



The combination of adjacent diketone moieties in cyclic ring systems further favors the formation of *gem*-diols. Oxidation of **30** with bromine afforded the hydrated ketone in good yield (Equation (17)) <2000JA7811>, while oxidation of **31**, using Des-Martin periodinane, gave ketone hydrate as the major product **32** (Equation (18)) <1998JCS(P1)3141>. Minor amounts of a regioisomer that is presumed to be derived from silyl group migration was also observed in this reaction.



Although the hydrogenolytic removal of the *o*-oxalyl protecting group in substrates analogous to **33** has been previously discussed, liberation of the free cyclopropane **34** may also be achieved with Pd/C (Equation (19)) <2001TL3183>. It is anticipated that cyclopropanes such as **34** will act as transition state analog inhibitors of hydrolytic enzymes.

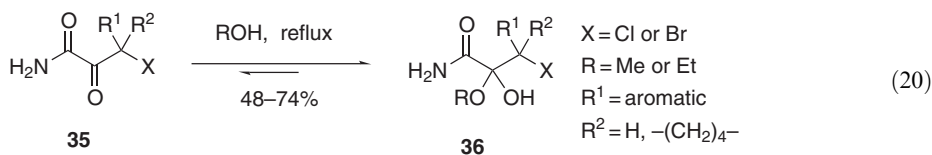


#### 4.04.2 HEMIACETALS— $R^1C(OH)OR^2$

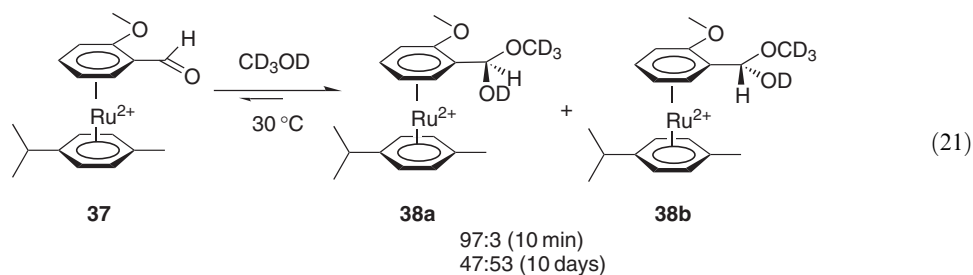
##### 4.04.2.1 Hemiacetals from Aldehydes and Ketones by Addition of Alcohols

###### 4.04.2.1.1 Acyclic hemiacetals

Electron-withdrawing groups adjacent to a ketone are frequently used to stabilize acyclic hemiacetals. For example,  $\beta$ -cyanovinyl trifluoromethyl ketone readily adds MeOH to give the corresponding hemiacetal in 30 min <2002S71>, while refluxing racemic pyruvamide **35** in the appropriate solvent yields stable hemiketal **36** exclusively as one diastereomer after selective crystallization (Equation (20)) <1997T13739>.



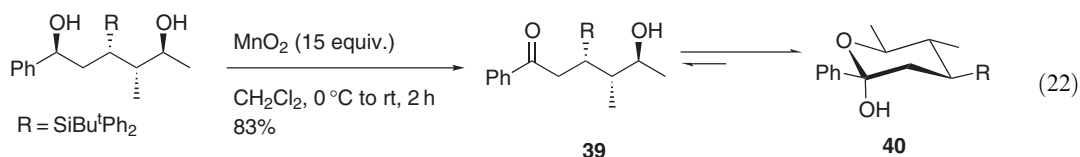
In a manner analogous to that previously discussed for the synthesis of  $\alpha$ -diols, acyclic hemiacetals may be synthesized by the addition of methanol to dicationic bis(arene) ruthenium complexes. To assess the stereoselectivity of the carbonyl addition reaction, the *o*-anisaldehyde complex **37** was reacted with  $CD_3OD$  at 30 °C, which gave within 10 min, two diastereomeric hemiacetal complexes, **38a** and **38b**, with a de of 94% (Equation (21)) <2003JA1188>.



#### 4.04.2.1.2 Cyclic hemiacetals from hydroxy carbonyl derivatives

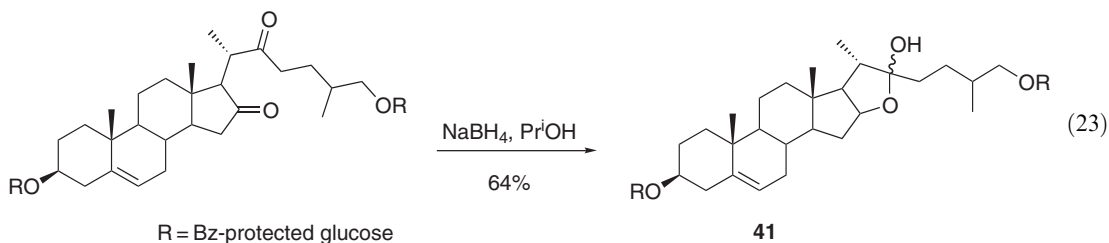
##### (i) By oxidation of diols

Manganese dioxide is a mild and selective oxidizing reagent for the oxidation of one hydroxy group in the presence of another. This is illustrated in the synthesis of the  $C_{33}$ – $C_{38}$  fragments of Amphotericin B and Nystatin, whereby the benzylic hydroxyl was selectively oxidized (Equation (22)). Through the intermediacy of ketone **39**, hemiacetal **40** was derived in 83% yield <1998SL201>.



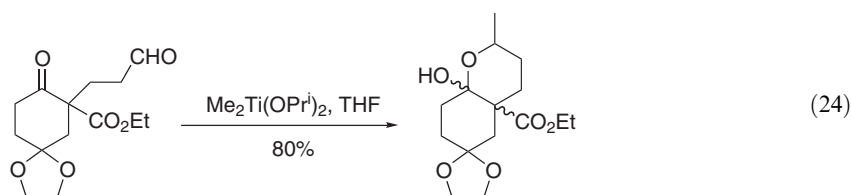
##### (ii) By reduction of dicarbonyl derivatives

Although  $\text{NaBH}_4$  is frequently used for the reduction of symmetrical dicarbonyl compounds, it may also be used for the selective reduction of one carbonyl derivative in the presence of another, as illustrated by the well-reported reduction of the 16-ketone of the cholestan-16,22-dione. Such intramolecular hemiacetal formation has been applied in the synthesis of furostan **41** (Equation (23)) <2001TL77>.



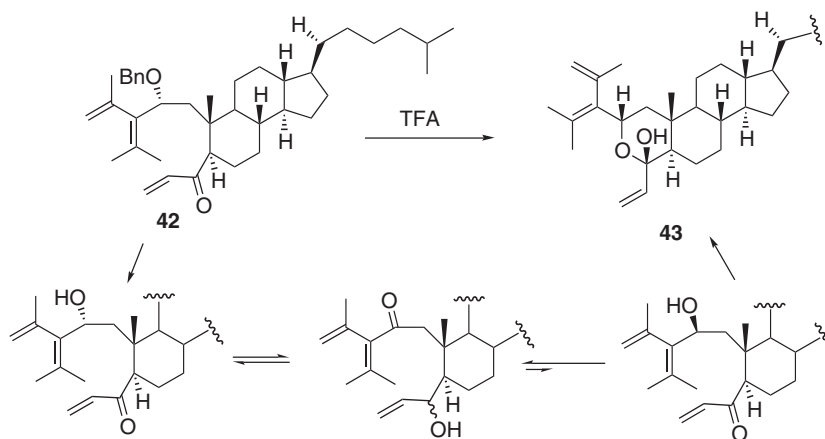
##### (iii) By addition of carbanions to dicarbonyl derivatives

The selective alkylation of an aldehyde in the presence of a ketone provides a convenient means to synthesize hemiacetal derivatives (Equation (24)). Here the aldehyde is methylated, using an excess of  $\text{Me}_2\text{Ti}(\text{O}i\text{-Pr})_2$ , giving rise to four cyclic hemiacetals. The major isomer ( $2R^*$ ,  $4aR^*$ ,  $8aS^*$ ) was, however, easily separated by flash chromatography <1995HCA663>.



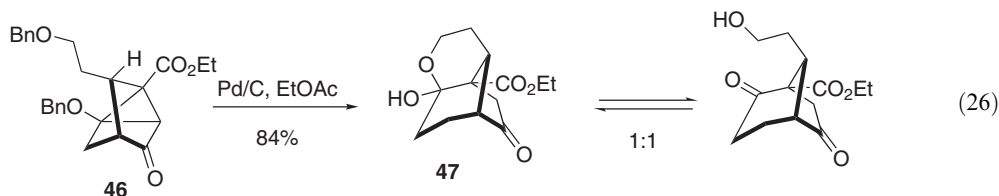
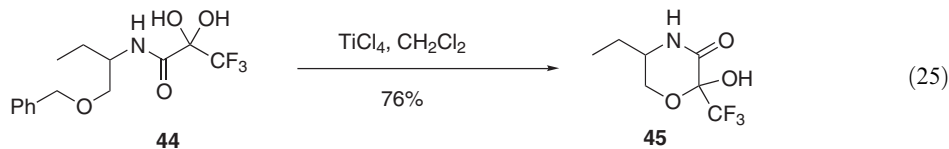
## (iv) Miscellaneous methods for the generation of hydroxy carbonyl derivatives

Numerous natural product syntheses involve the formation of hemiacetals via the cyclization of an unmasked hydroxy or phenoxy group in the presence of a carbonyl functionality. The deprotection of silyl ethers using tetrabutylammonium fluoride or hydrogen fluoride, followed by intramolecular hemiacetal formation, is particularly common in the synthesis of many natural products such as apoptolidin <2000OL1439>, the callipeltoside A aglycons <2002AG(E)841>, the acyl side chain segment of polyoxypeptin A <2002TL9391>, and the C(19)–C(27) fragment of rifamycin S <2001OL481>. Deprotection of an acetate group using a solution of sodium methoxide in methanol was a key step during studies toward the synthesis of brevetoxin/ciguatoxin <2002T1921>, while debenzoylation, followed by hemiacetal cyclization, was the final step in the synthesis of isofebrifugine <2001OL477> and the B-ring system of Taxol <1995CL181>. Surprisingly, during studies into the synthesis of the AB subsection of the taxanes, the treatment of benzylate derivative **42** with trifluoroacetyl (TFA) or with  $Zn(OTf)_2$  gave, via a reversible 1,5-hydride migration, hemiacetal **43** in 40–45% yield, Scheme 1 <1995TL1015>.



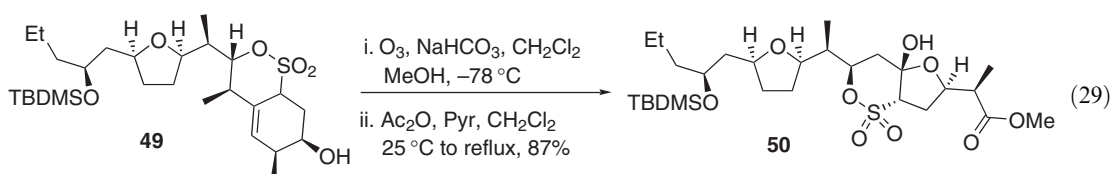
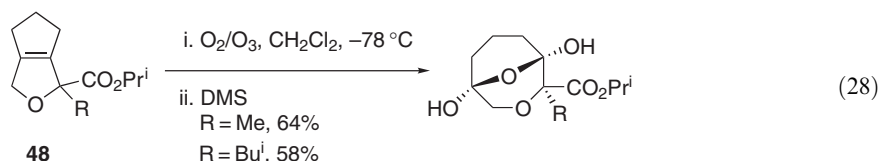
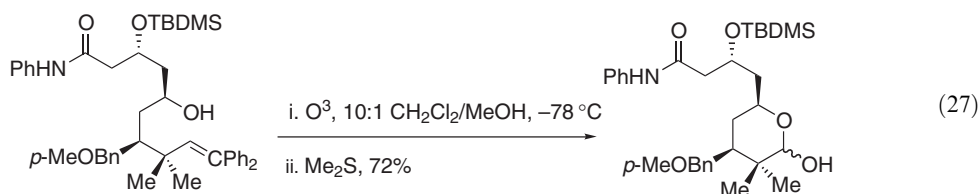
Scheme 1

Alternative examples include the debenzoylation of fluoro-pyruvamide **44** with titanium tetrachloride to form the new morpholine derivative **45** as a single diastereomer (Equation (25)) <1998T3799>. Upon hydrogenation with Pd/C, the highly strained tricyclo[3.2.1.0]octane **46** underwent concurrent debenzoylation and ring expansion to form hemiacetal **47** (Equation (26)) <2001T997>. Similarly, the collective acid hydrolysis of both an imine-protected carbonyl and a silyl-protected hydroxyl moiety lead to the formation 2,2-dichloro-5-hydroxypentan-2-one in a 14:86 equilibrium mixture with its cyclic form <1996S1131>.

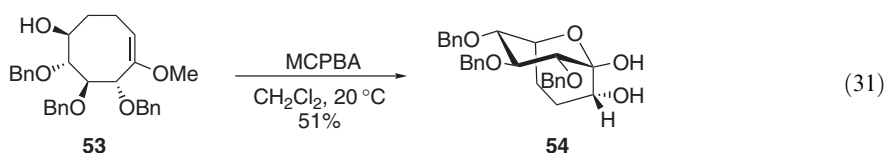
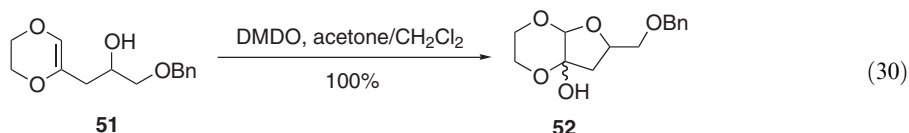


Numerous oxidative strategies have been adapted for the synthesis of hemiacetals. Ozonolysis can be used to generate a ketone moiety to participate in intramolecular cyclization with a neighboring hydroxyl group (Equation (27)) <1999JA7540>. Similar methods have been applied to the synthesis of sialic acid derivatives <2000OL2003, 2000SL865>. Interesting variations on

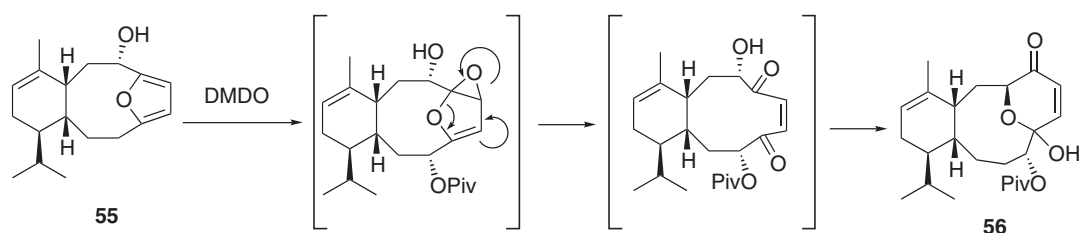
this method include the ozonolysis of dihydrofurans **48** (Equation (28)) <2001OL861>, while ozonolysis of sultone **49**, followed by eliminative work-up, delivered the expected hemiacetal **50** as a single stereoisomer in excellent yield (Equation (29)) <2000TL7629, 1998EJO2073>.



The epoxidation of an olefin followed by the intramolecular attack of a hydroxy nucleophile is another versatile method for the synthesis of hemiacetals. Epoxidation of homoallylic alcohol **51** with dimethyldioxirane afforded tetrahydrofuran derivative **52** as a mixture of diastereomers (Equation (30)) <1995TL6475>. Similarly, the stereoselective epoxidation of cyclooctene **53** with 3-chloroperoxybenzoic acid (MCPBA), followed by acid-catalyzed intramolecular ring-closure, led to the isolation of L-idose analog **54** (Equation (31)) <2001TL1769>.

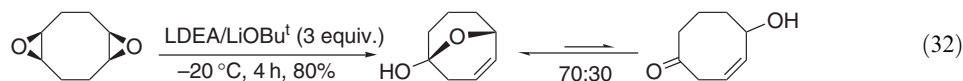


The regioselective epoxidation of furan derivatives such as **55**, followed by bond reorganization leading to pyranose derivatives of the type **56** (Scheme 2), has become a popular means by which to synthesize the core structures of many natural products <1998AG(E)185, 1999T3553, 2002EJO3974>. The free hydroxyl group accelerates oxidation of the proximal furan and yields for these reactions are typically good (76–93%). Similar oxidative ring expansions may be conducted using Achmatowicz conditions (*N*-bromosuccinimide (NBS)/THF/H<sub>2</sub>O) <2000OL863>. Another interesting adaptation of epoxides in the synthesis of hemiacetals

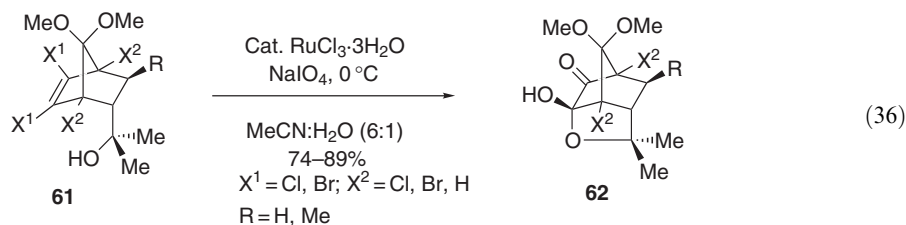
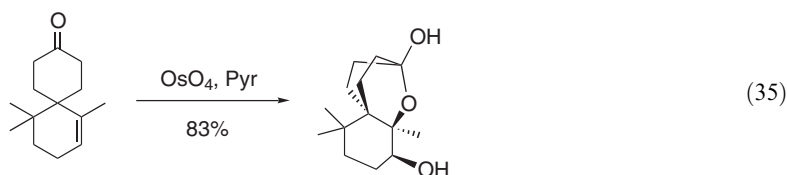
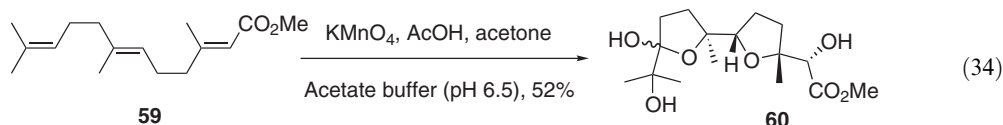
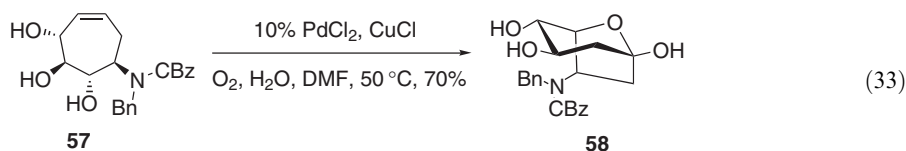


Scheme 2

involves the base induced rearrangement of *cis,cis*-1,5-cyclooctadiene dioxide (Equation (32)) <1997T1855>. Using a mixed lithium diethylamine/*t*-butoxide system, this method was successfully applied in the synthesis of functionalized bicyclo[3.3.0]octanes <2001OL441>.

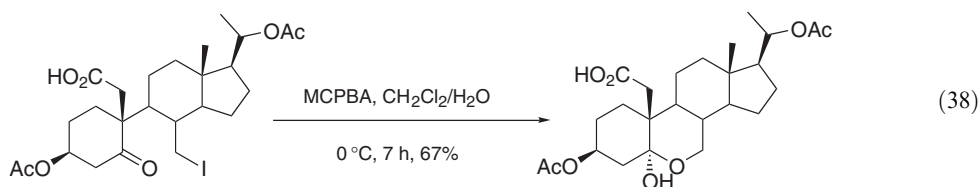
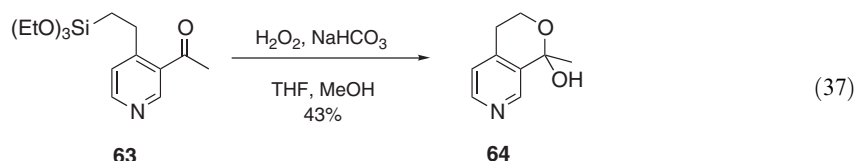


The versatility of alkenes as precursors in the synthesis of hemiacetals is further exemplified by the regioselective Wacker oxidation of cycloheptene **57** to yield hemiacetal **58** in 70% yield (Equation (33)) <2003JOC2115>. The potassium permanganate oxidation of 1,5,9-trienes, commencing with a kinetically controlled attack of the C=C bond of the  $\alpha,\beta$ -unsaturated ester **59**, provides lactol **60** as a 6:1 mixture of epimers (Equation (34)) <2000CC1735>. Additionally, osmium tetroxide has been used to dihydroxylate olefins, which in the presence of a carbonyl group cyclize to form hemiacetals, as illustrated during the synthesis of laurencial (Equation (35)) <1998T1395> or the C-ring of Taxol <1995JOC7849>. Oxidation of bicyclic derivatives **61** with catalytic RuCl<sub>3</sub> and NaIO<sub>4</sub> yields  $\alpha$ -keto hemiacetal **62** in good-to-high yields (Equation (36)) <2002JOC3783>. It has also been illustrated that Hyperforin, which contains a 1,3-diketone functionality and exists as a mixture of interconverting tautomers, is extremely easy to oxidize by MCPBA at the enolate double bond. The newly formed hydroxyl subsequently attacks a neighboring ketone to give a hemiacetal in 100% yield <2002MI433>.

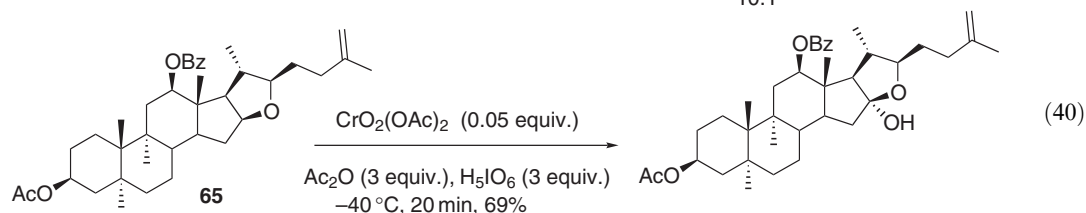
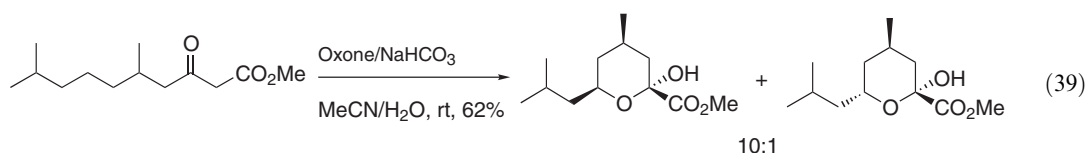


Although less prevalent, there are nevertheless numerous oxidative strategies for the synthesis of hemiacetals from nonalkene precursors. For example, the (EtO)<sub>3</sub>Si substituent in **63** was oxidatively removed to afford hemiacetal **64** in 43% yield (Equation (37)) <1997TL5737>, while the periodate cleavage of a 1,2-diol, followed by intramolecular nucleophilic attack on the newly formed carbonyl by a hydroxy substituent, was the final synthetic step in the synthesis of roflamycoin <1997JA2058>. Dimethyldioxirane has also been successively used to oxidize the benzyl ether carbon of flavinoids. This method is of interest as it shows opposite selectivity to that of other reagents that reportedly perform the oxyfunctionalization on the C-4 benzylic carbon <1997TL4651>. The oxidative cyclization of iodo ketones may also yield hemiacetals, as illustrated in the synthesis 6-oxa-5 $\alpha$ -pregnane (Equation (38)) <1996JOC6673>. Oxidation of the iodide to the highly labile iodoso intermediate, followed by displacement by the neighboring ketone to form an oxocarbenium ion and subsequent nucleophilic attack by H<sub>2</sub>O from the axial side, gives intermediate 5 $\alpha$ -hydroxy-6-oxasteroid in 67% yield.

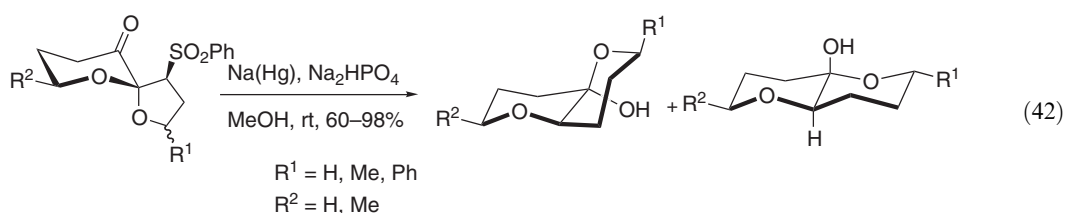
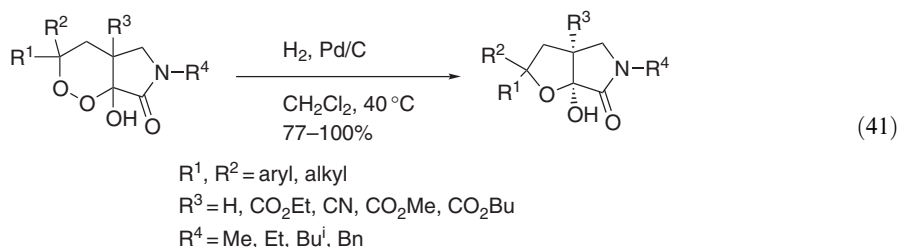




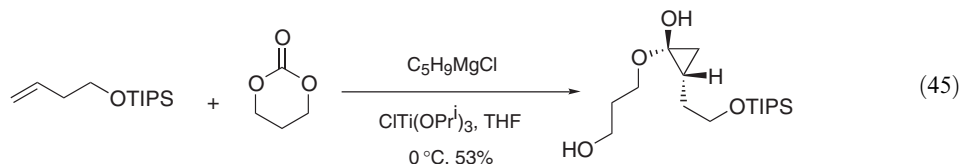
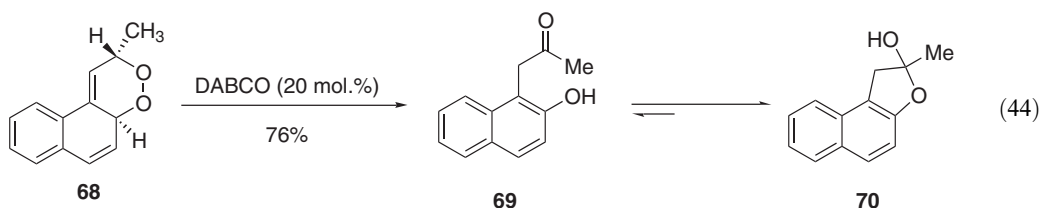
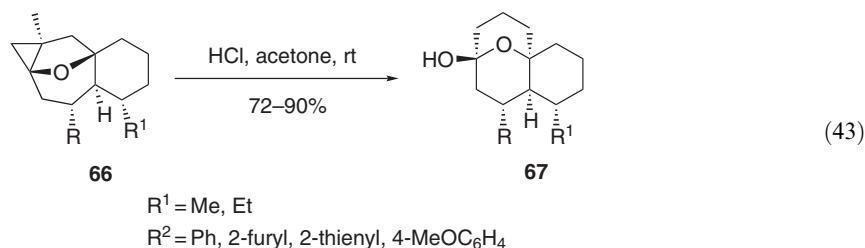
The stereoselective oxidation of unactivated C—H bonds represents a unique method for synthesizing hemiacetals. With oxone as an oxidizing agent, regioselective oxidation at a site  $\delta$  to that of a keto group affords a mixture of *trans*-hemiacetal and *cis*-hemiacetal (Equation (39)) <2003JA158, 2000JOC4179>. Alternatively, Cr[IV] can effect certain C—H oxidations, as illustrated by the unprecedented chemoselective oxidation of ether **65** (Equation (40)) <2002JA13978>. One other example has been reported, an unsaturated derivative, which provides the analogous epoxy hemiacetal in 66% yield <2002JA13978>.



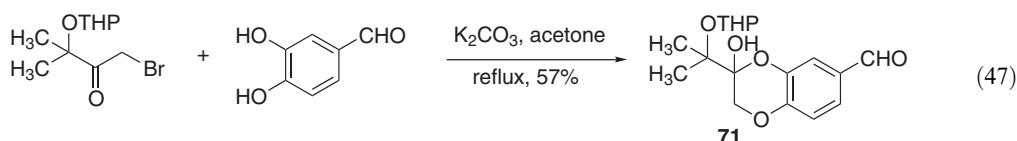
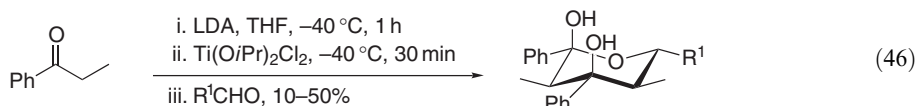
Reductive strategies may also be used for the synthesis of hemiacetals. Palladium on carbon catalyzes the reduction of azabicyclic peroxides under a hydrogen atmosphere to give the corresponding 7-aza-2-oxabicyclo[3.3.0]octan-8-ones in almost quantitative yields (Equation (41)) <1999TL3765>. 1,6-Dioxadecalins may be synthesized by the desulfonation of phenylsulfonyl[4,5] spiroketals. This process involves Na(Hg) desulfonation, cleavage of the axial  $\text{C}_5\text{—O}_1$  bonds to form diastereoselective enones, further *in situ* reduction of the conjugated double bond, and cyclization to the most stable *cis*- or *trans*-fused hemiacetal (Equation (42)) <1996TL3179>.



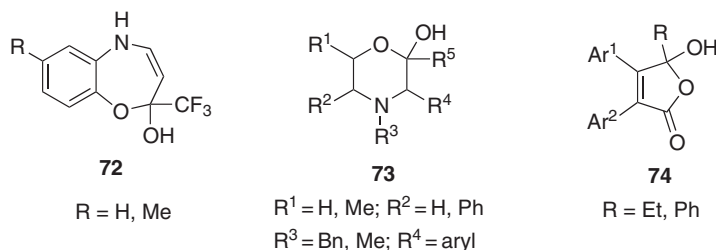
Cyclopropanes such as **66** may undergo acid-catalyzed ring expansion to afford eight-membered hemiketals **67** in good yield (Equation (43)) <2002JA9056>. The cyclopropane is synthesized in four steps from an alkenyl Fischer carbene with high enantioselectivity. Treatment of dioxane **68** with a base, such as 1,4-diazabicyclo[2.2.2]octane (DABCO), led to the rapid formation of ketone **69** that exists in equilibrium with hemiacetal **70** (Equation (44)) <1999T14739>. Alternatively, the mild decomposition of various  $\alpha$ -diazo carbonyl compounds in the presence of clay or zeolite catalysts yields 3-furanones in good yields <2002SL407, 2001TL5113>. More specifically, cyclopropane hemiacetals may be synthesized by using the Ti(II)-mediated coupling of monosubstituted olefins with carbonate derivatives (Equation (45)) <1996JOC4878>. While reaction yields are modest, a broad range of functional groups can be conveniently introduced and the specific example shown is produced as a single diastereomer.



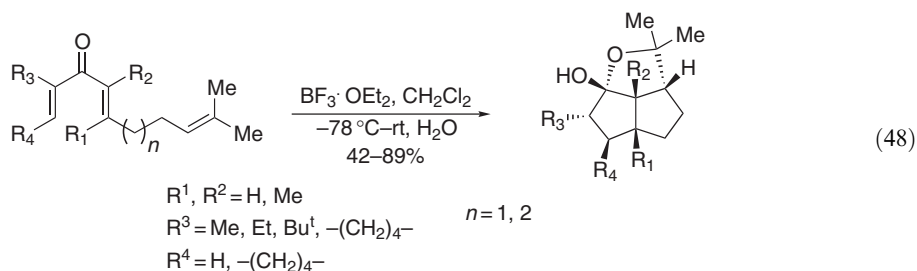
Hemiacetals may also arise as a consequence of aldol-type reactions. Tetrahydropyran-2,4-diols can be synthesized stereoselectively by a Ti(O*i*-Pr)<sub>2</sub>Cl<sub>2</sub>- <1999EJO2007> or ZnBr<sub>2</sub> <2001SL1992>-mediated domino aldol reaction (Equation (46)). A large number of aldehydes have been studied and reported. 5-Deoxy ketose derivatives may also be synthesized in modest yields from a one-pot 2-deoxyribose-5-phosphate aldolase and fructose-1,6-diphosphate aldolase catalyzed reactions <1995JA2947>. Alternative aldol-type reactions include the formation of dioxane derivative **71** in 57% yield after reaction of an  $\alpha$ -bromoketone with 3,4-dihydroxybenzaldehyde (Equation (47)) <1996TL7955>.



Other condensation-type reactions include the synthesis of oxazapines, such as **72**, synthesized via the condensation of 1,1,1-trifluoro-3-(isobutoxymethylene)-2-propanones with aromatic *o*-hydroxylamines under microwave irradiation conditions <1997T5847>. 2-Hydroxymorpholines **73** may be prepared through a three-component, one-pot, Petasis reaction involving the coupling of a 1,2-amino alcohol, a boronic acid, and a glyoxal derivative <2001TL3591>, while 5-alkyl(aryl)-5-hydroxy-3,4-diarylfuranones **74** are synthesized in good yields via a tandem esterification and oxidative cyclization process <2002TL8715, 2002SL947>.



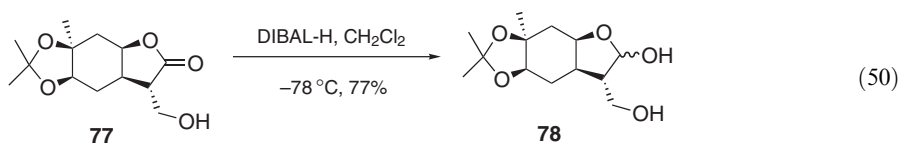
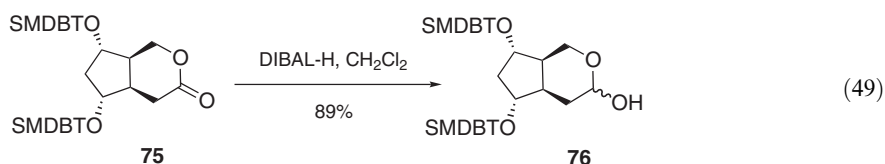
There are numerous other methods for the formation of hemiacetals, although many of these are substrate specific. Examples include the first synthesis of *cis,cis,cis,trans*-[5.5.5.5]-fenestranes using a novel lead tetraacetate mediated ring expansion of a bicyclo[3.3.0]octane subunit <1996TL7687>, studies toward the synthesis of the reduced furanochroman subunit involving cleavage of a silyl ether with concomitant retro-aldol reaction and epoxide ring opening to provide, upon cyclization, the desired hemiacetal <2000OL2507>; the preparation of trifluoromethyl lactol derivatives via base-induced cyclobutanol ring opening <1996SL57>, and the highly diastereoselective cycloisomerization of acyclic trienones, based upon the Nazarov reaction (Equation (48)) <1998JOC2430>. Finally, a nickel-catalyzed carbonylation of  $\alpha$ -keto alkynes under phase-transfer conditions affords unsaturated hydroxy lactones in the absence of sterically demanding groups on the keto function <1995OM5438>.



#### 4.04.2.2 Hemiacetals from Esters

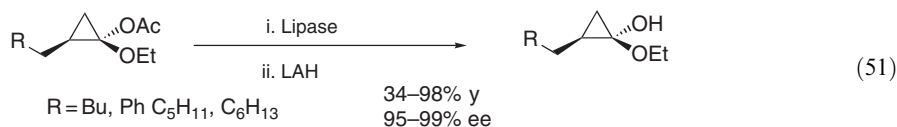
##### 4.04.2.2.1 By reduction

Ddiisobutylaluminum hydride (DIBAL-H) remains a popular reagent for the reduction of lactones. Reduction of lactone **75** in methylene chloride at  $-78^\circ\text{C}$ , followed by acidic work-up, afforded a mixture of lactol epimers **76** in 89% yield (Equation (49)) <1997TL3339>. Similarly, DIBAL-H reduction of lactone **77** yielded lactol **78** in 77% yield (Equation (50)) <1997TL3817>.



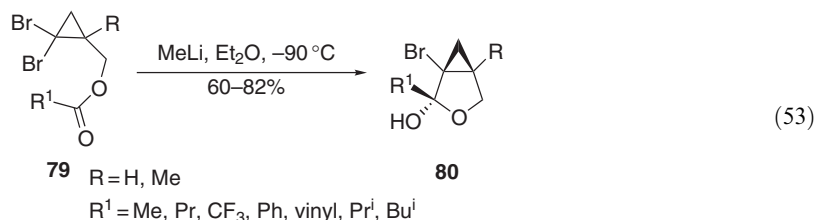
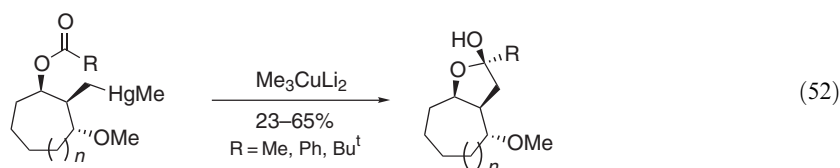
Enantiomerically pure cyclopropane hemiacetals may be obtained by the lipase-catalyzed kinetic resolution of their acylated congeners, followed by a reduction of the ester using lithium aluminum hydride (LAH). Lipases from *Candida antarctica* and *Pseudomonas cepia* are both

suitable for this purpose, showing enantiodivergent behavior towards the acyl derivatives and leading to products with high yields and high enantiomeric excess (Equation (51)) <2001OL189>.

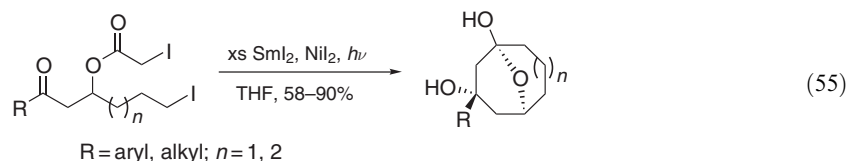
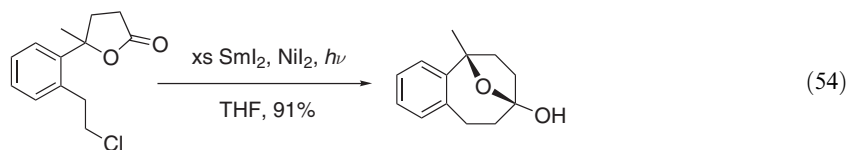


#### 4.04.2.2.2 By addition of carbanions

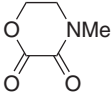
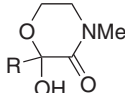
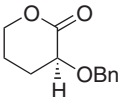
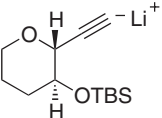
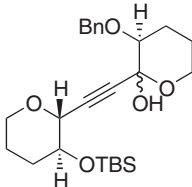
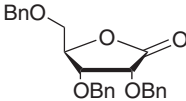
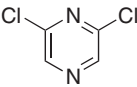
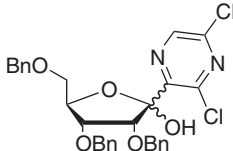
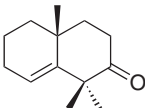
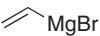
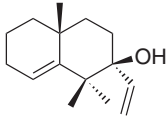

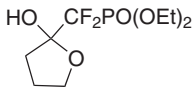
The intermolecular addition of carbanions to lactones remains an extremely versatile method by which to synthesize a variety of hemiacetals (Table 1). Because of the high reactivity of the reagents required to generate  $\text{R}_3\text{CMgX}$  or  $\text{R}_3\text{CLi}$ , the intramolecular version of the addition of Grignard and alkyllithium reagents to ketones has always proven to be problematic. However, developments involving the synthesis of organomercurials and their subsequent reaction with  $\text{Me}_3\text{CuLi}_2$  have led to the development of a novel and mild way for the intramolecular addition of organometallics across a carbonyl group (Equation (52)) <1995JOC1482>. Additionally, the reaction of methyllithium with dibromocyclopropanes **79** results in a lithium–bromide exchange and cyclization of the derived lithiocyclopropanes to form hemiacetals **80** stereoselectively (Equation (53)) <2000T4799>.



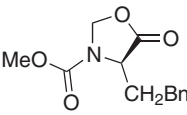
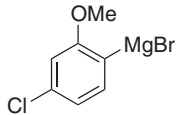
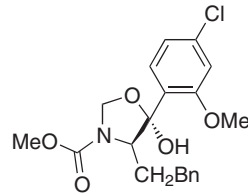
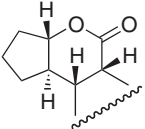
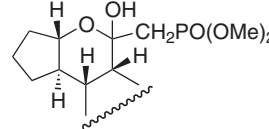
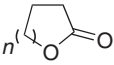
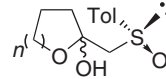
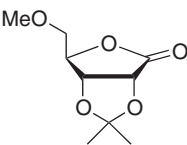
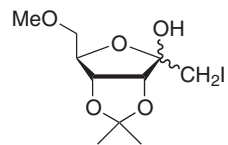
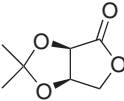
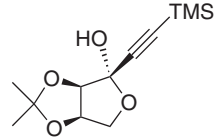
Samarium diiodide has become an increasingly versatile reagent in organic synthesis. For example, reduction of chloro lactones with  $\text{SmI}_2$ , in the presence of a catalytic amount of  $\text{NiI}_2$  and visible light, leads to nucleophilic acyl substitution, and provides a viable method by which to synthesize various hemiacetals (Equation (54)) <2000JOC8333, 2002JOC3861>. This method has been successfully applied toward the synthesis of natural products such as variecolin <2001OL2257> and the phorbol esters <2000OL2873>. Hemiacetals may also be synthesized from acyclic diiodoesters via an  $\text{SmI}_2$ -promoted Reformatsky-type reaction followed by a nucleophilic acyl substitution (Equation (55)) <2002JOC3459>.

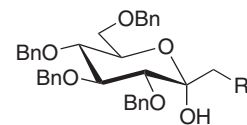
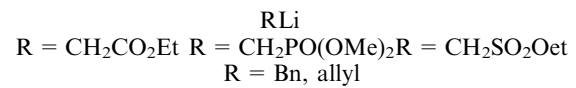
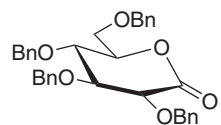


**Table 1** Hemiacetal formation by the addition of carbanions to lactones

<i>Substrate</i>	<i>Nucleophile</i>	<i>Product</i>	<i>Yield (%)</i>	<i>References</i>
	RMgBr R = alkyl, aryl 0°C		74-97	<1996BCJ2079>
			90	<1996JOC3003>
	 LDA, -78 °C		77	<1996TL5325>
	 rt, 24 h		80 ds = 7:3	<1996SL625>
	HCF <sub>2</sub> PO(OEt) <sub>2</sub> LDA, -78 °C		76	<1997T10623>

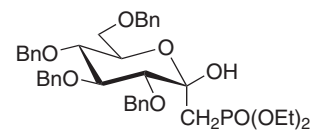
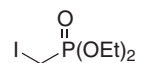
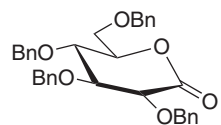
**Table 1** (continued)

<i>Substrate</i>	<i>Nucleophile</i>	<i>Product</i>	<i>Yield (%)</i>	<i>References</i>
			88 82% de	<1998OPRD186>
	MePO(OMe) <sub>2</sub> BuLi, -78 °C		93	<2000JOC8490>
	( <i>R</i> )-methyl tolyl sulfoxide		90 ( <i>n</i> = 1) 84 ( <i>n</i> = 2)	<2000T7927>
	CH <sub>2</sub> I <sub>2</sub>		58	<2000SL1691>
	H—C≡C—TMS		67	<2001T2345>



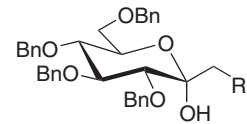
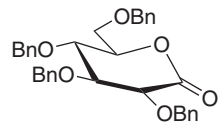
81–95

<2001TL6907>



70

<2002TL7101>



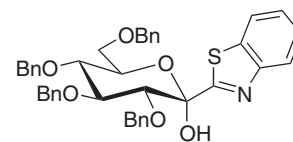
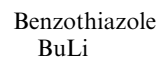
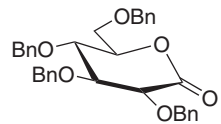
89

$R = \text{Me}$

69

$R = \text{Et}$

<2002TL7101>

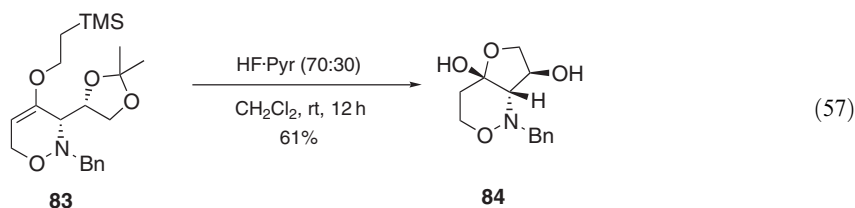
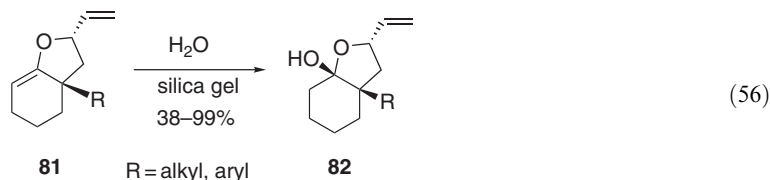


78

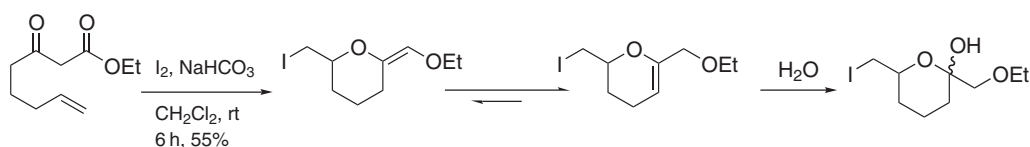
<2003TL13>

#### 4.04.2.3 Hemiacetals from Enol Ethers

Enol ethers are particularly facile to hydrolysis. Upon silica gel chromatography, enol ether **81** was hydrolyzed to give the more thermodynamically stable *trans*-hemiacetal **82** (Equation (56)) <1995JOC2668>. Such ease of hydrolysis upon silica gel chromatography was exploited in the synthesis of the taxoid C-ring system <2000EJC4029>. Under slightly more forcing conditions, enol ethers may be hydrolyzed with  $H_2SO_4/H_2O$  <2000EJO2145> or with *p*-toluenesulfonic acid in THF/ $H_2O$  <2000JA10482>. Treatment of enol ether **83** with pyridinium hydrogen fluoride in dichloromethane led to hemiacetal **84** as a single isomer (Equation (57)) <2002SL817>. The exact mechanism of this reaction is not known; however, it is well known that the  $HF \cdot Pyr$  cleaves silyl ethers as well as the dioxolane group, and it has thus been proposed that the reaction proceeds through an intermediate acetal. Halogens may also be added across the double bond of an enol ether during the synthesis of hemiacetals <2002AJC327, 2000JOC4679>.

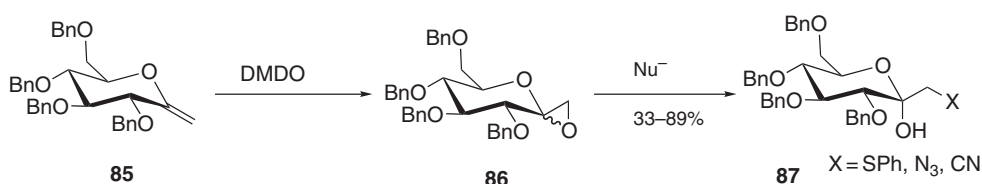


A novel method of synthesizing an enol ether, which undergoes subsequent hydrolysis upon work-up, involves the electrophilic-mediated cyclization of alkenyl-substituted  $\beta$ -keto esters. Iodine, phenylselenium bromide, or phenyltellurium trichloride have been used as electrophiles with yields in the range 38–65% (Scheme 3) <2002JOC4122>.



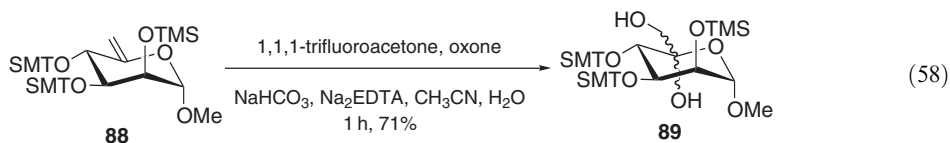
Scheme 3

Hemiacetals may be synthesized via the epoxidation, and subsequent ring opening, of enol ethers. Epoxidation of *exo*-glycal **85** with DMDO followed by nucleophilic ring opening of epoxide **86** yields a variety hemiacetals **87** in good-to-moderate yield (Scheme 4) <1995SL167>. However, when the *exo*-glycal was epoxidized with MCPBA, the intermediate epoxide reacted with the formed MCPBA directly to give the ring-opened product. Additionally, epoxidation and subsequent hydrolysis of pyranoside **88** produced hemiacetal **89** in 71% yield (Equation (58)) <2001OL3353>.



Scheme 4

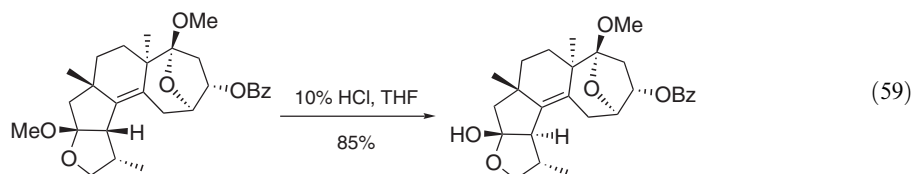




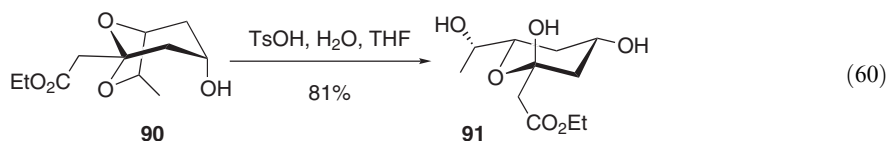
#### 4.04.2.4 Hemiacetals from Acetals by Deprotection

##### 4.04.2.4.1 From noncarbohydrate substances

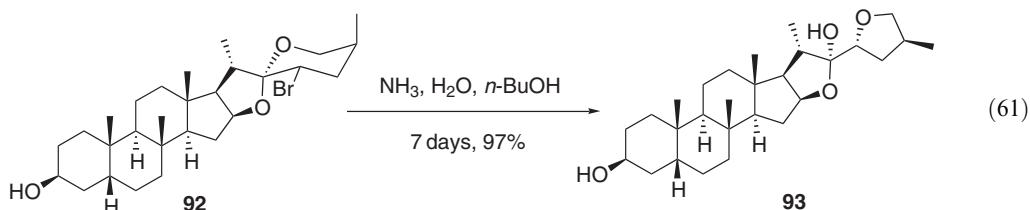
The formation of hemiacetals via the deprotection of their corresponding acetals is frequently applied in the synthesis of many natural products. In particular, hemiacetals are often derived from their methoxy acetal counterparts, as is the case for the synthesis of allocaythin B<sub>3</sub> (Equation (59)) <2000OL2125>. Synthesis of the nonisomerized hemiacetal was achieved using a solution of *p*-toluenesulfinic acid in acetone/H<sub>2</sub>O. Very mild hydrolysis conditions were also required for the synthesis of variecolin, whereby deprotection of a methoxy acetal was achieved using catalytic amounts of PdCl<sub>2</sub>(MeCN)<sub>2</sub> in CH<sub>3</sub>CN/H<sub>2</sub>O <2001OL2257>. The final sequence in the synthesis of (+)-phorboxazole A required the deprotection of a methoxy acetal, using 6% HCl in THF <2001JA4834>.



The final synthetic sequence in the formation of the C(1)–C(8) segment of (+)-aucutiphycin required hydrolysis of bicyclic ketal **90** to give target hemiketal **91** (Equation (60)). Under the hydrolysis conditions, the C(1)–C(3) side chain equilibrated to the equatorial position <2002TL1147>. Similarly, the final sequence in the synthesis of (–)-syringolide involved deprotecting a hemiacetal using a large excess of *p*-toluenesulfonic acid in acetone/water <2000CJC275>. During the asymmetric synthesis of *N*-acetylneuraminic acid, a triacetone was consecutively deprotected and cyclized using methanolic HCl <2000CC227>.



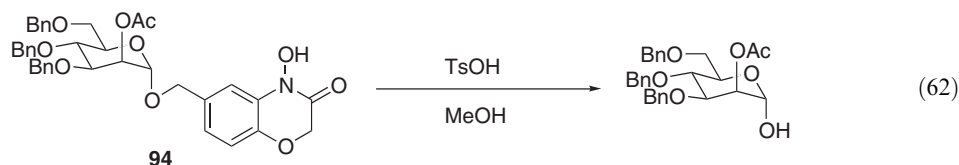
Hemiacetal **93** is formed from acetal **92** via a slightly more elaborate procedure involving neighboring group participation and weak alkaline hydrolysis (Equation (61)) <2001TL5989>. The mechanism suggested for this process consists of a departure of bromide, followed by addition of water to the transient carbocation.



##### 4.04.2.4.2 From carbohydrate substances

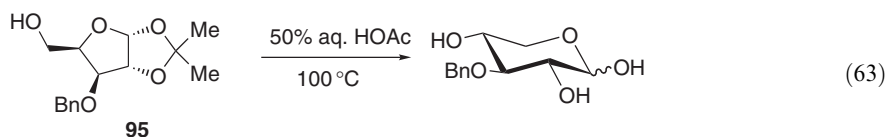
Protection and deprotection of the anomeric hydroxy group is an essential feature of oligosaccharide synthesis. Many glycosyl donors, however, have a transient lifetime and are used directly for glycosidation reactions. For a general review on carbohydrate chemistry, see

<2001AG(E)1576>. One of the more robust protecting groups for the anomeric hydroxyl is the benzyl acetal, which may be cleaved under a variety of conditions including standard hydrogenation <2002JA5380> or with  $\text{FeCl}_3$  in  $\text{CH}_2\text{Cl}_2$  <2002TL8879>. Several benzyl derivatives have been developed to allow for deprotection under a variety of conditions. Examples of such derivatives include the *p*-methoxybenzyl ether, oxidatively cleaved using cerium ammonium nitrate <2001JOC4233>; the *o*-nitrobenzyl ether, cleaved under photochemical conditions <2000JOC8011>; or the slightly more elaborate bicyclic derivative **94**, cleaved under acidic conditions with *p*-toluenesulfonic acid (Equation (62)) <2000SL1241>.



Methoxy acetals may be cleaved under acidic conditions similar to those previously discussed, while silyl ethers can be cleaved using a fluoride source such as tetra-*n*-butylammonium fluoride (TBAF), HF or Olah's reagent <2000EJO3541, 2000OL3043, 2002JA10036>. The allyl group is frequently used to protect the anomeric position with transition metal catalysts commonly used for the cleavage of this moiety <2003CEJ307, 2000S2263>. Alternatively, allenyl ethers may be cleaved under relatively mild conditions using catalytic  $\text{OsO}_4$  and *N*-methyl morpholine *N*-oxide <1999T11331>. The *n*-pentenyl glycoside protecting group remains, in the early 2000s, a popular choice for protection of the anomeric position <2001JOC8165>.

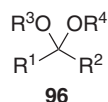
A variety of methods exist for the selective deprotection of an anomeric acetate in the presence of other acetate moieties. These include the use of *t*-butylamine <2002JCS(P1)242>, hydrazine acetate <2001TL1007>, and ammonia <2001MI165>. Acetals are hydrolyzed under acidic conditions, including the use of trifluoroacetic acid <2000MI549> or aqueous acetic acid <2000JA619>. Under the latter conditions, the furan derivative **95** equilibrated to the pyranose form (Equation (63)).



#### 4.04.3 ACETALS— $R_2^1C(OR^2)_2$

Reviews of the preparation and use of acetals as protecting groups <B-1999MI002, 1991COS(6)631> and chiral reagents <1999PAC1511> have appeared. The synthesis of certain specific types of acetals will not be covered here unless methods have more general applicability. The reader should therefore consult reviews for more details on the preparation of spiroacetals <1999JHC1373, 1999T7661, 1998CUOC395, 2001CUOC233> and glycoside coupling methods <B-2000MI003, B-1997MI001, 2000CRV4423>.

This section is divided into three parts: general methods (suitable for symmetrical and unsymmetrical acetals), methods for symmetrical acetals **96** ( $R^1 = R^2$ ), and those for unsymmetrical acetals **96** ( $R^1 \neq R^2$ ). The methods described in the general section (Section 4.04.3.1) can be applied to the preparation of symmetrical acetals; however, some of these methods are restricted to the preparation of cyclic unsymmetrical acetals from an unsymmetrical diol, and do not allow the use of two different monohydric alcohols. Such restrictions will be obvious or will be indicated at appropriate points in the discussion. Methods covered in the sections on symmetrical (Section 4.04.3.2) and unsymmetrical acetals (Section 4.04.3.3) represent the general situation found in the literature, but an appropriate choice of reaction components may result in the crossing of boundaries between sections. The reader should therefore consult all sections to avoid overlooking a potentially useful method. Intramolecular variants of many of the methods are also feasible.

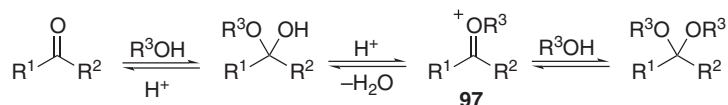


#### 4.04.3.1 General Methods

##### 4.04.3.1.1 From aldehydes and ketones

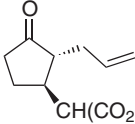
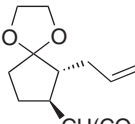
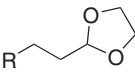
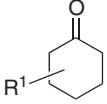
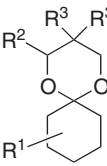
###### (i) With alcohols and protic or Lewis acid catalysts

The formation of acetals via the reaction of alcohols with aldehydes and ketones under acidic conditions is an equilibrium process that proceeds via the common, intermediate oxonium ion **97** (Scheme 5) <1981S501>. In general, it is necessary to shift the equilibrium in favor of the product by removing the water by-product, either by physical or chemical methods. The most commonly used method for the removal of water involves heating the carbonyl with an alcohol or diol in an inert solvent such as benzene, toluene, or xylene, which under continuous azeotropic distillation with a Dean–Stark or similar water separatory head <1938CB1803> results in removal of water. Examples are shown in Table 2 using monohydric alcohols and 1,2- or 1,3-diols. In general, cyclic acetals are usually formed more easily than acyclic acetals and functionalized alcohols may also be used.



Scheme 5

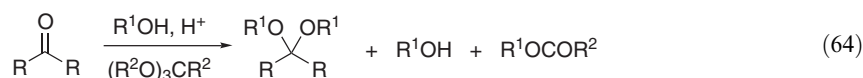
Table 2 Acetals prepared by azeotropic removal of water

Entry	Substrate	Conditi <sup>ns</sup>	Acetal	Yield (%)	References
1		HOCH <sub>2</sub> CH <sub>2</sub> OH PPTS, benzene 19 h		89	<1997CEJ441>
2	R-CH <sub>2</sub> -CH <sub>2</sub> -CHO R = squalene derivatives	HOCH <sub>2</sub> CH <sub>2</sub> OH TsOH, 4 h, benzene		86	<2002JCS(P1)1477>
3		HO-CH(R <sup>2</sup> )-C(R <sup>3</sup> ) <sub>2</sub> -CH <sub>2</sub> -OH R <sup>1</sup> = H, CH <sub>3</sub> or Bu <sup>t</sup> R <sup>2</sup> = H or CH <sub>3</sub> R <sup>3</sup> = H, CH <sub>3</sub> or CO <sub>2</sub> Et TsOH, benzene		60–82	<1997T6215>

<sup>a</sup> PPTS = pyridinium *p*-toluenesulfonate.

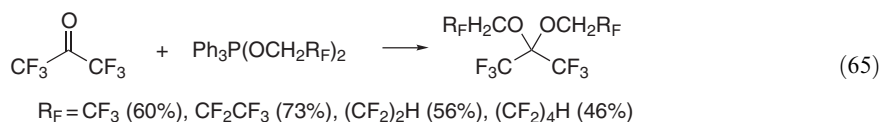
The order of carbonyl reactivity is generally: aliphatic aldehydes > aromatic aldehydes > acyclic ketones and cyclohexanones > cyclopentanones >  $\alpha,\beta$ -unsaturated ketones, and  $\alpha,\alpha$ -disubstituted ketones > aromatic ketones. This variation of reactivity thus makes chemoselectivity in polycarbonyl systems feasible. Steric hindrance in the alcohol slows down the rate of acetal formation. In some cases, particularly for saturated aliphatic aldehydes and primary alcohols, the equilibrium conversion to the acetal may be quite high.

In situations of an unfavorable equilibrium for acetal formation, the water can be completely removed by reaction with a suitable reagent. Orthoesters, the most widely used reagents for this purpose due to the mild conditions, react with the water to form an ester and an alcohol as shown in the general reaction in Equation (64). This is a general procedure that is particularly suitable for the preparation of ketone acetals and examples are illustrated in Table 3. The mechanism of this reaction is well established <1955JOC1695, 1969CC1175>. The orthoformate is usually chosen to match the alcohol, but with higher-boiling alcohols trimethyl or triethyl orthoformate can be used, and the ethanol or methanol and alkyl formate distilled out of the reaction mixture to displace the equilibrium. This may not be necessary for cyclic acetals if an excess of diol is used.



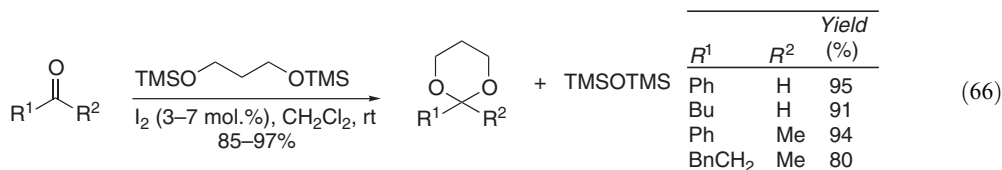
An alternative to the above removal of water are dehydrating reagents (the well-established references are supplied for convenience) such as molecular sieves <1971RTC1141, 1972S419, 1977RTC44>, calcium sulfate <1974JOC2815>, copper sulfate <1978JOC438> and alumina <1979CB3603>. Although this approach often allows acetalization to be carried out at room temperature (rt) or below, it appears to give high yields with only more reactive aldehydes or ketones.

In addition to the numerous examples of protic acids, Lewis acids and heterogeneous catalysts listed in chapter 4.04, COFGT (1995) <1995COFGT(4)159>; further catalysts have been reported in Table 4. The choice of catalyst is governed by the reactivity of the carbonyl group, the substrate chemical and thermal stability, and of course, the reaction conditions. The use of weaker acids, such as ammonium chloride, calcium chloride, alumina, or lanthanide halides can be used for the acetalization of aldehydes, but often acids such as TsOH are used for convenience. Ketones generally require stronger acids such as HCl,  $\text{H}_2\text{SO}_4$ , or TsOH. Protection under microwave irradiation in solvent-free conditions has also been reported <1997TL7867>. Acetal formation from ketones with electron-withdrawing groups, such as fluoro substituents, has been accomplished <1996TL8663>, and in addition the use of bis(fluoroalkoxy)triphenylphosphoranes leads to fluorinated acetals (Equation (65)) <1995JOC5696>.

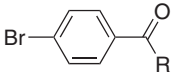
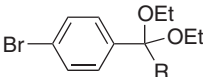
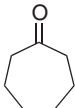
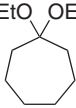
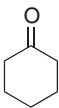
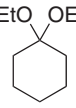


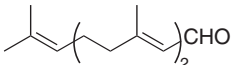
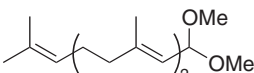
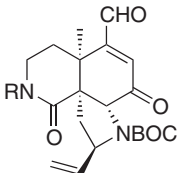
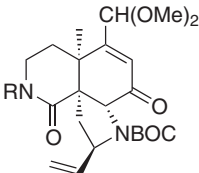


## (ii) With silyl ethers

The reaction of silyl ethers with carbonyl compounds, as in Equation (66), is well established and variations of trimethylsilyl triflate (TMSOTf) catalyzed reactions were reviewed in chapter 4.04, COGFT (1995) <1995COFGT(4)159>. Subsequent work has revealed that acid-sensitive groups such as tetrahydropyranyl (THP)-ethers are deprotected at temperatures higher than  $-78^\circ\text{C}$  using this protocol. Therefore, an alternative is the use of iodine, which gives excellent yields (with some shown) and is highly chemoselective. Complete selectivity for aldehydes was observed in the presence of ketones when using only 2 equiv. of the 1,3-bis(trimethylsiloxy)propane <2002S784>.



**Table 3** Acetal formation using orthoesters as dehydrating agents

Entry	Substrate	Conditions	Acetal	Yield (%)	References
1		EtOH, (EtO) <sub>3</sub> CH pTsOH, 12 h, rt		R = H, 89 R = Me, 72	<2000EJO3825>
2		EtOH, (EtO) <sub>3</sub> CH HCl, 3 days, rt		79	<2000T6299>
3		EtOH, (EtO) <sub>3</sub> CH HCl, 3 days, rt		77	<2000T6299>
4		EtOH, (EtO) <sub>3</sub> CH HCl, 3 days, rt		56	<2000T6299>
5		MeOH, (MeO) <sub>3</sub> CH LaCl <sub>3</sub> , 0.5 h, rt		82	<1999EJO2143>
6		MeOH, (MeO) <sub>3</sub> CH LaCl <sub>3</sub> , 0.5 h, rt		84	<1999JA866>

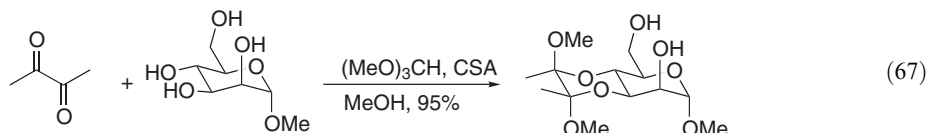
**Table 4** Catalysts for the acetalization of aldehydes and ketones

Alcohol or orthoformate	Catalyst	Yield (%)	References
HOCH <sub>2</sub> CH <sub>2</sub> OH	CsOH, CsF	49	<1997T16597>
HOCH <sub>2</sub> CH <sub>2</sub> OH, MeOH	ZnCl <sub>2</sub>	> 95	<2001EJO399>
MeOH, EtOH, (RO) <sub>3</sub> CH	Bu <sub>4</sub> NBr <sub>3</sub>	89–96	<2002JOC5842>
MeOH, EtOH, (RO) <sub>3</sub> CH	Bi(OTf) <sub>3</sub>	68–98	<2002JOC5202>
MeOH, (MeO) <sub>3</sub> CH	MCM-41 <sup>a</sup>	18–93	<1998TL9457>
HOCH <sub>2</sub> CH <sub>2</sub> OH, ROH	CdI <sub>2</sub> , microwave	80–92	<1999CL1283>
EtOH, (EtO) <sub>3</sub> CH	DDQ	79–98	<1999CL1199>
EtOH, (EtO) <sub>3</sub> CH	NBS	85–98	<1999SL1456>
HOCH <sub>2</sub> CH <sub>2</sub> OH, (EtO) <sub>3</sub> CH	ZrCl <sub>4</sub>	80–98	<1999SL321>
MeOH	Ce <sup>3+</sup> -montmorillonite	18–95	<1995JOC4039>
MeOH, (MeO) <sub>3</sub> CH	B <sub>10</sub> H <sub>14</sub>	85–93	<2002TL2699>
MeOH, (MeO) <sub>3</sub> CH	RhCl <sub>2</sub> CF <sub>3</sub> triphos	80	<2001HCA898>

<sup>a</sup> MCM-41 siliceous mesoporous material.

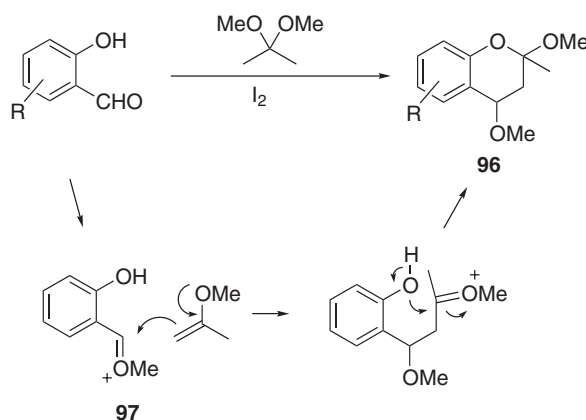
### (iii) Condensation of 1,2-diketones with 1,2-diols

Preparation of diacetals from 1,2-diketones and 1,2-diols was introduced by Ley as a method for the protection of *trans*-1,2-diols in carbohydrates (Equation (67)) <1997JCS(P1)2023>. This method is adaptable to commercially available phenanthrene-9,10-quinone and cyclohexane- or cycloheptane-1,2-diones. The method also includes the use of 2,2,3,3-tetramethoxybutane rather than butanedione <1996JOC3897>.

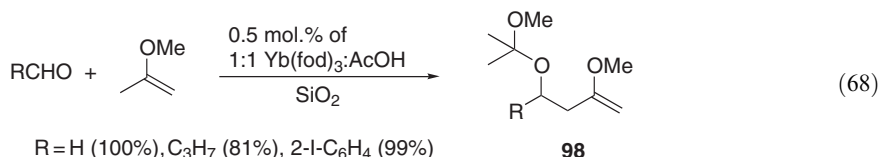


### (iv) Condensation of *o*-hydroxybenzaldehydes with dimethoxypropane

The formation of benzopyrans **96** (Scheme 6) is accomplished in high yields by iodine-catalyzed condensation of *o*-hydroxybenzaldehydes with dimethoxypropane <2000JCS(P1)3082>. Yields for this reaction ranged from 75% to 90% for the 13 substrates reported and include R = H (90%), 6-OMe (86%), 4-Me (88%), and 4-Br (84%). Mechanistically this was considered to occur via formation of **97**, which underwent nucleophilic attack by 2-methoxypropene and subsequently led to the products. This method has been extended to scandium triflate-catalyzed reactions <2000TL7943> and to the formation of 4-amino benzopyrans by using *o*-hydroxybenzaldimines <2001TL4405>.

**Scheme 6**

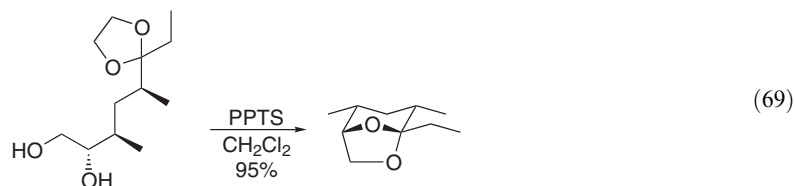
A similar reaction involves a catalytic ene-like reaction of aldehydes with vinyl ethers. For example, 2-methoxy propene gives **98** in high yields (Equation (68)) <1997T16299>. This methodology has been used in the synthesis of several natural products such as chlorovulone(II) and phyllanthocin.



#### 4.04.3.1.2 From acetals

##### (i) With alcohols

Acetals formed from low boiling alcohols such as methanol or ethanol can be exchanged with higher boiling alcohols under acidic conditions. A method that is often used is the treatment of 1,2-diols with 2,2-dimethoxypropane and an acid catalyst such as pyridinium *p*-toluenesulfonic acid (PPTS) <2001EJO1865>. Yields are generally very high (>90%) with these reactions. The method is also very useful for the preparation of chiral, optically active acetals when reaction with the corresponding ketone is low yielding. As depicted in Table 5, several chiral acetals have been prepared. Spiro acetals are also conveniently formed using acetal exchange (Equation (69)) <1995JA3653>.



##### (ii) By acetal interchange

No examples of this transformation have been reported in the period 1993–2003.

#### 4.04.3.1.3 From enol ethers and alcohols

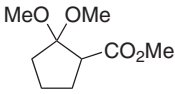
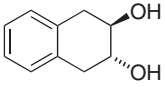
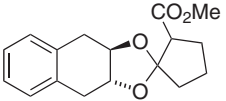
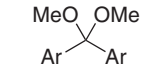
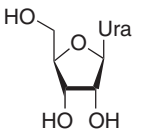
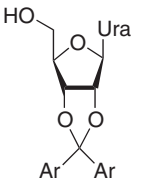
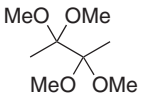
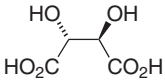
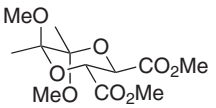
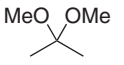
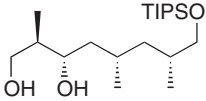
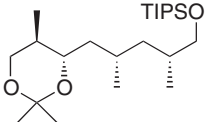
##### (i) By acid catalysis

Addition of alcohols to enol ethers via the acid-catalyzed formation of oxonium ion **99** is a standard method for the protection of alcohols. As shown in Scheme 7, excellent yields are obtained and these types of reactions often provide products of exceptional purity, thus bypassing the need for purification <2001JA9033, 1999JOC5301, 1995TL1653>. Typically, catalysts such as PPTS are used at 0 °C or room temperature.

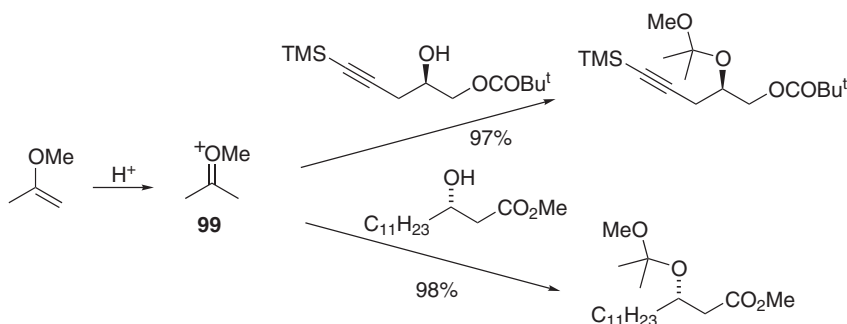
##### (ii) With electrophiles

Alcohols can also add to enol ethers with the aid of electrophiles. Past variations of this type of addition include the use of NBS (Equation (70)), in which reports have focused on tin-based radical chemistry of the subsequently formed acetal <1997T10479, 1998JOC1668> or elimination of HBr <2000JA12169>. This addition has also been extended to dienes of type **100** to provide 1,4-addition in modest yields (Equation (71)) <1999SL1841>. An additional variation on a past theme is asymmetric methoxyselenenylation of alkyl vinyl ethers <2001TL1559>, which allows for deselenenylation to give chiral acetals (Scheme 8). Diastereomeric ratios of the addition products **101** range from 1:1 to 9:1, and one example of a deselenenylation to provide a chiral acetal was performed. This gave **102** in 90% yield and 74% ee.

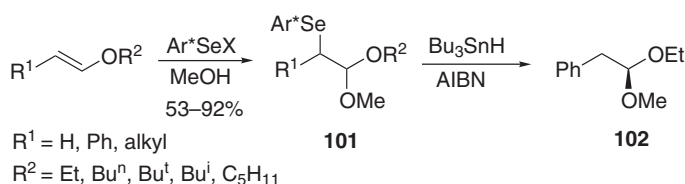
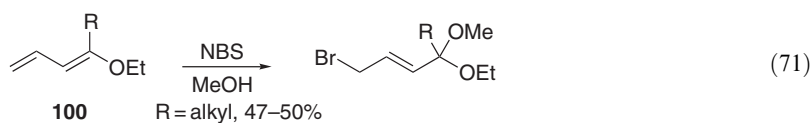
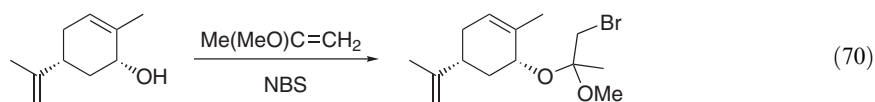
**Table 5** Acetal formation from chiral alcohols

Entry	Substrate	Chiral alcohol	Acetal	Yield (%)	References
1				70	<1997TA1039>
2	 Ar = <i>p</i> -C <sub>6</sub> H <sub>4</sub> OMe			95	<2001TL1789>
3				72	<1999TL1583>
4				71	<2001EJO1865>





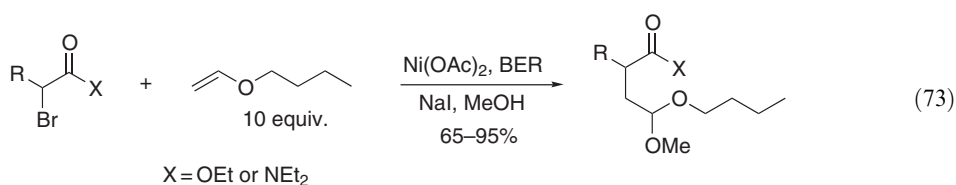
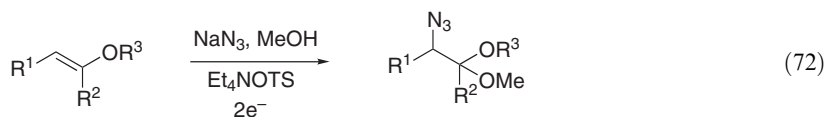
Scheme 7



Scheme 8

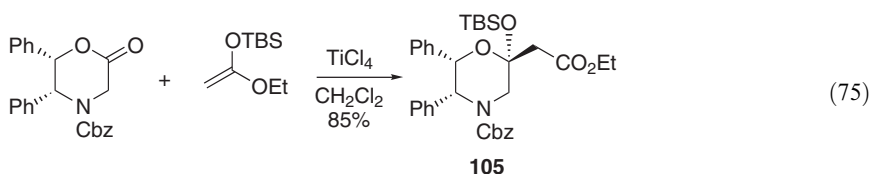
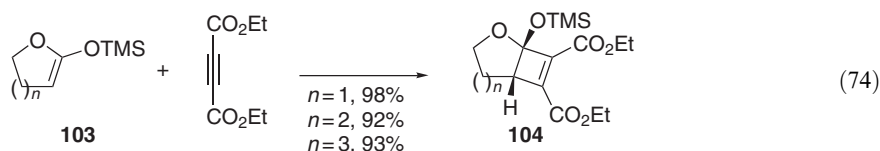
### (iii) Miscellaneous enol ethers

Two addition areas, involving anodic oxidation and radical coupling, have been reported. Azidomethoxylation of enol ethers by anodic oxidation gives regioselective addition in yields of 52–82% (Equation (72)) <1995TL7483>. Enol ethers used were  $R^1, R^2$  as cyclic systems from 5- to 12-membered rings or H and Me groups, with  $R^3$  generally a Me or  $Bu^t$  group. A 1:1 ratio of diastereomers was obtained in the single example of diastereoselective reaction. Additionally, the synthesis of  $\gamma$ -dialkoxy carboxylic acid derivatives has been achieved via a radical coupling with catalytic nickel and borohydride exchange resin (BER) (Equation (73)) <1996SL1224>.



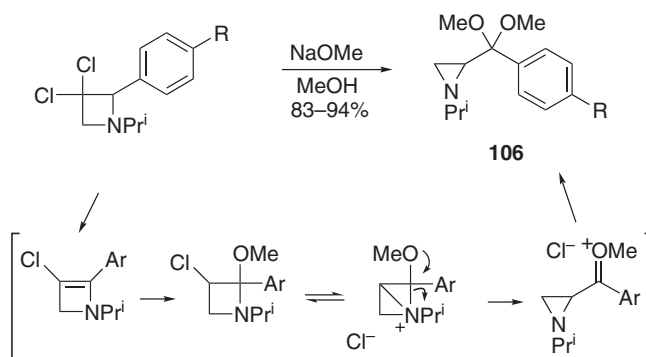
#### 4.04.3.1.4 From silyl enol ethers and enol acetates

As reported in chapter 4.04 of <1995COFGT(4)159>, silyl enol ethers react with alcohols in a similar manner as the enol ethers described above, but no new notable variations have been reported in this area up to 2003. However, two reactions of silyl ketene acetals have been reported that are of significant interest. Reaction of **103** with alkynes such as dimethyl acetylenedicarboxylate under solvent-free conditions gives the [2 + 2]-cycloaddition products **104** at room temperature (Equation (74)) <2000EJOC3381>. Ethyl propynoate and ethynyl methyl ketone were also used providing comparable yields. Acetals of type **105** were also obtained by Mukaiyama aldol reactions with lactone carbonyls (Equation (75)) <2001TL4437>. Aldol reaction and migration of the silyl group gave the acetal as a single diastereomer.



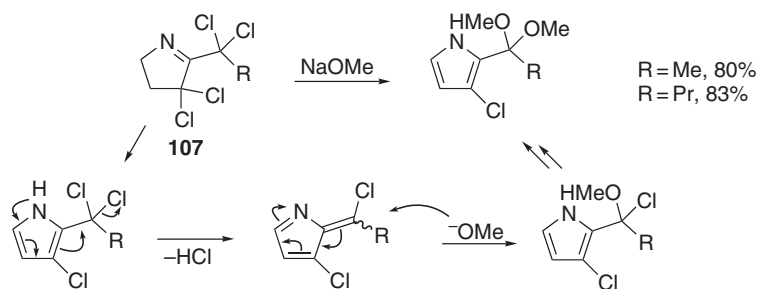
#### 4.04.3.1.5 From gem-dihalides by alkylation

Displacement of both halides from geminal dihalides with alkoxides is an additional method for the formation of acetals (see <1995COFGT(4)159> for an extended coverage) and is facilitated by a neighboring aromatic group. New work in this area has involved displacement with concurrent rearrangement upon treatment with alkoxides. For example, treatment of the dichloroazetidines with NaOMe gives high yields of the aziridines **106** (Scheme 9) <2002JOC2075>. The azetidines are synthesized in four convenient steps from benzaldehyde derivatives comprising electron donating and withdrawing groups in high yields.

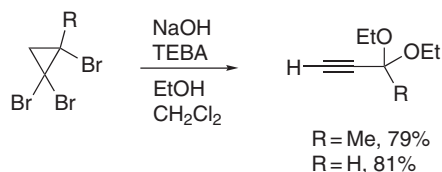


Scheme 9

Treatment of pyrrolines **107** with NaOMe gave pyrroles in good yields (Scheme 10) <1999T4133>. Mechanistically, the conversion was reported as initial aromatization of the pyrroline **107**, followed by a consecutive loss of HCl and attack of methoxide to produce the pyrrole after a sequential process. A final report involves the opening of trihalocyclopropanes (Equation (76)) in the presence of triethylbenzylammonium chloride (TEBA), which give good yields of acetylenic acetals <1998ACS1029>. Isopropanol has also been used in place of ethanol with comparable yields. The starting cyclopropanes are easily prepared via dihalocarbene addition to halogenated olefins <1996ACS446>.



Scheme 10



(76)

#### 4.04.3.2 Symmetrical Acetals

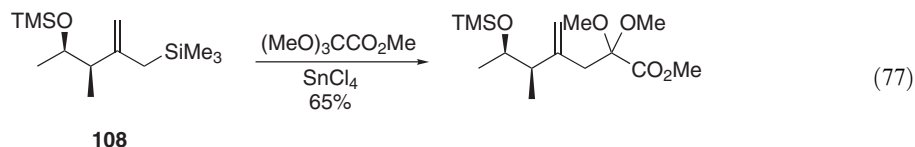
##### 4.04.3.2.1 From aldehydes and ketones

Formation of symmetrical acetals using orthoformates or acetal exchange is covered in Sections 4.04.3.1.1 and 4.04.3.1.2

##### 4.04.3.2.2 From orthoesters and nucleophiles

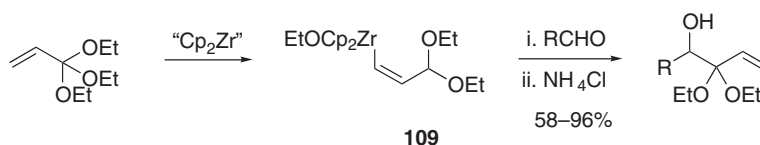
###### (i) With organometallic reagents

The displacement of an alkoxy group from an orthoester with a carbon nucleophile, specifically Grignard reagents, was covered in COGFT (1995) <1995COFGT(4)159>. Subsequent developments in this area involve the use of allyl silanes such as **108** as the nucleophile (Equation (77)), <1996HCA346>.



(77)

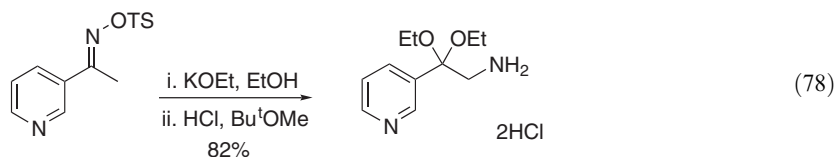
In a reversal of polarity, nucleophiles are generated from orthoesters by treatment with “ $\text{Cp}_2\text{Zr}$ .” The dialkoxyallylic zirconium species **109** is prepared from triethylorthoacrylate, which is then reacted with aldehydes as shown in Scheme 11 <1997TL5829>. In all cases, an  $sp^2$ -R group was used such as Ph (91%), furan (90%), or methylvinyl (58%). This reaction has also been applied to the reaction of chiral aldehydes giving diastereoselectivities in 8:1 to 12:1 ratios <2000JOC918>.



Scheme 11

(ii) *With enolate derivatives*

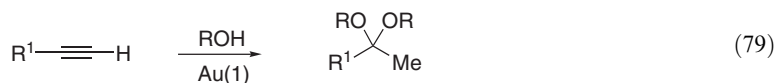
An example of the formation of a symmetrical diethyl acetal via a Neber rearrangement of a tosyl oxime has been reported (Equation (78)) <1999TL6739>.

4.04.3.2.3 *From alkenes and alkynes*(i) *From alkenes and alcohols with electrophilic metal derivatives*

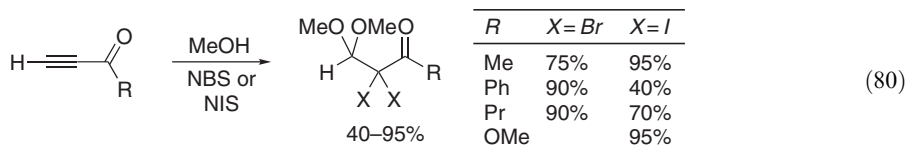
No examples of this transformation have been reported in the decade 1993–2003.

(ii) *From alkynes and alcohols with electrophilic metal derivatives*

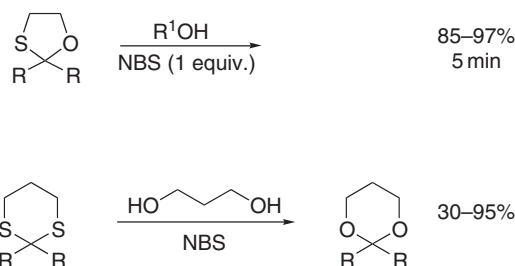
The mercury-catalyzed addition of alcohols to alkynes has been known since the 1930s. An alternative to the use of toxic mercury has been reported involving a cationic gold(I) complex. The catalyst, prepared from methyl(triphenylphosphine)gold, catalyzes a range of alkynes as shown in Equation (79) <1998AG(E)1415>. The majority of reactions were performed with  $R^1 = \text{Me}$  (with either methanol, ethanol, or isopropanol); thus, no yields are reported and only gas chromatography turnover numbers are given. The turnover numbers are up to  $10^5$ .

(iii) *From electron-deficient alkynes and alkenes by conjugate addition of alcohols*

Conjugate addition of methanol to a range of conjugated alkynes with both NBS and *N*-iodosuccinimide (NIS) has been reported (Equation (80)) <1998JOC4433>. A mechanism is postulated for the dihalo acetal formation, which could then be reduced with tributyltin hydride.

4.04.3.2.4 *From dithioacetals and O,S-acetals*

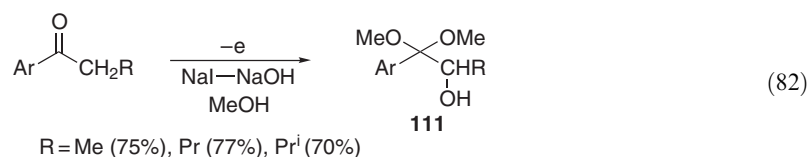
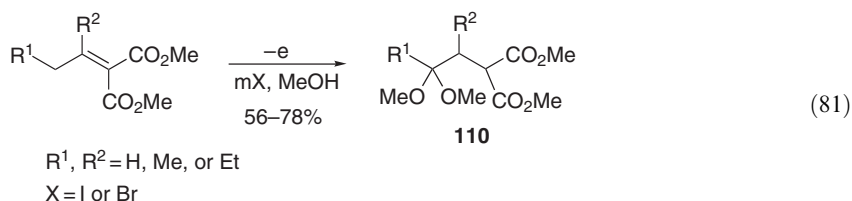
The alcoholysis of dithioacetals with  $\text{PhI}(\text{OCOCF}_3)_2$  is one of the standard methods for the formation of acetals from dithioacetals and the use of this in a complex natural product synthesis has been reported <1999AG(E)1669>. Another method is the use of NBS, which gives excellent yields of acetals from both *O,S*- and dithioacetals (Scheme 12) <2002T4513>. With *O,S*-acetals, both methanol and ethanol were used and an extensive range of substrates ranging from aliphatic to substituted aromatic derivatives were tested.



Scheme 12

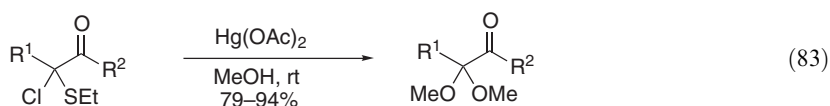
#### 4.04.3.2.5 Electrochemical methods

Several methods for acetal formation have been developed, although these are substrate specific. Electrolysis of alkylidenemalonates in methanol or ethanol in the presence of sodium or potassium halides gives modest-to-good yields of acetals **110** (Equation (81)) <1998T14529>. Similarly, electrolysis of aryl alkyl ketones in the presence of an NaI–NaOH system produces the hydroxy acetals **111** (Equation (82)) <2000T9999>. The majority of studies were performed with a phenyl aromatic moiety and several representative R groups are shown. The electrochemical cleavage of double bonds conjugated to aromatic groups has also been reported to give dimethoxy acetals; however, mixtures of products in modest yields are obtained <1996JOC3256>.

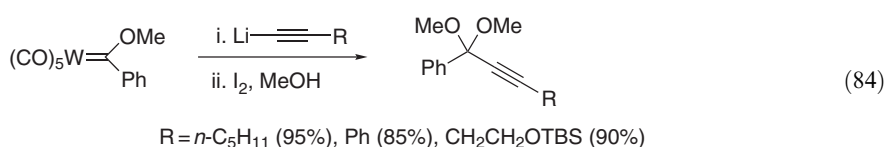


#### 4.04.3.2.6 Miscellaneous methods

Several reports on the conversion of  $\alpha$ -chloro- $\alpha$ -(alkylthio)carbonyls to acetals have appeared (Equation (83)) <2000T6541>, including its use in natural product synthesis <2000T6541>. R groups used were combinations of Me, Et, or Ph. Variations on this include the use of carboxylic acids <1998T4889> and the use of  $\alpha$ -chloro- $\alpha$ -phenylselenanyl esters <2000T7495>.



Fischer-type carbene complexes have also been converted to acetals by reaction with alkynyllithiums followed by treatment with iodine then methanol (Equation (84)) <1997OM5137>.



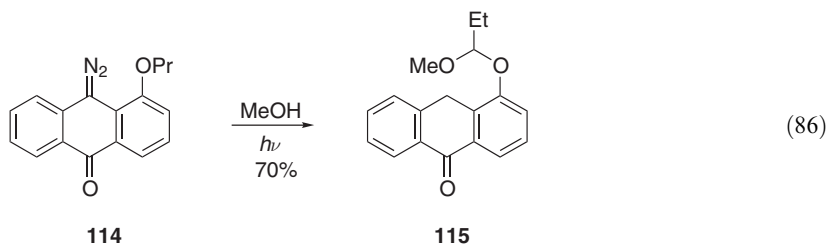
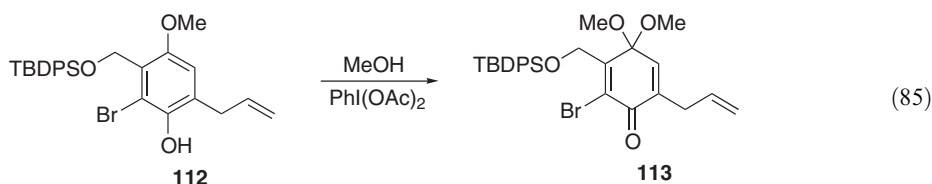
### 4.04.3.3 Unsymmetrical Acetals

#### 4.04.3.3.1 From $\alpha$ -substituted ethers and alcohols

The vast majority of glycoside-coupling methods involve the substitution of a leaving group from the anomeric carbon of a carbohydrate. Numerous methods and leaving groups have been developed for this process and the topic has been extensively reviewed <B-2000MI003, B-1997MI001, 2000CRV4423> and thus will not be covered here.

#### 4.04.3.3.2 From ethers

Two examples for the formation of acetals from ethers have been reported and these are both substrate specific. First, hypervalent iodine oxidation of allyl phenol **112** afforded quinone monoketal **113** in 70% yield as part of a two-step process (Equation (85)) <2000JA10484>. Second, the photolysis of diazoanthrone **114** gave acetal **115** as a mixture of product and starting material (Equation (86)) <1998TL6675>.



#### 4.04.3.3.3 From cyclic hemiacetals

Protection of cyclic hemiacetals as the acetal during a complex synthesis is usually accomplished with acidic conditions and an alcoholic solvent. Methanol is generally used as the solvent, as in the following <1999OL957, 1995T9393, 1999T4315>. These reactions are usually high yielding, 80–95%, and employ acid catalysts such as HCl or CSA.

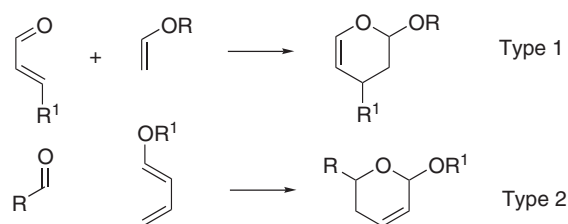
#### 4.04.3.3.4 By hetero-Diels–Alder reactions

Two modes of reaction are possible in the hetero-Diels–Alder reaction as shown in Scheme 13. Promotion of type 1 via Eu(fod)<sub>3</sub> and SnCl<sub>4</sub> <2002EJOC514>, high pressure <2002EJOC3126>, and high-temperature <1997S628> have all been reported. Yields for the Eu(fod)<sub>3</sub> catalyst were in the range 60–98% and SnCl<sub>4</sub> in 10–99%, and in both cases complex mixtures of diastereomers were obtained. Alternatively, high-temperature reactions gave yields of 66–71%, while high-pressure reactions gave a modest 35–45%. Reports on type 2 were briefly discussed in <1995COFGT(4)159>. There have not been any new reports in the period up to 2003.

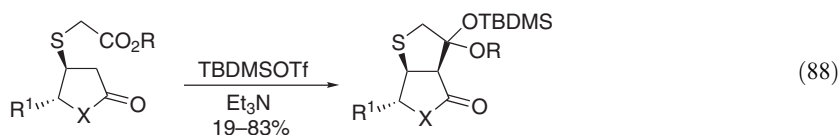
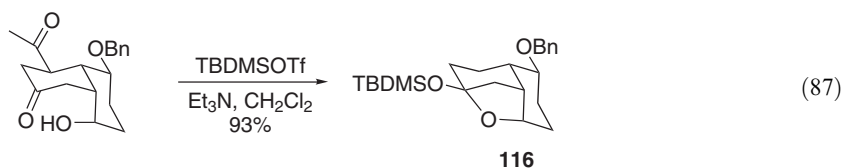
#### 4.04.3.3.5 Mixed alkyl silyl acetals

Several methods for the preparation of mixed alkyl silyl acetals such as **116** have appeared (Equation (87)). A general method involves treatment of the *in situ* formed hemiacetal with silyltriflates in the presence of a base. Examples of *t*-butyldimethylsilyl <1997TL6577>,

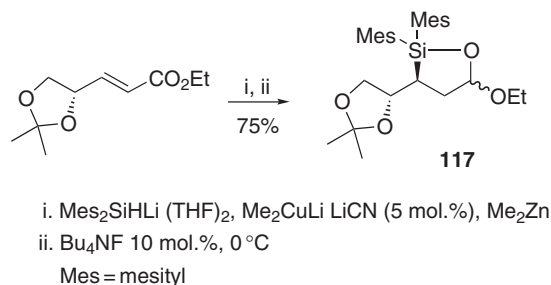
triethylsilyl <2000AG(E)2533>, and triisopropylsilyl <1998T3495> have all appeared. Similarly, intramolecular nucleophilic attack at esters and trapping of the resulting acetal oxide with silyltriflates has been reported (Equation (88)) <1996T9035>. Methyl, ethyl, and butyl esters were used in both lactam and lactone systems, with the  $R^1$  group primarily methyl.



Scheme 13



Formation of oxasilacyclopentane acetals, such as **117**, has been an active area of interest in the period 1993–2003. These are conveniently formed via diastereoselective conjugate addition of the hydrosilyl anion [ $\text{Mes}_2\text{SiHLi}(\text{THF})_2$ ] to an  $\alpha,\beta$ -unsaturated ester followed by intramolecular hydrosilylation using catalytic  $n\text{-Bu}_4\text{NF}$  (Scheme 14) <2002JA12648>. Diastereoselectivity in the example shown was 98:2, with several other examples reported in which the lowest ds was 93:7 in 63% yield.



Scheme 14

#### 4.04.4 OTHER DIOXYGEN DERIVATIVES

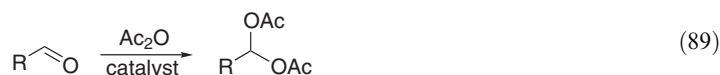
##### 4.04.4.1 Synthesis of $R_2^1C(OCOR^2)_2$

###### 4.04.4.1.1 From aldehydes and ketones

###### (i) From aldehydes

The reaction of aldehydes with acetic anhydride and a catalyst is the most common procedure for the preparation of 1,1-diacetoxy alkanes (Equation (89)). In addition to the protic and Lewis acids reported in COGFT (1995) <1995COGFT(4)159>, more recent catalysts include NBS

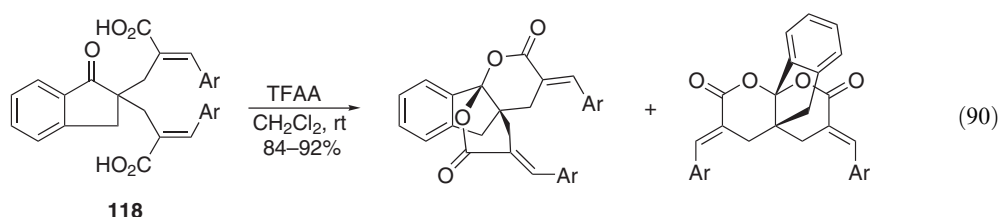
<2000SL623>, bismuth triflate <2001TL8133>, and lithium tetrafluoroborate <2001SL1921>. Heterogeneous catalysts include zeolites <1995TL601, 1995S1077>, sulfated zirconia <2002TL2709>, and expansive graphite <1997SC3379>. Yields for most of these catalysts were modest to good and differences in yields between aliphatic and aromatic are observed. Additional anhydrides can be used in this reaction. For example, the reaction of pent-4-enoic anhydride with benzaldehyde and sulfuric acid catalyst gave the corresponding acylal in 96% yield <1995JOC772>.



#### (ii) From ketones

The reaction of anhydrides with ketones and an acid catalyst is usually not as general as with aldehydes. However, some catalysts have been developed for this. Solid sulfated zirconia has been reported to give high yields of the diacetate <1996JCR(S)68>, while  $Sc(OTf)_3$  has been used for the preparation of mixed derivatives <2000TL2389>.

Keto diacids such as **118** (Equation (90)) can also be dehydrated to produce spirolactones <2001OL3619>. Aromatic groups used were phenyl, 4-alkyl, 4-methoxy, and 2- or 3-chlorophenyl substituted, all in excellent yields.

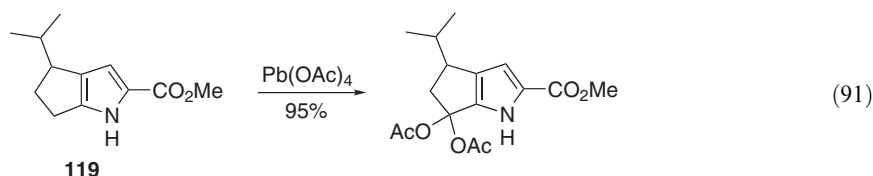


#### 4.04.4.1.2 From carboxylic acids

No examples of this transformation have been reported in the period 1993–2003.

#### 4.04.4.1.3 By oxidation of aromatic methyl and methylene groups

Oxidation of aromatic appendages is a standard method and several examples are given in <1995COFGT(4)159>. An example, shown in Equation (91) involves oxidation of bicyclic **119** using lead(IV) acetate in refluxing chloroform <1999TL6117>.



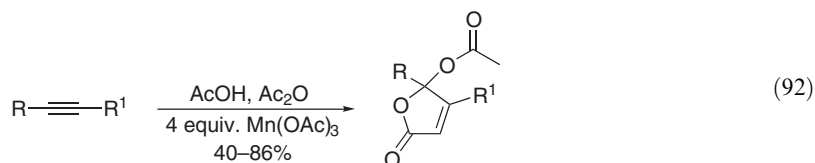
#### 4.04.4.1.4 By oxidation of furan derivatives

No examples of this transformation were reported within the decade 1993–2003.

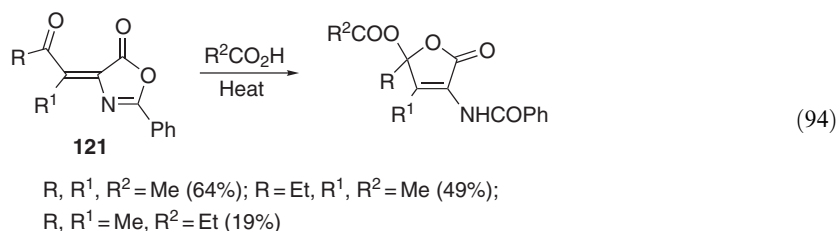
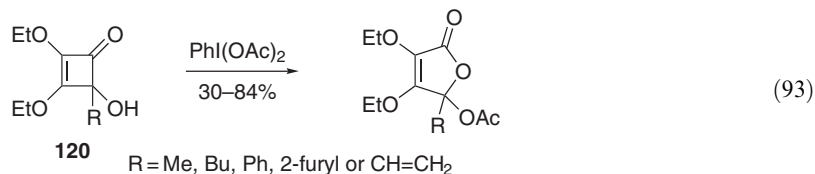
#### 4.04.4.1.5 Miscellaneous methods

In a new variation of an old reaction, alkynes yield furanones when treated with acetic acid in the presence of manganese triacetate (Equation (92)) <2000T9339>. Substrates involved in the study were  $R = Ph$  with  $R^1$  as H, Me, propyl, Ph, and  $SiMe_3$ ;  $R = SiMe_3$ ,  $R^1 = butyl$ ,  $R = octyl$ ,  $R^1 = H$ , and  $R, R^1 = propyl$ .





As expected, the Baeyer–Villiger oxidation of spirocyclic 1,3-ketones and lactones led to spirocyclic bis-lactones with good regioselectivity and yields of 38–90% [<1998TL4459>](#). Also reported was the reaction of hydroxy cyclobutenones **120** with  $\text{PhI(OAc)}_2$ , which give rise to 5-acetoxy-2(5*H*)-furanones ([Equation \(93\)](#)) [<1999JOC8995>](#). An additional report on the formation of acetoxy furanones was the rearrangement of **121** with either acetic or propanoic acid. However, only modest yields were obtained ([Equation \(94\)](#)) [<1997T1843>](#).

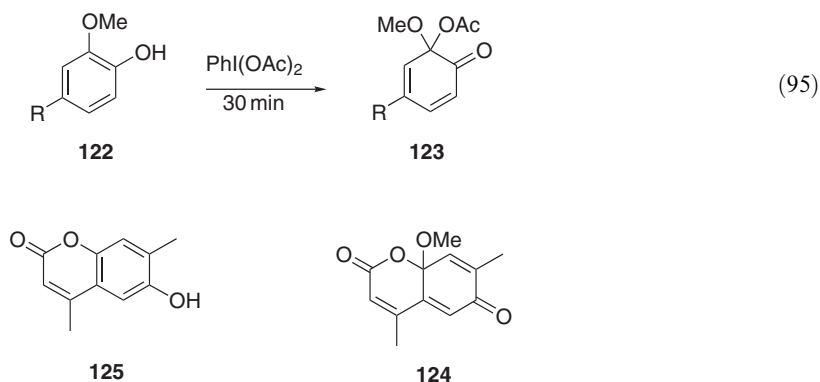


#### 4.04.4.2 Synthesis of $R_2^1C(OCOR^2)OR^3$

Numerous spiroacetals contain this functional group and reviews on their formation have appeared [<1999JHC1373, 1999T7661, 1998CUOC395, 2001CUOC233>](#). However, a few are mentioned below.

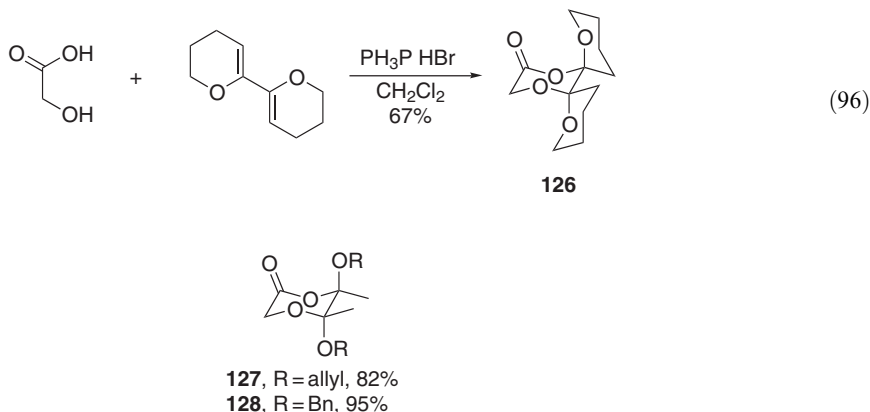
##### 4.04.4.2.1 From ethers

Oxidation of aliphatic ethers is a commonly used procedure as discussed in [<1995COFGT\(4\)159>](#), and a variation of this is the oxidation of methoxyphenols. Treatment of the methyl ethers **122** with  $\text{PhI(OAc)}_2$  in dichloromethane led to the formation of **123** in 93–99% yields ([Equation \(95\)](#)). In all cases, the R substituent was an alkyl group that was terminated by a silyl-protected alcohol. The advantages of using  $\text{PhI(OAc)}_2$  instead of typical lead oxidants such as  $\text{Pb(OAc)}_4$  are the absence of toxic lead salts and the removal of PhI and residual AcOH by-products by drying under vacuum [<1998JOC9597>](#).  $\text{PhI(OAc)}_2$  was also used in the formation of benzopyranone **124**, which was obtained in 97% yield from **125** [<2002JOC9475>](#).

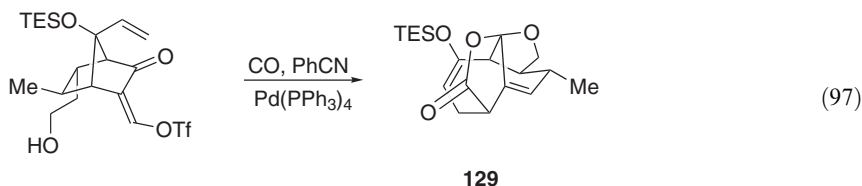


#### 4.04.4.2.2 From enol ethers and enol esters

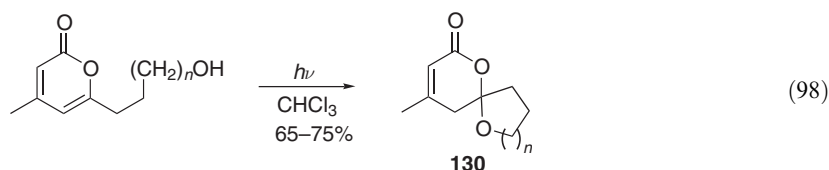
Dispiroketal are conveniently prepared by the reaction of glycolic acid with bi(dihydropyran) and catalytic  $\text{Ph}_3\text{P}\cdot\text{HBr}$  (Equation (96)) <1999JCS(P1)1647>. Glycolate **126** is obtained as a single racemic diastereoisomer, and this strategy has also been adapted to the synthesis of **127** and **128** <2001SL1793>.



Carbonylation of an enol triflate followed by tandem silyloxy-Cope rearrangement gives exclusively **129** in 46% yield (Equation (97)) <1999JA890>. Variations and mechanistic discussions of this procedure have also been presented <2000OL2905>. In brief, a mechanism involving isomerization of a  $\pi$ -allyl palladium species generated through an allenic intermediate is proposed.

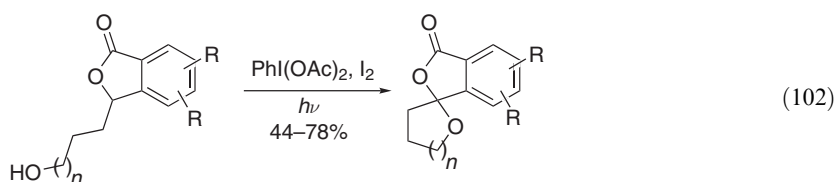
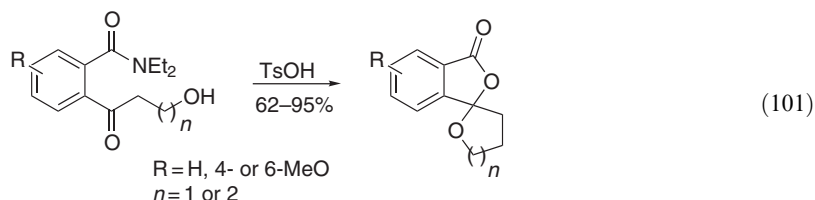
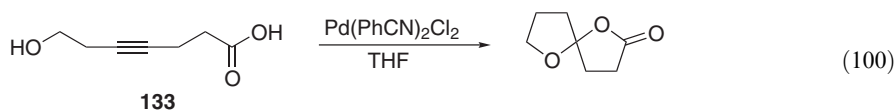
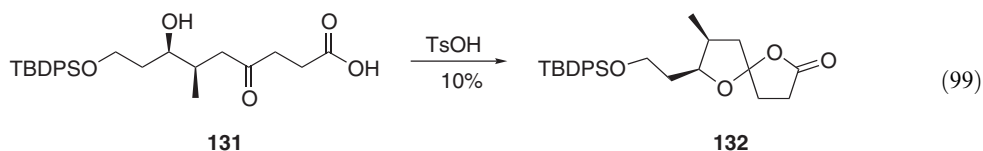


A final, less complex, transformation involves irradiation of pyranones bearing pendant alcohols (Equation (98)). These undergo intramolecular 1,6-addition to furnish the spirolactones **130** in yields of 65% for  $n = 1$  and 75% for  $n = 2$  <1995TL8531>.



#### 4.04.4.2.3 From carboxylic acids and carboxylic derivatives

Several methods for the formation of spirolactones from acids have appeared. Treatment of **131** with *p*-toluenesulfonic acid gave **132**, albeit in low yields (Equation (99)) <2000AJC845>. Alternatively, a similar spirolactone has been prepared by a palladium-induced cyclization of hydroxyalkynoic acid **133** (Equation (100)) <1995JCS(P1)1309>. This is reported as an unstable molecule and no yield is given. A more general method involves cyclization of the keto alcohols as shown in Equation (101) <1996T9553>. Yields are generally very good (62–95%) and the keto alcohols are prepared in one step by reaction of the ortho-lithiated diethylbenzamides with lactones. A similar general method involves oxidative cyclization using iodobenzene diacetate and iodine under photolytic conditions (Equation (102)) <2000TL3955>. In all cases with the latter example, the aromatic ring contains one or two methoxy groups, and when  $n = 1$  good yields are obtained (72–82%) while with  $n = 2$  a 44% yield results. Various substituents on the pendent alkyl chain are used as well.

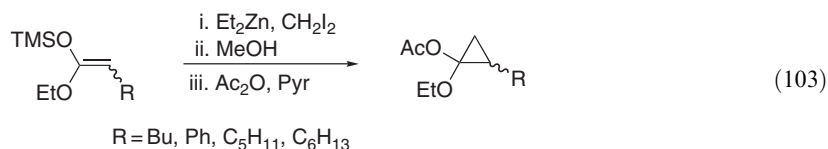


#### 4.04.4.2.4 From alcohols and carboxylate derivatives

No examples of this transformation have been reported in the period 1993–2003.

#### 4.04.4.2.5 From hemiacetals

Acylation of hemiacetals is a general method and an example is shown in Equation (103). The cyclopropane hemiacetals were readily prepared via cyclopropanation of the silylketene acetals followed by methanolysis. Acetylation with acetic anhydride gave the acyl alkyl acetals in high yield <2001OL189>.



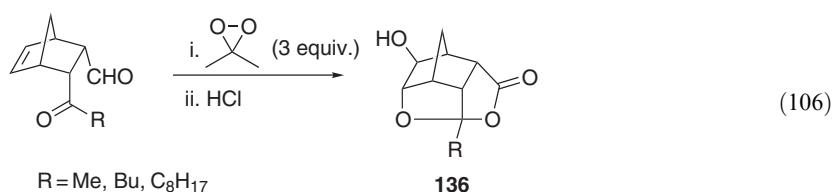
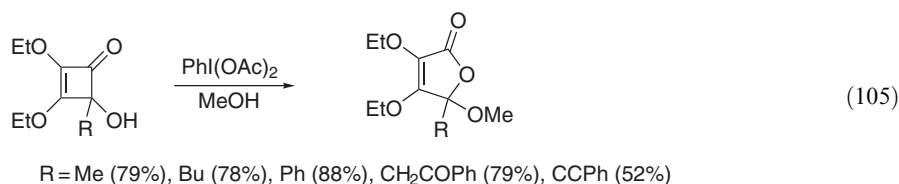
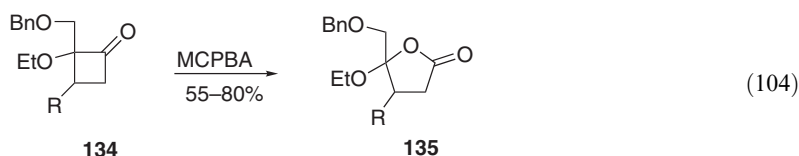
#### 4.04.4.2.6 From acetals

No examples of this transformation have been reported in the period 1993–2003.

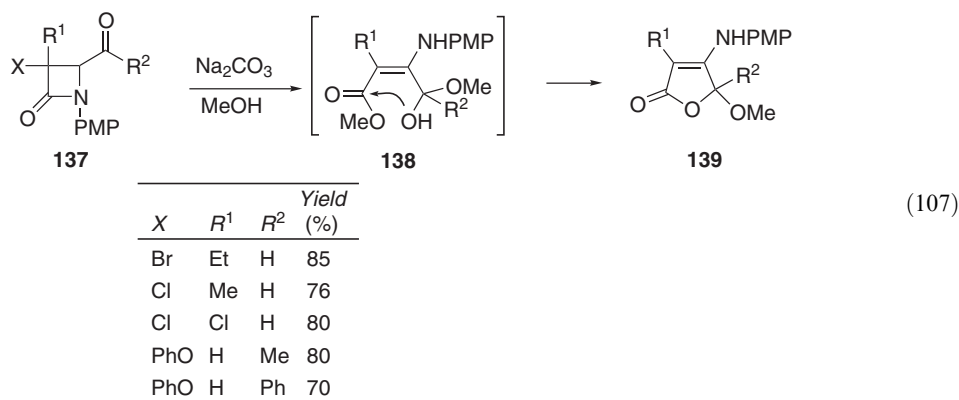
#### 4.04.4.2.7 From aldehydes and ketones by oxidation

Baeyer–Villiger oxidation of  $\alpha$ -alkoxy ketones to acyl alkyl acetals is a high-yielding method (Equation (104)). Application to lactones has been developed extensively. For example, **135** can be routinely prepared from the corresponding cyclobutanones **134** in high yields <2002JOC7649>, where R is a chiral oxazolidinone. An alternative ring expansion involves the reaction of hydroxycyclobutenones with PhI(OAc)<sub>2</sub> in methanol (Equation (105)). This gave the furanones in yields of 52–88%, in which an acyl cation is proposed as the key intermediate

<1999JOC8995>. The synthesis of diacetal compounds **136** via dimethyldioxirane-induced sequential cyclization of bicyclic olefins has also been reported (Equation (106)). Yields of 86–90% were obtained <2000T341>.



A final ring expansion, only involving pendant carbonyls and treatment with base, involves the rearrangement of azetidinones **137** (Equation (107)). Good yields of the enaminones **139** were obtained, in which a tandem E1cB-elimination–rearrangement followed by ring opening to give intermediate **138** was postulated <2000JOC3453>. A limiting factor appears to be the required use of the *p*-methoxyphenyl (PMP) protecting group.



#### 4.04.4.3 Other Derivatives

##### 4.04.4.3.1 1,2,4-Trioxalanes (ozonides)

No discussion is offered here and the reader is referred to <1995COFGT(4)159> for references to reviews on the subject.

##### 4.04.4.3.2 1,2,4-Trioxane

No discussion is offered here as these have been reviewed elsewhere <2002PHC317>.

4.04.4.3.3  $R_2^1C(OR^2)O_2R^3$ 

No discussion is offered here, however, a review on the chemistry of artemisinin and other  $C(OR)O_2R$  antimalarials has been published <1999H1681>.

4.04.4.3.4  $R_2^1C(OR^2)OX$  and  $R_2C(OX)_2$  ( $X = \text{heteroatom}$ )

No discussion is offered here, however, a review on general methods for the preparation of  $\alpha$ -hydroxy hydroperoxides and their application in oxidations has been published <1996S179>.

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## Biographical sketch



**John Hoberg** was born in the United States in 1962. He received his B.A. in chemistry from Jamestown College and his Ph.D. from Montana State University with Professor P. W. Jennings in 1990. After two years of postdoctoral work with G. Molander at the University of Colorado, he joined the National Renewable Energy Laboratory in Golden, CO. In 1998 he moved to Victoria University of Wellington, New Zealand and in 2004 joined the chemistry department at the University of Wyoming, USA. His research interests lie in the area of carbohydrate and organometallic chemistry, asymmetric and natural product synthesis.



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## 4.05

# Functions Incorporating Oxygen and Another Chalcogen

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### 4.05.1 FUNCTIONS CONTAINING OXYGEN AND SULFUR

This section contains methods for the synthesis of compounds containing a substituted carbon connecting oxygen to sulfur. Monothioacetals are reviewed first, which are not only useful carbonyl protecting groups, but also useful intermediates in organic synthesis. This is followed by a description of the corresponding molecules with tri- and tetracoordinated sulfur.

#### 4.05.1.1 Monothioacetals and Other Derivatives with Dicoordinate Sulfur

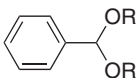
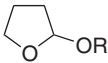
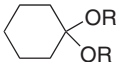
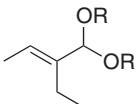
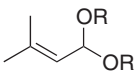
##### 4.05.1.1.1 *Acyclic compounds*

(i) *From carbonyl compounds, enols, and other acetals*

Generally, monothioacetals have been synthesized by Lewis acid mediated transacetalization of acetals such as  $\text{RSH}/\text{BF}_3 \cdot \text{Et}_2\text{O}$ ,  $\text{RSH}/\text{MgBr}_2$ ,  $\text{Me}_2\text{BBR}/\text{RSH}/\text{Pr}^i\text{NEt}_2$ ,  $\text{Bu}_{4-n}\text{Sn}(\text{SPh}_2)_n/\text{BF}_3 \cdot \text{Et}_2\text{O}$ , and  $\text{PhSH}/\text{Et}_3\text{Al}$ . As an alternative, two milder catalytic approaches have been developed as shown in [Table 1](#).

Catalytic lithium bromide reacts chemoselectively with acetals to produce the corresponding monothioacetals efficiently <2001SL1581>. Competitive monothioacetalizations demonstrate preferential reaction with benzylic acetals over tertiary carbon centered *O,O*-acetals which are more reactive than quaternary carbon centered *O,O*-acetals. Additionally, tetrahydropyranyl (THP) and methoxymethyl (MOM) ethers are less reactive than benzylic and trisubstituted acetals. In this chapter, no comparison is made between ethers and quaternary acetals. Dicyanoketene ethylene acetal (DCKA) is also used to catalyze the monothioacetalization of acetals <1995T10477>. This catalyst is an alternative to Lewis acids and is efficient particularly for the conversion of  $\alpha,\beta$ -unsaturated acetals to monothioacetals. DCKA catalysis has been further developed as a polymer support that is recyclable <1998TL5799>.

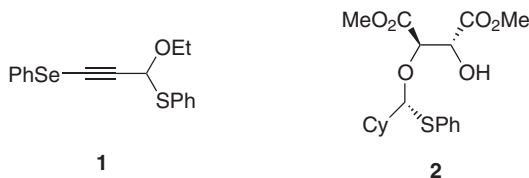
**Table 1** Monothioacetalization of acetals

Acetal	Conditions <sup>a</sup>	Nucleophile	R	Yield (%)	References
PHCH(OR) <sub>2</sub>	A	PhSH	Me	99	<2001SL1581>
	A	PhSH	Pr <sup>i</sup>	93	<2001SL1581>
	A	EtSH	Me	68	<2001SL1581>
	C	PhSH	Me	83	<1998TL5799>
	B	PhSH	CH <sub>3</sub>	77	<1995T10477>
	B	TMS-SPh	CH <sub>3</sub>	90	<1995T10477>
	A	PhSH	Bu	82	<2001SL1581>
	B	PhSH	<i>n</i> -C <sub>5</sub> H <sub>11</sub>	93	<1995T10477>
	C	PhSH	<i>n</i> -C <sub>5</sub> H <sub>11</sub>	86	<1998TL5799>
	B	TMS-SPh	Me	87	<1995T10477>
	C	TMS-SPh	Me	80	<1998TL5799>
	B	TMS-SPh	CH <sub>3</sub>	74	<1995T10477>
	B	TMS-SPh	CH <sub>3</sub>	91	<1995T10477>

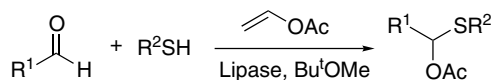
<sup>a</sup> Conditions A: LiBr (20%), toluene, 25 h, B: Dicyanoketene dimethyl acetal (0.2 equiv.), DMF, C: DCKA polymer, CH<sub>3</sub>CN.

*O,S*-Acetals can be formed selectively from enol ethers in one step with thiophenol or ethanethiol <1995SC3155>. Acyclic enol ethers do not require an acid catalyst while the cyclic enol ethers require Lewis acids such as BF<sub>3</sub>·OMe<sub>2</sub>.

$\gamma$ -Selenopropynal diethyl acetals provide stabilized cations that can react with mild nucleophiles to afford monothio- and monoselenoacetals <1995CCC149>. Monothioacetal **1** is synthesized from the diethyl acetal upon treatment with Bu<sub>2</sub>AlSPh in 72% yield. Opening tartrate acetals is another route to form thioacetals <2003JA428>. The addition of bromodimethyl borane to acetals followed by thiophenol produces hemithioacetal **2** in 68% yield with 6:1 diastereoselectivity.



Enantioselective acetylation of hemiacetals is achieved by a dynamic kinetic resolution <1995TL8493>. A thiol and aldehyde condense to form a racemic hemithioacetal in which one enantiomer is acylated by “*pseudomonas fluorescens*” lipase as shown in Table 2. This method has been applied to the enantioselective enzymatic synthesis of lamivudine, an antiviral agent <1995TL6961>.

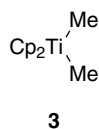
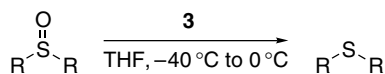
**Table 2** Enantioselective acetylation of hemithioacetals

Entry	$R^1$	$R^2$	Time (days)	Yield (%)	ee %, Configuration
1	MeO(CO)	Bu <sup>n</sup>	9	63	>95, (S)
2	MeO(CO)	EtSiO(CH <sub>2</sub> ) <sub>2</sub>	9	87	90, (S)
3	BnOCH <sub>2</sub>	Bu <sup>n</sup>	5	79	62, (R)
4	AcOCH <sub>2</sub>	EtSiO(CH <sub>2</sub> ) <sub>2</sub>	6	73	>90, (S)
5	AcOCH <sub>2</sub>	(MeO) <sub>2</sub> CH(CH <sub>2</sub> ) <sub>2</sub>	4	78	55, (S)

Source: &lt;1995TL8493&gt;.

## (ii) From sulfoxides

A novel deoxygenation of sulfoxides to the corresponding sulfides can be achieved using a titanocene methylidene complex **3** generated from the Tebbe or Petasis reagents <2000AG(E)2529>. In contrast to previous methods with harsh reagents and long reaction times, this reaction method is complete within 3 h, proceeds at low temperatures (−40 to 0 °C), and tolerates various functional groups as shown in Table 3. Kobayashi and co-workers have reduced sulfoxides with an equimolar amount of ferrocene and trifluoroacetic anhydride (TFAA) to give a mixture of sulfides and α-trifluoroacetoxy-methyl sulfides <2000CL400>. The latter product is a result of a Pummerer rearrangement, typical for sulfides containing an α-methyl group.

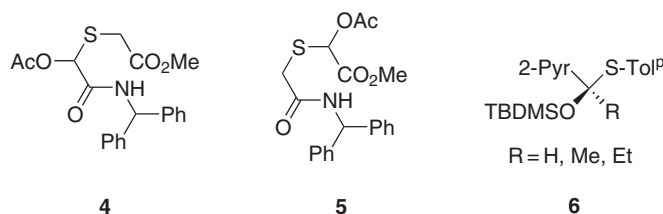
**Table 3** Reduction of sulfoxides

Starting Material	Product	Time (h)	Yield (%)
		2	50
		1	76
		0.5	84

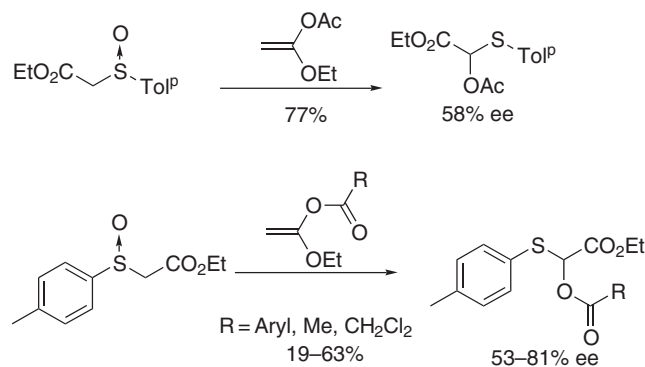
Source: &lt;2000AG(E)2529&gt;.

<sup>a</sup> PMB = *para*-methoxy benzyl.

Pummerer-type reactions provide various  $\alpha$ -substituted sulfides from the corresponding sulfoxides. The reaction of sulfinyl diacetic acid amide ester with *t*-butyldimethylsilyl triflate (TBDMSOTf) affords the corresponding amide  $\alpha$ -acetoxy sulfide **4** or the ester  $\alpha$ -acetoxy sulfide **5** by a chemoselective Pummerer reaction <2002TL1519>. Chemoselectivity can be tuned by the use of different solvents: more polar aprotic solvents favor **5** and less polar protic solvent favors **4**.

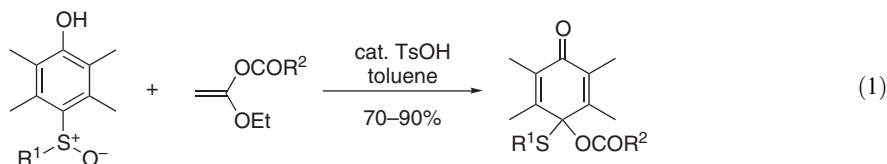


Asymmetric Pummerer-type reactions have been reported in which the deprotonation of the sulfoxides is the enantio-determining step. For example, ethoxy vinyl esters react with chiral sulfoxides as shown in Scheme 1 <1997TA303>. A highly stereoselective Pummerer reaction was achieved by reacting chiral  $\alpha$ -substituted sulfoxides with *O*-silylated ketene acetals in the presence of catalytic  $\text{ZnI}_2$  in tetrahydrofuran (THF) <1997JCS(P1)1763>. The  $\alpha$ -siloxo sulfides **6** were obtained in good yields (49–75%) and excellent enantioselectivity (>99%).



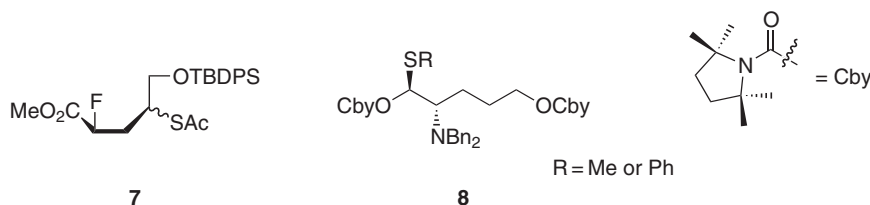
Scheme 1

An aromatic Pummerer-type reaction affords quinone *O,S*-acetals as shown in Equation (1) <2001JOC2434>. These quinone thioacetals aromatize when reacted with nucleophiles to afford sulfonylation products.



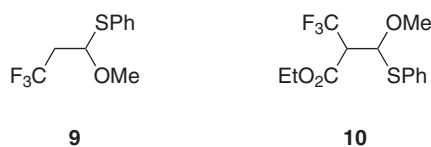
(iii) From vinyl sulfides,  $\alpha,\beta$ -unsaturated nitriles, and other reactions

Monothioacetals are also produced from  $\alpha$ -halo sulfides,  $\alpha$ -halo ethers and thiols, as reported in COFGT (1995) <1995COFGT(4)215>. An application of  $\alpha$ -ether sulfides is the synthesis of  $\beta$ -thionucleosides <2003JMC389>. An iodo ester is treated with potassium thioacetate in dimethylformamide (DMF) to afford the corresponding thioacetate **7**.

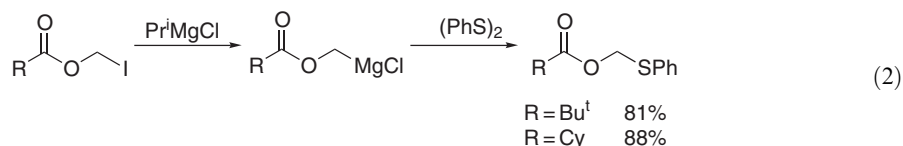


A regio- and stereoselective lithiation with *s*-butyllithium is achieved by deprotonation of a dicarbamate via a bis-chelate complex to afford a stereohomogeneous and regioisomerically pure product **8** <1998S1274>. This method is also used to form the seleno product (see Section 4.05.2.1.1, Equation (31)).

Vinyl sulfides react with sodium trifluoromethanesulfonate ( $\text{CF}_3\text{SO}_2\text{Na}$ ) and *t*-butyl hydrogen peroxide by a single electron transfer producing a stabilized cation <1999PS(153)323>. This cation is then trapped by a nucleophile such as methanol to afford  $\alpha$ -trifluoromethylthioacetal **9**. Fuchigami and co-workers have reported an electrosynthesis of 3,3,3-trifluoropropyl phenyl sulfide <1998JFC209>. Platinum electrodes are used to carry out this anodic oxidation in methanol containing  $\text{Et}_3\text{N}\cdot 3\text{HF}$  to afford  $\beta$ -trifluoromethylated *O,S*-acetal **10**.



Mixed thioacetals can also be formed from reactions of magnesium carbenoids as shown in Equation (2) <1999SL1820>. The magnesium carbenoid containing an ester reacts with various electrophiles such as diphenyl disulfide.



Monothioacetals **11** are also prepared from Michael addition of benzenethiolate to substituted acrylonitriles <1995JOC4299>. This method provides  $\beta$ -phenylsulfenyl nitriles without competitive addition to the nitrile. Oxetanes **12** are synthesized from the Paternò–Büchi photocycloaddition of aromatic aldehydes with silyl *O,S*-ketene acetals <2000JA4005>. Similar reactions are conducted with the corresponding *O,Se*-acetals (*vide infra*).



#### 4.05.1.1.2 Compounds with oxygen in a ring

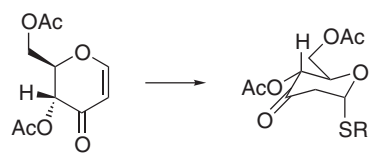
##### (i) From ethers, enols, aldehydes, and other acetals

Hex-1-ene-3-ulose reacts with various sulfur nucleophiles in a Michael-type addition to afford  $\alpha$ -deoxy-thioulosides <1996TL3453>.  $\text{ZnI}_2$  or KCN/18-crown-6 is used to catalyze the reaction shown in Table 4.

Radical additions to alkenes are promoted by hypervalent iodine as shown in Equation (3) <1996TL1889>. Iodobenzene diacetate (IBDA) oxidizes a thiocyanate anion to a radical that can

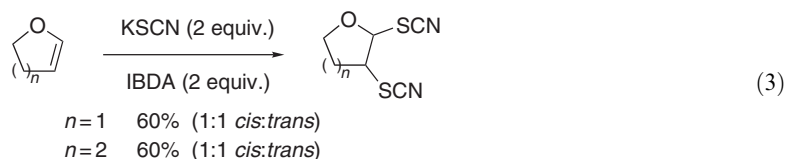
subsequently add to alkenes to provide dithiocyanate derivatives. In addition, dialkyl ethers react with IBDA, sodium azide, and diphenyl sulfide to afford mixed *O,S*-acetals in good yields [<1995SL1129>](#). This method can also be applied to *O,Se*-acetals (see [Table 13](#)).

**Table 4** Michael-type addition to hex-1-ene-3-ulose

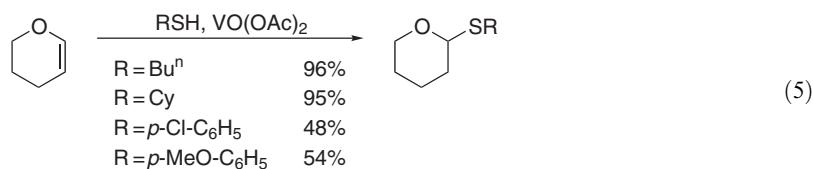
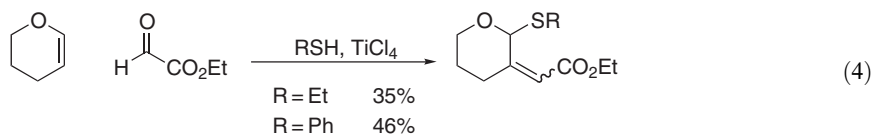


Nucleophile	Catalyst	Yield (%)
Bu <sup>n</sup> STMS	KCN/18-crown-6	46
allylSH	ZnI <sub>2</sub>	22
Z-Cys- <i>O</i> -allyl	ZnI <sub>2</sub>	41

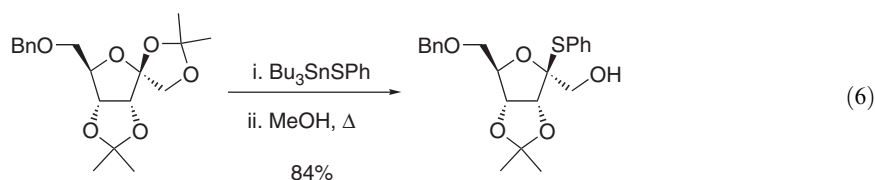
Source: [<1996TL3453>](#).



A three-component reaction process is described with dihydropyran, oxo-acetic acid ethyl ester, and sulfur nucleophile as shown in [Equation \(4\)](#) [<1999TL4751>](#). The reaction is promoted by TiCl<sub>4</sub> and affords functionalized tetrahydropyrans. Additionally, thiols readily add to dihydropyran in the presence of vanadyl(IV) acetate [<2001JMOC\(A\)169>](#). This method is a mild, heterogeneous reaction that provides the corresponding THP thioacetals in good yield as depicted in [Equation \(5\)](#). This is the first reported transition metal-catalyzed tetrahydropyranylation with thiols.

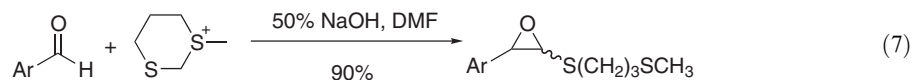


A regioselective opening of a substituted furanose with organostannanes provides the corresponding thioacetal as shown in [Equation \(6\)](#) [<1995TL5469>](#). Trimethylsilyl triflate mediates the *S*-glycosidation in which the  $\beta$ -anomer is formed preferentially.





Oxiranes are produced by the reaction of sulfonium ylides with aldehydes [<1995T10593>](#). This chapter includes ylides that contain thioalkyl substituents, which are unexpectedly stable as shown in [Equation \(7\)](#).

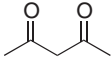
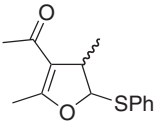
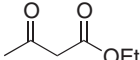
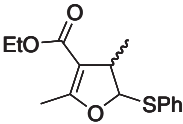
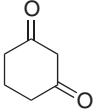
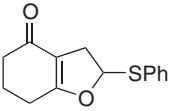
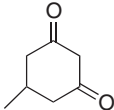
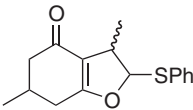
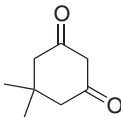
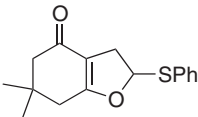


(ii) *By cycloadditions, photochemistry, and Pummerer-type reactions*

This section does not include hetero Diels–Alder reactions, although a number of papers have been published in the period 1995–2003.

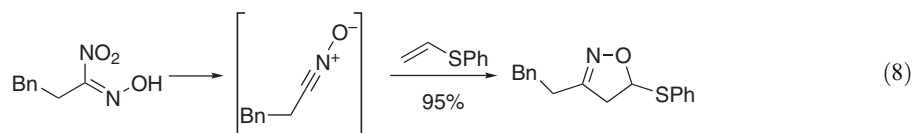
Oxidative cycloadditions of 1,3-dicarbonyls with vinyl phenyl sulfides have been reported [<1997TL2095, 1997TL5671>](#). These radical reactions can be mediated by metal salts of Mn(III), Ce(IV), Co(II), and Ag(I). Dicarbonyls react with various alkenes in acetonitrile with  $\text{Ag}_2\text{CO}_3$  and celite to form 3-acyl-furans and -dihydrofurans in good yields as shown in [Table 5](#).

**Table 5** Oxidative radical cycloaddition of 1,3-dicarbonyls to form dihydrofurans

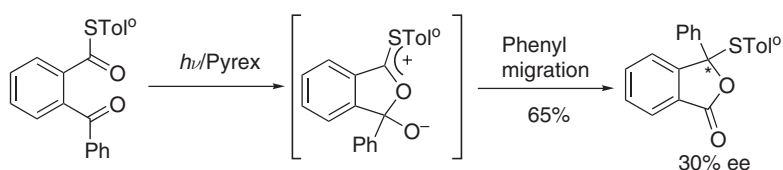
Dicarbonyl	$R^3$	Product	Yield (%)
	Me		83
	Me		63
	H		77
	Me		86
	H		77

Source: [<1997TL5671>](#).

1,3-Dipolar cycloadditions provide access to five-membered heterocycles. Isoxazoles are obtained by heating nitrolic acids, forming nitriles that subsequently undergo cyclizations in the presence of alkenes (Equation (8)) <2000TL1191>.

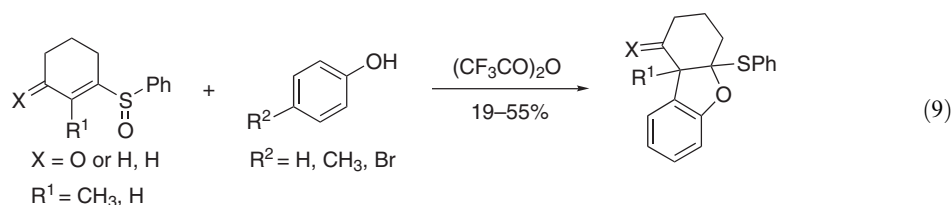


Solid-state photochemistry of aroylbenzothioates affords asymmetric phthalide formation <1998JA12770>. Scheme 2 depicts a novel absolute asymmetric reaction involving an intramolecular cyclization and phenyl migration.

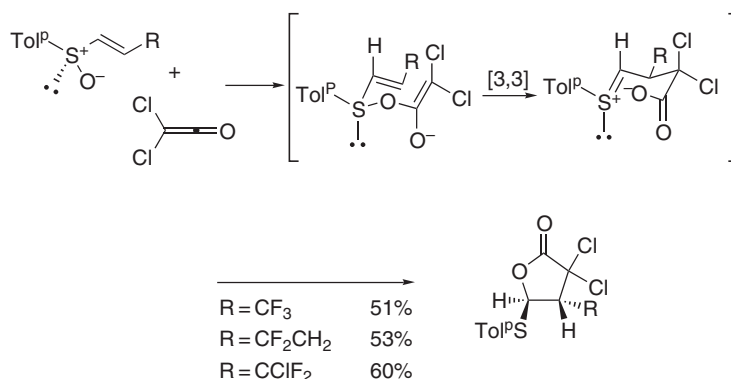


Scheme 2

A two-component [3,3]-sigmatropic rearrangement provides dihydrobenzofurans as shown in Equation (9) <2000OL2729>. This reaction proceeds via reduction of the sulfoxide and oxidation of the carbons involved. Elimination of thiophenol leads to substituted benzofurans.

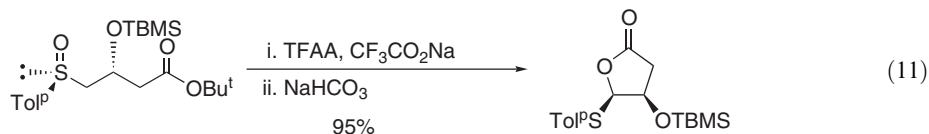
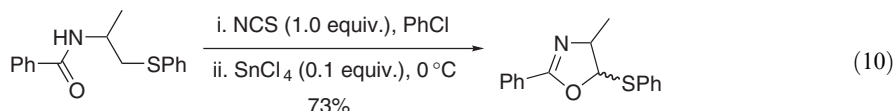


Sulfoxide-directed lactonization affords a stereoselective synthesis of enantiomerically pure  $\gamma$ -butyrolactones by a Pummerer-type reaction followed by a [3,3]-sigmatropic rearrangement as shown in Scheme 3 <1999EJO111>. Trichloroacetyl chloride with zinc dust and copper(II) chloride generate dichloroketene which reacts with vinyl sulfide derivatives to afford lactones.

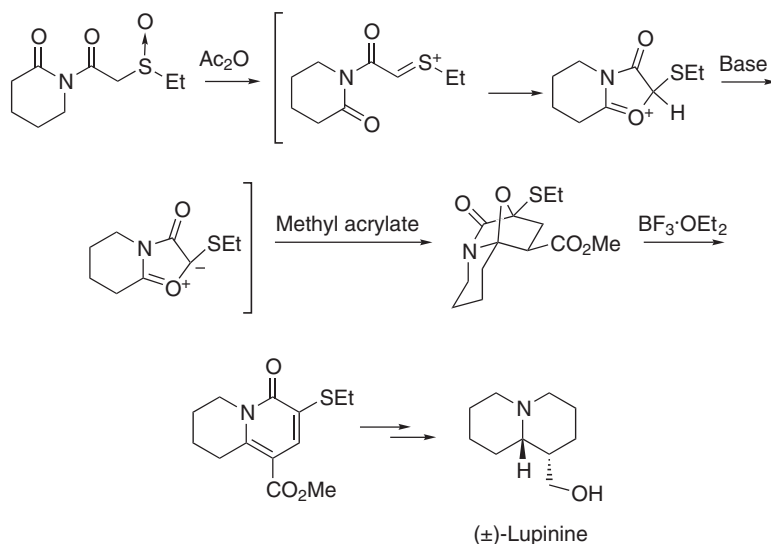


Scheme 3

Treatment of *N*-acylamino-2-thiophenol with *N*-chlorosuccinimide (NCS) followed by addition of  $\text{SnCl}_4$  affords the corresponding monothioacetal in good yield as shown in Equation (10) <2002TL7393>. An asymmetric Pummerer-type reaction provides a stereoselective synthesis of  $\beta$ -hydroxy- $\gamma$ -sulfenyl- $\gamma$ -butyrolactone as shown in Equation (11) <2000TL4189>. This is the first highly diastereoselective (>98% de) formation of the lactone under the Pummerer conditions.



Padwa and co-workers have explored a Pummerer cyclization–deprotonation–cycloaddition sequence to access naturally occurring alkaloids <2000JOC2368>.  $\alpha$ -Acyl sulfoxides generate thionium ions that are good electrophiles to react with various nucleophiles as shown in Scheme 4.



Scheme 4

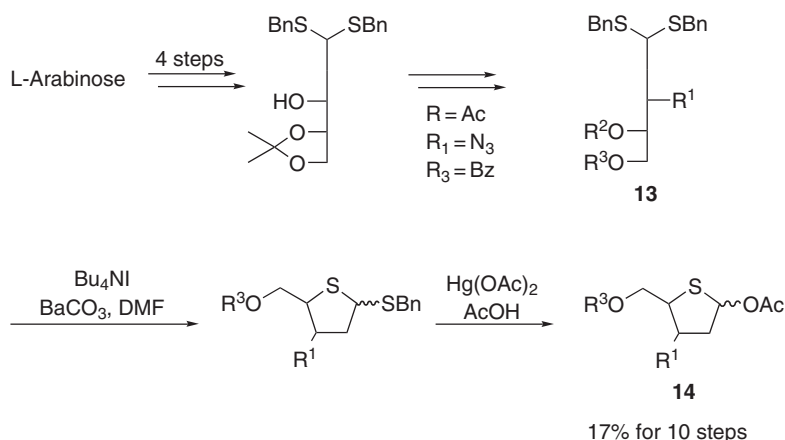
### (iii) By phase transfer catalyst

Phase transfer catalysis (PTC) is a convenient and useful method for carbohydrate synthesis because mild conditions can be used and reactions can be performed on large scale. Anomeric nucleophilic substitutions have been reported using mild PTC conditions for stereospecific entry to 1-thio- $\beta$ -D-mannosides and 1-thio- $\beta$ -L-rhamnosides <1996MI27>. Glycosyl bromides and chlorides are treated with thiophenol as the nucleophile and tetrabutylammonium hydrogen sulfate (TBAHS) as the phase transfer reagent to afford the corresponding phenyl thioglycosides. Ethyl acetate is shown to be a superior solvent in comparison to dichloromethane because the thiols can react with the latter to form bis(4-nitrophenylthio)methane. Allyl mercaptan can also serve as a nucleophile <2000JOC(A)9>.

Tetrabutylammonium thiocyanate and tetrabutylphosphonium bromide are also used in PTC for the synthesis of alkyl and aryl thioglycosides <1999JMOC(A)65>. The phosphonium salt is more effective than the ammonium salt.

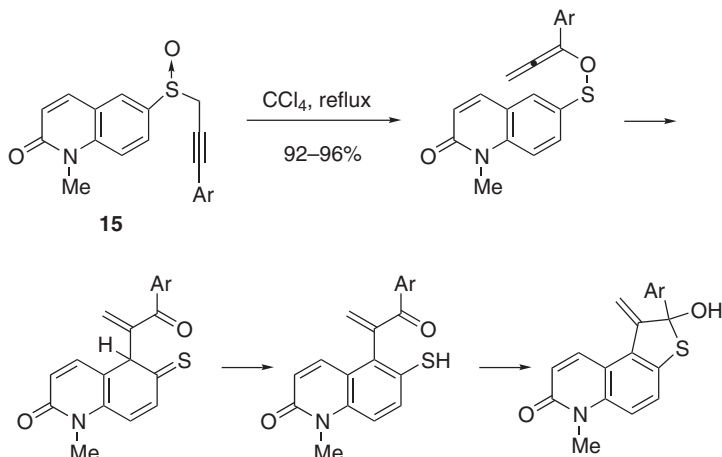
#### 4.05.1.1.3 Compounds with sulfur in a ring

Starting material **13** is obtained in four steps from L-arabinose for the synthesis of pentofuranose derivatives **14** as shown in Scheme 5 <1996JCS(P1)1665>. This mild method allows incorporation of sensitive functional groups as well as stereocontrol of the substituent at C-3.



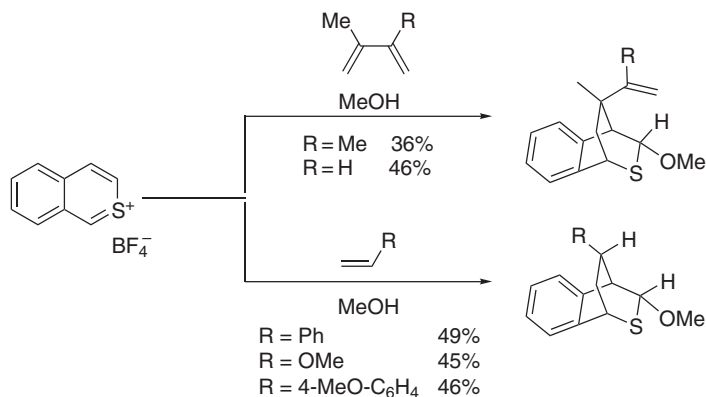
Scheme 5

Synthesis of a five-membered thiophene in a thienoquinolone system is accomplished via a sulfoxide rearrangement <1998T11603>. Sulfoxide **15** undergoes a [2,3]-sigmatropic rearrangement to give an intermediate allene. The allene subsequently undergoes a [3,3]-sigmatropic rearrangement followed by aromatization and formation of the monothio hemiacetal as shown in Scheme 6.



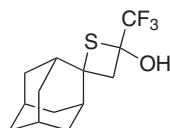
Scheme 6

Shimizu and co-workers have reported the  $[4^+ + 2]$ -type polar cycloadditions of 2-benzothiopyrylium salt with alkenes and dienes as shown in [Scheme 7](#) <1996CC2185, 2000TL2161>. For the dienes, a  $[2^+ + 4]$ -type reaction competes with the desired reaction to afford another cycloadduct.



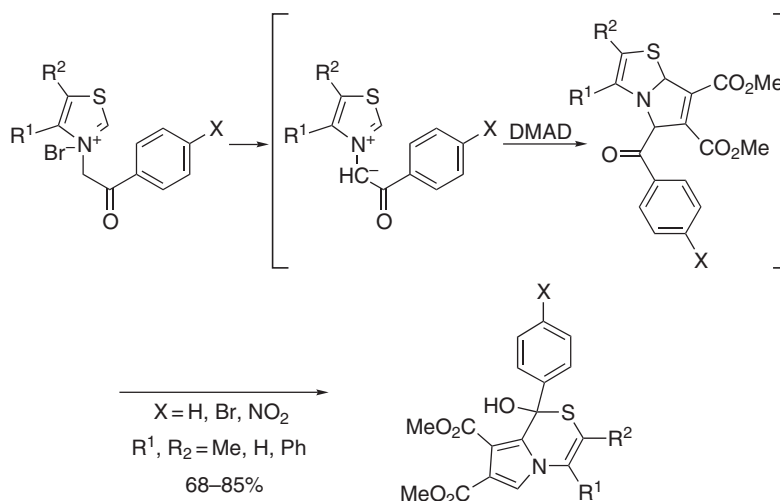
Scheme 7

Thietanes **16** are derived from the  $2\pi + 2\pi$  reaction of ammonium hydrosulfide with 3-adamantylidene-1,1,1-trifluoropropane-2-one <1996JOC1986>. This 2-thietanol is stabilized by the trifluoromethyl and geminal fragments as well as the adamantane structure.

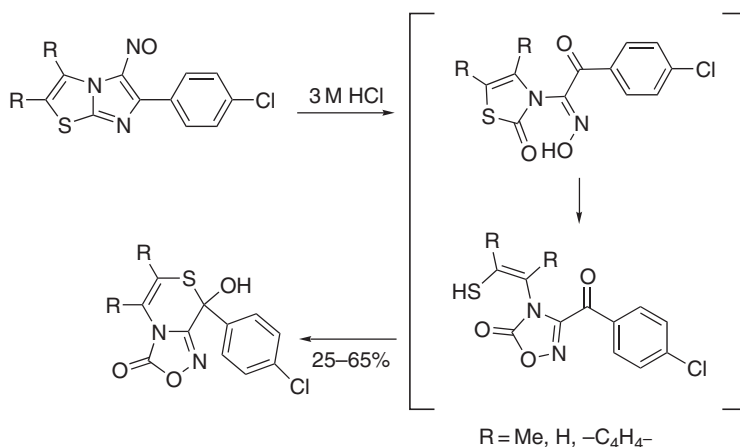


16

Reaction of thiazoliums and benzothiazolium *N*-phenylacylides with electron-deficient acetylenes and dimethyl acetylenedicarboxylate (DMAD) in wet DMF affords the corresponding hemiacetals as shown in [Scheme 8](#) <1996JCS(P1)629>. The proposed mechanism begins with the reaction with DMAD followed by interaction of the carbonyl and sulfur in a [1,5]-sigmatropic rearrangement. Thiazoles are also prepared from a ring-ring interconversion as shown in [Scheme 9](#) <2000SC875>.



Scheme 8



Scheme 9

#### 4.05.1.1.4 Cyclic monothioacetals

Thioacetals are commonly used protecting groups for aldehydes and ketones in multistep syntheses. They also serve as acyl carbanion equivalents.

##### (i) From carbonyl compounds, *O,O*-acetals, and xanthates

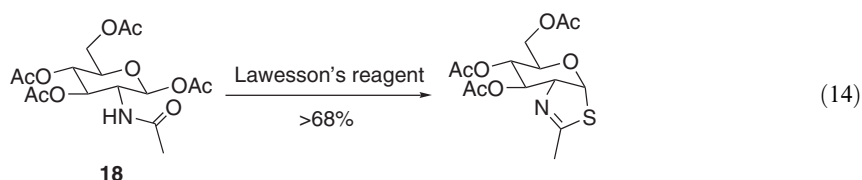
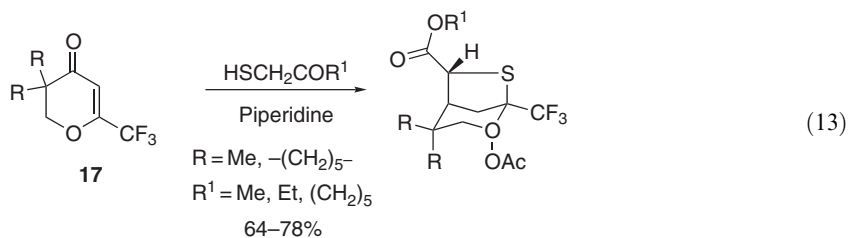
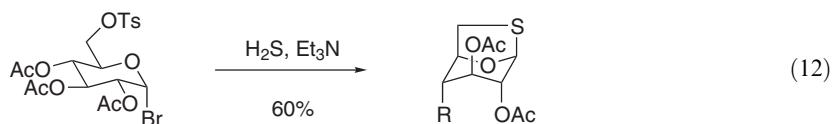
Monothioacetals are commonly prepared from 2-mercaptoethanol using strongly acidic conditions. Various catalysts are reported that avoid these harsh conditions. These catalysts are used with 2-mercaptoethanol or propanol and are highly selective for aldehydes over ketones. Bismuth trichloride is used as a catalyst for the protection of carbonyls as 1,3-oxathiolanes <1995SL984>. The bismuth salt is nontoxic, inexpensive, and easy to handle. Khan and co-workers report perchloric acid as well as organic tetra-*n*-butylammonium tribromide as catalysts to form monothioacetals <2002SL463, 2002TL2843>. Chlorinated silica gel is used in a ratio of 500 mg per mmol acylal <2001PS(176)165>. One report covers the use of bromine, *N*-bromosuccinimide (NBS) and 2,4,4,6-tetrabromo-2,5-cyclohexadienone <2002PS(177)1047>. NBS is further investigated for oxathioacetalization, thioacetalization, and transthioacetalization <2002TL6947>. Zirconium tetrachloride, lithium tetrafluoroborate, and indium trifluoromethanesulfonate are also efficient and chemoselective catalysts. <2000SL805, 2001SL238, 2002SL1535>.

For the synthesis of  $\alpha,\beta$ -unsaturated oxathiones, thiols can add 1,2 or 1,4 to  $\alpha,\beta$ -unsaturated carbonyls. Various Brønsted and Lewis acids were screened and the heterogeneous catalyst aminopropyl silica gel hydrochloride (APSG-HCl) as a supported catalyst proved to be superior <2002T10455>. This catalyst is simply removed by filtration.

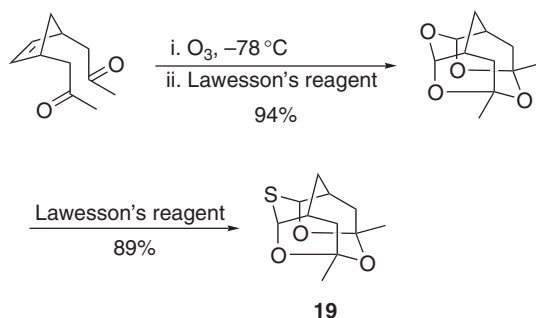
The reduction of cyclic xanthates 1,3-oxathiolane-2-thiones to 1,3-oxathiolanes has been reported using 2,2'-azobisisobutyronitrile (AIBN) and tributyltin hydride <1995HAC325>. A competing reaction forms the corresponding alkene stereoselectively. Using higher concentrations of tributyltin hydride diminishes the formation of alkene.

##### (ii) By intramolecular alkylation

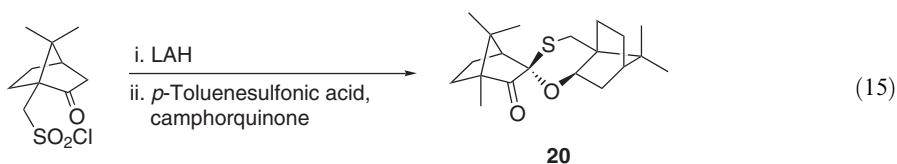
The synthesis of a 1,6-epithio bridge sugar is achieved from the corresponding bromo tosylate as shown in Equation (12) <1996AJC343>. This method is also applied to seleno sugars (*vide infra*). Thiabicyclic **17** is synthesized from the addition of mercaptoacetates to dihydropyrones as shown in Equation (13) <1998MC198>. Acetoamide pyranose **18** is converted to the thioamide by treatment of Lawesson's reagent as shown in Equation (14) <1996JA6804>.



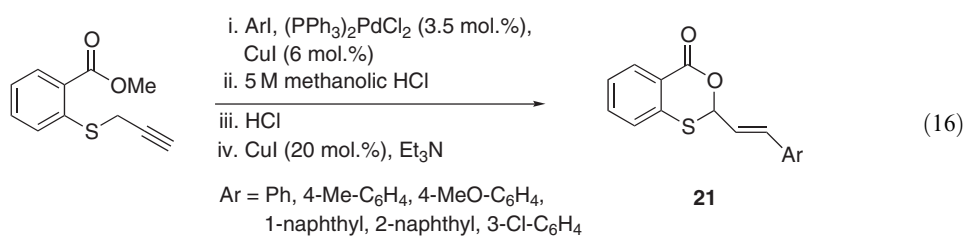
Thia-cage compounds **19** are synthesized from the tetraoxa-cage compounds when exposed to Lawesson's reagent as shown in [Scheme 10](#) [<2001JOC4610>](#). Novel camphor thioacetal **20** is synthesized from the reduced *exo* product of camphor-10-sulfonyl chloride as shown in [Equation \(15\)](#) [<2001JCR\(S\)405>](#).



Scheme 10

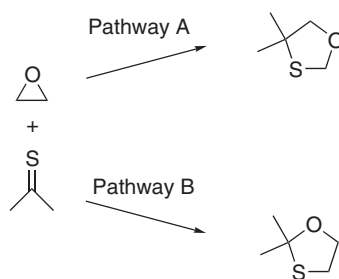


Benzoxathiinones are synthesized by a highly regio- and stereoselective method as shown in [Equation \(16\)](#) [<2001JCS\(P1\)1649, 2001SL415>](#). Copper(I) iodide is used to achieve cyclization and affords **21** in 25–70% yield.

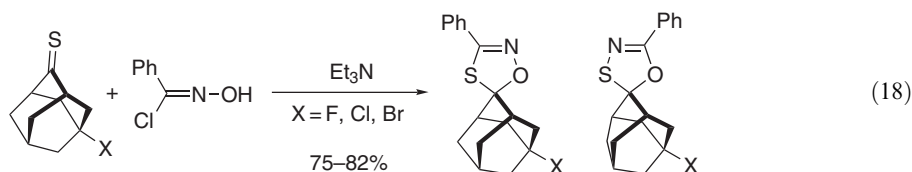
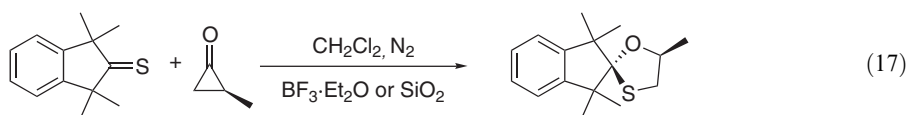


## (iii) By cycloaddition reactions

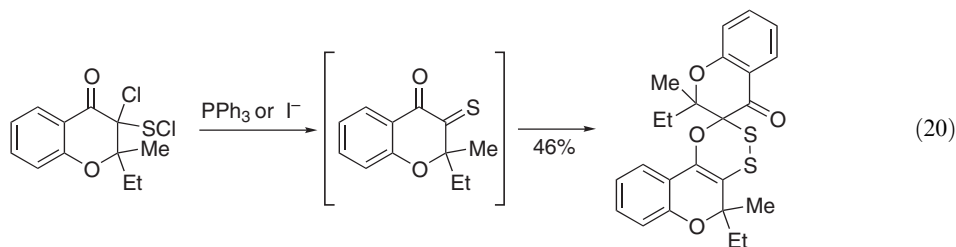
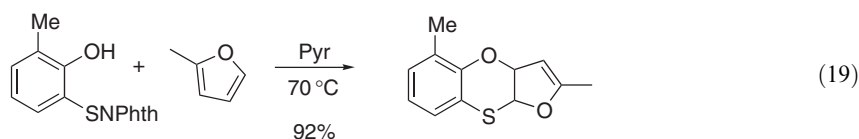
Thiocarbonyls react with oxiranes as shown in [Scheme 11](#) <1999HCA2316>. Pathway A is believed to proceed via a 1,3-dipolar cycloaddition of an intermediate carbonyl ylide. Pathway B occurs with cleavage of the carbon–oxygen bond and results in opening of the oxirane when activated by an electrophile. A silica gel mediated reaction of thiocarbonyls with oxiranes affords 1,3-oxathiolanes as shown in [Equation \(17\)](#) <2002H333>. 1,3-Dipolar additions are also reported for adamantane-2-thiones with benzonitrile oxides to provide oxathiazoles as shown in [Equation \(18\)](#) <1997JOC4672>.



Scheme 11

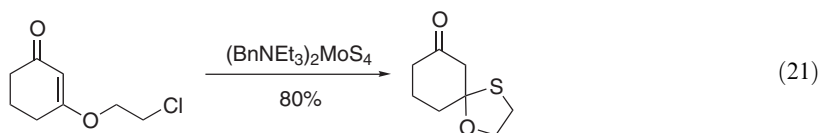


*o*-Thioquinones undergo a hetero-Diels–Alder reaction with 2-methylfuran as shown in [Equation \(19\)](#) <2000SL61>. In an attempt to reduce  $\alpha$ -chloro sulfonyl chlorides, the thiocarbonyl compound is formed and undergoes a dimerization via a [4 + 2]-cycloaddition as shown in [Equation \(20\)](#) <1998SUL19>.

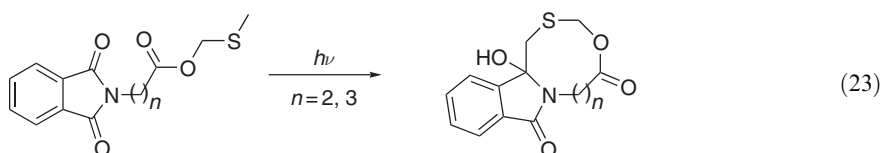
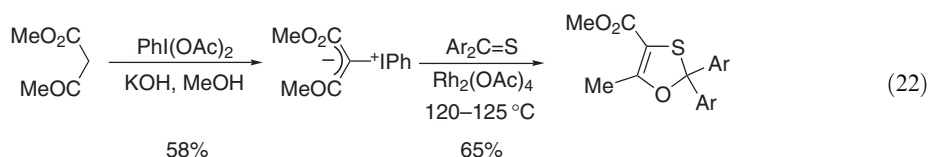


A tandem reaction mediated by benzyltriethylammonium tetrathiomolybdate results in the formation of monothioacetals as shown in [Equation \(21\)](#) <2000AG(E)4316>. The first step involves a sulfur transfer reaction mediated by the molybdenum to afford a ketosulfide followed by reduction and subsequent Michael addition.

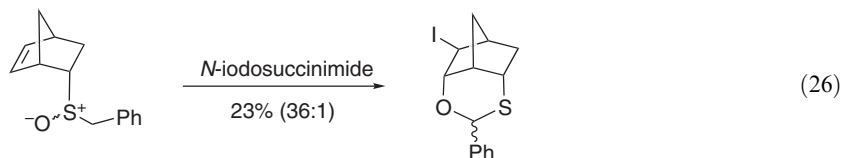
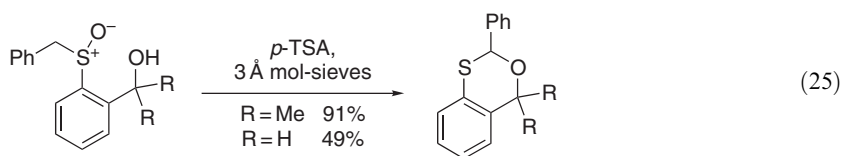
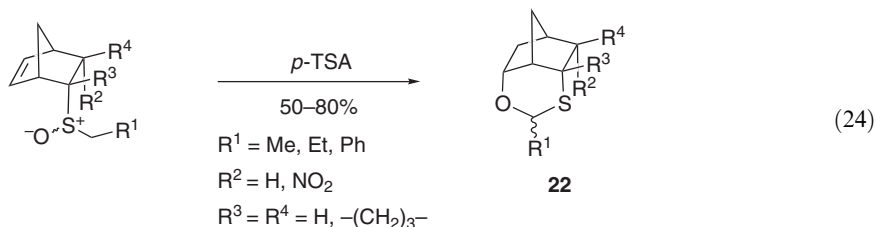




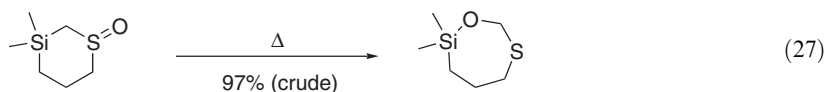
Oxathioles are produced from a rhodium(II) catalyzed cycloaddition as shown in Equation (22) <2002TL5997>. Methyl acetoacetate affords carbomethoxy iodonium ylides that cyclize when treated with diaryl thiones and rhodium acetate. Macrocyclization via photolysis of methylthio-methyl (MTM) ester has been reported and is shown in Equation (23) <2000JOC9028>.



1,3-Oxathianes are also synthesized via intramolecular Pummerer reactions.  $\gamma,\delta$ -Unsaturated sulfinyl compounds are treated with *p*-toluenesulfonic acid (*p*-TSA) to afford the oxathianes **22** as shown in Equation (24) <1995CC1197>.  $\gamma$ -Hydroxy sulfoxides also undergo this rearrangement as shown in Equation (25) <1999H291>. Furthermore, iodooxathianes are synthesized from the  $\gamma,\delta$ -unsaturated sulfinyl compound via an iodonium-promoted intramolecular Pummerer reaction depicted in Equation (26) <2000H465>.



A sila-Pummerer rearrangement of cyclic sulfoxides leads to a 1,3-oxathioacetal as shown in Equation (27) <1999TL185>. This thermal conversion is the first example of a sila-Pummerer rearrangement leading to a ring expansion.

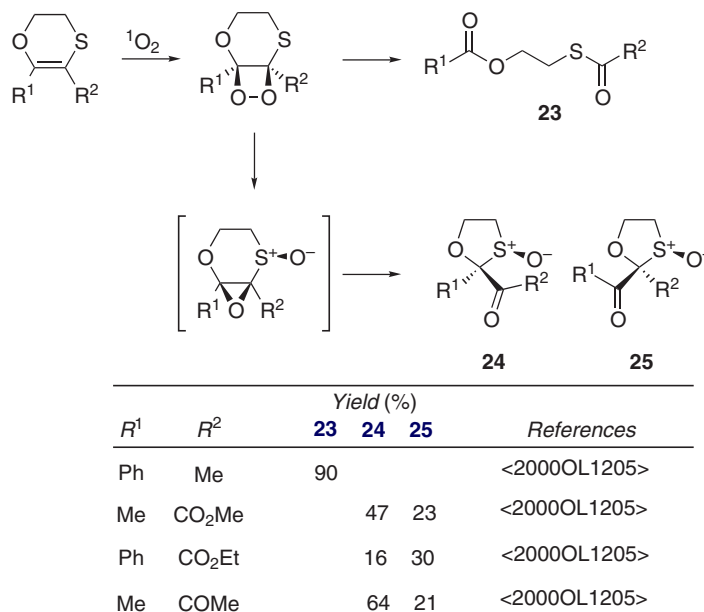


### 4.05.1.2 Derivatives with Tricoordinate Sulfur

#### 4.05.1.2.1 $\alpha$ -Alkoxy sulfoxides

Oxidation of sulfides to sulfoxides is commonly achieved by 3-chloroperoxybenzoic acid (MCPBA) or hydrogen peroxide. On large-scale operations of glycosyl sulfides, however, this method is problematic because low temperatures are required to prevent sulfone formation and completion of the reaction is not realized at low temperatures. In addition, the by-product *m*-chlorobenzoic acid is formed and is difficult to remove. To circumvent these drawbacks, Karkala and co-workers screened conditions to find a simple, inexpensive approach for the preparation of glycosyl and noncarbohydrate sulfides <1996JOC8347>. The oxidation method they support is a combination of hydrogen peroxide (1.2 equiv.), and acetic anhydride (1.1 equiv.) in dichloromethane. Reaction times can be reduced by using aprotic perfluorinated solvent mixtures without overoxidation to the sulfones <2001TA2389>.

Asymmetric oxidation of racemic 2-substituted-1,3-oxathianes was achieved using a catalytic di- $\mu$ -oxo Ti(salen) and urea hydrogen peroxide system <2003CHIR24>. Kinetic resolution led to the corresponding sulfoxides with high enantiomeric excess. Ketosulfoxides were unexpectedly produced from 5,6-dihydro-1,4-oxathiins when exposed to singlet oxygen <2000OL1205>. The proposed rearrangement shown in Scheme 12 details the formation of the ketosulfoxides in preference to the dicarbonyl.



Scheme 12

#### 4.05.1.2.2 $\alpha,\beta$ -Epoxy sulfides

A general approach to sulfinyloxiranes involves deprotonation of an  $\alpha$ -halo sulfoxide, then addition of a ketone or aldehyde, followed by cyclization of the resulting halohydrin. Satoh has reviewed oxiranyl anions that included sulfinyloxiranes <1996CRV3303>. Hydroxy chloro sulfoxides are treated with potassium *t*-butoxide to afford sulfinyloxiranes.

Asymmetric epoxidation of electron-deficient alkenes is achieved by nucleophilic epoxidation of vinyl sulfoxides <1998JOC4954>. The epoxidation of both vinyl and dieny sulfoxides was studied, as shown in Table 6. Alkene geometry is preserved in the resulting oxiranes with good yield and facial selectivity. Sodium proved to be the superior counterion compared to lithium and potassium by providing shorter reaction times and decreased amounts of overoxidized by-products. Increased substitution on the alkene leads to reduced or no reactivity. Cyclic substrates were also examined (Entries 9–11). Cyclohexenyl sulfoxides afford mixtures of products

when treated under oxidative conditions while the activated keto sulfoxides afford the  $\alpha,\beta$ -epoxy sulfides smoothly. When epoxidizing (*E*)-2-sulfinyl dienes, the metal cation influences facial selectivity (Entries 12–15). This sulfur-directed synthetic strategy is displayed in the formal syntheses of (–)-*trans*-Kumausyne and (+)-Kumausallene <1998JOC9612>.

**Table 6** Epoxidation of vinyl sulfoxides

Alkenyl sulfoxide		$\xrightarrow[\text{THF, 0 } ^\circ\text{C}]{\text{MOO-Bu}^t}$		$\alpha,\beta$ -Epoxy sulfoxides		
Entry	Product <sup>a</sup>	$R^1$	$R^2$	$M$	Time	Yield (%) <sup>b</sup>
1		Bu <sup>n</sup>	Tol <sup>P</sup>	Na	90 min	75 (13:83:4)
2		Bu <sup>n</sup>	Tol <sup>P</sup>	K	9 min	65 (94:6)
3		(CH <sub>2</sub> ) <sub>2</sub> Ph	Tol <sup>P</sup>	Na	220 min	67 (2:97:1)
4		Bu <sup>n</sup>	Bu <sup>t</sup>	K	75 h	65 (8:82)
5		Me	Tol <sup>P</sup>	Li	150 min	63 (6:92:2)
6		Me	Tol <sup>P</sup>	Na	100 min	80 (98:2)
7		Pr <sup>i</sup>	Tol <sup>P</sup>	Na	2 days	90 (13:85:2)
8		Pr <sup>i</sup>	Bu <sup>t</sup>	K	1 days	87 (3:73:1)
9 <sup>c</sup>		$n = 1$		Na	17 min	44 (36:5)
10 <sup>c</sup>				Li	10 min	48 (9:91)
11		$n = 0$		Na	160 min	60 (3:92:5)
12		H		Li	120 min	75 (20:80)
13		H		Na	90 min	61 (8:84:8)
14 <sup>d</sup>		Ph		Li	2 h	74 (2:12:86)
15		CH <sub>2</sub> OH		Na	120 min	80 (3:97)
16		H	H	Na	25 min	81 (95:5)
17		H	H	Na	90 min	94 (2:98)
18		H	Me	Na	160 min	60 (3:92:5)

Source: <1998JOC4954>.

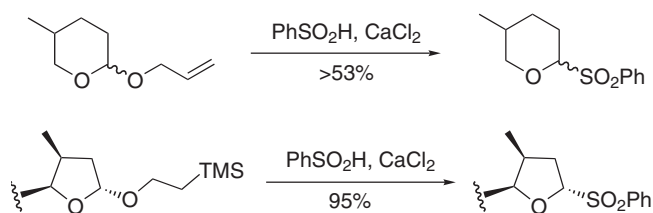
<sup>a</sup>  $\alpha$ -Epoxy sulfoxide shown; <sup>b</sup> Combined yield of pure products followed by ratio of sulfone: $\alpha$ -epoxide:  
 $\beta$ -epoxide; <sup>c</sup> Reaction carried out at  $-78^\circ\text{C}$ ; <sup>d</sup> Reaction carried out at  $-20^\circ\text{C}$ .

The above method is further developed using  $\alpha'$ -hydroxy sulfoxides and sulfones (*vide infra*) <2002JOC8166>. For (*E*)- $\alpha'$ -hydroxyalkyl vinyl sulfoxides, as the size of the substituent at the allylic position increases, so does stereoselectivity to afford the antiepoxides. Substitution at the  $\beta$ -carbon has a greater effect upon selectivity. Finally, changes in the metal cation can also enhance the reaction selectivity. Cyclic  $\alpha'$ -hydroxyalkyl sulfoxides were also investigated resulting in sulfone formation. The (*Z*)- $\alpha'$ -hydroxyalkyl vinyl sulfoxides are more reactive than the (*E*)-isomers.

#### 4.05.1.3 Derivatives with Tetracoordinate Sulfur

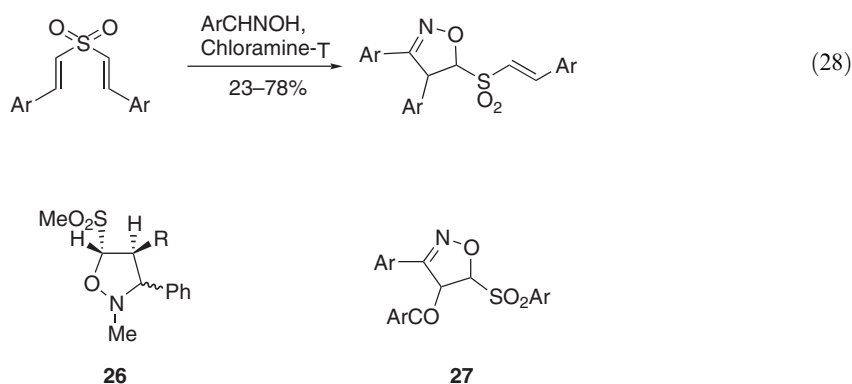
##### 4.05.1.3.1 $\alpha$ -Alkoxy sulfones and related compounds

Common oxidants used to oxidize sulfides to sulfones are MCPBA, hydrogen peroxide, and KMnO<sub>4</sub> <2003TA79>. Conversion of monocyclic *O,O*-acetals to the corresponding 1,3-oxathiane dioxides can be achieved in one step using phenylsulfinic acid and CaCl<sub>2</sub> as shown in Scheme 13 <1996JOC7860>. This method was applied in the enantioselective total synthesis of (+)-amphidinolide T1 <2003JA2374>.

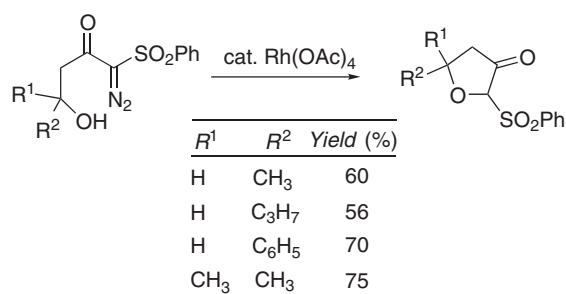


Scheme 13

1,3-Dipolar cycloadditions provide entry to five-membered heterocycles. Aryl sulfonylethenes undergo 1,3-dipolar cycloadditions in the presence of chloramine-T to afford bifunctional bispyrazoline and bisisoxazolines as shown in Equation (28) <2003PS(178)171>. Nitrones can also add to unsaturated methylsulfones via a 1,3-dipolar cycloaddition <1999JCR(S)566>. This reaction provides trisubstituted isoxazolidines **26** as a mixture of regioisomers. Isoxazolidines **27** are also prepared from araldoximes in the presence of chloramine-T <1999JCR(S)610>.



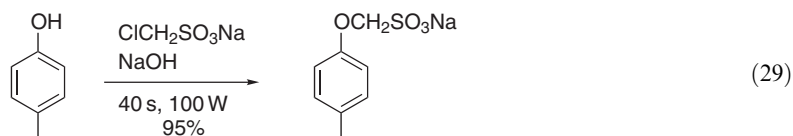
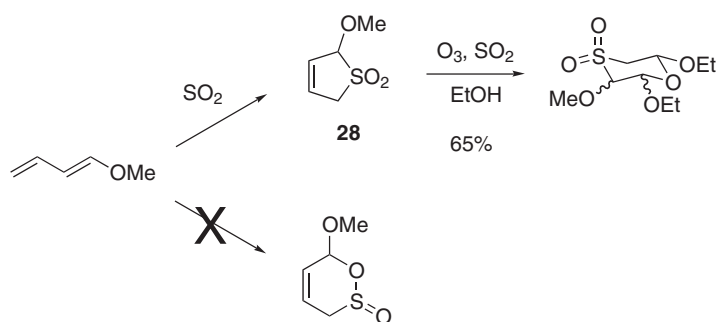
A rhodium catalyzed C—H insertion of phenyl sulfones leads to cyclization as shown in Scheme 14 <2000TL4773>.  $\text{Rh}_2(\text{OAc})_4$  forms the carbenoid from the diazo compound to provide access to furan derivatives.



Scheme 14

Sulfur dioxide reacts without any additives to electron-rich dienes, such as 1-methoxy-1,3-butadiene, below  $-60^\circ\text{C}$  to provide sulfolene **28** as shown in Scheme 15 <2000CEJ1858>. Reactions also proceed at  $-110^\circ\text{C}$  in the presence of Lewis acids. The corresponding sultine is not detected and **28** is used *in situ* to form sulfur heterocycles.

Sodium aryloxymethanesulfonates can be synthesized using microwave irradiation to promote the condensation of aryl alcohols with sodium chloromethanesulfonate <1999JCR(S)720>. A typical reaction is shown in Equation (29). The phenol can be derived from cresol, naphthol, allylphenol, etc. This method is superior to the Barber method, which generally uses temperatures up to  $220^\circ\text{C}$  for 4 h.



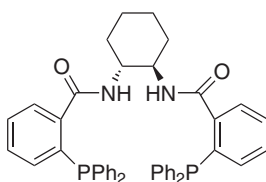
Trost and co-workers have demonstrated the use of sulfinates as nucleophiles in asymmetric allylic alkylation reactions. They are used in catalytic asymmetric synthesis of  $\alpha$ -acetoxysulfones as desymmetrizing reagents of allylic *gem* diesters as shown in Table 7 <2000JA6120>. Trisubstituted alkenes react slower than disubstituted alkenes, and electron-withdrawing groups do not affect the reaction. The chirality of the product can be inverted by changing the chirality on the ligand. The acetoxysulfones serve as aldehyde equivalents that allow for differentiation of the enantiotopic faces of  $\alpha,\beta$ -unsaturated aldehydes.

**Table 7** Asymmetric allylic alkylation of allylic *gem* diesters

$R^1$	$R^2$	Time (h)	Yield (%)	ee (%)
$C_6H_5$	$CH_3$	24	85	95
$o\text{-NO}_2\text{-C}_6\text{H}_4$	H	2	93	85
$n\text{-C}_3\text{H}_7$	H	4	94	98
$n\text{-C}_6\text{H}_{13}$	H	6	73	95
$EtO_2C$	$CH_3$	12	85	98

Source: <2000JA6120>.

Conditions: 6 mol.% **29**, 2 mol.%  $\pi$ -allylpalladium chloride dimer, sodium benzenesulfonate.

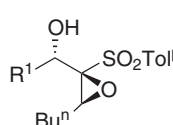
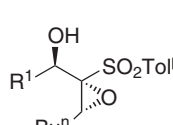
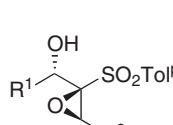


**29**

4.05.1.3.2  $\alpha,\beta$ -Epoxy sulfones

Stereoselective formation of  $\alpha,\beta$ -epoxy sulfones has been reported, using metal alkyl peroxides as well as metal-catalyzed reactions. Stereocontrolled nucleophilic epoxidations of  $\alpha'$ -hydroxyalkyl vinyl sulfones have been studied by Jackson and co-workers <1995JCS(P1)141>. Epoxidation of  $\beta$ -unsubstituted- $\alpha'$ -hydroxyalkyl sulfones yields *syn* epoxides in high diastereoselectivity using lithium *t*-butyl peroxide. In contrast, triisopropylsilyl ethers lead to the antiepoxyde. Epoxidation of (*E*)- $\alpha'$ -hydroxyalkyl- $\beta$ -phenyl vinyl sulfones provides antiepoxydes and their corresponding triisopropylsilyl ethers afford *syn* epoxides. These initial findings have been expanded by de la Pradilla and co-workers in the epoxidation of both vinyl sulfoxides and sulfones and are shown in Table 8 <2002JOC8166>.

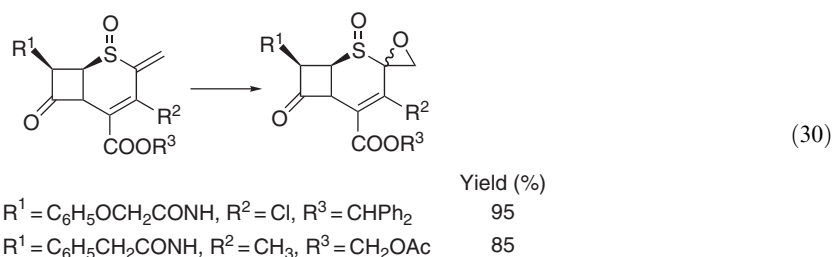
**Table 8** Epoxidation of  $\alpha'$ -hydroxy vinyl sulfoxides

alkenyl sulfoxide $\xrightarrow{\text{MOO-Bu}^t}$ $\alpha,\beta$ -epoxy sulfones					
Entry	Product <sup>a</sup>	$R^1$	$R^2$	Conditions	Yield (%) <sup>b</sup>
1		Et		Li, THF	75 (50:50)
2		Pr <sup>i</sup>		Li, THF	63 (68:32)
3		Bu <sup>t</sup>		Li, THF	81 (75:25)
4		Et		Li, Et <sub>2</sub> O	75 (5:95)
5		Pr <sup>i</sup>		Li, Et <sub>2</sub> O	60 (15:85)
6		Bu <sup>t</sup>		Li, Et <sub>2</sub> O	88 (24:76)
7		Et		Li, THF	70 (28:72)
8		Et		Li, Et <sub>2</sub> O	73 (2:98)
9		Et	Bu <sup>n</sup>	Li, THF	76 (97:3)
10		Ph	Bu <sup>n</sup>	Li, THF	86 (93:7)
11		Ph	Bu <sup>n</sup>	Li, Et <sub>2</sub> O	68 (94:6)
12		Et	Ph	Li, THF	67 (100)

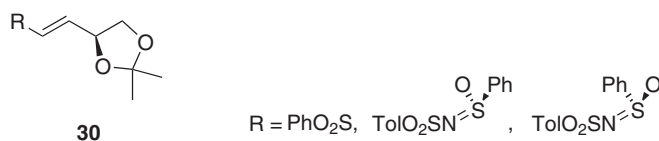
Source: &lt;2002JOC8166&gt;.

<sup>a</sup> Syn sulfone shown where the stereochemistry is defined for the hydroxyl and epoxide functionalities, relative to the extended conformation of the longest carbon chain. <sup>b</sup> Combined yield of pure products followed by ratio of *anti:syn* sulfone.

A mild oxidation of cephalosporins is accomplished using dimethyldioxirane. Dimethyldioxirane can be used under neutral conditions as a solution in acetone. The oxidant is examined for cephem sulfones and their derivatives as shown in Equation (30) <1995TL7111>.



Epoxidation of vinyl sulfones and *N*-(*p*-tolylsulfonyl)vinylsulfoximines proceeds with varying selectivity based on metal cation and substitution <1998JCS(P1)4097>. Substrate **30** gave the best yield and selectivity when treated with lithium *t*-butyl peroxide in THF.



Another method reports catalytic oxidation of sulfur followed by epoxidation of acyclic  $\alpha'$ -hydroxyl vinyl sulfones to afford the corresponding epoxy sulfones as shown in Table 9 <1999JCS(PI)1247>. These reactions are highly stereo- and regioselective for electron-deficient alkenes and can be expanded to carbohydrate fragments.

**Table 9** Metal-catalyzed epoxidation of hydroxy vinyl sulfones

$R^1$	$R^2$	$R^3$	<b>31</b>	<b>32</b>	References
Et	Bu	Tol <sup>P</sup>	76		<1999JCS(PI)1247>
(CH <sub>2</sub> ) <sub>2</sub> Ph	Bu	Bu <sup>t</sup>	54		<1999JCS(PI)1247>
Et	Ph	Tol <sup>P</sup>		60	<1999JCS(PI)1247>
Ph	vinyl	Tol <sup>P</sup>	67		<1999JCS(PI)1247>

The Darzens reaction is also used to synthesize  $\alpha,\beta$ -epoxysulfones. An asymmetric Darzens' reaction using chloromethyl phenyl sulfone with aromatic and aliphatic aldehydes is accomplished using phase-transfer catalyzed conditions to afford  $\alpha,\beta$ -epoxysulfones <2002T1407>. Chiral quaternary ammonium salts from cinchona alkaloids act as the catalyst to produce enantioselectivities up to 83%.

#### 4.05.2 FUNCTIONS CONTAINING OXYGEN AND EITHER SELENIUM OR TELLURIUM

##### 4.05.2.1 Dicoordinate Selenium and Tellurium Derivatives

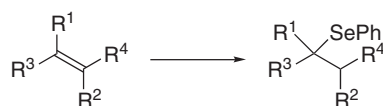
This section contains methods for compounds containing oxygen with selenium or tellurium. Novel examples are described that parallel and expand the chemistry generally associated with sulfur compounds.

##### 4.05.2.1.1 From enol ethers, ethers, lactones, other acetals, and other compounds

###### (i) From enol ethers and $\alpha,\beta$ -unsaturated nitriles

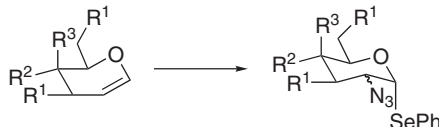
Monoselenoacetals are produced from enol ethers under mild conditions upon treatment with benzeneselenol as shown in Table 10 <1996JCR(S)206>. Furthermore, Michael addition of benzeneselenide anions to activated alkenes has been reported and was expanded to  $\alpha,\beta$ -unsaturated nitriles to provide functionalized selenides <1995JOC4299>. The addition is chemoselective; no addition to the nitrile moiety is observed, thus providing only  $\beta$ -phenylsulfenyl nitriles.

Azido-benzeneselenylation is achieved using sodium azide, IBDA, and diphenyl diselenide (Table 11) <1995CJC343>. The azido radical is generated *in situ* and adds to alkenes. The resulting radical is trapped by the selenium reagent to afford vicinal phenylseleno azides. This method has been applied to various glycols, but there are limitations. For the perbenzylated glycols, reaction conditions were modified to prevent oxidative cleavage of the benzyl group.

**Table 10** Monoselenoacetals prepared from enol ethers

$R^1$	$R^2$	$R^3$	$R^4$	Time (h)	Yield (%)	References
OEt	H	H	H	2	80 <sup>a</sup>	<1996JCR(S)206>
OMe	H	Me	H	3	85 <sup>a</sup>	<1996JCR(S)206>
OMe	—[CH <sub>2</sub> ] <sub>3</sub> —		H	5	85 <sup>a</sup>	<1996JCR(S)206>
OMe	—[CH <sub>2</sub> ] <sub>4</sub> —		H	4	80 <sup>a</sup>	<1996JCR(S)206>
O—[CH <sub>2</sub> ] <sub>3</sub> —	H		H	10	90 <sup>a</sup>	<1996JCR(S)206>
O—[CH <sub>2</sub> ] <sub>4</sub> —	H		H	10	90 <sup>a</sup>	<1996JCR(S)206>
H	H	OMe	CN	23	74 <sup>b</sup>	<1995JOC4299>

Conditions: <sup>a</sup> PhSeH; <sup>b</sup> KH, HMPA, PhSeH.

**Table 11** Selenoglycosides via azidoselenation

$R^1$	$R^2$	$R^3$	Procedure <sup>a</sup>	Yield (%)	References
OAc	OAc	H	A	91 <sup>b</sup>	<1995CJC343>
OAc	H	OAc	A	92 <sup>c</sup>	<1995CJC343>
OBn	OBn	H	B	82 <sup>b</sup>	<1995CJC343>
OBn	H	OBn	B	75 <sup>c</sup>	<1995CJC343>

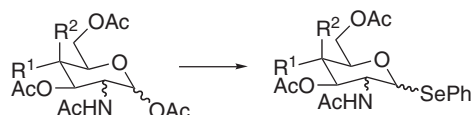
<sup>a</sup> Procedure A: (PhSe)<sub>2</sub>, NaN<sub>3</sub>, PhI(OAc)<sub>2</sub>; B: *N*-phenylselenophthalimide, (CH<sub>3</sub>)<sub>3</sub>SiN<sub>3</sub>, (Bu<sup>n</sup>)<sub>4</sub>NF. <sup>b</sup> Inseparable mixture of equatorial (gluco) and axial (manno) isomers. <sup>c</sup> Only the equatorial isomer is formed.

It is noted that this addition works well for D-galactal. However, D-glucal leads to a mixture of gluco and manno products. In addition, disaccharide-based glycols are low yielding because of their low reactivity. Novel one- and two-pot selenoglycosylations overcome these setbacks as shown in Table 12 <2002OL4623>.

#### (ii) From ethers

Similar to the reactions of enol ethers, dialkyl ethers react with iodobenzene diacetate, sodium azide, and diphenyl diselenide to afford the monoselenoacetals in good yields (Table 13) <1995SL1129>. The azido radical reacts with the ethers generating an  $\alpha$ -oxyradical, which is trapped by the selenium reagent.



**Table 12** One- and two-pot selenoglycoside formation

$R^1$	$R^2$	Procedure <sup>a</sup>	Yield (%)	References
OAc	H	A	82 <sup>b</sup>	<2002OL4623>
OAc	H	B	92 <sup>b</sup>	<2002OL4623>
H	OAc	A	46 <sup>b</sup>	<2002OL4623>
H	OAc	B	80 <sup>b</sup>	<2002OL4623>
OAc	H	A	44 <sup>c</sup>	<2002OL4623>
OAc	H	B	72 <sup>c</sup>	<2002OL4623>

<sup>a</sup> A: i. TMSOTf, ii. PhSeH, CSA, B: PhSeTMS, TMSOTf. <sup>b</sup> Both substituents equatorial. <sup>c</sup> Both substituents axial.

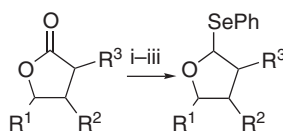
**Table 13** Monoselenoacetals prepared from ethers

Ether	Time (h)	Product <sup>a</sup>	Yield (%)	References
	5		71	<1995SL1129>
	5		55	<1995SL1129>
	3		86	<1995SL1129>
Bu <sup>t</sup> -OCH <sub>3</sub>	6	Bu <sup>t</sup> -OCH <sub>2</sub> SePh	90	<1995SL1129>

<sup>a</sup> Conditions: PhI(OAc)<sub>2</sub>, NaN<sub>3</sub>, and (PhSe)<sub>2</sub> at rt.

### (iii) From lactones

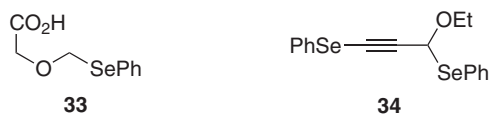
Phenylselenanyl tetrahydrofurans are prepared via a one-pot procedure from  $\gamma$ -lactones as shown in Table 14 <2001S867>. This reaction proceeds via nucleophilic attack of the selenophenol to the cyclic oxonium ion. This method cannot be extended to  $\gamma$ -lactols because they react via  $\gamma$ -hydroxy aldehydes, rather than a cyclic oxocarbenium ion, to afford acyclic diselenide products.

**Table 14** One-pot procedure from lactones

i. HAl(Bu<sup>t</sup>)<sub>2</sub>; ii. PhSeH, BF<sub>3</sub>·OEt<sub>2</sub>; iii. H<sub>2</sub>O

$R^1$	$R^2$	$R^3$	Yield (%)	trans:cis	References
H	H	Me	91	85:15	<2001S867>
H	Me	H	83	54:46	<2001S867>
Me	H	H	84	26:74	<2001S867>

$\gamma$ -Lactones open to acyclic acids when treated with sodium phenylselenide. Analogously, dioxolanone rings open with the selenium anion in THF-hexamethylphosphoramide (HMPA) at reflux to produce selenide acid **33** <2001JOC1966>.

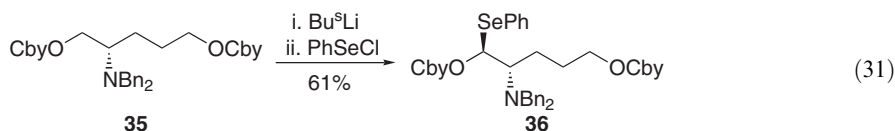


(iv) *From acetals*

The reaction of *O,O*-acetals with benzeneselenol is reported using tris(phenylseleno)borane, diisobutylaluminum benzeneselenonate, and various Lewis acids <1995COFGT(4)215>. Furthermore, a regioselective cleavage can be accomplished by modification of solvent systems <2002JOC3301>. The synthesis of  $\gamma$ -selenium-substituted propynal monoselenoacetals can provide propargyl cations stabilized by the chalcogen atom. Nucleophilic addition of the  $\text{Bu}_2\text{AlSePh}$  to  $\gamma$ -selenopropynal diethylacetal affords the monoselenoacetal **34** in 41% yield <1995CC149>.

(v) *From other*

(a) *From carbamates*. A regio- and stereoselective lithiation can be achieved by deprotonation of dicarbamate **35** via a bis-chelate complex to afford a stereohomogeneous and regioisomerically pure seleno product **36** (Equation (31)) <1998S1274>.

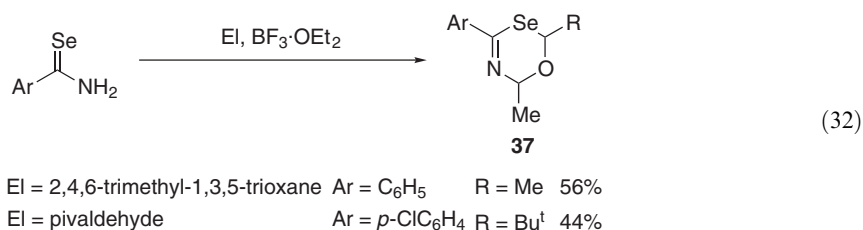


(b) *Ring-forming reactions*. Oxetanes can be synthesized from the Paternò-Büchi reaction, a [2+2]-photocycloaddition of excited carbonyl compounds with alkenes <2001S1243>. There is high regioselectivity as shown in Table 15. These compounds are useful as synthetic intermediates for functionalized oxetanes.

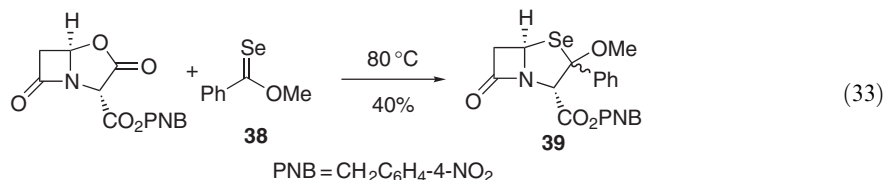
**Table 15** Synthesis of 3-selanyl-3-siloxyoxetanes via photocyclizations

Ar	R	Yield (%)	trans:cis	References
<i>p</i> -CNC <sub>6</sub> H <sub>4</sub>	Ph	94	68:32	<2001S1243>
<i>p</i> -CNC <sub>6</sub> H <sub>4</sub>	Me	70	86:14	<2001S1243>
Ph	Ph	84	68:32	<2001S1243>
2-Naph	Ph	0		<2001S1243>

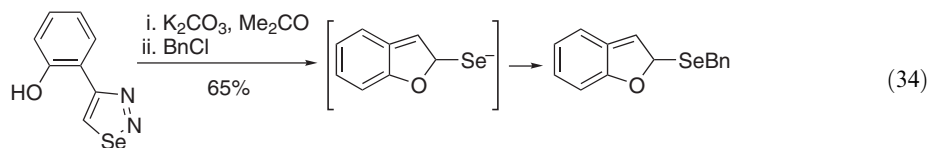
Oxaselenazines **37** can be prepared from the corresponding selenoamide <2001BCJ511>. As shown in Equation (32), the amide can react with 2,4,6-trimethyl-1,3,5-trioxane as well as pivaldehyde to afford the all-*cis* oxaselenazine products. However, treatment with benzaldehyde only afforded recovery of the starting material.



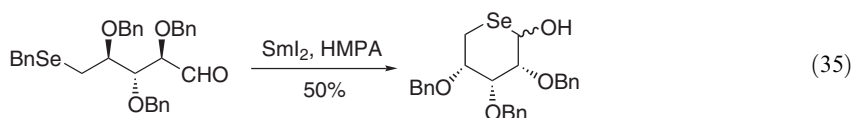
Gallagher and co-workers have extended an azomethine ylide strategy from  $\beta$ -lactam-based oxazolidinone to selenoketones [<2000T5579>](#). Compound **38** reacts as a 1,3-dipolarophile to afford selenapenam **39** with total regiocontrol ([Equation \(33\)](#)).



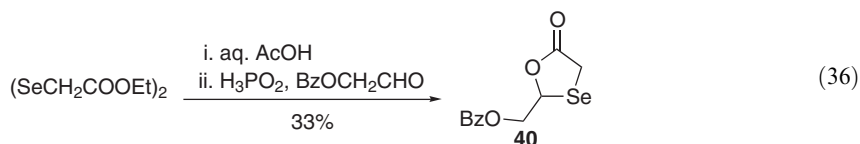
In an attempt to prepare acetylenic selenolates, Petrov and co-workers have treated selenodiazole with a weak base to afford 2-benzylselenobenzofuran as shown in [Equation \(34\)](#) [<2000RJOC605>](#). The mechanism proceeds by formation of a phenolate followed by intramolecular proton transfer to the heterocycle. This heterocyclic anion extrudes nitrogen to form an alkyneselenolate followed by intramolecular cyclization generating a selenium anion. This anion is trapped *in situ* by benzyl chloride.



A novel samarium(II) iodide mediated cyclization provides 5-selenopentopyranose carbohydrates as shown in [Equation \(35\)](#) [<2000T3995>](#). The ketyl radical adds to the selenium atom, which is followed by loss of the benzyl group.



Oxaselenolanone **40** is prepared from hydrolysis of the  $\beta$ -ester selenium dimer. The dimer is reduced and then condensed with an aldehyde to afford the desired lactone as shown in [Equation \(36\)](#) [<1997JMC2991>](#).



Dihydroselenophenes **41** are synthesized from 1,2,3-selenadiazoles via thermal [<2000JOM\(611\)488>](#) or radical [<2002JOC1520>](#) reactions (see [Table 16](#)). The vinyl radical is generated by extrusion of nitrogen, which then adds to alkenes. The resulting alkyl radical subsequently cyclizes. A competing reaction is dimerization of the selenadiazole to produce the 1,4-selenide **42**.

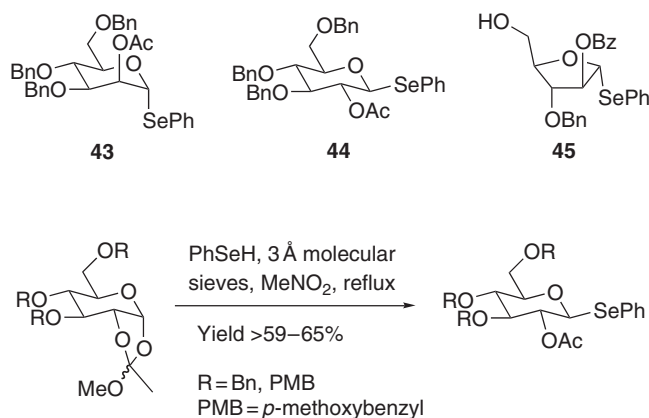
**Table 16** Reactions of 1,2,3-selenadiazole with olefins

<i>R</i>	<i>Conditions</i>	<i>Yield (%)</i>		<i>References</i>
		<b>41</b>	<b>42</b>	
OBu	130 °C	12	74	<2000JOM(611)488>
OBu	cat. Bu <sub>3</sub> SnH/AIBN, 80 °C	11	56	<2002JOC1520>
OCOCH <sub>3</sub>	cat. Bu <sub>3</sub> SnH/AIBN, 80 °C	7	67	<2002JOC1520>

#### 4.05.2.1.2 From ring-opening reactions and $\alpha$ -halo ethers

##### (i) From ring-opening reactions

(a) *From orthoesters.* There are many examples of ring opening of sugar orthoesters using benzeneseleninol. Examples include reactions in the presence of catalytic amounts of HgBr<sub>2</sub> to afford the selenoglycosides **43** <2000CEJ1416> and **44** <2002CEJ2608>. In addition, orthoesters of D-arabinose that are treated with SnCl<sub>4</sub> undergo an acid-catalyzed ring opening to yield  $\alpha$ -glycoside **45** <2000TL7447>. Another method avoids the use of mercury and tin and introduces the selenium at the  $\beta$ -position (Scheme 16) <2000TL2391, 2000JOC4315>.

**Scheme 16**

(b) *From epoxides.* Selenoglycosides can also be accessed from the corresponding epoxides (Table 17) <2000JOC5547>. Under basic conditions, this reaction is stereospecific.

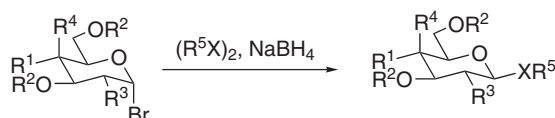
**Table 17** Synthesis of selenoglycosides

i. dimethyldioxirane; ii. PhSeH, conditions

<i>Conditions</i>	<i>R</i>	<i>Yield (%)</i>	<i>References</i>
(CF <sub>3</sub> CO <sub>2</sub> )O	TBS	53 $\alpha$ , 28 $\beta$	<2000JOC5547>
Et <sub>3</sub> N	Tr	> 56 $\alpha$ only	<2000JOC5547>

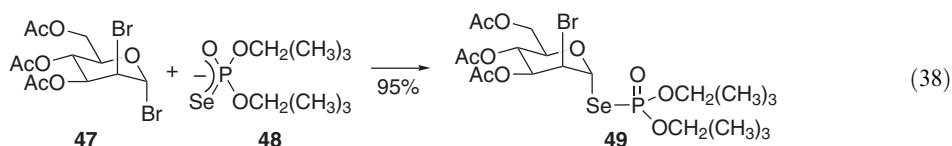
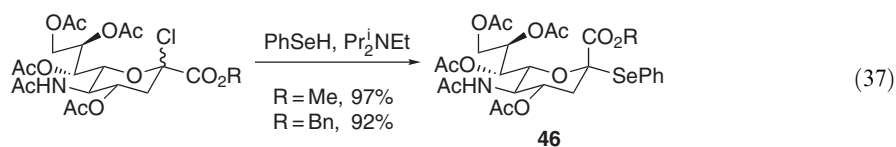
(ii)  $\alpha$ -Halo ethers

The displacement of a halide or acetate by benzeneselenol and potassium selenobenzoate under basic or acidic conditions has been reported to prepare selenoglycosides. Additionally, treatment of various halo glycosides with sodium borohydride and either diselenides or diaryltellurides affords the corresponding chalcogen glycoside (Table 18) <1996SL929, 1997AJC233>. This is an efficient one-pot synthesis that is mild and proceeds with inversion of stereochemistry.

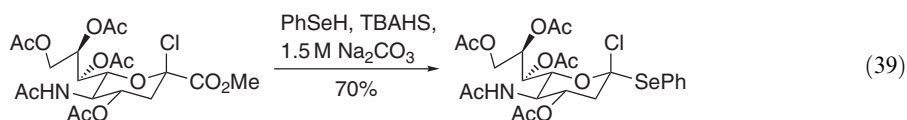
**Table 18** Synthesis of chalcogenoglycosides

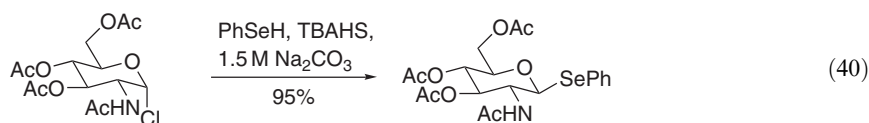
$R^1$	$R^2$	$R^3$	$R^4$	$R^5$	$X$	Yield (%)	References
OBz	Bz	OBz	H	Ph	Te	80	<1996SL929>
OBz	Bz	OBz	H	<i>p</i> -MeC <sub>6</sub> H <sub>4</sub>	Te	89	<1996SL929>
OBz	Bz	OBz	H	<i>p</i> -MeOC <sub>6</sub> H <sub>4</sub>	Te	88	<1996SL929>
OBz	Bz	OBz	H	<i>p</i> -Me <sub>2</sub> NC <sub>6</sub> H <sub>4</sub>	Te	68	<1996SL929>
OAc	Ac	OAc	H	<i>p</i> -MeOC <sub>6</sub> H <sub>4</sub>	Te	75	<1996SL929>
H	Bz	OBz	OBz	<i>p</i> -MeC <sub>6</sub> H <sub>4</sub>	Te	60	<1996SL929>
OAc	Ac	OAc	H	<i>p</i> -MeC <sub>6</sub> H <sub>4</sub>	Te	54	<1996SL929>
OAc	Ac	OAc	H	Ph	Se	94	<1997AJC233>
OAc	Ac	OAc	H	Me	Se	87	<1997AJC233>
OBn	Bz	OBz	H	Ph	Se	88	<1997AJC233>
OAc	Ac	OAc	H	Ph	Te	93	<1997AJC233>

Ikeda and co-workers have reported a novel procedure for the synthesis of phenylselenoglycoside **46** that avoids elimination side products. Using *N,N*-di-isopropylethylamine, **46** is synthesized in excellent yield through S<sub>N</sub>2 displacement of the corresponding chloro glycosides (Equation (37)) <2002BMCL2309>. This can be expanded to seleno phosphonates as shown in Equation (38). Condensation of bromo sugar **47** and seleno acid salt **48** yields phosphoroate **49** <2000HAC292>.

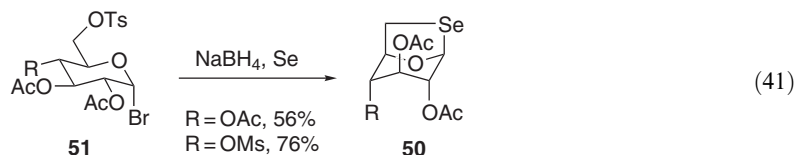


PTC is another method for the synthesis of selenoglycosides. Carrière and co-workers use TBAHS under mildly basic conditions in ethyl acetate to synthesize the glycosides as shown in Equations (39) and (40) <2000JMOC(A)9>.





The synthesis of 1,6-episeleno bridged sugar **50** is accomplished from bromo tosylate **51** (Equation (41)) <1996AJC343, 1999AJC885>. Attempts to prepare the 1,6-epitelluro sugar analogs with sodium hydrogen telluride were unsuccessful.



#### 4.05.2.1.3 Rearrangements and multicomponent reactions

Homolytic cleavage of diphenyl diselenide can be accomplished using irradiation with visible light. A highly selective three-component reaction is achieved starting from diphenyldiselenide using a tungsten lamp. The resulting benzeneseleno radical adds selectively to alkynes to afford the  $\beta$ -phenylselenovinyl radical, which subsequently adds to alkenes as shown in Table 19 <1999AG(E)2027>.

**Table 19** Three-component coupling using ethyl propiolate<sup>a</sup>

Alkene	Product	Yield (%)	References
		89	<1999AG(E)2027>
		78	<1999AG(E)2027>
		71	<1999AG(E)2027>
		70	<1999AG(E)2027>

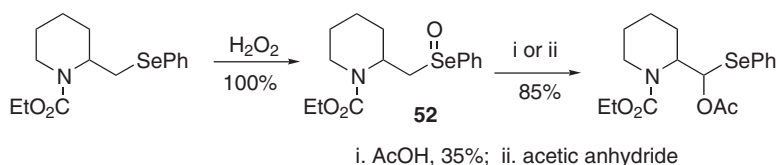
<sup>a</sup> Conditions: Ethyl propiolate, alkene, (PhSe)<sub>2</sub>, 15°C,  $h\nu > 300$  nm.

The examples of seleno-Pummerer reactions are not as prevalent as their sulfur counterparts because of the facile elimination of the selenoxides. In these reactions, most substrates lack  $\beta$ -hydrogens to the selenoxide. When selenoxide **52** is heated at reflux in a mixture of acid and carbon tetrachloride, the Pummerer-type reaction is obtained with no elimination side products (Scheme 17). The excess acid protonates **52**, thereby hindering the *syn* elimination <1995AJC445>.

While developing methods for  $\alpha$ -functionalization of arylseleninylacetates, Shimada and co-workers observed some novel transformations when selenides were treated under acidic conditions as shown in Table 20 <2000TL4637>.

A domino Michael-seleno Pummerer-type reaction occurs with 1,3-dicarbonyl compounds and vinyl phenyl selenoxide in the presence of hexamethyldisilane and various chlorosilanes to yield

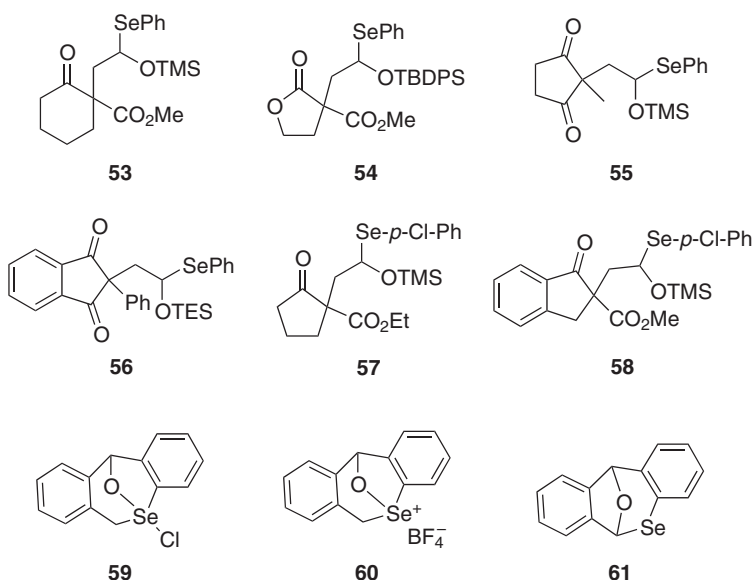
compounds **53–56** <2000JCS(P1)2577>. (This method also provides a means to add the formyl-methyl unit to carbonyl compounds.) In addition, it can be extended to *p*-chlorophenyl vinyl selenoxides **57** and **58**. Because of the lack of  $\beta$ -hydrogens, selenurane **59** and selenium salt **60** undergo a 1,2-rearrangement to provide **61** upon treatment with triethylamine <2001HAC317>.



Scheme 17

Table 20 Synthesis of  $\alpha$ -acetoxyselenides

<i>n</i>	<i>R</i> <sup>1</sup>	Conditions	Comments
1	CH <sub>3</sub> CO	(CH <sub>3</sub> CO) <sub>2</sub> O, allyltrimethylsilane	62% yield
1	CF <sub>3</sub> CO	TFAA, CDCl <sub>3</sub>	decomposition upon purification
0	H	MCPBA	stable compound, no yield reported



#### 4.05.2.2 Tricoordinate Selenium Derivatives

Phenyl selenides can be treated with MCPBA or ozone to provide selenoxides that are susceptible to elimination due to the  $\alpha$ -oxygen. No further advances on the information in chapter 4.05, COFGT (1995) <1995COFGT(4)215> have occurred in this area, in the period 1993–2003.

## ACKNOWLEDGMENTS

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## Biographical sketch



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## 4.06

# Functions Incorporating Two Chalcogens Other Than Oxygen

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### 4.06.1 FUNCTIONS CONTAINING TWO SULFURS— $R_2^1C(SR^2)SO_2R^3$ , etc.

#### 4.06.1.1 Introduction

Dithioacetals and their various oxides are versatile tools in organic synthesis. The former have been routinely used for the protection of the carbonyl group.

The impetus given by the Umpolung strategy continues to be largely exploited. These acyl anion equivalents were used in a sequence of deprotonation and treatment with a variety of electrophiles. A review <2003T6147> has highlighted the applications of 1,3-dithianes in the field

of total synthesis of natural products from 1990 to 2000. Chemoselective oxidation reactions have been achieved to allow access to the various oxides of dithioacetals. The late 1990s and early 2000s have seen the achievement of efficient enantioselective syntheses of dithioacetal oxides, mostly using the Andersen reaction or asymmetric oxidation. Addition to the double bond of ketene dithioacetal oxides has also been proved to be useful.

#### 4.06.1.2 Two Dicoordinated Sulfurs— $R_2C(SR^2)_2$

There are three types of compounds that contain two dicoordinated sulfur atoms: *gem*-dithiols, hemidithioacetals, and dithioacetals. The first two have received little attention since 1995 but dithioacetal functions have been much studied.

##### 4.06.1.2.1 *gem*-Dithiols

No further advances have occurred in this area since the publication of chapter 4.06.1.2 in COFGT (1995) <1995COFGT(4)243>.

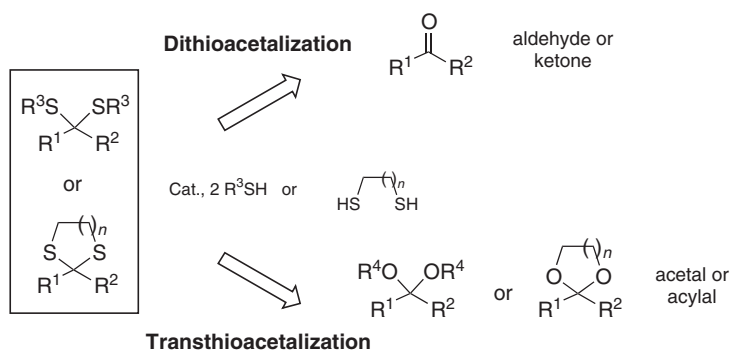
##### 4.06.1.2.2 Hemidithioacetals

No further advances have occurred in this area since the publication of chapter 4.06 in COFGT (1995) <1995COFGT(4)243>.

##### 4.06.1.2.3 Dithioacetals

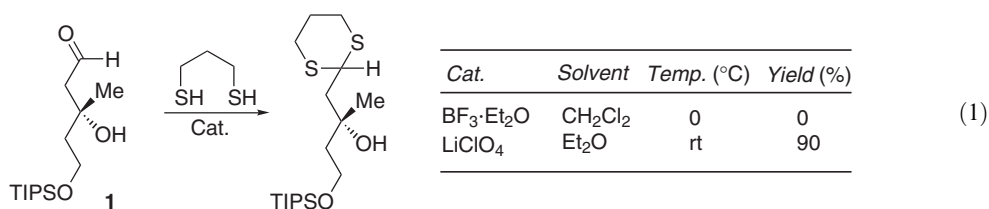
###### (i) From aldehydes, ketones, and related compounds

For the preparation of dithioacetals, two general reactions have been described: “dithioacetalization” from aldehydes or ketones and “tranthioacetalization” from acetals or acylals (*gem*-diacetates) (Scheme 1). Few examples have been reported from carbonyl derivatives such as enol ethers or hydrazones. These transformations involved thiols or dithiols in the presence of Brønsted or Lewis acids as catalysts.



Scheme 1

Among all the catalysts, boron trifluoride etherate ( $BF_3 \cdot Et_2O$ ) remained the most favored one. However, this reagent was not always efficient and it was necessary to find useful alternatives. For example, reaction of the sensitive hydroxy aldehyde **1** and propane-1,3-dithiol, in the presence of boron trifluoride etherate, led only to decomposition of **1** (Equation (1)). Using lithium perchlorate in anhydrous diethyl ether, the corresponding dithiane was obtained in a remarkable 90% yield <2000S69>.



Thus, since 1995, many new methodologies have been developed and it is frequently not easy to perceive the improvements. Indeed, the yields were often excellent (>90%) and it is possible to discriminate the types of the carbonyl functions. The usual order of reactivity observed is: aliphatic aldehyde > aliphatic ketone >  $\alpha,\beta$ -unsaturated aldehyde or aromatic aldehyde >  $\alpha,\beta$ -unsaturated ketone or aromatic ketone. These methods have been partially surveyed in two reviews in 1995 and 2000 [<B-1995MI133, 2000RCR947>](#). The new catalysts for the dithioacetalization reaction of aldehydes and ketones are listed in [Table 1](#).

**Table 1** Catalysts for dithioacetalization reaction of aldehydes and ketones

Catalysts	Amount (mol.%)	Solvent (mol l <sup>-1</sup> )	Temp.	Time	References
BiX <sub>3</sub> or Bi <sub>2</sub> (SO <sub>4</sub> ) <sub>3</sub> X = Cl, Br, I	0.04–10	CH <sub>3</sub> CN (1.25)	rt	2–10 h	<a href="#">&lt;1995SL984&gt;</a>
CAN	10	CHCl <sub>3</sub> (0.20)	rt	16 h	<a href="#">&lt;1995T7823&gt;</a>
LiBr	25–40	Neat	75–80 °C	15–180 min	<a href="#">&lt;1999S58&gt;</a>
HCl (anhyd.) <sup>a</sup>	5	MeOH (0.28)	rt	5–30 min	<a href="#">&lt;1999SC697&gt;</a>
InBr <sub>3</sub>	10	CH <sub>2</sub> Cl <sub>2</sub> or H <sub>2</sub> O (0.40)	rt	15–120 min	<a href="#">&lt;2000TL9695&gt;</a>
LiBF <sub>4</sub>	10	CH <sub>3</sub> CN (1.00)	rt	30–210 min	<a href="#">&lt;2001SL238&gt;</a>
CdI <sub>2</sub>	50	Neat	MW <sup>d</sup>	75 s	<a href="#">&lt;2001JCR(S)313&gt;</a>
InCl <sub>3</sub>	30	CH <sub>2</sub> Cl <sub>2</sub> (n.d)	rt	10 min–28 h	<a href="#">&lt;2001TL359&gt;</a>
InCl <sub>3</sub>	10	CH <sub>2</sub> Cl <sub>2</sub> (0.33)	rt	2–7 h	<a href="#">&lt;2002SC715&gt;</a>
I <sub>2</sub>	10	THF (0.50)	rt	0.5–7 h	<a href="#">&lt;2001TL4425&gt;</a>
NBS	15	CH <sub>2</sub> Cl <sub>2</sub> (0.10)	rt	30–180 min	<a href="#">&lt;2002SL474&gt;</a>
NBS	30	CH <sub>2</sub> Cl <sub>2</sub> (0.10)	rt	20–25 min	<a href="#">&lt;2002TL6947&gt;</a>
Sc(OTf) <sub>3</sub>	4	CH <sub>2</sub> Cl <sub>2</sub> (0.08)	rt	20–360 min	<a href="#">&lt;2002TL1347&gt;</a>
TBAB <sup>b</sup>	30	Neat	110–115 °C	40–120 min	<a href="#">&lt;2002JCS(P1)1520&gt;</a>
DBSA <sup>c</sup>	1–10	H <sub>2</sub> O (1.00)	40 °C	4 h	<a href="#">&lt;2002JA11971&gt;</a>
NiCl <sub>2</sub>	10	CH <sub>2</sub> Cl <sub>2</sub> –MeOH: 5–1 (0.33)	rt	8 min–18 h	<a href="#">&lt;2003TL919&gt;</a>

<sup>a</sup> From acetyl chloride and MeOH. <sup>b</sup> TBAB “tetrabutylammonium bromide”. <sup>c</sup> DBSA “dodecylbenzensulfonic acid”. <sup>d</sup> MW “microwave irradiation”.

Transthioacetalization has been used as an alternative method for the preparation of dithioacetals ([Table 2](#)).

**Table 2** Catalysts for transthoacetalization of acetals

Catalysts	Amount (mol.%)	Solvent (mol l <sup>-1</sup> )	Temp.	Time	References
ZrCl <sub>4</sub>	3–5	CH <sub>2</sub> Cl <sub>2</sub> (0.2)	rt	2 min–24 h	<a href="#">&lt;1999SL319&gt;</a>
InCl <sub>3</sub>	5	ClCH <sub>2</sub> CH <sub>2</sub> Cl (0.5)	81–85 °C	7–20 min	<a href="#">&lt;2002SL727&gt;</a>

Frequently, the same catalyst can be employed for both dithioacetalization and transthoacetalization reactions ([Table 3](#)).

**Table 3** Catalysts for both dithioacetalization and transthiacetalization reactions from aldehydes, ketones, and acetals

Catalysts	Amount (mol.%)	Solvent (mol <sup>-1</sup> )	Temp.	Time	References
WCl <sub>6</sub>	4–10	CH <sub>2</sub> Cl <sub>2</sub> (0.2)	0–5 °C	2–60 min	<1998SL739>
LiOTf	5	Neat	90–110 °C	5–180 min	<1999TL4055, 2001BCJ2401>
MoCl <sub>5</sub>	1–10	CH <sub>2</sub> Cl <sub>2</sub> (0.2)	rt	2–180 min	<2001PS207>
Trichloro-isocyanuric acid	10	CHCl <sub>3</sub> (0.2)	rt	0.75–2 h	<2001SL1641>
I <sub>2</sub>	10	CHCl <sub>3</sub> (0.2)	rt	5–420 min	<2001JOC7527>
H <sub>3</sub> PW <sub>12</sub> O <sub>40</sub>	0.1–2	Neat	rt	1 min–24 h	<2002S59>
NBS	10–40	CHCl <sub>3</sub> (0.2)	rt	5–170 min	<2002PS1047>
NBS	30	CH <sub>2</sub> Cl <sub>2</sub> (0.1)	rt	20–25 min	<2002TL6947>
TABCO <sup>a</sup>	20–50	CHCl <sub>3</sub> (0.2)	rt	3–240 min	<2002PS1047>
Br <sub>2</sub>	10–40	CHCl <sub>3</sub> (0.2)	rt	4–160 min	
In(OTf) <sub>3</sub>	8–10	CH <sub>2</sub> Cl <sub>2</sub> (0.2)	rt	6 min–4 h	<2002T7897>
Sc(OTf) <sub>3</sub>	2	[bmim] <sup>+</sup> [PF <sub>6</sub> ] <sup>-</sup> (1.0) <sup>b</sup>	rt	8–15 min	<2003TL3337>

<sup>a</sup> TABCO “2,4,4,6-tetrabromo-2,5-cyclohexadienone”. <sup>b</sup> [bmim]<sup>+</sup> “1-butyl-3-methylimidazolium cation”.

Heterogeneous catalysts have also been developed in view of their usually easier work-up (Table 4).

**Table 4** Heterogeneous catalysts for the preparation of dithioacetals from carbonyl compounds, from acetals, or from acylals

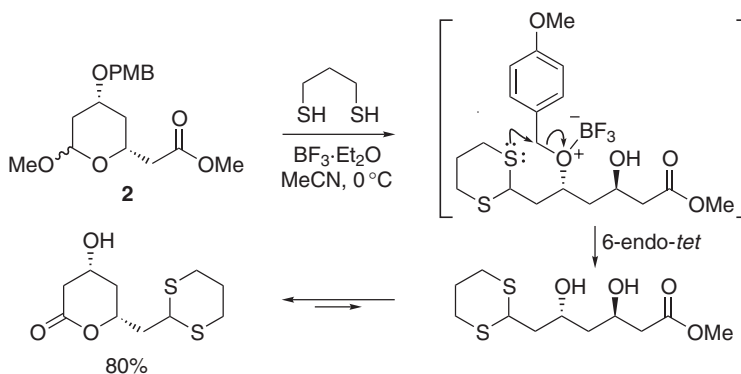
Catalysts	Amount	Solvent (mol <sup>-1</sup> )	Temp.	Time	References
Dowex-50W-X8	0.01 g/mmol	Neat	rt	35–200 min	<1995JCR(S)108>
ZrCl <sub>4</sub> –SiO <sub>2</sub>	10–60 mol.%	CH <sub>2</sub> Cl <sub>2</sub> (0.20)	rt	1 min–3 h	<1996TL4621>
TaCl <sub>5</sub> –SiO <sub>2</sub>	10 mol.%	CH <sub>2</sub> Cl <sub>2</sub> (0.50)	rt	2–10 min	<1997T14997>
Cu(OTf) <sub>2</sub> –SiO <sub>2</sub>	20 mol.%	Neat	75–80 °C	30 min–5 h	<1999SL415>
“Silica chloride” <sup>a,b</sup>	0.2–0.3 g/mmol	CH <sub>2</sub> Cl <sub>2</sub> (0.20)	rt	10–240 min	<2000SL263>
“Silica chloride” <sup>a,c</sup>	0.5 g/mmol	CH <sub>2</sub> Cl <sub>2</sub> (0.08)	rt	0.5–4.25 h	<2001PS165>
I <sub>2</sub> –Al <sub>2</sub> O <sub>3</sub>	10 mol.%	Neat	rt	9–40 min	<2001CL794>
H-Rho zeolite	0.5 equiv. <sup>d</sup>	Hexane (0.50)	70 °C	1–6 h	<1996JCR(S)494>
Envirocat EPZG	0.01 g/mmol	C <sub>6</sub> H <sub>6</sub> (0.67)	80 °C	30–140 min	<1996SC1579>
Fe <sup>3+</sup> –Montmorillonite	0.033 g/mmol	CH <sub>2</sub> Cl <sub>2</sub> (n.d.)	rt	4 h	<1996SC2993>
Envirocat EPZ10	0.02 g/mmol	CH <sub>2</sub> Cl <sub>2</sub> (0.33)	40 °C	4 h	<1998JCR(S)452>
Koalinitic clay	0.01 g/mmol	C <sub>6</sub> H <sub>6</sub> or CCl <sub>4</sub> (0.40)	Reflux	4 h	<1998JCS(P1)965 <sup>e</sup> , 1998JOC1058>
Zeolite HY, CaY or MgY	1 equiv. <sup>d</sup>	Hexane (ND)	70 °C	1 h	<1999GC173>
Bentonitic clay (TAFF)	0.109 g/mmol	Toluene (0.12)	105 °C under 585 mmHg	3 h	<2001SC1587>
POCl <sub>3</sub> –Montmorillonite clay	0.10 g/mmol	CH <sub>2</sub> Cl <sub>2</sub> (0.60)	rt	2 min–3 h	<2001SC1669>

<sup>a</sup> Prepared by refluxing silica gel with SOCl<sub>2</sub> for 48 h. <sup>b</sup> Only for transthiacetalization of acetals. <sup>c</sup> Only for transthiacetalization of acylals. <sup>d</sup> By weight with respect to carbonyl compound. <sup>e</sup> Preparation of dithioacetals also from oximes, enamines, and tosylhydrazones.

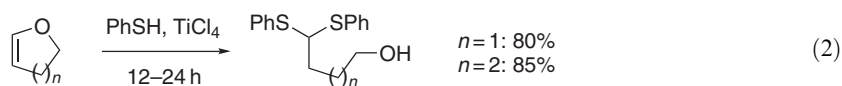
In the case of acetal **2** (Scheme 2), the catalyst was used not only for the transdithioacetalization reaction but also to facilitate the deprotection of the paramethoxybenzyl (PMB) group <2001OL177>.

Acetals can also be synthesized from enol ether derivatives. Thus, the reaction of methyl propenyl ether with ethanethiol can be conducted without solvent, or in the presence of BF<sub>3</sub>·Et<sub>2</sub>O (82% yield) or HCl gas (53% yield) <1995SC3155>. Ethyl-3,3,3-trifluoropropenyl ether can be also transformed to the corresponding dithioacetal in 91% yield by reaction with 1,3-propanedithiol <1998JCS(P1)279>. With endocyclic enol ethers, the reaction generally requires a stronger Lewis acid such as TiCl<sub>4</sub> (Equation (2)).

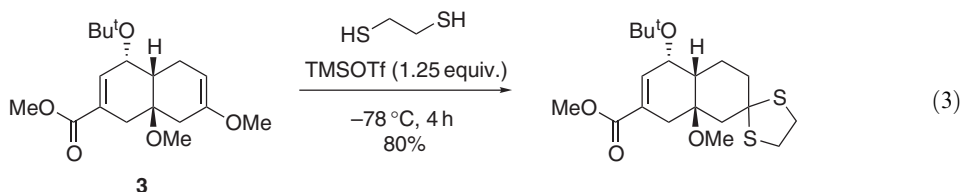




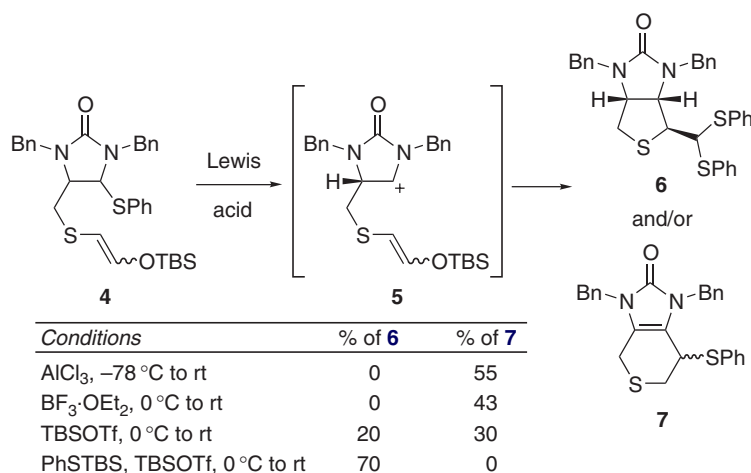
Scheme 2



However, in the case of acid-sensitive substrates like enol ether **3** (presence of the *O,O*-ketal and the *t*-butoxy group), this titanium Lewis acid led only to degradation products. This problem was solved using a slight excess of trimethylsilyltrifluoromethanesulfonate (TMSOTf) at  $-78^{\circ}\text{C}$  (Equation (3)) <2003TL1491>. This unusual thioacetalization procedure has also been employed with success for aldehydes or ketones as starting material (80–93% yield).

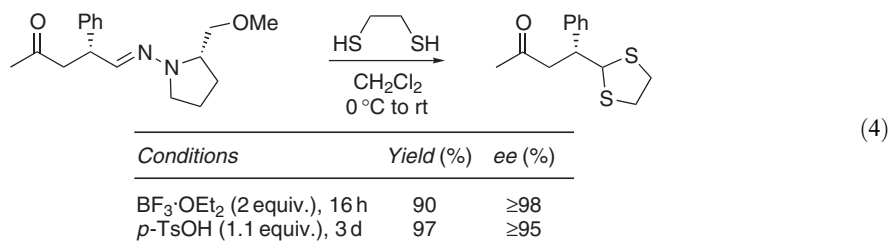


In connection with the synthesis of biotin, Lewis acids were also used for the intramolecular cyclization of silyl enol ether **4** (Scheme 3). Depending on the conditions, the thioacetal **6** and/or the bicyclic compound **7** were formed. The reaction proceeded via the generation of an immonium ion **5** and liberation of thiophenol. When *t*-butyldimethylsilyl phenyl sulfide (PhSTBS) was added, followed by a catalytic amount of TBSOTf, thioacetal **6** was the exclusive product obtained in 70% yield <2001JOC6197>.

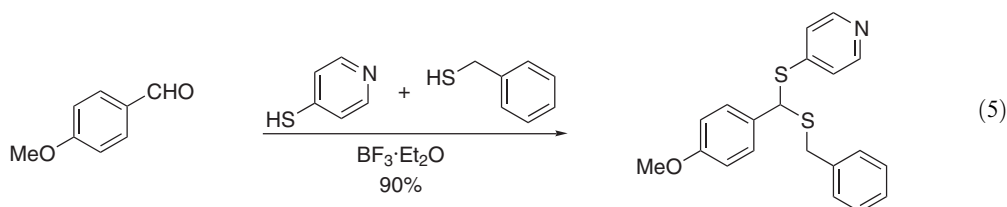


Scheme 3

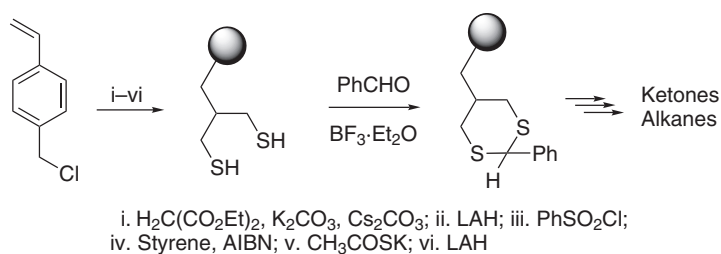
The direct dithioacetalization of *N,N*-dialkylhydrazones by 1,2-ethanedithiol could be promoted with  $\text{BF}_3 \cdot \text{Et}_2\text{O}$  or *p*-TsOH (Equation (4)) to afford the corresponding dithiolanes in nearly quantitative yields <1998TL7955>. This transformation should find further applications, in particular when the (*S*)- and (*R*)-1-amino-2-(methoxymethyl) pyrrolidine auxiliaries are used (SAMP/RAMP methodology). Dithioacetalizations of other tosylhydrazones, oximes, and enamines have also been examined <1998JCS(P1)965>.



Only one example dealing with unsymmetrical dithioacetals synthesis from aldehydes has been described (Equation (5)). An electron-deficient thiol (e.g., 4-mercaptopyridine) and an electron-rich thiol (e.g., benzyl mercaptan), in the presence of  $\text{BF}_3 \cdot \text{Et}_2\text{O}$ , must be used for this purpose <1998SL289>. Mechanistic considerations have been discussed <2002SL984>.

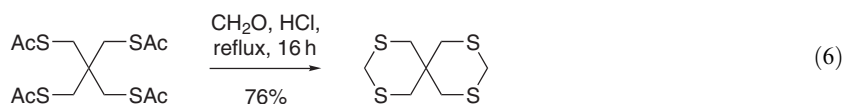


The synthesis of a polymeric reagent containing an odorless propane-1,3-dithiol function has been reported (Scheme 4). It was applied to the solid-phase synthesis of ketones <1998TL9263, 2000JOC4839, 2002EJO1546> and subsequent reduction to alkanes <2003SL1201>.

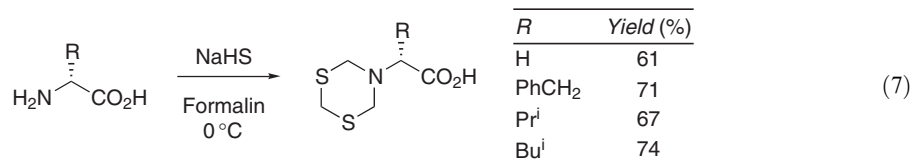


Scheme 4

Instead of thiols or dithiols, various compounds were used as alternative sources of the sulfur moiety:  $\text{Bu}_2\text{AlSPh}$  for the transformation of  $\gamma$ -phenylselenopropynal diethyl acetal <1995CC149>; mercapto-thioacetic acid in the presence of an aldehyde to give the 1,3-dithiolane-4-one, a precursor of 1,3-dithiolane nucleosides <1999CC1245>; thioacetate derivatives (Equation (6)) under acidic conditions (HCl), for the synthesis of photolabile molecular systems as dithiane-spiro-crown ethers <2001S1133, 2001OL2633>; or in the presence of a polystyrene supported sulfonic acid (10 mol.% in water) <2003OL101>.



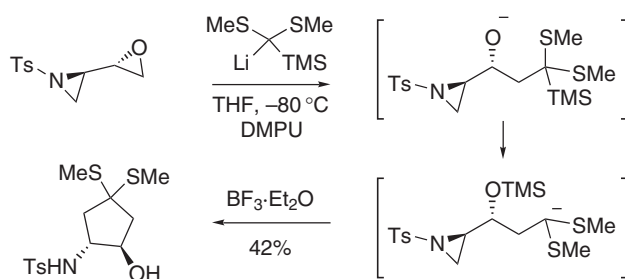
$\alpha$ -Amino acids were transformed into dithiazines (Equation (7)) via the reaction with sodium hydrosulfide in aqueous formaldehyde <2002OL4129>.



Finally, an electrochemical reduction of diaryl or dialkyl disulfide compounds in the presence of a ketone or an aldehyde and trimethylchlorosilane afforded dithioacetals in moderate yield (55–80%) <1996MI272>.

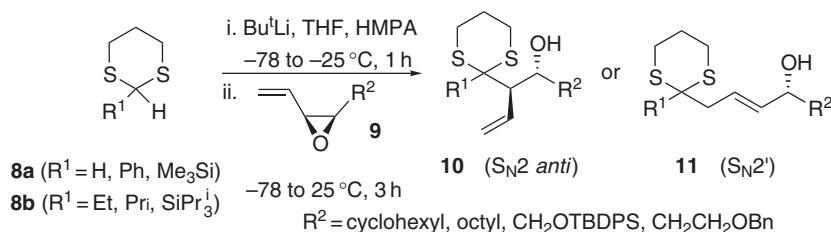
#### (ii) From other dithioacetals and related compounds

The preparation of dithioacetals from other dithioacetals is, of course, the archetypal synthetic reaction of the dithioacetals. Although in the strictest sense of the term such reactions are not really functional group transformations, they permit the conversion of a dithioacetal derived from an aldehyde to the dithioacetal of a ketone. These compounds have found particularly wide use for the Umpolung reactions of the carbonyl moiety, since the anions generated from dithioacetals are strongly stabilized by sulfur atoms and are equivalent to acyl anions. Surprisingly, no review on this area has been published since the publication of chapter 4.06 in COFGT (1995) <1995COFGT(4)243>. Thus, the report in 1989 by Page *et al.* is strongly recommended for a more thorough account of the possibilities of such reactions <1989T7643>. It is not intended to cover this area again, and this subsection will only be devoted to the chemistry that has received much attention since 1995. The addition of lithiated dithianes to epoxides and aziridines has been described. The reaction of lithiated dithianes with enantiopure *N*-sulfonylated aziridines leads, via regioselective nucleophilic ring opening, to enantiopure *N*-tosyl 2-(2'-dithianyl) secondary amines in good yields <1995JCS(P1)2439>. Both the conversion of vicinal diols into epoxides and nucleophilic epoxide opening with 2-lithio-1,3-dithiane can be performed in an efficient one-pot operation <1995JOC8122>. The synthesis of enantiomerically pure 1,2-epimino-3,4-epoxybutane has been described. This 1,4-bis electrophile offers a new route to targets with a 1,2-aminohydroxyl functionality, as in the cyclopentane synthesis depicted in Scheme 5 <2001S577>. This silicon-mediated domino approach was also used for the synthesis of pyrrolidine <2000SL92> and highly functionalized carbocycles <1999TL2921>.



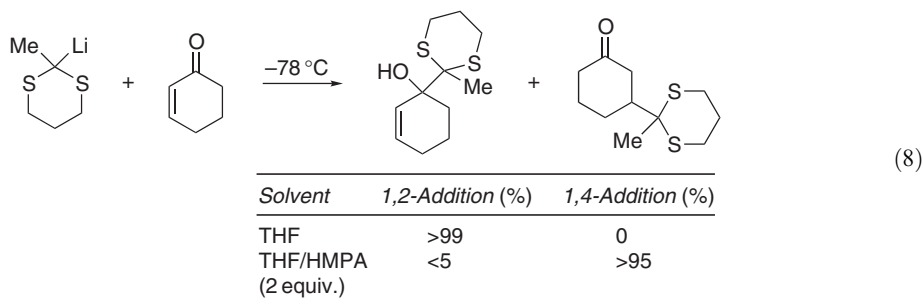
Scheme 5

High chemoselectivity was achieved for the addition of lithium dithiane anions to vinyl epoxides by making use of the steric nature of the dithiane substituent. Thus, addition of unencumbered lithiated dithianes **8a** to vinyl epoxides **9** gave S<sub>N</sub>2 adducts **10**, whereas sterically hindered anions derived from **8b** led primarily to S<sub>N</sub>2' adducts **11** (Scheme 6). Furthermore, the S<sub>N</sub>2 addition to *cis* vinyl epoxides provided exclusively *anti*-adducts, while *trans* epoxides gave the corresponding *syn*-adducts <2002JA14516>.

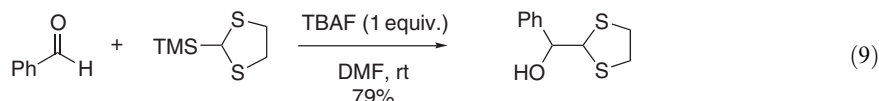


Scheme 6

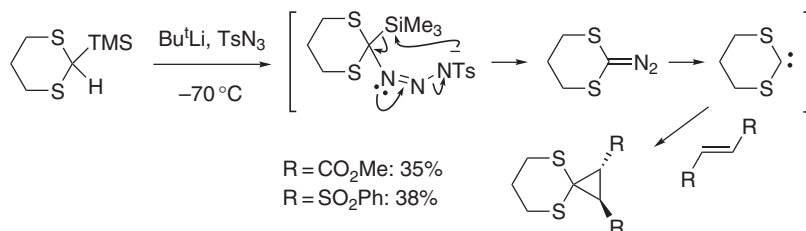
1,3-Dithiane can also be efficiently deprotonated by sodium 2-(2-ethoxyethoxy)ethoxide/sodium amide complex base [<1996T15147>](#). The effect of hexamethylphosphoramide (HMPA) on the reactivity of epoxides, aziridines, and alkyl halides with bis-thio substituted organolithium reagents has been examined. This cosolvent displayed either rate accelerating or rate retarding effects on the  $\text{S}_{\text{N}}2$  reactivity [<2002JA13386>](#). The role of HMPA in controlling the ratio of 1,2- to 1,4-addition to cyclohexenones and hexenal by sulfur-substituted organolithium reagents has also been studied (Equation (8)) [<1999JOC14, 2001JA6527>](#). The complexation effect of HMPA to lithium causes ion pair separation and lowers the Lewis acidity of the lithium cation which enhances 1,4-addition. The use of quinuclidine *N*-oxide has also been proposed as another alternative to the carcinogenic HMPA [<1999CC59>](#).



2-Trimethylsilyl-1,3-dithiolane was described as a masked dithiolane anion [<2001TL4557>](#). Under fluoride-ion catalysis, this compound reacted with different aldehydes, ketones, and allyl bromide. A representative example is given in Equation (9).

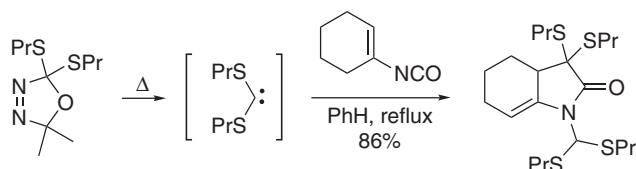


2-Lithio-2-(trimethylsilyl)-1,3-dithiane reacted with tosyl azide to give transient 2-diazo-1,3-dithiane, which decomposed to give the corresponding carbene (Scheme 7), whose  $\beta$ -reactivity toward various alkenes and alkynes has been examined [<1995CC1999, 1997T9269>](#).



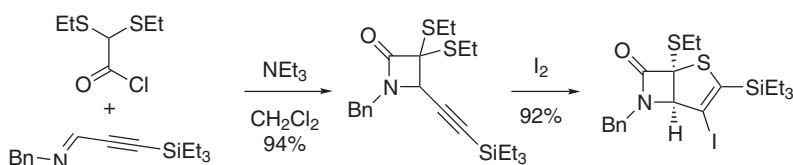
Scheme 7

A carbene can also be generated from dithioxadiazoline by heating. This species undergoes cycloaddition reactions with isocyanates (generated *in situ* from acyl azides) to produce pyrrolones and indolones (Scheme 8) [<1999JOC1766>](#). This methodology was applied to the synthesis of isatin derivatives [<1999TL6891, 2000T10101>](#).



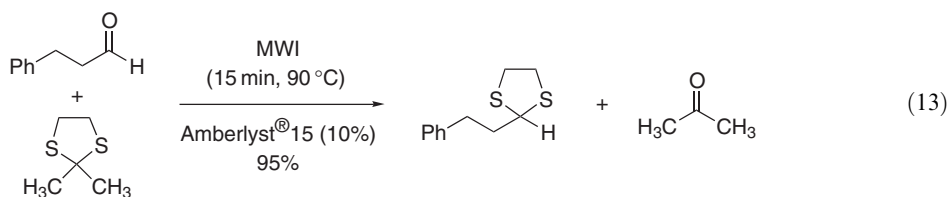
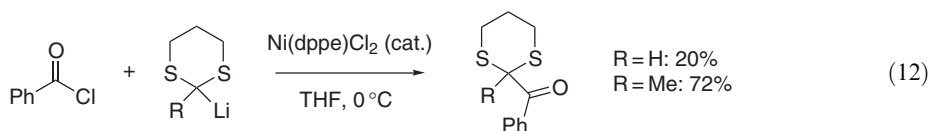
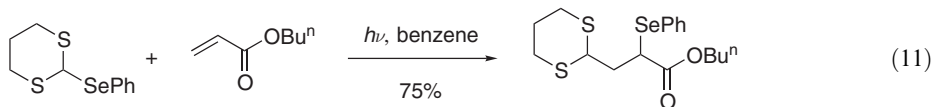
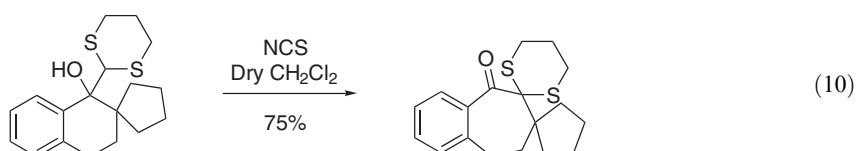
Scheme 8

Nonconventionally fused bicyclic  $\beta$ -lactams have been synthesized in two steps [<1998JOC8898>](#): [2 + 2]-cycloaddition of bis(ethylthio)acetyl chloride with propargyl imines and the subsequent iodination reaction ([Scheme 9](#)).



Scheme 9

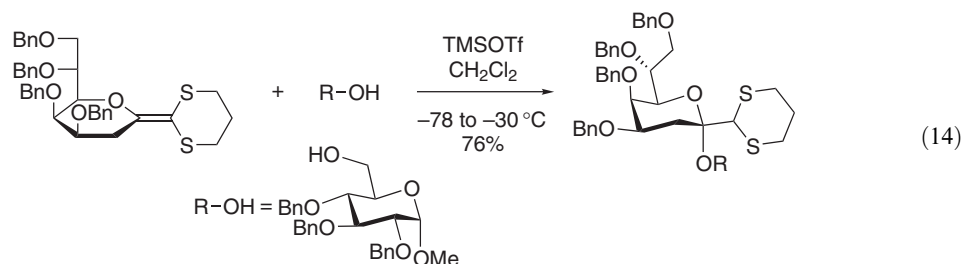
A reaction involving rearrangement of an aromatic ring fused cyclic dithiane alcohol by *N*-chlorosuccinimide has been developed ([Equation \(10\)](#)) [<1999JOC6380>](#). The corresponding one-carbon ring expanded 1,2-diketones was thus obtained. Photolysis of 2-phenylseleno-1,3-dithiane in the presence of electron-deficient alkenes, gave the addition products ([Equation \(11\)](#)). These reactions illustrate a radical atom transfer process arising from a heteroatom-stabilized radical [<1996TL2743>](#). A catalytic amount of Ni(0) allowed the conversion of an acyl chloride into 2-acyldithianes, not directly obtainable by other methodologies ([Equation \(12\)](#)) [<1995TL9185>](#). Aldehydes and ketones were protected as thioacetals ([Equation \(13\)](#)) by an exchange reaction with 2,2-dimethyl-1,3-dithiolane, catalyzed by an acidic solid catalyst without solvent under microwave irradiation [<2000GC252>](#).



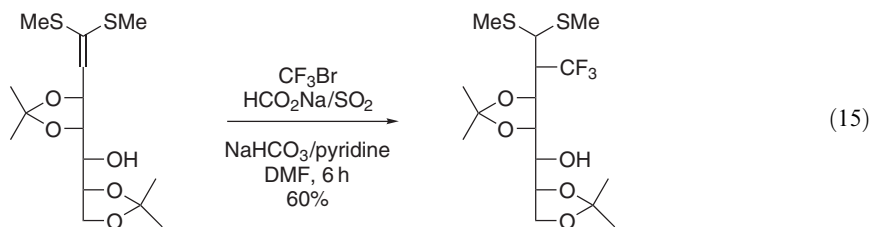
## (iii) From ketene dithioacetals

The transformation of a ketene dithioacetal to a saturated dithioacetal can be achieved either with a C—H bond formation or with the creation of a C—C bond at the  $\alpha$  carbon.

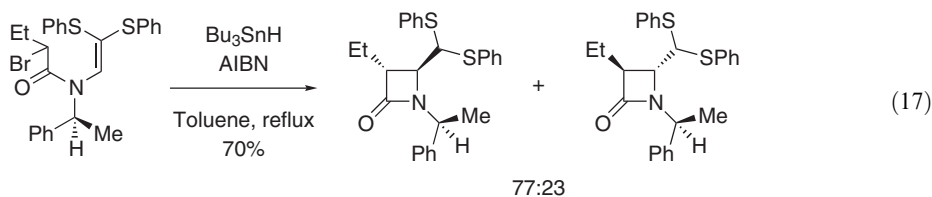
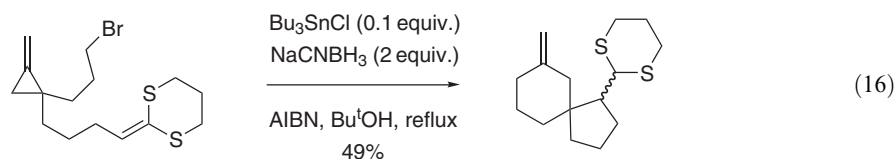
(a) *With C—H Bond Formation.* Two general methods have been developed allowing the reduction of ketene dithioacetals to substituted dithianes: zinc in acetic acid and magnesium in methanol <1997T17151>. Ketene dithioacetals have been used as glycosyl donors for the synthesis of *O*-glycosides <1999PJC973> and disaccharides (Equation (14)) <2000TA3737>.



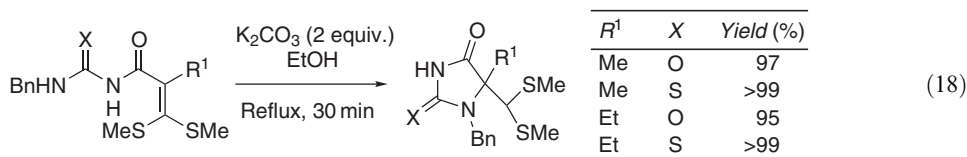
Various radical reactions with ketene dithioacetals have been investigated. The trifluoromethylation of ketene dithioacetals derived of mannose was carried out in the presence of trifluoromethyl bromide, sulfur dioxide, and sodium formate (Equation (15)) <1997JOC9107>.



The intramolecular radical cyclization of a brominated ketene dithioacetals was used for the synthesis of spiroundecane compounds (Equation (16)) <1995TL1365> and for the asymmetric synthesis of the lactam ring of carbapenem antibiotics (Equation (17)) <1996T489>.

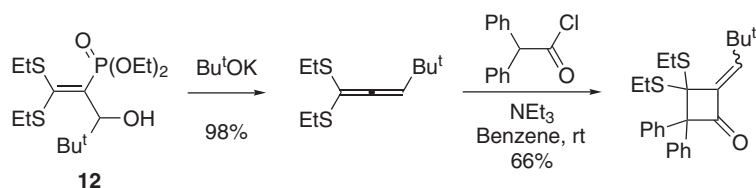


Base-induced cyclization of ureas or thioureas (Equation (18)) led to the formation of hydantoin derivatives in excellent yields <1995TL6257>.



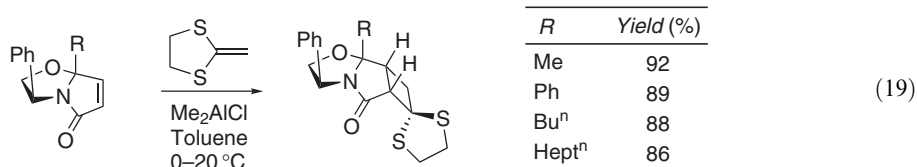
(b) *With C—C bond formation.* Ketene dithioacetals can be used as starting materials for cycloaddition. The dithioallene, obtained in quantitative yield by treatment of the alcohol **12** with

Bu<sup>t</sup>OK, treated with an excess of diphenyl ketene (generated *in situ*), led to [2 + 2]-cycloadducts (Scheme 10) in moderate yield <1996JOC8132>.

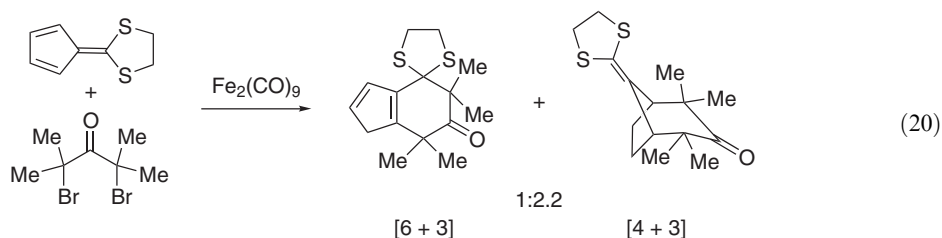


Scheme 10

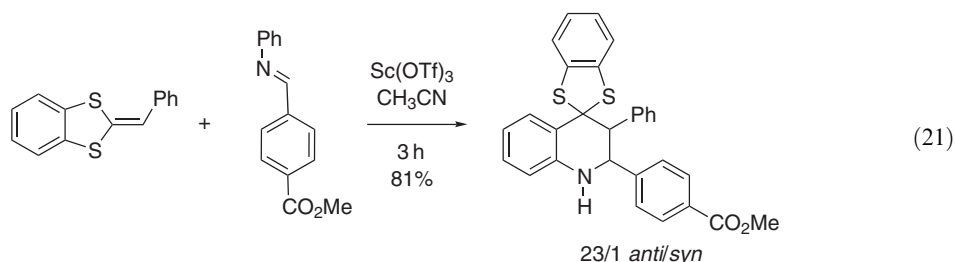
Additions of methylene dithiolane to unsaturated chiral lactams, mediated by dimethyl aluminum chloride, gave very high *endo*-selectivity of the cyclobutane [2 + 2]-adducts (Equation (19)) <1995JOC4359>. Under the same conditions, ethylene dithiomethyl ketal did not afford the cyclobutane adduct.



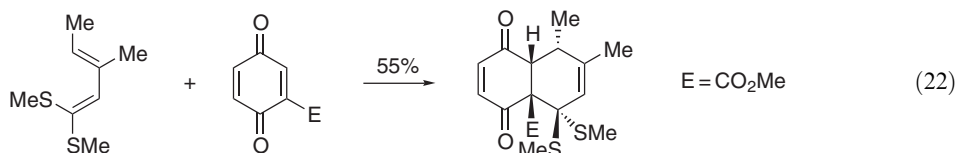
Both the [4 + 3]- and [6 + 3]-cycloadditions (Equation (20)) were observed when fulvene ketene dithioacetal reacted with 2-oxallyl cation (generated *in situ*) <1997JOC7717>.



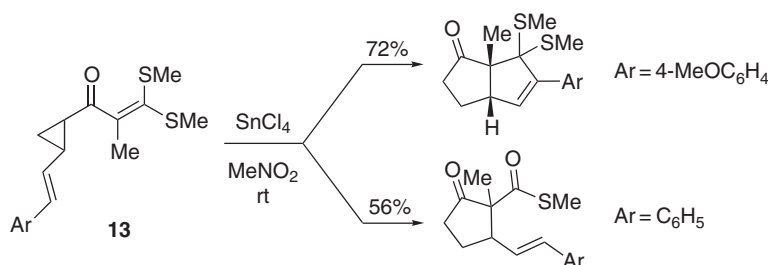
Ketene dithiolane can also be used as a dienophile in the aza-Diels–Alder reaction with *N*-arylimines (Equation (21)). Among the dienophiles tested, 1,4-benzodithiafulvenes were the most effective in the construction of the tetrahydroquinoline core <2002OL4411>.



The reaction of dialkylated vinyl ketene dithioacetal with *in situ* generated 2-methoxycarbonyl-*p*-quinone furnished the Diels–Alder adduct in 55% yield (Equation (22)) <1995TL4625>.

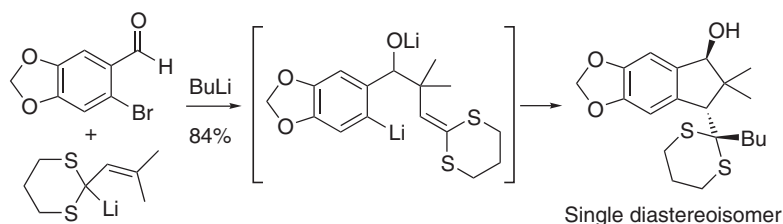


The rearrangement of cyclopropyl ketone **13** catalyzed by  $\text{SnCl}_4$  afforded two types of products with regard to the nature of the substituents of the aryl ring (Scheme 11). With a phenyl group, only the carboxythioate was obtained. However, with the *p*-methoxy group, the bicyclo[3.3.0]octenone was isolated as a single product <1998T531>.



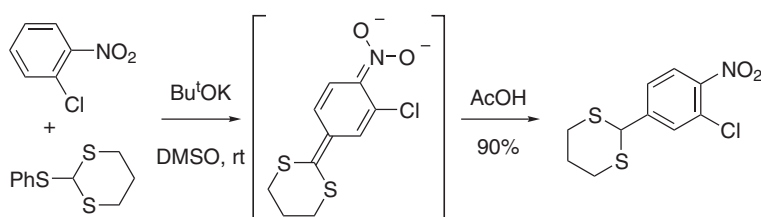
Scheme 11

A triple Umpolung sequence has been described for the preparation of substituted indanes <1996T14951>, in which a ketenedithioacetal was generated *in situ* (Scheme 12).



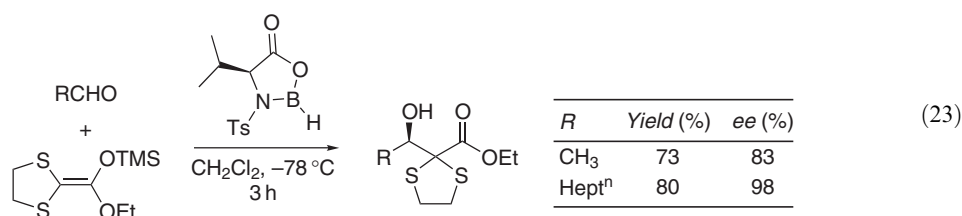
Scheme 12

2-Phenylthio-1,3-dithiane underwent vicarious nucleophilic substitution with various nitroarenes <2000TL5111> to provide *p*-dithianyl nitroarenes regioselectively in one step in good yields (Scheme 13).



Scheme 13

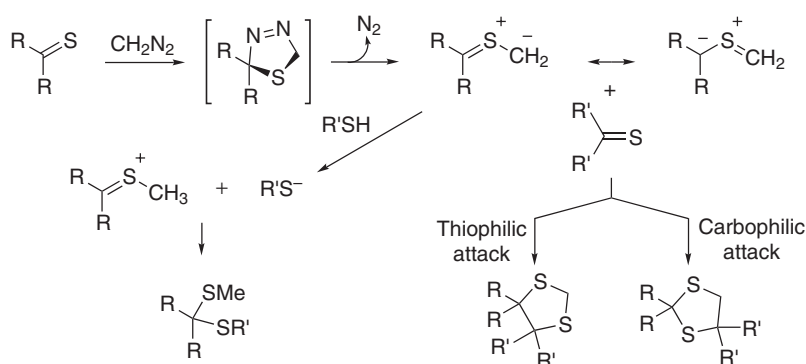
An asymmetric synthesis of dithiolane aldols was achieved (Equation (23)) by using silyl ketene acetals and a chiral oxazaborolidinone <1996TA2181>.





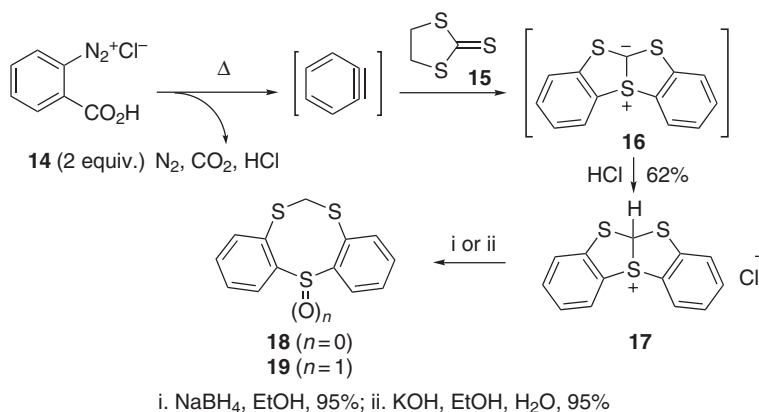
## (iv) From thiocarbonyl compounds

The only cycloaddition reactions that have been investigated involve dithioesters, thioketones, or trithiocarbonates. Mloston *et al.* have developed an easy access to thiocarbonyl ylides (Scheme 14), generated from the cycloadduct of a thiocarbonyl compound and diazomethane <1999T11475>. This 1,3-dipole reacts *in situ* with thiocarbonyl compounds (thione or dithioester) to afford the corresponding 1,3-dithiolanes. Two cycloadducts can thus be obtained depending on the “thiophilic” or “carbophilic” attack of the 1,3-dipole. This regioselectivity was controlled by steric or electronic effects <2000EJO1685, 2000EJO1695>. The dipole can also react with thiols to lead to dithioacetals via thionium ions <1999PJC635, 2001T145>.



Scheme 14

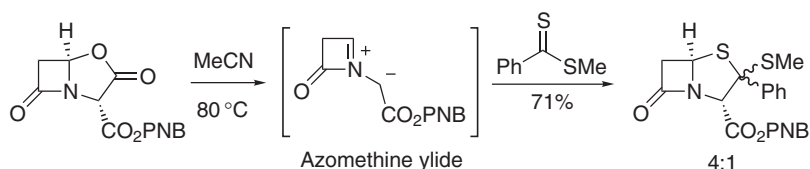
The sulfur ylide **16**, generated by a 1,3-dipolar cycloaddition of a benzyne derivative (formed by thermolysis of 2-carboxybenzenediazonium chloride **14**) to the ethylene trithiocarbonate **15**, can be trapped by hydrogen chloride (generated from **14**) to give a sulfonium chloride **17** (Scheme 15). Reduction of this sulfonium salt with  $NaBH_4$  afforded the dithiacetal **18** in excellent yield, while treatment with  $KOH$  led to the sulfoxide **19** <1996BCJ2349, 1998BCJ1187>.



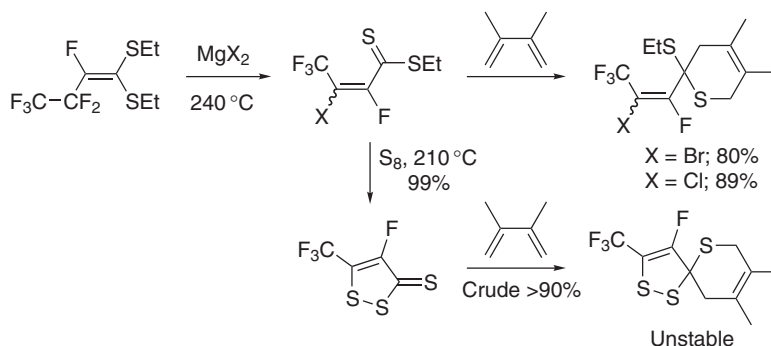
Scheme 15

An azomethine ylide and a dithioester as dipolarophile have been used for the synthesis of bicyclic  $\beta$ -lactams (Scheme 16) <1997JOC3438>. A similar reactivity was reported with phthalazinium-2-methanide and cyanodithioformate <1998JCS(P1)869>.

Portella and co-workers have described the [4 + 2]-cycloaddition between 2,3-dimethyl-1,3-butadiene and fluorinated thiocarbonyl compounds as dienophiles (Scheme 17) <2001TL2133, 2002TL5809>.



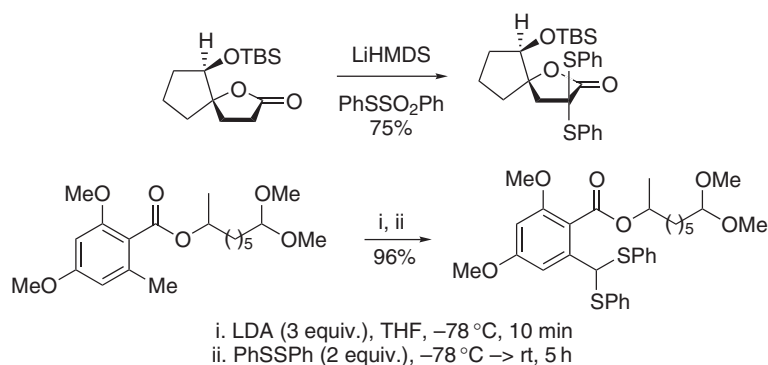
Scheme 16



Scheme 17

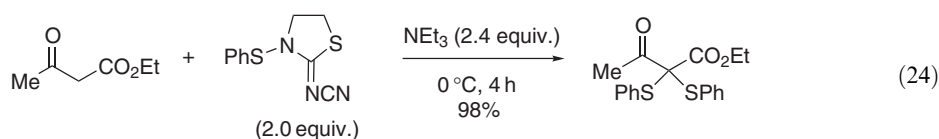
## (v) From various precursors

Compounds bearing an acidic methylene group may be disulfenylated by the action of a base followed by a reaction with a sulfenylating reagent. Only a few examples of sulfenylation have been described, and two of them are depicted in [Scheme 18](#). One employs a thiosulfonate [\[1999S258, 2001JOC2828\]](#) and the second uses a disulfide [\[1997TA2433, 2000JOC7990\]](#) as the sulfenylating agent.

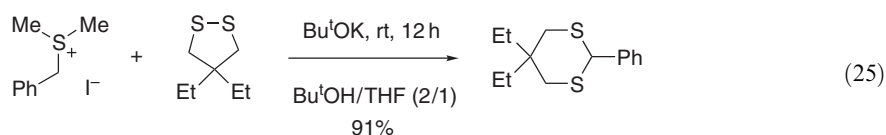


Scheme 18

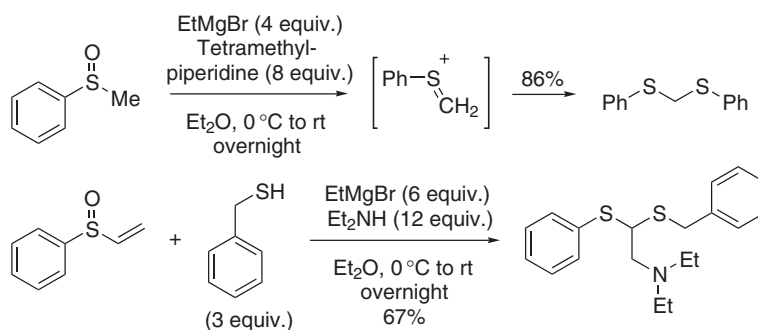
A new and efficient sulfenylation agent has been developed by Tanaka and co-workers: 3-phenylsulfenyl-2-(*N*-cyanoimino)thiazolidine ([Equation \(24\)](#)) [\[2000SL33\]](#).



1,2-Dithiolane is a convenient precursor for dithioacetals by reaction with sulfonium ylides (Equation (25)) <1995PS(106)227> or sulfoxonium ylides <1996PS(116)253>. Instead of ylides, pyridylmethylithium can also be used for the synthesis of 2-pyridyl-1,3-dithianes <1996PS(112)101>.

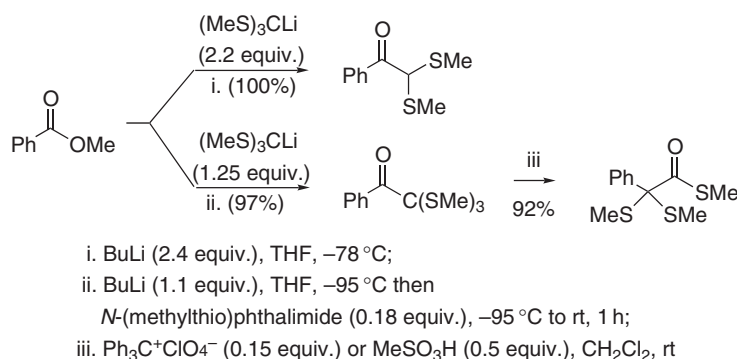


Other functional groups can be transformed into dithioacetals, e.g., sulfoxides (Scheme 19). Indeed, Kobayashi *et al.* have revealed that the reaction of sulfoxides bearing an acidic proton with magnesium amides (generated *in situ*) afforded the corresponding symmetrical dithioacetals via a Pummerer-type carbonium ion <1995BCJ1401>. This reaction was used to approach akuammiline alkaloids <1996JOC1239> and for the racemic synthesis of ethoxycarbonylmethyl-2-hydroxy-cyclohexanones <1998TA3445>. In the presence of thiols, unsymmetrical dithioacetals can be synthesized using the same strategy <1996BCJ2645, 2002BCJ1367>. This reaction has also been extended to vinyl sulfoxides <1997JOC8015>.



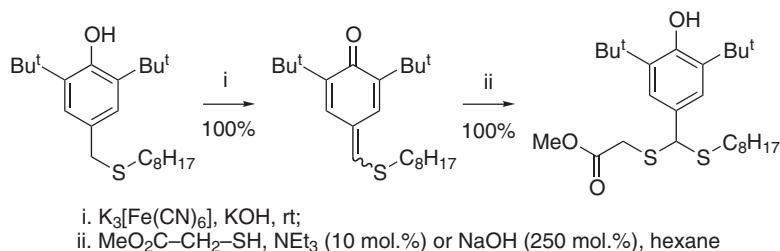
Scheme 19

The reaction of tris(methylthio)methylithium with aromatic, heteroaromatic, and aliphatic esters afforded, in excellent yields, the dimethyl  $\alpha$ -keto dithioacetals (Scheme 20) <1995JOC6017>. This reaction was then applied to acyl chlorides, anhydrides, thiol esters, and *N,N*-dimethylamides <1996JOC9572>. Depending on the reagent ratios and the reaction conditions, the trimethyl  $\alpha$ -keto trithioorthoesters can also be selectively obtained. By rearrangement in the presence of catalytic amounts of trityl perchlorate or methanesulfonic acid, these compounds led to  $\alpha,\alpha$ -bis(methylthio)thiolcarboxylates in very good yield <1997JOC7228>.



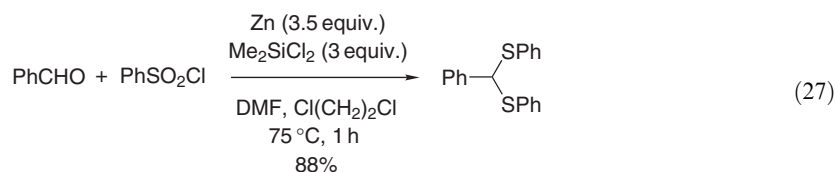
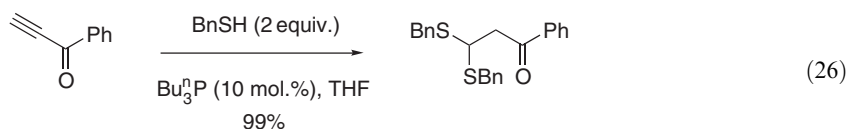
Scheme 20

Reaction of allyl silanes with tris(phenylthio)methane in the presence of  $\text{ZnBr}_2$  furnished the corresponding homoallylthioacetals in moderate yields <1996TL6085>. Regioselective oxidation of the *p*-alkylthiomethylphenols to the monosubstituted *p*-quinone methides with  $\text{K}_3[\text{Fe}(\text{CN})_6]$  followed by the addition of thiols provided the corresponding dithioacetals in excellent yields (Scheme 21) <1995PS(107)119>.

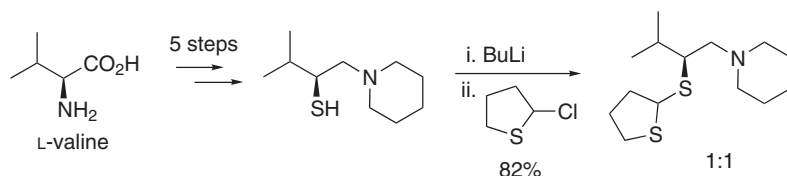


Scheme 21

Preparation of dithioacetals can be achieved by the double conjugate addition of a thiol derivative to acetylenes bearing electron-withdrawing groups (esters or ketone). Thus, by reaction with benzyl thiol in the presence of  $\text{Bu}_3\text{P}$  as catalyst, the ethynyl phenyl ketone was transformed to the corresponding dithioacetal in almost quantitative yield (Equation (26)) <1996SC1539>. Dithioacetalization of aldehydes can also be performed from sulfonyl chlorides <1999TL3179>. For this purpose, the corresponding thiols were generated *in situ* by reduction with the combined use of zinc metal and dichloromethylsilane in dimethylformamide (Equation (27)). This reaction is promoted by zinc chloride, formed during the reduction process, acting as a Lewis acid.



Preparation of an enantiopure hemicyclic dithioacetal from L-valine (Scheme 22) and 2-chlorothioline has been described <1996T12745>.

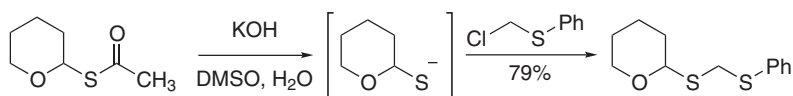


Scheme 22

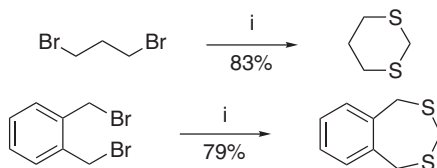
Using the same strategy, unsymmetrical dithioacetals (hemithioacetals) were synthesized by a one-pot reaction of thioacetic acid esters and  $\alpha$ -chlorosulfides (Scheme 23) <2002PS(177)709>.

Dihalides can also be used for the direct formation of dithianes and dithiepinines via a one-pot reaction with carbon disulfide and sodium borohydride (Scheme 24) <2000OL1133>.

Finally, the dithioacetal function was obtained accidentally as a by-product or with a poor yield. Two interesting examples are depicted in Scheme 25: the conversion of trichloromethyl compounds <1999S225> and the transformation of 1,2-diol to the corresponding dithioacetals <1998TL6027>.

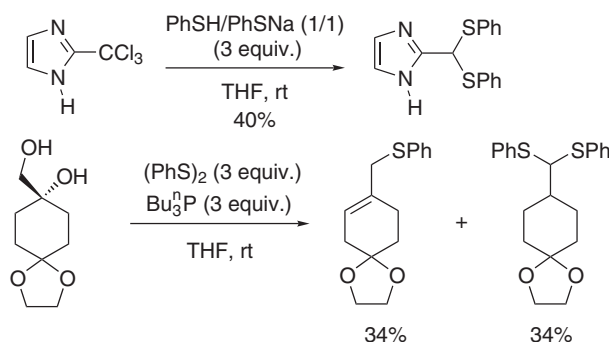


Scheme 23



i. CS<sub>2</sub> (1.5 equiv.), NaBH<sub>4</sub> (3 equiv.), THF, reflux overnight

Scheme 24



Scheme 25

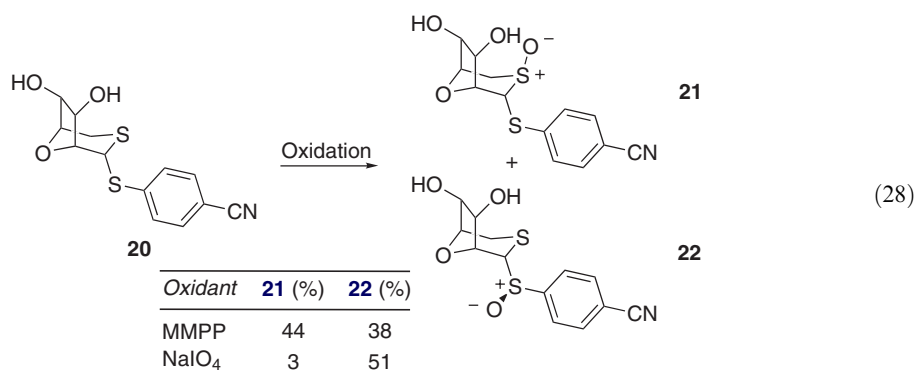
#### 4.06.1.3 One Dicoordinated Sulfur and One Higher Coordinated Sulfur—R<sub>1</sub><sup>2</sup>C(SR<sup>2</sup>)SO<sub>2</sub>R<sup>3</sup>, etc.

##### 4.06.1.3.1 $\alpha$ -Thiosulfoxides

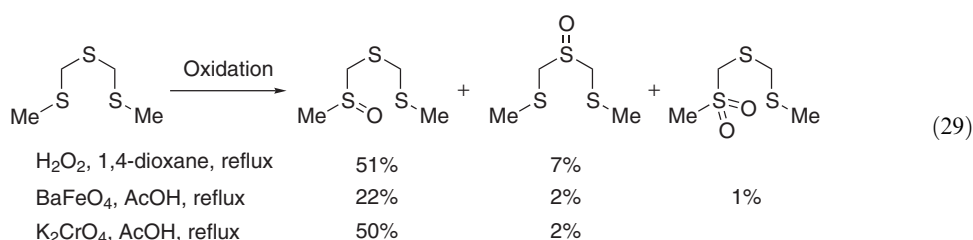
###### (i) Oxidation of dithioacetals

Following the trend of chapter 4.06 in COFGT (1995) <1995COFGT(4)243>, the mono-oxidation of dithioacetals remains a widely used transformation toward  $\alpha$ -thio sulfoxide derivatives. The efficiency of this approach has to be considered in terms of selectivity: (i) the regioselectivity of unsymmetrical dithioacetals; (ii) the chemoselectivity, in order to prevent overoxidation reactions leading to bis-sulfoxides or sulfones formation; (iii) the diastereoselectivity, usually associated with the facial discrimination of cyclic 2-substituted 1,3-dithioacetals; and, eventually, (iv) the enantioselectivity, allowing the differentiation of the enantio- or diastereotopic sulfur atom lone pairs. As far as the asymmetric synthesis of sulfoxides is concerned, the reader is advised to have a look at Chapter 2.03.2, which provides a more general discussion.

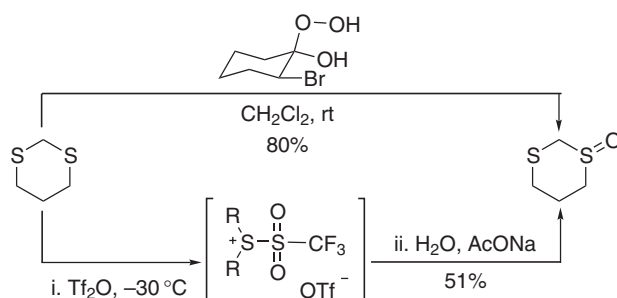
The selective oxidation of thioglycosides of type **20** (Equation (28)) has been investigated in order to gain insight into the structure–activity relationship of these potential antithrombotic drugs <2002TA3423>. With magnesium monoperoxyphthalate (MMPP) as oxidant, an almost equal amount of *endo* **21** and *exo* **22** sulfoxides was obtained. By using 1 equiv. of NaIO<sub>4</sub>, however, the *exo*-(*R*)-sulfoxide **22** was formed as the main product. During the course of the reaction, minor analogs such as bis-sulfoxides and sulfones were also characterized. Similarly, the oxidation of a related compound, namely the 4-cyanophenyl 1,5-dithio- $\beta$ -D-xylopyranoside derivative, proceeded with 3-chloroperoxybenzoic acid (MCPBA), but a single *endo*-sulfoxide was isolated <1997CAR53>.



The conversion of 2,4,6-trithiaheptane to the corresponding unsymmetrical sulfoxide is a relevant example of a regioselective and chemoselective reaction (Equation (29)). For this specific case, it has been shown that potassium chromate in hot acetic acid was more selective than hydrogen peroxide or barium ferrate <1999SUL141>, in spite of the harsh reaction conditions.



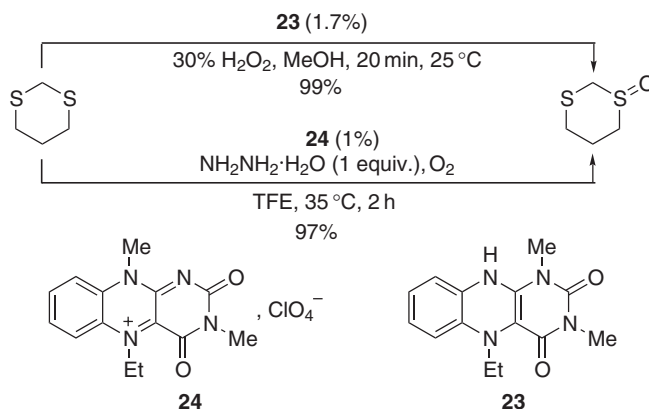
With unfunctionalized 1,3-dithiane as a model substrate, different approaches have been employed displaying no overoxidation reactions (Scheme 26). Carnell *et al.* have described the synthesis of a stable perhydrate derived from  $\alpha$ -bromocyclohexanone and 30% H<sub>2</sub>O<sub>2</sub> <2000T6571>. This oxidant yielded the corresponding  $\alpha$ -thio sulfoxide chemoselectively in dichloromethane as solvent albeit no reaction was observed in tetrahydrofuran (THF). This perhydrate is considered to be a useful selective oxidant in synthesis because of its poor reactivity toward alkenes or ketones. Another approach (Scheme 26) consisted of treating a dialkyl sulfide precursor with triflic anhydride to give a dialkyl(trifluoromethanesulfonyl)sulfonium salt intermediate <1997JOC2483>. Subsequent treatment with water provided the corresponding sulfoxide without sulfone formation.



Scheme 26

One important trend since 1995 in the field of the oxidation reaction has been the elaboration of organocatalysis processes, which has been reviewed <2001CRV3499>. Organic substances able to mediate selective catalytic oxidation of dithioacetals, in the presence of a co-oxidant, have been successfully described. For instance, Page *et al.* showed that simple oxime derivatives promoted the mono-oxidation of 2-phenyl-1,3-dithiane with hydrogen peroxide as co-oxidant <1997SL1355>. Efficient biomimetic processes, by analogy with microsomal flavin adenine dinucleotide containing monooxygenase (FADMO), have been established (Scheme 27).

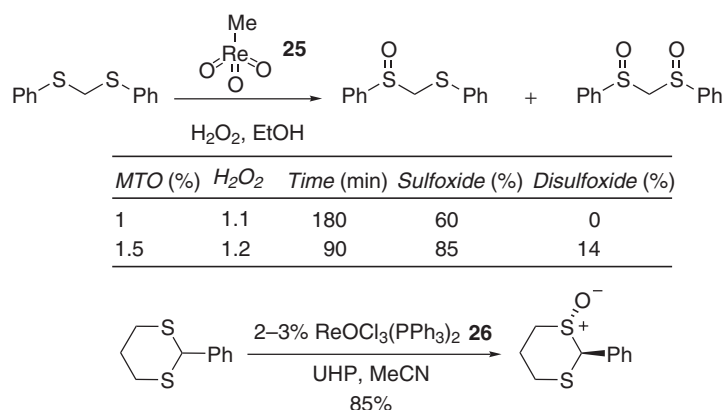
A detailed examination of the substitution pattern of various flavin derivatives showed the effectiveness of structure **23** to promote the oxidation of 1,3-dithiane [2001CEJ297](#). Even with 2 equiv. of  $\text{H}_2\text{O}_2$  after a 1h reaction, the formation of overoxidized products was not detectable. Further development of this process toward an aerobic catalyzed oxidation reaction has also been successfully demonstrated with lumiflavin **24** in the presence of hydrazine monohydrate [2003JA2868](#). The use of trifluoroethanol as solvent, given its high solubility of molecular oxygen, turned out to be essential to allow a smooth and selective mono-oxidation. Due to the low loading of these kinds of catalysts and the reaction conditions, these oxidative approaches can be considered to be economical and environmentally friendly systems.



Scheme 27

Given the wide application of 1,3-dithiane-1-oxides in chemistry affording the diastereoselective preparation of various organic compounds, their syntheses from the oxidation of the corresponding 1,3-dithioacetals have been realized with a variety of reagents. Readers should check chapter 4.06 of COFGT (1995) [1995COFGT\(4\)243](#), as well as subsequent papers of the Page group [1997T1061](#), [1998T14581](#), which provide an overview of the various classical oxidative conditions being employed. Indeed, most of the work has been achieved with 2-substituted 1,3-dithianes or 1,3-dithiolanes, and the chemo- as well as the stereoselectivity of the oxidation seems to be substrate and reaction-condition dependent. In the case of seven-membered rings, high diastereoselectivity has been reported for the resulting *trans*-sulfoxides [2001RJGC960](#).

Organometallic catalysis remains an active field of chemistry in the early 2000s, displaying great improvement toward the smooth and selective oxidative reaction of sulfur atoms. With only 1% of the air stable methyltrioxorhenium **25** (Scheme 28), the mono-oxidation reaction of an acyclic dithioacetal proceeded selectively at low conversion [1996BCJ2955](#). Nonetheless, the stoichiometry of the reagents has to be controlled in order to prevent overoxidation processes. Furthermore, using ethanol as the solvent seems to be crucial for the success of the reaction. A striking



Scheme 28

solvent effect has also been observed with rhenium complex **26** as a homogeneous catalytic activator of urea-hydrogen peroxide (UHP) <1998TL5655>. Although the oxidative transformation afforded the corresponding sulfoxide with *trans* selectivity in acetonitrile, a slow reaction rate was measured in CH<sub>2</sub>Cl<sub>2</sub> or CHCl<sub>3</sub>. The tolerance of other oxidant sensitive functional groups such as alkenes is another point of interest of rhenium catalysis.

An important systematic examination of the titanium-catalyzed oxidation of various 2-substituted 1,3-dithianes and 1,3-dithiolanes (Table 5) has been published by Della Sala *et al.* <2002S505>. They demonstrated that Cp<sub>2</sub>TiCl<sub>2</sub> gave comparable selectivities to that of the classical Ti(Pr<sup>i</sup>O)<sub>4</sub> but improved yields considering the chemoselectivity. This cyclopentadienyl Ti(IV) complex turned out to be less moisture sensitive and could be used with as little as 1% loading in the presence of 4 Å activated molecular sieves and *t*-butyl hydroperoxide (TBHP) as a co-oxidant. The diastereoselectivity of the reaction is generally excellent, affording *trans* derivatives, except for 2-carbonyl dithianes, which are known to be problematic substrates due to epimerization at the α-position of the carbonyl function.

**Table 5** Representative examples of titanium catalyzed oxidation of cyclic dithioacetals to monosulfoxides<sup>a</sup>

Substrate	Catalyst (%)	Time (h)	Yield (%)	Trans:cis
	5	5	86	98:2
	5 <sup>b</sup>	3	72	98:2
	5	5	91	96:4
	1	16	85	98:2
	5	25	63	80:20
	1	30	69	72:28
	1	22	69 <sup>c</sup>	93:7

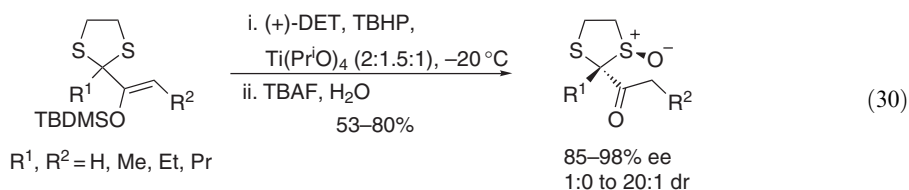
<sup>a</sup> CH<sub>2</sub>Cl<sub>2</sub>, molecular sieves 4 Å, TBHP, 0 °C. <sup>b</sup> Ti(Pr<sup>i</sup>O)<sub>4</sub> was used. <sup>c</sup> 4% of bis-sulfoxide was obtained.

As has already been discussed in COFGT (1995) <1995COFGT(4)243>, singlet oxygen can oxidize dithioacetals, and insights into the mechanism of this reaction have been provided <1999JOC5620, 2001JA4966>. Advances in the chemistry of dithiiranes, a unique three-membered ring dithioacetal, have been reviewed and the synthesis of dithiane-1-oxide derivatives has been described <1996MI869, 1999RHA1>.

The elaboration of enantiomerically enriched 1,3-dithioacetal 1-oxide is an important field of research, taking into account the richness of such derivatives as chiral nonracemic auxiliaries. Within chapter 4.06 of COFGT (1995) <1995COFGT(4)243>, the relevance of the modified

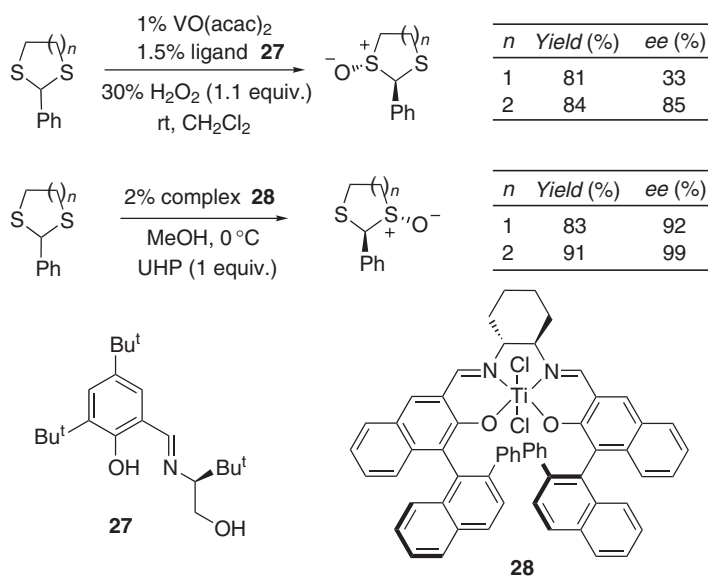


Sharpless reagent for the asymmetric synthesis of cyclic 2-substituted 1,3-dithioacetals has been pointed out. The reaction is usually performed by either the Kagan-modified procedure (dithioacetal: TBHP:titanium tetrakisopropoxide:diethyl tartrate (+ or -) (DET):water in a ratio of 1:1.1:1:2:1 or the Modena-modified procedure (1:0.5:0.25:1:0)). As a rule of thumb, a coordinated group at the 2-position, for instance encountered within cyclic 2-acyl-1,3-dithioacetals, is required for a highly enantioselective process, and the formation of the *anti* diastereoisomer is usually predominant. In the case of acyl dithiolanes, Maycock and co-workers have reported an improved diastereoselectivity by using anhydrous modified Sharpless conditions [<1995TL6537>](#). Although a three-step sequence is required (enol ether formation–oxidation–ketone regeneration), they showed subsequently (Equation (30)) that a better stereoselectivity was obtained when the oxidation step was realized with enol silyl ethers [<1997TL5047>](#). Up to 19% enantioselectivity improvement was measured in the dithiolane series, in comparison with the direct oxidation of the corresponding ketone. This technique was, however, not general to six-membered ring dithiane compounds.



Since the publication of COFGT (1995) [<1995COFGT\(4\)243>](#), several examples of asymmetric synthesis of 1,3-dithiane 1-oxides (DiTOX) have been described with closely related Sharpless modified protocols [<1995JCS\(P1\)2673, 2000T9683>](#). A subsequent paper by Page and co-workers giving a compilation of various results with those substrates [<1996T2125>](#) should be consulted. The preparation of simple chiral building blocks lacking a coordinating group, such as the 1,3-dithiane 1-oxide, occurred with low selectivity with the previously mentioned method. Alternatively, the diastereoselective oxidation reaction of 1,3-dithianes bearing a removable chiral auxiliary at the 2-position, such as diacetone-D-glucose (DAG), has been successfully reported [<1996JCS\(P1\)1879>](#).

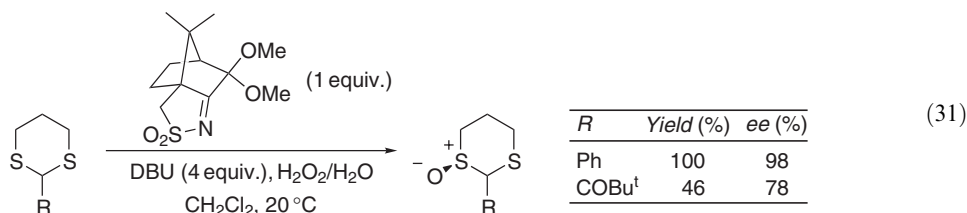
In 1995, Bolm and Bienewald established an efficient catalytic asymmetric sulfoxidation (Scheme 29). This reaction is promoted by vanadium complexes and successfully applied on dithioacetals with nonchelating groups. This process is easily performed in an open reaction vessel with the cheap  $\text{H}_2\text{O}_2$  as the oxidizing agent [<1995AG\(E\)2640>](#). The best results were obtained with *N*-salicylidene-amino alcohol ligand **27** in the 2-aryl-1,3-dithiane series [<1998SL1327>](#) and a catalyst loading of 0.1% was still successful. An erosion of the enantioselectivity was, however, measured with



Scheme 29

2-alkyl-dithiane derivatives. Sharzewski and co-workers further extended this approach with salen ligand analogs synthesized from D- or L-valinol, both enantiomers of which are readily available <1999TA3457>. Katsuki *et al.* have published an impressive enantioselective mono-oxidation with Ti(salen) complex **28** <2002TL3259>. Up to 99% enantiomeric excess (ee) was obtained and the reaction does not require a halocarbon solvent. These two methods proved to be very chemo- and diastereoselective for a large range of cyclic dithioacetals.

Page *et al.* have continued to improve the efficiency of novel camphorsulfonyl oxaziridine oxidants and have reported a reliable synthesis (1(*S*))-(-)-1,3-dithiane 1-oxide <1999OS37> in large quantities. These nonmetal catalysis methods have been recently reviewed <2001CRV3499> and generally provide an environmentally preferable approach to that of transition metal catalyzed methods. It has also been shown that the oxidation reaction could take place with H<sub>2</sub>O<sub>2</sub> as the terminal oxidant (Equation (31)) in the presence of enantiomerically pure sulfonylimines <1995SL773>. The reverse selectivity obtained compared to their oxaziridine analogs suggested the formation of an  $\alpha$ -hydroperoxyamine intermediate <1995TA2911, 1999PS(153/4)247>. The same method has been applied to acyclic 1,3-dithioacetals <2001IJC(B)1132>.

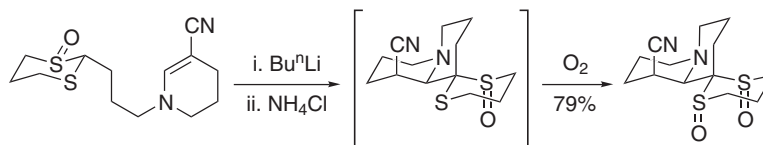


Biocatalysis constitutes an important alternative to chemical oxidative processes and provides an ecologically tolerant approach. Progress in the field of dithioacetals has allowed broadening of the scope of biosulfoxidation reactions with regard to both their usual substrate dependence and scale-up performances. Colonna *et al.* <1995CC1123, 2002HAC467> have reported a high-yielding mono-oxidation of unsubstituted 1,3-dithiane, 1,3-dithiolane, and bis(methylthio)-methane with a cyclohexanone monooxygenase (CMO) from *Acinetobacter calcoaceticus* NCIMB 9871. More than 98% ee values were measured in favor of the (*R*)-monosulfoxides, and with the formation of sulfone derivatives a kinetic resolution has been assumed in some cases. This method was extended to 2-substituted analogs but an erosion of the enantioselectivity was observed for the major *trans*-products <1996TA565>. Unfortunately, these enzymes are dependant upon an expensive cofactor, namely nicotinamide adenine dinucleotide phosphate (NADPH). Alternatively, Furstoss and co-workers have developed a whole-cell approach using, for instance, a culture of *Acinetobacter calcoaceticus* NCIMB 9871 <1996TL6117, 1997T9695> on a preparative scale that turned out to be as efficient as the pure CMO. A recombinant strain of Baker's yeast expressing cyclohexanone mono-oxygenase, and designed to perform oxidation reactions, has shown promising results with 2-substituted 1,3-dithiane or 1,3-dithiolane <1999JHC1533>. Almost complete enantioselectivities were obtained with cyclic dithioacetals bearing an ether or ester functionality at the C-2 position in order to improve their water solubility. A readily available chloroperoxidase from the marine fungus *Caldariomyces fumago* as noncofactor dependent enzyme revealed oxidative properties toward benzo[1,3]dithiole, but low yield and selectivity were obtained <1998CHIR246>. Cultures of a mutant strain (UV4) of *Pseudomonas putida* containing dioxygenase enzymes afforded a selective mono-oxidation of (methylthio)methyl phenyl sulfide <1995CC119> giving 97% ee but with a moderate yield. Contrary to the chemical oxidation, this system favored the reaction of the alkylaryl over the dialkyl sulfur atom <2001JCS(P1)3288>.

## (ii) From $\alpha$ -thio sulfoxide carbanions

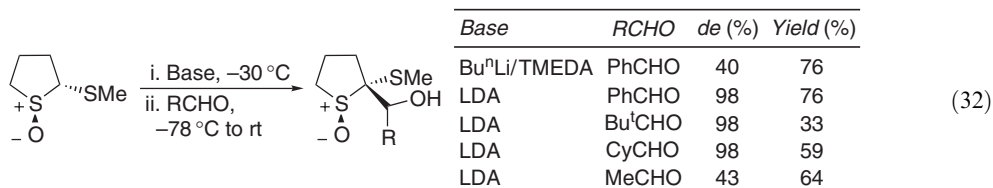
Alkylation of  $\alpha$ -thio sulfoxide carbanion derivatives <1995COFGT(4)243> has continued to attract some interest in the late 1990s and early 2000s as an acyl anion equivalent leading to ketone or ester functions. The deprotonation of the dithioacetal 1-oxide precursor usually occurred with strong bases such as Bu<sup>n</sup>Li, lithium diisopropylamide (LDA) or NaH, and these Umpolung reagents have been exemplified in total synthesis of naturally occurring Ciguatoxin <2002S1835> and new  $\beta$ -lactam drugs <2001BMCL137>. Intramolecular reactions allowing the synthesis of cyclic ketones have been also described toward the elaboration of cyclopropanated sugars <1996ZN(B)1517>. Similarly,

Fleming *et al.* have developed a straightforward synthesis of the indolizidine and quinolizidine cores (Scheme 30) by an intramolecular conjugate addition of a thio sulfoxide anion to an  $\alpha,\beta$ -unsaturated nitrile <1997JOC1305>. The high diastereoselectivity obtained is noteworthy in this series.



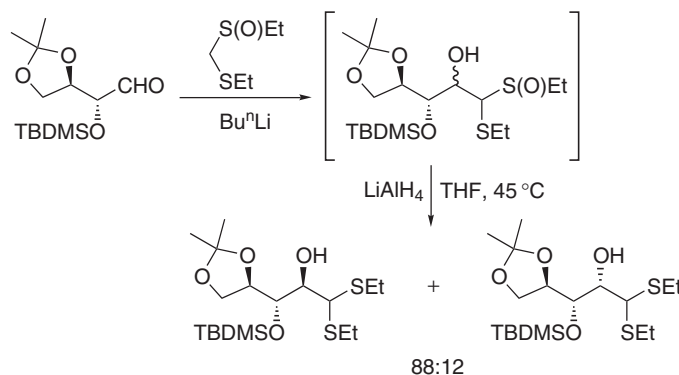
Scheme 30

The diastereoselective course of the intermolecular process is another point of interest. In this regard, Voss and co-workers <1997T2459> have studied the alkylation of the supposed configurationally stable 2-(methylthio)thiolane 1-oxide  $\alpha$ -carbanion (Equation (32)) generated by means of various sodium and lithium bases. Up to 98% of diastereoisomeric excess was obtained with LDA and an aromatic aldehyde. Complete selectivities were even obtained with aliphatic aldehydes, which are considered to be more difficult electrophiles than their aromatic homologs, in correlation to their steric hindrance. By using methyl iodide as the electrophile, the alkylated product was formed with an 80% de, but the more bulky 2-(*tert*-butylthio)thiolane 1-oxide has to be used. A related study was subsequently realized with epoxides as the electrophile <1999EJO1481>.



(32)

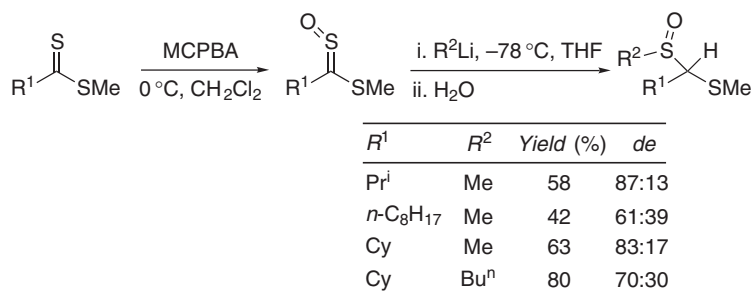
During a study aiming at the formation of polyhydroxylated structures <1999TA973>, the selective addition of the lithium salt of the commercially available ethyl ethylthiomethyl sulfoxide (EETMS) to a chiral aldehyde led to the major *anti* diol with an 88:12 ratio after LiAlH<sub>4</sub> sulfinyl group reduction (Scheme 31). The synthesis of the other polyhydroxylated isomers was also examined.



Scheme 31

Metzner and co-workers have developed an alternative procedure <1996TL4507> to prepare dithioacetal oxides starting from aliphatic sulfine derivatives, easily obtained by oxidation of the corresponding dithioesters (Scheme 32). These sulfines underwent a rapid thiophilic addition of alkyl lithium nucleophiles at low temperature affording the thioacetal compounds after protonation. The alkylation reaction of the  $\alpha$ -thio sulfoxide anion intermediates by MeI was also achieved. However, the obtained products spontaneously formed the corresponding ketones. It was also shown that the stereochemistry could be reversed by converting the lithiated anion

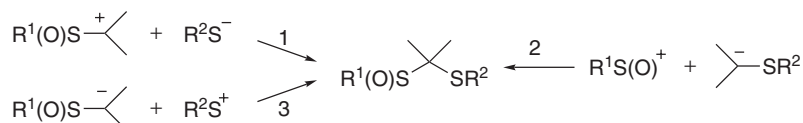
intermediate to an aluminum ate complex <1999EJO2859>. This methodology was applied to the elaboration of 2-cyclopenten-1-ones derivatives through a domino process <1999TL2319>. Similarly, the thiophilic attack of allyl silanes onto sulfoxes derived from aromatic and aliphatic dithioester via fluoride ion activation has been reported <1996JOC7174>.



Scheme 32

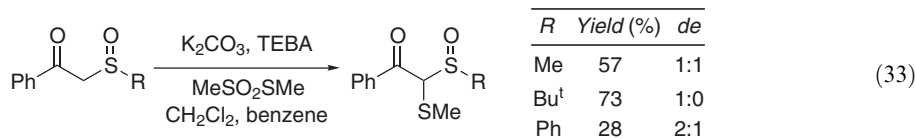
(iii) By various methods

In comparison with the previous approaches, other methods have been used sparingly in the literature for the elaboration of  $\alpha$ -thio sulfoxide moieties. As already disclosed in chapter 4.06 of COFGT (1995) <1995COFGT(4)243>, this building block has been envisaged via three different routes (Scheme 33). The first consisted of the reaction between a thiolate nucleophile and a chloromethyl sulfoxide <1997JCR(S)90>. The second route was applied according to the Andersen reaction via the addition of an  $\alpha$ -phenylthio methyl lithium to menthyl *p*-chlorobenzene sulfinate <1999NJC973>. Then, the corresponding thio sulfoxide was obtained in enantiopure form after recrystallization.

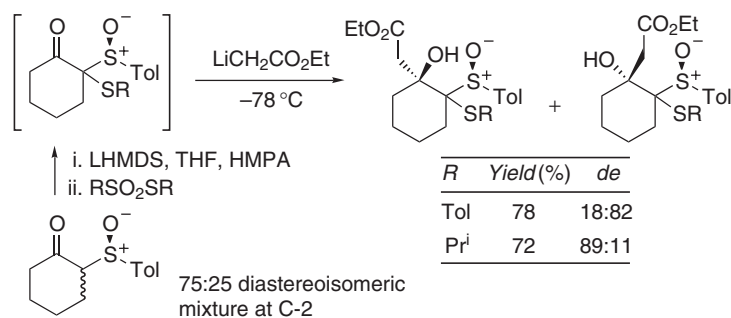


Scheme 33

In the period 1998–2003, improved procedures were described for the third pathway (Scheme 33). Wladislaw *et al.* have reported the sulfonylation reaction of  $\beta$ -keto sulfoxides (Equation (33)) in a two-phase solid–liquid system, by means of a phase-transfer catalyst, e.g., benzyltriethylammonium chloride (TEBA) <2000PS(157)139>. The best result was obtained with a bulky *t*-butyl group (R = Bu<sup>t</sup>). In the case of the phenylsulfinyl group (R = Ph), an improved diastereoselectivity was achieved (4:1) with *N*-benzylquininium chloride as chiral phase-transfer catalyst but no enantioselective process took place <1999T12023>.

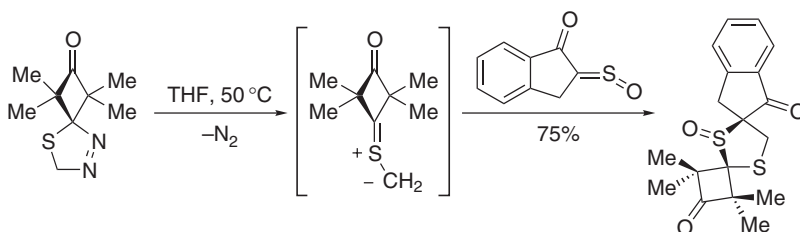


Enantio-enriched  $\beta$ -keto sulfoxides (Scheme 34) have been successfully used to carry out a diastereoselective sulfonylation reaction affording the acetal products that proved to be unstable <1998TA3445>. However, the subsequent *in situ* aldol reaction revealed a 1,2-asymmetric induction of the thioacetal *S*-oxide moiety. Interestingly, with respect to the sulfonyl group, the opposite induction was observed during the addition of the enolate. It is believed that the configuration of the  $\alpha$ -thio sulfoxide depends upon the thiosulfonate (R = Tol or Pr<sup>i</sup>) used as the electrophile for the first step of this sequence. After deprotection, these structures led to nonracemic  $\alpha$ -hydro keto derivatives.



Scheme 34

A completely different approach, based on 1,3-dipolar cycloaddition (Scheme 35), has been validated by Mloston and Heimgartner [<1995PJC1649>](#). Even though this method was applied to a specific substrate, it has been shown that the *in situ* generated thiocarbonyl-*S*-ylide could react with a sulfine as dipolarophile to give an  $\alpha$ -thio sulfoxide compound.

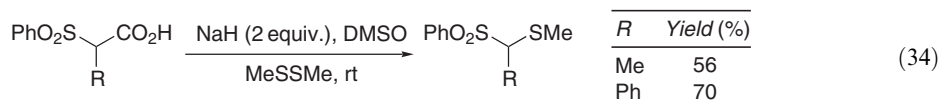


Scheme 35

#### 4.06.1.3.2 $\alpha$ -Thio sulfones

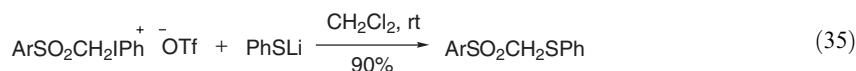
$\alpha$ -Thio sulfone derivatives are also a classical equivalent of the ketone functionality involved in various synthetic transformations, though less studied than their  $\alpha$ -thio sulfoxide counterparts. Most of the preparative methods based on C—S bond formation or alkylation of the thioacetal *S,S*-dioxide anion were already described in chapter 4.03 of COFGT (1995) [<1995COFGT\(4\)243>](#). Therefore, we will first focus on improved procedures and then describe the subsequently developed methods.

The synthesis of optically active 2-acyl-2-alkyl-1,3-dithiolane-1,1-dioxides [<2002HCA4079>](#) (see also [<1995COFGT\(4\)243>](#)) has been achieved by the oxidation of their sulfoxide precursors. The best conditions made use of OsO<sub>4</sub> and *N*-methylmorpholine *N*-oxide (NMO) in acetone. The sulfanylation reaction of an  $\alpha$ -sulfonyl carbanion, resulting from the deprotonation with a strong base such as Bu<sup>n</sup>Li, is, however, a more widely used pathway to  $\alpha$ -thio sulfone derivatives [<1995TL7531>](#). An alternative approach has been described (Equation (34)) via a decarboxylative sulfanylation sequence [<2000PS\(161\)1>](#). A mechanistic examination revealed that the decarboxylation reaction took place either before the C—S bond formation with R = Ph or subsequently with an alkyl group (e.g., R = Me). By analogy with the synthesis of  $\alpha$ -thio sulfoxide synthesis, the sulfanylation process of  $\alpha$ -sulfonyl substituted esters and thioesters, i.e., bearing an electron withdrawing group, can be smoothly effected in a two-phase solid–liquid system, by means of a phase transfer catalyst, e.g., TEBA [<1997PS\(123\)197>](#).

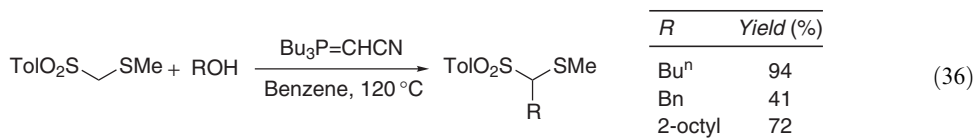


Alternatively, the construction of  $\alpha$ -thio sulfones via, on the one hand, the addition of a thiolate derivative to an aryl or an alkylsulfonylhalogenomethane has been achieved [<2000BMCL847>](#),

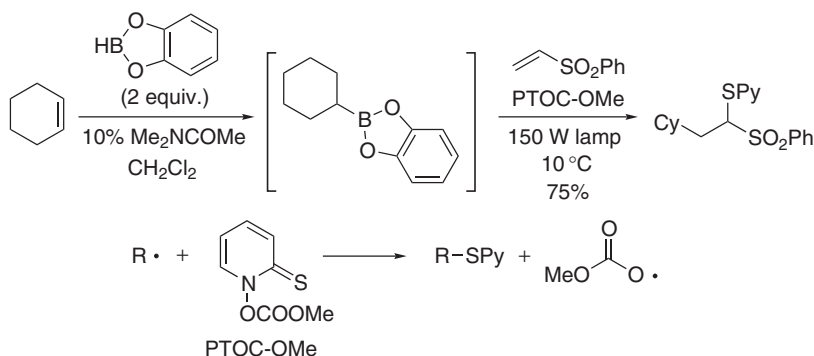
1995H2263>. On the other hand, an ((arylsulfonyl)methyl)iodonium salt (Equation (35)) can be used as an efficient electrophilic reagent with thiophenolate anion <1997JA4775>.



The alkylation of the methylene carbon of the anion of  $\alpha$ -thio sulfone building blocks is usually performed after deprotonation with  $\text{Bu}^n\text{Li}$  and reaction with good electrophiles such as aziridines, aldehydes, methyl iodide, etc. <1998TL147, 2001JHC579, 1995COFGT(4)243>. Moreover, the difluorination reaction at the  $\alpha$ -position of these acetals has been achieved with  $\text{IF}_5\text{-Et}_3\text{N-3HF}$  as a reagent <2002BCJ1597>. Furthermore, the development of cyanomethylenetriphenylphosphane, as a new Mitsunobu like reagent (Equation (36)), allowed a straightforward reaction of (methylsulfonyl) (4-tolylsulfonyl)methane with alcohols <1995TL2531>. This process has to be carried out at high temperature and a double alkylation reaction with benzyl alcohol as electrophile could be observed.

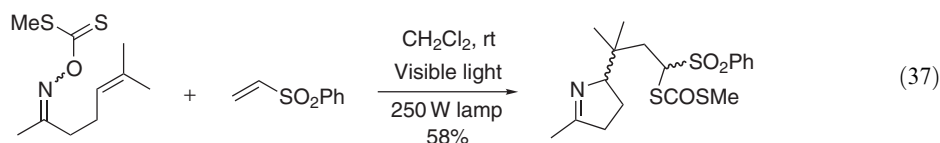


As described in (1995) <1995COFGT(4)243>, phenyl vinyl sulfone derivatives can act as an efficient radical trap at the  $\beta$ -position of alkyl radicals generated from the so-called Barton ester.  $\alpha$ -Pyridylthio sulfone compounds are then formed by recombination of the *in situ* formed pyridylthio group and the  $\alpha$ -radical of the sulfonyl moiety. This methodology has been exemplified by Barton's group to effect the one-carbon homologation of carboxylic acids <1995AJC407>. Taking advantage of this process, Gester and Renaud have investigated the stereochemical outcome of 1,3-dioxolan-4-yl and oxiranyl cyclic radicals in order to gain insight into the 1,2-asymmetric induction <1997S1261>. It has been shown that boronate ester intermediates (Scheme 36), generated *in situ* by hydroboration of the corresponding alkenes, are efficient radical precursors in this reaction upon irradiation <2000AG(E)925, 2000CC1017>. The success of this one-pot method is based on the Barton carbonate pyridine-2-thione-*N*-oxycarbonyl (PTOC-OMe) as a chain transfer reagent as depicted in Scheme 36.



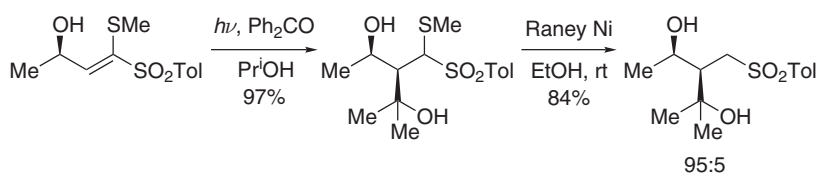
Scheme 36

The intramolecular cyclization of an iminyl radical onto an olefinic moiety (Equation (37)) has been examined by Gagosz and Zard <1999SL1978>. The new carbon-centered radical formed upon irradiation of the corresponding ketoxime xanthate was trapped by an external phenyl vinyl sulfone to give a functionalized  $\alpha$ -thio sulfone product. This xanthate chemistry was also applied to the trifluoromethylation reaction of vinyl sulfone, but poor yields were obtained <2001OL1069>.





Ketene dithioacetal *S,S*-dioxides proved to be efficient radical acceptors due to the captodative effect of both sulfur groups, allowing thereby a thioacetal *S,S*-dioxide synthesis via alkylation reactions. Ogura and co-workers have established (Scheme 37) that the photochemical addition of 1-hydroxyalkyl radical, generated by hydrogen abstraction from the corresponding alcohol with excited triplet benzophenone, occurred with high yield on the allylic alcohol double bond <1997T12101>, as depicted in Scheme 37. After removal of the thiomethyl ether function, it turned out that the addition proceeded with high diastereoselectivity due to an efficient 1,2-asymmetric induction. This group also applied this methodology to acyl radical addition <1999TL2537>. It has also been demonstrated that even hydrocarbons possessing no activated C–H bond such cyclohexane could react with ketene dithioacetal *S,S*-dioxides under the same conditions <2000JOC297>. In the same paper, an alternative source of radical precursors was successfully based on the C–Sn bond activation of tetraalkylstannanes via photoinduced electron transfer (PET) oxidation.

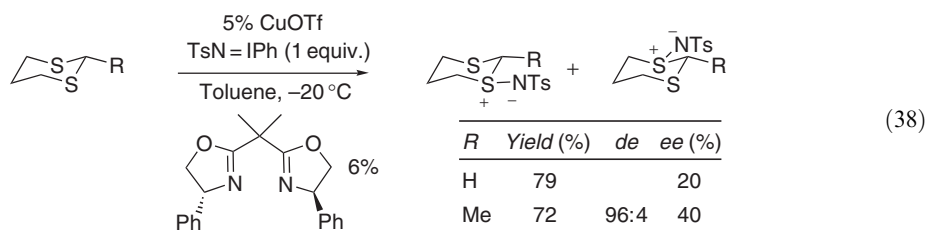


Scheme 37

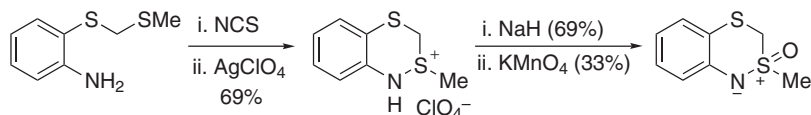
Finally, as will be shown with ketene thioselenoacetal *S,S*-dioxides in Section 4.06.2.3, ketene dithioacetal *S,S*-dioxides can undergo a cyclopropanation reaction <1997JCS(P1)3035>.

#### 4.06.1.3.3 Other derivatives

Despite the widespread chemistry of  $\alpha$ -thio sulfoxides (Section 4.06.1.3.1),  $\alpha$ -thio sulfilimines, their nitrogen analogs, have been far less studied <1996JCS(P1)313>. The sulfimination reaction of dithioacetal precursors has been described by means of chloramine-T with moderate yields <1998HAC29>. Interestingly, the asymmetric synthesis of various cyclic dithioacetals (Equation (38)) has been examined with *N*-(*p*-tolylsulfonyl)imino(phenyl)iodinane as the sulfiminating reagent <1998JCS(P1)2373>. The copper catalyzed sulfimination of the simplest 1,3-dithiane ( $R = \text{H}$ ) showed poor enantioselectivity with a chiral bis-oxazoline as the best ligand. The asymmetric induction was slightly improved with 2-functionalized dithianes together with a high diastereoselectivity in favour of the *trans*-isomers.

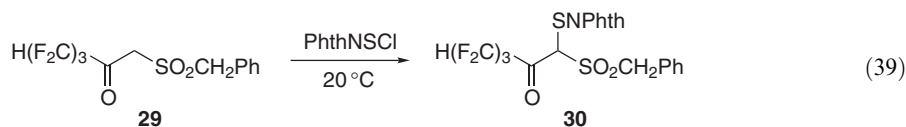


The formation of an  $\alpha$ -thio sulfilimide derivative with a cyclization approach onto a sulfonium intermediate is described in Scheme 38 <1995HAC167>. Moreover, the subsequent potassium permanganate oxidation took place regioselectively to the sulfilimine moiety.



Scheme 38

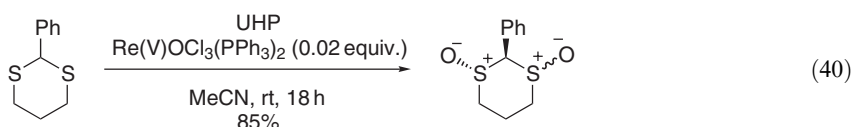
During the study of the reactivity of 1-benzylsulfonyl-1,1-dihydropolyfluoroketone precursor **29**, various types of  $\alpha$ -thio sulfones **30** were synthesized as shown in Equation (39) <2002JFC175>.



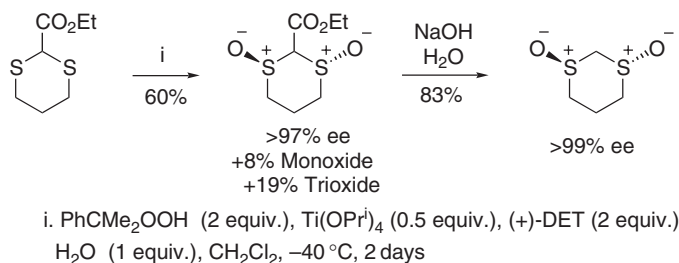
#### 4.06.1.4 Bis(sulfoxides)

##### 4.06.1.4.1 Oxidation

The standard oxidation of dithioacetals and  $\alpha$ -sulfanyl sulfoxides has been efficiently used either for producing new synthetic intermediates or in the context of biologically active molecules. The most common reagents are 3-chloroperoxybenzoic acid (MCPBA) <1998JOC3481, 1998JOC7306, 1998BMCL731> and NaIO<sub>4</sub> <2002TA3423, 1998BMCL3331>, but UHP catalyzed by rhenium(V) oxides <1998TL5655> or MMPP <2002TA3423> have also been used for a generally selective oxidation (Equation (40)). However, oxone <1995TL833> was not selective.



In connection with the interest of C<sub>2</sub> symmetric, enantioenriched bis(sulfoxides), the groups of Aggarwal <1998JOC3481, 1998JOC7306, 1998JCS(P1)2771> and Maycock <1995TL6537> have further investigated the enantio- and diastereoselective oxidation of a number of dithianes and dithiolanes. Optimum conditions for ethyl 1,3-dithiane-2-carboxylate involved <1998JOC7306> the Modena version of the Sharpless-type oxidation, leading to the *trans*-bis(sulfoxide) with high enantioselectivity and in good yield (Scheme 39). Hydrolysis and decarboxylation furnished the unsubstituted ((*R*),(*R*))-*trans*-1,3-dithiane-1,3-dioxide.

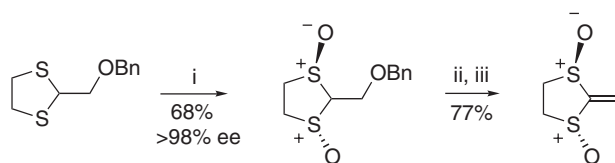


Scheme 39

In search of a practical synthesis of (1(*R*),3(*R*))-2-methylene-1,3-dithiolane-1,3-dioxide, Aggarwal *et al.* investigated the enantioselective oxidation of 1,3-dithiolanes bearing a methylene with an eliminatable group linked to carbon 2 <1998JCS(P1)2771>. They found again that, for these substrates, the Modena oxidizing system is more reactive than the Kagan reagent and that the enantioselectivity is largely dependent upon the substrate. The benzyl ether was found to give the optimum yield and enantio- and diastereoselectivity (Scheme 40).

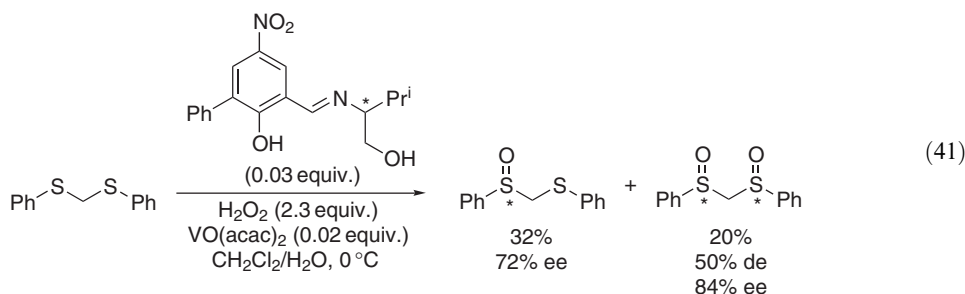
The synthesis of an acyclic derivative has also been investigated using a Bolm-type oxidizing agent: hydrogen peroxide with vanadium catalysis, in the presence of a Schiff base in a catalytic amount (Equation (41)). Imines prepared from a variety of salicylaldehydes and enantiopure 1,2-amino alcohols have been screened, leading to some success with a leucinol derivative <2001JCR(S)263>.





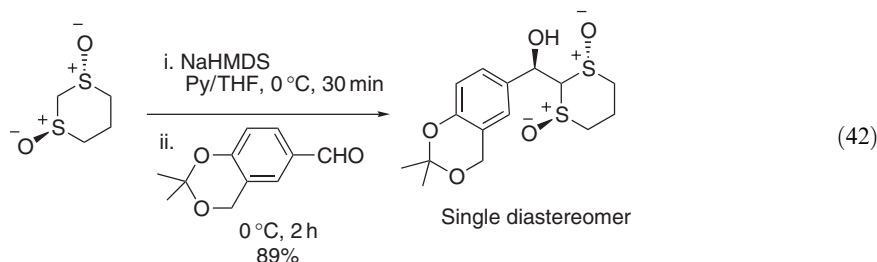
- i. PhCMe<sub>2</sub>OOH (2 equiv.), Ti(OPr<sup>i</sup>)<sub>4</sub> (0.5 equiv.), (+)-DET (2 equiv.), H<sub>2</sub>O (1 equiv.), CH<sub>2</sub>Cl<sub>2</sub>, -30 °C, 40 h  
 ii. NHMe<sub>2</sub>, MeCN; iii. EtN(Pr<sup>i</sup>)<sub>2</sub>, MeI, MeCN

Scheme 40



#### 4.06.1.4.2 From methylene bis(sulfoxides)

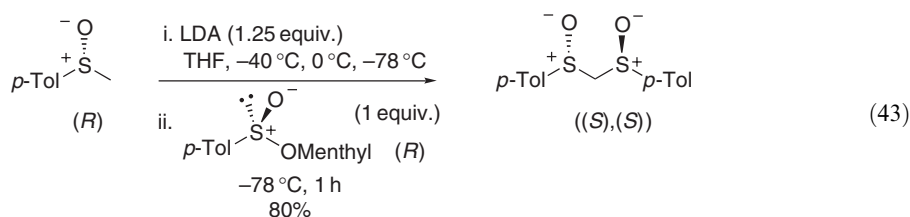
As *trans*-1,3-dithiane-1,3-dioxide is available (Scheme 39) with both relative and absolute stereocontrol, it has been used as a chiral acyl anion equivalent, and full papers have appeared on this. Deprotonation with sodium hexamethyldisilylazide (NaHMDS) and reaction with aromatic aldehydes provided [<1995JOC2174, 1997T16213>](#) alcohols with excellent stereocontrol of the new stereogenic center. It has been explained by an equilibration of the diastereomeric sodium alcoholates. It was elegantly applied [<2002JOC8618>](#) to the synthesis of (*R*)-salbutamol (Equation (42)).



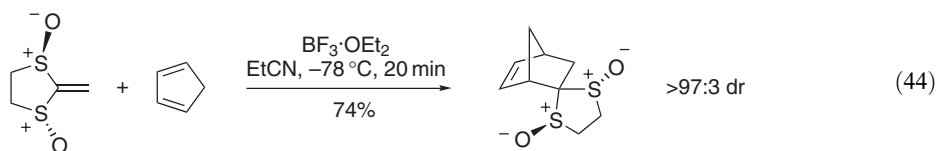
Analogous condensation reactions with aldehydes have been performed [<1997JOC1139>](#) with five-membered analogs, with good stereoselectivity under kinetically controlled conditions. In the acyclic series, ((*S*),(*S*))-bis-*p*-tolylsulfynylmethane has been used in the synthesis of ketenedithioacetal dioxides [<2002JOM130>](#). The latter have been used as chiral electron poor alkenes for cycloaddition with dienophiles [<1997TA409>](#).

#### 4.06.1.4.3 From various precursors

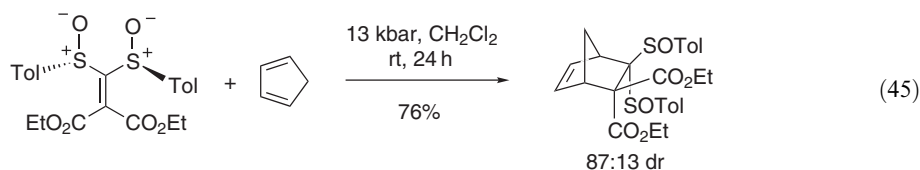
Though it requires a stoichiometric amount of a chiral source, the Andersen reaction of a carbanionic species with a stereodefined sulfinate is an attractive entry to enantiopure sulfoxides. In the main, two cheap sources, menthol and DAG, have been used for the easy preparation of diastereomerically pure sulfinate esters and their subsequent reaction [<1997TA3647, 2000T3749, 2000TA2991, 2000TA1183>](#) with sulfoxide carbanions (Equation (43)). Detailed procedures have been reported for the synthesis of the C<sub>2</sub> symmetrical (*S,S*)-bis-*p*-tolylsulfynylmethane from both menthyl [<1997TA3647>](#) and DAG [<2000TA2991>](#) *p*-toluenesulfonates in, respectively, 80 and 82% yields.



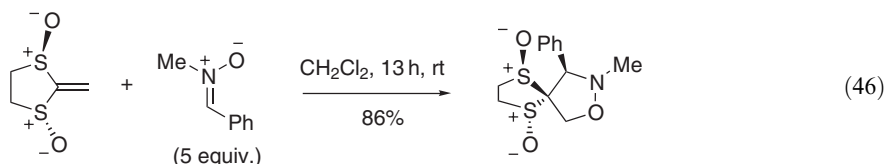
[4+2]-Cycloaddition of dienes to ketenedithioacetal dioxides provided spiro-bicyclic bis(sulf-oxides), as shown by Aggarwal and co-workers [\[1995JOC4962, 1998JCS\(P1\)2771\]](#). It took advantage of the  $C_2$  symmetry of (1(*R*),3(*R*))-2-methylene-1,3-dithiolane-1,3-dioxide in reaction with cyclopentadiene and electron-rich acyclic dienes. Under Lewis acid catalysis the reaction was very rapid. The adducts were obtained as single diastereoisomers (Equation (44)) [\[1995JOC4962, 1998JCS\(P1\)2771\]](#). Other dienes were examined: e.g., furan and dihydropyridines.



For the reaction of acyclic compounds bearing electron-withdrawing groups with cyclopentadiene and acyclic dienes, it was necessary to use 13 kbar of pressure and a Lewis acid catalyst (Equation (45)) [\[1997TA409\]](#), but a good-to-high stereoselectivity was attained.



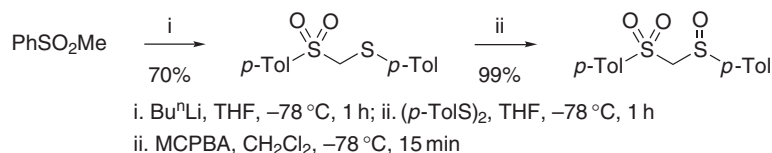
1,3-Dipolar cycloaddition was investigated with nitrones. It is regioselective in favor of isoxazolidines, and a single diastereomer was obtained [\[1998JOC3481\]](#) (Equation (46)). The ketenedithioacetal is a chiral ketene equivalent, as was demonstrated in the construction of the tropane skeleton with oxidopyridinium betaines as the dipole [\[2003OBC1884\]](#).



Dimerization of transient unsaturated sulfines afforded unsaturated dithiane dioxides [\[2002TL499\]](#).

#### 4.06.1.5 One Tricoordinated and One Higher Coordinated Sulfur— $R_2^1CS(O)R^2S(O)_2R^3$

Few literature reports have appeared on this type of compounds. Oxidation of  $\alpha$ -sulfanyl sulfones by MCPBA provided  $\alpha$ -sulfinyl sulfones in good yields in the acyclic [\[1998JOC2993\]](#) (Scheme 41) or cyclic series [\[1999BMC837\]](#).



Scheme 41

#### 4.06.1.6 Two Tetracoordinated Sulfurs— $R_2C[S(O)_2R^2]_2$

##### 4.06.1.6.1 Bis(sulfones)

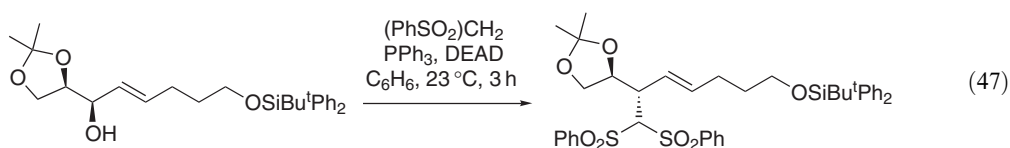
###### (i) From dithioacetals and their derivatives

The direct introduction of two oxygen atoms per sulfur atom was achieved for 1,3,5-trithiane using a combination of inexpensive UHP and trifluoroacetic anhydride in acetonitrile <1999SC2235>.

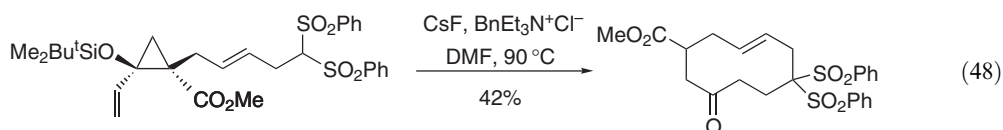
###### (ii) From methylene and alkylidene disulfones

As these compounds exhibit a high acidity of the CH adjacent to both sulfonyl groups, a great deal of synthetic work has involved their carbanions and subsequent treatment with electrophiles. It is a popular synthon for step-to-step construction of functionalized molecules.

Standard conditions have been used throughout the period 1995–2002: phase-transfer catalysis was efficient <2001EJO2659, 2000JOC2528> and strong bases, such as NaH, were also employed <1999CEJ187, 1998S1052, 1997HCA623, 1997HCA2047>, efficiently providing the alkylated products. In place of an alkyl halide, an alcohol was used <2002TL3939> through a Mitsunobu-type reaction (Equation (47)), again in connection with the significant acidity of the  $CH_2$  of diphenylsulfonylmethane, which is necessary for this process.



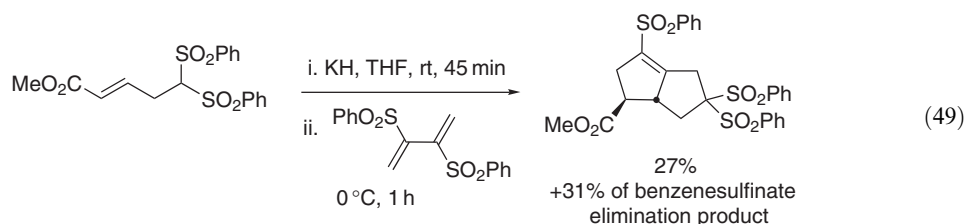
An intramolecular Mitsunobu reaction version has led to bicyclic fused carbocycles <1995TL8577>. Three-membered ring electrophiles were utilized in conjunction with carbanions of bis(sulfones). An oxirane was used <1998AG(E)633>. Reissig and co-workers have extensively studied the ring opening of activated vinylcyclopropanes by soft nucleophiles, such as the anions of bis(sulfones) <1995SL1223, 1998S1052, 1999CEJ187>. They have developed an elegant method for the formation of medium to large carbocycles (Equation (48)).



N-Alkylamides have been obtained by the reaction of a sodium (bis)sulfone carbanion with oxazolinium salts <1996JOC10>.

Treatment of a lithiated (bis)sulfone with cyclohexadienyl tricarbonyl iron salts furnished tricarbonyl iron complexes of dienes <1997TL505>.

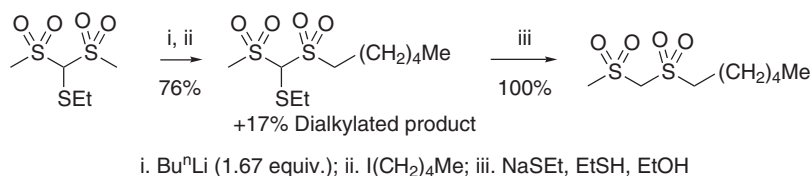
The soft nature of bis(sulfone) carbanions makes them prone to perform a conjugate addition with acceptors. As an application, Padwa *et al.* have used “multisulfone” reagents for a new synthesis of fused cyclopentenones (Equation (49)) <1996JOC3829, 1995JA7071>.



Other Michael acceptors have included a pyrrolidinyl enone <1999SL1307> and conjugated hydrazones <1998T7581>.

The scope of the Michael addition has been extended by the use of a ruthenium catalyst,  $[\text{RuH}_2(\text{PPh}_3)_4]$ , leading to a practical reaction of bis(sulfones) with an unsaturated aldehyde and a ketone <1996JA8553>.

When it is desired to alkylate a (bis)sulfone not classically on the carbon adjacent to both sulfonyl groups, but rather on the terminal methyl group, a possible route is to use a dianion. For that example, a methylsulfanyl group was added on the central position. The dianion of [methylsulfanyl] [bis(methylsulfonyl)]methane was prepared, alkylated on the more reactive terminal anion site, and subsequently desulfanylated <2002TL1377>. The monoalkylation is, however, not fully selective (Scheme 42). Geranyl and farnesyl derivatives have also been prepared by alkylation of the trianion <1996BOC242>.



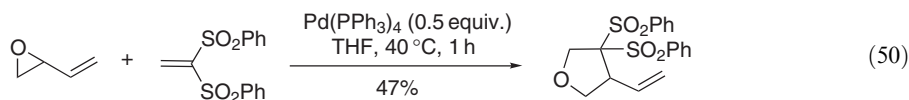
Scheme 42

### (iii) From ketene dithioacetal tetraoxides

The activated double bond of such compounds is susceptible to undergoing a variety of cycloaddition reactions.

The formation of a cyclopropane ring has been achieved by the addition of trimethylsulfoxonium ylide in moderate yields <1997JCS(P1)3035>. The dipolar cycloaddition reaction of diazomethane has been effected regioselectively to produce 5,5-bis(sulfonyl)-4,5-dihydro-3H-pyrazoles, which could be cleaved photochemically (simply with room light) to afford the previous cyclopropanes <1997JCS(P1)695>.

Construction of functionalized tetrahydrofuran rings was achieved by Yamamoto and co-workers using palladium-catalyzed [3 + 2]-cycloaddition reactions to unsaturated alkenes and a variety of sources of  $\pi$ -allyl complexes: allyl carbonates <2001JOC7142>, vinyl oxiranes (Equation (50)) <1998JOC3067>, and allenes <1999JOC694>.

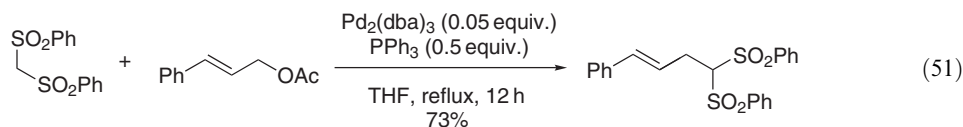


Bis(cyclopentadienyl)zirconocene underwent conjugate addition to unsaturated bis(sulfones) <2002JOC7019>.

### (iv) Palladium(0) catalysis

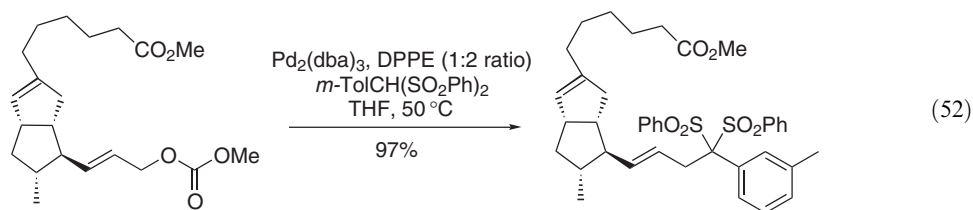
Tremendous developments have appeared on this topic in the period 1995–2002, as bis(sulfones) usually accompany malonates as a source of nucleophiles for the model investigations and applications of the palladium catalyzed allylation reactions. Bis(sulfones) feature CH acidity, easy construction of various starting materials, and versatile transformations.

The quest for a reaction achieved under neutral conditions has been successful due to Poli and co-workers <1998JOC9608> using a standard  $\pi$ -allyl intermediate (Equation (51)).



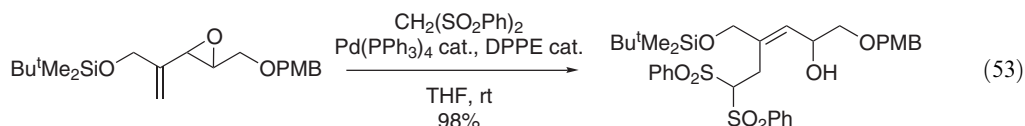
Titanated nucleophiles have been shown to perform an efficient heterobimetallic-catalyzed allylation <1999JOC2962>. Diethylzinc has been used as a base for an asymmetric process catalyzed by an (*R*)-binap palladium complex, with 92% ee, but with very moderate yield <1999CC1895>.

Most developments have dealt with applications to the construction of complex structures, natural products, and bioactive molecules. As a typical example (Equation (52)), a bis(sulfone) has been prepared in the field of prostacyclins by reaction of an allyl carbonate and a palladium catalyst in the presence of a phosphine <1999CC307>. Subsequent bis(desulfonylation) provided the corresponding alkene.



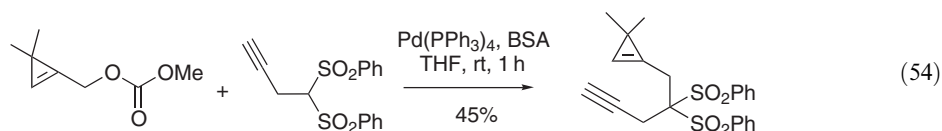
The efficiency of this process has been exploited <2000T8263> for the rapid synthesis of a  $^{11}\text{C}$ -labeled tracer for radio imaging of receptors in a living human brain (using the position emission tomography technique).

Cyclohexenyl carbonates <1999T3467> and esters <1997T3957>, derived from sugars, have been used as a source of  $\pi$ -allyl palladium complexes. Fürstner *et al.* have used functionalized vinyl oxiranes in the palladium catalyzed reaction with bis(phenylsulfonyl)methane as a key step for the total synthesis of cristic acid (Equation (53)) <2000OL2467> and furanoterpene ircinin-4 <1999SL29>.

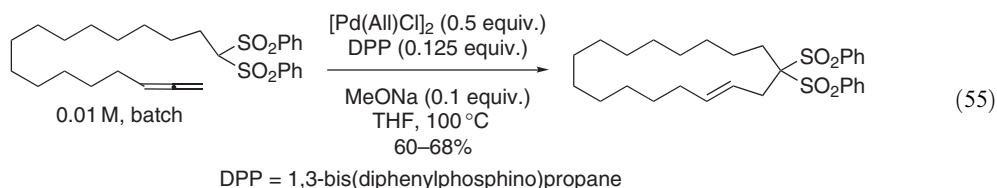


An intramolecular version was shown to be efficient for the macrocyclization of the aglycon part of fluviricin B1 <1997AG(E)1486>.

Other three-membered rings were successful for similar allylation reactions: vinyl aziridines bearing an *N*-phosphinyl group <1996SL847> with opening of the ring, and cyclopropenyl methyl carbonates with attack on the external terminus of the attractive 1,2-methano- $\pi$ -allyl-palladium intermediate (Equation (54)) <2000SL1467>.

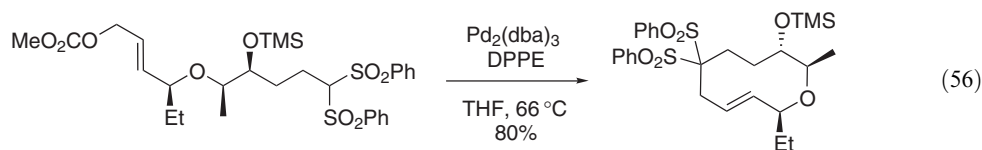


A great deal of variation has been reported for the source of the allylating agent: simple alkynes are efficient <1998JA10262>. Allenes have been largely employed, either in an intermolecular version or for the synthesis of a variety of rings by an intramolecular process <1995JA5156>. Yamamoto and co-workers have developed a smooth formation of five- or six- membered carbocycles <1996TL7453>, and six- to eight-membered cyclic ethers <1999TL1747>. Trost *et al.* explored the synthesis of larger rings and obtained a remarkably good yield of a 17-membered ring product (Equation (55)) <1997AG(E)1750>. The efficiency of this process is largely dependent upon the substrates and ring size formation.

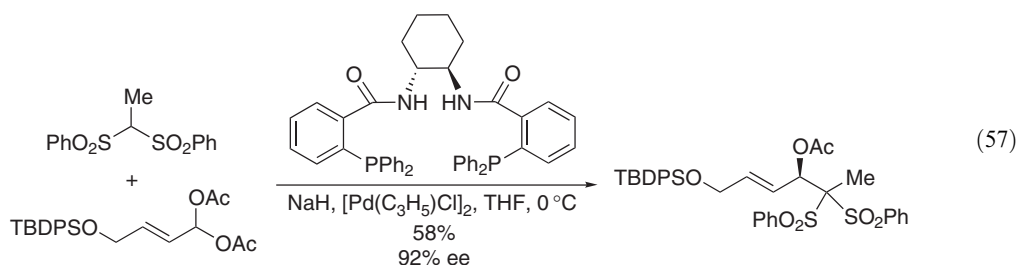


Abundant results from Hoffmann and co-workers have dealt with the cyclization of allyl acetates as a key step for the synthesis of natural products incorporating medium-sized ring ethers. Access to an eight-membered ring was optimized for the synthesis of enantiopure (–)-*trans*-lanthisan <1995T155>. The best result was obtained with an allyl chloride. Conditions

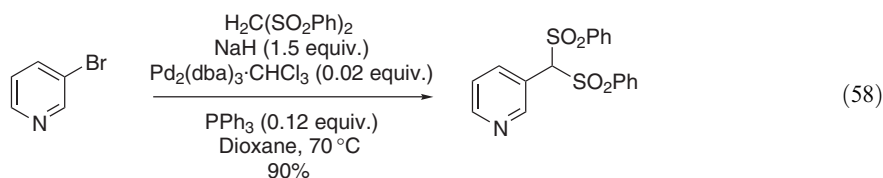
for the formation of (*Z*) or strained (*E*)-configured nine-membered rings were investigated <1998AG(E)633, 1995T145>. Preparation of 10-membered ring ethers (Equation (56)) was effected in 80–81% yield <1998TL7085>.



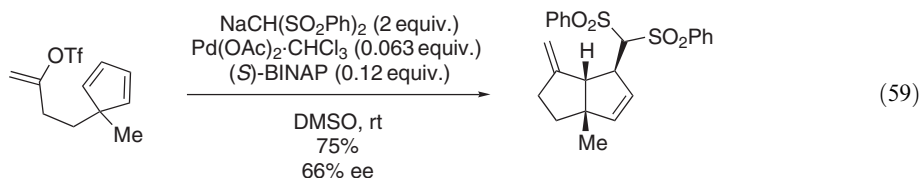
Further developments have appeared on the enantioselective allylation of nucleophiles using a chiral  $C_2$  symmetric palladium ligand, ((*R*),(*R*))-1,2-di(2'-diphenylphosphinobenzamido)cyclohexane). Trost and co-workers have studied allyl bis(esters), in which two C—O bonds are enantiotopic (Equation (57)). The reaction with bis(sulfones), as pro-nucleophiles, led to moderate-to-good enantioselectivities <1995JA7247, 2001JA3687>. Derivatives of tartaric acid (TADDOL) have been tested with almost no enantioselectivity <1995HCA1636>.



Reactions other than allylation have involved sulfones as C—H acids. An efficient arylation of bis(sulfones) has been disclosed <2002TL2539>, using aryl bromides and iodides in the presence of 2 mol.% of  $Pd_2(dba)_3 \cdot CHCl_3$ ,  $PPh_3$ , and NaH as a base in dioxane at 70 °C (Equation (58)). As expected, aryl chlorides are less reactive.



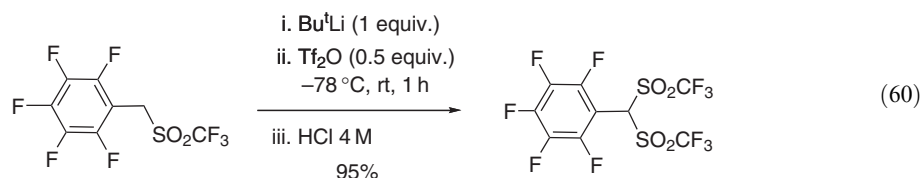
An elegant asymmetric Heck reaction <1996JA7108>, with attack of the intermediate  $\pi$ -allyl palladium complex by a sodium (bis)sulfone afforded a bicyclic skeleton (Equation (59)) that could be further elaborated into a sesquiterpene, (–)-capnellene.



#### (v) Various precursors

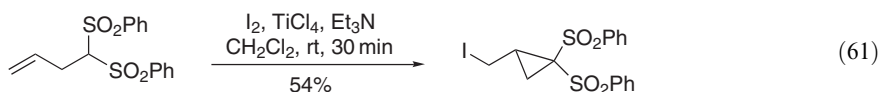
Double oxidation of sulfanyl sulfones by hydrogen peroxide gave a bis(sulfone) <2001EJO2659>.

In search of a Brønsted acid with high catalytic activity, Yamamoto and co-workers <2001AG(E)4077> and also Barrett <1999JOC2910, 2002SL1299, 2002T3835> have synthesized a variety of bis(triflyl)methanes. Reaction of a pentafluorobenzyltriflate with *t*-butyllithium and subsequent treatment with triflic anhydride led to pentafluorophenyl[bis(triflyl)methane] in excellent yield <2001AG(E)4077>. This was extended to a practical synthesis of a polystyrene-bound reagent, which was used for various acid catalyzed reactions with high turnover number and frequency (Equation (60)) <2001AG(E)4077, 2002SL1299>.



Bis(triflyl)methanes have been produced by reaction of trimethylsilylmethyl lithium with triflic anhydride [<1999JOC2910, 2002T3835>](#). They were used for conversion into tris(triflyl)methanes and subsequently to their ytterbium(III) and scandium(III) anions, for new applications to acid catalysis. This was extended to a fluorous biphasic system [<2000SL847>](#) in order to recycle and reuse the catalyst. Carbene generation by photochemical irradiation of bis(sulfonyl)diazomethane, followed by C–H insertion with cyclohexane, or addition to cyclohexene afforded bis(sulfone) derivatives [<2001EJO3771>](#).

Sulfonyl sulfenes may be generated [<1995LA2137, 1995LA2151>](#) by basic reaction of sulfonyl chlorides (elimination and addition of two molecules), and subsequent [4 + 2]-cycloaddition to cyclopentadiene, in modest yields versus the addition of the parent sulfene. A bis(sulfonyl)cyclopropane was produced [<2002JOC922>](#) by an iodocarbocyclization reaction involving iodine and an unsaturated bis(sulfone) (Equation (61)). Homolysis of the carbon–iodine bond produced the corresponding radical, which was reacted with electron-rich alkenes to cyclize with subsequent trapping of the resulting radical.

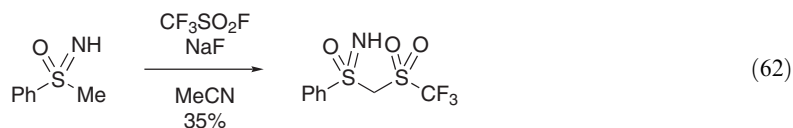


#### 4.06.1.6.2 Bis(sulfonic) acids and their derivatives

No significant further advances have occurred in this area since the publication of chapter 4.06 in COFGT (1995) [<1995COFGT\(4\)243>](#).

#### 4.06.1.6.3 Other compounds

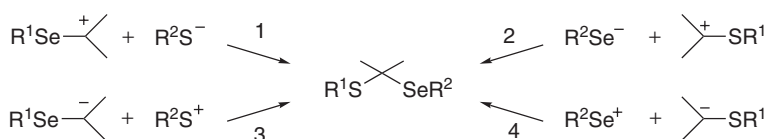
Sulfonylation of sulfoximines was achieved with trifluoromethanesulfonyl fluoride in the presence of NaF or CsF (Equation (62)) [<1998RJOC1117>](#).



### 4.06.2 FUNCTIONS CONTAINING ONE SULFUR AND ONE SELENIUM OR TELLURIUM—R<sup>1</sup>CSR<sup>2</sup>SeR<sup>3</sup>, etc.

#### 4.06.2.1 Dicoordinated Sulfur Derivatives

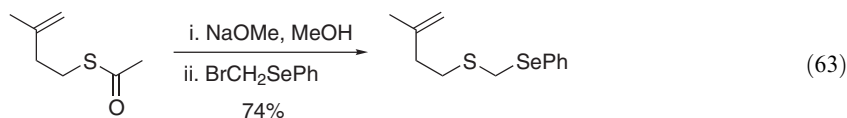
The preparation of thioselenoacetal functions could be realized via the four ionic pathways shown in Scheme 43. The classical methods following these routes, already covered in chapter 4.06 of COFGT (1995) [<1995COFGT\(4\)243>](#), are still in use in the early 2000s, with the standard conditions.



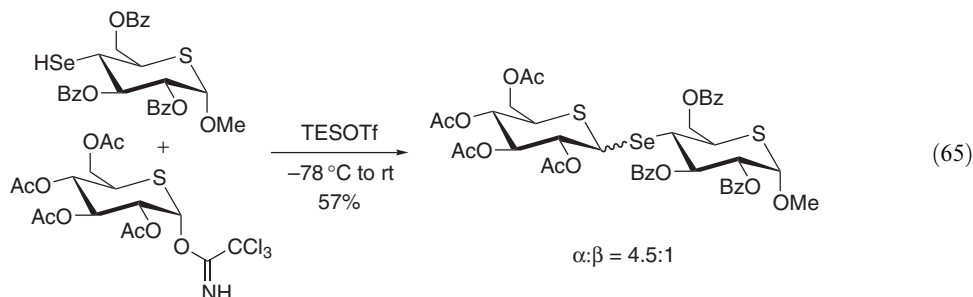
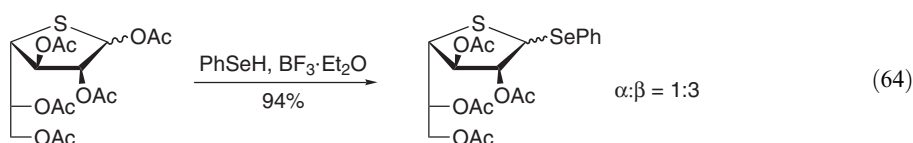
Scheme 43



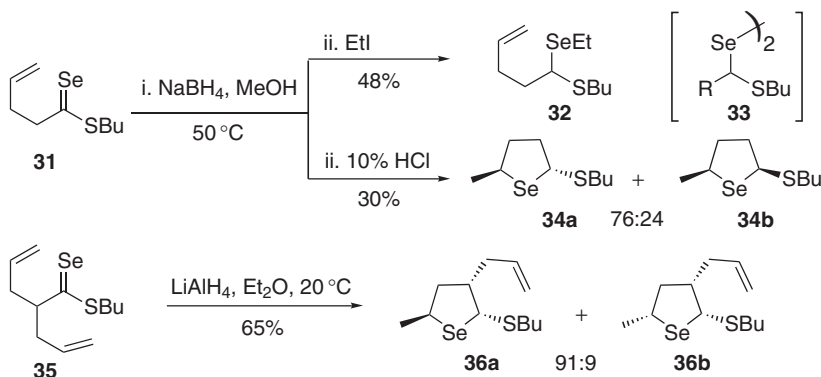
Since then, according to the first route (Scheme 43), it has been shown (Equation (63)) that the thiolate intermediate could be generated *in situ* from the corresponding thioacetate <2002OL4065>.



During the synthesis of heteroanalogs of sugars, the thioacetal moiety turned out to be a convenient formal precursor of an alkylthiocarbocation (Scheme 43, route 2). For instance, a selenium-containing glycosyl donor (Equation (64)) was used for further elaboration of an oligosaccharide fragment containing 4-thio-*Galf* <2000TA207>. This 4-thio-D-selenogalactofuranoside was prepared by the reaction of its acetylated precursor with phenylselenol and  $\text{BF}_3 \cdot \text{Et}_2\text{O}$  as Lewis acid. A second approach (Equation (65)) <1995JA9783> made use of the reactivity of the trichloroacetimidate function at the anomeric position of the glycosyl donor. It was shown that the coupling reaction took place with triethylsilyl triflate when the temperature was allowed to rise to room temperature.



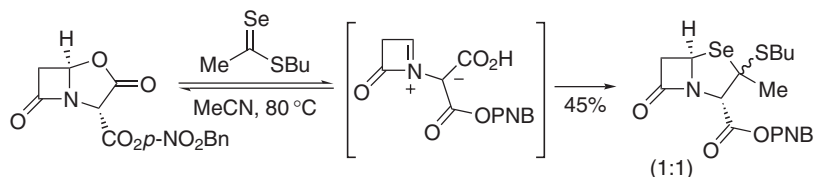
Selenothioic acid *S*-esters of type **31** (Scheme 44) proved to be an interesting precursor of thioselenoacetal derivatives <1996CC1461>. On the one hand, upon reduction of compound **31** with sodium borohydride, the obtained intermediate could be trapped by an electrophile such as iodoethane to give the acetal **32**. On the other hand, an acidic aqueous work-up, subsequent to the reduction step, led selectively to a 5-*exo*-trig cyclization allowing the synthesis of compounds **34** in moderate yield. Whatever the substrate, the formation of the diselenide **33** was also observed. This method was extended to  $\alpha$ -di or  $\alpha$ -trisubstituted precursors of type **35**, providing a straightforward approach to polyfunctionalized tetrahydrosephenes **36**. For those more substituted substrates, the reduction step has to be performed with  $\text{LiAlH}_4$  instead of  $\text{NaBH}_4$ . The anti-selectivity with respect to both methyl and sulfanyl groups is worth noting.



Scheme 44

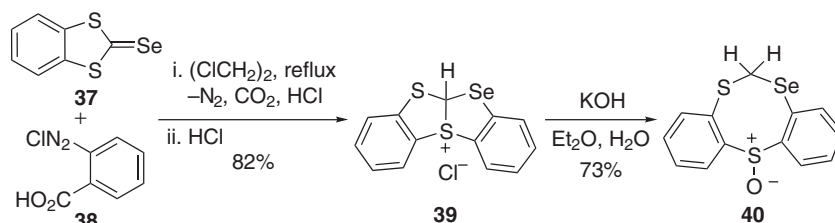


The selenothioic acid *S*-ester function may also be considered as a dipolarophile. After the generation of the azomethine ylide intermediate (Scheme 45), the assembly of a variety of novel bicyclic  $\beta$ -lactam skeletons, incorporating heteroatoms, was realized <2000T5586>.



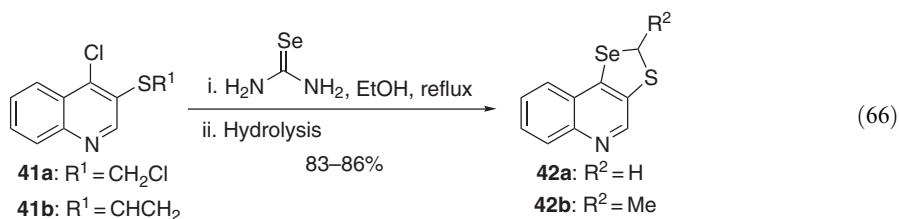
### Scheme 45

Another type of related 1,3-dipolar cycloaddition has been described between 1,3-benzodithiole-2-selone **37** and a benzyne intermediate (Scheme 46), generated from diazo precursor **38** [\[1996BCJ2349\]](#). Basic treatment of the obtained sulfonium **39** led to the eight-membered ring selenoacetal **40**.

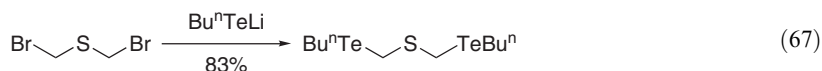


### Scheme 46

Thioselenoacetal functions could be found within heterocycles (Equation (66)) such as 1,3-thiaselenolo[5,4-*c*]quinoline [<1996PJC54>](#). Their syntheses consisted of an aromatic nucleophilic substitution performed on structure **41** with selenourea, followed by the formation of the acetal **42** in good yields after hydrolysis. Maslankiewicz and co-workers [<1996PJC54>](#) pointed out that these 1,3-selenido-sulfides appeared less stable than the corresponding 1,3-dithiole analogs. The alkylation of an  $\alpha$ -thio carbanion with sulfur electrophiles (Scheme 43, route 4) is also an important pathway toward thioselenoacetal formation [<2000JA11340>](#).



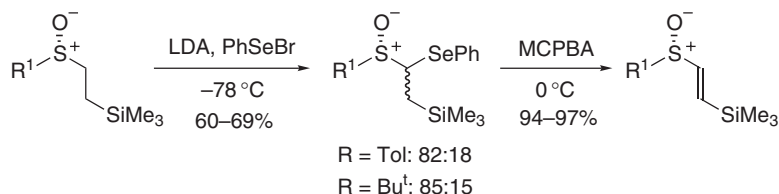
The preparation of thiotelluroacetals (Equation (67)), hardly described in the literature, could be realized by treating  $\text{S}(\text{CH}_2\text{Br})_2$  with  $\text{BuTeLi}$  [<1996AG\(E\)528>](#).



#### 4.06.2.2 Tricoordinated Sulfur Derivatives

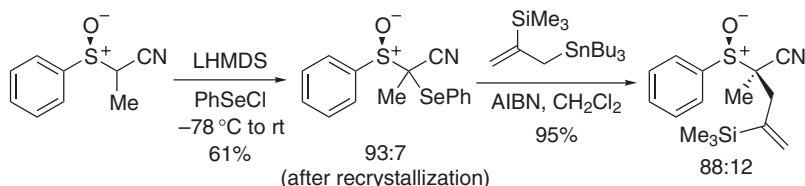
$\alpha$ -Seleno sulfoxides have gained some interest since 1995, especially for the preparation of vinyl sulfoxides, after an oxidative elimination reaction, and also as (arylsulfinyl)methyl radical precursors. However, their syntheses still take advantage of the classical methods, i.e., reactions between an electrophilic selenol derivatives ( $\text{R}^1\text{Se}^+$ ) and an  $\alpha$ -sulfoxide carbanion generated with a base, as fully

exemplified in the previous COFGT (1995) (chapter 4.06.2.1). Two examples are shown in [Scheme 47](#). The deprotonation of an enantioenriched sulfoxide with LDA ([Scheme 47](#)) led to the corresponding  $\beta$ -silylseleno derivatives by reaction with PhSeBr at low temperature [<2002JOC640>](#).



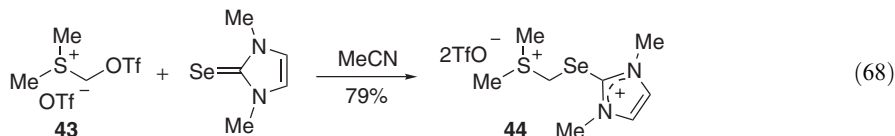
Scheme 47

Renaud *et al.* ([Scheme 48](#)) have made use of the base lithium bis(trimethylsilyl)amide (LHMDS) and PhSeCl as electrophile to form the  $\alpha$ -seleno sulfoxide. They subsequently performed a radical addition reaction with homolytic cleavage of the carbon–selenium bond [<1998HCA1048>](#). Following this approach, other reagents could be employed such as LDA/(PhSe)<sub>2</sub> [<1997TL233>](#) or MeLi/(PhSe)<sub>2</sub> [<2000JOC7083>](#).



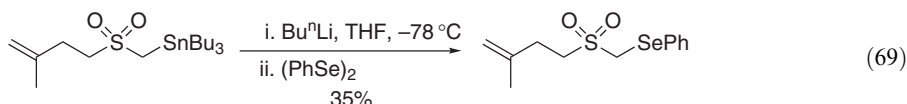
Scheme 48

Weiss *et al.* have introduced a novel type of 1,1-biselectrophile **43** ([Equation \(68\)](#)) [<1998ZN\(B\)916>](#). It reacts easily with a selenourea to give the  $\alpha$ -seleno sulfonium compound **44**, a tricoordinated sulfur derivative other than sulfoxide. Using the same approach,  $\alpha$ -thio sulfonium salts have also been synthesized (Chapter 4.06.1.3.3).



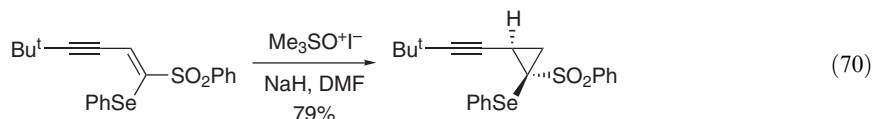
#### 4.06.2.3 Tetracoordinated Sulfur Derivatives

As was already fully exemplified in the previous chapter 4.06.2.3 of COFGT (1995), the most common approach to the synthesis of  $\alpha$ -seleno sulfones remains the selenenylation ( $RSe^+$ ) of an  $\alpha$ -sulfone carbanion ( $RSO_2C^-$ ). Although usually generated by means of a base [<1999JOC9521, 1999JCS\(P1\)71>](#), the carbanion at the  $\alpha$ -position of the sulfonyl group could also be prepared via a tin–lithium exchange as described in [Equation \(69\)](#), yielding the selenylated product in moderate yield [<2002OL4065>](#).

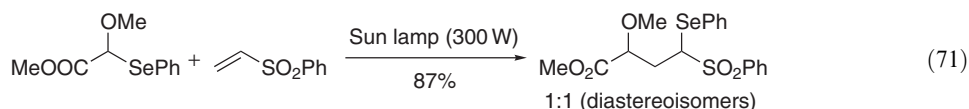


It has been shown that ketene thioselenoacetal *S,S*-dioxides, functionalized with an alkyne moiety ([Equation \(70\)](#)), could undergo a cyclopropanation reaction by means of a sulfoxonium

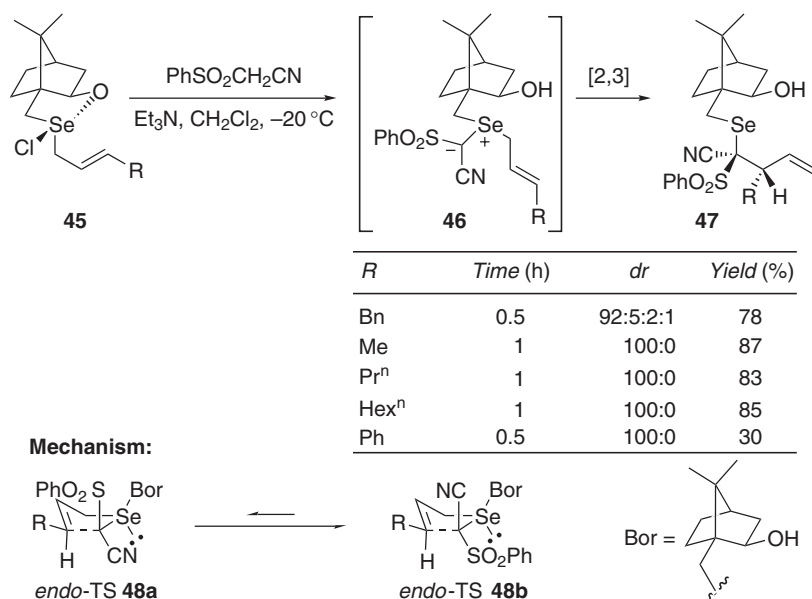
ylide reagent [<1997JCS\(P1\)3035>](#). The cyclopropane structure with an  $\alpha$ -seleno sulfone function is thereby obtained in good yield. In the same manner, the analogous  $\alpha$ -thio sulfones could also be formed from the corresponding ketene derivatives (Chapter 4.06.1.3.2).



An ester substituted *O*,*Se*-acetal (Equation (71)) proved to be an efficient radical precursor upon irradiation [<1996S253>](#), allowing addition to electron poor alkenes, such as vinyl sulfones, together with phenylselenyl group transfer. The overall radical process gives a functionalized  $\alpha$ -seleno sulfone even in the absence of radical initiators such as 2,2'-azobisisobutyronitrile (AIBN).

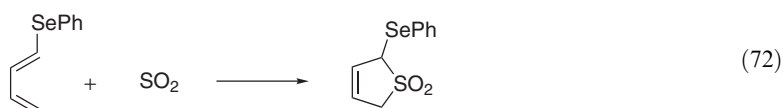


Koizumi and co-workers have developed a synthesis of diastereoenriched  $\alpha$ -seleno sulfones **47** (Scheme 49) from chiral nonracemic hypervalent selenium compounds **45** [<1997JOC4562>](#). The selenonium ylide intermediate **46**, generated *in situ*, gave rise to a highly selective asymmetric [2,3]-sigmatropic rearrangement. The stereochemical outcome of this process was explained by assuming a more stable *endo* transition state **48**. Steric interactions between R and PhSO<sub>2</sub> would therefore favor the transition structure **48b** and lead to homoallylic selenides **47**.



Scheme 49

During the investigation of the competition between the hetero Diels–Alder reaction and the cheletropic addition of sulfur dioxide (Equation (72)), the formation of 2-seleno-2,5-dihydrothiophene-1,1-dioxide was proven [<2002HCA733>](#). However, these compounds are described as unstable at room temperature, which has to be taken into account for preparative purposes.

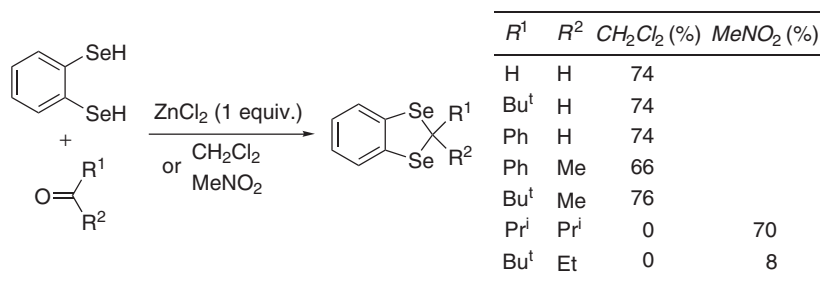


### 4.06.3 FUNCTIONS CONTAINING SELENIUM AND/OR TELLURIUM— $R_2^1C(SeR^2)_2$ , $R_2^1C(SeR^2)TeR^3$ , etc.

#### 4.06.3.1 Diselenium Derivatives

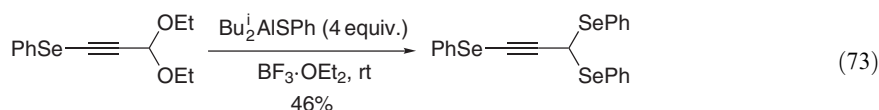
The literature covered a huge amount of work done toward the formation and the chemistry of diselenoacetals. An examination of chapter 4.06 in COFGT (1995) <1995COFGT(4)243> as well as, in some instances, *Comprehensive Heterocyclic Chemistry II* <1996CHECHII679> is recommended. These reviews provide an overview of the experimental conditions and chemistry that has been done within that field, especially the important contributions of Krief and co-workers. It could therefore be pointed out that the main approach toward diselenoacetals, i.e., the reaction of a carbonyl group with selenol derivatives, is still usually achieved with the originally described procedures through Brønsted or Lewis catalyst such as the routinely used  $ZnCl_2$  <2000JCS(P1)2211, 2002MI481>.

The aforementioned approach has been extended to the synthesis of 1,3-benzodiselenolane derivatives (Scheme 50) <1999TL6571>. In dichloromethane as solvent, the reaction worked properly with different kinds of aldehydes and reasonably hindered ketones such as *t*-butyl methyl ketone. In terms of reactivity, the selenoacetalization with 1,3-benzodiselenolanes are indeed closely related to methylselenol but are more efficient than phenylselenol. For more difficult cases with highly shielded ketones ( $R^1 = Pr^i$ ,  $Bu^t$ ;  $R^2 = Pr^i$ , Et; etc.), zinc chloride in nitromethane turned out to be more efficient than dichloromethane, affording selenoacetal products in moderate-to-good yield. As a general trend, some difficulties could be met for selenoacetalization of aromatic and very hindered ketones. A closely related approach has been also applied to cyclic aliphatic diselenols <1996TL2667>. Furthermore, the selenoacetalization reaction of enol ether derivatives in place of ketones has been carried out in the presence of  $BF_3 \cdot Et_2O$  as Lewis acid <1996JCR(S)206>.

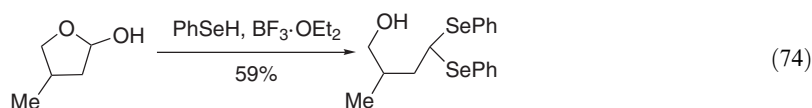


Scheme 50

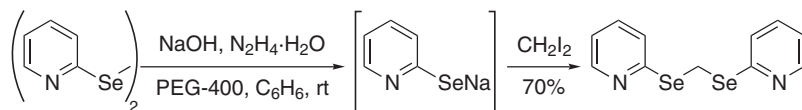
Like the selenoboranes and selenosilanes, already described in COFGT (1995) <1995COFGT(4)243>, the aluminum analogs (Equation (73)) <1995CC149> could be employed instead of selenol derivatives in order to perform a transacetalization reaction. An electrochemical synthesis of thioacetals, from the corresponding ketones or aldehydes, was achieved <1996MI272> in the presence of diaryl or dialkyl selenides and trimethylchlorosilane.



$\gamma$ -Hydroxydiselenoacetal compounds could be obtained from the corresponding  $\gamma$ -lactols (Equation (74)) <2001S867>. It is assumed that this process involves the opened lactol form, i.e., the  $\gamma$ -hydroxy aldehyde, which undergoes a Lewis acid catalyzed selenoacetalization.

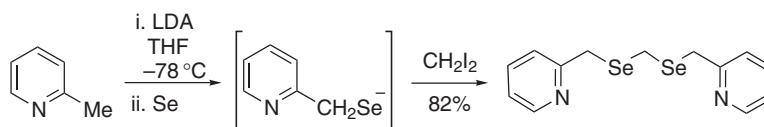


The addition of selenide salts to *gem*-dihalides provided another general approach toward diselenoacetal derivatives. For instance, Bhasin and Singh have reported (Scheme 51) a convenient method for the elaboration of 2-pyridylselenomethanes via the *in situ* formation of the corresponding 2-pyridylselenolate <2002JOM71>. This intermediate is quantitatively obtained from the reduction of 2,2'-dipyridyl diselenide using hydrazine hydrate in the presence of NaOH in aprotic solvents. The introduction of polyethylene glycol-400 as the phase transfer catalyst is believed to facilitate the substitution reaction with halo methanes. A closely related method has been also described via the reduction of diselenide derivatives with sodium or potassium borohydride <2001JCS(P1)1140, 2001HAC358>.



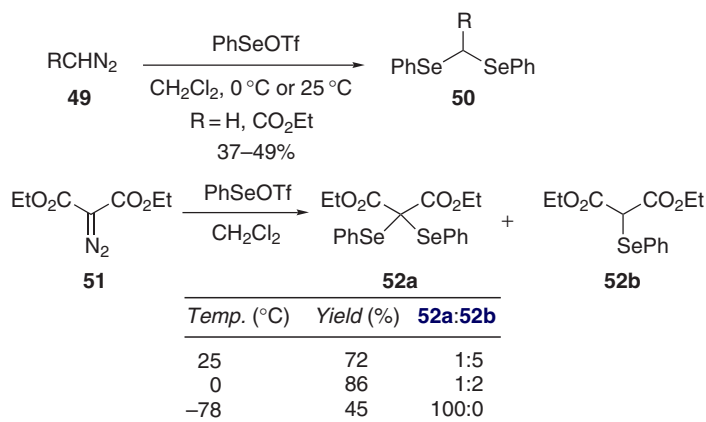
Scheme 51

A similar approach, but with the *in situ* formation of the 2-picolyl selenolate anion from elemental selenium and the lithiated 2-picoline, has also been reported (Scheme 52) <2002PS(177)597>. This intermediate reacts with iodomethane to afford the diselenoacetal in a good yield.



Scheme 52

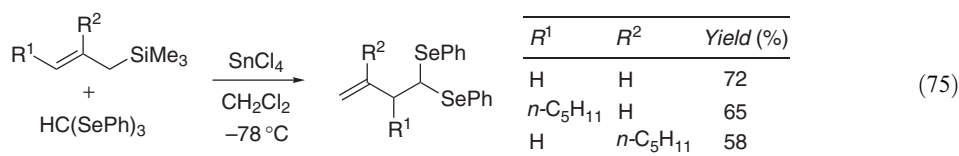
Diselenide derivatives (RSe)<sub>2</sub> are known as precursors of diselenoacetals by reacting with diazomethane <1996JCS(D)2719>. In this context, the reaction between diazocompounds **49** (Scheme 53) and divalent selenium species such as phenylselenenyl triflate has been studied <2000SL1813>. As long as mono-substituted diazoprecursors of type **49** are employed, the acetal products **50** are selectively formed in moderate yield. Nevertheless, with more substituted diazo precursors **51**, different mixtures of mono- and di-selenylated products **52** are obtained with respect to the temperature at which the reaction has been performed. The diselenoacetals **52a** were eventually obtained, as the sole product, when the reaction was carried out at  $-78^{\circ}\text{C}$ .



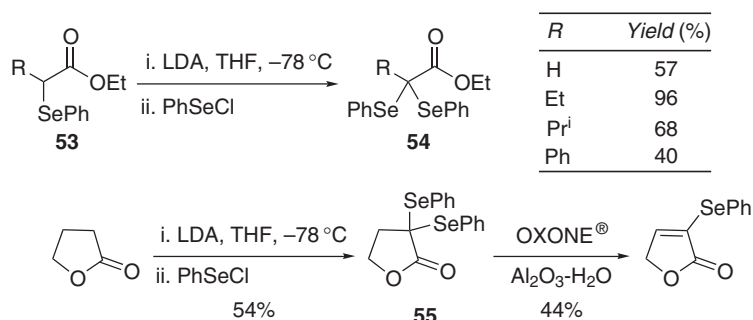
Scheme 53

The straightforward reaction of allyl silanes with tris(phenylseleno)methane, an easily prepared reactant, furnished the corresponding homoallyldiselenoacetals via a carbon-carbon bond formation (Equation (75)) <1996TL6085>. It has been shown that  $\text{SnCl}_4$  was the most effective catalyst

and few side products such as allylmonoselenides have been detected. These compounds are interesting precursors of seleno-1,4-butadienes or  $\beta,\gamma$ -unsaturated aldehydes. The same approach could be used for the synthesis of homoallyldithioacetal (Chapter 4.06.1.2.3) with  $\text{ZnBr}_2$  as the Lewis acid.

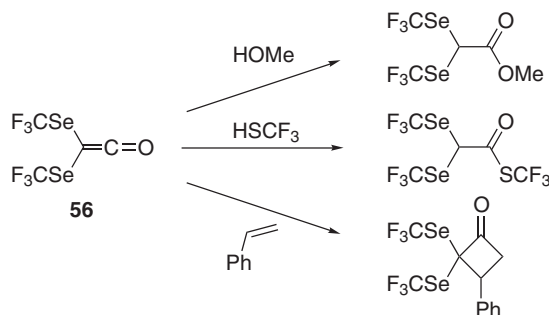


$\alpha,\alpha$ -Bis(phenylselenanyl)carbonyl compounds are encountered in the literature as, for example, precursors to  $\alpha,\beta$ -unsaturated carbonyl derivatives as outlined in Scheme 54. In that field, Paulmier and co-workers described the selenenylation <2000T7483> of  $\alpha$ -selenyl ester **53** with LDA as a base. Compounds **54** were obtained in good yields except for phenyl derivatives ( $R = \text{Ph}$ ). The direct introduction of the diphenylselenium moiety, providing product **55**, was also demonstrated in the lactone series <1996JCS(P1)1913>. This approach was also used with ketones <1997T6365>, lactams <1998T6369>, and 2-methyloxazolines <1997TA2433>. For base sensitive structures  $N$ -phenylselenanyl morpholine could be employed directly in some cases <1997T16767>.



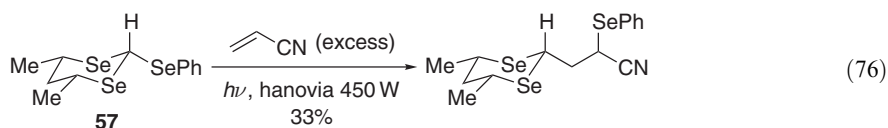
Scheme 54

A systematic investigation of the reactivity of the stable ketene **56** (Scheme 55) was undertaken by Haas and Radau <1998JFC9>. They disclosed the elaboration of a variety of novel perfluoro-diselenoacetals via addition reactions or  $[2+2]$ -cycloaddition reactions.



Scheme 55

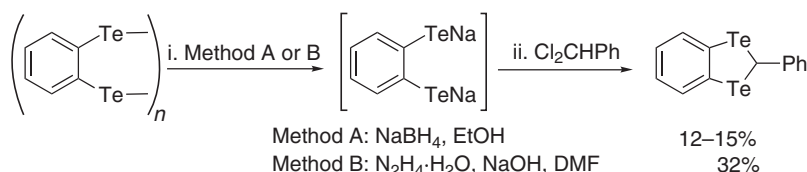
During the study of 1,3-diselenanes of type **57** (Equation (76)), Krief and Defrère <1996TL8015> demonstrated the ability to perform an addition reaction to acrylonitrile upon irradiation.



In the same way as for dithioacetals, diselenoacetals can be alkylated with various electrophiles after deprotonation [<1996TL8015, 2000AG\(E\)414, 1996TL8011>](#), as already described in COFGT (1995) [<1995COFGT\(4\)243>](#). A general review on selenium-stabilized carbanions has appeared [<2000TCC113>](#). Finally, the synthesis of arylselenoacetals has been carried out on neutral alumina from  $\alpha$ -chloro-(phenylseleno)alkanes [<1995SC117>](#).

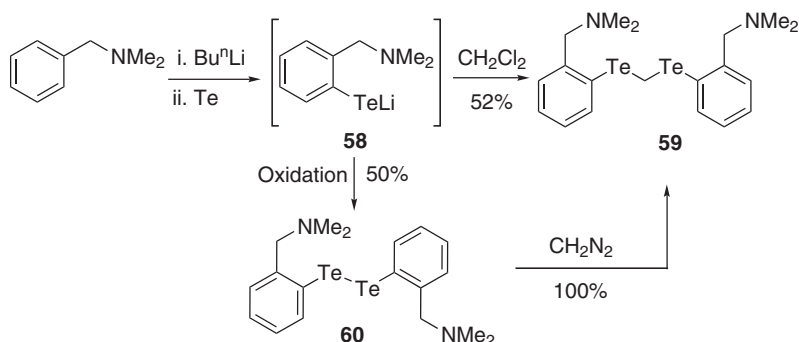
#### 4.06.3.2 Ditellurium Derivatives

Since COFGT (1995) [<1995COFGT\(4\)243>](#), the ditelluroacetal function could be found within several structures, especially for their properties as soft donor ligands with metals. A general discussion on their characteristics and synthesis has been given in the papers of Singh and Khandelwal and co-workers [<1996JOM65, 2002PIA357>](#). Obviously, the most general method for the synthesis of ditelluroacetal derivatives consists of the reaction between tellurolate anions ( $\text{RTe}^-$ ) and dihalogenomethane compounds. The success of those processes seems to depend upon the methods used for the preparation of tellurolate ( $\text{RTe}^-$ ) precursors. During their investigations toward the synthesis of benzo-1,3-ditelluroles (Scheme 56) [<2000MI1127>](#), Gadzhieva and Sadekov first tried to generate the sodium salt intermediate with sodium borohydride (method A) but low yields were obtained for the alkylated products. It was assumed that poorly reactive trialkylborate complexes with tellurolate anions were formed. Hence, they performed the same reaction by means of hydrazine in basic media as reductant (method B) and slightly improved the yield.



Scheme 56

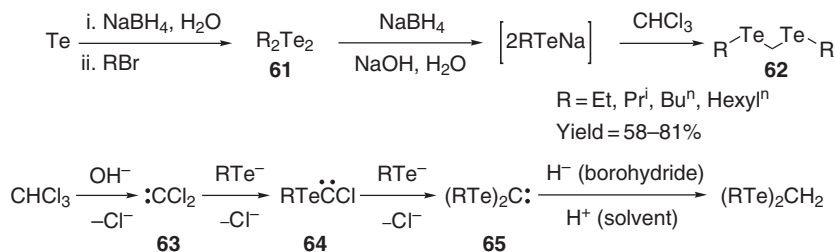
A multidentate tellurium ligand (Scheme 57), designed for complexation of chromium metals [<1995OM4755>](#), was prepared from the corresponding anion **58** obtained by insertion of tellurium metal in the C—Li bond of the corresponding *ortho*-metallated precursor. The alkylation reaction of dichloromethane afforded the target ligand **59** as an impure product. Its synthesis was eventually achieved through a classical two-step synthesis via the dimer **60** which gave a smooth transformation with diazomethane.



Scheme 57

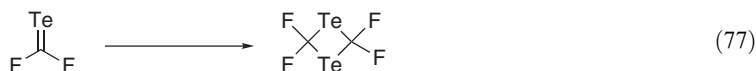


Selvakumar *et al.* have developed a convenient route to bis(alkyltelluro)methane ligands **62** shown in Scheme 58 <2001PS(171)501>. They carried out the reduction of precursors **61** by means of sodium borohydride in the presence of chloroform to yield ligands **62**. In order to explain this process (Scheme 54), the formation of carbene species **63–65** generated from chloroform under the basic conditions was proposed, followed by hydride reduction and solvent protonation.



Scheme 58

The dimerization of tellurocarbonyl compound <1995JOC4657, 1997TL2501>, usually considered a transient species, to the thermodynamically more stable 1,3-ditellurethane, can be formally considered as an access to the ditelluroacetal moiety. An example is given in Equation (77) in the perfluoroalkyl series <2001PS(171)113>.



The alkylation of ditelluroacetals after deprotonation with lithium amides bases <2000MI1127, 1995CBR861>, is still used, in the early 2000s, for the synthesis of new ditelluroacetals.

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## Biographical sketch



**Vincent Reboul** was born in France in 1968. He studied at Orsay University, where he obtained a B.Sc. in biochemistry in 1991 and his Ph.D. in 1996 under the direction of Dr. C. Thal at ICSN, Gif-sur-Yvette, France, working on organo-iron complexes. He spent a year and a half in a postdoctoral position in the laboratory of Professor R. Holton, at Florida State University (Tallahassee), being involved in the total synthesis of taxol. In 1998, he obtained his present position as “Maître de conférences” in organic chemistry, at the University of Caen, in the laboratory of P. Metzner. His scientific interests include all aspects of asymmetric synthesis with organo-sulfur chemistry.



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**Patrick Metzner** was born in 1946. He studied at the University of Caen (France), where he obtained his Ph.D. in 1973 under the direction of Prof. J. Vialle. He joined the group of Prof. B. M. Trost at the University of Madison-Wisconsin in 1978–1979. He returned to Caen with a CNRS position. He was promoted “Directeur de Recherche” in 1990, within the ENSI Caen and the University, and now heads the CNRS Unit #6507 there. His research topics focus on sulfur chemistry and asymmetric synthesis. They involve thiocarbonyl compounds, enethiolates, sulfines, sulfides, and sulfoxides, sulfur ylides, formation of C—C bonds with full stereocontrol and reactions such as the Claisen rearrangement, epoxidation mediated by sulfur ylides, chemoselective oxidation of low coordinence sulfur compounds, and metal catalyzed couplings.



# 4.07

## Functions Incorporating a Chalcogen and a Group 15 Element

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### 4.07.1 FUNCTIONS CONTAINING A CHALCOGEN AND A NITROGEN FUNCTION

#### 4.07.1.1 Functions Bearing Oxygen and Nitrogen

##### 4.07.1.1.1 *Hemiaminals with tricoordinate nitrogen bearing alkyl, aryl, or acyl substituents*

(i) *From compounds containing multiply bonded functional groups*

(a) *From aldehydes and ketones.* As highlighted in COFGT (1995), the most general method to generate the O—C—N synthon is by the condensation of an amine with either an aldehyde or a ketone. There are, however, many factors inherent in the substrate and reaction conditions that

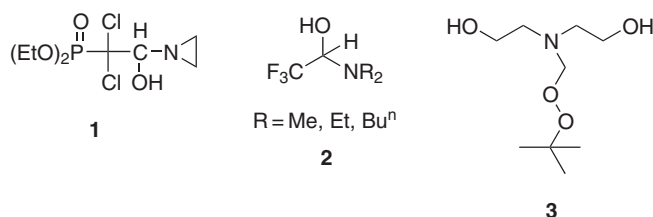
influence the outcome of the reaction. For more detailed background of the behavior of various ketones and aldehydes with amines, see chapter 4.07.1.1.1 of <1995COFGT(4)293>.

Recently, several groups have contributed research concerning the mechanistic nature of these reactions <2000JCS(P2)941, 2001JOC7596> along with kinetic and equilibrium data <1997JCS(P2)909>.

The reaction of phosphoroyldichloroacetaldehyde with ethyleneimine was shown to furnish the crystalline hemiaminal (hydroxyaziridine) **1**, which is known to be stable at room temperature for long periods of time <1999T8423>.

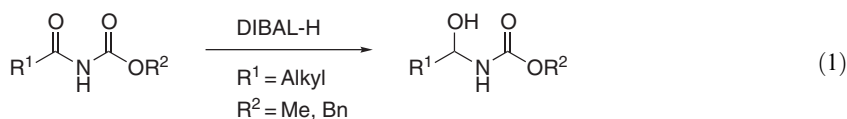
Hemiaminals **2** derived from trifluoroacetaldehyde act as trifluoromethylating agents, although there is a need for improvement in terms of the yield and reaction efficiency <2000TL6411>.

In a final example, a variety of *t*-butylperoxamines were synthesized via the addition of secondary amines with formaldehyde and *t*-butyl hydroperoxide (70% aq.) in MeOH. The products were tested as anti-malarial agents, in which compound **3** showed the highest potency <2001BMCL2269>.



(b) *From amides/imides*. The condensation reaction of imides with aldehydes has been widely used recently, particularly toward the synthesis of ampicillin and thalidomide prodrugs <1997BMCL3107, 2001BMC1279>.

Acyl carbamates can be selectively reduced with diisobutylaluminum hydride (DIBAL-H) to provide *N*-acyl hemiaminals in high yields (Equation (1)). The stable intermediates undergo intra- and intermolecular addition reactions with the aid of a Lewis acid <1997TL6545, 2001JOC6988>. Alternatively, the reduced hemiaminal is trapped to afford the *N,O*-acetal TMS ether in excellent yield as a stable precursor for the *N*-acyliminium ion <2002CC1064>.



The cathodic reaction of phthalimide anion in methanol afforded a novel product, *N*-hydroxy-methyl-3-hydroxyphthalimidine **4** <1998T7517>.

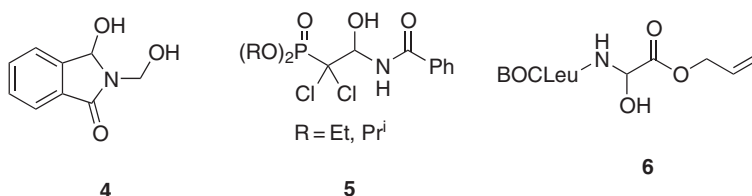
Recently, it was shown that the condensation of phosphochlorals with benzamide resulted in the formation of stable phosphorylated hemiamidals, **5** <1999T8423>.

The reaction of *N*-Cbz-L-phenylalanyl and acrylamide under standard Baylis–Hillman reaction conditions furnished an unexpected non-Baylis–Hillman adduct, which was later identified as the *N*-acyl hemiaminal. The scope of this reaction was further explored by using several enantiopure and racemic aldehydes to provide the corresponding products in moderate-to-very good yields (Table 1) <1998CL787>.

The  $\alpha$ -hydroxy allyl ester **6**, derived from the condensation reaction of BOC-leucine amide with allyl glyoxalate hydrate, was homologated further to arrive at a desired synthon to be incorporated into a variety of modified peptides that represent a novel class of HIV replication inhibitors <1996BMCL609>.

**Table 1** Reactions of aminoaldehydes with acrylamide in the presence of DABCO

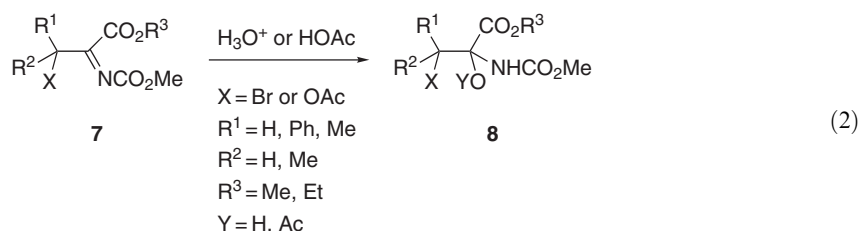
Aldehyde	Time (h)	Yield (%)
<i>N</i> -BOC-L-Valinal	13	73
<i>N</i> -BOC-L-Phenylalanal	18	63
<i>N</i> -BOC-L-Tryptophanal	15	40
<i>N</i> -BOC-L-Prolinal	15	70
<i>N</i> -BOC-L-Serinal(OBn)	15	29
<i>N</i> -BOC-Glycinal	18	82
<i>N</i> -BOC-L-Lysinal	18	48
<i>N</i> -Cbz-L-Valinal	15	78
<i>N</i> -Cbz-Glycinal	14	85
<i>N</i> -BOC-L-Leucinal	13	80



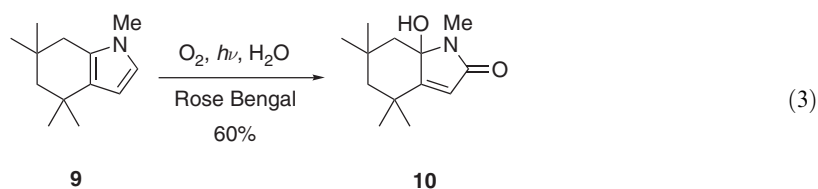
The total synthesis of (±)-mesembrine utilizes an intramolecular nucleophilic attack of an allyl anion onto an imide intermediate to furnish the desired N—C—O moiety en route to the natural product <1997TL1893>.

Recent syntheses of 15-desoxyspergualin have demonstrated the reaction of key amide intermediates with suitable electrophiles to furnish the central α-hydroxyglycine unit of the natural product <1998JOC9723, 2000TA3665, 2001T2757>.

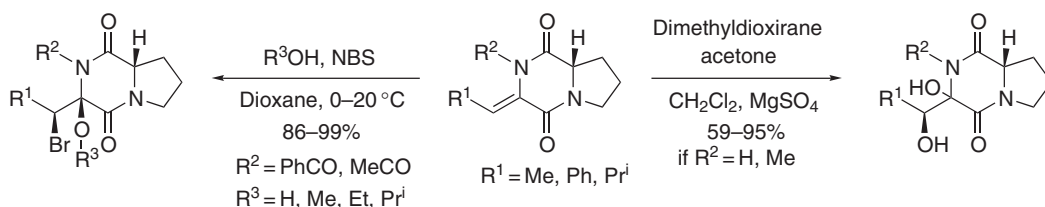
(c) *From imines/iminium salts.* In a report by Danion and co-workers, it was demonstrated that the addition of water or acetic acid to iminoesters **7** furnishes the corresponding hemiaminals and α,β-diacetoxy amino esters **8** (Equation (2)) <1996JCS(P1)1833>. In the last few years no further pertinent examples have been reported, therefore see chapter 4.071.1.1.i.c of <1995COFGT(4)293> for other reactions under this subheading.



(d) *Alkenes.* The oxidation of *N*-methylpyrrole **9**, via photooxygenation reaction conditions with Rose Bengal as a photosensitizer, afforded hydroxy pyrrolidinone **10** (Equation (3)). This intermediate underwent a key spiro-rearrangement reaction to furnish the desired spirosuccinimide product <2000TL4519>.



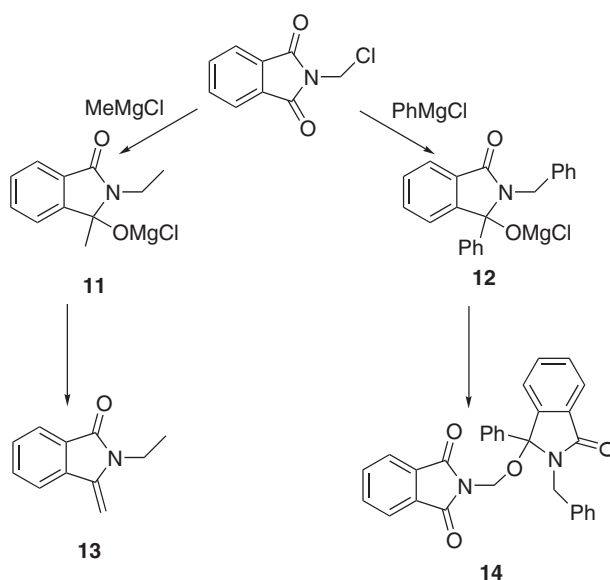
The bromohydroxylation or alkoxylation of enamide moieties is often used to achieve the N—C—O synthon. This transformation has been demonstrated recently in two approaches toward the synthesis of Thaxtomins A and B, where the resulting bromine functionality is removed along with protecting groups by catalytic hydrogenation with  $\text{H}_2/\text{Pd}$  on charcoal in both the reports <1996T8525, 1993JOC3473>. In another example, 3-ylidenepiperazine-2,5-diones (or 3-ylidene-2,5-diketopiperazines) were selectively epoxidized and bromoalkylated to furnish the N—C—O synthon in high yields (Scheme 1) <2003S67>.



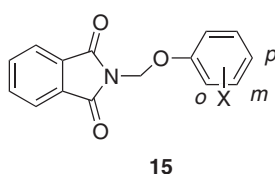
Scheme 1

(ii) From compounds containing two singly bonded functional groups

(a) From  $X\text{—C—N}$  functions ( $X = \text{hal}, \text{OR}, \text{SR}, \text{SO}_2\text{R}, \text{NR}_2$ ). When *N*-chloromethylphthalimide is reacted with organomagnesium reagents, the substrate underwent consecutive chloride substitution and mono-carbonyl addition to afford substrates **11** and **12** (Scheme 2). When **11** is treated with a mild acid, the corresponding dehydrated product **13** is obtained. **12** was often found to react further via intermolecular coupling with the starting material to provide the addition by-product **14** <2000CJC1285>. A variety (**15a–h**) of other phthalimide derivatives were synthesized by the condensation of *N*-chlorophthalimide with commercially available substituted phenols with base in DMF or DMSO at room temperature. These compounds were then reacted in various ways to afford the cyclized or eliminated products <1998JHC1477>. Interestingly, a series of readily hydrolyzable basic and dibasic esters of ampicillin were produced by alkylation of the carboxylate function of ampicillin to obtain various prodrugs. Many of the prodrugs possess the substituted N—C—O functional group <2001BMC493>.

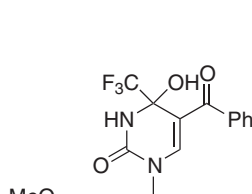
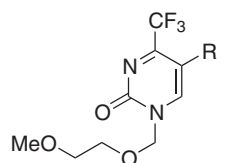


Scheme 2

**15**

Substrate	X
<b>a</b>	H
<b>b</b>	<i>o</i> -Br
<b>c</b>	<i>p</i> -Br
<b>d</b>	<i>o</i> -Cl
<b>e</b>	<i>m</i> -Cl
<b>f</b>	<i>o</i> -F
<b>g</b>	<i>o</i> -Br, <i>p</i> -Cl
<b>h</b>	<i>m</i> , <i>m</i> -OMe

(b) From  $O-C-X$  functions ( $X = \text{hal or OR}$ ). Acyclic nucleoside analogs **16** and **17** were prepared from MEM-Cl and silylated pyrimidines. NaI was used to facilitate nucleophilic displacement <2001T7369>. Danikiewicz and Szmigielski provide an efficient, two-step synthesis of *N*-alkoxymethyl derivatives of acetanilide, formanilide, and benzanilide by phase-transfer catalysis (PTC) conditions with MOM-Cl. Upon heating the resultant anilides with an excess of aliphatic alcohols and a catalytic quantity of *p*-TsOH, a variety of *N*-alkoxymethyl derivatives were obtained as shown in Table 2 <2001SC3047>.

**16**

R = C(=O)Ph, CH<sub>2</sub>Ph, Et, Pr<sup>i</sup>

**17**

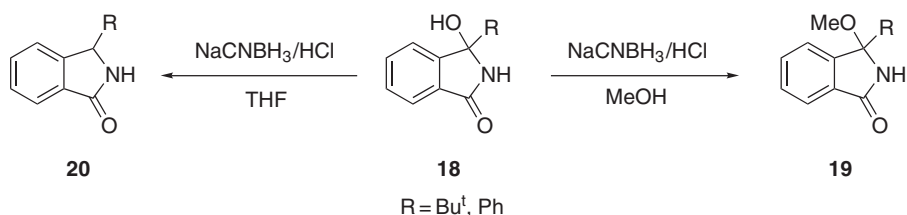
**Table 2** Preparation of *N*-alkoxymethylanilides from the appropriate *N*-methoxymethylanilides

$R^1$	$R^2$	$T$ (°C)	Time (h)	Yield (%)
Me	Et	78	1.5	92
Me	Pr <sup>n</sup>	60	1	90
Me	Pr <sup>i</sup>	82	1.5	83
Me	Bu <sup>n</sup>	75	3	70
Me	Bu <sup>i</sup>	80	4	74
Me	Bu <sup>s</sup>	85	3	90
Me	Bu <sup>t</sup>	60	2	60
Me	CH <sub>2</sub> CH=CH <sub>2</sub>	rt	24	81
H	Et	78	3	67
Ph	Et	78	2.5	93

*N*-Alkylated fluorouracil and fluorodeoxyuridine derivatives have been prepared in attempts to improve the biological activity against certain types of cancer <1996CPB1196, 2002HAC211>.

(c) By functionalization of a preformed *O,N*-acetal. Kawai and co-workers reported a method for the preparation of Cbz–Gly(OR)–OR derivatives using Cbz–Gly(OH)–OH and ROH that has been shown to be applicable to many primary and secondary alkoxyglycine substrates <1996SC1545>. In an unexpected result, when R = Bu<sup>t</sup> or Ph, upon reaction with NaCNBH<sub>3</sub>/HCl in MeOH, **18** underwent dehydration thereby forming a resonance-stabilized acyliminium ion, and

was subsequently attacked by solvent (MeOH) to afford **19**. In contrast, when the reaction was carried out in aprotic solvents such as THF and TFA, the acyliminium ion was reduced by NaCNBH<sub>3</sub> to furnish the desired compound **20** (Scheme 3) <2002TL9163>.

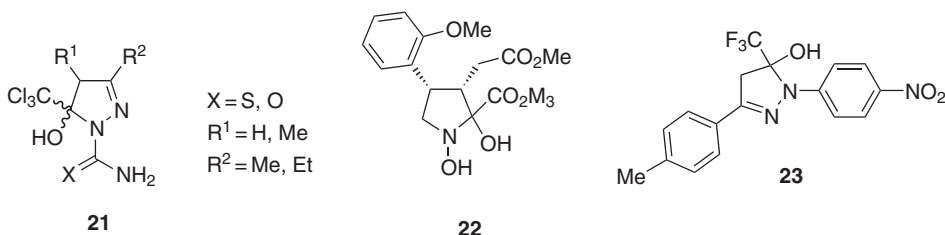


Scheme 3

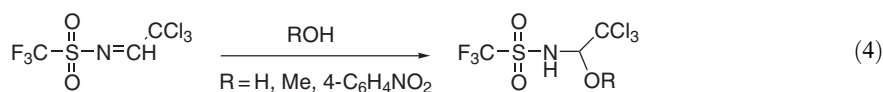
#### 4.07.1.1.2 Functions with tricoordinate nitrogen-bearing heteroatom substituents

##### (i) From compounds containing a multiply bonded functional group

(a) *From aldehydes and ketones.* Several novel 5-hydroxy-1*H*-pyrazolines were synthesized by reacting a series of trichlorobutenones with semicarbazide hydrochloride or thiosemicarbazide, **21** <1999T345>. Reduction of a nitro diester function with Pd/C and ammonium formate in methanol provided **22** in 89% yield, and this was converted directly to the nitron due to its instability <1997JOC2314>. The cyclic pyrazoline-5-ol **23** was prepared by the reaction of 4-nitrophenylhydrazine with 1-(4-methylphenyl)-4,4,4-trifluorobutane-1,3-dione and transformed to the pyrazole after loss of water with HOAc under refluxing conditions <2001JMC3039>.



(b) *From imines/nitrones.* Schiff bases react readily with oxygen and nitrogen nucleophiles, yielding products as shown in Equation (4) <1999ZOR1361, 2001ZOR1635>.

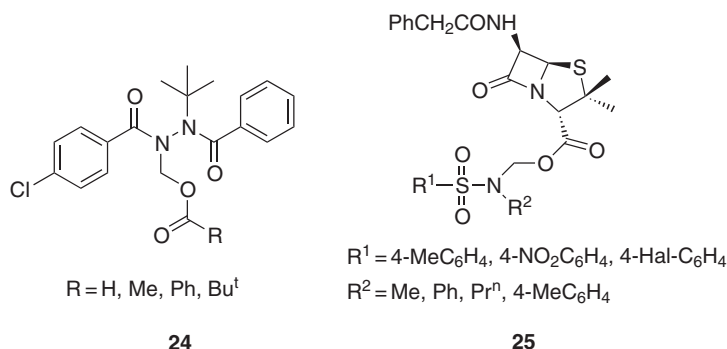


(c) *From alkenes.* No further advances have occurred in this area since the publication of chapter 4.07.1.1.2.i.c in <1995COFGT(4)293>.

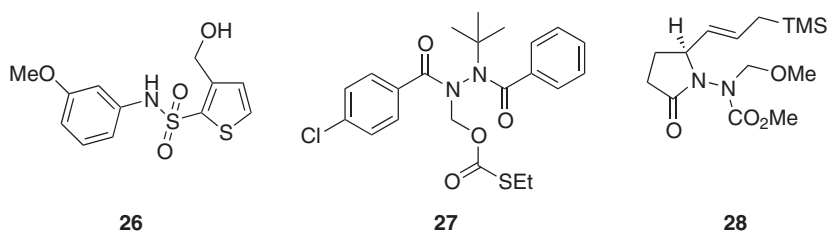
##### (ii) From compounds containing two singly bonded functional groups

(a) *From X—C—N functions (X = hal).* Various novel insecticides and environmentally safe halofenozide-*N*-(acyloxy)alkyl derivatives **24** were prepared by reacting the corresponding chloroalkyl derivatives with suitable carboxylic acids and diisopropylethylamine (DIEA) in

THF <2002S53>. Similarly, substitution of *N*-chloromethylsulfonamide intermediates with the sodium salt of various carboxylic acids afforded the corresponding benzylpenicillin ester derivatives **25**, albeit in low yields <2000BMC1629>. In a different substitution protocol, several phenyl esters were lithiated ( $\text{Bu}^n\text{Li}$ ) and subsequently trapped with suitable electrophiles to provide various benzotriazole derivatives en route to polysubstituted thiophenes <1998JCS(P1)1059>.



(b) *From O—C—X functions (X = hal)*. Interestingly, treatment of chloromethyl methyl ether with **26** and *N,N*-diisopropylamine afforded the *N*-alkylated product without formation of the ether substrate <1999JHC65>. In a different example, thiocarbonate **27** was synthesized from the reaction of the potassium salt of halofenozide with the appropriate thiocarbonic acid <2002S53>. Finally, even with an allyl silane side-chain present, methoxymethyl derivative **28** was generated from the reaction of the amide precursor with NaH and MOM—Cl <2000TL395>.



#### 4.07.1.1.3 Functions with dicoordinate nitrogen

##### (i) From compounds containing a multiply bonded functional group

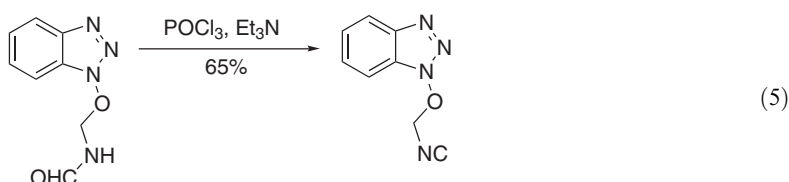
(a) *From aldehydes and ketones*. The N—C—O bond formation of the hydroxythiazolanyl-thiazole ring system was achieved by the reaction of a thioamide with a thiazole in the presence of molecular sieves <2001OL2811>. Oxathiazines and oxaselenazines bearing a variety of substituents were prepared by treating a solution of arenecarbochalcogenoamides with a trioxane or pivaldehyde and  $\text{BF}_3 \cdot \text{OEt}_2$  as shown in Table 3 <2001BCJ511>.

As a new method to access the isocyanomethyl moiety, a carbonyl precursor underwent dehydration with phosphorus oxychloride and triethylamine to afford the 1-(isocyanomethoxy) benzotriazole in 65% yield (Equation (5)) <1997CPB1369>.

**Table 3** Preparation of 6*H*-1,3,5-oxathiazines and 6*H*-1,3,5-oxaselenazines

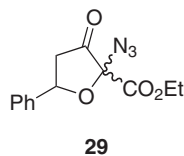
$$\text{R}^1-\text{C}(=\text{X})\text{NH}_2 \xrightarrow[\text{BF}_3 \cdot \text{OEt}_2, \text{CH}_2\text{Cl}_2, \text{rt, 1-3 h}]{\text{2,4,6-Trimethyl-1,3,5-trioxane (A) or pivaldehyde (B)}} \text{R}^1-\text{C}(\text{X})(\text{R}^2)-\text{N}(\text{R}^2)-\text{O}-\text{R}^2$$

$\text{R}^1$	$\text{X}$	Reagent	$\text{R}^2$	Yield (%)
$\text{C}_6\text{H}_5$	S	A	$\text{CH}_3$	95
$\text{C}_6\text{H}_5$	S	B	$\text{C}_4\text{H}_9$	43
<i>p</i> -Cl $\text{C}_6\text{H}_4$	S	A	$\text{CH}_3$	38
<i>p</i> -Cl $\text{C}_6\text{H}_4$	S	B	$\text{C}_4\text{H}_9$	32
$\text{C}_6\text{H}_5$	Se	A	$\text{CH}_3$	56
$\text{C}_6\text{H}_5$	Se	B	$\text{C}_4\text{H}_9$	32
<i>p</i> -Cl $\text{C}_6\text{H}_4$	Se	A	$\text{CH}_3$	53
<i>p</i> -Cl $\text{C}_6\text{H}_4$	Se	B	$\text{C}_4\text{H}_9$	44



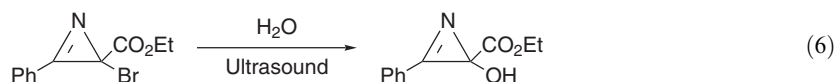
(b) From hydrazones and oximes. No further advances have occurred in this area since the publication of chapter 4.07.1.1.3.i.b in <1995COFGT(4)293>.

(c) From alkenes. Azido-substituted diazoketoesters were reacted with  $\text{Rh}_2(\text{OAc})_4$  to give rise to unexpected 3(2*H*)-furanones, such as **29**, in excellent yields via a [3,3]-sigmatropic shift of the enol form of the initial furanone <1997TL5087>.



(ii) From compounds containing two singly bonded functional groups

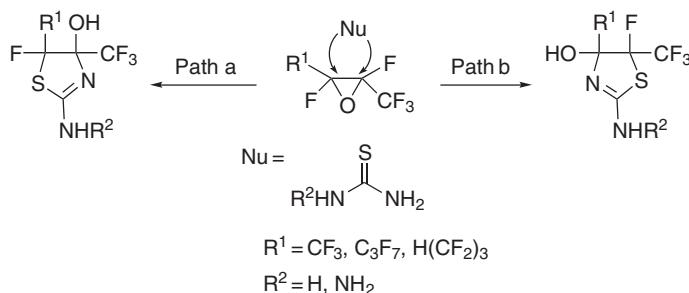
(a) From  $\text{X}-\text{C}-\text{N}$  functions ( $\text{X} = \text{hal}$ ). Under ultrasonic conditions, 2*H*-azirines undergo halide displacement to give rise to 3-hydroxy-2*H*-azirines (Equation (6)) <2000TL7217, 2002JOC66>. The reaction of isocyanates with 3-alkoxyphenols in toluene and triethylamine affords phenylurethane intermediates that cyclize in an intramolecular fashion to generate benzozazineones in moderate yields <2002JFC(116)97>.



(b) From  $\text{O}-\text{C}-\text{X}$  functions ( $\text{X} = \text{hal, OR}$ ). The reaction of haloethers with sodium azide in solvents such as DMF, acetonitrile, or DMSO provide azidoalkyl alkyl ethers in reliable yields and is most often used in nucleoside and carbohydrate chemistry <1997MI1115, 1996JMC949, 1999SL1151, 2000MI1977, 2002JCS(P1)1982>. Trimethylsilyl azide and a catalytic amount of TMSOTf are used often to accomplish the aforementioned transformation <1996T9057, 2002JA3263>.

Notably, the reaction of polyfluoro-epoxy alkanes with either camphor-thiosemicarbazone or thiourea and thiosemicarbazide yield thiazolinyldiazones and polyfluoroalkylated 1,3-thiazolines, respectively (Scheme 4) <2000JFC(104)155, 2003JFC(120)41>.





Scheme 4

#### 4.07.1.2 Functions Bearing Sulfur and Nitrogen

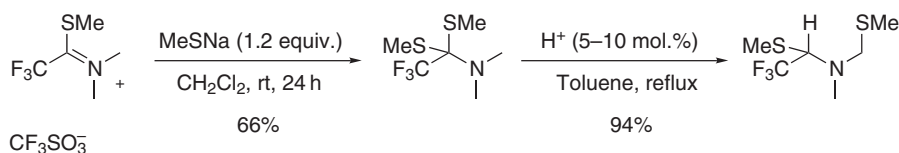
##### 4.07.1.2.1 Dicoordinate sulfur derivatives

(i) Functions with tetra- and tricoordinate nitrogen bearing alkyl or aryl substituents

(a) From compounds containing multiply bonded functional groups. From aldehydes and ketones. No further advances have occurred in this area since the publication of chapter 4.07.1.2.1.i.a.1 in <1995COFGT(4)293>.

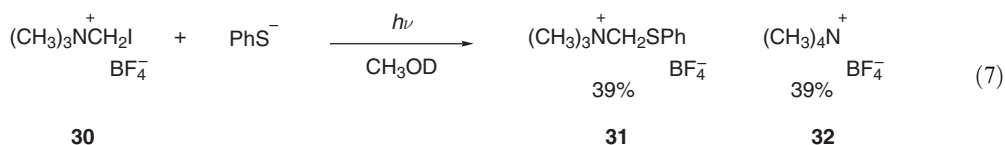
From thiocarbonyl compounds. No further advances have occurred in this area since the publication of chapter 4.07.1.2.1.i.a.1 in <1995COFGT(4)293>.

From imines and iminium salts. Dithioethers, such as *N,N*-dimethyl-bis(methylthio)-orthotrifluoroacetamide, formed by the nucleophilic reaction of sodium methyl sulfide with the trifluoro-thioamidium salt were found to rearrange on treatment with acid to the bis-hemiaminal moiety (Scheme 5) <1996TL5515>.

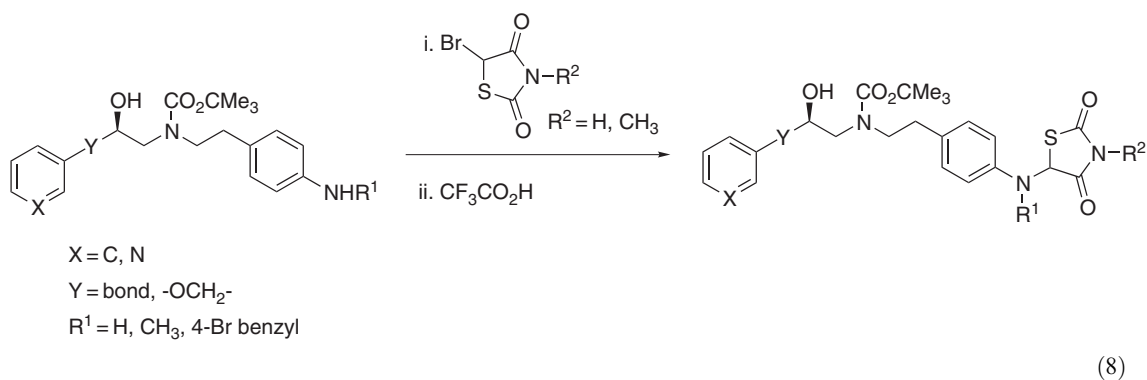


Scheme 5

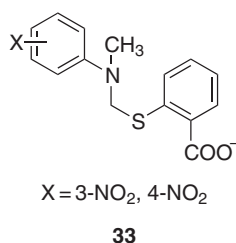
(b) From compounds containing two singly bonded functional groups. From X—C—N functions (X = Hal, CN, OR, NR<sub>2</sub>, or a metal). The photoinduced reaction of ammonium salt **30** provides equal amounts of the anticipated S<sub>RN</sub>1 product **31** and hydrogen transfer reduction product **32** (Equation (7)) <2000JOC3460>.



From S—C—X functions (X = Cl, Br, SR). Treatment of a variety of anilines first with bromothiazolidinediones in the presence of triethylamine and second with trifluoroacetic acid produced the corresponding thiazolidinediones (Equation (8)) <2000MI164>.

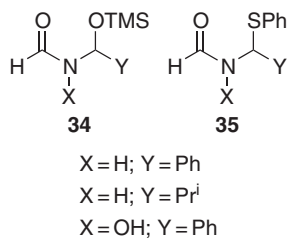


(c) By functionalization of a preformed *S,N*-acetal. Anilino thioethers **33** undergo concerted bimolecular nucleophilic substitution with sulfur nucleophiles in aqueous solutions at room temperature. The mechanism is supported by the lack of an iminium ion intermediate <1995JA9415>.



(ii) Functions with tricoordinate nitrogen bearing acyl or heteroatom substituents

(a) From compounds containing multiply bonded functional groups. From aldehydes and ketones. Addition of thiophenol to a solution of bis(trimethylsilyl)-formamide (BSF)-aldehyde adducts **34** and a catalytic amount of TMS-OTf provided compounds **35** <1996JCS(P1)895>.



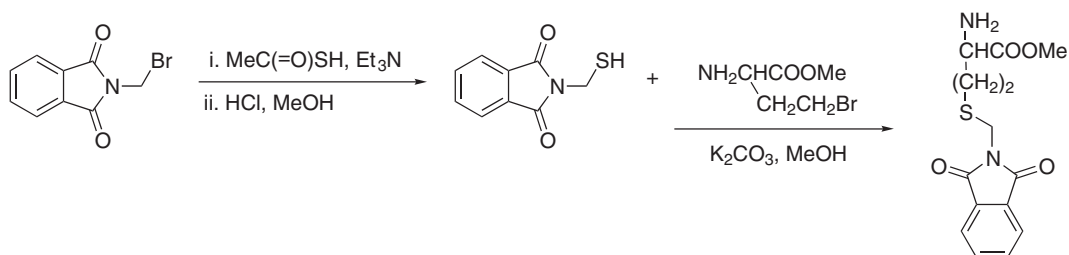
From imines. No further advances have occurred in this area since the publication of chapter 4.07.1.2.1.ii.a.2 in <1995COFGT(4)293>.

From compounds possessing an  $\text{S} = \text{N}$  unit. No further advances have occurred in this area since the publication of chapter 4.07.1.2.1.ii.a.3 in <1995COFGT(4)293>.

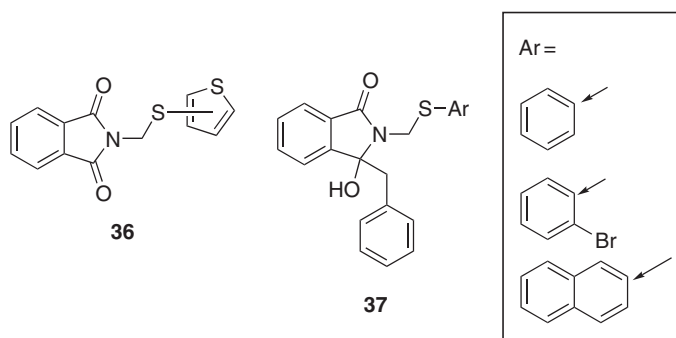
From alkenes. No further advances have occurred in this area since the publication of chapter 4.07.1.2.1.ii.a.4 in <1995COFGT(4)293>.

(b) From compounds containing two singly bonded functional groups. From  $\text{X}-\text{C}-\text{N}$  functions ( $\text{X} = \text{Hal}, \text{OR}, \text{NR}_2$ , or a metal). Thiol displacement of *N*-halomethylphthalimides was the most prevalent reaction found in recent literature examples <2000JMC1620, 2001EJO1831>. For example, treatment of *N*-bromomethylphthalimide with thioacetic acid in the presence of

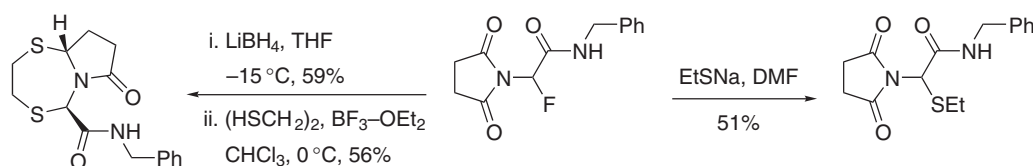
triethylamine followed by deacetylation (conc. HCl) affords the thiol in good yields (Scheme 6). The resulting thiol was then reacted with a suitable alkyl halide to form a more complex thioether <1999H1789>. The reaction of chloromethylphthalimide with either 2- or 3-mercaptothiophene yields the corresponding thienylthiomethylphthalimides **36** in moderate yields <1996JHC321>.  $\omega$ -Benzyl- $\omega$ -carbinol lactams **37** were prepared by, first, *S*-alkylation of *N*-chloromethylphthalimide followed by subsequent Grignard carbophilic addition <2000OL1201>.



Scheme 6

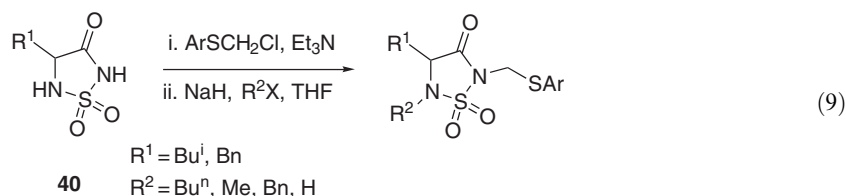
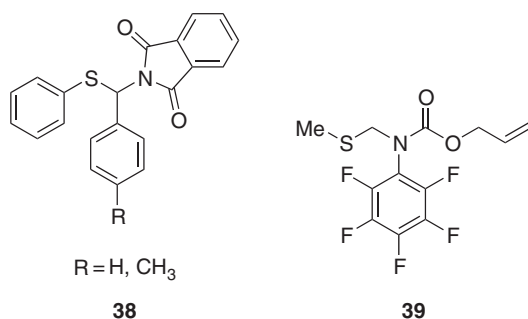


The  $\alpha$ -fluorophthalimide (Scheme 7) was reacted to afford either thioether substitution at the  $\alpha$ -fluoro position or a reduction and subsequent cyclization product <1998TL7755>.



Scheme 7

From S—C—X functions (X = Hal). Reaction of  $\alpha$ -chlorothioethers with potassium phthalimide provides the corresponding substituted products **38** <1998JOC3706>. *N*-Allyloxycarbonylpentafluoroaniline was converted into the *N*-methylthiomethyl derivative **39** after conversion to its sodium salt and subsequent alkylation with chloromethyl methyl sulfide in high yield <1999T6945>. In a different manner, compound **40** was alkylated to give the desired N—C—S bond followed by *N*-5 alkylation (Equation (9)) <1998BMC661>.

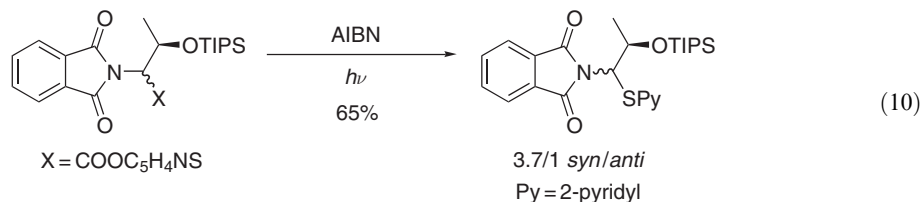


(c) *By functionalization of a preformed S,N-acetal.* The trimethylsilyl trifluoromethanesulfonate (TMS-OTf) promoted  $\beta$ -lactam fragmentation of 4-alkylthioazetidin-2-ones demonstrates a novel method to access *N,S*-acetals in moderate-to-excellent yields <1996JCS(P1)2321>. The reaction occurs by a nucleophilic attack of a nitrile group on the generated cation intermediate. Examples of the scope of this method are provided in Table 4.

**Table 4**  $\beta$ -Lactam fragmentation of 4-alkylthioazetidin-2-ones

$\beta$ -Lactam	R <sup>1</sup>	R <sup>2</sup>	Yield (%)	Diastereomeric ratio
	Bn	Me	50	2.8:1
	<i>p</i> -MeOBn	Me	47	2.9:1
	Allyl	Me	45	2:1
	Pr <sup>i</sup>	Me	64	2:1
	Cyclohexyl	Me	84	1.8:1
	Bu <sup>t</sup>	Me	89	1:1
	Bu <sup>t</sup>	Ph	63	1.1:1
	Bu <sup>t</sup>	Me	46	1.3:1
	Bu <sup>t</sup>	Ph	91	1.2:1
	Bu <sup>t</sup>	Pr	77	1.4:1
	Bu <sup>t</sup>	Ph	53	1:1
	Bu <sup>t</sup>	Me	65	NA
	Bu <sup>t</sup>	Me	54	1:1

(d) *Miscellaneous reactions.* Irradiation of the Barton ester using a 300 W sun lamp provides pyridylthio derivatives as a 3.7/1 *syn/anti* mixture of isomers in an overall yield of 65% (Equation (10)) <1996TL2569>.



(iii) *Functions with dicoordinate nitrogen*

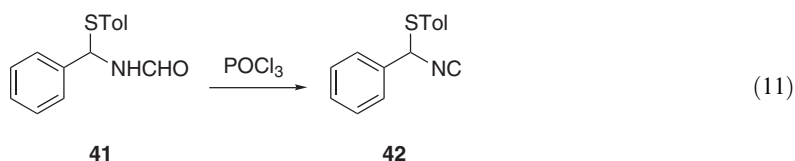
(a) *From compounds containing multiply bonded functional groups.* From aldehydes and ketones. No further advances have occurred in this area since the publication of chapter 4.07.1.2.1.iii.a.1 in <1995COFGT(4)293>.

From acid chlorides. No further advances have occurred in this area since the publication of chapter 4.07.1.2.1.iii.a.2 in <1995COFGT(4)293>.

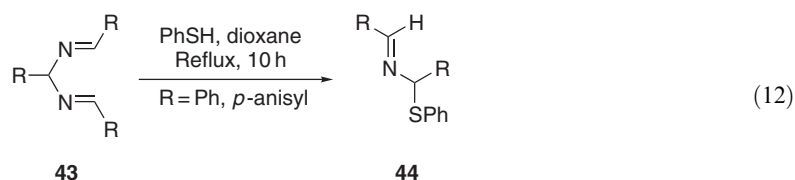
From thiocarbonyl compounds. No further advances have occurred in this area since the publication of chapter 4.07.1.2.1.iii.a.3 in <1995COFGT(4)293>.

From imines. No further advances have occurred in this area since the publication of chapter 4.07.1.2.1.iii.a.4 in <1995COFGT(4)293>.

From a preformed *S,N*-acetal. Reaction of **41** with POCl<sub>3</sub> provides the tolyl sulfide isocyanide **42** in moderate yields (Equation (11)) <1996JMC3929>.



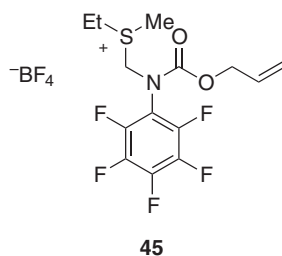
(b) *From compounds containing two singly bonded functional groups.* From X—C—N functions (X = Hal, OR, NR<sub>2</sub>). The reaction of diimines **43** with thiophenol in refluxing dioxane affords imines **44** in good yields (Equation (12)) <1997TL4281, 1998T4375>.



From S—C—X functions (X = Hal or SR). No further advances have occurred in this area since the publication of chapter 4.07.1.2.1.iii.b.2 in <1995COFGT(4)293>.

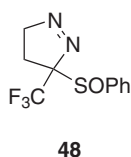
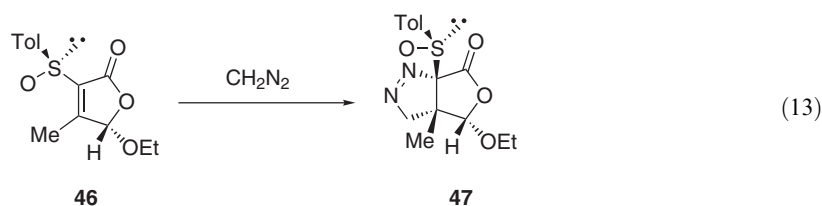
#### 4.07.1.2.2 Tricoordinate sulfur derivatives

Recently, the first example of a sulfonium salt *S,N*-acetal has been described in the literature. Reaction of the triethyloxonium tetrafluoroborate in dichloromethane with the corresponding *N*-methyl thiomethyl parent compound provided the crystalline sulfonium tetrafluoroborate salt **45** in 76% yield <1999T6945>.



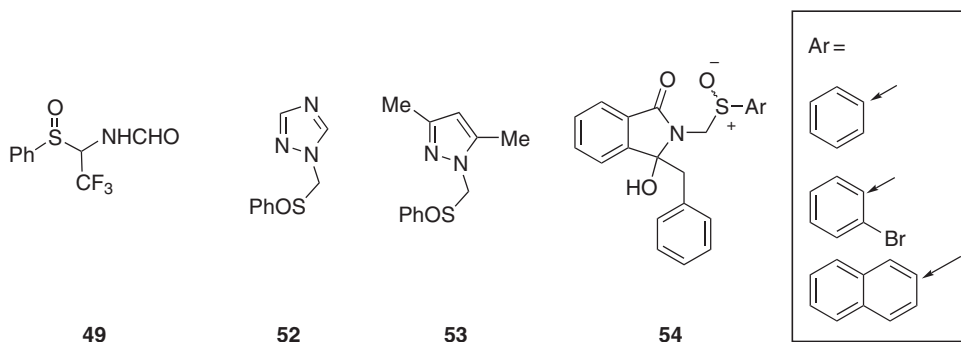
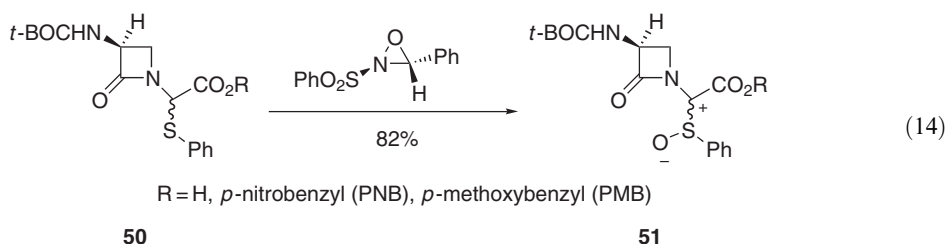
(i) *From compounds containing multiply bonded functional groups*

The 1,3-dipolar cycloaddition of **46** with diazomethane generates **47** as the sole adduct in very good yield with complete regio- and stereoselectivity (Equation (13)) <1996TA1943>. Similarly, pyrazoline **48** was synthesized by the cycloaddition of diazomethane with the appropriate tri-fluoropropene; however, this product readily eliminated PhSOH on thermolysis at 80 °C to afford the pyrazole <1996T4383>.



(ii) *By functionalization of a preformed S,N-acetal*

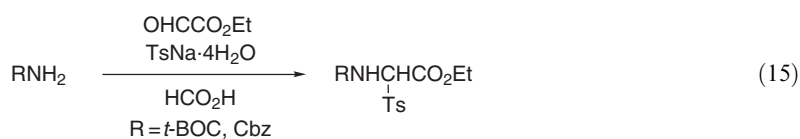
This area mainly comprises different methods to oxidize a variety of sulfides to the corresponding sulfoxides. Ozonolysis is one way to achieve such an oxidation <2001SL712>. Another method utilizes dimethyldioxirane (DMDO) to oxidize the formamide to the sulfoxide **49** in a 58:19 diastereomeric mixture <1996BCJ1763>. The use of an interesting oxaziridine reagent often provides controlled oxidation of a thioether to the corresponding sulfoxide. Specifically, the reaction of **50** with 2-(phenylsulfonyl)-3-phenyloxaziridine gave **51** as a mixture of four diastereomers (Equation (14)) <1999T13301>. Sulfoxides **52** and **53** were obtained by the oxidation of the sulfide precursors with NaIO<sub>4</sub> <2000T7273>. In the case of MCPBA, short reaction times are often necessary to avoid over-oxidation to the sulfones. In this manner, sulfoxides **54** were obtained after reacting with MCPBA for 1–3 min at 0 °C <2000OL1201>.



#### 4.07.1.2.3 Tetra- and higher-coordinate sulfur derivatives

##### (i) From compounds containing multiply bonded functional groups

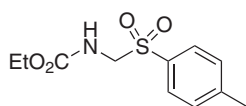
(a) *From aldehydes and ketones.* Kinoshita and Nagano recently reported that the reaction of *t*-butyl or benzyl carbamate, with ethyl glyoxylate, and sodium *p*-toluenesulfinate tetrahydrate produces ethyl *N*-BOC and *N*-Cbz- $\alpha$ -tosylglycinates (Equation (15)) <2000BCJ1605>.



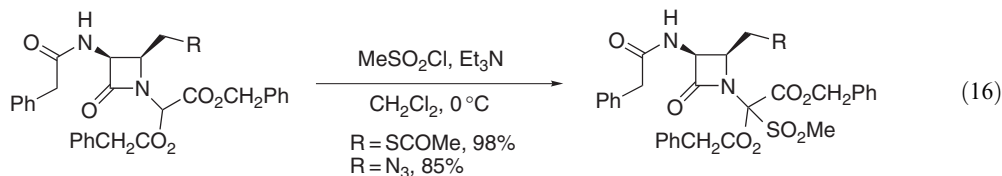
The Ugi reaction is often employed to afford tosylated products. In one case, a variety of aldehydes or ketones were coupled with L-homoserine along with substituted isocyanides to afford *N*-carbamoyl methyl- $\alpha$ -aminobutyrolactones in good-to-excellent yields (Table 5) <1998TL7109>. The Ugi reaction may also be applied to the solid-phase synthesis of substrates <1997T6573>. A variety of  $\alpha$ -amidoalkyl-*p*-tolyl sulfones were synthesized by reacting suitable aldehydes with crude *t*-butyl carbamate, anhydrous sodium *p*-toluenesulfinate, water, methanol, and formic acid and stirring for 15 min <2001TL5093, 2002TL1079>. Carbamate **55** was synthesized using similar reaction conditions, yet required longer times for the completion of the reaction <2000TL5489>. Sisko and co-workers reported an efficient method for the synthesis of substituted tosylmethyl isocyanide (TosMIC) precursors. By heating an aldehyde, formamide, TMSCl, and *p*-toluenesulfinic acid in a 1:1 solution of toluene:acetonitrile, a wide array of substituted tosylmethyl formamides were generated. Dehydration of the subsequent products with POCl<sub>3</sub> and triethylamine provided TosMIC derivatives cleanly, even on a 13 kg scale <1996TL8113>.

**Table 5** Synthesis of *N*-carbamoylmethyl- $\alpha$ -aminobutyrolactones via the Ugi reaction

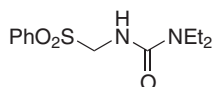
$R^1$	$R^2$	Time (h)	Yield (%)	Diastereomeric ratio
$\text{CH}_3(\text{CH}_2)_2-$	H	60	73	3:1
$(\text{CH}_3)_2\text{CH}-$	H	94	97	7:1
$(\text{CH}_3)_3\text{C}-$	H	94	92	3:1
	H	47	71	8:1
$-(\text{CH}_2)_5-$		70	72	NA

**55**

(b) *From sulfonic acid derivatives.* Hwu and co-workers have demonstrated that the treatment of  $\beta$ -lactams with  $\text{MeSO}_2\text{Cl}$  and  $\text{Et}_3\text{N}$  in  $\text{CH}_2\text{Cl}_2$  provides the corresponding sulfone derivatives in excellent yields (Equation (16)) <1999CEJ2705, 1998JMC4681>.



(c) *From sulfones.* The sulfone carbanion derived from  $\text{PhSO}_2\text{CH}_3$  was aminated by *N*-carboxamido oxaziridine to provide a novel and direct route to the corresponding  $\alpha$ -amino compound **56** <2000TL2247>.

**56**

(ii) *From compounds containing two singly bonded functional groups*

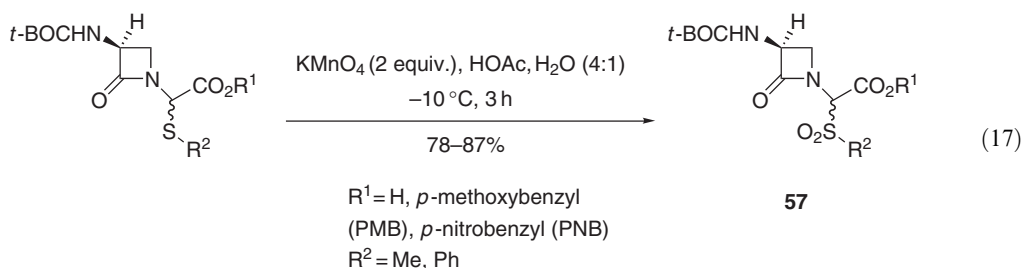
(a) *From  $X-C-N$  functions* ( $X = \text{Hal}$ ,  $\text{OR}$ ,  $\text{NR}_2$ , or a metal). No further advances have occurred in this area since the publication of chapter 4.07.1.2.3.ii.a in <1995COFGT(4)293>.

(b) *From  $S-C-X$  functions* ( $X = \text{Metal}$ ). No further advances have occurred in this area since the publication of chapter 4.07.1.2.3.ii.b in <1995COFGT(4)293>.

(iii) *By functionalization of a preformed *S,N*-acetal*

Sulfones **57** were synthesized by oxidation with potassium permanganate in aqueous acetic acid in good yields (Equation (17)) <1999T13301>.  $\alpha$ -Substituted *S,N*-acetals were obtained by lithiation and subsequent trapping by electrophiles or deuterium <1997T4835>.





#### 4.07.1.3 Functions Bearing Selenium or Tellurium, Together with Nitrogen

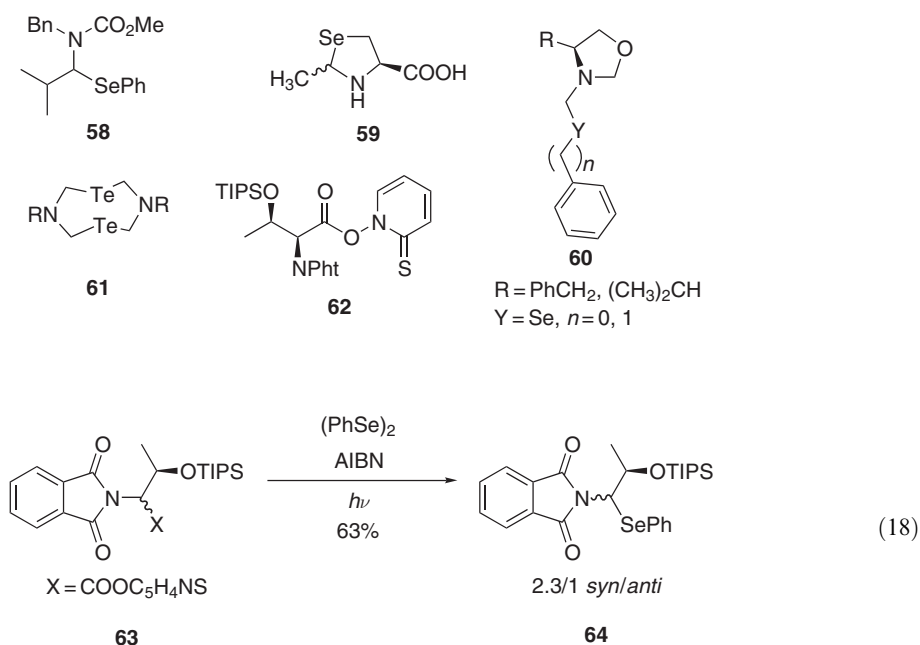
In recent years, more applications of organoselenium compounds have been presented in the literature, specifically transformations stemming from selenocarbonyl compounds. Conversely, the progress of organotellurium chemistry is slow in comparison, thus providing an opportunity for future growth in this area. For previous reviews of both organoselenium—and tellurium see chapter 4.07.1.3 in <1995COFGT(4)293>.

##### 4.07.1.3.1 From compounds containing a multiply bonded functional group

###### (i) From carbonyl compounds

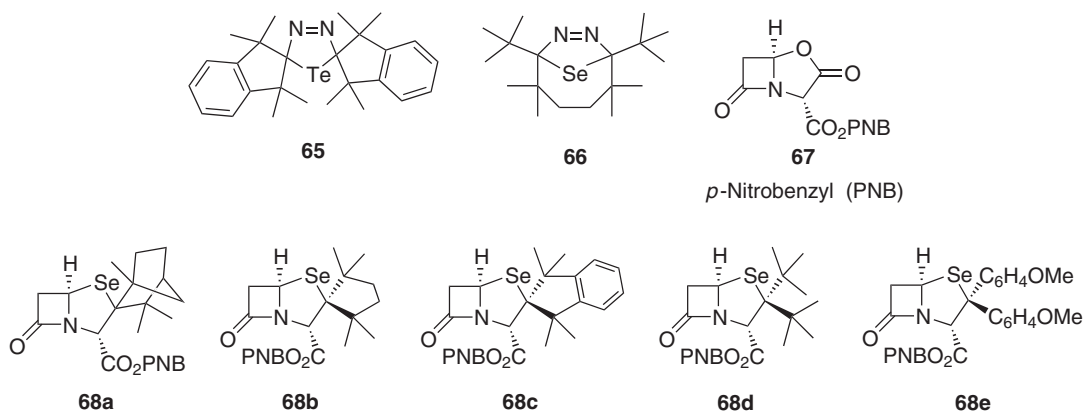
Reaction of an isobutyraldehyde-derived imine with ClCO<sub>2</sub>Et followed by PhSeH/Et<sub>3</sub>N provides the expected *Se,N*-acetal **58** <1996TL9199>. Selenocysteine can react with acetaldehyde to afford the cyclic *Se,N*-acetal **59** <2001BMCL2911>. A new and easily accessible class of chiral selenides **60** containing oxazolidine was prepared from the reaction of amino alcohols with paraformaldehyde and selenol <2002S2338>. Treatment of an aqueous or ethanolic solution of primary arylamines with formalin and NaTeH at rt provided 2*H*,6*H*-tetrahydro-1,3,5,7-ditelluradiazocines **61** as solids <2000CL870>.

Irradiation of Barton ester **62** using a 300 W sun lamp provides the corresponding *N,Se*-acetal as a 2.3/1 *syn/anti* mixture of isomers in an overall yield of 63% <1996TL2569>. In a similar manner, Barton ester **63** was transformed into the *N,Se*-acetal, **64**, by sun lamp irradiation in the presence of diphenyl diselenide in 63% yield (Equation (18)) <1998HCA268>.



## (ii) From seleno- or tellurocarbonyl compounds

It is somewhat challenging to synthesize selenocarbonyl compounds from aldehydes and ketones because of their instability and preference for oxidation and oligomerization. Despite this, there are a variety of options to access stabilized substrates. Reaction of a telluroketone–tungsten complex with a diazo compound affords telluradiazoline **65** in 76% yield [<1996CC123>](#). This process is much superior to traditional methods to arrive at the telluradiazoline by the reaction of ketone hydrazones with  $\text{TeCl}_2$  (via the *in situ* formation of a telluroketone and diazo compound) in 26% yield [<1997T8137>](#). Similarly, selenadiazoline **66** was obtained by reacting dihydrazone **66** was obtained by reacting dihydrazone with  $\text{Se}_2\text{Cl}_2$  in the presence of  $\text{Bu}_3\text{N}$  in an intramolecular fashion [<2000JOC1799>](#). Thermolysis of oxazolidinone **67** with a variety of selenoketones provides racemic selenapenamams **68a–e** in moderate yields (25–37%) [<2000T5579>](#).



## (iii) From iminium salts

No further advances have occurred in this area since the publication of chapter 4.07.1.3.1.iii in [<1995COFGT\(4\)293>](#).

## (iv) From diazoalkanes

No further advances have occurred in this area since the publication of chapter 4.07.1.3.1.iv in [<1995COFGT\(4\)293>](#).

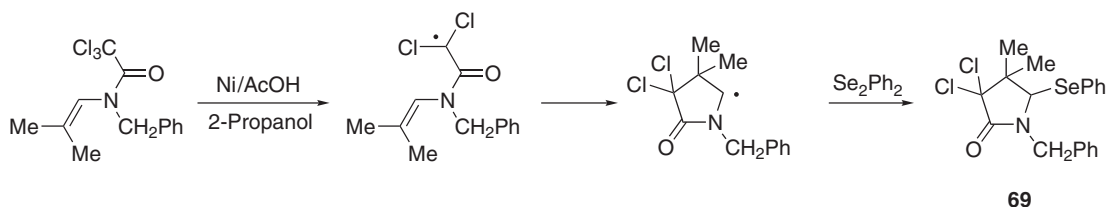
## (v) From alkenes

Selenide **69** was formed as a minor product via the capture of the  $\text{Ni}/\text{AcOH}$  promoted radical with diphenyl diselenide after an initial 5-endo-dig cyclization ([Scheme 8](#)) [<1996T1397, 1998T1029>](#).

## 4.07.1.3.2 From compounds containing singly bonded functional groups

(i) From compounds containing two singly bonded  $X\text{—C—N}$  groups ( $X = \text{Li}, \text{Na}$ )

Azabicyclo[2.2.2]octan-3-one is easily lithiated by LDA, and addition of phenylselenenyl chloride provides the 2-substituted product **70** in good yield [<2000T1139>](#). Similarly,  $\alpha$ -selenation of the ester moiety of a proline proceeded in good yields to afford **71** with the use of  $\text{LiHMDS}$  as the base and  $\text{PhSeCl}$  as the electrophile. The *N*-BOC deprotection protocol ( $\text{TFA}/\text{CH}_2\text{Cl}_2/\text{rt}$ ) gave



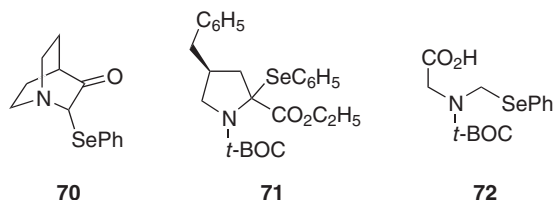
Scheme 8

the  $\Delta^1$ -pyrroline by  $\beta$ -elimination of the selenide [<1995TL6149, 1996TA2613>](#). A variety of other novel compounds, shown in [Table 6](#), were synthesized in a similar manner via lithiation and subsequent trapping with a suitable selenium electrophile [<2000AG\(E\)2175, 2000AG\(E\)694, 2000JCS\(P1\)2415, 2000JOC3716, 2002OL3329, 1996JOC7147, 1996H577>](#).

**Table 6** *N*,Se-acetal formation via lithiation and selenium trapping

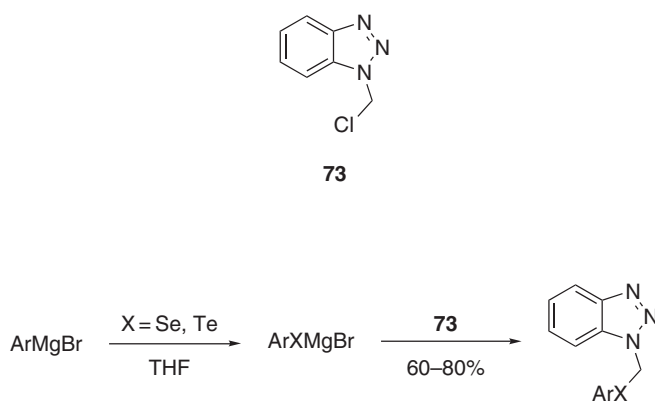
Reaction conditions	Product	References
PhSeH, TsOH, CH <sub>2</sub> Cl <sub>2</sub>		<a href="#">&lt;2000AG(E)2175, 2000AG(E)694&gt;</a>
PhSeH, TsOH		<a href="#">&lt;2000JCS(P1)2415&gt;</a>
(PhCH <sub>2</sub> Se) <sub>2</sub> , NaBH <sub>4</sub>		<a href="#">&lt;2000JOC3716&gt;</a>
NaBH <sub>4</sub> , HSePh, BF <sub>3</sub> -OEt <sub>2</sub>		<a href="#">&lt;2002OL3329&gt;</a>
(PhSe) <sub>2</sub>		<a href="#">&lt;1996JOC7147&gt;</a>
PhSeCl, AcOH		<a href="#">&lt;1996H577&gt;</a>

PhSeNa was used to open a type of  $\gamma$ -lactone ring to provide the corresponding Se,*N*-acetal, **72** <2001JOC1966>.



(ii) From silyl tellurides and magnesium arylselenolate- or tellunolate bromides

Silyl tellurides have been shown to display a unique reactivity toward a variety of electrophilic substrates, particularly in polar solvents <2000AG(E)3669, 2000OL3671>. Recently, trimethylsilyl phenyl telluride [Me<sub>3</sub>SiTePh] was reacted with 1-chloromethylbenzotriazole **73** to give the corresponding Te—C—N acetal products <2001TL5061>. A second new use for selenium and tellurium arises from the formation of magnesium arylselenolate and aryltellunolate bromides (Grignard reagents) from arylmagnesium bromide and the elemental Se and Te precursors. Reaction of the corresponding Grignard reagents with **73** provided the aryl products in good yields (Scheme 9) <2001MI477>.



Scheme 9

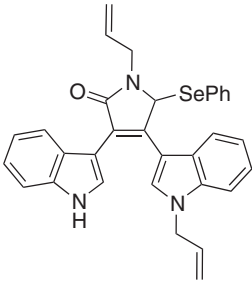
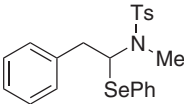
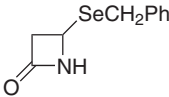
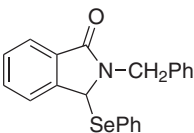
(iii) From a preformed *N,O*-acetal

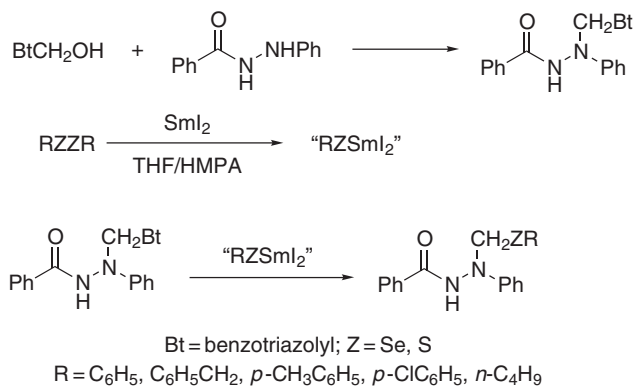
The following *N*,Se-acetals were synthesized from the *N,O*-acetal precursor under a variety of conditions as shown in Table 7 <1996JA2825, 1998HCA353, 2001TL4737, 2001TL9225>.

(iv) Miscellaneous reactions

Lu and Zhang reported that unsymmetrical  $\alpha$ -(2-arylcarbonyl-1-phenylhydrazino) diorganyl selenides (and sulfides) were synthesized through a nucleophilic displacement of benzotriazole by selenolates (or thiolates) promoted by SmI<sub>2</sub> as shown in Scheme 10 <1998SC4501>.

**Table 7** Preparation of *N*,*Se*-acetals from *N*,*O*-acetals

Reaction conditions	Product	References
PhSeH, TsOH, CH <sub>2</sub> Cl <sub>2</sub>		<1996JA2825>
PhSeH, TsOH		<1998HCA353>
(PhCH <sub>2</sub> Se) <sub>2</sub> , NaBH <sub>4</sub>		<2001TL4737>
NaBH <sub>4</sub> , HSePh, BF <sub>3</sub> ·OEt <sub>2</sub>		<2001TL9225>

**Scheme 10**

## 4.07.2 FUNCTIONS CONTAINING A CHALCOGEN AND PHOSPHORUS, ARSENIC, ANTIMONY, OR BISMUTH

### 4.07.2.1 Functions Bearing Oxygen

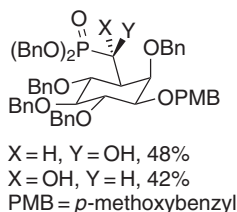
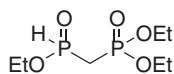
#### 4.07.2.1.1 Oxygen and phosphorus

(i) From compounds containing multiply bonded functional groups

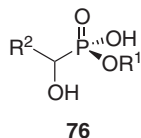
(a) From carbonyl compounds.  $\alpha$ -Heterophosphonates can be obtained by the addition of the corresponding phosphite precursor ((RO)<sub>2</sub>PX) with an aldehyde (ArCHO) via a modified

Arbromov reaction <2001TL3219>. A “green chemistry” application of a modified Arbromov reaction was recently demonstrated by the successful formation of  $\alpha$ -hydroxyphosphonates under microwave irradiation and solvent-free conditions <2002SL2633>.

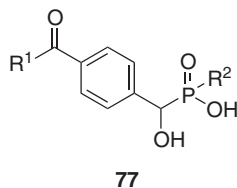
Reaction of an L-quebrachitol-derived aldehyde with lithium dibenzyl phosphite afforded two phosphonate intermediates **74** en route to the formation of phosphatidylinositol ether lipid analogs. Interestingly, the resulting analogs were shown to inhibit human colon and breast cancer cell growth in biological activity studies <2002TL2835>. The first synthetic example of *H*-phosphonylphosphonate **75** as well as a thorough study of its reactivity with a variety of aldehydes were reported (Table 8). The resulting hydroxyphosphinyl phosphonate products are particularly desirable substrates due to their significance in biological and medicinal chemistry <2001TL8451>. Both *syn*- and *anti*- $\beta$ -amino- $\alpha$ -hydroxy-*H*-phosphinates were prepared via an ALibis(binaphthoxide) (ALB)-catalyzed hydrophosphinylation of *N,N*-dibenzyl- $\alpha$ -aminoaldehydes in a diastereoselective manner <2001TL5033>. In recent years, there have also been several examples of solid-phase syntheses of a variety of O—C—P substrates, including  $\alpha$ -hydroxy phosphonates **76** as well as unsymmetrical phosphinic acids **77** (see Tables 9 and 10 <1996TL6073, 2001TL1855, 2001TL125>).

**74****Table 8** Reaction of **75** with various aldehydes**75**

Substrate	Conditions	Products	Yield (%)
	Et <sub>3</sub> N, CH <sub>2</sub> Cl <sub>2</sub> , 40 °C, 5 h		60
	Et <sub>3</sub> N, CH <sub>2</sub> Cl <sub>2</sub> , 40 °C, 5 h		47
	Et <sub>3</sub> N, CH <sub>2</sub> Cl <sub>2</sub> , 40 °C, 1.5 h		73
	K <sub>2</sub> CO <sub>3</sub> , CH <sub>2</sub> Cl <sub>2</sub> –DMF (9:1) 40 °C, 2 h		45
	Et <sub>3</sub> N, CH <sub>2</sub> Cl <sub>2</sub> , 40 °C, 3 h		50

**Table 9**  $\alpha$ -Hydroxy phosphonates **76** synthesized on solid support

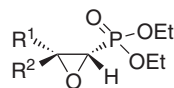
$R^1$	$R^2$	Yield (%)
H	<i>p</i> -F-Ph	86
CH <sub>3</sub> CH <sub>2</sub>	<i>p</i> -F-Ph	90
PhCH <sub>2</sub>	Pr <sup>n</sup>	87
PhCH <sub>2</sub>	Ph	92
PhCH <sub>2</sub>	<i>p</i> -MeO-Ph	77
PhCH <sub>2</sub>	<i>p</i> -F-Ph	88
PhCH <sub>2</sub>	2-Naphthyl	72
PhCH <sub>2</sub>	3-Thienyl	72
2-CF <sub>3</sub> -PhCH(CH <sub>3</sub> )	Ph	79

**Table 10** Phosphinic acid products from solid-phase synthesis

$R^1$	$R^2$	Yield (%)
OH	H	70
OH		95
OH		95
	H	95
		95
		95

(b) From other multiply bonded functional groups. (*E*)- and (*Z*)-phosphonic esters react with dioxirane in a two-phase system to provide the corresponding *trans* and *cis* isomers of diethyl 1,2-epoxyethyl phosphonate **78** <1998JOM(571)189, 2000TL9781, 2002PS(177)1153>. In

a different epoxidation example, the first asymmetric epoxidation catalyzed by cyclohexanone monooxygenase (CHMO) was recently reported to provide ee values  $\geq 98\%$  for dimethyl and diethyl vinylphosphonates <2002TL1797>.



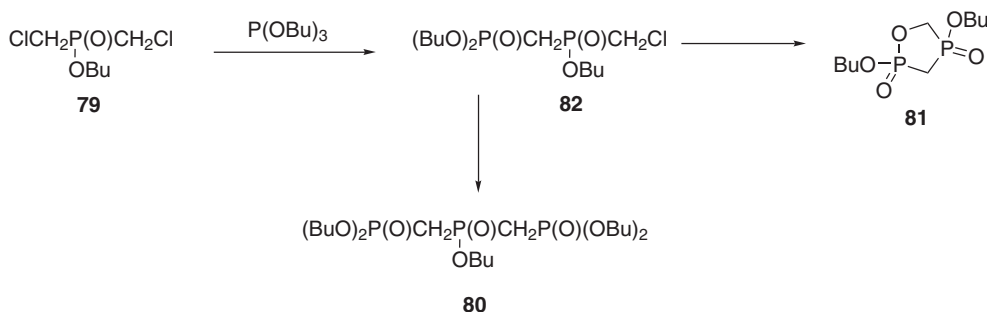
$R^1 = \text{H, Pr}^n$

$R^2 = \text{Ph, hexyl, anisyl, tolyl, naphthyl}$

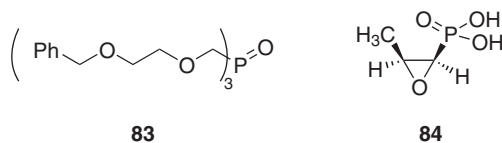
78

(ii) From compounds containing two singly bonded functional groups

(a) From  $X-C-P$  functions ( $X = \text{hal}$ ). The reaction of bis(chloromethyl) phosphinate **79** with tributyl phosphite in a 1:2 molar ratio yielded pentabutyl ester **80**, a standard Arbuzov product. Interestingly, in an equimolar ratio of the starting compounds, cyclic diphospholane **81** was obtained instead of the anticipated butyl(chloromethyl)(dibutoxyphosphorylmethyl) phosphinate **82** as shown in Scheme 11. The authors suggest that the high temperature and removal of butyl chloride from the reaction favors this cyclization <2002ZOB521>. Trisubstituted phosphine oxide **83** was obtained by the phase-transfer catalyzed Williamson reaction of tris-(chloromethyl)phosphine oxide with a slight excess of 2-benzyloxyethanol <1999HAC307>. Phosphine oxides are unique in their ability to complex hard cations, like actinides, and have the potential use to recover actinides from nuclear waste. Alkoxide displacement of  $\alpha$ -haloalkyl phosphorus compounds can provide a variety of phosphine oxides via inter- and intramolecular reactions. In the case of intermolecular reactions, tertiary phosphine oxides containing pyridine rings were obtained by the nucleophilic substitution of chloride by the sodium salts of hydroxypyridines and 8-hydroxyquinolines <1996PS(108)189>. Epoxide **84** was obtained via intramolecular nucleophilic displacement of an  $\alpha$ -bromide intermediate <1995JA2931>. Interestingly, formation of epoxide **84** completed the concise total synthesis of the natural product fosfomycin, which has been used clinically as an antibiotic.



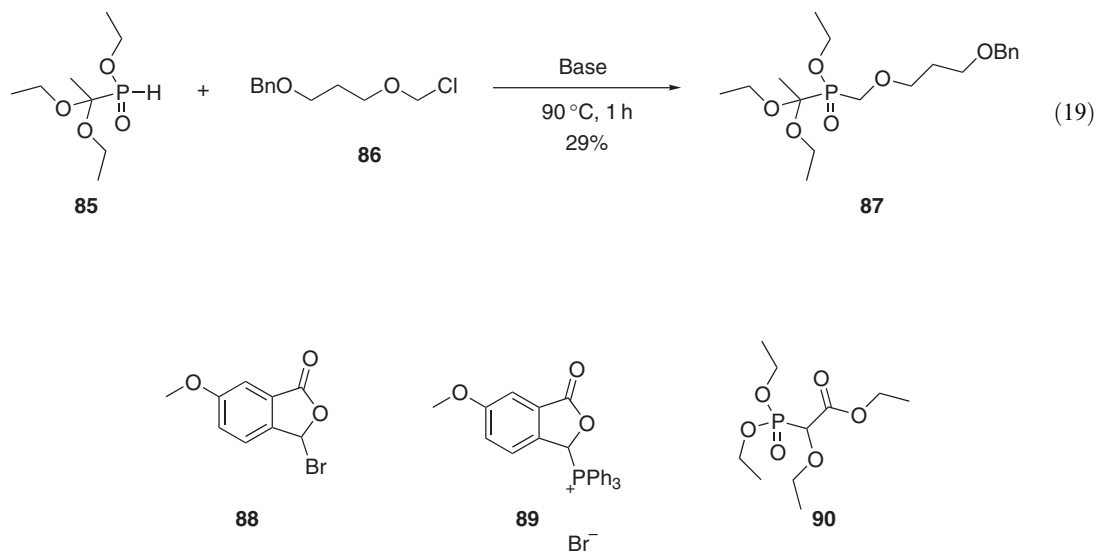
Scheme 11



(b) From  $O-C-X$  functions ( $X = \text{hal}$ ). The Arbuzov reaction remains a common approach for the formation of  $P-C$  bonds. For example, the reaction of compound **85** with chloromethyl ether **86** provided the  $O-C-P$  bond of **87**, albeit in only 29% yield (Equation (19)) <2001BMCL1451>.

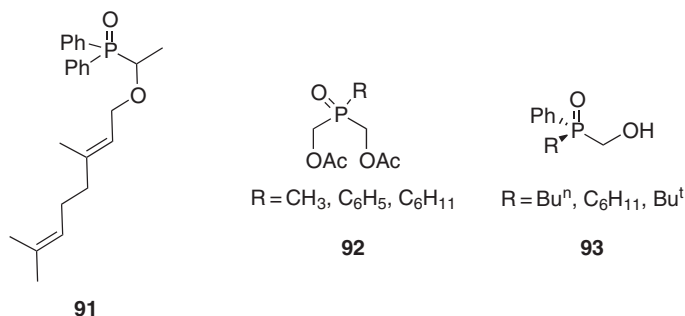


Reaction of triphenylphosphine with compound **88** provided the Wittig reagent precursor **89** <2001BMCL33>. Similarly, treatment of 2-chloro-2-ethoxyacetate with triethyl phosphite (at 150 °C) afforded triethyl 2-ethoxyphosphonoacetate **90** in 99% yield, and this was subsequently reacted with a suitable aldehyde in a Horner–Wadsworth–Emmons fashion. Notably, this sequence was successfully scaled up for use in a pilot plant <2003OPRD82>.



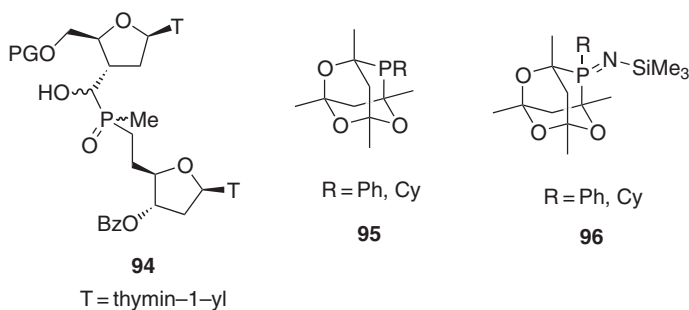
(iii) By functionalization of a preformed *O,P*-acetal

(a) *Functionalization on oxygen.* Coupling of geranyl bromide and a phosphinyl alcohol provided phosphinoyl ether **91**, which was utilized toward the synthesis of (±)-(15(*E*)) and (15(*Z*))-16-oxa-2,3-oxidosqualenes <1995TL5719>. Several phosphine oxide diacetates **92** were synthesized and subsequently reacted with a variety of enzymes in order to achieve an enzymatic resolution <2002PS(177)1557>. Optically active 1-hydroxymethylalkylphenylphosphine oxides **93** were prepared by lipase-catalyzed optical resolution in moderate-to-good yields <2001TL6569>. In an extension of this result, it was later discovered that the enzymatic resolutions were up to six times more enantioselective in the ionic liquid 1-butyl-3-methylimidazolium hexafluorophosphate (BMIM-PF<sub>6</sub>) than in most common organic solvents <2002TA735>. Calix[4]arenes bearing four diphenylphosphinylmethoxymethyl groups have been synthesized by the halogen displacement of chloromethylcalix[4]arene by diphenylmethylolphosphine oxide. These calix[4]arenes have the potential to act as binders for metal cations <2002PS(177)1537>.



(b) *Functionalization on carbon.* No further examples have occurred in this area since the publication of chapter 4.07.2.1.1.i.d.2 in <1995COFGT(4)293>.

(c) *Functionalization on phosphorus.* In a standard example of phosphorus homologation, diphenylphosphine oxide was added to acetaldehyde in the presence of catalytic triethylamine to afford diphenylphosphinoyl-1-ethanol in 96% yield <1995TL5719>. In a similar transformation, novel tertiary phosphine oxides such as **94** were synthesized to construct modified DNA analogs, which were then tested via hybridization to complementary RNA and DNA <1998SL283>. Treatment of phosphaadamantyl ligands, **95** with a slight excess of  $\text{Me}_3\text{SiN}_3$  effected oxidation to the corresponding (trimethylsilyl)phosphinimines, **96**, in high yields. The products were then treated with  $\text{CpTiCl}_3$  to afford the corresponding titanium complexes that were shown to effect only minimal catalytic activity in ethylene polymerization <2000OM3791>. In another effort to prepare ligands for catalysis, the Staudinger reaction was employed in the resolution of C2-symmetric diphosphines (BINAPFu) with an enantiopure azide to yield a 1:1 mixture of diastereomeric phosphinimines <2001JOC7478>.



#### 4.07.2.1.2 Oxygen and arsenic, antimony, or bismuth

No further examples have been reported in this area since the publication of chapter 4.07.2.1.2 in <1995COFGT(4)293>.

### 4.07.2.2 Functions Bearing Sulfur

This section outlines the chemistry of compounds containing sulfur and a group 15 element. Notably, the past decade has provided novel examples involving As, Sb, and Bi.

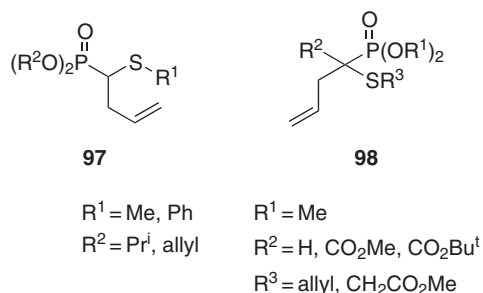
#### 4.07.2.2.1 Sulfur and phosphorus

##### (i) From compounds containing multiply bonded functional groups

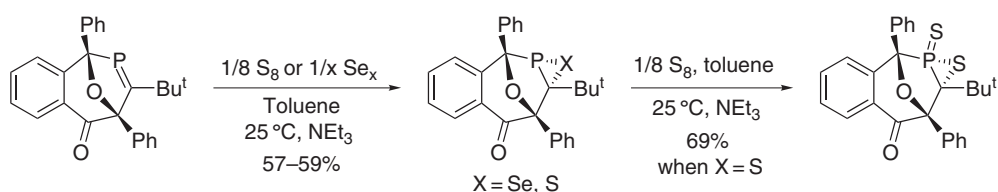
(a) *From carbonyl compounds.* For standard examples utilizing aldehydes and ketones, see chapter 4.07.2.2.1.i.a in <1995COFGT(4)293>.

(b) *From thiocarbonyl compounds.* The reaction of a trialkylphosphine ( $\text{PR}_3$ ) and carbon disulfide ( $\text{CS}_2$ ) affords a 1,3-dipolar moiety, which reacts further with either a phosphonylalkyne or phosphonylalkene to generate a reactive ylide species. This resulting ylide provides 1,3-dithiolanes after treatment with an aldehyde via a Wittig reaction <2002HAC633>.

(c) *From diazoalkanes.* There have been many examples of carbene insertion of diazoalkanes into either a C—S or S—S bond. Both copper(II) and rhodium catalysts were tested in the [2,3]-sigmatropic Wittig rearrangement of an intermediate sulfonium ylide to provide phosphonates **97** <1998S1635>. A similar example utilizing this carbene method afforded **98** as a ring-closing metathesis (RCM) precursor that was used to generate a cyclic  $\alpha$ -thiophosphonate <2001SL605, 2002JOC8123>.

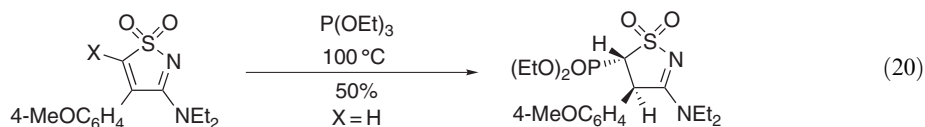


(d) *From phosphorus ylides.* The reaction of polycyclic phosphalkene with sulfur affords thiaphosphirane compounds with high selectivity (Scheme 12) <2000T6259>. Upon treatment with a second equivalent of sulfur, selective formation of thioxothiaphosphirane occurs.



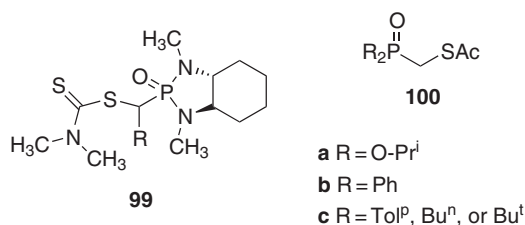
Scheme 12

(e) *From S-containing heterocycles.* Macrocyclic structures, potentially useful in molecular recognition studies, can be obtained in one step by the reaction of lithiated thiophene with the bis-electrophile, PhPCl<sub>2</sub> <1995JOC7406>. Triethyl phosphite (TEP) can be reacted with a substituted isothiazole to afford the desired product via a nucleophilic addition at the most electrophilic center (Equation (20)) <2000T5455>. Addition of triflic acid to a trithio heterocycle produces an unstable 1,3-dithiolium cation salt which was immediately reacted with triethyl phosphite to yield a Horner–Wadsworth–Emmons reagent <2001EJO933>.

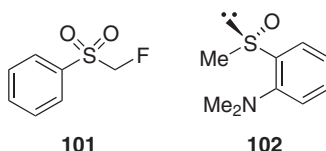


(ii) *From compounds containing two singly bonded functional groups*

(a) *From X–C–P functions (X = Hal, OTs, Li).* Lithiation of a di-phosphonic diamide followed by sulfuration with dithiuram [(CH<sub>3</sub>)<sub>2</sub>NCS<sub>2</sub>]<sub>2</sub> provided the S–C–P bond of **99** in very good yields and moderate selectivity <1996JA11668>. Displacement of a halide by a nucleophilic sulfur species is a standard method to obtain a variety of thioesters **100a,b** <2001TL5137, 2001OL9>. In the example of a tosylate displacement, the desired α-thiophosphine oxides **100c** were synthesized under milder and more versatile conditions than by utilizing the corresponding Arbuzov reaction of (*O*-ethyl) diphenylphosphinite with an appropriate (chloromethyl) thioether <1997T10527>. In general, (chloromethyl) thioethers (RS–C–X) are limited in availability, thereby further highlighting this strategy.



(b) From S—C—X functions (*X* = Hal, Li). The Arbuzov reaction of R<sub>2</sub>P(OR) and a desired S—C—X (*X* = Hal) component leads to α-thio-phosphonates readily, yet application of this reaction is limited to the relatively few α-halothioesters available commercially. Not surprisingly, there are more examples of lithiated C—S species used in recent examples. The formation of diethyl fluoro(phenylsulfonyl)methylphosphonate begins with the addition of LiHMDS to a solution of fluoromethyl phenyl sulfone **101** and diethyl chlorophosphate in THF at −70 °C <1995SC3583>. In the deprotonation of (*S*)-2,2-(*N,N*-dimethylamino)phenyl methyl sulfoxide **102**, LDA was used to generate an anion that was subsequently reacted with diethyl chlorophosphate <2000OL1451>. Both sulfinylmethyl phosphonates were then reacted with a variety of aldehydes in Horner–Emmons reactions.



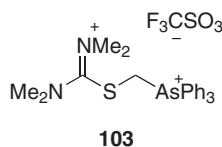
#### (iii) By functionalization of a preformed *S,P*-acetal

No further advances have occurred in this area since the publication of chapter 4.07.2.2.1.iii in <1995COFGT(4)293>.

### 4.07.2.2.2 Sulfur with arsenic, antimony, or bismuth

#### (i) Arsenic compounds

Treatment of Ph<sub>3</sub><sup>+</sup>AsCH<sub>3</sub>OTf with (Me<sub>2</sub>N)<sub>2</sub>CS provided the first S—C—As bond **103** reported to date <1998MI599>.



### 4.07.2.3 Functions Bearing Selenium or Tellurium

#### 4.07.2.3.1 Selenium or tellurium with phosphorus

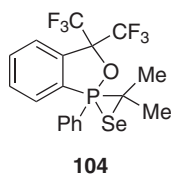
In recent years, more examples of *Se,P*-acetals have surfaced. The known compounds still appear to be restricted to those containing phosphorus(IV) or phosphorus(V) functions. *Te,P*-acetals are much less explored, therefore offering considerable promise for future research.

*(i) From phosphines*

Phosphaalkynes and elemental selenium (or tellurium) react to give the corresponding 1,2,4-selenadiphospholes <1999S1642>. In a similar synthetic pathway, phospho-tetracycles of selenium compounds were formed <2000CC1745, 2001HAC406>. These tetracyclic cage compounds have been shown to complex with tungsten and iron carbonyl fragments and have potential application in transition metal chemistry.

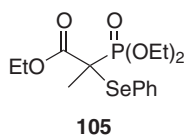
*(ii) From phosphorus ylides*

The stabilized ylide in Scheme 12 (Section 4.07.2.2.1.i.d) reacts with gray selenium at room temperature to provide a polycyclic compound with high selectivity <2000T6259>. Similarly, treatment of a phosphorus ylide and elemental selenium in THF at room temperature successfully provided selenaphosphirane **104** in excellent yield. The molecular structure was established by X-ray crystallographic analysis, thus providing a great deal of information concerning these novel structures <2002JA9706>.

*(iii) From phosphonates and phosphine oxides*

(a) *With selenium nucleophiles.* There are no recent examples using Se compounds as nucleophiles. See chapter 4.07.2.3.1.iii.a in <1995COFGT(4)293> for prior examples.

(b) *With selenium electrophiles.* This is the most commonly used method for compounds containing a phosphorus(V) functional group. Phosphonates bearing either a  $\beta$ -carbonyl group or an  $\alpha$ -sulfoxide are easily deprotonated ( $\text{Bu}^n\text{Li}$ , THF,  $-78^\circ\text{C}$ ) and subsequently selenenylated with  $\text{PhSeX}$  ( $\text{X} = \text{Br}, \text{Cl}$ ). Compound **105** <2001TL619> was obtained by this procedure. This compound is most often used to obtain vinyl phosphonates via selenoxide elimination.



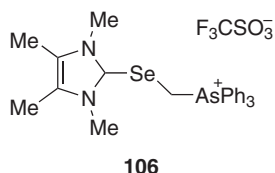
Lithiation of difluoromethylphosphonates followed by quenching with  $\text{PhSeCl}$  or  $\text{PhSeSePh}$  yields the corresponding selenyldifluorophosphonate, a good source of phosphonodifluoromethyl radicals <2001OL185>. Phosphorylated allenes can be deprotonated using LDA in THF and trapped with  $\text{PhSeCl}$  to provide phenylseleno-substituted phosphorylated allenes <2000PS(166)265>.

**4.07.2.3.2 Selenium or tellurium with arsenic, antimony, or bismuth**

There is only one example of a function with  $\text{Se-C-As}$  units possessing an  $sp^3$  hybridized carbon. Similar examples incorporating  $\text{Se-C-Sb}$  or  $\text{Se-C-Bi}$  remain unknown and unexplored.

## (i) From a selenediamide

Treatment of a selenide with triphenylarsenic triflate affords the triphenylselenenylarsenic salt **106** in 95% yield <1998MI599>.



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## Biographical sketch



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## 4.08

# Functions Incorporating a Chalcogen and a Silicon, Germanium, Boron, or Metal

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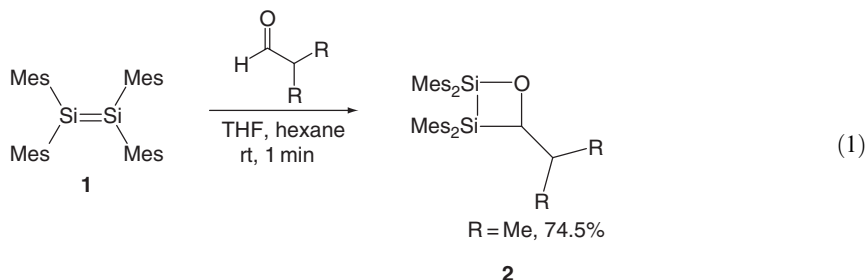
**4.08.1 FUNCTIONS CONTAINING A CHALCOGEN AND A METALLOID****4.08.1.1 Functions Bearing Oxygen****4.08.1.1.1 Oxygen and silicon— $R_2^I C(OR^2)SiR_3^3$ , etc.**

The major synthetic pathways leading to systems containing an oxygen with an  $\alpha$  silicon have been reviewed in COFGT (1995). The various routes included are those from halomethyl silanes, which involve displacement of the halide from a halomethylsilane with an oxygen nucleophile, from the reduction of acyl silanes with LAH,  $NaBH_4$ , and borane–methyl sulfide complex, from aldehydes and ketones, which involves nucleophilic addition with silyl anions, from the hydroboration of vinyl silanes, from epoxidation of vinyl silanes, from alkoxy silanes which involves the rearrangement of alkoxy silanes to  $\alpha$ -hydroxysilyl anions under conditions of strong base—the mechanism of which appears more closely related to the Brook rearrangement. The trapping of metallated ethers, nitriles, esters, and amides with trialkylchlorosilanes yields the corresponding  $\alpha$ -silyl compounds.

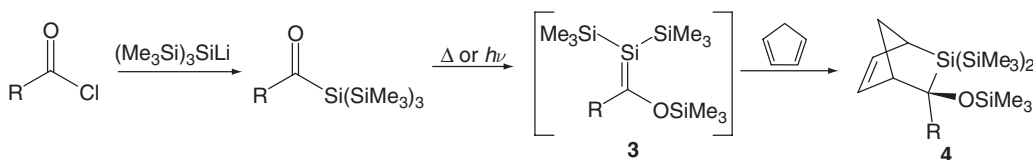
Moser has recently published a review on silicon compounds <2001T2065>. The major synthetic pathways to generate systems containing oxygen with an  $\alpha$  silicon are reviewed below.

*(i) From silenes*

2-Methylpropionaldehyde reacted with tetramesityldisilene **1** to give the corresponding cycloaddition product **2** in 74.5% yield (Equation (1)) <1996JOM363>.



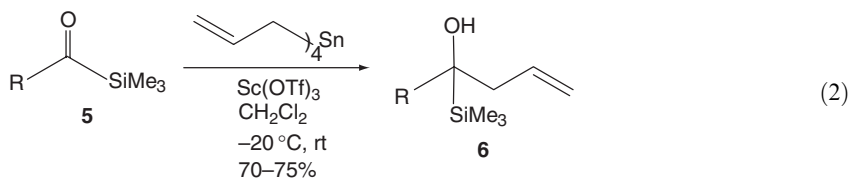
The siloxysilene **3** derived from thermolysis of benzoylpolysilane underwent a facile *in situ* cycloaddition with a range of dienes to produce the corresponding cycloadducts **4** with modest-to-good diastereoselectivity (Scheme 1) <1996TL2491>.



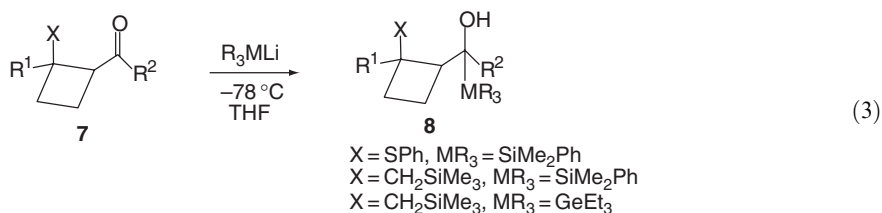
Scheme 1

*(ii) By nucleophilic addition*

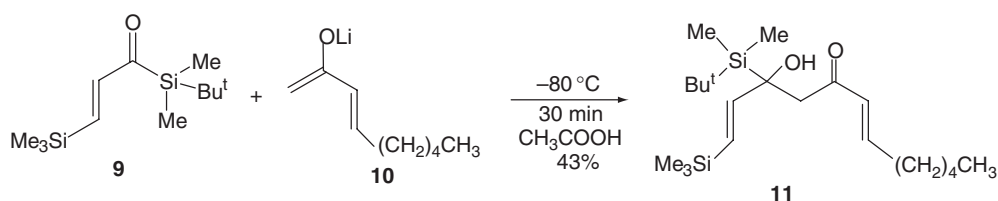
The allylation of acyl silanes **5** with tetraallyltin in the presence of catalytic amounts of  $Sc(OTf)_3$  proceeded smoothly to afford the silylated homoallylic alcohols **6** in good yields (Equation (2)) <1998TL6737>.



The diastereoselective addition of dimethylphenylsilyllithium to the *trans*-2-phenylthiocyclobutyl ketones **7** provided cyclobutanemethanol derivatives **8**. The Lewis acid-promoted stereospecific ring-opening reactions of the resulting cyclobutanemethanol derivatives has been studied. Similar diastereoselective addition of triethylgermyllithium to *trans*-2-phenylthiocyclobutyl ketones has also been reported (Equation (3)) <1997T8349>.

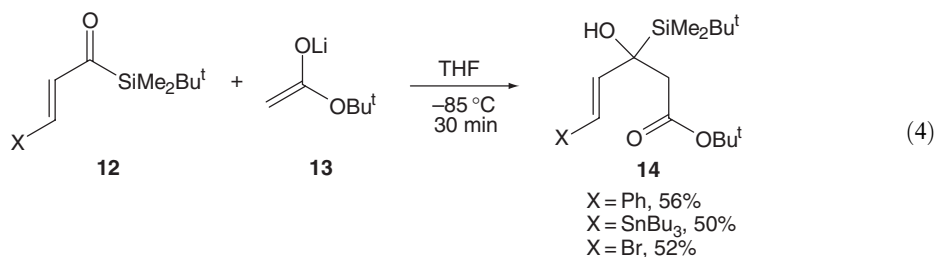


Reactions of the (*E*)- and (*Z*)-isomers of ( $\beta$ -(trimethylsilyl)acryloyl)(*t*-butyl)dimethylsilanes **9** with lithium enolate **10** of  $\alpha,\beta$ -unsaturated methyl ketones at  $-80$  to  $-30$  °C afforded the corresponding silylated alcohols **11** (Scheme 2) <1998JA4947>.

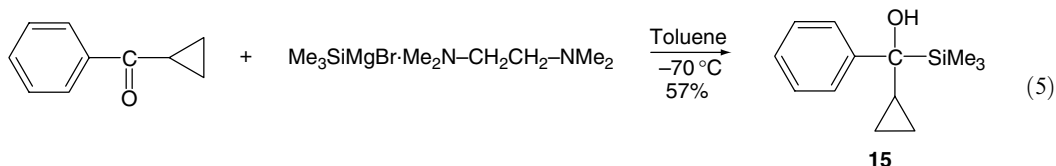


Scheme 2

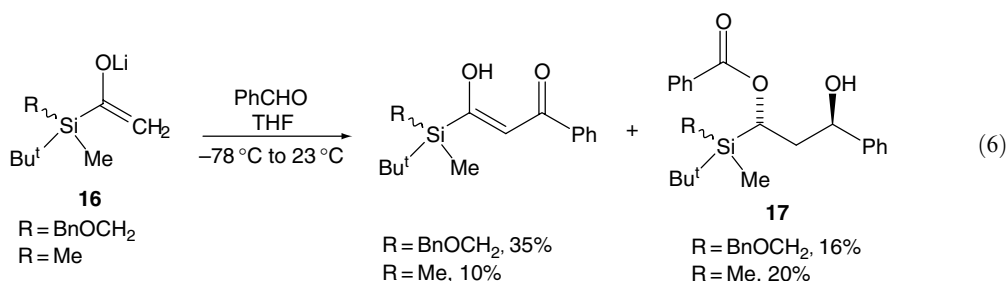
The acyl silanes **12** reacted with lithium enolate **13** derived from the *t*-butylacetate to provide the corresponding silylated alcohols **14** (Equation (4)) <1998TL5243>.



The amine-stabilized trimethylsilylmagnesium halides reacted with cyclopropyl phenyl ketone to provide the corresponding silylated alcohols **15** (Equation (5)) <1995AG(E)1030>.

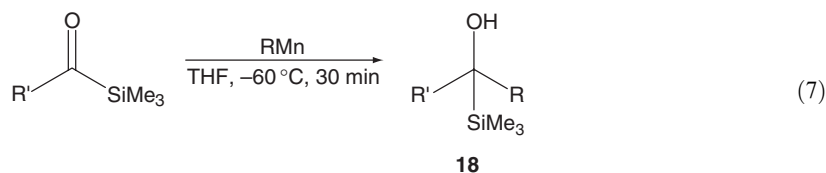


The reaction of acyl silane-enolates **16** with benzaldehyde gave rise to  $\alpha$ -benzoyloxy- $\gamma$ -hydroxysilanes **17** in a reaction cascade involving aldol addition, hemiacetal formation, stereospecific intramolecular Cannizzarro-type disproportionation, and transesterification. This reaction pathway was supported by the separate transformation of the proposed intermediates to the final products (Equation (6)) <1995T3749>.

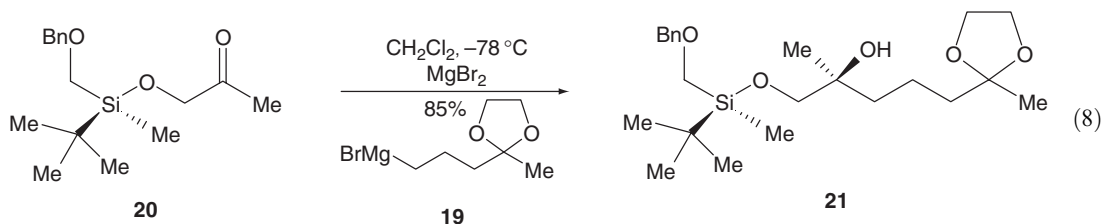


The reaction of bis(acyl silanes) with trifluoromethyltrimethylsilane (TFMTMS) resulted in a new family of 2,2-difluoro-3-trialkylsilyl ketols. These compounds were submitted to a facile and effective defluorosilylation. The overall process constituted a new synthesis of cyclic six- and seven-membered 2-fluoro-1,3-diketones with regiospecific introduction of fluorine. The keto–enol equilibrium of cyclic 1,3-diketones and the mechanism of the defluorosilylation reaction were also studied <2001JOC4543>.

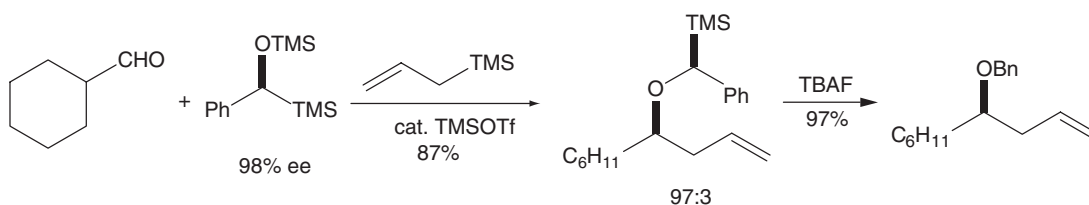
Organomanganese halides and organomanganates prepared by transmetalation of organolithium and Grignard reagents added smoothly to the carbonyl group of acyl silanes and of the substituted aldehydes bearing a chiral center at the  $\alpha$ -position affording the desired alcohols **18** in good-to-excellent yields and with essentially no undesired products from enolization. Comparison of the stereochemical outcome with that observed for other organometallic species outlined the capability of organomanganese reagents to induce uniformly good diastereoselectivities in a number of cases significantly higher than reported previously for these reactions. The key role displayed by the trimethylsilyl group in promoting high 1,2-asymmetric induction clearly emerged in the comparison of acyl silane with the corresponding aldehyde. The sense of the Cram/anti-Cram selectivity depended upon the nature of the carbonyl reagents engaged in these reactions (Equation (7)) <2001JOM223>.



Chiral silicon groups, attached as protective groups in proximity to a prostereogenic functionality by means of an ether linkage, can act as efficient stereochemical directors, at least in specific cases. The addition of Grignard reagent **19** to  $\alpha$ - and  $\beta$ -silyloxy carbonyl compounds such as **20** (silyloxy is the stereogenic (Me<sub>3</sub>C)(BnOCH<sub>2</sub>)MeSiO-group) afforded the respective product **21** with stereofacial selectivity of up to 85%. The source of the selectivity was discussed along with its dependence upon structural parameters (Equation (8)) <2002T5885>.

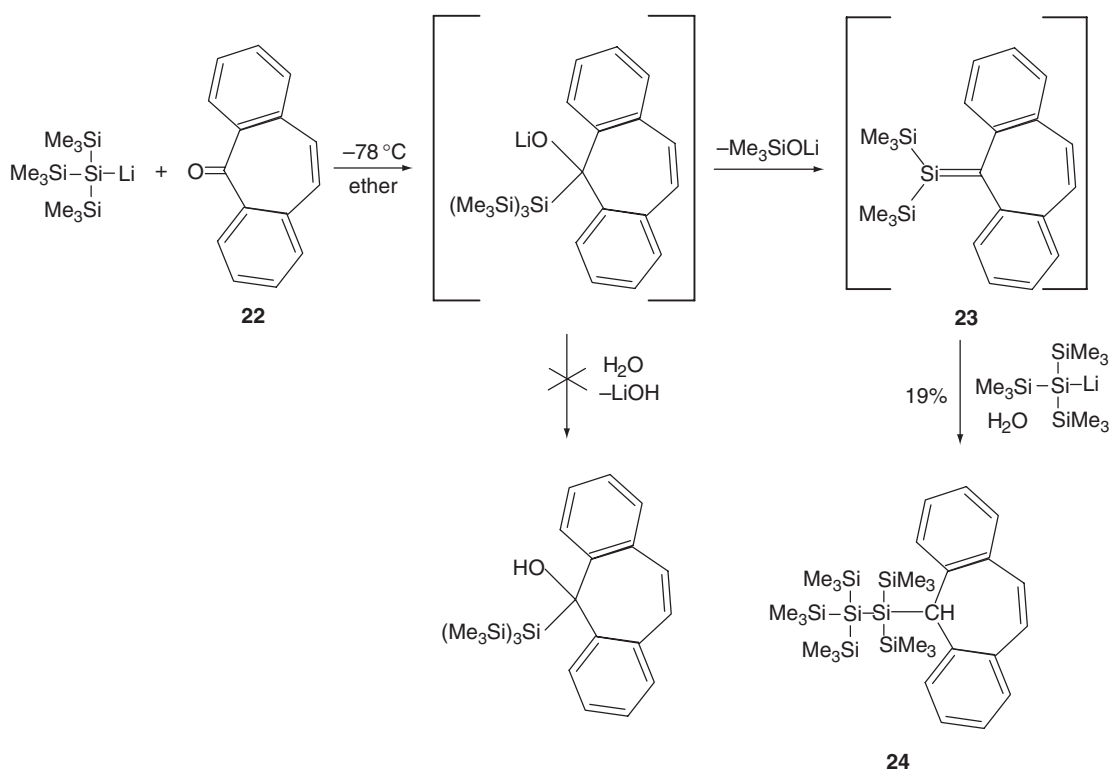


Enantiopure (*S*)- $\alpha$ -(trimethylsilyl)benzyl alcohol (98% ee) was prepared by Noyori's transfer hydrogenation of benzoyltrimethylsilane. The corresponding trimethylsilyl ether was subjected to Marko's silyl-modified Sakurai conditions with a variety of aldehydes to afford homoallylic ethers in high diastereoselectivity. The practicality of the  $\alpha$ -trimethylsilylbenzyl group as an oxocarbenium ion auxiliary was further demonstrated by its efficient deprotection or conversion to a benzyl protecting group (Scheme 3) <2002OL147>.



Scheme 3

Tris(trimethylsilyl)silyllithium reacted with dibenzosuberone **22** in ether to give, after carbonyl addition of the lithium silanide and lithium trimethylsilanolate elimination according to a modified Peterson mechanism, the transient silene **23** which was trapped by addition of the excess tris(trimethylsilyl)lithium to the silicon–carbon double bond to afford the corresponding silane **24** (Scheme 4) <1996JOM185>.



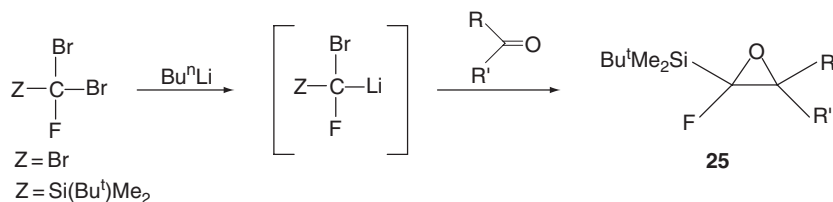
Scheme 4

Lewis acid-catalyzed reaction of allyl- and benzyltrichloroacetimidates with  $\alpha$ -silyl alcohols was found to be a general method for the synthesis of  $\alpha$ -alkoxysilanes. Upon exposure to CsF, these  $\alpha$ -alkoxysilanes could be made to undergo a [2,3]-Wittig rearrangement with an efficiency similar to that realized by the analogous but inherently more toxic  $\alpha$ -alkoxystannanes <1999OL1111>.

A carbenoid reagent was generated by treatment of dibromofluoromethyl(*t*-butyl)dimethylsilane with *n*-butyllithium in THF at  $-78^\circ\text{C}$  and was allowed to react with aldehydes and ketones to give 1-fluoro-1-silyloxiranes **25** in good yields. Alkylation of the silyl-substituted carbenoid was also achieved efficiently in good yields (Scheme 5) <1997TL4591>.

Addition of benzaldehyde to an ethereal solution of *t*-butyldimethylsilyldibromomethylithium, derived from *t*-butyldimethylsilyldibromomethane and lithium diisopropylamide, provided  $\alpha$ -bromo- $\alpha$ -silyl ketone. The use of ketone instead of aldehyde afforded  $\alpha$ -bromoacyl silane via the bromosilyl epoxide intermediate. Further treatment of the  $\alpha$ -bromo- $\alpha$ -silyl ketone with *n*-butyllithium afforded lithium enolate, which provided  $\beta$ -hydroxy- $\alpha$ -silyl ketone upon treatment with

aldehyde in ether. The enolate gave the  $\alpha,\beta$ -unsaturated ketone or the monosilyl ether of 2-acyl-1,3-diol in tetrahydrofuran instead of the ether. The use of isopropylmagnesium bromide in place of *n*-butyllithium also resulted in a formation of the corresponding magnesium enolate <1996T14533>.



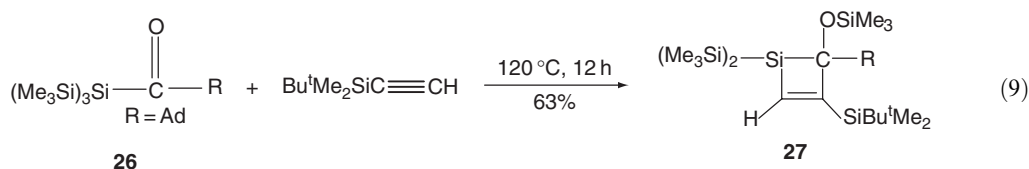
Scheme 5

A series of acyl silanes including aliphatic-, aromatic-, and bis-acyl silanes, as well as the acyl silanes bearing other substituents such as a bromine atom and alkenyl, succinimide, and carbonyl groups, were prepared, and their reactions with samarium diiodide or tributylstannane were studied. The acyl silanes underwent transformations such as reductions, reductive alkylations, intramolecular radical cyclizations, pinacol couplings, aldol reactions, and Tishchenko reactions, depending on the nature of the substrates and reaction conditions. Acylsilanes were generally reduced to give the corresponding  $\alpha$ -silyl alcohols without transfer of silyl groups. Intramolecular radical cyclizations of 5-hexenoylsilanes and 1-silyl-1,5-pentanedione were realized to give  $\alpha$ -silylcyclopentanols and 1,2-cyclopentanediol derivatives, respectively. On treatment with samarium diiodide in tetrahydrofuran, 1-(trimethylsilyl)-1,6-hexanedione underwent a pinacol coupling reaction in the presence of  $\text{Bu}^t\text{OH}$ , whereas it underwent a Tishchenko reaction in the presence of  $\text{MeOH}$ . The Tishchenko reaction of 1-silyl-1,5-pentanedione gave an  $\alpha$ -silyllactone. On reaction with samarium diiodide, 1-(trimethylsilyl)-1,5-hexanedione and 1,5-bis(trimethylsilyl)-1,6-hexanedione, underwent, respectively, intramolecular aldol reactions <1996JOC1794>.

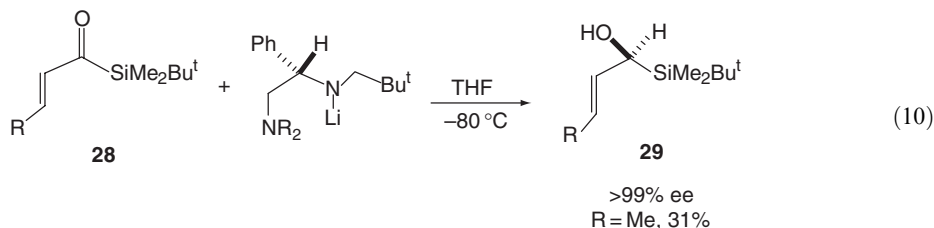
Silylated vinyloxiranes substituted on the double bond have been synthesized and reacted under very mild conditions in the presence of a catalytic amount of palladium(0). They rearranged into  $\alpha$ -silylated- $\beta,\gamma$ -unsaturated aldehydes not only with complete chirality transfer but also with total retention of the double bond stereochemistry <1997TL5493>.

Optically active 2-alkylcyclopropanecarboxylic acids were efficiently synthesized from the chiral  $\alpha$ -hydroxytrimethyl silanes via a diastereoselective cyclopropanation as the key step <1998TL4311>.

The reaction of adamantoyltris(trimethylsilyl)silane **26** with *t*-butyldimethylsilylacetylene at  $120^\circ\text{C}$  proceeded to give 2-adamantyl-3-*t*-butyldimethylsilyl-2-trimethylsiloxy-1,1-bis(trimethylsilyl)-1-silacyclobut-3-ene **27** in 63% isolated yield (Equation (9)) <2000JOM248>.

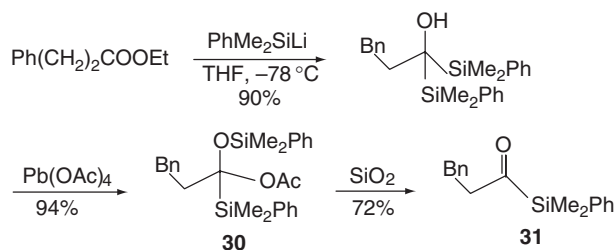


Reaction of  $\beta$ -substituted acryloylsilanes **28** with lithium amides afforded  $\alpha$ -silylallylic alcohols **29** in high enantiomeric excess (>99%) via the formal hydride transfer from the chiral lithium amide (Equation (10)) <1999OL237>.



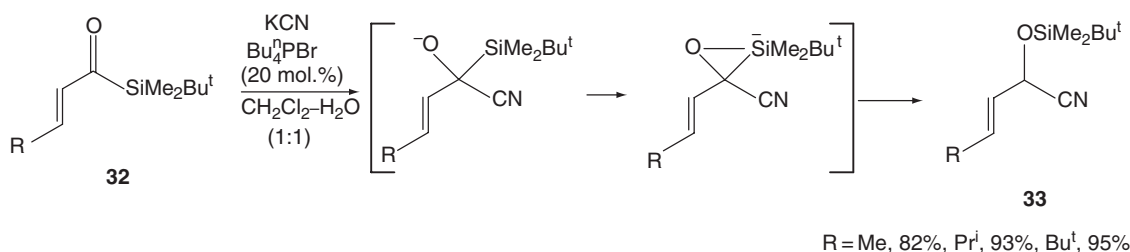
The reaction of lead tetraacetate with the  $\alpha,\alpha$ -disubstituted  $\alpha$ -silyl alcohol, readily available via the nucleophilic addition of dimethylphenylsilyllithium with an ester, proceeded to give the  $\alpha$ -silyloxy dimethylphenylsilyl compound **30**. This material upon reaction with silica provided acylsilane **31** in 72% yield (Scheme 6) <2000JOC2292>.





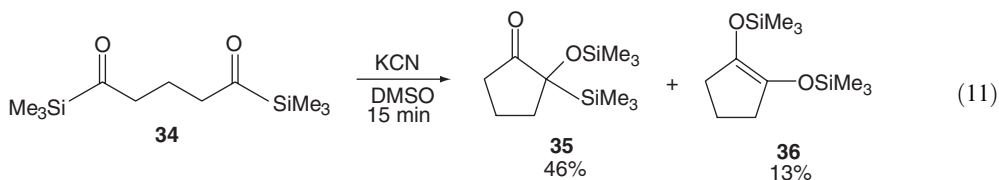
Scheme 6

The reactions of acyl silanes **32** with KCN under liquid–liquid phase-transfer catalytic conditions proceeded smoothly via the Brook rearrangement to produce *O*-silylated cyanohydrin derivatives **33** in excellent yields (Scheme 7) <2000TL4169>.

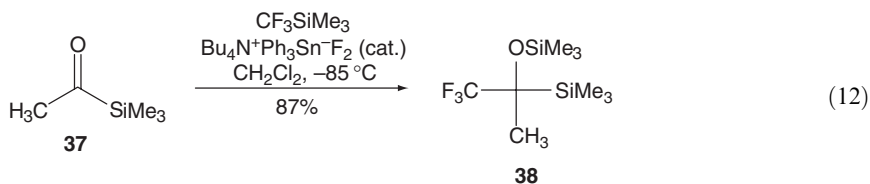


Scheme 7

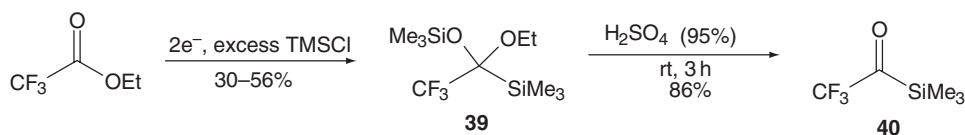
Cyclization of 1,5-bis(acyl silanes) **34** with potassium cyanide gave new silylated cyclopentanones **35** and **36** via a multistep sequence combining nucleophilic addition, two silyl migrations, and  $\beta$ -elimination. The nature of the products was very dependent on the competition between [1,2] carbon-to-oxygen and [1,4] oxygen-to-oxygen silyl migration (Equation (11)) <2001TL6535>.



The reaction of an acyl silane **37** under catalysis by trimethylsilyl trifluoromethanesulfonate in dichloromethane provided the corresponding trimethylsilyl ether of methyl(trifluoromethyl)-trimethylsilyl carbinol **38** (Equation (12)) <2001JOC4348>.



A practical synthesis of trifluoroacetyltrimethyl silane **40** was achieved via its ethyltrimethylsilyl ketal **39**. It involved electrochemical reduction of the ethyltrifluoroacetate to the corresponding ketal, which upon treatment with sulfuric acid provided acyl silane in 86% yield (Scheme 8) <2003TL3741>.

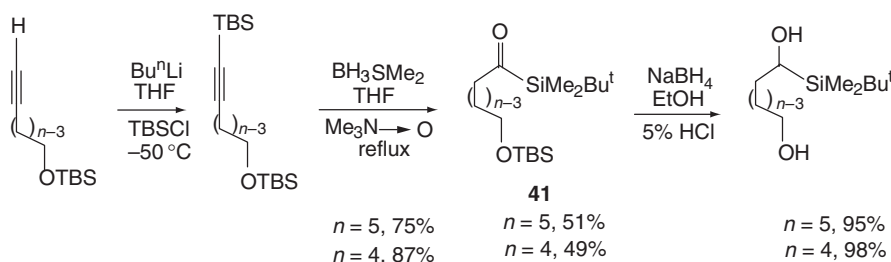


Scheme 8

The 4,6-dideoxyfuranoses have been synthesized by starting from the readily available (*E*)-5-dimethylphenylsilyl-2-hexene-4-ol and employing successively three versatile oxyfunctionalization methods, namely photooxygenation, metal-catalyzed epoxidation, and oxidative desilylation <2001JOC7365>.

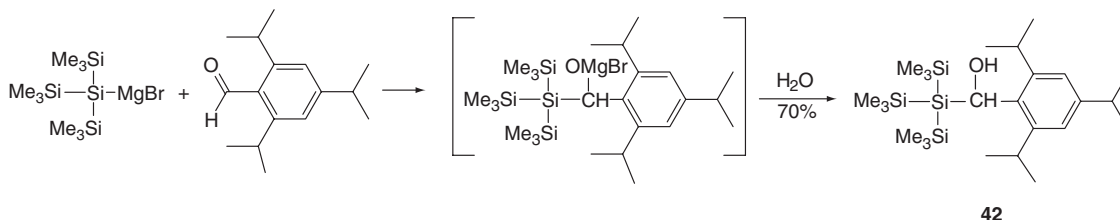
The generation and reactions of oxiranyl anions stabilized by a trifluoromethyl group are described. Treatment of (*S*)-2,3-epoxy-1,1,1-trifluoropropane (75% ee) with Bu<sup>n</sup>Li followed by electrophiles gave the corresponding 2-alkylated epoxide with retention of stereochemistry in moderate-to-good yields. The reaction was applicable to a general synthesis of optically active trifluoromethylated tertiary alcohols <2002OL173>.

The terminal alkyne was deprotonated with *n*-butyllithium followed by silylation *t*-butyldimethylsilyl chloride. Hydroboration followed by oxidation provided the corresponding acyl silane **41**, which was reduced to silyl alcohol by sodium borohydride (Scheme 9) <1999SL705>.



Scheme 9

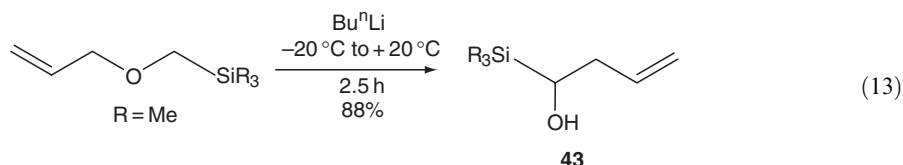
Tris(trimethylsilyl)silylmagnesium bromide underwent nucleophilic addition to 2,4,6-triisopropylbenzaldehyde followed by hydrolysis to provide the corresponding silyl alcohol **42** (Scheme 10) <1997JOM185>.



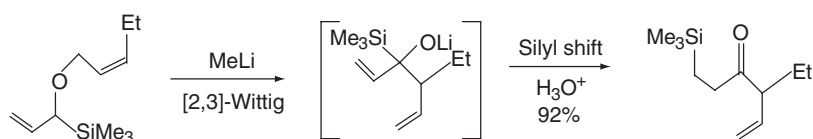
Scheme 10

### (iii) By Wittig rearrangement

A Wittig–Still-type [2,3]-sigmatropic rearrangement of (trimethylsilyl)methyl allyl ethers via silicon–lithium exchange to provide the silylated alcohols **43** has been developed (Equation (13)) <1996TL2403>.



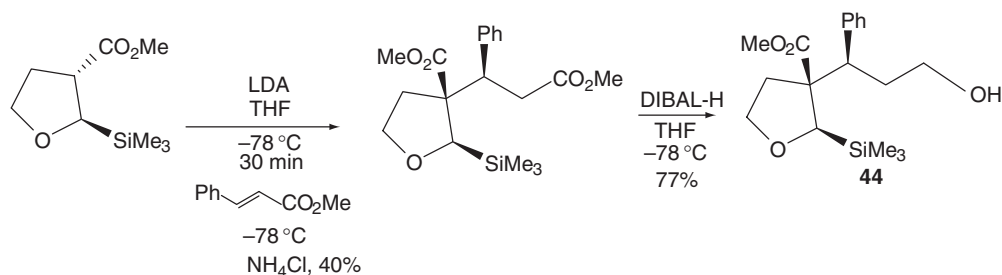
Wittig rearrangements of  $\alpha$ -alkoxysilanes, promoted by the action of methyllithium, were studied. Depending on both the substrate and reaction conditions employed, [2,3]-, [1,2]-, or [1,4]-Wittig rearrangements can be realized. These rearrangements were shown to be initiated by either Si/Li exchange or deprotonating  $\alpha$  to the silane. Furthermore, the sigmatropic shifts can often be followed by other synthetically useful *in situ* chemical events (Scheme 11) <1999OL1115>.



Scheme 11

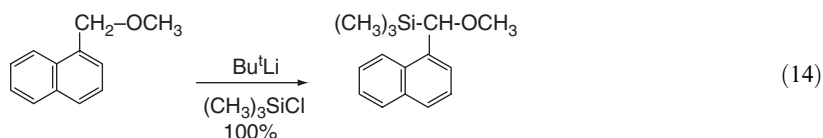
(iv) From deprotonation

Methyl (2-trimethylsilyl)tetrahydrofuran-3-carboxylates were deprotonated with LDA to form the enolates, which underwent Michael reaction with methylcinnamate. It was believed that the silicon moiety in such substrates controlled the sense of asymmetric induction observed in Michael reactions of the derived enolates with methylcinnamate. The LAH reduction of the conjugate addition product gave the corresponding alcohol **44** (Scheme 12) <1996TL9119>.

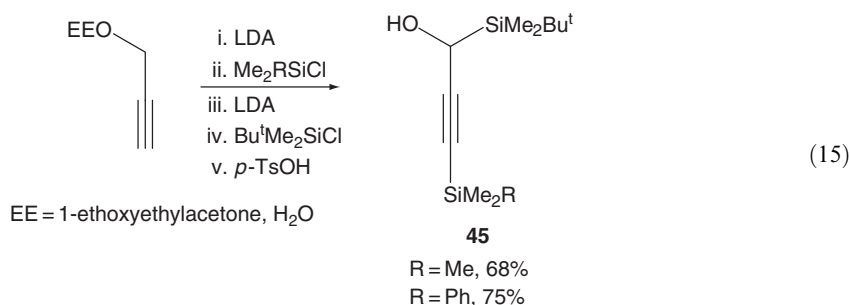


Scheme 12

[Methoxy(trimethylsilyl)methyl]arenes were readily prepared by reactions of chlorotrimethyl silane with ( $\alpha$ -methoxy)arenylmethyllithium reagents as obtained from (methoxymethyl)arenes and *tert*-butyllithium (Equation (14)) <1999JOC4247>.

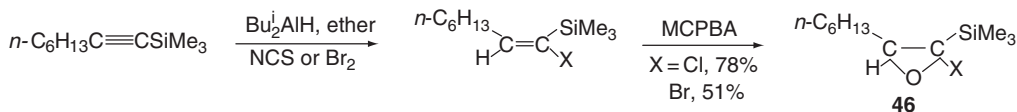


It has been reported that the propargylic ether was deprotonated with lithium diisopropylamide followed by silylation to provide the corresponding silylated alkyne. Further treatment with lithium diisopropylamide followed by reaction with *t*-butyldimethylchlorosilane and deprotection of ethoxyethyl group with *p*-toluenesulfonic acid provided the corresponding  $\alpha$ -hydroxysilanes **45** (Equation (15)) <2002JOC1786>.



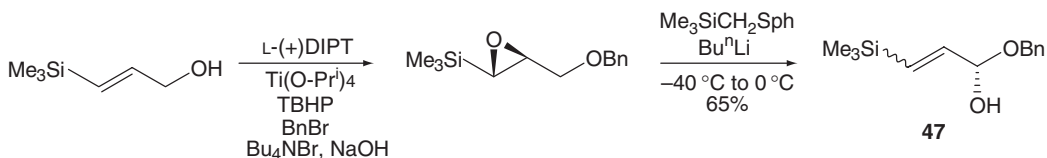
## (v) From silylated alkenes

The preparation of 2-halo-2-trimethylsilyloxirane **46** was achieved by the hydroalumination of an alkynylsilane with diisobutylaluminum hydride followed by halogenation with either halogens or NCS and further epoxidation with MCPBA. Treatment of 2-halo-2-trimethylsilyloxirane with metal salts such as  $\text{ZnCl}_2$ ,  $\text{ZnBr}_2$ ,  $\text{NaI}$ , and  $\text{AgBF}_4$  gave the corresponding  $\alpha$ -haloacylsilanes in good yields (Scheme 13) <1995TL5353>.



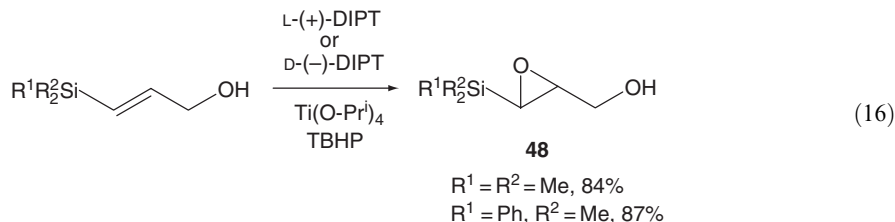
Scheme 13

3-(Trimethylsilyl)allyl alcohol was epoxidized followed by phase-transfer benzylation to yield an epoxide, which was reacted with *n*-butyllithium to give, after aqueous work-up, a vinyl silane **47** (Scheme 14) <1996TA763>.



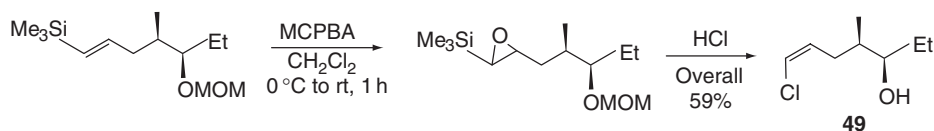
Scheme 14

Catalytic epoxidation of the allylic alcohols using D-(–)-diisopropyltartrate (DIPT) or L-(+)-DIPT afforded the corresponding epoxides **48** (Equation (16)) <1995TA577>.



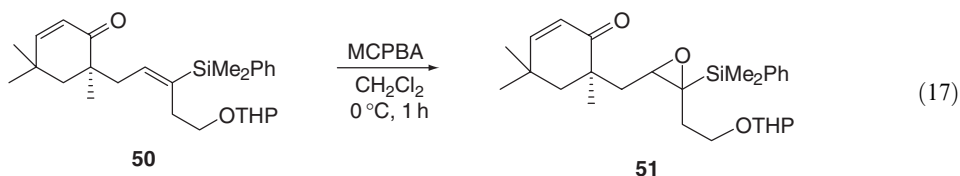
Cyclopropanation of the title compounds was possible under certain conditions ( $\text{CH}_2\text{I}_2/\text{Sm}(\text{Hg})$ ) in special cases, but epoxidation of these alkenes is apparently a general reaction, which occurred readily in a stereospecific manner with *m*-chloroperbenzoic acid <1995JOM239>.

The *Z* vinyl chloride **49** was prepared in a simple way from vinyl silane by oxidation with *m*-chloroperbenzoic acid, followed by treatment with hydrochloric acid in 59% overall yield (Scheme 15) <2000EJO3581>.

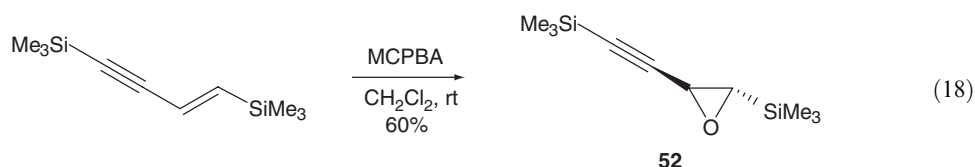


Scheme 15

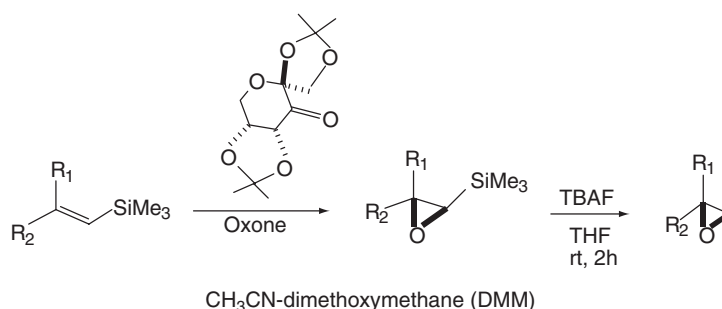
The one-pot epoxidation of the cyclohexenone derivative **50** with MCPBA provided the corresponding  $\alpha$ -silylated epoxide **51** (Equation (17)) <2001TL9123>.



A new chemoselective approach to the synthesis of an epoxide containing an  $\alpha$ -trimethylsilyl group and the trimethylsilyl-substituted ethynyl group **52** has been developed based on (3*E*)-1,4-bis(trimethylsilyl)-3-buten-1-yne (Equation (18)) <2001T549>. A simple epoxidation reaction, followed by regioselective  $\alpha$ -opening of the epoxide ring by metal halides afforded the corresponding halohydrins with a high degree of stereoselectivity. A subsequent  $\beta$ -elimination reaction from these compounds leads to (*Z*),(*E*)-dienylhalides and to (*Z*)-enynyl halides <2001T549>.



The epoxidation of 2,2-disubstituted vinyl silanes using a fructose-derived chiral ketone as catalyst and oxone as oxidant provided 2,2-disubstituted  $\alpha,\beta$ -epoxysilanes with high enantioselectivity (Scheme 16) <1999JOC7675>.

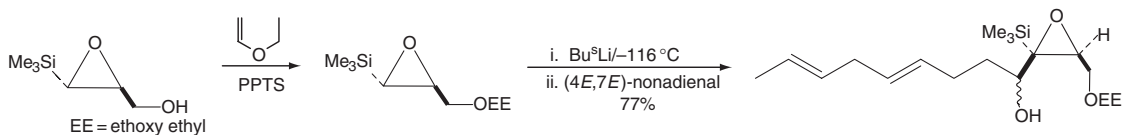


Scheme 16

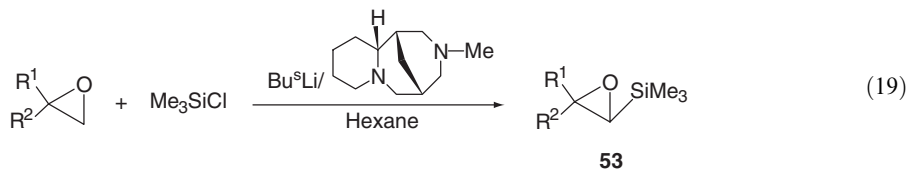
#### (vi) From epoxides

(+)-Cerulenin, a potent fungal inactivator of fatty acid synthases, has been prepared in optically pure form by a sequence involving reaction of a chiral oxiranyllithium with (4*E*), (7*E*)-nonadienal. The synthesis of the former took advantage of a particularly favorable Sharpless epoxidation and metalation to a configurationally stable organolithium, while the latter was available in quantity by a direct and improved route (Scheme 17) <1997JOC636>.

The presence of a suitable diamine ligand is the key to achieving ring lithiation–substitution of epoxides without the need for activating substituents on the epoxide and constituted a new synthetic entry to *trans*- $\alpha,\beta$ -epoxysilanes **53** (Equation (19)) <2001OL461>.

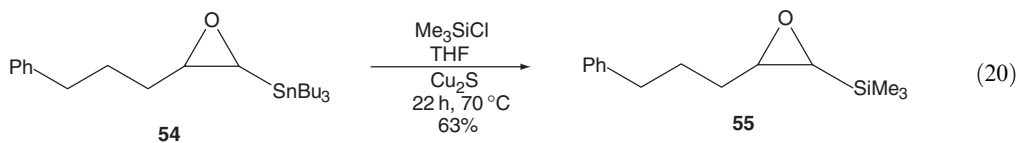


Scheme 17

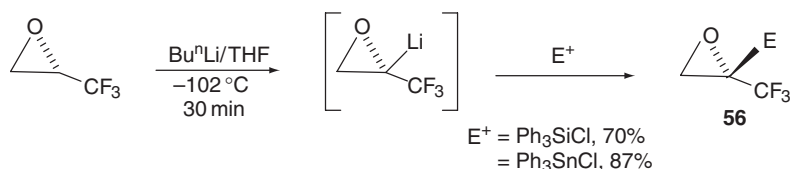
**Table 1** Direct synthesis of  $\alpha,\beta$ -epoxy silanes from epoxides

Epoxide	Product	Yield (%)
		73
		71
		61
		74
		65
		67
		71

Copper(I) sulfide mediated the cross-coupling in tetrahydrofuran of  $\alpha$ -stannylepoxide **54** with an electrophile such as trimethylsilyl chloride and afforded  $\alpha$ -trimethylsilyl epoxide **55** in moderate yield (Equation (20)) <1997SL481>.



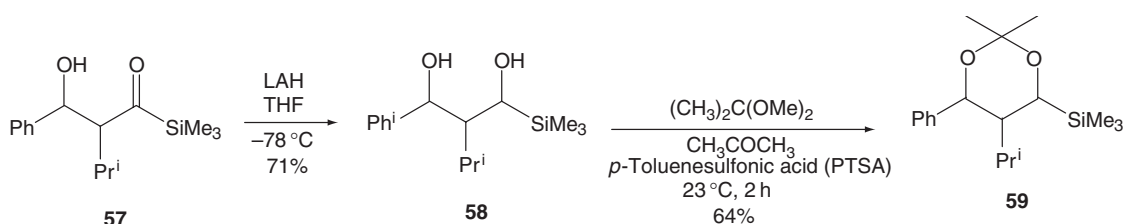
Treatment of (*S*)-2,3-epoxy-1,1,1-trifluoropropane with *n*-butyllithium followed by electrophiles such as triphenylsilyl chloride and triphenyltin chloride provided the corresponding 2-silyl and 2-stannylsubstituted epoxides **56** (Scheme 18) <2002OL173>.



Scheme 18

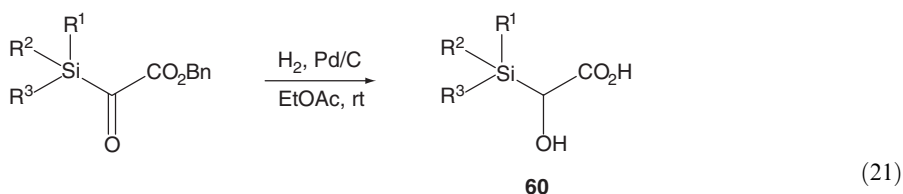
## (vii) From the reduction of carbonyl compounds

The acyl silane **57** was reduced with LAH to give 1,3-dihydroxypropylsilane derivative **58** which was treated with acetone dimethylacetal affording the 2-silyl-1,3-dioxane derivative **59** (Scheme 19) <2002T6815>.



Scheme 19

Rhodium-catalyzed oxygen transfer was used to generate benzyl 2-silyl-2-oxoacetates in good yields. The hydrogenation of these compounds led to chiral  $\alpha$ -silyl-substituted  $\alpha$ -hydroxyacetic acids **60** (Equation (21)) <2002OL2265>. Resolution by means of HPLC using a chiral stationary phase afforded an enantiomerically pure representative of this class of compounds, which was successfully applied as a chiral ligand in an asymmetric aldol-type reaction <2002OL2265>.



$\text{R}^1 = \text{R}^2 = \text{R}^3 = \text{Me}, 78\%$

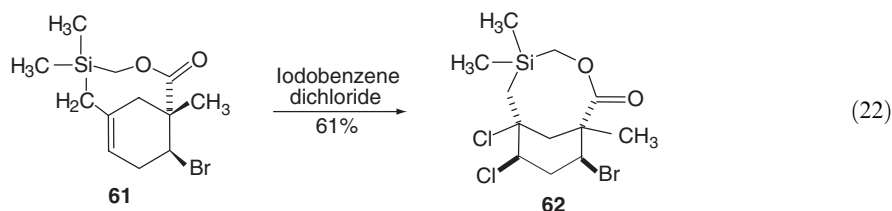
$\text{R}^1 = \text{R}^2 = \text{R}^3 = \text{Et}, 85\%$

$\text{R}^1 = \text{R}^2 = \text{Me}, \text{R}^3 = \text{Bu}^t, 89\%$

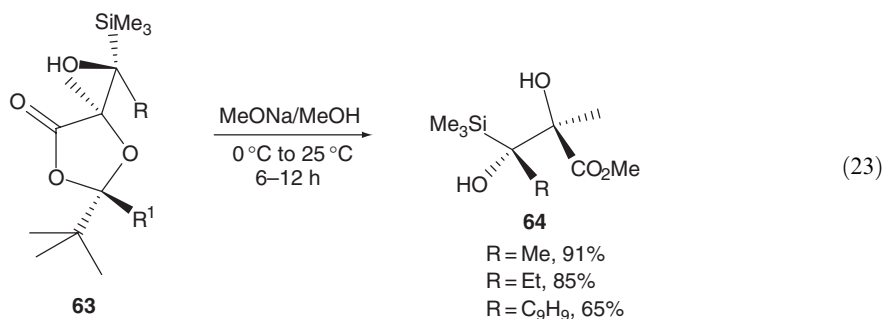
## (viii) Miscellaneous methods

The  $\alpha$ -(trimethylsilyl)allenyl ketones were prepared in a one-pot operation from propargylic chlorides and acetyltrimethylsilane. The reaction proceeded through an intermediate containing an  $sp^3$  carbon attached to an oxygen and trimethylsilyl group <1996SC803>.

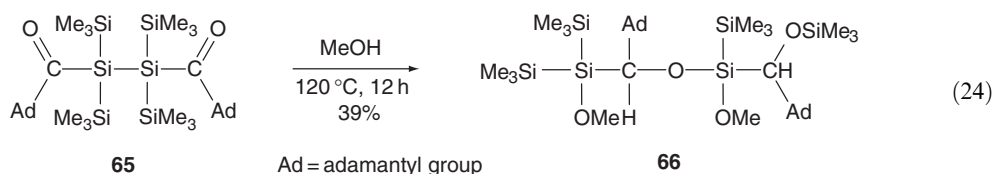
The bridgehead allyl silane cycloadduct **61** was chlorinated with iodobenzene dichloride to give the polyhalogenated cyclohexane **62** (Equation (22)) <1997JOC8962>.



Methanolysis of the silylated alcohol **63** induced by sub-stoichiometric amounts of methoxide ion gave the corresponding (2*R*,3*R*)-3-trimethylsilyl-2,3-dihydroxy methyl esters **64** in good yields (Equation (23)) <2002TA1825>.



Heating a benzene solution of 1,2-diadamantoyltetrakis(trimethylsilyl)disilane at 120 °C gave an isomerization product, 3,4-diadamantyl-2,2-bis(trimethylsiloxy)-1,1-bis(trimethylsilyl)-1,2-disilacyclobutene in 24% yield. A mechanistic interpretation including a 2,3-disiladiene intermediate was described. Similar treatment of 1,2-diadamantoyltetrakis(trimethylsilyl)disilane **65** in the presence of an excess of methanol at 120 °C afforded a methanol adduct **66** in 39% yield (Equation (24)) <2003JOM72>.



A new method for the synthesis of optically active  $\alpha$ -hydroxyalkynylsilanes was described. The key step of the conversion was the use of the reverse Brook rearrangement of the 2-alkynylsilyl ether <2000TL6589>.

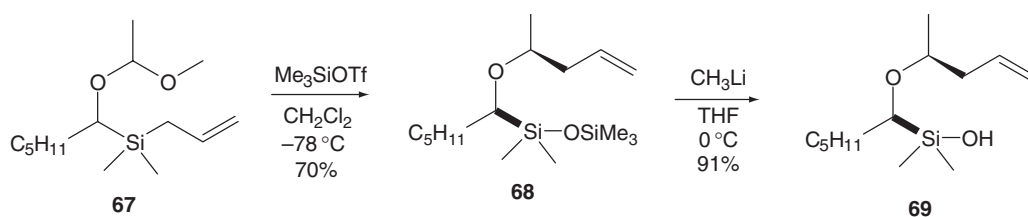
Treatment of  $\alpha$ -silylated allylic alcohols with epoxidizing reagents afforded  $\alpha$ -silylated aldols in a highly stereocontrolled fashion. The transformation is proposed to proceed either by a reaction cascade involving stereospecific epoxidation of the allylic alcohol moiety followed by an acid-supported pinacol-type rearrangement, or by a sequence consisting of a  $\pi$ -face-selective electrophilic attack at the allylic silane moiety with hyperconjugative stabilization of the evolving carbocation, followed by rearrangement of the thus obtained pentacoordinated silanium ion. Depending on the reaction conditions, the  $\pi$ -face selectivity of the oxidation step is controlled by the stereogenic C-atom or the more remote Si-center of chirality <1999HCA561>.

The reaction of mixed acetal **67** with trimethylsilyl triflate at  $-78^\circ\text{C}$  resulted in the somewhat hydrolytically unstable allyl transfer product in good yield. The trimethylsilyl ether derivative **68** with excess methylolithium provided the trimethylsilyl-substituted derivative **69** as a 34:1 diastereomeric mixture (Scheme 20 and Table 2) <1996JOC2441>. The substituted allyl silanes were prepared by displacement of methoxy group on silicon (prepared by ozonolysis of **67** in the presence of methanol) by allyllithio reagents which were in turn generated by transmetalation of the corresponding allylstannanes. The results are summarized in Table 2 <1996JOC2441>.

#### 4.08.1.1.2 Oxygen and germanium— $\text{R}_2^1\text{C}(\text{OR}^2)\text{GeR}_3^1$ , etc.

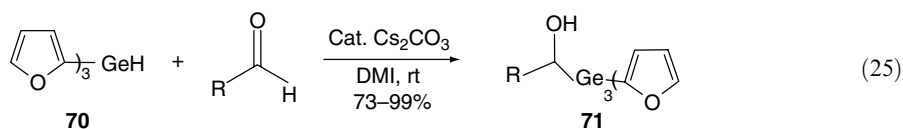
In COFGT (1995), the preparation of  $\alpha$ -alkoxygermane systems has been described from halo-methyl ethers, aldehydes, ketones, and nucleophilic substitution of halogermenes.



**Table 2** Synthesis of substituted allyl silanes

<i>Allylstannane</i>	<i>Allylsilane</i>	<i>Yield (%)</i>
		65
		71
		75
		75
		64

Nucleophilic addition of tri-2-furylgermane **70** to various aldehydes and  $\alpha,\beta$ -unsaturated carbonyl compounds in the presence of a catalytic amount of base such as  $\text{Bu}^t\text{OK}$  and  $\text{Cs}_2\text{CO}_3$  afforded  $\alpha$ -hydroxy germanes and  $\beta$ -germyl carbonyl compounds, respectively, in good-to-excellent yields. The reaction of aldehydes proceeded with high chemoselectivity under mild conditions to produce  $\alpha$ -hydroxy germanes **71** bearing various functional groups effectively (Equation (25)) <2001T9827>.  $\alpha$ -Hydroxy germanes could be converted into acylgermanes by Swern oxidation <2001T9827>.



In an in-depth study, the capability of acylgermanes to function as acceptors in radical cyclization was reported <1997JA4797>. The addition of radicals to acylgermanes followed by rapid fragmentation of the resulting  $\alpha$ -germylalkoxy radicals provided ketones and germyl free radicals <1997JA4797>.

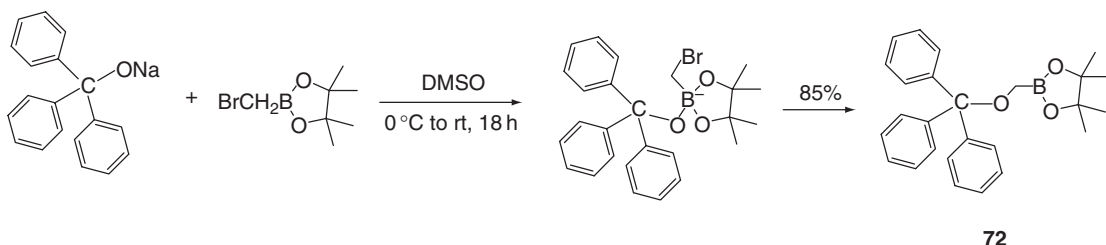
**4.08.1.1.3 Oxygen and boron— $R_2^1C(OR^2)BR_2^3$ , etc.**

The different synthetic pathways leading to  $\alpha$ -alkoxyborane systems have been outlined in COFGT (1995) from  $\alpha$ -haloboranes,  $\alpha$ -haloboronates, carbonylation of organoboranes, and homologation of dioxaborinanes.

The following synthetic routes represent methods to generate systems containing oxygen  $\alpha$  to boron.

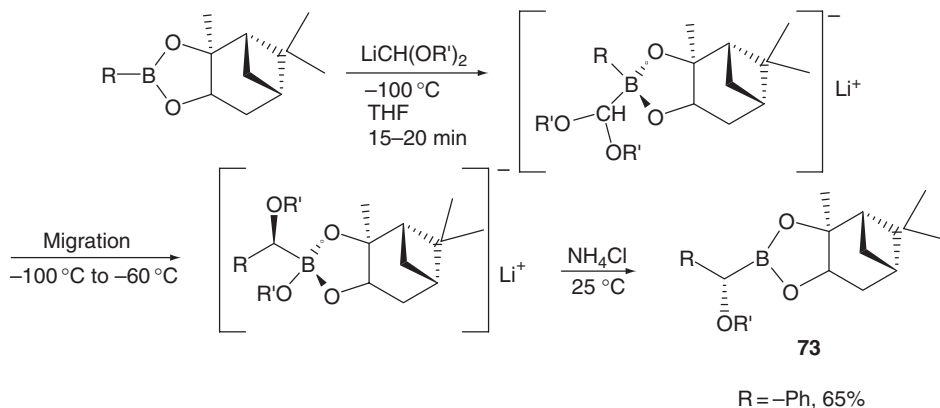
*(i) From  $\alpha$ -haloboronates and alkylboronates*

Sodium trityloxyde with 2-(bromomethyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane efficiently yielded 4,4,5,5-tetramethyl-2-[(triphenylmethoxy)methyl]-1,3,2-dioxaborolane **72** (Scheme 21) <1995OM2855> which can be transesterified with chiral diols to form other [(triphenylmethoxy)methyl]-1,3,2-dioxaborolanes <1995OM2855>. These can undergo chain extension with (dichloromethyl)lithium in the normal manner and are potentially useful synthetic intermediates <1995OM2855>.



Scheme 21

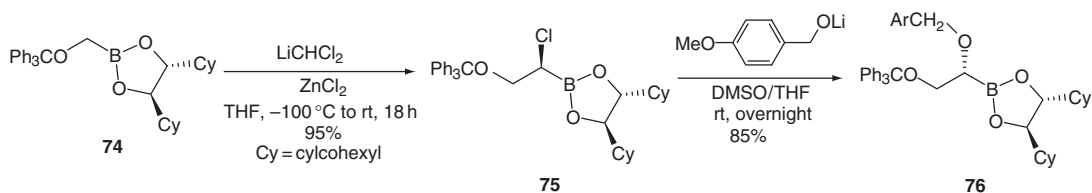
Matteson and co-workers have developed a new homologation reaction <2000JOC5403> of boronic esters with (dialkoxymethyl)lithium reagents. This new process provided a convenient one-step synthesis of  $\alpha$ -alkoxy boronic esters **73**. When the reaction was catalyzed by zinc chloride, high diastereoselection was achieved from aryl and *sec*-alkylboronates (Scheme 22) <2000JOC5403>.



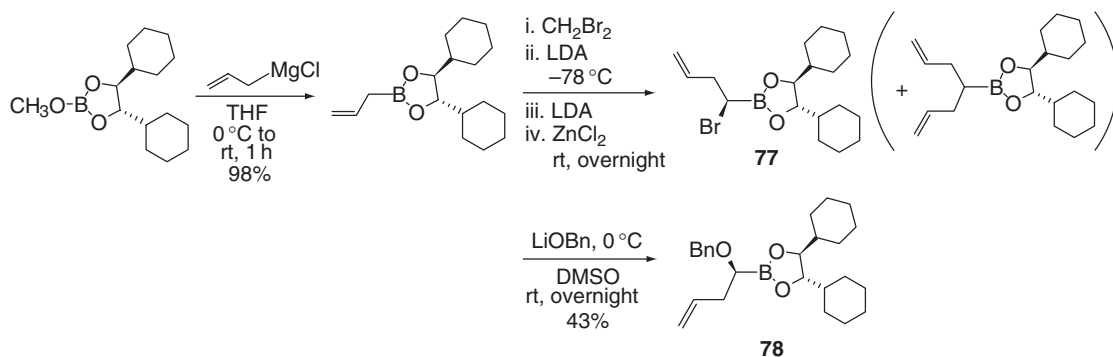
Scheme 22

(Trityloxy)methylboronate **74** reacted with (dichloromethyl)lithium to provide chloro boronic ester **75**. Subsequent substitution with sodium *p*-methoxybenzyl oxide efficiently yielded (*R*)-[1-(*p*-methoxybenzyloxy)-2-(trityloxy)ethylboronate] **76** (Scheme 23) <1997TA3855>.

The  $\alpha$ -bromo boronate ester **77** was also reacted with lithium benzyloxyde (easily prepared from benzylalcohol and *n*-butyllithium) to produce the corresponding  $\alpha$ -benzyloxy boronate ester **78** (Scheme 24) <1996OM152>.

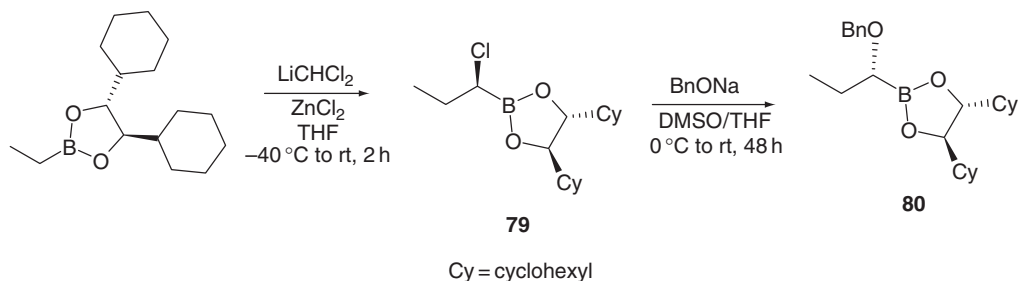


Scheme 23



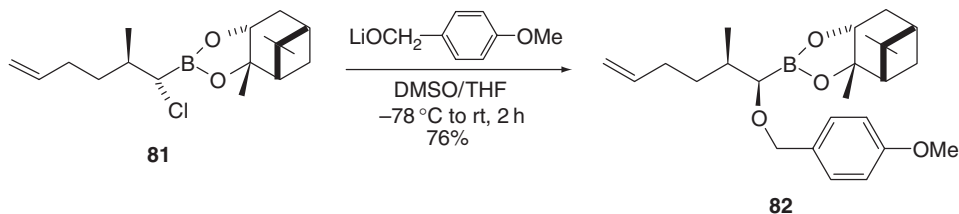
Scheme 24

$\alpha$ -Chloro boronate ester **79** was reacted with sodium benzyloxide to give  $\alpha$ -benzyloxy boronate esters **80** (Scheme 25) <1996JA4560>. The stereoselective boronic ester has been used to install all three chiral centers in a convergent synthesis of highly pure stegobinone, the epimerically labile pheromone of the drugstore beetle, *Stegobium paniceum*, and the furniture beetle, *Anobium punctatum*. The asymmetric centers were installed via the reaction of (dichloromethyl)lithium with 1,2-cyclohexylethane-1,2-diol boronic esters <1996JA4560>.



Scheme 25

The reaction of  $\alpha$ -chloro boronic ester **81** with lithium *p*-methoxybenzyloxide generated the corresponding  $\alpha$ -alkoxy boronate ester **82** (Scheme 26) <1996JOC3106> in 76% yield.



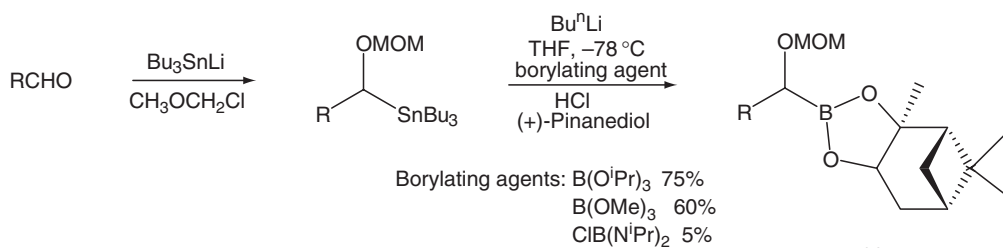
Scheme 26

(ii) *From  $\alpha$ -alkoxystannanes*

Various  $\alpha$ -alkoxy boronic esters have been synthesized by borylation of  $\alpha$ -alkoxyorganolithium reagents generated via tin/lithium exchange. The results are summarized in Table 3 <1998TL555>. This reaction occurred with retention of configuration and gave access to  $\alpha$ -alkoxy boronic esters **83** (Scheme 27) <1998TL555>.

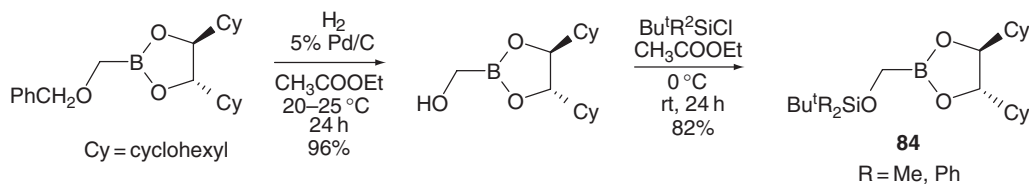
**Table 3** Synthesis of alpha-alkoxyboronic esters

$\alpha$ -Alkoxystannane	Product	Yield (%)
		75
		70
		58
		73
		30
		45
		55

**Scheme 27**

(iii) From  $\alpha$ -alkoxyboronates

The catalytic hydrogenolysis of 2-(benzyloxymethyl)-1,3,2-dioxaborolane to the hydroxymethyl derivative was immediately followed by silylation with *t*-butyldimethylsilyl chloride to form the 2-(trialkylsilyloxymethyl)-1,3,2-dioxaborolane **84** or with *t*-butyldiphenylsilyl chloride to form the analogous derivative (Scheme 28) <2000JOC6650>.



Scheme 28

## 4.08.1.2 Functions Bearing Sulfur

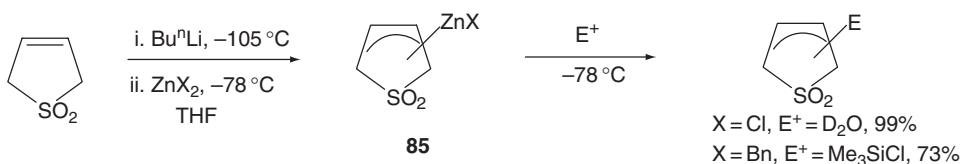
The importance of acyl silanes and functionalization of sulfur-containing compounds is reflected in two useful reviews <1998JOM181, 2000EJO2171>.

4.08.1.2.1 Sulfur and silicon— $R_2^1C(SR^2)SiR_3^3$ , etc.

The major synthetic routes to generate  $\alpha$ -silylated derivatives from sulfur-stabilized carbanions, halomethyl silanes, from silylthioethers, reverse Brook rearrangement, from vinyl silanes, from  $\alpha$ -arylthiovinyl silanes, from rearrangements of ylides prepared from  $\alpha$ -thiosilanes, from  $\alpha$ -silylorganomagnesium compounds, from  $\alpha$ -silylated *O,S*-acetals, and from trimethylsilylthiones have been described in COFGT (1995). Listed below are the major synthetic routes to prepare compounds containing sulfur  $\alpha$  to silicon.

## (i) From sulfur-stabilized carbanions

Zinc sulfolenylates **85** have been generated by metal exchange processes from lithium sulfoenylate. These organozinc compounds show very interesting regioselectivity in the reactions with electrophiles (Scheme 29) <1995TL7105>.



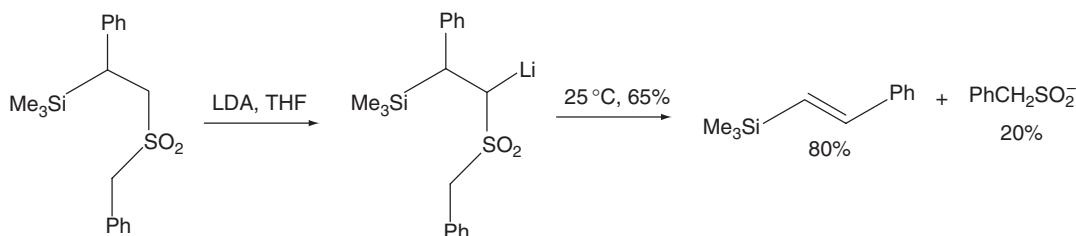
Scheme 29

The double alkylation of bis[2-(2-lithio-1,3-dithian-yl)]diorganosilane with bis(bromomethyl)diorganosilanes proceeded smoothly in good yields in a mixture of THF-hexamethylphosphoric triamide (HMPA) or THF-1,1,3,3-tetramethylurea (TMU) to give 1,4-disilacyclohexanes whose conformation was shown to be a twist-boat on the basis of X-ray analysis (Scheme 33) <1998TL3197>.

The multicomponent linchpin couplings of silyldithianes via solvent-controlled Brook rearrangement has been studied <1997JA6925>.

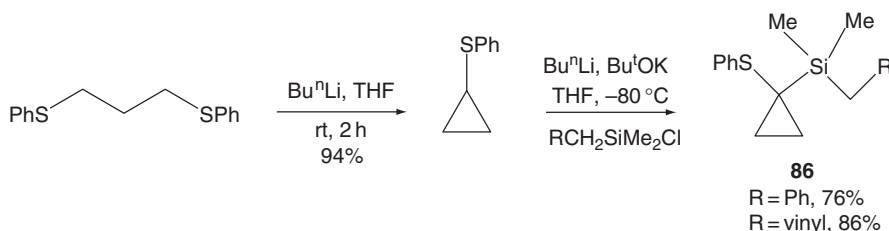
Treatment of trimethylsilyl ethanes bearing  $\alpha$ -phenyl groups and  $\beta$ -phenylthio, phenylsulfonyl, or cyano groups with LDA caused elimination–rearrangement mediated by the  $\beta$ -carbanionic species. Mechanistic conclusions were based on the isotopic labeling experiments, the effects of substituents, and approximate kinetics. These suggested that trimethylsilyl is the migrating group,

that cleavage of the bond to the leaving group was little advanced in the transition structure and that placing of a substituent to encourage silicon-carbon bond cleavage was mandatory (Scheme 30) <1996JCS(P1)1511>.



Scheme 30

The  $\alpha$ -dimethyl(1-phenylthio)cyclopropylsilyl group was used as a new masked hydroxyl group. The phenylcyclopropyl thioether was deprotonated with *n*-butyllithium in the presence of potassium-*t*-butoxide followed by silylation with chlorotrialkylsilanes to provide the  $\alpha$ -thiosilanes **86** (Scheme 31) <2000T2025>.



Scheme 31

Trimethylsilyldiazomethane was compared with ethyldiazoacetate for the rhodium, copper, and cobalt catalyzed formation and [2,3] rearrangement of allylsulfonium ylides. At room temperature, the reaction could be carried out using the allyl sulfide as the limiting reagent by slow addition of 3 equiv. of the diazo compound. Slightly better yields were obtained with trimethylsilyldiazomethane than with ethyldiazoacetate to generate the  $\alpha$ -trimethylsilyl thioethers <1999TL1617>.

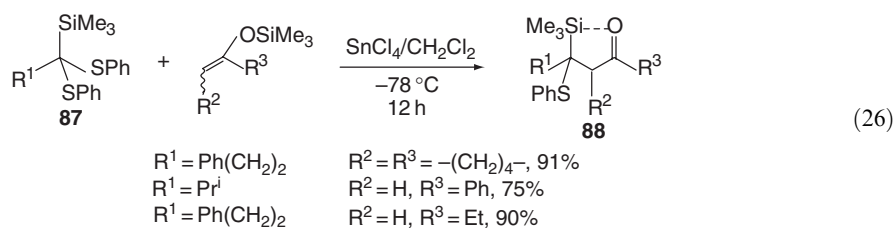
The reaction of mono- or bisilylated thioanisole derivatives with 3,4-epoxybutyltosylate afforded the cyclopentanol. Migratory aptitudes of two different silyl groups in the Brook 1,4-rearrangement was examined giving the order SiMe<sub>2</sub>Ph > SiMe<sub>3</sub> > SiMePh<sub>2</sub> <1998T11481>.

Successive treatment of the (*Z*)- $\gamma$ -trimethylsilyl allylic alcohols with copper(I) *t*-butoxide and allylic halides followed by the tetrabutylammonium fluoride-assisted hydrolysis produced the allylation products, 2,5-alkadien-1-ols, with complete retention of configuration. Similar treatment of the organometallic intermediates with aryl and vinylic halides in the presence of palladium(0) catalyst gave the corresponding cross-coupling products in good yields. The stereoselective preparation of the starting materials was also described <2002JOC8450>.

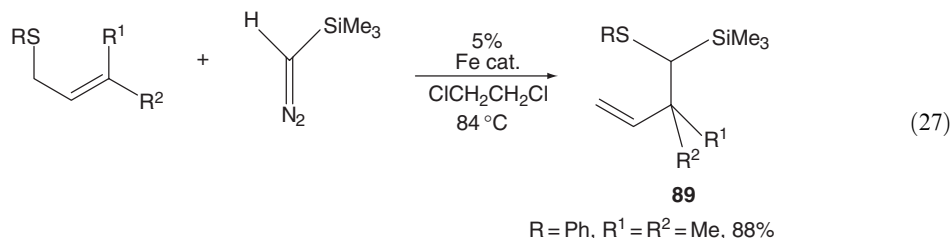
A cumene solution of  $\alpha$ -stannylbenzylphenyl sulfide was treated with Bu<sup>n</sup>Li and bis(oxazoline)-Pr<sup>i</sup> at -78 °C and subsequently with benzophenone to give the product with 99% ee. It was confirmed that the reaction of  $\alpha$ -lithio benzylphenyl sulfide proceeds through a dynamic kinetic resolution pathway. The enantioselective reactions of  $\alpha$ -lithio benzyl 2-pyridyl sulfide gave the products with stereochemistry reverse to that obtained in the reaction of benzylphenyl sulfide. It was established that this reaction proceeded through a dynamic thermodynamic resolution pathway in which the reaction with an electrophile proceeded faster than interconversion between the diastereomeric complexes <2000JA11340>.

(ii) *From thioethers, ethers, and silylated acetals and thioacetals*

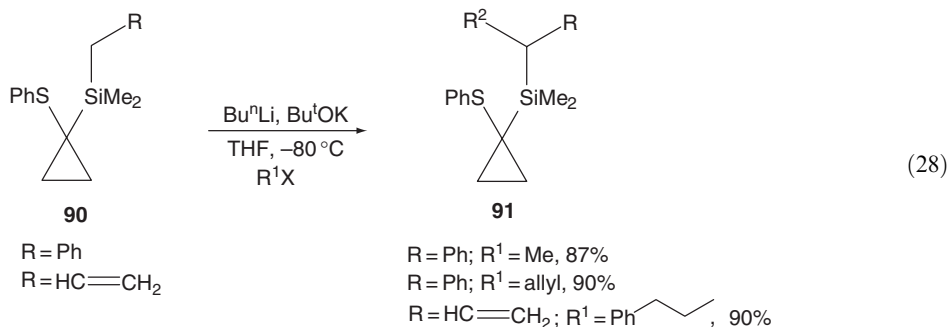
The tin(IV) chloride promoted reaction of  $\alpha$ -trimethylsilylthioacetals **87** with trimethylsilyl enol ethers gave  $\beta$ -phenylthio ketones **88** (Equation (26)) <2002JOC8450>.



Iron salts efficiently catalyzed the Doyle–Kirmse reaction of allyl sulfides with (trimethylsilyl)diazomethane and ethyldiazoacetate in dichloroethane at  $83^\circ\text{C}$  to provide the  $\alpha$ -thiosilyl compound **89**. Competitive dimerization was less of a problem with (trimethylsilyl)diazomethane than with ethyldiazoacetate. Good results were obtained using only 1.5 equiv. of (trimethylsilyl)diazomethane, even without slow addition. Phosphine ligands affect the kinetics, but not the diastereoselectivity. DPPE and BINAP led to higher yields than DPPP, but no enantioselection was detected with *R*-(+)-BINAP (Equation (27)) <2000OL1303>.

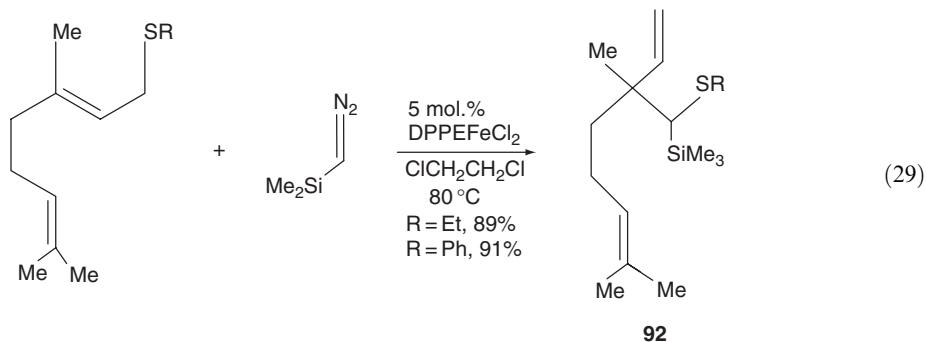


The  $\alpha$ -thiosilyl compound **90** was deprotonated with  $\text{Bu}^n\text{Li}/\text{Bu}^i\text{OK}$  followed by alkylation with alkyl halides to afford the corresponding alkylated products **91** (Equation (28)) <1995TL3861>. The dimethyl(1-phenylthio)cyclopropylsilyl group has been used as a masked hydroxyl group <1995TL3861>.

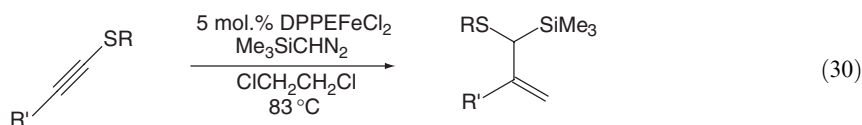


Organolithium reagents stabilized by halogeno, thio, silyl, vinyl, and/or phenyl substituent(s) could cleave THF effectively under the influence of boron trifluoride etherate at lower temperatures. The softness of these carbanionic reagents seemed to be important for successful reaction <1995CL355>.

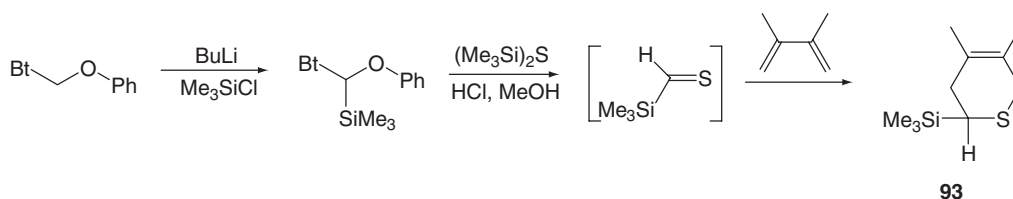
The iron-catalyzed Kirmse reaction was used to generate  $\alpha$ -silyl thioethers **92** via the reaction of allylthio ether with (trimethylsilyl)diazomethane (Equation (29)) <2002JOC6711>.



Propargyl sulfides were shown to be efficient partners for the iron-catalyzed addition/rearrangement reaction with trimethylsilyldiazomethane (Equation (30)) <2001JOC5256>.



A general method for the synthesis of  $\alpha$ -silylated thio cyclic compounds **93** has been described that employed a Diels–Alder cycloaddition reaction (Scheme 32) <2000JOC9206>.



Scheme 32

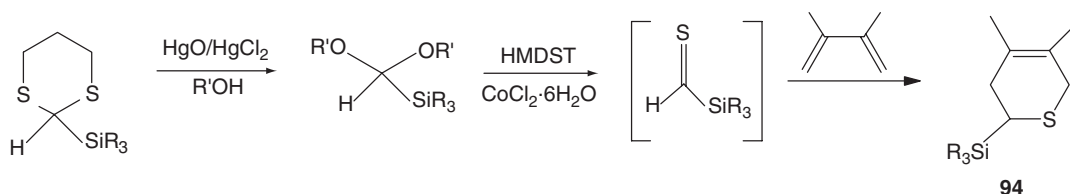
Acyl silanes with terminal  $\alpha$ -stannyl bromide or xanthate functionalities have been prepared.  $\alpha$ -Stannyl radicals generated from these acyl silanes undergo intramolecular cyclizations to give cyclic silyl enol ethers regiospecifically. The radical processes involve radical cyclization, Brook rearrangement, and  $\beta$ -fragmentation in sequence. A tributylstannyl group serves as the radical leaving group. The newly formed  $\sigma$ -bond and  $\pi$ -bond are located between the same two carbon atoms. This approach is limited to the formation of five-membered rings. In another route,  $\omega$ -bromo- $\alpha$ -phenylsulfonylacyl silanes are synthesized. The radical cyclizations of these  $\alpha$ -sulfonylacyl silanes also give cyclic silyl enol ethers. The phenylsulfonyl moiety is the radical leaving group in this system. Furthermore, the newly formed  $\sigma$ -bond and  $\pi$ -bond are located at adjacent positions sharing a single carbon atom. The latter approach is effective for both five- and six-membered ring formation <2001JOC8983>.

Thioacyl silanes containing the ferrocene moiety, easily prepared from the corresponding acyl silanes with Lawesson's reagent at room temperature, could be transformed into vinyl silanes, sulfur heterocycles, and sulfoxides <1999TL6473>.

A number of 1,4- and 1,5-acylsilane dicarbonyl compounds were synthesized using Corey–Brook dithiane methods. These dicarbonyl substrates were annulated with the bis(trimethylsilyl) enol ether of methylacetoacetate in the presence of TMSOTf, affording bicyclic ethers bearing silicon substituted at the bridgehead position. The annulation reactions proceeded with excellent regiochemical and good-to-excellent stereochemical control via a neighboring group participation mechanism <1995JOC130>.

### (iii) From dienes and allenes

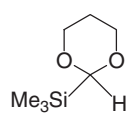

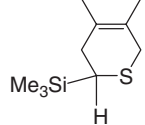
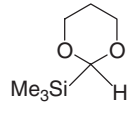

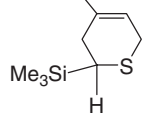
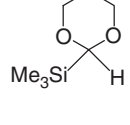

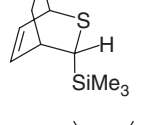
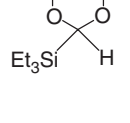

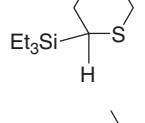
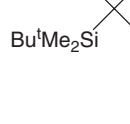

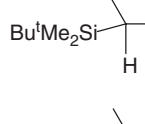
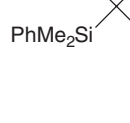

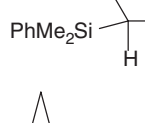
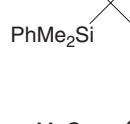

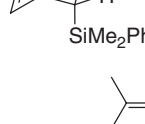
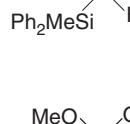

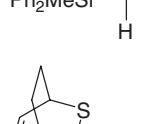
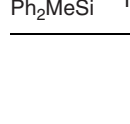

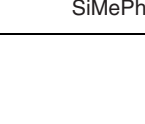
Reaction of several silylated acetals with hexamethyldisilathiane (HMDST) in the presence of cobalt(II) chloride hexahydrate afforded a simple, novel, and general entry to thioformylsilanes, directly trapped *in situ* as their Diels–Alder cycloadducts **94** (Scheme 33) <1997SL361>. The results are summarized in Table 4 <1997SL361>.



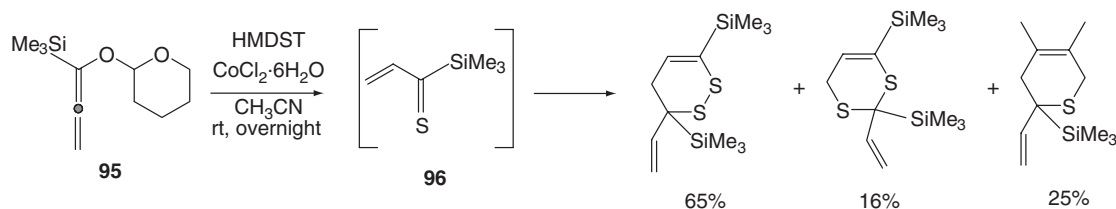
Scheme 33



**Table 4** Synthesis of thioformylsilanes

<i>Acetal</i>	<i>Diene</i>	<i>Product</i>	<i>Yield (%)</i>
			41
			37
			64
			51
			41
			56
			58
			62
			54

Treatment of different silylated allenes **95** with hexamethyldisilathiane (HMDST) in the presence of cobalt(II) chloride hexahydrate afforded an easy and high yielding access to  $\alpha,\beta$ -unsaturated thioacyl silanes **96**, which undergo a self-dimerization reaction to afford polyfunctionalized 1,2-dithiodienes as the major products (Scheme 34) <2003TL2831>. The representative examples thioacyl silanes are outlined in Table 5 <2003TL2831>.



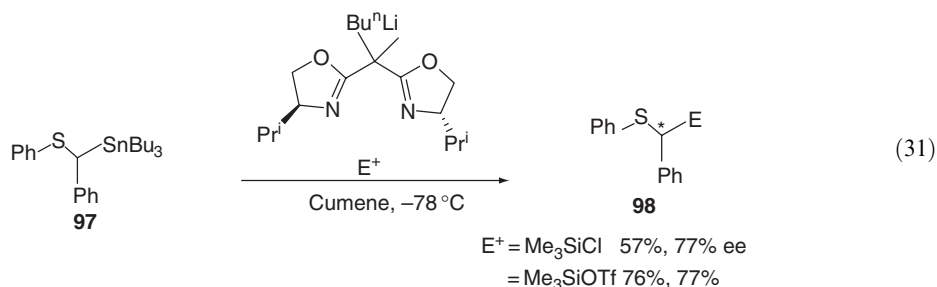
Scheme 34

Table 5 Thionation of silylated allenes

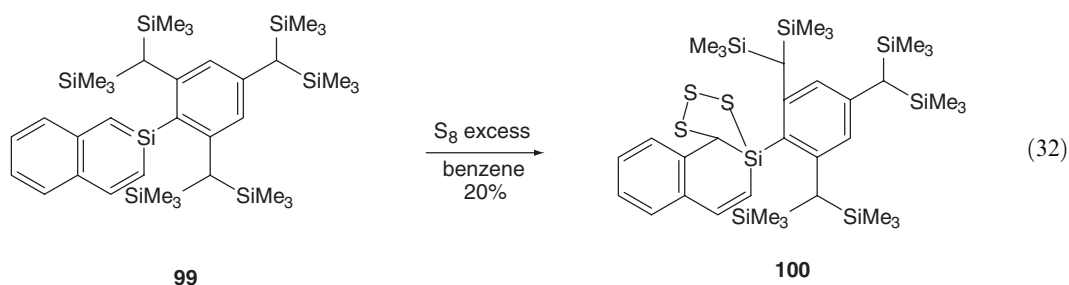
Allene	Product	Yield (%)
		65
		59
		36
		42
		57
		29

## (iv) Other routes

A cumene solution of  $\alpha$ -stannylbenzylphenyl sulfide **97** was treated with  $\text{Bu}^n\text{Li}$  and bis(oxazoline)- $\text{Pr}^i$  and subsequently with benzophenone to give the corresponding chiral  $\alpha$ -thiosilane **98** (Equation (31)) <2000JA11340>.



It has been demonstrated that the reaction of 2-silanaphthalene **99** with excess sulfur afforded a cyclic trisulfide **100** (Equation (32)) <1999JA11336>.



#### 4.08.1.2.2 Sulfur and germanium— $R_2^I C(SR^2)GeR_3^3$ , etc.

Different methods have been reviewed in COFGT (1995) to generate  $\alpha$ -germylsulfur systems from  $\alpha$ -germylorganomagnesium compounds or from germylthioethers: reverse Brook rearrangement, from halomethylgermanes, and from vinylgermanes. No further advances have occurred in this area since the publication of chapter 4.08.1.2.2 in <1995COFGT(4)351>.

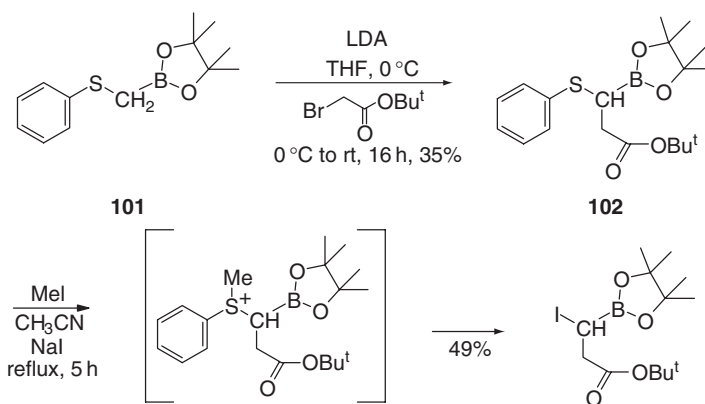
#### 4.08.1.2.3 Sulfur and boron— $R_2^I C(SR^2)BR_3^3$ , etc.

The examples of systems containing an  $\alpha$ -thioalkylboron unit have been described in COFGT (1995) from methylphenylthio ethers, diphenyldithioacetals,  $\alpha$ -haloboronates, alkylation of  $\alpha$ -phenylthioboronates, and other miscellaneous methods. The following synthetic routes describe the preparation of systems containing sulfur  $\alpha$  to boron.

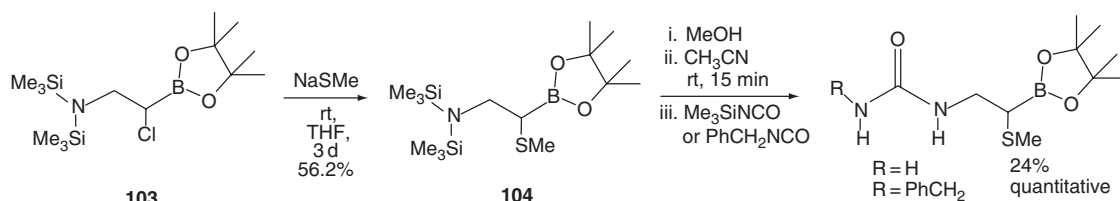
##### (i) From $\alpha$ -thioboronates

Specifically,  $\text{BrCH}_2\text{CHF}_2$ ,  $\text{BrCH}_2\text{COOBu}^t$ , and  $\text{CH}_2=\text{CHCOOMe}$  were allowed to react with the stabilized anion of (phenylthio)methane boronate,  $\text{PhSCH}_2\text{BO}_2\text{C}_6\text{H}_{12}$  derived from deprotonation of the corresponding (phenylthio)methane boronate **101** to give the substituted boronate **102**. The substituted (phenylthio)methane boronate was converted to the corresponding sulfonium ion by treatment with methyl iodide and subsequently displaced with iodide. The  $\alpha$ -iodo derivative was converted to the amine by conventional methods (Scheme 35) <2001JOC6375>.

The  $\alpha$ -thioboronate ester was generated from the 2-bromomethyl-4,4,5,5-tetramethyl-1,3,2-dioxaborolane. The boronate ester was reacted with lithio(hexamethyl)disilazane followed by (dichloromethyl)lithium to provide the corresponding  $\alpha$ -chloro boronate ester **103** which reacted further with sodiomethanethiol to produce the  $\alpha$ -thioboronate ester **104** (Scheme 36) <1997HAC487>. It should be noted that  $\alpha$ -chloro boronate ester failed to react with lithium benzyloxide.



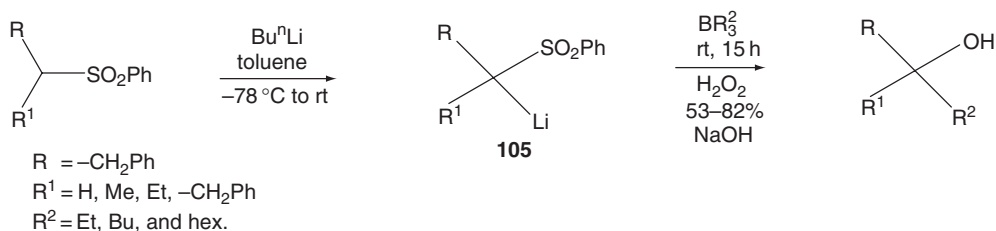
Scheme 35



Scheme 36

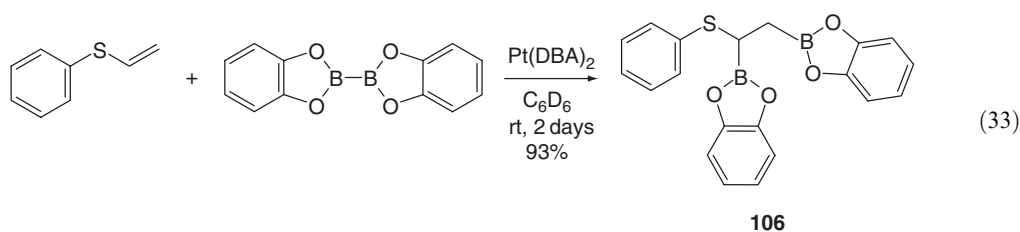
## (ii) From sulfones and vinyl sulfides

The reaction of sulfone anions **105** with trialkylboranes followed by thermal isomerization of the obtained boron compounds in the presence of excess borane–methyl sulfide complex and by alkaline hydroperoxide oxidation gave primary alcohols (Scheme 37) <2003TL4451>.



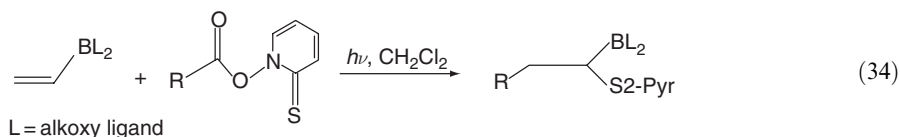
Scheme 37

$\alpha$ -Thioboronate esters **106** are obtained directly in high yield and selectively from metal-catalyzed additions of B–X bonds (X = H, B) to thiocarbonyl compounds and vinyl sulfides (Equation (33)) <2001OM2130>.



## (iii) From vinylboronates

The vinylboronic esters when reacted with the *O*-acyl derivative of *N*-hydroxypyridine-2-thione underwent the abstraction of thiopyridyl fragment that opened an interesting route to  $\alpha$ -thio boronic esters (Equation (34)) <1995T6999>.

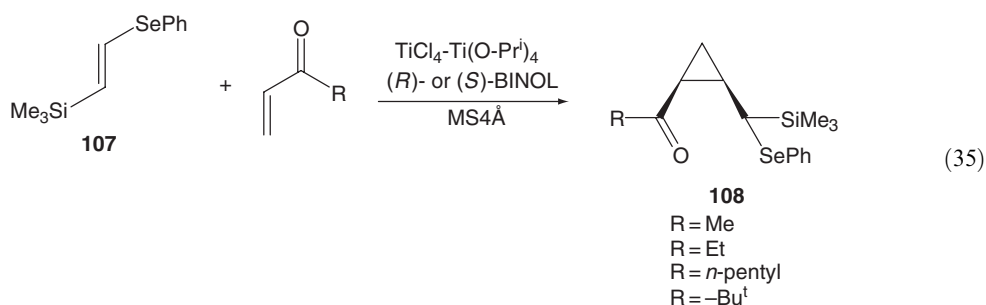


## 4.08.1.3 Functions Bearing Selenium or Tellurium

4.08.1.3.1 Selenium or tellurium and silicon— $R_2C(SeR^2)SiR_3^3$ , etc.

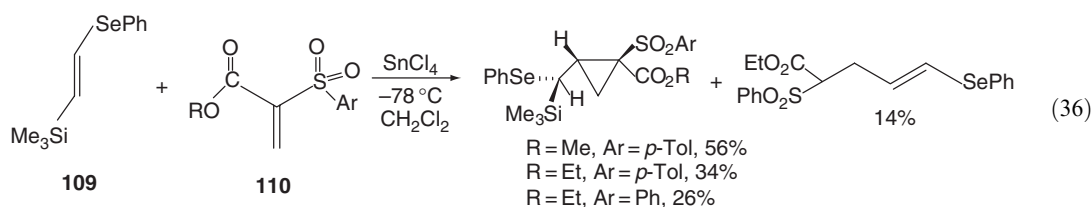
The different routes to selenium systems containing an  $\alpha$ -silicon functionality have been described in COFGT (1995) by direct deprotonation of selenium compounds, from selenoacetals and selenoketals, from vinyl selenides, from aldehydes and thioaldehydes, from vinyl silanes, and from (halomethyl)trimethyl silanes. The preparation of dialkyl tellurides has been achieved by alkylation of sodium tellurides with alkyl chlorides. Described below are synthetic routes based on 1-seleno-2-silylethenes leading to systems containing selenium  $\alpha$  to silicon.

The reaction of (*E*)-1-(phenylseleno)-2-(trimethylsilyl)ethene **107** and vinylketones in the presence of a chiral Lewis acid prepared from  $TiCl_4$ ,  $Ti(O^iPr)_4$ , (*R*)- or (*S*)-1,1'-binaphthol (BINOL), and 4 Å molecular sieves (MS4 Å) gave enantiomerically enriched *cis* cyclopropane products **108**. The enantiomeric excess and chemical yield varied depending on the ratio of  $TiCl_4$  and  $Ti(O^iPr)_4$  to (*E*)-1-(phenylseleno)-2-(trimethylsilyl)ethene. Reproducible results (43–47% ee/33–41% yields) for *cis*-1-acetyl-2-[(phenylseleno)(trimethylsilyl)methyl]cyclopropane were obtained using 1.1 equiv. of  $TiCl_4$ , 0.54–0.65 equiv. of  $Ti(O^iPr)_4$  and 1.65 equiv. of BINOL. The observed enantioselectivity was explained by consideration of the structure of the postulated intermediates, alkoxy titanium–carbonyl complexes, via *ab initio* MO calculations (Equation (35)) <1996JOC4046>.



The reactions of 1-seleno-2-silylethenes with highly electrophilic tricarbonyl-substituted olefins in the presence of Lewis acids have been investigated. The reaction of 1-(phenylseleno)-2-(trimethylsilyl)ethane with tris(alkoxycarbonyl) olefins or 1,1-bis(alkoxycarbonyl)-2-acyl olefins in the presence of  $ZnBr_2$  at  $-30^\circ C$  gave *cis*-substituted cyclopropanes exclusively. The origin of the *cis* stereochemistry was ascribed to the synclinal addition path of the  $ZnBr_2$ -coordinated electrophilic olefin. Application of the highly functionalized selenium- and silicon-substituted cyclopropane products to the preparation of a useful synthetic intermediate for the pyrethroid class of insecticides was also demonstrated <1997JOC2968>.

The reaction of 1-seleno-2-silylene and methylenemalonate ester in the presence of Lewis acid (zinc bromide) provided highly functionalized cyclopropanes <1995JOC6546> which were utilized for further functional group transformations <1999JOC282>. The [2 + 1]-cycloaddition reactions of a 1-seleno-2-silylene **109** to 2-sulfonylacrylates **110** were also studied (Equation (36)) <1999JOC9521>.



The stereoselective [2+1]-cycloaddition reactions of 1-seleno-2-silylethenes with di(–)-menthyl-ethane-1,1-dicarboxylates has also been explored [<1999JOC2367>](#).

#### 4.08.1.3.2 Selenium or tellurium and germanium— $R_2^1C(\text{Se}R^2)\text{Ge}R_3^3$ , etc.

According to COFGT (1995), few examples of compounds containing a germyl group  $\alpha$  to a selenium or tellurium are known. One important method to generate  $\alpha$ -selenogermane has been through iodide displacement from (iodomethyl)trimethylgermane using lithium phenylselenide. No further advances have occurred in this area since the publication of COFGT (1995) (chapter 4.08.1.3.2).

#### 4.08.1.3.3 Selenium or tellurium and boron— $R_2^1C(\text{Se}R^2)\text{BR}_2^3$ , etc.

As indicated in COFGT (1995), there are no reports of significant routes to systems containing a boron function  $\alpha$  to a selenium or tellurium.

The selenoalkenyldicyclohexylboranes, readily prepared by the hydroboration of internal alkylselenoacetylenes with dicyclohexylborane followed by iodination under basic conditions, produced *cis/trans* 1,2-disubstituted alkenyl selenides. The mechanism of the reaction probably would involve a system containing a boron function  $\alpha$  to a selenium [<1996JOM139>](#).

### 4.08.2 FUNCTIONS CONTAINING A CHALCOGEN AND A METAL

#### 4.08.2.1 Functions Bearing Oxygen— $R_2^1C(\text{OR}^2)\text{M}$ , etc.

The formation of carbanions adjacent to an oxygen function has been reviewed in COFGT (1995). A recent review describes the asymmetric [2,3]-Wittig rearrangement as a general tool for the asymmetric synthesis [<1997PAC595>](#). Another review on the functions bearing oxygen has appeared in the literature [<1997AG\(E\)2282>](#).

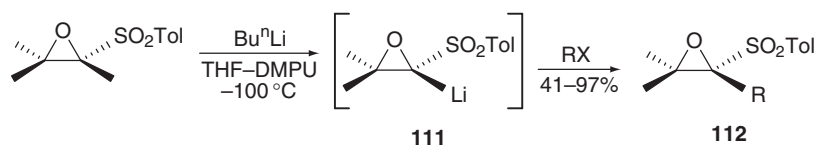
##### 4.08.2.1.1 Lithium, sodium, or potassium

The synthetic routes leading to an  $sp^3$  carbon attached to oxygen and lithium, sodium, or potassium have been outlined in COFGT (1995), and include direct deprotonation of a saturated carbon adjacent to oxygen, tin–lithium exchange, reductive lithiation of  $\alpha$ -phenylthioethers, halogen–lithium exchange, lithiation of allylic and benzylic ethers, lithiation of  $\alpha$ -cyano ethers, and lithiation of *O*-alkylcarbonates and *O*-alkylcarbamates. Listed below are routes leading to an  $sp^3$  hybridized carbon attached to oxygen and lithium, sodium, or potassium.

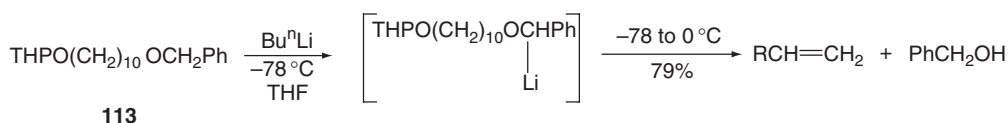
##### (i) By direct deprotonation

Oxiranyllithium compounds **111** generated from epoxy sulfones by deprotonation with *n*-butyllithium in THF at  $-100^\circ\text{C}$  react with alkylhalides to give new substituted epoxides **112** in high yields (Scheme 38) [<1996TL2605>](#).

Treatment of benzyl ethers of primary alcohols **113** with *n*-butyllithium afforded terminal alkenes in good yield (Scheme 39) [<1996CL1039>](#).

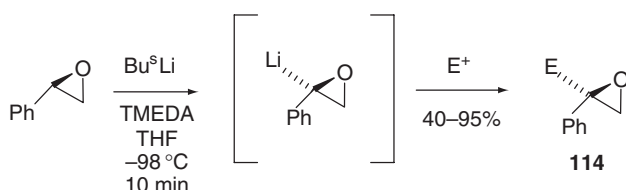


Scheme 38



Scheme 39

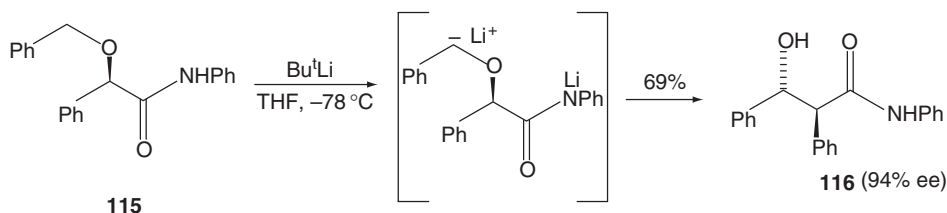
The stereospecific  $\alpha$ -lithiation of optically active styrene oxides and the trapping reaction of the corresponding highly reactive intermediates with electrophiles to produce optically active styrene oxide derivatives **114** have been described. This method has been applied to the synthesis of an optically active oral antifungal agent of industrial interest (Scheme 40) <2002OL2445>.



Scheme 40

Enantioselective  $\alpha$ -deprotonation–rearrangement of a chiral-substituted cyclooctene oxides using organolithiums in the presence of (–)-sparteine or (–)- $\alpha$ -isosparteine gave the functionalized bicyclo[3.3.0]octan-2-ols in 56–72% yields and 83–89% ees <2001OL441>.

Treatment of chiral  $\alpha$ -benzyloxy-oxycarboxamide **115** with  $\text{Bu}^t\text{Li}$  gave  $\beta$ -hydroxycarboxamides **116** in high optical purity through the formation of  $\alpha$ -lithiated ethers and subsequent 1,2-Wittig rearrangement (Scheme 41) <2001TL4865>.

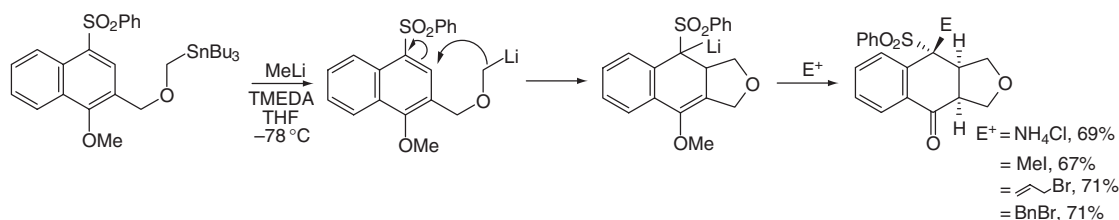


Scheme 41

The cyclization induced by tin–lithium transmetalation of the enantio-defined stannanes was shown to proceed with complete retention of configuration at the Li-bearing  $sp^3$ -carbon to afford the enantio-enriched  $\alpha,\beta$ -disubstituted tetrahydrofurans <1997TL8939>.

The phenylsulfonyl group promotes the dearomatizing cyclization of tethered organolithiums onto aromatic rings. With an ether tether, the cyclizations create a new tetrahydrofuran ring, and both cyclization and subsequent electrophilic quenches proceed with high levels of diastereoselectivity.

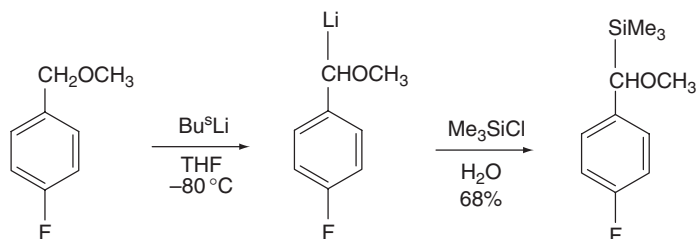
The sulfonyl group can be removed from the cyclized products oxidatively or reductively. The dearomatizing cyclization of a naphthylsulfone was used in the synthesis of a close structural analog of podophyllotoxin (Scheme 42) <2003OL831>.



Scheme 42

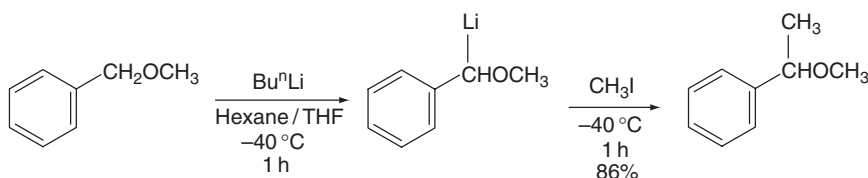
MOM-protected  $\alpha$ -hydroxytrimethylstannanes do not undergo tin–lithium exchange cleanly as their tributyl-counterparts do. Other protecting groups (e.g., *N,N*-diethylcarbamate) allow for clean transmetalation to occur presumably due to the formation of a more stable  $\alpha$ -alkoxyorganolithium species <1998TL9617>.

Aryl methyl alkyl ethers were metallated with  $\text{Bu}^n\text{Li}$  or  $\text{Bu}^s\text{Li}$  in THF at different temperatures, affording  $\alpha$ -alkoxy-substituted aryl methyllithium derivatives. At low temperatures, the organometallics derived from methyl and isopropyl ethers are sufficiently stable to react with added electrophiles affording the expected products. On the contrary, under similar conditions, lithium derivatives of primary alkyl benzyl ethers rapidly decay to benzyl alcohol (Scheme 43) <1998T12389>.



Scheme 43

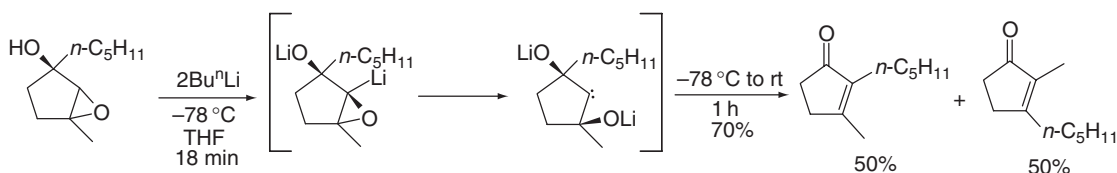
Stable  $\alpha$ -methoxy aryl methyl carbanions can be generated by metallation of aryl methyl methyl ethers with  $\text{Bu}^n\text{Li}$  in THF at  $-40^\circ\text{C}$ , avoiding Wittig rearrangement to the corresponding alkoxides. Reaction of these carbanions with various electrophiles afforded the expected products in satisfactory yields. Connection between the metallation procedure and the reductive electrophilic substitution of aryl methyl methyl ethers allowed the transformation of compounds into 2-arylpropanoic acids (Scheme 44) <1995TL5641>.



Scheme 44

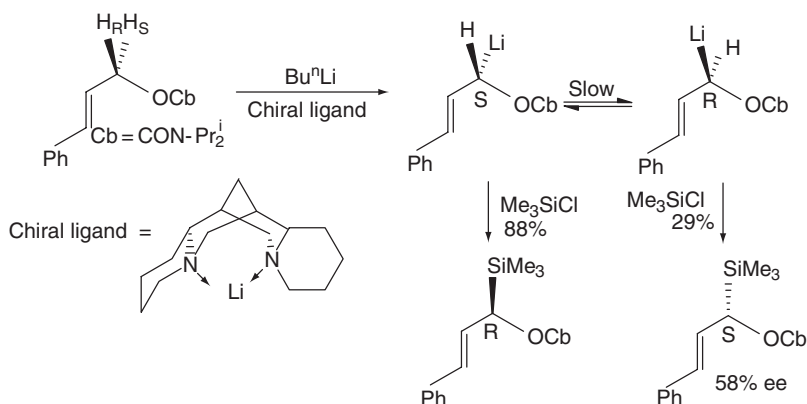


Several substituted five- and six-membered cyclic  $\alpha,\beta$ -unsaturated ketones were readily available by treatment of the corresponding  $\alpha$ -hydroxy epoxides with an organolithium reagent. The reaction involves a new carbenoid 1,2-alkyl rearrangement. Evidence for the carbenoid intermediate has been obtained by intramolecular trapping of the highly reactive species (Scheme 45) <1995JA12700>.



Scheme 45

The enantioselective lithiation and substitution of (*E*)-cinnamyl *N,N*-diisopropylcarbamate through the use of (–)-sparteine complexes reactions lead to diastereomeric lithium carbanion pairs that are configurationally unstable and equilibrate even at temperatures below  $-50^\circ\text{C}$ . The initially formed epimer (1*S*)-*epi*- is rapidly converted to the thermodynamically more stable (1*R*)- (in toluene solution). Carboxylation, acylation with acid chlorides, stannylation, and silylation take place at the  $\alpha$ -position with stereoinversion (79%–86% ee) (Scheme 46) <1998EJO2397>.



Scheme 46

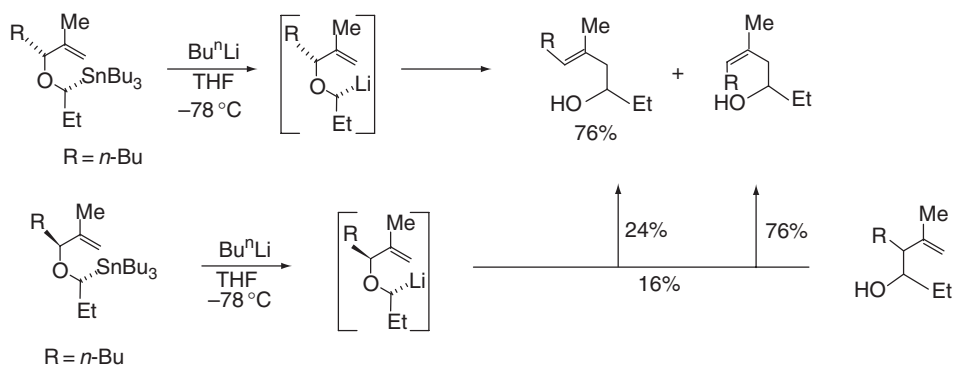
The metallated epoxides have been used as sources of carbenoids, and the solvent effects on competing intramolecular carbon–hydrogen and intermolecular carbon–lithium insertions in  $\alpha$ -alkoxy epoxide systems have been studied. The slow addition of the organolithium reagent to a dilute solution of the epoxide favored an intramolecular C–H insertion over an intramolecular C–Li insertion into the epoxide-derived carbenoids. Solvation of the carbenoid lithium atoms was decisive as regards the stereoselectivity of the process <1999JOC9279>.

Treatment of benzyl ethers of primary alcohols with *n*-butyllithium ( $\text{Bu}^n\text{Li}$ ) afforded terminal olefins in good yield <1996CL1039>.

#### (ii) By tin–lithium exchange

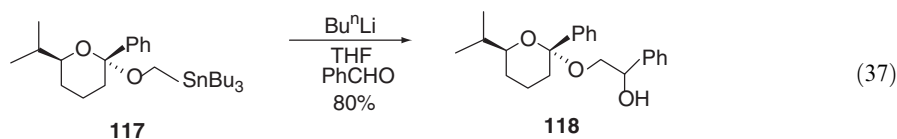
The [2,3]-Wittig rearrangement of (*E*)-crotyl propargylic ethers, when induced with a  $\text{Bu}^t\text{Li}$ /chiral bis(oxazoline) complex, was shown to provide high enantioselectivity (up to 89% ee) along with high diastereoselectivity <1998TL5513>.

The (*E*)/(*Z*)-selectivities in the [2,3]-Wittig rearrangements of secondary  $\beta$ -(methyl or silyl)-allylic ethers were shown to depend critically on the nature of groups on the carbanion terminus, thereby permitting elucidation of the structural requirements for attaining high (*Z*)-selectivity (Scheme 47) <1999TL6257>.

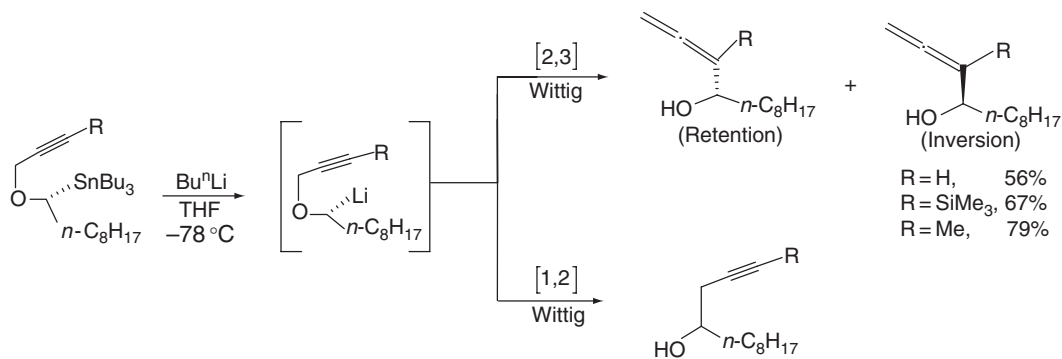


Scheme 47

A chiral derivative of tributylstannylmethanol **117**, readily prepared from L-valine, underwent Sn–Li exchange to provide an  $\alpha$ -alkoxyorganolithium that added to aldehydes to provide products **118** with up to 91:9 dr. The diastereoselectivity depended on the solvent and alkyl lithium used for transmetalation. Treatment of adducts with acid allowed recovery of the chiral auxiliary and diol with complete stereochemical integrity (Equation (37)) <2001OL2903>.

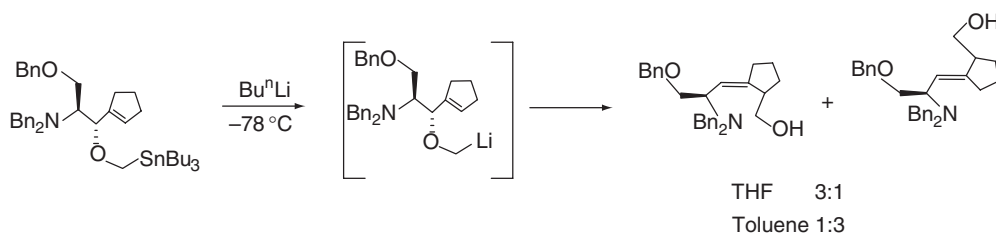


The [2,3]-Wittig rearrangement of an enantiomerically defined  $\alpha$ -propargyloxy stannane with butyllithium was shown to proceed with complete inversion of configuration at the Li-bearing terminus. The periselectivity ([2,3]- versus [1,2]-) of the rearrangement depended upon the nature of substituents on the group (Scheme 48) <1997SL1045>.



Scheme 48

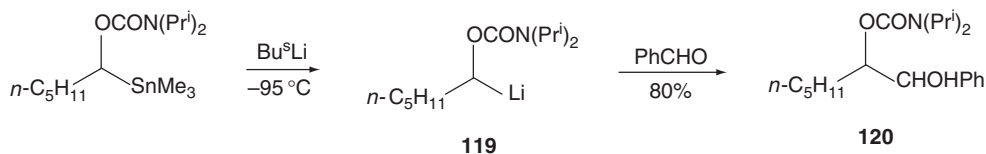
The Still–Wittig rearrangement gave opposite selectivities for (*Z*):(*E*)-alkenes in THF(3:1) versus toluene (1:3) in the synthesis of serine–proline dipeptide amide isoesters (Scheme 49) <2001OL1789>.



Scheme 49

Treatment of benzyl  $\gamma$ -(trimethylsilyl)propargyl ether with *n*-butyllithium was shown to afford the *ortho*-[2,3]-Wittig product in remarkable preference to the [1,2]-Wittig product. The factors governing the periselectivity in this type of carbanion rearrangement were discussed <2000CL1394>.

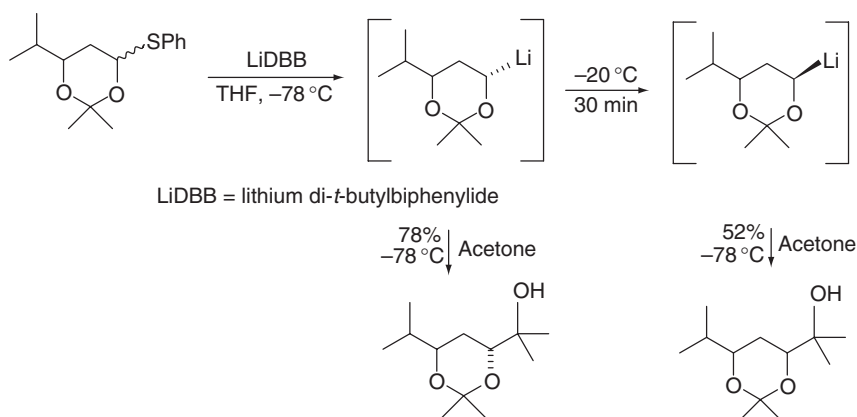
The carbamate-protected  $\alpha$ -alkoxyorganolithium **119** derived from the stannane could be trapped with benzaldehyde to provide the corresponding secondary alcohol **120** (Scheme 50) <1998TL9617>.



Scheme 50

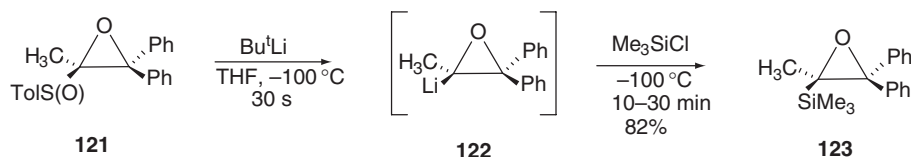
(iii) By reductive lithiation of thioethers and sulfoxides

Configurationally defined  $\alpha$ -alkoxylithium reagents were prepared by reductive lithiation of 4-(phenylthio)-1,3-dioxanes. A new and more general synthesis of 4-(phenylthio)-1,3-dioxanes has been developed on the basis of the reduction and *in situ* acetylation of 1,3-dioxan-4-ones. For each of the substitution patterns examined reductive lithiation gave the axial alkylolithium with 99:1 stereoselectivity. Equilibrations of these alkylolithium reagents were possible with unhindered substrates to give the equatorial alkylolithiums with excellent stereoselectivities. The more hindered axial alkylolithium reagents did not equilibrate efficiently. The equilibrium between alkylolithium reagents strongly favored the equatorial isomer. The inefficient equilibration with this hindered substrate was attributed to a slow rate of equilibration rather than insufficient driving force. These alkylolithium reagents could be coupled with a variety of electrophiles with retention of configuration by direct addition, copper-mediated coupling, or transmetalation to the corresponding alkylzinc reagents followed by copper-mediated coupling (Scheme 51) <1999JOC6849>.



Scheme 51

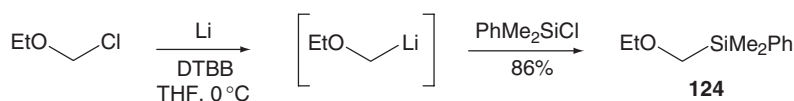
The first generation of destabilized oxiranyllithium and oxiranyl Grignard reagent from sulfinyloxiranes with Bu<sup>t</sup>Li or EtMgCl was described. Treatment of  $\alpha$ -methyl  $\alpha,\beta$ -epoxy sulfoxide (sulfinyloxirane) **121** with Bu<sup>t</sup>Li in THF at  $-100^\circ\text{C}$  gave oxiranyllithium **122** having a carbanion destabilizing group. The oxiranyllithium reacted with trimethylsilyl chloride to give a new epoxide **123** in good yield. Oxiranyl Grignard reagent could be generated by the reaction of the sulfinyloxirane having at least one aromatic group on its  $\beta$ -position with EtMgCl (Scheme 52) <1995TL8235>.



Scheme 52

(iv) *By halogen–lithium exchange*

The reaction of equimolecular amounts of chloromethyl ethyl ether and dimethylphenylsilyl chloride with excess lithium powder (1:7 molar ratio) and a catalytic amount of 4,4'-di-*t*-butylbiphenyl (DTBB) (5 mol.%) in THF at  $0^\circ\text{C}$  provided the corresponding ethyl (dimethylphenyl)-methyl silyl ether **124** (Scheme 53) <1996T1643>.



Scheme 53

#### 4.08.2.1.2 Magnesium

The systems containing magnesium  $\alpha$ - to an oxygen have been described in COFGT (1995). The most notable example was the preparation of a Grignard reagent through chloromethyl methyl ether in diethyl ether as a solvent. No further advances have occurred in this area since the publication of COFGT (1995) (chapter 4.08.2.1.2).

#### 4.08.2.1.3 Titanium or aluminum

As outlined in COFGT (1995), lithiated carbamates have been metal-exchanged with tris(dimethylamino)titanium chloride or diisobutylaluminum methanesulfonate resulting in titanium and aluminum intermediates, which were used in stereoselective aldol reactions with aldehydes and ketones.

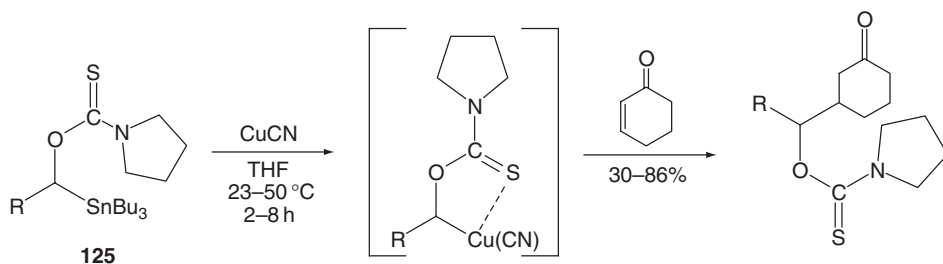
A metallocycle containing  $\alpha$ -alkoxy titanium species has been shown to be an intermediate in the reductive cyclization of enones to cyclopentanol catalyzed by bis(trimethylphosphine)titanocene <1996JA3182>. Lewis acid-assisted cleavage of an orthoformate could give rise to  $\alpha$ -alkoxy organozinc carbenoids in the synthesis of alkoxycyclopropanation reaction <1998CC2191>.

(*E*)-But-2-enyl *N,N*-diisopropylcarbamate after deprotonation to its lithium/(–)-sparteine complex gave with trialkyltin chlorides mixtures of the 3-oxy- and 1-oxy-substituted, enantiomerically enriched allylstannanes in high regioselectivity and in enantiomeric purity (95% ee) via a delithiotitanation (inversion) and detitanostannylation (*anti*- $\text{S}_{\text{E}}'$ ) sequence. The titanium tetrachloride mediated condensation of (*S*)- and (*R*)-allylstannanes with aldehydes or ketones proceeded via titanodestannylation to yield (*Z*)-*anti*-homoaldol products with complete chirality transfer <1996S141>.

#### 4.08.2.1.4 Copper or zinc

In COFGT (1995), several methods were described to generate  $\alpha$ -alkoxycuprates and  $\alpha$ -alkoxyzinc compounds. The major method to prepare  $\alpha$ -alkoxycuprates included a route from  $\alpha$ -alkoxystannanes by transmetalation with *n*-butyllithium, followed by the addition of copper(I) cyanide. The  $\alpha$ -alkoxyzincates have been prepared from iodomethyl esters with activated zinc in tetrahydrofuran.

The conjugate addition of  $\alpha$ -alkoxystannanes **125** via *in situ* transmetallation using catalytic copper(I) cyanide proceeded through  $\alpha$ -alkoxy copper species (Scheme 54) <1996TL3811>.



Scheme 54

#### 4.08.2.1.5 Mercury

The  $\alpha$ -alkoxyorganomercury compounds have been prepared by the photochemistry of  $\alpha$ -diazo-mercurials and the reaction of mercuric oxide/mercuric acetate with dialkyl-aralkylhydrazones. No further advances have occurred in this area since the publication of COFGT (1995) (chapter 4.08.2.1.5).

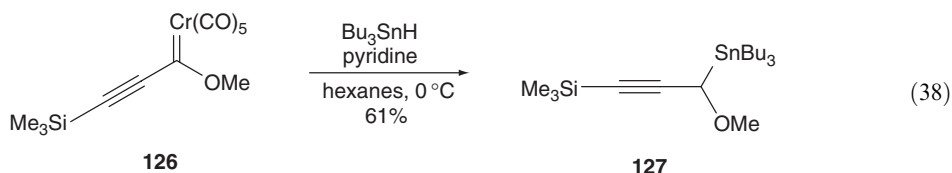
#### 4.08.2.1.6 Tin

The  $\alpha$ -alkoxystannanes were prepared from acylstannanes, from aldehydes and ketones, from tributylstannylmethyl iodide, from tributyltin chloride, and from tributylstannylacetals as described in COFGT (1995).

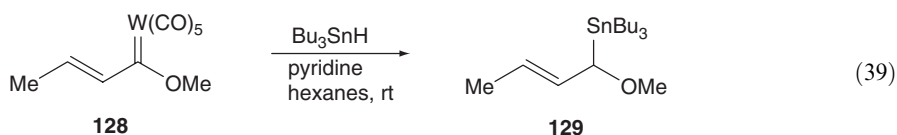
The following section outlines the generation of systems containing oxygen  $\alpha$  to tin.

##### (i) From hydrostannation

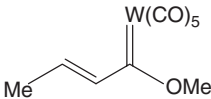
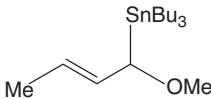
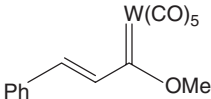
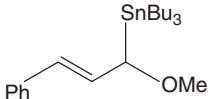
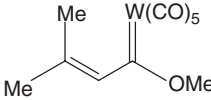
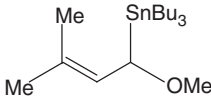
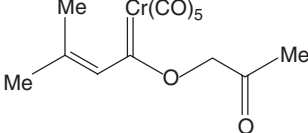
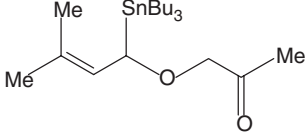
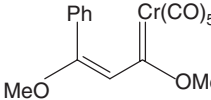
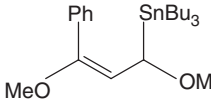
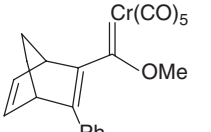
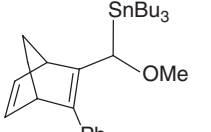
Hydrostannation of chromium alkynylcarbene complexes **126** with tributyltin hydride provided a facile, sterically controlled synthesis of alkoxy-substituted propargylstannanes **127**. The synthetic scope and mechanistic implications were reported (Equation (38)) <1995TL1011>.



Hydrostannation of readily available chromium and tungsten vinylcarbene complexes **128** with tributyltin hydride provided a facile synthesis of alkoxy-substituted allylstannanes **129**. The results are summarized in Table 6 <1995TL1007>. The preparation of acetal, keto, methoxy, and silyl-substituted stannane reagents was demonstrated (Equation (39)) <1995TL1007>.

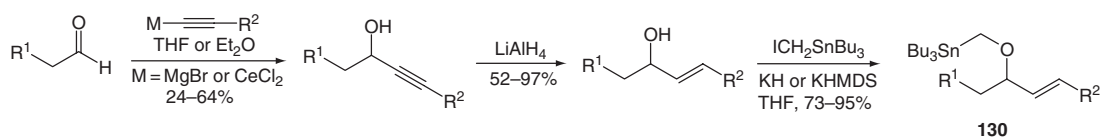


**Table 6** Hydrostannation reactions of carbene complexes

Carbene	Conditions	Product	Yield (%)
	Bu <sub>3</sub> SnH, 3.0 equiv. Pyridine, 6.0 equiv. Hexanes, rt		73
	Bu <sub>3</sub> SnH, 1.4 equiv. Pyridine, 3.0 equiv. Hexanes, 0 °C		58
	Bu <sub>3</sub> SnH, 3.0 equiv. Pyridine, 6.0 equiv. Hexanes, rt		71
	Bu <sub>3</sub> SnH, 1.4 equiv. DMAP, 3.0 equiv. Hexanes, THF, 0 °C		42
	Bu <sub>3</sub> SnH, 1.5 equiv. DMAP, 3.0 equiv. Hexanes, THF, 0 °C		69
	Bu <sub>3</sub> SnH, 1.1 equiv. DMAP, 3.0 equiv. Hexanes, THF, 0 °C		55

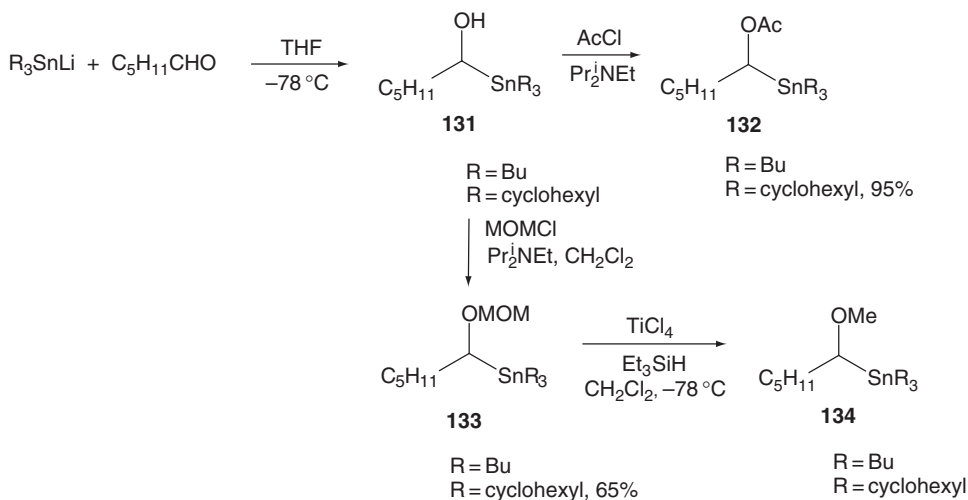
## (ii) From carbonyl compounds

The aldehydes were treated with metallated acetylide to give propargyl alcohol. After reduction of alkynes with LAH to obtain (*E*) alkenes, the allylic hydroxy group was deprotonated with KH or KHMDS and alkylated with iodomethyltributyltin to afford the desired stannylated methylallylic ether derivatives **130** (Scheme 55) <1996TL389>.

**Scheme 55**

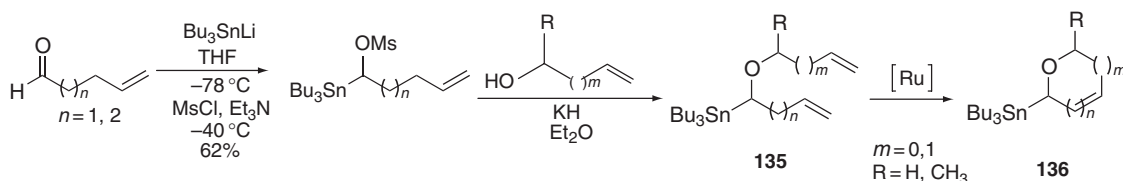
A method has been reported for the synthesis of chiral cyclopentanes using tin–lithium exchange and cycloalkylation reactions. The *sec*-butyllithium/(–)-sparteine-mediated deprotonation of an alkylcarbamate and subsequent substitution furnished a highly enantioenriched stannane as a stable carbanion equivalent. It was transformed into suitable cyclization precursors, which underwent tin–lithium exchange and stereoselective cycloalkylation when reacted with *n*-butyllithium, giving highly enantioenriched cyclopentanes in very good yields. A kinetic resolution was observed with a higher substituted stannane <2002OL2189>.

The nucleophilic addition of trialkyltinlithium with 1-hexanal resulted in the formation of  $\alpha$ -hydroxystannane **131**, which was acetylated to give acetylated stannane **132** in 95% yield. The corresponding MOM derivative **133** was also prepared in 65% yield. The Lewis acid-catalyzed reduction of the MOM ether with triethylsilane then provided the simple methyl ether derivative **134** (Scheme 56) <1996JOC6492>.



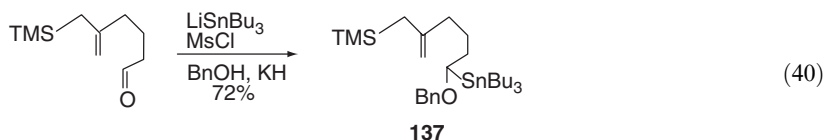
Scheme 56

The synthesis of  $\alpha$ -(alkoxyalkyl)stannane-substituted dienes and their conversion into eight-membered cyclic ethers via ring-closing metathesis was reported. The condensation of lithiotri-*n*-butylstannane 4-pentenal provided the hydroxystannane which was immediately converted to the mesylate in 62% overall yield. The displacement of the mesylate with allyl alcohol or 3-butenol provided dienes **135** followed by ring-closing metathesis with ruthenium **136** (Scheme 57) <1997JA6919>. The results are summarized in Table 7 <1997JA6919>.



Scheme 57

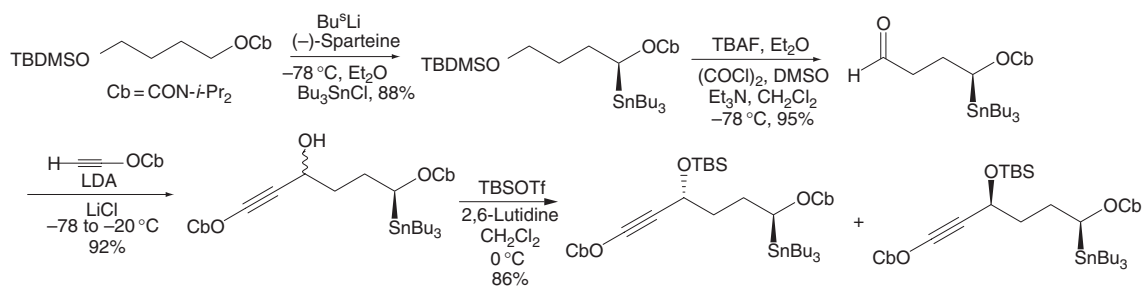
The allylsilane-tethered  $\alpha$ -stannyl ether **137** was prepared by the nucleophilic addition of the aldehyde with lithiotri-*n*-butylstannane followed by treatment with mesyl chloride, potassium hydride, and benzyl alcohol in 72% yield (Equation (40)) <2000JOC3252>.



The intramolecular *trans*-cyclocarbolithiation of the  $\alpha$ -lithiated 4-substituted 5-hexynylcarbamate (1*S*,4*RS*)- employing lithioestannylation was presented. The *cis*-/*trans*-5-*exo-dig* cyclization products were formed exclusively. The highly enantioenriched organotin precursor was synthesized via an asymmetric deprotonation of the corresponding alkylcarbamate by the chiral complex *sec*-butyllithium/( $-$ )-sparteine and subsequent substitution with tributyltin chloride (Scheme 58) <2002OL2193>.

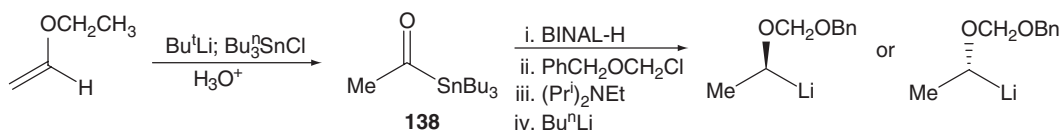
**Table 7** Ring-closing metathesis of acyclic tributylstannyl substituted dienes

Diene	Product	Yields (%)
		92
		74
		38
		84
		96
		96

**Scheme 58**

## (iii) From acylstannanes

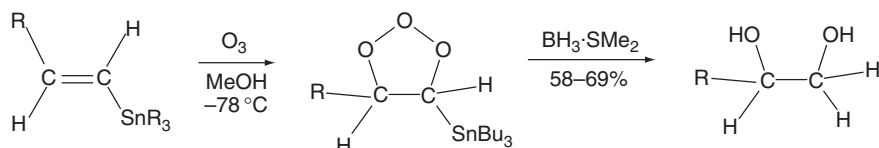
The acylstannane **138** was reduced with (*R*)-2,2'-dihydroxy-1,1'-binaphthyl-modified lithium aluminum hydride (*R*)-BINAL-H or (*S*)-BINAL-H followed by the protection of the hydroxyl group as the (benzyloxy)methyl ether. The reaction provided the nonracemic ( $\alpha$ -alkoxyalkyl)stannanes (Scheme 59) <1995JA10889>.

**Scheme 59**



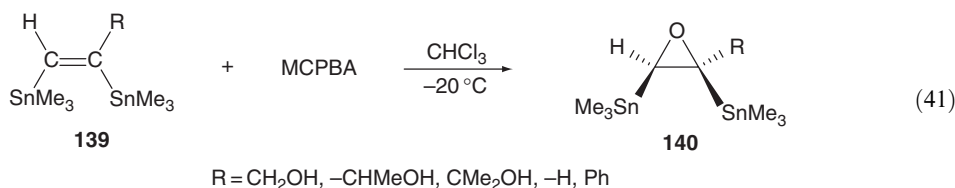
## (iv) From alkenylstannanes

Primary ozonides derived from alkenylstannanes displayed an unusual stability and can be transformed into 1,2-diols by treatment with dimethyl sulfide and borane–methyl sulfide complex. The observation has been incorporated into the development of a novel one-pot strategy for the conversion of alkynes into 1,2-diols (Scheme 60) <2002OL383>.

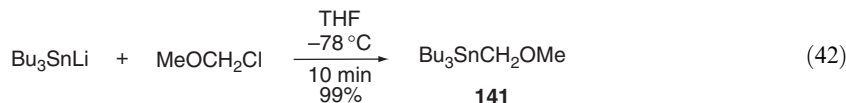


Scheme 60

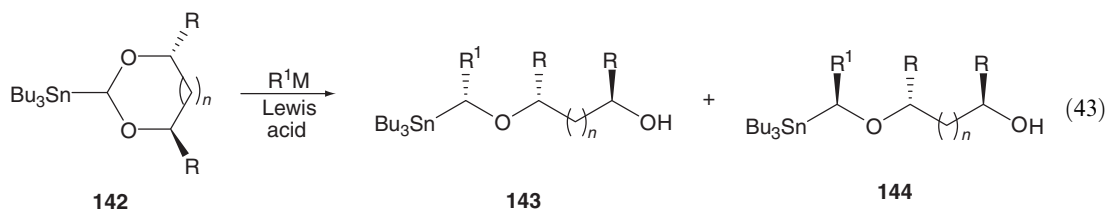
The *cis*-1,2-bis(trimethylstannyl) ethene **139** underwent smooth epoxidation with MCPBA to provide the corresponding *cis*-1,2-bis(trimethylstannyl)-substituted epoxides **140** (Equation (41)) <1995JOM239>.

(v) From tri-*n*-butylstannyllithium

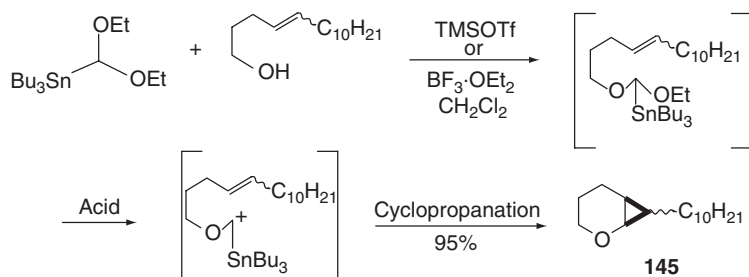
A convenient, general, and efficient one-pot synthesis of primary  $\alpha$ -alkoxy organostannanes **141** useful as hydroxymethyl anion equivalents was reported (Equation (42)) <1997SL1377>.

(vi) From tri-*n*-butylstannyl acetals

$\alpha$ -Tributylstannylacetals **142** derived from chiral C<sub>2</sub> symmetrical diols were reacted with miscellaneous organometallic reagents to give chiral  $\alpha$ -oxygenated organostannanes **143** and **144** in high yields. The Lewis acid-promoted ring opening of these chiral  $\alpha$ -tributylstannylacetals by organocopper reagents, allyltins, or silylenol ethers has been considered to occur mainly according to an *anti* process (dr = 70/30 to 93/7), the absolute configuration of the newly created center is *S* when the reaction was performed with Me<sub>2</sub>CuLi/BF<sub>3</sub> on the  $\alpha$ -stannylacetal derived from (2*S*,4*S*)-2,4-pentanediol. Of interest was the reverse stereochemical trend obtained using organo-aluminum reagents (dr = 30/70 to 15/85) since it becomes possible to reach selectively the new chiral center with a preferential (*R*)- or (*S*)-configuration from the same precursor. The obtained  $\alpha$ -alkoxyalkylstannanes can be transmetalated with *n*-butyllithium (THF, –78 °C) to give configurationally stable  $\alpha$ -alkoxyalkyllithiums. Furthermore, if desired, the enantioenriched  $\alpha$ -alkoxyalkylstannanes derived from 2,4-pentanediol can be converted into enantioenriched  $\alpha$ -hydroxyalkylstannanes (subsequently protected as MOM derivatives) with retention of configuration at the asymmetric carbon using an appropriate oxidation- $\beta$ -elimination sequence (Equation (43)) <1997T7615>.



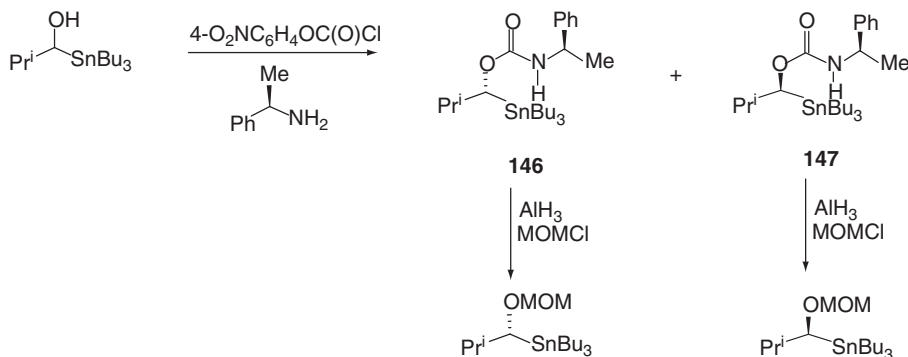
Reactions of a tin-substituted acetal with alkenols in the presence of an acid resulted in a facile transacetalization followed by intramolecular cyclopropanation to give the cyclized products **145** in high yields and stereoselectivity (Scheme 61) <1999TL1717>.



Scheme 61

(vii) Kinetic resolution of  $\alpha$ -hydroxystannanes

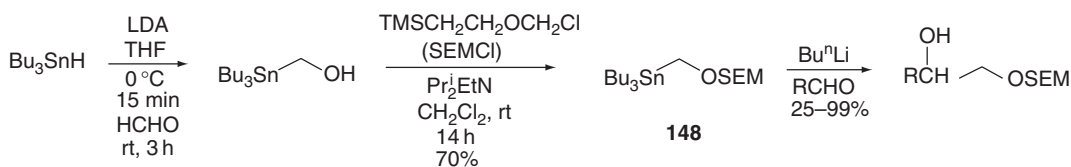
Norephedrine carbamate derivatives of  $\alpha$ -hydroxystannanes **146** and **147** could be readily prepared and the resulting diastereomers were separable by column chromatography. Removal of the carbamate moiety by reduction provided enantiomerically enriched  $\alpha$ -hydroxystannanes (Scheme 62) <2002T10287>.



Scheme 62

(viii) From nucleophilic displacement

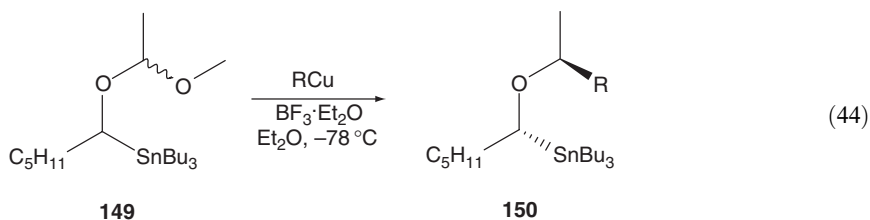
Tri-*n*-butyl[2-(trimethylsilyl)-ethoxymethoxymethyl]stannane **148** was used as a protected precursor for a hydroxymethyl anion which was added to various carbonyl and carboxyl electrophiles (Scheme 63) <2000SL455>.



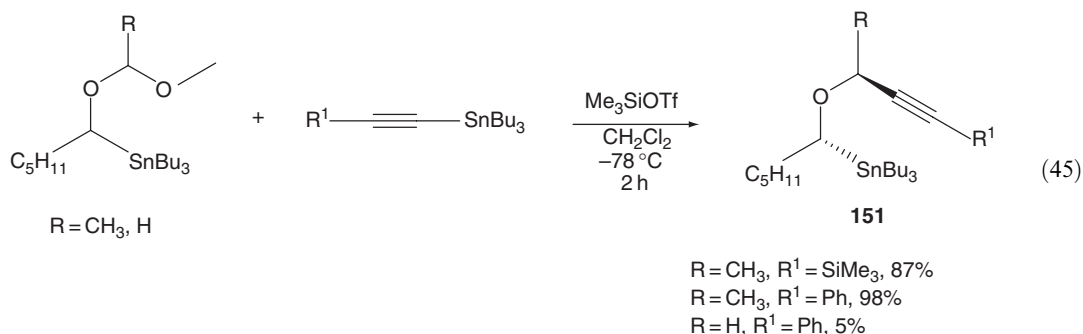
Scheme 63

## (ix) From nucleophilic addition

The reaction of a stannyl-substituted mixed acetal **149** with organocopper reagent was performed in the presence of a Lewis acid. The stannyl-substituted ether **150** was obtained in good yield using boron trifluoride as the Lewis acid (Equation (44)) <1995TL7799>.

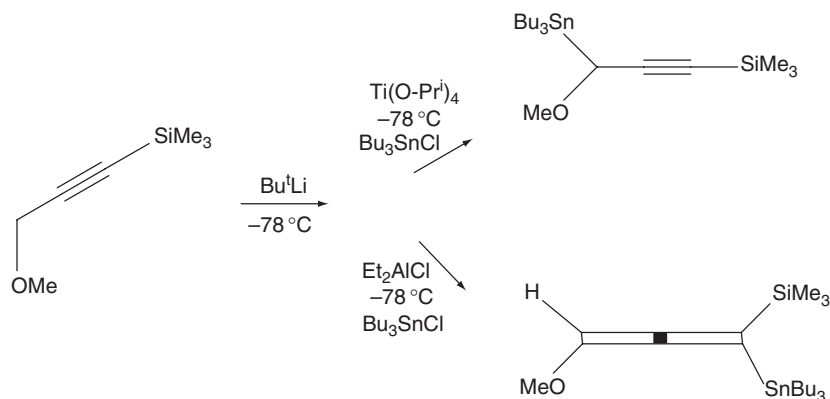


The regio- and stereoselective addition of alkynylstannanes to the stannyl-substituted mixed acetals resulted in propargylic ether derivatives **151** in excellent yields (Equation (45)) <1996TL3819>.



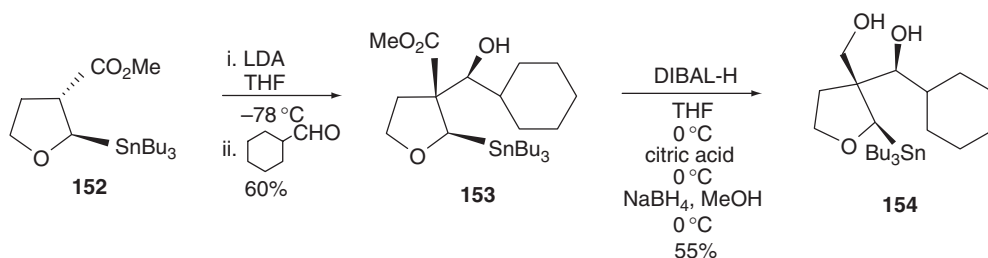
## (x) From deprotonation of ethers

The reactivity of the propargyl and allenyllithium intermediates was examined when submitted to transmetalation and subsequent tri-*n*-butyltin chloride quench. The metallation was conducted with *t*-butyllithium. After transmetalation of propargyllithium and allenyllithium with titanium tetrakisopropoxide, tri-*n*-butyltin chloride addition to the mixture gave propargylstannane in 89% yield. When the transmetalation was carried out with diethylaluminum chloride, quenching with tri-*n*-butyltin chloride resulted in the formation of the allenylstannane in 83% yield (Scheme 64) <1996TL5519>.



Scheme 64

The reaction of (tetrahydrofuran-2-yl)tri-*n*-butylstannane **152** with LDA followed by treatment with cyclohexane carbaldehyde afforded the alcohol **153** which upon reduction with DIBAL-H and sodium borohydride gave the corresponding stannane diol **154** (Scheme 65) <1996TL9115>.

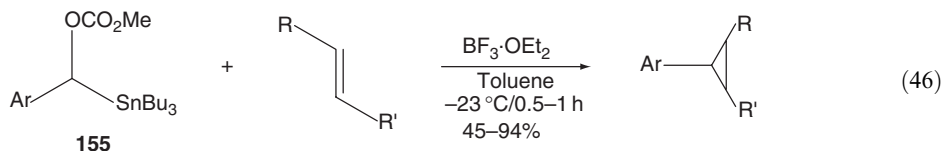


Scheme 65

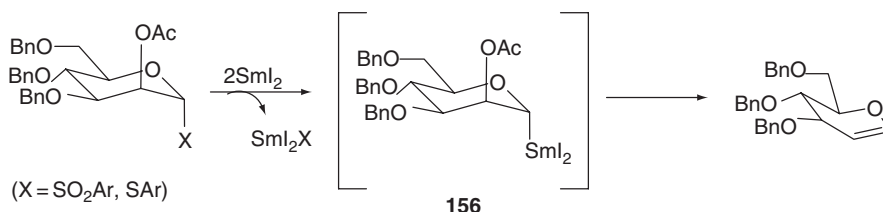
*(xi) Miscellaneous methods*

The synthesis of substituted lactones has been carried out by the reaction of  $\alpha$ -(benzyloxy)crotyl-stannane with aldehydes in the liquid phase and on a solid support <2001JOC7195>. The reaction of  $\alpha$ -stannylmethylithium with carbon monoxide generated the acyllithium, which underwent anionic 1,2-stannyl rearrangement to give the enolate derivative of an acyltin. The acyltin underwent reaction with aldehydes to provide the corresponding  $\alpha$ -alkoxystannyl compounds <1999JOM171>.

The acid-promoted cyclopropanation reactions of  $\alpha$ -((alkoxycarbonyl)oxy)stannanes **155** with alkenes were studied (Equation (46)) <1997JA11986>.

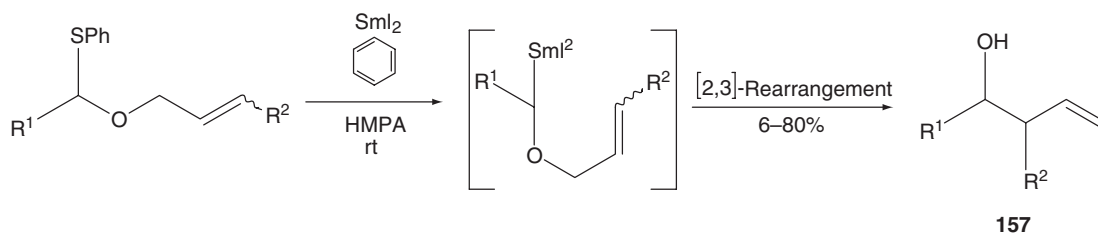
**4.08.2.1.7 Samarium**

The samarium-promoted reaction of cyclohexanone with mannosyl pyridylsulfones has been shown to proceed with  $\alpha$ -alkoxy samarium species <1997TL1767>. The samarium diiodide promoted radical cyclization leading to the synthesis of 1,2-*cis*-C-glycoside has been shown to proceed through  $\alpha$ -alkoxy samarium species **156** (Scheme 66) <1997CEJ1342>.



Scheme 66

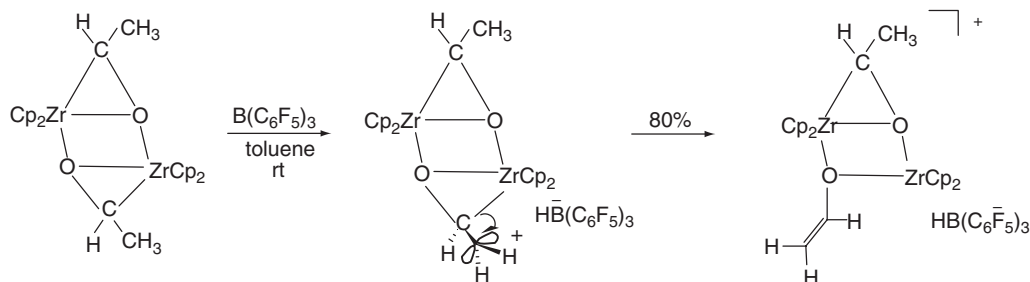
The samarium iodide promoted [2,3]-Wittig rearrangement of *O,S*-acetals yielding homoallyl alcohols **157** has been shown to occur through  $\alpha$ -alkoxy samarium species (Scheme 67) <2001TL415>.



Scheme 67

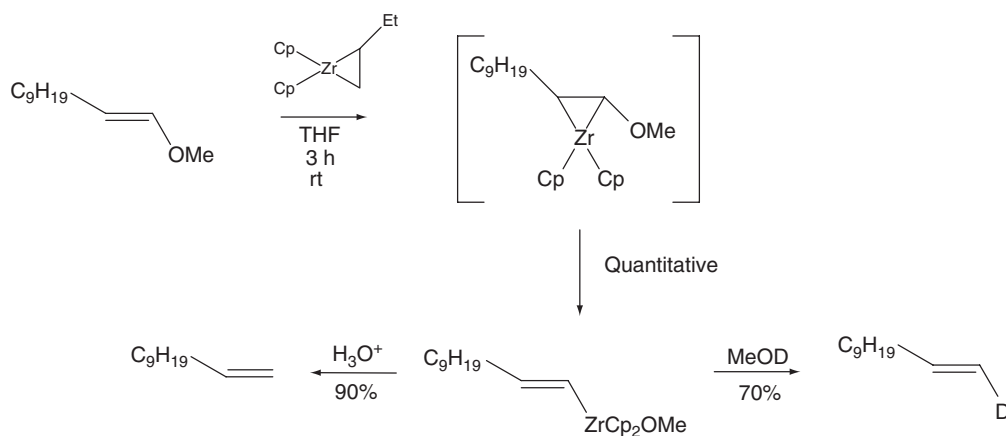
## 4.08.2.1.8 Zirconium

Tris(pentafluorophenyl)borane, a strong Lewis acid, reacted with the ( $\eta^2$ -acetaldehyde)zirconocene dimer by hydride transfer from the methyl group of an acetaldehyde ligand to boron. One of the metallaoxirane moieties of the dizirconium complex was then opened to give a salt that was isolated with an 80% yield (Scheme 68) <1996JOM263>.



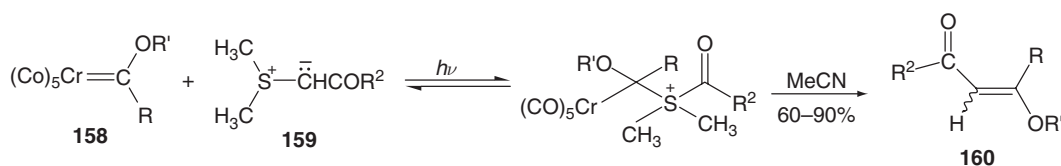
Scheme 68

Lithiated epoxynitriles inserted efficiently into alkenylzirconocene chlorides via a 1,2-metalate rearrangement to form intermediates containing an  $sp^3$  carbon attached to oxygen and zirconium, which resulted in substituted 2-cyano-1,3-dienes <2000TL6201>. The addition of (*E*)-methoxy enol ether to the zirconocene complex provided a vinylzirconium derivative, which was hydrolyzed to the corresponding alkene and underwent reaction with MeOD to provide deuterium substituted (*E*)-alkene (Scheme 69) <2000JOC7218>.



Scheme 69

It has been demonstrated that the reaction of chromium carbene complexes **158** with sulfur ylides **159** represented a new stereoselective entry to 2-acylvinylethers **160** (Scheme 70) <1996OM4612, 1996OM2764>.

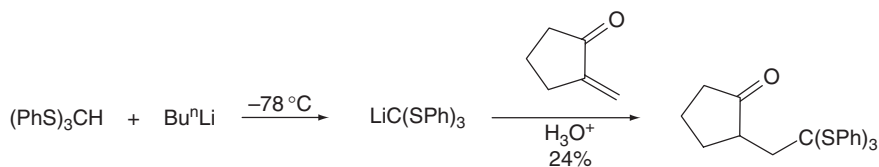


Scheme 70

**4.08.2.2 Functions Bearing Sulfur— $R_2^1C(SR^2)M$ , etc.****4.08.2.2.1 Lithium***(i) By direct deprotonation*

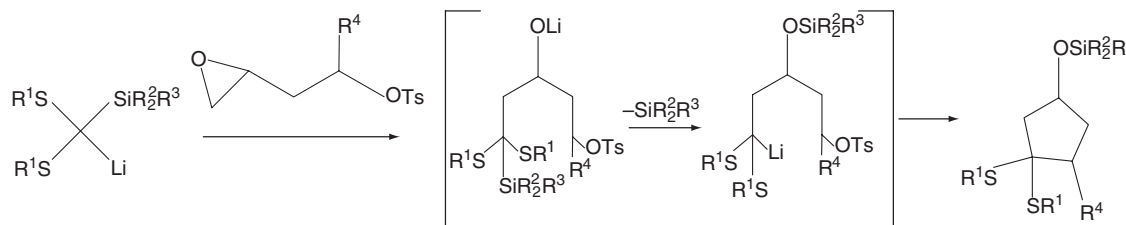
*(a) From sulfides.* The intramolecular carbolithiation of vinyl sulfides at  $-105^\circ\text{C}$  in THF had been found to be stereospecific regarding the formation of the new carbon–carbon bond and nonstereospecific regarding the formation of the new carbon–lithium bond. The resulting  $\alpha$ -durylthioalkyllithium compounds were configurationally stable at  $-105^\circ\text{C}$  and epimerized at  $-90^\circ\text{C}$  <1999JCS(P2)183>.

Tris(methylthio)methane was deprotonated with *n*-butyllithium to give tris(phenylthio)methyl-lithium, which reacted with 2-exomethylene cyclopentanone to provide the corresponding conjugated product bearing a phenylthio group after hydrolysis. Better yields were realized in the presence of trimethylsilyl chloride (Scheme 71) <1995TL8925>.

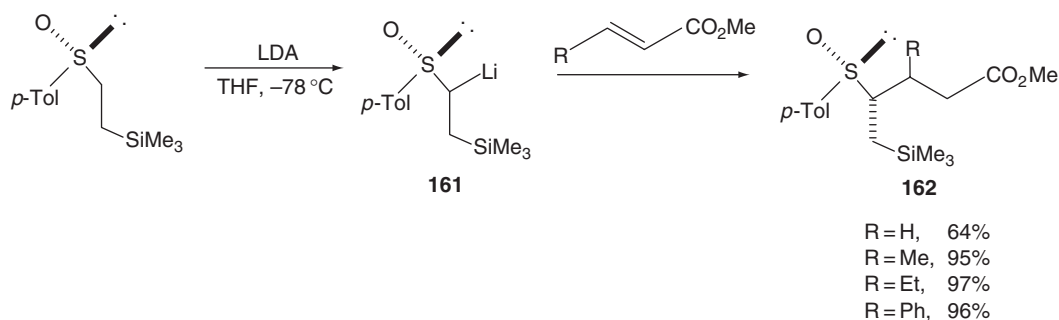
**Scheme 71**

The reaction of phenylcyclopropyl thioether with *n*-butyllithium in the presence of TMEDA and an electrophile such as an aldehyde or a ketone provided the corresponding addition product. The addition product was treated with an excess of lithium powder and a catalytic amount of 4,4'-di-*t*-butylbiphenyl (DTBB), and finally reaction with a second carbonyl compound, either an aldehyde or a ketone gave, after hydrolysis, the expected cyclopropane 1,3-diols derivatives <2001T4411>.

1,3-Functionalized cyclopentanes, cyclohexanes, and cycloheptanes were obtained by addition of lithiated silyldithioacetals to epoxyhomoallyltosylates. The reaction involved a cascade of epoxide ring opening, Brook 1,4-rearrangement, and tosylate substitution. The method was particularly suitable for the preparation of cyclopentanes, whereas cyclohexanes and cycloheptanes were formed in yields less than 49%. Use of enantiomerically pure epoxides provided optically active cyclopentanes as well as oxetanes (Scheme 72) <1996LA1811>.

**Scheme 72**

*(b) From sulfoxides.* A stereoselective conjugate addition of the  $\alpha$ -carbanion derived from *p*-tolyl-2-(trimethylsilyl)ethylsulfoxide have been studied. Reaction of *p*-tolyl  $\alpha$ -lithio- $\beta$ -(trimethylsilyl)ethylsulfoxide **161** with  $\alpha,\beta$ -unsaturated esters gave the conjugate addition products **162** as a single diastereomer (Scheme 73) <1997SL449, 2000JOC1758>.

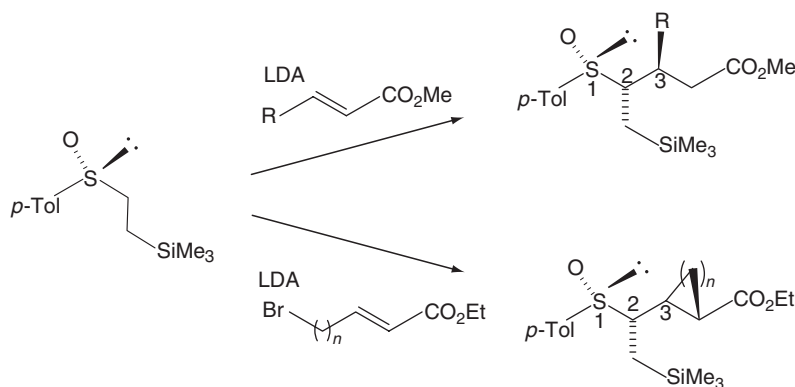


Scheme 73

Reactions of  $\alpha$ -sulfinylcarbanions, derived from *p*-tolylsulfoxides bearing various alkyl groups, with a variety of electrophiles were examined. The reaction of  $\alpha$ -sulfinylcarbanions, derived from the  $\beta$ -silylethylsulfoxides, with ketones or trimethyl phosphates gave the *syn* products with high stereoselectivity. Interaction between the silicon in the trialkylsilyl group and the carbonyl oxygen in nucleophiles was postulated to stabilize the transition state, leading preferably to the *syn* diastereoisomers. This novel silicon–oxygen interaction was supported by an MO calculation study using the MOPAC 93/PM3 and the Gaussian 94 Beche3LYP/3-21 + G\* methods [\[2000JOC469\]](#).

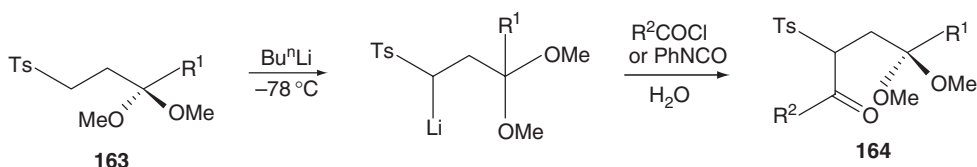
Reaction of thiomethylphosphonates with aryl (or butyl) tellurenyl halides and aldehydes under basic conditions provides moderate-to-good yields of ketone thio (telluro) acetals, with vinylic sulfides being by-products of this transformation. Tellurium–lithium exchange by reaction with Bu<sup>n</sup>Li yielded vinylorganolithium species, which were captured with several electrophiles. In the case of DMF, *Z*- $\alpha$ -phenylthio- $\alpha,\beta$ -unsaturated aldehydes were obtained [\[1999T7421\]](#).

The reaction of lithiated (*R*)-2-(trimethylsilyl)ethyl *p*-tolylsulfoxide with  $\alpha,\beta$ -unsaturated esters gave 1,4-conjugate addition products as single stereoisomers, whereas the reaction of (*R*)-2-(trimethylsilyl)ethyl *p*-tolylsulfoxide with 4-, 6-, or 7-haloalkenoates afforded cyclopropane-, cyclopentane-, or cyclohexanecarboxylates, respectively, with high stereoselectivity (Scheme 74) [\[1997SL449\]](#).



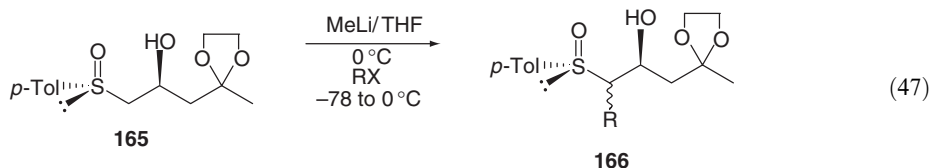
Scheme 74

The lithiation of 1,1-dimethoxy-3-tosylpropane **163** followed by reaction with acylchlorides afforded the corresponding keto-ether **164** (Scheme 75) [\[1995T2763\]](#).



Scheme 75

With the  $\delta$ -carbonyl functionality properly protected,  $\beta$ -hydroxy- $\delta$ -dioxolane sulfoxides **165** could be regioselectively alkylated by treatment with methyl lithium in THF and quenching the resulting dianion with a variety of simple alkyl halides to yield sulfoxides **166** in good yields (Equation (47)) <1995TL4559>.



A new pathway of remote asymmetric induction in Michael reactions involving allylic  $\alpha$ -phenylsulfonylcarbanions in chiral donors has been disclosed. The transmission of asymmetry was found to depend on the presence of an aromatic nucleus bound to the chiral center <1999JOC8>.

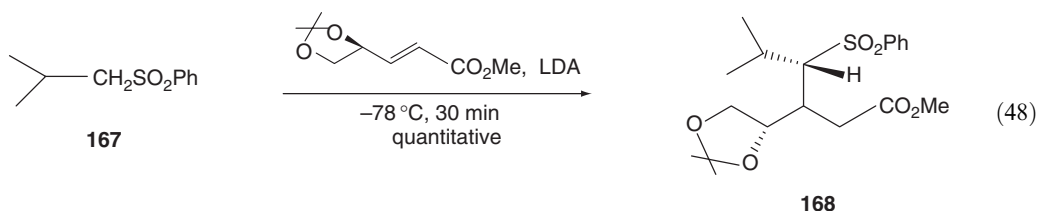
(*E*)- and (*Z*)-1-(Phenylsulfonyl)-4-(trimethylsilyl)-2-butenes were converted by Bu<sup>n</sup>Li to (*E*)- and (*Z*)-1-lithio-1-(phenylsulfonyl)-4-(trimethylsilyl)-2-butenes with retention of the initial stereochemistry. Reactions with electrophiles (protio and deuterio acids, primary, secondary, and benzyl halides, chloroformates, chlorothioformates, acid chlorides, epoxides, trialkylsilyl chlorides, and triethylgermanylchloride) in THF or THF/HMPA gave the corresponding (*E*)- and (*Z*)-1-(phenylsulfonyl)-1-substituted-4-(trimethylsilyl)-2-butenes with stereochemical retention <1998JOC4181, 1998JOC4193>.

The reactions of  $\alpha$ -arylsulfonylcarbanions generated from 3-hydroxy- and 3-alkoxy-1-(arylsulfonyl)cyclohexane with some electrophiles were suggested to proceed with inversion of configuration at the carbanionic centers <1998JCS(P1)3519>.

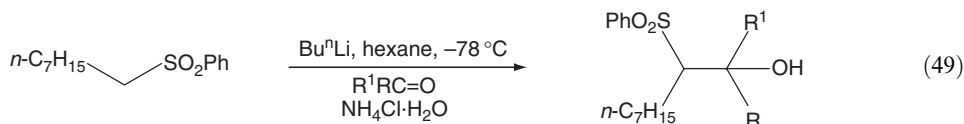
Trimethylsilyldithiane was metallated with *t*-butyllithium in HMPA followed by treatment with epoxide to afford the corresponding product <1997JA6925>. Similarly, the deprotonated dithiane was reacted with an aldehyde to provide the corresponding secondary alcohol <1997TL8667>. The dithiane was metallated with *t*-butyllithium in HMPA/THF followed by alkylation with an epoxide and silylation to afford the corresponding product <1997TL8671>.

The thia-Sommelet rearrangement of sulfonium salts with lithium diisopropylamide at low temperature leading to the formation of hexatrienes containing quaternary stereogenic centers was reported <1998JA841>.

(*c*) From sulfones. The sulfone **167** depicted was deprotonated with lithium diisopropylamide and treated with a Michael acceptor to provide the corresponding conjugate addition product **168** (Equation (48)) <1996TA2423>.

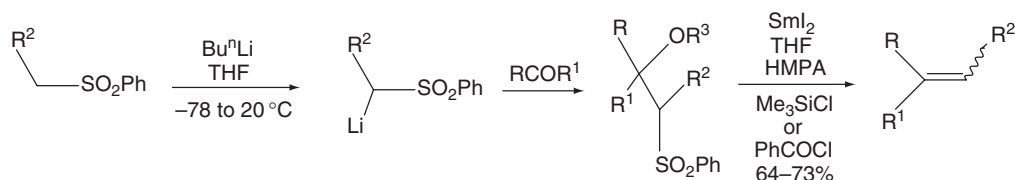


Using 1,2-dimethoxyethane as solvent in the addition of metallated sulfones to aldehydes can increase yields in the first step of the Julia–Lythgoe olefin synthesis. The addition of metallated sulfones to ketones was also discussed (Equation (49)) <1996TL5283>.



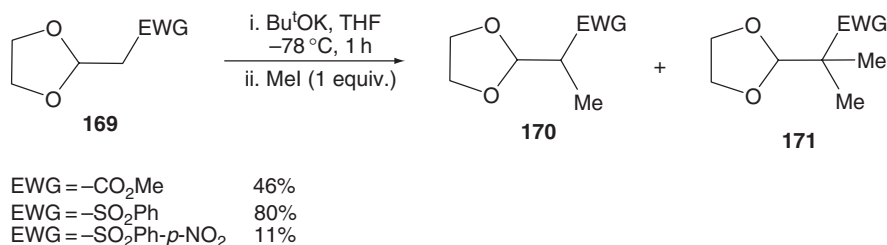
Modification of the Julia–Lythgoe olefination reaction between ketones and primary sulfones leads to trisubstituted alkenes in good overall yields. Samarium diiodide was shown to play a crucial role in the reductive elimination step (Scheme 76) <1996TL2089>.





Scheme 76

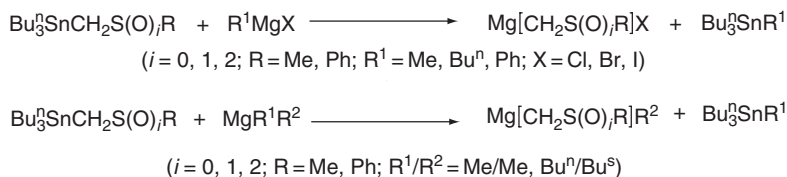
Tetrahydrofuran solutions of acetals **169** reacted with a stoichiometric amount of potassium *t*-butoxide, and the resulting carbanion was quenched with methyl iodide to provide the corresponding methylated products **170** and **171** (Scheme 77) <2001T4461>.



Scheme 77

#### 4.08.2.2.2 Beryllium or magnesium

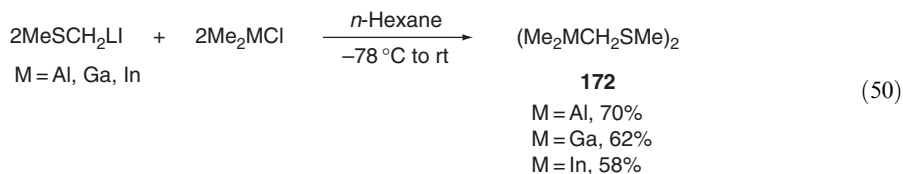
Diorganomagnesium and Grignard reagents were found to react with sulfur-stabilized methyltin compounds in a 1:1 molar ratio yielding sulfur-functionalized methylmagnesium compounds (Scheme 78) <2002JOM111>.



Scheme 78

#### 4.08.2.2.3 Aluminum, indium, or gallium

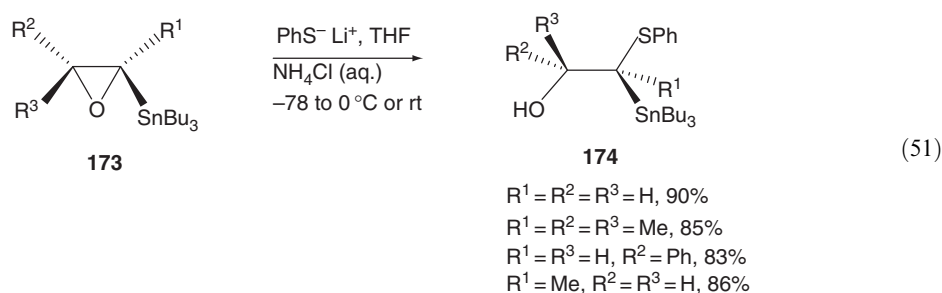
The dimethyl(methylthiomethyl)metal compounds **172** (Me<sub>2</sub>MCH<sub>2</sub>SMe)<sub>2</sub> (M = Al, Ga, In) have been prepared from LiCH<sub>2</sub>SMe and the respective dimethylmetal chlorides. Unlike the corresponding lithium compounds, the thiomethyl compounds with AlMe<sub>2</sub> and GaMe<sub>2</sub> groups are sublimable and soluble in nonpolar solvents. The compounds (Me<sub>2</sub>MCH<sub>2</sub>SMe)<sub>2</sub> have been characterized by elemental analyses, multinuclear NMR spectroscopy, and, in the cases M = Al and Ga, by single-crystal X-ray crystallography. The Al and Ga compounds are dimeric in the solid and in nondonor solvents, but are cleaved by stronger donors such as ethers and amines (Equation (50)) <2002OM3471>.



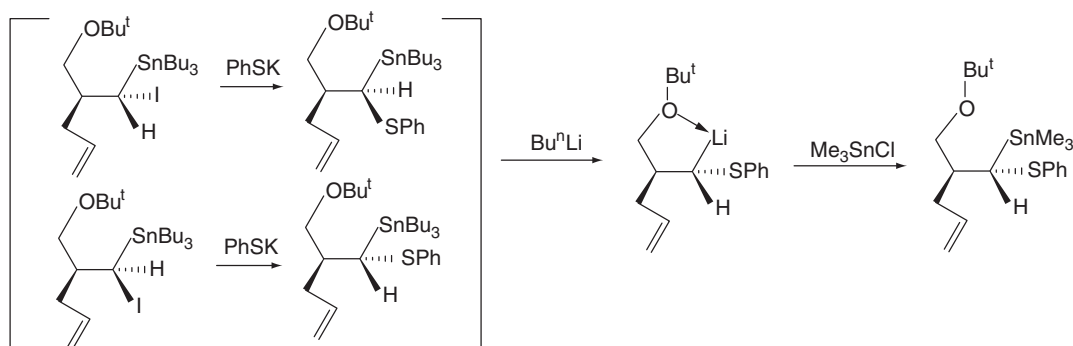
**4.08.2.2.4 Tin**

As outlined in COFGT (1995), the reaction between alkyl- and arylthiomethylolithiums prepared from the corresponding sulfides and  $\text{Bu}^n\text{Li}/\text{TMEDA}$ , and trialkyltin chlorides was reported to give  $\alpha$ -stannyl thioethers.

Unsubstituted and  $\alpha$  or  $\beta$  C-substituted epoxystannanes **173** reacted with lithium phenyl sulfide to give regio- and stereodefined  $\alpha$ -phenylthio- $\beta$ -hydroxystannanes **174** resulting from the  $\alpha$ -opening with inversion of configuration. Alternatively,  $\alpha$ - or  $\beta$ -*trans*-silylepoxytannanes afforded stereospecific  $\alpha$ - or  $\beta$ -silylated vinyl sulfides formed by nucleophilic attack at the carbon which bore the tin group and subsequent *syn*-elimination of  $\text{HOSnBu}_3$  (Equation (51)) <2001TL8993>.



It was reported that various chelated organo-*gem*-bismetallics could react with two different electrophiles leading to a new asymmetric stereogenic center with good diastereoselectivity (Scheme 79) <1995SL723>.



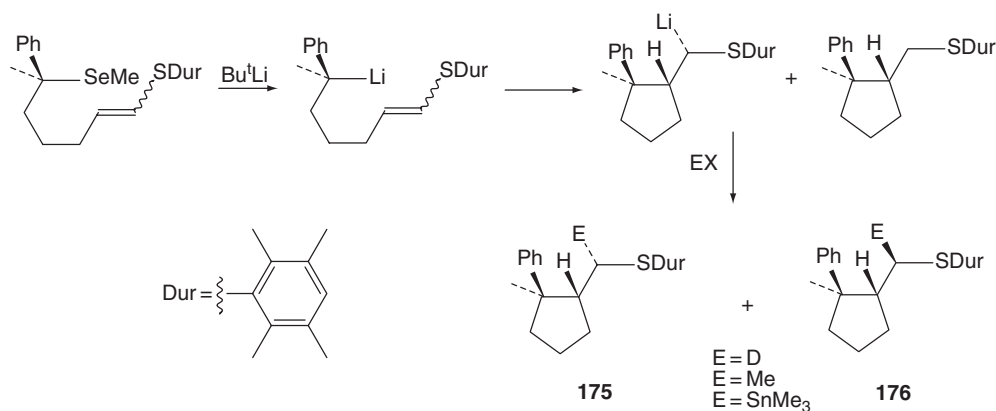
**Scheme 79**

Intramolecular carbolithiation of vinyl sulfides to generate configurationally stable  $\alpha$ -durylthioalkyllithium compounds at  $-105^\circ\text{C}$  in THF showed carbolithiation to be nonstereospecific regarding the newly formed lithium bearing stereocenter.  $\alpha$ -Durylthioalkyllithium could undergo reaction with trimethyltin chloride to provide  $\alpha$ -thio tin compounds **175** and **176** (Scheme 80) <1997CC2189, 1999JCS(P2)183>.

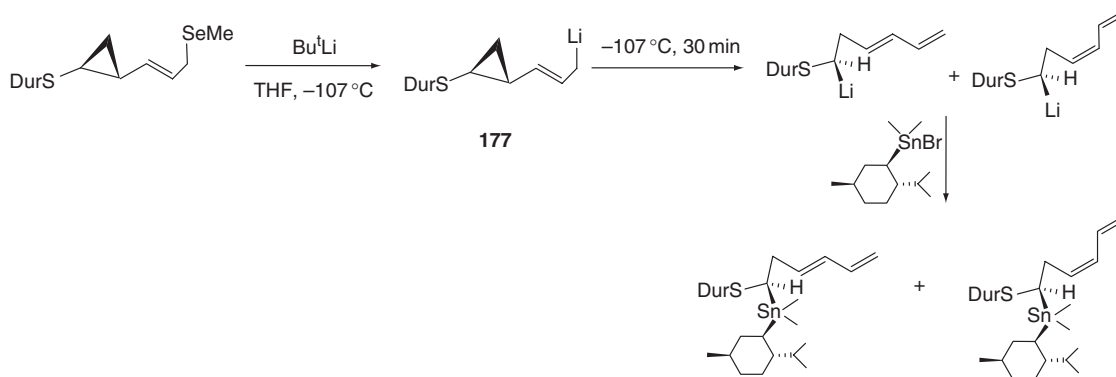
Ring opening of the cyclopropylallyllithium compound **177** to give the  $\alpha$ -duryl thio-substituted alkylolithium compound proceeded in a stereochemically defined manner at the lithium-bearing stereocenter (Scheme 81) <1999CC33>.

**4.08.2.2.5 Iron**

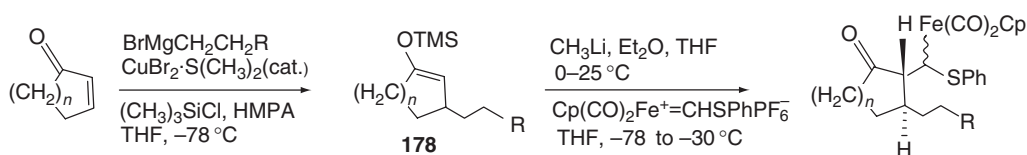
Silyl enol ethers **178** were prepared by copper-promoted conjugate addition of Grignard reagents to cyclopentenone in the presence of trimethylsilyl chloride. The silyl derivative reacted with methylolithium to generate enolates. Addition to the thiocarbene complex produced the substrates as mixtures of diastereomers with respect to the iron-bearing carbon atom (Scheme 82) <2001JOC3449>.



Scheme 80



Scheme 81



Scheme 82

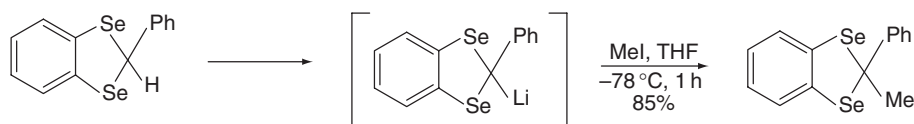
#### 4.08.2.3 Functions Bearing Selenium or Tellurium— $\text{R}_2^1\text{C}(\text{SeR}^2)\text{M}$ , etc.

##### 4.08.2.3.1 Lithium

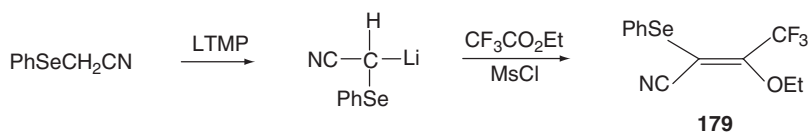
The synthesis and reactivity of 1,3-benzodiselenolanes toward lithium diisopropylamide and butyllithiums were described as well as the original syntheses of aromatic compounds bearing selenium atoms (Scheme 83) <1999TL6571>.

(Phenylselenenyl) acetonitrile was treated with lithium 2,2,6,6-tetramethylpiperidide (LTMP) to give  $\alpha$ -seleno carbanion, which was reacted with ethyltrifluoroacetate to provide the corresponding enol ether **179** (Scheme 84) <2002JOC5678>.

After a detailed study of the hydrozirconation of the acetylenic selenides, it was established that the initial hydrozirconated product would involve an intermediate containing  $\alpha$ -seleno zirconium intermediate <1998T2371>.



Scheme 83

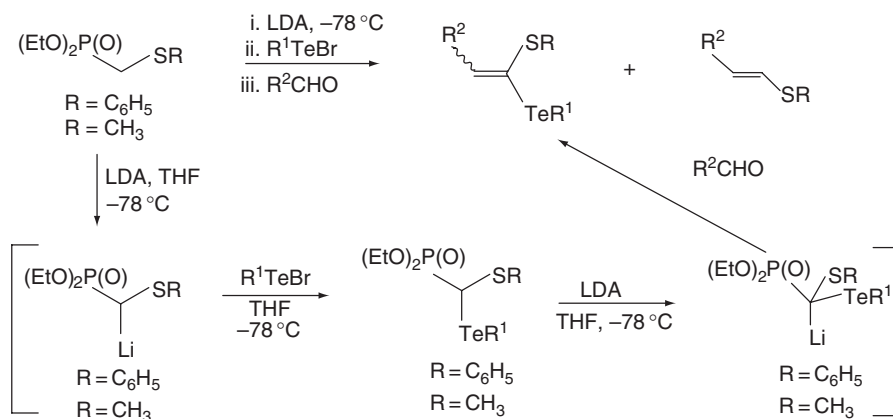


Scheme 84

#### 4.08.2.3.2 $\alpha$ -Telluro lithium species

As indicated in COFGT (1995), selenium–lithium exchange with an alkyllithium has been successfully used to generate  $\alpha$ -telluro lithium species.

The semistabilized telluronium ylides generated *in situ* from the corresponding telluronium salts reacted with  $\alpha,\beta$ -unsaturated ketones to afford *cis*-2-vinyl-*trans*-3-substituted cyclopropyl ketones with high stereoselectivity and in high-to-excellent yields. Conversely, these enones gave *trans*-2-vinyl-*trans*-3-substituted cyclopropyl ketones, when the corresponding arsonium ylides were employed. Other factors such as solvent and amount of base also influenced the stereochemistry of this reaction. A mechanistic rationale was discussed briefly (Scheme 85) <1999T7421, 1997JOC954>.



Scheme 85

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# 4.09

## Functions Bearing Two Nitrogens

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## 4.09.1 INTRODUCTION

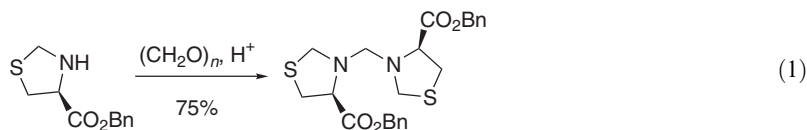
Although the title of this series implies absolute comprehensiveness, the ubiquity of the functions bearing two nitrogen atoms connected to an  $sp^3$ -carbon atom certainly prevents complete coverage of the topic. Nevertheless, an attempt has been made to be as comprehensive as possible, and the author apologizes to colleagues whose published work was not considered during the preparation of this chapter. The number of general reaction schemes is limited in favor of detailed explicit examples. Less important work (from the standpoint of the author) was summarized within the text by using systematic names of compounds that will allow the specialist to identify any work of interest. Few speculative statements have been made concerning the potential generality of the summarized procedures. The interested reader should consult the original literature to draw conclusions about whether or not a certain method may be of value for his/her intention. The most significant progress has been made in the chemistry of benzotriazole derivatives, which would certainly justify its own review. The same may be true for bis-imidazolium compounds, but they are not included in this chapter.

## 4.09.2 GEMINAL DIAMINO ALKANES-AMINALS

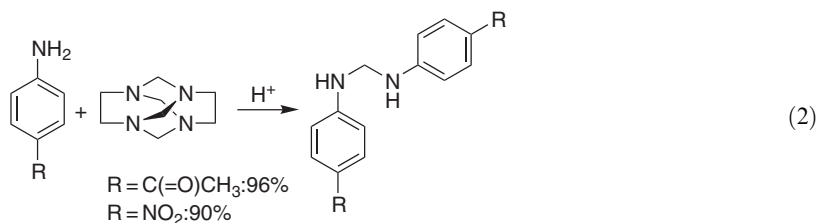
### 4.09.2.1 Condensation of Aldehydes and Ketones with Amines

#### 4.09.2.1.1 Acyclic amins

$C_2$ -Symmetric chiral methylene amins have been prepared using a standard procedure (amine + formaldehyde + acid) summarized in COFGT (1995) (Equation (1)) <2001SC1697, 2002T4439>. This procedure may be of general interest for the synthesis of chiral ligands provided the amins are sufficiently stable.

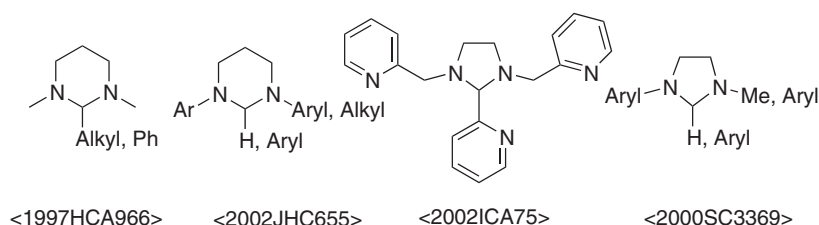


1,3,6,8-Tetraazatricyclo[4.4.1.1<sup>3,8</sup>]-dodecane (TATD) has been used as a methylene source for the synthesis of amins based on substituted anilines (Equation (2)) <2002SC1407>. This procedure is of limited generality since it is restricted to acceptor-substituted anilines.



#### 4.09.2.1.2 Cyclic amins

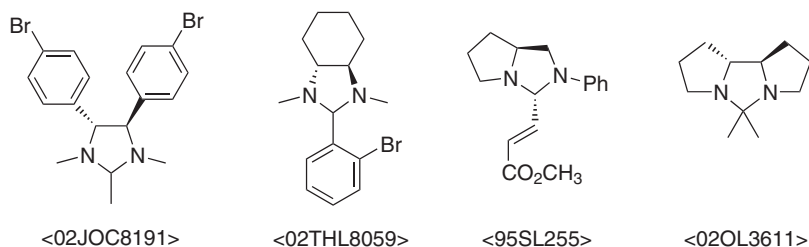
Simple achiral imidazolidines and hexahydropyrimidines have been synthesized by condensing aromatic and aliphatic aldehydes (including aqueous formaldehyde) with 1,2- or 1,3-diamines <1996JOC3646, 1997HCA966, 2000BMC2113, 2000JOC1200, 2000SC3369, 2002JHC655, 2002ICA75>. Alcohols, toluene, ether, and CH<sub>2</sub>Cl<sub>2</sub> have been used as solvents. The reaction temperature depends on the substrate structures, and molecular sieves or acid catalysts are utilized occasionally. Selected examples are depicted in Scheme 1.



Scheme 1

2,3-Dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) has been used as a catalyst for imidazolidine formation from aliphatic and aromatic aldehydes <1995T5813>. Increased reaction times and inferior yields were reported for the uncatalyzed reaction. The condensation reaction of aromatic aldehydes and *N,N'*-disubstituted ethylenediamines to imidazolidines in a water suspension medium has been developed <2000GC272>. Diazabicycloalkanes containing medium and large rings have been synthesized from *N*-alkenylpropane-1,3-diamines by a sequence consisting of rhodium-catalyzed double bond hydroformylation and subsequent amins formation <1999CC1279, 1999AJC1131>.

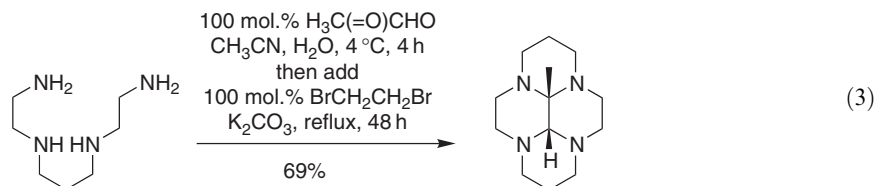
Chiral 1,3-diamines are frequently employed as covalently bonded chiral auxiliaries <1995SL255, 1995S1038, 1995JA10767, 1999CC2061, 1999AG(E)2556, 1999TL6241, 2002SL423> or as synthetic intermediates for the synthesis of organocatalysts <2002OL3611> and chiral metal ligands <2002JOC8191, 1997TA2607, 2000AG(E)4093, 2002TL8059, 2002TA1379>. Representative examples are depicted in Scheme 2. A three-component reaction to tricyclic amins from



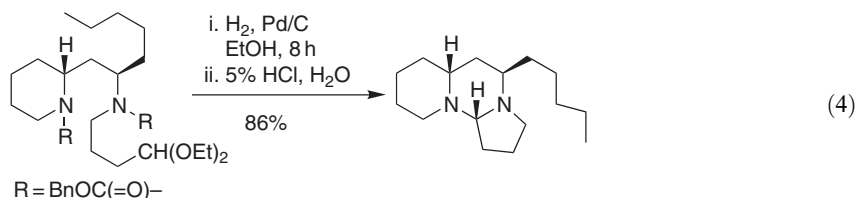
Scheme 2

acyclic starting materials has been developed <2001OL2145>. The ring-chain tautomerism of 2-aryl-substituted *cis*- and *trans*-configured decahydroquinazolines has been studied by NMR spectroscopy <2002JOC4734>.

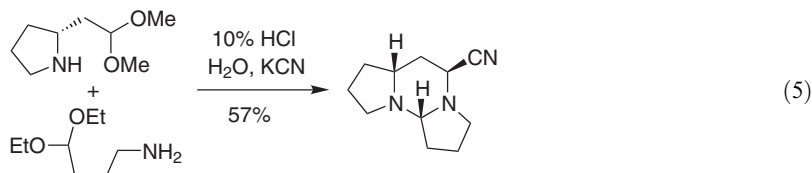
Polycyclic bis(aminals) are accessible by the condensation reaction between  $\alpha$ -dicarbonyl compounds and a linear tetraamine (Equation (3)). The stereochemical course of this condensation as well as the complexation properties of the polycyclic bis(aminals) have been studied <1998TL6861, 1999JOM259>. Polycyclic bis(aminals) are also useful synthetic intermediates in the synthesis of cyclen (1,4,7,10-tetraazacyclododecane) and cyclam (1,4,8,11-tetraazacyclotetradecane) <1999TL2517, 2002CC312, 2003T4573>.



An intramolecular aminal formation was the final step in the total synthesis of the alkaloid tetraponerine <2000JA9584>. After the removal of the nitrogen protective groups, an acetal served as carbonyl precursor in the presence of dilute aqueous  $\text{HCl}$  (Equation (4)).



An alternative approach utilized the intermolecular condensation between a cyclic and an acyclic aminoacetal in the presence of potassium cyanide for the synthesis of another member of this class of alkaloids (Equation (5)) <1996JOC4949>.



#### 4.09.2.2 Reaction of Amines with Geminal Dihalo Compounds

As summarized in COFGT (1995), amines and geminal dihalo compounds form aminals following an  $\text{S}_{\text{N}}2$ -type process. A recent report describes the copper(0)-mediated conversion of 1,1,1-trifluoro-2,2-dichloroethane and dialkylamines into 1,1-bis(dialkylamino)-2,2,2-trifluoroethanes <1997JOC1576>. This transformation is limited to dimethylamine and cyclic secondary amines. The chemistry of 1,1-bis(dialkylamino)-2,2,2-trifluoroethanes has also been the subject of a detailed study <1997JOC6503>.

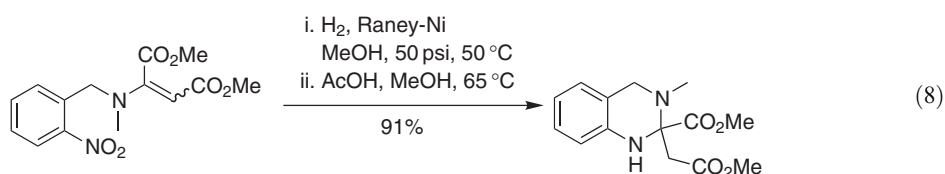
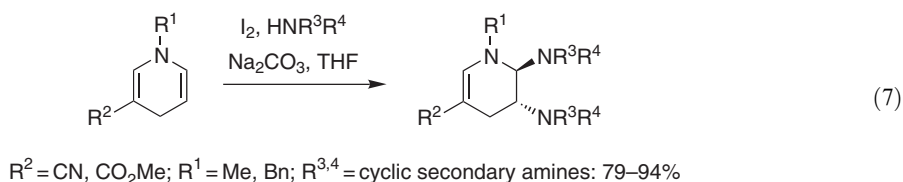
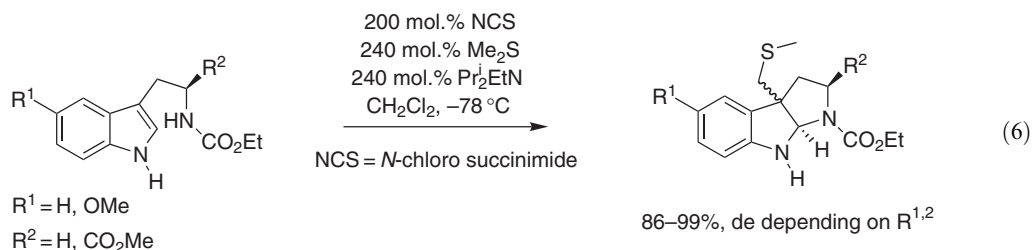
#### 4.09.2.3 Amine Addition to Imines and Iminium Salts

##### 4.09.2.3.1 To imines

As was summarized in COFGT (1995), the nucleophilic addition of an amine to an imine has found only limited application in the literature. This situation has not changed since 1995 and the interested reader is referred to chapter 4.09.2.3.1 of <1995COFGT(4)403>.

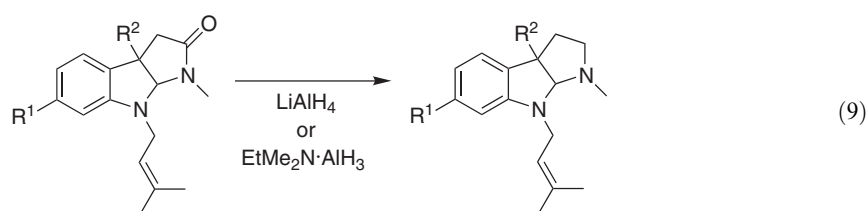
## 4.09.2.3.2 To iminium salts or enamines

Enamines react with amines inter- or intramolecularly in the presence of an electrophile to afford an aminoral <1998T14845, 1998CC2715, 1999JOC7381, 1999OL1315, 2001CEJ41>. Various electrophiles can be used to activate the enamine moiety as an intermediate iminium ion for nucleophilic attack by the amine (Equations (6)–(8)) <2000OL675, 2000CEJ1763, 2001TL4915>.

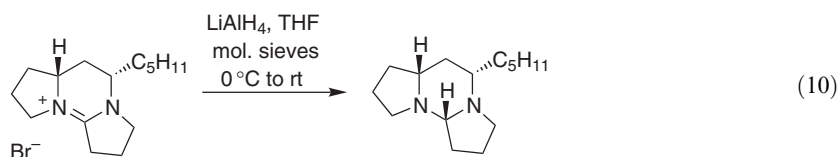


## 4.09.2.4 Reductive Processes

Indole alkaloids featuring the general framework depicted in Equation (9) have been synthesized by the reduction of the corresponding amid <1999JOC1086, 2001JOC1186>. Further examples prove the general utility of this transformation for the synthesis of cyclic aminorals <1999JOC8594>.



The reduction of amidines, amidinium ions, and cyanamides has been covered in chapter 4.09.2.4 of <1995COFGT(4)403>. Recent applications of the reduction of amidinium ions by complex metal hydrides have been reported <1998TA2245, 2002SC1457>. An application in natural product synthesis is outlined in Equation (10) <2002OL4697>. Examples have been reported in which the amidinium ion is generated and reduced *in situ* <1996CPB715, 1998JA6500, 2001H1029>. The stereoelectronic control of the addition of various nucleophiles to the 1,3-dimethyl-5-phenyl-1,4,5,6-tetrahydropyrimidinium ion has been investigated <2001JA4451>. An example of the dissolving metal reduction of amidines has been reported <1997T5359>.

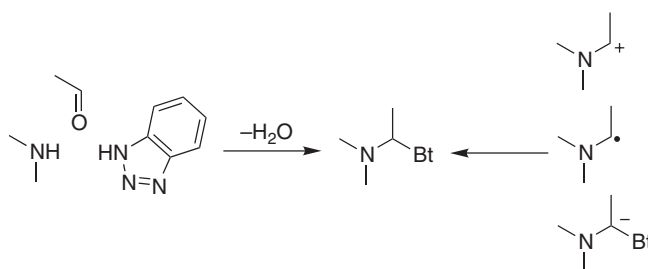


### 4.09.2.5 Reduction of Ureas

The reduction of five- and six-membered ureas has been summarized in chapter 4.09.2.5 of <1995COFGT(4)403>. Recent publications report the utilization of complex metal hydrides for this transformation <2001EJOC1625, 2002EJOC301>.

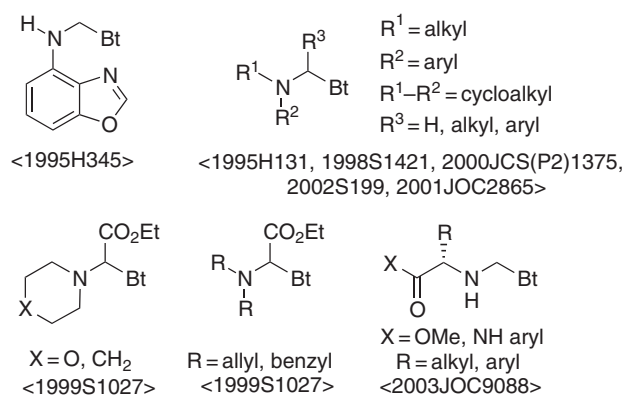
### 4.09.2.6 Benzotriazole Derivatives

Aminomethylbenzotriazoles are usually generated by the condensation of an amine with an aldehyde (ketone <1995H131>) and 1*H*-benzotriazole. They can be converted under appropriate reaction conditions to synthons that represent nitrogen-stabilized cations <1995H345, 1998S1421, 1999S1027, 2001JOC2865, 2002S199, 2003JOC9088>, anions <1995H131>, or radicals <2000JCS(P2)1375> (Scheme 3). These synthons can be used for a plethora of useful C/C- or C/heteroatom-bond forming reactions. This chapter will be limited to a short summary on the synthesis of the readily available aminomethylbenzotriazoles.



Scheme 3

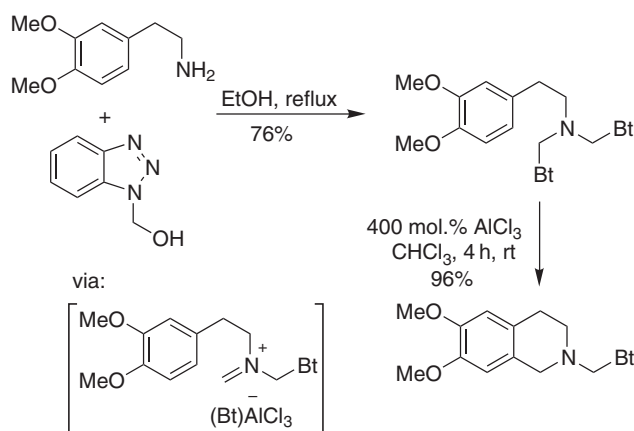
Scheme 4 depicts the general formulas for acyclic aminomethylbenzotriazoles that can be prepared by stirring of the appropriate aldehyde and amine with 1*H*-benzotriazole at room or elevated temperature.



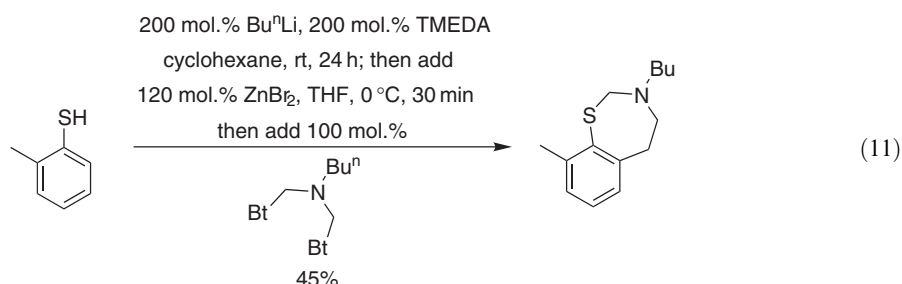
Scheme 4

The synthesis and reactivity of 2-benzotriazolylaziridines and 2*H*-azirines have been investigated <1999JOC346, 2003JOC9105>.

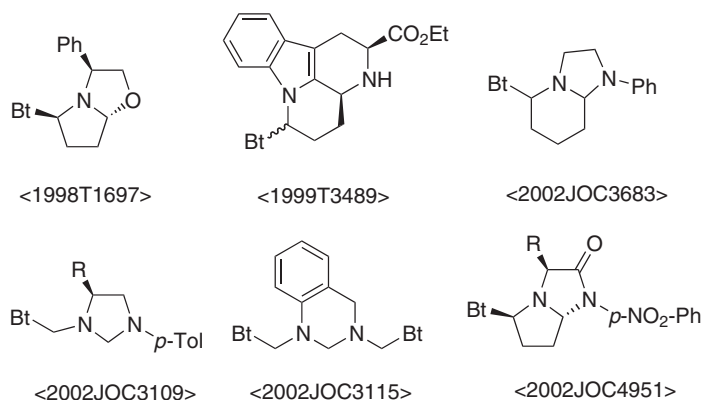
*N,N*-Bis(benzotriazolylmethyl)alkanamines can be prepared from primary amines and a two-fold excess of 1*H*-benzotriazole and formaldehyde. *N,N*-Bis[(benzotriazol-1-methyl)alkanamines have been utilized for the synthesis of various heterocycles <2002JCS(P1)592, 2002S601, 2002JOC8220, 2002JOC8237>. Two examples are depicted in Scheme 5 and Equation (11) <1999JCS(P1)179, 2002JOC8234>.



Scheme 5



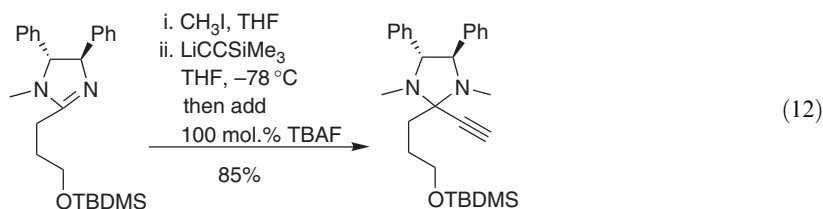
Several benzotriazolyl- or benzotriazolylmethyl-substituted heterocycles have been prepared using the well-established condensation chemistry [<1998TL1697, 1998JOC6699, 1999T3489, 2000JOC3683, 2002JOC3109, 2002JOC3115, 2002JOC4951, 2002JOC8224, 2002S1646>](#). Some representative examples are depicted in [Scheme 6](#).



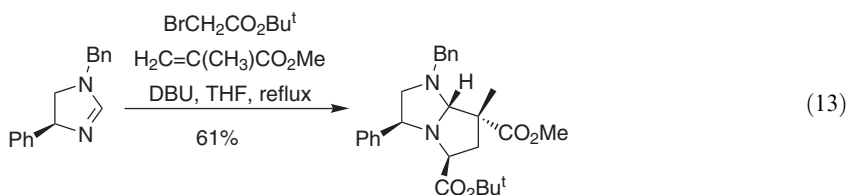
Scheme 6

#### 4.09.2.7 Miscellaneous Procedures

The synthesis of aminals from carbonyl compounds and *N,N*-dialkyl-1,2-diamines is restricted to aldehydes whereas ketones often fail to afford the desired amina. An alternative access to chiral 2,2-dialkyl-substituted imidazolidines utilized the nucleophilic addition of an acetylide anion to an imidazolinium ion ([Equation \(12\)](#)) [<2000OL2659>](#).



Chiral 4,5-dihydroimidazolium ylides, generated *in situ* from chiral dihydroimidazoles and an alkylating agent in the presence of a base, undergo an inter- or intramolecular 1,3-dipolar cycloaddition with suitable dipolarophiles to provide bicyclic and tricyclic aminsals [<1997TL1647, 2001TL3951>](#). A representative example is depicted in [Equation \(13\)](#) [<1996TL1707>](#).



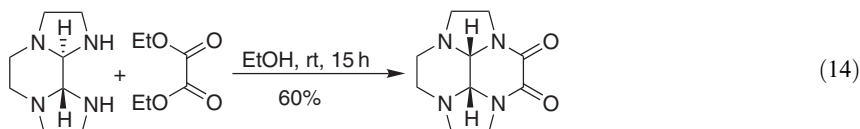
The low-valent titanium-mediated reductive cyclization of acyclic imines in tetrahydrofuran (THF) to imidazolines has been described [<1996TL4767>](#). The reaction of [60]fullerene with diethyl diazidomalonate afforded an aminsal-functionalized fulleroid [<1995CC1725>](#). The [4 + 1]-cycloaddition between vinylketenes and a nucleophilic *N*-heterocyclic carbene that was generated thermally from 2-trichloromethyl-1,3-imidazoline afforded spirocyclic aminsals [<2003OL263>](#).

#### 4.09.3 GEMINALLY SUBSTITUTED ALKANES BEARING ONE AMINO AND ONE ACYLATED OR SULFONATED AMINO GROUP

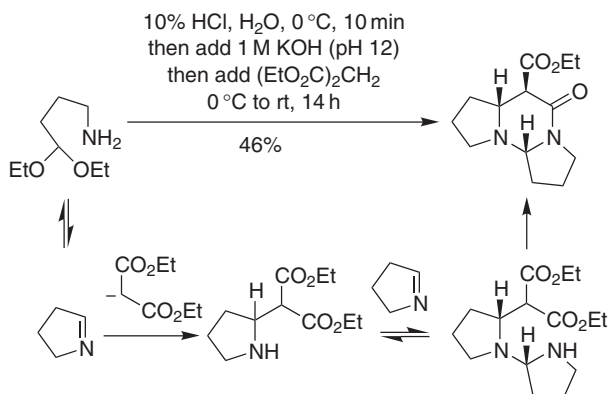
##### 4.09.3.1 Acylated Derivatives

##### 4.09.3.1.1 Acylation of aminsals

Condensation of a tricyclic bis-aminal with diethyl oxalate afforded a tetracyclic bis-acylated bis-aminal ([Equation \(14\)](#)) [<2000EJOC33>](#).



A two-component multistep reaction between  $\Delta^1$ -pyrroline and 4-aminobutanal diethylacetal culminated in the intramolecular acylation of an aminsal to afford an advanced intermediate for the total synthesis of tetraopnerine alkaloids ([Scheme 7](#)) [<2000CJC1030>](#).

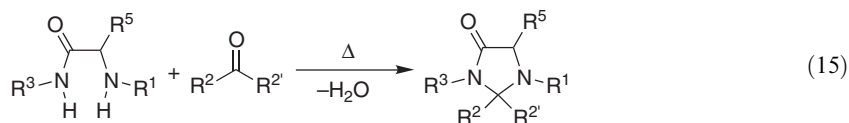


Scheme 7

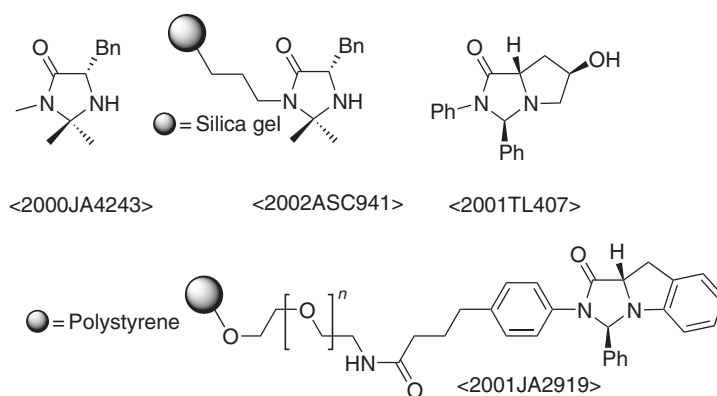


#### 4.09.3.1.2 Condensation of amines and amides with carbonyl compounds

The condensation of 2-aminoamides with aldehydes or ketones leads to the formation of imidazolidin-3-ones (Equation (15)). The reaction mixture is usually heated in methanol dimethylformamide (DMF) or toluene, and the use of a catalytic amount of acid has been reported.



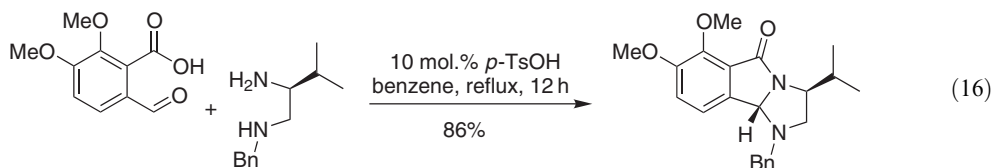
Chiral imidazolidin-3-ones and pyrrolo[1,2-*c*]imidazolones have been prepared and utilized as (immobilized) organocatalysts <2000JA4243, 2000JA9874, 2001TL407, 2001TL411, 2002ASC941>, (immobilized) transition metal ligands <2001JA2919, 2002TA1769>, covalently bonded chiral auxiliaries <1995T3423, 1998CJC234, 2001OL425>, or as synthetic intermediates <1996TA2233, 2000OL2781, 2001TA101>. Representative examples are depicted in Scheme 8.



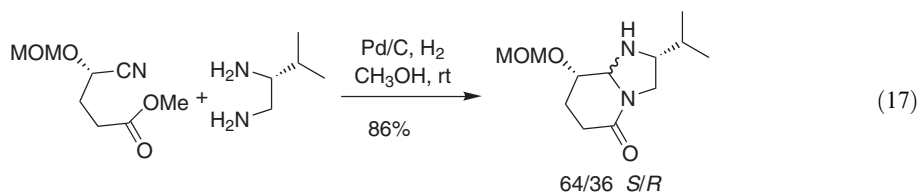
Scheme 8

6,7-Dimethoxy-3-methyl-1,2,3,4-tetrahydroisoquinoline-1-acetamides have been condensed with formaldehyde or benzaldehyde to provide pyrimido[6,1-*a*]isoquinolin-2-ones <1997LA1165>.

2-Formyl- or 2-acetylbenzoic acid was condensed with chiral 1,2-diamines to afford the corresponding polycyclic monoacylated aminals (Equation (16)) <2002TA933>.



Enantiomerically enriched cyanohydrins have been hydrogenated to oxo carbonic acids and condensed with chiral diamines in a one-pot procedure to afford the corresponding bicyclic, monoacylated aminals (Equation (16)) <2003ASC483>. When comparing Equations (16) and (17), it is instructive to notice the different regioselectivity of the amination formation.

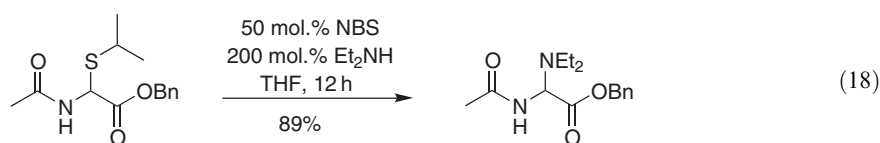


The condensation of *O*-methyl lactimes with ethyl-6,7-dimethoxy- $\alpha$ -[1-(1,2,3,4-tetrahydroisoquinolyl)]acetate afforded mixtures of tetracyclic, monoacylated amins (8,13-diazasteroids) and the corresponding medium-sized tricyclic diamides <1998MI375>. Treatment of 2,3-diaminonaphthalene with 4-isothiocyanato-4-methyl-2-pentanone led to the formation of a tetracyclic, thioacylated amina <2000M501>. A tricyclic amina has been prepared in which one nitrogen is part of a pyrrole <2000TL4295>.

#### 4.09.3.1.3 Nucleophilic displacement reactions

The nucleophilic displacement of a leaving group from an  $sp^3$ -hybridized, *N*-acyl-substituted carbon atom may proceed via an  $S_N2$ - or  $S_N1$ -type (iminium ion intermediate) process. The corresponding transformations are summarized in this chapter regardless of their actual mechanism. Developments and applications in this area during the 1990s are apparently very limited. The interested reader is referred to chapter 4.09.3.1.2 of <1995COFGT(4)403> for a more sound summary.

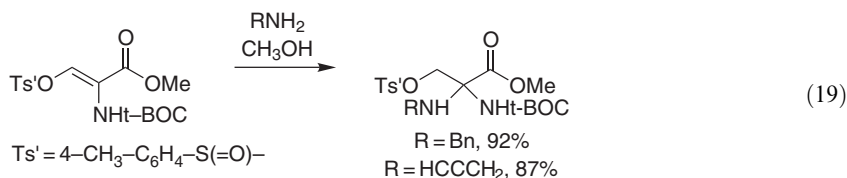
Treatment of  $\alpha$ -isopropylthioglycines with a variety of different amines in the presence of *N*-bromo succinimide (NBS) afforded the corresponding amins with chemical yields that are not always useful, depending on the nature of the amine. The best example is depicted in Equation (18) <2002JOC5408>.



5-Alkylaminopyrrolones have been synthesized by the reaction between 5-chloro-1,5-dihydro-2*H*-pyrrol-2-ones and primary aromatic, aliphatic as well as alkoxyamines in reasonable yields <2001S89>. Methyl-*N*-benzoyl-2-bromoglycinate was trimerized by treatment with  $NH_3$ . The corresponding trimethyl-2,2',2'-nitrilotris[2-(benzoylamino)acetate] was used for the synthesis of  $C_3$ -symmetric peptide derivatives <1995TL857>.

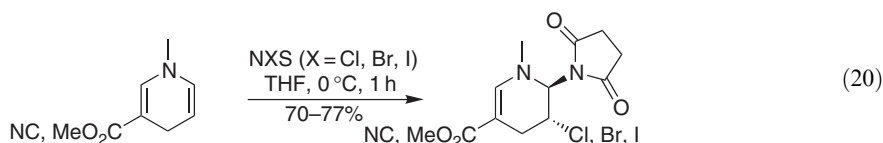
#### 4.09.3.1.4 Addition of amines and amides to C—N multiple bonds

Two examples of the nucleophilic addition of amines to the *N*-acylenamine moiety of a  $\beta$ -(4-toluenesulfinyl)-substituted dehydroamino acid have been reported (Equation (19)) <2002TL4495>.

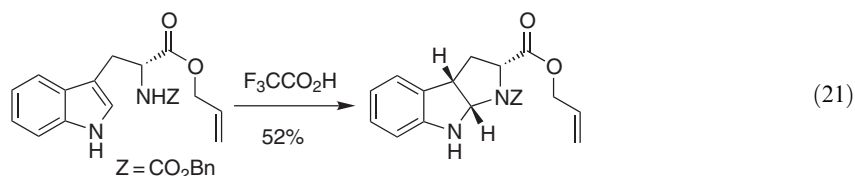


The nucleophilic addition of a phthalimide ion to a di(ethoxycarbonyl)-substituted imine has been reported <2000TL9713>.

Several examples for the addition of an *N*-nucleophile to an iminium ion have been reported <1995JA5604, 1996T13111, 1999S1022, 2002TL3347>. For instance, three-acceptor-substituted *N*-methyl-1,4-dihydropyridines add halosuccinimides to afford the corresponding amins (Equation (20)) <1998JOC2728>.



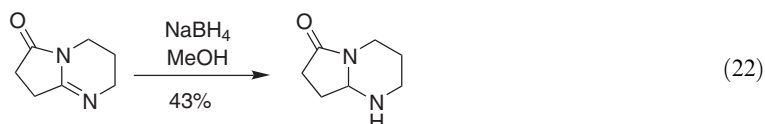
Acid-catalyzed cyclization of a benzyloxycarbonyl-protected tryptophan afforded a tricyclic amina (Equation (21)) <2001JMC2276>.



A Fischer indole synthesis of *N',N'*-diphenylcyclopentyl-*N*-trifluoroacetyl-enehydrazines that proceeds under particularly mild conditions (due to the presence of the *N*-trifluoroacetyl moiety) has been reported [<1999TL3601>](#).

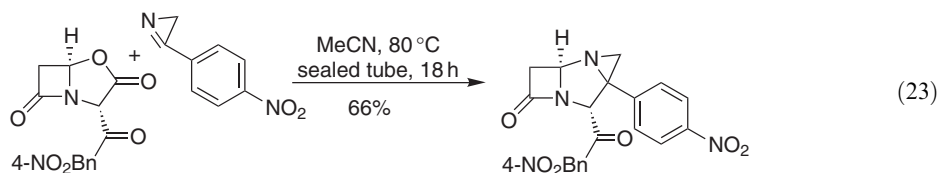
#### 4.09.3.1.5 Reductive methods

The reduction of imines and iminium ions has been summarized in chapter 4.09.3.1.2 of [<1995COFGT\(4\)403>](#). A recently reported example for the reduction of a bicyclic amidine to a bicyclic amina is depicted in [Equation \(22\)](#) [<2002T7177>](#).



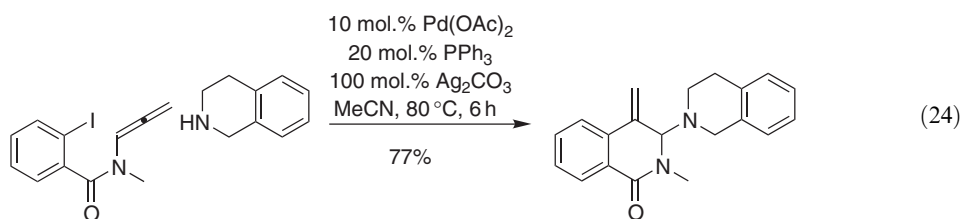
#### 4.09.3.1.6 Cycloaddition procedures

The thermal 1,3-dipolar cycloaddition between *in situ* generated  $\beta$ -lactam-based azomethine ylides and 2*H* azirines afforded tricyclic amina [<2002JCS\(P1\)2014>](#). The generality of this procedure is hampered by low-to-moderate yields and diastereoselectivities. The best example is depicted in [Equation \(23\)](#).

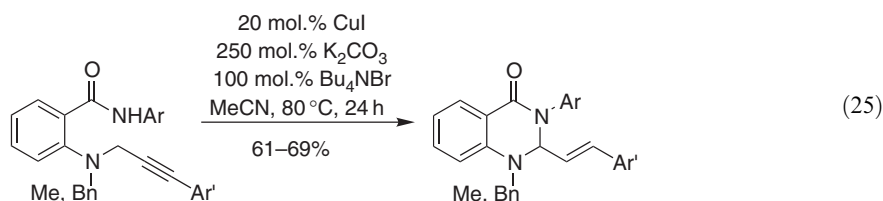


#### 4.09.3.1.7 Metal-catalyzed procedures

The palladium-catalyzed intramolecular cyclization of an aryl iodide onto a 1,2-dienamide afforded a  $\pi$ -allylpalladium complex that was intercepted by a secondary amine to provide the corresponding amina ([Equation \(24\)](#)) [<1995CC1903>](#). The regioselectivity of the intermolecular attack of the amine onto the  $\pi$ -allylpalladium complex was determined by the nature of the inorganic base. Related examples for the intramolecular attack of the  $\pi$ -allylpalladium complex by an amine have also been reported [<2001CC964>](#).

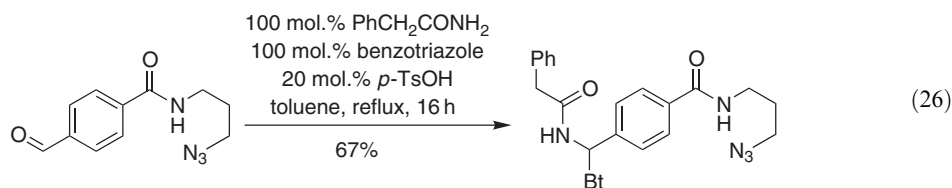


Quinazolinones have formed by the copper-catalyzed cyclization of *N*-alkynyl-substituted 2-aminobenzamide ([Equation \(25\)](#)) [<2001TL2883>](#).

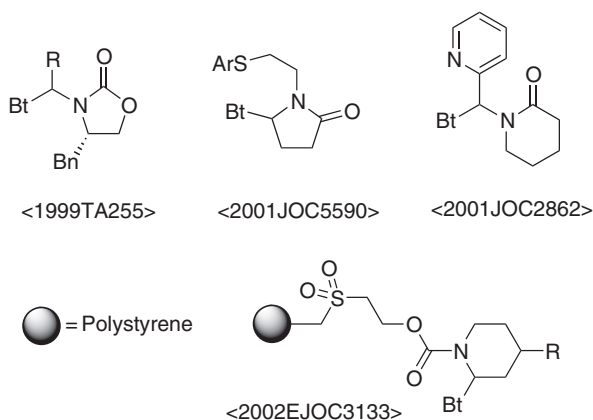


#### 4.09.3.1.8 Benzotriazole derivatives

The preparation of acyclic *N*-(1-benzotriazol-1-yl-alkyl)amides by the condensation of primary or secondary amides and aliphatic or aromatic aldehydes with 1*H*-benzotriazole is well established <1995SC1197, 1995JCS(P1)1, 1999JOC7622, 2000TL9691, 2000JOC8066, 2002JOC4957>. An instructive example is depicted in Equation (26) <1998TL3819>. Alternative procedures using 2,2-dichloroacetamides or enamides as the acylamino source have been reported <2002JOC8239, 1997JOC700>. *N*-(1-Benzotriazol-1-yl-alkyl)amides may be used according to the reactivity pattern outlined in Scheme 3.

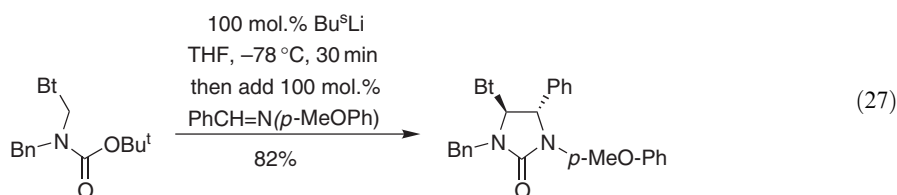


The synthesis of *N*-(benzotriazolymethyl)thioamides using the condensation chemistry outlined above has been reported <1995T8703, 1995T13271, 2000JOC8819>. Several benzotriazolyl- or benzotriazolymethyl-substituted heterocycles have been prepared using the reliable condensation strategy <1999TA255, 2001JOC5590, 2001JOC2862, 2002EJOC3133>. Some representative examples are depicted in Scheme 9.



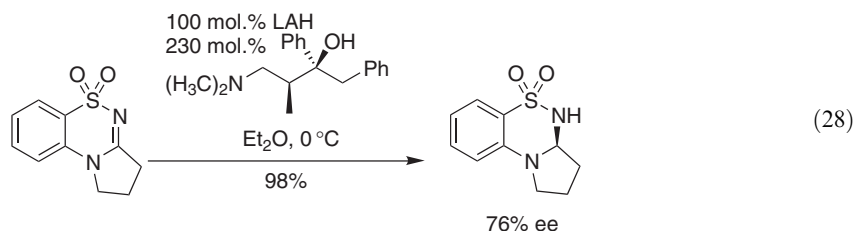
Scheme 9

The preparation of benzotriazolylimidazolidinone derivatives represents a noteworthy exception of the general condensation strategy (Equation (27)) <2001JOC2858>.



### 4.09.3.2 Sulfonated Derivatives

A limited number of examples for the synthesis of this specific functionality have been reported since the publication of COFGT (1995). A tricyclic aminal was regioselectively monosulfonated to the corresponding sulfonamide by treatment with TsCl [<2000H483>](#). The reduction of a pyrrolo-benzothiadiazine with various chiral and achiral complex hydrides has been investigated [<1996BMC3003>](#). The highest enantioselectivity was observed using the combination of lithium aluminum hydride (LAH) and (+)-(2(*S*),3(*R*))-4-dimethylamino-3-methyl-1,2-diphenyl-2-butanol (Chirald<sup>®</sup>) ([Equation \(28\)](#)).



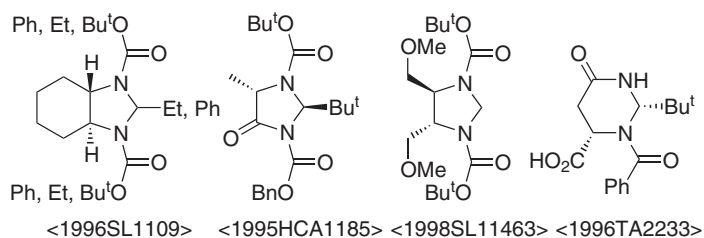
The oxidation of substituted indoles with *N*-sulfonyloxaziridines afforded an unusual 1,3-oxazolidinoindole ring system containing an *N*-monosulfonated aminal [<1997JA1159>](#). 3,5-Dimethyl-*N*-*p*-tolylsulfonyl-2,6-dichloro-1,4-benzoquinone imine containing a highly electrophilic *N*-tosylimine was treated with aromatic amines to afford the corresponding acyclic monosulfonated aminal [<2000JOU245>](#).

### 4.09.4 GEMINALLY SUBSTITUTED ALKANES BEARING TWO ACYLATED OR SULFONATED AMINO GROUPS

#### 4.09.4.1 Acylated Derivatives

##### 4.09.4.1.1 Acylation of monoacylated aminals

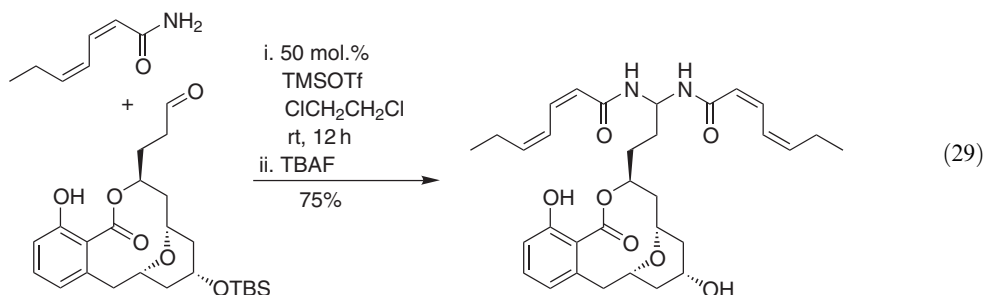
Cyclic monoacylated aminals, either isolated or generated *in situ*, are frequently acylated using the corresponding acid chlorides [<1995HCA1185, 1996TA1567, 1996SL1109, 1996TA2233, 1998S1463, 2000OL2781, 2001TA101, 2001JMC2276>](#). Some representative diacylated aminals prepared by this strategy are depicted in [Scheme 10](#).



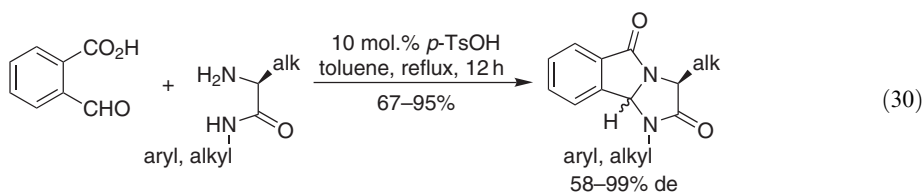
Scheme 10

##### 4.09.4.1.2 Condensation of amides with carbonyl compounds

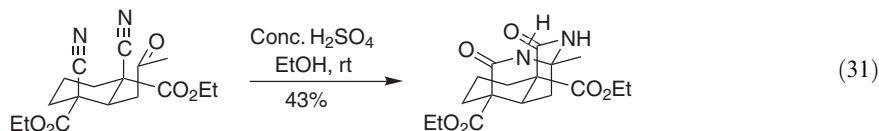
Acyclic *N,N*-alkylidene-bis-amides can be synthesized by the acid-catalyzed condensation of amides with aldehydes. An application in the context of natural product synthesis is depicted in [Equation \(29\)](#) [<2001TL2645, 2002AG\(E\)3701>](#). A more general study on this topic is also available [<1996S1299>](#).



The *N*-BOC-*N'*-Fmoc-protected imidazolidine-2-carboxylic acid was prepared by the condensation between *N*-BOC-*N'*-Fmoc-protected ethylenediamine and glyoxylic acid [<1998TL2569>](#).  $\alpha$ -BOC-amino-Fmoc-glycine was synthesized from 9-fluorenylmethylcarbamate, glyoxylic acid, and *t*-butyl carbamate by a two-step condensation sequence [<1996SC3237>](#). The sequential intermolecular condensation and intramolecular acylation between 2-formylbenzoic acid and  $\alpha$ -aminoamides afforded 1*H*-imidazo[2,1-*a*]isoindole-2,5(3*H*,9*bH*)-diones ([Equation \(30\)](#)) [<2001JCS\(P1\)1767>](#).



A similar intramolecular strategy was used to synthesize tricyclic *N,N'*-diacylaminals from a cyclic dicyanoketone ([Equation \(31\)](#)) [<2000JOC3255, 2002JA13686>](#).



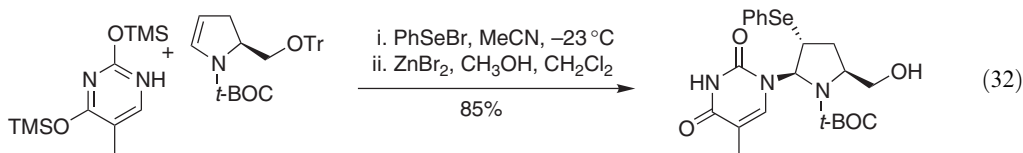
An example has been reported for a one-pot Rh-catalyzed double bond hydroformylation, succeeded by an intramolecular condensation of the resulting aldehyde with two acylated amino groups to afford a diazabicyclo[4.4.0]decane [<2002OL4575>](#).

#### 4.09.4.1.3 Reductive methods

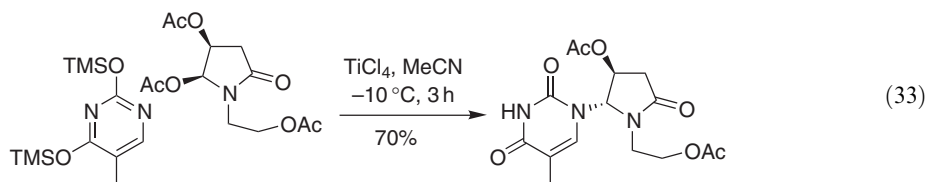
The few reductive methods for the synthesis of *N,N'*-diacylated aminals have been summarized in chapter 4.09.4.1.2 of [<1995COFGT\(4\)403>](#). No significant progress has been reported since the 1990s.

#### 4.09.4.1.4 Nucleophilic addition to imines and enamines

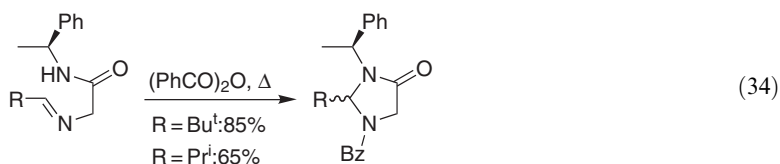
Addition of electrophiles ( $H^+$ ,  $PhSe^+$ ,  $I^+$ ,  $Br^+$ ) to *N*-acylenamines has been used to generate *N*-acyliminium ions *in situ*, which react with *N*-acylnitrogen nucleophiles to afford the corresponding *N,N'*-diacylated aminals [<1995TL7705, 1999JOC7218, 1999JA11953, 2000OL4205>](#). An example is depicted in [Equation \(32\)](#) [<2001TL1599>](#).



The generation of a cyclic *N*-acyliminium ion from a cyclic *N*-acyl-*N,O*-acetal followed by the *in situ* reaction with a heterocyclic nitrogen nucleophile afforded a related nucleoside analog ([Equation \(33\)](#)) [<1999CL687>](#).



1-Benzoyl-2-*t*-butyl- and 1-benzoyl-2-isopropyl-3-(1'(*S*)-methylbenzyl)imidazolidin-4-ones were prepared by the treatment of the corresponding imino amide with benzoic anhydride at elevated temperature (Equation (34)) <1995JOC6408>.

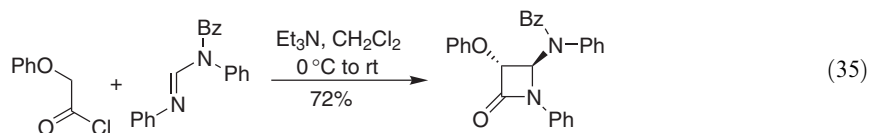


The alkylation of imidazoles in the 2-position was achieved with *in situ* generated allylic stannanes in the presence of chloroformates to afford the cyclic bis-acylated amins <1995SL1117>. It is reasonable to assume that the reaction proceeds via the intermediate formation of an *N*-(alkoxycarbonyl)imidazolium ion.

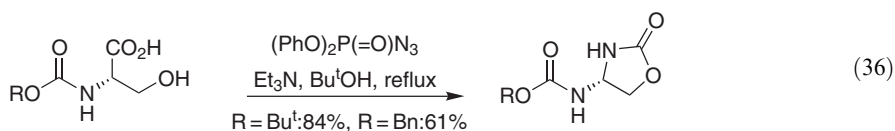
Little work has been published about the addition of nucleophiles to unactivated imines. It was shown that the succinimide anion adds to an *in situ* generated di(ethoxycarbonyl)-substituted *N*-acylimine <1995SC2723>.

#### 4.09.4.1.5 Miscellaneous procedures

4-Acylamino and 4-sulphonamido  $\beta$ -lactams have been prepared by the [2+2]-cycloaddition between acyclic trisubstituted amidines and the ketene generated *in situ* from 2-aryloxy or 2-arylamino-substituted acetic acid chlorides <2000T7811>. A representative example is depicted in Equation (35).



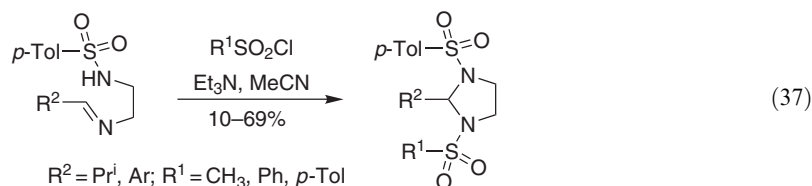
A Curtius rearrangement of *N*-benzyloxycarbonyl- or *N*-*t*-butyloxycarbonyl-substituted (*S*)-serine has been exploited to synthesize the corresponding protected 4-amino-2-oxazolidinone (Equation (36)) <2000JOC6595>. A related intermolecular Curtius rearrangement has been reported <1999JOC8537>.



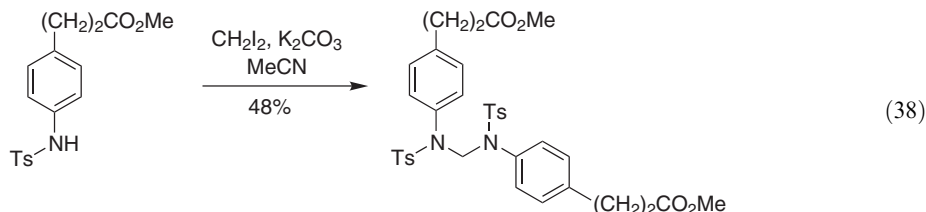
The direct bis-amidation of ethyl acetate using ethyl-*N*-[(4-nitrobenzenesulfonyl)oxy]carbamate (NsONHCO<sub>2</sub>Et) was observed. However, the reaction conditions were optimized to support the formation of the monoamidated product <2001TL1171>.

#### 4.09.4.2 Sulfonated Derivatives

2-Substituted *N,N*-disulfonated imidazoles have been prepared by the reaction of sulfonic acid chlorides with imines generated from *N*-sulfonated ethylenediamines and aldehydes (Equation (37)) <2000MI894>.



Treatment of  $\text{CH}_2\text{I}_2$  with an aromatic sulfonamide afforded an acyclic bis-sulfonated amina in moderate yield (Equation (38)) <1995JCS(P1)83>. In a related alkylation reaction, *N,N*-bis(chloromethyl)amides served as the methylene donors for the formation of cyclic *N,N'*-disulfonated amins <1998MI2201>.



The investigation of the chemical properties of *N*-(2,2,2-trichloroethylidene)trifluoromethanesulfonamide revealed, not unexpectedly, the high electrophilicity of the imine carbon atom. The reaction of that imine with benzenesulfonamide led to the formation of *N*-(2,2,2-trichloro-1-phenylsulfonylaminoethyl)-trifluoromethanesulfonamide <2001JOU1559>.

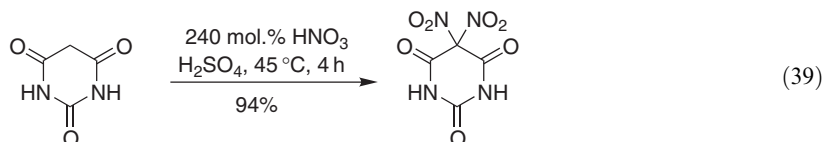
A limited number of geminally substituted alkanes bearing one acylated and one sulfonated amino group have been reported <1998MI2201, 2000TL5479, 2002JCS(P1)1105>.

#### 4.09.5 GEMINALLY SUBSTITUTED ALKANES BEARING TWO SIMILAR DICOORDINATE OR HETEROSUBSTITUTED NITROGENS

##### 4.09.5.1 *gem*-Dinitro Alkanes

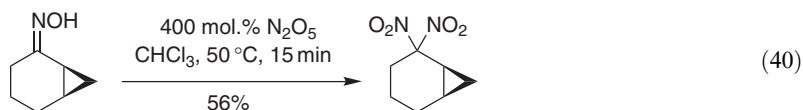
Limited work concerning *gem*-dinitro alkanes has apparently been published since 1995. A comprehensive summary of the synthesis of *gem*-dinitro alkanes can be found in chapter 4.09.5.1 of <1995COFGT(4)403>.

A common strategy toward *gem*-dinitro alkanes utilizes the direct bis-nitration of a methylene group with acidic protons. Some examples of this strategy have been published recently. The synthesis of 3,3,5,7-tetranitrooxindole by the treatment of oxindole with a mixture of sulfuric and nitric acid has been described <1996TL9263>. Ring-opening reactions of 3,3,5,7-tetranitrooxindole and its transformations into indoles, indazoles, and benzoxazinones have been investigated <1999T10447>. Bis-nitration of pyrimidin-4,6-diones with nitric acid in concentrated sulfuric acid afforded 5,5-*gem*-dinitropyrimidin-4,6-diones in high yields. One of three examples is depicted in Equation (39) <2000TL2011, 2001TL1793, 2002JOC7833>. The 5,5-*gem*-dinitropyrimidin-4,6-diones were thermally stable up to 150 °C, but hydrolyzed vigorously with water.



The oxidative nitration of oximes of spiro[2.*n*]alkan-4-ones and bicyclo[*n*.1.0]alkan-2-ones with nitrogen pentoxide afforded the corresponding *gem*-dinitro bicycles <1999JOU839>. The highest yielding example is depicted in Equation (40). Trinitroazetidine has been prepared by the treatment of *N*-*p*-tosyl-3-azetidinone oxime with nitric acid, urea, and ammonium nitrate <1995JOC1959>.

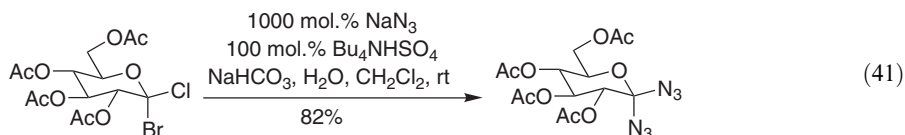




Cyclopent-1-en-1-ol was converted in low yield to 2,2-dinitrocyclopentanone oxime using a mixture of ceric ammonium nitrate (CAN) and  $\text{NaNO}_2$  [<1998TL6617>](#). 1-Trimethylsilylcyclooctene yielded 2,2-dinitrocyclooctylnitrate when treated with acetylnitrate [<1999CC1079>](#).

#### 4.09.5.2 *gem*-Diazidoalkanes

Treatment of peracetylated 1-bromo- $\beta$ -D-glycopyranosyl chlorides with sodium azide under phase-transfer conditions afforded the corresponding glycopyranosylidene 1,1-diazides [<1996S577>](#). One of three examples is depicted in [Equation \(41\)](#).



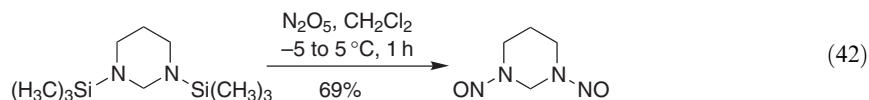
Benzylidene diacetate was converted into diazidophenylmethane (decomposes violently when exposed to elevated temperature) when refluxed with sodium azide in benzene [<1998TL6361>](#).

#### 4.09.5.3 *gem*-Diisocyanates and *gem*-Diisothiocyanates

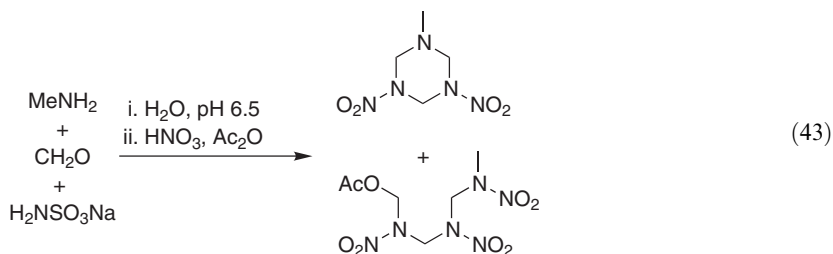
No further advances have occurred in this area since the publication of chapter 4.09.5.3 [<1995COFGT\(4\)403>](#).

#### 4.09.5.4 *gem*-Dinitrosamines and *gem*-Dinitramines

Silylamines can be converted into nitrosamines by treatment with dinitrogen pentoxide in  $\text{CH}_2\text{Cl}_2$ . The application of this method afforded 1,3-(dinitroso)hexahydropyrimidine from 1,3-bis(trimethylsilyl)hexahydropyrimidine ([Equation \(42\)](#)) [<1997T4371>](#).

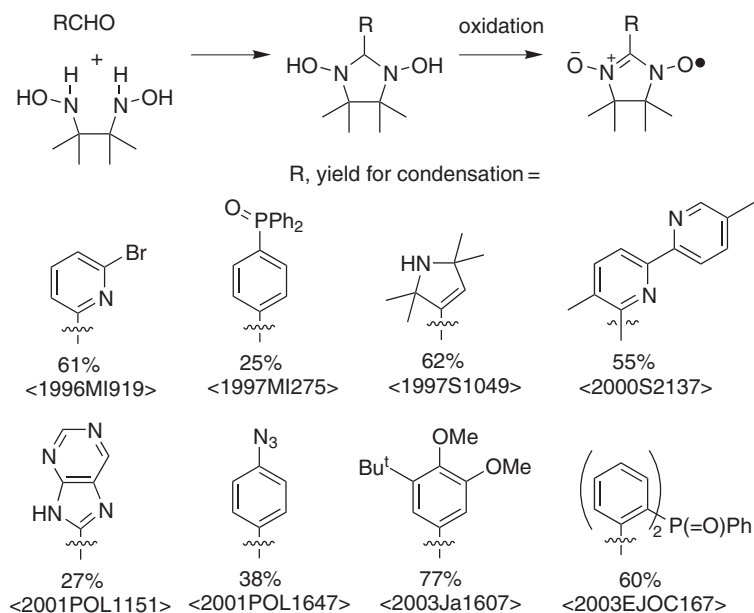


The nitration of cyclic 1,3-disulfonates afforded a mixture of cyclic *gem*-dinitro compounds and acyclic linear polynitramines in low-to-moderate yield. The product distribution depended on the reaction conditions for the nitration and for the formation of the cyclic 1,3-disulfonates from formaldehyde, primary amines, and potassium sulfamate ([Equation \(43\)](#)) [<2000MI1079, 2000MI1082>](#).



#### 4.09.5.5 *gem*-Dihydroxylaminoalkanes

4,4,5,5-Tetramethyl-4,5-dihydro-1*H*-imidazolyl-1-oxyl-3-oxides (cyclic nitronylnitroxides) are being intensively studied for their properties as organic ferromagnets. They can be synthesized by the oxidation of 4,4,5,5-tetramethyl-imidazolidine-1,3-diols, which in turn are most frequently synthesized by the condensation of 2,3-bis(hydroxyamino)-2,3-dimethylbutane with aldehydes <1996MI919, 1997MI275, 1997T16911, 1997S1049, 2000S2137, 2000IC6091, 2001POL1151, 2001CEJ2007, 2001POL1647, 2002ZNB677, 2003JA1607, 2003EJOC167>. Some representative examples are depicted in Scheme 11.



Scheme 11

#### 4.09.5.6 *gem*-Dicarbodiimides

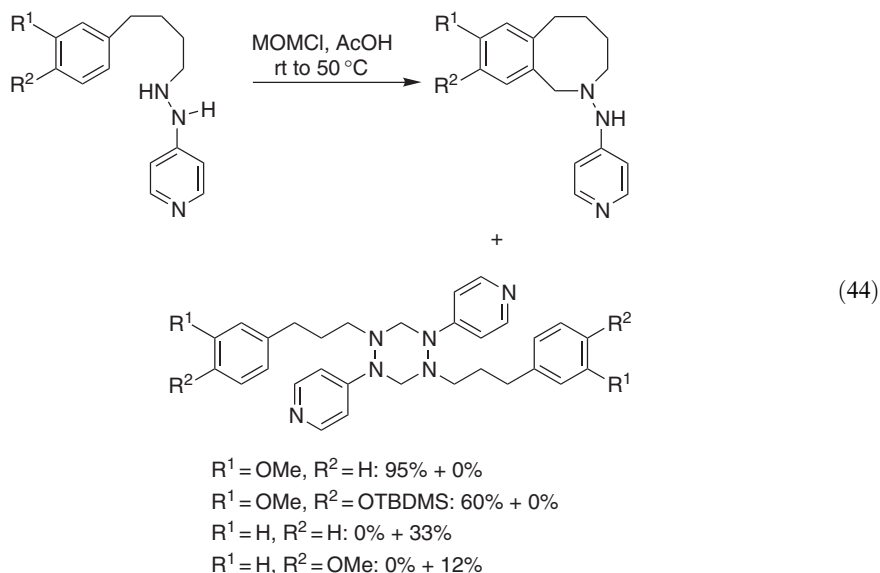
No further advances have occurred in this area since the publication of chapter 4.09.5.6 <1995COFGT(4)403>.

#### 4.09.5.7 *gem*-Diazo Alkanes

Treatment of benzyl cyanide with nitric oxide (NO) in the presence of sodium methoxide afforded a bis-diazeniumdiolated imideate,  $\text{PhC}(\text{OMe})=\text{NH}[\text{N}(\text{O})=\text{N}(\text{ONa})]_2$  in low yield <2000TL8421>. No further advances have occurred in this area since the publication of chapter 4.09.5.7 <1995COFGT(4)403>.

#### 4.09.5.8 *gem*-Dihydrazino Alkanes

1,2,4,5-Tetrazines were formed unintentionally during the attempted Pictet–Spengler cyclization of the corresponding hydrazines. The chemoselectivity of this reaction is highly dependent on the nature of the substituents (Equation (44)) <2000SL137>.



The synthesis of bis(7-azaindol-1-yl)methane and two structural isomers by the reaction between  $\text{CH}_2\text{Br}_2$  and 7-azaindol under phase-transfer conditions has been reported <2002OL4049>. The preparation and determination of physical properties of silver(I) complexes of bis(1,2,4-triazol-1-yl)methane have been achieved <2003IC112>. *N,N*-bis(pyrazol-1-yl-methyl)-alkylamines have been synthesized by the condensation of 3,5-disubstituted 1-(hydroxymethyl)-pyrazoles with primary aliphatic amines <2001SC1315>.

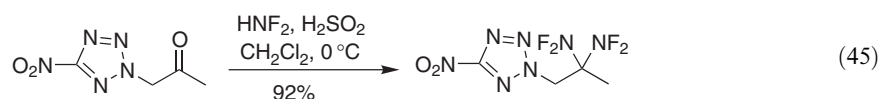
#### 4.09.5.9 *gem*-Diiminoalkanes and *gem*-Diisocyanides

Treatment of benzaldehyde with ammonia under pressure ( $\sim 7$  atm) afforded the corresponding *gem*-diimino alkane, 1,3,5-triphenyl-2,4-diazapenta-1,4-diene, in quantitative yield <2002MI2308>. Alternatively, benzaldehyde can be treated with hexamethyldisilazane and LiBr in THF at elevated temperatures to afford the identical *gem*-diimino alkane in 94% yield <2001MI29>.

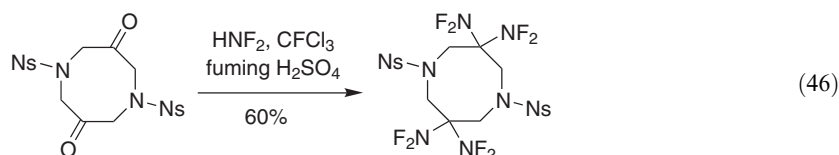
Diisocyanomethane synthesized from bis(formylamido)methane by treatment with  $\text{POCl}_3$  and  $\text{Et}_3\text{N} \cdot \text{H}_2\text{C}(\text{N}\equiv\text{C})_2$  decomposes violently at temperatures above  $-10^\circ\text{C}$ . Highly diluted solutions of diisocyanomethane are reasonably stable at room temperature (<2002ZAAC863>).

#### 4.09.5.10 *gem*-Difluoroaminoalkanes

2-[2,2-Bis(difluoroamino)propyl]-5-nitrotetrazole was prepared from the corresponding ketone by treatment with difluoroamine, which was in turn generated from triphenyl(difluoroamino)-methane (Equation (45)) <2000MI949>.

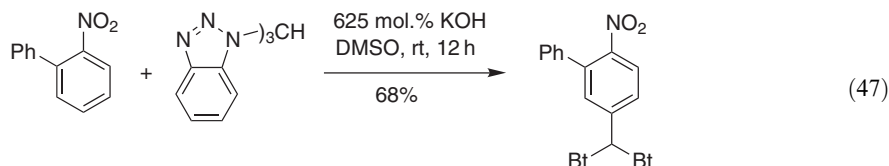


A more general study investigated the scope of the bis(difluoroamination) of ketones with difluoroamine, which was generated *in situ* from triphenyl(difluoroamino)methane <2002CC1712>. *gem*-Bis(difluoroamino)-substituted heterocyclic nitramines have been synthesized from the corresponding diketones using difluoroamine that was generated from *N,N*-difluorourea (Equation (46)) <1998JOC1566, 1999JOC960>.



#### 4.09.5.11 *gem*-Benzotriazol-1-yl Alkanes

Reaction of tris(benzotriazol-1-yl)methane with nitroarenes under basic reaction conditions afforded *p*-bis(benzotriazol-1-yl)methyl-substituted nitroarenes (Equation (47)) <1996TL347>.



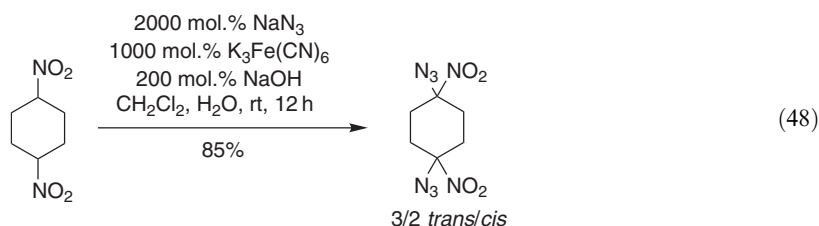
Bis(benzotriazol-1-yl)methane can be prepared from phenyldichloromethane and 1*H*-benzotriazole in the presence of *p*-toluenesulfonic acid in toluene at reflux <1997TL903>.

### 4.09.6 GEMINALLY SUBSTITUTED ALKANES BEARING TWO DIFFERENT DICOORDINATE OR HETEROSUBSTITUTED NITROGENS

#### 4.09.6.1 Nitroalkane Derivatives

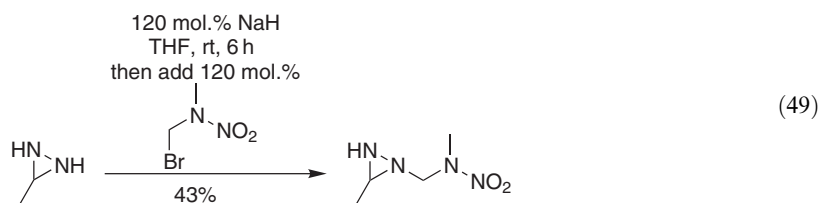
2-Nitro-2-nitroso-butyric and propionic acid ethyl ester have been prepared in low yield (20% and 15%, respectively) by treatment of [1-(ethoxycarbonyl)ethylidene]triphenylphosphorane with dinitrotetroxide <1996LA845>.

Nitroethane and 1-nitrobutane were converted into the corresponding 1-azido-1-nitroalkanes (80% and 83% yield, respectively) by treatment with sodium azide and ammonium peroxodisulfate (NH<sub>4</sub>)<sub>2</sub>S<sub>2</sub>O<sub>8</sub> <2002MI1466>. An alternative procedure utilized potassium ferricyanide K<sub>3</sub>Fe(CN)<sub>6</sub> as the oxidant. A representative example is depicted in Equation (48) <1997JOC1872>.



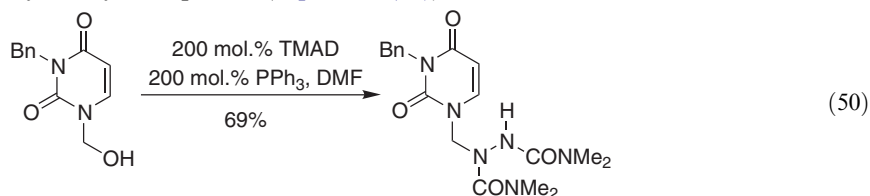
#### 4.09.6.2 Nitraminoalkane Derivatives

3-Methyl-1-(2-nitrazapropyl)diaziridine was prepared by the alkylation of 3-methyldiaziridine with the corresponding alkyl bromide (Equation (49)) <1999MI112>.



#### 4.09.6.3 Azoalkanes and Hydrazino Alkane Derivatives

Treatment of *N*<sup>3</sup>-benzyluracil with *N*-hydroxymethylphthalimide in the presence of *N,N,N',N'*-tetramethylazodicarboxamide (TMAD) and PPh<sub>3</sub> afforded, under optimized conditions, the corresponding 1-hydrazylmethyl compound (Equation (50)) <2002TL2633>.



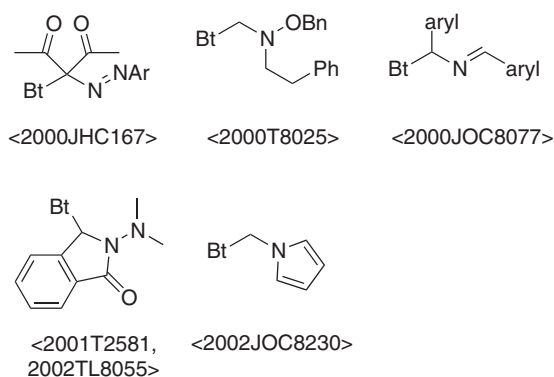
No further advances have occurred in this area since the publication of COFGT (1995) (chapter 4.09.6.3 of <1995COFGT(4)403>).

#### 4.09.6.4 Isocyanato Alkane Derivatives

No further advances have occurred in this area since the publication of COFGT (1995) (chapter 4.09.6.4 of <1995COFGT(4)403>).

#### 4.09.6.5 Benzotriazole Derivatives

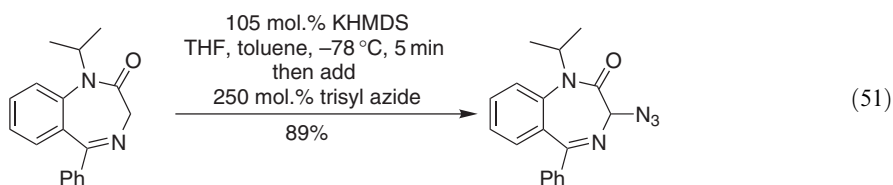
A number of 1*H*-benzotriazol-1-yl-substituted alkanes bearing dicoordinated or heterosubstituted nitrogens are known <2000JHC167, 2000T8025, 2000JOC8077, 2001T2581, 2002TL8055, 2002JOC8230>. These benzotriazole derivatives are usually prepared by the inter- or intramolecular condensation of an appropriate amine and an aldehyde with 1*H*-benzotriazole. Some representative examples are depicted in Scheme 12.



Scheme 12

#### 4.09.6.6 Miscellaneous Derivatives

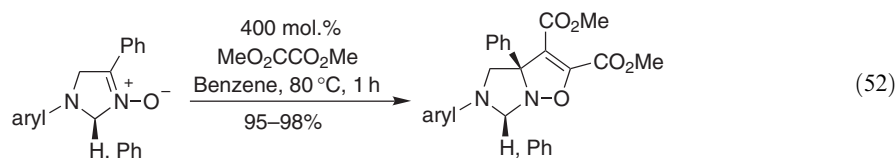
The direct azidation of enolates of benzodiazepines with 2,4,6-triisopropylbenzenesulfonyl azide (trisyl azide) afforded the corresponding 3-azidobenzodiazepines <1996TL6685>. A representative example is depicted in Equation (51).



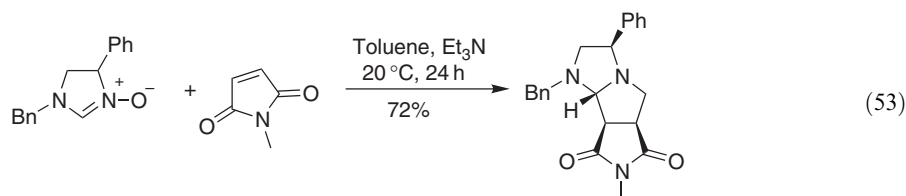
#### 4.09.7 GEMINALLY SUBSTITUTED ALKANES BEARING ONE AMINO GROUP AND ONE DICOORDINATE OR HETEROSUBSTITUTED NITROGEN

##### 4.09.7.1 Aminomethylhydroxylamines

The thermal 1,3-dipolar cycloaddition between imidazolin-3-oxides and dimethyl acetylenedicarboxylate afforded the corresponding 3a,4,5,6-tetrahydroimidazo[1,5-*b*]isoxazoles with a remarkable yield (Equation (52)) <2000TL5407, 2001T3413>. (1(*S*))-(-)- $\beta$ -pinene has been employed as a dipolarophile for the analogous transformation <2001TA1463>.



A structurally modified imidazolin-3-oxide underwent the 1,3-dipolar cycloaddition with a variety of different alkenes in low-to-moderate yield. The highest yielding example is depicted in Equation (53) <2000SL967>.

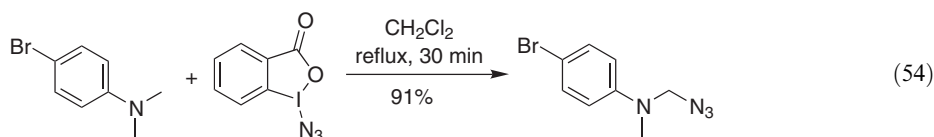


##### 4.09.7.2 Aminomethyl Nitramines and Nitrosamines

No further advances have occurred in this area since the publication of COFGT (1995) (chapter 4.09.7.2 of <1995COFGT(4)403>).

##### 4.09.7.3 Aminomethyl Azides and Triazines

Azide has been incorporated into *N,N*-dimethylarylamines to afford the corresponding *N*-azido-*N*-methylanilines <1997JA7408>. A representative example is depicted in Equation (54) <1996JA5192>.



*N*-Azido-*N*-methylanilines have also been prepared in moderate yield by treatment of either *N*-(methoxymethyl)anilines or 1,3,5-triarylhexahydro-1,3,5-triazines with TiCl<sub>4</sub> and trimethylsilylazide <1995SC969>. A related investigation employed the combination of iodosylbenzene and trimethylsilylazide as reagent for the azidation of *N,N*-dimethylarylamines <1998S547>.

##### 4.09.7.4 Aminomethylazo and -hydrazino Compounds

No further advances have occurred in this area since the publication of COFGT (1995) (chapter 4.09.7.4 of <1995COFGT(4)403>).

#### 4.09.7.5 Aminomethylamines

3-Amino-1,4-benzodiazepines have been prepared by the reduction of the corresponding azides (Equation (47)) with triphenylphosphine <1996TL6685>.

#### 4.09.8 GEMINALLY SUBSTITUTED ALKANES BEARING ONE ACYLATED OR SULFONATED AMINO GROUP AND ONE DICOORDINATE OR HETEROSUBSTITUTED NITROGEN

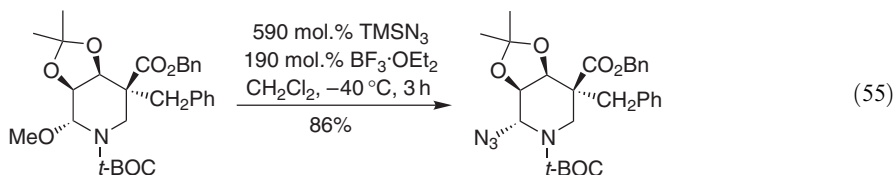
As was concluded in chapter 4.09.8 of <1995COFGT(4)403>, work on compounds that bear one dicoordinate nitrogen substituent and a sulfonated amino substituent on the same carbon are very rare. An example can be found in <2000JOU816>.

##### 4.09.8.1 Acylaminomethylisocyanates and -isothiocyanates

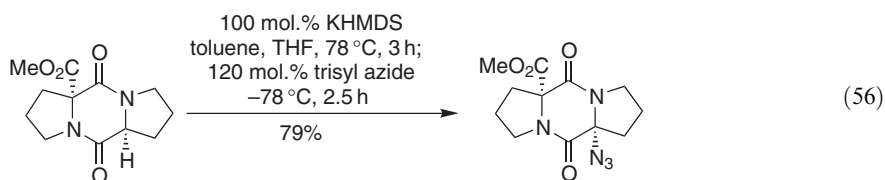
No further advances have occurred in this area since the publication of chapter 4.09.8.1 <1995COFGT(4)403>.

##### 4.09.8.2 Acylaminomethylazides

Treatment of a highly functionalized, cyclic *N*-acyl-*N*,*O*-acetal with trimethylsilyl azide afforded the corresponding substituted 6-azido-*N*-(*t*-butoxycarbonyl)piperidine in high yield (Equation (55)) <2000OL4037>.



Tricyclic diketopiperazin-2,5-diones have been deprotonated and treated with different electrophiles. Equation (56) depicts an azidation with 2,4,6-triisopropylbenzenesulfonyl azide (trisyl azide) as the electrophile <2002OL2645>.



3-Azidomethyl-2-oxazolidinone was prepared by condensation from 2-oxazolidinone, paraformaldehyde, and HN<sub>3</sub> <2000OL3777>.

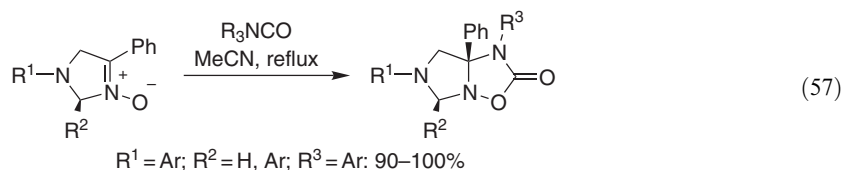
##### 4.09.8.3 Acylaminomethyl Nitramines

No further advances have occurred in this area since the publication of chapter 4.09.8.3 <1995COFGT(4)403>.

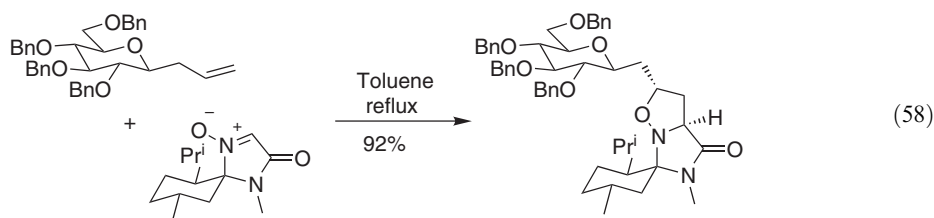
##### 4.09.8.4 Acylaminomethylhydroxylamines and -hydrazines

This chapter verifies that a large number of reactions have been described that provide diverse compounds containing the acylaminomethylhydroxylamine- and hydrazine-structural element. The 1,3-dipolar cycloaddition between substituted  $\Delta^3$ -imidazoline-3-oxides and arylisocyanates

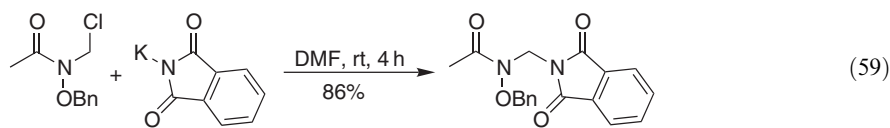
afforded substituted imidazoloxadiazol-2-ones in high yields (Equation (57)) <1997TL2299, 1997T13873, 1999SC3889>. A related 1,3-dipolar cycloaddition of *N*-oxides derived from polyhydroxylated piperidines has been described <1996T4467>.



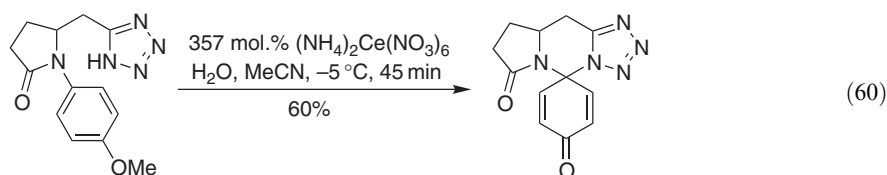
The 1,3-dipolar cycloaddition between a spirocyclic chiral nitron and different allylglycosides afforded the expected tricyclic isoxazolidines in good yield and auxiliary-induced diastereoselectivity <2001OL1375>. A representative example is depicted in Equation (58).



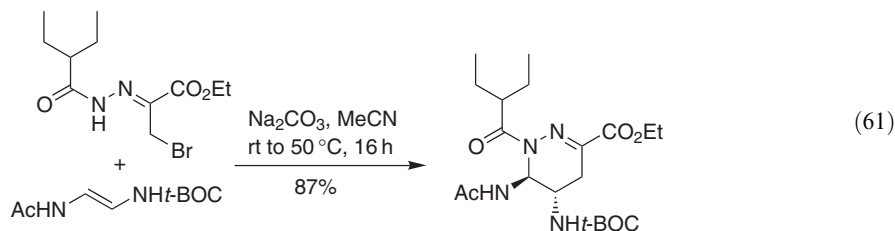
Treatment of *N*-chloromethyl-*N*-benzyloxyacetamide with potassium phthalimide afforded the *N*-(phthalimidomethyl)-*N*-benzyloxyacetamide (Equation (59)) <1995SL97>.



The mechanism of the formation of a spirocyclic tetrazole by treatment of the corresponding pyrrolidinone with cerium(IV) ammonium nitrate has been investigated Equation (60) <1996T10169>.



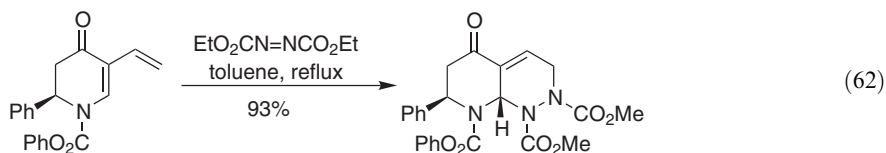
The synthesis of a 1,4,5,6-tetrahydropyridazine derivative by an intermolecular hetero-Diels–Alder reaction has been reported (Equation (61)) <1999BMCL1751>.



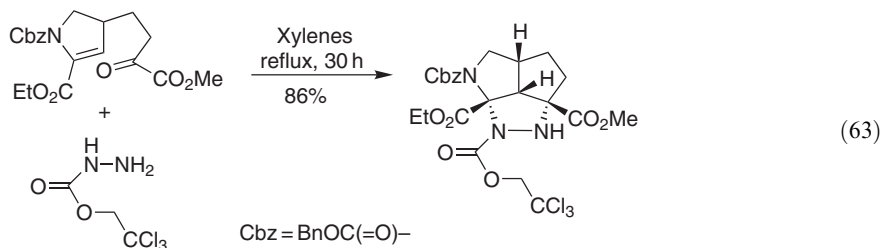
A microwave-promoted addition of the *N*-phenylhydrazone of 1-phenylpyrazol-4-carbaldehyde onto the imine function of *N*-trichloroethylidenecarbamate afforded the corresponding addition product <1999T9623>.

The Diels–Alder cycloaddition between 5-vinyl-2,3-dihydro-1*H*-pyridin-4-one and diethylazodicarboxylate afforded the corresponding cycloadduct in good yield (Equation (62)) <2003OL321>.

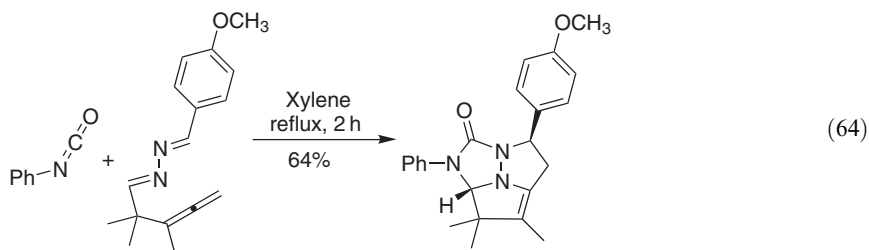




The condensation of 2,2,2-trichloroethylcarbazate with a dihydropyrrole  $\alpha$ -ketoester was followed by an intramolecular azomethine imine 1,3-dipolar cycloaddition to afford a tricyclic cycloadduct (Equation (63)) <2002JOC7880>.

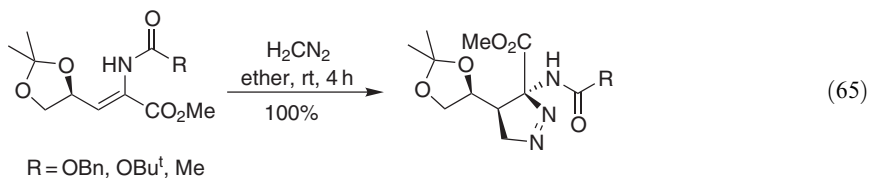


A proposed sequence consisting of an intra- and an intermolecular 1,3-dipolar cycloaddition was employed to synthesize a triazatricyclic compound (Equation (64)) <2002TL6431>.

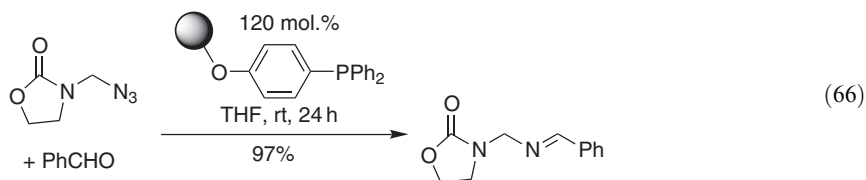


#### 4.09.8.5 Acylaminomethyl Azoalkanes and Iminoalkanes

$\Delta^1$ -Pyrazolines have been prepared by the 1,3-dipolar cycloaddition of dehydroamino acid and diazomethane (Equation (65)) <1996TA537, 1997T3777, 2000TA4903>.

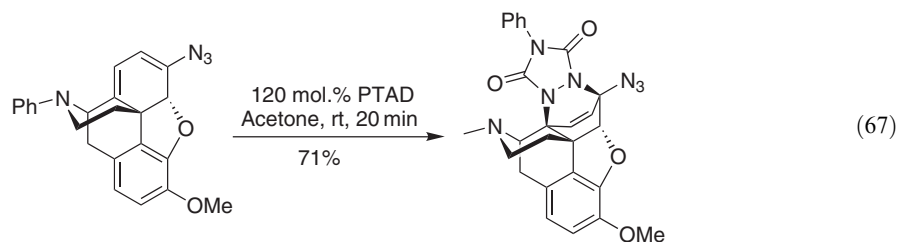


An aza-Wittig reaction that utilized a polymer-supported phosphine (polystyrene-based) afforded the 3-[(benzylidene-amino)-methyl]-oxazolidin-2-one from 3-azidomethyl-2-oxazolidinone and benzaldehyde (Equation (66)) <2000OL3777>.



#### 4.09.8.6 Miscellaneous Compounds

The intermolecular Diels–Alder reaction of 6-azido-6-demethoxythebaine and 4-phenyl-4*H*-1,2,4-triazoline-3,5-dione (PTAD) afforded the corresponding polycyclic cycloadduct (Equation (67) <1997M1267>).



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**Biographical sketch**

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# 4.10

## Functions Incorporating a Nitrogen and Another Group 15 Element

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### 4.10.1 FUNCTIONS CONTAINING ONE NITROGEN AND ONE PHOSPHORUS: $R_2^1C(NR_2^2)PR_2^3$ , etc.

It can be said that the chemistry of organophosphorus compounds stands among the most prolific and utile domains of organic chemistry today. As there exist a number of categories of organophosphorus functionalities, this chapter will focus on the chemistry of the N—C—P array, which appears extensively in the literature. This array of atoms has proven itself to be an attractive substructure to chemists, as it has been employed as a building block in natural product synthesis, as ligand architecture in organometallic catalysis, and as the basis of novel biologically active species in hapten and peptidomimetic synthesis. Although these topics are meritorious and demonstrate the utility of the N—C—P array, this work will focus not on the applications of these substructures, but on the preparations thereof.

Over the period of 1995–2003, a number of publications (ca. 2,500) have appeared that invoke the preparation and use of organophosphorus compounds of this description. Although most preparations fall under a narrow number of methods, the scope of these methods has shown itself to be broad and tolerant of various other functional groups. New methods have also come about, most notably, methods that effect the highly efficient installation of a stereocenter at the central carbon. These methods will be offered special attention, as they are both novel and presumably of great interest to the synthetic chemist.

#### 4.10.1.1 Amino Functions: $R^1C(NR_2^2)PO$ , $R^1C(NR_2^2)PR_2^3$ , $R^1C(NR_2^2)P(O)R_2^3$ , etc.

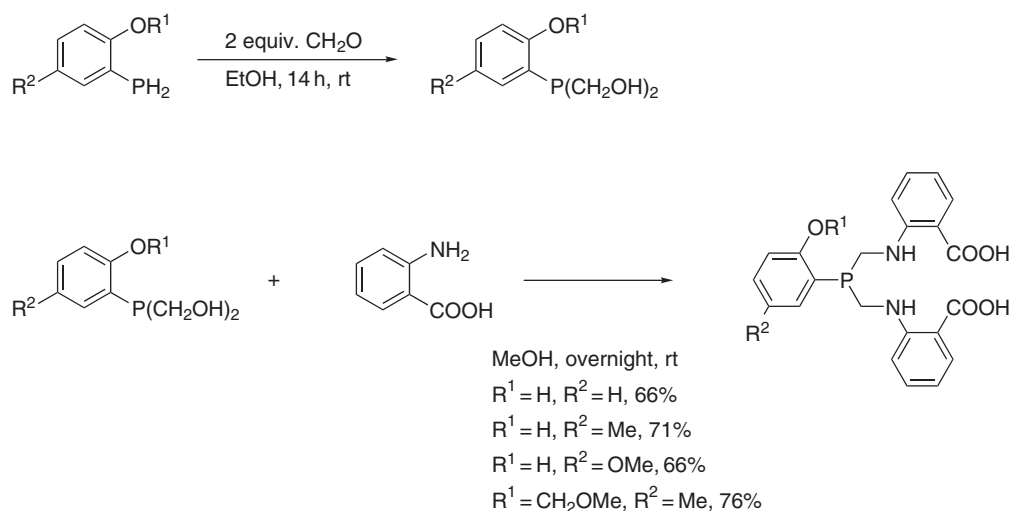
##### 4.10.1.1.1 Dicoordinate phosphorus functions: $R^1C(NR_2^2)PO$ , etc.

During the period 1995–2003, there were no published reports detailing the preparation of the N–C–P array in which phosphorus had a coordination number of 2.

##### 4.10.1.1.2 Tricoordinate phosphorus functions: $R^1C(NR_2^2)PR_2^3$ , etc.

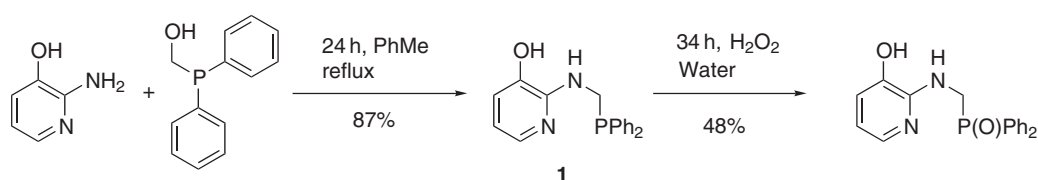
###### (i) Tricoordinate phosphorus functions by condensation of amines with $\alpha$ -hydroxymethylphosphorus compounds

Condensation of amines with phosphorus bearing hydroxymethyl groups has become a versatile and convenient method for the preparation of relevant tricoordinate phosphorus compounds. In general, a phosphine reacts with an excess of formaldehyde to generate a reactive species. Elimination of the hydroxyl group followed by attack with an amine generates the desired product with loss of water. An example of this reaction as employed by Karasik and co-workers [<2001POL3321>](#) is shown in [Scheme 1](#). The hydroxymethylphosphine is prepared and observed spectroscopically prior to the introduction of amine. The authors also report that although heating does accelerate the condensation of formaldehyde and phosphine, it can lead to unwanted polymerization by-products.



Scheme 1

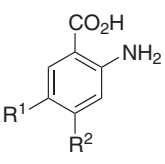
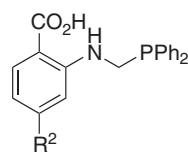
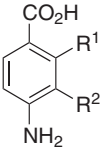
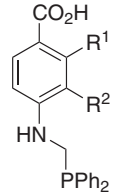
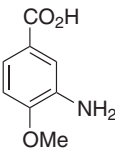
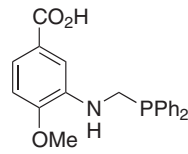
Smith and co-workers [<2000JCS\(D\)2771>](#) have reported similar results leading to the synthesis of novel pyridylphosphine ligands as shown in [Scheme 2](#). The second step of the scheme demonstrates a means of oxidizing the tricoordinate phosphorus function **1** to a tetracoordinate motif to be discussed in [Section 4.10.1.1.3.\(i\)](#).



Scheme 2

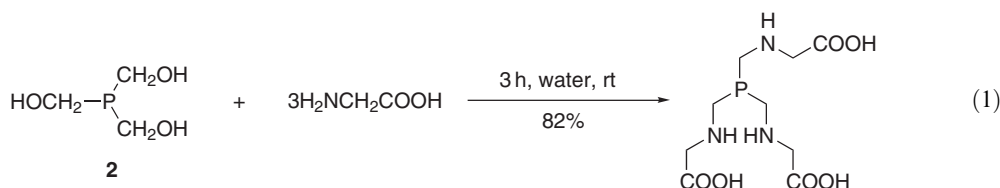
Condensations of this sort have also found use in the elaboration of aminobenzoic acids. Smith and co-workers have produced examples, shown in Table 1, in which diphenylphosphinomethanol reacts with a series of substrates in suitable yields with small aromatic groups <2002TL1299>.

**Table 1** Condensation of aminobenzoic acids with diphenylphosphinomethanol<sup>a,b</sup>

Aminobenzoic acid	R <sup>1</sup>	R <sup>2</sup>	Yield (%)	Product
	H	H	88	
	F	H	55	
	Cl	H	76	
	H	Cl	90	
	Br	H	77	
	I	H	66	
	OH	H	80	
	COOH	H	94	
	OMe	OMe	63	
	H	H	63	
	H	OMe	96	
			93	

<sup>a</sup> <2002TL1299>. <sup>b</sup> Conditions: 2 equiv. Ph<sub>2</sub>PCH<sub>2</sub>OH, MeOH, rt.

Reactions of this sort also appear applicable to phosphorus bearing three hydroxymethyl groups. In the following example published by Katti and co-workers, compound **2** accepts 3 equiv. of glycine (Equation (1)) <1999JA1658>.

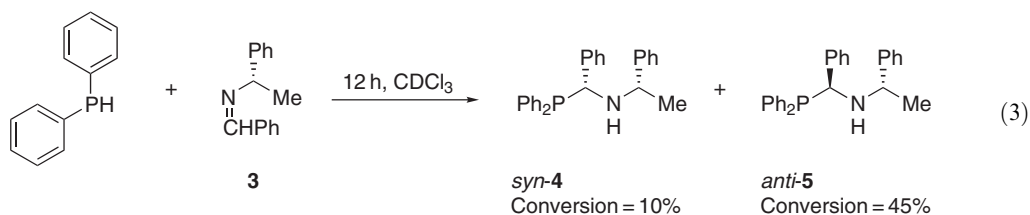


In systems bearing two proximal phosphorus atoms, it is possible to achieve either multiple additions such as those described above by employing secondary amines, or cyclization by using primary amines, which can attack once at each hydroxymethylated phosphorus. Examples of both processes involving tetrahydroxymethyldiphosphines appear in Table 2 <1999JA1658>.

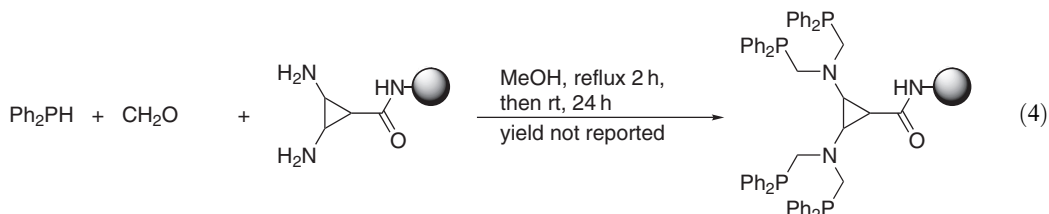
Through the condensation of a primary phosphine, 2 equiv. of a primary amine, and excess formaldehyde, it is possible to achieve cyclization via a different pathway. The nitrogen of both amines attacks the activated phosphorus species, and a third equivalent of formaldehyde effects

<i>Tetrahydroxymethyldiphosphine</i>	<i>Amine</i>	<i>Product</i>	<i>Yield (%)</i>
	PhNHMe		90
	NHEt <sub>2</sub>		62
	NH <sub>2</sub> CH <sub>2</sub> COOH		85
	NH <sub>2</sub> CHMeCOOH		78
	NH <sub>2</sub> CH <sub>2</sub> COOH		78

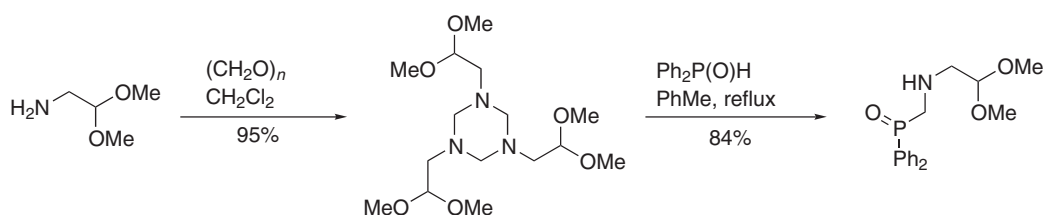
In the conversion of **3** to a mixture of **4** and **5**, Andrieu and co-workers [<2001XXX1015>](#) exploited the inherent stereochemistry of **3** to achieve preferential formation of the *anti* product after 12 h of equilibration, though with modest selectivity (Equation (3)).



Reports have surfaced demonstrating the preparation of bis(diphenylphosphinomethyl) amino compounds on solid phase. Arya and co-workers have shown that the condensation of amines on solid support with formaldehyde and diphenylphosphine leads to dendrimers (Equation (4)), which the authors have applied to heterogeneous catalysis <2000JOC1881>.

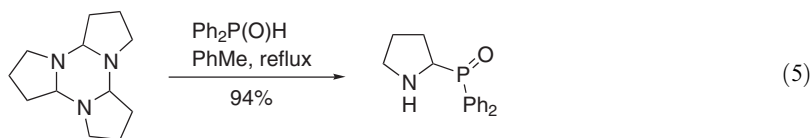


Typically, the imines employed in the reactions of this class are generated from an aldehyde and an amine, either *in situ* or in a separate pot. There are, however, other ways to generate imine equivalents for use in the condensation. One such method is the use of a triazine as the electrophile. Couture and co-workers offer two examples of such a transformation. In the synthesis of lennoxamine, Couture and co-workers <2000T1491> utilize this approach to generate an early intermediate, as shown in Scheme 3.



Scheme 3

Couture and co-workers <1998JCS(P1)1403> use a similar transformation to generate a derivative of pyrrole (Equation (5)).



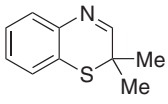
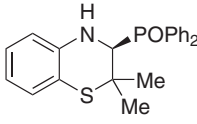
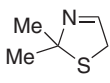
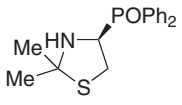
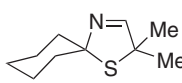
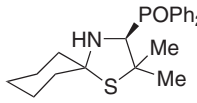
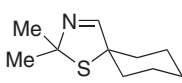
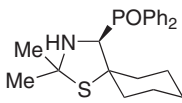
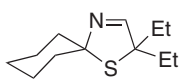
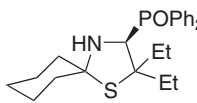
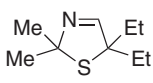
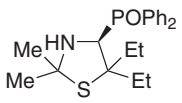
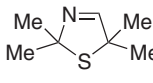
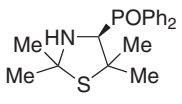
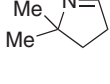
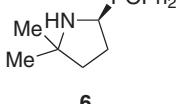
#### 4.10.1.1.3 Tetracoordinate phosphorus functions: $R_2^1\text{C}(\text{NR}_2^2)\text{P}(\text{O})\text{R}_2^3$ , $R_2^1\text{C}(\text{NR}_2^2)\text{P}(\text{O})(\text{OR}^3)_2$ , etc.

(i) Tetracoordinate phosphorus functions (phosphine oxides,  $R_2^1\text{C}(\text{NR}_2^2)\text{P}(\text{O})\text{R}_2^3$ ) by addition of dialkylphosphine oxides to imines

A reaction similar to that discussed above generates the phosphine oxide directly, without the need for subsequent oxidation. Shibasaki and co-workers have shown that the addition of diphenylphosphine oxide to various imines in the presence of (*R*)-PrPB, Pr(binaphthylOH)

(binaphthylOK)<sub>2</sub>, generates the desired products in good yields and selectivities as shown in Table 3. Shibasaki and co-workers <sup><1999TL2565></sup> also detail the use of trialkylphosphine oxide **6** in asymmetric reduction of a carbonyl.

**Table 3** Asymmetric addition of diphenylphosphine oxide to imines<sup>a,b</sup>

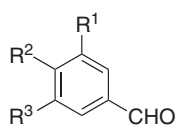
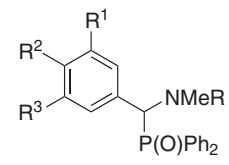
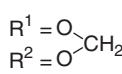
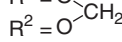
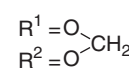
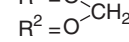
Imine	Product	Yield (%)	ee (%)
		72	82 <sup>c</sup>
		98	91 <sup>c</sup>
		98	93 <sup>c</sup>
		95	92 <sup>c</sup>
		98	81 <sup>c</sup>
		76	82 <sup>c</sup>
		50	92 <sup>c</sup>
		63	75 <sup>d</sup>

**6**

<sup>a</sup> <sup><1999TL2565></sup>. <sup>b</sup> Conditions: (*R*)-PrPB (3,3), Ph<sub>2</sub>P(O)H, PhMe/THF 7:1. <sup>c</sup> 50 °C, 50 h. <sup>d</sup> rt, 96 h.

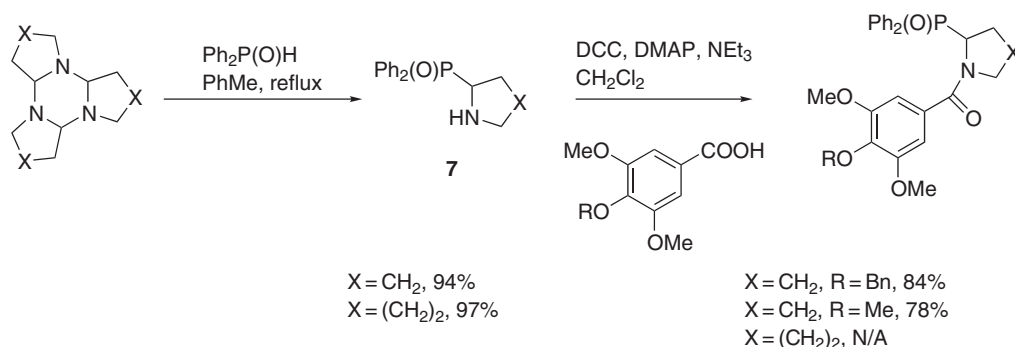
Couture and co-workers <sup><2001EJO2559></sup> have exploited a similar reaction to generate substituted aryl derivatives (Table 4). The aldehyde condenses with the primary amine *in situ*, followed by the addition of diphenylphosphine oxide with azeotropic removal of water.

**Table 4** Reactions of aldehydes with amines and diphenylphosphine oxide<sup>a,b</sup>

	Amines		Yield (%)
R <sup>1</sup> = H R <sup>2</sup> = H R <sup>3</sup> = H	NHMe( <i>p</i> -methoxybenzyl)	R <sup>1</sup> = H R <sup>2</sup> = H R <sup>3</sup> = H	75
R <sup>1</sup> = H R <sup>2</sup> = OMe R <sup>3</sup> = H	NHMe( <i>p</i> -methoxybenzyl)	R <sup>1</sup> = H R <sup>2</sup> = OMe R <sup>3</sup> = H	77
R <sup>1</sup> = OMe R <sup>2</sup> = OMe R <sup>3</sup> = OMe	NHMe( <i>p</i> -methoxybenzyl)	R <sup>1</sup> = OMe R <sup>2</sup> = OMe R <sup>3</sup> = OMe	85
R <sup>1</sup> =  R <sup>2</sup> =  R <sup>3</sup> = OMe	NHMe( <i>p</i> -methoxybenzyl)	R <sup>1</sup> =  R <sup>2</sup> =  R <sup>3</sup> = OMe	78
R <sup>1</sup> = H R <sup>2</sup> = OMe R <sup>3</sup> = OMe	NH <sub>2</sub> Me	R <sup>1</sup> = H R <sup>2</sup> = OMe R <sup>3</sup> = OMe	94

<sup>a</sup> <2001EJO2559>.<sup>b</sup> Conditions: 0 °C, PhMe, 1 h, then add Ph<sub>2</sub>P(O)H, reflux for 1 h with Dean-Stark trap.

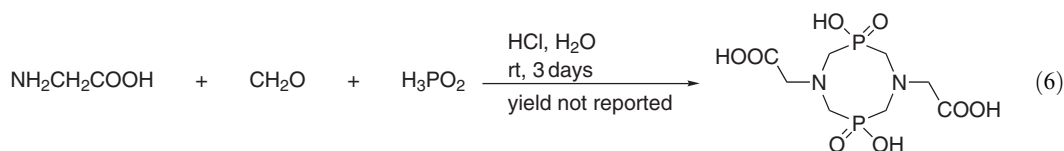
Couture and co-workers <2000BMC2113> also published access to the desired atomic array using imines generated *in situ* by the thermal decomposition of triazines. After isolation of  $\beta$ -aminotrialkylphosphine oxide **7**, the amine is coupled to an acid to generate a  $\beta$ -amidotrialkylphosphine oxide (Scheme 4).

**Scheme 4**

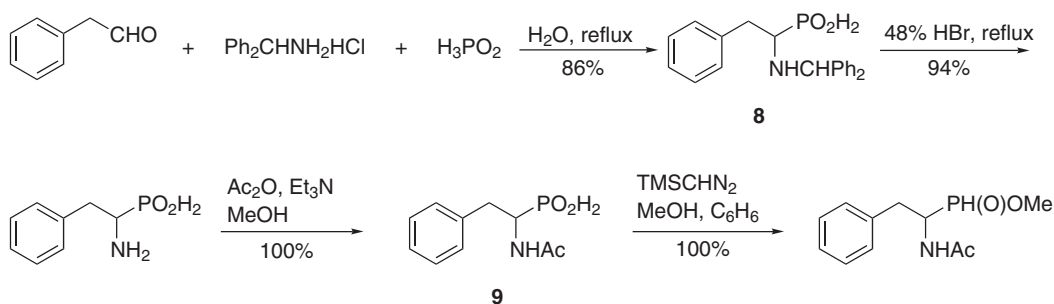
(ii) Direct synthesis of tetracoordinate phosphorus functions in which phosphorus bears a hydroxyl group via addition of phosphorus to imines

Although there do exist a number of references that document the generation of the above-mentioned functionality, most such sources arrive at the desired compound via generation of the phosphonate ester or analogous species and subsequent hydrolysis to acquire the P—OH array. Examples of such endeavors will appear later in Section 4.10.1.1.3.(iii), which details the generation of  $\beta$ -aminophosphonate esters. This section focuses on the direct generation of the targets without the intermediacy of a phosphonate ester or analogous compound.

In the search for novel ligand architecture, Giovenzana and co-workers have prepared an eight-membered bidentate ring through the condensation of glycine and formaldehyde in the presence of hypophosphorous acid (Equation (6)). In addition to its synthesis, the authors describe its coordination properties <2002TL8387>.

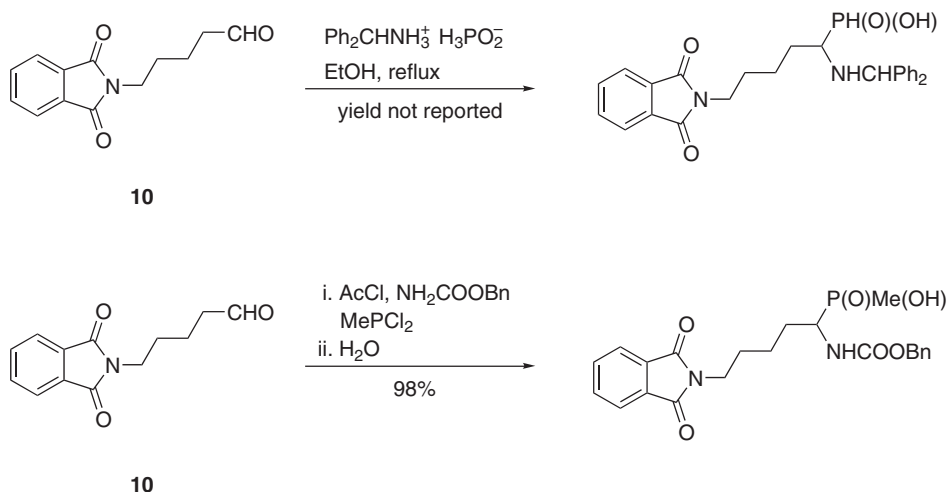


In course of the synthesis of phosphinyl peptidomimetics, Ebetino and co-workers have exploited a similar transformation to generate compound **8**. The amine and aldehyde are efficiently condensed in the presence of hypophosphorous acid to yield **8**, which in turn undergoes further transformations as shown in Scheme 5 <2002JOM212>. Although amides similar to  $\beta$ -amidophosphonate **9** can be realized through acylation, as shown here, the direct synthesis of such compounds is discussed in Section 4.10.1.2.3.



Scheme 5

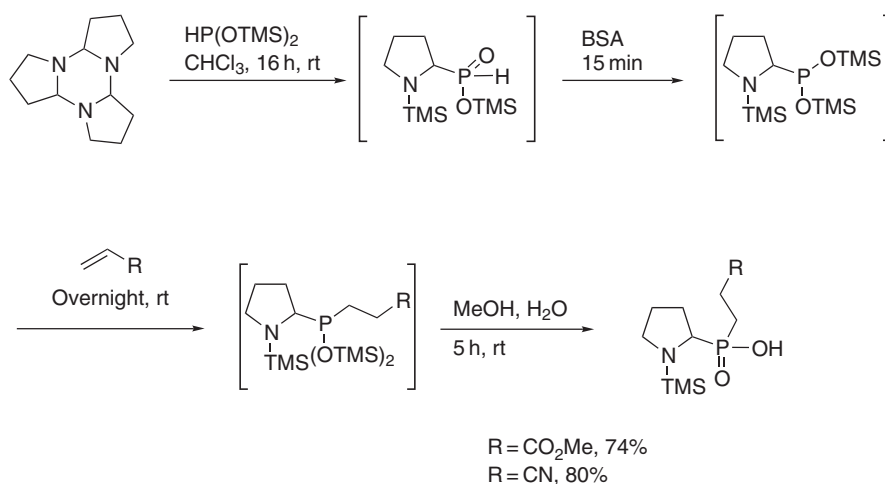
While studying nitric oxide synthase, Massa and co-workers utilized this approach to generate racemates of potential inhibitors. Condensation of an aldehyde, **10**, with one of the two sources of nitrogen produces the transitory imine, which is trapped by a phosphorus nucleophile, as depicted in Scheme 6 <2000HAC505>. The products were further elaborated to the final targets.



Scheme 6



Haemers and co-workers have utilized an alternative approach, in which a triazine serves as an imine surrogate, in the preparation of proline analogs. Reaction of the triazine with bis(trimethylsilyl) phosphonite renders an intermediate, which is further silylated with BSA, alkylated, and finally hydrolyzed to the phosphinic acid as shown in [Scheme 7 <1995SI074>](#).

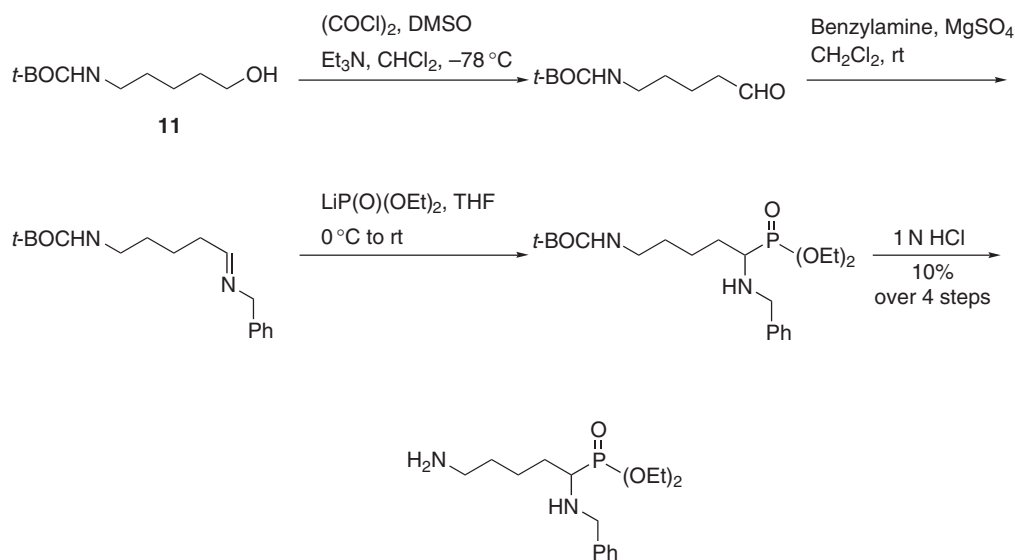


Scheme 7

(iii) Preparation of compounds bearing phosphonate esters and closely derived functionalities via addition of phosphorus to imines

Among all classes of molecules bearing the N—C—P array of interest, undoubtedly the most widely prepared and studied group is that which includes phosphonate esters. These compounds appear prolifically in the literature, and offer the greatest number of examples of the condensation reactions typical to the synthesis of the functionality discussed in this chapter. The first method of interest, condensation of nucleophilic phosphorus with imines, resembles reactions described previously.

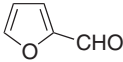
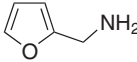
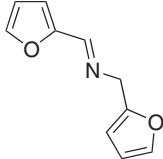
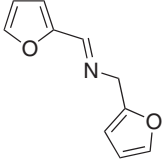
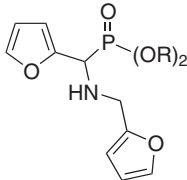
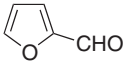
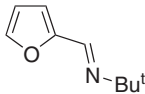
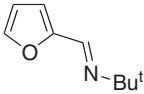
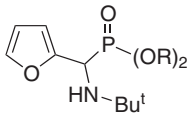
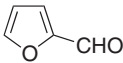
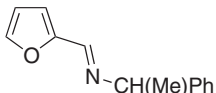
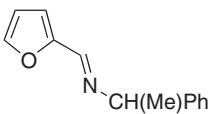
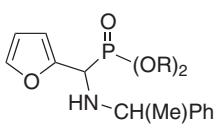
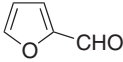
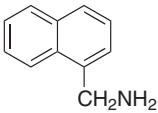
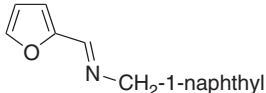
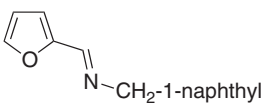
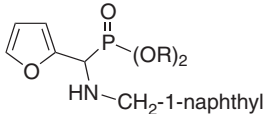
The first example of reactions of this class comes from Massa and co-workers. Oxidation of alcohol **11** to the aldehyde, followed by condensation with benzylamine, addition of  $\text{LiP}(\text{O})(\text{OEt})_2$ , and deprotection, renders diamine **12** in 10% yield with only one purification over four steps as shown in [Scheme 8 <2000HAC505>](#).



Scheme 8

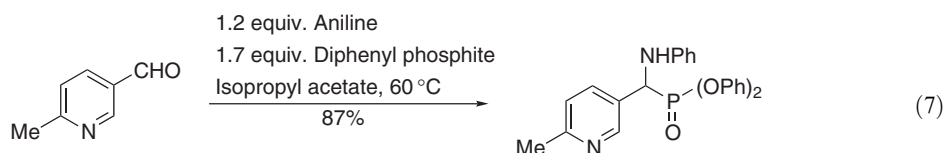
Condensations of a similar nature have also rendered unique furyl-substituted aminophosphonates. Lewkowski and co-workers have produced a series of compounds with various alkyl substituents in their search for novel plant protection agents (Table 5) <2000OPP453>.

**Table 5** Generation of furan-substituted amino phosphonates<sup>a</sup>

Substrate	Reagent	Conditions	Yield (%)	Product
		Neat, rt, 5 h	74	
	HP(O)(OR) <sub>2</sub> R = Et R = PhCH <sub>2</sub> R = Ph	1 equiv. Phosphite, toluene, 40 °C, 7 h, rt, 12 h	NA 54 69	
	Bu <sup>t</sup> NH <sub>2</sub>	Neat, rt, 5 h	78	
	HP(O)(OR) <sub>2</sub> R = Et R = PhCH <sub>2</sub> R = Ph	1 equiv. Phosphite, toluene, 40 °C, 7 h, rt, 12 h	52 73 57	
	PhCH(Me)NH <sub>2</sub>	Neat, rt, 5 h	64	
	HP(O)(OR) <sub>2</sub> R = Et R = PhCH <sub>2</sub> R = Ph	1 equiv. Phosphite, toluene, 40 °C, 7 h, rt, 12 h	59 69 53	
		Neat, rt, 5 h	88	
	HP(O)(OR) <sub>2</sub> R = Et R = PhCH <sub>2</sub> R = Ph	1 equiv. Phosphite, toluene, 40 °C, 7 h, rt, 12 h	59 53 53	

<sup>a</sup> <2000OPP453>.

In course of the development of a Cox-2 inhibitor, a Merck team prepared an aminophosphonate for use as a nucleophile in a Horner–Wadsworth–Emmons (HWE) coupling. 6-Methylnicotinate was condensed with aniline and diphenylphosphate to render aminophosphonate **13** (Equation (7)), which was coupled with another aldehyde <2000JOC8415>.



13

Couture and co-workers expounded further on the competence of such compounds for use in HWE reactions. The group prepared a series of aminophosphonates via condensation (Table 6) and demonstrated their efficacy in olefination reactions. Couture and co-workers [\[2001SI462\]](#) also demonstrate the applicability of these reactions to diphenylphosphine oxides (see Section 4.10.1.1.3.(i)).

**Table 6** Formation of aminophosphonate HWE substrates<sup>a,b</sup>

$R^1$	$R^2$	$R^3$	$R^4$	$R^5$	$R^6$	Yield (%)
H	OMe	OMe	Br	Me	Ph	70
H	H	H	H	Me	Ph	75
H	OMe	H	H	Me	Ph	77
OMe	OMe	H	H	Me	Ph	78
—OCH <sub>2</sub> O—		H	H	Me	Ph	78
OMe	OMe	OMe	H	Me	Ph	85
H	OMe	H	H	Et	Ph	82
H	OMe	H	H	Bu	Ph	75
OMe	OMe	H	H	Me	OEt	66
—OCH <sub>2</sub> O—		H	H	Me	OEt	62
H	OMe	H	H	Et	OMe	71
H	OMe	H	H	Bu	OMe	65

<sup>a</sup> [\[2001SI462\]](#). <sup>b</sup> Conditions: 1 equiv. aldehyde, 1 equiv. amine, toluene 0 °C to reflux for 1 h, added 1 equiv. P source, reflux for 1 h with Dean-Stark trap.

Del Pozo and co-workers have applied aminophosphonates to their search for potent HIV inhibitors. In the generation of a series of peptide mimics, the condensation of imines with phosphates gives rise to the target molecules. Del Pozo and co-workers [\[2000SL698\]](#) have also synthesized trialkylphosphines via the same protocol and note that they spontaneously oxidize to the trialkylphosphine oxide on work-up (Table 7).

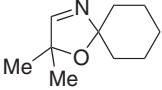
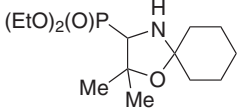
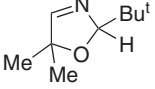
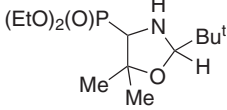
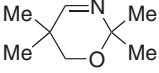
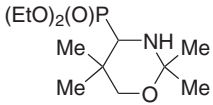
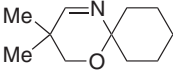
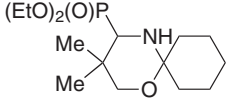
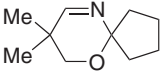
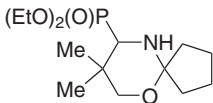
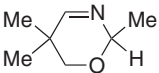
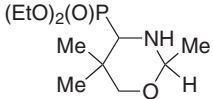
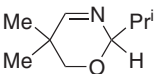
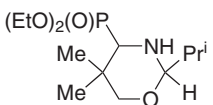
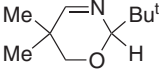
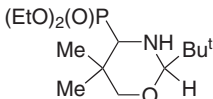
**Table 7** Synthesis of peptide mimics<sup>a</sup>

$R^1$	$R^2$	$R^3$	Conditions <sup>b</sup>	Yield (%)
(CH <sub>3</sub> ) <sub>2</sub> CHCH <sub>2</sub>	Ph	CH <sub>3</sub> CH <sub>2</sub> O	A	78
(CH <sub>3</sub> ) <sub>2</sub> CHCH <sub>2</sub>	Ph	CH <sub>3</sub> O	A	73
(CH <sub>3</sub> ) <sub>2</sub> CHCH <sub>2</sub>	2-Furyl	CH <sub>3</sub> O	A	74
PhCH <sub>2</sub>	Ph	Ph	B	58
Me	Ph	Ph	B	45
PhCH <sub>2</sub>	3-Pyridyl	Ph	B	42
(CH <sub>3</sub> ) <sub>2</sub> CHCH <sub>2</sub>	Ph	Ph	B	64
H	Ph	Ph	B	45
(CH <sub>3</sub> ) <sub>2</sub> CHCH <sub>2</sub>	2-Furyl	Ph	B	31

<sup>a</sup> [\[2000SL698\]](#). <sup>b</sup> A: (R<sup>3</sup>)<sub>2</sub>P(O)H, neat, 100 °C, 3 h; B: (R<sup>3</sup>)<sub>2</sub>PH, Bu<sup>n</sup>Li, THF, −78 °C to rt, then [O].

Interesting aminophosphonates can be prepared from *N,O*-acetals. The result is a heterocycle bearing a pendant phosphonate ester. Martens and co-workers [<1996SC3685>](#) have exploited this protocol as shown in [Table 8](#).

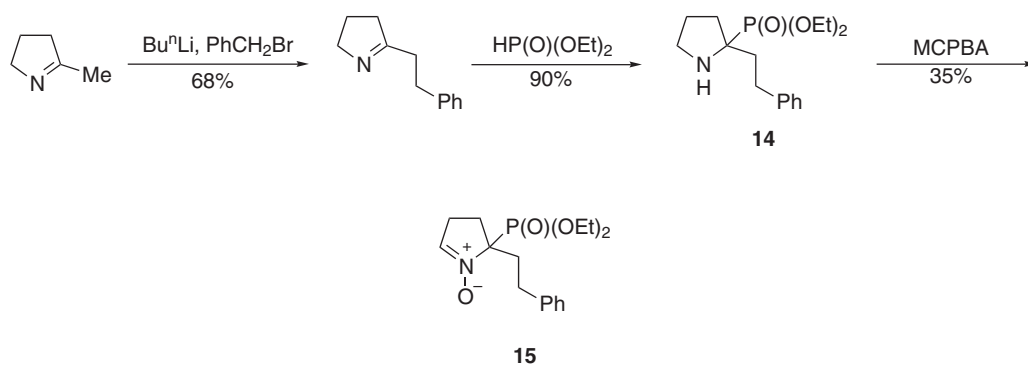
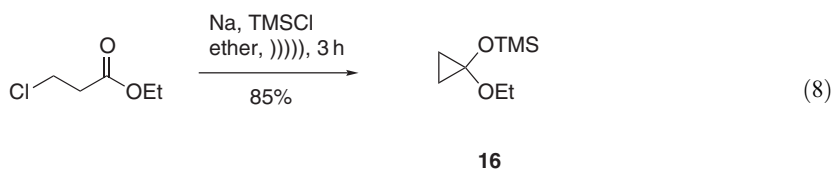
**Table 8** Preparation of phosphonates with *N,O*-heterocycles<sup>a,b</sup>

<i>N,O</i> -Acetal	Product
	
	
	
	
	
	
	
	

<sup>a</sup> [<1996SC3685>](#). <sup>b</sup> Yields = 35–75%.

An intriguing use of heterocycle-pendant phosphonates appears in the work of Liu and co-workers. The authors achieve convenient assembly of compound **14**, which is oxidized to dihydro-2*H*-pyrrole-*N*-oxide **15** as described in [Scheme 9](#). This compound finds use as a spin trap in ESR experiments [<2002JOC7624>](#).

In addition to serving as appendages to heterocycles and medium-sized rings, phosphonates can also be prepared as pendants to cyclopropyl groups. Fadel has published a useful synthesis of 1-aminocyclopropane phosphonates from cyclopropanone mixed acetals. Ethyl-3-chloropropionate is sonochemically converted directly into mixed ketal **16** ([Equation \(8\)](#)), which undergoes *in situ* hydrolysis to the hemiketal and participates in the three-component condensation as portrayed in [Table 9](#) [<1999JOC4953>](#).

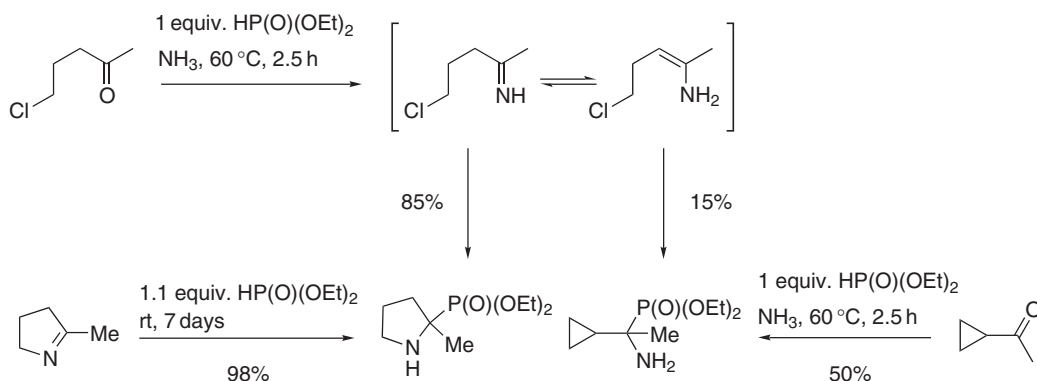
**Scheme 9****Table 9** Synthesis of 1-aminocyclopropane phosphonates from **16**<sup>a</sup>

Amine	Phosphorus source	Conditions <sup>b</sup>	Time (days)	Solvent	Product	Yield (%)
PhCH <sub>2</sub> NH <sub>2</sub>	P(OEt) <sub>3</sub>	A	3	EtOH		68
PhCH(Me)NH <sub>2</sub>	P(OEt) <sub>3</sub>	A	3	EtOH		68
PhCH(Me)NH <sub>2</sub>	P(OEt) <sub>3</sub>	A	4	EtOH/THF (1:1)		87
PhCH(Me)NH <sub>2</sub>	P(OMe) <sub>3</sub>	A	3	MeOH		71
PhCH(Me)NH <sub>2</sub>	P(OEt) <sub>3</sub>	B	1	EtOH		95

<sup>a</sup> <1999JOC4953>. <sup>b</sup> 1 equiv. **16**, 1.5 equiv. phosphorus source, 55 °C; A: 1.5 equiv. amine HCl; B: 1.5 equiv. free amine and 4 equiv. HOAc.

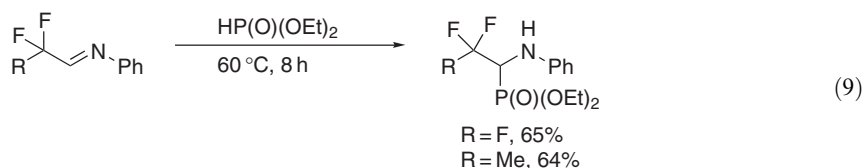
It is also possible to generate  $\alpha$ -amino- $\beta$ -cyclopropyl phosphonates, the study of which has offered insights into the reactivity of  $\gamma$ -chloroimines. Tordo and co-workers have found that while such imines tend to cyclize to five-membered heterocycles, they exist in equilibrium with enamines that give rise to cyclopropyl derivatives. Tordo and co-workers <1999S2036> have explored the

mechanism by preparing both products directly and comparing the results to those obtained from the aforementioned equilibrium (Scheme 10).

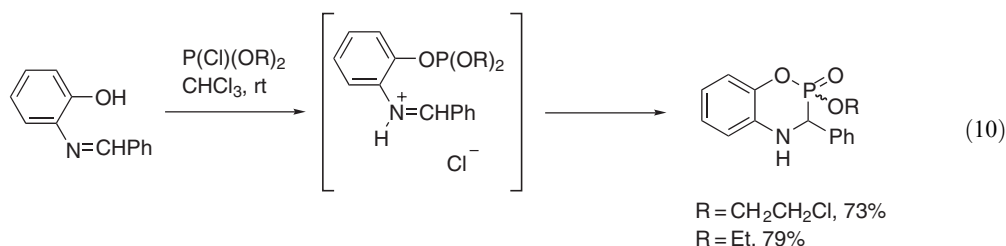


Scheme 10

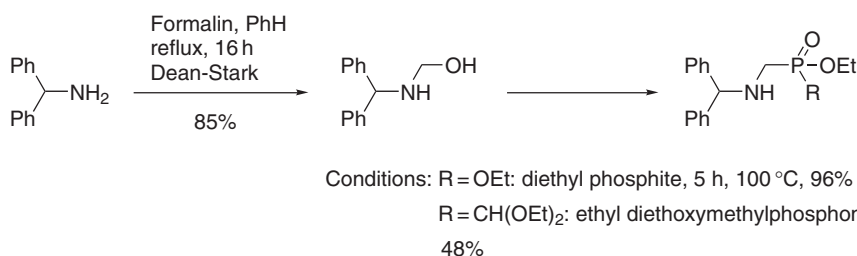
Hägele and co-workers have applied the addition of diethyl phosphite to imines in fluorinated systems. The reaction proceeds in decent yield (Equation (9)) <1996JFC75>.



Another unique reaction appears in the work of Dimukhametov and co-workers, wherein the authors employ phosphorus compounds both as electrophiles and nucleophiles. An imine-bearing phenol attacks phosphorus, and phosphorus subsequently attacks the imine intramolecularly. The yields are good and represent mixtures of diastereomers (Equation (10)) <2001MC196>.



Honek and co-workers <1999OL1395> have demonstrated the stepwise condensation by isolating the intermediate hemiaminal in good yield and adding nucleophiles in a subsequent step (Scheme 11).



Scheme 11

Although the conventional method for the condensation of imines with sources of phosphorus is a stalwart procedure that continues to find widespread use, as with all methods it lends itself to

novel improvements. Certainly the alluring utility of these compounds has enticed groups to discover more expedient routes to the products and reagents to enhance efficiency.

Yadav and co-workers have formulated a highly attractive method for the preparation of these compounds. The montmorillonite, KSF-catalyzed condensation of diethyl phosphite with imines generated *in situ* proves itself to be quite effective in toluene at reflux, yet far more so under microwave irradiation at room temperature. Several examples of this truly remarkable rate and yield enhancement appear in Table 10 <2001S1131>.

**Table 10** Preparations of aminophosphonates under heating vs. microwave irradiation<sup>a</sup>

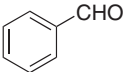
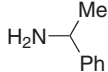
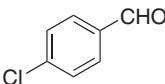
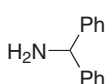
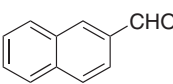

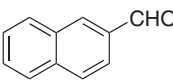
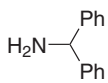
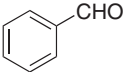
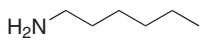
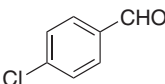

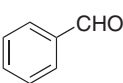
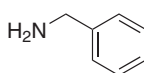
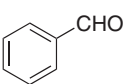
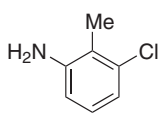

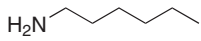
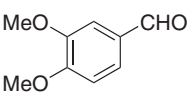
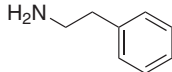
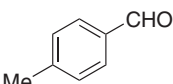

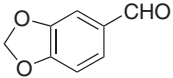
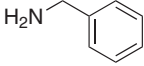
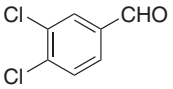
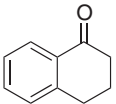
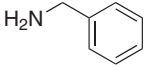
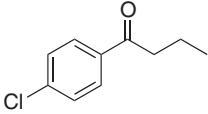
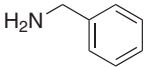
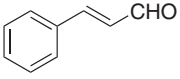
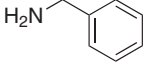
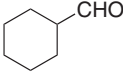
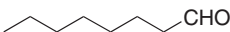
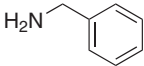
Carbonyl	Amine	Heating <sup>b</sup> : time, yield (%)	Microwave <sup>c</sup> : time, yield (%)
		6 h, 70	3 min, 85
		8 h, 75	3 min, 82
		10 h, 72	5 min, 90
		8 h, 70	6 min, 81
		5 h, 74	4 min 89
		7 h, 80	5 min, 83
		5 h, 72	3 min, 90
		7 h, 70	5 min, 85
		10 h, 65	6 min, 80
		8 h, 75	5 min, 91
		6 h, 77	4 min, 88

Table 10 (continued)

Carbonyl	Amine	Heating <sup>b</sup> : time, yield (%)	Microwave <sup>c</sup> : time, yield (%)
		5 h, 80	3 min, 92
	$\text{H}_2\text{NPh}$	6 h, 73	5 min, 87
		12 h, 68	8 min, 78
		10 h, 70	7 min, 75
		6 h, 75	5 min, 90
	$\text{H}_2\text{NPh}$	6 h, 78	4 min, 85
		7 h, 80	3 min, 87

<sup>a</sup> <2001SI131>. <sup>b</sup> 5 mmol amine, 5 mmol aldehyde, 5 mmol diethyl phosphite, 1.5 g montmorillonite clay, toluene, reflux. <sup>c</sup> 5 mmol amine, 5 mmol aldehyde, 5 mmol diethyl phosphite, 1.5 g montmorillonite clay, toluene, irradiation.

Other catalysts, particularly Lewis acids, have found applications to the synthesis of amino phosphonates. Chandrasekhar and co-workers <2001TL5561> have demonstrated the utility of  $\text{TaCl}_5\text{--SiO}_2$  as a catalyst for the condensation. Mixtures of equimolar portions of an aniline, an aldehyde, and a diethylphosphate in the presence of 10 mol.%  $\text{TaCl}_5\text{--SiO}_2$  lead to the efficient construction of a number of targets as displayed in Table 11.

Qian and co-workers have screened a number of metal complexes, mostly triflates, in search of an effective catalyst for the three-component condensation. Upon testing a series of Lewis acids on a system of benzaldehyde, benzylamine, and diethyl phosphite (Table 12), Qian and Huang <1998JOC4125> found  $\text{Yb}(\text{OTf})_3$  to be a promising candidate.

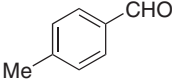
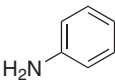
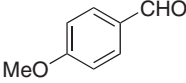
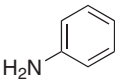
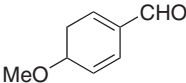
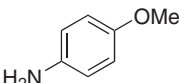
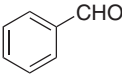
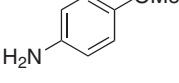
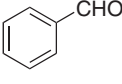
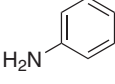
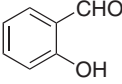
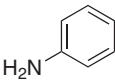
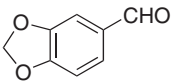
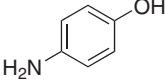
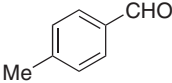
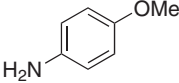
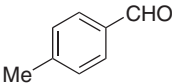
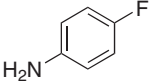
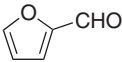
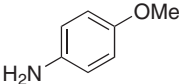
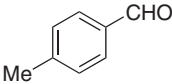

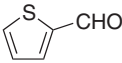
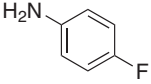
After further studies, Qian demonstrated  $\text{Yb}(\text{OTf})_3$  to be highly effective in the reaction of amines and diethyl phosphite with several aldehydes as depicted in Table 13 <1998JOC4125>.

Qian has also applied these conditions to chiral amines in an effort to achieve stereinduction from the intrinsic chirality of the system (Table 14). The yields are excellent, and the selectivities observed suggest that the method holds potential <1998JOC4125>.

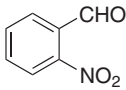
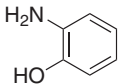
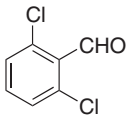
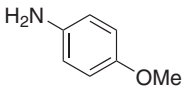
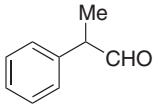
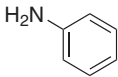
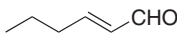
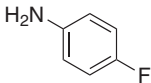
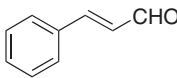
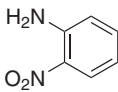

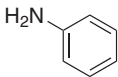
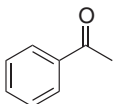
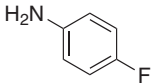
Other Lewis acids and conditions have also proven themselves effective in promotion of the three-component reaction. Ranu and co-workers have published a thorough examination of the use of  $\text{InCl}_3$  as a catalyst, both with and without sonication, in the condensation of both aldehydes and ketones with amines and diethyl phosphite. Although aldehydes react swiftly at room temperature and ketones perform well in THF at reflux, sonication greatly enhances reaction rate, in some cases reducing reaction time by more than half (Table 15) <1999OL1141>.



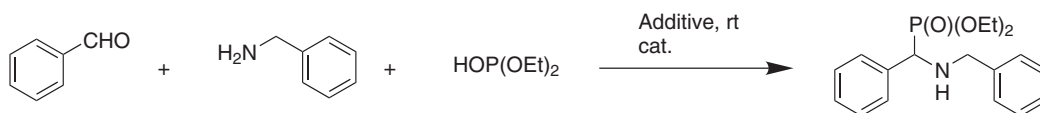
**Table 11** Preparations of aminophosphonates catalyzed by TaCl<sub>5</sub>–SiO<sub>2</sub><sup>a,b</sup>

Carbonyl	Amine	Time (h)	Yield (%)
		22	92
		19	88
		18	94
		18	93
		20	90
		24	84
		24	81
		18	93
		18	94
		20	92
		77	88
		20	93

**Table 11** (continued)

Carbonyl	Amine	Time (h)	Yield (%)
		24	87
		18	88
		20	92
		22	85
		24	82
		22	81
		24	87

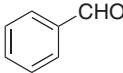
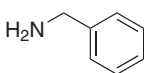
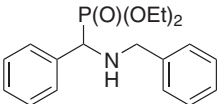
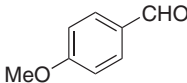
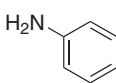
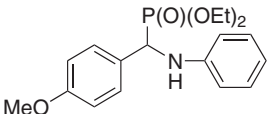
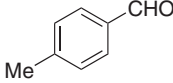
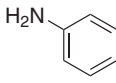
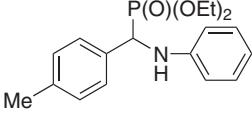
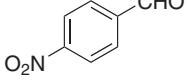
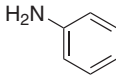
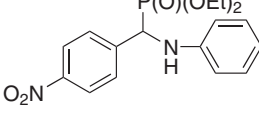
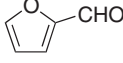
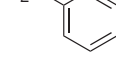
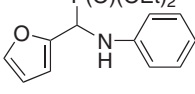
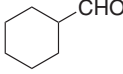
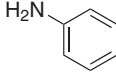
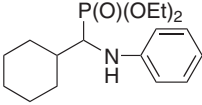
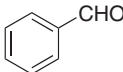
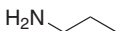
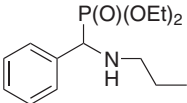
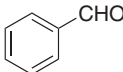
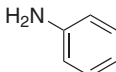
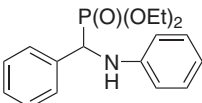
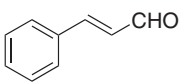
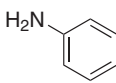
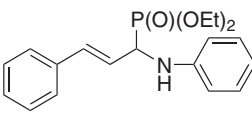
<sup>a</sup> <2001TL5561>. <sup>b</sup> 1 mmol amine, 1 mmol aldehyde, 1 mmol diethyl phosphite, 10 mol.% TaCl<sub>5</sub>–SiO<sub>2</sub>, CH<sub>2</sub>Cl<sub>2</sub>, rt.

**Table 12** Evaluation of a series of metal complexes<sup>a</sup>

Catalyst	Solvent	Additive	Yield (%)
None	CH <sub>2</sub> Cl <sub>2</sub>	MgSO <sub>4</sub>	Trace
La(OTf) <sub>3</sub> (10 mol.%)	CH <sub>2</sub> Cl <sub>2</sub>	MgSO <sub>4</sub>	34
Sm(OTf) <sub>3</sub> (10 mol.%)	CH <sub>2</sub> Cl <sub>2</sub>	MgSO <sub>4</sub>	56
Yb(OTf) <sub>3</sub> (10 mol.%)	CH <sub>2</sub> Cl <sub>2</sub>	MgSO <sub>4</sub>	89
Yb(OTf) <sub>3</sub> (10 mol.%)	CH <sub>2</sub> Cl <sub>2</sub>	4 Å mol. sieves	87
Yb(OTf) <sub>3</sub> (10 mol.%)	THF	MgSO <sub>4</sub>	67
Yb(OTf) <sub>3</sub> (10 mol.%)	CH <sub>3</sub> CN	MgSO <sub>4</sub>	71
Yb(OTf) <sub>3</sub> (10 mol.%)	PhMe	MgSO <sub>4</sub>	30
SnCl <sub>4</sub> (100 mol.%)	CH <sub>2</sub> Cl <sub>2</sub>	MgSO <sub>4</sub>	21
SnCl <sub>4</sub> (120 mol.%)	CH <sub>2</sub> Cl <sub>2</sub>	MgSO <sub>4</sub>	68

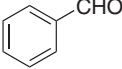
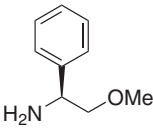
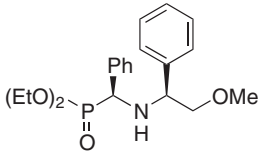
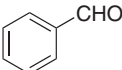
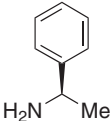
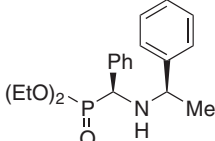
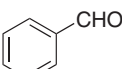
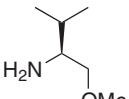
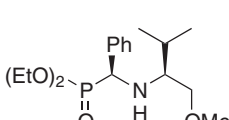
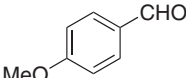
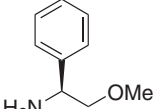
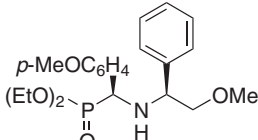
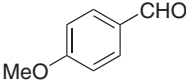
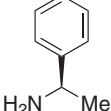
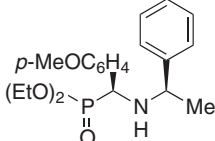
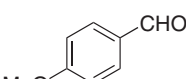
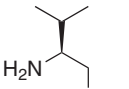
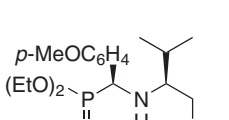
<sup>a</sup> <1998JOC4125>.

**Table 13** Evaluation of 10 mol.% Yb(OTf)<sub>3</sub> as a catalyst<sup>a,b</sup>

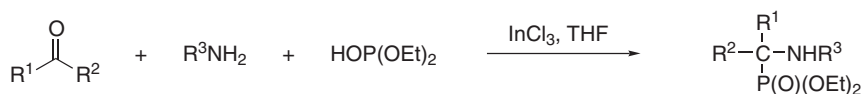
Aldehyde	Amine	Product	Yield (%)
			89
			92
			88
			93
			85
			71
			65
			89
			79

<sup>a</sup> <1998JOC4125>.<sup>b</sup> Conditions: 1.1 equiv. amine, 1.2 equiv. diethyl phosphite, 125 mg MgSO<sub>4</sub>, CH<sub>2</sub>Cl<sub>2</sub>, rt.

**Table 14** Use of 10 mol.% Yb(OTf)<sub>3</sub> in condensations generating stereochemistry<sup>a,b</sup>

Aldehyde	Amine	Product (major isomer)	Yield (%)	Selectivity
			95	78:22
			92	57:43
			82	74:26
			91	78:22
			88	57:43
			81	74:26

<sup>a</sup> <1998JOC4125>. <sup>b</sup> Conditions: 1.1 equiv. amine, 1.2 equiv. diethyl phosphite, 125 mg MgSO<sub>4</sub> CH<sub>2</sub>Cl<sub>2</sub>, rt.

**Table 15** Condensations catalyzed by InCl<sub>3</sub> both with and without sonication<sup>a,b</sup>

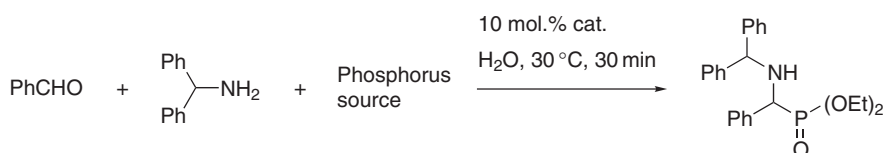
<i>R</i> <sup>1</sup>	<i>R</i> <sup>2</sup>	<i>R</i> <sup>3</sup>	Time with/without sonication (h)		Yield with/without sonication (%)	
H	Ph	Ph	5	11	93	92
H	Ph	PhCH <sub>2</sub>	5	12	95	93
H	Ph	PhCH(Me)	6	12	90	90
H	Ph	Pr <sup>n</sup>	5	12	90	89
H	Ph	Cyclohexyl	7	15	90	88
H	<i>p</i> -MeOPh	Ph	6	10	92	92

Table 15 (continued)

$R^1$	$R^2$	$R^3$	Time with/without sonication (h)		Yield with/without sonication (%)	
H	<i>p</i> -MeOPh	Me <sub>2</sub> CH	7	12	90	88
H	<i>p</i> -O <sub>2</sub> NPh	Ph	7	12	82	80
H	( <i>E</i> )-PhCH=CH	Ph	6	10	85	85
H	<i>m</i> -HOPh	Ph	6	10	93	91
H	2-Pyridyl	Ph	7	11	92	92
H	2-Pyridyl	PhCH(Me)	7	14	90	90
H	( <i>E</i> )-Pr <sup>n</sup> CH=C(Et)	PhCH <sub>2</sub>	7	14	89	88
H	Me <sub>2</sub> CH	PhCH <sub>2</sub>	6	13	88	86
H	Pr <sup>n</sup>	Me <sub>2</sub> CH	6	14	87	85
H	( <i>E</i> )-Me <sub>2</sub> C=CH(CH <sub>2</sub> ) <sub>2</sub> C(Me)=CH	PhCH <sub>2</sub>	6	13	89	87
Et	Et	PhCH <sub>2</sub>	9	11	82	80
Me	Ph	PhCH <sub>2</sub>	9	12	85	81
CH(Me)CH(OH)Ph	PhCH(OH)CH(Me)	PhCH <sub>2</sub>	9	14	90	89
	Cyclohexanone	PhCH <sub>2</sub>	6	9	87	85
	4-Bu <sup>t</sup> cyclohexanone	PhCH <sub>2</sub>	7	10	80	80
	Indanone	PhCH <sub>2</sub>	6	9	80	79
Me	( <i>E</i> )-PhCH=CH	PhCH <sub>2</sub>	7	12	76	75
CH <sub>2</sub> COOEt	Me	PhCH <sub>2</sub>	7	10	85	82

<sup>a</sup> <1999OL1141>. <sup>b</sup> Conditions: 1 mmol aldehyde, 1 mmol amine, 1 mmol diethyl phosphite, 10 mol.% InCl<sub>3</sub>, ketones at reflux, aldehydes at rt.

Kobayashi and co-workers have not only applied new Lewis acids to the reaction, but have done so in a way that results in a more environmentally compatible protocol. They have found that the employment of a Lewis acid surfactant, scandium(III) trisdodecyl sulfate, enables the condensation to progress effectively in aqueous media as opposed to the more typical organic solvents. Table 16 illustrates Kobayashi's search for effective conditions, and Table 17 offers a number of examples of this quick and reliable condensation <2000CC669>.

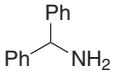
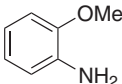
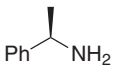
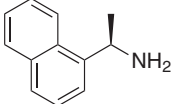
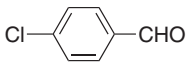
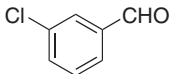
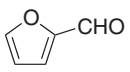
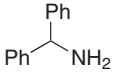
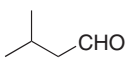
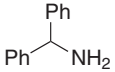
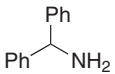
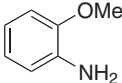
Table 16 Inspection of surfactant catalysts<sup>a,b</sup>

Catalyst	Phosphorus source	Yield (%)
Sc(OSO <sub>3</sub> (CH <sub>2</sub> ) <sub>11</sub> CH <sub>3</sub> ) <sub>3</sub>	P(OEt) <sub>3</sub>	71
NaOSO <sub>3</sub> (CH <sub>2</sub> ) <sub>11</sub> CH <sub>3</sub>	P(OEt) <sub>3</sub>	8
Sc(OTf) <sub>3</sub>	P(OEt) <sub>3</sub>	6
<i>p</i> -HOSO <sub>3</sub> C <sub>6</sub> H <sub>4</sub> (CH <sub>2</sub> ) <sub>11</sub> CH <sub>3</sub>	P(OEt) <sub>3</sub>	18
Sc(OSO <sub>3</sub> (CH <sub>2</sub> ) <sub>11</sub> CH <sub>3</sub> ) <sub>3</sub>	P(OEt) <sub>3</sub>	31 <sup>c</sup>
Sc(OSO <sub>3</sub> (CH <sub>2</sub> ) <sub>11</sub> CH <sub>3</sub> ) <sub>3</sub>	HOP(OEt) <sub>2</sub>	Trace

<sup>a</sup> <2000CC669>. <sup>b</sup> Conditions: 1 equiv. aldehyde, 1 equiv. amine, 2.5 equiv. phosphorus source. <sup>c</sup> Neat.

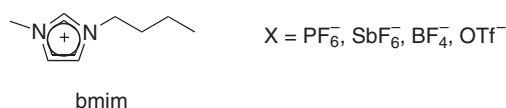
Lee and co-workers have also made progress in both finding an effective Lewis acid catalyst and formulating an environmentally sound protocol. This group has screened lanthanide triflates for use in the three-component condensation exploiting an ionic liquid solvent. Use of [bmim][X] (Figure 1) as a reaction medium allows recovery and recyclability of solvent and appears to promote the reaction as effectively as the traditional solvents. The authors examined several combinations of catalyst and solvent in the condensation of benzaldehyde, aniline, and diethyl phosphonate and found many systems effective (Table 18) <2001CC1698>.

**Table 17** Catalytic activity of  $\text{Sc}(\text{OSO}_3(\text{CH}_2)_{11}\text{CH}_3)_3$  in water<sup>a,b</sup>

$\text{R}^1\text{CHO}$	$\text{R}^2\text{NH}_2$	$\text{P}(\text{OEt})_3$	10 mol.% cat. $\text{H}_2\text{O}$ , 30 °C, 30 min	$\begin{array}{c} \text{R}^2 \\ \diagup \\ \text{NH} \\ \diagdown \\ \text{R}^1 \end{array} \text{P}(\text{O})(\text{OEt})_2$
$\text{R}^1\text{CHO}$	$\text{R}^2\text{NH}_2$		Time (min)	Yield (%)
PhCHO			60	83
PhCHO	PhNH <sub>2</sub>		20	88
PhCHO			20	86
PhCHO	PhCH <sub>2</sub> NH <sub>2</sub>		60	84
PhCHO			60	78
PhCHO			60	80
	PhNH <sub>2</sub>		30	85
	PhNH <sub>2</sub>		20	80
			120	78
			60	83
PhCH <sub>2</sub> CH <sub>2</sub> CHO			60	95
PhCH=CHCHO			20	53

<sup>a</sup> <2000CC669>. <sup>b</sup> Conditions: 1 equiv. aldehyde, 1 equiv. amine, 4 equiv. triethyl phosphite.

Lee and co-workers <2001CC1698> went on to demonstrate the utility of recycled catalysts, showing that reactivity is retained after use especially with  $\text{Sc}(\text{OTf})_3$ , which shows efficacy in five iterations (Table 19).

**Figure 1** [bmim] [X] as reaction medium.**Table 18** Screening of lanthanide triflates in ionic liquids<sup>a,b</sup>

$\text{PhCHO} + \text{H}_2\text{NPh} + \text{HP(O)(OEt)}_2 \xrightarrow[\text{[bmim][X], 20 }^\circ\text{C}]{10 \text{ mol.}\% \text{ cat.}}$				$\text{Ph}-\text{CH}(\text{NHPH})-\text{P(O)(OEt)}_2$
Solvent	Catalyst			Yield (%)
[bmim][PF <sub>6</sub> ]	Yb(OTf) <sub>3</sub>			95
[bmim][PF <sub>6</sub> ]	Sc(OTf) <sub>3</sub>			80
[bmim][PF <sub>6</sub> ]	Dy(OTf) <sub>3</sub>			94
[bmim][PF <sub>6</sub> ]	Sm(OTf) <sub>3</sub>			99
[bmim][PF <sub>6</sub> ]	Yb(OTf) <sub>3</sub> ·H <sub>2</sub> O			63
[bmim][PF <sub>6</sub> ]	La(OTf) <sub>3</sub> ·H <sub>2</sub> O			39
[bmim][PF <sub>6</sub> ]	Sm(OTf) <sub>3</sub> <sup>c</sup>			95
[bmim][PF <sub>6</sub> ]	Sm(OTf) <sub>3</sub> <sup>d</sup>			74
[bmim][SbF <sub>6</sub> ]	Sm(OTf) <sub>3</sub>			71
[bmim][BF <sub>4</sub> ]	Sm(OTf) <sub>3</sub>			18
[bmim][OTf]	Sm(OTf) <sub>3</sub>			89
[bmim][PF <sub>6</sub> ]	In(OTf) <sub>3</sub>			90

<sup>a</sup> <2001CC1698>.<sup>c</sup> 1 mol.% catalyst.<sup>b</sup> Conditions: 0.25 mmol benzaldehyde, 0.25 mmol aniline, 1 mmol diethyl phosphonate.<sup>d</sup> The catalyst used was that recovered from the previous entry.**Table 19** Efficacy of catalysts on successive use<sup>a</sup>

Catalyst	Yield of iterative use (%)				
	1st	2nd	3rd	4th	5th
Sc(OTf) <sub>3</sub>	97	94	97	93	99
Yb(OTf) <sub>3</sub>	57	54	NA	NA	NA
Sm(OTf) <sub>3</sub>	87	87	NA	NA	NA
Gd(OTf) <sub>3</sub>	84	77	NA	NA	NA
InCl <sub>3</sub>	86	50	NA	NA	NA

<sup>a</sup> <2001CC1698>.

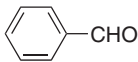
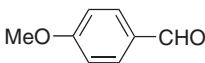
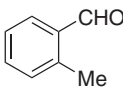
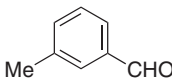
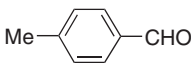
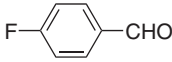
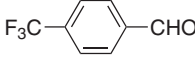
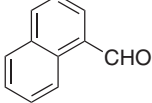
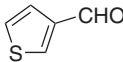
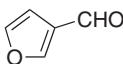
The authors document the condensation of a number of aldehydes with aniline and triethyl phosphite in [bmim][PF<sub>6</sub>] with catalytic Sc(OTf)<sub>3</sub> (Table 20). In addition to being high yielding, the procedure is claimed to be more environmental friendly than the previous protocols <2001CC1698>.

Though the use of metals as catalysts for these reactions is quite common, the incorporation of aminophosphonates into stable metal complexes appears scant in the literature. A particularly notable example of such a complex is found in the synthesis of a series of ferrocenylaminophosphonic esters by Lewkowski and co-workers. Even in the presence of the pendant ferrocenyl moiety, the reactions proceed in useful yields (Table 21) <2001JOM105>.

As seen in previous examples, it is possible to utilize a triazine as a masked imine. Stevens and co-workers <1998SL180> provide an example of the use of tri-(*N*)-allyltriazine as a component of the condensation, though the yields are low (Scheme 12).

Another interesting route that avoids the direct use of the imine is the amino hydroxylation protocol developed by Doye and co-workers. Amino hydroxylation, both intermolecular (Table 22) and intramolecular (Table 23) followed by attack with a phosphorus source, perfects an efficient one-pot procedure for generation of the targets <2002EJO457>.

**Table 20** Use of  $\text{Sc}(\text{OTf})_3$  in  $[\text{bmim}][\text{PF}_6]^{\text{a,b}}$ 

$\text{RCHO} + \text{H}_2\text{NPh} + \text{P}(\text{OEt})_3 \xrightarrow[\text{[bmim][PF}_6\text{], 20 }^\circ\text{C}]{1 \text{ mol.}\% \text{ Sc}(\text{OTf})_3}$			$\text{R}-\text{CH}(\text{NHPH})-\text{P}(\text{O})(\text{OEt})_2$
Aldehyde			Yield (%)
			97
			>99
			90
			>99
			>99
			93
			97
			>99
			93
			90

<sup>a</sup> <2001CC1698>. <sup>b</sup> Conditions: 0.25 mmol aldehyde, 0.25 mmol aniline, 1 mmol triethyl phosphite.

The literature offers a small number of examples of the generation of stereochemistry in the condensation of amines with aldehydes and phosphates. A notable example is found in the work of Houghten and co-workers, who in the course of devising phosphono peptides condense the components in solid phase and set a stereocenter between nitrogen and phosphorus by exploiting an existing stereocenter. The true product of the condensation is the resin-bound dimethyl phosphonate, though the reported yields are for the phosphonic acid recovered after liberation from the resin with concomitant hydrolysis (Table 24) <2002TL4103>.

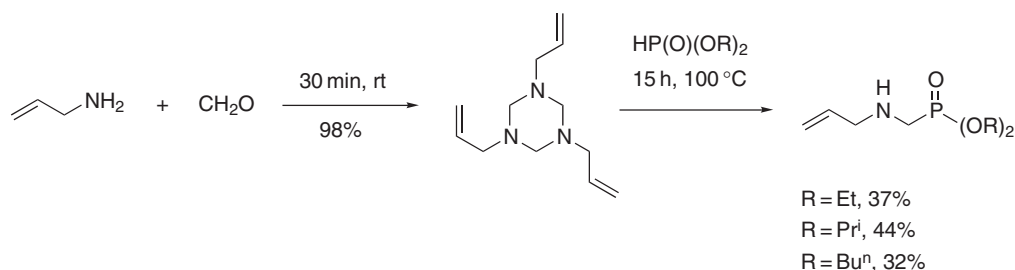
Royer and co-workers have devised a moderately selective method of adding phosphates to imines bearing chiral auxiliaries to generate substituted piperidines. The product of the condensation can be elaborated into a series of related compounds (Scheme 13). The authors also demonstrate the use of an  $\alpha$ -cyanoamine in a similar system (Scheme 14) <1997T3627>.



**Table 21** Synthesis of ferrocenyl aminophosphonates<sup>a,b</sup>

$R^1$	$R^2$	Yield (%)
$\text{CH}_2\text{Ph}$	Et	75
$\text{CH}_2\text{Ph}$	$\text{CH}_2\text{Ph}$	62
$\text{CH}_2(2\text{-Fur})$	Et	51
$\text{CH}_2(2\text{-Fur})$	$\text{CH}_2\text{Ph}$	88
$\text{C}(\text{CH}_3)_3$	Et	59 <sup>c</sup>
$\text{C}(\text{CH}_3)_3$	$\text{CH}_2\text{Ph}$	70
$\text{CHPh}_2$	Et	75
$\text{CHPh}_2$	$\text{CH}_2\text{Ph}$	72
$(R)\text{-CH}(\text{CH}_3)\text{Ph}$	Et	62
$(R)\text{-CH}(\text{CH}_3)\text{Ph}$	$\text{CH}_2\text{Ph}$	65
$\text{CHPh}_2$	Ph	72

<sup>a</sup> <2001JOM105>. <sup>b</sup> Conditions: 5 mmol imine, 5 mmol dialkyl phosphite, toluene, reflux, 7 h, then rt 12 h. <sup>c</sup> Reaction run in acetonitrile.

**Scheme 12****Table 22** Intermolecular amino hydroxylation route<sup>a,b</sup>

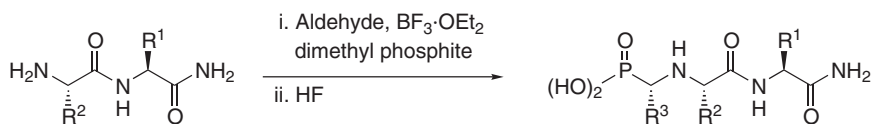
Alkyne	Amine	Product	Yield (%)
$\text{Ph}\text{---}\text{C}\equiv\text{C}\text{---}\text{Ph}$			68
$\text{Et}\text{---}\text{C}\equiv\text{C}\text{---}\text{Et}$			76
$\text{Ph}\text{---}\text{C}\equiv\text{C}\text{---}\text{Me}$			97 <sup>c</sup>
$\text{Ph}\text{---}\text{C}\equiv\text{C}\text{---}\text{Et}$			88 <sup>c</sup>

<sup>a</sup> <2002EJO457>. <sup>b</sup> Conditions: i. 1.4 mmol alkyne, 1.4 mmol amine, 3 mol.%  $\text{Cp}_2\text{TiMe}_2$ , toluene, 110 °C, 72 h; ii. 1.4 mmol diethyl phosphite, 5 mol.%  $\text{Me}_2\text{AlCl}$ , 25 °C, 2 h. <sup>c</sup> Neat, dimethyl phosphite was used.

**Table 23** Intramolecular amino hydroxylation route<sup>a,b</sup>

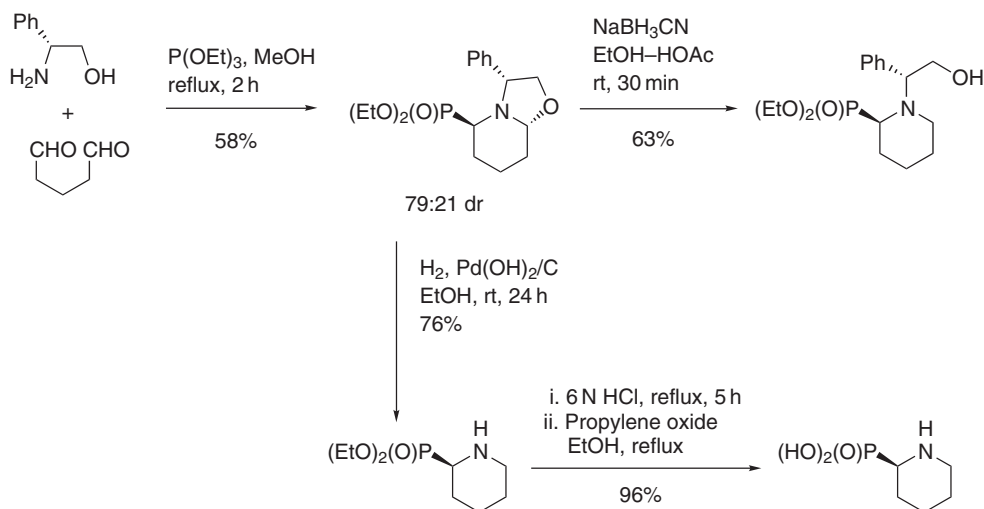
Aminoalkyne	Product	Yield (%)
		78
		86
		85
		52
		66
		58

<sup>a</sup> <2002EJO457>. <sup>b</sup> Conditions: i. 1 mmol aminoalkyne, 5 mol.% Cp<sub>2</sub>TiMe<sub>2</sub>, toluene, 110 °C, 9 h; ii. 1 mmol diethyl phosphite, 5 mol.% Me<sub>2</sub>AlCl, 25 °C, 2 h.

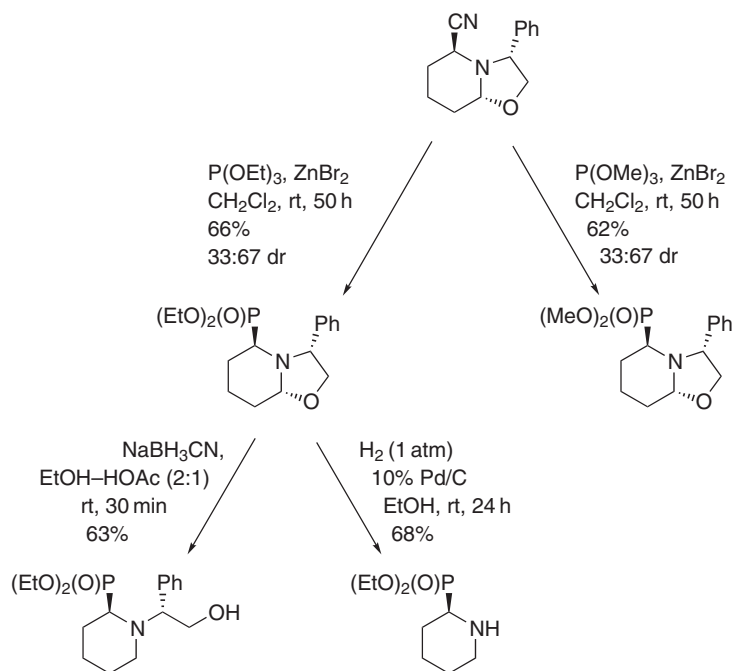
**Table 24** Solid-phase synthesis of phosphono peptides<sup>a,b</sup>

<i>R</i> <sup>1</sup>	<i>R</i> <sup>2</sup>	<i>R</i> <sup>3</sup> CHO	Yield (%)	<i>dr</i>
PhCH <sub>2</sub>	PhCH <sub>2</sub>	Ph	85	4:1
PhCH <sub>2</sub>	HOOCCH <sub>2</sub>	Ph	79	2:3
PhCH <sub>2</sub>	Me	Ph	83	1:2
PhCH <sub>2</sub>	Me	Pr	88	1:4
PhCH <sub>2</sub>	HOOCCH <sub>2</sub>	Pr	86	NA
PhCH <sub>2</sub>	PhCH <sub>2</sub>	Pr	92	NA
PhCH <sub>2</sub>	(CH <sub>3</sub> ) <sub>2</sub> CH <sub>2</sub>	Bu	80	2:3
Me	PhCH <sub>2</sub>	Bu	71	NA
Me	PhCH <sub>2</sub>	Ph	53	NA
Me	PhCH <sub>2</sub>	Pr	65	NA
H	PhCH <sub>2</sub>	Bu	88	5:3
PhCH <sub>2</sub>	Me	4-Pr <sup>i</sup> C <sub>6</sub> H <sub>4</sub>	70	4:5

<sup>a</sup> <2002TL4103>. <sup>b</sup> Conditions: i. 10 equiv. aldehyde, 10 equiv. dimethyl phosphite, 3 equiv. BF<sub>3</sub>·OEt<sub>2</sub>, rt, 16 h; ii. HF, 0 °C, 7 h.

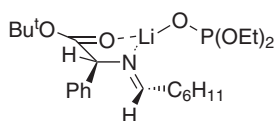


Scheme 13



Scheme 14

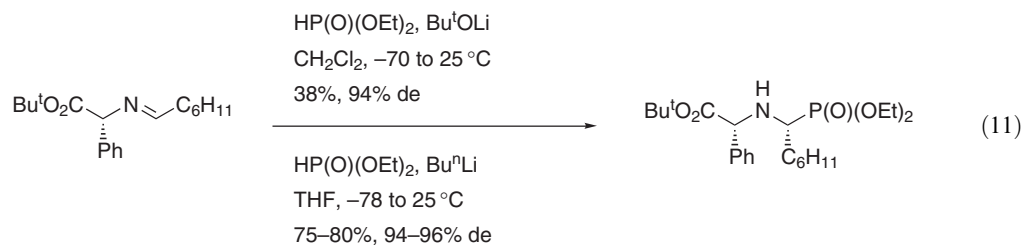
Two novel chiral auxiliaries appear in a paper by Smith and co-workers that allow stereoselective addition of lithium diethyl phosphite to an imine via the chelation-controlled transition state **17** (Figure 2). Although the results acquired for the use of *t*-butyl ester auxiliary seen in



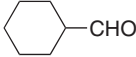
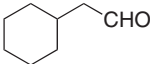

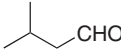

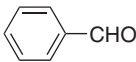
17

Figure 2 Chelation-controlled transition state **17**.

Equation (11) appears inconsistent, the methyl ether-derived auxiliary found in Table 25 furnishes highly reliable selectivities. Both auxiliaries are liberated by hydrogenolysis <1995JA10879>.



**Table 25** Stereoselective addition of LiP(O)(OEt)<sub>2</sub> to imines<sup>a</sup>

<i>RCHO</i>	<i>Imine yield (%)</i>	<i>Addition product yield (%)</i>	<i>Free amine yield (%)</i>	<i>Free amine ee (%)</i> <sup>b</sup>
	90	68	94	96
	89	70	87	99
	82	82	86	97
	84	81	89	99
MeCHO	90	77	99	99
	95	78	98	98
MeS-CH <sub>2</sub> -CH <sub>2</sub> -CHO	84	69	89 <sup>c</sup>	75
BnO-CH <sub>2</sub> -CHO	92	38	100	98
Bu <sup>t</sup> O <sub>2</sub> C-CH <sub>2</sub> -CH <sub>2</sub> -CHO	95	37	83	96
	82	90	88	71

<sup>a</sup> <1995JA10879>. <sup>b</sup> as per Mosher amide. <sup>c</sup> 5 equiv. Pd black, H<sub>2</sub>, AcOH, 25°C, 48 h.

One can also fathom a system in which the phosphorus moiety bears the chiral auxiliary. Kolodiazny and co-workers have described the use of two auxiliaries in good yield with variable selectivity. Bornyl and menthyl groups pendant to the phosphonate induce asymmetry at the neighboring carbon as seen in Table 26 <1998TA1645>.

**Table 26** Synthesis of amino phosphonates with chiral auxiliaries on phosphorus<sup>a</sup>

$(R^1O)_2P(O)H \xrightarrow{\text{PhCHO, PhCHR}^2\text{NH}_2} \begin{array}{c} \text{O} \\ \parallel \\ (R^1O)_2\text{P}-\text{CH}(\text{Ph})-\text{NHCHR}^2\text{Ph} \end{array}$			
$R^1$	$R^2$	Yield (%)	de (%)
(-)-Bornyl	H	90	50
(-)-Menthyl	H	94	50
(-)-Menthyl	Me	85	84

<sup>a</sup> <1998TA1645>.

Martens and co-workers have developed a highly efficient protocol for the addition of binaphthylphosphorus esters to certain imines. The results of the addition, catalyzed by  $\text{BF}_3 \cdot \text{OEt}_2$ , are shown in Table 27 <2000TL7285>.

**Table 27** Asymmetric hydrophosphorylation of imines with binaphthylphosphorus esters<sup>a</sup>

$R^1/R^2$	$R^3/R^4$	Yield (%)	dr <sup>b</sup>
Me/Me	Me/Me	47	83:17
Me/Me	-(CH <sub>2</sub> ) <sub>5</sub> -	47	>95:5
-(CH <sub>2</sub> ) <sub>5</sub> -	Me/Me	37	80:20
-(CH <sub>2</sub> ) <sub>5</sub> -	-(CH <sub>2</sub> ) <sub>5</sub> -	68	>95:5
H/H	-(CH <sub>2</sub> ) <sub>5</sub> -	30	>95:5

<sup>a</sup> <2000TL7285>. <sup>b</sup> Determined by NMR.

Similar imines find use in the highly effective protocol developed by Martens and co-workers. Various binaphthol-lanthanide metal complexes catalyze the hydrophosphonylation with dimethyl phosphite, in some cases in both high yield and selectivity (Table 28) <1998JA3089>.

**Table 28** Hydrophosphonylation catalyzed by lanthanide-binaphthol complexes<sup>a,b</sup>

Catalyst <sup>c</sup> (20 mol. %)	Solvent	Temp. (°C)	Time (h)	Yield (%)	ee <sup>d</sup> (%)
(R)-LPB	THF/PhMe 1:7	rt	144	53	61
(R)-LPB	THF/PhMe 1:7	50	50	55	64
(R)-PrPB	THF/PhMe 1:7	50	50	51	84
(R)-SmPB	THF/PhMe 1:7	50	40	97	93
(R)-GdPB	THF/PhMe 1:7	50	50	77	95
(R)-DyPB	THF/PhMe 1:7	50	50	76	97
(R)-YbPB	THF/PhMe 1:7	rt	20	42	97
(R)-YbPB	THF/PhMe 1:7	rt	50	86	98

**Table 28** (continued)

Catalyst <sup>c</sup> (20 mol. %)	Solvent	Temp. (°C)	Time (h)	Yield (%)	ee <sup>d</sup> (%)
( <i>R</i> )-YbPB	THF/PhMe 1:7	50	20	89	94
( <i>R</i> )-YbPB	THF/PhMe 1:7	50	50	90	96
( <i>R</i> )-YbPB	THF	50	50	52	95
( <i>R</i> )-YbPB	PhMe	50	50	79	85
( <i>R</i> )-YbPB	THF/PhMe 1:7	50	60	56	94
( <i>R</i> )-YbPB	THF/PhMe 1:7	50	60	39	94

<sup>a</sup> <1998JA3089>. <sup>b</sup> 0.3 mmol imine, 1.5 mmol HP(O)(OMe)<sub>2</sub>. <sup>c</sup> P = potassium, S = sodium, L = lithium, B = (*R*)-(+)-binaphthol.  
<sup>d</sup> ee determined by chiral stationary phase HPLC.

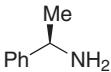
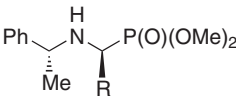
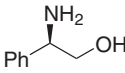
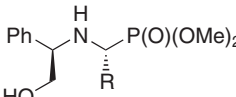
The inherent chirality of the imine can play an important role in directing the stereochemical outcome of the reaction. Heydari and co-workers present an example of the application of lithium perchlorate/diethyl ether (LPDE) in the condensation of imines with dimethyl phosphite. After demonstrating the utility of the protocol in achiral systems (Table 29), the authors apply the reaction to chiral imines to achieve reasonable selectivities (Table 30) <1998TL6729>.

**Table 29** Use of LPDE as a catalyst in condensation<sup>a</sup>

$R^1CHO + HN(R^2)_2 + HP(O)(OMe)_2 \xrightarrow[\text{rt, 10 min}]{5 \text{ M LPDE}} (R^2)_2N\underset{\substack{  \\ R^1}}{C}P(O)(OMe)_2$		
<i>R</i> <sup>1</sup>	<i>R</i> <sup>2</sup>	Yield (%)
Pr <sup>i</sup>	Et	97
Pr <sup>n</sup>	Et	95
Bn	Et	99
Ph	Et	90
4-MeOPh	Et	87
Pr <sup>i</sup>	Bn	93
Pr <sup>n</sup>	Bn	97
Bn	Bn	95
Ph	Bn	95
4-MeOPh	Bn	90

<sup>a</sup> <1998TL6729>.

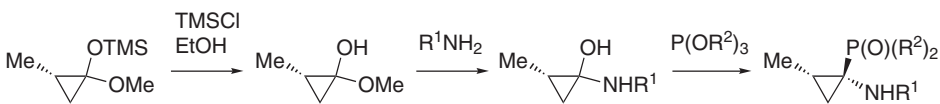
**Table 30** Use of LPDE as a catalyst in condensation using chiral imines<sup>a</sup>

$RCHO + \text{Amine} + HP(O)(OMe)_2 \xrightarrow[\text{-15 °C, 30 min}]{2 \text{ M LPDE}} \text{Product}$				
Amine	<i>R</i>	Product	Yield (%)	<i>dr</i>
	Pr <sup>i</sup>		95	79:21
	Bu <sup>t</sup>		96	82:18
	C <sub>6</sub> H <sub>11</sub>		92	80:20
	Bn		90	83:17
	Pr <sup>i</sup>		90	88:12
	Bu <sup>t</sup>		95	91:9
	C <sub>6</sub> H <sub>11</sub>		94	90:10

<sup>a</sup> <1998TL6729>.

Fadel and co-workers have furnished examples of the preparation of aminocyclopropane phosphonate esters by exploiting the substitution pattern on the cyclopropyl group. A series of hemiaminals is heated in a phosphate solvent to effect solvolysis with moderate facial selectivity directed by a pendant methyl group (Table 31) <2000EJO2153>.

**Table 31** Generation of aminocyclopropane phosphonates<sup>a</sup>



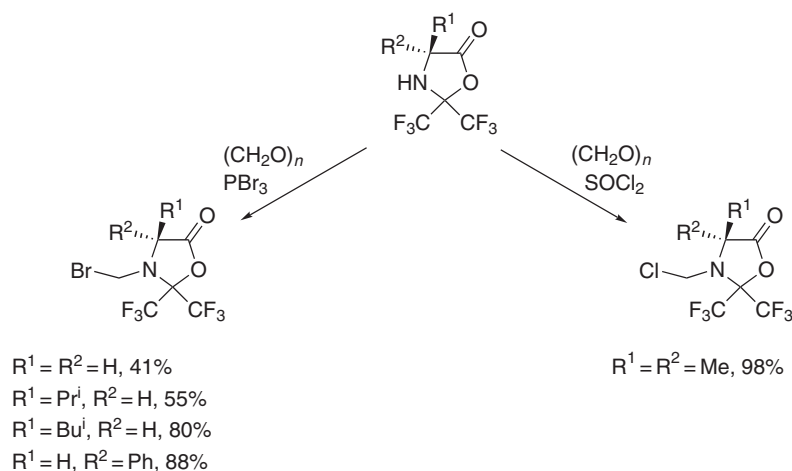
$R^1$	$P(O)(OR^2)_2$	Time (h)	Yield (%)	$dr$
$CH_2Ph$	$P(OEt)_3$	140	62 <sup>b</sup>	88:12
$(S)\text{-CH(Me)Ph}$	$P(OMe)_3$	65	48 <sup>b,d</sup>	73:27
$(S)\text{-CH(Me)Ph}$	$P(OEt)_3$	68	80 <sup>b</sup>	87:13
$CH_2Ph$	$P(OEt)_3$	22	69 <sup>c</sup>	86:14
$(S)\text{-CH(Me)Ph}$	$P(OMe)_3$	21	67 <sup>c,d</sup>	80:20
$(S)\text{-CH(Me)Ph}$	$P(OEt)_3$	22	82 <sup>c</sup>	87:13
$(R)\text{-CH(Me)Ph}$	$P(OEt)_3$	22	82 <sup>c</sup>	87:13

<sup>a</sup> <2000EJO2153>. <sup>b</sup> cat. TMSI, 3 mmol acetal, 4.5 mmol amine-HCl, 3.6 mmol  $P(OR^2)_3$ , 55 °C. <sup>c</sup> As per previous reference<sup>b</sup> with free amine and 4 equiv. AcOH. <sup>d</sup> In MeOH.

(iv) Preparation of compounds bearing phosphonate esters and closely derived functionalities via nucleophilic substitution

While not so common as the attack of phosphorus on an imine, the nucleophilic addition of phosphorus sources to amines with neighboring leaving groups is a motif that appears quite attractive as a means of generating the systems in question. The lone pair on nitrogen enhances the efficacy of halogens and other leaving groups, thus availing an effective method.

Burger and co-workers provide an example of the utility of both bromomethyl- and chloromethylamines in the synthesis of aminophosphonates and aminophosphine oxides. An amine reacts with *p*-formaldehyde in the presence of a halogen source to render the halomethylamine (Scheme 15), which is then treated with one of the several nucleophiles to furnish the product in very good yields (Table 32) <1998JCS(P1)2091>.



**Scheme 15**

A similar approach manifests itself in the work of Katritzky and co-workers, who have demonstrated the utility of the benzotriazolyl moiety as an effective leaving group for use with phosphorus nucleophiles, among many others. Katritzky offers examples of the zinc

**Table 32** Reaction of halomethylamines with phosphorus nucleophiles<sup>a</sup>

	<i>R</i> <sup>1</sup>	<i>R</i> <sup>2</sup>	<i>R</i> <sup>3</sup>	<i>R</i> <sup>4</sup>	Time	Yield (%)
	H	H	OMe	OMe	30 min	66
	Pr <sup>i</sup>	H	OMe	OMe	30 min	95
	Bu <sup>i</sup>	H	OMe	OMe	30 min	83
	Bu <sup>i</sup>	H	OMe	Ph	30 min	94
	H	Ph	OMe	OMe	30 min	90
	H	Ph	Ph	Ph	30 min	95
	Me	Me	OMe	OMe	3 h	83
	Me	Me	Ph	Ph	5 days	62

<sup>a</sup> <1998JCS(P1)2091>.

bromide-catalyzed addition of triethyl phosphite to a spectrum of nitrogen compounds including cyclic amines, anilines, diamines, *N,O*-acetals, and other heterocycles. The couplings tend to be high yielding and efficient (Table 33) <2002JOC3115, 2002JOC3109, 1999JOC1979, 2002S601, 2002JCS(P1)592>.

**Table 33** Addition of P(OEt)<sub>3</sub> to benzotriazolylmethylamines catalyzed by ZnBr<sub>2</sub>

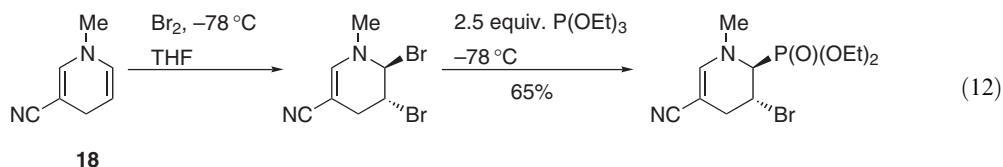
Amine	Product	Yield (%)	References
		75	<2002JOC3115>
		70	<2002JOC3109>
		77	<1999JOC1979>
		87	<2002S601>
		79	<2002JCS(P1)592>



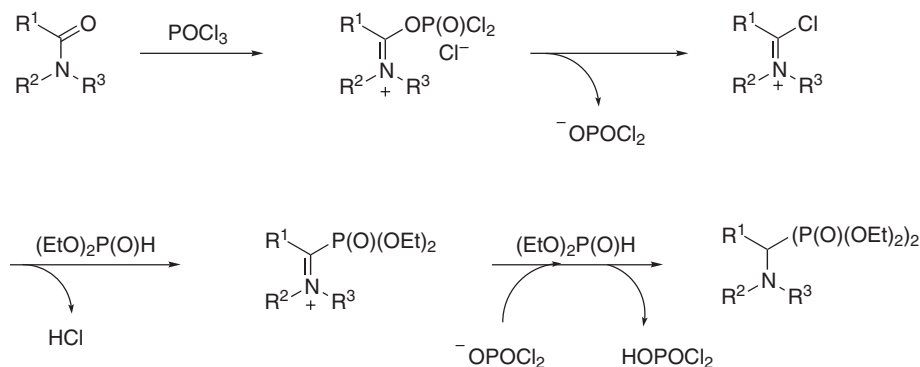
Table 33 (continued)

Amine	Product	Yield (%)	References
		76	<2002JCS(P1)592>
		70	<2002JCS(P1)592>
		73	<2002JCS(P1)592>

Lavilla and co-workers provide an example of the use of a transient electrophile generated *in situ* from a parent dihydropyridine. Compound **18** is treated with bromine, and the dibromide is immediately introduced to triethyl phosphite to render the aminophosphonate ester as shown in Equation (12) <2000XXX1763>.



An interesting variant on the substitution motif appears in the work of Liu and co-workers. Electrophiles are prepared via the Vilsmeier reaction and 2 equiv. of diethyl phosphite is added. The first equivalent displaces chloride, and the second adds to the resultant iminium ion (Scheme 16). Liu generates a series of  $\alpha$ -amino-*gem*-bisdiethyl phosphonates through this protocol (Table 34). Compounds derived from formamides undergo HWE couplings with aldehydes to render  $\alpha$ -diethyl phosphonoenamines (Table 35) <1999HAC271>.



Scheme 16

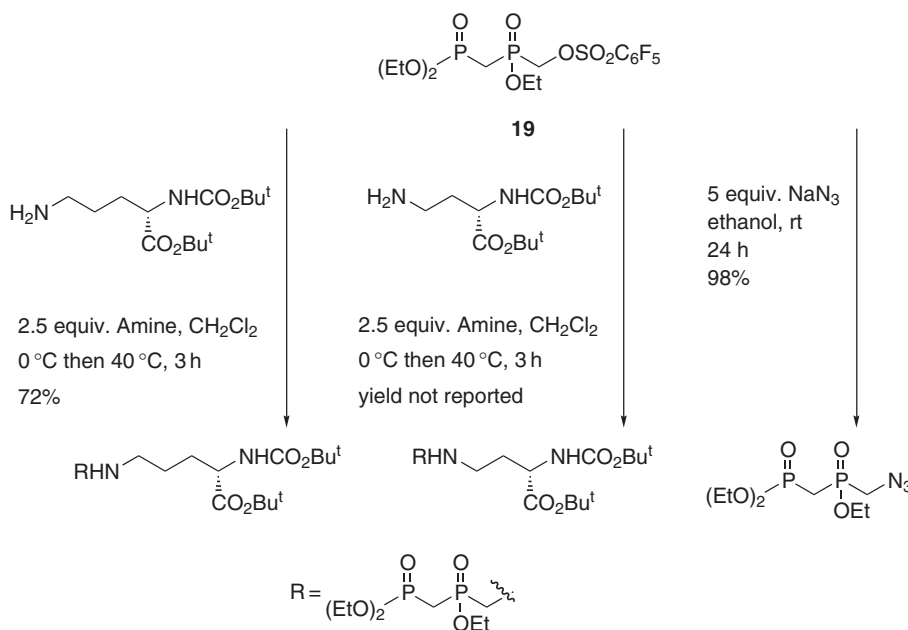
$$\begin{array}{ccc} \text{R}^1\text{C(=O)N(R}^2\text{)(R}^3\text{)} & \xrightarrow[\text{CH}_2\text{Cl}_2, 0-30^\circ\text{C, 10 h}]{\begin{array}{l} \text{i. 1 equiv. POCl}_3 \\ \text{ii. 2 equiv. HP(O)(OEt)}_2 \end{array}} & \text{R}^1\text{CH(P(O)(OEt)}_2\text{)N(R}^2\text{)(R}^3\text{)} \end{array}$$

<sup>a</sup> <1999HAC271>.

$$\text{(EtO)}_2\text{(O)P}(\text{N}(\text{R}^1)\text{R}^2)\text{P}(\text{O})(\text{OEt})_2 \xrightarrow[\text{THF, 15 to 30 }^\circ\text{C, 1 h}]{1 \text{ equiv. NaH, 1 equiv. R}^3\text{CHO}} \text{(EtO)}_2\text{(O)P}(\text{N}(\text{R}^1)\text{R}^2)=\text{CH-R}^3 \quad (\text{Z})$$

<sup>a</sup> <1999HAC271>.

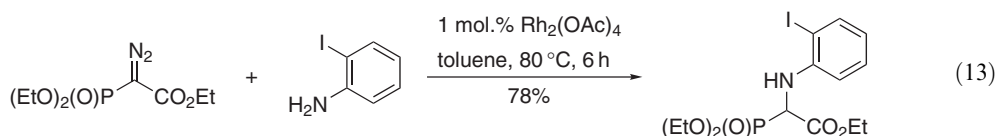
Recent advances in transition metal chemistry have popularized the use of  $\alpha$ -azido esters in synthesis on account of their ability to form reactive metal-carbene complexes with certain transition metals. This utility has translated into the use of  $\alpha$ -azidocarbethoxymethyldiethyl phosphonates



Scheme 17

for the preparation of  $\alpha$ -aminocarbethoxymethyldiethyl phosphonates by treatment with a metal complex in the presence of an amine. Although only one example appears here, others involving the generation of amido- and carbamatophosphonates are available in Section 4.10.1.2.4.

Kondo and co-workers demonstrated the efficacy of this reaction with 2-iodoaniline. Heating in toluene with the azide and  $\text{Rh}_2(\text{OAc})_4$  as a catalyst furnished the product in 78% yield as shown in Equation (13) <2002CC210>.



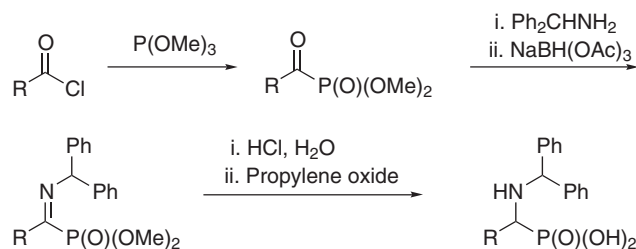
(vi) Preparation of  $\alpha$ -aminophosphonates via generation and reduction of  $\alpha$ -iminophosphonates

Reduction of imines neighboring phosphonates provides a useful entry into the desired system, though the reaction is not highly exploited in the literature. The three references that follow demonstrate the versatility of this method.

Ryglowski and Kafarski published the reductive amination of acylphosphonates. Addition of trimethyl phosphite to a series of acid chlorides provides the acylphosphonates, which are reductively aminated and hydrolyzed to the corresponding acids as shown in Table 36 <1996T10685>.

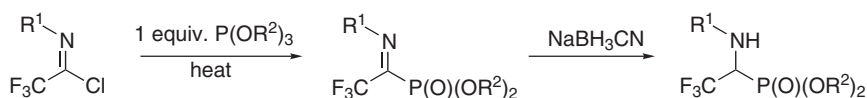
Yuan and co-workers offer an alternative approach. Phosphites add into imidoyl chlorides, and the resultant imines are reduced. Thus, Yuan and co-workers <1998HAC139> produce a series of  $\alpha$ -trifluoromethyl- $\alpha$ -aminophosphonates in high yields (Table 37).

A similar procedure proves itself applicable to the reduction of oximes. Demir and co-workers show that the treatment of an  $\alpha$ -oximinophosphonate with sodium borohydride in the presence of either  $\text{MoO}_3$  or  $\text{NiCl}_2$  effects reduction to the amine. Yields vary, and in some cases are quite good (Table 38) <1996TL407>.

**Table 36** Reductive amination of acylphosphonates<sup>a,b</sup>

<i>R</i>	Yield <sup>c</sup> (%)
Me	60
Et	60
Bu <sup>i</sup>	55
PhCH <sub>2</sub> CH <sub>2</sub>	35
2-FC <sub>6</sub> H <sub>4</sub>	30

<sup>a</sup> <1996T10685>. <sup>b</sup> Specific conditions not provided. <sup>c</sup> Yields from acylphosphonates to phosphonic acids.

**Table 37** Use of imidoyl chlorides<sup>a</sup>




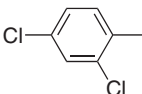
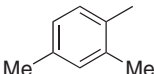
<i>R</i> <sup>1</sup>	<i>R</i> <sup>2</sup>	Step one			Step two Yield <sup>b</sup> (%)
		Temp. (°C)	Time (h)	Yield (%)	
Ph	Et	80	6	94	60 <sup>c</sup>
4-MeOC <sub>4</sub> H <sub>5</sub>	Et	80	10	95	99
PhCHMe	Et	100	40	80	99
PhCHMe	Me	100	40	82	99
PH <sub>2</sub> CH	Et	100	40	67	99

<sup>a</sup> <1998HAC139>. <sup>b</sup> NaBH<sub>3</sub>CN, glacial AcOH, rt, 10 h. <sup>c</sup> NaBH<sub>3</sub>CN, EtOH, rt, 20 h.

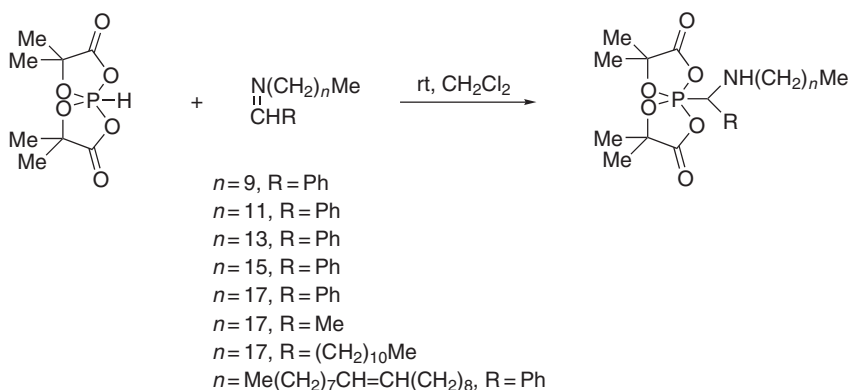
#### 4.10.1.1.4 Higher-coordinate phosphorus functions

Although pentacoordinate phosphorus rarely appears in the manifestation of the P—C—N array and is an uncommon substructure in synthesis, one unique example presented here depicts the generation of such compounds. Etemad-Moghadam and co-workers publish the coupling of spiroposphoranes to a number of long-chain imines on route to novel phosphorus acid amphiphiles. The products of the couplings ( $\alpha$ -aminoalkyl)spiroposphoranes prove unstable to purification, so yields are not reported, and the stereochemical outcomes of the couplings are not clearly defined. Nonetheless, the chemistry found in Equation (14) is noteworthy <2000EJO281>.

**Table 38** Reduction of oximinophosphonates to aminophosphonates<sup>a</sup>

$  \begin{array}{ccc}  \text{HO}-\text{N} & & \\  \parallel & & \\  \text{R}-\text{C} & \xrightarrow[\text{cat.}]{\text{5 equiv. NaBH}_4, \text{MeOH, rt, 6 h}} & \text{NH}_2 \\    & &   \\  \text{P(O)(OEt)}_2 & & \text{P(O)(OEt)}_2  \end{array}  $		
	Yield (%)	
<i>R</i>	1.5 equiv. <i>MoO</i> <sub>3</sub>	2 equiv. <i>NiCl</i> <sub>2</sub>
Me	59	51
Et	64	61
Pr <sup>i</sup>	68	67
PhCH <sub>2</sub>	71	73
	69	52
	67	61
	71	66
Ph	92	79
	77	76
	91	83

<sup>a</sup> <1996TL407>.



(14)

#### 4.10.1.2 Other Nitrogen Functions: $R_2C(NY)PR_2^2$ , $R_2C(NHX)PR_2^2$ , etc.

#### 4.10.1.2.1 Dicoordinate phosphorus functions

During the period 1995–2003, there were no published reports detailing the preparation of the N—C—P array in which phosphorus had a coordination number of 2.

#### 4.10.1.2.2 Tricoordinate phosphorus functions

Although compounds of this class do appear in the literature, the reports tend largely toward the coupling of a compound such as those found in [Section 4.10.1.1.2](#) to an electrophile so as to generate an amido or a carbamato tricoordinate phosphorus function by methods beyond the scope of this chapter.

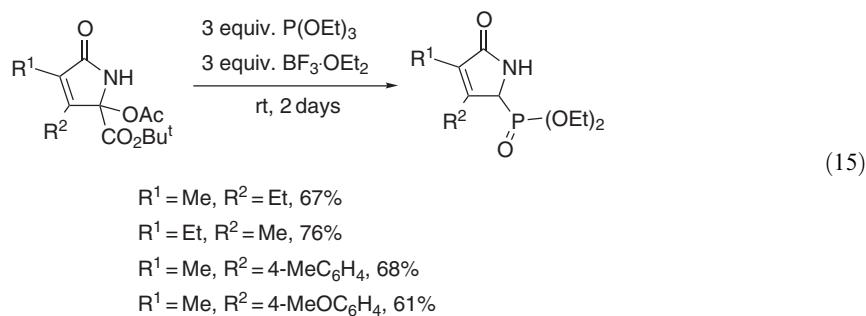
#### 4.10.1.2.3 Tetracoordinate phosphorus functions

Compounds of this category appear prolifically in the literature and take the form of various nitrogen functions: amides, carbamates, ureas, hydrazines, imines, etc. The chemistry employed to generate such compounds is quite similar to the methods discussed in [Section 4.10.1](#); so many such reactions are revisited herein.

##### (i) Preparation of tetracoordinate phosphorus compounds via addition of phosphorus to C—N double bonds

Reactions found here closely resemble those described previously in [Section 4.10.1.1.3.\(iii\)](#), and constitute the most widely executed protocol toward the tetracoordinate phosphorus products. The generic mechanism involves the attack of the appropriate phosphorus nucleophile on a C—N double bond either pre-existing or generated *in situ*. Several examples follow.

In their efforts toward the synthesis of phycocyanobilin, Kinoshita and co-workers prepared a series of lactams bearing exocyclic diethyl phosphonates. The authors explain that the parent lactams, upon treatment with  $\text{BF}_3 \cdot \text{OEt}_2$ , eliminate acetate to generate an electrophilic site for the attack by triethyl phosphite. Note that complete conversion to the products also involves loss of the *t*-butyl group followed by decarboxylation ([Equation \(15\)](#)) [<2000BCJ497>](#).



Cristau and co-workers provide an example for the generation of  $\alpha$ -amidophosphonates by the attack of sodium diethyl phosphite on a series of acylimines. The authors also apply this protocol to the synthesis of a sulfonamide ([Table 39](#)) [<1998S1167>](#).

*N*-Benzyloxycarbonyl- $\alpha$ -aminoalkylphosphinic acids succumb to synthesis via the three-component condensation as shown by Coward and co-workers. The condensation of an alkylphosphonous acid, or its adamantylammonium salt, with benzyl carbamate and an aldehyde renders the products in useful yields through a convenient protocol ([Table 40](#)) [<1996TL4335>](#).

Chloro phosphites have proven themselves competent partners in similar condensations. Xu and co-workers have published the condensation of benzyl carbamate and various aldehydes with both chloro phosphites and chlorodithioalkyl phosphites as shown in [Table 41](#). The authors propose that water liberated during imine formation hydrolyzes the chloro phosphates and chlorodithioalkyl phosphates to dialkyl phosphates and dithioalkyl phosphates, respectively, which subsequently serve as nucleophiles [<2000HAC417>](#).

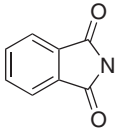
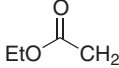
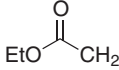
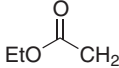
Similar chemistry is possible with alkoxydichlorophosphine and dichlorophenylphosphine. Dai and co-workers demonstrate the efficiency of both with benzyl carbamate and aromatic aldehydes, as shown in [Table 42](#). The authors suggest that the tetracoordinate phosphorus product results from hydrolysis of P—Cl bonds [<1997SC3341, 1997S415>](#).

**Table 39** Addition of NaP(O)(OR<sup>3</sup>)<sub>2</sub> to acyl imines<sup>a,b</sup>

$\text{Ph}-\text{C}(\text{NR}^1)=\text{R}^2 \xrightarrow[\text{ii. 1 N HCl, 0}^\circ\text{C}]{\text{i. NaP(O)(OR}^3)_2, \text{ THF, 12 h, 20}^\circ\text{C}} \text{R}^1\text{HN}-\text{C}(\text{Ph})(\text{R}^2)-\text{P(O)(OR}^3)_2$			
<i>R</i> <sup>1</sup>	<i>R</i> <sup>2</sup>	<i>R</i> <sup>3</sup>	Yield (%)
PhC(O)	Ph	Et	85
PhC(O)	2-MeC <sub>6</sub> H <sub>4</sub>	Et	75
PhC(O)	1-Naphthyl	Et	90
2-MeC <sub>6</sub> H <sub>4</sub> C(O)	Ph	Et	60
MeC(O)	Ph	Et	35
PhCH <sub>2</sub> OC(O)	Ph	Et	52
PhC(O)	Ph	CH <sub>2</sub> Ph	85
Ts	Ph	Et	96

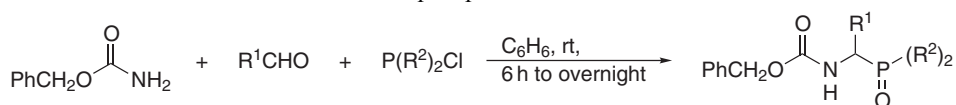
<sup>a</sup> <1998SI1167>. <sup>b</sup> 6.37 mmol NaP(O)(OR<sup>3</sup>)<sub>2</sub>, 7 mmol acylimine, −78 °C to 20 °C.

**Table 40** Three-component condensation rendering alkylphosphonic acids<sup>a,b</sup>

$\text{R}^1\text{H}_2\text{C}-\text{P}(\text{OR}^2)(\text{H}) + \text{R}^3\text{CHO} + \text{PhCH}_2\text{O}-\text{C}(=\text{O})\text{NH}_2 \xrightarrow[\text{to rt, 6 h}]{\text{AcCl, 0}^\circ\text{C}} \text{PhCH}_2\text{O}-\text{C}(=\text{O})\text{NH}-\text{CH}(\text{R}^3)-\text{P}(\text{OH})(\text{OR}^1)\text{R}^2$			
<i>R</i> <sup>1</sup>	<i>R</i> <sup>2</sup>	<i>R</i> <sup>3</sup>	Yield (%)
H	Adamantyl-NH <sub>3</sub> <sup>+</sup>	H	67
H	Adamantyl-NH <sub>3</sub> <sup>+</sup>	Bu <sup>t</sup>	69
H	Adamantyl-NH <sub>3</sub> <sup>+</sup>	Ph	61
H	Adamantyl-NH <sub>3</sub> <sup>+</sup>	4-MeOC <sub>6</sub> H <sub>4</sub>	72
Pr <sup>n</sup>	H	H	50
	H	Ph	73
	H	Me	75
	H	Et	48
	H	4-MeOC <sub>6</sub> H <sub>4</sub>	71

<sup>a</sup> <1996TL4335>. <sup>b</sup> Conditions: 1 equiv. alkylphosphonous acid, 1 equiv. aldehyde, 1 equiv. carbamate, 0 °C for 30 min, then rt for 6 h.

A unique approach to the preparation of *N*-Cbz- $\alpha$ -phosphono acids appears in the work of Toone and co-workers. Treatment of a protected  $\alpha$ -hydroxy- or  $\alpha$ -methoxy amino acid with PCl<sub>3</sub> and P(OMe)<sub>3</sub> results in the elimination of the oxygenic substituent followed by the addition of trimethyl phosphite as depicted in Equation (16) <1999JOC9153>.

**Table 41** Three-component condensation with chloro phosphites and chlorodithioalkyl phosphites<sup>a,b</sup>

$R^1$	$R^2$	Yield (%)
Ph	OEt	87
2-MeOC <sub>6</sub> H <sub>4</sub>	OEt	71
4-ClC <sub>6</sub> H <sub>4</sub>	OEt	69
4-BrC <sub>6</sub> H <sub>4</sub>	OEt	74
PhCH <sub>2</sub>	OEt	67
Bu <sup>i</sup>	OEt	69
Pr <sup>i</sup>	OEt	67
Me	OEt	56
Ph	OMe	78
2-MeOC <sub>6</sub> H <sub>4</sub>	OMe	64
4-ClC <sub>6</sub> H <sub>4</sub>	OMe	66
4-BrC <sub>6</sub> H <sub>4</sub>	OMe	64
PhCH <sub>2</sub>	OMe	50
Bu <sup>i</sup>	OMe	57
Pr <sup>i</sup>	OMe	58
Me	OMe	55
Ph	SPR <sup>i</sup>	43
2-MeOC <sub>6</sub> H <sub>4</sub>	SPR <sup>i</sup>	38
4-ClC <sub>6</sub> H <sub>4</sub>	SPR <sup>i</sup>	40

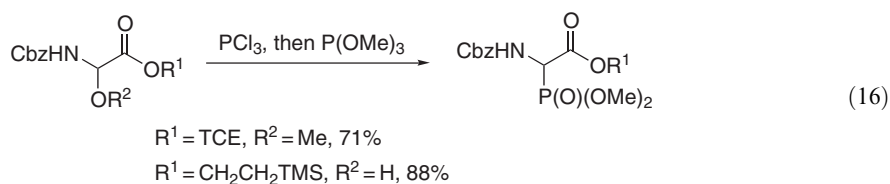
<sup>a</sup> <2000HAC417>. <sup>b</sup> 3 mmol benzyl carbamate, 3.1 mmol aldehyde, 3.3 mmol phosphorus compound.

**Table 42** Three-component condensation with dichlorophosphorus compounds

$R^1$	$R^2$	Yield (%)	References
H	Ph	85	<1997S415> <sup>a</sup>
4-Me	Ph	76	<1997S415> <sup>a</sup>
3-Cl	Ph	72	<1997S415> <sup>a</sup>
4-Cl	Ph	68	<1997S415> <sup>a</sup>
2,4-Cl	Ph	80	<1997S415> <sup>a</sup>
2-MeO	Ph	66	<1997S415> <sup>a</sup>
4-MeO	Ph	83	<1997S415> <sup>a</sup>
3-NO <sub>2</sub>	Ph	77	<1997S415> <sup>a</sup>
4-NO <sub>2</sub>	Ph	79	<1997S415> <sup>a</sup>
H	OMe	80	<1997SC3341> <sup>b</sup>
4-Cl	OMe	67	<1997SC3341> <sup>b</sup>
H	OEt	87	<1997SC3341> <sup>b</sup>
4-Me	OEt	72	<1997SC3341> <sup>b</sup>
2-MeO	OEt	69	<1997SC3341> <sup>b</sup>
4-MeO	OEt	66	<1997SC3341> <sup>b</sup>
4-Cl	OEt	72	<1997SC3341> <sup>b</sup>
3-NO <sub>2</sub>	OEt	74	<1997SC3341> <sup>b</sup>
4-NO <sub>2</sub>	OEt	83	<1997SC3341> <sup>b</sup>
H	Pr <sup>n</sup>	79	<1997SC3341> <sup>b</sup>
4-Cl	Pr <sup>n</sup>	67	<1997SC3341> <sup>b</sup>
H	Bu <sup>n</sup>	72	<1997SC3341> <sup>b</sup>
4-Cl	Bu <sup>n</sup>	68	<1997SC3341> <sup>b</sup>

<sup>a</sup> Conditions: 5 mmol benzyl carbamate, 5 mmol aldehyde, 5 mmol dichlorophenylphosphine, AcCl, 0 °C for 0.5 h then rt for 1 h, concentrated then stirred in 10:1 C<sub>6</sub>H<sub>6</sub>/H<sub>2</sub>O at rt for 2 h. <sup>b</sup> Conditions: 5 mmol benzyl carbamate, 5 mmol aldehyde, 5 mmol alkoxydichlorophosphine, AcCl, rt for 6 h then 40 °C for 4 h, concentrated then stirred in 10:1 C<sub>6</sub>H<sub>6</sub>/H<sub>2</sub>O at rt for 2 h.



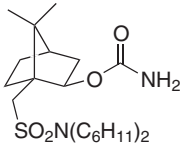
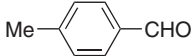
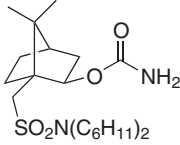
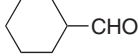
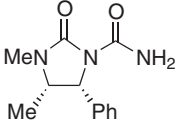
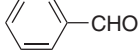
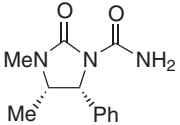
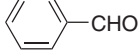
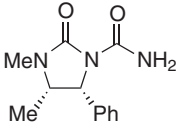
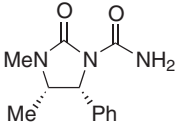



Three-component condensations have proven themselves amenable to enhancements involving chiral auxiliaries. Both Chung and co-workers and Roos and co-workers demonstrate the applicability of several auxiliaries to condensations involving diethyl phosphite, which in some cases offer *dr* values greater than 100:1. Results appear in [Table 43](#) [<1996TA21, 1998SC3877>](#).

**Table 43** Three-component condensations involving diethyl phosphite aided by chiral auxiliaries

Chiral material	Aldehyde	Yield (%)	<i>de</i> (%) or <i>dr</i>	References
		71	14.4	<a href="#">&lt;1996TA21&gt;<sup>a</sup></a>
		84	34.1	<a href="#">&lt;1996TA21&gt;<sup>a</sup></a>
		75	>99	<a href="#">&lt;1996TA21&gt;<sup>a</sup></a>
		73	96.4	<a href="#">&lt;1996TA21&gt;<sup>a</sup></a>
		77	96.7	<a href="#">&lt;1996TA21&gt;<sup>a</sup></a>
		76	>99	<a href="#">&lt;1996TA21&gt;<sup>a</sup></a>
		79	>99	<a href="#">&lt;1996TA21&gt;<sup>a</sup></a>

Table 43 (continued)

Chiral material	Aldehyde	Yield (%)	de (%) or dr	References
		75	>99	<1996TA21> <sup>a</sup>
		76	>99	<1996TA21> <sup>a</sup>
		70	>100:1	<1998SC3877> <sup>b</sup>
		52	>100:1	<1998SC3877> <sup>b</sup>
	MeCHO	42	66:34	<1998SC3877> <sup>b</sup>
		68	>100:1	<1998SC3877> <sup>b</sup>

<sup>a</sup> Conditions: 3 mmol chiral material, 4 mmol diethyl phosphite, 5 mmol aldehyde, AcCl, 0 °C for 30 min, rt for 1 h. <sup>b</sup> Conditions: 1 mmol chiral material, 1.5 mmol diethyl phosphite, 1.5 mmol aldehyde, AcCl, 0 °C for 30 min, rt for 1 h.

The addition of phosphorus nucleophiles to C—N double bonds also proves to be a useful route to  $\alpha$ -ketosulfiniminophosphonates. Davis and co-workers have been successful in the asymmetric addition of lithium diethyl phosphite to enantiopure keto sulfinimines in both high yields and selectivities as shown in Table 44 <2001OL1757>.

Evans and co-workers <1997JOC7532> have executed similar experiments also in good yield and selectivity, as shown in Table 45.

Hou and co-workers have demonstrated similar asymmetric additions in the presence of a nearby chiral azirine, which also has the potential to influence the stereochemical outcome of the reaction. Despite the second source of chirality, good selectivities seem attainable with either epimeric azirine (Table 46) <2002JOC2902>.

The examples discussed thus far have explored the generation of systems in which nitrogen bears a common electron-withdrawing group, amides, carbamates, etc. Although of less routine interest to the chemist than the compounds discussed previously, the three-component condensation has also found applications to systems bearing *N*-heteroatom bonds. Heydari and co-workers have demonstrated the efficacy of condensations involving dimethylhydrazine and *N*-hydroxyaniline. Acidic catalysts aid the reaction, which tends to be high yielding and fast. In reactions

**Table 44** Asymmetric addition of lithium diethyl phosphite to enantiopure keto sulfinimines<sup>a</sup>

$R^1$	$R^2$	Yield (%)	<i>de</i> (%)
Me	4-MeOPh	73	>95
Me	4-MePh	91	>95
Me	Ph	92	>95
Et	Ph	93	>95
Me	4-NO <sub>2</sub> Ph	93	>95
Me	Bu <sup>t</sup>	97	>95

<sup>a</sup> <2001OL1757>.**Table 45** Asymmetric addition of metallated phosphites to keto sulfinimines<sup>a</sup>

$R^1$	$R^2$	$M$	Yield (%)	<i>de</i> (%)
Ph	Et	Li	85	84
Ph	Et	Na	80	93
4-MeOPh	Et	Li	50	84
4-MeOPh	Et	Na	50	90
Ph	Pr <sup>i</sup>	Li	82	97

<sup>a</sup> <1997JOC7532>.**Table 46** Asymmetric additions to a pair of epimers<sup>a</sup>

$R$	$M$	Yield (%)	<i>syn:anti</i>
<div style="text-align: center;"> </div>			
NEt <sub>2</sub>	Li	96	84:16
NEt <sub>2</sub>	Na	92	62:38
OMe	Li	95	85:15
<div style="text-align: center;"> </div>			
NEt <sub>2</sub>	Li	94	<1:99
NEt <sub>2</sub>	Na	93	22:78
OMe	Li	94	<1:99

<sup>a</sup> <2002JOC2902>.

involving  $\text{P(OMe)}_2(\text{OTMS})$ , note the transfer of TMS from the phosphite to the hydroxylamine (Table 47) <2002CL1146, 2001TL3629>.

**Table 47** Three-component condensations in the presence of N—N and N—O bonds

$$\text{R}^1\text{CHO} + \text{P(OMe)}_2(\text{OR}^2) + \text{R}^3\text{—NHR}^4 \xrightarrow[\text{LiClO}_4\cdot\text{OEt}_2]{\text{Cat., rt}} \text{R}^5\text{—N}(\text{R}^3)\text{—CH(R}^1\text{)—P(=O)(OMe)}_2$$

$\text{R}^1$	$\text{R}^2$	$\text{R}^3$	$\text{R}^4$	$\text{R}^5$	Catalyst	Yield (%)	References
$\text{Pr}^i$	Me	$\text{NMe}_2$	H	H	TMSCl	94	<2002CL1146> <sup>a</sup>
$\text{Pr}^n$	Me	$\text{NMe}_2$	H	H	TMSCl	90	<2002CL1146> <sup>a</sup>
$\text{Bu}^t$	Me	$\text{NMe}_2$	H	H	TMSCl	94	<2002CL1146> <sup>a</sup>
Hexyl	Me	$\text{NMe}_2$	H	H	TMSCl	95	<2002CL1146> <sup>a</sup>
2-furyl	Me	$\text{NMe}_2$	H	H	TMSCl	76	<2002CL1146> <sup>a</sup>
4- $\text{NO}_2\text{Ph}$	Me	$\text{NMe}_2$	H	H	TMSCl	86	<2002CL1146> <sup>a</sup>
4-BrPh	Me	$\text{NMe}_2$	H	H	TMSCl	89	<2002CL1146> <sup>a</sup>
$\text{Pr}^i$	Me	Ph	OH	OH	AcOH	89	<2002CL1146> <sup>a</sup>
$\text{Pr}^n$	Me	Ph	OH	OH	AcOH	96	<2002CL1146> <sup>a</sup>
$\text{Bu}^t$	Me	Ph	OH	OH	AcOH	90	<2002CL1146> <sup>a</sup>
$\text{C}_6\text{H}_{11}$	Me	Ph	OH	OH	AcOH	87	<2002CL1146> <sup>a</sup>
3-Pyridyl	Me	Ph	OH	OH	AcOH	87	<2002CL1146> <sup>a</sup>
4- $\text{NO}_2\text{Ph}$	Me	Ph	OH	OH	AcOH	85	<2002CL1146> <sup>a</sup>
$\text{Pr}^i$	TMS	Ph	OH	OTMS		97	<2001TL3629> <sup>b</sup>
$\text{Pr}^n$	TMS	Ph	OH	OTMS		95	<2001TL3629> <sup>b</sup>
$\text{Bu}^n$	TMS	Ph	OH	OTMS		99	<2001TL3629> <sup>b</sup>
Hexyl	TMS	Ph	OH	OTMS		90	<2001TL3629> <sup>b</sup>
$\text{C}_6\text{H}_{11}$	TMS	Ph	OH	OTMS		87	<2001TL3629> <sup>b</sup>
Ph	TMS	Ph	OH	OTMS		90	<2001TL3629> <sup>b</sup>
4-MeOPh	TMS	Ph	OH	OTMS		85	<2001TL3629> <sup>b</sup>
2-Furyl	TMS	Ph	OH	OTMS		90	<2001TL3629> <sup>b</sup>
3-Pyridyl	TMS	Ph	OH	OTMS		95	<2001TL3629> <sup>b</sup>
( <i>E</i> )-PhCH=CH	TMS	Ph	OH	OTMS		95	<2001TL3629> <sup>b</sup>

<sup>a</sup> Conditions: 0.8 mmol  $\text{LiClO}_4\cdot\text{OEt}_2$ , 2.2 mmol nitrogen source, 2 mmol aldehyde, 2.2 mmol phosphite, 2.2 mmol catalyst, 1 h.

<sup>b</sup> Conditions: 0.8 mmol  $\text{LiClO}_4\cdot\text{OEt}_2$ , 2.2 mmol nitrogen source, 2 mmol aldehyde, 2.2 mmol phosphite, 15 min.

(ii) *Preparation of tetracoordinate phosphorus compounds via nucleophilic displacement of leaving groups*

The displacement of leaving groups as a means of coupling to the products discussed here is just as common and useful as it is in the synthesis of amino compounds and proceeds via the same mechanisms as reactions discussed in Section 4.10.1.1.3.(iv). Typically, the phosphorus source acts as the nucleophile, though there do exist a few examples of reactions in which the nitrogen source serves such a role.

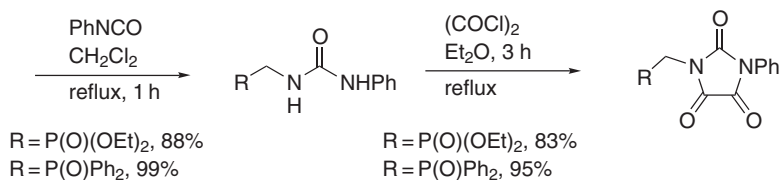
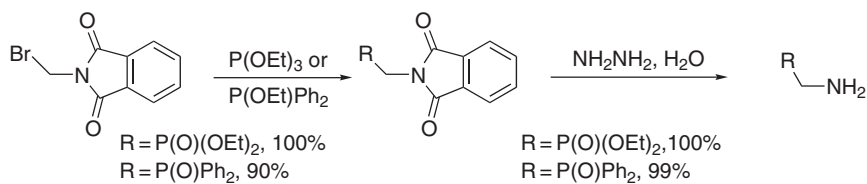
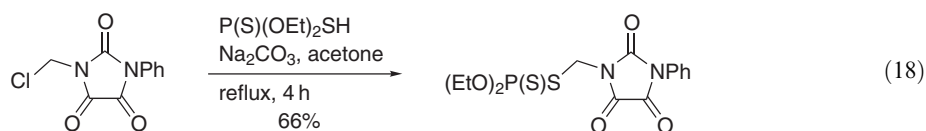
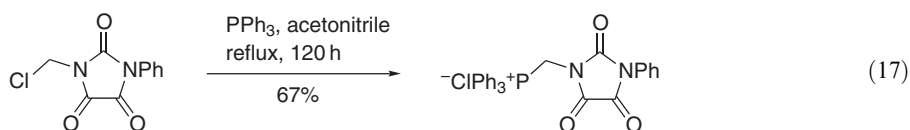
Couture and co-workers have developed a method for the synthesis of tetracoordinate phosphorus compounds bearing formamides and *N*-BOC-amines. The reaction involves the condensation of the nitrogen source with *p*-formaldehyde and TMSCl to generate an  $\alpha$ -chloroamide or carbamate, which reacts with a phosphorus nucleophile to render the products in good yield (Table 48) <1995TL2483>.

Plénat and co-workers have exploited the displacement of halogens in their synthesis of 2,4,5-imidazolidinetriones. Displacement of chloride from *N*-chloromethyl-2,4,5-imidazolidinetrione by either triphenylphosphine (Equation (17)) or *O,O*-diethyl dithiophosphate (Equation (18)) affords the desired products in suitable yields. Better yields are realized when other nucleophiles attack *N*-bromomethylphthalimide. Those products are then converted to the desired products through a three-step protocol (Scheme 18) <1995T9551>.

**Table 48** Attack of phosphorus nucleophiles on chloromethylamides and carbamates<sup>a</sup>

$$R^1-\overset{\text{O}}{\parallel}{C}-\underset{\text{R}^2}{\text{NH}} \xrightarrow[\text{TMSCl}]{(\text{CH}_2\text{O})_n} \left[ R^1-\overset{\text{O}}{\parallel}{C}-\underset{\text{R}^2}{\text{N}}-\text{CH}_2\text{Cl} \right] \xrightarrow[\text{Toluene, reflux}]{\text{P(OEt)(R}^3)_2, 1 \text{ h}} R^1-\overset{\text{O}}{\parallel}{C}-\underset{\text{R}^2}{\text{N}}-\text{CH}_2-\text{P(=O)(R}^3)_2$$

$R^1$	$R^2$	$R^3$	Yield (%)
H	Me	OMe	71
H	CH <sub>2</sub> Ph	OMe	70
H	Me	OEt	72
H	CH <sub>2</sub> Ph	OEt	75
H	Ph	OEt	70
H	Me	Ph	82
H	CH <sub>2</sub> Ph	Ph	80
H	Ph	Ph	75
OBu <sup>t</sup>	CH <sub>2</sub> Ph	OEt	65
OBu <sup>t</sup>	CH <sub>2</sub> Ph	Ph	68

<sup>a</sup> <1995TL2483>.**Scheme 18**

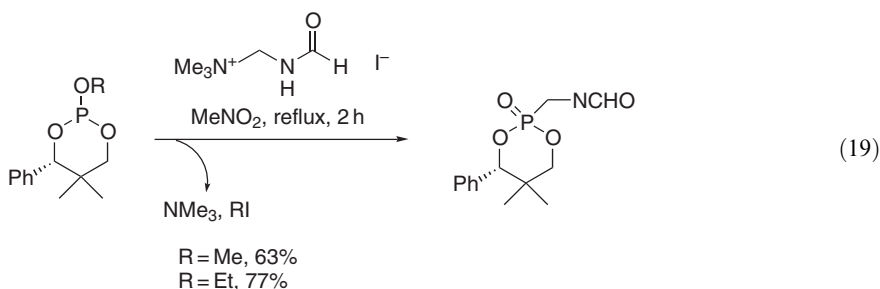
Katritzky and co-workers have applied the benzotriazole (Bt) group to this reaction. A mixture of triethyl phosphite and  $\alpha$ -Bt-lactam reacts in the presence of a zinc bromide catalyst to render products in good yield as shown in Table 49 <2000JOC4364>.

**Table 49** Use of benzotriazole as a leaving group<sup>a,b</sup>

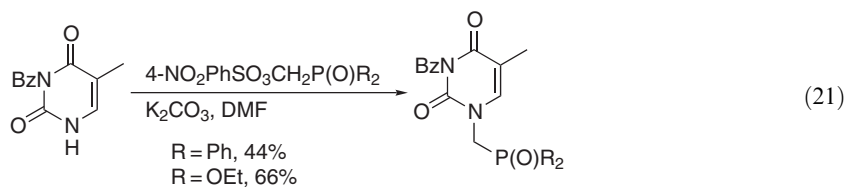
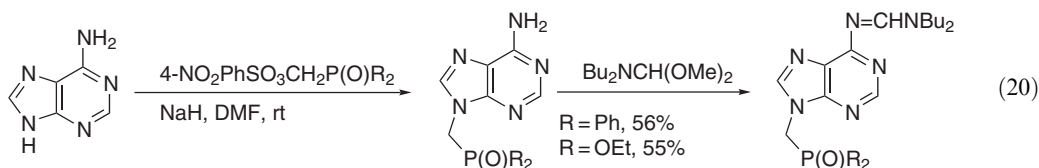
<i>R</i>	Yield (%)
CH <sub>2</sub> CH <sub>2</sub> OH	49
4-MeOPhCH <sub>2</sub>	79
3,4-MeOPhCH <sub>2</sub>	78
4-MeOPhCH <sub>2</sub> CH <sub>2</sub>	76
	85
	67

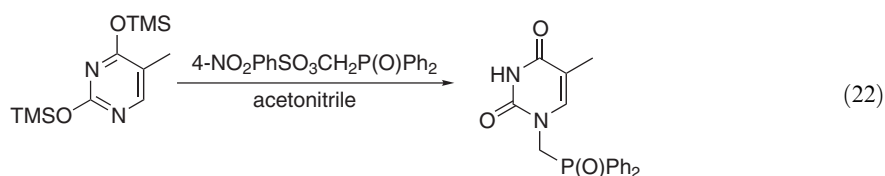
<sup>a</sup> <2000JOC4364>. <sup>b</sup> Conditions: 1.3 mmol lactam, 1.3 mmol ZnBr<sub>2</sub>, 2.1 mmol P(OEt)<sub>3</sub>.

An example of a cyclic phosphite acting as the nucleophile appears in the work of Leusen and co-workers. Two similar cyclic phosphites react with cationic formamides to displace trimethylamine as found in Equation (19) <1998EJO1511>.



Cases in which nitrogen acts as a nucleophile displacing a leaving group from the phosphorus compound are less prominent in the literature, though equally useful as the methods seen thus far. In the synthesis of a series of nucleobase compounds, Dahl and co-workers <2000JCS(P1)2015> utilize this reaction to displace 4-nitrobenzene sulfonates from phosphines and phosphonates (Equations (20)–(22)).





Yuanand and co-workers have demonstrated the synthesis of 1-hydrazinoalkylphosphonic acids via displacement of  $\alpha$ -mesylates from phosphonates with hydrazine. The reactions proceed in moderate yields, as shown in Table 50, and the products were subsequently converted to their oxalate salts <1996S507>.

**Table 50** Displacement of mesylates with hydrazine<sup>a</sup>

$\text{R}-\text{CH}(\text{OMs})-\text{P}(\text{O})(\text{OEt})_2$	$\xrightarrow[\text{EtOH, 50 } ^\circ\text{C, 15 h}]{\text{NH}_2\text{NH}_2 \cdot \text{H}_2\text{O}}$	$\text{R}-\text{CH}(\text{NHNH}_2)-\text{P}(\text{O})(\text{OEt})_2$
<i>R</i>	<i>Yield (%)</i>	
H	50	
Me	53	
Et	56	
PhCH <sub>2</sub>	61	
Ph	55	
4-MePh	60	
4-MeOPh	52	
4-FPh	54	
4-ClPh	53	

<sup>a</sup> <1996S507>.

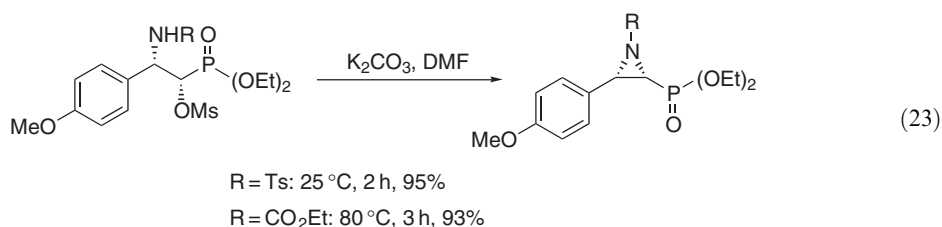
While involved in hapten synthesis, Gouverneur and co-workers have used the combination of DEAD and triphenylphosphine to couple *N*-(phenoxy carbonyl)-*O*-*t*-BOC hydroxylamine to  $\alpha$ -hydroxy phosphonates. The yields vary widely, yet the reactions are still clean (Table 51). Removal of the *t*-BOC group completes the synthesis <1996TL6331>.

**Table 51** Displacements assisted by DEAD/PPh<sub>3</sub><sup>a</sup>

$\text{HO}-\text{CH}(\text{R})-\text{P}(\text{O})(\text{OBn})_2$	$\xrightarrow[\text{THF, rt, 1-2 h}]{\begin{smallmatrix} 2 \text{ equiv. DEAD}/2 \text{ equiv. PPh}_3, \\ 1.5 \text{ equiv. PhOCO-NHO-t-BOC} \end{smallmatrix}}$	$\text{PhOCO}-\text{N}(\text{t-BOCO})-\text{CH}(\text{R})-\text{P}(\text{O})(\text{OBn})_2$
<i>R</i>	<i>Yield (%)</i>	
Me	53	
Et	50	
Pr <sup>i</sup>	29	
Bu <sup>i</sup>	64	
CH <sub>2</sub> CH <sub>2</sub> Ph	96	

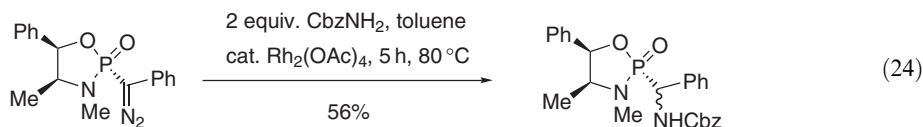
<sup>a</sup> <1996TL6331>.

Sharpless and co-workers offer examples of an intramolecular displacement that affords *N*-substituted azirines in high yield (Equation (23)) <1999JOC8379>.



## (iii) Preparation of tetracoordinate phosphorus compounds via metal carbenoid insertions

As the reactions of diazo compounds with transition metals become increasingly popular in synthesis, this method becomes useful in the synthesis of compounds of interest here. Moody and co-workers [<2001TA1657>](#) have demonstrated the reactions of diazophosphonic acid derivatives with a variety of nucleophiles including a carbamate as shown in [Equation \(24\)](#). Moody has published a similar reaction by using  $\alpha$ -diazo- $\beta$ -phosphonate esters in the synthesis of phosphonoglycine derivatives and in peptide synthesis ([Table 52](#)) [<1995SL921, 1997CC2391>](#).

**Table 52** Carbenoid insertions

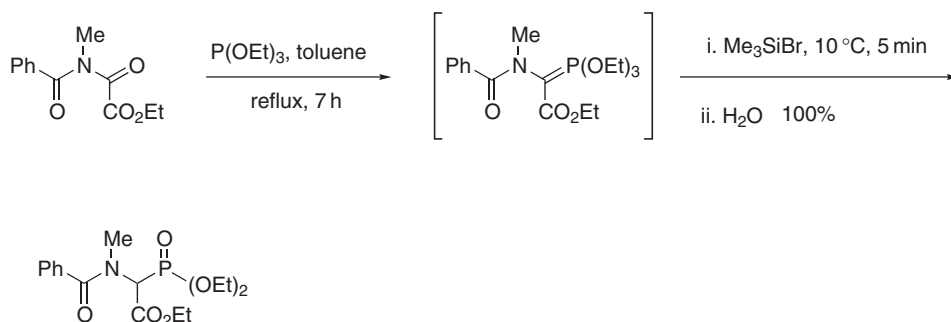
Substrate	$R^1$	$R^2$	$R^3$	Yield (%)	References
$R^1-C(=O)-NHR^2$	OBu <sup>t</sup>	H		75	<a href="#">&lt;1995SL921&gt;</a> <sup>a</sup>
	OCH <sub>2</sub> Ph	H		73	<a href="#">&lt;1995SL921&gt;</a> <sup>a</sup>
	Me	H		79	<a href="#">&lt;1995SL921&gt;</a> <sup>a</sup>
	Et	H		66	<a href="#">&lt;1995SL921&gt;</a> <sup>a</sup>
	OBu <sup>t</sup>	Pr		46	<a href="#">&lt;1995SL921&gt;</a> <sup>a</sup>
	NHMe	H		40	<a href="#">&lt;1995SL921&gt;</a> <sup>a</sup>
$R^2-P(R^3)-CH(R^1)-C(=O)-NH_2$	H	H	Cbz	81	<a href="#">&lt;1997CC2391&gt;</a> <sup>b</sup>
	Me	H	<i>t</i> -BOC	88	<a href="#">&lt;1997CC2391&gt;</a> <sup>b</sup>
	Me	H	Cbz	80	<a href="#">&lt;1997CC2391&gt;</a> <sup>b</sup>
	Pr <sup>i</sup>	H	<i>t</i> -BOC	80	<a href="#">&lt;1997CC2391&gt;</a> <sup>b</sup>
	Bu <sup>i</sup>	H	<i>t</i> -BOC	82	<a href="#">&lt;1997CC2391&gt;</a> <sup>b</sup>
	—(CH <sub>2</sub> ) <sub>2</sub> —		Cbz	80	<a href="#">&lt;1997CC2391&gt;</a> <sup>b</sup>

<sup>a</sup> Conditions: 1 mmol triethyldiazophosphono acetate, 5 mmol NH compound, toluene, 2 mol.% Rh<sub>2</sub>(OAc)<sub>4</sub>, reflux overnight.

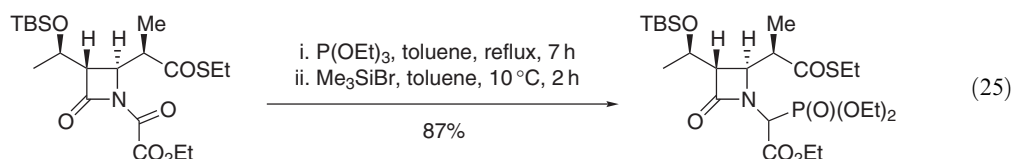
<sup>b</sup> Conditions: triethyldiazophosphono acetate, toluene, Rh<sub>2</sub>(OAc)<sub>4</sub>.

## (iv) Preparation of tetracoordinate phosphorus compounds via miscellaneous methods

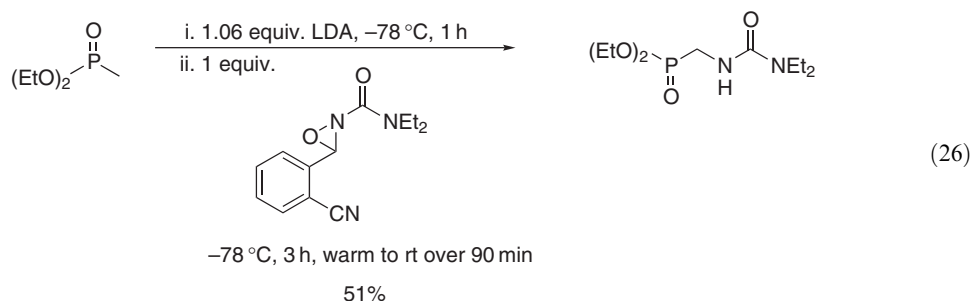
In addition to the more widely employed methods, the literature offers a small number of interesting and unique entries into the desired system. Kondo and co-workers have developed a means of generating  $\alpha$ -carbamato- $\alpha$ -phosphono esters. The reaction stands distinct from others seen thus far in which it involves the direct attack of triethylphosphine on a carbonyl. The yields are high, as shown in [Scheme 19](#) and [Equation \(25\)](#), and the conditions seem suitable for the functionalization of  $\beta$ -lactams [<1996JCS\(P1\)3>](#).

**Scheme 19**



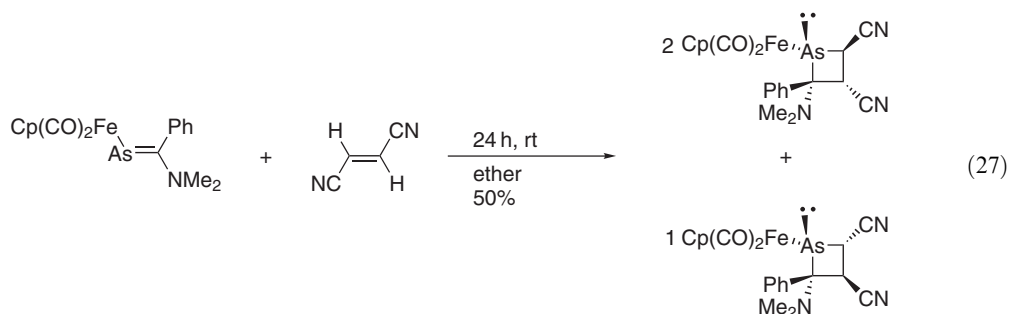


Armstrong and co-workers have demonstrated the amination of phosphonate ester enolates by *N*-carboxamido oxaziridines. Attack by the enolate on the *N*-carboxamido oxaziridine results in formation of the desired compound with loss of 2-cyanobenzaldehyde, as shown in Equation (26) <2000TL2247>.



#### 4.10.2 FUNCTIONS CONTAINING ONE NITROGEN AND ONE ARSENIC, ANTIMONY, OR BISMUTH

Compounds of this description are seldom the target of synthesis and the literature offers only one example from the years surveyed. Weber and co-workers have studied the reaction of arsa alkenes with fumarodinitrile (Equation (27)). The organometallic species adds to the electron deficient olefin effecting cyclization to a 2:1 mixture of diastereomers <2002OM1998>.



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## Biographical sketch



**Craig S. Kenesky** is currently a graduate student at the University of Pennsylvania working in the laboratories of Professor Amos B. Smith, III. He received his B.A. in chemistry from The Johns Hopkins University in 1999, whereupon he began his graduate studies. His research interests include the synthesis of architecturally complex natural products of biological significance, and the design, synthesis, and evaluation of novel nonpeptidal peptidomimetics, carbohydrate-derived scaffolds, and drugs targeting HIV and cancer.



**Professor Gary Molander** was born in Cedar Rapids, Iowa. He received his B.S. degree at Iowa State University in 1975 working with Professor Richard C. Larock. He 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 as a National Institutes of Health post-doctoral fellow in 1980, and in 1981 he accepted an appointment at the University of Colorado, Boulder, as an assistant professor of chemistry. He was promoted to Associate Professor in 1988 and Professor of Chemistry in 1990. 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 area of research has also been the application of organolanthanide reagents and catalysts to selective organic synthesis.

## 4.11

# Functions Incorporating a Nitrogen and a Silicon, Germanium, Boron, or a Metal

C. CHU

*AstraZeneca R&D Charnwood, Loughborough, UK*

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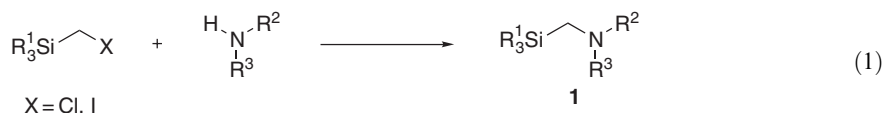
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**4.11.1 FUNCTIONS CONTAINING A NITROGEN AND A METALLOID:****4.11.1.1 Nitrogen and Silicon Functions****4.11.1.1.1  $\alpha$ -Aminosilanes**

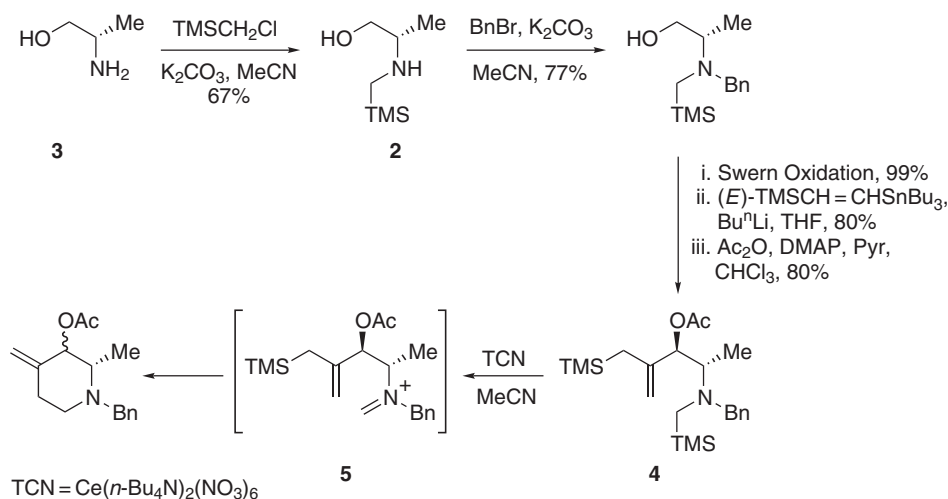
The chemistry of  $\alpha$ -aminosilanes has been a growing area of interest because  $\alpha$ -aminosilanes have been shown to be useful intermediates in synthesis, most notably as ylide precursors. A recent review by Aizpurua and Palomo [<2002MI411-01>](#) has covered the main synthetic routes to  $\alpha$ -aminosilanes and in this section some of these methodologies will be discussed.

*(i) Reaction of an amine with a halomethyl silane and its further functionalization*

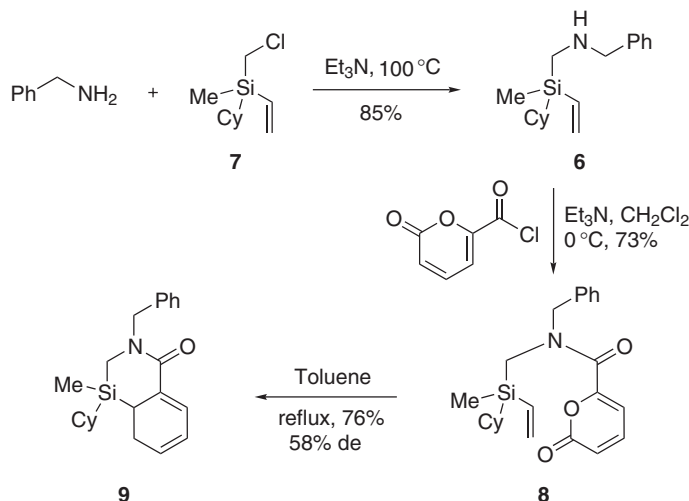
The alkylation of ammonia or an amine by halomethyl silanes in an inert solvent is the most straightforward method used to prepare  $\alpha$ -aminosilanes **1** (Equation (1)), but its development is restricted by the limited availability of functionalized halomethyl silanes and the complication of overalkylation. Only chloromethyl- and iodomethyltrimethylsilane are widely used to prepare trimethylsilylmethylamines. In order to overcome the problem of overalkylation, either a large excess of amines was needed or a two-step procedure using a masked amino group (such as an azido or phthalimide group) was employed (see Sections 4.11.1.1.4 and 4.11.1.1.2). Despite these issues, a number of publications on this reaction have been listed in chapter 4.11 of COFGT (1995) and will not be repeated here.



A typical example of  $\alpha$ -aminosilane synthesis from an amine and its subsequent use as an ylide precursor was published by Mariano and co-workers [<1996TL571>](#) in their studies of the stereochemical features of oxidative Mannich cyclizations. They prepared  $\alpha$ -aminosilane **2** in moderate yield from the alkylation of an amino alcohol **3** with chloromethyltrimethylsilane. The resulting  $\alpha$ -aminosilane **2** was further functionalized by *N*-benzylation. After the introduction of the vinyl trimethylsilyl group, the intermediate **4** was treated with TCN, which underwent single electron transfer (SET) and transformed the  $\alpha$ -silylamine into an amine radical cation. This was followed by rapid desilylation to generate the iminium ion **5**, which is the substrate for Mannich cyclization (Scheme 1). The results of the oxidative Mannich cyclization of related  $\alpha$ -aminosilanes were informative regarding the stereochemical selectivity of this reaction.

**Scheme 1**

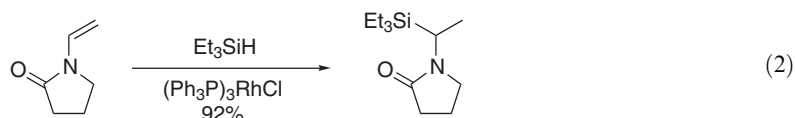
Coelho and Blanco <2001SL1455> in their study of the selectivity of intramolecular reactions of chiral silicon compounds also made use of a similar alkylation reaction. They synthesized the chiral  $\alpha$ -aminosilane **6** in moderate yield by direct alkylation of benzylamine with chloromethylsilane **7** at 100 °C (Scheme 2). This intermediate **6** was then acylated to give silatriene **8**, which was shown to undergo intramolecular Diels–Alder reaction to give product **9** as a mixture of diastereomers with a moderate de of 58%.



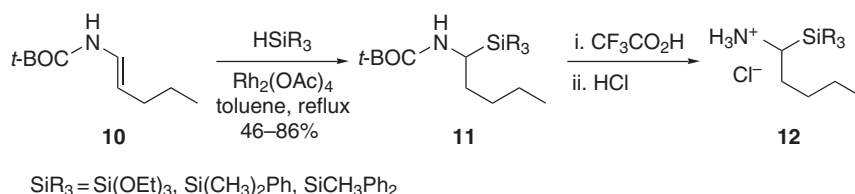
Scheme 2

## (ii) Hydrosilylation of enamines

An alternative direct synthesis of  $\alpha$ -aminosilanes is the hydrosilylation of enamines, but it has not been widely studied. Pioneering efforts by Skoda-Földes and co-workers <1991JOM(408)297> have demonstrated a rhodium-induced hydrosilylation of enamides with trialkylsilanes (Equation (2)). Murai and co-workers <1998OM926> have widened the scope of this reaction to allow other *N*-substitutions including those on *N*-alkenylureas and identified rhodium acetate as the preferred catalyst.



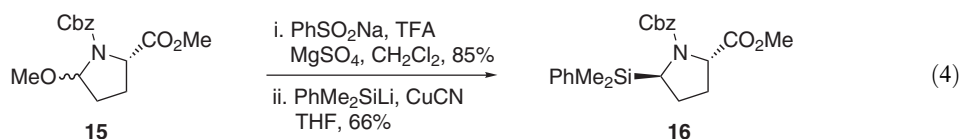
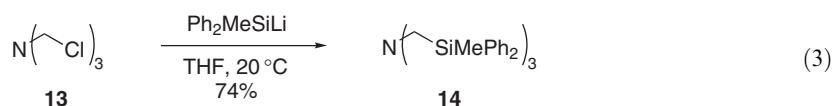
Sieburth and co-workers in their study of peptidomimetics developed a practical synthesis of BOC-protected  $\alpha$ -aminosilanes by hydrosilylation. The *N*-BOC enamine **10** (prepared using Overman's Curtius rearrangement protocol) was reacted with slight excess of silanes in the presence of 5% rhodium acetate in refluxing toluene to provide moderate-to-good yields of the hydrosilylation products **11** (Scheme 3) <2000TL10175>. The difference in product yields was consistent with a combination of steric and electronic effects for this transformation. Deprotection of product **11** using TFA proceeded smoothly and the  $\alpha$ -silylamine products **12** were characterized as their hydrochloride salts.



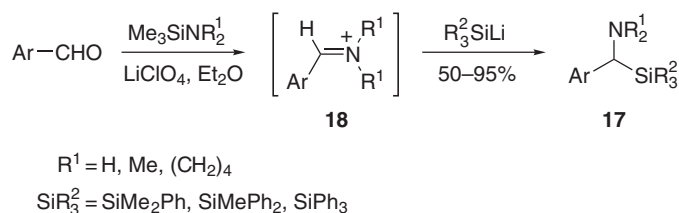
Scheme 3

## (iii) Reaction of halomethylamines and methyleneiminium salts with metallosilanes

Halomethylamines and methyleneiminium salts are considered synthetically equivalent entities, but the availability of  $\alpha$ -chloroalkylamines and related compounds is poor in comparison. An example of metallosilane displacement of halomethylamine was shown in Equation (3) where tris(chloromethyl)amine **13** is exhaustively silylated to give the amine **14** in 74% yield <1973HCA1117>. A related example of the use of metallosilane to prepare  $\alpha$ -aminosilanes was reported by Sun and Moeller where the phenyl sulfonyl proline derivative **15** was silylated using a cuprate reagent to give the *N*-Cbz protected silylated proline derivative **16** (Equation (4)) <2002OL1547>.



Maimi-Jamal and co-workers <1999JCS(P1)3709> reported a one-pot three-component synthesis of a variety of  $\alpha$ -silylated *N,N*-dialkylamines **17** by the addition of a metallosilane (e.g., phenyldimethylsilyllithium) to iminium intermediates **18** generated *in situ* from aryl aldehydes and (trimethylsilyl)dialkylamines in a 5 M ethereal LiClO<sub>4</sub> solution (Scheme 4). This methodology is general for most aryl aldehydes to give the corresponding  $\alpha$ -aminosilane in good-to-excellent yields. In the case of enolizable aldehydes such as isobutyraldehyde, the yield of the reaction was lowered by the formation of enamine as side product in the iminium ion formation step.



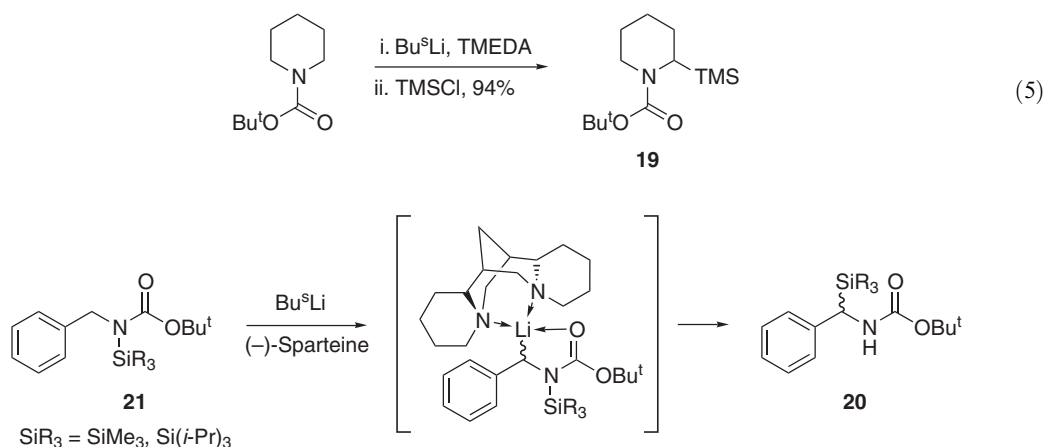
Scheme 4

## (iv) Silylation of aminomethylolithium reagents

In general, this approach to the synthesis of  $\alpha$ -aminosilanes is only applicable to alkyl species with an “activated”  $\alpha$ -nitrogen atom or that with additional anionic stabilization. This is due to the fact that carbanionic centers are not noticeably stabilized by an  $\alpha$ -amino functionality; hence, the deprotonation of methylamines even with strong bases is normally unsuccessful. The “activated”  $\alpha$ -nitrogen atom could be part of an *N*-nitrosoamine or amidine group that facilitates lithiation, and a few examples of these reactions could be found in chapter 4.11 of COFGT (1995).

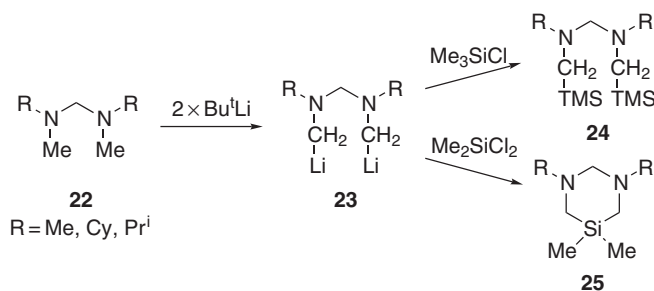
The use of directed metallation groups also facilitates the preparation of silanes via aminomethylolithium intermediates. *t*-BOC-piperidine is readily metallated by *s*-BuLi/TMEDA to afford, after quenching with TMSCl, the 2-silylpiperidine **19** (Equation (5)) <1989TL1197>. In an extension of this methodology, Barberis and Voyer published the first example of an enantioselective [1,2] silicon rearrangement to afford an *N-t*-BOC  $\alpha$ -aminosilane **20**. When *N*-silyl-protected *N-t*-BOC-benzylamine **21** was subjected to enantioselective deprotonation using the chiral complex *s*-BuLi/(–)-sparteine, the chiral benzyllithium intermediates underwent a [1,2] silicon shift to give good yields of product **20** with ee up to 72% (Scheme 5) <1998TL6807>.





Scheme 5

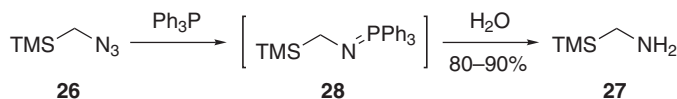
A more direct route to a lithiated methylamine has been investigated by Karsch and co-workers [\[1997CB1777\]](#). They have successfully dilithiated a series of *N,N'*-dimethyl-methylenediamine derivatives **22** with *t*-BuLi and reacted the doubly lithiated species **23** with a range of halosilanes to give the corresponding silylated products such as **24** and **25** (Scheme 6). It is interesting to note that the deprotonation takes place exclusively at the methyl groups rather than the methylene carbon atom. Furthermore, the monolithiated species was not detected spectroscopically, and in subsequent reactions no monosubstitution product was found. This can be explained by a kinetically favored second metallation step due to complexation of the lithium ion.



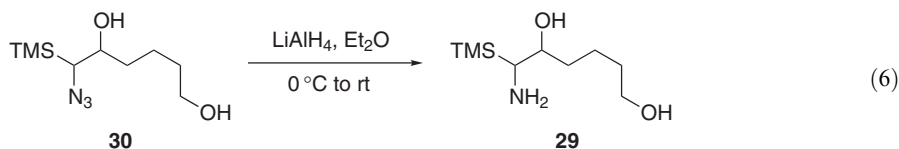
Scheme 6

#### (v) Reduction of silylmethyl azides

Many methods are known for azide reduction and they may be applied to silylmethyl azides. Chapter 4.11 of COFGT (1995) has reported two publications that made use of the Staudinger reaction to reduce silylmethyl azides **26** to the respective amine **27** via the iminophosphorane intermediate **28** (Scheme 7) [\[1986BCJ2537, 1988SC1975\]](#). Other groups have shown that LiAlH<sub>4</sub> is also an effective reducing agent for conversion of silylmethyl azides into the desired  $\alpha$ -aminosilanes [\[1996TL555, 2001OL3955\]](#). For example, Chakraborty and Laxman [\[2002TL2645\]](#) prepared the  $\alpha$ -trimethylsilylamine intermediate **29** from trimethylsilylmethylazide derivative **30** using LiAlH<sub>4</sub> reduction in their total synthesis of (+)-crocacin D (Equation (6)).

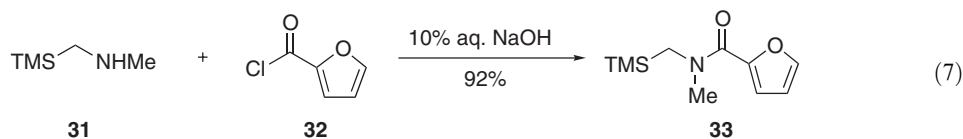


Scheme 7

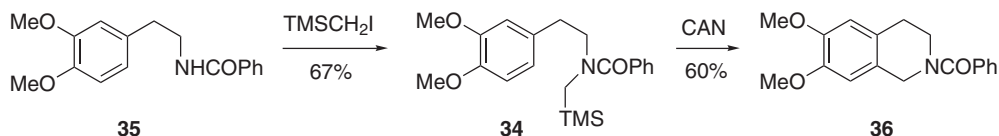


#### 4.11.1.1.2 *N*-Acyl- $\alpha$ -aminosilanes

Acylation of aminosilanes is the most straightforward and common method to access the title compounds. A cross section of examples covering a broad range of circumstances has been discussed in chapter 4.11 of COFGT (1995). A typical example is demonstrated by the following acylation reaction. *N*-Methyl trimethylsilylmethylamine **31** was acylated with 2-furylformyl chloride **32** to afford the  $\alpha$ -amidosilane **33** in excellent yield (Equation (7)) <1992JOC5419>.

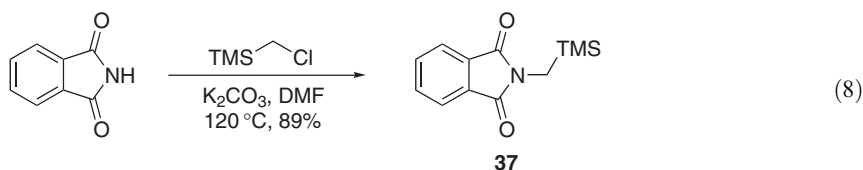


Primary and secondary amides are readily alkylated by silylmethyl halides. Mariano and co-workers have utilized this procedure to prepare some intermediates for oxidative Pictet–Spengler cyclizations. For example, 2-arylethyl- $\alpha$ -silylamide **34** was synthesized by alkylation of 2-arylethylamide **35** with TMSCH<sub>2</sub>I. The  $\alpha$ -silylamide **34** readily underwent CAN oxidation to afford the corresponding tetrahydroisoquinoline **36** (Scheme 8) <1998JOC860>. They have demonstrated an alternative Pictet–Spengler cyclization reaction that is mild and is applicable to systems that possess particularly acid-sensitive functionalities.

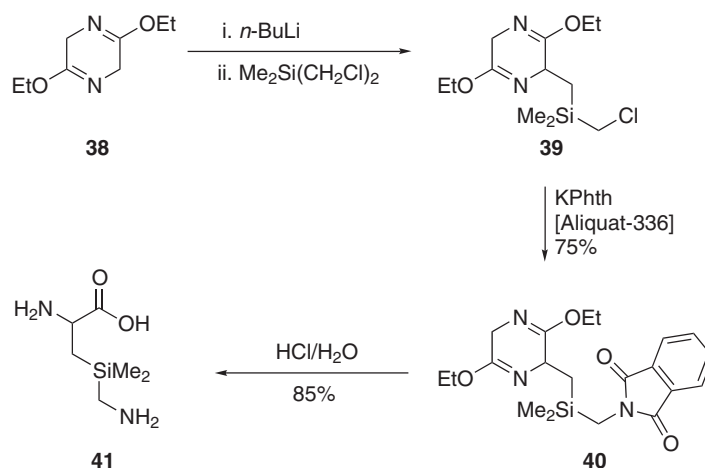


Scheme 8

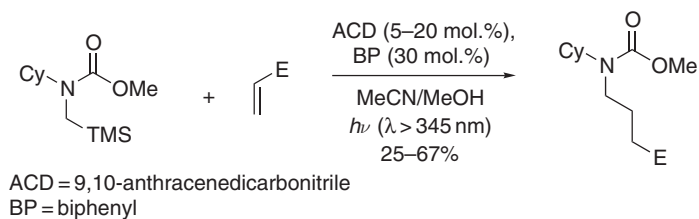
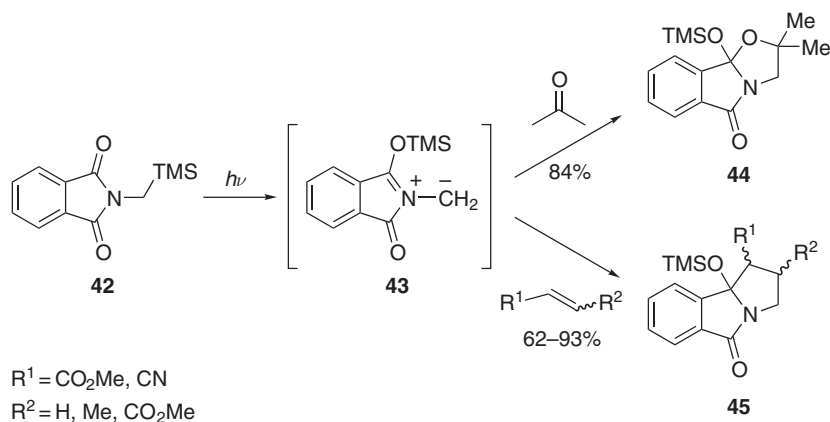
Sommer and Rockett <1951JA5130> first prepared *N*-silylmethylphthalimides from phthalimide **37** (Equation (8)). A more recent example was reported by Tacke and Handmann <2002OM2619> in pursuit of the synthesis of silicon-containing  $\alpha$ -amino acids. Using 3,6-diethoxy-2,5-dihydropyrazine **38** as a masked amino acid, they first prepared the chloromethylsilane derivative **39** and reacted that with potassium phthalimide to afford **40**. The amino acid and  $\alpha$ -aminosilane functionalities were unmasked by acid hydrolysis to give target compound **41** (Scheme 9). This chemistry was also applied asymmetrically based on Schöllkopf's methodology <1983T2085>.



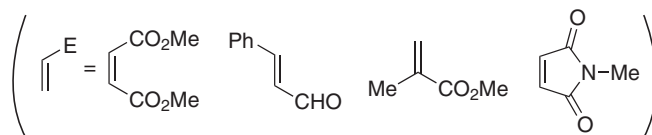
*N*-Silylmethylphthalimides (and *N*-silylmethylimides) **42** themselves are substrates for photochemical reaction, and this has been the subject of investigation by Mariano and co-workers. In three publications, they described the synthesis of a wide range of unusual polycyclic compounds starting from *N*-silylmethylimide or *N*-silylmethylphthalimide derivatives <1995JOC2353, 1995JA2698, 1996JOC3304>. In all cases the silyl analogs **42** were irradiated, and they underwent a process involving the excited state C to O migration of a TMS group to generate azomethine



ylide species **43**. This high-energy intermediate then reacted in a number of different ways to provide a range of *N*-heterocycles such as **44** and **45**. A selection of them is shown in [Scheme 10](#). A related reaction using  $\alpha$ -silylcarbamates as starting material was reported by Meggers and co-workers ([Equation \(9\)](#) <1995AG(E)2137>).

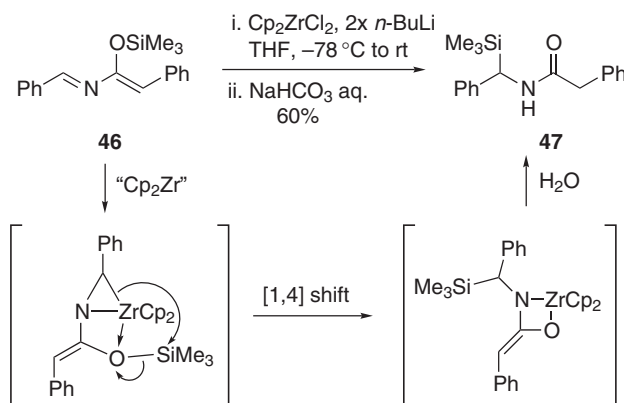


(9)



A novel method to generate *N*-acyl- $\alpha$ -aminosilane has been published by Szymoniak and co-workers. They used a zirconocene catalyst similar to that used by Honda and Mori (in their research into aza-Brook rearrangement of  $\alpha$ -silylallylamine) <1996JOC1196> to mediate an unusual retro-Brook rearrangement of 2-aza-1,3-dienes **46** to produce  $\alpha$ -silylated amides after hydrolysis <2000TL3053>. The azadiene **46** was treated with the Negishi zirconium reagent which, after

base hydrolysis, gave  $\alpha$ -silylamide **47** in 60% yield (Scheme 11). They theorized that the driving force of the retro-Brook rearrangements was the strongly oxophilic character of zirconium, and they proposed the mechanism shown in Scheme 11. It is interesting to find that no trace of the silylation at C-4 was detected, possibly because of the steric bulk of the C-5 phenyl group.

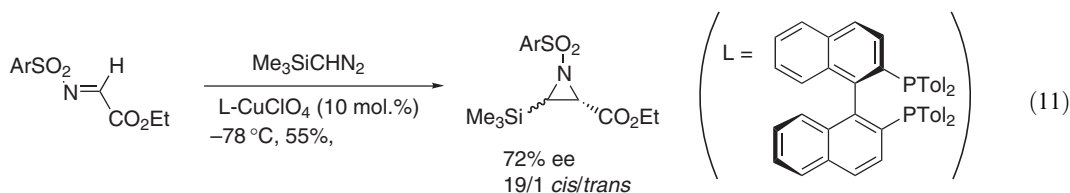
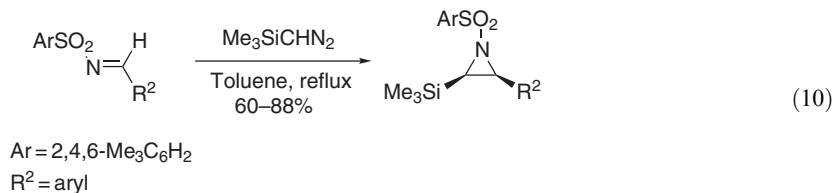


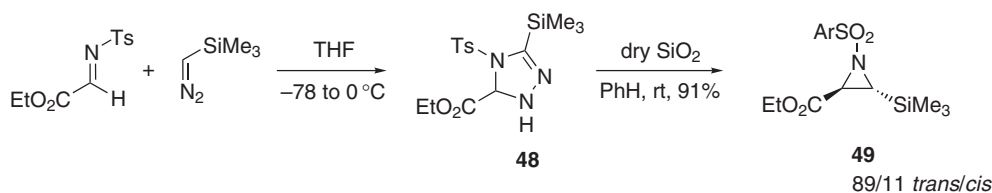
Scheme 11

#### 4.11.1.1.3 C-Silylaziridines

There exist a number of synthetic routes to silylaziridines, but it is most common to assemble the silylaziridines by the reaction of suitable silylalkenes with either nitrenes or azide. Direct intramolecular nucleophilic displacement of halides can also lead to the preparation of silylaziridines, but they are not as well investigated. A number of examples have been described in chapter 4.11 of COFGT (1995); therefore, this section will be focusing on some new syntheses of silylaziridines and their application as versatile synthetic intermediates.

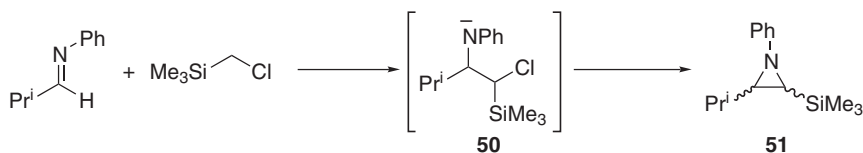
Since 1999 a few reports have been published highlighting the preparation of silylaziridines from *N*-sulfonylaldimines using trimethylsilyldiazomethane (TMSD). Both Jørgensen and co-workers <1999JCS(P1)2293>, and independently, Shioiri and co-workers <2000TL9455>, have demonstrated that TMSD is a versatile reagent for the aziridination of  $\alpha$ -imino esters and aryl-*N*-sulfonylaldimines (Equation (10)). Good yields of silylaziridines with high *cis* selectivity were afforded. Jørgensen and co-workers also carried out the reaction asymmetrically using a chiral Lewis acid complex and moderate enantioselectivity was obtained (Equation (11)). In 2002, Aggarwal and co-workers <2002JOC2335> expanded this methodology to a range of *N*-sulfonylimines derived from aromatic, heteroaromatic, aliphatic, and unsaturated aldehydes. In most cases average-to-good yields of products were obtained and high diastereoselectivity for *cis* product was also observed. In contrast, they found that an  $\alpha$ -imino -ester gave predominantly the *trans* product in high yield and they proposed an alternative mechanism involving intermediate **48**, which was broken down to the desired silylaziridine **49** upon treatment with silica gel (Scheme 12).



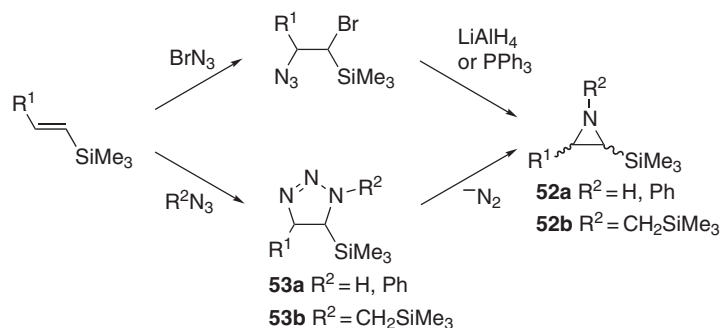


Scheme 12

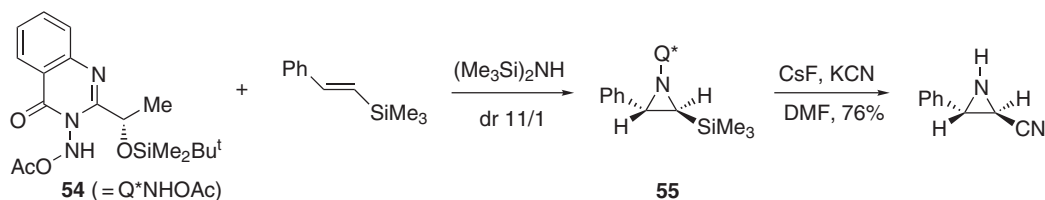
Taylor and co-workers also reported a related reaction, but instead of TMSD, they used the carbanion **50** derived from chloromethyltrimethylsilane and *s*-BuLi to carry out a Darzens-like reaction to afford the silylaziridine **51** (Scheme 13) <2000JCS(P1)1173>. In the same paper they explored other preparations of silylaziridines from vinyl silanes. They found that the addition of bromoazide to vinyl silanes followed by the reduction of the azide with a reducing agent (such as  $\text{LiAlH}_4$  or  $\text{PPh}_3$ ) gave average-to-good yields of silylaziridines **52** via intermediate **53** (Scheme 14). This could also be achieved by using an organoazide reagent instead of bromoazide. Atkinson and co-workers have also investigated the use of vinyl silanes as precursors to silylaziridines. They devised a diastereoselective aziridination reaction using enantiopure 3-acetoxyaminoquinazolinone derivative **54** to obtain an 11:1 ratio of diastereoisomers of aziridines **55** (Scheme 15) <1996TL5179>.



Scheme 13



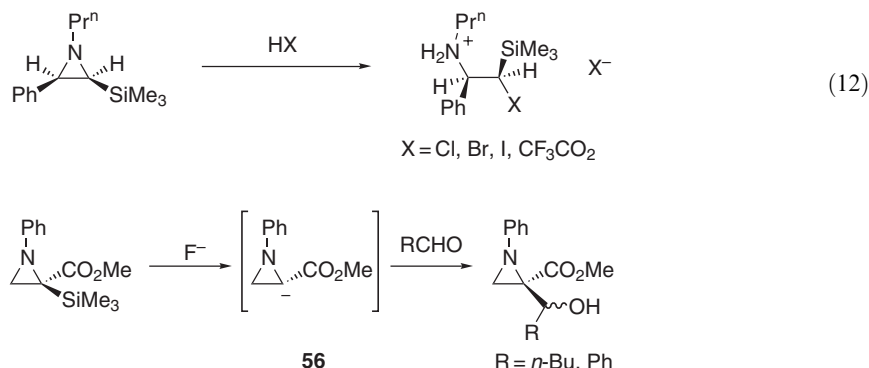
Scheme 14



Scheme 15

Silylaziridines can undergo a variety of reactions and it is beyond the scope of this review to go into details. For example, they readily ring open when treated with nucleophiles under strongly acid conditions (Equation (12)) <2000JCS(P1)439>. The same publication also showed that silylaziridines are good intermediates for the synthesis of other aziridine derivatives. Silylaziridines undergo desilylation when treated with fluoride ion and the aziridine anion **56** can be trapped

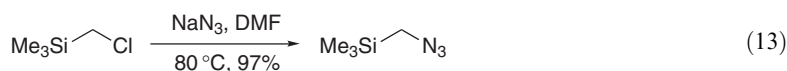
with electrophiles such as aldehydes (Scheme 16) <2000JCS(P1)439>. Alternatively if the nitrogen atom of the silylaziridine bears a potential leaving group **55**, elimination of the silyl group to give the azirine intermediate followed by the addition of the cyanide ion is observed in the presence of CsF and KCN (Scheme 15) <1997JCS(P1)897>.



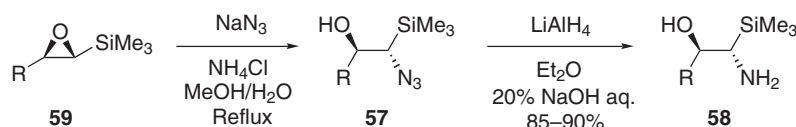
Scheme 16

#### 4.11.1.1.4 Trimethylsilylmethyl azide and $\alpha$ -silyl azides

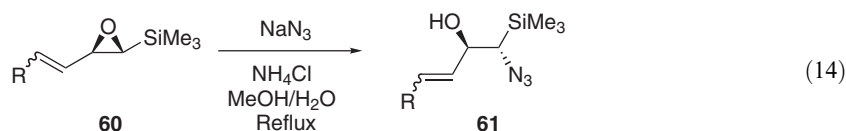
Trimethylsilylmethyl azide (TMS-MA, b.p. 58–61°C/80 mmHg) is a relatively stable alternative synthon for reactions, which formally require the shock-sensitive methyl azide. TMS-MA is reportedly stable in refluxing toluene and is stable at refrigerator temperatures for at least six months. Both Tsuge and co-workers <1983CL1131> and Nishiyama and Tanaka <1983CC1322> independently reported its synthesis (Equation (13)). Other applications of TMS-MA include its use in the preparation of trimethylsilylmethylisocyanate and isothiocyanate (see Sections 4.11.1.1.5) and as a 1,3-dipolarophile to generate triazolines **52b**, which readily give silylaziridines **53b** (Scheme 14) <1984H1955>.



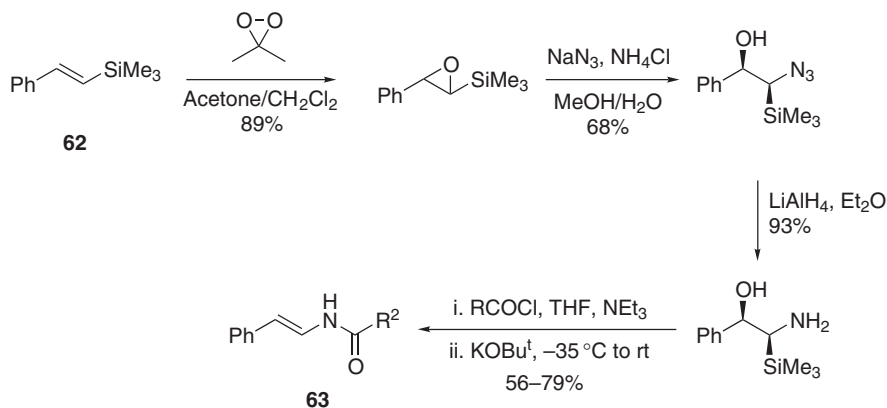
The most common synthesis of  $\alpha$ -silyl azides is by nucleophilic addition to silyloxiranes to afford  $\beta$ -hydroxy- $\alpha$ -silyl azides <1986CL1193>. The silyl group exerts a powerful directing effect such that the nucleophilic attack occurs exclusively at the carbon bearing the silicon, resulting in regioselective ring opening of the silyloxiranes. Chakraborty and Reddy <1990TL1335, 1991TL679> demonstrated that the normal preference for C-3 ring opening of 2,3-epoxy alcohols by nucleophiles is reversed when a silyl group is attached to C-2. Bassindale and co-workers made use of this chemistry to prepare a selection of alkyl  $\beta$ -hydroxy- $\alpha$ -silyl azides **57** with good-to-excellent yields (Scheme 17) <1996TL(37)555>. They were then reduced to the corresponding silylamino alcohols with no loss of ee compared to that of the initial  $\alpha$ -silyloxiranes **59**. In their related study of the regioselective ring opening of  $\alpha,\beta$ -epoxy- $\gamma,\delta$ -vinyl silanes, Malacria and co-workers <2002SL553> also found azide ion attack solely on the carbon bearing silicon giving a single regioisomer and diastereomer **61** (Equation (14)).



Scheme 17



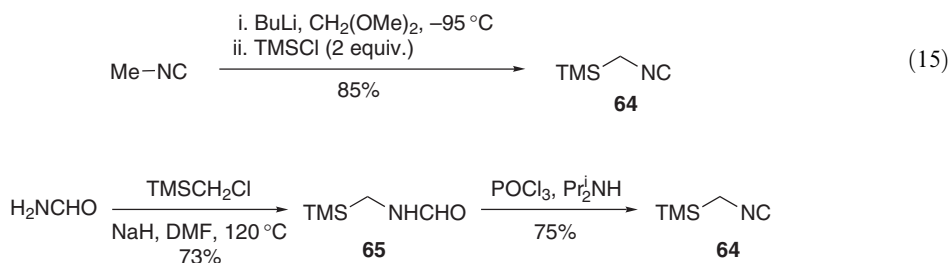
Furstner and co-workers reported a useful synthesis of enamides from vinyl silanes via the corresponding  $\alpha$ -silyl azides <2001OL3955>. The conversion of (*E*)-alkenylsilanes **62** into (*E*)-enamides **63** is outlined in Scheme 18. The regio- and stereospecific epoxysilane ring opening with azide ion was followed by reduction and Peterson elimination. All products were obtained as a single diastereomer, and the configuration of the starting material was transferred to the final product with high integrity. This sequence of reactions to afford enamide from vinyl silane has also been reported by Chakraborty and Laxman <2002TL2645> in their total synthesis of (+)-crocacin D.



Scheme 18

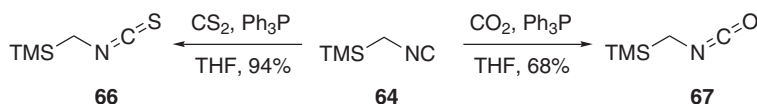
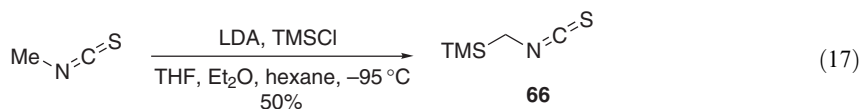
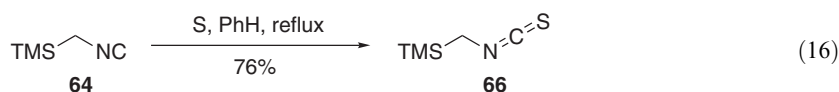
#### 4.11.1.1.5 Trimethylsilylmethylisocyanide, -isocyanate, and -isothiocyanate

The title compounds have received considerable attention as small molecule synthons for a range of imine derivatives and heterocycles. Numerous syntheses of trimethylsilylmethylisocyanide **64** have been reported. Smith and Livinghouse published a practical account of its synthesis by lithiation of methylisocyanide followed by silylation with TMSCl (Equation (15)) <1984SC639>. An alternative preparation involved the silylmethylation of formamide via its sodium salt and gave the formamido silane **65**, which was dehydrated under Ugi conditions to liberate trimethylsilylmethylisocyanide **64** (Scheme 19) <1986SC865>. The advantage of the latter method is that it avoids the use of the toxic, volatile, and odorous MeNC.



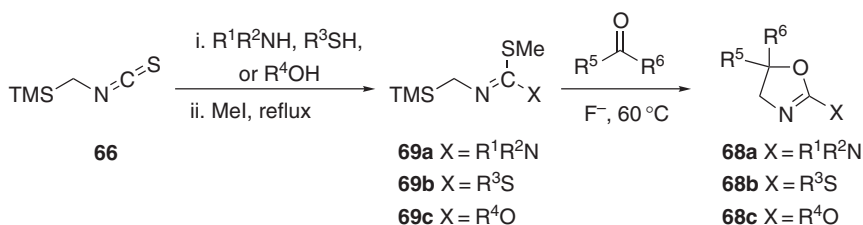
Scheme 19

If trimethylsilylmethylisocyanide **64** is heated with elemental sulfur in an inert solvent, the trimethylsilylmethylisothiocyanate **66** is produced (Equation (16)) <1982BCJ1163>. A more accessible route to the isothiocyanate **66** involves direct lithiation of methylisothiocyanate and trapping of the anion with TMSCl (Equation (17)) <1997S423>. This method could be applied to the synthesis of bis- and tris(trimethylsilyl)methylisothiocyanates by increasing the equivalents of LDA and TMSCl used. An improved synthesis of isothiocyanate **66**, which uses CS<sub>2</sub> as the sulfur source is reported to give reproducibly better yields and is readily adapted to afford trimethylsilylmethylisocyanate **67** by using CO<sub>2</sub> (Scheme 20) <1984JOC2688, 1985H2489>.



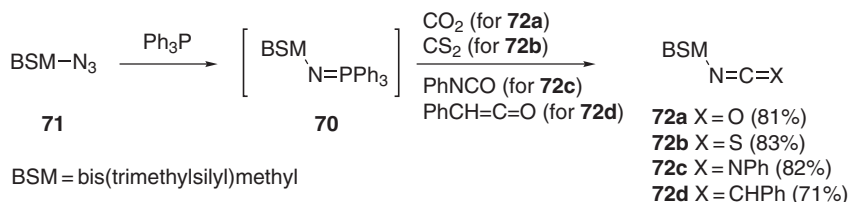
Scheme 20

Trimethylsilylmethylisothiocyanates are versatile intermediates for building small heterocycles. Nishiyama and co-workers <1997H1405, 1997H1913> published a three-step synthesis of oxazolines **68a–68c** starting from silylthiocyanate **66**. The silylthiocyanate **66** serves as a precursor for the generation of an aminonitrile ylide functional group equivalents (such as isothiureas **69a**, dithiocarbonates **69b**, or iminothiocarbonates **69c**). They are prepared by the addition of amines, thiols, or alcohols, respectively, to a silylthiocyanate. All the above aminonitrile ylide equivalents readily undergo 1,3-dipolar cycloadditions with aldehydes to give the corresponding oxazolines **68** (Scheme 21) <1997H1405, 1997H1913>. A similar reaction was reported by Tsuge and co-workers <2001H249> where the same aminonitrile ylide equivalents were treated with alkenes as the 1,3-dipolarophiles to give pyrrolines.



Scheme 21

The synthesis and reactivity of other *N*-silylmethylheterocumulenes were published by Seconi and co-workers <1995JOC6032>. They prepared the intermediate **70** from bis(trimethylsilyl)methyl azide **71** and Ph<sub>3</sub>P. This intermediate was transformed into isocyanate **72a**, isothiocyanate **72b**, carbodiimides **72c**, or ketene imines **72d** by the addition of a range of reagents (Scheme 22). The reactivity of these *N*-silylmethylheterocumulenes and their use in synthesis were also investigated in the paper.



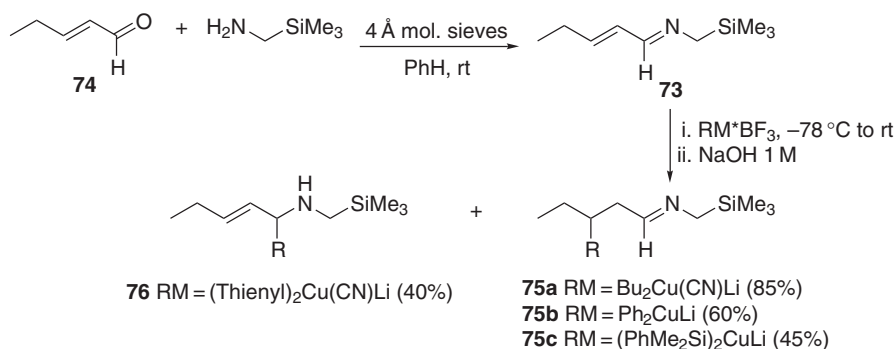
Scheme 22

#### 4.11.1.1.6 $\alpha$ -Iminosilanes and related compounds

Silylmethylimines are readily prepared from  $\alpha$ -aminosilanes and carbonyl compounds, particularly trimethylsilylmethylamine. Bonini and co-workers <1997SL1321> investigated the regioselective addition of organocuprates to 1-aza-1,3-dienes **73**, which were synthesized by the

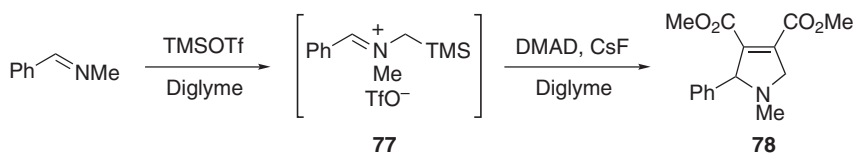


condensation of  $\alpha,\beta$ -unsaturated aldehyde **74** with trimethylsilylmethylamine or bis(trimethylsilyl)methylamine. The treatment of the 1-aza-1,3-dienes **73** with a range of organocuprates gave satisfactory-to-good yields of highly selective 1,4-addition products (**75a–75c**) apart from one exception. It was surprising to find that heteroaromatic ligands gave predominantly 1,2-products **76** over 1,4-addition products (Scheme 23).

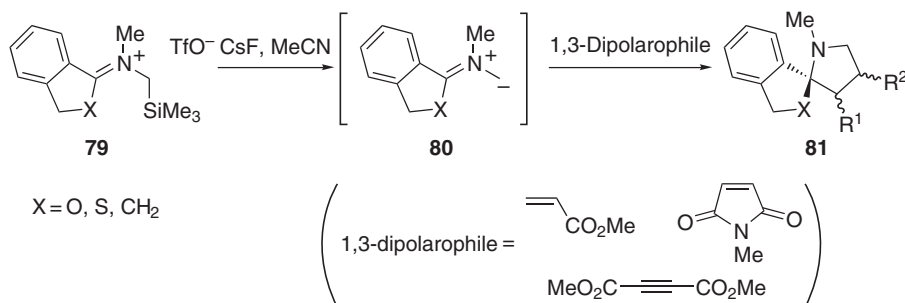


Scheme 23

Vedejs and Martinez first disclosed the potential of *N*-(trimethylsilylmethyl)iminium salts such as **77** for the generation of azomethine ylides and subsequently a range of nitrogen heterocycles (Scheme 24) <1979JA6452, 1980JA7993>. Since then, the desilylation of  $\alpha$ -iminosilanes has become the most frequently used means of producing azomethine ylides, prompting considerable interest in efficient routes to the iminosilane precursors. The communication from Fishwick and Foster clearly demonstrated this methodology as a mean to synthesize a number of spiro-fused pyrrolidines <1996TL5163>. The  $\alpha$ -silyliminium salts **79** are prepared by standard synthetic methods, and the introduction of fluoride ions leads to the generation of 1,3 dipole intermediate **80**. In the presence of alkenes, alkynes, or other dipolarophiles, dipoles **80** undergo highly regioselective cycloaddition to afford novel spirocycles **81** in good-to-excellent yields (Scheme 25). A similar method has been used by Pearson and Mi <1997TL5441> to synthesize a collection of indolizidines and pyrrolizidines.



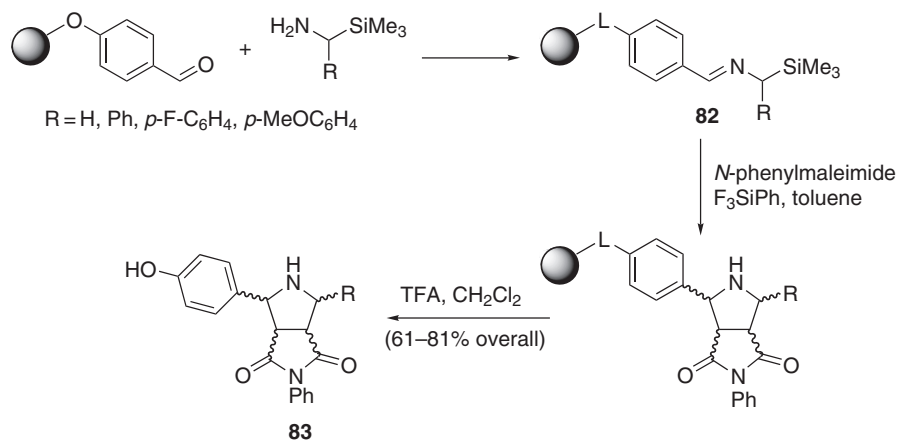
Scheme 24



Scheme 25

Recently, Komatsu and co-workers <2003T197> applied this reaction to solid-phase synthesis of pyrrolidines and pyrroles. Polymer-supported azomethine ylides were generated from the corresponding  $\alpha$ -silylimines **82** either by treatment with a trifluorosilane, or by thermal

1,2-silatropy (Scheme 26). The resulting azomethine ylides were then reacted with dipolarophiles and good yields of cyclization products **83** were afforded after cleavage from the resin. The stereoselectivity of the reaction was dependent on the method used to generate the azomethine ylide and substrate dependent, but when the corresponding reaction was carried out in solution phase, higher selectivity was observed.

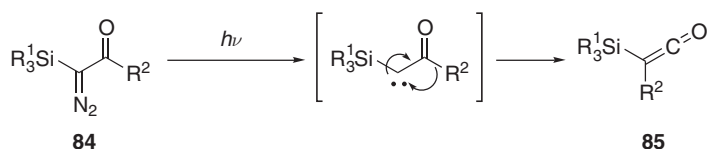


Scheme 26

Other related compounds such as  $\alpha$ -silylmethylamidines and thioimidates have been discussed in detail in COFGT (1995) and will not be repeated here.

#### 4.11.1.1.7 $\alpha$ -Diazosilanes

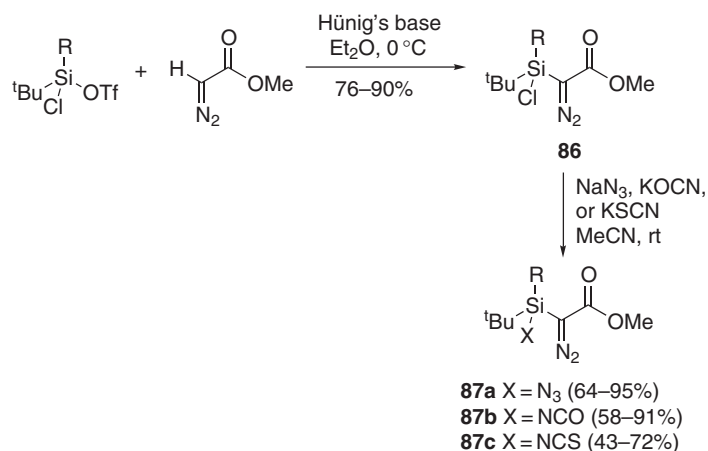
Silyl-substituted diazoalkanes and diazocarbonyl compounds **84** are important precursors for silylcarbenes or -carbenoids. The most widely used application of these compounds is their ability to undergo photochemical Wolff rearrangement to give the corresponding silylketenes **85** (Scheme 27). Silylketenes are stable to typical [2+2]-cycloaddition reactions and readily isolable compounds unlike their nonsilylated counterparts, which makes them versatile synthetic intermediates.



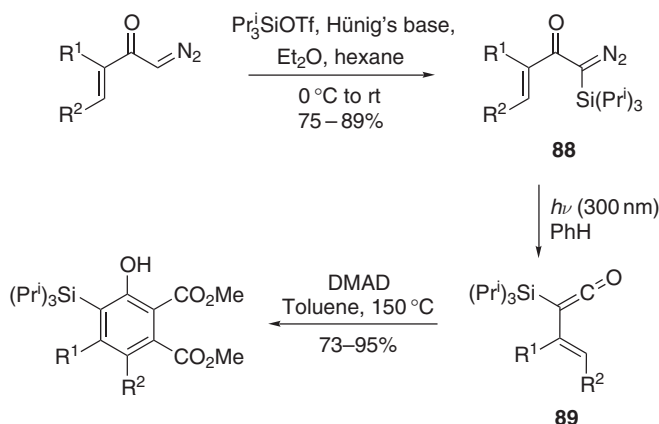
Scheme 27

In 1985, Maas and Brückmann <1985JOC2801> reported the first synthesis of  $\alpha$ -silyldiazocarbonyl compounds from diazocarbonyl- and trialkylsilyl triflate in the presence of Hünig's base. This method is applicable to a range of diazocarbonyl derivatives <1999CC1199>, and it not only tolerates alkyl or aryl groups on the silicon, but even a chloride. Maas and Bender prepared  $\alpha$ -(chlorosilyl) diazoacetates **86** and showed that they can be converted into azidosilyl- **87a**, isocyanatosilyl- **87b**, or isothiocyanatosilyl- **87c** substituted diazoacetates (Scheme 28) <1999SI1175>.

Other silyldiazocarbonyl derivatives have been prepared to give silylketenes with unique properties. A number of silyl vinylketenes had been synthesized from  $\alpha'$ -silyl- $\alpha'$ -diazo- $\alpha,\beta$ -unsaturated ketones **88** by Danheiser and co-workers <1998JOC8380>. They found that the silyl vinylketenes **89** behave as the diene components in Diels–Alder reactions with electron-deficient alkenes and alkynes rather than undergo [2+2]-cycloaddition reactions like other vinylketenes (Scheme 29). In a separate paper, Danheiser and co-workers <2002OL2465>

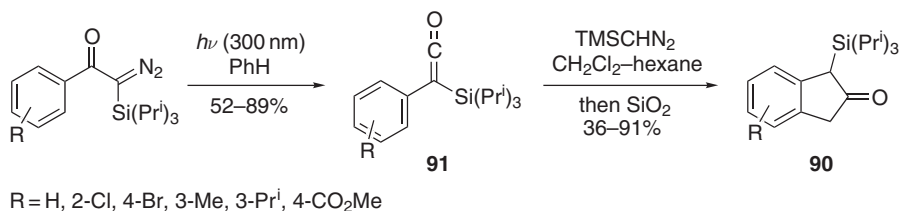


Scheme 28



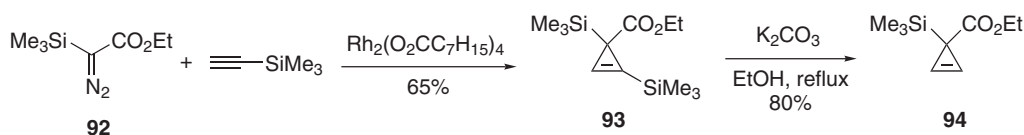
Scheme 29

reported a [4 + 1]-annulation process between silyl arylketenes and TMSD to afford 2-indanone derivatives **90** (Scheme 30). The silyl arylketenes **91** were synthesized using the same methodology developed by Maas and Brückmann.



Scheme 30

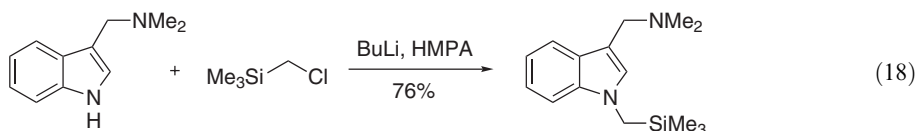
In 1999, Arrowood and Kass <1999T6739> published a different synthetic use for silyldiazo-carbonyl derivatives. They treated ethyl trimethylsilyldiazoacetate **92** with trimethylsilylacetylene either under irradiation or in the presence of rhodium(II) octanoate dimer catalyst to give cyclopropane **93**. This was followed by selective desilylation of the vinylsilyl group to afford the target 3-carbomethoxy-3-(trimethylsilyl)cyclopropane **94** in an overall yield of 48% (Scheme 31). Cyclopropane **94** was shown to be a stable and interesting compound that could be subjected to a range of further functional group interconversions to afford other cyclopropane derivatives.



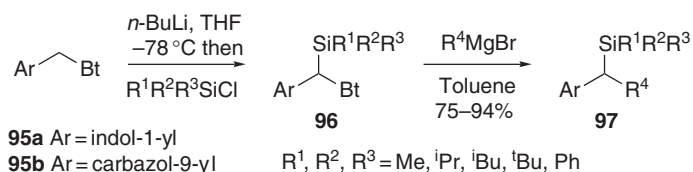
Scheme 31

#### 4.11.1.1.8 *N*-(Silylmethyl) heterocycles

Vedejs' methodology for the generation of azomethine ylides from aminosilanes is readily extended to allow access to ylides formed from  $\alpha$ -silyl heterocycles (Section 4.11.1.1.6). Alternatively, silylmethylation of a wide range of heterocycles under basic conditions is an efficient and popular process. The five-membered azoles and related heterocycles are readily alkylated with trimethylsilylmethyl chloride under a variety of conditions (Equation (18)) and the details can be found in chapter 4.11 of COFGT (1995).

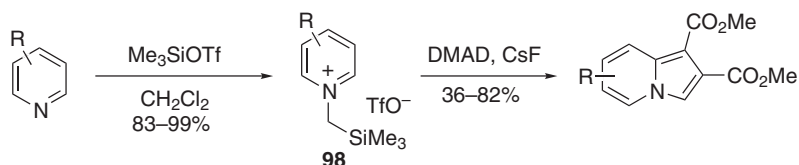


Although *N*-alkylation is usually dominant, varying amounts of *C*-alkylation can also be observed depending on the substrates and reaction conditions. Katritzky and co-workers have been investigating the use of benzotriazole (Bt) as a synthetic auxiliary, and they found that it could be applied to a novel synthesis of highly branched and sterically hindered *N*-silylalkylated carbazoles and indoles <1995OM734>. The *N*-(benzotriazole-1-ylmethyl)carbazole **95a** and -indole **95b** derivatives are readily synthesized from alkylation of carbazole or indole with BtCH<sub>2</sub>Cl. Deprotonation of **95** followed by silylation with a selection of alkyl- and/or arylsilyl chlorides afforded the corresponding intermediates **96**. When they were treated with an excess of Grignard reagents in toluene under reflux good-to-excellent yields of desired *N*-silylmethylcarbazole and indole derivatives **97** were achieved (Scheme 32).



Scheme 32

The silylmethylation of pyridine and substituted pyridines is also possible by alkylation with TMS—CH<sub>2</sub>OTf, affording the pyridinium salts **98** (Scheme 33). The triflate salts can be desilylated with fluoride ions generating an azomethine ylide species which in turn can be intercepted by DMAD and other dipolarophiles <1984CL279, 1984H701>.

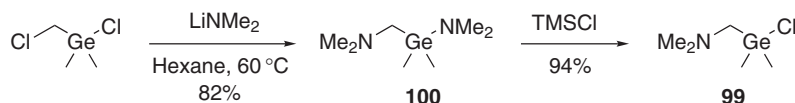


Scheme 33

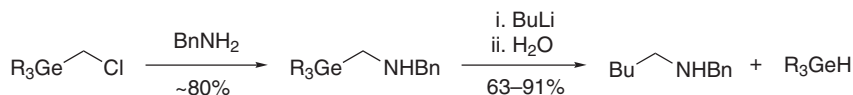
#### 4.11.1.2 Nitrogen and Germanium Functions

Synthetic routes to  $\alpha$ -aminogermanes closely parallel those already described for the corresponding silanes. This parallel stretches across almost all of the established synthetic organogermanium chemistry and is discussed in depth in a useful review of that subject <1982COMC-I(2)365>.

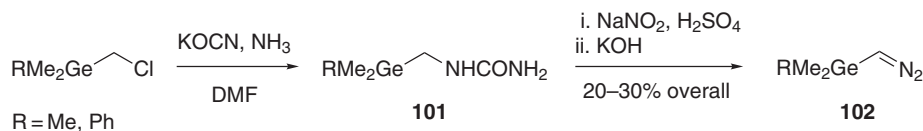
Alkylation of amines by germylmethyl halides is by far the most frequently encountered preparative route. An early example is the synthesis of the germylmethylamine **99** (Scheme 34). Interestingly, the chlorogermene **99**, which cannot be obtained by reaction with a single equivalent of lithium amide, is accessible by the treatment of **100** with TMSCl <1977JOM(132)77>. Terunuma and co-workers have prepared a series of germylmethylamines (Scheme 35) and demonstrated their base-catalyzed fragmentation to trialkylgermanes. This is contrary to the reactivity pattern of silylmethylamines, which undergo a Brook rearrangement under the same conditions <1991CL97>. The reaction of germylmethyl halides with potassium cyanate and ammonia affords  $\alpha$ -germylureas **101**, which have been used to prepare germyldiazomethanes **102** (Scheme 36). The transiently produced isocyanates are not isolated <1985TL5547, 1986CPB3273>.



Scheme 34

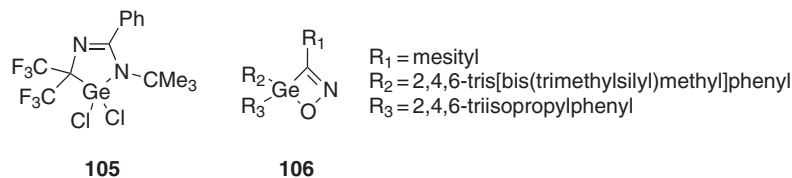
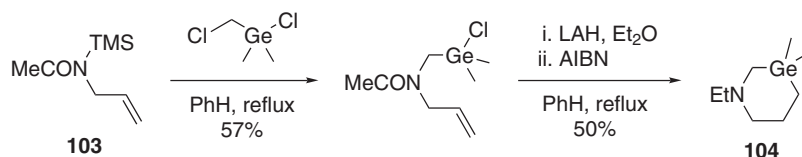


Scheme 35



Scheme 36

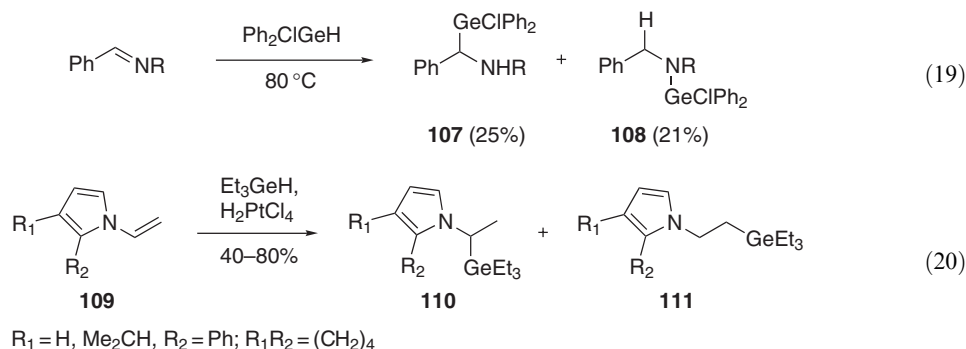
Silylated amides **103** will also react readily with chloromethylgermanes, typically under neutral conditions, in a nonpolar solvent (Scheme 37). This chemistry and a subsequent radical-mediated, intramolecular hydrogermylation have been used to prepare the azagermine **104** <1988JOM(346)1>. A benzo-fused version of **104** is accessible by similar chemistry <1988JOM(339)259>. Other germanium-containing heterocycles such as **105** and **106** have also been synthesized by cycloaddition reactions <1995ZN(B)289, 1997CC1553>.



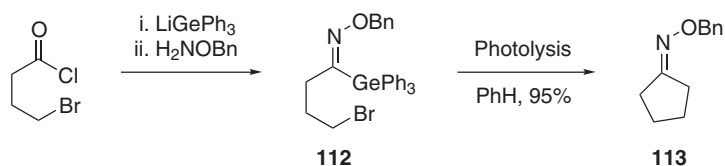
Scheme 37

Germanium hydrides will add to aldimines in a nonregioselective manner to generate a mixture of germylmethylamines **107** and aminogermanes **108** (Equation (19)). The selectivity is reagent

and substrate sensitive. The authors ascribe the product distribution to the operation of two competing (radical and ionic) mechanisms although the ionic mechanism, favoring formation of a C—Ge bond, generally predominates <1979JOM(168)43>. A similar addition to nitrones and related compounds has also been demonstrated <1972JOM(34)C18>. Germanium hydrides will also undergo hydrogermylation with 2- and 2,3-substituted 1-vinylpyrroles **109** including 1-vinyl-4,5,6,7-tetrahydro-indole in the presence of  $\text{H}_2\text{PtCl}_6$  to give a mixture of  $\alpha$ - **110** and/or  $\beta$ - **111** germano substituted adducts (Equation (20)) <1996ZOB(66)86>.

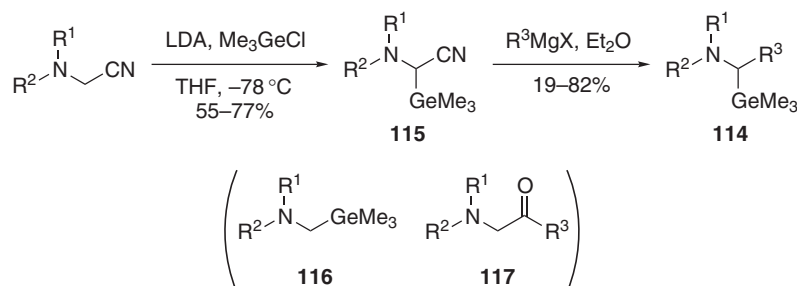


Acylgermane hydrazones and oxime ethers undergo radical cyclizations to give good yields of cyclic hydrazones and oximes <1998JOC4711>. The acylgermane derivatives **112** are accessible via a copper-mediated coupling of acid chlorides and  $\text{LiGePh}_3$  followed by condensation with *N,N*-dimethylhydrazine or *o*-benzylhydroxylamine (Scheme 38). Thus, under photolysis,  $\omega$ -halo-, phenylseleno-, and vinylacylgermane hydrazones and oxime ethers cyclize to their respective cyclic adducts **113**.

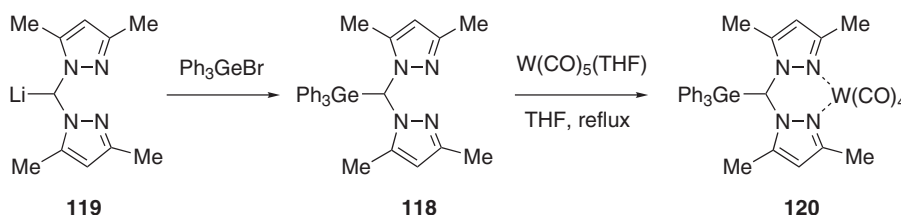


Scheme 38

Lastly, and perhaps the most usefully, Sato and co-workers have established a flexible lithiation-germylation reaction of aminoacetonitriles which uses readily available reagents to prepare a host of  $\alpha$ -aminogermanes **114** (Scheme 39). The intermediate germynitriles **115** can be isolated and purified. Both alkyl and aryl substituents are tolerated although the yields of the Grignard addition vary dramatically with substitution. The Grignard reaction also generates variable amounts of the by-products **116** and **117** <1991SI169>. Analogous chemistry is reported in the preparation of an organogermynylbis(pyrazol-1-yl)methane ligand **118** from bis(pyrazol-1-yl)methylolithium **119** with  $\text{Ph}_3\text{GeBr}$  (Scheme 40). Treatment of this ligand **118** with  $\text{W(CO)}_5(\text{THF})$  in refluxing THF results in the heterobimetallic complex  $\text{Ph}_3\text{GeCHPz}_2\text{W(CO)}_4$  **120** as the major product <2002JOM(658)198>.



Scheme 39



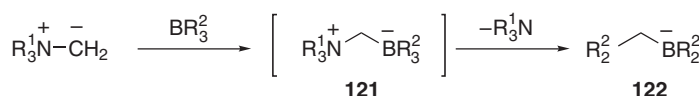
Scheme 40

#### 4.11.1.3 Nitrogen and Boron Functions

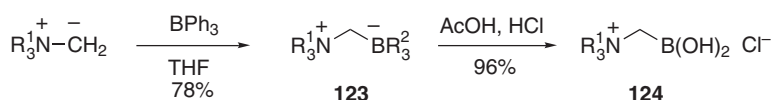
The research into the chemistry of aminomethylboron compounds has traditionally been limited, primarily due to the reactivity of  $\alpha$ -aminoboranes, which are frequently air or moisture sensitive and readily undergo  $\alpha$ -transfer rearrangements. However, a growing awareness of the value in medicinal chemistry of  $\alpha$ -aminoboronic acids as serine protease inhibitors has prompted a steadily increasing output of synthetic work in this area since the first disclosure of significant biological relevance in 1977.

##### 4.11.1.3.1 $\alpha$ -Aminoboranes and borohydrides

$\alpha$ -Aminoboranes have generally been synthesized by reactions between a nitrogen ylide and a trialkyl- or triarylborane. Muster and Stevens <1967TL995> first described the reaction of an unstabilized *N*-ylide with boranes (Scheme 41). The presumed initial zwitterionic borohydride intermediate **121** rapidly underwent  $\alpha$ -transfer reactions to a new borane **122** with loss of the amine substituent. The overall process amounted to methylene insertion by the ylide. Bickelhaupt and Barnick <1968RTC188> subsequently isolated the relatively stable adduct **123** (Scheme 42) and demonstrated its conversion into the boronic acid **124** as part of a chemical proof of the structure of intermediate **123**.

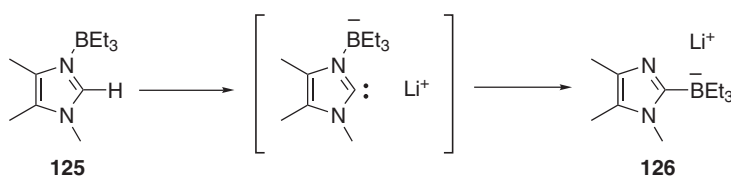


Scheme 41

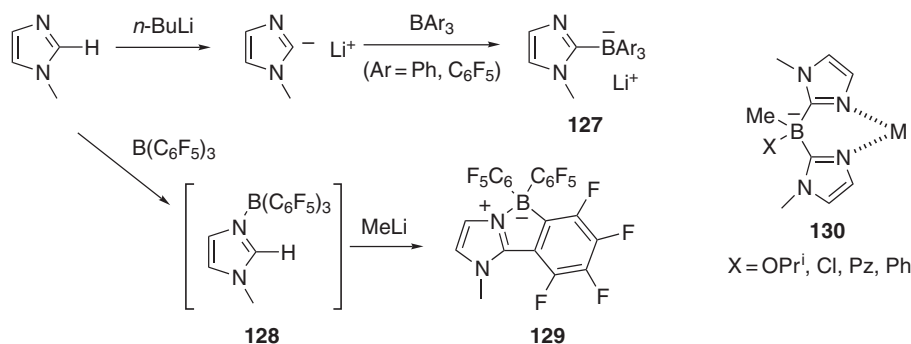


Scheme 42

Stable imidazol-2-ylidene carbenes are related to nitrogen ylides and they too react with a trialkyl- or triarylborane to give a zwitterionic adduct. Seibert and co-workers <1998EJI843, 1999EJI789> have reported the synthesis and rearrangement of **125** when treated with *n*-BuLi to give the lithium salt **126** (Scheme 43). Vagedes and co-workers reported an alternative synthesis to the related arylborane derivatives **127** (Scheme 44) since they demonstrated that when the arylborane derivative **128** was deprotonated with MeLi, instead of rearrangement as reported by Seibert, aryl substitution took place to give **129** <2002EJI2015>. Both compounds **127** and **129** were characterized by X-ray crystallography. This methodology has been used to prepare a new class of bisimidazole-borate ligands **130** <2000JCS(D)1255>.

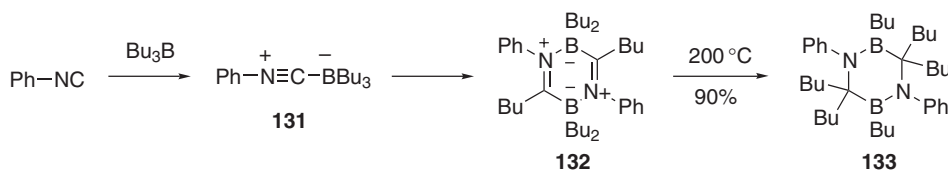


Scheme 43

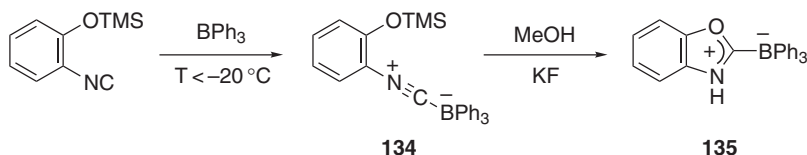


Scheme 44

Trialkylboranes will also react with isocyanides to generate dipolar adducts which are prone to thermal dimerization processes. Phenylisocyanide and tributylborane react together to generate a zwitterion **131**, which quickly dimerizes to the isolated diboradihydropyrazine **132** (Scheme 45) <1965LA(687)1, 1972LA(755)67>. Thermolysis of the pyrazine **132** prompts a second B–C migration, giving the diborapiperazine **133**. Tamm and co-workers isolated the thermally unstable monomeric iminoborane adduct **134** at low temperature (–20 °C). It is converted into the ylidene **135** when treated with a catalytic amount of KF in methanol (Scheme 46). The X-ray structure of **134** and **135** was reported. Dimerization of **134** was also observed upon heating <1996OM1251>. The benzoxazol-2-ylidene **135** was also synthesized via a different route by Lambert and co-workers <1996OM452> in the same year.



Scheme 45

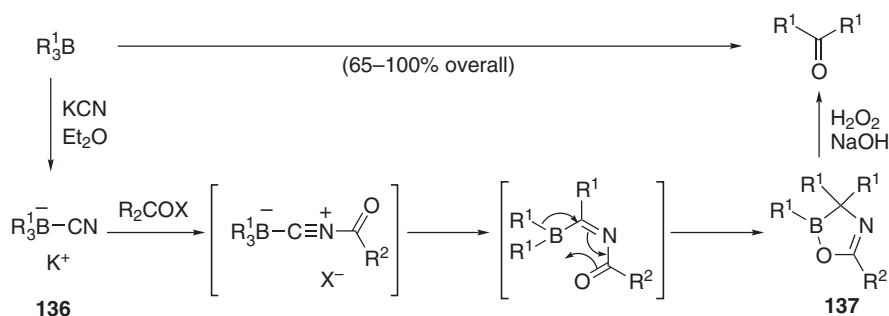


Scheme 46

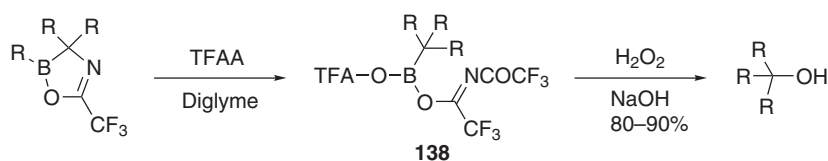
Despite the handling difficulties experienced with many borane derivatives, the ease with which alkyl migration from boron to an adjacent carbon can occur has led to some useful synthetic methodology. Pelter and co-workers have extensively characterized the utility of cyanoborate salts as precursors for  $\alpha$ -migration chemistry. The salts **136** are readily prepared from trialkylboranes and KCN in organic solvents and react with any of a range of acylating agents (usually AcCl, PhCOCl, or trifluoroacetic anhydride (TFAA)) to generate the oxazaborolines **137** in which two alkyl groups have transferred from boron to carbon (Scheme 47). Oxidative cleavage of the heterocycles **137** completes an overall synthesis of symmetrical ketones in excellent yield <1975JCS(P1)129>. A feature of the alkyl migration is the general insensitivity to steric congestion in the transition state, such that secondary alkyl groups also migrate readily. Use of TFAA as the acylating reagent in diglyme can induce the third and final B-alkyl substituent to migrate, giving the presumed intermediate boronate derivative **138** (Scheme 48). Oxidative cleavage liberates tertiary carbinols, again in good yield, usually associated with small amounts of ketone <1975JCS(P1)138>.

The chemistry of oxazaboroline such as **139** has also been investigated by Denniel and co-workers <1995TL6875>. They reported the synthesis of oxazaborolines **139** and **140** by hydroboration of acetamidoacrylate, deprotonation and *N*-acylation or *N*-alkylation of the resulting complex (Scheme 49). These boron complexes could in turn be converted to *N*- or C-substituted alaninate derivatives. When **140** was treated with a strong acid at room temperature, methylalaninate **141** was afforded in almost



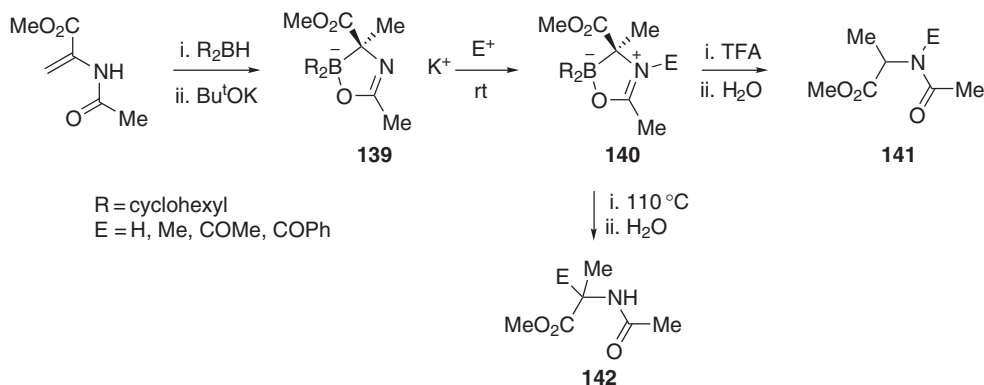


Scheme 47



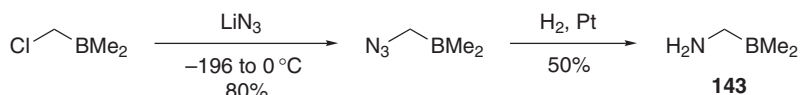
Scheme 48

quantitative yields, while refluxing in toluene with one molar equivalent of pyridine, the betaine **140** rearranges and **142** was generated after hydrolysis (Scheme 49). It is interesting to find that, unlike most oxydialkylorganoborates, no B—O migration of the cyclohexyl group was observed <1975JCS(P1)129>.

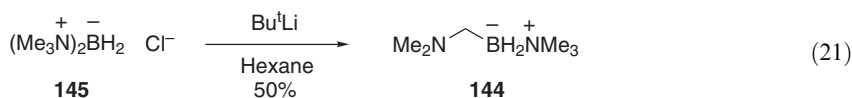


Scheme 49

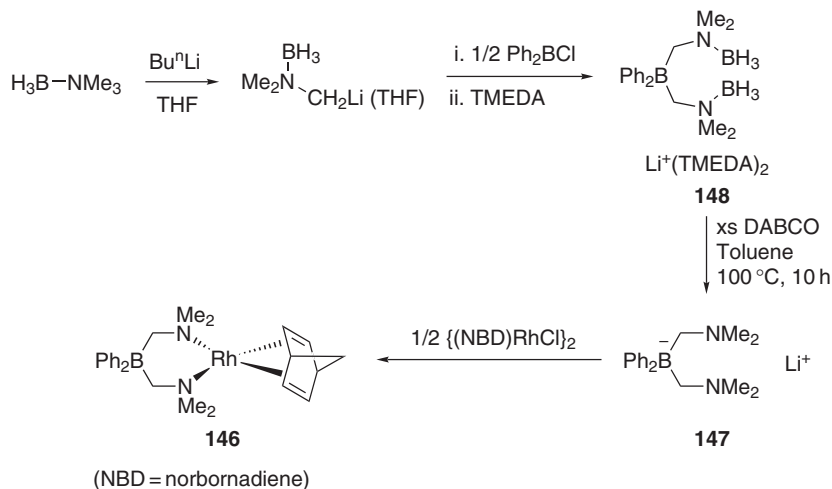
The chemistry of low-molecular weight  $\alpha$ -aminoboranes is made more challenging by their extreme volatility. Nevertheless, some synthetic details are available. Chloromethyldimethylborane undergoes straightforward  $S_N2$  displacement with nucleophiles including lithium azide, which generates the gaseous azidomethyl species (Scheme 50). Hydrogenation of the azide over platinum gave aminomethyldimethylborane **143**, which is essentially monomeric <1965JA488>. Miller and co-workers <1983OM1529> have synthesized the isomeric  $\alpha$ -aminoborane **144** as its trimethylamine complex by the reaction of the cationic borane **145** with *t*-butyllithium (Equation (21)). It is characterized as a nonvolatile liquid that behaves as a nucleophile and strong base <1964IC1196, 1969IC275>. Related chemistry has been extensively surveyed by Miller and co-workers, which has been covered in chapter 4.11 of COFGT (1995).



Scheme 50

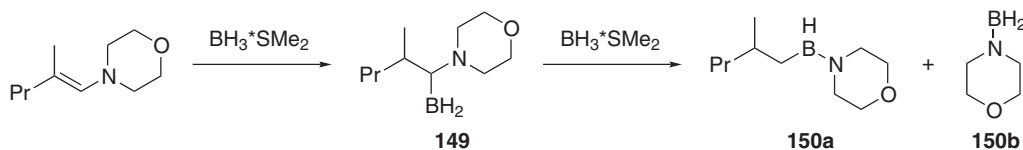


This methodology has recently been extended to the preparation of an *N*-chelated rhodium(I) (dialkylamino)borate complex **146** <2002IC6541>. The ligand **147** was synthesized according to Scheme 51, and interestingly it was found that clean deprotection of **148** only took place in the presence of a large excess of DABCO. The lithium salt **147** underwent facile transmetalation with {(NBD)RhCl<sub>2</sub>} to afford the rhodium complex **146** as a yellow crystal. The reactivity of the [Ph<sub>2</sub>B(CH<sub>2</sub>NMe<sub>2</sub>)<sub>2</sub>]Rh(I) fragment has been explored by exchanging the NBD ligand for other ligands such as CO, PR<sub>3</sub>, and CH<sub>3</sub>CN.



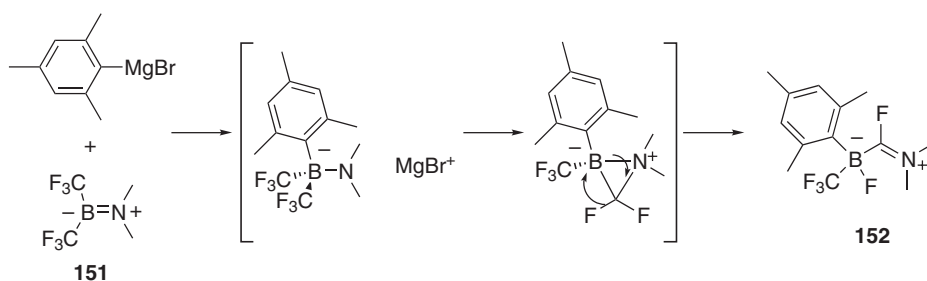
Scheme 51

The hydroboration of unsubstituted enamines generally gives  $\beta$ -boron addition but Singaram and co-workers have demonstrated that  $\beta,\beta$ -disubstituted enamines can give good yields of  $\alpha$ -boron addition products **149** (Scheme 52) <1991JOC5691>. In the absence of an oxidative work-up, the aminoborane intermediate **149** reacts further with borane to give decomposition products containing B—N bonds (**150a** and **150b**). Wipke and co-workers have used organic reaction prediction software (IGOR2) to compare computational and experimental observations of the outcome of enamine hydroboration and have achieved a good agreement <1993JA440>. Boronates can also be obtained by this methodology, using an aqueous work-up protocol.

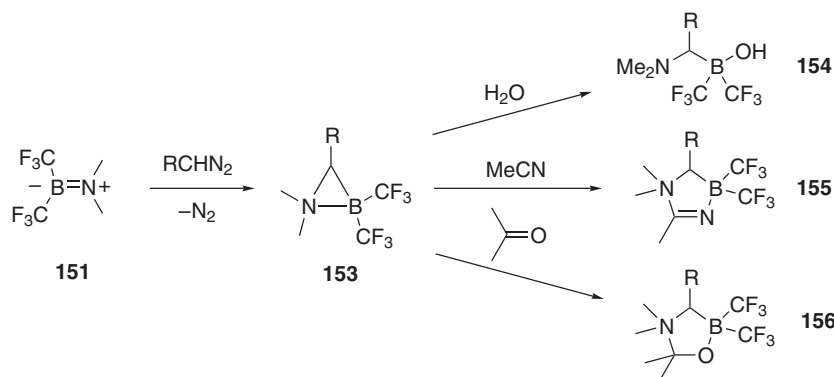


Scheme 52

(Dimethylamino)bis(trifluoromethyl)borane **151** possesses unique properties in aminoborane chemistry, and it provides a synthetic route to some novel  $\alpha$ -boroamino compounds. Brauer and co-workers <1996JOM(524)225> reported the formation of zwitterion **152** by treating borane **151** with aryl Grignard reagents. They hypothesize the rearrangement mechanism as shown in Scheme 53. In a separate publication, they found a simple entry to the azonia-boratacyclopropane **153** from borane **151** and diazomethane derivatives. The three-membered heterocycle intermediate **153** undergoes hydrolysis to form **154**, while nitriles and carbonyl compounds insert into the B—N bond to give five-membered heterocycles **155** and **156**, respectively (Scheme 54) <1999EJI255>. Investigation of the influence of the diazomethane substituents on reactivity and stability of the intermediate **153** was described.



Scheme 53

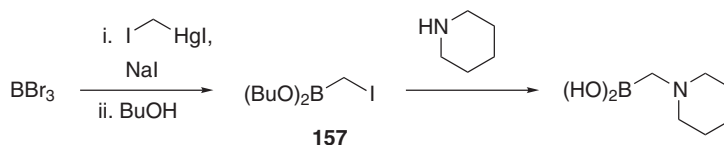


Scheme 54

#### 4.11.1.3.2 $\alpha$ -Aminoboronic acids

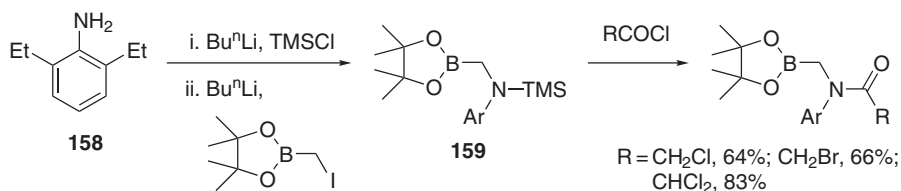
Although several examples of aminomethylboronate syntheses were described up to 1977, the appearance of a landmark publication in that year documenting a boronate amino acid isostere as a useful inhibitor of the serine protease chymotrypsin [<1977JA6435>](#) triggered a surge in synthetic and medicinal interest which is ongoing. Aspects of aminomethylboronic acid chemistry including methods for their synthesis have appeared as subsections in three general reviews of boronic acids and boronates by Matteson [<1989CRV1535, 1989T1859, 1991PAC339>](#).

Matteson and Cheng [<1966JOM\(6\)100>](#) reported the first general synthetic method (Scheme 55) relying on the generation of an  $\alpha$ -iodoboronate **157** and subsequent displacement by a secondary amine. This preparative method failed when ammonia or primary amines were used [<1978JA1325, 1979JOM\(170\)259>](#), but it can be overcome in the case of primary aromatic amines by using *N*-silyl-*N*-lithioamines (Scheme 56). Metallation and silylation of hindered arylamines such as **158** followed by remetallation gives a nucleophilic species that reacts cleanly with pinacol iodomethaneboronate to give a stable aminomethyl derivative **159** that can readily be distilled and directly acylated without the need to desilylate [<1986JOC1610>](#).



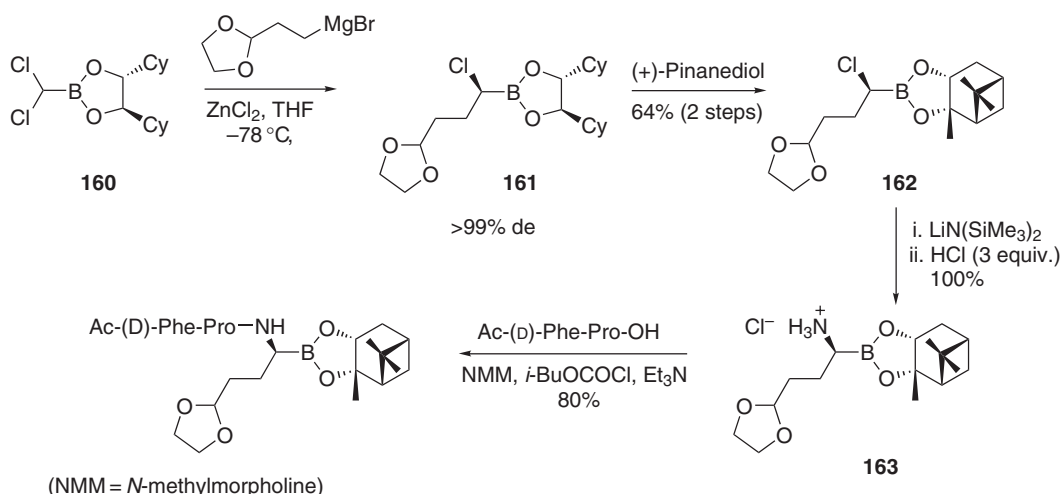
Scheme 55

Much of the research in this area is concentrated on the synthesis of novel  $\alpha$ -aminoboronic acids as amino acid isosteres. These  $\alpha$ -aminoboronic acids can be incorporated into peptides to give possible serine protease inhibition properties. Almost all of these exploitations of aminomethylboronates have relied upon essentially the same strategy for assembly of the N—C—B functionality, specifically, the homologation, amination sequence pioneered by Matteson and co-workers.



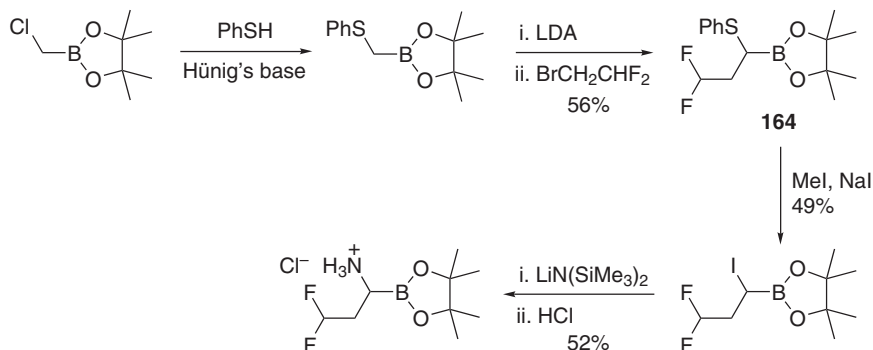
Scheme 56

This methodology was demonstrated by Mantri and co-workers [\[1996JOC5690\]](#) in their synthesis of  $\alpha$ -aminoboronic acids. They treated dichloromethylboronates **160** with Grignard reagents to give an intermediate ate complex that efficiently rearranges to the  $\alpha$ -chloroboronate **161** (Scheme 57). Substitution reactions of  $\alpha$ -chloroboronates **162** with primary amines have been shown to be sluggish by early research; therefore, lithium hexamethyldisilazide (LHMDS) is used to introduce the amino function after acidic work-up to give the desired  $\alpha$ -aminoboronic ester **163** [\[1981JA5241, 1984OM614\]](#). Direct acylation of the HMDS intermediate is also possible.



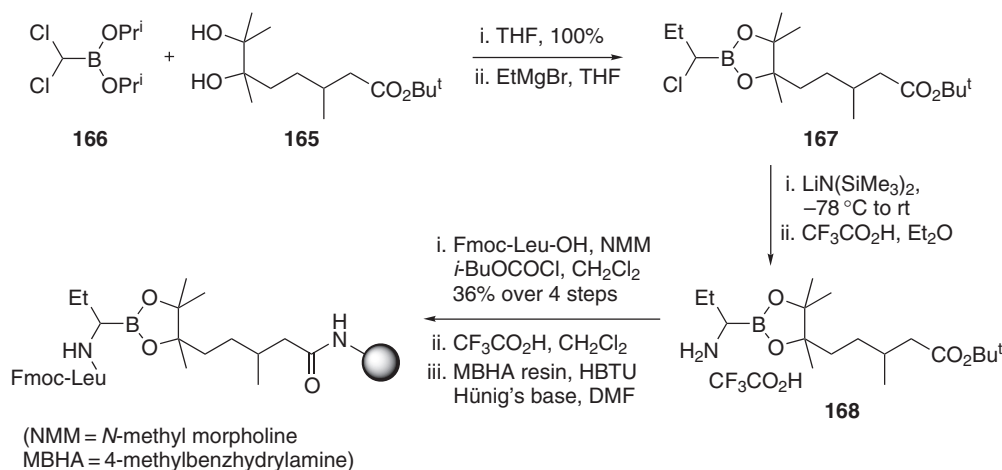
Scheme 57

The above approach is widely used in the preparation of  $\alpha$ -aminoboronic acids, but it depends greatly on the availability of the side chain as Grignard or organolithium reagents. A modified approach was reported by Kettner and co-workers where the  $\alpha$ -side chain substituent is derived from the reaction of an electrophile with the stabilized  $\text{PhSCH}_2\text{BO}_2$ -pinacol methide anion to give **164** and the amino group is installed afterwards using the typical route [\[2001JOC6375\]](#). The overall synthesis is shown in Scheme 58 and three different side chains have been prepared using this methodology.



Scheme 58

The choice of boronate ester is diverse, both achiral, cyclic boronates derived from ethylene glycol or pinacol have been used as well as the esters of (+)- or (–)-pinanediol, which give up to 99% ee in the equivalent diastereoselective chloroboronate synthesis [<1983OM1536, 1984OM1284>](#). More recently, Wilson and co-workers reported a solid supported synthesis of peptide boronic acids, which made use of a pinacol-like diol linker to resin [<2000BMCL1577>](#). The diol **165** was synthesized by a three-step sequence, and it was treated with boronate ester **166** to give  $\alpha$ -chloroboronate **167**. Using the methodology described previously,  $\alpha$ -aminoboronic ester **168** was generated (Scheme 59). It was then attached to resin followed by conventional high throughput peptide synthesis to give novel  $\alpha$ -aminoboronic acid incorporated peptides after acidic cleavage from the polymer support.



Scheme 59

Since the initial disclosure of aminomethylboronates as chymotrypsin inhibitors, many disclosures of increasingly more complex structures designed to inhibit key serine proteases (including elastase, thrombin and cathepsin G) have appeared. An overview of these inhibitors has been covered in book by Powers [<B-1986MI411-01>](#) and a brief summary of them can be found in chapter 4.11 of COFGT (1995).

#### 4.11.2 FUNCTIONS CONTAINING A NITROGEN AND A METAL: $R_2^1C(NR_2^2)ML_n$ (M = Li, K, Mg, Sn, Zn), etc.

This section reviews the synthesis of  $\alpha$ -metallated nitrogen compounds, focusing on those in which the nitrogen atom is a component of an amine, imine, or equivalent species. The synthesis of metallated nitroalkanes (nitronates) is beyond the scope of this article to review in depth, but general methods are briefly surveyed, with emphasis on other comprehensive reviews.

##### 4.11.2.1 $\alpha$ -Metallated Amine Functions

A thorough and well-organized review of nitrogen-stabilized carbanions by Gawley and Rein appeared in 1991 which underscores the need for additional carbanion-stabilizing groups to ensure the stability and utility of many  $\alpha$ -lithiated amines, exemplifying this with amidines in particular [<1991COS\(3\)65>](#). This review will aim to give an update on currently available methods for synthesis of unstabilized  $\alpha$ -amino anions and their masked, stabilized equivalents. Some further specific examples and discussions on the nature of the C—M bond will be found in two general reviews of carbanion chemistry [<1980T2531, 1987MI411-01>](#).

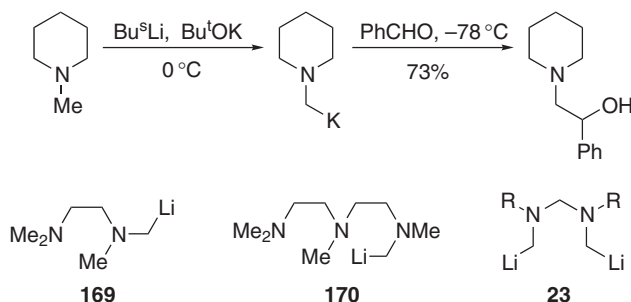
The literature contains a vast array of  $\alpha$ -metallated amines in which the metal is either tin or, particularly, lithium. Potassium, magnesium, and zinc have all found occasional utility. The remaining metals that occur with regularity in most aspects of organic chemistry are very poorly represented in this area, despite the apparently obvious potential for transmetallation from accessible organolithium species.

#### 4.11.2.1.1 Lithium, potassium, and magnesium

A comprehensive review on lithiation adjacent to a nitrogen can be found in Clayden's book on organolithium compounds [<B-2002MI411-01>](#). He concentrates mainly on the chemistry of "dipole stabilized"  $\alpha$ -lithiation and their use in synthesis. This section will cover a broader range of the preparation of  $\alpha$ -lithiated amine functional groups.

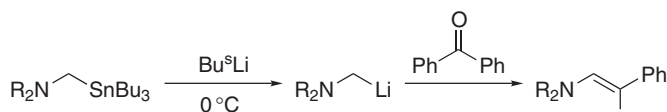
##### (i) Unstabilized carbanion equivalents

Alkali metallation of unstabilized tertiary amines has been achieved using strong bases and generally proceeds in a nonspecific manner, producing the most thermodynamically stable anion. One of the most efficient examples, by Ahlbrecht, is the metallation of *N*-methylpiperidine by the Lochmann–Schlosser base (*s*-BuLi/*t*-BuOK) as shown in [Scheme 60](#) [<1984TL1353>](#). The reaction is successful for most *N*-methyl tertiary amines. The lithium analogs are known, but direct deprotonation often required an extra amino group in the molecule. The  $\alpha$ -lithio amines such as **169** [<1987CB2081>](#), **170** [<1990RTC305>](#), and **23** [<1997CB1777>](#) are formed by treating the respective amine with BuLi. This is presumably due to intramolecular chelation of the metal.



Scheme 60

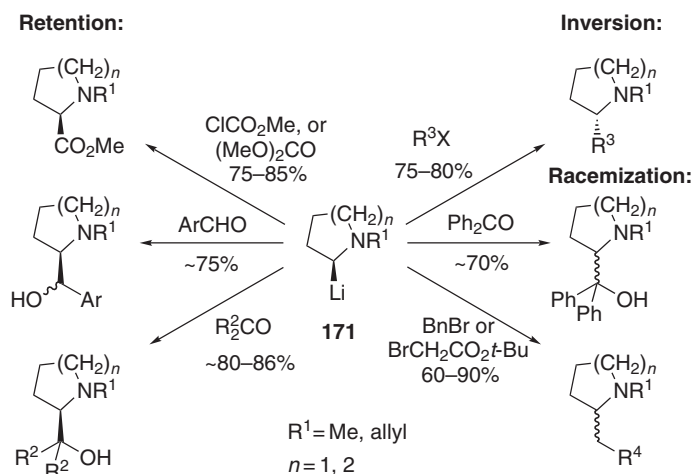
In the case of amines without extra coordinating groups present, the lithiated species can be prepared by transmetalation. Peterson established one of the earliest site-specific protocols ([Scheme 61](#)), which relies on prior synthesis of the  $\alpha$ -aminostannane and transmetalation by BuLi [<1971JA4027>](#). Tsunoda and co-workers described an alternative methodology which requires a thioaminal precursor [<1991TL1975>](#). In 2000, Gawley and co-workers reported an investigation on the stereoselectivity of  $\text{S}_{\text{E}}2$  reactions of unstabilized  $\alpha$ -aminoorganolithiums [<2000JA3344>](#). 2-Lithiopyrrolidines and -piperidines **171** generated from transmetalation of the respective aminostannane derivatives were quenched with a selection of electrophiles, and they found there is evidence for both polar and SET mechanisms depending on the nature of the electrophile. The results are summarized in [Scheme 62](#).



Scheme 61

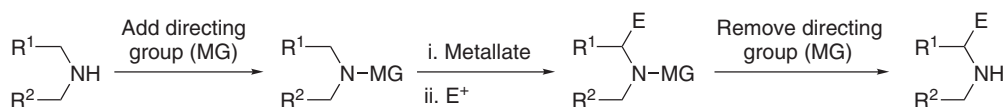
##### (ii) Dipole-stabilized carbanion equivalents

A very wide range of carbanion-stabilizing groups has been appended to the amino group itself to stabilize the metallation process. These groups include amides, carbamates, formamidines, nitrosamines, dithiocarbamates, thioamides, and allyl groups, which are readily removed after metallation. The typical sequence of reactions is shown in [Scheme 63](#), where MG denotes a metallation directing group. A review by Beak and co-workers comprehensively surveys essentially all of the known examples of  $\alpha$ -metalloamine synthetic equivalents to that date [<1984CRV471>](#). They are



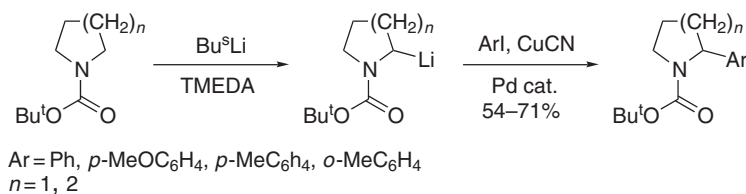
Scheme 62

also covered in detail in Clayden's book on organolithium compounds [<B-2002MI411-01>](#). Other groups such as carbonyl or cyano can also be present  $\alpha$  to the amino group to stabilize the carbanion by delocalizing electron density into enolate equivalents, but they are not easily removed to reveal the amino function and are not discussed in detail here.



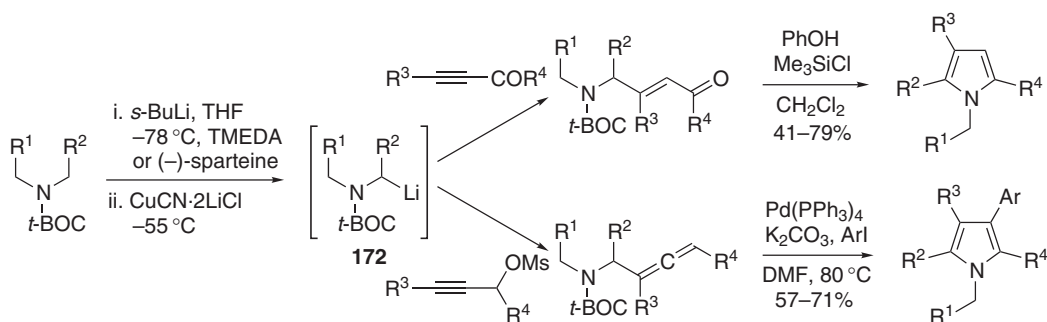
Scheme 63

The metallation of amides and carbamates by directed deprotonation is the most widely applied method to generate  $\alpha$ -litho amines. These intermediates have been shown by Dieter and co-workers to be versatile reagents for palladium-catalyzed coupling with aryl iodides in the presence of CuCN (Scheme 64) [<1995TL3613>](#). They have also reported the preparation of  $\alpha$ -aminoalkylcuprates from the corresponding  $\alpha$ -lithiocarbamates **172** and their subsequent addition reactions to alkynyl species (Scheme 65) [<2000OL2283, 2001OL3855>](#). Adducts from the addition reactions are good precursors for pyrrole synthesis.

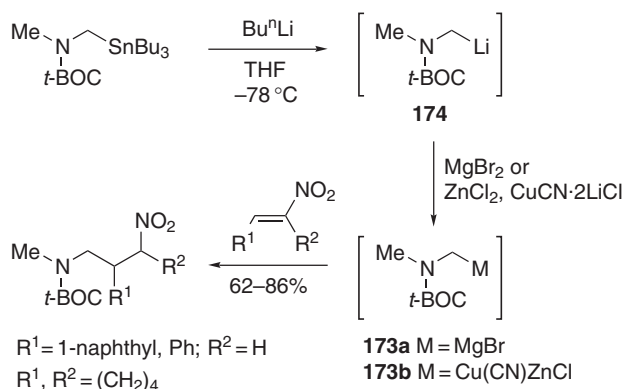


Scheme 64

Transmetallation from lithium to magnesium has infrequently been used to generate  $\alpha$ -amino Grignard reagents in situations where the change of metal enhances yield or selectivity. For example, Strekowski and co-workers have investigated the conjugate addition of  $\alpha$ -metalloamine **173** with nitroalkenes [<1995TL225>](#). They found that the  $\alpha$ -lithioamino adduct only gave good yield of addition product at  $-100^\circ\text{C}$  and the yield decreased at higher temperature. By contrast, the Grignard reagent **173a** generated from transmetallation of  $\alpha$ -lithioamine **174** gave good yields at  $-78^\circ\text{C}$  and the range of substrates can be extended if the corresponding organocuprate reagent **173b** is formed (Scheme 66).

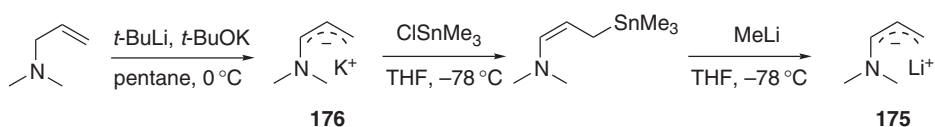


Scheme 65



Scheme 66

The  $\alpha$ -metallated amino compounds have received little attention from structural chemists in the past. In 1999, Weston and Ahlbrecht reported the first structural investigation of 1-dimethyl-aminoallylalkali compounds. They synthesized the simple  $\alpha$ -lithioamine **175** through a Sn–Li exchange reaction (Scheme 67) and its potassium analog **176** by direct deprotonation with the Lochmann–Schlosser base (*t*-BuLi/*t*-BuOK) (Scheme 67). Their research has concluded that both lithium and potassium derivatives exist exclusively in the endo conformation in THF as demonstrated by NMR studies. *Ab initio* calculations also reveal that the endo-structure is thermodynamically more stable than the exo conformation <1999T2289>.



Scheme 67

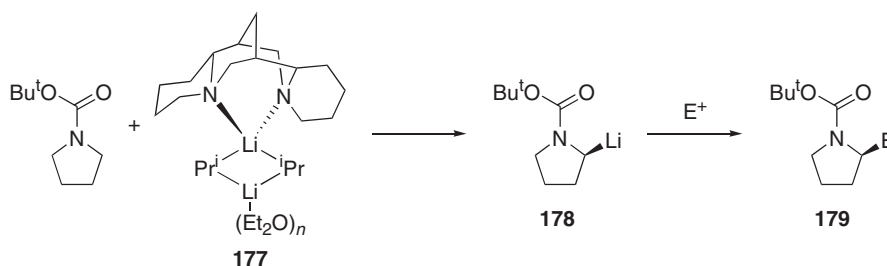
### (iii) Chiral, nonracemic $\alpha$ -aminolithium reagents

A number of  $\alpha$ -lithiated amine equivalents have been established in which the stabilizing group is chiral resulting in a configurationally stable carbanion, retaining its formal  $sp^3$ -hybridization. High ee values are readily achieved in cyclic systems, although when low ee values are obtained, they are probably the result of poor selectivity in removal of one diastereotopic proton from a pair. Consequently, methods which rely on transmetalation to lithium from more stable organometallics (usually stannanes) can achieve excellent selectivity, especially at low temperature <1991JA8546, 1992JOC2220>.

The use of organolithium and chiral diamine complexes for asymmetric deprotonation of BOC-protected amines has also been published. Beak and co-workers reported that *i*-PrLi/(–)-sparteine complexes **177** carry out the asymmetric lithiation of BOC-pyrrolidine and the resulting

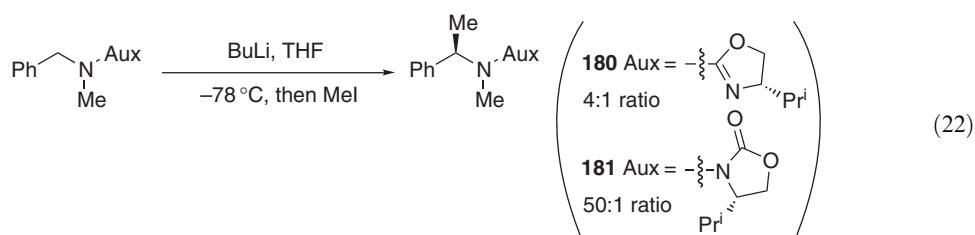


configurationally stable lithiated species **178** can be trapped with electrophiles to give 2-substituted BOC-pyrrolidines **179** with high ee (Scheme 68) <1994JA3231>. They have also studied the mechanism and kinetics of the deprotonation reaction. Their results show that there is evidence for a prelithiation complex of pyrrolidine and chiral lithium base **177**, and that the deprotonation reaction is the rate determining step <1995JOC7092>.



Scheme 68

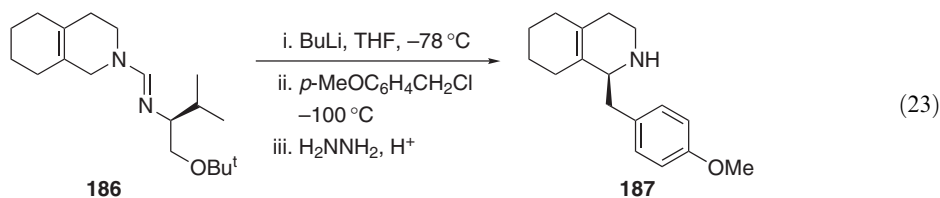
Gawley and co-workers have made an elegant comparison of the effectiveness of chiral auxiliaries oxazoline **180** and oxazolidinone **181** in lithiation and methylation reactions. They demonstrated that **181** gave almost complete diastereocontrol, while **180** proceeded with poor selectivity (Equation (22)) <1989JOC3002>. They further studied the difference in selectivity observed in the reaction of  $\alpha$ -metallated pivalamides and oxazolines **182–185** with carbonyls. They found that when  $\alpha$ -lithiotetrahydroisoquinoline **182** or **183** was treated with benzophenone, a deep blue solution was produced, indicative of the presence of a ketyl radical, and that transmetalation to **184** or **185** with  $MgBr_2 \cdot OEt_2$  prior to the addition of benzophenone showed no indication of ketyl formation <1991TL1941>. The results are summarized in Table 1. They explained their findings by the competing SET and polar mechanisms. Thus, in some instances, the polar process is slower for the lithiated species, and SET followed by radical coupling produces racemic addition products nonselectively.

Table 1 Addition of  $\alpha$ -metallated tetrahydroisoquinoline to benzophenone

	Z	M	ESR	Selectivity
<b>182</b>	Pivalamide	Li	+	NA
<b>183</b>	Oxazoline	Li	+	1:1
<b>184</b>	Pivalamide	Mg	—	NA
<b>185</b>	Oxazoline	Mg	—	10:1

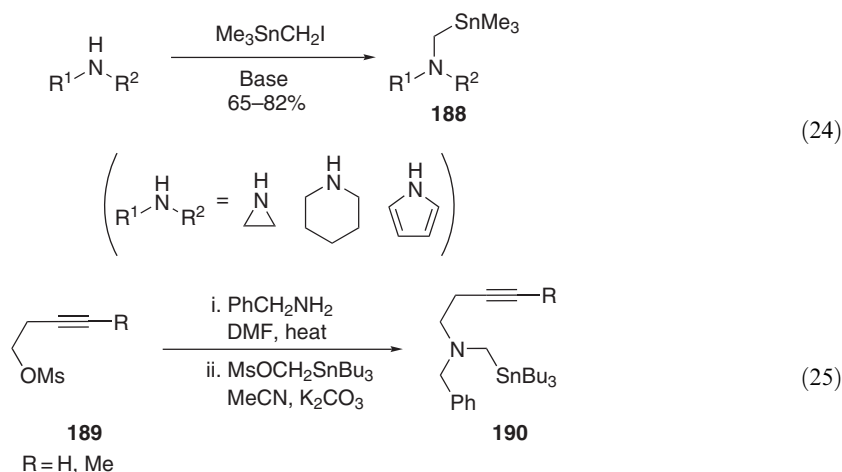
The seminal work of Meyers and co-workers in developing chiral formamidines as dipolar, carbanion-stabilizing groups represents perhaps the most effective means of generating nonracemic  $\alpha$ -aminolithium reagents <1984T1361>. Many representative examples are included in the

aforementioned review by Gawley with a fuller discussion than is possible here. High induction is best achieved when the metallated amine forms part of a five-, six-, or seven-membered ring, and benzo-fused systems such as tetrahydroisoquinolines give near perfect diastereoselection. For example, metallation of octalin **186** followed by benzylation and removal of the formamidine chiral auxiliary gives a key intermediate **187** in the synthesis of dextrophan (Equation (23)) <1986JOC872>.



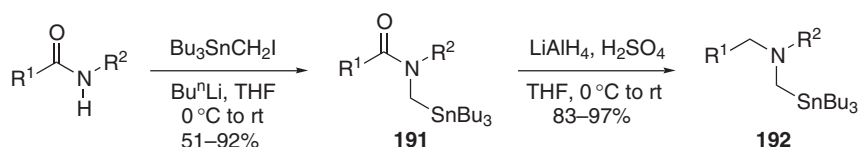
#### 4.11.2.1.2 Tin and zinc

The synthesis of  $\alpha$ -aminostannanes parallels to some extent the methods available for preparation of the analogous silanes (Section 4.11.1.1). Thus, Abel and co-workers <1975JOM(97)159> have described a complementary synthetic approach to the foregoing methods using  $\text{R}_3\text{SnCH}_2\text{I}$  (cf.  $\text{TMS-CH}_2\text{I}$ ) as the tin source. Secondary amines gave a good yield of the  $\alpha$ -aminostannane products **188**, but reaction with primary amines often result in a mixture of mono- and dialkylated products (see also reference <1976JOM(113)C13>). This method is particularly well suited to the synthesis of  $\alpha$ -stannylmethylaziridines, -piperidines, and some heteroaromatic systems (see Equation (24)). Coldham and co-workers also reported a similar reaction where an acyclic secondary amine **189** was treated with  $\text{Bu}_3\text{SnCH}_2\text{OMs}$  to afford the corresponding  $\alpha$ -aminostannane **190**, which was a key intermediate for their investigation into the synthesis of pyrrolidines by anionic cyclization (Equation (25)) <1997TL7621>.

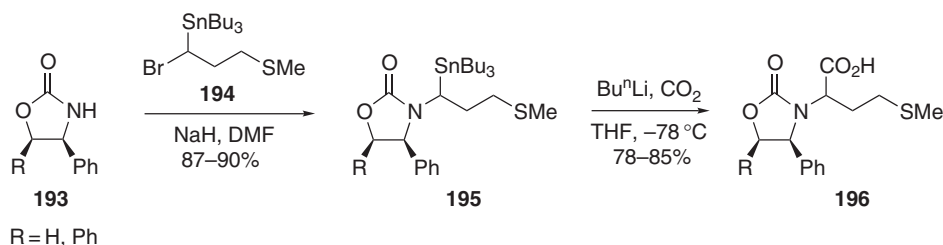


Besides alkylation of amines, alkylation of amide and carbamate NH functions have shown to be an alternative method to synthesize  $\alpha$ -aminostannanes. Chong and co-workers published a simple preparation of  $\alpha$ -aminostannanes by alkylation of amides to first give  $\alpha$ -amidostannane intermediate **191**. After reduction with alane ( $\text{LiAlH}_4$  gave competing destannylation), the desired  $\alpha$ -aminostannanes **192** were produced in good-to-excellent yields (Scheme 69) <1996JOC7627>. Alkylation of carbamates has also been reported by Jeanjean and co-workers <2000EJO1297>. The oxazolidinone chiral auxiliary **193** was alkylated with  $\alpha$ -bromo-organostannane **194** to give a good yield of  $\alpha$ -stannylcarbamate **195**. The stannane **195** was then treated with *n*-BuLi and  $\text{CO}_2$  to provide the protected amino acid derivative **196** in 78–85% yields (Scheme 70).

A different approach was carried out by Quintard and co-workers, who used readily available amins such as **197** that react with  $\text{Bu}_3\text{SnMgCl}$  (prepared *in situ* from  $\text{Bu}_3\text{SnH}$  and  $\text{Pr}^i\text{MgCl}$ ) to give excellent yields of the stannanes **198** (Scheme 71). Yields for the two-step process were in the range 45–90% overall <1984S495>. Coldham and co-workers have also shown that iminium ions

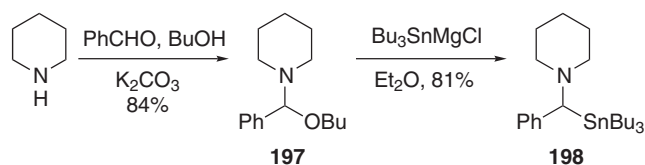


Scheme 69

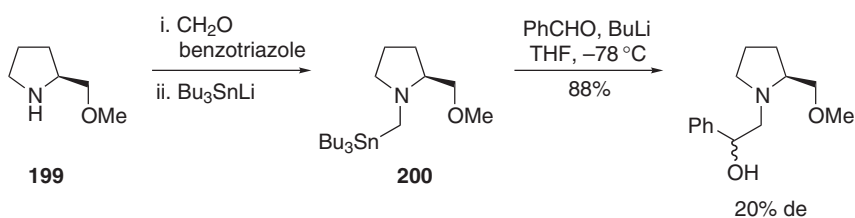


Scheme 70

also react with  $Bu_3SnLi$  to give stannanes as shown in [Scheme 72](#). The iminium ion was prepared by the condensation of pyrrolidines **199** with formaldehyde in the presence of benzotriazole catalyst, prior to reaction with  $Bu_3SnLi$  [\[1997JCS\(P1\)1481\]](#). The stannane intermediate **200** provided access to the corresponding  $\alpha$ -amino-organolithium by Li–Sn exchange, which undergoes addition to aldehydes to give  $\beta$ -amino alcohols in good yields and modest diastereoselectivities. Yields were generally comparable to the amination process, although the versatility is undoubtedly greater.

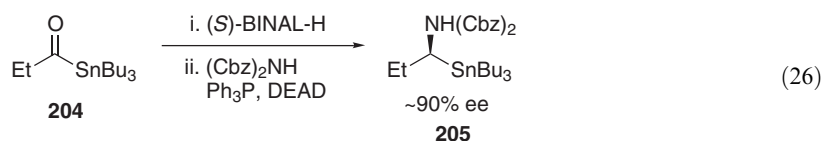
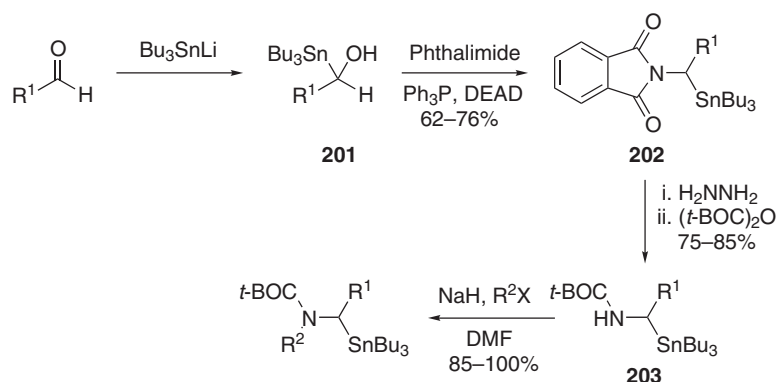


Scheme 71

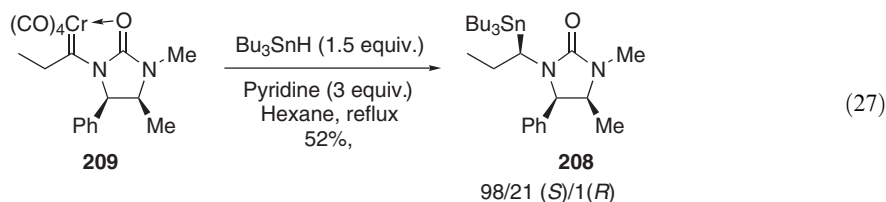
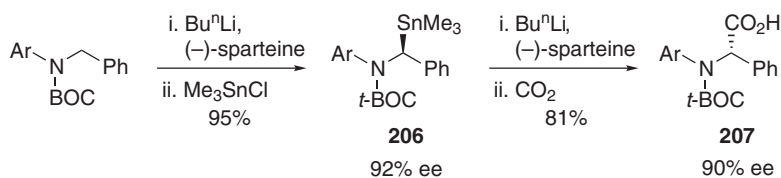


Scheme 72

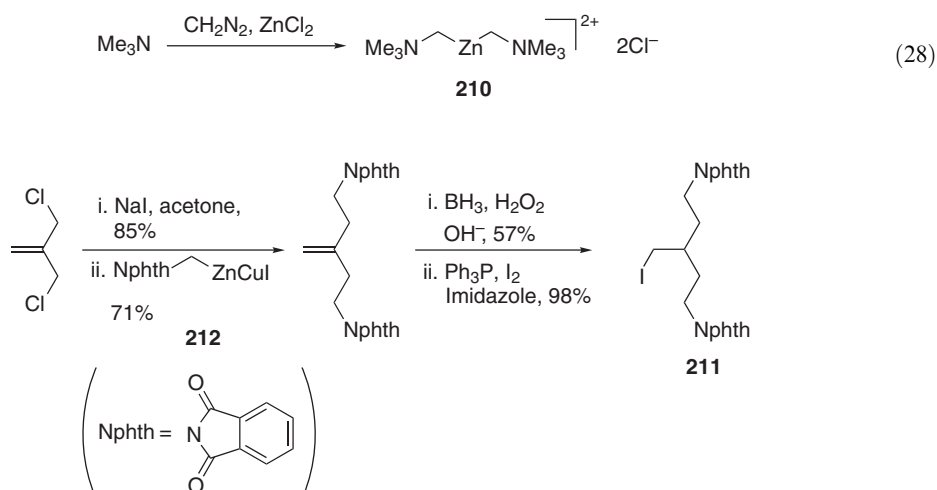
Stannylcarbinols **201**, prepared by the addition of  $Bu_3SnLi$  to aldehydes, can be converted into phthalimidomethylstannanes **202** under Mitsunobu conditions as shown in [Scheme 73](#). Hydrazinolysis and BOC protection gives an acylaminostannane **203**, which can be further alkylated at nitrogen under standard conditions [\[1992JOC2220, 2002JOC3625\]](#). Enantiomerically enriched aminomethyltin species are accessible in a similar manner; enantioselective reduction of acylstannane **204** with (*S*)-BINAL-H gives a carbinol, which is readily converted into imide **205** with inversion of the carbinol stereochemistry ([Equation \(26\)](#)). The overall enantioselectivity of the process is dependent on the reduction step [\[1992JOC2220\]](#).



The interchangeability of Sn and Li by transmetallation in either direction is a straightforward process and several  $\alpha$ -aminostannanes have been prepared from lithium derivatives discussed in the previous section. For example, the BOC-protected benzylamine derivative was asymmetrically deprotonated by *n*-BuLi/(–)-sparteine and the anion was quenched with Me<sub>3</sub>SnCl to give stannane **206** as an intermediate for the synthesis of novel amino acids **207** (Scheme 74) <1997JOC1574>. A related reaction, which utilizes the 1,1-addition of stannanes to Fischer carbene complexes to generate chiral organostannane derivative **208** was published by Wulff and co-workers. The imidazolidinone carbene complex **209** was treated with Bu<sub>3</sub>SnH in refluxing hexane, and high stereoselectivity of the product **208** can be achieved in the synthesis of the product depending on the side chain (Equation (27)) <1998OM3696>.



Few reports give details of  $\alpha$ -aminozinc derivatives despite evidence in those papers that such species are relatively stable and can in some cases be isolated. Wittig and Schwarzenbach <1961LA(650)1> were the first to prepare bis(trimethylaminomethyl)zinc chloride **210** by the reaction of ZnCl<sub>2</sub>, diazomethane, and Me<sub>3</sub>N (Equation (28)). Recently, Zhu and co-workers have reported the use of the  $\alpha$ -zinc-substituted methylphthalimide in their synthesis of a modified uridine derivative. They required the iodide fragment **211** to couple to a ribose derivative in which the two phthalimide groups were introduced by using the organozinc derivative **212** in the presence of CuI in good yield (Scheme 75) <2002MI(21)723>.



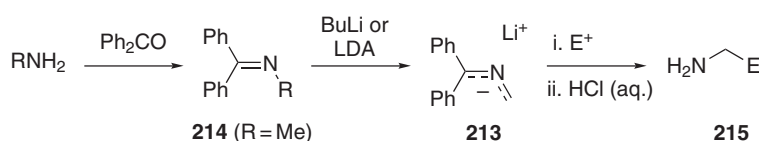
Scheme 75

#### 4.11.2.2 $\alpha$ -Metallated Imine Functions

##### 4.11.2.2.1 Lithium

This section addresses lithiation by deprotonation; lithiation by metal exchange with organostannanes was briefly discussed in [Section 4.11.2.1.2](#).

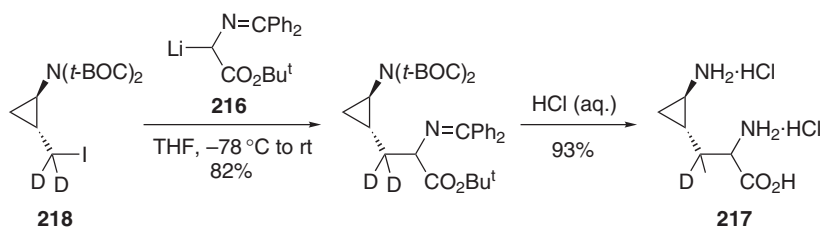
The lithiation of unactivated amines can be achieved by first generating an aldimine or ketimine, which is able to delocalize the new carbanion as the aza-allyl anion **213**. The process is most successful with *N*-methylbenzophenone imine **214**, which offers increased anion stability and complete regiocontrol of the alkylation site [<1977CB2659>](#). Hydrolysis then releases the newly substituted amine **215** as shown in generic form in [Scheme 76](#). Examples of  $\alpha$ -lithiated imines are tabulated in Beak's 1984 review [<1984CRV471>](#).



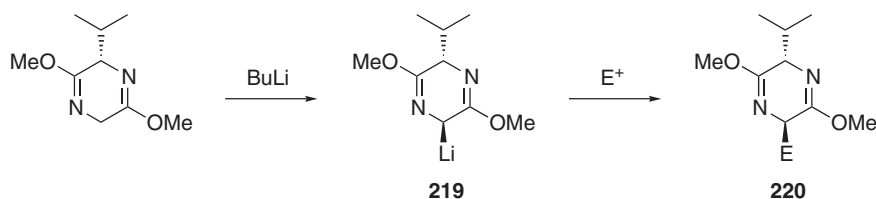
Scheme 76

Additional stabilization of the incipient aza-allyl carbanion increases the lifetime of the metallated intermediate. Lithiated imines of glycine **216** have been used as glycine carbanion synthons, especially in the synthesis of unnatural  $\alpha$ -amino acids. In a recent example de Meijere and co-workers have reported the preparation of deuterated amino acid **217** containing a cyclopropyl group as part of the total synthesis of the novel antibiotic belactosin A. They utilized the lithiated aminoacetate derivative **216** to add the amino acid function to the iodide **218** in good yield ([Scheme 77](#)) [<2000SL1741>](#). Other glycine synthons have been published such as Schöllkopf's elegant bis-lactim ether. This can be deprotonated asymmetrically to  $\alpha$ -lithio carbanion **219**, which can be quenched with a variety of electrophiles to yield **220** selectively ([Scheme 78](#)) [<1983T2085>](#). The details of this methodology are covered in chapter 4.11 of COFGT (1995).

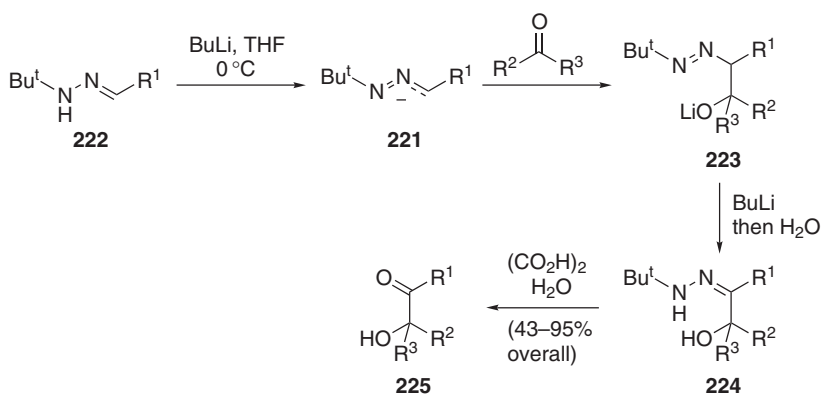
The related diaza-allyl anion **221** can be generated by metallation of the azo compound **222**. Baldwin and co-workers have extensively investigated the lithiation of *t*-butylhydrazone **222** and its subsequent reaction with an aldehyde or ketone. The initial azo intermediate **223** was easily isomerized back to a hydrazone **224** on exposure to BuLi. Final hydrolysis of the hydrazone **224** completes a useful and general synthesis of  $\alpha$ -hydroxyketones **225** ([Scheme 79](#)) [<1983CC1040, 1986T4223>](#).



Scheme 77



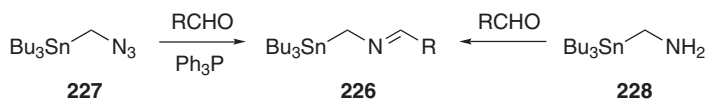
Scheme 78



Scheme 79

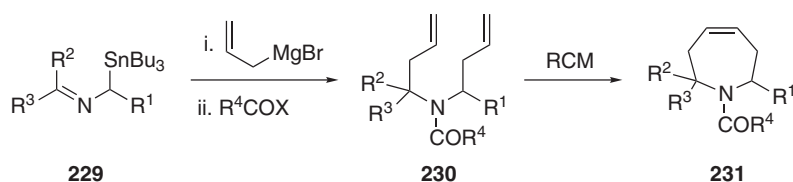
#### 4.11.2.2.2 Tin

Pearson and co-workers have published a number of creative syntheses using  $\alpha$ -stannylimine derivatives **226** as precursors to lithio imines, which undergo  $[\pi 4s + \pi 2s]$ -cycloadditions to anionophilic alkenes, generating pyrrolidines and related compounds. They have reported a variety of synthetic routes to  $\alpha$ -stannylimine derivatives **226**, such as the Staudinger reaction of azidomethylstannane **227** with  $\text{Ph}_3\text{P}$  in the presence of an aldehyde, and the more conventional condensation of aldehydes or ketones with  $\alpha$ -aminostannanes **228** (Scheme 80) <1992JOC6354>. This chemistry has been applied successfully to the synthesis of complex polycyclic pyrrolidines containing natural products <1995JA12336, 1997TL3369>.



Scheme 80

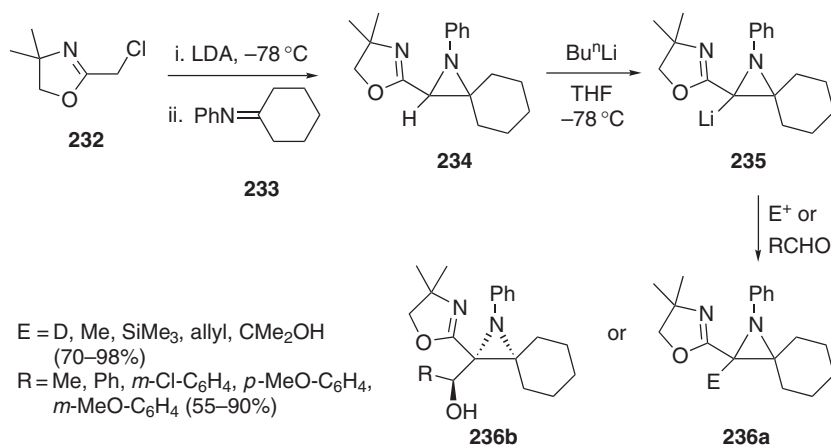
Recently, Pearson and Aponick have extended the use of  $\alpha$ -stannylimines to prepare tetrahydroazepines via ring-closing metathesis. They found that treatment of (2-azaallyl)stannanes **229** with 2 equiv. of allyl Grignard reagent afforded good yields of dienes **230**, which were subjected to ring-closing metathesis to give 2,3,6,7-tetrahydroazepines **231** in 75–98% yields (Scheme 81) <2001OL1327>.



Scheme 81

#### 4.11.2.3 $\alpha$ -Metallated Aziridines

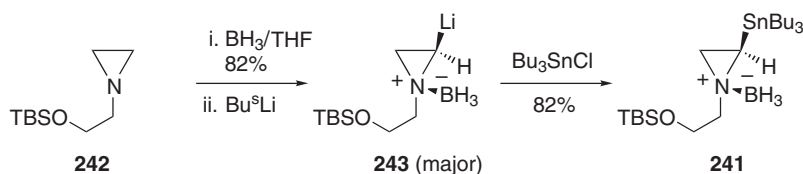
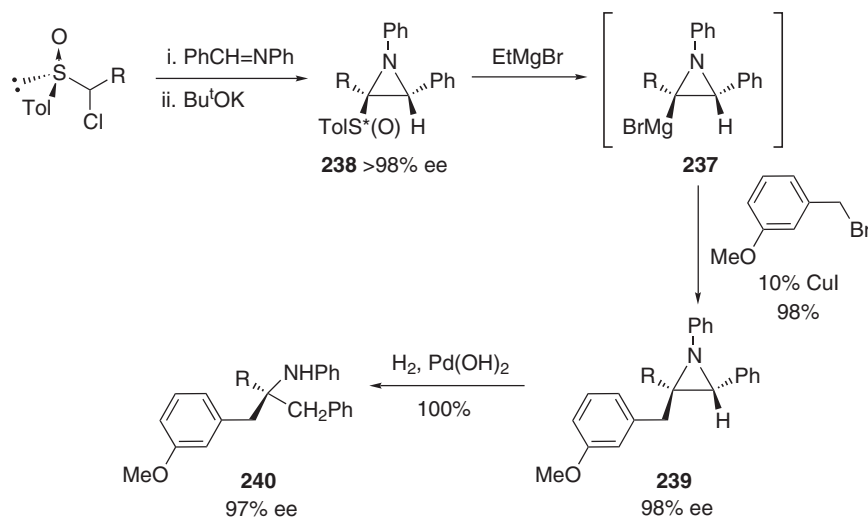
The chemistry of aziridinyl anions was not widely known and studied until Satoh published a review on this subject in 1996 <1996CRV3303>.  $\alpha$ -Metallated aziridines can serve as key intermediates for the synthesis of more complex aziridines and amines bearing a chiral quaternary center. Florio and co-workers have reported a convenient route to oxazolinylaziridines based on the deprotonation and alkylation of simpler oxazolinylaziridines. Treatment of oxazoline **232** with LDA then Schiff base **233** afforded aziridine **234**. Lithiation of aziridine **234** with *n*-BuLi at  $-78^\circ\text{C}$  resulted in the formation of aziridinyl lithium **235**, which could be trapped with a number of electrophiles to give functionalized aziridines **236a–236b** (Scheme 82) <1999TL6101>. If the electrophile is an arylaldehyde, the reaction takes place with complete *anti*-diastereoselectivity to give **236b**. (Acetaldehyde was shown to be much less *anti*-diastereoselective (*anti*/*syn* ratio = 2/1).) It is noteworthy that deprotonation–alkylation reactions of oxazolinylloxiranes are nonstereoselective.



Scheme 82

The generation of aziridinylmagnesium is possible as Satoh and co-workers have demonstrated. They prepared the aziridinylmagnesium species **237** by the sulfoxide-metal exchange of sulfinylaziridines **238**, and in the presence of catalytic amounts of CuI good-to-excellent yields of alkylation products were afforded with a variety of electrophiles <2000TL6495>. The alkylated aziridines **239** were converted regioselectively to the corresponding amines **240** by hydrogenation with Pd(OH)<sub>2</sub> in quantitative yield. If the sulfoxide starting material is optically pure, this methodology leads to the asymmetric synthesis of amines bearing a quaternary chiral center with little to no loss of chirality (Scheme 83).

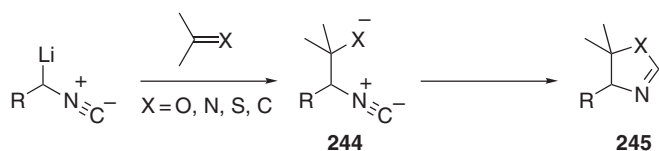
Finally, it is also possible to prepare  $\alpha$ -stannylaziridines **241** as shown by Vedejs and Kendall <1997JA6941>. The  $\alpha$ -lithioaziridines **243** generated from lithiation of the aziridines **242** were treated with Bu<sub>3</sub>SnCl to give the desired  $\alpha$ -stannylaziridines **241** (Scheme 84). The borane acts as an activator for substituted aziridine synthesis and it is easily cleaved in refluxing ethanol.



#### 4.11.2.4 $\alpha$ -Metallated Isocyanides and Isothiocyanates

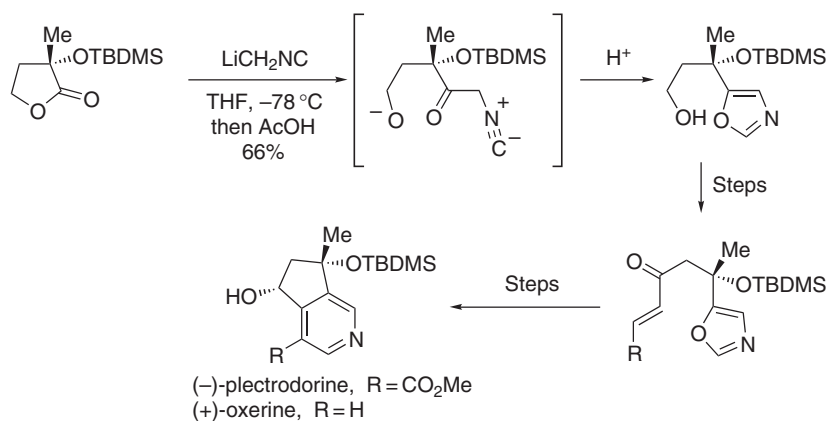
##### 4.11.2.4.1 Isocyanides

Lithiated isocyanides are readily generated by alkyllithiums and are unusual stabilized carbanions in that the terminal isocyanide carbon is an electrophilic center; the immediate products of alkylation **244** often react further, typically by a cyclization to generate five-membered heterocycles **245**. The synthesis and chemistry of  $\alpha$ -lithiated isocyanides are the subject of two comprehensive reviews [<1977AG\(E\)339, 1984CRV471>](#) and well-described preparative details are available for the generation and silylation of  $\text{LiCH}_2\text{NC}$  [<1984SC639>](#). The potential of these reagents for the synthesis of oxazolines, thiazolines, imidazolines, pyrrole derivatives, and related compounds are summarized in [Scheme 85](#).



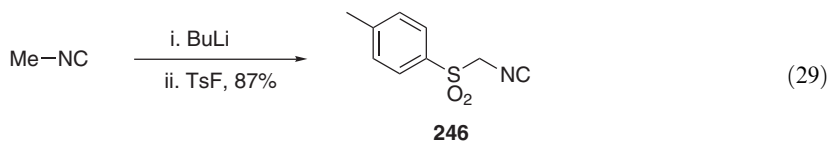
For example, cyclization of lithiated isocyanides with carbonyl equivalents generates a new heterocyclic carbanion, which is generally protonated on work-up. This reaction is applied in an elegant synthesis of the cyclopenta[*c*]pyridine ring system in natural products (–)-plectordorine and (+)-oxerine ([Scheme 86](#)) [<2000TL10251>](#). The anionic intermediate can undergo further tandem reactions to give disubstituted heterocycles [<1980JOC2548>](#).





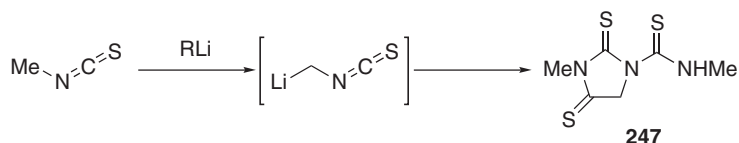
Scheme 86

Tosylmethylisocyanide (TosMIC, **246**) is a versatile isonitrile that has been utilized in the synthesis of substituted  $\alpha$ -hydroxyaldehydes, nitriles, pyrroles, imidazoles, and thiazoles. Van Leusen and co-workers have described the synthesis of TosMIC by the lithiation of MeNC followed by reaction with TsF (Equation (29)) <1972TL2367>. Details of the chemistry of TosMIC can be found in several useful leading references and overviews <1977TL2949, 1979CPB2857, 1980S325>.

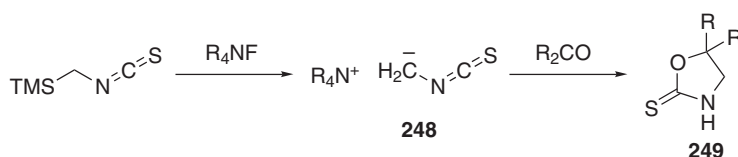


#### 4.11.2.4.2 Isothiocyanates

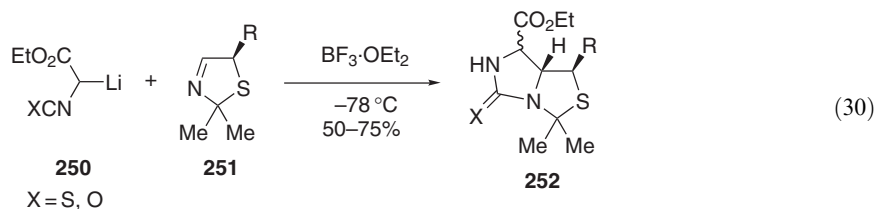
Lithiated isothiocyanates without additional carbanion-stabilizing groups are only rarely invoked as intermediates in the literature. Metallation of MeNCS is reported to give the thiazolinethione **247** (Scheme 87) <1981AG(E)126>. A much more practical method for the generation of an equivalent carbanion has been achieved by desilylation of TMS-CH<sub>2</sub>NCS using tetraalkylammonium fluorides <1981AG(E)126, 1982BCJ1163> (see also Section 4.11.1.1.5). The resultant salt **248** has been intercepted with a range of electrophiles, including carbonyl compounds which afford oxazolinethiones **249** (Scheme 88). Stabilized lithiated isothiocyanate have been used in the preparation of functionalized thiazolidines. The lithium salt of isothiocyanate (and isocyanate) **250** was reacted with cyclic imine **251** to give a bicyclic product **252** in 75% yield as a pair of diastereomers <1983TL4503> (Equation (30)).



Scheme 87

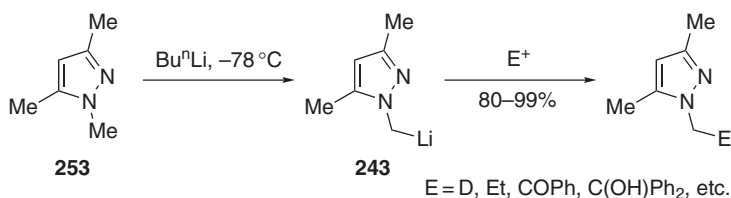


Scheme 88



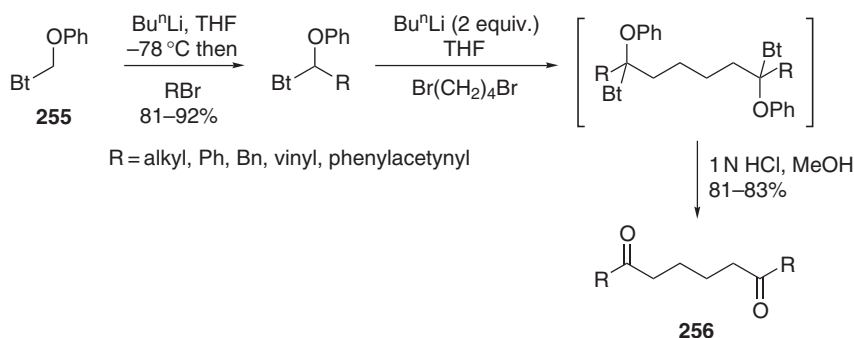
#### 4.11.2.5 Metallation of *N*-Methyl Heterocycles

Nitrogen heterocycles, especially  $\pi$ -excessive heteroaromatic systems bearing an *N*-methyl substituent, can frequently be lithiated on that  $sp^3$ -carbon, either by deprotonation or transmetallation from Si and Sn species, to give a dipole-stabilized carbanion. An important consideration and a major restriction is that the reaction is only practical if competing  $\alpha$ -metallation of the aromatic ring is suppressed or impossible. This aspect is discussed in more detail in Gschwend and Rodriguez' monumental review of heteroatom-facilitated lithiations <1979OR(26)1>. This could be demonstrated by the  $\alpha$ -lithiation of *N*-alkyl group in pyrazoles published by Katritzky and co-workers <1983T2023>. The 1,3,5-trimethylpyrazole **253** was deprotonated exclusively at the *N*-methyl group and the lithio-derivative **254** was successfully trapped with a range of electrophiles (Scheme 89). A list of other examples can be found in chapter 4.11 of COFGT (1995).



Scheme 89

Among the variety of  $\alpha$ -metallated *N*-methyl heterocycles reported, the benzotriazole derivatives have found the most use in synthesis. As described in Section 4.11.1.1.8, benzotriazole **95** was  $\alpha$ -lithiated and subsequently quenched with electrophile TMSCl to give **96**. Application of a similar chemistry was again published by Katritzky and co-workers where they found that some  $\alpha$ -benzotriazole ethers **255** can be used as masked acyl anion equivalents and can be used to prepare alkyl, aryl, alkenyl, and alkynyl ketones. For example, the 1,6-diketone **256** was synthesized in good yields following the protocol in Scheme 90 <1999JOC2124>.



Scheme 90

#### 4.11.2.6 $\alpha$ -Metallated Nitroalkanes

The synthesis and chemistry of  $\alpha$ -anions derived from nitroalkanes is a vast, mature area which cannot be accommodated in this review. A comprehensive coverage of the topic can be found in Ono's book on the chemistry of nitro group <B-2001MI411-01>. Two named reactions embrace the majority of nitroalkane chemistry and both require  $\alpha$ -nitro anions as intermediates. These are the Henry reaction and the Nef reaction. The Henry reaction covers the condensation of aldehydes and ketones (and usually Michael acceptors) with nitroalkanes and has been reviewed <1959OR(10)179, 1970MI411-01, B-2001MI411-01>. The Nef reaction covers all hydrolyses of nitronates to carbonyl compounds. A review in 1990 comprehensively surveyed the known examples of, and conditions for, the Nef reaction <1990OR655>. There has been no significant breakthrough in this area even though much research has been devoted to the new developments and application of these reactions in modern organic synthesis.

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## Biographical sketch



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## 4.12

# Functions Containing One Phosphorus and Either Another Phosphorus or As, Sb, Bi, Si, Ge, B, or a Metal

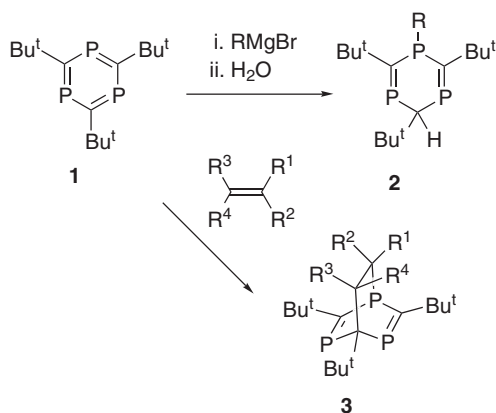
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*University of St. Andrews, St. Andrews, UK*

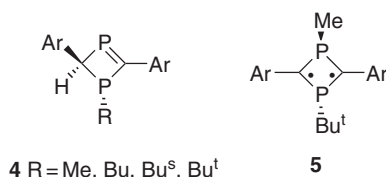
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Scheme 1

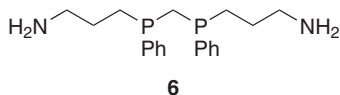


#### 4.12.1.3 Symmetrical Tricoordinate Phosphorus Functions

There have been a large number of developments in the synthesis of compounds of this type since the publication of chapter 4.12.1.3 in <1995COFGT(4)543> and these are categorized according to the starting materials used.

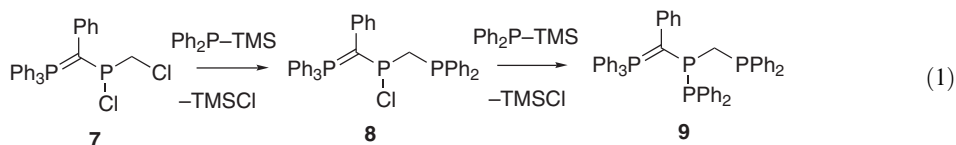
##### 4.12.1.3.1 From 1,1-dihalo alkanes

Sequential treatment of tri-*p*-tolylphosphine with lithium, Bu<sup>t</sup>Cl, and CH<sub>2</sub>Cl<sub>2</sub> gives the bis(phosphine) Tol<sub>2</sub>PCH<sub>2</sub>PTol<sub>2</sub> in 37% yield <1997JPC(A)4666>. Reaction of the aminophosphine PhPH(CH<sub>2</sub>)<sub>3</sub>NH<sub>2</sub> with sodium in liquid ammonia followed by CH<sub>2</sub>Cl<sub>2</sub> affords the product **6** of interest as a polydentate ligand <1996BCJ1947>.



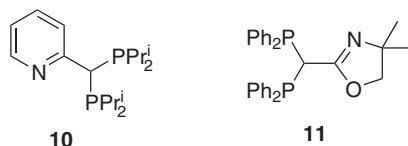
##### 4.12.1.3.2 By nucleophilic substitution on 1-haloalkylphosphines

A further example of this rather uncommon approach is provided by the reaction of chloromethylphosphine-containing ylide **7** with Ph<sub>2</sub>P-TMS to give first **8** and then **9** (Equation (1)) <2000ZN(B)519>.



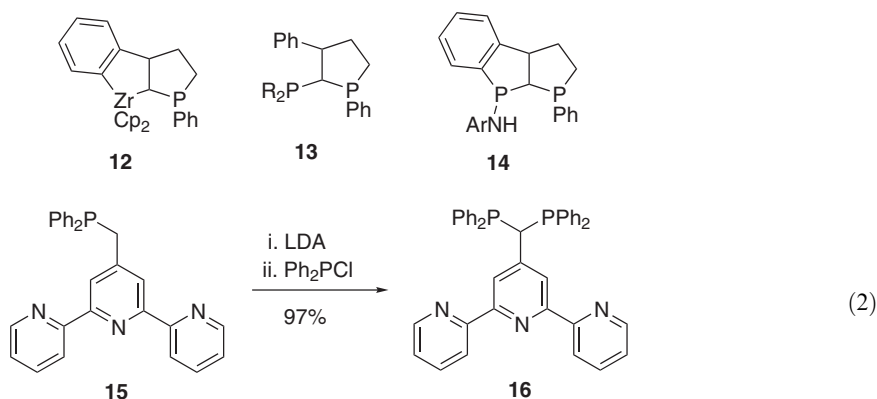
#### 4.12.1.3.3 From 1,1-dimetallo alkanes

Further examples of this approach have appeared including the treatment of 2-picoline twice with BuLi followed by  $\text{Pr}^i_2\text{PCl}$  to give **10** in 40% overall yield [<1999M783>](#) and formation of **11** by treating the trimethyloxazoline with 2equiv. of LDA followed by 2equiv. of  $\text{Ph}_2\text{PCl}$  [<2000JCS\(D\)1067>](#).

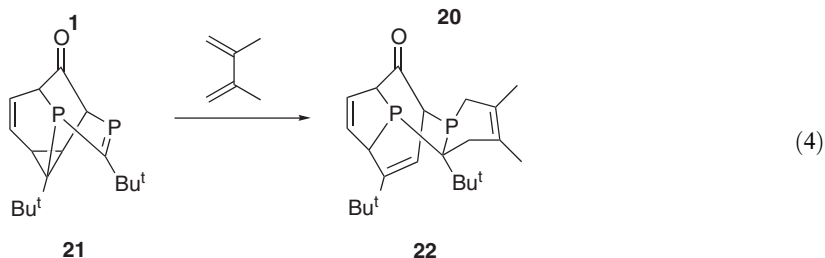
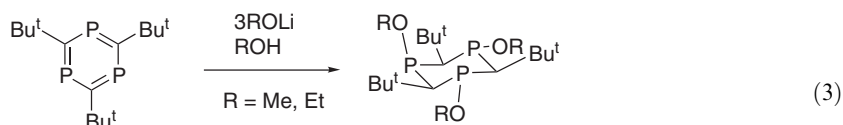


#### 4.12.1.3.4 By electrophilic substitution on 1-metalloalkylphosphines

Reaction of  $\text{Me}_2\text{PCH}_2\text{Li}$  with dichlorophosphines,  $\text{R}_2\text{PCl}_2$ , gives  $\text{Me}_2\text{PCH}_2\text{P(R)CH}_2\text{PMe}_2$  while with  $\text{PCl}_3$  the tetrakis(phosphine)  $(\text{Me}_2\text{PCH}_2)_3\text{P}$  is formed [<1997JOM\(529\)151>](#). A range of unsymmetrical bis(phosphines),  $\text{R}^1_2\text{PCH}_2\text{PR}^2_2$  can be prepared by the treatment of  $\text{R}^1_2\text{PCH}_2\text{SnPh}_3$  or  $\text{R}^1_2\text{PCH}_2\text{SnMe}_3$  either with an alkyllithium followed by  $\text{R}^2_2\text{PCl}$  or with  $\text{R}^2_2\text{PCl}$  alone at  $240^\circ\text{C}$  [<1999JCS\(D\)1867>](#). Reaction of the zirconacycle **12** with  $\text{Et}_2\text{PCl}$  or  $\text{Ph}_2\text{PCl}$  gives phosphinophospholanes **13** [<1997CC1239>](#) while treatment of **12** with  $\text{ArN}=\text{PCl}$  (Ar = 2,4,6-tri-*t*-butylphenyl) followed by water gives the aminophosphine product **14** [<2003AG\(E\)2176>](#). Reaction of the terpyridyl-containing phosphine **15** with LDA followed by  $\text{Ph}_2\text{PCl}$  gives the diphosphine **16** in 97% yield (Equation (2)) [<2000CC1125>](#).

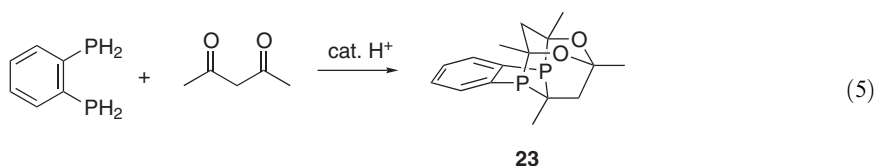


one axial (Equation (3)) <2000CC2015>. The polycyclic compound **21**, formed from tropone and  $\text{Bu}^t\text{C}\equiv\text{P}$ , undergoes Diels–Alder reaction with 2,3-dimethylbutadiene followed by a rearrangement to afford product **22** (Equation (4)) <1996PS(109)425>.



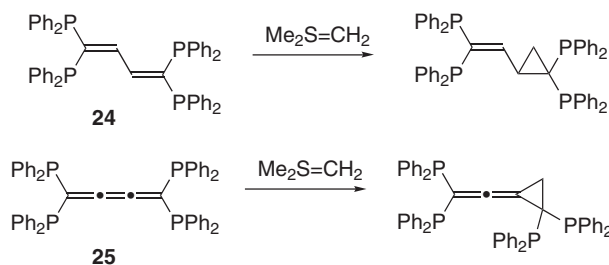
#### 4.12.1.3.7 From carbonyl compounds

Acid-catalyzed reaction of benzene-1,2-diphosphine with 1,3-pentanedione gives the remarkable polycyclic product **23** (Equation (5)) <1999CC901>.



#### 4.12.1.3.8 From 1,1-diphosphino alkenes

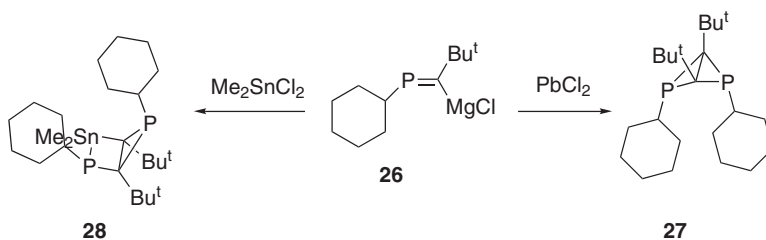
The tetraphosphinobutadiene **24** and the butatriene **25** both undergo cyclopropanation upon treatment with  $\text{Me}_2\text{S}=\text{CH}_2$  (Scheme 2) <1995CB365>.



Scheme 2

#### 4.12.1.3.9 From phosphalkenes

Treatment of the phosphalkenyl Grignard reagent **26** with  $\text{PbCl}_2$  gives the diphosphabicyclo [1.1.0]butane derivative **27** <2001CC663>, while with  $\text{Me}_2\text{SnCl}_2$  the bicyclo[2.1.0] system **28** is formed <2000JCS(D)3233> (Scheme 3).

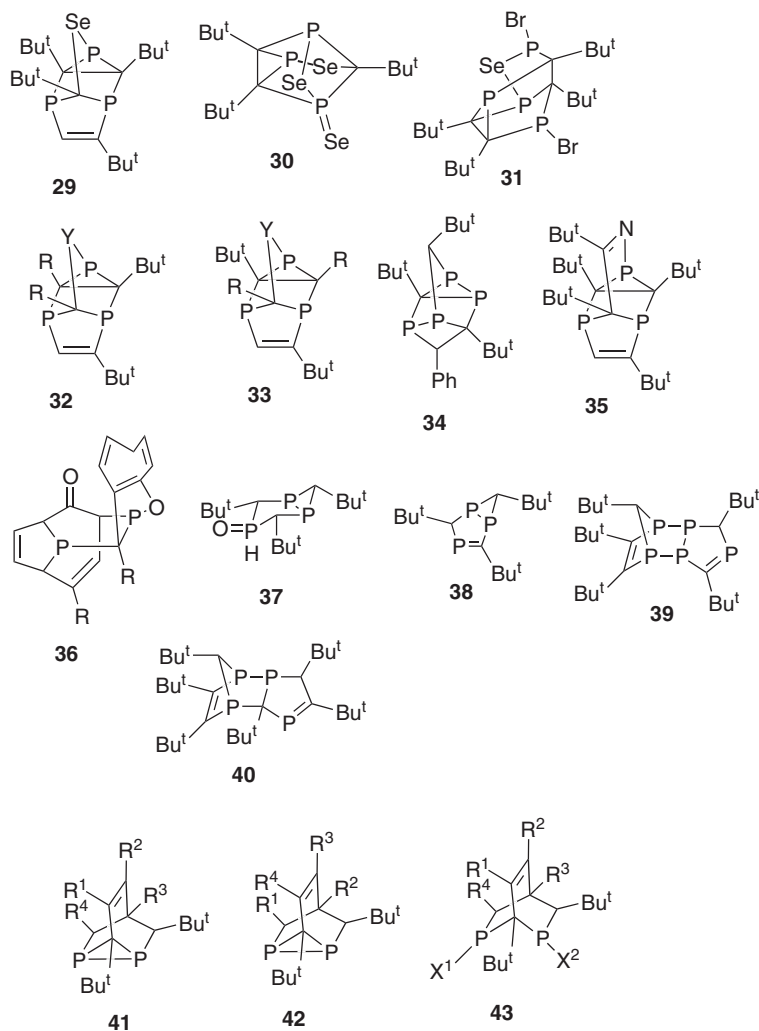


Scheme 3

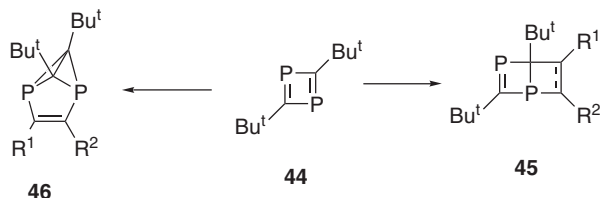
## 4.12.1.3.10 From phosphalkynes

There has been a great deal of progress in this area largely due to the work of Regitz since the publication of chapter 4.12.1.3.15 in <1995COFGT(4)543>. A short review has been published <1997CB823>. New products containing one or more P—C—P functions derived from  $\text{Bu}^t\text{C}\equiv\text{P}$  include **29** obtained in 95% yield by the reaction with selenium <1999SI642> and **30** obtained in 5% yield from the same reaction <2000CC1745>. Remarkably, treatment of **29** with bromine gives **31** <1999SI642>. Tetracyclic products **32** and/or **33** analogous to **29** can also be formed by the reaction of  $\text{Bu}^t\text{C}\equiv\text{P}$  with 3,5-disubstituted 1,2,4-oxadiphospholes <1999EJO587>, 1,2,4-thiadiphospholes <2002JOM(655)7>, or 1,2,4-selenadiphospholes <2001HAC406> giving products with  $\text{Y} = \text{O}, \text{S},$  and  $\text{Se}$ , respectively. While reaction with tungsten pentacarbonyl-complexed aminophosphinidenes gives products analogous to **32** [ $\text{Y} = \text{ArNHP}\rightarrow\text{W}(\text{CO})_5$ ], benzylphosphinidene,  $\text{PhCH}_2\text{P}:$ , first rearranges to  $\text{PhCH}=\text{PH}$  which gives **34** <1995CB991>. Reaction of  $\text{Bu}^t\text{C}\equiv\text{P}$  with 4,6-di-*t*-butyl-1,3,2-diazophosphinine gives compound **35** in 70% yield <1998EJO2039>. Reaction of cycloheptatrienone (tropone) with  $\text{Bu}^t\text{C}\equiv\text{P}$  and similar phosphalkynes takes a remarkable course to give the pentacyclic 2:1 adducts **36** <1995JOC5884>. When butadienylcyclo-octatetraenylhafnium is treated with  $\text{Bu}^t\text{C}\equiv\text{P}$  and the resulting adduct hydrolyzed, the products include **37** and **38** <1999EJI763>. Reduction of  $\text{Bu}^t\text{C}\equiv\text{P}$  with sodium amalgam gives a mixture of diphospholide and triphospholide salts and when these are treated with acid or  $\text{PdCl}_2(\text{COD})$ , the Diels–Alder dimers **39** and **40** are formed <1997JOM(536)273>.

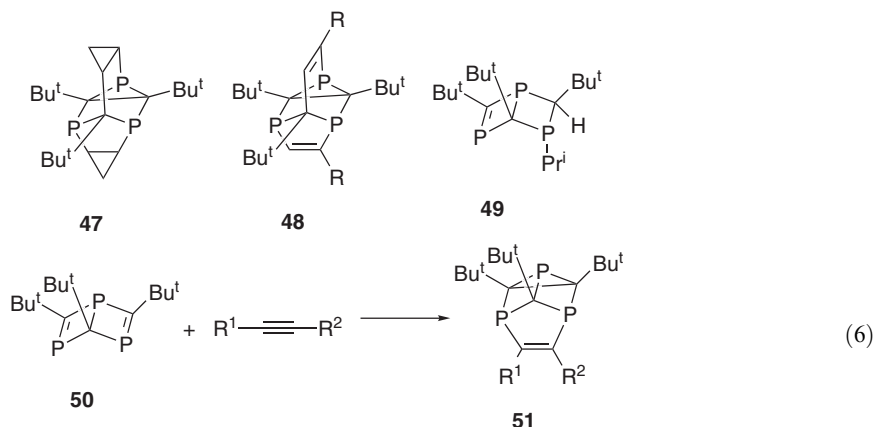
The reaction of  $\text{Bu}^t\text{C}\equiv\text{P}$  and other phosphalkynes with 1,3-dienes,  $\text{R}^1\text{CH}=\text{C}(\text{R}^2)-\text{C}(\text{R}^3)=\text{CHR}^4$ , to give products of structure **41** or **42**, has been further examined <1995BSF652>, and adducts of this type have been obtained from  $\text{Bu}^t\text{C}\equiv\text{P}$  and 1-trimethylsilylbutadiene <1999EJO1041> as well as from 2,4,6- $\text{Me}_3\text{C}_6\text{H}_2-\text{C}\equiv\text{P}$  and butadiene <1998SI305>. Treatment of such adducts with  $\text{Br}_2$  or  $\text{ICl}$  leads to cleavage to give **43** <1998S427>.



In addition to methods starting from monomeric phosphalkynes, there have been several new reactions reported, which begin from readily accessible cyclic dimers or trimers, and these are also considered here. The diphosphacyclobutadiene **44** undergoes cyclo-addition with *N*-methylmaleimide and electron-rich alkynes to give adducts **45** but with electron-poor alkynes to give the isomeric products **46** (Scheme 4) <2002JOM(643)409>. As already mentioned, the triphosphabenzene **1** undergoes Diels–Alder cyclo-addition with a wide variety of alkenes to give bicyclic products **3** but with cyclopropene there is a further homo-Diels–Alder reaction to give **47** <2001EJO3425>. With terminal alkynes  $\text{RC}\equiv\text{CH}$  this also occurs to give products **48** <2000S529>. Treatment of **1** with  $\text{Pr}^i\text{MgCl}$  followed by hydrolysis takes a different course than for  $\text{MeMgBr}$  and  $\text{PhMgBr}$  and gives the product **49** <2003AG(E)1863>. Homo-Diels–Alder reaction between the Dewar isomer of **1**, compound **50**, and alkynes gives tetracyclic products **51** (Equation (6)) <1997JOM(529)215, 1999S1363>.

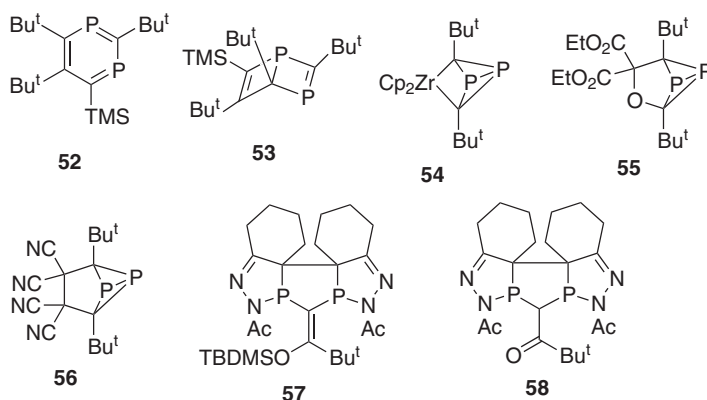


Scheme 4



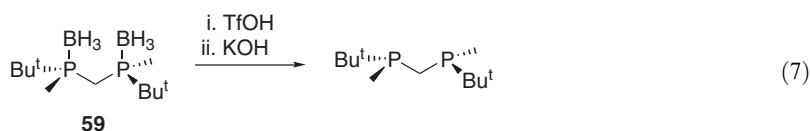
#### 4.12.1.3.11 Miscellaneous methods

Upon prolonged heating the 1,3-diphospha benzene **52** undergoes cyclization to give products including **53** <2001S463>. The tricyclic zirconium compound **54** reacts with diethyl oxomalonate to give **55** and with tetracyanoethylene to give **56** both in low yield <1999S639>. Prolonged storage of compound **57**, prepared by a complex sequence of reactions, resulted in partial hydrolysis of the silyl enol ether to give **58** <1999EJO2633>.



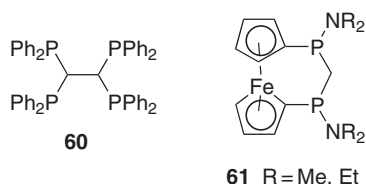
#### 4.12.1.3.12 By reduction of tetracoordinate systems

A new method for deprotection of chiral bis(phosphine–borane adducts) such as **59** involves treatment with TfOH followed by KOH (Equation (7)) <2000TL6461>.



#### 4.12.1.3.13 Interconversions

Conversion of  $\text{Cl}_2\text{PCH}_2\text{PCl}_2$  into  $\text{Ar}_2\text{PCH}_2\text{PAR}_2$  may be achieved by reaction with  $\text{ArLi}$  <1994T4303, 2001CC699>, while treatment with  $\text{Me}_3\text{SnF}$  gives  $\text{F}_2\text{PCH}_2\text{PF}_2$  in 63% yield <1995ZN(B)1583>. Niobium-catalyzed hydrogenation of  $\text{Ph}_2\text{PCH}_2\text{PPh}_2$  to give  $(\text{C}_6\text{H}_{11})_2\text{PCH}_2\text{P}(\text{C}_6\text{H}_{11})_2$  has been reported <1995CC849>, and lithiation of  $\text{Ph}_2\text{PCH}_2\text{PPh}_2$  followed by iodine oxidation gives the tetrakis(phosphine) **60** in 15% yield <1995BSF691>. The ferrocene derivatives **61** have been prepared by reacting dilithiated ferrocene with  $(\text{R}_2\text{N})\text{ClPCH}_2\text{P}(\text{NR}_2)\text{Cl}$  <2003EJ1169>.

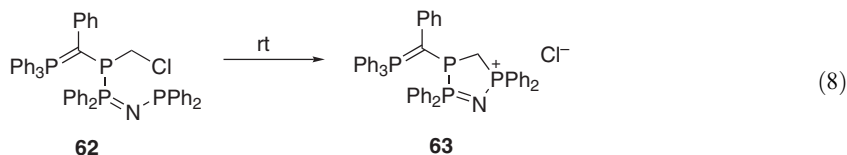


#### 4.12.1.4 Asymmetrical Systems Containing at Least One Tricoordinate Phosphorus

There have been relatively a few developments in the synthesis of compounds of this type since the publication of chapter 4.12.1.4 in <1995COFGT(4)543>. These are categorized according to the starting materials used.

##### 4.12.1.4.1 From 1-haloalkylphosphines

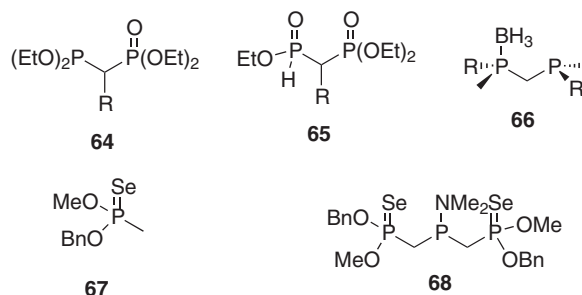
Interaction of the  $\text{NPPH}_2$  and  $\text{CH}_2\text{Cl}$  functions present in **62** occurs spontaneously at room temperature resulting in the formation of the salt **63** (Equation (8)) <2000ZN(B)519>.



##### 4.12.1.4.2 From 1-metalloalkylphosphorus compounds

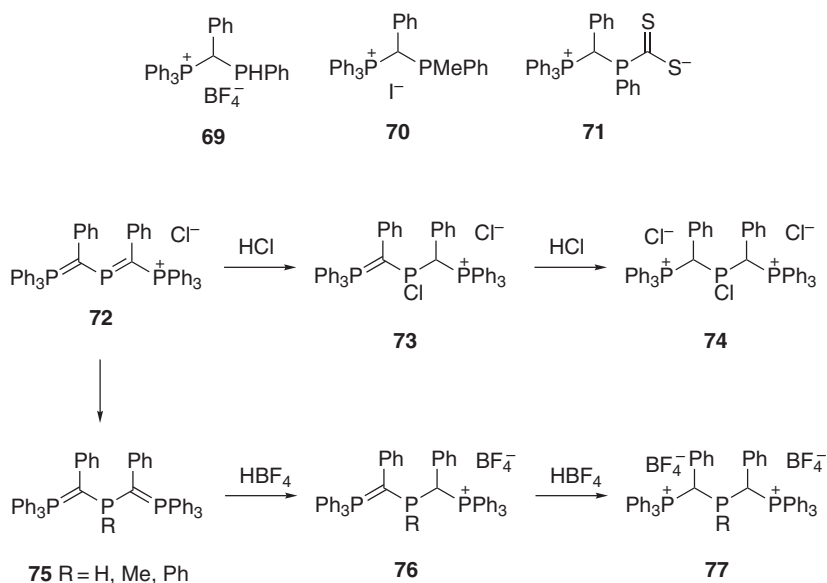
Problems in the synthesis of  $(\text{Pr}^i\text{O})_2\text{P}(\text{O})\text{CH}_2\text{PPh}_2$  from  $(\text{Pr}^i\text{O})_2\text{P}(\text{O})\text{CH}_2\text{Li}$  and  $\text{Ph}_2\text{PCl}$  can be overcome by using  $\text{Ph}_2\text{PBr}$ , which gives the product in 72% yield <1995PS(102)91>. Treatment of functions such as  $\text{RCH}_2\text{P}(\text{O})(\text{OEt})_2$  with  $\text{Bu}^s\text{Li}$  followed by  $(\text{EtO})_2\text{PCl}$  initially gives **64** but on addition of water this is hydrolyzed to **65** <1995JMC2596>. Asymmetric synthesis of compounds **66** has been achieved by the reaction of  $\text{RPM}_2\cdot\text{BH}_3$  with  $\text{Bu}^s\text{Li}$  in the presence of sparteine, followed by  $\text{RPCl}_2$  and finally  $\text{MeMgCl}$  <2001MI118>. Treatment of the selenophosphonate **67** with  $\text{BuLi}$  followed by  $\text{Me}_2\text{N---PCl}_2$  gives the product **68** <2002JOC146>.



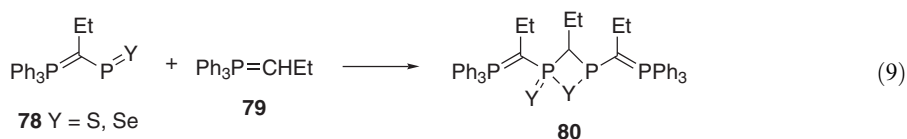


#### 4.12.1.4.3 By electrophilic attack on phosphorus ylides

The phosphine-substituted ylide,  $\text{Ph}_3\text{P}=\text{C}(\text{Ph})-\text{P}^+\text{HPh}$ , reacts with  $\text{HBF}_4$  to give **69**, with  $\text{MeI}$  to give **70**, and with  $\text{CS}_2$  to give **71** <1998EJI381>. The compound **72**, obtained from  $\text{Ph}_3\text{P}=\text{CHPh}$  and  $\text{PCl}_3$ , undergoes twofold addition of  $\text{HCl}$  to give first **73** then **74** (Scheme 5) <1997JOM(529)87>. Prior treatment with  $\text{LiAlH}_4$ ,  $\text{MeLi}$ , or  $\text{PhLi}$  gives compounds **75** which are similarly converted into **76** and **77** <1996ZN(B)267>. Both the sulfur and selenium compounds **78** react with ylides such as **79** to give products **80** (Equation (9)) <1995CB1015>.

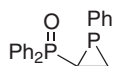


Scheme 5



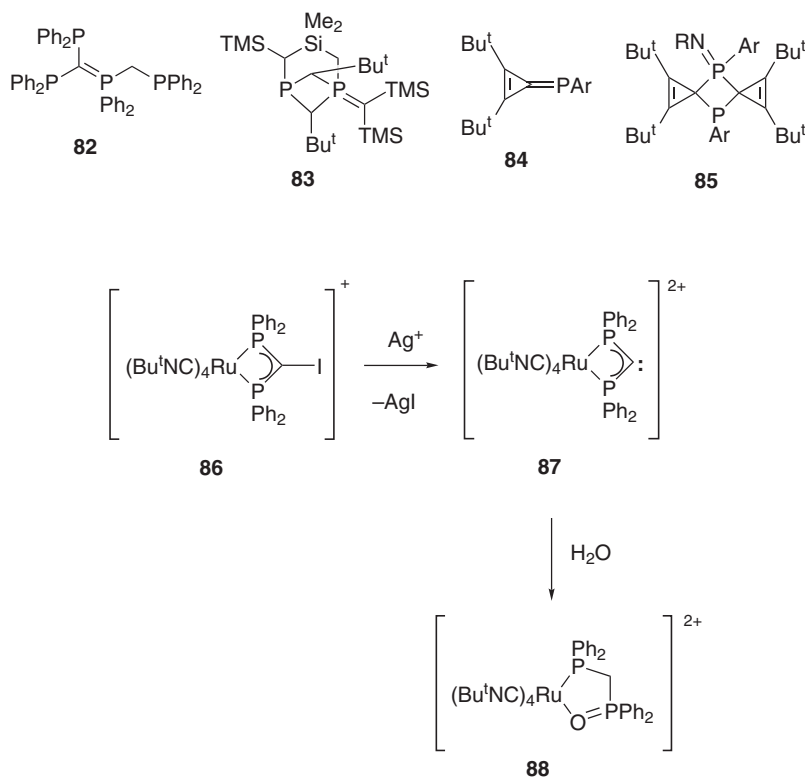
#### 4.12.1.4.4 From vinylphosphorus compounds

Treatment of the vinylphosphine oxide  $\text{Ph}_2\text{P}(\text{O})\text{CH}=\text{CH}_2$  with  $\text{Cp}_2\text{Zr}$  followed by  $\text{PhPCl}_2$  gives the phosphirane **81** <1998CC1177>.



#### 4.12.1.4.5 Miscellaneous methods

The lithiation of  $\text{Ph}_2\text{PCH}_2\text{PPh}_2$  followed by iodine oxidation, which was already mentioned to give **60** as a minor product, gives **82** as the main product <1995CC37, 1995BSF691>. Reaction of  $\text{Bu}^t\text{C}\equiv\text{P}$  with  $\text{LiCH}(\text{TMS})_2$  takes a complex course to afford the remarkable product **83** in 64% yield <2002JOM(645)256>. The compound **84** ( $\text{Ar} = 2,4,6\text{-tri-}t\text{-butylphenyl}$ ) reacts in a 2:1 ratio with azides,  $\text{RN}_3$ , to give the spirodiphosphetanes **85** as minor products <1994TL1527>. Treatment of the ruthenium(II) complex **86** with  $\text{AgClO}_4$  or  $\text{AgBF}_4$  gives the dicationic diphosphinocarbene complex **87**, which reacts with water to afford **88** in 70% yield (Scheme 6) <2003AG(E)4767>.



Scheme 6

#### 4.12.1.4.6 By oxidation of symmetrical tricoordinate systems

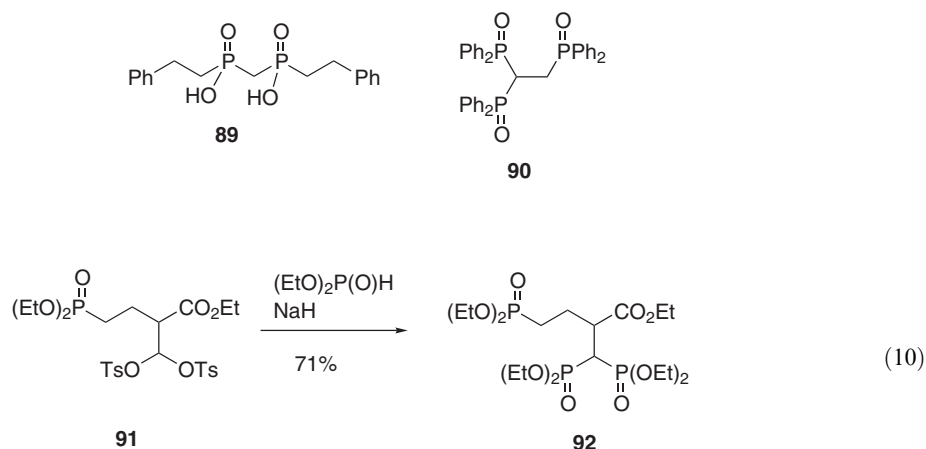
A convenient new method for oxidation of  $\text{Ph}_2\text{PCH}_2\text{PPh}_2$  to  $\text{Ph}_2\text{P}(\text{O})\text{CH}_2\text{PPh}_2$  involves Pd-catalyzed reaction with 1,2-dibromoethane and  $\text{NaOH}$  in a two-phase system <1999JA5831>, while conversion of the same bis(phosphine) into  $\text{Ph}_2\text{P}(=\text{NAr})\text{CH}_2\text{PPh}_2$  using a variety of fluorinated aryl azides has been examined <1998JA11364>. Competition between the phosphine and phosphinite functions is observed upon reaction of the pentacyclic compound **36** with electrophiles: alkyl halides lead to quaternization of the phosphine center while oxidation, treatment with sulfur or selenium, and reaction with azides all lead to oxidation at the phosphinite center <1996S87>.

#### 4.12.1.5 Symmetrical Tetracoordinate Systems

There have been a large number of developments in the synthesis of compounds of this type since the publication of chapter 4.12.1.5 in <1995COFGT(4)543>. These are categorized according to the starting materials used.

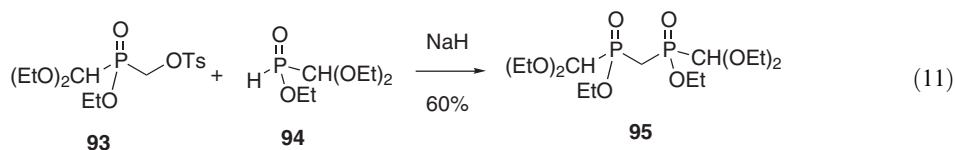
#### 4.12.1.5.1 From reactions of 1,1-dihalo alkanes with phosphorus nucleophiles

Reaction of  $\text{PhCH}_2\text{CH}_2\text{P}(\text{OTMS})_2$  with  $\text{CH}_2\text{Br}_2$  followed by hydrolysis gives the bis(phosphinic acid) **89** in 47% yield [<1997JGU1857>](#), while the tris(phosphine oxide) **90** may be formed by the reaction of either 1,1,2-trichloroethane, 1,1-dichloroethene, or (*E*)-1,2-dichloroethene with  $\text{Ph}_2\text{P}(\text{O})\text{H}$  and a base under phase-transfer catalysis conditions [<1994JGU1134>](#). The conversion of the 1,1-ditosylate **91** into the tris(phosphonate) **92** in 71% yield using  $(\text{EtO})_2\text{P}(\text{O})\text{H}/\text{NaH}$  (Equation (10)) may also be considered in this category [<1997PS\(129\)13>](#).



#### 4.12.1.5.2 From reactions of 1-haloalkylphosphorus compounds with phosphorus anions

A new example of this type is the reaction of **93** with the anion derived from **94** to give **95** in 60% yield (Equation (11)) [<1995MI129>](#).



#### 4.12.1.5.3 From reactions of 1-haloalkylphosphorus compounds with phosphines

Reaction of  $(\text{R}^1\text{O})_2\text{P}(\text{O})\text{CH}_2\text{OTf}$  with  $\text{R}^2_3\text{P}$  may be used to obtain the following phosphonate/phosphonium salts:  $(\text{MeO})_2\text{P}(\text{O})\text{CH}_2\text{P}^+\text{Ph}_3 \text{OTf}^-$  (83%),  $(\text{EtO})_2\text{P}(\text{O})\text{CH}_2\text{P}^+\text{Ph}_3 \text{OTf}^-$  (82%),  $(\text{BnO})_2\text{P}(\text{O})\text{CH}_2\text{P}^+\text{Ph}_3 \text{OTf}^-$  (84%), and  $(\text{EtO})_2\text{P}(\text{O})\text{CH}_2\text{P}^+\text{Bu}_3 \text{OTf}^-$  (72%) [<1996JOC7697>](#).

#### 4.12.1.5.4 From Arbuzov reactions of 1-haloalkylphosphorus compounds

Significant new developments in this area include the use of microwave irradiation to promote the reaction of  $(\text{EtO})_2\text{P}(\text{O})\text{CH}_2\text{I}$  with  $(\text{EtO})_3\text{P}$  giving a 91% yield of  $(\text{EtO})_2\text{P}(\text{O})\text{CH}_2\text{P}(\text{O})(\text{OEt})_2$  in 3 min [<2000PS\(160\)195>](#), and use of the silyloxyphosphine  $\text{Bu}_2\text{POTMS}$  to convert  $\text{R}_2\text{P}(\text{O})\text{CH}_2\text{Cl}$  into  $\text{R}_2\text{P}(\text{O})\text{CH}_2\text{P}(\text{O})\text{Bu}_2$  for  $\text{R} = \text{Ph}$  (63%) and  $\text{Bu}$  (80%) [<1999JGU1047>](#). By working at high temperature under vacuum to ensure the removal of the otherwise troublesome benzyl chloride, the Arbuzov reaction can now be achieved with tribenzyl phosphite and this has allowed, for example, the conversion of  $(\text{BnO})_2\text{P}(\text{O})\text{CH}_2\text{Cl}$  into  $(\text{BnO})_2\text{P}(\text{O})\text{CH}_2\text{P}(\text{O})(\text{OBn})_2$  in 92% yield and  $\text{BnOP}(\text{O})(\text{CH}_2\text{Cl})_2$  into compound **96** in 71% yield [<1995TL5183, 1995HCA670>](#). This has been applied also in the synthesis of compounds such as **97** [<2001T9149>](#) and of  $(\text{BnO})_2\text{P}(\text{O})\text{CH}_2\text{P}(\text{O})(\text{OBn})_2$  from  $(\text{BnO})_2\text{P}(\text{O})\text{CH}_2\text{Br}$  in 37% yield [<1999BMCL3069>](#). Reaction of  $\text{BuOP}(\text{O})(\text{CH}_2\text{Cl})_2$  with 2 equiv. of  $(\text{BuO})_3\text{P}$  gives the product

molecular Arbuzov reaction to give the cyclic product **99** in 83% yield [<2002JGU486>](#).



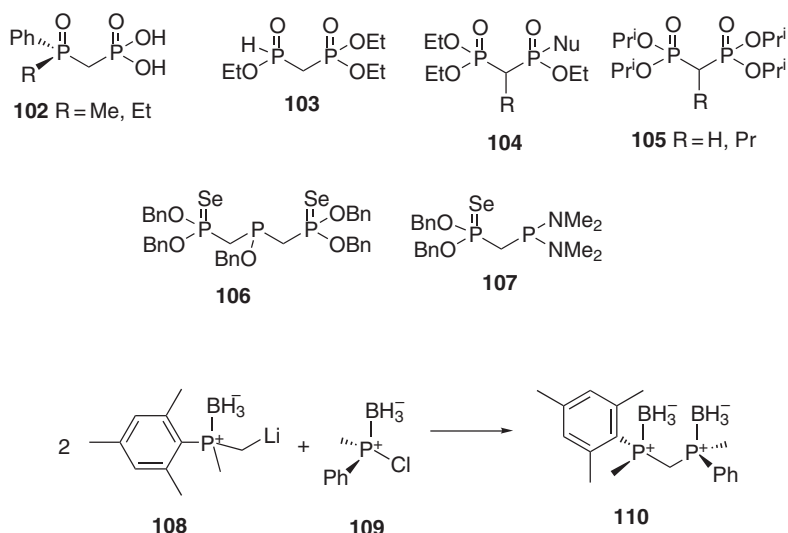
#### 4.12.1.5.5 From 1,1-dimetallor alkanes

monophosphonate.



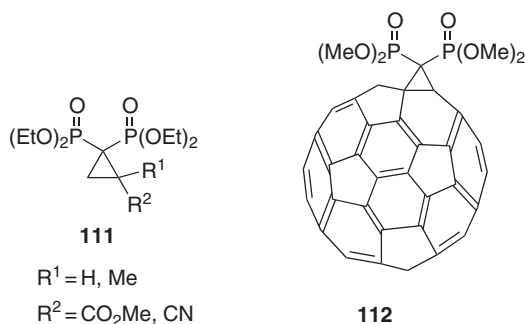
#### 4.12.1.5.6 From electrophilic substitution on 1-metalloalkylphosphorus compounds

selectivity (Equation (12))  $\langle 2001C694 \rangle$ .



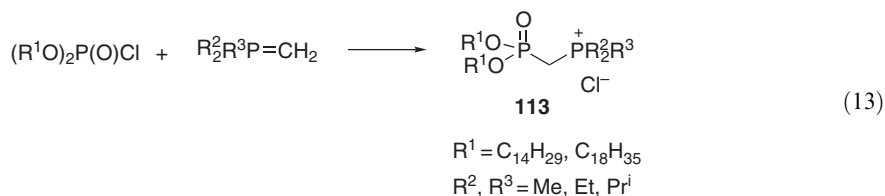
#### 4.12.1.5.7 From diphosphorus-substituted carbenes

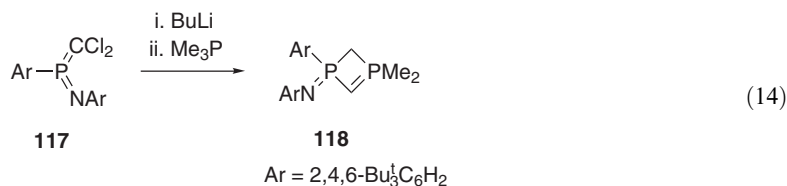
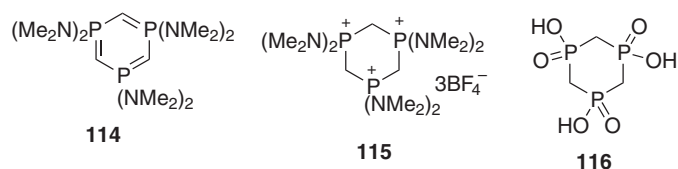
Electrolysis of  $(\text{EtO})_2\text{P}(\text{O})\text{CCl}_2\text{P}(\text{O})(\text{OEt})_2$  in the presence of activated alkenes such as methyl acrylate and acrylonitrile gives the cyclopropanediphosphonates **111** in 40–75% yield <1999S1903>. Treatment of  $\text{C}_{60}$  with  $(\text{MeO})_2\text{P}(\text{O})\text{CH}(\text{Br})\text{P}(\text{O})(\text{OMe})_2$  and DBU gives **112** in 41% yield and subsequent reaction with TMSI gives the corresponding diphosphonic acid <2000SL1816>.



#### 4.12.1.5.8 By electrophilic attack on phosphorus ylides and from 1,3-diphosphaalkenes generated in other ways

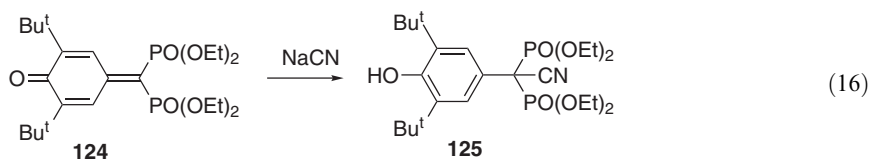
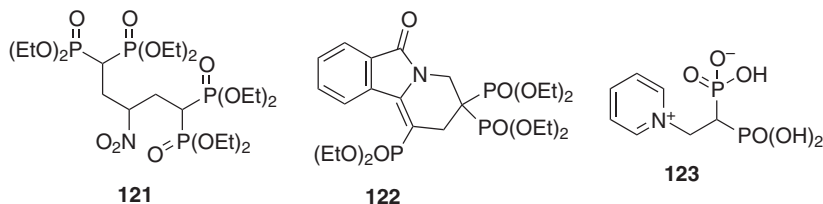
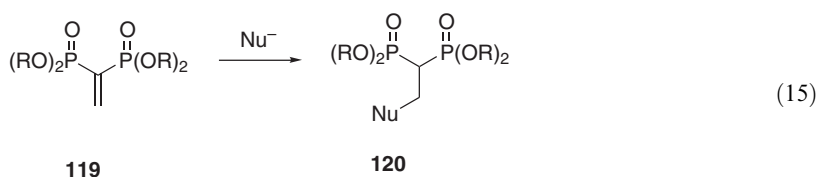
A range of cationic phosphonolipids **113**, of interest for gene transfection, have been prepared in 60–80% yield by the reaction of long-chain dialkoxyphosphoryl chlorides with simple nonstabilized ylides (Equation (13)) <2000JMC4617>. The unusual cyclic triylide **114** reacts with  $\text{HBF}_4$  in  $\text{Et}_2\text{O}$  to give the salt **115** <1997AG(E)2349> and with aqueous  $\text{HCl}$  to give the triphosphinic acid **116** <1999AG(E)829>. Treatment of compound **117** with  $\text{BuLi}$  followed by  $\text{Me}_3\text{P}$  results in carbenoid formation, interaction with  $\text{Me}_3\text{P}$  to give an ylide, and a series of proton transfers to produce **118** (Equation (14)) <1994AG(E)982>.





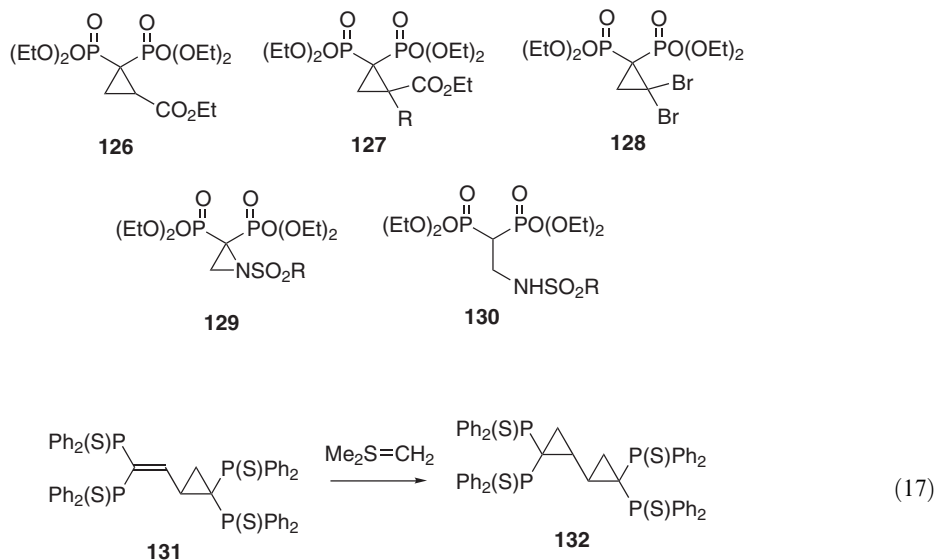
#### 4.12.1.5.9 From 1,1-diphosphorus-substituted alkenes

The addition of nucleophiles to diphosphonates **119** to give products **120** (Equation (15)), described in chapter 4.12.1.5.14 of <1995COFGT(4)543>, has been used widely and the range of nucleophiles used has been extended considerably. Examples include addition of the anion of Meldrum's acid <2001JOC3704>, a carbohydrate-derived amide in the synthesis of sialidase inhibitors <1998HCA1896>, PH phosphoranes <1995PS(103)125>, the anions of aryl and heteroaryl methyl ketones in the synthesis of antiinflammatory and antiarthritic compounds <1998BMCL1093>, sulfur-containing aryllithium and aryl Grignard reagents <1999PS(144)325>, 3-pyridyllithium <2003S1971>, substituted imidazoles <1998CPB1703>, and a variety of enolate anions <1994JMC4449>. Addition of the anion of nitromethane to the tetraethyl ester has been re-examined and found to give either the previously reported monoadduct or the double addition product **121** depending on the conditions <1996PS(112)137>. Treatment of the tetraethyl ester with sodium phthalimide results in double Michael addition followed by a Wadsworth–Emmons reaction to afford **122** <2000PS(156)107>. Pyridine and a range of other nitrogen heterocycles add to vinylidenediphosphonic acid to give zwitterionic products such as **123** <1995BAU1528>. The diphosphonate **124** reacts with NaCN to give product **125** in 70% yield (Equation (16)) <1994PS(86)13>.



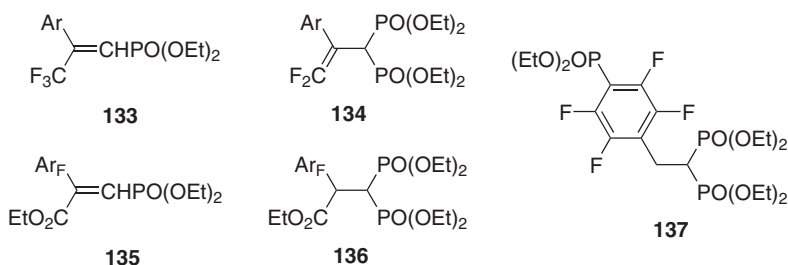
A number of methods involving the formation of cyclopropanediphosphonates have been reported. Treatment of tetraethyl vinylidenediphosphonate with ethyl bromoacetate and LDA

results in cyclopropanation to give **126** in 72% yield <1999SC4251>, and use of substituted  $\alpha$ -bromo esters similarly gives **127** <2002SC1543>. Addition of tribromomethyl lithium followed by base treatment gives **128** <2003S1971>, and the aziridines **129** resulting from reaction with sulfonamides and iodosobenzene undergo transfer hydrogenation with ammonium formate to afford **130** <2003S1971>. Cyclopropanation of the double bond in **131** with  $\text{Me}_2\text{S}=\text{CH}_2$  gives **132** (Equation (17)) <1995CB365>.



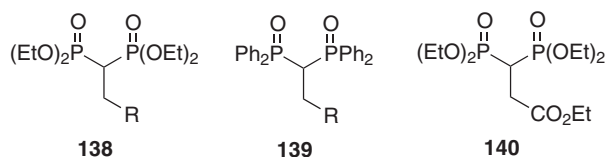
#### 4.12.1.5.10 From vinylphosphorus compounds

Addition of phosphite anions to a variety of fluorine-containing vinylphosphonates has been examined. Thus, sodium diethylphosphite adds to compounds **133** with loss of  $\text{F}^-$  to give **134** <1995PS(104)197, 1996PS(111)62>, and the fluoroaryl compounds **135** similarly give **136** <1996JFC(77)71>. Removal of the ethyl ester group in compounds **135** generally results in a change in the site of addition to give 1,2-diphosphonates, but for  $\text{Ar}_\text{F} = \text{C}_6\text{F}_5$  only the original regioselectivity is preserved with additional ring substitution to afford **137** <1996JFC(77)71>.



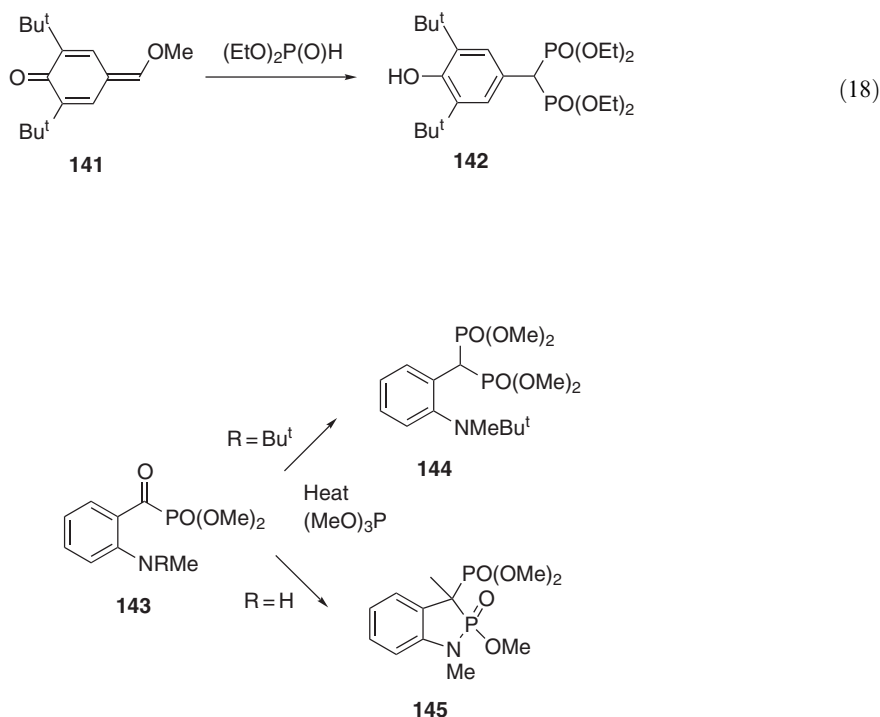
#### 4.12.1.5.11 From alkynes

A detailed mechanistic study on the twofold addition of compounds such as  $(\text{EtO})_2\text{P}(\text{O})\text{H}$  and  $\text{Ph}_2\text{P}(\text{O})\text{H}$  to alkynes,  $\text{RC}\equiv\text{CH}$ , in the presence of  $\text{KOH}$  to give products **138** and **139** has appeared. A variety of conditions including thermal, photochemical, ultrasound, and radical were examined <1997JOC2414>. An improved method involving the treatment of  $\text{HC}\equiv\text{C}-\text{CO}_2\text{Et}$  with  $(\text{EtO})_2\text{P}(\text{O})\text{H}$ ,  $\text{KOH}$  and alumina gives **140** in 95% yield <1999TL2311>.



#### 4.12.1.5.12 Miscellaneous methods

Treatment of compound **141** with an excess of diethyl phosphite gives **142** in 81% yield (Equation (18)) <1994PS(86)13>. Heating the benzoylphosphonate **143** with trimethyl phosphite gives **144** for R = Bu<sup>t</sup>, while for R = H the cyclic product **145** is obtained (Scheme 7) <1997JCS(P1)2545>.

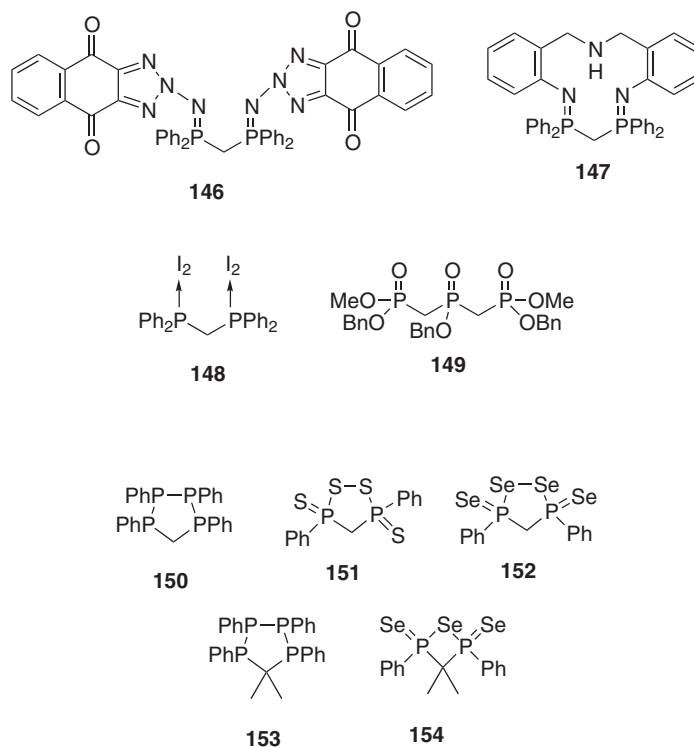


Scheme 7

#### 4.12.1.5.13 By oxidation of tricoordinate species

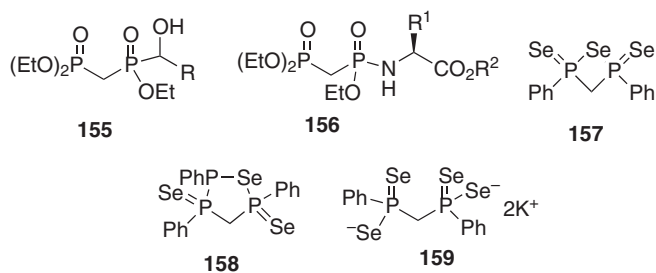
New oxidative transformations of Ph<sub>2</sub>PCH<sub>2</sub>PPh<sub>2</sub> include its conversion, by oxidation and reaction with ArN<sub>3</sub>, into the previously unknown oxide/imines Ph<sub>2</sub>P(O)CH<sub>2</sub>P(=NAr)Ph<sub>2</sub> <2000S2085>, reaction with 2,3-diazido-1,4-naphthoquinone to give **146** in 51% yield <1997JOC4082>, and with di(2-azidobenzyl)amine to give a 97% yield of **147** <1997JOM(529)121>. Treatment with iodine gives the expected bis(iodophosphonium salt) in solution but in the solid state this exists as the molecular complex **148** <1998JCS(D)2379>. Electrochemical oxidation of tetraphenylporphine in the presence of Ph<sub>2</sub>PCH<sub>2</sub>PPh<sub>2</sub> leads to dimeric structures linked by —Ph<sub>2</sub>P<sup>+</sup>CH<sub>2</sub>P<sup>+</sup>Ph<sub>2</sub>— <2001EJ1659>. Reaction of compound **68** with benzyl alcohol followed by MCPBA gives **149** <2002JOC146>. More radical oxidation processes are observed with cyclopolyphosphines. When compound **150** is treated with sulfur and DBU the dithiadiphospholane **151** is produced in 40% yield, while the treatment with selenium gives **152** in 94% yield. The dimethyl analog **153** reacts with selenium to give a 68% yield of the selenadiphosphetane product **154** <2001CC2288>.





#### 4.12.1.5.14 Interconversions

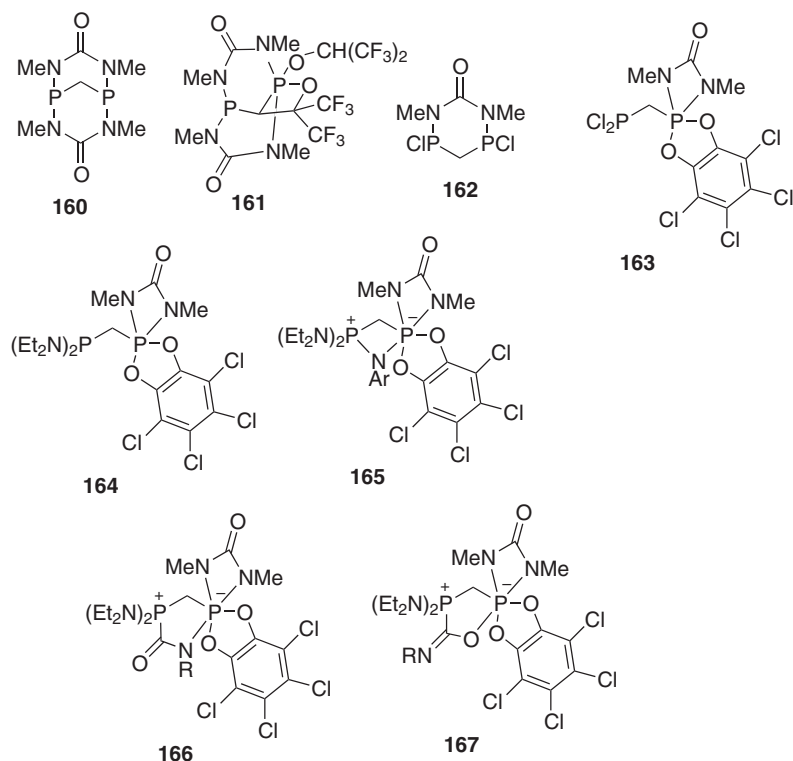
New interconversions based on  $\text{Cl}_2\text{P}(\text{O})\text{CH}_2\text{P}(\text{O})\text{Cl}_2$  include its reaction with  $\text{CF}_3\text{CH}_2\text{OH}$  and  $\text{Et}_3\text{N}$  to give  $(\text{CF}_3\text{CH}_2\text{O})_2\text{P}(\text{O})\text{CH}_2\text{P}(\text{O})(\text{OCH}_2\text{CF}_3)_2$  in 90% yield [\[1998TL6263, 1999PS\(144\)681\]](#), an improved preparation of  $(\text{BnO})_2\text{P}(\text{O})\text{CH}_2\text{P}(\text{O})(\text{OBn})_2$  [\[2002SC211\]](#), and formation of symmetrical diphosphonic acid diesters  $(\text{RO})(\text{HO})\text{P}(\text{O})\text{CH}_2\text{P}(\text{O})(\text{OH})(\text{OR})$  and tetraesters  $(\text{RO})(\text{MeO})\text{P}(\text{O})\text{CH}_2\text{P}(\text{O})(\text{OMe})(\text{OR})$  and  $(\text{RO})_2\text{P}(\text{O})\text{CH}_2\text{P}(\text{O})(\text{OR})_2$  using tetrazole as a catalyst [\[2001T8637, 2002SC2683\]](#). The PH of hydrogen phosphinates such as  $(\text{EtO})_2\text{P}(\text{O})\text{CH}_2\text{P}(\text{O})\text{H}(\text{OEt})$  reacts with aldehydes to give **155** [\[2001TL8451\]](#) and may be replaced by an aryl group in a palladium-catalyzed process [\[2002SC2951\]](#) or by Me using  $\text{NaN}(\text{TMS})_2$  and MeI [\[1995JMC2596\]](#). Selective mono-deprotection of  $(\text{BnO})_2\text{P}(\text{O})\text{CH}_2\text{P}(\text{O})(\text{OBn})_2$  can be achieved with DABCO or quinuclidine [\[1995JOC2946\]](#) and the resulting  $\text{P}-\text{OH}$  converted into  $\text{P}-\text{Cl}$  using oxalyl chloride [\[1995TL4785\]](#). The new compounds  $(\text{HO})\text{PhP}(\text{O})\text{CH}_2\text{P}(\text{O})\text{Ph}(\text{OH})$  and  $(\text{HO})\text{MeP}(\text{O})\text{CH}_2\text{P}(\text{O})\text{Me}(\text{OH})$  have been prepared by HCl hydrolysis of the corresponding diethyl esters [\[2000BAU1045\]](#). Transesterification of  $(\text{MeO})_2\text{P}(\text{O})\text{CH}_2\text{P}(\text{O})(\text{OMe})_2$  occurs on treatment with chloromethyl pivalate and NaI to give the tetrakis(pivaloyloxymethyl) ester [\[1999TL8491\]](#). Amino acid-functionalized phosphonates **156** have been prepared from *in situ* generated  $(\text{EtO})_2\text{P}(\text{O})\text{CH}_2\text{P}(\text{O})\text{Cl}(\text{OEt})$  and amino acid esters [\[1994TL5425\]](#). Reaction of compound **152** with  $\text{TMS}-\text{CN}$  removes one selenium atom to give **157**, while with  $\text{Bu}_3\text{P}$  a more profound change results to give **158** and with potassium reductive cleavage affords **159** [\[2003EJI1461\]](#).



The range of interconversions involving functionalization of the central carbon of  $(\text{EtO})_2\text{P}(\text{O})\text{CH}_2\text{P}(\text{O})(\text{OEt})_2$  and related compounds has been extended considerably. Preparation of  $(\text{EtO})_2\text{P}(\text{O})\text{CD}_2\text{P}(\text{O})(\text{OEt})_2$  with 93% D has been reported [<1994JCS\(P1\)821>](#), and new compounds  $(\text{EtO})_2\text{P}(\text{O})\text{CH}(\text{R})\text{P}(\text{O})(\text{OEt})_2$  have been prepared with  $\text{R} = \text{CH}_2\text{TMS}$  [<2001T4423>](#),  $\text{CH}_2\text{CO}_2\text{Me}$  [<1999S1056>](#),  $\text{CO}_2\text{Bn}$  [<1997CC87>](#),  $\text{CH}_2\text{CH}(\text{OBn})\text{CH}_2\text{NEt}_2$ , and  $\text{CH}_2\text{CH}(\text{OH})\text{CH}_2\text{N}(\text{Bn})_2$  [<2001JCS\(P1\)1086>](#). Alkylation using farnesyl bromide [<1997BMCL2435>](#) and bromoalkylphosphonates [<2002PS\(177\)231>](#) has also been reported. Radical addition by either selenide [<1995TL6403>](#) or xanthate-functionalized [<2003SL387>](#) bis(phosphonates) to alkenes has also been used to access 2-alkylated products. Conjugate addition of the anion of  $(\text{EtO})_2\text{P}(\text{O})\text{CH}_2\text{P}(\text{O})(\text{OEt})_2$  may be carried out using phase-transfer catalysis conditions [<1998JOU52>](#) and a range of heterocyclic Michael acceptors have also been used [<2003SL785>](#). If iodine is added, ring closure to cyclopropane diphosphonates occurs and this provides an alternative approach to compounds such as **126** [<1994SC1425>](#). Functionalization of  $\text{C}_{60}$  with methylenediphosphonate groups has been achieved using  $(\text{EtO})_2\text{P}(\text{O})\text{CH}_2\text{P}(\text{O})(\text{OEt})_2$ ,  $\text{I}_2$ , and a large excess of NaH to give both mono- [<2000TL3947>](#) and difunctionalized [<2001T7331>](#) products, while the latter may also be obtained as a mixture of isomers by the treatment with  $(\text{EtO})_2\text{P}(\text{O})\text{CHBrP}(\text{O})(\text{OEt})_2$  and NaH [<2002JCS\(P2\)1173>](#). A detailed study of the C-2 alkylation of  $(\text{BnO})_2\text{P}(\text{O})\text{CH}_2\text{P}(\text{O})(\text{OBn})_2$  has also been reported [<1999BMC901>](#).

#### 4.12.1.6 Penta- and Hexacoordinate Systems

There have been relatively few developments in this area since the publication of chapter 4.12.1.6 in [<1995COFGT\(4\)543>](#). Reaction of  $(\text{Et}_2\text{N})_2\text{PCH}_2\text{P}(\text{NEt}_2)_2$  with either hexafluoroacetone followed by HF [<1999EJI1665>](#) or hexafluorothioacetone dimer followed by warming to room temperature [<2001EJI2377>](#) gives  $(\text{Et}_2\text{N})_2\text{F}_2\text{PCH}_2\text{PF}_2(\text{NEt}_2)_2$ . The bicyclic compound **160** reacts with hexafluoroacetone to give the remarkable structure **161** [<2001EJI195>](#). Treatment of the heterocycle **162** with tetrachloro-*o*-benzoquinone affords compound **163**, which reacts with diethylamine to give **164**. This interacts both with aryl azides [<1996PS\(109\)493>](#) and simple isocyanates [<1995TL2021>](#) in a most unusual way to give products **165** and a mixture of **166** and **167**, respectively.



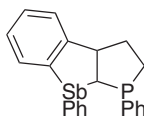
## 4.12.2 FUNCTIONS CONTAINING ONE PHOSPHORUS AND ONE ARSENIC, ANTIMONY, OR BISMUTH

### 4.12.2.1 Phosphorus and Arsenic Functions

There have been very few developments in this area since the publication of chapter 4.12.2.1 in <1995COFGT(4)543>. Treatment of  $\text{Me}_2\text{PCH}_2\text{Li}$  with  $\text{AsCl}_3$  gives  $(\text{Me}_2\text{PCH}_2)_3\text{As}$  <1997JOM(529)151> and five compounds of the type  $\text{R}^1_2\text{PCH}_2\text{AsR}^2_2$  have been prepared from  $\text{R}^1_2\text{PCH}_2\text{SnPh}_3$ ,  $\text{PhLi}$ , and  $\text{R}^2_2\text{AsCl}$  <1999JCS(D)1867>. Two compounds  $\text{Me}_3\text{As}^+\text{CH}_2\text{P}(\text{O})(\text{OR})_2\text{I}^-$  ( $\text{R} = \text{C}_{14}\text{H}_{29}$ ,  $\text{C}_{18}\text{H}_{35}$ ), of interest as lipids for DNA transfection, have been obtained by the reaction of  $\text{Me}_3\text{As}=\text{CH}(\text{TMS})$  with  $(\text{RO})_2\text{P}(\text{O})\text{Cl}$  followed by acid hydrolysis <2000AG(E)629>.

### 4.12.2.2 Phosphorus and Antimony Functions

There have been very few developments in this area since the publication of chapter 4.12.2.2 in <1995COFGT(4)543>. Treatment of  $\text{Me}_2\text{PCH}_2\text{Li}$  with  $\text{SbCl}_3$  gives  $(\text{Me}_2\text{PCH}_2)_3\text{Sb}$  <1997JOM(529)151>, and reaction of the zirconacycle **12** with  $\text{PhSbCl}_2$  results in transmetallation to give **168** <1997CC1239>.



**168**

### 4.12.2.3 Phosphorus and Bismuth Functions

The first compound containing this function has now been described. Treatment of  $\text{Me}_2\text{PCH}_2\text{Li}$  with  $\text{BiCl}_3$  gives  $(\text{Me}_2\text{PCH}_2)_3\text{Bi}$  <1997JOM(529)151>.

## 4.12.3 FUNCTIONS CONTAINING PHOSPHORUS AND A METALLOID

### 4.12.3.1 Dicoordinate Phosphorus Derivatives

There have been no significant developments in this area since the publication of chapter 4.12.3.1 in <1995COFGT(4)543>.

### 4.12.3.2 Tricoordinate Phosphorus Derivatives

#### 4.12.3.2.1 Tricoordinate phosphorus and silicon functions

There have been a large number of developments in the synthesis of compounds of this type since the publication of chapter 4.12.3.2.1 in <1995COFGT(4)543>. These are categorized according to the starting materials used.

##### (i) From 1-metalloalkylsilanes

Several routes from  $\text{TMS}-\text{CH}_2\text{MgCl}$  to products of the type  $\text{TMS}-\text{CH}_2\text{PR}^1\text{R}^2$  have been described including transmetallation with  $\text{CdCl}_2$  followed by reaction with  $\text{ArPCl}_2$  to give  $\text{TMS}-\text{CH}_2\text{P}(\text{Cl})\text{Ar}$  in 53% yield ( $\text{Ar} = 2,4,6-(\text{CF}_3)_3\text{C}_6\text{H}_2$ ) <1994JOM(469)125>, reaction

with  $\text{Bn}^*\text{PBr}_2$  followed by  $\text{MeMgCl}$  to afford  $\text{TMS}-\text{CH}_2\text{P}(\text{Me})\text{Bn}^*$  ( $\text{Bn}^* = 2\text{-bromobenzyl}$ ) <1994ZN(B)1606>, and reaction with  $\text{PhP}(\text{Cl})\text{N}(\text{Me})\text{Ph}$  followed by  $\text{MeLi}$  to give  $\text{TMS}-\text{CH}_2\text{P}(\text{Me})\text{Ph}$  in 85% yield <1998CC149>. Grignard reagents with other groups on silicon have also been used and  $\text{PhMe}_2\text{SiCH}_2\text{MgCl}$  reacts with  $\text{Ph}_2\text{PCl}$  to give  $\text{PhMe}_2\text{-SiCH}_2\text{PPh}_2$  <2001JOM(629)7>, while  $(\text{Pr}^i\text{O})_3\text{SiCH}_2\text{MgCl}$  and  $\text{PCl}_3$  give  $[(\text{Pr}^i\text{O})_3\text{SiCH}_2]_3\text{P}$  which is reduced by  $\text{LiAlH}_4$  to afford  $(\text{H}_3\text{SiCH}_2)_3\text{P}$  <1998JMAC1749>.

(ii) From 1-haloalkylsilanes

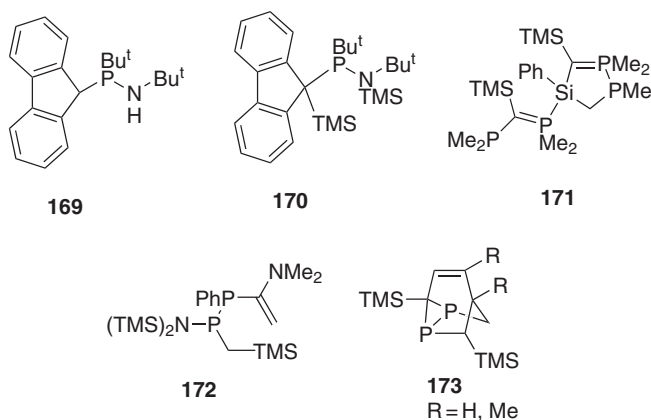
Treatment of  $\text{MeSi}(\text{CH}_2\text{Cl})_3$  with  $\text{Ph}_2\text{PLi}$  gives  $\text{MeSi}(\text{CH}_2\text{PPh}_2)_3$  <1995ICA(235)215>. In the course of studies on P/N macrocycles,  $\text{ClCH}_2\text{SiMe}_2\text{NHSiMe}_2\text{CH}_2\text{Cl}$  has been reacted with  $\text{PhPHLi}$  to give  $\text{PhPHCH}_2\text{SiMe}_2\text{NHSiMe}_2\text{CH}_2\text{PHPh}$  <1996CC2783>, while treatment of  $\text{PhNHSiMe}_2\text{CH}_2\text{Cl}$  with  $\text{BuLi}$  and  $\text{PhPH}_2$  gives  $\text{PhN}(\text{Li})\text{SiMe}_2\text{CH}_2\text{P}(\text{Ph})\text{CH}_2\text{SiMe}_2\text{N}(\text{Li})\text{Ph}$  <2001JA3960>.

(iii) From 1-metalloalkylphosphines

An improved procedure for the reaction of  $\text{Me}_2\text{PCH}_2\text{Li}$  with  $\text{MeSiCl}_3$  gives  $\text{MeSi}(\text{CH}_2\text{PMe}_2)_3$  in 52% yield <1997JA11244>. Treatment of  $\text{HC}(\text{SiMe}_2\text{Br})_3$  with  $\text{Ph}_2\text{PCH}_2\text{Li}$  gives  $\text{HC}(\text{SiMe}_2\text{CH}_2\text{PPh}_2)_3$  in 69% yield <2000JCS(D)2183> and the same reagent has been used to convert terminal  $-\text{SiMe}_2\text{Cl}$  functions in dendrimers into  $-\text{SiMe}_2\text{CH}_2\text{PPh}_2$  <1999CC1623, 2002EJO1085>. Dendrimers with terminal  $-\text{SiCl}_3$  groups are similarly converted into the analogs with  $-\text{Si}(\text{CH}_2\text{PMe}_2)_3$  using  $\text{Me}_2\text{PCH}_2\text{Li}$  <2002JCS(D)1997>. Treatment of the fluorenylphosphine **169** with  $\text{BuLi}$  followed by  $\text{TMS}-\text{Cl}$  gives a 67% yield of **170** <2002EJ1678>, while reaction of  $(\text{Me}_2\text{P})_2\text{C}(\text{TMS})\text{Li}$  with  $\text{PhSiCl}_3$  leads via a series of rearrangements to the unexpected product **171** <1995JOM(501)167>.

(iv) From 2-silylphosphaalkenes and -phosphaalkynes

An ene reaction between  $(\text{TMS})_2\text{N}-\text{P}=\text{CH}(\text{TMS})$  and  $\text{PhP}=\text{C}(\text{Me})\text{NMe}_2$  gives the product **172** <1997JOC7605>, while  $\text{TMS}-\text{C}\equiv\text{P}$  reacts with butadiene and 2,3-dimethylbutadiene to give products **173** <1999EJO363>.

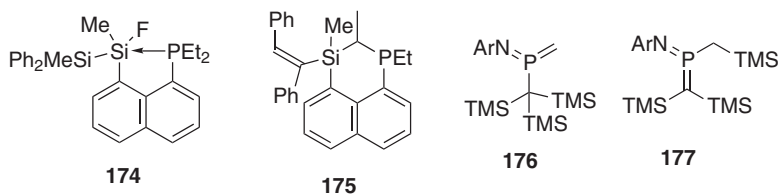


(v) From phosphino(silyl)carbenes

Full details of the addition of  $(\text{Pr}^i_2\text{N})_2\text{P}-(\text{TMS})\text{C:}$  to alkenes to give 1-phosphino-1-silylcyclopropanes have appeared <2000JA4464>, and by using acrylates and acrylamides with a chiral auxiliary group this addition has been achieved asymmetrically <2001JOC8240>.

(vi) *Miscellaneous methods*

Heating compound **174** with diphenylacetylene leads to the loss of  $\text{Ph}_2\text{MeSiF}$  and rearrangement to afford **175** in 78% yield [<2001JA9210>](#), while compound **176** rearranges by a 1,3-silyl shift on boiling in toluene to give **177** ( $\text{Ar} = 2,4,6\text{-Bu}^t_3\text{C}_6\text{H}_2$ , 85%) [<1997CC293>](#).

(vii) *Interconversions*

Treatment of  $\text{TMS}-\text{CH}(\text{Ph})\text{PCl}_2$  with  $\text{HSiCl}_3$  and  $\text{Et}_3\text{N}$  gives  $\text{TMS}-\text{CH}(\text{Ph})\text{P}(\text{SiCl}_3)_2$  [<1996JOM\(521\)417>](#).

(viii) *By reduction of tetracoordinate phosphorus functions*

Deprotection of the bis(borane) adduct of compounds such as  $\text{Ph}_2\text{PCH}_2\text{SiMe}_2\text{CH}_2\text{PPh}_2$  may be achieved using  $\text{HBF}_4 \cdot \text{Me}_2\text{O}$  [<1995T7655>](#).

4.12.3.2.2 *Tricoordinate phosphorus and germanium or boron functions*

There have been no significant developments in this area since the publication of chapters 4.12.3.2.2 and 4.12.3.2.3 in [<1995COFGT\(4\)543>](#).

4.12.3.3 *Tetracoordinate Phosphorus Derivatives*4.12.3.3.1 *Tetracoordinate phosphorus and silicon functions*

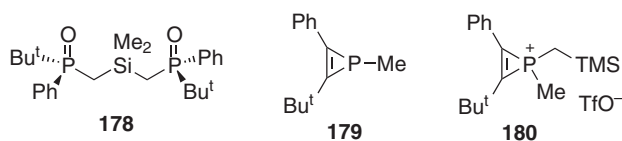
There have been a large number of developments in the synthesis of compounds of this type since the publication of chapter 4.12.3.3.1 in [<1995COFGT\(4\)543>](#). These are categorized according to the starting materials used.

(i) *From 1-metalloalkylsilanes*

The Grignard reagent  $\text{TMS}-\text{CH}_2\text{MgCl}$  reacts with  $(\text{EtO})_2\text{CH}-\text{P}(\text{O})\text{H}(\text{OEt})$  to give  $(\text{EtO})_2\text{CH}-\text{P}(\text{O})\text{H}(\text{CH}_2-\text{TMS})$  in 72% yield [<1999SL1633>](#), while the organocerium reagent  $\text{TMS}-\text{CH}_2\text{CeCl}_2$  reacts with  $\text{Ph}_2\text{P}(\text{O})\text{Cl}$  to give  $\text{TMS}-\text{CH}_2\text{P}(\text{O})\text{Ph}_2$  in 54% yield [<1999EJO2299>](#). The compound **83** mentioned earlier in [Section 4.12.1.4.5](#) also contains a function of this type.

(ii) *From reactions of 1-haloalkylsilanes with phosphorus nucleophiles*

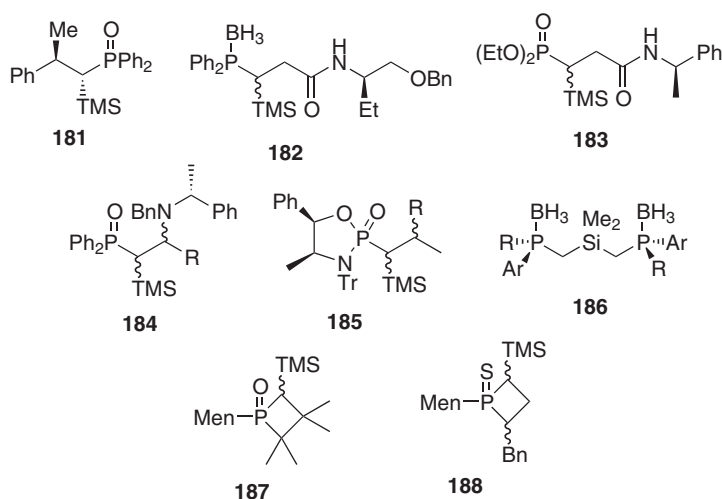
Treatment of enantiomerically pure  $\text{Ph}(\text{Bu}^t)\text{P}(\text{O})\text{H}$  with LDA followed by  $\text{ClCH}_2\text{SiMe}_2\text{CH}_2\text{Cl}$  gives the chiral product **178** with no racemization [<2000EJO3205>](#). Reaction of the phosphirene **179** with  $\text{TMS}-\text{CH}_2\text{OTf}$  gives the salt **180** [<1998S175>](#).



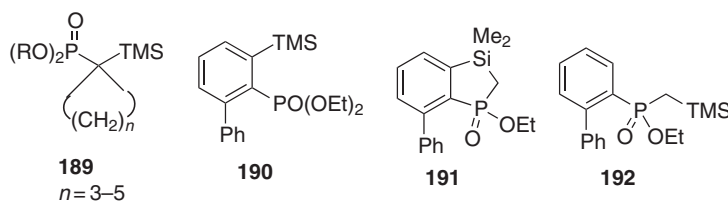
(iii) From 1-metalloalkylphosphorus compounds

The reaction of  $(\text{MeO})_2\text{P}(\text{O})\text{CH}_2\text{Li}$  with  $\text{R}_3\text{SiCl}$ ,  $\text{R}_2\text{SiCl}_2$ , and  $\text{RSiCl}_3$  to give  $\text{R}_3\text{SiCH}_2\text{P}(\text{O})(\text{OMe})_2$ ,  $\text{R}_2\text{Si}[\text{CH}_2\text{P}(\text{O})(\text{OMe})_2]_2$ , and  $\text{RSi}[\text{CH}_2\text{P}(\text{O})(\text{OMe})_2]_3$ , respectively, has been carried out for  $\text{R} = \text{C}_{12}\text{H}_{25}$  and  $\text{C}_{18}\text{H}_{37}$  [\[1999JOM\(575\)126\]](#). Treatment of  $\text{Ph}_2\text{P}(=\text{N}-\text{TMS})\text{Me}$  with  $\text{BuLi}$  followed by  $\text{Et}_2\text{NSiMe}_2\text{Cl}$  gives  $\text{Ph}_2\text{P}(=\text{N}-\text{TMS})\text{CH}_2\text{SiMe}_2\text{NEt}_2$  in 72% yield [\[1999JCS\(D\)3413\]](#).

Various attempts to control the relative and absolute stereochemistry of silylation adjacent to phosphorus have been described. A  $\beta$ -stereocenter directs  $\alpha$ -silylation to give predominantly the *anti* product such as in **181** [\[1996TL7461, 1998JCS\(P1\)3405\]](#), while more remote auxiliary groups have been examined in lithiation and silylation to obtain products such as **182** [\[2001JOC5566\]](#) and **183** [\[2001EJO3031\]](#). Control of the stereochemistry of conjugate addition of organometallics to vinylphosphine oxides followed by trapping with  $\text{TMS}-\text{Cl}$  has also been achieved using both chiral organometallics to give products such as **184** [\[1998TL1637\]](#) and a chiral phosphorus compound to give products such as **185** [\[2000SL1771\]](#). Further examples of the reaction of lithiated chiral phosphine-borane adducts with both  $\text{Me}_2\text{SiCl}_2$  and  $\text{Ph}_2\text{SiCl}_2$  to give products such as **186** have been described. The lithium compounds may be obtained either from an enantiomerically pure phosphine-borane adduct [\[1998OM668, 2001JOM\(624\)333\]](#) or, for  $\text{R} = \text{Me}$ , by enantioselective deprotonation of  $\text{ArP}(\text{BH}_3)\text{Me}_2$  in the presence of sparteine [\[1995JA9075, 2001S2341\]](#). Silylation of phosphetane oxides and sulfides bearing a *P*-menthyl group to give products such as **187** [\[1996JOM\(522\)223\]](#) and **188** [\[1997T4363\]](#) has also been examined.

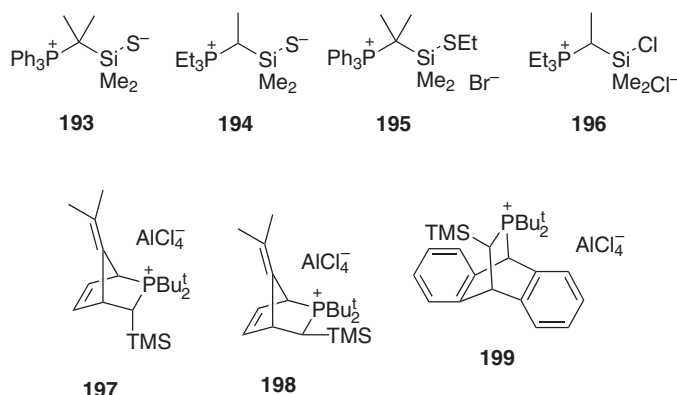


The regioselectivity of lithiation and silylation of  $\alpha,\beta$ - and  $\beta,\gamma$ -unsaturated phosphonates has been further examined and, although  $\alpha$ -silylation usually predominates, there are cases where  $\gamma$ -silylation occurs [\[1996JCS\(P1\)931, 2000JOC4175\]](#). The *P*-methyl groups of cyclophosphazenes may be converted into  $\text{CH}_2\text{Si}(\text{OMe})_3$  by the treatment with  $\text{BuLi}$  followed by  $(\text{MeO})_3\text{SiCl}$  [\[1999M89\]](#). Reaction of  $(\text{RO})_2\text{P}(\text{O})\text{CCl}_3$  with 2 equiv. of  $\text{BuLi}$  and  $\text{TMS}-\text{Cl}$  initially gives the carbenoid  $(\text{RO})_2\text{P}(\text{O})\text{C}(\text{Cl})(\text{Li})-\text{TMS}$  and when this reacts with  $\alpha,\omega$ -dihalides the cyclic products **189** result [\[1995S239\]](#). In an unusual process, reaction of **190** with an excess of  $\text{MeLi}$  gives both the cyclic product **191** (42%) and the acyclic product **192** (26%) [\[1998JOC2338\]](#).



(iv) From reactions of phosphorus ylides with silyl halides and from 2-silyl phosphalkenes generated in other ways

Reaction of  $(\text{Me}_2\text{N})_3\text{P}=\text{CH}_2$  with  $\text{TMS}-\text{OTf}$  and  $(\text{MeO})_3\text{SiOTf}$  gives the expected phosphonium triflates, while with  $\text{Pr}^i_2\text{PCl}_2$  only one chlorine is displaced to give  $(\text{Me}_2\text{N})_3\text{P}^+\text{CH}_2\text{PPr}^i_2(\text{Cl})\text{Cl}^-$  <1997ZN(B)669>. The cyclic oligomers of  $\text{R}^1\text{R}^2\text{Si}=\text{S}$  react with a wide range of simple ylides to give zwitterionic products such as **193** and **194** <2000BAU920> and these may undergo further transformations as illustrated by reaction of **193** with  $\text{EtBr}$  to give **195** and of **194** with  $\text{AcCl}$  to give **196** <2000BAU933>. The phosphonium salt  $\text{Bu}^t_2\text{P}^+=\text{CH}-\text{TMS}\text{AlCl}_4^-$  undergoes Diels-Alder cycloaddition with dimethylfulvene to give **197** and **198** and with anthracene to give **199** <1997JOM(535)91>.



(v) From 1-silyl-1-phosphorus-substituted alkenes

Catalytic hydrogenation of **200** gives **201** in 99% yield <1998JOC6239>. Conjugate addition of alkylolithiums to  $\alpha$ -silylallenylphosphonates **202** gives products **203** <1994RTC547>. Stereoselective addition of a chiral heterocyclic anion to  $(\text{EtO})_2\text{P}(\text{O})\text{C}(\text{=CH}_2)-\text{TMS}$  to give **204** has been examined <2002TA233>.

#### 4.12.3.3.2 Tetracoordinate phosphorus and germanium or boron functions

There has only been one significant development in the synthesis of compounds of this type since the publication of chapters 4.12.3.3.2 and 4.12.3.3.3 in <1995COFGT(4)543>. The cyclic trimer of  $\text{Me}_2\text{Ge}=\text{S}$  reacts with  $\text{Et}_3\text{P}=\text{CHMe}$  to give the zwitterionic product **205** in 84% yield <2001BAU1679>.

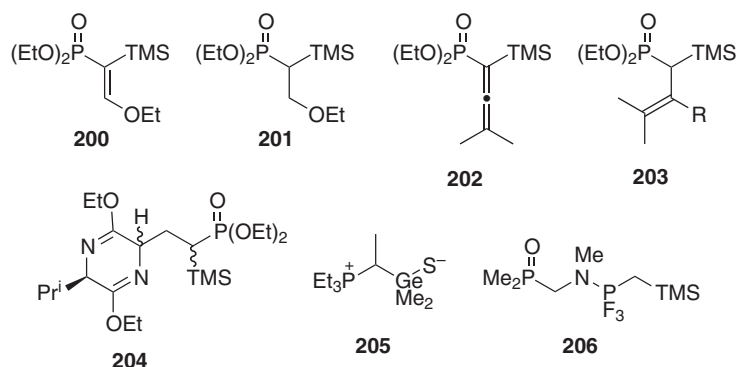
#### 4.12.3.4 Higher-coordinate Phosphorus Derivatives

##### 4.12.3.4.1 Higher-coordinate phosphorus and silicon functions

There has only been one significant development in the synthesis of compounds of this type since the publication of chapter 4.12.3.4.1 in <1995COFGT(4)543>. The compound  $\text{F}_4\text{PCH}_2-\text{TMS}$



(whose preparation remains unpublished) reacts with  $\text{Me}_2\text{P}(\text{O})\text{CH}_2\text{N}(\text{Me})\text{—TMS}$  with loss of  $\text{TMS—F}$  to afford **206** in 90% yield [<1995ZN\(B\)1818>](#).



#### 4.12.3.4.2 Higher-coordinate phosphorus and germanium or boron functions

As stated in chapters 4.12.3.4.2 and 4.12.3.4.3 of [<1995COFGT\(4\)543>](#) compounds of this type remain unknown.

### 4.12.4 FUNCTIONS CONTAINING PHOSPHORUS AND A METAL

#### 4.12.4.1 Group 1 and 2 Derivatives

##### 4.12.4.1.1 Compounds containing phosphorus and lithium

A detailed study of the configurational stability of  $\alpha$ -lithiated phosphine oxides  $\text{R}^1\text{P}(\text{O})\text{CH}(\text{Li})\text{R}^2$  has concluded that they are not configurationally stable even at  $-78^\circ\text{C}$  on a short timescale [<1995TL8473, 1996JCS\(P1\)2567>](#). The X-ray structure of  $(\text{Ph}_2\text{P}(\text{O})\text{CH}_2\text{Li})_2(\text{TMEDA})_2$  has been reported [<1999CC1401>](#) and X-ray structures of  $\text{Me}_2\text{P}(=\text{N—TMS})\text{CH}_2\text{Li}$ , which exists as a cyclic tetramer, and  $\text{Pr}^1\text{P}(=\text{N—TMS})\text{CMe}_2\text{Li}$ , which exists as a dimer, show considerable “aza-enolate” character in each case with the lithium located closer to N than to C [<1996CB253>](#). Treatment of nitriles  $\text{RCH}_2\text{CN}$  with  $(\text{EtO})_2\text{P}(\text{O})\text{Cl}$  and 2 equiv. of LDA gives the  $\alpha$ -lithiated phosphonates **207** [<2000JCS\(P1\)3311, 1994RTC45>](#). Reaction of (2-methoxybenzyl)di-*p*-tolylphosphine with BuLi in diethyl ether gives a lithiated derivative, which exists in the solid state as the dimeric structure **208** [<2001AG\(E\)183>](#).

##### 4.12.4.1.2 Compounds containing phosphorus and sodium

Reaction of compound **208** with  $\text{NaOBu}^1$  results in transmetalation to give the sodium derivative **209** [<2001AG\(E\)183>](#).

##### 4.12.4.1.3 Compounds containing phosphorus and potassium

The ease of conversion of  $\text{R}^1\text{R}^2\text{P}(\text{O})\text{CH}_2\text{CN}$  into the potassium derivatives  $\text{R}^1\text{R}^2\text{P}(\text{O})\text{CH}(\text{K})\text{CN}$  has been determined for a range of phosphonates, phosphinates, and phosphine oxides by the measurement of their  $\text{p}K_a$  values in DMSO using  $\text{MeS}(\text{O})\text{CH}_2^- \text{K}^+$  as a base [<1994JGU1735>](#).



#### 4.12.4.1.4 Compounds containing phosphorus and beryllium

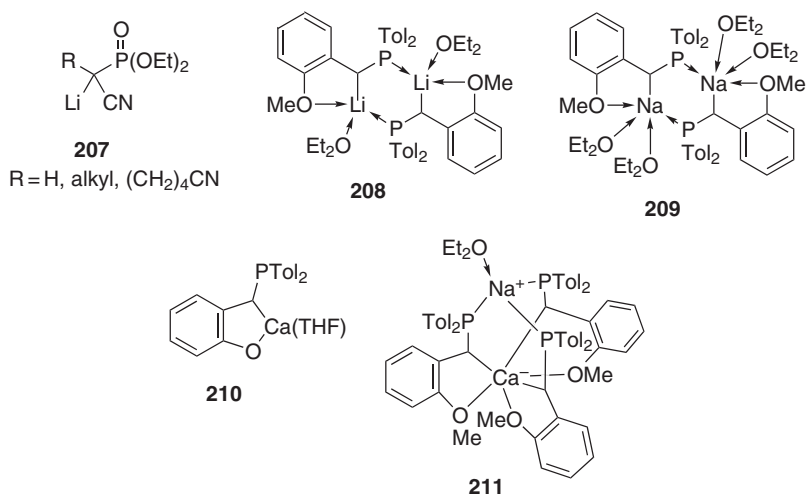
There have been no significant developments in this area since the publication of chapter 4.12.4.1.4 in <1995COFGT(4)543>.

#### 4.12.4.1.5 Compounds containing phosphorus and magnesium

There have been no significant developments in this area since the publication of chapter 4.12.4.1.5 in <1995COFGT(4)543>.

#### 4.12.4.1.6 Compounds containing phosphorus and heavier group 1 and 2 metals

The first compounds containing a P—C—Ca function have been prepared by the treatment of **208** and **209** with  $\text{CaI}_2$ . In the first case the reaction proceeds with loss of Me to give **210**, which exists in the solid state as a cubane tetramer, while in the second case the methoxy groups are retained to give the sodium calcate structure **211** <2001AG(E)183>.



#### 4.12.4.2 Compounds Containing Phosphorus and a Lanthanide

There have been no significant developments in this area since the publication of chapter 4.12.4.2 in <1995COFGT(4)543>.

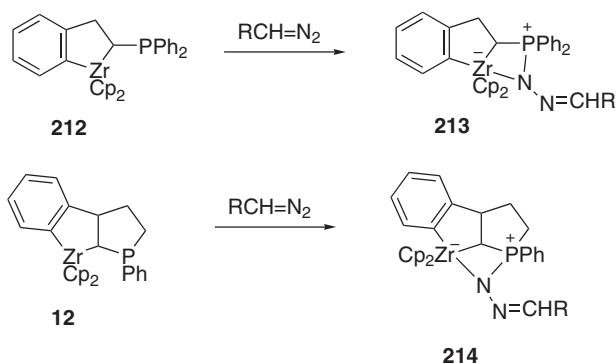
#### 4.12.4.3 Transition Metal Derivatives

##### 4.12.4.3.1 Compounds containing phosphorus and scandium or yttrium

There have been no significant developments in this area since the publication of chapter 4.12.4.3.1 in <1995COFGT(4)543>.

##### 4.12.4.3.2 Compounds containing phosphorus and titanium, zirconium, or hafnium

The zirconacycles **212** and **12** react with diazo compounds to give the zwitterionic adducts **213** and **214**, respectively (Scheme 8) <2003NJC675>.



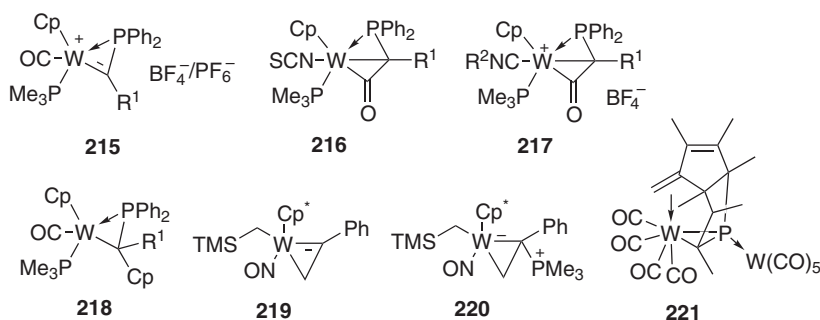
Scheme 8

#### 4.12.4.3.3 Compounds containing phosphorus and vanadium, niobium, or tantalum

There have been no significant developments in this area since the publication of chapter 4.12.4.3.3 in <1995COFGT(4)543>.

#### 4.12.4.3.4 Compounds containing phosphorus and chromium, molybdenum, or tungsten

The only significant developments in this area since the publication of chapter 4.12.4.3.4 in <1995COFGT(4)543> have involved compounds containing phosphorus and tungsten. Treatment of cationic carbene complexes **215** with NaSCN <1994ICA(222)77> or isocyanides  $\text{R}^2\text{NC}$  <1998JOM(553)103> results in rearrangement to give **216** and **217**, respectively, while with sodium cyclopentadienide there is simple addition to give **218** <1996JOM(520)59>. Addition of trimethylphosphine to tungstacyclopentene complex **219** gives **220** <1999OM3414>. In a remarkable process, the phosphinidene complex  $\text{Cp}^*\text{P}[\text{W}(\text{CO})_5]_2$  reacts with but-2-yne under thermal or photochemical conditions to give **221** <2000JCS(D)2493>.

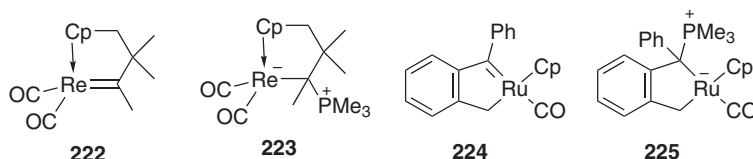


#### 4.12.4.3.5 Compounds containing phosphorus and manganese or rhenium

The only significant development in this area since the publication of chapter 4.12.4.3.5 in <1995COFGT(4)543> is a report that the rhenium carbene complex **222** reacts with  $\text{Me}_3\text{P}$  to give **223** <1997JA5750>.

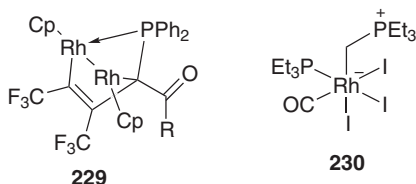
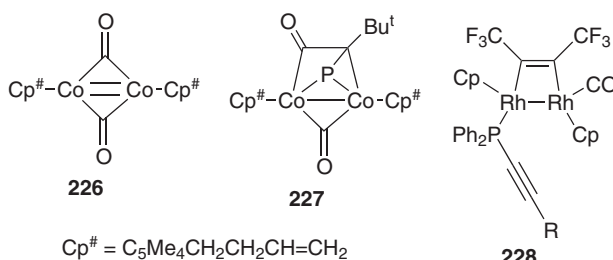
#### 4.12.4.3.6 Compounds containing phosphorus and iron, ruthenium, or osmium

The only significant development in this area since the publication of chapter 4.12.4.3.6 in <1995COFGT(4)543> is a report that the ruthenium carbene complex **224** reacts with  $\text{Me}_3\text{P}$  to give **225** <1994OM971>.



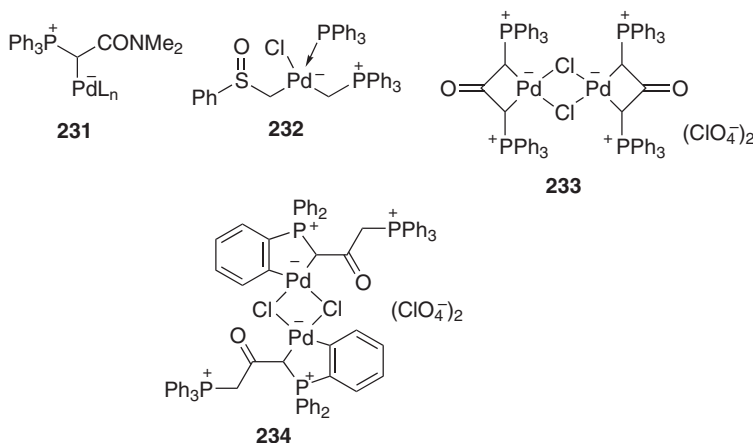
#### 4.12.4.3.7 Compounds containing phosphorus and cobalt, rhodium, or iridium

Reaction of the cobalt complex **226** with  $\text{Bu}^t\text{C}\equiv\text{P}$  results in insertion to give **227** <1994ICA(222)13>. Oxidation of the dinuclear rhodium complex **228** with oxygen in the presence of silica gives **229** <1997OM1531>. Products from the interaction of  $\text{CH}_2\text{I}_2$  with  $\text{RhI}(\text{CO})(\text{PET}_3)_2$  include **230** <1998ICA(280)99>.

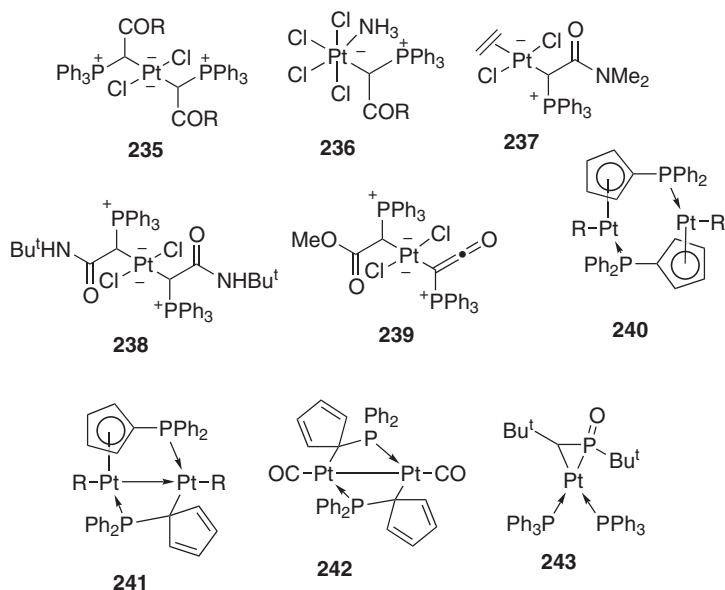


#### 4.12.4.3.8 Compounds containing phosphorus and nickel, palladium, or platinum

The ylide  $\text{Ph}_3\text{P}=\text{CH}-\text{C}(\text{O})\text{NMe}_2$  coordinates to a variety of palladium compounds exclusively through C rather than O or N to give products of the type **231** <1998JCS(D)1699>. Reaction of  $\text{PhS}(\text{O})\text{CH}_2\text{PdCl}(\text{PPh}_3)_2$  with  $\text{Ph}_3\text{P}=\text{CH}_2$  takes place with displacement of one  $\text{Ph}_3\text{P}$  to give **232** <1994OM441>. Reaction of the bis(ylide)  $\text{Ph}_3\text{P}=\text{CH}-\text{C}(\text{O})-\text{CH}=\text{PPh}_3$  with  $\text{PdCl}_2$  first gives **233** <1998OM5887> but when this is heated it undergoes cyclopalladation to afford **234** whose chemistry has been examined <1999IC2455>.

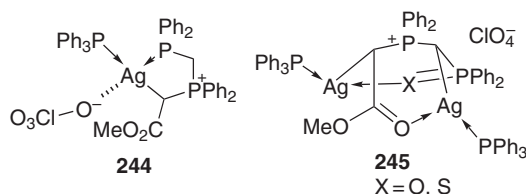


The reaction of  $K^+ [PtCl_3 CH_2=CH_2]^-$  with stabilized ylides to give products such as **235** has been described <1996ICA(245)157> and the Pt(IV) anion  $PtCl_5NH_3^-$  reacts similarly to give **236** <2002OM3744>. Reaction of  $Ph_3P=C=C=O$  with  $K^+ [PtCl_3 C_2H_4]^-$  or  $PtCl_2(C_2H_4)_2$  followed by a range of nucleophiles leads to systems such as **237–239** <2000OM1373>. The dinuclear platinum complexes **240** are found to exist predominantly in the isomeric  $\eta^5\eta^1$  form **241** <1992JA4687> and when these compounds are treated with CO and then heated the  $\eta^1\eta^1$  compounds **242** are produced with loss of the ketone  $R_2CO$  <1994OM478>. The carbonyls in **242** may then be stepwise displaced by phosphines while retaining the  $\eta^1\eta^1$  structure <1994OM830>. Controlled peracid oxidation of the  $Bu^tCH=PBu^t-Pt(PPh_3)_2$  adduct gives the oxide **243** <2003CC1092>.



#### 4.12.4.3.9 Compounds containing phosphorus and copper, silver, or gold

Compounds of the type  $(RO)_2P(O)CH_2Cu$  and  $(R_2N)_2P(O)CH_2Cu$ , formed by the treatment of the corresponding methylphosphonates or phosphoramidates with BuLi followed by CuI, are stable at room temperature and undergo palladium-catalyzed coupling with aryl iodides <2001JGU172>. Treatment of  $Ph_2PCH_2PPh_2^+CH_2CO_2Me ClO_4^-$  with  $Ag(acac) \cdot Ph_3P$  gives **244** whereas the corresponding oxide or sulfide  $Ph_2P(=X)CH_2PPh_2^+CH_2CO_2Me ClO_4^-$  give the bicyclic structure **245** <1995JCS(D)805>.



#### 4.12.4.3.10 Compounds containing phosphorus and zinc, cadmium, or mercury

The only significant development in this area since the publication of chapter 4.12.4.3.10 in <1995COFGT(4)543> is a report that palladium-catalyzed reaction of  $(EtO)_2P(O)CH_2I$  with  $PhZnCl$  results in formation of  $(EtO)_2P(O)CH_2ZnCl$  <2001JGU172>.

#### 4.12.4.4 Group 13 and 14 Derivatives

##### 4.12.4.4.1 Compounds containing phosphorus and aluminum

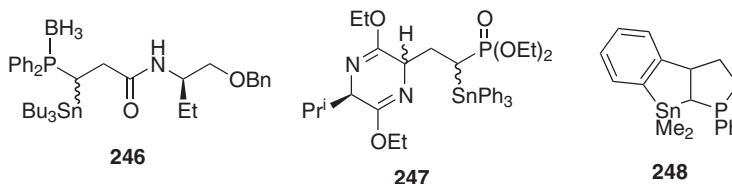
There have been no significant developments in this area since the publication of chapter 4.12.4.4.1 in <1995COFGT(4)543>.

##### 4.12.4.4.2 Compounds containing phosphorus and gallium, indium, or thallium

There have been no significant developments in this area since the publication of chapter 4.12.4.4.2 in <1995COFGT(4)543>.

##### 4.12.4.4.3 Compounds containing phosphorus and tin or lead

Reaction of  $\text{Ph}_2\text{P}(\text{S})\text{CH}_2\text{Li}$  with  $\text{Ph}_3\text{SnCl}$ ,  $\text{Ph}_2\text{SnCl}_2$ ,  $\text{PhSnCl}_3$ , and  $\text{SnCl}_4$  has been used to prepare, respectively,  $\text{Ph}_3\text{SnCH}_2\text{P}(\text{S})\text{Ph}_2$ ,  $\text{Ph}_2\text{Sn}[\text{CH}_2\text{P}(\text{S})\text{Ph}_2]_2$ ,  $\text{PhSn}[\text{CH}_2\text{P}(\text{S})\text{Ph}_2]_3$ , and  $\text{Sn}[\text{CH}_2\text{P}(\text{S})\text{Ph}_2]_4$  <1994POL1705>. In contrast  $\text{Ph}_2\text{P}(\text{O})\text{CH}_2\text{Li}$  reacts only once with  $\text{Ph}_2\text{SnCl}_2$  to afford  $\text{Ph}_2\text{Sn}(\text{Cl})\text{CH}_2\text{P}(\text{O})\text{Ph}_2$  <1994POL1705>. The influence of a remote chiral auxiliary on the stereoselectivity of deprotonation and stannylation of a phosphine–borane adduct to give **246** has been examined <2001JOC5566>, and the addition of a chiral heterocyclic anion to  $(\text{EtO})_2\text{P}(\text{O})\text{C}(=\text{CH}_2)\text{SnPh}_3$  to give **247** has been reported <2002TA233>. Reaction of  $\text{Me}_3\text{SnCH}_2\text{I}$  and  $\text{Ph}_3\text{SnCH}_2\text{I}$  with  $\text{BuLi}$  followed by  $\text{R}_2\text{PCl}$  has been used to prepare a range of products such as  $\text{Me}_3\text{SnCH}_2\text{P}(\text{menthyl})_2$ ,  $\text{Ph}_3\text{SnCH}_2\text{P}(\text{menthyl})_2$ , and  $\text{Ph}_3\text{SnCH}_2\text{P}(\text{mesityl})_2$  <1999JCS(D)1867>. Treatment of the zirconacycle **12** with  $\text{Me}_2\text{SnCl}_2$  results in transmetallation to give **248** <1997CC1239>. Hydrostannylation of phosphalkynes,  $\text{RC}\equiv\text{P}$ , using  $\text{Ph}_3\text{SnH}$  results in twofold addition to give  $\text{RCH}(\text{SnPh}_3)\text{PH}(\text{SnPh}_3)$  in 75–80% yield <1998EJI227>. Finally, the bicyclic compound **28** described earlier in Section 4.12.1.3.9 contains a function of this type.



#### 4.12.4.5 Actinide Derivatives

There have been no significant developments in this area since the publication of chapter 4.12.4.5 in <1995COFGT(4)543>.

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- 1994OM478 K. A. Fallis, G. K. Anderson, M. Lin, N. P. Rath, *Organometallics* **1994**, 13, 478–488.  
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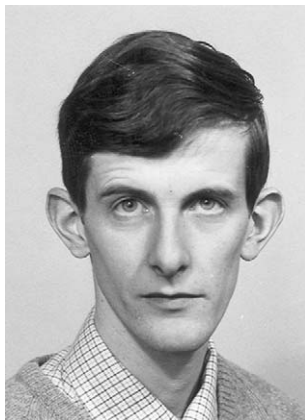
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## 4.13

# Functions Containing at Least One As, Sb, or Bi with or without a Metalloid (Si or Ge) or a Metal

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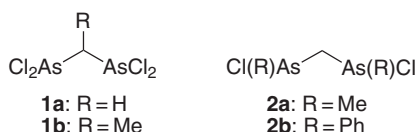
### 4.13.1 FUNCTIONS CONTAINING TWO ARSENIC, ANTIMONY, OR BISMUTH GROUPS

#### 4.13.1.1 Functions with Two Similar Elements: $R_2^1AsCR_2^2AsR_2^3$ , etc.

##### 4.13.1.1.1 Arsenic functions

###### (i) Chloro derivatives

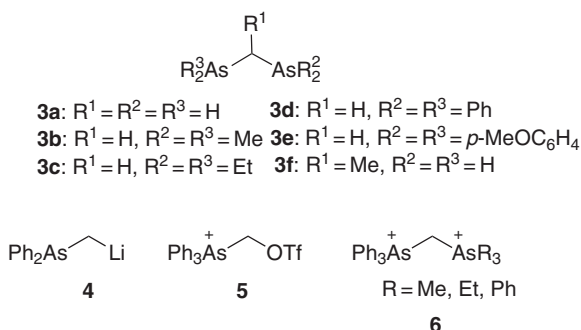
Bis(dichloroarsino)-, bis(chloroalkylarsino)-, and bis(chloroarylarsino)methane derivatives are precursors of a wide range of bis(arsino)methane derivatives. Bis(dichloroarsino)methane **1a** is prepared in good yield by the reaction of arsenic oxide  $As_2O_3$  with acetyl chloride and  $AlCl_3$  at  $170^\circ C$  followed by treatment with  $SOCl_2$  <1949CB152>. Acetyl chloride and  $AlCl_3$  are also used as reagents to transform arsenic acids  $MeAsO(OH)_2$  and  $PhAsO(OH)_2$  into the corresponding chloroarsines **2a** and **2b** <1949CB152> (Scheme 1).



Scheme 1

###### (ii) Hydride, alkyl, and aryl derivatives

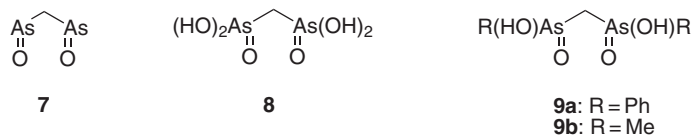
Bis(dichloroarsino)methane **1a** is a particularly useful substrate for the preparation of tetraalkyl and tetraaryl derivatives. Thus, its reactions with methylmagnesium chloride and ethylmagnesium chloride afford the corresponding tetramethyl and tetraethyl derivatives **3b** and **3c** <1987CB1281>. Chloroarsine **1a** is also reduced on treatment with LAH to give bisarsinomethane **3a** (m.p.  $91-96^\circ C$ ). An alternative method for the synthesis of alkyl and aryl derivatives **3** is the reaction of chlorodialkyl- or chlorodiarylarsines with dialkyl- or diarylarsinomethylsodium and lithium derivatives as exemplified by the synthesis of bis(diphenylarsino)methane **3** via the reaction of diphenylchloroarsine  $Ph_2AsCl$  with diphenylarsinomethyl lithium **4**. Symmetrical derivatives can also be synthesized by the reaction of dialkyl- or diarylarsino sodium or lithium with 1,1-dichloromethane or 1,1-dichloroethane. Thus, arsine **3e** is prepared by the reaction of  $(p-MeOC_6H_4)_2AsLi$  with 1,1-dichloromethane, while derivative **3f** is formed by mixing  $Ph_2AsNa$  with 1,1-dichloroethane. Finally, symmetrical and unsymmetrical bisarsonium methyltrifluoromethanesulfonate salts **6** are prepared by the reaction of triphenylarsine  $R_3As$  ( $R = Ph, Et, Me$ ) in acetonitrile at room temperature and are isolated in yields ranging from 38% to 96% <1998ZN599> (Scheme 2).



Scheme 2

## (iii) Acid derivatives

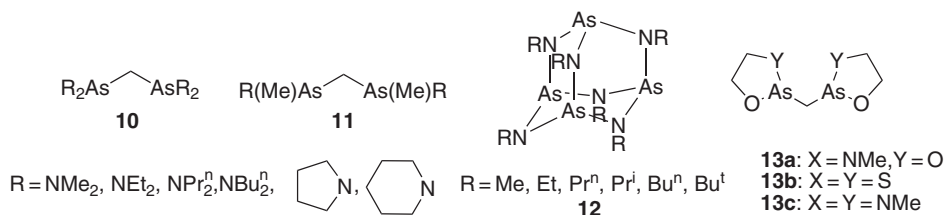
Hydrolysis of (dichloromethane)arsine **1a** readily affords the corresponding dimeric bisoxide **7**, which gives bisarsenic acid derivative **8** on further oxidation with  $\text{H}_2\text{O}_2$  <1949CB152>. Methylene bis(phenylarsenic acid) **9a** is prepared by the reaction of phenylarsenic oxide with dibromomethane, while methylene bis(methylarsenic acid) **9b** is formed by mixing oxide **7** with methyl iodide <1970ZAAC120>. Bisphenylarsenic acid **9a** can also be obtained by dephenylation of compound **3d** on treatment with LAH (Scheme 3).



Scheme 3

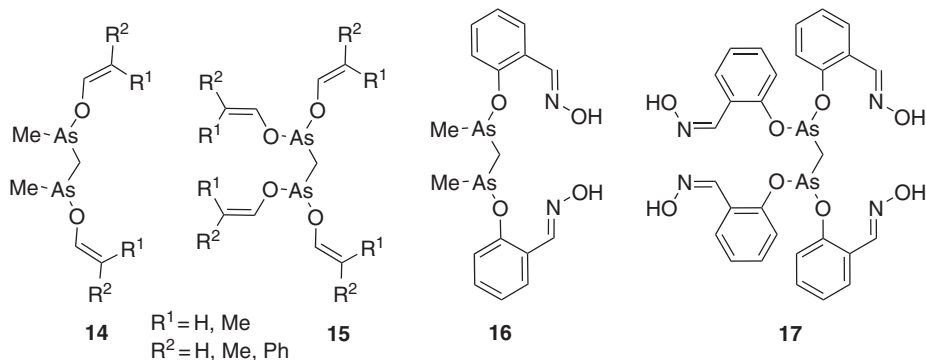
## (iv) Amino derivatives

Reactions of chloroarsines of type **1** or **2** with nucleophiles open routes to various compounds. Thus, compounds **1a** and **2a** react with secondary amines in  $\text{Et}_2\text{O}$  at  $-30^\circ\text{C}$  to lead to the corresponding tetraamino and diamino derivatives **10** <1975JOM393> and **11** <1975ZAAC202>. Bis(dichloroarsine) **1a** also reacts with primary amines, thus providing the 2,4,6,8-tetraaza-1,3,5,7-tetraarsadamantanes **12** oils. The chemistry of amino arsines and related compounds has been reviewed <1982S173> (Scheme 4).



Scheme 4

Tetramethylamino arsine (**10**;  $\text{R} = \text{NMe}_2$ ) undergoes As—N bond fission on reaction with nucleophiles. Thus, its reaction with 2-(methylamino)ethanol affords the cyclic arsenic derivative **13a** (45%, b.p.  $155^\circ\text{C}/0.01$  mm Hg), while ethane-1,2-dithiol furnishes compound **13b** (40%, b.p.  $175^\circ\text{C}/0.001$  mm Hg). All these derivatives can be obtained directly from bis(dichloroarsino)methane **1a**, as illustrated by the formation of compound **13c** in 55% yield by the reaction of **1a** with 1,2-bis(*N*-methylamino)ethane <1991ZAAC151>. Aminoarsines **10** ( $\text{R} = \text{NMe}_2$ ) and **11** ( $\text{R} = \text{NMe}_2$ ) also react with oximes of general form  $\text{R}^1\text{R}^2\text{C}=\text{N}-\text{OH}$  to give the corresponding arsenic oxide derivatives **14** and **15** in yields ranging from 75% to 100% <1992JPR716> (Scheme 5).

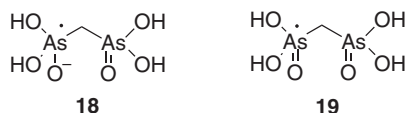


Scheme 5

It is interesting to note that when mixing with salicylaldehyde  $\text{C}_6\text{H}_4(\text{OH})\text{CH}=\text{NOH}$ , compounds **10** and **11** react exclusively with the phenolic hydroxyl to afford the phenoxy derivatives **16** and **17** in 95% and 65% yields, respectively (Scheme 5).

(v) *Radicals*

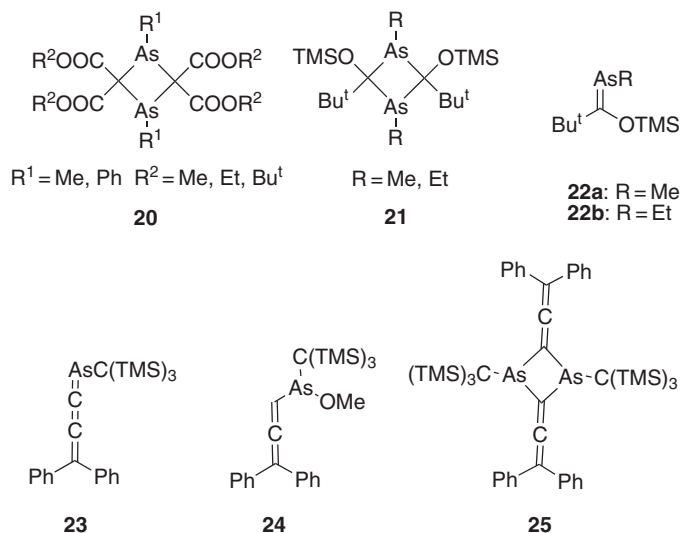
X-ray irradiation of single crystals of methylene diarsenic acid **8** gives rise to a variety of radicals in which the arsenic-centered radicals **18** and **19** have been identified by electron spin resonance <1981HCA329> (Scheme 6).



Scheme 6

(vi) *Cyclic compounds*

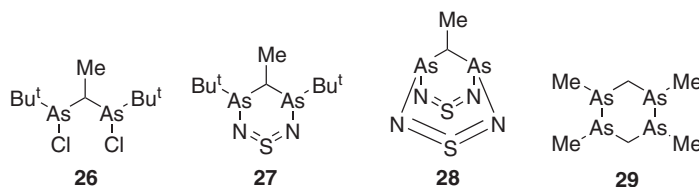
Alkyl- and arylarsenic dichlorides react readily with malonic esters to afford the 1,3-dialkyl- and 1,3-diaryl-1,3-diarsacyclobutanes **20** in yields ranging from 10% to 75% <1976AG(E)56, 1978JCR252> (Scheme 7).



Scheme 7

Alternatively, 1,3-diarsacyclobutanes **21** can be prepared by the photodimerization of the corresponding arsoranes **22a** and **22b**, and are isolated in 86% (m.p. 94 °C) and 95% (m.p. 123 °C) yields, respectively <1980ZAAC(470)144, 1980ZAAC(470)157>. Thermal dimerization of cumulene **23**, generated by the treatment of **24** with butyllithium in THF at -78 °C, furnishes diarsacyclobutane **25** (47%, m.p. 224 °C). Other cyclic derivatives can be synthesized by the reaction of chloroarsines with  $\text{K}_2\text{SN}_2$ : thus, compound **27** is formed from **26** <1987ZN(B)118>. Similarly, compound **28** is obtained from chloroarsine **1b** by a double reaction with  $\text{K}_2\text{SN}_2$ . Finally, reductive elimination of chlorine from bis(methylchloroarsino)methane by sodium amalgam provides a convenient route to 1,2,4,5-tetramethyl-1,2,4,5-tetraarsacyclohexane **29** <1975ZAAC202> (Scheme 8).



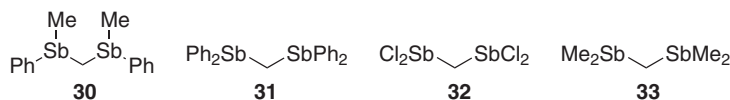


Scheme 8

#### 4.13.1.1.2 Antimony functions

##### (i) Alkyl and aryl derivatives

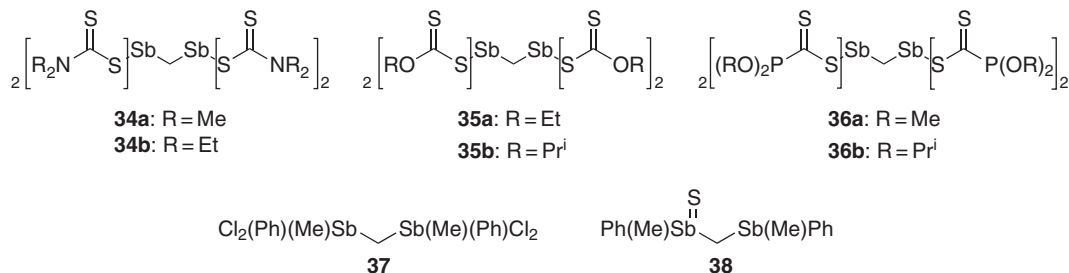
A general route to groups flanked by two antimony atoms derives from the reaction of dialkyl- or diarylstibino sodium or lithium with 1,1-dichloromethane. Thus, the treatment of diphenylmethylstibine with sodium in liquid  $\text{NH}_3$  and subsequent reaction with 1,1-dichloromethane affords bis(phenylmethylstibino)methane **30** (b.p. 130–168 °C/0.01 mmHg) <1972JOM333>. Alternatively, alkyl or aryl derivatives such as bis(dimethylstibino)methane **33**, are formed by the reaction of bis(dichlorostibino)methane **32**, generated by dephenylation of bis(diphenylstibino)methane **31**, with alkylmagnesium chloride ( $\text{MeMgCl}$ ) (Scheme 9).



Scheme 9

##### (ii) Thio derivatives

Tetrachlorodistibine **32** also reacts with dithioamides, dithioesters, or dithiophosphonates to furnish the corresponding compounds **34–36** <1992ZAAC164>. Finally, reduction of antimony(V) chloride **37** occurs easily on treatment with sodium sulphide in methanol at room temperature, allowing isolation of the stable asymmetric monosulfide **38** (40 %, m.p. 89–90 °C) <1975JOM57> (Scheme 10).

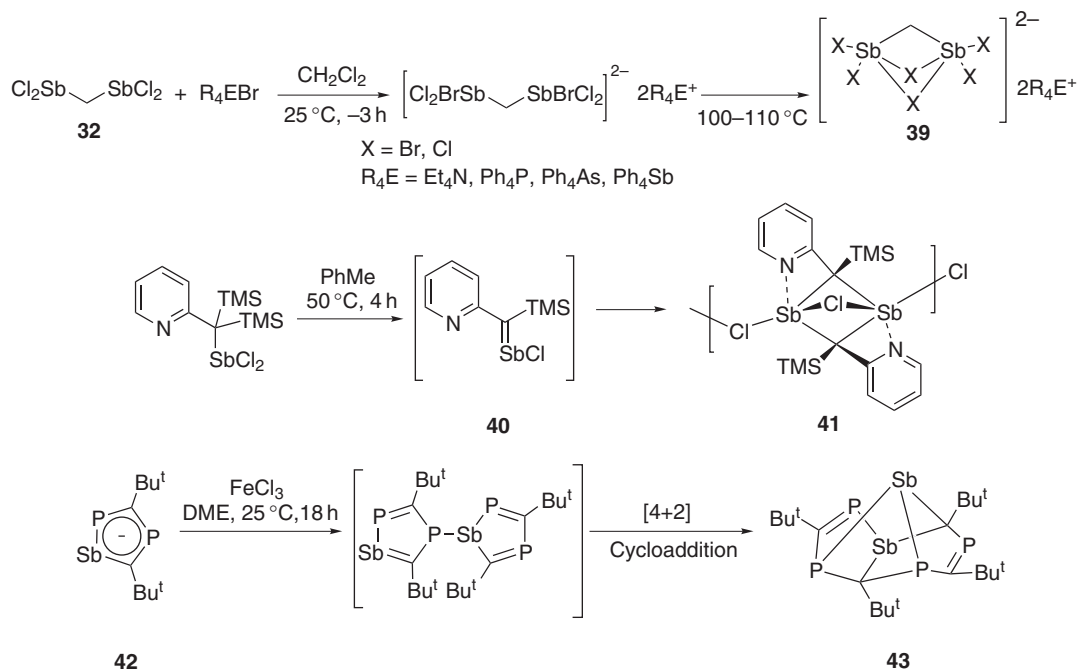


Scheme 10

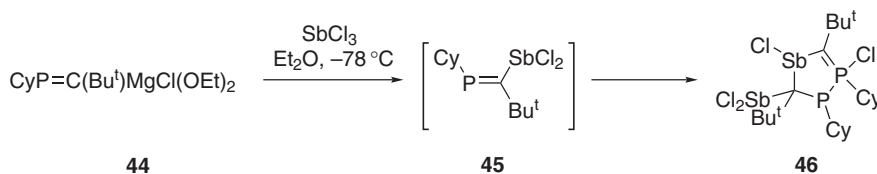
##### (iii) Cyclic compounds

Complex salts such as **39** are obtained by the reaction of tetrachlorodistibine **32** with the suitable quaternary bromide salts and subsequent heating <1992ZAAC157>. The chloro-bridged polymeric geminal C-centered distibine complex **41** is formed by mild thermolysis of (2-pyridyl)  $(\text{SiMe}_3)_2\text{CSbCl}_2$  via elimination of  $\text{TMSCl}$  and a [2 + 2]-stereospecific *cis*-cycloaddition of stibaalkene **40** <1998CC575>. Hexastibino-cage compound **43** is synthesized by the treatment of a DME solution of  $\text{FeCl}_3$  with 1 equiv. of the diphosphastibolyl ring anion **42** (61 %, m.p. 82 °C) <1997CC305> (Scheme 11).

Finally, reaction of the phosphavinyl Grignard reagent  $[\text{CyP}=\text{C}(\text{Bu}^t)\text{MgCl}(\text{OEt})_2]$  **44** with  $\text{SbCl}_3$  leads to compound **46** (66 %, m.p. 83–85 °C) probably via a coupling and a subsequent rearrangement of two molecules of the supposed intermediate **45** <2002MI1209> (Scheme 12).



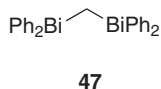
Scheme 11



Scheme 12

#### 4.13.1.1.3 Bismuth functions

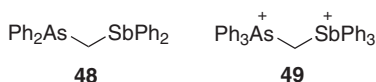
Bismuthinomethane derivatives are prepared analogously to their distibino counterparts. Thus, bis(diphenylbismuthino)methane **47** is obtained from  $\text{Ph}_2\text{BiNa}$  by reaction with 1,1-dichloromethane <1980AG(E)723, 1985CB1039> (Scheme 13).



Scheme 13

#### 4.13.1.2 Functions with Two Dissimilar Elements: $\text{R}_2^1\text{AsCR}_2^2\text{SbR}_2^3$ , etc.

To the best of our knowledge, only compounds containing arsenic and antimony have been prepared. A convenient approach to such compounds is illustrated by the reaction of stibino-methylolithium, obtained from bis(diphenylstibino)methane **31** on treatment with  $\text{PhLi}$ , with diphenylchloroarsine in THF to afford the derivative **48** in 23% yield <1983CB473, 1985CB2353>. Another example is the formation in 57% yield of the trifluoromethanesulfonate salt **49** by the reaction of triphenylarsonium methyltrifluoromethanesulfonate **5** with triphenylstibine in refluxing acetonitrile (Scheme 14).



Scheme 14

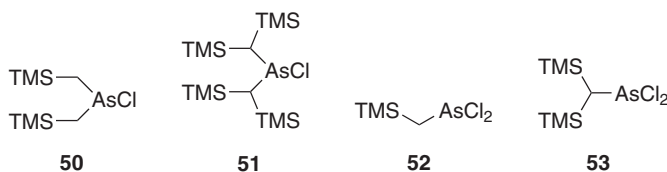
#### 4.13.2 FUNCTIONS CONTAINING ARSENIC, ANTIMONY, OR BISMUTH AND A METALLOID (Si OR Ge)

##### 4.13.2.1 Arsenic Derivatives

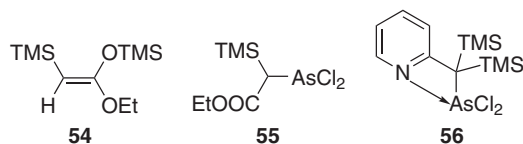
##### 4.13.2.1.1 Arsenic and silicon functions

###### (i) Arsines

(a) *Chloroarsines*. In general, chloroarsines containing an  $sp^3$ -carbon flanked with one arsenic and one silicon are prepared from arsenic trichloride and a silylated lithium or Grignard reagent. Thus, bis(trimethylsilylmethyl)chloroarsine **50** is formed by the reaction of arsenic trichloride with trimethylsilylmethylmagnesium chloride in a 1:1 molar ratio in THF <1991PS(57)1>. In a similar fashion, arsenic trichloride reacts with bis(trimethylsilyl)methyl lithium in  $\text{Et}_2\text{O}$  to furnish chloroarsine **51** (m.p.  $70\text{--}72^\circ\text{C}$ , 61%) <1980JCS(D)2428>. Other derivatives can be obtained in the same manner. Reaction of bis(diethylamino)chloroarsine with trimethylsilylmethylmagnesium chloride or bis(trimethylsilyl)methylmagnesium chloride at  $-78^\circ\text{C}$ , followed by aqueous work-up, readily affords dichloro(trimethylsilylmethyl)arsines **52** (81%) and **53** <1991MI413-01, 1990POL319>. Arsenic trichloride also reacts with silylated ketene acetals such as **54** in either THF or  $\text{Et}_2\text{O}$  at room temperature to quantitatively afford dichloroarsine **55** <1989TL349>. The final example is the intramolecularly complexed dichloride **56** generated in 55% yield by mixing arsenic trichloride with  $\text{Pyr-2'C(TMS)}_2\text{Li}$  in  $\text{Et}_2\text{O}$  at  $-80^\circ\text{C}$  <1991CC1560> (Schemes 15 and 16).

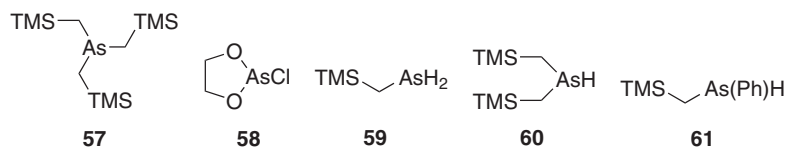


Scheme 15



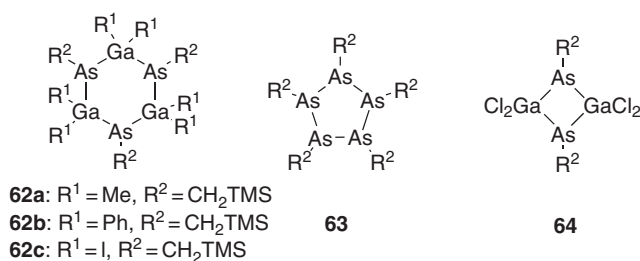
Scheme 16

(b) *Tertiary arsines, secondary and primary alkyl- or arylarsines*. Tertiary arsine **57** is prepared by the reaction of  $\text{AsCl}_3$  with an excess of trimethylsilylmethylmagnesium chloride in THF (80%, m.p.  $67\text{--}68^\circ\text{C}$ ). An alternative approach to **57** is the use of chloro derivative compound **58** in place of arsenic chloride. Under these conditions, compound **57** is obtained in 95% yield <1990IC3502>. Chloro derivatives **52** and **50** are reduced by LAH in  $\text{Et}_2\text{O}$  at  $-78^\circ\text{C}$  to afford the corresponding primary arsines **59** <1990POL319> and **60**, respectively <1991PS(57)1>. Finally, secondary arsine **61** is synthesized in 75% yield by metallation of phenylarsine with sodium in liquid  $\text{NH}_3$  followed by a coupling reaction with  $\text{TMSCH}_2\text{Cl}$  <1996OM84> (Scheme 17).



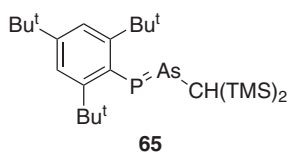
Scheme 17

(c) *Cyclic arsines.* Reaction of arsine **59** with triphenyl- or trimethylgallane in benzene at 55 °C gives the corresponding trimeric mono(arsino)gallanes **62a** and **62b** in quantitative and 85% yield, respectively. However, its reaction with tris(trimethylsilylmethyl)gallane results in the formation of the pentacyclic arsine **63** <1990POL319>. Bis[bis(trimethylsilyl)methyl]trimethylsilyl arsine  $[(\text{TMS})_2\text{CH}]_2\text{AsTMS}$  reacts with  $\text{GaCl}_3$  in a 1:1 ratio in pentane to give the six-membered ring **62c** (67%, m.p. 180–184 °C), whereas the use of a twofold excess of arsine affords the four-membered ring **64** (80%, m.p. 101–108 °C) <1986OM1266> (Scheme 18).



Scheme 18

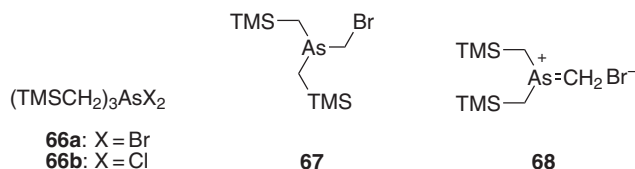
(d) *Miscellaneous.* Finally, a derivative containing an  $\text{As}=\text{P}$  double bond has been prepared. Thus, reaction of chloroarsine **60** with  $(2,4,6\text{-Bu}^t\text{C}_6\text{H}_2)\text{PH}_2$  in THF in the presence of excess 1,5-diazabicyclo[5.4.0]undec-5-ene affords phospharsene **65** as an orange crystalline solid <1983CC881> (Scheme 19).



Scheme 19

## (ii) Arsoranes

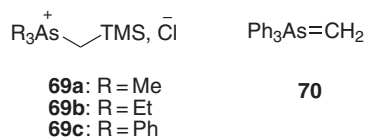
Reaction of tris(trimethylsilylmethyl)arsine **57** with bromine provides the corresponding arsorane **66a** (m.p. 118–120 °C) <1958JA1336>. This arsorane is thermally unstable and, at 170 °C, it rearranges to the trivalent derivative **67**, probably via the salt **68**. Chloro derivative **66b** is prepared by the addition of arsenic trichloride in  $\text{Et}_2\text{O}$  to a hexane/benzene solution of **57** and isolated in 17% yield after recrystallization (m.p. 112–114 °C) <1991PS(57)1> (Scheme 20).



Scheme 20

## (iii) Quaternary salts

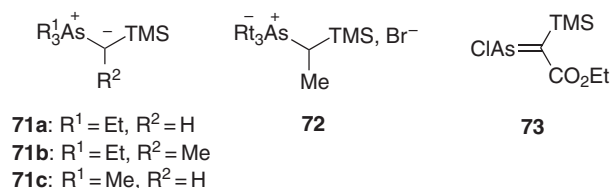
A general method to prepare quaternary salts incorporating arsenic and silicon consists of reaction of the corresponding trialkylarsine and trimethylsilylmethyl chlorides. Thus, reaction of trimethylarsine with  $\text{TMSCH}_2\text{Cl}$  in a sealed tube at  $170^\circ\text{C}$  gives the corresponding salt **69a**. In a similar fashion, salt **69b** is formed in 79% yield by reaction of triethylarsine with trimethylsilylmethyl chloride. Compound **69c**, used for silylcyclopropanation reactions, can also be prepared by the treatment of methylenearsorane **70** with trimethylsilyl chloride in  $\text{Et}_2\text{O}$  at  $-70^\circ\text{C}$  under an inert atmosphere <1984TL4425> (Scheme 21).



Scheme 21

## (iv) Ylides and cumulenes

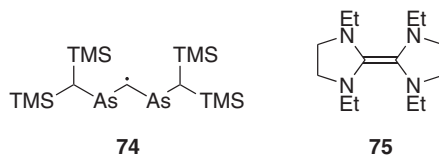
All salts of the type **69** mentioned above react readily with BuLi to afford the corresponding ylides **71** in high yields. The chemistry of arsenium ylides has been reviewed <1982AOC115> and several spectroscopic studies have been reported <1975CB2649, 1976CB473>. Such ylides also react with alkyl halide electrophiles. Thus, ylide **71a** reacts with methyl bromide to afford the corresponding salt **72**. This latter can again be converted into the ylide **71b**. Finally, ylides such as **71c** react with trimethylsilanol in a desilylation reaction to lead to the corresponding (trialkylarsine)methylene  $\text{Me}_3\text{As}=\text{CH}_2$  and hexa-trimethyldisiloxane <1967IC168>. A more esoteric example is the formation of the unstable arsorane **73** by dehydrohalogenation of the dichloroarsine **55** by DABCO <1989TL349> (Scheme 22).



Scheme 22

## (v) Photoreactions

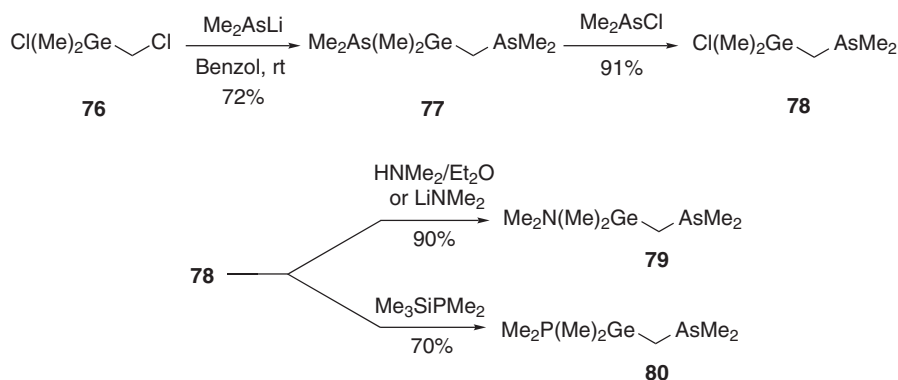
Photolysis of degassed toluene solutions of chloroarsine **53** in the presence of the electron-rich olefin **75** furnishes the corresponding arsenic centered radical **74** characterized by its electron spin resonance spectrum <1976CC623> (Scheme 23).



Scheme 23

## 4.13.2.1.2 Arsenic and germanium functions

Reaction of  $\text{ClGe}(\text{Me})_2\text{CH}_2\text{Cl}$  **76** (prepared in three steps from germanium tetrachloride) with dimethylarsinolium  $\text{Me}_2\text{AsLi}$  in benzol affords **77** in 72% yield. The latter reacts with dimethylarsino chloride to lead to derivative **78** (91%). Aminolysis of **78** with dimethylamine gives **79**, which can also be obtained by treatment of **78** with  $\text{Me}_2\text{NLi}$ . Finally, compound **80** is formed by the reaction of **78** with dimethyltrimethylsilylphosphine <1977JOM77> (Scheme 24).



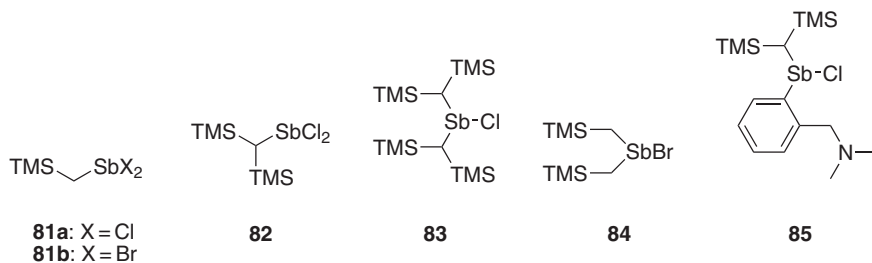
Scheme 24

### 4.13.2.2 Antimony Derivatives

#### 4.13.2.2.1 Stibines

##### (i) Chlorostibines

Treatment of diphenyl(trimethylsilylmethyl)stibine (prepared from diphenylstibino chloride and trimethylsilylmagnesium chloride) with HCl in chloroform led to dichlorostibine **81a**. <1995JOM117> Its bromide counterpart **81b** is obtained in 79% yield from tris(trimethylsilylmethyl)stibine **86** by treatment with a twofold excess of antimony tribromide <1993JOM119>. Use of a twofold excess of antimony tribromide affords the monobromide derivative **84**. Reaction of antimony trichloride with bis(trimethylsilyl)methylmagnesium chloride at  $-78^\circ\text{C}$  in  $\text{Et}_2\text{O}$  affords compound **82** <1983POL291, 1984IC2582>. The latter reacts with 2-(*N,N*-dimethylaminomethyl)phenyllithium at  $-80^\circ\text{C}$  to give the chiral chlorostibine **85** (96%, m.p.  $80^\circ\text{C}$ ) <2003IC1751> (Scheme 25).



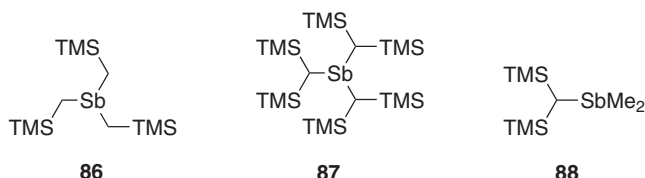
Scheme 25

##### (ii) Tertiary stibines, secondary and primary stibines

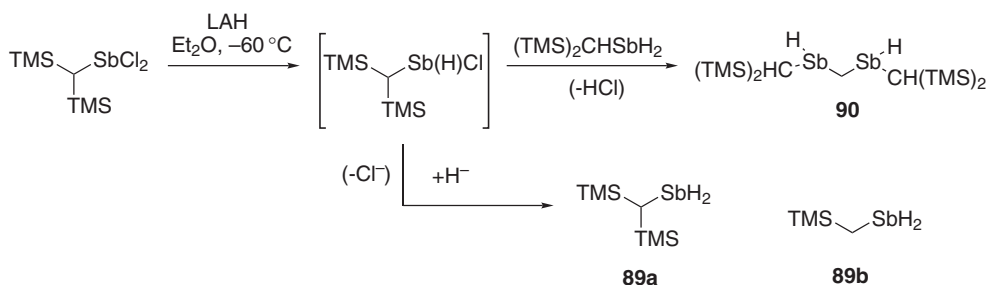
Various stibines are prepared by the reaction of substituted alkylolithiums or Grignard reagents with antimony trichloride. Thus, reaction of trimethylsilylmethylmagnesium chloride with  $\text{SbCl}_3$  in THF and subsequent hydrolysis affords tris(trimethylsilylmethyl)stibine **86** as a white solid (74%, m.p.  $64\text{--}65^\circ\text{C}$ ) <1958JA1336, 1992OM2163>. Tertiary stibine **87** (98%, m.p.  $80\text{--}82^\circ\text{C}$ ) is obtained in a similar fashion by reacting antimony trichloride with bis(trimethylsilyl)methylmagnesium chloride, while dimethyl-bis(trimethylsilylmethyl)stibine **88** (76%, b.p.  $32^\circ\text{C}/2 \times 10^{-1}$  mmbar) is prepared by alkylation of dichlorostibine **82** with methylmagnesium iodide in a 2:1 molar ratio <2002JOM33> (Scheme 26).

The preparation of stable primary and secondary stibines has been reported. Thus, addition of dichlorostibine **82** in  $\text{Et}_2\text{O}$  to LAH at  $-60^\circ\text{C}$  affords the primary stibine **89a** in 69% yield <2001OM2666>. It can be noted that hydrides of main group 15 elements are important compounds, frequently used as reducing agents <1998JOM297> or precursors for electronic

materials. However, many of them, such as  $\text{RSbH}_2$  ( $\text{R} = \text{Me}, \text{Ph}$ ) and  $\text{R}_2\text{SbH}$  ( $\text{R} = \text{Me}, \text{Et}$ ), decompose in minutes or hours at room temperature. By contrast, stibine **89a** is stable at room temperature in a sealed tube for weeks, and at  $-28^\circ\text{C}$  it is stable indefinitely. Distibine **90** is formed in 93% yield from the same reagents as **89a** but in a “reverse addition” reaction <2003OM576>. The mixed compound bis(trimethylsilyl)methylstibino chloride  $(\text{TMS})_2\text{CH}(\text{H})\text{SbCl}$  is postulated to be an intermediate in the formation of **90** via reaction of  $(\text{TMS})_2\text{CHSbCl}_2$  with LAH and loss of  $\text{H}_2$ . Similarly, primary stibine **89b** is obtained in 51% yield from the corresponding bromostibine **81b** by treatment with LAH in tetraglyme <1993JOM119> (Scheme 27).

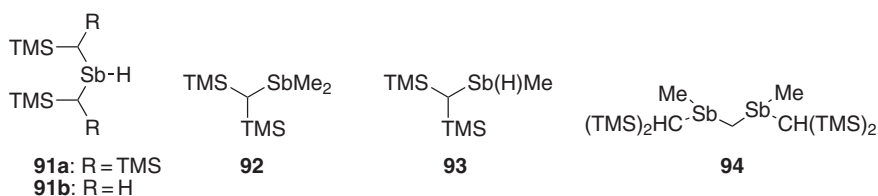


Scheme 26



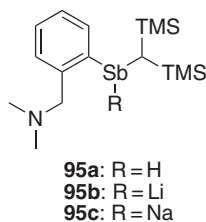
Scheme 27

In a similar fashion, the secondary stibines **91a** (m.p.  $-14^\circ\text{C}$ ) and **91b** are obtained in 66% and 45% yields by reacting the corresponding chlorides **83** and **84** with LAH <2002OM2584, 1993JOM119>. Stibine **89a** reacts with methyl iodide/DBU with substitution of hydrogen by methyl to give the corresponding tertiary stibine **92** <2003OM576>. Use of the reagents in a 1:1:1 molar ratio exclusively affords the secondary stibine **93** in 82% yield. Also distibine **90** reacts with methyl iodide and DBU to furnish distibine **94** in 69% yield (Scheme 28).



Scheme 28

An efficient synthesis of the three unsymmetrical organoantimony compounds **95** from the corresponding chloride has been reported <2003IC1751>. Unsymmetrical stibines are of particular interest due to the potential activity of antimony and bismuth compounds bearing three different substituents as chiral reagents or catalysts for enantioselective synthesis. Thus, chloride **85** is reduced by LAH in  $\text{Et}_2\text{O}$  to give the secondary unsymmetrical stibine **95a** in 87% yield. Treatment of **95a** with *n*-butyllithium in THF at  $-80^\circ\text{C}$  and subsequent crystallization gives compound **95b** (62%, m.p.  $48-52^\circ\text{C}$ ). The latter is transmetalated with sodium *t*-butoxide in the presence of TMEDA at  $-50^\circ\text{C}$  and subsequent crystallization gives compound **95c** (44%, m.p.  $65-70^\circ\text{C}$ ) (Scheme 29).

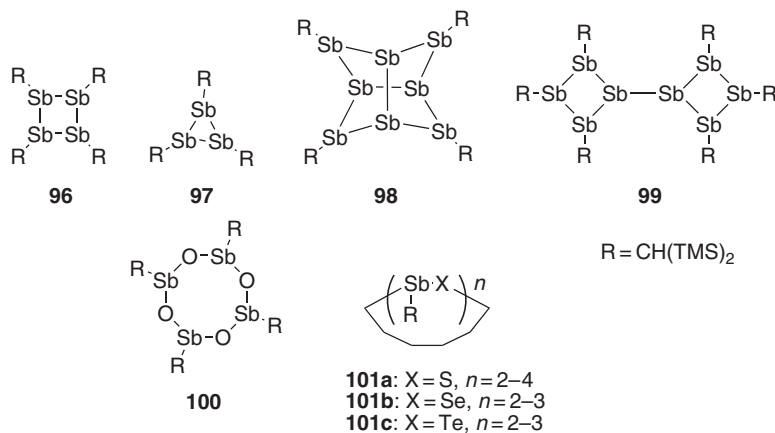


Scheme 29

## (iii) Cyclic stibines

It is noteworthy that the heating of **89a** to 110–120 °C leads to the cyclic compound  $R_4Sb_4$  **96** <2001OM2666>. Distibine **90** is also used for the preparation of antimony homocycles. Controlled removal of hydrogen is achieved when LAH is added to a solution of **90** in Et<sub>2</sub>O at room temperature: tristibine **97** and tetrastibine **96** are formed and isolated in 11% and 12% yields, respectively <2003OM576>. These two compounds can also be formed from chloride **82**. Thus, treatment of compound **82** with  $n$  equivalents ( $n = 3$  or 4) of magnesium turnings in THF affords the corresponding homocycle **97** ( $n = 3$ ) or **96** ( $n = 4$ ) in 88% yield <1992OM145, 1984JOMC27>. The three-membered ring compound **97** is also prepared by reacting chloride **82** with Li<sub>3</sub>Sb at –40 °C (58%, m.p. 94–98 °C) and by UV irradiation of its four-membered counterpart **96** (quantitative yield) <1998OM5594>. Reaction of stibine **89a** with antimony trichloride in the presence of pyridine yields the polycycle **98** in 32%. Exposure to light leads to photochemical ring contraction with formation of the tristibine **97**. Finally, the bicyclic compound **99** (2%, m.p. 152–153 °C) is formed in low yield in an attempt to metallate distibine **94** with sodium *t*-butoxide in the presence of 18-crown-6.

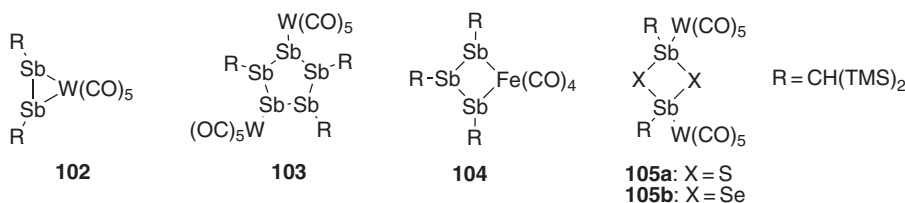
Preparation of heterocyclic organoantimony derivatives has been described. Treatment of chloride **82** with KOH in water/Et<sub>2</sub>O at –25 °C and subsequent recrystallization affords the cyclic stibane oxide **100** <1994ZN877> whereas its reactions with sodium chalcogenides furnish the corresponding cyclic antimony chalcogenides **101a**, **101b**, and **101c** in 84%, 75%, and 70% yields, respectively <1996ZN149> (Scheme 30).



Scheme 30

The synthesis of several cyclic metal complexes of organoantimony ligands has also been reported. Thus, complexes **102** (15%, m.p. 99 °C) and **103** (70%, m.p. 138 °C) are prepared by reacting distibine **90** and cyclo [TMSCH<sub>2</sub>Sb]<sub>5</sub> with W(CO)<sub>5</sub>·THF <1998OM5594, 2001ZAAC1855> whereas complex **104** (69%, m.p. 159 °C) is prepared by an insertion reaction of Fe<sub>2</sub>(CO)<sub>9</sub> in the three-membered ring **97**. The ring–ring equilibria [(TMS)<sub>2</sub>CH]<sub>2</sub>Sb<sub>2</sub>S<sub>2</sub>/[(TMS)<sub>2</sub>CH]<sub>3</sub>Sb<sub>3</sub>S<sub>3</sub> and [(TMS)<sub>2</sub>CH]<sub>2</sub>Sb<sub>2</sub>Se<sub>2</sub>/[(TMS)<sub>2</sub>CH]<sub>3</sub>Sb<sub>3</sub>Se<sub>3</sub> also react with W(CO)<sub>5</sub>·THF to form the corresponding complexes **105a** <2002MI547> and **105b** <2002JOM130> in quantitative and 42% yields, respectively (Scheme 31).



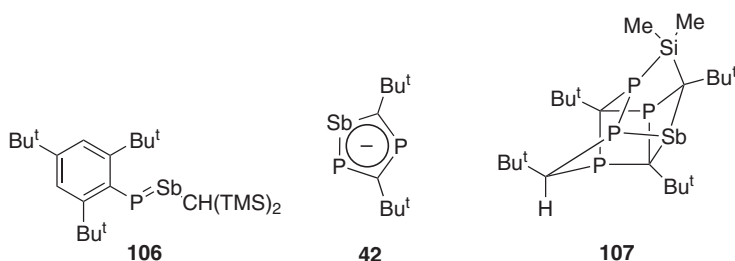


Scheme 31

(iv) Miscellaneous

In analogy to dichloroarsine **60**, dichlorostibine **82** reacts with  $(2,4,6\text{-Bu}_3\text{C}_6\text{H}_2)\text{PH}_2$  in THF in the presence of excess 1,5-diazabicyclo[5.4.0]undec-5-ene to afford the phosphastibene **106** <1983CC881>.

Finally, the preparation of the hexastibino-cage compound **107** has been reported. This compound (41%, m.p. 203 °C) is synthesized by the reaction of the potassium complex of diphosphastibolyl ring anion **42** with dimethylsilyl dichloride <2001JOM61> (Scheme 32).

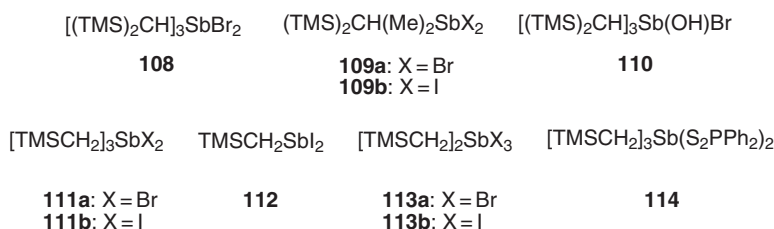


Scheme 32

#### 4.13.2.2.2 Stiboranes

(i) Chloro- and bromostiboranes

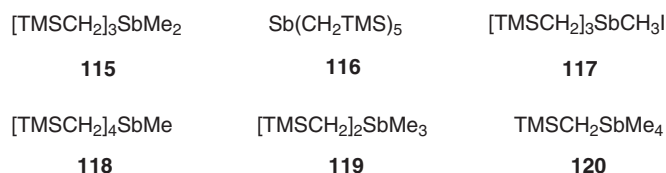
Bromination of tertiary stibines affords the corresponding dibromostiboranes. Thus, reaction of stibine **89a** with bromine in petroleum ether at 0 °C furnishes dibromo-tris(trimethylsilylmethyl)stiborane **108** (m.p. 158–160 °C) <1958JA1336>. In a similar fashion, addition of  $\text{Br}_2$  or  $\text{I}_2$  in  $\text{Et}_2\text{O}$  at 0 °C to a solution of tertiary stibines **87** and **88** affords the corresponding trialkylantimony halides **108**, **109a**, and **109b** in 84% (m.p. 174 °C), 61% (m.p. 149–151 °C), and 98.5% (m.p. 116–118 °C) yields, respectively. Moreover, hydrolysis of stiborane **108** with a solution of potassium hydroxide in water surprisingly gives the hydroxy bromide **110** (m.p. 120–123 °C, 70%). This compound is also obtained in 72% yield by reacting dibromostiborane **109a** with potassium hydroxide in water <2002JOM33>. Similarly, pentavalent compounds **111b** (92%, m.p. 164–165 °C) and **111a** are prepared in 92% yield by the addition of iodide or bromide to the tristibine **86**. Thermal decomposition of **111b** gives the iodide derivative **112** (91%) which, on further treatment with  $\text{I}_2$ , furnishes bis(trimethylsilylmethyl)antimony triiodide **113b** <1992OM2163>. Bis(trimethylsilylmethyl)antimony tribromide **113a** is quantitatively formed by addition of excess  $\text{Br}_2$  to bromide **84** in petroleum ether at –20 °C <1999JOM256>. Its reaction with 2 equiv. of diphenyldithiophosphinate in refluxing  $\text{CHCl}_3$  affords tris(trimethylsilylmethyl)antimony bis(diphenyldithiophosphinate) **114** (m.p. 103 °C) in 42% yield (Scheme 33).



Scheme 33

*(ii) Alkylstiboranes*

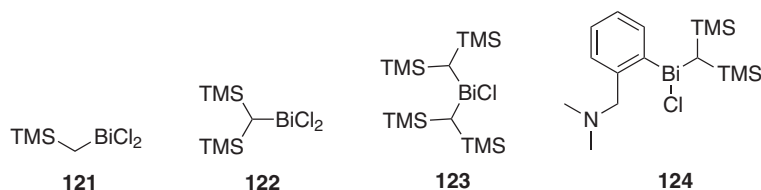
A general and versatile route to alkylstiboranes is the reaction of suitable lithium reagents with an appropriate antimony derivative <1978CB2702>. Thus, reaction of stiborane **111b** with methyl-lithium (2equiv.) in Et<sub>2</sub>O at 0°C affords stiborane **115** (78%, m.p. 51–53°C), while its reaction with trimethylsilylmethyl-lithium (2equiv.) gives pentakis derivative **116** (89%, m.p. 93°C) <1978CB2702>. The same lithium reagent is used to convert the salt **117** (obtained by the reaction of tristibine **86** with methyl iodide) into stiborane **118** (68%, m.p. 33°C). This salt also reacts with methyl-lithium (2equiv.) to afford stiborane **115** (78%). Similarly, stiborane **119** (83%, b.p. 65°C/0.1 torr) is prepared by the reaction of trimethyldibromostiborane Me<sub>3</sub>SbBr<sub>2</sub> (generated by bromination of trimethylstibine) with trimethylsilylmethyl-lithium. This lithiated reagent is also used to transform tetramethyliodostiborane Me<sub>4</sub>SbI (obtained by the reaction of trimethyldibromostiborane with methyl-lithium) to tetramethylstiborane **120** (37%, b.p. 68°C/5.5 torr) (Scheme 34).



Scheme 34

**4.13.2.3 Bismuth Derivatives****4.13.2.3.1 Bismuth and silicon functions***(i) Chlorides*

Trimethylsilylmethylbismuthino dichloride **121** is prepared in two steps from diphenylbismuthino chloride. First, diphenylbismuthino chloride Ph<sub>2</sub>BiCl is transformed into diphenyl(trimethylsilylmethyl)bismuthine Ph<sub>2</sub>(TMSCH<sub>2</sub>)Bi by reaction with trimethylsilylmethylmagnesium bromide. Then, substitution of the phenyl groups is achieved on treatment with gaseous HCl <2002AG(E)2309>. The same reaction sequence allows the synthesis of chloride **122** (77%) from diphenylbismuthino chloride and bis(trimethylsilyl)methylmagnesium chloride <1999OM328>. Bismuthino chloride **123** is prepared in 93% yield by the reaction of bis(trimethylsilyl)methyl-lithium with bismuth trichloride in a 2:1 molar ratio <1999OM328>. Finally, the chiral bismuthino chloride **124** is formed in 91% yield by reaction of **122** with 2-(Me<sub>2</sub>NCH<sub>2</sub>)-C<sub>6</sub>H<sub>4</sub>Li in toluene at –80°C <2003IC1751> (Scheme 35).

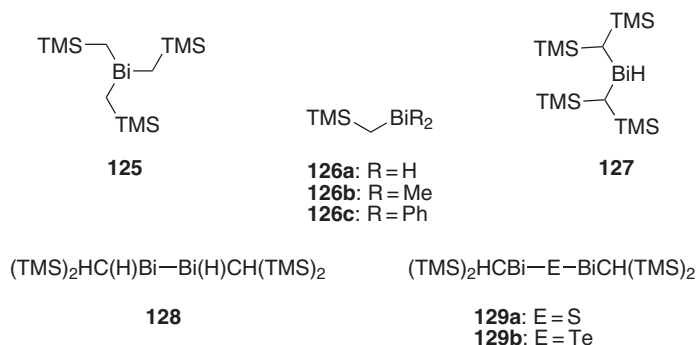


Scheme 35

*(ii) Tertiary bismuthines, secondary and primary bismuthines*

As with the arsenic and antimony derivatives, reaction of bismuth trichloride BiCl<sub>3</sub> with trimethylsilylmethylmagnesium chloride in THF affords tertiary bismuthine **125** in 35% yield <1958JA1336>. Dialkyl(trimethylsilylmethyl)bismuthines **126b** and **126c** are synthesized by the reaction of dialkylbismuthinosodium with chloromethyltrimethylsilane <1988ZN(B)739, 2002AG(E)2309>. Primary and secondary stibines are also obtained from the corresponding chlorides on treatment with LAH. Thus, chlorides **121** and **123** react with LAH in Et<sub>2</sub>O at

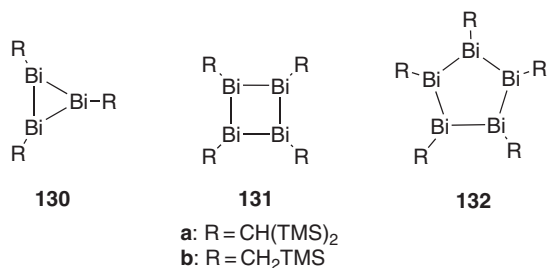
$-80^{\circ}\text{C}$  to lead to trimethylsilylbismuthine **126a** <2002AG(E)2309> and bis(trimethylsilyl)methylbismuthine **127** (66%, m.p.  $-14^{\circ}\text{C}$ ), respectively <2002OM2584>. The latter decomposes at room temperature to give the corresponding dibismuthine **128** (73%, m.p.  $104^{\circ}\text{C}$ ) and 1 equiv. of dihydrogen. Finally, chloride **123** reacts with sodium sulfide and disodium telluride in liquid  $\text{NH}_3$  to afford di(bis(trimethylsilyl)methylbismuth) tellurides **129a** ( $\text{E} = \text{S}$ , 88%, m.p.  $87^{\circ}\text{C}$ ) and **129b** ( $\text{E} = \text{Te}$ , 53%, m.p.  $83^{\circ}\text{C}$ ), respectively <2002JOM130> (Scheme 36).



Scheme 36

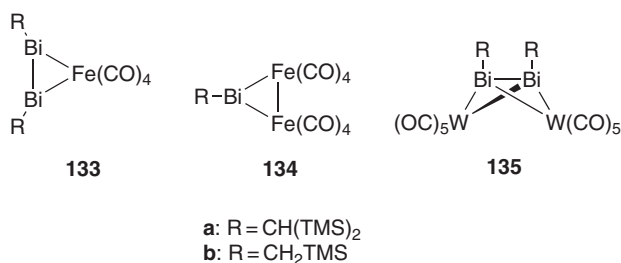
### (iii) Cyclic bismuthines

Cyclic bismuthines **130a** and **131a** are synthesized in 68% global yield by the reduction of chloride **123** with magnesium filings in THF at  $-35^{\circ}\text{C}$  <1998AG(E)3175>. In solution, there is an equilibrium between the two organobismuth rings. The equilibrium constant  $K = [\text{R}_3\text{Bi}_3]/[\text{R}_4\text{Bi}_4]^3$  is  $40.5 \text{ mol l}^{-1}$  in  $\text{C}_6\text{D}_6$  at  $23^{\circ}\text{C}$ . This equilibrium is shifted in favor of the four-membered ring when the solution is cooled. Above  $-50^{\circ}\text{C}$ , bismuthine **126a** decomposes to furnish a mixture of the three-membered and the five-membered ring compounds **130b** and **132b** in 90% global yield <2002AG(E)2309> (Scheme 37).



Scheme 37

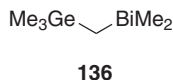
Bis(trimethylsilyl)methylbismuthino chloride **123** also reacts with  $\text{Na}_2[\text{Fe}(\text{CO})_4]$  to afford compounds **133a** (20%, m.p.  $111\text{--}113^{\circ}\text{C}$ ) and **134a** (14%, m.p.  $84\text{--}86^{\circ}\text{C}$ ). Finally, reaction of the ring–ring equilibrium **130b** and **132b** with  $\text{W}(\text{CO})_5 \cdot \text{THF}$  affords the bismuthene complex **135b** (m.p.  $95\text{--}96^{\circ}\text{C}$ ) <2002AG(E)2309> (Scheme 38).



Scheme 38

**4.13.2.3.2 Bismuth and germanium functions**

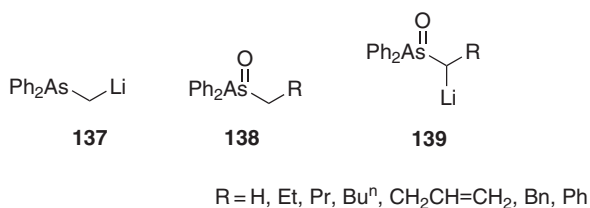
The germylated derivative **136** is synthesized from dimethylbismuthinosodium and chloromethyltrimethylgermane <1988ZN(B)739> (Scheme 39).



Scheme 39

**4.13.3 FUNCTIONS CONTAINING ARSENIC, ANTIMONY OR BISMUTH, AND A METAL****4.13.3.1 Arsenic Derivatives****4.13.3.1.1 Arsenic and group 1 metals**

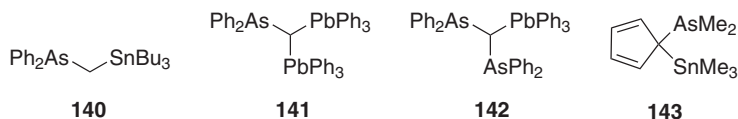
Dialkyl- and diarylarsinomethyl lithium derivatives can be prepared from the corresponding bis(dialkylarsino)- and bis(diarylarsino)methanes as exemplified by the synthesis of diphenylarsinomethyl lithium **137** by the treatment of bis(phenylarsino)methane **3c** (74%) with *n*-butyllithium in THF at  $-40^\circ\text{C}$  <1978TL4391>. An alternative approach for the preparation of **137** consists in mixing diphenylarsinomethyl iodide with *n*-butyllithium or phenyllithium at  $-78^\circ\text{C}$  with quantitative yield <1982TL2301>. Finally, lithium derivatives **139** are formed almost quantitatively on treatment of alkyl diphenylarsane oxides **138** with lithium diisopropylamide in THF at  $-40^\circ\text{C}$ . Lithium derivatives **139** readily react with organic halides or carbonyl compounds with C—C linkage. The resulting arsane oxides can be easily reduced to arsines <1977AG(E)53, 1977AG(E)709> (Scheme 40).



Scheme 40

**4.13.3.1.2 Arsenic and group 14 metals**

Derivatives containing arsenic and tin such as diphenyl(tributylstannylmethyl)arsine **140** (73%) are prepared by the reaction of tributylstannylmethyl lithium  $\text{Bu}_3\text{SnCH}_2\text{Li}$  with diphenylchloroarsine  $\text{Ph}_2\text{AsCl}$  <1982CB1810> or by the addition of tributyltin chloride to diphenylarsinophenyllithium <1985CB2353>. A similar route is used to prepare lead derivatives. Thus, compound **142** is synthesized in two steps from tris(triphenyllead)methane. Treatment with 2 equiv. of phenyllithium affords bis(triphenyllead)methyl lithium  $\text{Ph}_3\text{PbCH}_2\text{Li}$  (98%), which reacts with diphenylarsino chloride  $\text{Ph}_2\text{AsCl}$  to give compound **141** in 65% yield. Addition of phenyllithium and subsequent reaction with another equivalent of diphenylchloroarsine led to derivative **142** in 53% yield <1980TL2807>. Another example is the dimethylarsino trimethylstannylcyclopentadiene **143** prepared in 26% yield by the reaction of dimethylaminotrimethylstannane with dimethylarsino cyclopentadiene in pentane at room temperature <1979JOM57> (Scheme 41).



Scheme 41

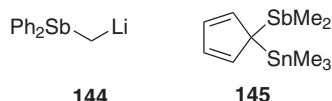
### 4.13.3.2 Antimony Derivatives

#### 4.13.3.2.1 Antimony and group 1 metals

Phenyllithium reacts with bis(diphenylstibino)methane in THF at  $-70^{\circ}\text{C}$  to afford diphenylstibinomethylithium **144** quantitatively <1978TL4391, 1983CB473, 1985CB2353>.

#### 4.13.3.2.2 Antimony and group 14 metals

Dimethylstibinotrimethylstannylcyclopentadiene **145** is synthesized in 80% yield by following the same procedure as described above for compound **143** <1979JOM57> (Scheme 42).



Scheme 42

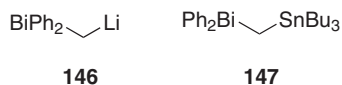
### 4.13.3.3 Bismuth Derivatives

#### 4.13.3.3.1 Bismuth and group 1 metals

Diphenylbismuthinomethylithium **146** is generated by following the same procedure as for its arsino and stibino counterparts, i.e., by transmetalation of bis(diphenylbismuthino)methane with phenyllithium in  $\text{Et}_2\text{O}$  at  $-78^{\circ}\text{C}$  <1980AG(E)723, 1985CB1039>.

#### 4.13.3.3.2 Bismuth and group 14 metals

Reaction of dimethylbismuthinosodium with chloromethyltrimethyltin furnishes derivative **147** <1988ZN(B)739> (Scheme 43).



Scheme 43

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### Biographical sketch



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## 4.14

# Functions Containing at Least One Metalloid (Si, Ge, or B) Together with Another Metalloid or Metal

N. G. BHAT

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## 4.14.1 FUNCTIONS CONTAINING TWO METALLOIDS

4.14.1.1 Functions Bearing Two Silicons:  $R_2C(SiR_3)_2$ , etc.

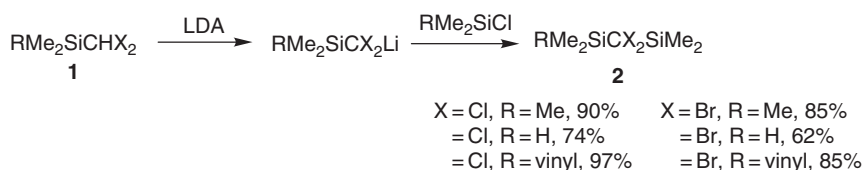
The COFGT (1995) details the synthetic methods for the preparation of an  $sp^3$ -hybridized carbon connected to two silyl groups and either protons or carbon fragments. Recently, a useful review on silenes has appeared <2002POL467>. A review describing the synthesis, structure, and reactions of groups 1–3 containing bulky silicon-substituted alkyl groups has been published <1995JOM89>.

## 4.14.1.1.1 Formation of the Si—C—Si linkage

In COFGT (1995), the different methods to form the Si—C—Si linkage are reported. The different routes involve the quenching of a carbanion with a silyl electrophile, quenching a silyl anion with a carbon electrophile, construction from silenes or disilenes, the generation of 1,1-bis(silyl) alkanes through rearrangements involving silenes, hydrosilylation, and the synthesis of 1,1-bis(silyl) alkanes via the replacement of functionality on the central methylene by either protons or carbon fragments.

## (i) Quenching a carbanion with a silyl electrophile

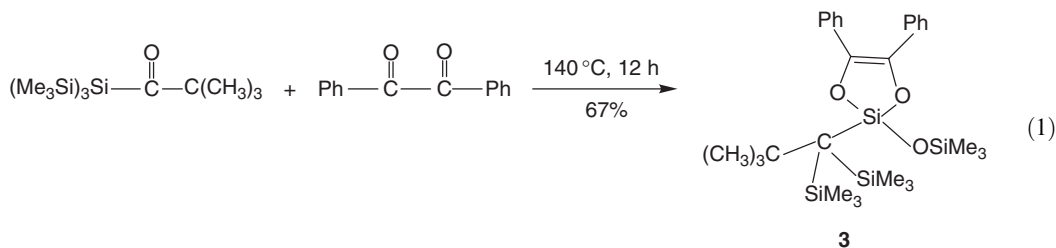
*gem*-Disilyl compounds **2** could also be prepared by the deprotonation of dihalotrimethylsilylmethane **1** with lithium diisopropylamide followed by silylation with trialkylsilyl chlorides (Scheme 1) <1997JOM185>.



Scheme 1

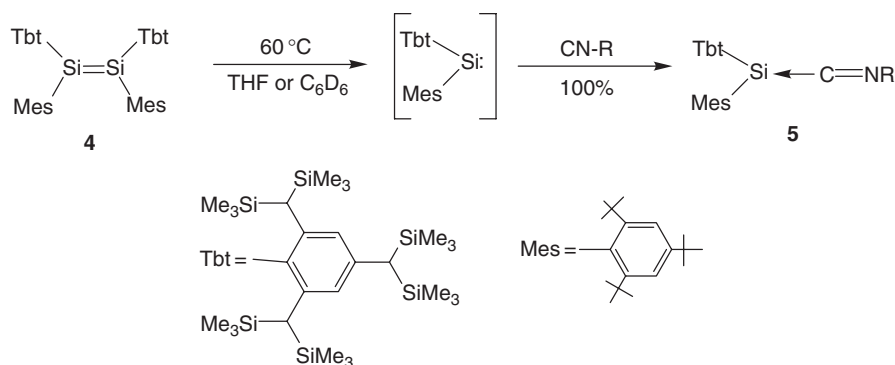
## (ii) From silenes and silylenes

When the co-thermolysis of pivaloyltris(trimethylsilyl)silane with benzil was carried out in a sealed tube at 140 °C for 12 h, 1-[(*t*-butyl)bis(trimethylsilyl)methyl]-3,4-diphenyl-1-trimethylsiloxy-2-5,dioxa-1-silacyclopent-3-ene **3** was obtained in 67% yield (Equation (1)) <2003JOM1>.

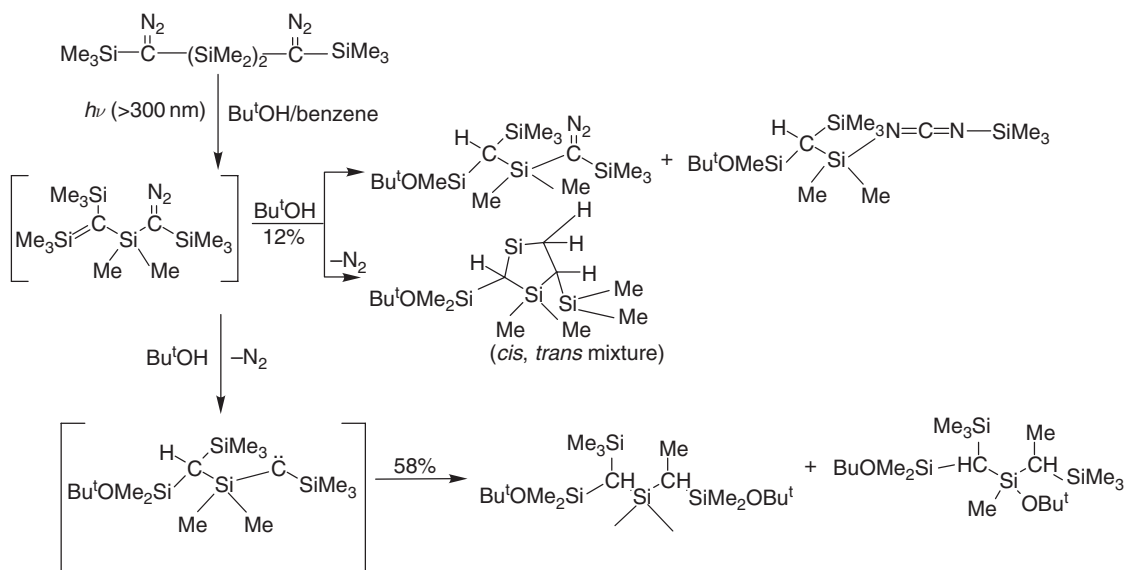


The reaction of a sterically hindered silylene **4** with isocyanides provided the first stable silylene–Lewis base complexes **5** (Scheme 2) <1997JA1456>.

The photolysis of bis(trimethylsilyldiazomethyl)disilane **6** in *t*-butyl alcohol provided the *t*-butyl alcohol adducts **7** and **8**. The structures of these products revealed the stepwise formation of asymmetric silenes as intermediates (Scheme 3) <1995JOM99>.



Scheme 2



Scheme 3

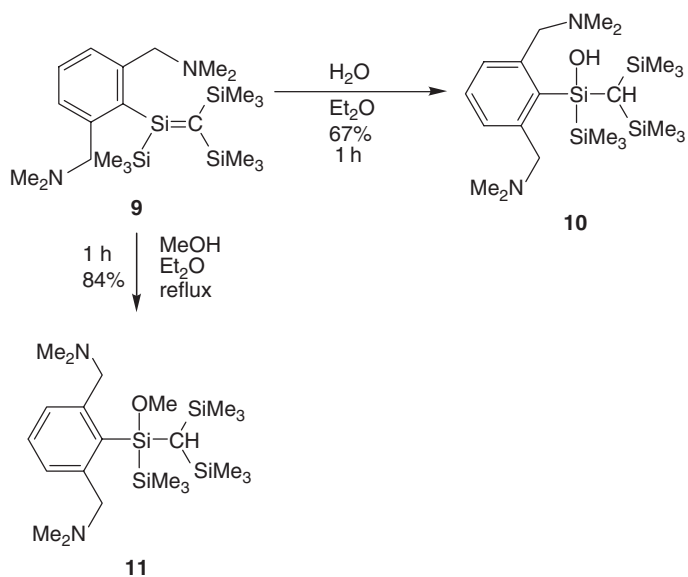
1-[2,6-Bis(dimethylaminomethyl)phenyl]-1,2,2-tris(trimethylsilyl)silene) was prepared by the treatment of (dichloromethyl)tris-(trimethylsilyl)silane with 2,6-bis(dimethylaminomethyl)phenyllithium (molar ratio 1:2). The product is a crystalline compound, indefinitely stable at room temperature. The reaction of trimethyl-substituted silene **9** with water or methanol led to the addition of these nucleophiles to the silicon—carbon double bond, producing the silanol **10** and the methoxysilane **11** respectively. The reaction pathway leading to these products was discussed (Scheme 4) <2001JOM261>.

The silylated alcohol **12** was deprotonated with methyllithium in ether at low temperature. This resulted in the elimination of lithium trimethylsilanoate to provide the transient silene **13**, which underwent readdition of lithium trimethylsilanoate to give the observed product **14** after silylation with chlorotrimethylsilane (Scheme 5) <1996JOM181>.

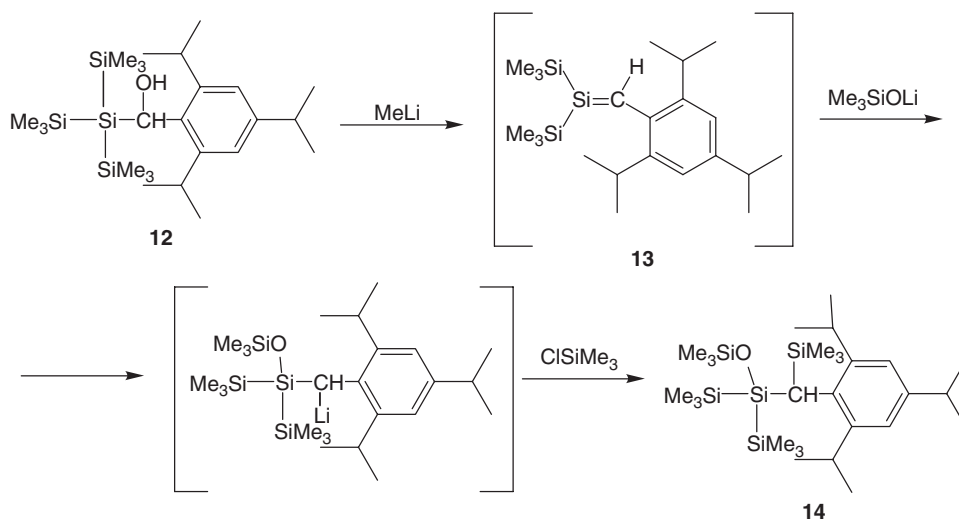
### (iii) Other routes

The reaction of 1-boraadamantane with 1-alkynylsilicon compounds led to adamantylbis(silyl) compound **15** upon reaction with methanol (Scheme 6) <2001JOM51>.

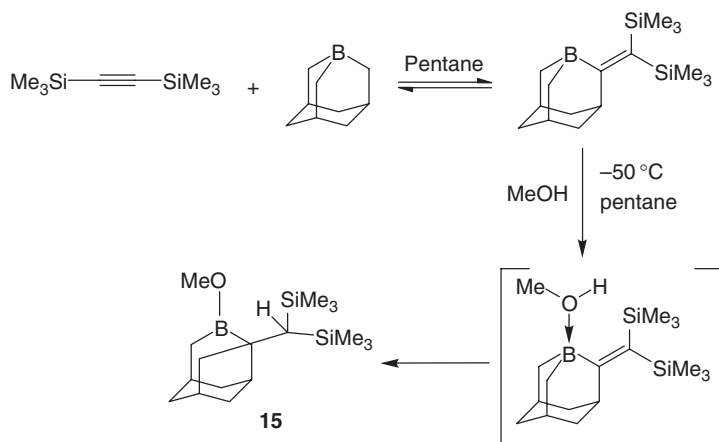
A one-pot procedure for the transformation of the  $\alpha$ -silylated amide **16** to  $\alpha,\alpha$ -disilylated amide **17** has been reported via the deprotonation of the  $\alpha$ -silylated amide with *n*-butyllithium followed by silylation with trimethylsilyl chloride (Equation (2)) <2000T4467>.



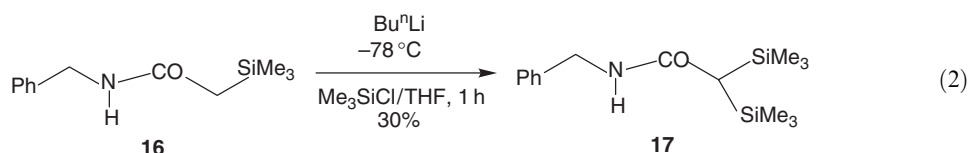
Scheme 4



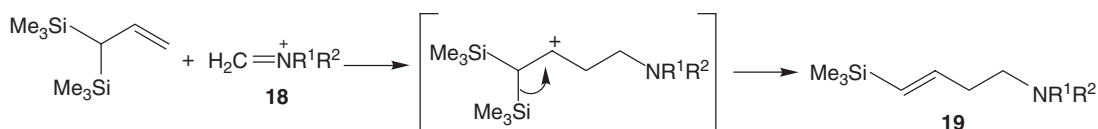
Scheme 5



Scheme 6

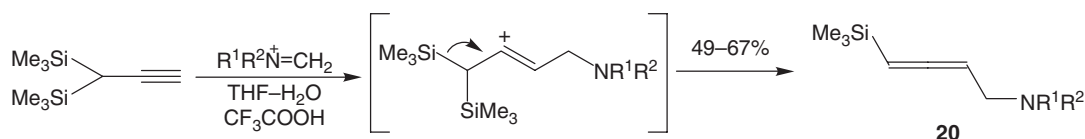


3,3-Bis(trimethylsilyl)propene reacted with iminium ions **18** generated *in situ* from secondary amines by an aminomethylation–desilylation process, leading to (*E*)- $\beta$ -aminovinylsilanes **19**. When a secondary amine with two secondary groups was used the reaction failed, probably due to steric hindrance (Scheme 7) <2000JOM186>.



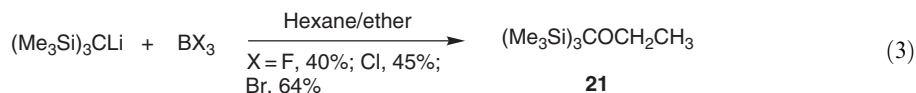
Scheme 7

The synthesis of pure trimethyl-substituted  $\alpha$ -allenic amines **20** was achieved by the reaction of 1,1-bis(trimethylsilyl)-2-propyne with iminium ions, via an aminomethano desilylation process (Scheme 8) <1996SC3351>.

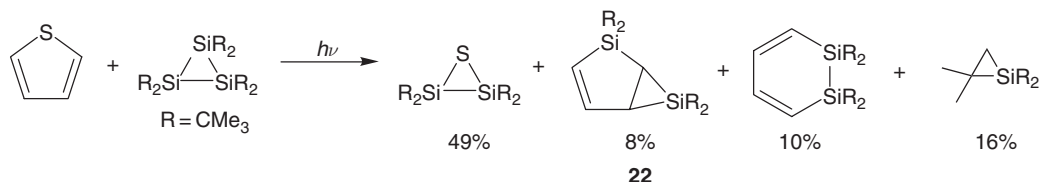


Scheme 8

Facile cleavage of Et<sub>2</sub>O occurred with [tris(trimethylsilyl)methyl]lithium in the presence of BX<sub>3</sub> (where X = F, Cl, or Br) yielding ethyl tris(trimethylsilyl)methyl ether **21** instead of the expected [tris(trimethylsilyl)methyl]boron dihalide; an analogous Et<sub>2</sub>O cleavage also occurred with AlCl<sub>3</sub>. The sterically hindered ether formed was unreactive toward carbon–oxygen bond cleavage by HBr, BCl<sub>3</sub>, and Me<sub>3</sub>SiI (Equation (3)) <1995OM3098, 1995OM5695>.



The photolysis of hexa *t*-butylcyclotrisilane in the presence of thiophene generated 2,2,6,6-tetra *t*-butyl-2,6-disilabicyclo[3.1.0]hex-3-ene **22** as one of the products in 8% yield (Scheme 9) <1995OM5695>.

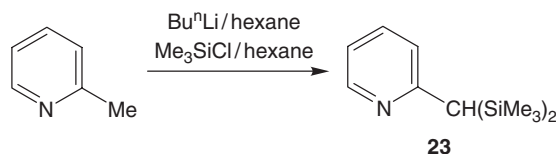


Scheme 9

#### 4.14.1.1.2 Changing the groups attached to the central methylene

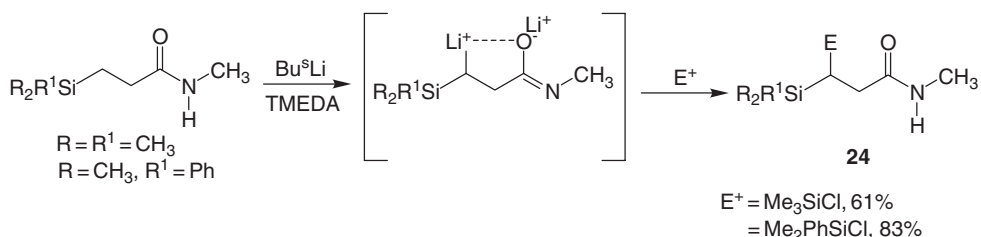
In COFGT (1995), the preparation of 1,1-bis(silyl) alkanes through the manipulation of the central group of an existing 1,1-bis(silyl)methane was outlined. The simplest route to such a change would involve metallation followed by an electrophilic quench.

2-Methylpyridine was deprotonated with *n*-butyllithium followed by silylation with chlorotrimethylsilane to afford the bis(silylated) product **23**. The latter was reacted further with *n*-butyllithium followed by treatment with chlorotrimethylsilane to produce the tris(trimethylsilyl) compound (Scheme 10) <1995JOM89>.



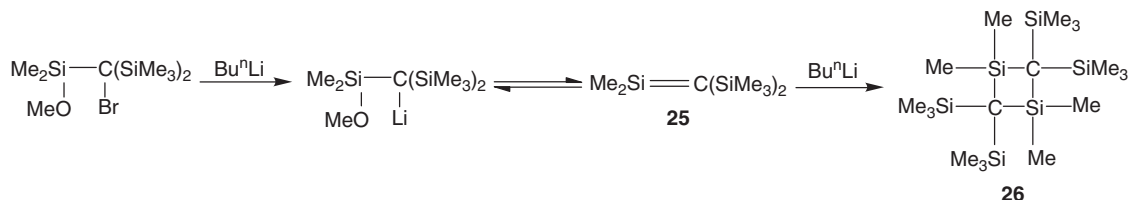
Scheme 10

*N*-Methyl-3-(trimethylsilyl)propanamide was reacted with *s*-butyllithium and *N,N,N',N'*-tetramethylethylenediamine (TMEDA) and subsequent quenching with chlorotrimethylsilane gave the silylated product **24** in 61% yield (Scheme 11) <1999JCS(P1)2433>.



Scheme 11

The trimethyl-substituted silene was formed by the reaction of  $\alpha$ -bromotrimethylsilane with *n*-butyllithium. The silene **25** in the presence of *n*-butyllithium was transformed into the corresponding 1,3-disilacyclobutane **26** (Scheme 12) <2000JOM304>.

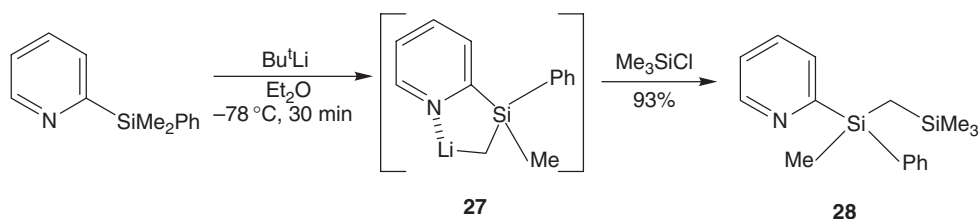


Scheme 12

#### 4.14.1.1.3 Changing the ligands on silicon

In COFGT (1995), silicon-based substitution reactions on 1,1-bis(silyl)alkanes to generate new systems are described. The most common process by which an existing 1,1-bis(silyl) alkane could be functionalized is through the displacement of chlorine bound to silicon by a nucleophilic carbon.

A novel method for the deprotonation of a methyl group on silicon has been developed. The demonstrated  $\alpha$ -lithiation protocol was based on intramolecular pyridyl group coordination to stabilize the  $\alpha$ -silylcarbanion together with the inherent silicon  $\alpha$ -effect. It was found that the deprotonation ( $\text{Bu}^n\text{Li}/\text{Et}_2\text{O}/-78^\circ\text{C}$ ) occurred with 2-pyridyltrimethylsilane but not with other related silanes such as phenyltrimethylsilane, 3-pyridyltrimethylsilane, and 4-pyridyltrimethylsilane. It seemed that this deprotonation proceeded through the agency of the complex-induced proximity effect (CIPE) of a 2-pyridyl group on silicon.  $^1\text{H}$ -NMR analysis of (2-pyridyldimethylsilyl)methyl-lithium revealed the intramolecular coordination of a pyridyl group to lithium. The (2-pyridyldimethylsilyl)methyl-lithium **27** was found to react with chlorosilanes to give the desired compounds **28** in excellent yields (Scheme 13) <2001JOC3970>. The results are outlined in Table 1.

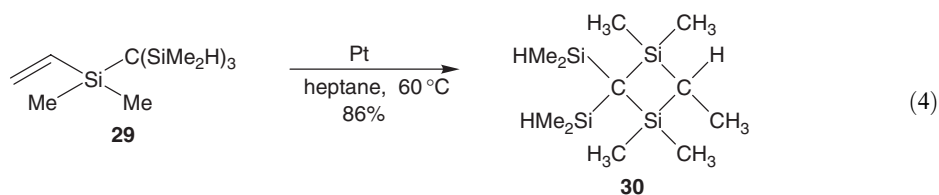


Scheme 13

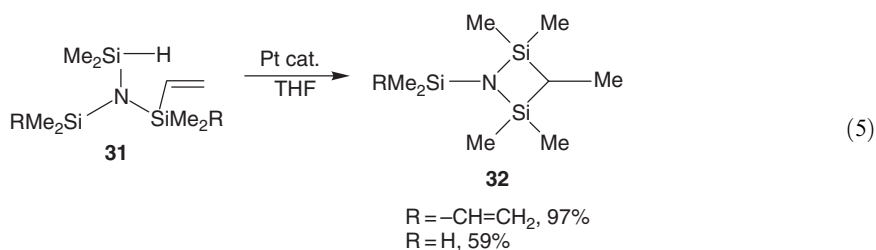
**Table 1** The reaction of (2-pyridyldimethylsilyl) methyl lithium with various silyl electrophiles

Nucleophile	Electrophile	Product	Yield (%)
	$\text{Me}_3\text{SiCl}$		93
	$\text{PhMe}_2\text{SiCl}$		99
	$2\text{-PyrMe}_2\text{SiH}$		63

The platinum-catalyzed intramolecular hydrosilylation of a vinyl silane **29** was achieved in heptane to produce the 1,3-disilacyclobutane derivative **30** (Equation (4)) <2001JOM127>.



The addition of platinum catalyst to trisilyl-substituted amines **31** resulted in the formation of intramolecular cyclization products **32**. Unexpectedly, four-membered-ring products were formed predominantly, rather than the thermodynamically more stable five-membered rings resulting from endo-cyclization. The products were quite thermally stable and resisted reaction with  $\text{Bu}^n\text{Li}$  and  $\text{Bu}^n\text{Li/TMEDA}$ . The trisilyl-substituted amine starting materials were prepared from lithium bis(silyl)amides and chlorosilanes in high yields (Equation (5)) <1999OL423>.



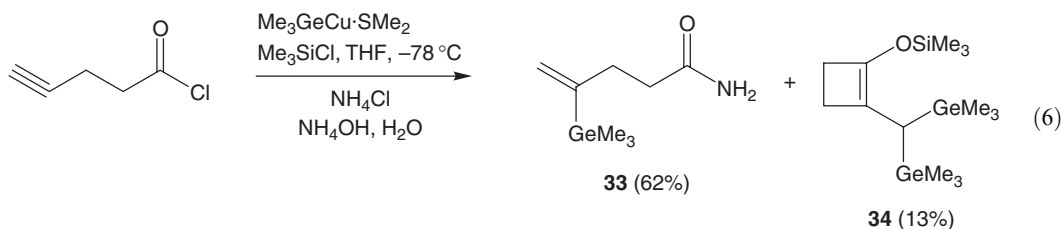
#### 4.14.1.2 Functions Bearing Two Germaniums: $R_2C(GeR_3)_2$

1,1-Bis(germyl)alkanes could be prepared by the formation of either one or both of the Ge—C bonds or modification of the groups attached to either the germaniums or to the central carbon. The different methods to generate an  $sp^3$ -hybridized carbon connected to two germanium atoms and either protons and carbon fragments are outlined in COFGT (1995).

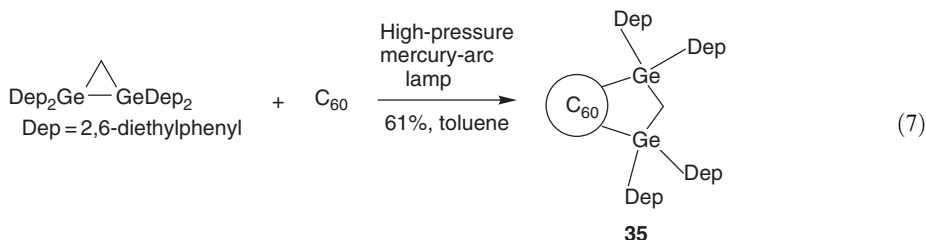
##### 4.14.1.2.1 Formation of the Ge—C—Ge linkage

In COFGT (1995), the formation of the Ge—C—Ge linkage via quenching of a carbanion with a germyl electrophile, quenching a germyl anion with a carbon electrophile, and from germenes or digermenes is described.

The reaction of 4-pentenoyl chloride with (trimethylgermyl)copper(I)-dimethyl sulfide and trimethylsilyl chloride in dry THF at  $-78^\circ\text{C}$  followed by work up with aqueous ammonium chloride and ammonium hydroxide gave two products; the major product was shown to be an amide (62%) **33** and the minor product was shown to be the *gem*-digermyl compound **34** (Equation (6)) <1995OM5011>.



In the photochemical bis-germylation of  $\text{C}_{60}$  with 1,1,2,2-tetrakis(2,6-diethylphenyl)-1,2-digermirane, a cycloadduct **35** was obtained in high yield for the first time. Spectroscopic analysis and theoretical investigation confirmed that the product resulted from 1,4-cycloaddition. Control experiments and laser flash photolysis experiments suggested that an exciplex intermediate was responsible for the formation of the cycloadduct. The redox properties of the cycloadduct were examined by differential pulse voltammetry (Equation (7)) <2000OL2671>.



##### 4.14.1.2.2 Changing the groups attached to the central methylene

In COFGT (1995), the only method reported is the metallation of bis(trimethylgermyl)methane with *t*-butyllithium and subsequent reaction with an electrophile. No further advances have occurred in this area since the publication of chapter 4.14.1.2.2 in <1995COFGT(4)601>.

##### 4.14.1.2.3 Changing the ligands on germanium

In COFGT (1995), the preparation of the 1,1-bis(germyl)alkanes by changing the ligands on germanium present in 1,1-bisgermylalkanes is reported. No further advances have occurred in this area since the publication of chapter 4.14.1.2.3 in <1995COFGT(4)601>.



#### 4.14.1.3 Functions Bearing Two Borons: $R_2C(BR_2)_2$ , etc.

In COFGT (1995), systems containing two boryl groups and either proton or carbon fragments bound to an  $sp^3$ -hybridized carbon were reviewed. A useful review has appeared on highly Lewis acidic bifunctional organoboranes <2000EJI131>.

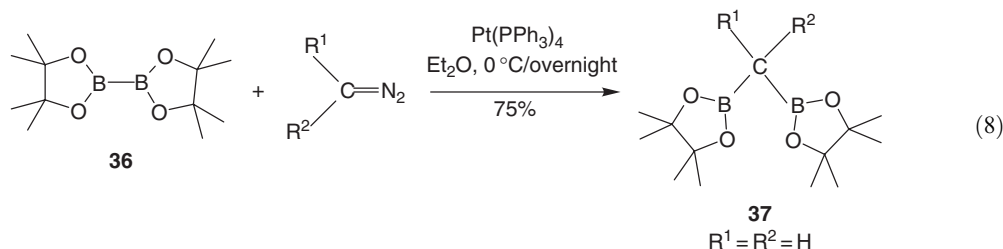
##### 4.14.1.3.1 Formation of the B—C—B linkage

The formation of the B—C—B linkage through the hydroboration of terminal alkynes, internal alkynes, vinylboranes, and through the quenching of a carbanion with a boryl electrophile is outlined in COFGT (1995). In addition to hydroboration, vinylboranes have been boroborated to give 1,1,2-trisborylalkanes.

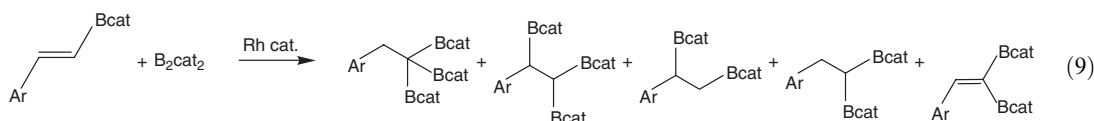
##### (i) From diboration

The catechol-substituted diboranes reacted with the catechol-substituted borylacetylenes, in the presence of  $[Pt(PPh_3)_2(C_2H_4)]$  or  $[Pt(PPh_3)_4]$ , to give tetra- and hexaborylethane derivatives. When  $[Pt(COD)_2]$  was used as catalyst, the tetraborylethane was formed exclusively. Catalytic hydrogenation of the tetraborylethane afforded the 1,1,1',1'-tetraborylethane which has been studied by X-ray structure analysis <1999EJI1693>.

The insertion reaction of bis(pinacolato)diborane **36**,  $[(Me_4C_2O_2)BB(O_2C_2Me_4)]$ , with various diazoalkanes provided novel representatives of a new class of substituted C1-bridged bis(pinacolato)diborane derivatives **37** in 75–78% isolated yields. The reaction was efficiently catalyzed by  $Pt(PPh_3)_4$  in toluene at  $110^\circ C$ . Single-crystal X-ray diffraction, GCMS, and NMR multinuclear spectroscopies fully confirmed the structure and configuration of the new compounds (Equation (8)) <2002OM1870, 1995AG(E)809>.

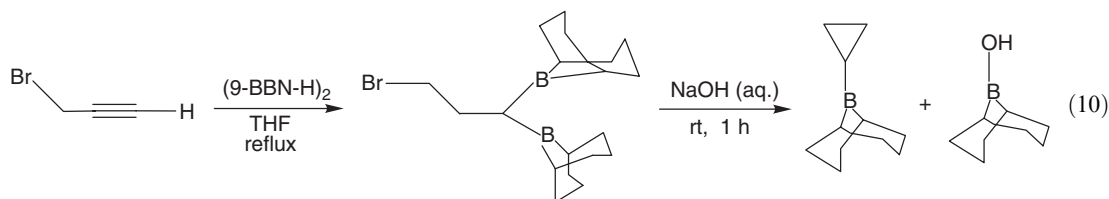


Diboration of the styrylboronate esters (*E*)-*p*-R-C<sub>6</sub>H<sub>4</sub>-CH=CH-Bcat (R = H, MeO; cat = 1,2-O<sub>2</sub>C<sub>6</sub>H<sub>4</sub>), with bis(catechol)diborane (B<sub>2</sub>cat<sub>2</sub>), in the presence of a variety of rhodium phosphine catalysts gave the corresponding hydroborated products. The formation of the products apparently involved regiospecific insertion of the vinylboronates into a rhodium—boron bond followed by  $\beta$ -hydride elimination, another regiospecific insertion of the 2,2-diboration, and a 2,1-hydrogen shift (Equation (9)) <2002JOM77>.

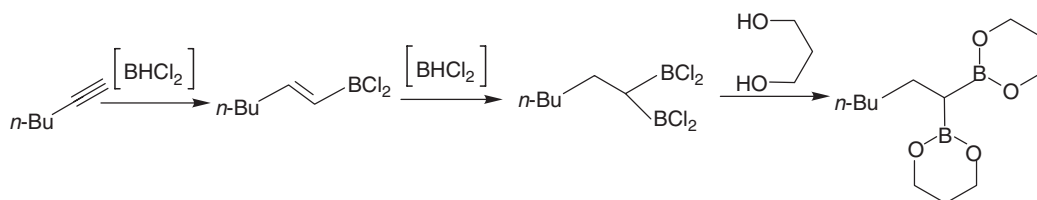


##### (ii) From dihydroboration terminal alkynes

Dihydroboration of propargyl bromide with 9-BBN-H followed by the treatment of the adduct with aqueous sodium hydroxide afforded the hydroxyl(cyclopropyl)borate complex (Equation (10)) <2000TL4251>, which underwent efficient palladium-catalyzed cross coupling to produce a variety of aryl- and vinylcyclopropanes in good-to-excellent yields <2000TL4251>.



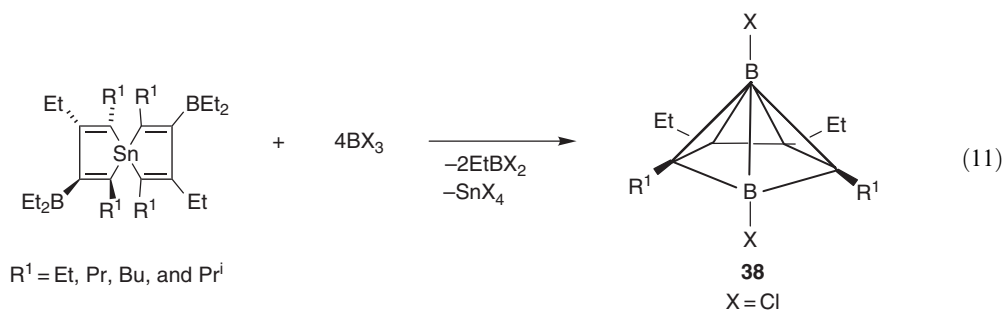
Trialkylsilanes or dialkylsilanes reacted rapidly with boron trichloride in the absence of ethereal solvents or other nucleophiles to form unsolvated dichloroborane. If no substrate was present, dichloroborane disproportionated to trichloroborane and two geometric isomers of chloroborane dimer, which in turn yielded monochlorodiborane and, slowly but irreversibly, diborane. All of the B—H compounds in the mixture except diborane were highly active hydroborating agents. With alkenes in the presence of sufficient boron trichloride, the products were alkyl-dichloroboranes. These were free from detectable contamination by dialkylchloroboranes unless more than 1 mol of hydride was present. Similar hydroboration of terminal acetylenes could be controlled to yield either (*E*)-1-(dichloroboryl)alkenes or 1,1-bis(dichloroboryl)alkanes, each free from significant contamination by the other. Alkyl-dichloroboranes with trialkylsilanes at 25 °C produce alkyl-monochloroboranes, detected by  $^{11}\text{B}$ -NMR. 1,1-Bis(dichloroboryl) alkanes similarly yielded 1,1-diborylalkane dimers. An alkylmonochloroborane could hydroborate a second alkene to form a dialkylchloroborane. For this purpose, differing alkyl groups may be introduced in either order, regardless of their relative steric properties. With 2 mol of trialkylsilane, alkyl-dichloroboranes were converted to alkylborane dimers. Boron tribromide and its bromoborane derivatives behaved similarly to the chloro compounds in the examples tested (Scheme 14) <1995OM4157>.



Scheme 14

### (iii) Other route

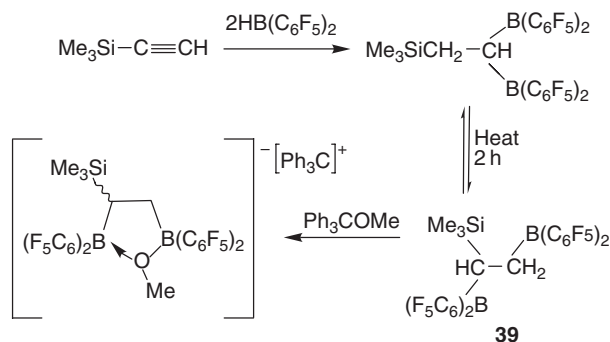
Tetraalkynyltin compounds were reacted with triethylborane to provide 1,1'-spirobisstannols. These provided carboranes **38** when reacted with boron halides. The intermediates prior to the formation of carboranes were 3-borolenes bearing boryl groups in the 2,5-positions with the boryl groups at the same side of the ring (Equation (11)) <1995JOM87>.



#### 4.14.1.3.2 Changing the groups on the central methylene

According to COFGT (1995), the simplest method for adding functionality to the central methylene was by direct deprotonation followed by an electrophilic quench.

The dihydroboration of trimethylsilylacetylene with diperfluorophenylborane followed by thermal treatment provided 1,2-diborylethane derivative **39** (Scheme 15) <1995TL987, 1995AG(E)809>.

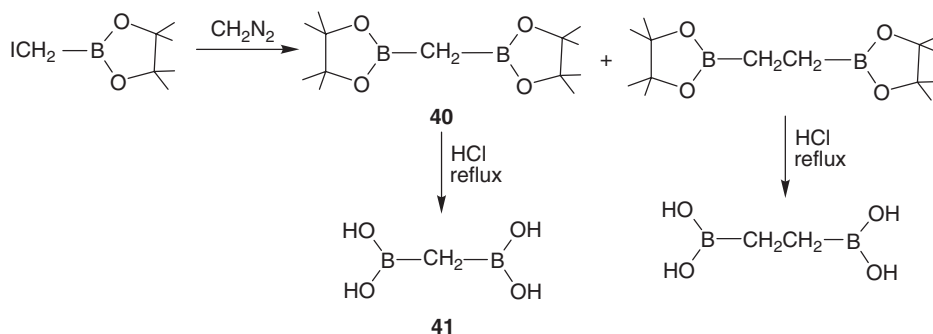


Scheme 15

#### 4.14.1.3.3 Changing the ligands on boron

The route to the generation of 1,1-bis(boryl)alkanes was through the modification of ligands on boron. In COFGT (1995), several such reactions have been demonstrated on bis(boryl)alkanes.

It has been discovered that diazomethane reacted with  $\alpha$ -iodo boronate ester to insert methylene to give the corresponding *gem*-diboronate **40** in 83% yield which could be easily hydrolyzed to the corresponding boronic acid **41** (Scheme 16) <2001OM3962>.



Scheme 16

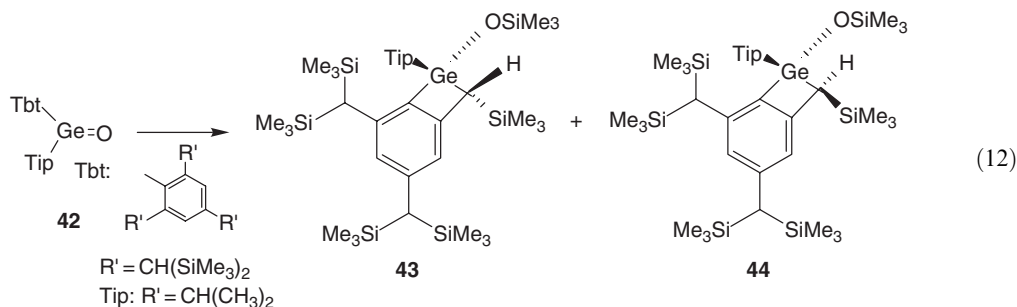
#### 4.14.1.4 Functions Bearing a Silicon and a Germanium Group: $R_2CSiR_3^2GeR_3^3$ , etc.

The generation of systems containing both a silyl group and a germyl group attached to the same  $sp^3$ -hybridized carbon along with either hydrogen or carbon fragments is outlined in COFGT (1995).

##### 4.14.1.4.1 Formation of the Si—C—Ge linkage

The formation of the Si—C—Ge linkage has been outlined in COFGT (1995) by quenching a carbanion with a germyl electrophile, quenching a carbanion with a silyl electrophile, quenching a metalloid anion with a carbon electrophile, and hydrogermylation of silyllallene.

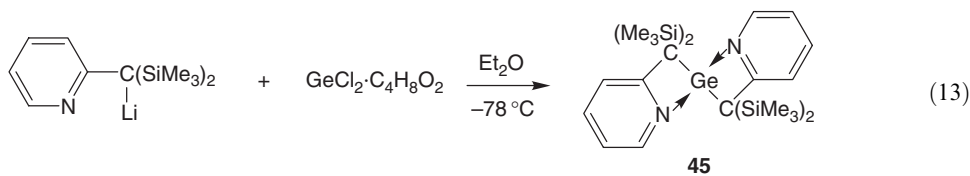
It has been reported that a germanone **42** readily underwent intramolecular carbon–silicon insertion in solution to give a mixture of stereoisomers **43** and **44** containing  $\alpha$ -trimethylsilyl-germyl moieties (Equation (12)) <2002POL563>.



#### 4.14.1.4.2 Changing the groups attached to the central methylene

In COFGT (1995), metallation of the central carbon has been demonstrated by the deprotonation of trimethylgermyl(trimethylsilyl)methane with *t*-butyllithium. The same intermediate could also be prepared from the corresponding  $\alpha$ -chloro derivative through metal-halogen exchange with lithium metal.

Bis[2-pyridyl]bis(trimethylsilyl)-*C,N*]germanium(II) **45** was prepared by the reaction of lithiated 2-[bis(trimethylsilyl)methyl]pyridine and germanium(II) chloride-dioxane in ether at  $-78^\circ\text{C}$ . The structure of the product was confirmed by an X-ray diffraction study (Equation (13)) <1997OM2116>.



#### 4.14.1.4.3 Changing the groups attached to the metalloids

According to COFGT (1995), one of the most frequently used transformations was the replacement of a halogen by a carbon nucleophile, a reaction that has also been applied to 1-silyl-1-germylalkanes. The alkoxide ligands on the metalloids have been replaced by both oxygen and nitrogen ligands. The silyl(germyl)methane moiety has also been used as a ligand for transition metals. No further advances have occurred in this area since the publication of chapter 4.14.1.4.3 in <1995COFGT(4)601>.

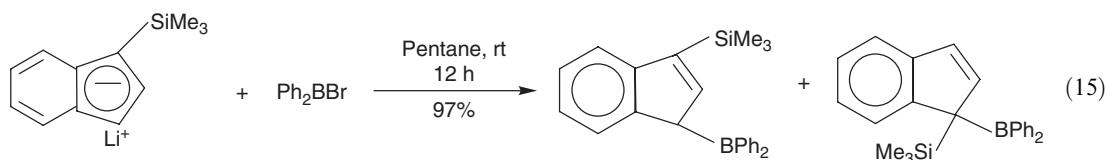
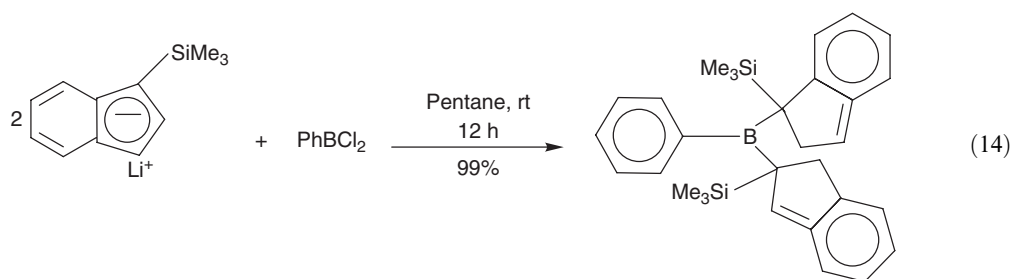
### 4.14.1.5 Functions Bearing a Silicon and a Boron Group: $\text{R}_2^1\text{CSiR}_3^2\text{BR}_2^3$ , etc.

#### 4.14.1.5.1 Formation of the Si—C—B linkage

COFGT (1995) detailed the different methods to form the Si—C—B linkage by quenching a carbanion with a boryl electrophile, quenching a carbanion with a silyl electrophile, hydroboration of vinyl silane, and borylboration of vinyl silane. Described below are the synthetic routes to generate systems containing silicon  $\alpha$  to boron.

##### (i) Quenching a carbanion with a boryl electrophile

The reaction of boron halides with indenyllithium reagents was studied. In this case, the indenyl moiety was readily transferred and bis(indenyl)boranes were formed (Equations (14) and (15)) <1997JOM361>.



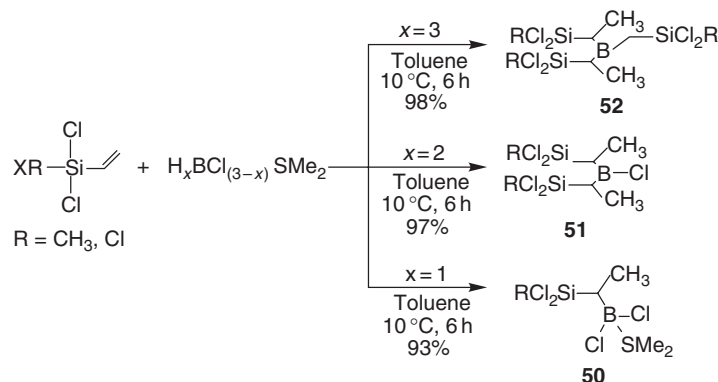
The stereocontrolled synthesis of 1-silyl-1-boryl-2-alkenes by *gem*-silylborylation of  $\alpha$ -chloroallyllithiums has been reported. The  $\alpha$ -chloroallyllithiums generated *in situ* from allylic chlorides with lithium diisopropylamide (LDA) in tetrahydrofuran were reacted with (dimethylphenylsilyl) (pinacolato)borane **46** to provide the corresponding *gem*-silylboryl reagents **47**. The results are summarized in Table 2 (Equation (16)) <2001AG(E)4283>.

**Table 2** Synthesis of 1-silyl-1-boryl-2-alkenes from allylic chlorides

<i>Allylic chloride</i>	<i>Product</i>	<i>Yield (%)</i>
		82
		86
		75
		79
		75
		72
		73

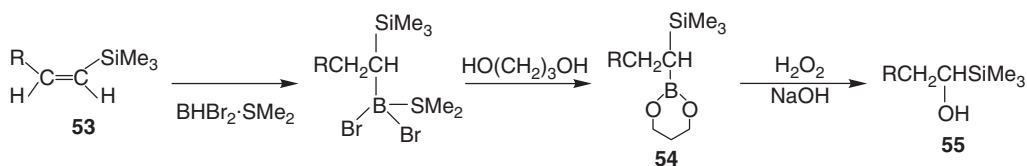


Hydrocarbon reactions of dichloroborane-, monochloroborane-, and borane-dimethyl sulfide with dichloromethylvinylsilane and trichlorovinylsilane were investigated. The first addition appeared strictly regioselective in the  $\alpha$ -position to silicon, producing one chiral methine group between silicon and dichloroborane in the compound formed **50**. The second addition of borane- or monochloroborane-dimethyl sulfide at the vinyl groups of dichloromethylvinylsilane and trichlorovinylsilane also took place in the  $\alpha$ -position to silicon, forming a second chiral methine group **51**. In the case of borane-dimethyl sulfide the third addition occurred in the  $\beta$ -position owing to the steric hindrance to boron in tris[(dichloromethylsilyl)ethyl] borane **52** (Scheme 20) <2000POL323>.



Scheme 20

(*Z*)-1-Trimethylsilyl-1-alkenes **53**, easily prepared by the hydroboration of the corresponding 1-trimethylsilyl-1-alkynes followed by protonolysis with acetic acid, readily reacted with dibromoborane-methyl sulfide complex in dichloromethane for 6 h. The resulting solution was then treated with 1,3-propanediol in a 1:1 mixture of dichloromethane and *n*-pentane at  $0^\circ\text{C}$  for half an hour to provide the corresponding *gem*-dimetalloalkanes **54** containing boron and silicon. These  $\alpha$ -trimethylsilylalkylboronate esters were purified by vacuum distillation in high yields (72–84%) and the structures of these novel intermediates were further confirmed by selective oxidation with alkaline hydrogen peroxide to provide the corresponding alcohols **55** containing the trimethylsilyl group (Scheme 21) <2003TL6833>. Representative examples of boronate esters with an  $\alpha$ -trimethylsilyl group are provided in Table 3.



Scheme 21

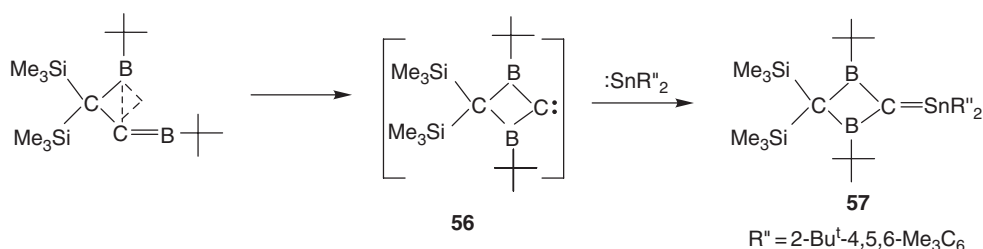
### (iii) Other routes

Addition of diarylstannylenes to an electrophilic carbene **56** furnished the corresponding stannaethene **57**. The X-ray structure analysis of the stannaethene revealed a strictly planar environment of the tricoordinated tin and carbon atoms and a slight twisting of the tin–carbon double bond (Scheme 22) <1997JOM255>.

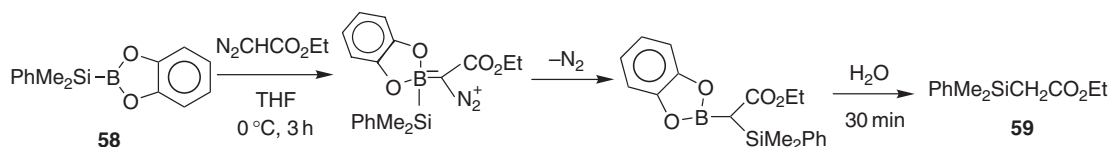
Several representative silylboranes, including *B*-(phenyldimethylsilyl) catecholborane, were prepared and their reactivity was explored. The reaction of silylboranes with either vinyl lithium or lithium acetylide generated the corresponding silylborates, which rearranged upon treatment with iodine producing the vinyl silanes and silylacetylide, respectively. The reaction of *B*-(phenyldimethylsilyl)catecholborane **58** with ethyl diazoacetate yielded ethyl(phenyldimethylsilyl) acetate **59** upon hydrolysis (Scheme 23) <1995OM3112>.

**Table 3** Synthesis of *gem*-dimetalloalkanes containing boron and silicon  
 (*Z*)-1-Trimethylsilyl-1-alkene      *Product*      *Yield (%)*

$\begin{array}{c} n\text{-C}_4\text{H}_9 \quad \text{SiMe}_3 \\ \diagdown \quad \diagup \\ \text{C}=\text{C} \\ \diagup \quad \diagdown \\ \text{H} \quad \text{H} \end{array}$	$\begin{array}{c} \text{SiMe}_3 \\   \\ n\text{-C}_4\text{H}_9\text{CH}_2\text{CH}-\text{B} \begin{array}{c} \diagup \quad \diagdown \\ \text{O} \quad \text{O} \end{array} \end{array}$	84
$\begin{array}{c} n\text{-C}_5\text{H}_{11} \quad \text{SiMe}_3 \\ \diagdown \quad \diagup \\ \text{C}=\text{C} \\ \diagup \quad \diagdown \\ \text{H} \quad \text{H} \end{array}$	$\begin{array}{c} \text{SiMe}_3 \\   \\ n\text{-C}_5\text{H}_{11}\text{CH}_2\text{CH}-\text{B} \begin{array}{c} \diagup \quad \diagdown \\ \text{O} \quad \text{O} \end{array} \end{array}$	82
$\begin{array}{c} n\text{-C}_6\text{H}_{13} \quad \text{SiMe}_3 \\ \diagdown \quad \diagup \\ \text{C}=\text{C} \\ \diagup \quad \diagdown \\ \text{H} \quad \text{H} \end{array}$	$\begin{array}{c} \text{SiMe}_3 \\   \\ n\text{-C}_6\text{H}_{13}\text{CH}_2\text{CH}-\text{B} \begin{array}{c} \diagup \quad \diagdown \\ \text{O} \quad \text{O} \end{array} \end{array}$	78
$\begin{array}{c} \text{Cl}(\text{CH}_2)_3 \quad \text{SiMe}_3 \\ \diagdown \quad \diagup \\ \text{C}=\text{C} \\ \diagup \quad \diagdown \\ \text{H} \quad \text{H} \end{array}$	$\begin{array}{c} \text{SiMe}_3 \\   \\ \text{Cl}(\text{CH}_2)_3\text{CH}_2\text{CH}-\text{B} \begin{array}{c} \diagup \quad \diagdown \\ \text{O} \quad \text{O} \end{array} \end{array}$	72
$\begin{array}{c} (\text{CH}_3)_3\text{C} \quad \text{SiMe}_3 \\ \diagdown \quad \diagup \\ \text{C}=\text{C} \\ \diagup \quad \diagdown \\ \text{H} \quad \text{H} \end{array}$	$\begin{array}{c} \text{SiMe}_3 \\   \\ (\text{CH}_3)_3\text{CCH}_2\text{CH}-\text{B} \begin{array}{c} \diagup \quad \diagdown \\ \text{O} \quad \text{O} \end{array} \end{array}$	74
$\begin{array}{c} \text{CH}_3\text{CH}_2\text{CHCH}_3 \quad \text{SiMe}_3 \\ \diagdown \quad \diagup \\ \text{C}=\text{C} \\ \diagup \quad \diagdown \\ \text{H} \quad \text{H} \end{array}$	$\begin{array}{c} \text{SiMe}_3 \\   \\ \text{CH}_3\text{CH}_2\text{CHCH}_2\text{CH}-\text{B} \begin{array}{c} \diagup \quad \diagdown \\ \text{O} \quad \text{O} \end{array} \end{array}$	80



**Scheme 22**



**Scheme 23**

#### 4.14.1.5.2 Changing the groups attached to the central methylene

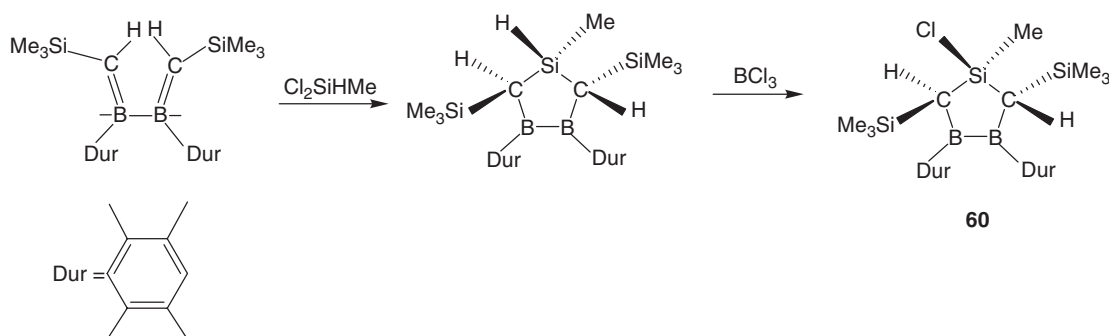
As described in COFGT (1995), the only method described for the manipulation of functionality on the central methylene of  $\alpha$ -borylsilylalkanes is through deprotonation followed by electrophilic quench. No further advances have occurred in this area since the publication of chapter 4.14.1.5.2 in <1995COFGT(4)601>.



#### 4.14.1.5.3 Changing the groups attached to the metalloids

As indicated in COFGT (1995), ester exchange provided a simple route to the manipulation of the functionality on boronic acids. A carbon–boron bond may be formed by the displacement of an alkoxide ligand, such as the reaction of an allyl Grignard reagent with  $\alpha$ -trimethylsilyl-*B*-methoxyborolane.

The cyclic compounds **60** containing boron and silicon were prepared by reacting 2,3-diborata-1,3-butadiene with dichloromethylsilane followed by treatment with boron trichloride (Scheme 24) <2002JOM262>.



Scheme 24

#### 4.14.1.6 Functions Bearing a Germanium and a Boron Group: $R_2^1CBR_2^2GeR_3^3$ , etc.

In COFGT (1995), very little work was reported concerning systems containing both boron and germanium on the same  $sp^3$ -hybridized carbon. One example was the hydroboration of dimethyl(divinyl)germane with borane–methyl sulfide complex, which resulted in a mixture of regioisomers as evidenced by the alcohols produced upon oxidative work-up. No further advances have occurred in this area since the publication of chapter 4.14.1.6 in <1995COFGT(4)601>.

### 4.14.2 FUNCTIONS CONTAINING A METALLOID AND A METAL

#### 4.14.2.1 Silicon and a Metal: $R_2^1CSiR_3^2M$ , etc.

According to COFGT (1995), the most important route for the preparation of 1-metallo-1-silylalkanes is deprotonation. This has been most generally performed when the resultant carbanion is stabilized by, for example, aryl, allyl, or carbonyl groups. Two useful reviews have appeared recently on organometallic compounds in <1995JOM101> and <2001T2065>.

##### 4.14.2.1.1 Silicon and a group 1 or group 2 metal: $R_2^1CSiR_3^2Li$ , etc.

In COFGT (1995), different methods have been outlined to synthesize  $\alpha$ -lithiosilylalkanes from  $\alpha$ -lithiosilylalkanes involving deprotonation, addition of organolithium to vinyl silane, halogen-lithium exchange, transmetallation, sulfur–lithium exchange,  $\alpha$ -sodio- or  $\alpha$ -potassiosilylalkanes,  $\alpha$ -magnesosilylalkanes involving halogen–magnesium exchange, addition of a Grignard reagent to vinyl silane, transmetallation, and rearrangement.

##### (i) By deprotonation of alkyl silanes and allyl silanes

The generation of [bis(2-pyridyldimethylsilyl)methyl]lithium was easily accomplished by the deprotonation of [bis(2-pyridyldimethylsilyl)methane] using *n*-butyllithium in diethyl ether. The bis(2-pyridyldimethylsilyl)methyl]lithium thus generated was found to react with a variety of

aldehydes and ketones to give the corresponding vinyl silanes in extremely high yields with complete stereoselectivities <2000OL1299>.

The formation of benzocyclobutenol derivatives by intramolecular cyclizations of *o*-acylbenzyl-lithiums is described. Treatment of *o*-(trialkylsilylmethyl)phenyl ketones with LDA followed by the quenching of the corresponding 1-trialkylsiloxy-2-(trialkylsilyl) benzocyclobutenes provided the desired products in good yields. Subsequently, *o*-acyl-*m*-methoxybenzylolithiums were found to work well in cyclizations to benzocyclobuten-1-ol derivatives. The reaction of 2-benzoyl-3,4,5-trimethoxybenzylolithium, generated *in situ* by deprotonation of 6-methyl-2,3,4-trimethoxybenzophenone with LDA, and subsequent treatment with chlorotrimethylsilane afforded the corresponding 1-(trimethylsiloxy) benzocyclobutene. Cyclization of 2-pivaloyl-3-methoxybenzylolithiums, generated *in situ* from *t*-butyl-2-methyl-6-methoxyphenyl ketones upon deprotonation with LDA, proceeded spontaneously at  $-78^{\circ}\text{C}$  to give the corresponding benzocyclobuten-1-ols. The results of thermal isomerization of these 1-trimethylsiloxy-2-(trialkylsilyl) benzocyclobutenes were also described <1999JOC3557>.

Both (*Z*)- and (*E*)-allylic silanes were prepared with high stereoselectivity by copper-mediated substitution of allylic carbamates by organometallic reagents. The reaction of alkylmagnesium reagents with (*E*)-allylic carbamates provides (*Z*)-allylic silanes, whereas both alkylmagnesium and alkylolithium reagents react with (*Z*)-allylic carbamates to afford (*E*)-allylic silanes. Because the Grignard reagents are often more facile to prepare than alkylolithium species, these reagents are the optimal nucleophiles for the synthesis of both (*Z*)- and (*E*)-allylic silanes. This method also allows readily available nonracemic allylic carbamates to be converted to chiral, nonracemic (*Z*)- and (*E*)-allylic silanes with high stereoselectivity <2000JOC1601>. The selective deprotection of acetals with trimethylsilylmethylmagnesium chloride to the corresponding diols has been achieved <2000JOC4694>. The organomercury compounds containing the bulky silyl ligands have been prepared <1996JOM143>.

Treatment of a tetrahydrofuran solution of *t*-butyldimethylsilyldihalomethylolithiums with *p*-MeOC<sub>6</sub>H<sub>4</sub>CHO or *n*-butanal followed by an addition of HMPA and benzaldehyde gave the corresponding 1,3-diol monosilyl ether in 83% or 45% yield, respectively. The use of oxirane in place of aldehyde as the first electrophile followed by addition of benzaldehyde provided 1,4-diol monosilyl ether <1996T503>.

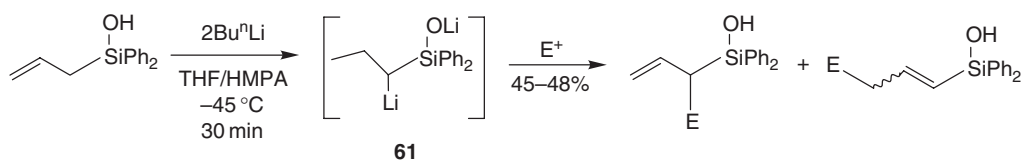
The reaction of 1-triphenylsilyl-2-propenylolithium with ethylene oxide afforded an adduct, a lithium salt of 3-triphenylsilyl-4-penten-1-ol, which regenerated an allyllithium species, 3-lithio-5-triphenylsiloxy-1-pentene via anionic rearrangement of a silyl group from carbon to oxygen in the presence of HMPA. This allylic lithium compound could be trapped in one pot by various electrophiles to provide the corresponding adducts as regioisomeric mixtures. A successive addition of epoxides, aldehydes, and HMPA to 1,3-bis(triphenylsilyl)-2-propenylolithium gave 1,4-diol monosilyl ethers in one pot with high regioselectivity <1998TL2575>. Reactions of aliphatic ketones with lithium trimethylsilyldiazomethane in the presence of excess olefins afforded methylenecyclopropanes in moderate-to-good yields <1999T3687>.

Allylation of the radical generated from  $\alpha$ -silyl- $\alpha$ -phenylselenoacetic esters with various allyltributyltin substrates led to good yields of the corresponding homoallylsilanes. A study on the nature of the radical thus generated was performed using comparative allylation rates with electronically different allyltributyltin compounds. Finally, these homoallylsilanes were converted into the corresponding homoallylic-1,2-diols after reduction of the ester function and oxidation of the C—Si bond <1995T12097>. The preparation of  $\alpha$ -(alkoxy)silylacetic esters has been achieved <1995T12083>. LDA treatment of 2-silylated benzamides afforded 2-fluorosilylated acetophenones in a general process likely driven by complex-induced proximity effect (CIPE)-facilitated  $\alpha$ -silyl carbanion formation and rearrangement; oxidation (H<sub>2</sub>O<sub>2</sub>) of the products gives 2-hydroxyacetophenones and catechols <1996TL2915>.

The synthesis of 2-substituted allylic alcohols from esters has been achieved by the reaction of trimethylsilylmethylmagnesium chloride with esters <1996JOC9617>. The enantioselective synthesis of (2-substituted-2-hydroxyethyl)allylsilanes by cerium-mediated trimethylsilylmethylmagnesium chloride addition on the ester group of optically active  $\beta$ -hydroxy esters. The reaction of ester acetals with trimethylsilylmethylmagnesium chloride to afford the alcohol acetals has also been achieved <1997TL3861>. An efficient synthesis of substituted vinylcarbamates, from benzylcarbamates via the Peterson olefination was described <1997TL1851>.

Reactions of aliphatic ketones with lithium trimethylsilyldiazomethane in the presence of excess olefins afforded methylenecyclopropanes in moderate-to-good yields. The multiplicity of the alkylidene carbene intermediate in the reaction has been revealed to be a singlet <1999T3687>. The reaction of  $\gamma$ -ketoaldehyde acetals with lithium trimethylsilyldiazomethane afforded 2-cyclopentenones via the 1,5-carbon-hydrogen insertion of alkylidene carbene in high-to-moderate yields <2000TL6859>.

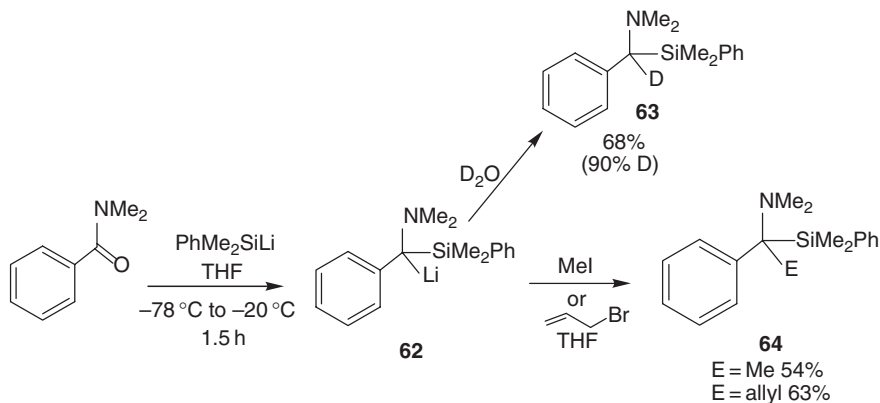
Treatment of 1-[axial]-(trimethylsilylethynyl)cyclohexan-1-ol with dicobalt octacarbonyl results in a conformational ring flip such that the bulky dicobalt-alkyne cluster moiety now occupies the favored equatorial site. However, when a 4-*t*-butyl substituent is present, the coordinated alkynyl group retains its original axial or equatorial position. Complexation of *trans*-[diaxial]-1,4-bis(triphenylsilylethynyl)cyclohexane-1,4-diol brings about a chair-to-chair conformational inversion such that both cluster fragments now occupy equatorial sites. In contrast, *cis*-1,4-bis(triphenylsilylethynyl)-cyclohexane-1,4-diol reacts with  $\text{Co}_2(\text{CO})_8$  to yield the twist-boat conformer in which the two axial hydroxyl substituents exhibit *intra*-molecular hydrogen bonding. Likewise, the corresponding reaction of *cis*-1,4-bis(trimethylsilylethynyl)cyclohexane-1,4-diol with  $\text{Co}_2(\text{CO})_8$  leads to a twist-boat, but in this case, the molecules are linked through *inter*-molecular hydrogen bonds. Eight of these cobalt clusters have been characterized by X-ray crystallography, and the potential participation of twist-boats in synthesis is discussed <2001JOC8585>. *t*-Butyldimethylsilyldibromomethyl lithium acted as a dibromomethylene dianion synthon in the reaction with aldehydes followed by 1,3-rearrangement of silyl group from carbon to oxygen <1996T503>. The hydroxymethylating reagent [dimethyl(phenylthiomethyl)silyl]methylmagnesium chloride adds to a sugar aldehyde with high selectivity to give stable *syn*-product <1995SL1069>. Treatment of allyldiphenylsilanol with 2 equiv. of *n*-butyllithium in the presence of HMPA provided silylallyllithium **61** bearing an oxide anion on the silicon atom. The reaction of silylallyllithium with different electrophiles was also investigated (Scheme 25) <1997TL5189>.



Scheme 25

(ii) By nucleophilic addition

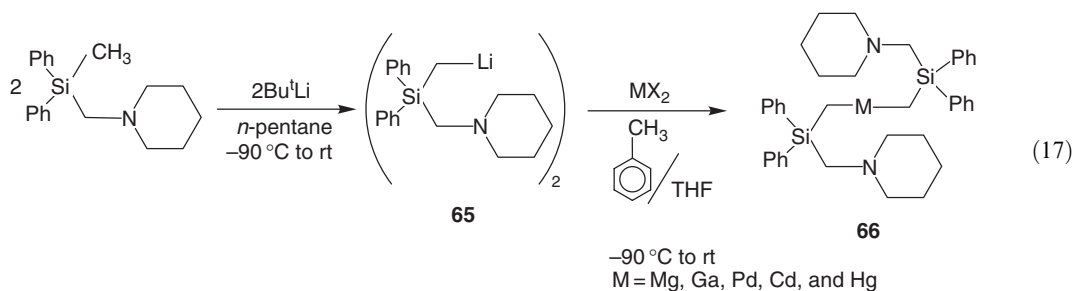
*N,N*-Dimethylbenzamide was reacted with dimethylphenylsilyllithium to provide the corresponding  $\alpha$ -silyllithium **62** and gave deuterated  $\alpha$ -silylamine **63** on quenching with D<sub>2</sub>O. The reaction of  $\alpha$ -silyllithium with alkyl halides provided the corresponding  $\alpha$ -silyl alkylated products **64** (Scheme 26) <1998CC713>.



Scheme 26

(iii) Another route

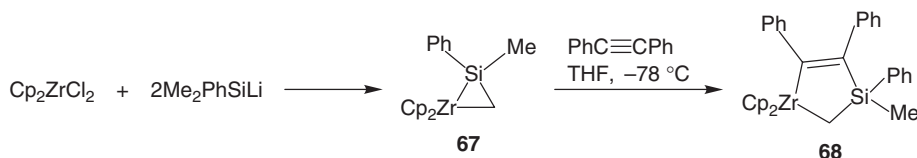
Starting from the lithium alkyl **65**, the bis[(diphenyl)(piperidinomethyl)silyl]methyl metal compounds **66** containing metals such as magnesium, cadmium, gallium, palladium, and mercury were synthesized in different solvents (toluene and tetrahydrofuran) by metathesis reactions, using the corresponding metal(II) halides (Equation (17)) <2002JOM149>.



#### 4.14.2.1.2 Silicon and a transition metal: $R^1CSiR^2CuX$ , etc.

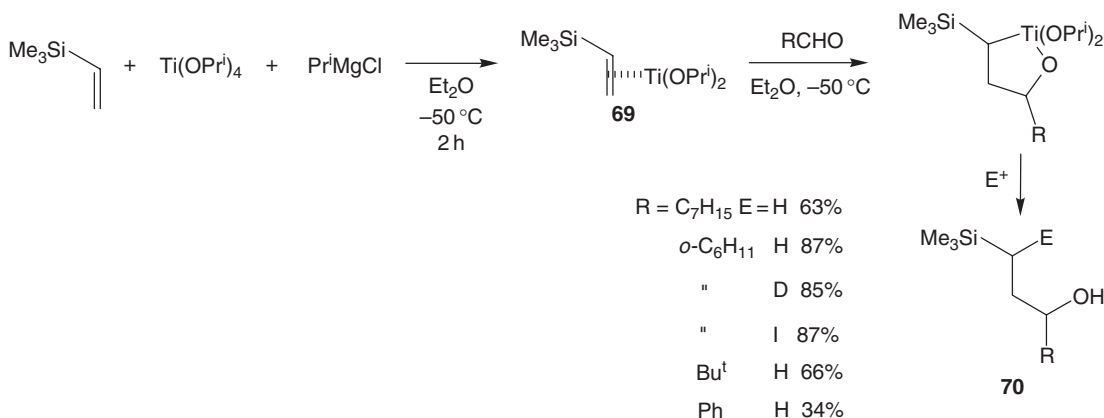
According to COFGT (1995), there have been many reports of systems containing both silicon and a transition metal (including zinc) bound to the same carbon together with either protons or carbonyl groups. They have been prepared mainly by the reactions of transition metal complexes with an  $\alpha$ -silylmethyl anion, by the reaction of an  $\alpha$ -metallomethyl transition metal with a silyl electrophile, and changing the groups attached to the central methylene or to the metal.

The zirconium–silene complex **67** was formed from dicyclopentadienyl chloride and dimethylphenylsilyllithium, which reacted with diphenylacetylene to provide the silazirconacyclopentene **68** (Scheme 27) <2000JOM304>.



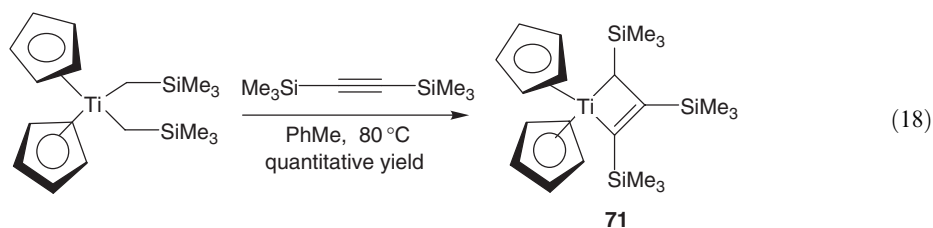
Scheme 27

The (trimethylsilyl)ethylene–titanium alkoxide complex **69** was generated from trimethyl(vinyl)silane with titanium tetraisopropoxide and isopropylmagnesium chloride. The preformed alkene–titanium complex reacted with aldehydes to form the corresponding  $\gamma$ -silyl alcohol **70**. The reaction was believed to go through oxatitanacycles (Scheme 28) <2000JOC6217>.

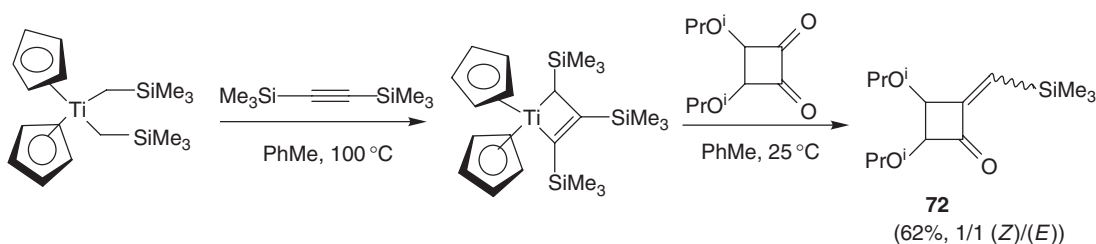


Scheme 28

The reaction of  $Cp_2Ti(CH_2SiMe_3)_2$  with bis(trimethylsilyl)acetylene in toluene formed tris(trimethylsilyl) titanacyclobutene **71**. Unlike other titanacyclobutenes, which underwent insertion with carbonyl compounds, this reagent converted carbonyl compounds to the corresponding alkenylsilanes (Equation (18)) <1995TL3619>.

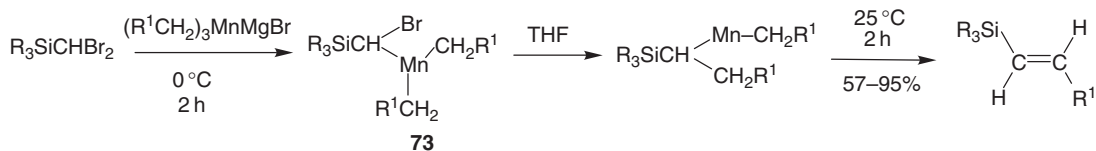


A variety of cyclobutanedione derivatives, including squaric esters, reacted with dicyclopentadienyltitanocene to afford the corresponding methylenation products **72**. With certain mixed-substituted substrates the reaction proceeded preferably at a ketonic carbonyl rather than a vinylogous ester (Scheme 29) <1995TL6001>.



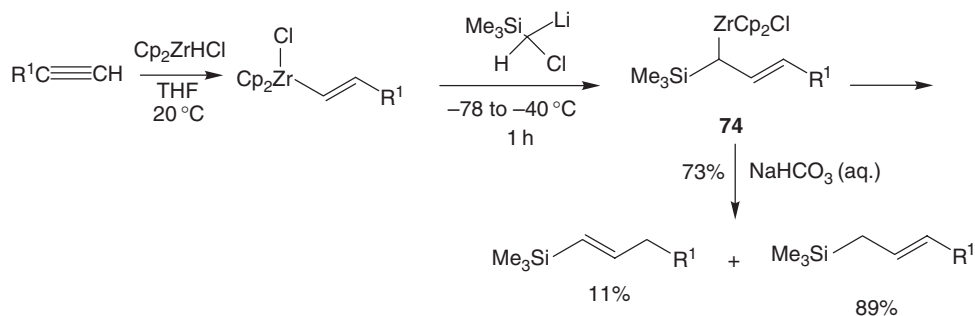
Scheme 29

Treatment of dibromomethyltrialkylsilanes with butylmagnesium bromide in the presence of a catalytic amount of manganese(II) chloride provided (*E*)-1-trialkylsilyl-1-pentenenes with high stereoselectivity in good yields. The reaction proceeded through  $\alpha$ -silylmanganese intermediate **73** (Scheme 30) <1997TL3275>.



Scheme 30

A convergent route to allylzirconocene reagents **74** by the insertion of a silyl-substituted carbenoid such as trimethylsilylchloromethylithium reagent ( $\text{LiCH}(\text{SiMe}_3)\text{Cl}$ ) into vinylzirconocene chlorides was reported (Scheme 31) <1999TL9353>.



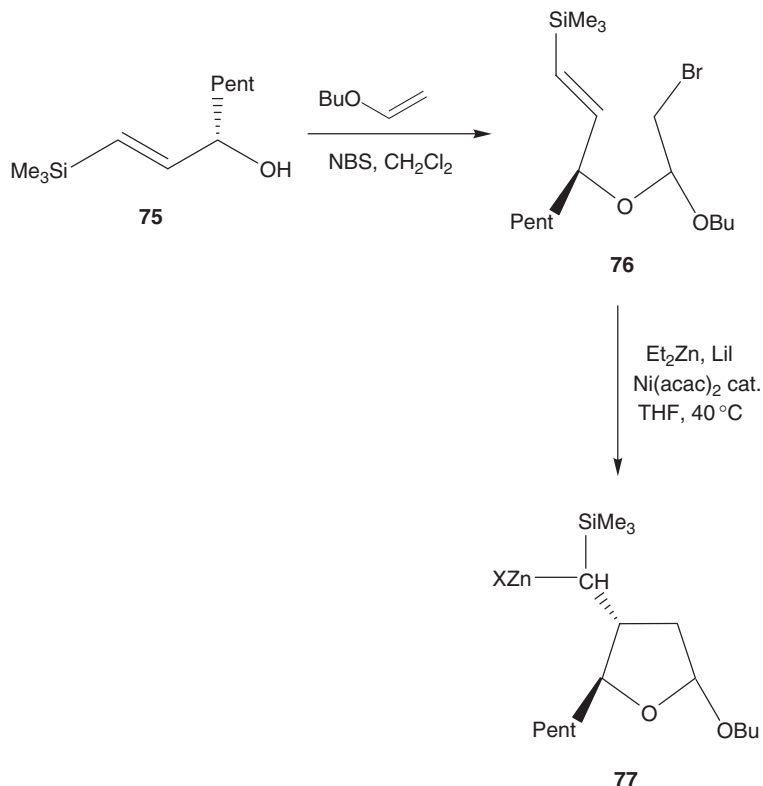
Scheme 31

A variety of aromatic aldehydes were converted to the corresponding vinyl silanes in a one-pot procedure involving the addition of (trimethylsilylmethyl)lithium to the aldehyde followed by treatment with  $\text{Cp}_2\text{TiCH}_2\text{-AlMe}_2\text{Cl}$  ("Tebbe's reagent"). Halide and alkoxide substituents were tolerated, and (*E*)-vinyl silanes were formed exclusively in good yield <2001TL1411>. An efficient synthesis of silylketenes via an unusual rhodium-mediated Wolff rearrangement involving  $\alpha$ -silylrhodium species has been reported <1999CC1199>. Trimethylsilylmethyl lithium has been utilized in the synthesis of  $\beta$ -ketosilanes via the reaction with (*Z*)-1-bromo-1-alkenylboronate esters <2000TL6541>. Mixed diorganozincs underwent selective transfer of the alkyl grouping in a 1,4-fashion to various Michael acceptors <1997JCS(P1)3117>. Highly enantioselective addition of mixed diorganozincs to aldehydes to provide the corresponding chiral alcohols has been investigated <1997JOC7895>.

The generation of  $(2\text{-PyMe}_2\text{Si})_2\text{CHLi}$  was easily accomplished by the deprotonation of  $(2\text{-PyMe}_2\text{Si})_2\text{CH}_2$  using *n*-BuLi in  $\text{Et}_2\text{O}$ . Thus, the generated  $(2\text{-PyMe}_2\text{Si})_2\text{CHLi}$  was found to react with a variety of aldehydes and ketones to give the corresponding vinyl silanes in extremely high yields with complete stereoselectivities <2000OL1299>. Tris(trimethylsilyl)methyl lithium has been prepared from tris(trimethylsilyl)methane by reaction with methyl lithium <1998TL4745>.

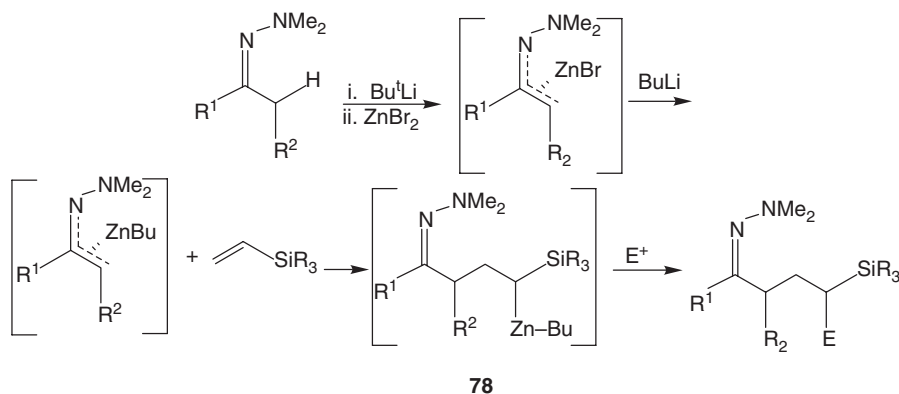
The compound  $\{(\text{Me}_3\text{Si})_2\text{CHSiMe}_2\text{CH}_2\}_2$  has been prepared and metallated with MeLi to give the chelated lithiate ion  $[\text{CH}_2\text{SiMe}_2\text{C}(\text{SiMe}_3)_2\text{LiC}(\text{SiMe}_3)_2\text{SiMe}_2\text{CH}_2]^-$ , which was isolated as its  $[\text{Li}(\text{TMEDA})_2]$  salt (TMEDA = *N,N,N,N*-tetramethylethylenediamine). The potential of this salt as a source of the very bulky dicarbanionic ligand  $\{(\text{Me}_3\text{Si})_2\text{CSiMe}_2\text{CH}_2\}_2$  was demonstrated by its reaction with  $\text{HgBr}_2$  in THF to give the chelated mercury compound  $[\text{CH}_2\text{SiMe}_2\text{C}(\text{SiMe}_3)_2\text{HgC}(\text{SiMe}_3)_2\text{SiMe}_2\text{CH}_2]$ . The crystal structures of the salt and the mercurial compound were determined <1996OM1651>.

The reaction of dipentylzinc with (*E*)-trimethylsilylpropenal in the presence of chiral catalyst provided allylic alcohol **75** in 70% yield and 92% ee. The reaction of allylic alcohol **75** with butyl vinyl ether and *N*-bromosuccinimide in dichloromethane afforded the bromoacetal **76** in 88% yield. The nickel-catalyzed cyclization proceeded smoothly with diethylzinc and lithium iodide to provide the  $\alpha$ -trimethylsilyl zinc reagent **77** (Scheme 32) <1995TL231>.



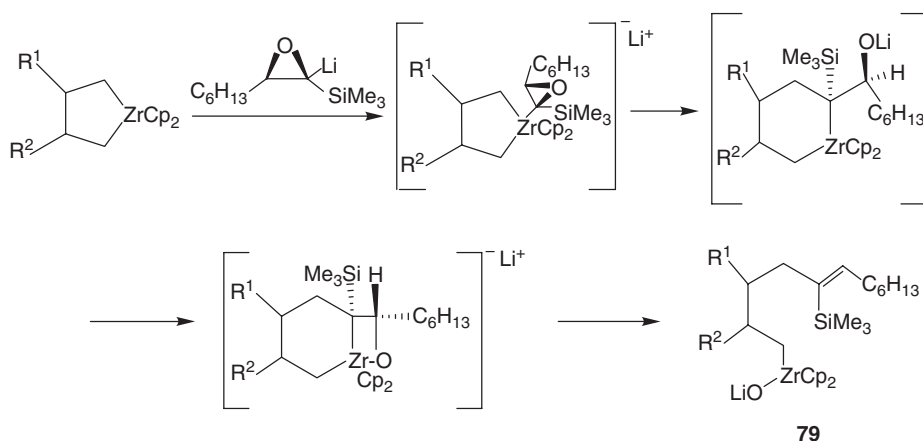
Scheme 32

It has been demonstrated that vinyl silanes were highly reactive and their reactions with zincated hydrazones were shown to be highly regioselective. The reaction was shown to proceed through  $\alpha$ -zincated silicon species **78**, which could undergo reaction with electrophiles (Scheme 33) <1997TL7099>.



Scheme 33

Silylketenes bearing a range of substituents (alkyl, alkenyl, aryl, heteroaryl) were prepared by an unusual rhodium-mediated Wolff rearrangement of the corresponding silyldiazo ketone and the reaction was shown to proceed through an  $\alpha$ -silylrhodium species <1999CC1199>. Metalated epoxides (epoxysilanes, epoxynitriles, and epoxystyrene) inserted efficiently into the zirconacyclohexane containing an  $\alpha$ -trimethylsilyl group (Scheme 34) <2000TL5275> via a 1,2-metallate rearrangement to afford the corresponding substituted alkenes **79**.



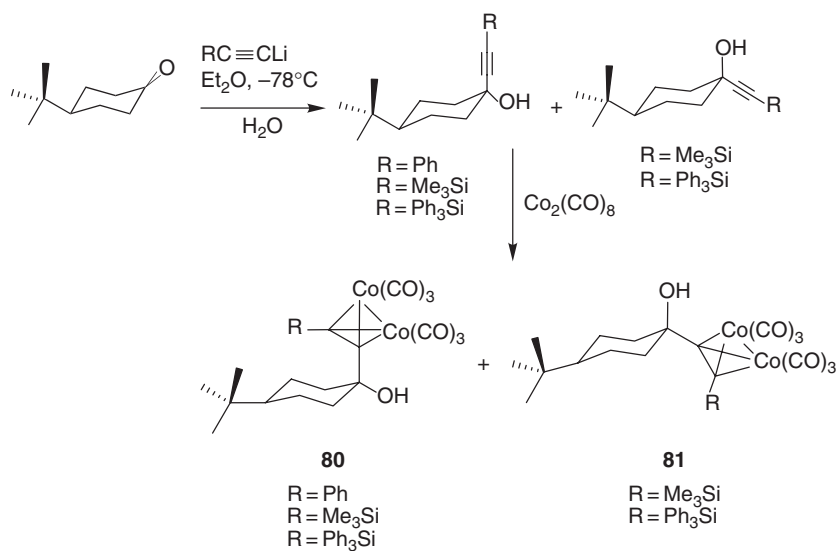
Scheme 34

4-*t*-Butylcyclohexanone was treated with (trimethylsilylethynyl)lithium and subsequent hydrolysis yielded two alkynols that were readily separable by column chromatography. The isomers with axial and equatorial alkynyl groups, respectively, formed in a 5:2 ratio. Each alkynol was stirred at room temperature for 24 h with an equimolar quantity of dicobalt hexacarbonyl to give the corresponding dicobalt hexacarbonyl clusters **80** and **81** (Scheme 35) <2001JOC8585>.

#### 4.14.2.1.3 Silicon and a group 13 or group 14 metal: $R^1CSiR^2_3SnR^3_3$ , etc.

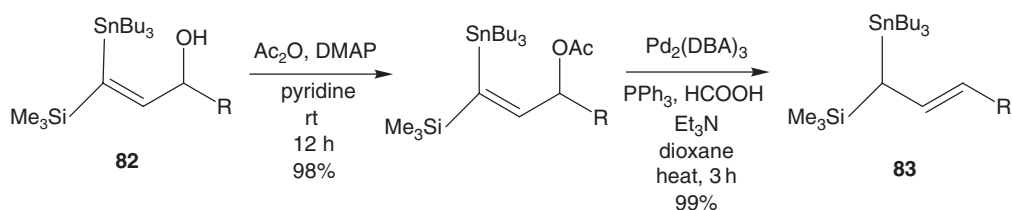
The most common methods for the preparation of compounds containing a silicon and a group 13 or 14 metal bound to the same carbon along with either protons or carbon atoms have been through transmetalation from easily accessible  $\alpha$ -lithio or  $\alpha$ -magnesiumsilylalkane derivatives.





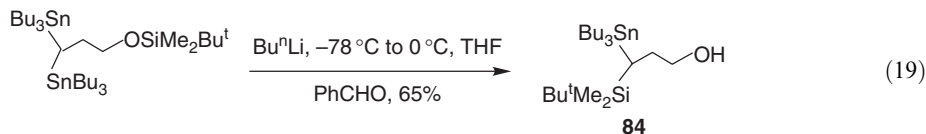
Scheme 35

The 1-hydroxy-3,3-heterobimetallic compound **82** containing tin and silicon was acetylated with acetic anhydride in pyridine, which underwent palladium-catalyzed hydrogenolysis of the resulting allylic acetate to the corresponding alkenes **83** containing *gem*-heterobimetallic species with tin and silicon (Scheme 36) <1996T7221>.

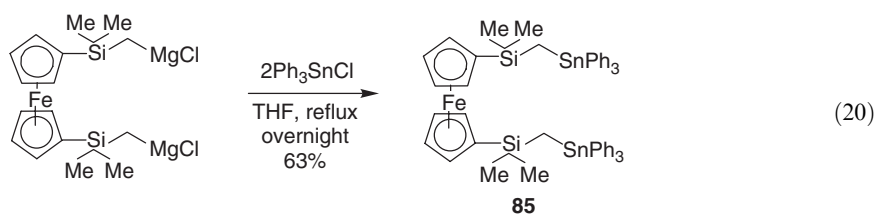


Scheme 36

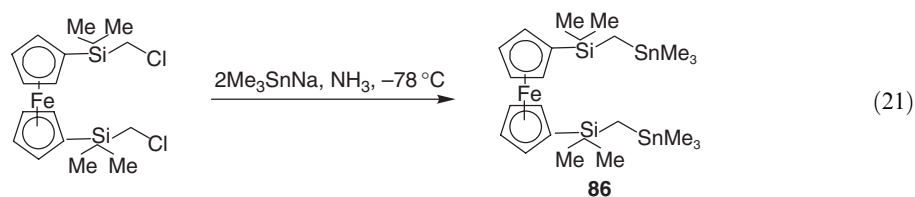
The *gem*-distannane containing a siloxy group was metallated with *n*-butyllithium and reacted with benzaldehyde to provide 3-(*t*-butyldimethylsilyl)-3-(tributylstannyl)propanol **84** exclusively (Equation (19)) <1998JOC1773, 1995TL9345>.



A variety of ferrocene-containing organotin compounds **85** and **86** has been synthesized by employing the (dimethylsilyl)methylene group as a spacer between the ferrocene units and tin (Equations (20) and (21)) <2000OM430>.

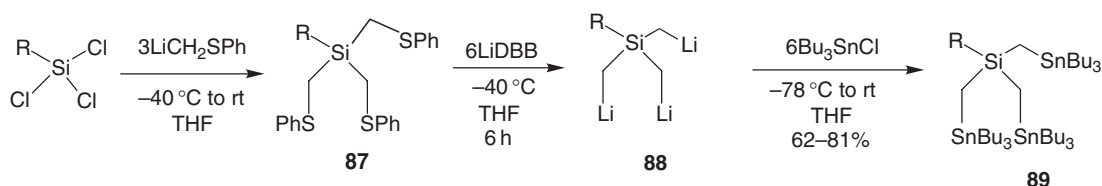






Starting from vinyl triflates, the corresponding allylsilanes were prepared using a cross coupling with tris[(trimethylsilyl)methyl]aluminum catalyzed by palladium(0) [<1997T15853>](#). The compounds containing  $\alpha$ -silylindium, aluminum, and gallium have been prepared [<1997ZAAC883, 1996CB1425, 1997CB417, 1998EJI1661, 1998EJI355, 1999JCS\(D\)2385, 1999ZAAC2095>](#). The preparation of compounds containing  $\alpha$ -silyltitanium species has also been reported [<1995TL6001, 2001AG\(E\)2890>](#). The reaction of tetrakis[bis(trimethylsilyl)methyl]digallane with 1,1'-ferrocenedicarboxylic acid afforded orange-red crystals of the macrocyclic compound in 84% yield [<2000OM1128>](#).

The tris(phenylthiomethyl)silanes **87** were prepared by the reaction of (phenylthiomethyl)-lithium with the corresponding chlorosilanes. The reductive carbon—sulfur bond cleavage was achieved through metallation using an electron-transfer reagent such as lithium *p,p'*-di-*t*-butylbiphenylide (LiDBB). The reaction was effective in replacing thiophenyl groups of tris(phenylthiomethyl)silanes with lithium to give the corresponding tris(lithiomethylsilanes) **88**, which were derivatized with tri-*n*-butyltin chloride to the corresponding tris(tri-*n*-butylmethyl)stannanes **89** (Scheme 37) [<2000OM4223>](#).



Scheme 37

#### 4.14.2.1.4 Silicon and other elements

In COFGT (1995), the systems in which the silicon and the group 15 and 16 elements (selenium, tellurium, arsenic, and antimony) attached to an  $sp^3$ -carbon are covered in chapters 4.13 and 4.08.

A study of the scope of the catalytic hydrogenation and hydrosilylation of chiral exomethylene-substituted cyclopentanes and cyclohexanes utilizing the organolanthanide precatalysts  $\text{Cp}_2\text{LnCH}(\text{SiMe}_3)_2$  ( $\text{Cp} = \text{C}_5\text{Me}_5$ ;  $\text{Ln} = \text{Sm}, \text{Yb}$ ) was undertaken. Both reaction types were sterically driven and lead to the *cis*-diastereomer as the major product. Additionally, the hydrosilylation was regiospecific, the silane being placed exclusively at the terminal position of the double bond [<1996JOM275>](#). The  $\alpha$ -trimethylsilylsamarium species has been used in the efficient regiospecific synthesis of pyrrolizidine and indolizidine skeletons [<1996JA707, 1996JA9295>](#). It has been reported that the lanthanide metallocenes such as  $\text{Cp}_2\text{LnCH}(\text{SiMe}_3)_2$  ( $\text{Ln} = \text{Sm}$  and  $\text{Nd}$ ,  $\text{Cp} = \text{C}_5\text{Me}_5$  and  $\text{C}_5\text{Me}_4$ ) catalyzed the regiospecific intermolecular addition of primary amines to acetylenic, olefinic, and diene substrates [<1996OM3770>](#).

#### 4.14.2.2 Germanium and a Metal: $\text{R}_2^1\text{CGeR}_3^2\text{M}$

There have been many reports on the generation of  $\alpha$ -metallogermylalkanes from the transmetallation of the corresponding  $\alpha$ -lithio derivatives as described in COFGT (1995). No further advances have occurred in this area since the publication of chapter 4.14.2.2 in [<1995COFG\(4\)601>](#).

##### 4.14.2.2.1 $\alpha$ -Lithiogermylalkanes

As reported in COFGT (1995), deprotonation of  $\alpha$  to the germyl group with LDA provides the most efficient route to these systems. The other route includes the addition of an organolithium

reagent to a vinylgermane. No further advances have occurred in this area since the publication of chapter 4.14.2.2.1 in <1995COFGT(4)601>.

#### 4.14.2.2.2 Other $\alpha$ -metallogermylalkanes

As outlined in COFGT (1995), the transmetalation of an  $\alpha$ -lithio derivative provided a rapid entry into other  $\alpha$ -metallogermylalkanes. A further route to  $\alpha$ -metallogermylalkanes was achieved by the displacement of the halide of (halomethyl)trimethylgermanes with anionic iron and tungsten complexes resulting in the generation of the  $\alpha$ -metallogermylalkanes. No further advances have occurred in this area since the publication of chapter 4.14.2.2.2 in <1995COFGT(4)601>.

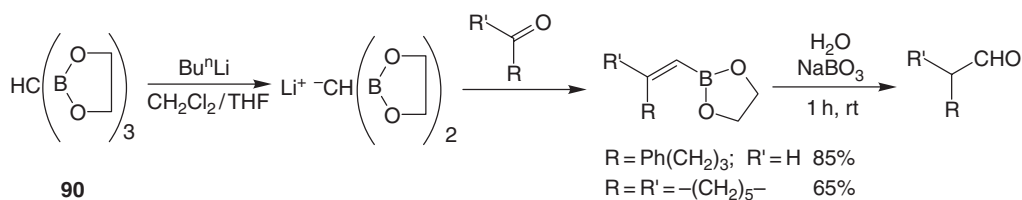
#### 4.14.2.3 Boron and a Metal: $R_2^1CBR_2^2M$

According to COFGT (1995), the most readily available derivatives are the  $\alpha$ -lithioorganoboranes.

##### 4.14.2.3.1 $\alpha$ -Lithioborylalkanes

In COFGT (1995), the preparation of compounds containing a carbon bound to a lithium, a boron, and either hydrogen or carbon atoms has been described by deprotonation, by halogen-metal exchange, or by transmetalation.

The preparation of tris(ethylenedioxyboryl)methane **90**, the reagent for the only known homologation of aldehydes and ketones under nonacidic conditions, was improved by avoiding the difficult isolation of the intermediate tris(dimethoxyboryl)methane and by direct crystallization of tris(ethylenedioxyboryl)methane **90** (Scheme 38) <1995T11219>.



Scheme 38

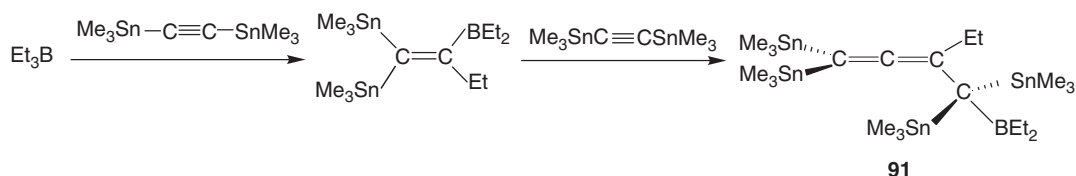
The condensation of dimesitylboron-stabilized carbanions with a variety of aromatic aldehydes followed by *in situ* oxidation at low temperature, is a unique, highly stereoselective process yielding predominantly erythro-1,2-diols <1996T1085>.

##### 4.14.2.3.2 Other $\alpha$ -metalloborylalkanes

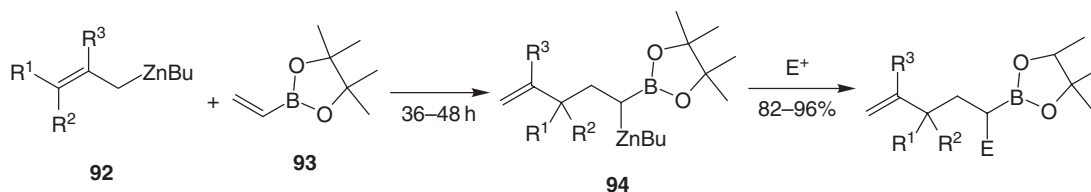
The other  $\alpha$ -metalloborylalkanes have been prepared by  $\alpha$ -haloalkylboronic esters as indicated in COFGT (1995). Rearrangements have been implicated during the preparation of a number of cyclic organotin compounds containing an  $\alpha$ -boryltin moiety.

In the preparation of novel organoborane Lewis acids via a selective boron-tin exchange process, the attack by a boron halide on an organotin substrate could be viewed as passing through a transition state containing boron and tin attached to an  $sp^3$ -carbon <1998EJ1761>. Stannylated allenes **91** have been prepared by 1,1-organoboration of 2 equiv. of bis(trimethylstannyl)ethyne with 1 equiv. of triethylborane or ferrocenyldimethylborane (Scheme 39) <1996JOM169>.

Boryl substitution on an olefin activated the olefinic double bond toward addition of an organozinc reagent. Addition of an allylic zinc reagent **92** to an alkenylboronate **93** thus took place smoothly to afford a variety of *gem*-zincio/boryl species **94**. Theoretical studies with density functional calculations on the reaction pathway revealed that the reaction proceeded via zincio-ene reaction rather than a bora-Claisen rearrangement (Scheme 40) <2001OL3137>.



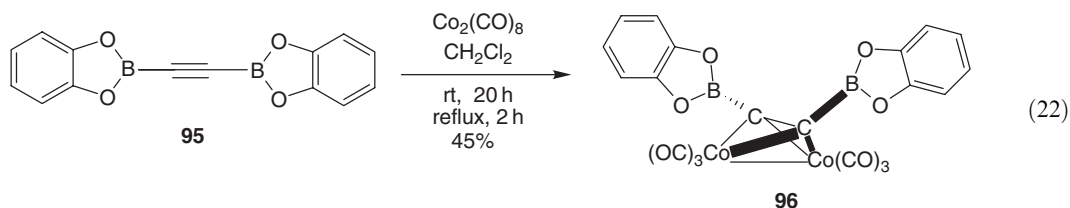
Scheme 39



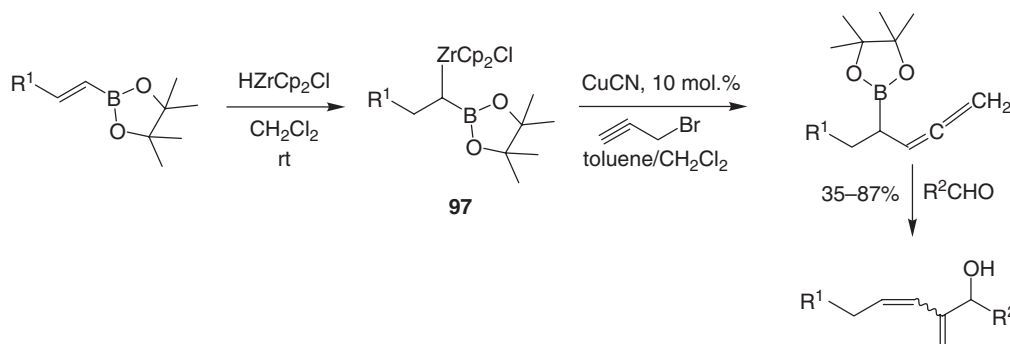
Scheme 40

Functionalized mixed alkyl(trimethylsilylmethyl)zinc reagents added efficiently to a wide variety of Michael acceptors in high yield and with exclusive 1,4-regioselectivity, without the need for transition metal catalysis. The trimethylsilylmethyl group behaved as a nontransferable group, and in no cases was transfer of this group observed [<1998T1471>](#). The addition reaction of  $\alpha$ -boryl carbanions to aldehyde was studied. Terminal alkenes and 1,2-alkanediols were obtained in high yields by the addition of  $[(\text{Me}_2\text{C})_2\text{O}_2\text{BCH}_2]\text{Cu}(\text{CN})\text{ZnI}$  from Knochel's (dialkoxyboryl)-methylzinc reagent. The reaction provided a simple procedure for the olefination or the hydroxymethylation of aldehydes [<1996T915>](#).

The bis(1,3,2-benzodioxaborolyl)diborane was shown to catalyze the trimerization of the diborylacetylene **95**, thus verifying the catalytic cycle with cobalt octacarbonyl. The diborylacetylene was allowed to react with a catalytic amount of cobalt octacarbonyl to provide the corresponding addition product **96** (Equation (22)) [<2000EJ1177>](#).

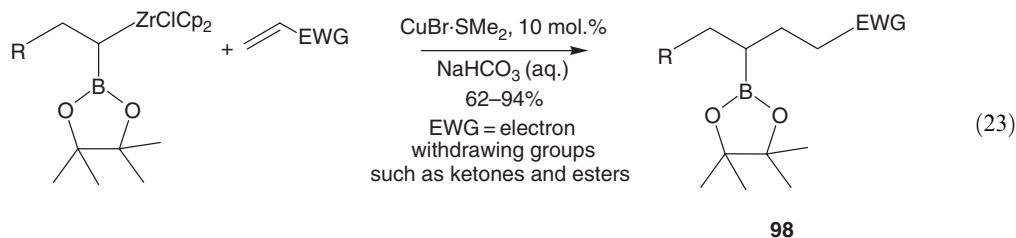


A novel class of organometallic complexes containing 1,1-bimetallics of boron and zirconium has been reported [<1996JST291>](#). The use of *gem*-borazirconocene alkanes in the regioselective synthesis of  $\alpha$ -allenic boronic esters has been demonstrated (Scheme 41) [<1995JOC486>](#).



Scheme 41

*gem*-Borazirconocenes readily added across Michael acceptors in the presence of  $\text{CuBr}\cdot\text{SMe}_2$ , to afford the 1,4-addition products **98** in good-to-excellent yields. In the case of cycloalkenones diastereomers were produced, with the *anti*-product favored. The selectivity with cyclopentenone was high (9:1), while with cyclohexenone it was less (3:1). In this context, *gem*-borazirconocene alkanes could be regarded as  $\alpha$ -hydroxyl anion equivalents (Equation (23)) <1995TL1805>.



Reaction of acid chlorides and *gem*-borazirconocene alkanes produced enol borates by the rearrangement of  $\alpha$ -bora ketones. Reaction of the enol borates with NBS occurred with complete regioselectivity to give the corresponding unsymmetrical  $\alpha$ -bromo ketones <1995TL5665>. Some unusual chemistry involving boron migrations that resulted from the juxtaposition of boron and zirconium in the same molecule has been described <1995JOC4316>. The synthesis of 1,1-bimetallics of boron and zirconium via the hydrozirconation of the corresponding unsaturated boronates has been reported <1996JST291>.

In the diboration of allenes catalyzed by palladium complexes and organic iodides, the generation of the palladium-allyl species with the boryl attached to the central carbon of the  $\pi$ -allyl group has been shown <2001JA761>. In the facile titanium-catalyzed dehydrogenative borylation of ethylene,  $\alpha$ -boryltitanium species have been shown to be the intermediate <1995JA6615>. Treatment of  $\alpha$ -chloroalkylboronic esters with  $\text{CrCl}_2$  in the presence of  $\text{LiI}$  and TMEDA generated  $\alpha$ -boryl radicals, which added to  $\alpha,\beta$ -unsaturated esters in a 1,4-fashion under mild conditions in excellent yields <1998SL253>. Synthetically useful (*E*)-1-alkenylboronic esters were prepared stereoselectively from aldehydes with one-carbon extension by using a geminal dichromium reagent derived from a dichloromethylboronic ester chromium(II) chloride and lithium iodide <1995SL963>.

## ACKNOWLEDGMENTS

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## 4.15

# Functions Containing Two Atoms of the Same Metallic Element

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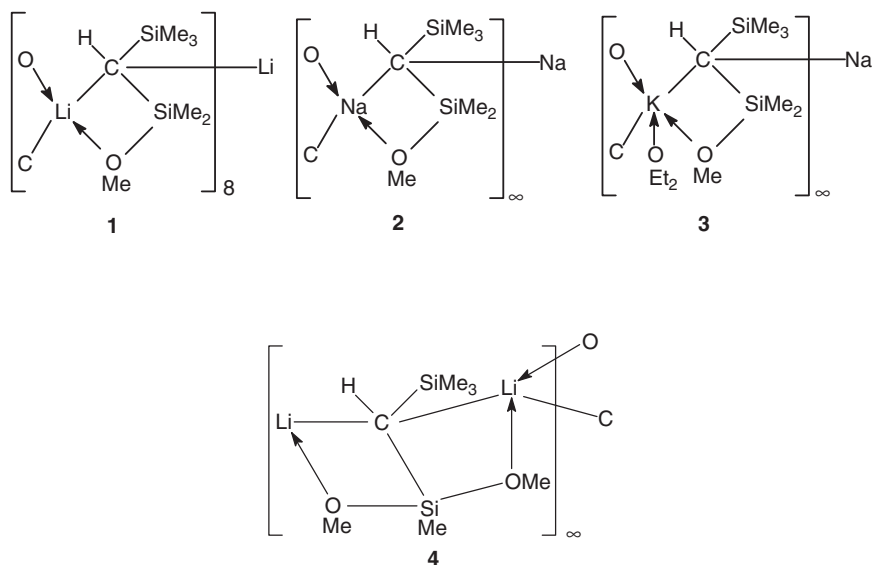
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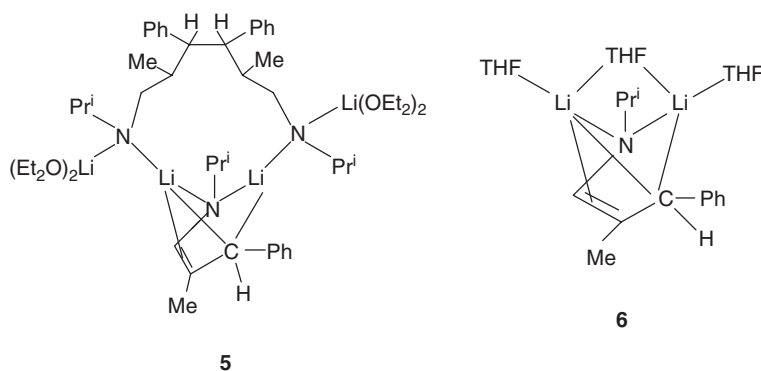
### 4.15.1 FUNCTIONS CONTAINING TWO GROUP 1 METALS

The species  $[(\eta^5\text{-Cp})\text{K}]_\infty$  has a classical zigzag polymeric structure [<1997OM3855>](#). Crystallization of  $[(\eta^5\text{-3,5-Me}_2\text{C}_6\text{H}_3)_5\text{C}_5\text{Li}(\text{THF})_2]$  from toluene leads to the species with an infinite chain one-dimensional structure containing alternating  $[(\eta^5\text{-3,5-Me}_2\text{C}_6\text{H}_3)_5\text{C}_5\text{Li}]^-$  and  $[(\text{THF})\text{Li}((\eta^5\text{-3,5-Me}_2\text{C}_6\text{H}_3)_5\text{C}_5)\text{Li}((\eta^5\text{-3,5-Me}_2\text{C}_6\text{H}_3)_5\text{C}_5)\text{Li}(\text{THF})]^+$  moieties in a manner similar to the formation of the polydecker complexes [<2003JCS\(D\)2658>](#). Such extended structures are observed in the solid state of the cyclopentadienyls of lithium, sodium, and potassium [<1997OM3855>](#), 1,2,4-tris(trimethylsilyl)cyclopentadienylpotassium [<2001JCS\(D\)1128>](#), as well as in the solvated complexes such as  $[(\text{THF})\text{K}(\mu\text{-}\eta^5\text{-Cp}^*)]_x$  [<2002JOM\(649\)252>](#),  $[(\text{DME})\text{Na}(\mu\text{-}\eta^5\text{-Cp})]_x$  [<2002JCS\(D\)896>](#), and  $[\text{Li}(\eta^5\text{-C}_5(\text{CH}_2\text{Ph})_5)_2(\text{C}_6\text{D}_6)]$  [<1996OM4702>](#).

Tetranuclear species of composition  $[(\text{PMDETA})\text{K}\{\mu\text{-CH}(\text{SiMe}_3)_2\}\text{K}\{\mu\text{-CH}(\text{SiMe}_3)_2\}\text{K}\{\mu\text{-CH}(\text{SiMe}_3)_2\}\text{K}(\text{PMDETA})]$  is an example of compounds with KCK frameworks [<2000OM4030>](#). The ligand  $\text{CH}_2(\text{SiMe}_3)(\text{SiMe}_2\text{OMe})$  with *t*-butyllithium in pentane gives **1** [<2003OM2505>](#). The latter reacts with potassium *t*-butylate in hexane and then with diethyl ether to yield **2**. With  $\text{NaCH}_2\text{Ph}$  in ether, the starting ligand produces **3**. The behavior of the ligand  $\text{CH}_2(\text{SiMe}_3)\{\text{SiMe}(\text{OMe})_2\}$  in the reaction with *t*-butyllithium in pentane is different and the product is **4**.

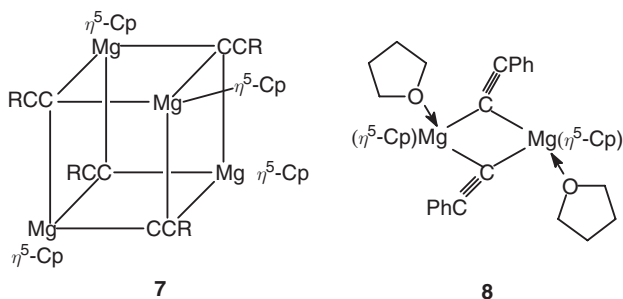


1-Aza-1,3-diene with excess lithium in ether gives *N,N*-dilithium-hexa-1,5-diene-1,6-diamide <2003AG(E)2253>. If the same reaction is run in THF under ultrasound, species **5** is formed. Prolonged treatment finally gives **6**.



#### 4.15.2 FUNCTIONS CONTAINING TWO GROUP 2 METALS

Three-coordinate homoleptic organomagnesium compounds are rare, among them  $[(2,6\text{-Et}_2\text{Ph})_2\text{Mg}]_2$  <2001IC6004> and  $[t\text{-Bu}_2\text{Mg}]_2$  <2003OM2458>. They contain the  $\mu\text{-C}$  skeletons in their dimeric structures. Organomagnesium species  $[(\eta^5\text{-Cp})\text{Mg}(\text{Me})(\text{OEt}_2)]_2$  when reacted with acetylenes  $\text{RC}\equiv\text{CH}$  ( $\text{R} = \text{Ph}, \text{Fc}$ ) yield the cubic tetramers **7** ( $\text{R} = \text{Ph}, \text{Fc}$ ) <2003OM1793>. When **7** ( $\text{R} = \text{Ph}$ ) is dissolved in THF, the dimer **8** with the bridging acetylide moieties results.



### 4.15.3 FUNCTIONS CONTAINING TWO TRANSITION METALS

#### 4.15.3.1 Introduction

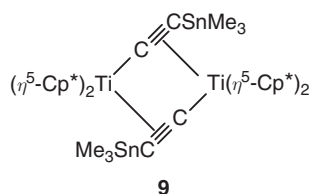
This has been discussed in detail in COFGT (1995).

#### 4.15.3.2 Functions Containing Two Sc, Y, or La Atoms

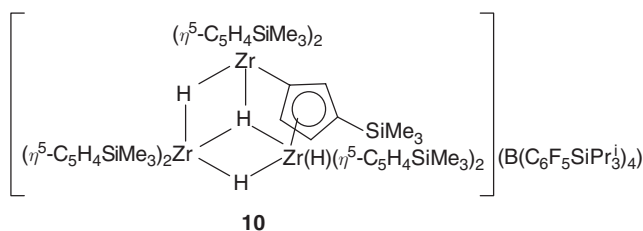
No substantial new data is available for inclusion since the publication of COFGT (1995).

#### 4.15.3.3 Functions Containing Two Ti, Zr, or Hf Atoms

Interaction of  $[(\eta^5\text{-Cp})_2\text{ZrMe}_2]$  with  $[\text{CPh}_3][\text{B}(\text{C}_6\text{F}_5)_4]$  gives unusual dinuclear cationic species with the bridging methyl group,  $\{[(\eta^5\text{-Cp})_2\text{ZrMe}_2]_2(\mu\text{-Me})\}[\text{B}(\text{C}_6\text{F}_5)_4]$  <1996JMOC67, 2001JA223, 2003JOM(677)10>. Rearrangement of the species  $[(\eta^5\text{-Cp}^*)_2\text{Ti}(\eta^2\text{-Me}_3\text{SnC}=\text{CSnMe}_3)]$  followed by elimination of the  $\text{SnMe}_3$  groups gives a dinuclear complex **9** without any signs of the titanium–titanium interaction <2000ACR119, 2003AG(E)1794>. These and similar species possess dynamic behavior <1997AG(E)606, 1998JA6952, 2002OM2254, 2002OM2627>.

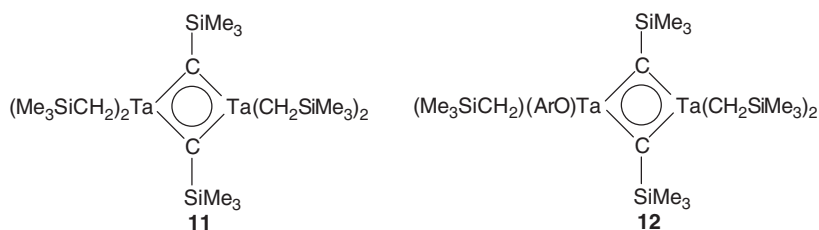


The reaction of  $[(\eta^5\text{-C}_5\text{H}_4\text{SiMe}_3)(\text{H})\text{Zr}(\mu\text{-H})_2\text{Zr}(\text{H})(\eta^5\text{-C}_5\text{H}_4\text{SiMe}_3)]$  yields among the other products cluster **10** where the assembly between the two zirconium sites is realized in an  $\eta^5:\eta^1$  mode <1999OM2933>.



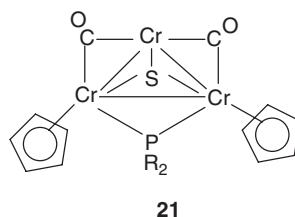
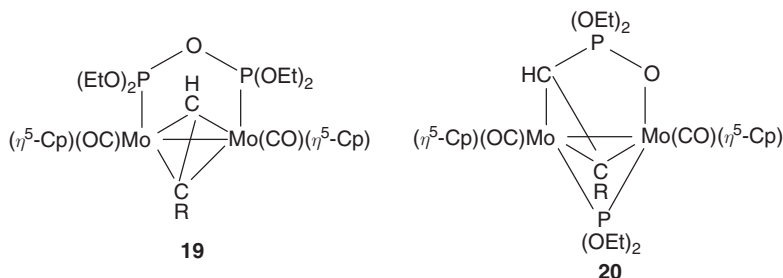
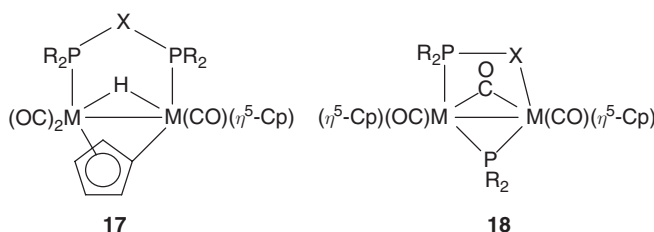
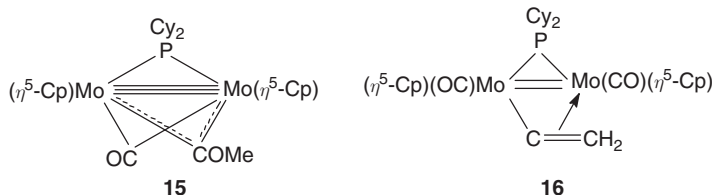
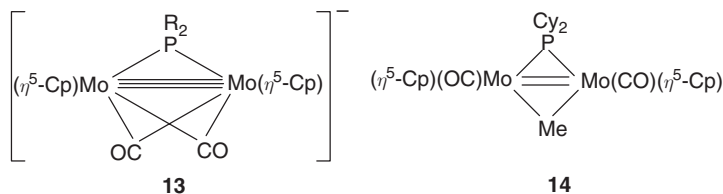
#### 4.15.3.4 Functions Containing Two V, Nb, or Ta Atoms

Terminal  $\text{Me}_3\text{SiCH}_2$  groups of the species **11** enter stepwise substitution with protic agents <1996OM5502>. Phenols substitute one of such groups and produce a series of compounds **12** (Ar =  $\text{C}_6\text{HPh}_{4-2,3,5,6}$ ,  $\text{C}_6\text{HPh}_{2-2,6-\text{Me}_{2-3,5}}$ ,  $\text{C}_6\text{HPh}_{2-2,6-t\text{-Bu}_{2-3,5}}$ ,  $\text{C}_6\text{H}_2\text{-Ph-2-}t\text{-Bu}_{2-4,6}$ ,  $\text{C}_6\text{H}_2(1\text{-Np})\text{-2-}t\text{-Bu}_{2-4,6}$ ) <1999OM3016>.

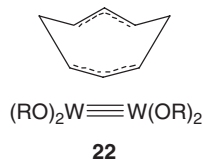


## 4.15.3.5 Functions Containing Two Cr, Mo, or W Atoms

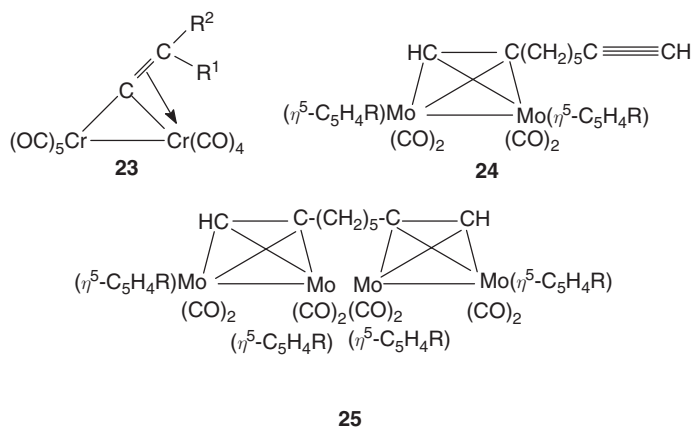
Species  $[(\eta^5\text{-Cp})(\text{OC})\text{Mo}(\mu\text{-PR}_2)(\mu\text{-Cl})\text{Mo}(\text{CO})(\eta^5\text{-Cp})]$  ( $\text{R} = \text{Cy}, \text{Ph}, \text{OEt}$ ) containing the double molybdenum–molybdenum bond can be reduced with  $\text{LiBHET}_3$ ,  $\text{Na}(\text{Hg})$ , or  $\text{KBH}(\text{i-Bu})_3$  to yield the anions of the respective alkali metals **13** ( $\text{R} = \text{Cy}, \text{Ph}, \text{OEt}$ ) <2003OM1983>. The latter possess an interesting reactivity pattern. Thus, the derivative **13** ( $\text{R} = \text{Cy}$ ) reacts with methyl iodide to give the neutral complex **14** containing the bridging methyl group.  $\text{Me}_3\text{OBF}_4$  gives rise to the methoxycarbyne compound **15**, where the triple bond between molybdenum atoms is retained. Addition of allyl chloride leads to **16**. The other possible ways of reacting the  $\text{Mo}_2$  or  $\text{W}_2$  compounds of similar nature is oxidative addition of the cyclopentadienyl ligand to generate species of the type **17** ( $\text{M} = \text{Mo}, \text{W}$ ;  $\text{R} = \text{Me}, \text{Ph}, \text{EtO}$ ;  $\text{X} = \text{CH}_2, \text{O}$ ) and the  $\text{P-X}$  bond addition to afford **18** ( $\text{M} = \text{Mo}, \text{W}$ ;  $\text{R}_2\text{PXP} = \text{dppm}, \text{dmpm}, (\text{EtO})_2\text{POP}(\text{OEt})_2$ ) <1997OM354, 1997OM624, 1997OM1378, 1997OM2581>. Among the compounds with the bridging carbonyl groups, there are  $[(\eta^5\text{-Cp})_2\text{W}_2(\mu\text{-X})(\mu\text{-CO})(\text{CO})_2(\mu\text{-dppm})](\text{PF}_6)$  ( $\text{X} = \text{F}, \text{Cl}$ ) <1999OM4509>. Species  $[(\eta^5\text{-Cp})_2\text{Mo}_2\{\mu\text{-OP}(\text{OEt})_2\}\{\mu\text{-P}(\text{OEt})_2\}(\text{CO})_2]$  reacts with  $\text{HC}\equiv\text{C}(\text{Tol-}p)$  to give a mixture of isomeric products **19** and **20** <2003OM2741>. One more example includes the representative of the species with a bridging methylene group,  $[(\eta^5\text{-Cp})_2\text{W}_2\{\mu\text{-C}(\text{OMe})=\text{CH}_2\}(\mu\text{-CH}_2)(\text{CO})_2(\mu\text{-dppm})]^+$  <2002OM1177>. One of the products of interaction of  $[(\eta^5\text{-Cp})\text{Cr}(\text{CO})_2(\text{SPR}_2)]$  ( $\text{R} = \text{Ar}$ ) is the compound **21** containing two bridging carbonyl groups <2002OM5287, 2003OM1657>.



Complex  $[\text{W}_2(\text{COT})(\text{NMe}_2)_4]$  <1996OM992> reacts with neopentanol, isopropanol, and *t*-butanol to yield  $[\text{W}_2(\text{COT})(\text{OR})_4]$  having the structural arrangement **22** <2002JCS(D)4077>. With lighter alcohols (methanol, ethanol, and *n*-propanol),  $[\text{W}_2(\text{COT})(\text{NMe}_2)_4]$  forms compounds of higher nuclearity  $[\text{W}_2(\text{COT})(\text{OR})_4]_2$  ( $\text{R} = \text{Me}, \text{Et}, \text{Pr}^n$ ) containing the  $[\text{W}_2(\mu-\eta^5, \eta^5\text{-COT})(\mu\text{-OR})(\text{OR})_2]$  <2003JOM(684)269>.



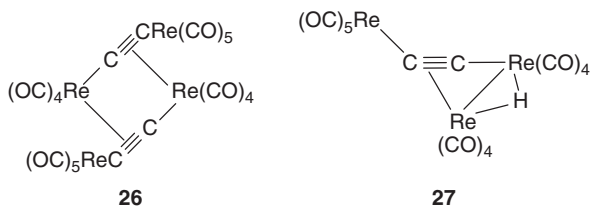
Alkynyl complexes of chromium tend to produce di-, tri-, and tetranuclear clusters containing bridging cyclobutenylidene ligands <1996OM3723, 1998EJI1225>. The vinylidene complexes of chromium  $[(\text{OC})_5\text{Cr}=\text{C}=\text{C}(\text{R}^1)(\text{R}^2)]$  ( $\text{C}(\text{R}^1)(\text{R}^2)=\text{CMe}_2$ ,  $\text{C}(\text{CH}_2)_5$ ,  $\text{C}(\text{Me})(\text{Et})$ ,  $\text{C}(\text{Me})(^t\text{Bu})$ ) on warming give the dinuclear species **23** with the same set of  $\text{R}^1$  and  $\text{R}^2$  <2003JOM(677)46>. Among the representatives of this group of complexes, it is interesting to mention  $[(\eta^5\text{-Cp})\text{-Mo}(\mu\text{-SiMe}_3)_3(\mu\text{-}\eta^1, \eta^2\text{-C}=\text{C}(\text{R})\text{H})\text{Mo}(\eta^5\text{-Cp})](\text{BF}_4)$  <2001OM1230>. 1,8-Nonadiyne reacts with  $[(\eta^5\text{-C}_5\text{H}_4\text{R})_2\text{Mo}_2(\text{CO})_6]$  ( $\text{R} = \text{H}, \text{COMe}, \text{COOEt}$ ) <1996OM4182> to yield clusters **24** and **25** ( $\text{R} = \text{H}, \text{COMe}, \text{COOEt}$ ) <1999OM3164, 2000OM5032>. Tris(isopropylsilyl)bis(pentalene) dimolybdenum has a sandwich structure, where the molybdenum–molybdenum bond length falls into the range of those for triple and quadruple molybdenum–molybdenum bonds <1998OM1934, 1999OM1087>. Alkyl and aryl aldehydes with  $[\text{W}_2(\text{OCH}_2^t\text{Bu})_6(\text{Pyr})_2]$  give  $[\text{W}_2(\mu\text{-CHR})(\text{O})(\text{OCH}_2^t\text{Bu})_6(\text{Pyr})]$  ( $\text{R} = \text{Alk}, \text{Ar}$ ) <2000OM884>.



#### 4.15.3.6 Functions Containing Two Mn, (Tc), or Re Atoms

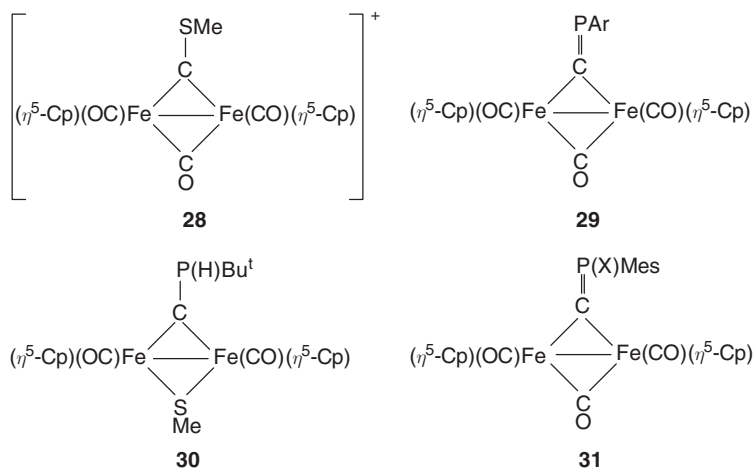
The complex  $[\text{Re}_2\text{Me}_4(\mu\text{-dppm})_2]$  on reaction with carbon monoxide produces the di- $\mu$ -methylene compound  $[\text{Re}_2(\mu\text{-CH}_2)_2(\text{CO})_4(\mu\text{-dppm})_2]$  <2003JOM(671)166>. Decarbonylation of  $[(\text{OC})_5\text{-ReC}\equiv\text{CRe}(\text{CO})_5]$  gives species **26** with no rhenium–rhenium interaction <1997JOM(541)423>. Cluster **27**, however, contains the rhenium–rhenium bond. Complex cation  $[(\eta^5\text{-Cp}^*)(\text{OC})_2\text{Re}(\eta^3\text{-CH}_2\text{C}\equiv\text{CH})]^+$  with pyridine forms the rhenacyclobutadiene species  $[(\eta^5\text{-Cp}^*)(\text{OC})_2\text{Re}(\eta^3\text{-CH}_2\text{C}(\text{Pyr})=\text{CH})]$ , which tends to isomerize to yield the allene of composition  $[(\eta^5\text{-Cp}^*)(\text{OC})_2\text{Re}(\eta^3\text{-CH}_2=\text{CH}(\text{Pyr}))]$  <1998JA722>. A cation containing the *t*-butyl substituent in the alkyne framework,  $[(\eta^5\text{-Cp}^*)(\text{OC})_2\text{Re}(\eta^3\text{-CH}_2\text{C}\equiv\text{CBu}^t)]$ , with 4-(dimethylamino)pyridine gives at the first stage the rhenacyclobutadiene, but isomerization of the product takes another route—to the alkyne species  $[(\eta^5\text{-Cp}^*)(\text{OC})_2\text{Re}(\eta^3\text{-NC}_5\text{H}_4\text{NMe}_2\text{CH}_2=\text{C}=\text{CBu}^t)]$ .

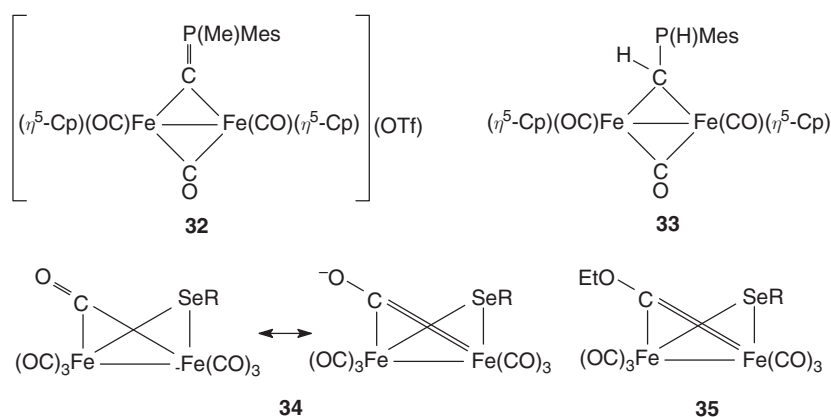
A number of similar propargyl derivatives with aldehydes give the  $\eta^1$ -2,5-dihydro-3-furyl-based clusters [<1996JA530>](#). They enter into alkoxycarbonylation reactions [<1996JA9279, 1996JOC3245, 1997JOC1986, 1997TL5209>](#), oxidative carbonylation [<1998OM2683>](#), and other reactions.



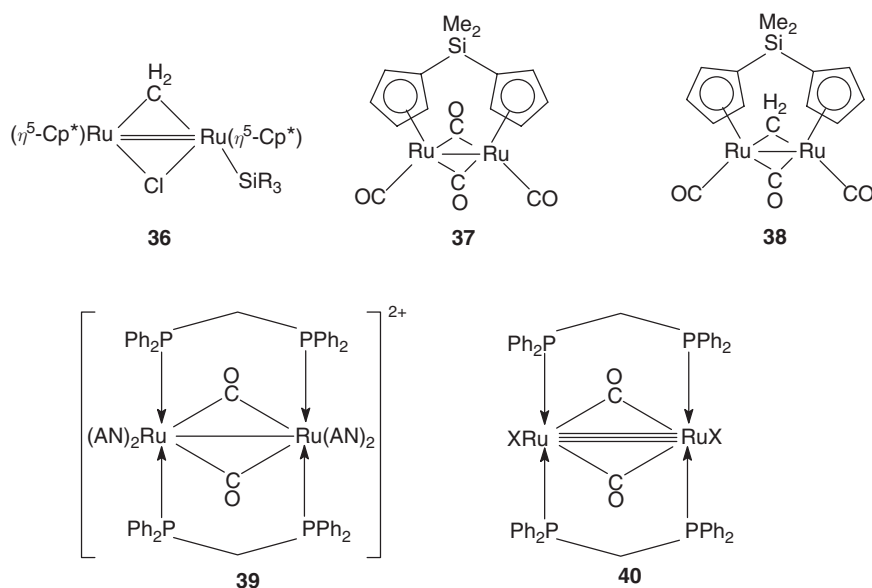
#### 4.15.3.7 Functions Containing Two Fe, Ru, or Os Atoms

Complex **28**, when reacted with aryl(silyl)phosphanes,  $\text{ArP(H)(SiMe}_3\text{)}$ , gives products **29** ( $\text{Ar} = 2,4,6\text{-R}_3\text{C}_6\text{H}_2$ ,  $\text{R} = \text{Me, Pr}^i, \text{Bu}^t, \text{CF}_3$ ) containing bridging isophosphaalkyne ligands. With  $\text{Bu}^t\text{P(H)SiMe}_3$ , however, the product is **30** [<1997ZN\(B\)655>](#). The mesityl complex **29** can be oxidized by sulfur or selenium to produce **31** ( $\text{X} = \text{S, Se}$ ). It can also be methylated using methyl triflate to yield **32** and subsequently reduced by sodium borohydride to afford **33**. Anionic species **34** ( $\text{R} = \text{Ar}$ ) possess ambidentate reactivity [<1996OM1535, 2001JOM\(627\)255>](#). One reactivity pattern is electrophilic attack at the iron site with a partial negative charge accompanied by replacement of the bridging carbonyl moiety, and another direction is the electrophilic attack at the oxygen site of a carbyne framework. In the latter case, reaction of  $\text{Et}_3\text{OBF}_4$  with **34** ( $\text{R} = o\text{-, } m\text{-, and } p\text{-MeC}_6\text{H}_4, \alpha\text{-C}_{10}\text{H}_7, p\text{-MeO-}, p\text{-Br-}, \text{ and } p\text{-ClC}_6\text{H}_4$ ) yields the products **35** with the same set of substituents  $\text{R}$  [<2003JOM\(676\)80>](#). Clusters with the bridging isocyanide moiety are exemplified by  $[(\eta^5\text{-Cp})_2\text{Fe}(\text{CO}(\text{COOR})(\mu\text{-CNMe}_2)_2)]^+$  [<2000JOM\(612\)18>](#). Interaction of the carbon nucleophiles with  $[(\eta^5\text{-Cp})_2\text{Fe}_2(\mu\text{-CX})(\mu\text{-CO})(\text{CO})_2](\text{SO}_3\text{CF}_3)$  ( $\text{X} = \text{SMe, N(R)Me}$ ;  $\text{R} = \text{Me, CH}_2\text{Ph}$ ) [<1997JCS\(D\)4665, 1997JCS\(D\)4671>](#) is the reaction of formation of carbon–carbon bonds. Thus, the acetonitrile complexes  $[(\eta^5\text{-Cp})_2\text{Fe}_2\{\mu\text{-CN(Me)R}\}(\mu\text{-CO})(\text{CO})(\text{AN})](\text{SO}_3\text{CF}_3)$  ( $\text{R} = \text{Me, CH}_2\text{Ph, Xyl}$ ) insert acetylenes followed by the acetonitrile displacement, to yield the vinyliminium compounds  $[(\eta^5\text{-Cp})_2\text{Fe}_2\{\mu\text{-}\eta^1\text{:}\eta^3\text{-C(R}^2\text{)=CHC=N(Me)R}^1\}(\mu\text{-CO})(\text{CO})](\text{SO}_3\text{CF}_3)$  ( $\text{R}^1 = \text{Me, XCH}_2\text{Ph, Xyl}$ ;  $\text{R}^2 = \text{SiMe}_3, \text{Me, Bu}^n, \text{Tol, Ph, H}$ ) [<2003OM1326>](#). In sharp contrast, the reaction with methyllithium gives the product of rearrangement of the acetonitrile ligand  $[(\eta^5\text{-Cp})_2\text{Fe}_2\{\mu\text{-CN(Me)R}\}(\mu\text{-CO})(\text{CO})(\text{CH}_2\text{CN})](\text{SO}_3\text{CF}_3)$  [<2002JOM\(649\)64>](#). Treatment of the  $\mu$ -amino-carbyne complex  $[(\eta^5\text{-Cp})_2\text{Fe}_2\{\mu\text{-CN(Me)Xyl}\}(\mu\text{-CO})(\text{CO})(\text{NCBu}^t)](\text{SO}_3\text{CF}_3)$  [<1996JOM\(509\)19, 2000JOM\(606\)163>](#) by *p*-tolylacetylide followed by triflic acid gives  $[(\eta^5\text{-Cp})_2\text{Fe}_2\{\mu\text{-}\eta^1\text{:}\eta^3\text{-C(p-Tol)=C=C(Bu}^t\text{)}\}\text{N(H)CN(Me)Xyl}\}(\mu\text{-CO})(\text{CO})](\text{SO}_3\text{CF}_3)$  [<2003JOM\(684\)37>](#).





Methoxinitrido clusters  $[\text{Ru}_3(\text{CO})_9(\mu_3\text{-CO})(\mu_3\text{-NOMe})]$  experience thermolytic cleavage of the N—O bond and produce, in particular, the hexanuclear species  $[\text{Ru}_6(\text{CO})_6(\mu\text{-CO})_2(\mu_4\text{-NH})(\mu\text{-OMe})_2]$  <1996JCS(D)1707>. This cluster also gives rise to heterometallic carbonyl clusters <1999JOM(577)323>. Ruthenium clusters with a bridging methylene group include  $[(\eta^5\text{-Cp})_2\text{Ru}_2(\mu\text{-CH}_2)(\text{CO})_2(\text{SiR}_3)(\text{H})]$  ( $\text{SiR}_3 = \text{SiMe}_3, \text{SiEt}_3, \text{SiPr}^n_3, \text{SiMe}_2\text{Ph}, \text{SiPh}_3, \text{Si}(\text{OMe})_3$ ) <1996OM4162> as well as the product of the reaction of  $[(\eta^5\text{-Cp}^*)\text{RuCl}]_4$  with  $\text{Mg}(\text{CH}_2\text{SiR}_3)_2$ , **36** ( $\text{SiR}_3 = \text{SiEt}_3, \text{SiMe}_2\text{Et}, \text{SiMe}_2\text{Ph}$ ) <1999OM1904>. The reaction of  $[\text{H}_4\text{Ru}_4(\text{CO})_{12}]$  with dimethylphenylphosphine in the presence of  $\text{Me}_3\text{NO}$  gives two products, one of which,  $[(\text{OC})_7\text{Ru}_4(\mu\text{-CO})_2(\mu\text{-H})_2(\text{PMe}_2\text{Ph})_4]$ , contains two bridging carbonyls <2003ICC675>. The reaction of  $[\text{Ru}_3(\text{CO})_{10}(\mu\text{-dppm})]$  with di-*i*-butylphosphine gives  $[(\mu_3\text{-H})(\mu\text{-H})\text{Ru}_3(\mu\text{-CO})(\text{CO})_4(\mu\text{-dppm})(\mu\text{-P}^t\text{Bu}_2)_2]$  <1996JOM(526)145>. With diphenylphosphine,  $[\text{Ru}_3(\mu\text{-CO})(\text{CO})_6(\mu\text{-PPh}_2)_2(\mu_3\text{-CH}_2\text{Ph})]$  is the main product <1999ICC128>. Cluster anion  $[\text{HRu}_3(\text{CO})_{11}]^-$  with tricyclohexylphosphine gives  $[\text{Ru}_3\text{CO}_4(\text{PCy}_3)_2(\mu\text{-H})(\mu\text{-CO})_2]^-$  in two isomeric forms <1999ICC247>. Complex **37** <1996JOM(512)11, 1997ICA(262)109> with  $\text{LiBHET}_3$  forms the methylene-bridged cluster **38** <1999OM3008>. The A-frame complex **39** reacts with different salts to yield **40** ( $\text{X} = \text{Cl}, \text{Br}, \text{I}, \text{SH}, \text{S}(p\text{-Tol}), \text{S}^i\text{Pr}, \text{N}_3$ ) <1999OM4244>. Species  $[(\mu\text{-H})_2(\text{Os}_3(\text{CO})_9\text{L})]$  ( $\text{L} = \text{PEt}_3, \text{PEt}_3\text{Ph}, \text{PPh}_3, \text{PPr}^i\text{Ph}_2, \text{PCy}_3$ ) with diazomethane give  $[(\mu\text{-H})_2\text{Os}_3(\text{CO})_9(\text{PPh}_3)(\mu\text{-CH}_2)]$  <2000OM761>. One of the products of interaction of 2,2,6,6-tetramethyl-3,5-heptanedionate (L) with  $[\text{Os}_3(\text{CO})_{12}]$  is  $[\text{Os}_4(\mu\text{-H})(\mu\text{-CO}_2)\text{L}(\text{CO})_{13}]$  containing a unique  $\text{CO}_2$  ligand <2001JCLS421>. Another unique situation is realized in the product of interaction of  $[\text{Os}_7(\text{CO})_{19}(\text{AN})_2]$  with 1,1'-bis(diphenylphosphino)ferrocene where the  $\mu_2\text{-CO}$ -bridged cluster  $[\text{Os}_7(\text{CO})_{17}(\mu_4\text{-}\eta^2\text{CO})(\text{AN})(\mu\text{-dppf})]$  is the product <1999ICC498>.

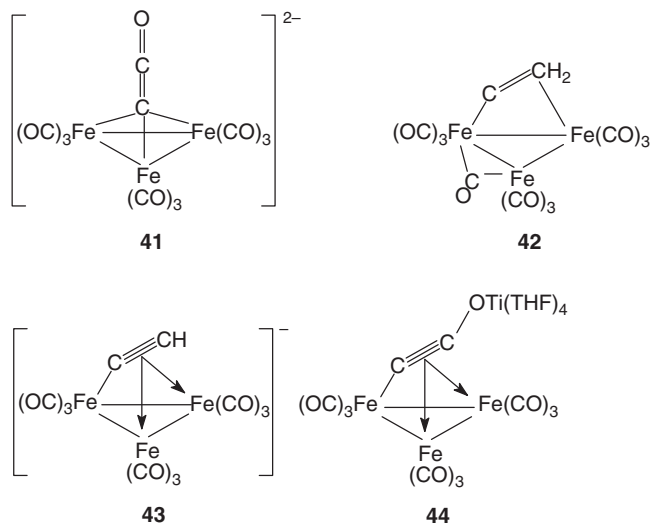




The diiron carbyne species of composition  $[(\eta^5\text{-Cp})(\text{OC})\text{Fe}(\mu\text{-CO})(\mu\text{-CR})\text{Fe}(\text{CO})(\eta^5\text{-Cp})](\text{BBr}_4)$  ( $\text{R} = \text{Ph}$ ,  $p\text{-Tol}$ ) and  $[(\eta^5\text{-C}_5\text{H}_4\text{SiMe}_3)(\text{OC})\text{Fe}(\mu\text{-CO})(\mu\text{-CR})\text{Fe}(\text{CO})(\eta^5\text{-C}_5\text{H}_4\text{SiMe}_3)](\text{BBr}_4)$  ( $\text{R} = \text{Ph}$ ,  $p\text{-Tol}$ ,  $p\text{-CF}_3\text{C}_6\text{H}_4$ ) react with nucleophiles like  $\text{NaSR}'$  ( $\text{R}' = \text{Et}$ ,  $\text{Ph}$ ,  $o\text{-Tol}$ ) in THF at low temperatures to yield  $[(\eta^5\text{-Cp})(\text{OC})\text{Fe}(\mu\text{-CO})(\mu\text{-C(R)SR}')\text{Fe}(\text{CO})(\eta^5\text{-Cp})]$  ( $\text{R} = \text{Ph}$ ,  $p\text{-Tol}$ ;  $\text{R}' = \text{Et}$ ,  $\text{Ph}$ ,  $p\text{-Tol}$ ), or  $\text{Na}[\text{M}(\text{CO})_5(\text{CN})]$  ( $\text{M} = \text{Cr}$ ,  $\text{Mo}$ ,  $\text{W}$ ) to produce  $[(\eta^5\text{-Cp})(\text{OC})\text{Fe}(\mu\text{-CO})(\mu\text{-CPh})\text{Fe}(\text{N}=\text{C}=\text{M}(\text{CO})_5)(\eta^5\text{-Cp})]$  ( $\text{M} = \text{Cr}$ ,  $\text{Mo}$ ,  $\text{W}$ ) [<2000OM3498, 2000OM3784, 2001OM4092>](#). Complexes  $[(\text{OC})_2\text{Fe}(\mu\text{-}\eta^8\text{-COT})(\mu\text{-C(R)(OEt)})\text{Fe}(\text{CO})_2]$  ( $\text{R} = \text{Ph}$ ,  $p\text{-Tol}$ ,  $p\text{-CF}_3\text{C}_6\text{H}_4$ ) with  $\text{HBF}_4$  in  $\text{Et}_2\text{O}$  at low temperature give  $[(\text{OC})_2\text{Fe}(\mu\text{-}\eta^8\text{-COT})(\mu\text{-CR})\text{Fe}(\text{CO})_2](\text{BF}_4)$  [<2003OM1816>](#). The product, where  $\text{R} = p\text{-CF}_3\text{C}_6\text{H}_4$ , when reacted with  $\text{NaSR}$  ( $\text{R} = \text{Et}$ ,  $p\text{-Tol}$ ) gives the neutral dinuclear complex  $[(\text{OC})_2\text{Fe}(\mu\text{-}\eta^8\text{-COT})(\mu\text{-C}(p\text{-CF}_3\text{C}_6\text{H}_4)(\text{SO}_2\text{R}))\text{Fe}(\text{CO})_2]$  ( $\text{R} = \text{Et}$ ,  $p\text{-Tol}$ ). Reaction of  $[(\text{OC})_2\text{Fe}(\mu\text{-}\eta^8\text{-COT})(\mu\text{-C(R)})\text{Fe}(\text{CO})_2](\text{BF}_4)$  with  $\text{NaBH}_4$  gives  $[(\text{OC})_2\text{Fe}(\mu\text{-}\eta^8\text{-COT})(\mu\text{-C(R)(H)})\text{Fe}(\text{CO})_2]$  ( $\text{R} = \text{Ph}$ ,  $p\text{-Tol}$ ,  $p\text{-CF}_3\text{C}_6\text{H}_4$ ). With  $[\text{NaM}(\text{CO})_5(\text{CN})]$  ( $\text{M} = \text{Cr}$ ,  $\text{Mo}$ ,  $\text{W}$ ), they give rise to  $[(\text{OC})_2\text{Fe}(\mu\text{-}\eta^8\text{-COT})(\mu\text{-C(R)(N}=\text{C}=\text{M}(\text{CO})_5)\text{Fe}(\text{CO})_2]$  ( $\text{R} = \text{Ph}$ ,  $o\text{-Tol}$ ,  $o\text{-C}_6\text{H}_4\text{CF}_3$ ;  $\text{M} = \text{Cr}$ ,  $\text{Mo}$ ,  $\text{W}$ ).

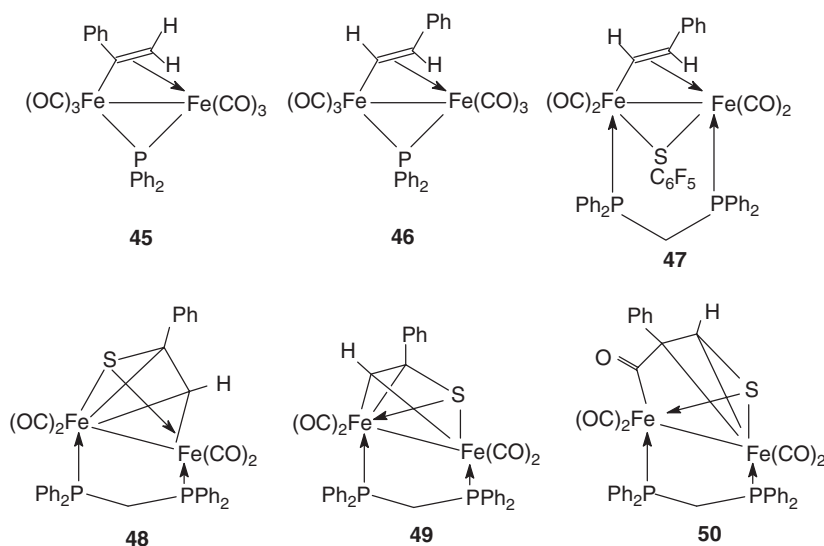
Clusters of the type  $[\text{Ru}_6\text{C}(\text{CO})_{17}]$  are active in hydrogenation reactions [<2001JCS\(CC\)2624>](#). A pentaruthenium carbide system was also developed [<1998JCS\(D\)1253>](#). The silica-supported clusters  $[\text{Ru}_6\text{C}(\text{CO})_{16}\text{SnCl}_3]^-$  and  $[\text{Ru}_6\text{C}(\text{CO})_{16}\text{SnCl}_2]$  are catalysts [<2001AG\(E\)1211>](#). Another cluster of this kind is  $[\text{Ru}_6\text{C}(\text{CO})_{16}]^{2-}$  [<2001JCLS273>](#). They form nanostructures, and the mixed palladium–ruthenium complexes are efficient as catalysts [<1999JCS\(CC\)1571, 2000AG\(E\)1131, 2000JCS\(CC\)1955, 2001AG\(E\)4638>](#), especially when immobilized by silica [<2001JCS\(D\)3295>](#). An illustrative example is the reaction of  $[\text{Ru}_3\text{C}(\text{CO})_{14}]^{2-}$  with  $[\text{PtCl}_2(\text{AN})_2]$  in the presence of silica to afford  $[\text{Ru}_5\text{PtC}(\text{CO})_{18}]$  and  $[\text{Ru}_{12}\text{Pt}_2\text{C}(\text{CO})_{32}(\text{AN})]$  [<2003EJI1325>](#). The pentaosmium analog  $[\text{Os}_5\text{C}(\text{CO})_{15}]$  is a popular starting agent for preparation of the heteronuclear clusters [<1996JCS\(D\)2887, 1996JOM\(524\)211, 1997JCS\(D\)2445, 1997JCS\(D\)2705>](#).

The reaction of **41** with a solution containing low-valent titanium ions, previously speculated [<1997AG\(E\)2234, 1997AG\(E\)2380>](#), leads to the formation of three new clusters containing three iron atoms, **42–44** [<1999OM534>](#). The ethynyl cluster **43** is the result of reduction of the carbonyl moiety, the other two may result from the rearrangement of the CCO group and subsequent protonation.

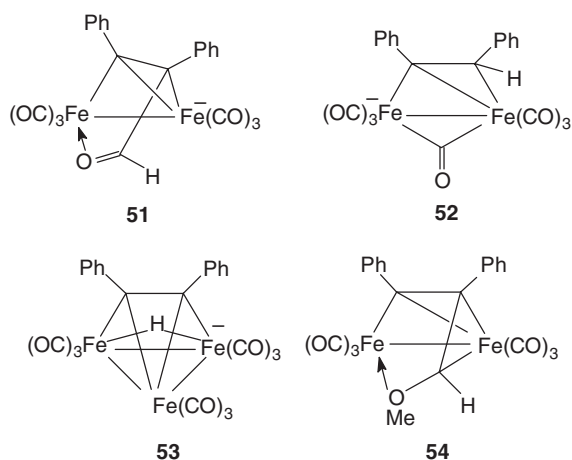


Species **45** [<1997JOM\(527\)247, 1998ICA\(291\)178, 1998ICC257>](#) undergoes isomerization to **46** [<1998JCS\(CC\)1815, 2000OM5696, 2001JCS\(D\)341>](#). The thiolate species  $[\text{Fe}_2(\text{CO})_6\{\mu\text{-O}=\text{C}-\text{C}(\text{Ph})=\text{CH}_2\}(\mu\text{-SC}_6\text{F}_5)]$  on reaction with diphenylphosinomethane gives **47–49** (isomers), as well as **50** [<2003JOM\(672\)22>](#).

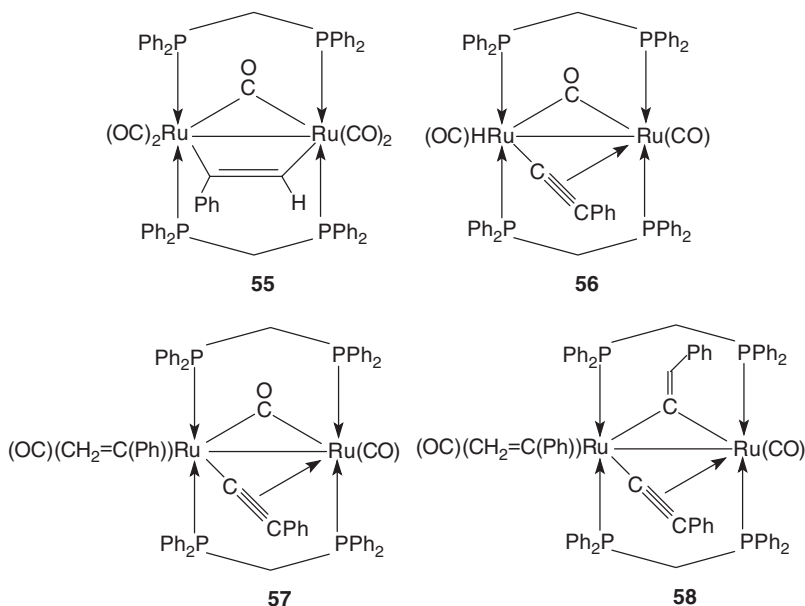




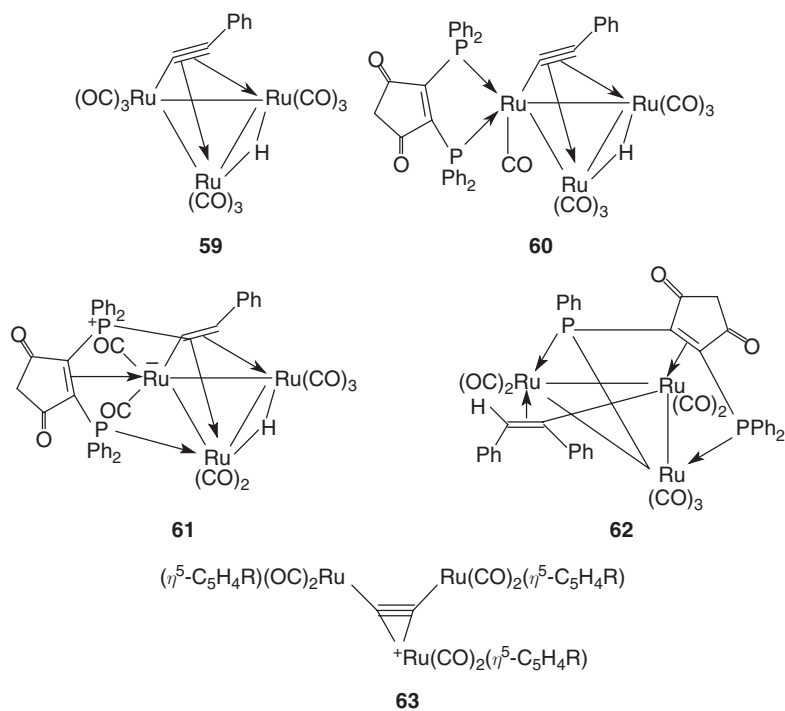
Interaction of  $[\text{PPh}_4][\text{HFe}_3(\text{CO})_{11}]$  with diphenylacetylene in the presence of methyl iodide gives **51** <2002JOM(642)107>, which rearranges at room temperature to the main product **52**. Prolonged reflux with excess diphenylacetylene and methyl iodide yields the trinuclear anionic cluster **53**. In excess methyl iodide only and at room temperature, the product is **54** <2003JOM(678)117>. Cluster  $[(\mu\text{-H})\text{Os}_3(\text{CO})_9(\text{PPh}_3)(\mu\text{-}\eta^2\text{-CH=CH}_2)]$  is known <1996OM4930, 1998OM3087>. Related examples include  $[\text{Os}_3(\text{CO})_{10}(\mu_3\text{-}\eta^2\text{-C}_2\text{R}_2)]$  ( $\text{R} = \text{Me}, \text{Ph}$ ) <1998ICA(274)82> and  $[\text{Ru}_3(\text{CO})_8(\mu\text{-dppm})(\mu_3\text{-}\eta^2\text{-C}_2(\text{COOMe})_2)]$  <1998JOM(552)109>.



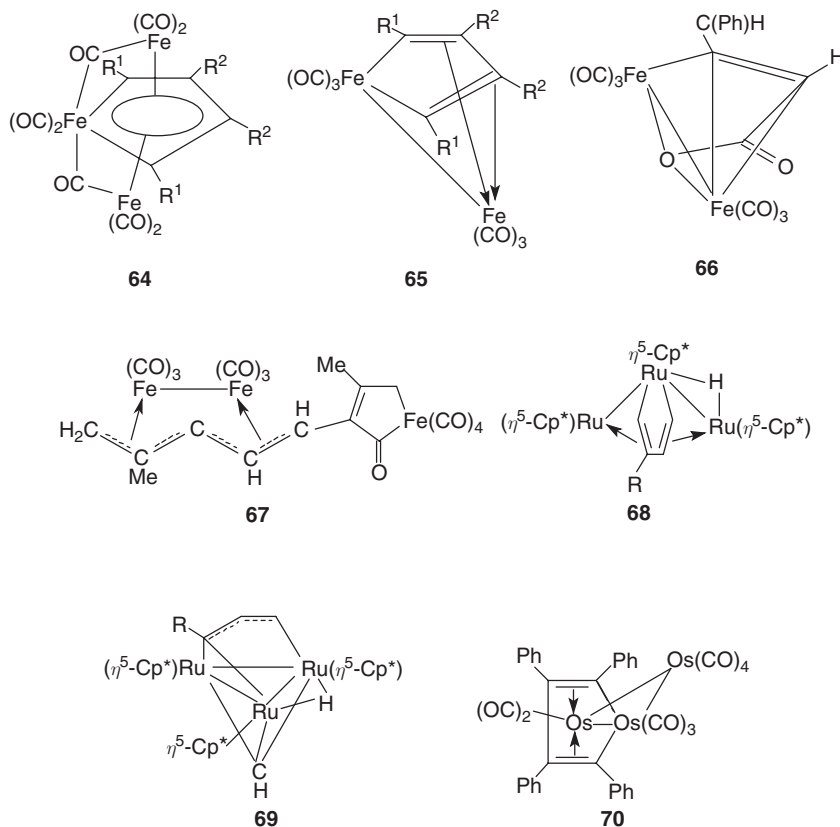
The complex  $[(\eta^5\text{-Cp})(\text{OC})(\mu\text{-CH}_2)(\mu\text{-CO})\text{Ru}(\text{CO})(\eta^5\text{-Cp})]$  is a convenient precursor for the coupling of alkynes <1997OM5572>. This is not a property for the cluster  $[(\text{OC})_2\text{Ru}(\mu\text{-CO})(\mu\text{-dppm})_2\text{Ru}(\text{CO})_2]$ , which reacts with alkynes in a traditional manner to yield the alkynyl, alkenyl, and vinylidene species without coupling <1999ICC197, 2000JOM(593)77>. Complex  $[(\text{OC})_2\text{Ru}(\mu\text{-CH}_2)(\mu\text{-dppm})_2\text{Ru}(\text{CO})_2]$  <2001OM1882> at elevated temperatures causes formation of the uncoordinated  $\text{PhC}\equiv\text{C}\text{-C}(\text{Ph})=\text{CH}_2$  on interaction with phenylacetylene <2003ICA(350)101>. At lower temperatures the formation of complex **55** is observed. The same product follows from  $[(\text{OC})_2\text{Ru}(\mu\text{-CO})(\mu\text{-dppm})_2\text{Ru}(\text{CO})_2]$  and phenylacetylene in toluene. In more polar media, the process is stepwise and can be governed by the amount of phenylacetylene added. First formed is the alkynyl-bridged product **56**, then the product with an alkynyl bridge and alkenyl side group follows **57** and finally the alkylidene bridge is added replacing the carbonyl bridge **58**.



Clusters  $[\text{HRu}_3(\text{CO})_9(\mu_3\text{-}\eta^2, \eta^2, \eta^1\text{-C}\equiv\text{CBu}^t)]$  enter substitution reactions with phosphorus donors and acetonitrile [<1996ICA\(241\)71, 1996JOM\(516\)65, 1999JCS\(CC\)1499, 1999JCS\(D\)479, 1999JOM\(589\)239, 2000OM2330>](#). Reactions of the osmium analogs containing the  $\text{—C}\equiv\text{CR}$  group ( $\text{R} = \text{H, Me, Ph, CMe}_2\text{OH}$ ) with a variety of two-electron donor ligands were also documented [<1996OM3916>](#). Thermolysis of **59** with the diphosphine ligand in methylene chloride in the presence of  $\text{Me}_3\text{NO}$  gives a mixture of products **60** and **61** [<2003OM1953>](#). If thermolysis is conducted in DCE, **62** is the additional product. A product similar to **60** but containing the  $\text{C}\equiv\text{CTol-}p$  moiety can be prepared from the relevant ruthenium cluster [<1997JCCR25>](#) and the diphosphine ligand [<2003OM1953>](#). The cationic species **63** ( $\text{R} = \text{H, Me}$ ) does not contain ruthenium–ruthenium bonds [<2002JCS\(CC\)2174>](#).

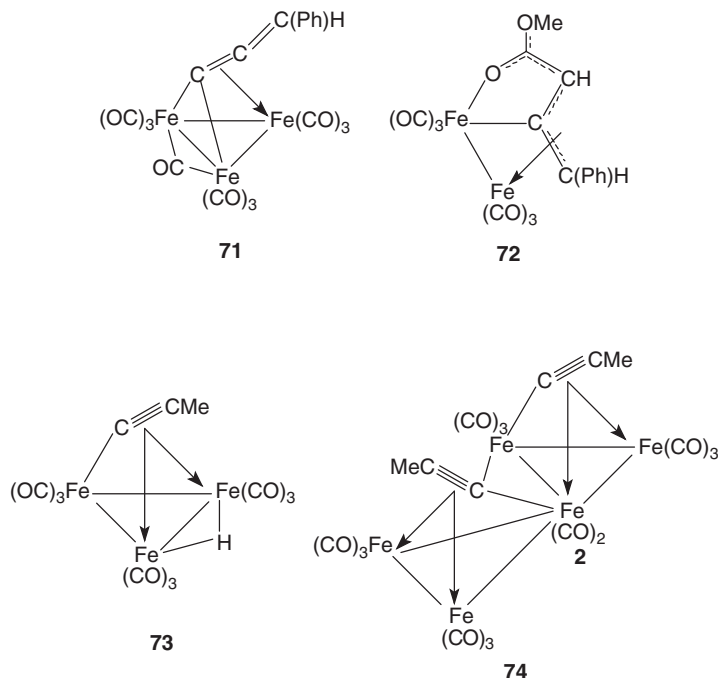


Complexes containing bridging polyyne-diyl moieties acquire substantial interest because of their efficiency in transmission of the electronic effects between the redox active metal sites <1996AG(E)414, 1996MC200, 1996OM477>, rich reactivity pattern involving functionalizations, oligomerization, and metal core enhancement <1996CJC2349, 1997JCLS293>, and possible applications in materials chemistry <1996ICA(247)99, 1997OM4882, 1997OM5988>. Alkynes react with  $[\text{Fe}_3(\text{CO})_{12}]$  to yield the ferrole-type complexes **64** ( $\text{R}^1 = \text{R}^2 = \text{Et}$ ;  $\text{R}^1 = \text{Me}$ ,  $\text{R}^2 = \text{Et}$ ;  $\text{R}^1 = \text{Ph}$ ,  $\text{R}^2 = \text{Et}$ ;  $\text{R}^1 = \text{R}^2 = \text{Ph}$ ;  $\text{R}^1 = \text{Me}$ ,  $\text{R}^2 = \text{NEt}_2$ ;  $\text{R}^1 = \text{R}^2 = \text{CH}=\text{CHNMe}_2$ ;  $\text{R}^1 = \text{R}^2 = \text{CH}=\text{CHS}$ ) <1997JCLS407>. The same structural principles apply to  $[(\eta^5\text{-Cp})_2\text{Ru}_3(\mu\text{-CO})_2(\text{C}_2(\text{CF}_3)_2)_2(\text{C}_2\text{Ph}_2)]$  <1996JCS(D)975>. Thermal degradation of complexes **64** gives **65** with the same set of  $\text{R}^1$  and  $\text{R}^2$  groups <1999JOM(573)139>. Similarly unusual transformations are known for the products of the coordinated diynes with carbenes and their metal fragment condensation <1996OM2855, 1997JCS(CC)483>. In a related transformation the allenylidene iron complex in methanol is converted to **66** <1997JCS(D)1851> and still other examples exist <1997JOM(533)31, 1997JOM(533)45>. The ruthenium analogs of ferrole complexes follow from  $[\text{Ru}_3(\text{CO})_{12}]$  and 1,4-diphenylbuta-1,3-diyne <1996ICA(250)129>. Reaction of isopropenylacetylene with  $[\text{Fe}_3(\text{CO})_{12}]$  gives the open cluster **67** among the isomeric products <2002JCS(D)1448>. Triruthenium clusters possess a remarkable ability to activate hydrocarbon substrates <1996JCS(D)975, 2002EJI1009, 2003JA9910>. The *nido*-ruthenacyclopentadiene complexes  $[\{(\eta^5\text{-Cp}^*)\text{Ru}(\mu\text{-H})\}_3(\text{CH}=\text{CMe}-\text{CR}=\text{CH})]$  ( $\text{R} = \text{H}$ ,  $\text{Me}$ ) on thermolysis give a mixture of the product of dehydrogenation **68** ( $\text{R} = \text{H}$ ,  $\text{Me}$ ) and then **69** ( $\text{R} = \text{H}$ ,  $\text{Me}$ ) <2003OM2196>. In the formation of **64**, the  $\text{Ru}_3$  core is partially cleaved but further on it is restored followed by the C—C bond cleavage. Osmacyclopentadiene cluster **70** originating from  $[\text{Os}_3(\text{CO})_{12}]$  and diphenylacetylene is characterized by rapid ligand substitution reactions occurring at the  $\text{Os}(\text{CO})_4$  moiety <1999OM5518>.

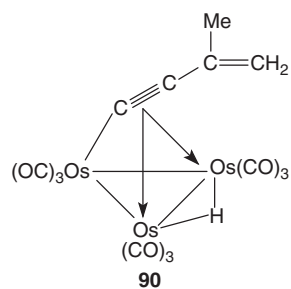
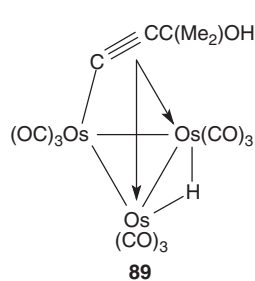
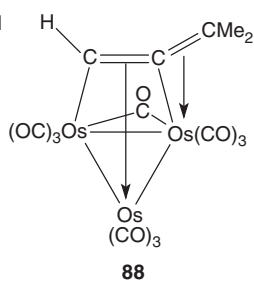
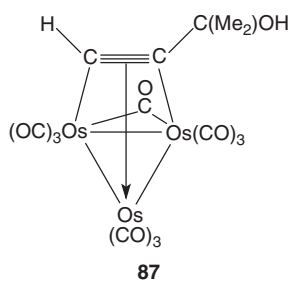
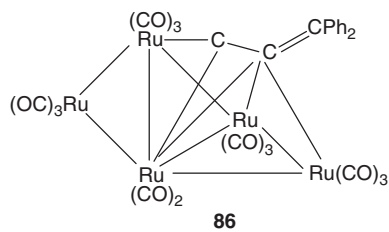
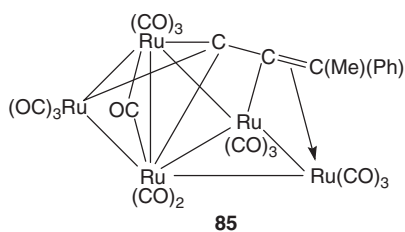
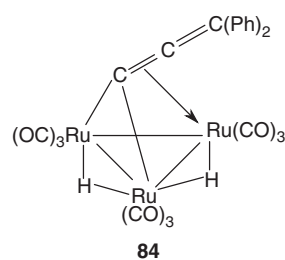
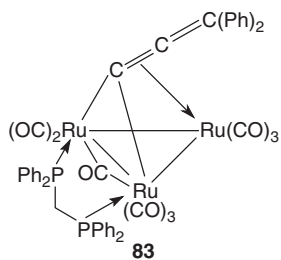
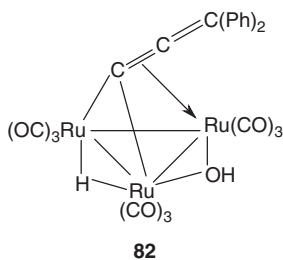
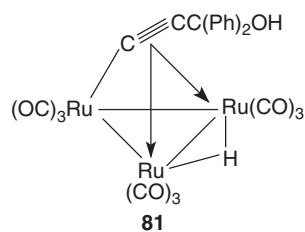
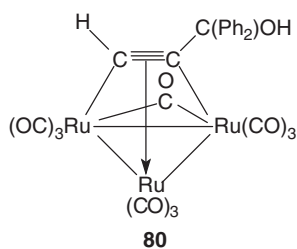
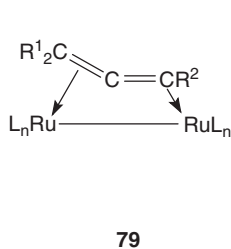
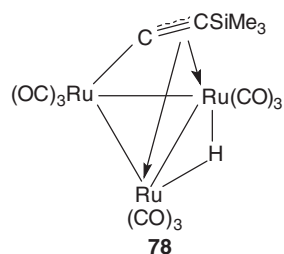
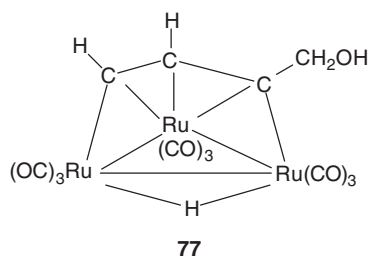
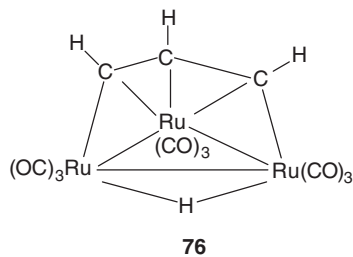
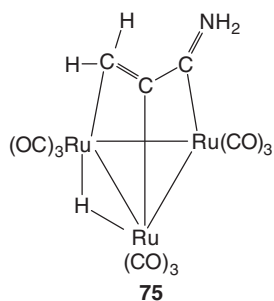


1-Ethynylcyclohexanol with  $[\text{Fe}_3(\text{CO})_{12}]$  gives  $[\text{Fe}_3(\text{CO})_9(\mu\text{-CO})(\mu_3\text{-}\eta^2\text{-1,2-HC}\equiv\text{CC}_6\text{H}_{11}\text{OH})]$ ,  $[\text{Fe}_3(\text{CO})_9(\mu\text{-CO})(\mu_3\text{-}\eta^2\text{-1,2-C}\equiv\text{CC}_6\text{H}_{10})]$ , and other products <2001JCS(D)1485>. Related examples on alkynol clusters were systematized <1999MI1>. Thus, 1-phenyl-1-propyn-2-ol reacts with  $[\text{Fe}_3(\text{CO})_{12}]$  to yield **71**, which further reacts with methanol to give **72** <1997JCS(D)1851>.

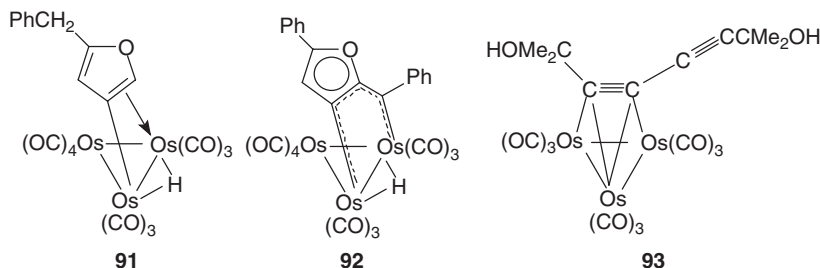
The product of interaction of alkynol  $\text{MeC}\equiv\text{CC}(\text{H})(\text{Et})\text{OH}$  with  $[\text{Fe}_3(\text{CO})_{12}]$ , **73**, experiences further transformation to the hydrido-acetylide cluster **74** <2000JCS(D)989>. Species  $[(\eta^5\text{-Cp})_2\text{Fe}_2(\mu\text{-CN}(\text{Me})(\text{Me}_2\text{C}_6\text{H}_3\text{-2,6}))(\mu\text{-CO})(\text{CO})(\text{Bu}^t\text{CN})](\text{OTf})$  reacts with *p*-tolyl acetylide and then triflic acid to give  $[(\eta^5\text{-Cp})_2\text{Fe}_2(\mu\text{-}\eta^1:\eta^3\text{-C}(4\text{-MeC}_6\text{H}_4)=\text{C}=\text{C}(\text{Bu}^t)\text{N}(\text{H})\text{CN}(\text{Me})\text{-}(\text{Me}_2\text{C}_6\text{H}_3\text{-2,6}))(\mu\text{-CO})(\text{CO})](\text{OTf})$  <2003JOM(684)37>.



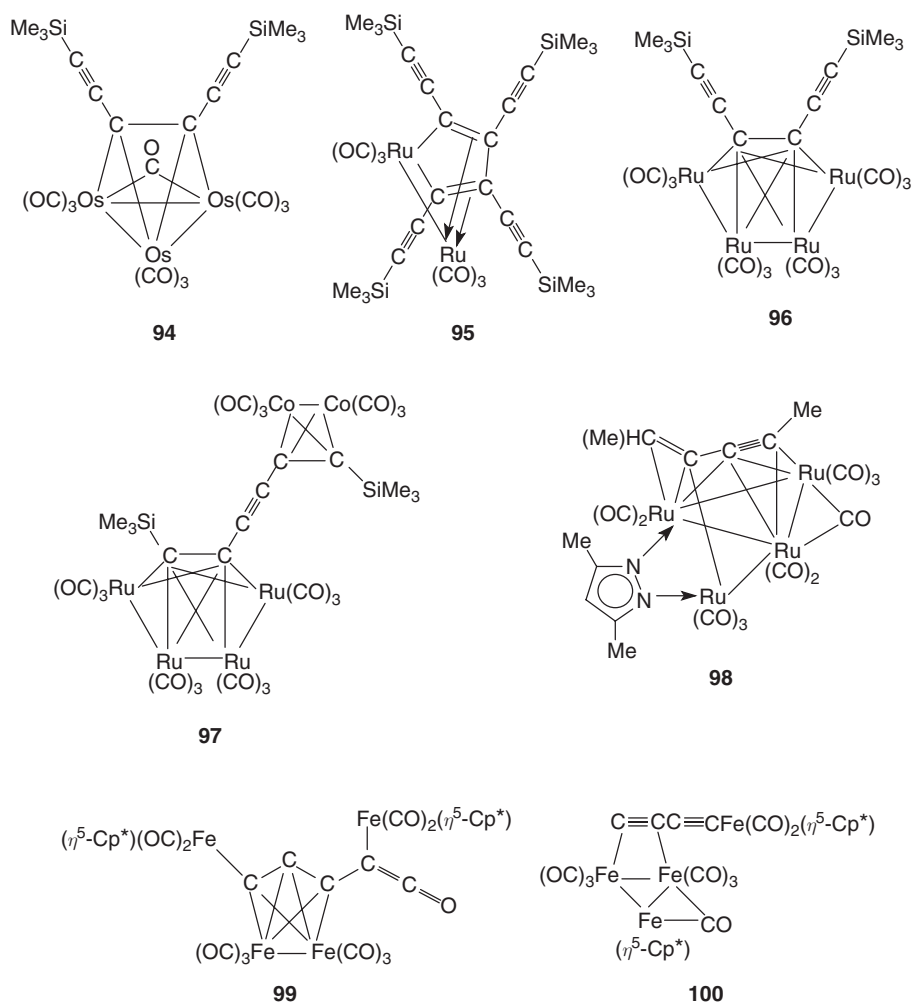
Thermolysis of dimethylaminopropyne with  $[\text{Ru}_3(\text{CO})_{12}]$  gives the product **75** along with **76** <2003JOM(671)137>. Trimethylsilylpropargyl alcohol under conditions gives **77** along with **76**. If the latter reaction is run in  $\text{MeOH}/\text{KOH}$  medium with subsequent acidification, species **76** becomes the main product which is formed along with **78**. Similar complexes include  $[(\mu\text{-H})\text{Ru}_3(\text{CO})_9\{\text{CHCH}\text{-}\text{C}(\text{OMe})\}]$  <2000JOM(609)169>,  $[(\mu\text{-H})\text{Ru}_3(\text{CO})_8(\text{PPh}_3)(\mu_3\text{-}\eta^3\text{-HCCCHCOH})]$  <1998ICC134, 1999JCS(D)2777>,  $[(\mu\text{-H})\text{Ru}_3(\text{CO})_9(\mu_3\text{-}\eta^3\text{-C}_{12}\text{H}_{17})]$  <1998JCS(D)751>,  $[(\mu\text{-H})\text{Ru}_3(\text{CO})_9(\mu_3\text{-}\eta^3\text{-C}_{12}\text{H}_{19})]$  <1996JOM(510)37>, and  $[(\mu\text{-H})\text{Ru}_3(\text{CO})_9(\mu_3\text{-}\eta^3\text{-HCCPhCH})]$  <1996OM4100>. A typical propargyl structure in the ruthenium chemistry is characterized by the  $\mu\text{-}\eta^1:\eta^2$  coordination mode of this three-electron-donor ligand **79** <1996OM164, 1997OM1159, 1997OM1476, 1998JA3243, 2000JOM(593)465, 2000OM3179, 2002ICC82>. Another option is the five-electron  $\mu\text{-}\eta^2:\eta^3$  arrangement <1998JA1938>. The alkynyl cluster  $[\text{Ru}_3(\mu\text{-H})(\mu_3\text{-C}_2\text{CPh}_2(\text{OH}))(\text{CO})_9]$  contains the hydroxyl group <1998CRV2797>. Propargyl alcohol  $\text{HC}\equiv\text{CC}(\text{Ph}_2)(\text{OH})$  with  $[\text{Ru}_3(\text{CO})_{10}(\text{AN})_2]$  forms first **80**, then on thermolysis eliminates the carbonyl ligand to afford **81** <2000JCS(D)881>. The latter can be protonated in three ways—by  $\text{HBF}_4$  to give **82**, by  $\text{HBF}_4$  in the presence of diphenylphosphino-methane to yield **83**, and using a combination of  $\text{K}(\text{BHBu}_3)/\text{HBF}_4$  to afford **84**. Protonation of the products of interaction of alkynols with  $[\text{Ru}_3(\text{CO})_{12}]$ , **80** (but  $\text{CPh}$ ,  $\text{R} = \text{Me}$ ,  $\text{Ph}$ , instead of  $\text{CPh}_2$ ) by tetrafluoroboric acid include **84** as well as species **85** and **86** <1998POL2937, 2000JCS(D)4390>. The range of clusters originating from  $\text{HC}\equiv\text{CC}(\text{H})(\text{OH})\text{Me}$  may be supplemented by the tetra-, penta-, hexa-, and heptaruthenium compounds <1998JCS(D)3391>. Complexes of the type **81** tend to produce the alkene-alkyne species and this process is usually catalyzed by the oxide supports <2001JCS(D)46, 2002ICA(334)131>. Protonation of the alkynol complex **87** is followed by elimination of water to yield **88** <1996JOM(508)39>. Interaction of  $\text{HC}\equiv\text{CC}(\text{Me}_2)\text{OH}$  with  $[\text{Os}_3(\text{CO})_{12}]$  leads to **89**, which can be dehydrated to form the alkene-alkyne complex **90**. Propargyl alcohols  $\text{HC}\equiv\text{CCR}_2\text{OH}$  ( $\text{R} = \text{H}$ ,  $\text{Me}$ ,  $\text{Ph}$ ) with  $[(\eta^5\text{-Cp})(\text{AN})\text{Ru}(\mu\text{-CH}_2)(\mu\text{-CO})\text{Ru}(\text{CO})(\eta^5\text{-Cp})]$  yield the allylidenes  $[(\eta^5\text{-Cp})(\text{OC})\text{Ru}(\mu\text{-}\eta^1:\eta^3\text{-C}(\text{C}(\text{R}_2\text{OH})\text{CH}=\text{CH}_2)(\mu\text{-CO})\text{Ru}(\eta^5\text{-Cp}))]$  ( $\text{R} = \text{H}$ ,  $\text{Me}$ ,  $\text{Ph}$ ) <2003ICA(354)29>. The products when reacted with tetrafluoroboric acid are dehydrated and the 2-butadienyl complexes  $\{[(\eta^5\text{-Cp})(\text{OC})\text{Ru}(\mu\text{-}\eta^2:\eta^3\text{-CR}_2=\text{CCH}=\text{CH}_2)(\mu\text{-CO})\text{Ru}(\eta^5\text{-Cp})](\text{BF}_4)$  ( $\text{R} = \text{H}$ ,  $\text{Me}$ ,  $\text{Ph}$ ) result.



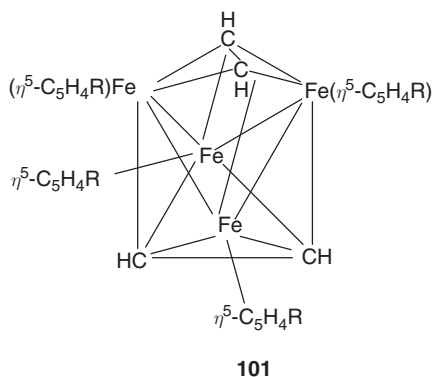
The conjugated diyne  $\text{PhC}\equiv\text{CC}\equiv\text{CCH}_2\text{OH}$  with  $[\text{H}_2\text{Os}_3(\text{CO})_{10}]$  gives the product of intramolecular cyclization **91** <1999JCS(D)2511> containing the  $\eta^2$ -coordinated 2-benzylfuran <2001OM3854, 2003OM3455>. If the starting diyne used is  $\text{PhC}(\text{O})\text{C}\equiv\text{CC}\equiv\text{CPh}$ , the product of cyclization is **92**, where the furan ring reveals aromaticity but coordination is fulfilled in the  $\eta^3$ -manner, in which the exocyclic carbon site participates. The final product of the reaction of  $\text{HOMe}_2\text{CC}\equiv\text{CC}\equiv\text{CCMe}_2\text{OH}$  is the trinuclear cluster **93** <2003OM3455>.  $[\text{H}_2\text{Os}_3(\text{CO})_{10}]$  also reacts with 1,4-diphenylbuta-1,3-diyne to yield  $[\text{Os}_3(\mu\text{-H})(\text{CO})_{10}(\mu_3\text{-}\eta^3\text{:}\eta^1\text{:}\eta^3\text{-Ph}(\text{C})\text{C}_9\text{H}_6)]$ , where the product experiences ring-closure and formation of the fused five- and six-membered ring ligand, interacting with the osmium triangle via the pseudo-allylic route <2003JOM(683)313>. The product can be decarbonylated to give  $[\text{Os}_3(\mu\text{-H})(\text{CO})_9(\mu_3\text{-}\eta^3\text{:}\eta^1\text{:}\eta^3\text{-Ph}(\text{C})\text{C}_9\text{H}_6)]$ .



Dimethyl- and diphenylacetylene react with  $[\text{Ru}_3(\text{CO})_9(\mu\text{-CO})(\mu_3\text{-C}\equiv\text{C}\equiv\text{CPh}_2)]$  ( $\text{R} = \text{Me}, \text{Ph}$ ) and  $[\text{Ru}_4(\text{CO})_{12}(\mu_4\text{-C}(\text{Ph})\text{C}(\text{Ph})\text{CCCPh}_2)]$  <2001JCS(D)46>. A related cluster is  $[\text{Ru}_3(\mu_3\text{-C}(\text{OCH}_2\text{CH}=\text{CH}_2)\text{CHCCPh}_2\text{OC}(\text{O})(\mu\text{-dppm})\text{-}(\mu\text{-CO})(\text{CO})_6)]$  <2001AJC319>.  $[\text{Ru}_2(\text{CO})_6(\mu\text{-PPh}_2)(\mu\text{-}\eta^1, \eta^2\text{-C}\equiv\text{CBu}^t)]$  experiences intermolecular coupling to yield  $[\text{Ru}_4(\text{CO})_8(\mu\text{-PPh}_2)_2(\text{Bu}^t\text{C}\equiv\text{CC}\equiv\text{CBu}^t)]$  <1996OM5269>. The reaction with the  $\mu\text{-}\eta^1, \eta^2\text{-C}\equiv\text{CPh}$  derivatives is followed by the formation of the tetranuclear clusters <1998OM2936>. The dialkynyl complex  $[\text{Ru}_2(\text{CO})_6(\mu\text{-PPh}_2)(\mu\text{-}\eta^1, \eta^2\text{-C}\equiv\text{CC}\equiv\text{CBu}^t)]$  gives among other products  $[\text{Ru}_4(\text{CO})_9(\mu\text{-PPh}_2)_2(\mu_4\text{-}\eta^1, \eta^2, \eta^2, \eta^1\text{-C}\equiv\text{CC}=\text{C}(\text{Bu}^t)\text{C}\equiv\text{CC}\equiv\text{CBu}^t)]$  <1998OM2477>. Similarly,  $[\text{Fe}_2(\text{CO})_6(\mu\text{-PPh}_2)(\mu\text{-}\eta^1, \eta^2\text{-C}\equiv\text{CPh})]$  gives  $[\text{Fe}_4(\text{CO})_8(\mu\text{-PPh}_2)_2(\mu_4\text{-}\eta^2, \eta^2, \eta^2, \eta^2\text{-PhC}\equiv\text{CC}\equiv\text{CPh})]$  <1997AG(E)2668, 1997JCS(CC)1883, 1998OM2970, 1999JCS(D)13>. Examples of coordinated 1,3-dienes can be found, e.g.,  $[\text{Ru}_3(\text{CO})_{10}(\mu_3\text{-}\eta^2\text{-C}_2\text{Ph}(\text{C}\equiv\text{CPh}))]$  <1996AJC155>,  $[\text{Ru}_3(\text{CO})_8(\text{dppm})\text{-}(\mu_3\text{-}\eta^2\text{-C}_2\text{Ph}(\text{C}\equiv\text{CPh}))]$  <1997JOM(536)93>, and others <1996JCLS109, 1996JCS(D)1551, 1997OM4276, 1998JOM(558)197, 2000JCS(D)2939, 2001AJC325>. The reaction of 1,4-diphenylbuta-1,3-diyne with  $[\text{Ru}_3(\text{CO})_{12}]$  in THF in the presence of  $\text{Me}_3\text{NO}$  gives  $[(\text{OC})_3\text{Ru}(\mu\text{-}\eta^2, \eta^5\text{-C}(\text{C}\equiv\text{CPh})=\text{C}(\text{Ph})\text{-C}(\text{C}\equiv\text{CPh})=\text{CPh})\text{Ru}(\text{CO})_3]$  <1996ICA(250)129>. The same reaction but in benzene and in the absence of an initiator gives  $[(\text{OC})_3\text{Ru}(\mu\text{-}\eta^2, \eta^5\text{-C}(\text{Ph})\text{C}(\text{C}\equiv\text{CPh})\text{-C}(\text{C}\equiv\text{CPh})\text{CPh})\text{Ru}(\text{CO})_3]$  <1997JOM(536)339>. Thermolysis where 1,4-bis(ferrocenyl)buta-1,3-diyne participates is similar <1996RCB1200>. 1,6-Bis(trimethylsilyl)hexa-1,3,5-triene with  $[\text{Os}_3(\text{CO})_{10}(\text{AN})_2]$  gives cluster **94** <1999JOM(578)103>. The products of interaction of the same alkyne with  $[\text{Ru}_3(\text{CO})_{12}]$  are different and can be formulated as **95** and **96**. Cluster **96** further interacts with  $[\text{Co}_2(\text{CO})_8]$  to produce the heterodimetallic species **97** containing two homonuclear metal cluster counterparts. The same reaction run at room temperature leads to  $[\text{Ru}_3(\text{CO})_{10}(\mu_3\text{-}\eta^2\text{-C}_2(\text{C}\equiv\text{CSiMe}_3)_2)]$  and  $[\text{Ru}_4(\text{CO})_{12}(\mu_4\text{-}\eta^2\text{-C}_2(\text{C}\equiv\text{CSiMe}_3)_2)]$  <1999JOM(578)55>. Similar structures based on triiron cores are known <2000JOM(604)150>. The osmium homolog of the latter is known <1998JOM(565)279> and is illustrated as **94**. Among the products of the ruthenium clusters with diynes,  $[\text{Ru}_3(\mu_3\text{-C}_5\text{H}_5\text{NMe})(\mu\text{-}\eta^3\text{-PhCH}=\text{C}\equiv\text{CPh})(\mu\text{-CO})_2(\text{CO})_6]$  <1998MI1> may be mentioned. The cluster  $[\text{Os}_3(\mu_3\text{-}\eta^2\text{-FcC}\equiv\text{CC}\equiv\text{CFc})(\text{CO})_{10}]$  <2000OM2411> reacts with water to give  $[\text{Os}_3(\mu\text{-H})(\mu_3\text{-}\eta^3\text{-FcCH}=\text{CC}\equiv\text{CFc})(\text{CO})_9]$  and  $[\text{Os}_3(\mu\text{-OH})(\mu_3\text{-}\eta^3\text{-FcCH}=\text{C}\equiv\text{CFc})(\text{CO})_9]$  <2000OM4090>. Similar products are formed between thienyl diyne and  $[\text{Os}_3(\text{CO})_{10}(\text{AN})_2]$  <2000JCS(D)4015>. The result of the coupling reaction is the cluster  $[\text{Ru}_3(\mu\text{-NS}(\text{OMePh}))(\mu\text{-}\eta^3\text{-PhCH}=\text{CC}\equiv\text{CPh})(\text{CO})_9]$  <1997JOM(549)275>. The  $[\text{Ru}_3(\mu\text{-H})(\mu\text{-}\eta^2\text{-3,5-Me}_2\text{pz})(\text{CO})_{10}]$  complex reacts with 2,4-hexadiyne to yield among the other products cluster **98** <2001ICC57>. Cluster  $[(\eta^5\text{-Cp}^*)(\text{OC})_2\text{FeC}\equiv\text{CC}\equiv\text{CFc}(\text{CO})_2(\eta^5\text{-Cp}^*)]$  with  $\text{Fe}_2(\text{CO})_9$  gives a mixture of **99** and **100** <1998JOM(565)49, 2000JCS(CC)1285>.



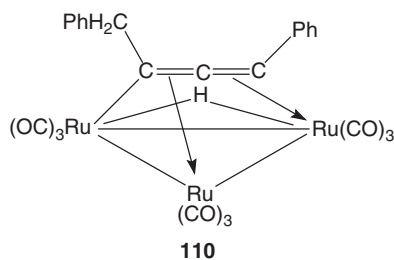
The tetrairon clusters  $[(\eta^5\text{-C}_5\text{H}_4\text{R})\text{Fe}_4(\mu_3\text{-CO})_4]$  ( $\text{R} = \text{H}, \text{Me}$ ) of the cubane type when treated with lithium aluminum hydride, give the acetylene clusters **101** ( $\text{R} = \text{H}, \text{Me}$ ) [<1998JA9135>](#). They enter into oxidation reactions with ammonium hexafluorophosphate and silver tetrafluoroborate to yield the cationic clusters, where the butterfly-type framework is retained [<2002IC6726>](#).



The reaction of  $[(\text{Cp}^*)(\text{OC})_2\text{FeC}\equiv\text{CC}\equiv\text{CH}]$  with  $[\text{Ru}_3(\text{CO})_{12}]$  leads to a mixture of cluster compounds **102–105**, [<2003JOM\(670\)2>](#). Thermolysis of the heterodimetallic complex  $[\text{Os}_3(\text{CO})_{10}(\mu\text{-H})(\mu\text{-}\eta^3\text{-C(=CHPh)C}\equiv\text{CW(O)}_2(\eta^5\text{-Cp}^*))]$  gives products **106** and **107**, both with the

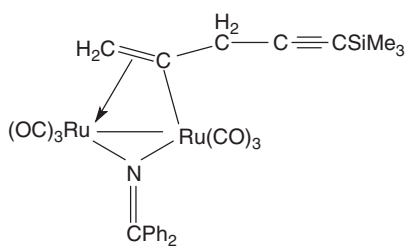
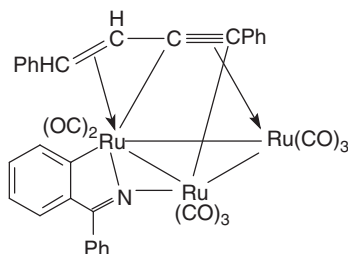
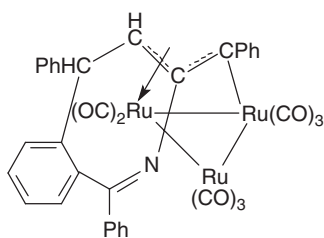
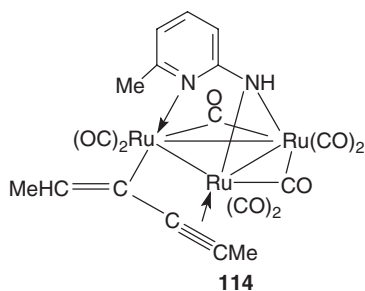
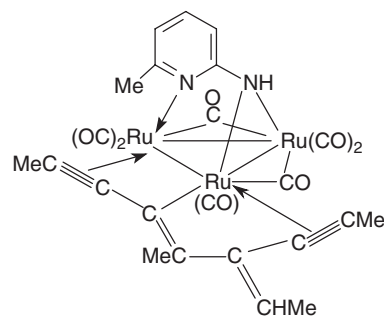
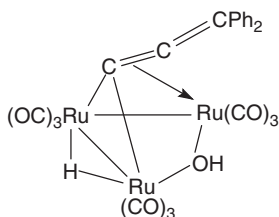
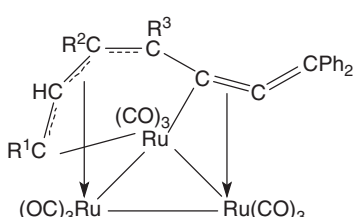
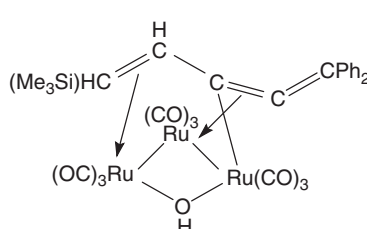
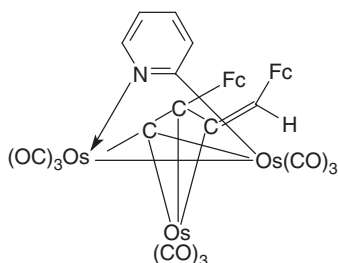
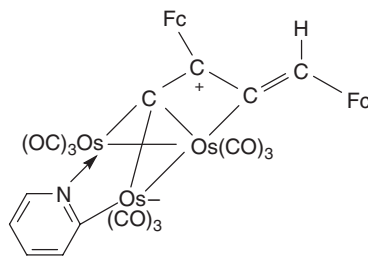


<2000JCS(D)4527>. Similar reactions of 1,3-dialkynes are known <1999JOM(589)213>.

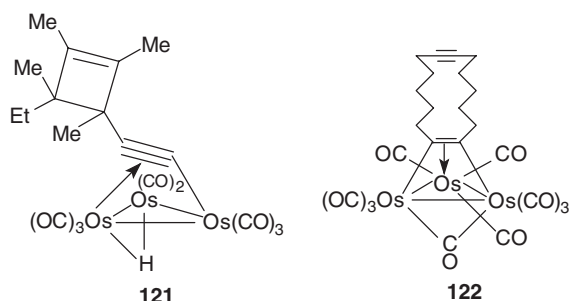




$[\text{Ru}_3(\text{CO})_9(\mu_2\text{-NCPH}_2)(\mu_2\text{-H})]$  reacts with  $\text{HC}\equiv\text{CCH}_2\text{C}\equiv\text{CSiMe}_3$  to give variously coordinated triruthenium clusters **111–113** <2000OM5424>. The ruthenium cluster based on 2-aminopyridine reacts with  $\text{MeC}\equiv\text{CC}\equiv\text{CMe}$  to yield **114**. With an excess of the dialkyne, cluster **115** is formed, both being examples of alkyne–alkene complexes <2001OM4973, 2003ICA(350)215>. Another illustration of the coupling reactions of the coordinated ligands pertains to the allenylidene complex **116**. With phenylacetylene, it experiences dehydration followed by the formation of **117** ( $\text{R}^1 = \text{Ph}$ ,  $\text{R}^2 = \text{H}$ ,  $\text{R}^3 = \text{Ph}$ ). With trimethylsilylacetylene, the first step is the coupling reaction leading to **118** and the second is dehydration to afford **117** ( $\text{R}^1 = \text{R}^3 = \text{Me}_3\text{Si}$ ,  $\text{R}^2 = \text{H}$ ) <1999JOM(589)239>.  $\text{MeC}\equiv\text{CC}\equiv\text{CMe}$  with  $[\text{Os}_3(\text{CO})_{10}(\text{AN})_2]$  gives  $[\text{Os}_3(\text{CO})_9(\mu\text{-CO})(\mu_3\text{-}\eta^2\text{:}\mu_3\text{-}\eta^1, \eta^1, \eta^3\text{-MeC}_2\text{C}_2\text{MeOC}_5\text{Me}_2)\text{Os}_3(\mu\text{-CO})(\text{CO})_9]$  and other clusters <2001JOM(635)119>. Cluster  $[\text{Os}_3(\text{CO})_{10}(\mu\text{-}\eta^2\text{-2-C}_5\text{H}_4\text{N})(\mu\text{-H})]$  reacts with 1,4-bis(ferrocenyl)butadiyne to yield isomers **119** and **120** <2001JOM(637)514, 2001OM5225>.

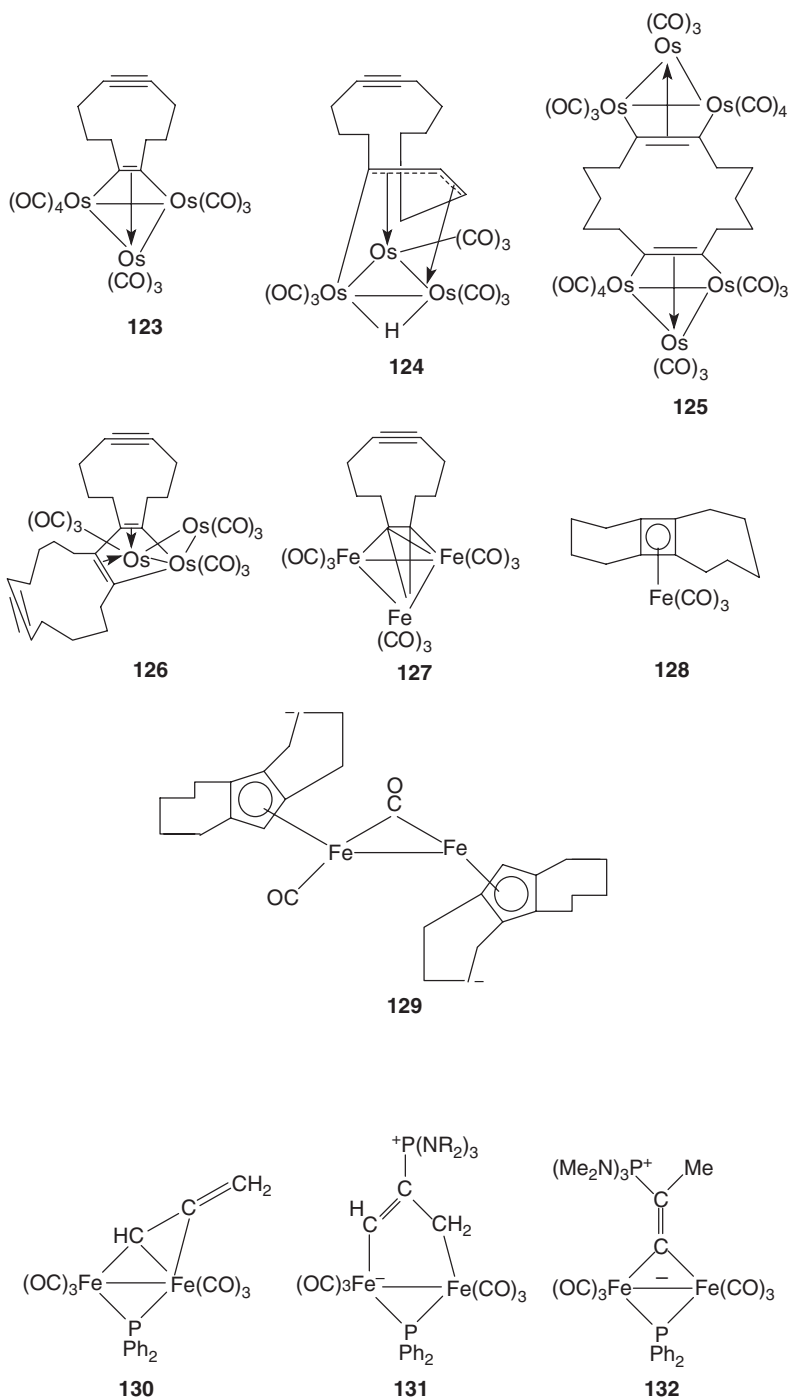
**111****112****113****114****115****116****117****118****119****120**

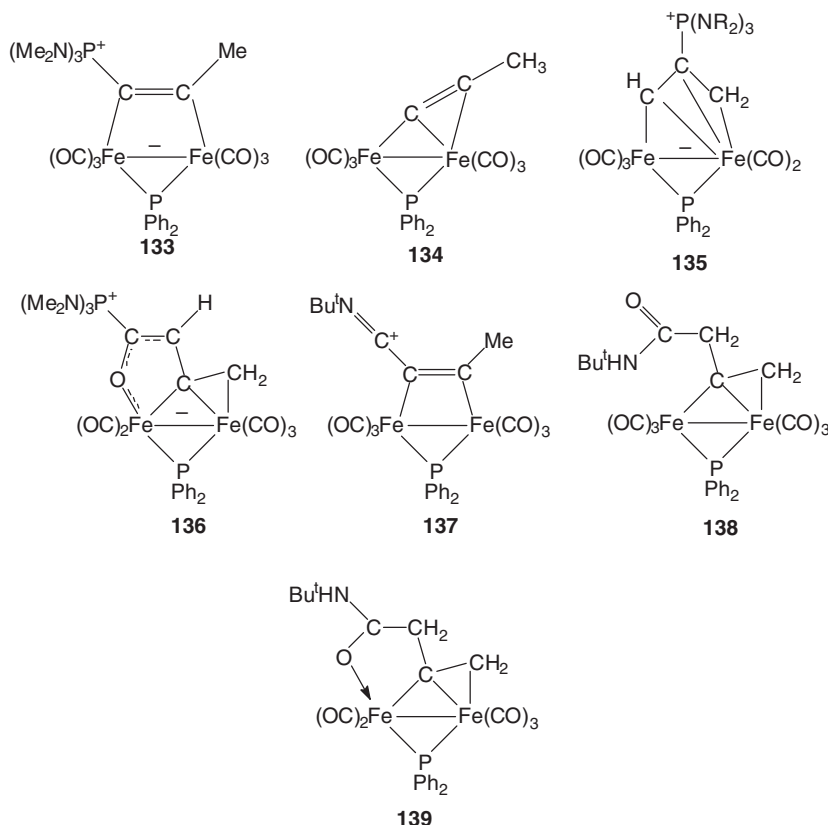
Interaction of a fourfold excess of hexamethyl Dewar benzene (L) with  $[\text{Os}_3(\text{CO})_{10}(\text{AN})_2]$  first gives  $[\text{Os}_3(\text{CO})_{10}(\eta^4\text{-L})]$ , then, under reflux, the product of decarbonylation,  $[(\mu\text{-H})_2\text{Os}_3(\text{CO})_9(\mu\text{-}\eta^3\text{-CH}(\text{C}_6\text{Me}_5))]$ , which can be thermally or photochemically transformed to **121** <2003OM2361>. The cyclotetradeca-1,8-diyne ( $\text{C}_{14}\text{H}_{20}$ ) complexes, for example,  $[\text{Os}_3(\text{CO})_{10}(\mu_3\text{-}\eta^2\text{-C}_{14}\text{H}_{20})_2]$ , **122** <1999OM880> further react with  $[\text{Os}_3(\text{CO})_{10}(\text{AN})_2]$  to yield derivatives  $[\{\text{Os}_3(\text{CO})_{10}\}_2(\mu_3, \mu_3\text{-}\eta^2, \eta^2\text{-C}_{14}\text{H}_{20})]$ , with the ligand in photochemical conditions to give  $[\text{Os}_3(\text{CO})_9(\mu\text{-}\eta^4\text{-C}_{14}\text{H}_{20})_2]$ , and with the ligand in  $\text{Me}_3\text{NO}/\text{AN}$  to afford  $[\text{Os}_3(\text{CO})_9(\mu_3\text{-}\eta^3\text{-C}_4\text{H}_{10})_2]$  <2003OM2990>. In excess ligand or on reaction of the products with complex **122**, more spacious complexes are formed that are likely to play a role in materials chemistry. Cyclodeca-1,8-diyne reacts with  $[\text{Os}_3(\text{CO})_{10}(\text{AN})_2]$  to give cluster **123** possessing a branched reactivity pattern <1999OM880>. On thermolysis, **123** is converted into **124**. In excess  $[\text{Os}_3(\text{CO})_{10}(\text{AN})_2]$  it gives species **125**, and on photochemical decarbonylation, product **126** is afforded.  $[\text{Fe}_3(\text{CO})_{12}]$  in this reaction behaves differently and forms the cluster product **127**, which on thermolysis undergoes unusual rearrangements to the  $\eta^4$ -cyclobutadienyl, **128**, and  $\eta^5$ -cyclopentadienyl, **129**, derivatives respectively. Ruthenium and osmium clusters containing 1,3-cyclohexadiene are characterized by either the  $\eta^4$ - or  $\mu_2\text{-}\eta^2\text{:}\eta^2$  coordination mode <1996JCS(D)2165>.  $[\text{Os}_4(\text{CO})_9(\text{RCCR})(\eta^6\text{-C}_6\text{H}_6)]$  ( $\text{R} = \text{Me}, \text{Ph}$ ) reacts with  $\text{Me}_3\text{NO}$  and 1,3- or 1,4-cyclohexadiene to afford  $[\{\text{Os}_4(\text{CO})_8(\text{RCCR})(\eta^6\text{-C}_6\text{H}_6)\}_2(\mu_2\text{-}\eta^2\text{:}\eta^2\text{-L})]$  ( $\text{R} = \text{Me}, \text{Ph}$ ;  $\text{L} = \text{C}_6\text{H}_8\text{-1,3}, \text{C}_6\text{H}_8\text{-1,4}$ ) <2003ICC1291>.



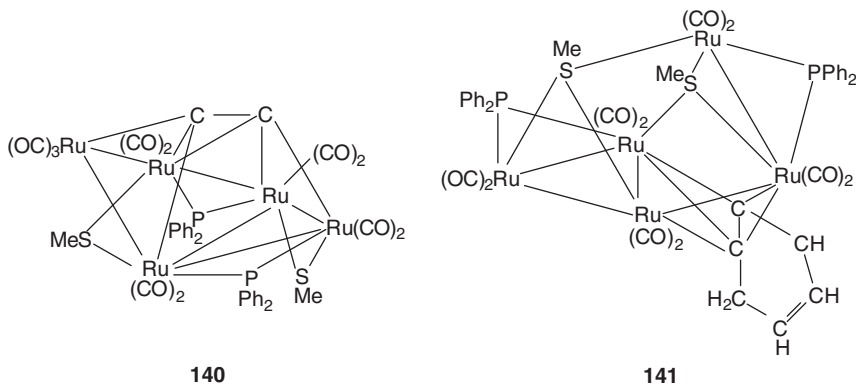
Nucleophilic attack of diphenylphosphine on the allenyl species  $[\text{Fe}_2(\text{CO})_6(\mu\text{-PPh}_2)(\mu\text{-}\eta^1\text{:}\eta^2\text{-(H)C=C=CH}_2)]$ , **130**, gives  $[\text{Fe}_2(\text{CO})_6(\mu\text{-PPh}_2)(\mu\text{-}\eta^1\text{:}\eta^2\text{-CH}_3\text{C=CH(PPh}_2))]$  <1996JCS(CC)1545, 1997OM3221>. Diphenylphosphinomethane produces  $[\text{Fe}_2(\text{CO})_6(\mu\text{-PPh}_2)(\mu\text{-}\eta^1(\text{P}):\eta^1(\text{C})\text{-}\eta^2(\text{C})\text{-Ph}_2\text{PCHPPH}_2(\text{H)C=CCH}_3)]$  and an iron-carbon-bridged phosphinomethanide complex <1996OM5302, 1997OM297>. Trialkylphosphites give  $[\text{Fe}_2(\text{CO})_6(\mu\text{-PPh}_2)(\mu\text{-}\eta^1\text{:}\eta^2\text{-CH}_3\text{C=CCH(PO(OR)}_2)]$  ( $\text{R} = \text{Me}, \text{Et}, \text{Pr}^n$ ) <1997OM4251>. Complex **130** reacts with  $\text{P}(\text{NR}_2)_3$  ( $\text{R} = \text{Me}, \text{Et}, \text{Pr}^n$ ) to yield the zwitterionic derivatives **131** ( $\text{R} = \text{Me}, \text{Et}, \text{Pr}^n$ ) <1999OM679> in accord with the reaction course of the same starting reagent with primary amines <1998OM3331>. However if species **130** is treated first with  $\text{HBF}_4$  and then with  $\text{P}(\text{NMe}_2)_3$ , a mixture of the vinylidene-bridged complex, **132**, and the dimetallacyclobutene, **133**, results <1999OM679>. Under  $\text{HBF}_4$  alone, species **130** isomerizes into the acetylide complex **134**. Complexes **131** ( $\text{R} = \text{Me}, \text{Et}, \text{Pr}^n$ ) slowly decarbonylate into **135** ( $\text{R} = \text{Me}, \text{Et}, \text{Pr}^n$ ). Thermolysis of **132** ( $\text{R} = \text{Me}$ ) gives the same product, **136** ( $\text{R} = \text{Me}$ ). For **131** ( $\text{R} = \text{Et}, \text{Pr}^n$ ), however, the products are **136** ( $\text{R} = \text{Et}, \text{Pr}^n$ ) and **137** ( $\text{R} = \text{Et}, \text{Pr}^n$ ). The structure of these complexes is similar to those of  $[\text{Fe}_2(\text{CO})_5(\mu\text{-PPh}_2)(\mu\text{-}\eta^1\text{:}\eta^2\text{-(NuC(O)CH}_2\text{)C=CH}_2)]$  ( $\text{Nu} = \text{OR}, \text{NHR}, \text{Alk}$ ) <1996OM2688, 1997OM1186, 1997OM3221, 1998JOM(569)39, 1998OM2953>. Complexes **137** also resemble analogous iron alkenyls <1997JOM(527)247>. Complex **130** on reaction with triphenylphosphine gives an analog where, instead of the  $\text{P}(\text{NR}_2)_3$  moiety, there is a  $\text{PPh}_3$  group carrying the partial positive charge <1999OM679>. The product reacts with  $\text{P}(\text{NEt}_2)_3$  to produce **131** ( $\text{R} = \text{Et}$ ). On

thermolysis, it gives an analog of **136** with  $\text{P}(\text{NR}_2)_3/\text{PPh}_3$  substitution. The latter reacts with  $\text{P}(\text{NEt}_2)_3$  to give **136** ( $\text{R} = \text{Et}$ ). Reactions with isocyanides were also studied [<1999OM3178>](#). Bis(phenylene)butatriene  $\text{Fe}_2(\text{CO})_6$  complexes are of interest [<1996OM1511>](#). Species **130** with *t*-butylisocyanide gives a mixture of **137** and **138** [<1999OM3178>](#). The latter is decarbonylated to give **139**.





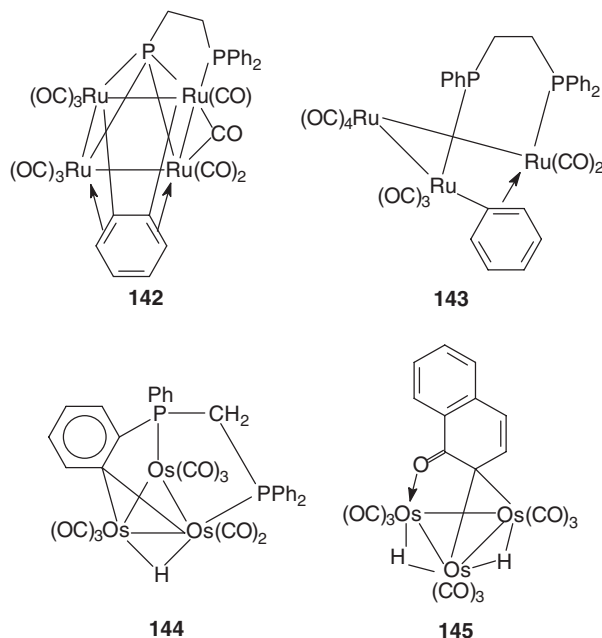
Cluster **140** <1997JCS(D)2937> has an interesting reactivity pattern manifested in reactions with molecular hydrogen, olefins, and cyclopentadiene <1997JCLS293>. Its reaction with buta-1,3-diene gives **141** containing a bridging benzene in the form of cyclohex-3-en-1-yne <1999JOM(573)134>. The related system is [Ru<sub>5</sub>(μ<sub>2</sub>, μ<sub>3</sub>-C<sub>2</sub>)(μ-SMe<sub>2</sub>)(μ-PPh<sub>2</sub>)<sub>2</sub>(CO)<sub>13</sub>] <1997JCS(D)371>.



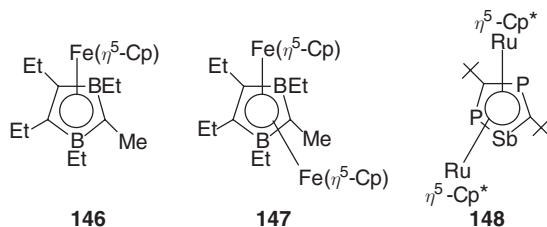
Heterogeneous precursors for the catalytic transformations of benzene and arenes are adsorption complexes of these ligands with transition metals <2001JCLS139, 2001SSCI18> and homogeneous catalytic precursors are cluster complexes, e.g., [(η<sup>6</sup>-C<sub>6</sub>H<sub>6</sub>)<sub>4</sub>Ru<sub>4</sub>H<sub>4</sub>Cl<sub>2</sub>] <1997JOM(539)163> and other similar species <1996JCS(D)2395>, where the bonding mode of the arene ligands is predominantly μ-η<sup>2</sup>, η<sup>2</sup>, η<sup>2</sup>. The μ-η<sup>1</sup>, η<sup>1</sup>, η<sup>1</sup> is observed, in particular, in the adsorption complex of benzene with ruthenium <1998JVST(A)1017>. In the species [(η<sup>5</sup>-Cp\*)Ru]<sub>3</sub>(μ-H)<sub>3</sub>(μ<sub>3</sub>-η<sup>3</sup>, η<sup>3</sup>-C<sub>6</sub>H<sub>6</sub>)<sup>2+</sup> <1997JA625>, the mode is different. Cluster complexes [(η<sup>6</sup>-C<sub>6</sub>Me<sub>6</sub>)<sub>2</sub>(η<sup>6</sup>-C<sub>6</sub>H<sub>6</sub>)Ru<sub>3</sub>(μ<sub>2</sub>-H)<sub>2</sub>(μ<sub>2</sub>-OH)(μ<sub>3</sub>-O)]<sup>+</sup> and [(η<sup>6</sup>-C<sub>6</sub>Me<sub>6</sub>)<sub>2</sub>(η<sup>6</sup>-C<sub>6</sub>H<sub>6</sub>)Ru<sub>3</sub>(μ<sub>3</sub>-H)<sub>3</sub>(μ<sub>3</sub>-O)]<sup>+</sup> are efficient catalysts of the hydrogenation of arenes <2001JOM(621)103>. Successive carbonylation of [Ru<sub>3</sub>(CO)<sub>6</sub>(μ-CO)(μ<sub>3</sub>-η<sup>5</sup>, η<sup>3</sup>, η<sup>3</sup>-C<sub>10</sub>H<sub>8</sub>)] leads

first to  $[\text{Ru}_3(\text{CO})_8(\mu_3\text{-}\eta^5, \eta^2, \eta^1\text{-C}_{10}\text{H}_8)]$  and then to  $[\text{Ru}_2(\text{CO})_5(\mu_2\text{-}\eta^5, \eta^3\text{-C}_{10}\text{H}_8)]$  <2001OM359>. Excess acenaphthylene with  $[\text{Os}_3(\text{CO})_{10}(\text{AN})_2]$  gives  $[\text{Os}_3(\text{CO})_{10}(\mu\text{-H})(\mu\text{-}\eta^2\text{-C}_{12}\text{H}_7)]$ , which on thermolysis transforms into  $[\text{Os}_3(\text{CO})_9(\mu\text{-H})_2(\mu_3\text{-}\eta^2\text{-C}_{12}\text{H}_6)]$  <2002IC5525, 2003JOM(683)421>. The product of thermolysis reacts with acenaphthylene to produce four clusters:  $[\text{Os}_4(\text{CO})_{12}(\mu_4\text{-}\eta^2\text{-}\eta^2\text{-C}_{12}\text{H}_6)]$ ,  $[\text{Os}_2(\text{CO})_6(\mu\text{-}\eta^4\text{-C}_{24}\text{H}_{12})]$ ,  $[\text{Os}_3(\text{CO})_9(\mu\text{-H})(\mu_3\text{-}\eta^4\text{-C}_{24}\text{H}_{13})]$ , and  $[\text{Os}_2(\text{CO})_5(\mu\text{-}\eta^4\text{-C}_{24}\text{H}_{12})(\eta^2\text{-C}_{12}\text{H}_8)]$ .

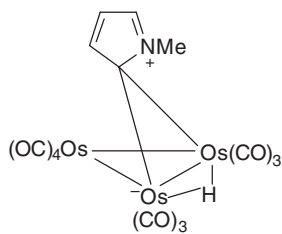
Pyrolysis of clusters containing phenyl-substituted P-ligands often leads to the appearance of benzyne ligands through the stages of *o*-metallation and cleavage of the phosphorus-carbon bond <2001JCLS139>.  $[\text{Ru}_3(\text{CO})_{10}(\text{dppe})]$  in benzene on heating produces clusters **142** and **143** <2002ICC414>. Bonding of the six-electron benzyne ligand occurs in a  $\mu_4\text{-}\eta^4$  manner. Cluster **143** is characterized by the  $\mu_1, \mu_2\text{-}\eta^3$  coordination mode of the three-electron  $\text{C}_6\text{H}_5$  moiety. The reactivity of the *o*-metallated derivative **144** is receiving much attention <1998JCS(D)1097, 2000ICC553, 2000JOM(616)157, 2000OM5623, 2001JCLS5, 2001JOM(625)112, 2003JOM(681)237>. Large clusters of osmium are  $[\text{Os}_6(\text{CO})_{14}(\mu\text{-H})(\mu\text{-CO})(\text{AN})(\text{Pyr})(\mu\text{-}\eta^2\text{-C}_5\text{H}_4)]$  <1997JCS(D)4357> and  $[\text{Os}_6\text{CO}]_{14}(\mu\text{-CO})(\mu\text{-H})(\mu\text{-}\eta^1\text{-}\eta^2\text{-C}_9\text{H}_8\text{N}_3)]$  <1998JCS(D)1939>.  $\text{MeC}\equiv\text{CC}\equiv\text{CMe}$  with  $[\text{Os}_3(\text{CO})_{10}(\text{AN})_2]$  gives  $[\text{Os}_3(\text{CO})_9(\mu\text{-CO})(\mu_3\text{-}\eta^2\text{-}\mu_3\text{-}\eta^1, \eta^1, \eta^3\text{-MeC}_2\text{C}_2\text{MeOC}_5\text{Me}_2)\text{Os}_3(\mu\text{-CO})(\text{CO})_9]$  and other clusters <2001JOM(635)119>. One of the products of interaction of  $[\text{Os}_3(\mu\text{-H})(\mu\text{-OH})(\text{CO})_{10}]$  with 1-naphthol is **145** <2003JOM(687)203>.



The triple-decker complex **146** is assumed to be formed via the sandwich **147**. These two species follow simultaneously from the corresponding 2,3-dihydro-1,3-diborole and  $[(\eta^5\text{-Cp})\text{Fe}(\eta^4\text{-COD})]$  <1996CEJ487>. A mixture of 1,4,2-diphosphastibolyl and 1,2,4-triphospholyl anions with  $[\text{RuCl}_2(\text{PPh}_3)_3]$  gives an isomeric mixture of antimony-containing sandwiches <1997JCS(D)2183>. In excess  $[(\eta^5\text{-Cp}^*)\text{Ru}(\text{AN})_3](\text{PF}_6)$ , the triple-decker **148** results.

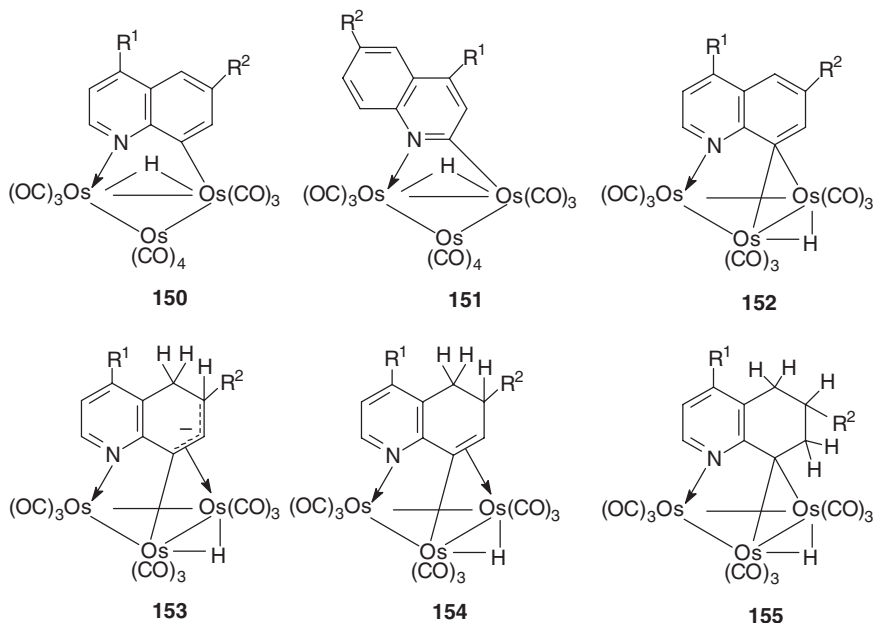


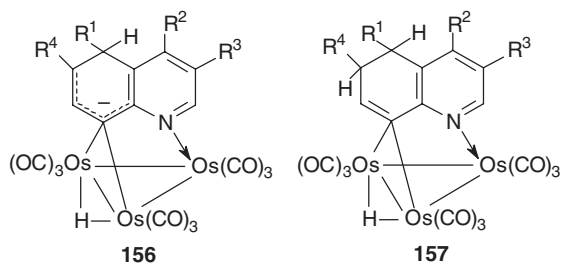
Activation of 1-methylpyrrole using triosmium clusters gives among the others zwitterionic product **149** <1997OM1735>.



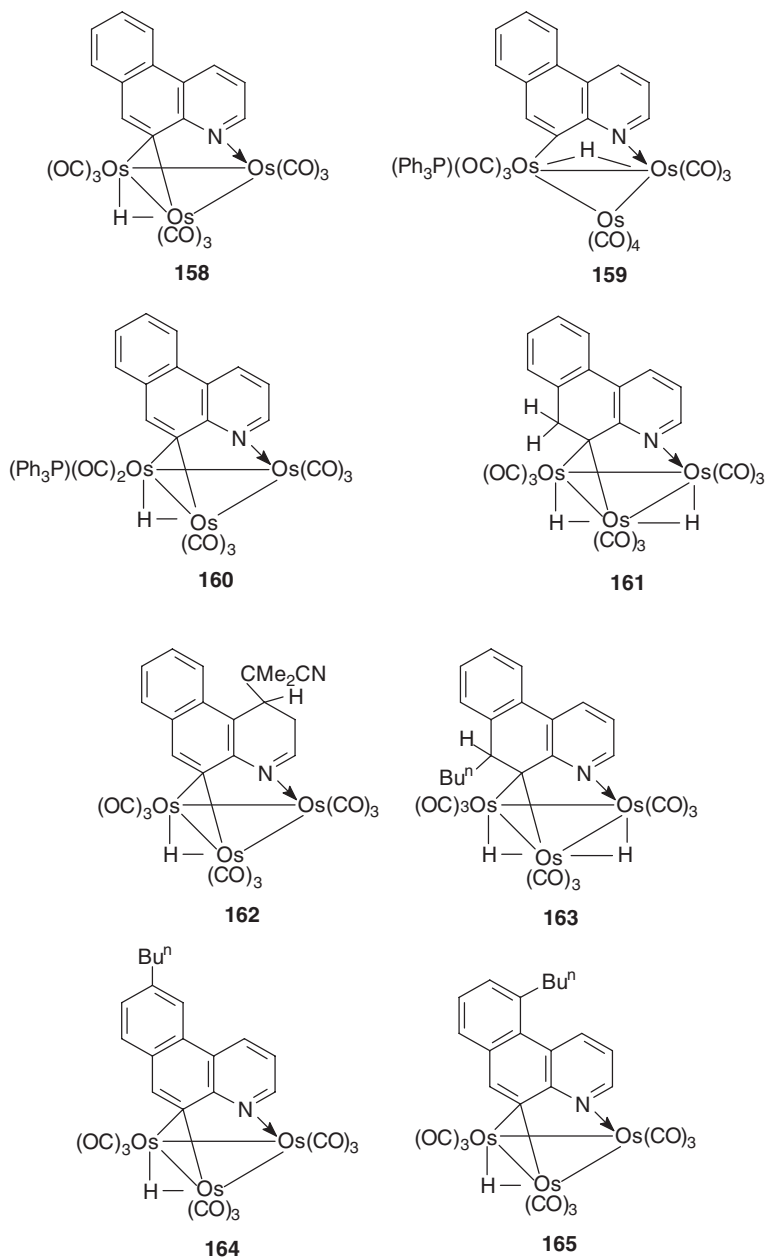
149

Quinoline and tetrahydroquinoline react with  $[M_3(CO)_{12}]$  ( $M = Ru, Os$ ) to give  $[(\mu-H)(\mu-\eta^2-C_9H_6N)M_3(CO)_{10}]$  ( $M = Ru, Os$ ), the product of oxidative addition of the C(2)—H bond of the quinoline ring to  $[M_3(CO)_{12}]$ . The same type of products, **150** ( $R^1 = R^2 = H$ ;  $R^1 = Me, R^2 = H$ ;  $R^1 = H, R^2 = Me$ ), results from the derivatives of quinoline and  $[Os_3(CO)_{10}(AN)_2]$  <1996OM1979, 1998OM415, 1998POL2975, 2002OM1508> but products **151** ( $R^1 = R^2 = H$ ;  $R^1 = Me, R^2 = H$ ;  $R^1 = H, R^2 = Me$ ) are also formed in minor amounts. At elevated temperatures, decarbonylation of **150** ( $R^1 = R^2 = H$ ;  $R^1 = Me, R^2 = H$ ;  $R^1 = H, R^2 = Me$ ) takes place, and the result is **152** ( $R^1 = R^2 = H$ ;  $R^1 = Me, R^2 = H$ ;  $R^1 = H, R^2 = Me$ ), the process being reversible. Complexes **152** ( $R^1 = R^2 = H$ ;  $R^1 = Me, R^2 = H$ ;  $R^1 = H, R^2 = Me$ ) enter hydrogenation with  $LiEt_3BH$  to give **153** ( $R^1 = R^2 = H$ ;  $R^1 = Me, R^2 = H$ ;  $R^1 = H, R^2 = Me$ ). Protonation of **153** ( $R^1 = R^2 = H$ ;  $R^1 = Me, R^2 = H$ ;  $R^1 = H, R^2 = Me$ ) by triflic acid gives **154** ( $R^1 = R^2 = H$ ;  $R^1 = Me, R^2 = H$ ;  $R^1 = H, R^2 = Me$ ), and further hydrogenation/protonation sequence gives **155** ( $R^1 = Me, R^2 = H$ ). A similar process occurs when **152** ( $R^1 = R^2 = H$ ) interacts with  $R^1Li$  [ $R^1 = Me, Bu^n, Bu^t, PhCH_2, Ph, vinyl, C_2(CH_2)_3Me, CH_2CN, CMe_2CN, CHS(CH_2)_2S, CH_2COOBu^t$ ] or  $R^1MgBr$  ( $R^1 = Me, CH_2=CHCH_2MgBr$ ) to yield **156** [ $R^1 = Me, Bu^n, Bu^t, PhCH_2, Ph, vinyl, CH_2=CHCH_2, C_2(CH_2)_3Me, CH_2CN, CHS(CH_2)_2S, CH_2COOBu^t, R^2 = R^3 = R^4 = H$ ] and on protonation **157** with the same set of substituents as in **156** <1998JA12818, 2000JOM(593)226>.

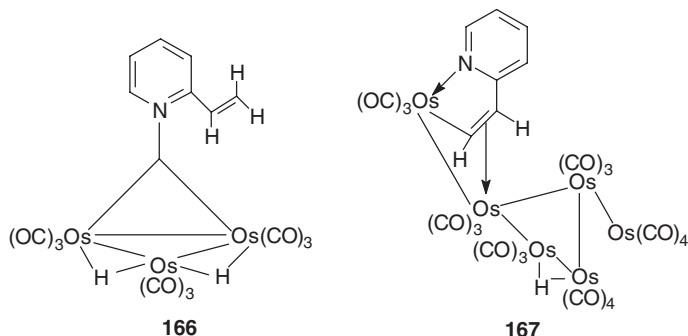




5,6-Benzoquinoline complex **158** is reactive toward triphenylphosphine to yield **159** <1998OM415, 1999OM3519>. Thermolysis of **159** gives **160**. Complex **158** with  $\text{LiEt}_3\text{BH}$  and then  $\text{CF}_3\text{COOH}$  gives **161** and with  $\text{LiMe}_2\text{CCN}/\text{CF}_3\text{COOH}$ , **162**. With *n*-butyllithium/ $\text{CF}_3\text{COOH}$ , a mixture of products is obtained, **163–165**.

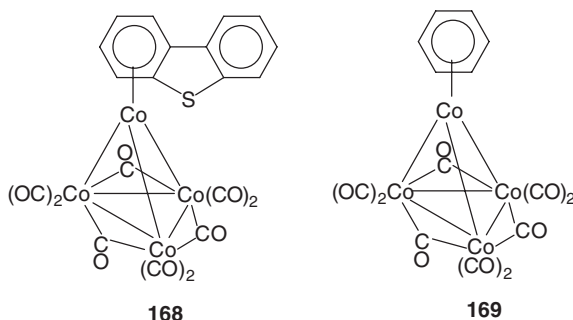


Cluster **166** upon thermolysis in the presence of  $[\text{Os}_3(\text{CO})_{10}(\text{AN})_2]$  rearranges into **167** <1996JOM(513)27> containing along with nitrogen-coordination, the  $\eta^2$ -coordination via the vinyl group.



#### 4.15.3.8 Functions Containing Two Co, Rh, or Ir Atoms

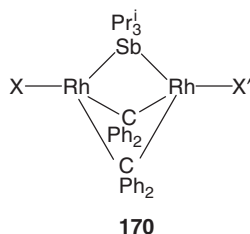
In the  $[\text{Co}_4(\text{CO})_{12}]$  structure, three of the carbonyl ligands are bridging between the cobalt atoms <1999JOM(573)60>. In the clusters  $[(\eta^5\text{-Cp})_3\text{Co}_3(\mu\text{-CO})_2(\mu_2\text{-CH}_2)]$  and  $[(\eta^5\text{-Cp})_3\text{Co}_3(\mu_3\text{-CO})(\mu_3\text{-NNCH}_2)]$ , the bridging methylene moieties have a dynamic behavior <2001JOM(617)561>. Bridging carbonyls are contained in  $[\text{Co}_4(\mu\text{-dppm})_2(\mu\text{-CO})_3(\text{CO})_5]$ ,  $[\text{Co}_4(\mu\text{-CO})_3(\text{CO})_6(\eta^6\text{-C}_6\text{H}_6)]$  <2001AJC277>,  $[\text{Co}_4(\mu_3\text{-AsPh})_2(\mu_4\text{-}\eta^2, \eta^2, \eta^1\text{-As}_4\text{Ph}_4)(\mu\text{-CO})_2(\text{CO})_8]$ , and the product of its thermolysis,  $[\text{Co}_4(\mu_3\text{-AsPh})_2(\mu_4\text{-}\eta^2, \eta^1\text{-As}_2\text{Ph}_2)(\mu\text{-CO})(\text{CO})_9]$  <2001JOM(625)245, 2003CCR(241)273>. Clusters  $[(\eta^5\text{-Cp})\text{Co}_3(\mu_3\text{-S})(\mu_3\text{-CS})]$  on reaction with RI or ROTf ( $\text{R} = \text{Me}, \text{Et}$ ) are converted into the cationic species  $[(\eta^5\text{-Cp})\text{Co}_3(\mu_3\text{-S})(\mu_3\text{CSR})]^+$  <2003ICA(354)54>. Dibenzothiophene with  $[\text{Co}_4(\text{CO})_{12}]$  or  $[\text{Co}_2(\text{CO})_8]$  forms cluster **168** <1999OM5721>. The product reacts with  $[\text{Cr}(\text{CO})_3(\text{AN})_3]$  to yield the  $\eta^6$ -benzene complex **169**. Species **169** also results from the reaction of benzothiophene with  $[\text{Co}_4(\text{CO})_{12}]$ . In  $[\text{Rh}_4(\text{CO})_{12}]$ , the carbonyl groups are fluxional, and mutual exchange of the terminal and bridging carbonyls is not accompanied by energy changes for the complexes in solution <1996ICA(252)311, 2003OM3448>. Clusters  $[\text{MoIr}_3(\mu\text{-CO})_3(\text{CO})_8(\eta^5\text{-Cp})]$  enter the ligand substitution reaction with isocyanides to yield  $[\text{MoIr}_3(\mu\text{-CO})_3(\text{CO})_{8-n}\text{L}_n(\eta^5\text{-Cp})]$  ( $\text{L} = \text{CNBu}^t$ ,  $\text{CNC}_6\text{H}_3\text{Me}_2\text{-2,6}$ ;  $n = 1\text{--}3$ ) <2003JOM(678)72>.  $[\text{Mo}_2\text{Ir}_2(\mu\text{-CO})_3(\text{CO})_7(\eta^5\text{-Cp})_2]$  reacts with *t*-butyl isocyanide to give a single product of composition  $[\text{Mo}_2\text{Ir}_2(\mu\text{-CO})_2(\text{CO})_6(\text{CNBu}^t)_2(\eta^5\text{-Cp})_2]$ . Species with the  $\text{Rh}_2(\mu\text{-CH}_2)_2$  units deserve mentioning <1998JOM(554)155>. Anionic carbide cluster  $[\text{Co}_{13}\text{C}_2(\text{CO})_{24}]^-$  is known <2003ICA(350)187>.



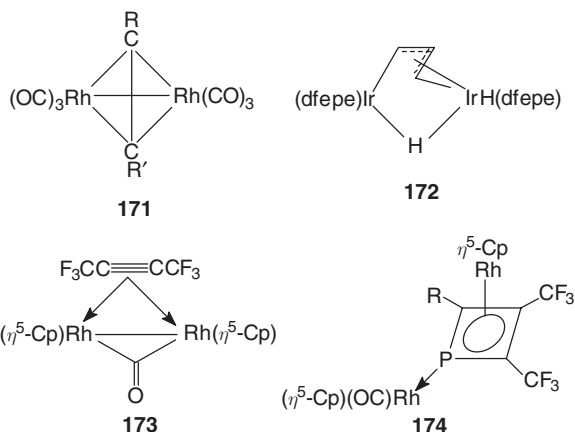
The carbene complexes of rhodium(I),  $\text{trans-}[\text{RhCl}(\text{=CR}_2)(\text{Sb}(\text{Pr}^i)_3)_2]$  on thermolysis give the dinuclear species **170** ( $\text{X} = \text{X}' = \text{Cl}$ ) <2000CEJ4471>. The bridging  $\text{Sb}(\text{Pr}^i)_3$  ligand can be replaced by carbon monoxide or *t*-butyl isocyanide. The chloride ligands can be substituted by acetylacetonate moieties <1999AG(E)1609, 2002CEJ309> to yield **170** ( $\text{X} = \text{X}' = \kappa^2\text{-acac}$ ). With various acetylacetonates, the products of incomplete (**170**,  $\text{X} = \text{Cl}$ ,  $\text{X}' = \kappa^2\text{-acac}$ ) and complete substitution follow. With sodium bromide or iodide, the products are **170** ( $\text{X} = \text{X}' = \text{Br}, \text{I}$ ) <2003JCS(D)1495>. Mixed acetylacetonato-carboxylato species of the type **170** are other illustrations.



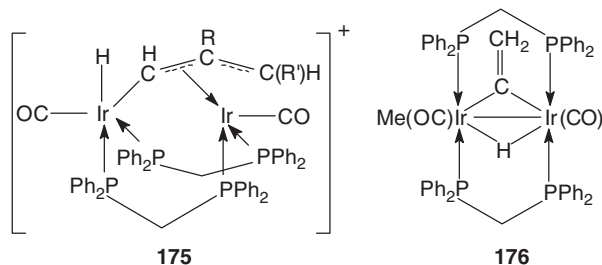
Dinuclear complex  $[(\kappa^2\text{-acac})_2\text{Rh}_2(\mu\text{-CPh}_2)_2(\mu\text{-PPh}_3)]$  is also known <2000AG(E)3909>. The dirhodium species  $[(\text{acac})\text{Rh}(\mu\text{-PMe}_3)(\mu\text{-CPh}_2)_2\text{Rh}(\text{acac})]$  and  $[\text{ClRh}(\mu\text{-PMe}_3)(\mu\text{-CPh}_2)_2\text{RhCl}]$  contain not only the  $\text{CPh}_2$  bridge but trimethylphosphine ligand, which is a rarity <2000AG(E)3909, 2002AG(E)2301>.  $[\text{Rh}_6(\text{CO})_{14}(\mu, \kappa^3\text{-Ph}_2\text{P}(\text{CH}=\text{CH}_2)]$  contains the framework where two adjacent rhodium atoms are bonded to the double bond of the vinyl group <2003JCS(D)2468>.



Interaction of  $[\text{Rh}_4(\text{CO})_{12}]$  with alkynes in an atmosphere of carbon monoxide or carbon monoxide/hydrogen leads to two types of complexes, one of which, **171**, contains the  $\text{CRh}_2$  functional groups <1999OM417, 1999OM1542, 1999OM3457>. Ethylene reacts with  $[(\text{dfepe})_2\text{Ir}_2(\mu\text{-H})_3(\text{H})]$  to give the  $\mu\text{-}\eta^1\text{:}\eta^3$ -coordinated dinuclear complex **172** <1999OM5717>. Several rhodium complexes contain metal- $\eta^2$ -acetylide interactions <1996OM506, 1998OM2553>. Phosphaalkynes  $\text{P}\equiv\text{CR}$  ( $\text{R} = \text{Bu}^t, \text{Ad}$ ) with the rhodium dimer **173** give the triple-decker products **174** ( $\text{R} = \text{Bu}^t, \text{Ad}$ ) <1999OM4838>.

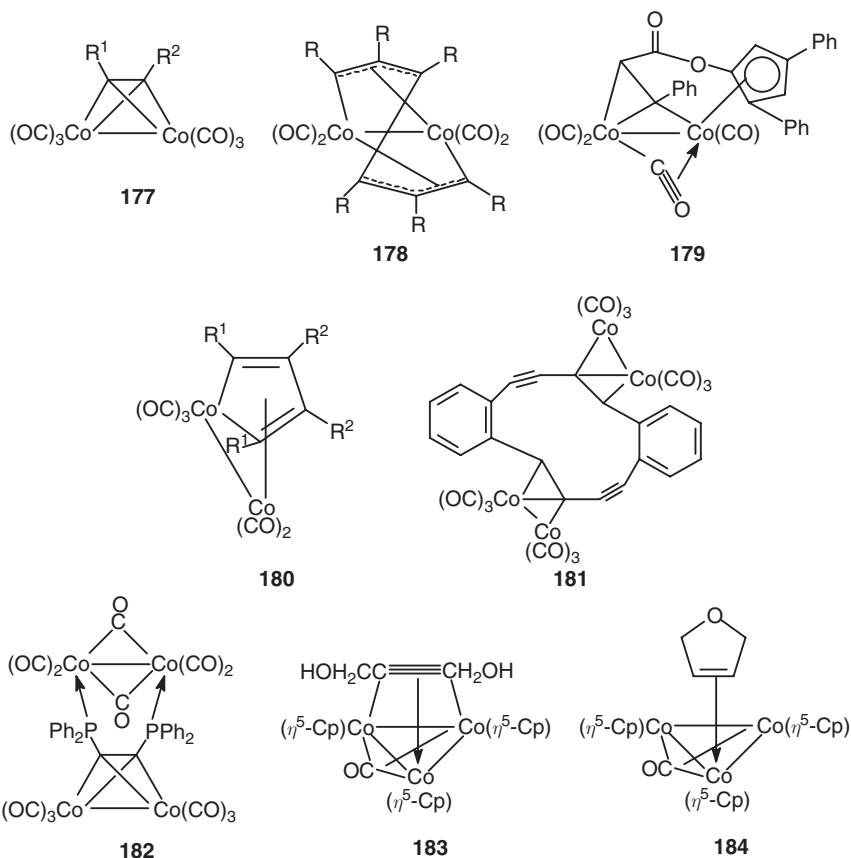


The iridium dimer  $[\text{Ir}_2\text{Me}(\text{CO})(\mu\text{-CO})(\text{dppm})_2](\text{OTf})$  reacts with  $\text{CO}$ ,  $\text{SO}_2$ ,  $\text{PR}_3$ ,  $\text{CNR}$  ( $\text{L}$ ) to rearrange its bridging moiety to  $[\text{Ir}_2\text{H}(\text{L})(\text{CO})_2(\mu\text{-CH}_2)(\text{dppm})_2](\text{OTf})$  <1998OM2553, 1999JA2613, 1999JA3666>. With alkynes, the bridging methylene normally forms vinylcarbenes <1996CJC2289, 1996OM506, 1996OM1042, 1997OM2297>. The cationic species  $[\text{MeIr}(\mu\text{-dppm})_2(\mu\text{-CO})\text{Ir}(\text{CO})]$  with acetylenes  $\text{R}^1\text{C}\equiv\text{CR}^2$  ( $\text{R}^1 = \text{R}^2 = \text{Me}, \text{Et}, \text{Pr}^n$ ;  $\text{R}^1 = \text{Me}, \text{R}^2 = \text{Et}$ ;  $\text{R}^1 = \text{Me}, \text{R}^2 = \text{Ph}$ ) finally form cluster structures **175** <1999OM1629, 1999OM2177, 1999OM4134>. The same starting complex with acetylene gives **176** <1997ICA(259)213, 1998JA4047, 1999OM4134>, and similar complexes are found in organoruthenium and -osmium chemistry <1996OM272, 1998JA4047>.

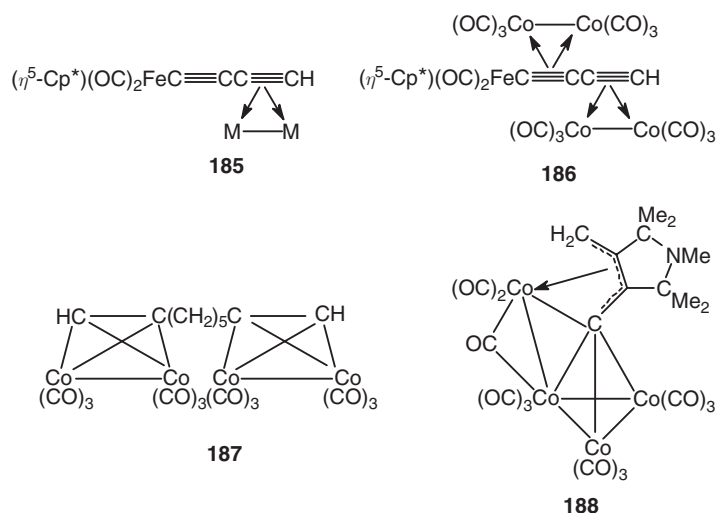


Electrochemical oxidation of  $[(\eta^5\text{-Cp})_3\text{Co}_3(\mu_3\text{-CPh})_2]$  gives the cationic cluster  $[(\eta^5\text{-Cp})_3\text{Co}_3(\mu_3\text{-CPh})_2]^+$  <2003POL3413, 2004ICA(357)533, 2004JOM(689)146>. With halogens, the starting cluster gives the adducts  $[(\eta^5\text{-Cp})_3\text{Co}_3(\mu_3\text{-CPh})_2(\mu\text{-Cl})](\text{PF}_6)\cdot\text{AN}$ ,  $[(\eta^5\text{-Cp})_3\text{Co}_3(\mu_3\text{-CPh})_2(\mu\text{-Br})](\text{SbF}_6)$ ,  $[(\eta^5\text{-Cp})_3\text{Co}_3(\mu_3\text{-CPh})_2(\mu\text{-I})](\text{SbF}_6)\cdot\text{CH}_2\text{Cl}_2$ , and  $[(\eta^5\text{-Cp})_3\text{Co}_3(\mu_3\text{-CPh})_2(\mu\text{-I})](\text{I}_3)$  <2004ICA(357)1236>.

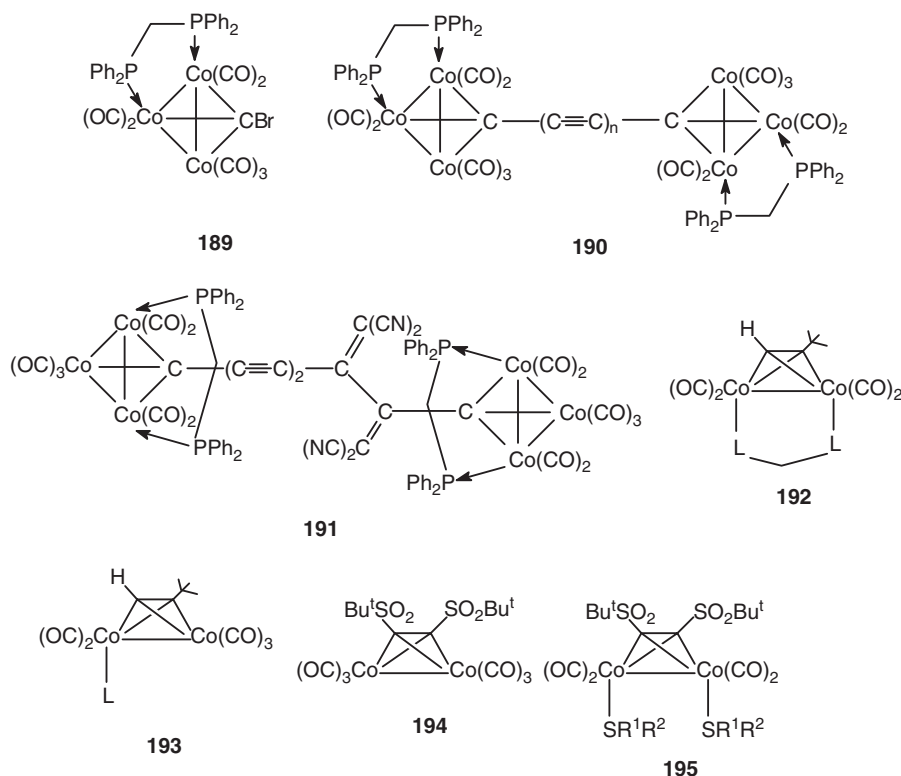
$[\text{Co}_3(\mu_3\text{-CR})(\mu\text{-(AsMe}_2)_2\text{O})(\text{CO})_3]$  ( $\text{R} = \text{Cl, Me}$ ) and  $[\text{Co}_2(\mu\text{-C}_2(\text{COOMe})_2)(\mu\text{-(AsMe}_2)_2\text{O})(\text{CO})_4]$  <2000JCS(D)395> react with hydrogen sulfide to yield the bisdimethylarsine sulfide bridges <2003JOM(681)102>. Alkynes with  $[\text{Co}_2(\text{CO})_8]$  typically form species **177**. Excess amounts of alkynes give **178** <1999OM206>. Complex **177** ( $\text{R}^1 = \text{Ph}$ ,  $\text{R}^2 = \text{H}$ ) with excess ethynylbenzene in the presence of trimethylamine *N*-oxide forms **179** <1999OM215> and **180** <1999OM197>. The cyclic tetrayne,  $\text{C}_{20}\text{H}_8$ , with  $[\text{Co}_2(\text{CO})_8]$  gives the double addition product **181** <1999JOM(578)91>. The structure of the cluster containing the propargyl moiety,  $[(\text{Bu}^t\text{C}\equiv\text{C})_3\text{C}(\text{Co}_2(\text{CO})_6)_2]^+$ , was determined <1998AG(E)161>. Bis(diphenylphosphino)acetylene with  $\text{Co}_2(\text{CO})_8$  gives **177** ( $\text{R}^1 = \text{R}^2 = \text{PPh}_2$ ) and in excess  $[\text{Co}_2(\text{CO})_8]$  species **182** is formed <1999ICC450>. The product of cluster formation of alkynediol **183** dehydrates by the cyclization pathway to yield **184** <1997OM2152>. Other routes of dehydration are possible <1999OM4552>. When bromoalkynes take part in the cluster formation, they couple to form coordinated diynes <2001JOM(634)74>. The other route for the transformation of coordinated alkynols, alkene-alkynes, and diynes is cyclization leading to the facile synthesis of metallacyclopentadiyne cobalt complexes <1999JCS(CC)2503, 2000AG(E)2732, 2001JOM(635)119>.

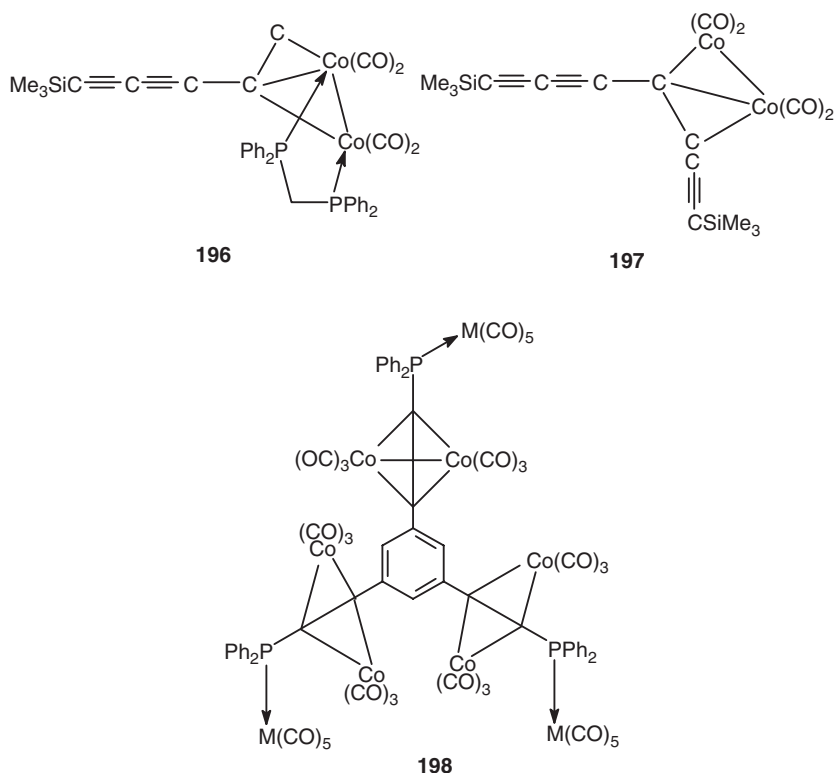


$[(\eta^5\text{-Cp}^*)(\text{OC})_2\text{FeC}\equiv\text{CC}\equiv\text{CH}]$  reacts with  $[\text{Co}_2(\text{CO})_8]$  and  $[(\eta^5\text{-Cp})\text{Mo}(\text{CO})_2]$  to yield **185** ( $\text{M} = \text{Co}(\text{CO})_3$ ,  $\text{Mo}(\text{CO})(\eta^5\text{-Cp})$ ) <1997JCS(CC)1557, 1999JCS(CC)101, 2003JOM(670)2>. Excess  $[\text{Co}_2(\text{CO})_6]$  leads to a 1:2 adduct **186**.  $[(\eta^5\text{-Cp}^*)(\text{OC})_2\text{FeC}\equiv\text{CC}\equiv\text{CFe}(\text{CO})_2(\eta^5\text{-Cp}^*)]$  with  $[\text{Co}_2(\text{CO})_8]$  gives **187** <1999OM4684>. 1,8-Nonadiyne reacts with  $[\text{Co}_2(\text{CO})_8]$  to yield cluster **187** <1999OM3164>.  $[\text{Co}_4(\text{CO})_{12}]$  and the corresponding diyne give cluster **188** <2002JOM(656)57>. Related examples can be found elsewhere <1996ICA(243)109, 1999JOM(578)155>.

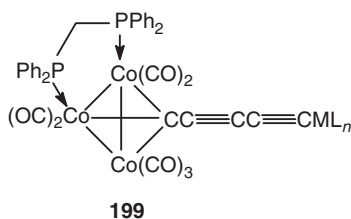


The  $\mu_3$ -bromocarbyne species **189**, on reaction with  $[\text{Au}(\text{P}(p\text{-Tol})_3)_2](\mu\text{-C}\equiv\text{C})_n$  ( $n = 2-4$ ) catalyzed by  $\text{Pd}(\text{PPh}_3)_4/\text{CuI}$ , gives the cluster-capped chain structures **190** ( $n = 2-4$ ) <2003JOM(670)170>. One of the products, **190** ( $n = 3$ ), with TCNE yields the adduct **191**.  $[(3,3'\text{-Dimethylbutyne})\text{Co}_2(\text{CO})_6]$  reacts with chelating diphosphine ligands (dppm, dppe) to yield clusters **192** ( $\text{L}_2 = \text{dppm}, \text{dppe}$ ). With monodentate ligands, clusters **193** ( $\text{L} = \text{CO}, \text{PPh}_3$ ) result <1999OM3859>. Bis(*t*-butylsulfonyl)-ethyne with  $[\text{Co}_2(\text{CO})_8]$  gives cluster **194** <1999OM4275>. The product reacts with various sulfides and produces **195** ( $\text{R}^1 = p\text{-Tol}, \text{R}^2 = \text{Me}; \text{R}^1 = \text{R}^2 = \text{PhCH}_2, \text{Et}, \text{THT}$  (tetrahydrothiophine)).  $\text{Me}_3\text{Si}(\text{C}\equiv\text{C})_3\text{SiMe}_3$  with  $[\text{Co}_2(\text{CO})_6(\text{dppm})]$  in benzene gives cluster products **196** and **197** <1999OM3885>. These species further react with  $[(\eta^5\text{-Cp})\text{RuCl}(\text{PPh}_3)_2]$  to give the products of substitution of the trimethylsilyl groups by the  $(\eta^5\text{-Cp})\text{RuCl}(\text{PPh}_3)_2$  moiety.  $1,3,5\text{-(OC)}_3\text{M-P}(\text{PPh}_2)(\text{C}\equiv\text{C})_3\text{C}_6\text{H}_3$  ( $\text{M} = \text{Mo}, \text{W}$ ) react with  $[\text{Co}_2(\text{CO})_8]$  to yield **198** ( $\text{M} = \text{Mo}, \text{W}$ ) <1999OM2565>. The same type of reaction was applied to  $[\text{H}\{\text{C}\equiv\text{C-}p\text{-C}_6\text{H}_4\}_n]_4$  ( $n = 1, 2, 3$ ) <1998C533, 1998JCS(CC)2661>.

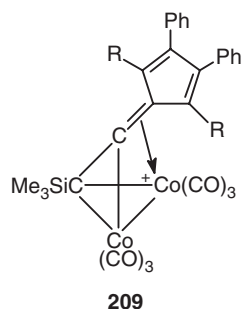
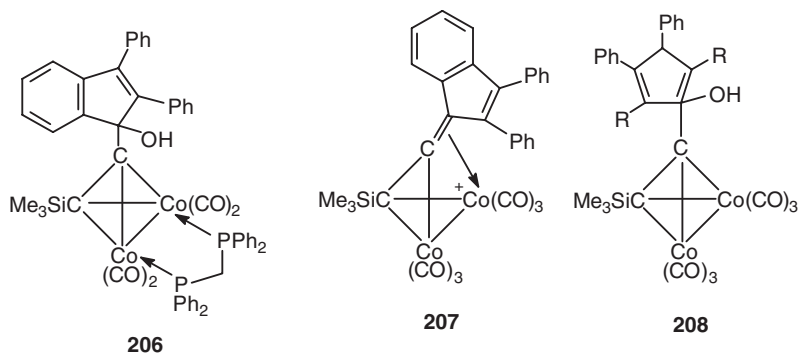
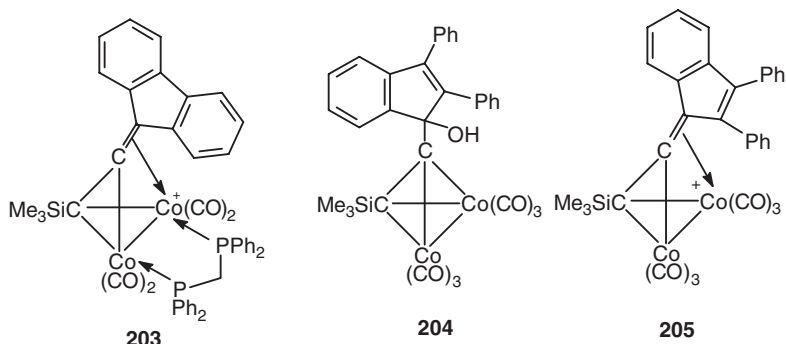
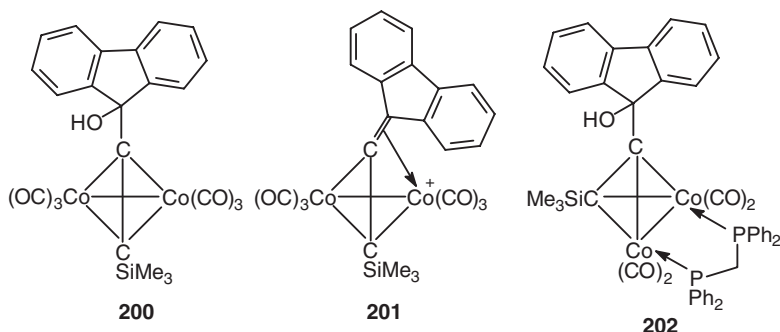




The reactivity studies of the complexes containing the  $\text{Co}_3$  framework were extended to alkynes capped by other transition metal moieties. Thus, **189** when reacted with  $[(\eta^5\text{-Cp})(\text{OC})_3\text{W}]\text{C}\equiv\text{CC}\equiv\text{CAuPPh}_3$  gives **199** ( $\text{ML}_n = \text{W}(\text{CO})_3(\eta^5\text{-Cp})$ ) [<2003JOM\(683\)398>](#). Interaction with  $[\text{Me}_3\text{Si}\equiv\text{CC}\equiv\text{CAuP}(p\text{-Tol})_3]$  gives **199** ( $\text{ML}_n = \text{SiMe}_3$ ), and subsequent reaction with sodium methoxide and then  $[\text{AuClP}(p\text{-Tol})_3]$  affords **199** ( $\text{ML}_n = \text{AuP}(p\text{-Tol})_3$ ).

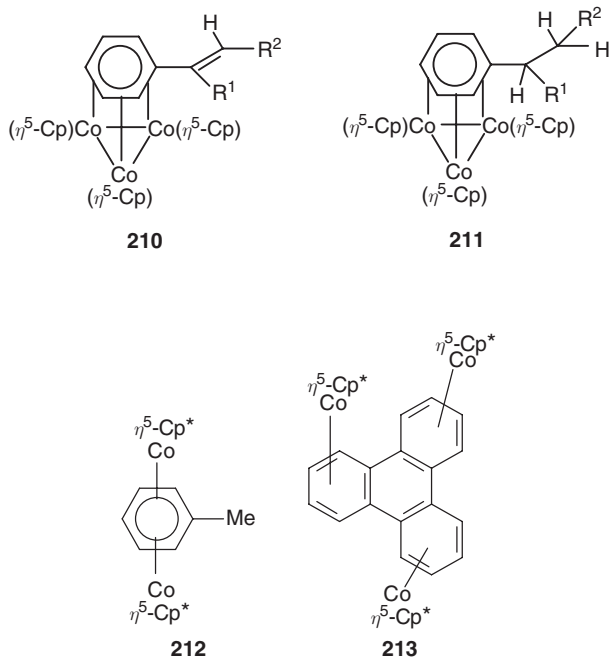


Organometallic clusters containing cyclopentadienyl, indenyl, and fluorenyl ions allow additional insight on the behavior of the short-lived ligands [<1996CRV1077, 1997OM2160>](#). 9-((Trimethylsilyl)ethynyl)-9-fluorenyl with  $[\text{Co}_2(\text{CO})_8]$  forms cluster **200** [<1999OM3372>](#). Protonation of the latter using  $\text{HBF}_4$  gives the cationic species **201**, and interaction of **200** with diphenylphosphinomethane gives the complex **202**. The product of protonation of the latter by  $\text{HBF}_4$  is **203**. The 1-(trimethylsilyl)-2,3-diphenylindenol cluster **204** prepared in a similar manner can be protonated to give the indenyl cationic complex **205**. Further combination with diphenylphosphinomethane/ $\text{HBF}_4$  gives **206** and **207**. Tetraphenylcyclopentadienone and 2,5-diethyl-3,4-diphenylcyclopentadienone give rise to clusters **208** ( $\text{R} = \text{Ph}, \text{Et}$ ) and **209** ( $\text{R} = \text{Ph}, \text{Et}$ ), respectively.

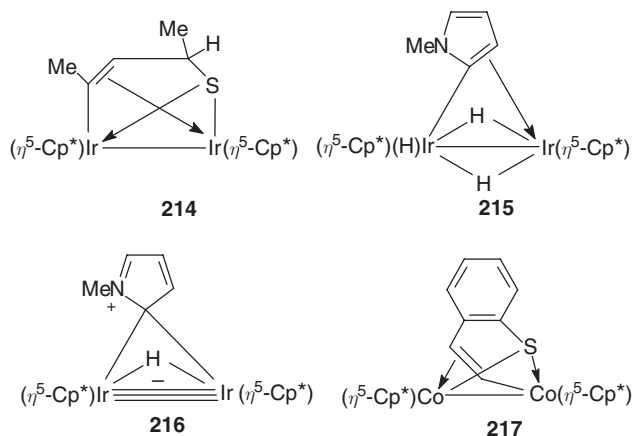


Cluster complexes **210** ( $R^1 = H$ ,  $R^2 = Me$ ;  $R^1 = Me$ ,  $R^2 = H$ ;  $R^1 = H$ ,  $R^2 = Ph$ ;  $R^1 = Ph$ ,  $R^2 = H$ ) follow from  $[(\eta^5\text{-Cp})\text{Co}(\text{C}_2\text{H}_4)_2]$  and a variety of 1-alkenylbenzenes <1996JOM(516)187, 1996OM5622>. The products when treated with molecular hydrogen in the presence of palladium/charcoal catalyst give species **211** with the same set of  $R^1$  and  $R^2$  <1999JOM(573)22>. The triple-decker complex of cobalt, **212**, possesses an interesting reactivity pattern with respect to the polycyclic hydrocarbons <1998CEJ1982, 1999JOM(579)139>. For example, the product of reaction of **212** with triphenylene is **213** where the threefold

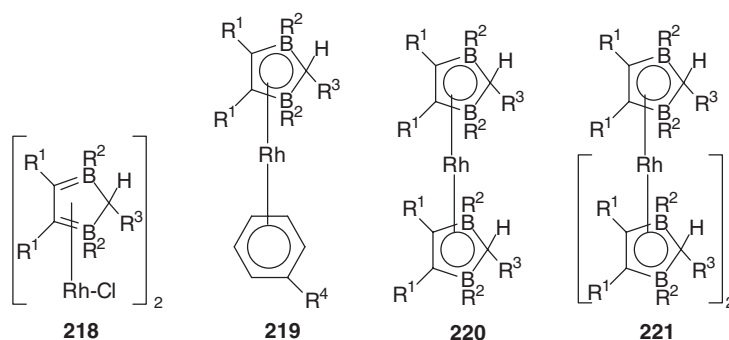
$\eta^4$ -coordination mode of three cobalt sites is realized [<2003ICA\(350\)625>](#). The structure of this product and some other related complexes was described in detail [<1998AG\(E\)155, 2000CEJ3686, 2002AG\(E\)1211>](#).



2-Methylthiophene with  $[(\eta^5\text{-Cp}^*)\text{IrH}_2(\mu\text{-H})_2\text{IrH}_2(\eta^5\text{-Cp}^*)]$  in the presence of *t*-butylethylene produces cluster **214** [<1999OM134>](#). Pyrrole in these conditions gives **215**, along with trace amounts of **216**. Some other examples are interesting with regard to the problem of desulfurization, e.g., the benzothiophene-derivatized cluster **217** [<1997POL3115>](#) and other clusters [<1999OM1786>](#).

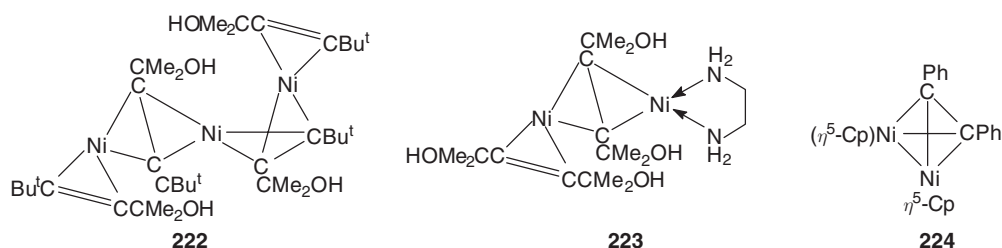


2,3-Dihydro-1,3-diborole derivatives react with  $[(\text{C}_2\text{H}_4)_2\text{RhCl}]_2$  to yield dimers **218** ( $\text{R}^1 = \text{R}^2 = \text{Me}$ ,  $\text{R}^3 = \text{MesCH}_2$ ;  $\text{R}^1 = \text{Et}$ ,  $\text{R}^2 = \text{R}^3 = \text{Me}$ ;  $\text{R}^1 = \text{Me}$ ,  $\text{R}^2 = \text{Bu}^t$ ,  $\text{R}^3 = \text{Me}$ ) [<1998JOM\(571\)107, 2001JOM\(619\)7>](#). Pure 1,3-diborolyl sandwich **220** ( $\text{R}^1 = \text{Me}$ ,  $\text{R}^2 = \text{Bu}^t$ ,  $\text{R}^3 = \text{Me}$ ) can be prepared from **219** ( $\text{R}^1 = \text{Me}$ ,  $\text{R}^2 = \text{Bu}^t$ ,  $\text{R}^3 = \text{R}^4 = \text{Me}$ ), methyllithium, and the 1,3-diborole ligand [<2001JOM\(619\)7>](#). The by-product of this reaction is the triple-decker species **221** ( $\text{R}^1 = \text{Me}$ ,  $\text{R}^2 = \text{Bu}^t$ ,  $\text{R}^3 = \text{Me}$ ).

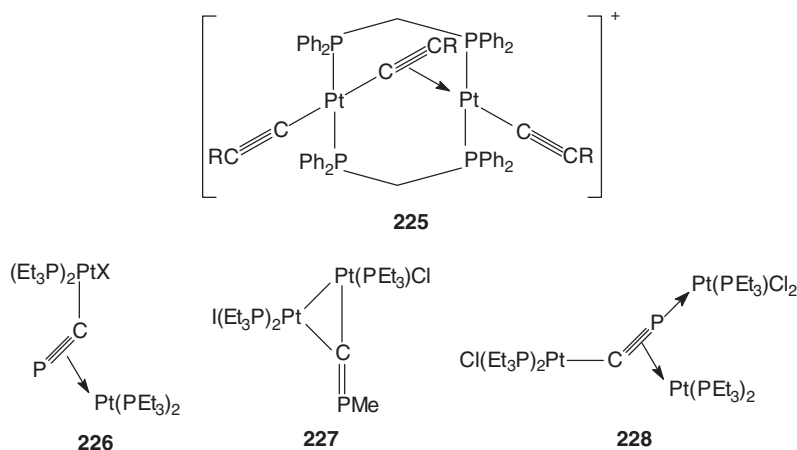


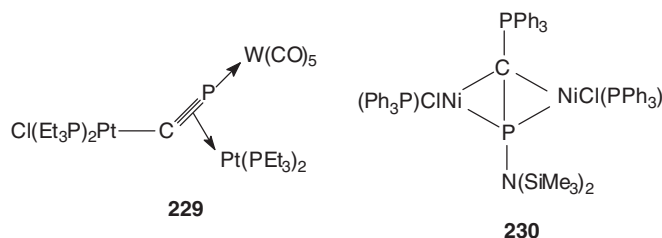
#### 4.15.3.9 Functions Containing Two Ni, Pd, or Pt Atoms

Cationic species  $\text{Pt}_2^+$  with methane experiences dehydrogenation to give the carbene cluster  $\text{Pt}_2\text{CH}_2^+$  <2000CPL53>. The product forms a 1:1 adduct with ammonia,  $\text{Pt}_2\text{C}^+\cdot\text{NH}_3$  <2003JA3676>. The nickel(0) complex  $[\text{Ni}(\text{Bu}^t\text{C}\equiv\text{CCMe}_2\text{OH})_2]$  can be trimerized to yield the product **222** followed by the evolution of two alkyne molecules. A related example is the dinuclear species **223** <1996OM2314, 1999OM4942>. Nickelocene reacts with methyllithium and diphenylacetylene to yield, in particular, species **224** <1996JOM(519)69, 1998JOM(566)217, 2000JOM(593)245, 2000JOM(613)37>. Nickelocene with methyl- or phenyllithium and bis(trimethylsilyl)acetylene gives  $[(\eta^5\text{-Cp})\text{Ni}(\mu\text{-}\eta^2\text{:}\eta^2\text{-Me}_3\text{SiC}\equiv\text{CSiMe}_3)\text{Ni}(\eta^5\text{-Cp})]$ ,  $[(\eta^5\text{-Cp})\text{Ni}(\mu\text{-}\eta^2\text{:}\eta^2\text{-PhC}\equiv\text{CSiMe}_3)\text{Ni}(\eta^5\text{-Cp})]$ , and  $[(\eta^5\text{-Cp})\text{Ni}]_4(\mu, \mu\text{-}\eta^2\text{:}\eta^2\text{:}\eta^2\text{-Me}_3\text{SiC}\equiv\text{CC}\equiv\text{CSiMe}_3)\text{Ni}(\eta^5\text{-Cp})]$  <2003ICA(350)520>.

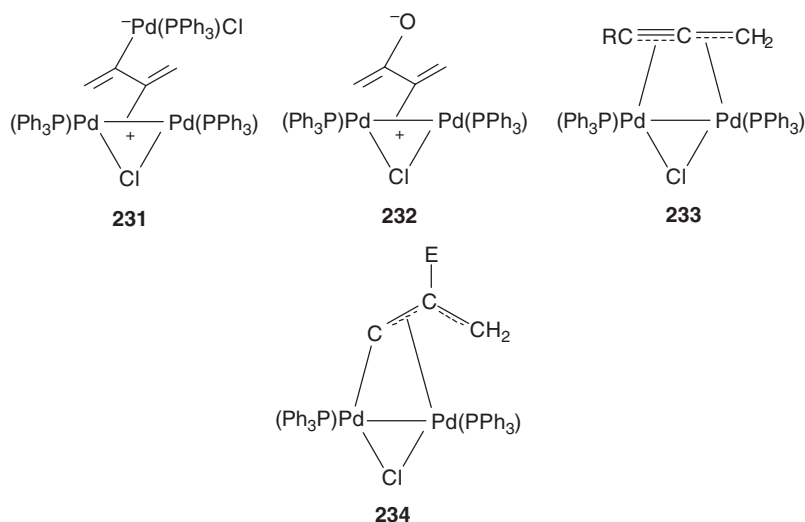


Dinuclear platinum(II) acetylides of the A-frame type, **225** ( $\text{R} = \text{Ph}, \text{C}_6\text{H}_4\text{Et-4}, \text{C}_6\text{H}_4\text{Ph-4}, \text{C}_6\text{H}_4\text{OMe-4}, \text{C}_6\text{H}_4\text{OEt-4}$ ) are luminescent materials <1998OM2590>. Reaction of  $[\text{XPt}(\text{PEt}_3)_2\text{C}(\text{X}) = \text{PMe}]$  ( $\text{X} = \text{Cl}, \text{Br}$ ) with  $[\text{Pt}(\text{PEt}_3)_4]$  gives the dinuclear complexes **226** ( $\text{X} = \text{Cl}, \text{Br}, \text{I}$ ) <1999OM258, 2003EJI1843>. The product with  $\text{X} = \text{Cl}$  with methyl iodide yields species **227**, with  $[\text{PtCl}_2(\text{PEt}_3)_2]$  to provide **228**, and with  $[\text{W}(\text{CO})_5(\text{THF})]$  to afford **229**.  $[\text{Cl}(\text{Ph}_3\text{P})\text{Ni}\{\text{P}(\text{N}(\text{SiMe}_3)_2)\text{C}(\text{PPh}_3)\}]$  reacts with  $[(\text{Ph}_3\text{P})_2\text{Ni}(\text{C}_2\text{H}_4)]$  to yield **230** <1998OM1569>.





Complex **231** is stable in its zwitterionic arrangement [<1997JOM\(530\)187>](#). The product of interaction of  $[\text{Pd}(\text{PPh}_3)_2\text{Cl}](\text{PF}_6)_2$  with  $[\text{Pd}_2(\text{DBA})_3]$  and 2-trimethylsiloxy-1,3-butadiene in the presence of triethylamine, or of ligand exchange of  $[(\text{Ph}_3\text{P})\text{Pd}(\mu\text{-1,3-butadiene})(\mu\text{-Cl})\text{Pd}(\text{PPh}_3)](\text{PF}_6)$  [<1996JCS\(CC\)825>](#) with 2-trimethylsiloxy-1,3-butadiene formulated as **232**, is also stable in its zwitterionic form [<1999JOM\(574\)142>](#). Reaction of *trans*- $[\text{Pd}(\text{PPh}_3)_2\text{Cl}(\eta^1\text{-C}(\text{R})=\text{C}=\text{CH}_2)]$  or *trans*- $[\text{Pd}(\text{PPh}_3)_2\text{Cl}(\eta^1\text{-CH}_2\text{C}\equiv\text{CR})]$  ( $\text{R} = \text{H}, \text{Bu}^t, \text{Ph}, \text{SiMe}_3$ ) with  $[\text{Pt}_2(\text{DBA})_3]$  gives the binuclear species **233** [<2001JA3223>](#). In the case of  $\text{R} = \text{Ph}$ , the bridging iodide and phenylsulfide complexes were prepared. The complex with  $\text{R} = \text{Ph}$  adds electrophilic agents  $\text{ECl}$  to yield **234** ( $\text{E} = \text{H}, \text{MeCO}$ ).

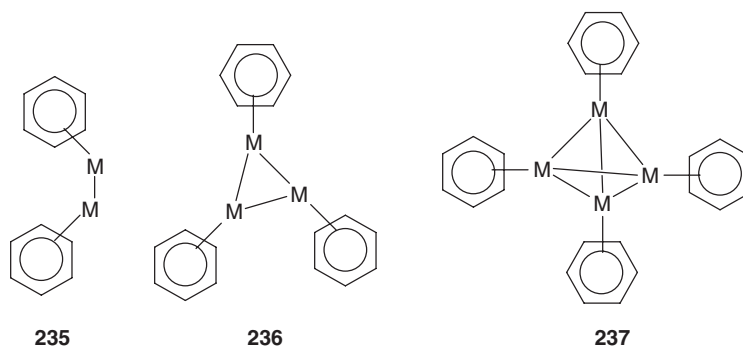


The complexes  $\mu\text{-}\eta^5\text{:}\eta^5\text{-(2-benzyl-1,3,4,5-tetramethyl-2,3-dihydro-1,3-diborolyl)(\eta^3\text{-allyl})(\eta^4\text{-1,5-hexadiene)dinickel}$  and  $\mu\text{-}\eta^5\text{:}\eta^5\text{-[2-(2,4,6-trimethylbenzyl)-1,3,4,5-tetramethyl-2,3-dihydro-1,3-diborolyl](\eta^3\text{-allyl})(\eta^4\text{-1,5-hexadiene)dinickel}$  may serve as the representative triple-decker complexes [<2001ZN\(B\)73>](#).

#### 4.15.3.10 Multidecker Sandwich Complexes of Transition Metals

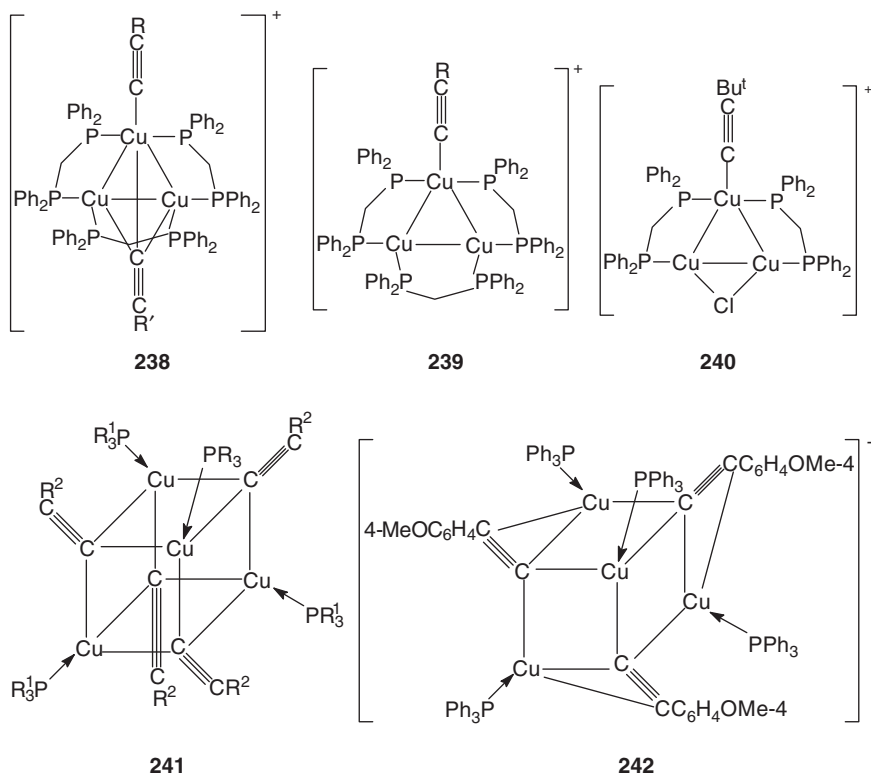
Using a combination of the laser-vaporization and flow tube reactor techniques, the whole range of benzene sandwiches and multideckers was synthesized for all of the first row transition metals [<1999OM1430>](#). For scandium, titanium, and vanadium [<1997JPC\(A\)8207, 1999OM1430>](#), ordinary multideckers with parallel benzene rings follow. For iron, cobalt, and nickel [<1997JCP3492, 1999OM1430>](#), the structures are more irregular and may include arrangements [235–237](#).

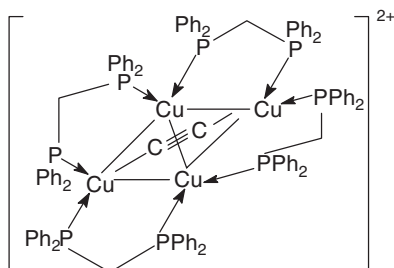




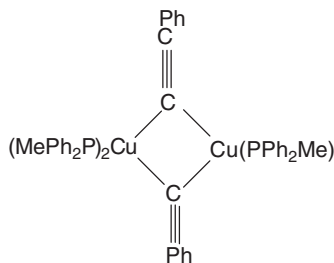
#### 4.15.3.11 Functions Containing Two Cu, Ag, or Au Atoms

Among the trinuclear copper(I) acetylides, there are complexes **238** ( $R^1 = R^2 = \text{Ph}$ ,  $\text{Bu}^t$ ,  $\text{C}_6\text{H}_4\text{NO}_2\text{-4}$ ,  $\text{C}_6\text{H}_4\text{Ph-4}$ ,  $\text{C}_6\text{H}_4\text{OMe-4}$ ,  $\text{C}_6\text{H}_4\text{NH}_2\text{-4}$ ,  $n\text{-C}_6\text{H}_{13}$ ;  $R^1 = \text{C}_6\text{H}_4\text{OMe-4}$ ,  $R^2 = \text{C}_6\text{H}_4\text{OEt-4}$ ;  $R^1 = \text{C}_6\text{H}_4\text{OMe-4}$ ,  $R^2 = \text{C}_6\text{H}_4\text{NO}_2\text{-4}$ ), **239** ( $R = \text{Ph}$ ,  $\text{Bu}^t$ ,  $\text{C}_6\text{H}_4\text{NO}_2\text{-4}$ ,  $\text{C}_6\text{H}_4\text{Ph-4}$ ,  $\text{C}_6\text{H}_4\text{OMe-4}$ ,  $\text{C}_6\text{H}_4\text{NH}_2\text{-4}$ ,  $n\text{-C}_6\text{H}_{13}$ ), **240**, and **241** ( $R^1 = \text{Ph}$ ,  $R^2 = \text{C}_6\text{H}_4\text{Et-4}$ ;  $R^1 = \text{Ph}$ ,  $R^2 = \text{C}_6\text{H}_4\text{OMe-4}$ ;  $R^1 = \text{Ph}$ ,  $R^2 = \text{C}_6\text{H}_4\text{Ph-4}$ ;  $R^1 = \text{Ph}$ ,  $R^2 = \text{C}_6\text{H}_4\text{NO}_2\text{-4}$ ;  $R^1 = R^2 = \text{Ph}$ ;  $R^1 = \text{C}_6\text{H}_4\text{F-4}$ ,  $R^2 = \text{Ph}$ ;  $R^1 = \text{C}_6\text{H}_4\text{Me-4}$ ,  $R^2 = \text{Ph}$ ;  $R^1 = \text{C}_6\text{H}_4\text{OMe-4}$ ,  $R^2 = \text{Ph}$ ), as well as the complexes of the type **238** but containing bridging ligands, bis(diphenylphosphino)alkyl and arylamines <1996JCS(D)2335, 1996JCS(D)3283, 1997JCS(CC)963, 1997OM1772, 1997JPP(A)75, 1998CCR(171)17, 1998OM3293, 1999JOM(578)3>. Analogs of **238** also exist where  $R^1$  and  $R^2$  are replaced by the  $(\text{OC})\text{Re}(\text{bpy})$  moieties <1998JCS(CC)777>. Cluster **242** is the product of interaction of  $[\text{Cu}(\text{AN})_4](\text{PF}_4)$  and  $[\text{Au}(\text{C}\equiv\text{CC}_6\text{H}_4\text{OMe-4})]$  in methylene chloride <1996JCS(CC)2067>. Reaction of trimethylsilylacetylene with  $[\text{Cu}_2(\text{dppm})_2(\text{AN})_2]^{2+}$  in the presence of  $n$ -butyllithium in THF gives the tetranuclear complex **243** <1996AG(E)1100>. The dinuclear species **244** is also of interest in materials chemistry <1996JCS(D)2889>. The alkene-alkyne complexes of copper may contain oxygen donor ligands <2001IC6167>.



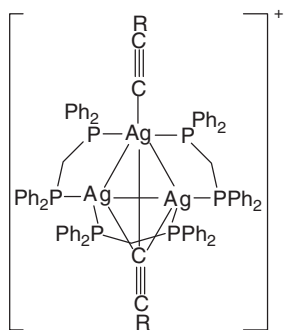


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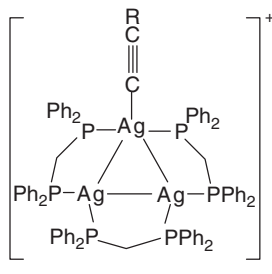


244

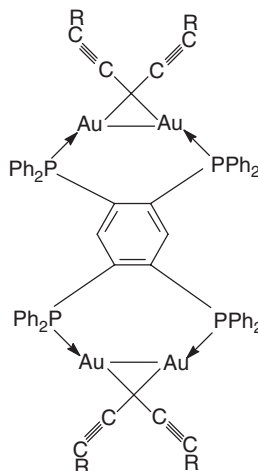
Silver acetylide forms a number of double salts, e.g.,  $\text{Ag}_2\text{C}_2 \cdot m\text{AgX}$  ( $\text{X} = \text{F}, \text{ClO}_4, \text{NO}_3$ , and others) as well as acetylides with six to nine silver atoms [<1998AG\(E\)630, 1998JCS\(CC\)339, 1999JA3136, 2000JA7608, 2001AG\(E\)1130, 2001JA1501, 2001JA7594, 2001JCS\(CC\)807, 2002AG\(E\)4135, 2002JCLS63, 2002JCS\(CC\)2682, 2002NJC513>](#). Some illustrative examples include  $[\text{Ag}_2\text{C}_2] \cdot 6\text{CHF}_2\text{COOAg}$ ,  $[\text{Ag}_2\text{C}_2] \cdot 5\text{CF}_3\text{SO}_3\text{Ag} \cdot 2\text{MeCN} \cdot 2\text{H}_2\text{O}$ , and  $[\text{Ag}_2\text{C}_2] \cdot 8\text{CF}_3\text{SO}_3\text{Ag} \cdot 2\text{EtCN} \cdot 3\text{H}_2\text{O}$  [<2003JOM\(670\)235>](#). Silver(I) acetylides **245** ( $\text{R} = \text{Ph}, \text{C}_6\text{H}_4\text{OMe-4}, \text{C}_6\text{H}_4\text{NO}_2\text{-4}$ ) and **246** ( $\text{R} = \text{Ph}, \text{C}_6\text{H}_4\text{NO}_2\text{-4}$ ) [<1996POL1853>](#) as well as the analog of **245** ( $\text{R} = \text{Ph}$ ) where instead of the diphenylphosphinomethane, the  $(\text{Ph}_2\text{P})\text{NPr}^n$  chelating ligand is used, [<1997OM2032>](#) possess interesting photochemical properties. Oligomeric and polymeric gold(I) acetylides deserve attention [<1996IC2490, 1996JCS\(CC\)181, 1996JCS\(D\)3411, 1996JCS\(D\)3699, 1996JCS\(D\)4227, 1996OM1734, 1997AG\(E\)1179, 1997OM3541, 1998JCS\(CC\)1055>](#). Species **247** ( $\text{R} = n\text{-C}_6\text{H}_{13}, \text{Ph}, \text{C}_6\text{H}_4\text{OMe-4}$ ) serve as an illustration [<1996OM1734>](#).



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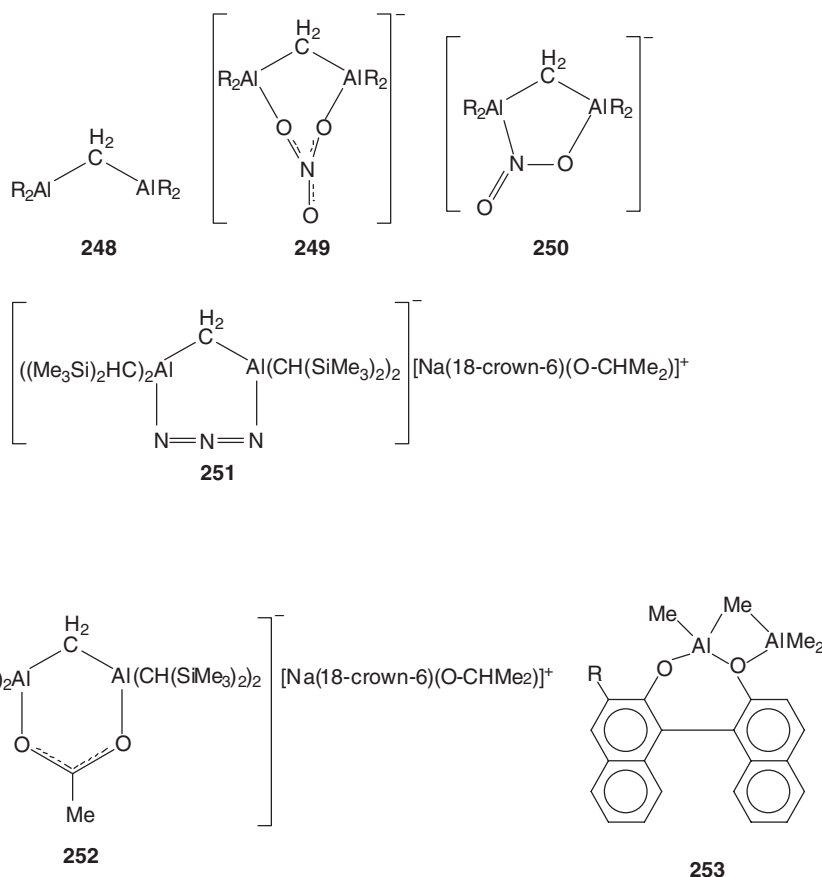
The tetrameric pentafluorophenyl copper,  $[\text{Cu}(\text{C}_6\text{F}_5)]_4$ , can be prepared using the appropriate Grignard reagent and copper(I) chloride in ether [<2003OM3526>](#). On recrystallization from toluene,  $[\text{Cu}(\text{C}_6\text{F}_5)]_4(\eta^2\text{-toluene})_2$  can be prepared. The latter contains one short and one long Cu—Cu diagonal distance.

#### 4.15.3.12 Functions Containing Two Zn, Cd, or Hg Atoms

No substantial new data is available for inclusion since the publication of COFGT (1995).

#### 4.15.4 FUNCTIONS CONTAINING TWO Al, Ga, In, OR TI ATOMS

Tetralkyldialuminum methylene-bridged species **248** are chelating Lewis acids <1998ZAAC937>, for example, with respect to nitrate **249** and nitrite **250** anions <1998EJI921>. Species **248**, when reacted with sodium azide in acetone in the presence of 18-crown-6, gives **251**, and under the same conditions but with sodium acetate yields **252** <1999JOM(579)18>. A similar trend is observed for the methylene-bridged tin compounds <1997OM5716>. The recent structural determination of  $[\text{Al}_2(\text{CD}_3)_6]$  should be noted <2000OM4398>. 3,3'-Bis(triphenylsilyl)-2,2'-dihydroxy-1,1'-binaphthyl with  $\text{Al}_2\text{Me}_6$  gives **253** <2003OM2318>.

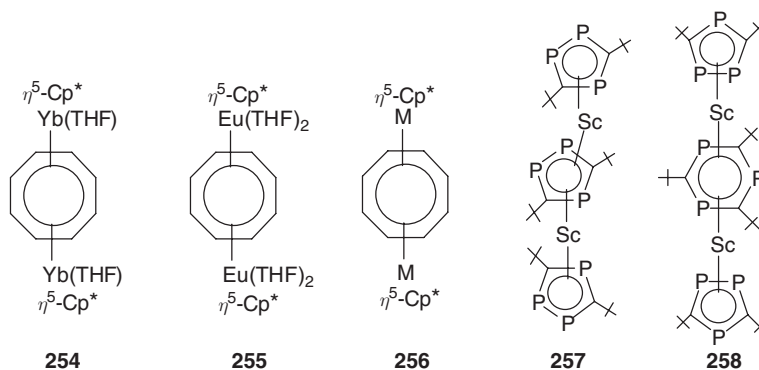


#### 4.15.5 FUNCTIONS CONTAINING TWO Sn OR Pb ATOMS

Anionic complexes  $[(\eta^5\text{-Cp})_5\text{Pb}_2]^-$  and  $[(\eta^5\text{-Cp})_9\text{Pb}_4]^-$  <1998CSR225> as well as  $[(\eta^5\text{-Cp})_2\text{Pb}]_\infty$  <1998IC163> are examples of the nontransition metal polydecker species.

#### 4.15.6 FUNCTIONS CONTAINING TWO LANTHANIDE OR ACTINIDE ATOMS

Multidecker structures for the rare-earth metals include  $[(\eta^5\text{-Cp}^*)\text{Sm}]_2(\mu\text{-}\eta^8, \eta^8\text{-C}_8\text{H}_8)$  <1998JA9555>. A general synthetic scheme for these complexes includes interaction of metal trichloride in THF followed by potassium cyclopentadienide <1999OM1460>. Complexes **254** and **255** were prepared this way. At elevated temperatures and reduced pressures, both **254** and **255** transform into **256** ( $\text{M} = \text{Eu}, \text{Yb}$ ).  $\text{Bu}^t\text{C}\equiv\text{P}$  reacts with scandium atoms to yield the triple-decker species **257** <1997JCS(CC)481>. Metal-vapor synthesis also allowed formation of the mixed ligand triple-decker scandium species **258** <1996JA7630>.



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## 4.16

# Functions Containing Two Atoms of Different Metallic Elements

A. P. SADIMENKO

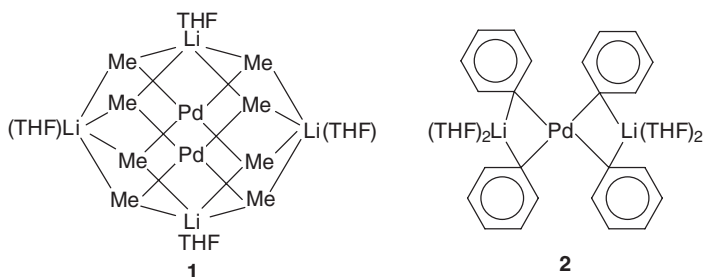
*University of Fort Hare, East London, South Africa*

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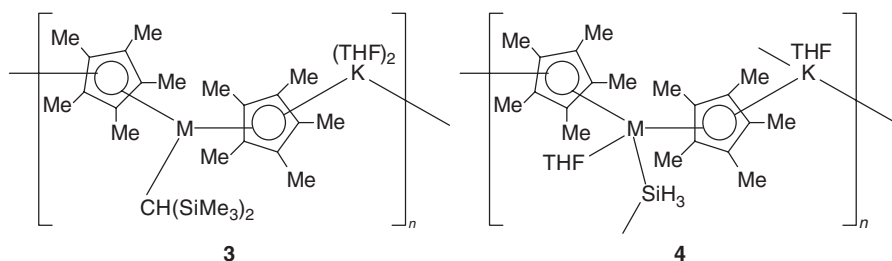
### 4.16.1 FUNCTIONS CONTAINING AT LEAST ONE GROUP 1 METAL

The general principle of synthesis of multidecker anions is to react sandwich complexes of tin or lead with the alkali metal complexes of crown or cryptand ligands [<1999OM1148>](#). Among the products are  $[(\eta^5\text{-Cp})_2\text{Pb}(\mu\text{-}\eta^5, \eta^5\text{-Cp})\text{Na}(15\text{-crown-5})]$ ,  $[(\eta^5\text{-Cp})_2\text{Pb}(\mu\text{-}\eta^5, \eta^5\text{-Cp})\text{Pb}(\mu\text{-}\eta^5, \eta^5\text{-Cp})\text{Cs}(18\text{-crown-6})]$ , and others. Interaction of  $[(\eta^5\text{-Cp})_2\text{Pb}]$  and  $[(\eta^5\text{-Cp}')\text{Na}(\text{THF})]$  ( $\text{Cp}' = 2\text{-tetrahydrofurfurylcyclopentadienyl}$ ) in toluene is a nucleophilic 1:1 stacking addition leading to the triple-decker  $[\{(\eta^5\text{-Cp})_2\text{Pb}(\mu\text{-}\eta^5\text{-Cp}')\text{Na}\} \cdot 0.5\text{THF}]$  [<2000JCS\(D\)2247>](#). The reaction between  $[(\eta^5\text{-Cp})\text{PbCl}]$  and  $[(\eta^5\text{-Cp}')\text{K}(\text{THF})]$  (the meaning of  $\text{Cp}'$  is the same as above) mixed in THF in a ratio of 1:2 proceeds differently and yields  $[\{(\eta^5\text{-Cp})_2\text{Pb}(\mu\text{-}\eta^5\text{-Cp}')\text{K}\} \cdot 2\text{THF}]$  not containing the  $\text{Cp}'$ -group [<2003OM2528>](#). Similar structure but with a differing coordination mode of the cyclopentadienyl ligands is observed for  $[\{(\eta^2\text{-Cp})_2\text{Mn}(\mu\text{-}\eta^2: \eta^5\text{-Cp})\text{K}(\text{THF})\} \cdot 0.5\text{THF}]$  [<2001JCS\(CC\)1956>](#).

The reaction of *N,N'*-bis(2-pyridylethyl)-1,2-bis-2,4,6-trimethylphenylimino)ethane-1,2-diamine or *N,N'*-bis(diphenylphosphino-3-propyl)-1,2-bis(2,4,6-trimethylphenylimino)-ethane-1,2-diamine with *n*-butyllithium and  $[(\eta^4\text{-COD})\text{PdMeCl}]$  followed by methylolithium in THF gives the dimer  $[(\text{THF})_4\text{Li}_4\text{Me}_8\text{Pd}_2]$  with the structure **1** [<2003JOM\(681\)24>](#). Similar cluster compounds are known [<1999ZAAC1904, 2000JPS\(A\)4764, 2001OM4221>](#). Starting with the dinuclear complex  $[(\text{acac})\text{Pd}(\text{oxam})\text{Pd}(\text{acac})]$  in the presence of phenyllithium in THF, complex **2** can be prepared [<2003JOM\(681\)24>](#). Interaction of  $(\text{Et}_8\text{-calix-pyrrole})[\text{Li}(\text{THF})_4]$  with  $[\text{SmCl}_3(\text{THF})_3]$  gives species with the  $\text{Li}(\mu\text{-Me})_2\text{Sm}$  moiety [<2000OM817>](#).



The lanthanide (II) compounds containing the alkali metal cyclopentadienyl moieties are stable [<1997OM2963, 1998M8650, 2000JA10533, 2001OM3323, 2001OM4565, 2002JOM\(647\)61>](#). The reaction of  $[(\eta^5\text{-Cp}^*)_2\text{M}(\text{THF})_2]$  ( $\text{M} = \text{Sm}, \text{Eu}, \text{Yb}$ ) with  $\text{KCH}(\text{SiMe}_3)_2$  gives complexes **3** ( $\text{M} = \text{Sm}, \text{Eu}, \text{Yb}$ ) [<2003OM129>](#), where the lanthanide site is characterized by the oxidation number  $2+$ . Compounds  $[(\eta^5\text{-Cp}^*)_2\text{M}(\text{THF})_2]$  ( $\text{M} = \text{Sm}, \text{Eu}, \text{Yb}$ ) react first with sodium hydride and phenyl silane and then an additional equivalent of phenyl silane to yield complexes **4** ( $\text{M} = \text{Sm}, \text{Eu}, \text{Yb}$ ).



#### 4.16.2 FUNCTIONS CONTAINING AT LEAST ONE GROUP 2 METAL (AND NO GROUP 1 METALS)

No substantial new data are found after the publication of COFGT (1995).

#### 4.16.3 FUNCTIONS CONTAINING AT LEAST ONE TRANSITION METAL (AND NO GROUP 1 OR 2 METALS)

##### 4.16.3.1 Two Different Transition Metals

##### 4.16.3.1.1 Two genuine transition metals (Ti and Pt)

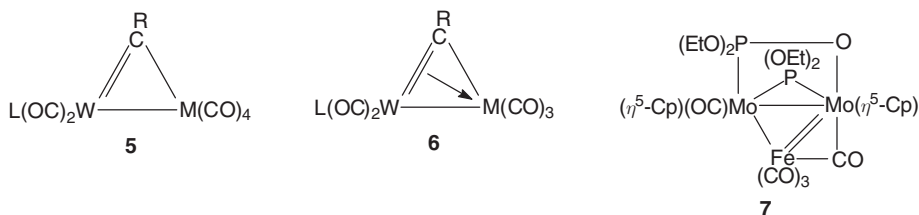
$[(\eta^5\text{-C}_5\text{H}_4\text{SiMe}_3)_2\text{Ti}(\text{C}\equiv\text{CFc})_2]$  with  $[\text{Pd}(\text{PPh}_3)_4]$  ( $\text{Fc} = \text{ferrocenyl}$ ) gives the heterotetranuclear cluster  $[(\eta^5\text{-C}_5\text{H}_4\text{SiMe}_3)_2\text{Ti}(\text{C}\equiv\text{CFc})_2\text{Pd}(\text{PPh}_3)_2]$  [<1999OM4119>](#).

The reaction between  $[(\eta^5\text{-Cp})_2\text{V}]$  and  $[\text{Co}_2(\text{CO})_8]$  gives the heterodinuclear complex  $[(\eta^5\text{-Cp})_2\text{V-Co}(\text{CO})_4]$  [<1999OM2452>](#).

A Mo—W complex containing the diphenylphosphinomethane (DPPM) bridge and the four-electron donor  $\mu\text{-}\eta^1\text{:}\eta^2\text{-CNR}$  ligand is known [<1997OM1378>](#). The other example is  $[(\text{OC})_3(\eta^5\text{-Cp})\text{Mo}(\mu\text{-Cy})\text{W}(\eta^5\text{-Cp})(\text{CO})_3]$  ( $\text{Cy} = \text{cyclohexyl}$ ) [<1999JOM\(578\)155, 2000JOM\(607\)137>](#).

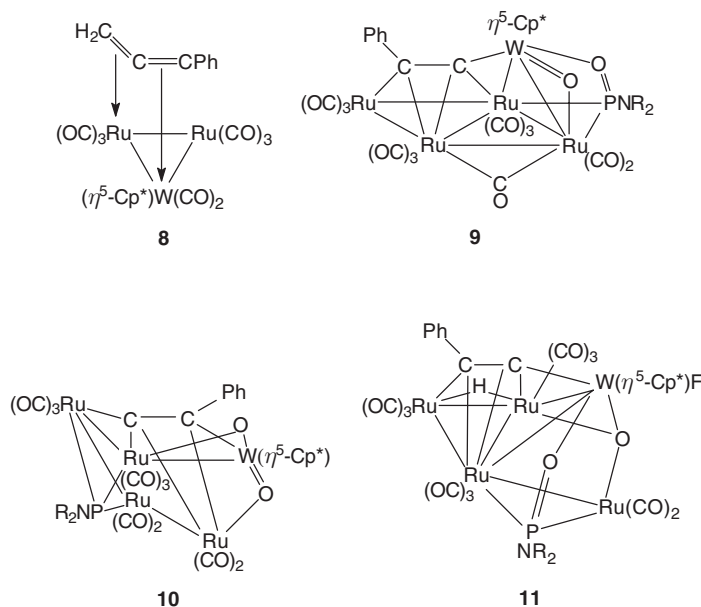
Complex  $[\text{Fe}(\text{CO})_4(\eta^2\text{-C}_2\text{H}_2)]$  reacts with  $[(\eta^5\text{-Cp})(\text{OC})_2\text{W}\equiv\text{CPh}]$  to yield **5** ( $\text{M} = \text{Fe}$ ,  $\text{R} = \text{Ph}$ ,  $\text{L} = \eta^5\text{-Cp}$ ) [<2003JOM\(681\)250>](#). Complex **5** ( $\text{M} = \text{Os}$ ,  $\text{R} = \text{Ph}$ ,  $\text{L} = \eta^5\text{-Cp}$ ) was prepared similarly. On decarbonylation, these compounds readily provide **6** ( $\text{M} = \text{Fe}, \text{Os}$ ;  $\text{R} = \text{Ph}$ ,  $\text{L} = \eta^5\text{-Cp}$ ). Compound  $[(\eta^5\text{-Cp})_2\text{Mo}_2\{\mu\text{-OP}(\text{OEt})_2\}\{\mu\text{-P}(\text{OEt})_2\}(\text{CO})_2]$  reacts with  $[\text{Fe}_2(\text{CO})_9]$  and one of the products is **7** [<2003OM2741>](#). Oxidative addition of molecular chlorine or iodine to  $[\text{MoRu}(\text{CO})_6(\mu\text{-DPPM})_2]$  gives  $[(\text{OC})_2\text{Mo}(\mu\text{-X})(\mu\text{-CO})(\mu\text{-DPPM})_2\text{Ru}(\text{CO})_2[\text{Mo}(\text{CO})_4\text{X}_3]$  [<2003IC1175>](#).



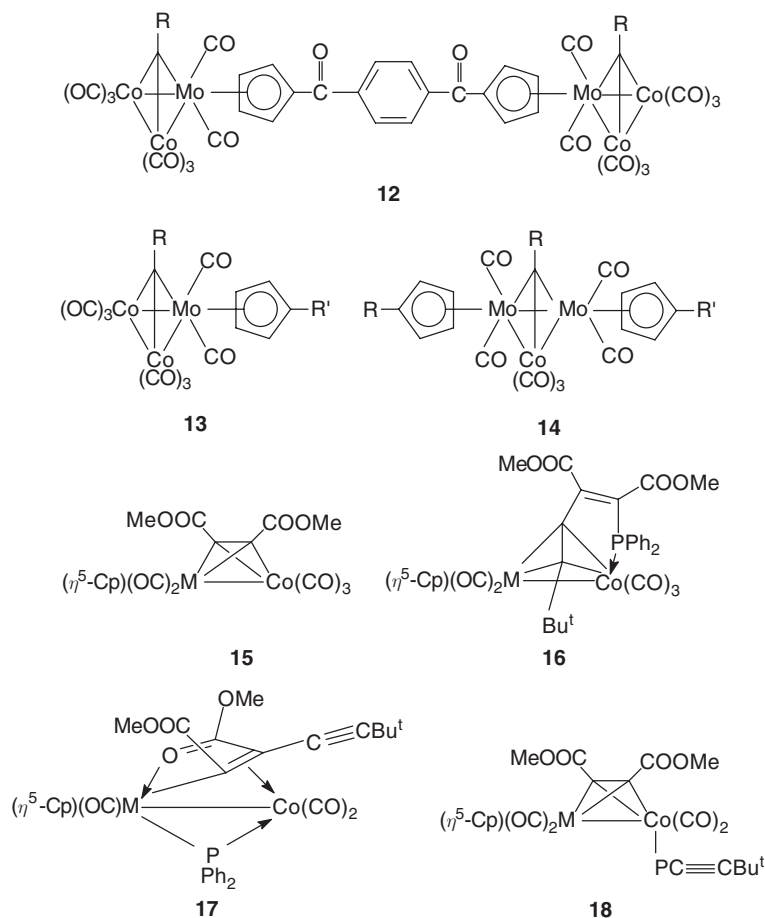


Species  $[(\eta^5\text{-Cp})_2\text{Mo}_2\text{Ir}_2(\mu\text{-CO})_3(\text{CO})_7]$  with diphenylacetylene yields  $[(\eta^5\text{-Cp})_2\text{Mo}_2\text{Ir}_2(\mu\text{-CO})_4(\text{CO})_4(\mu_4\text{-}\eta^2\text{-PhC}_2\text{Ph})]$ . The latter with *t*-butylisocyanide affords  $[(\eta^5\text{-Cp})_2\text{Mo}_2\text{Ir}_2(\mu\text{-CO})_4(\text{CO})_3(\text{CNBu}^t)(\mu_4\text{-}\eta^2\text{-PhC}_2\text{Ph})]$  <2003JOM(682)41>.

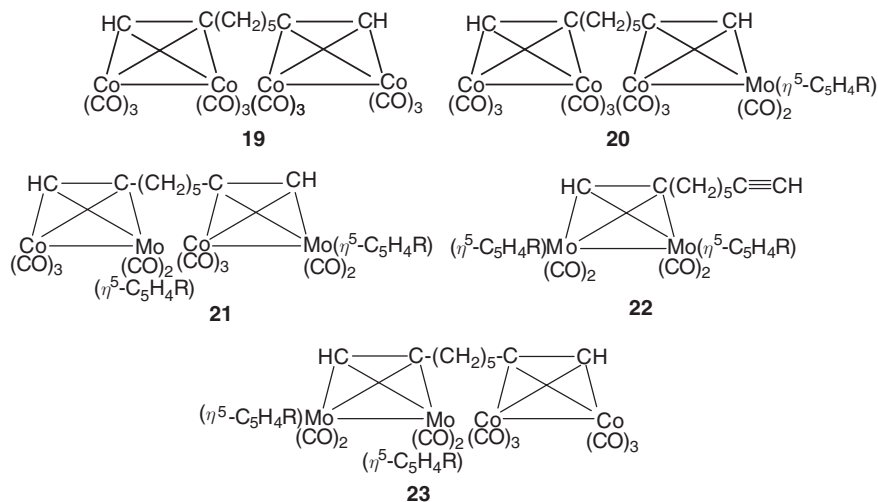
$[\text{Ru}_3(\text{CO})_{12}]$  reacts with  $[(\eta^5\text{-Cp}^*)(\text{OC})_3\text{WCH}_2\text{C}\equiv\text{CPh}]$  and gives the mixed-metal  $\mu$ -allenyl product **8** <1996ICA(243)109>. Complexes  $[\text{Ru}_4(\text{CO})_{13}(\mu\text{-PNR}_2)]$  ( $\text{R} = \text{Pr}^i, \text{Cy}$ ) under reflux with  $[(\eta^5\text{-Cp}^*)\text{W(O)}_2(\text{C}\equiv\text{CPh})]$  form the heteronuclear clusters **9** and **10** <1999JOM(577)126>. Cluster **8** reacts with  $\text{HBF}_4\cdot\text{OEt}_2$  to yield species **11** containing the tungsten–fluorine bond.  $[\text{Ru}_3(\text{CO})_{12}]$  and  $[(\eta^5\text{-C}_5\text{R}_5)\text{WRu}_3(\text{CO})_8(\text{C}_2\text{Ph})]$  ( $\text{R} = \text{H}, \text{Me}$ ) at elevated temperatures give  $[(\eta^5\text{-C}_5\text{R}_5)\text{WRu}_4(\mu_5\text{-C})(\text{CO})_{12}(\mu\text{-CPh})]$  and  $[(\eta^5\text{-C}_5\text{R}_5)\text{WRu}_5(\mu_6\text{-C})(\text{CO})_{14}(\mu\text{-CPh})]$  ( $\text{R} = \text{H}, \text{Me}$ ) <2001OM215>. Both these clusters are hydrogenated to  $[(\eta^5\text{-C}_5\text{R}_5)\text{WRu}_4(\mu_5\text{-C})(\text{CO})_{11}(\mu\text{-CPh})(\mu\text{-H})_2]$  ( $\text{R} = \text{H}, \text{Me}$ ) and  $[(\eta^5\text{-Cp}^*)\text{WRu}_5(\mu_6\text{-C})(\text{CO})_{13}(\mu\text{-CPh})(\mu\text{-H})_2]$ . The structure of the species  $[(\eta^5\text{-Cp})(\text{OC})_3\text{Ru}_2\text{Mo}(\mu_3\text{-}\eta^1\text{-CC})\text{Ru}(\text{CO})_2(\eta^5\text{-Cp})]$  <1998JCS(CC)1805> was later reformulated as  $[\mu_3\text{-}\eta^1\text{-}\{(\eta^5\text{-Cp})(\text{OC})_2\text{Mo}\equiv\text{C-C}\}\text{Ru}_3(\text{CO})_5(\eta^5\text{-Cp})_3]$  <2003JOM(672)17>.



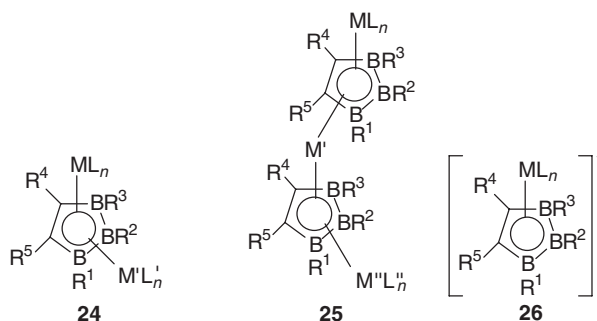
Mixed-metal clusters <1998JOM(559)157, 1999JOM(582)252, 1999OM3164, 2000JOM(616)140, 2000OM5032, 2001JOM(628)123, 2001NJC939, 2002OM5066> readily enter the metal exchange reactions. Thus, linked clusters **12** ( $\text{R} = \text{COOEt}, \text{Ph}$ ) with  $\text{Na}[\text{Mo}(\text{CO})_3(\text{C}_5\text{H}_4\text{R}')] ]$  ( $\text{R}' = \text{H}, \text{COMe}, \text{COOEt}, \text{CO-}p\text{-C}_6\text{H}_4\text{COOMe}$ ) give a set of heterometallic species **13** ( $\text{R} = \text{COOEt}, \text{R}' = \text{H}, \text{COMe}, \text{COOEt}, \text{CO-}p\text{-C}_6\text{H}_4\text{COOMe}$ ;  $\text{R} = \text{Ph}, \text{R}' = \text{COOEt}$ ) <2003JOM(676)55>. Clusters **13** ( $\text{R} = \text{COOEt}, \text{R}' = \text{COMe}, \text{CO-}p\text{-C}_6\text{H}_4\text{COOMe}$ ) react with  $\text{Na}[\text{Mo}(\text{CO})_3(\eta^5\text{-Cp})]$  and produce **13** ( $\text{R} = \text{COOEt}, \text{R}' = \text{H}$ ) and **14** ( $\text{R} = \text{R}' = \text{H}$ ;  $\text{R} = \text{H}, \text{R}' = \text{COMe}, \text{CO-}p\text{-C}_6\text{H}_4\text{COOMe}$ ,  $\text{R} = \text{R}' = \text{COMe}$ ). Reaction of the clusters **15** ( $\text{M} = \text{Mo}, \text{W}$ ) with  $\text{Ph}_2\text{PC}\equiv\text{CBu}^t$  gives the following products: **16** ( $\text{M} = \text{Mo}, \text{W}$ ), **17** ( $\text{M} = \text{W}$ ), and **18** ( $\text{M} = \text{Mo}, \text{W}$ ) <1999JOM(573)180>.



The  $\mu_3$ -CCo<sub>2</sub>M (M = Cr, Mo, W, Fe, Ni, Ru) and C<sub>2</sub>CoM (M = Mo, W) clusters are normally made using the metal-exchange approach <1997POL2387, 1997POL3067, 1997POL3273>. Thus, cluster **19** reacts with Na[( $\eta^5$ -C<sub>5</sub>H<sub>4</sub>R)Mo(CO)<sub>3</sub>] (R = H, COMe, COOEt) to give the metal-exchange products **20** and **21** (R = H, COMe, COOEt) <1999OM3164>. Cluster **22** with [Co<sub>2</sub>(CO)<sub>8</sub>] gives **23**, whose assignment is based on spectral characteristics <1996ICA(245)143, 1996POL4117, 1998JOM(568)157, 1998JOM(570)71> and X-ray structural determination <1999OM3164>.

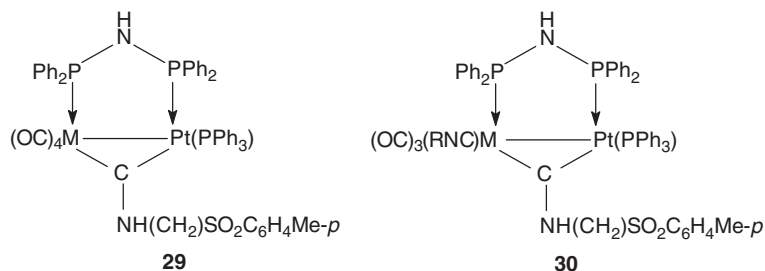
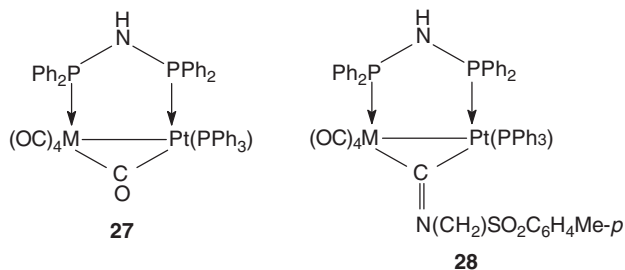


Anionic carborane complex  $[(\eta^5\text{-Cp}^*)\text{Co}(\text{Et}_2\text{C}_2\text{B}_3\text{H}_4)]^-$  with  $[\text{Mo}(\text{CO})_4\text{Cl}(\mu\text{-Cl})]_2$  gives triple-decker and tetradeccker species **24** [ $\text{ML}_n = \text{Mo}(\text{CO})_4$ ,  $\text{M}'\text{L}'_n = \text{Co}(\eta^5\text{-Cp}^*)$ ,  $\text{R}^1 = \text{R}^2 = \text{R}^3 = \text{H}$ ,  $\text{R}^4 = \text{R}^5 = \text{Et}$ ] and **25** [ $\text{ML}_n = \text{M}''\text{L}''_n = \text{Co}(\eta^5\text{-Cp}^*)$ ,  $\text{M}' = \text{Mo}(\text{CO})_2$ ,  $\text{R}^1 = \text{R}^2 = \text{R}^3 = \text{H}$ ,  $\text{R}^4 = \text{R}^5 = \text{Et}$ ], respectively [<1998IC102>](#). Compound **25** [ $\text{ML}_n = \text{M}''\text{L}''_n = \text{Co}(\eta^5\text{-Cp}^*)$ ,  $\text{M}' = \text{Mo}(\text{CO})_2$ ,  $\text{R}^1 = \text{R}^2 = \text{R}^3 = \text{H}$ ,  $\text{R}^4 = \text{R}^5 = \text{Et}$ ] is the only product of the interaction of  $[(\eta^5\text{-Cp}^*)\text{Co}(\text{Et}_2\text{C}_2\text{B}_3\text{H}_4)]^-$  and  $[\text{Mo}(\text{CO})_4\text{Br}(\mu\text{-Br})]_2$  but the triple-decker species is not formed [<1998IC102>](#). The reaction of the same cobalt precursor with  $[\text{W}(\text{CO})_4\text{Br}(\mu\text{-Br})]_2$  gives the tungsten analog of **24** [ $\text{ML}_n = \text{W}(\text{CO})_4$ ,  $\text{M}'\text{L}'_n = \text{Co}(\eta^5\text{-Cp}^*)$ ,  $\text{R}^1 = \text{R}^2 = \text{R}^3 = \text{H}$ ,  $\text{R}^4 = \text{R}^5 = \text{Et}$ ]. Complex **24** [ $\text{ML}_n = \text{Mo}(\text{CO})_4$ ,  $\text{M}'\text{L}'_n = \text{Co}(\eta^5\text{-Cp}^*)$ ,  $\text{R}^1 = \text{R}^2 = \text{R}^3 = \text{H}$ ,  $\text{R}^4 = \text{R}^5 = \text{Et}$ ] with phenyllithium in the presence of trimethyloxonium tetrafluoroborate in toluene gives **24** [ $\text{ML}_n = \text{Mo}(\text{CO})_4$ ,  $\text{M}'\text{L}'_n = \text{Co}(\eta^5\text{-Cp}^*)$ ,  $\text{R}^1 = \text{PhCH}_2$ ,  $\text{R}^2 = \text{R}^3 = \text{R}^4 = \text{R}^5 = \text{Et}$ ]. *nido*- $[(\eta^5\text{-Cp}^*)\text{Co}(\text{Et}_2\text{C}_2\text{B}_3\text{H}_4)]^-$  and  $\text{CpTaCl}_4$ ,  $\text{Cp}^*\text{TaCl}_4$ , and  $\text{CpNbCl}_4$  yield the triple deckers **24** [ $\text{ML}_n = \text{Co}(\eta^5\text{-Cp}^*)$ ;  $\text{M}'\text{L}'_n = \text{MXX}'(\eta^5\text{-C}_5\text{R}_5)$  ( $\text{M} = \text{Ta}$ ,  $\text{R} = \text{H}$ ,  $\text{X} = \text{X}' = \text{Cl}$ ;  $\text{M} = \text{Mo}$ ,  $\text{R} = \text{H}$ ,  $\text{X} = \text{X}' = \text{Cl}$ );  $\text{R}^1 = \text{R}^2 = \text{R}^3 = \text{H}$ ;  $\text{R}^4 = \text{R}^5 = \text{Et}$ ] as the main products. Upon reaction with an alkylating or arylating agent, complex **24** [ $\text{ML}_n = \text{Co}(\eta^5\text{-Cp}^*)$ ;  $\text{M}'\text{L}'_n = \text{MXX}'(\eta^5\text{-C}_5\text{R}_5)$  ( $\text{M} = \text{Ta}$ ,  $\text{R} = \text{H}$ ,  $\text{X} = \text{X}' = \text{Cl}$ );  $\text{R}^1 = \text{R}^2 = \text{R}^3 = \text{H}$ ;  $\text{R}^4 = \text{R}^5 = \text{Et}$ ] undergoes the following transformations: with  $\text{Me}_2\text{Zn}$  or  $\text{AlMe}_3$  to **24** [ $\text{ML}_n = \text{Co}(\eta^5\text{-Cp}^*)$ ;  $\text{M}'\text{L}'_n = \text{MXX}'(\eta^5\text{-C}_5\text{R}_5)$  ( $\text{M} = \text{Ta}$ ,  $\text{R} = \text{H}$ ,  $\text{X} = \text{Me}$ ,  $\text{X}' = \text{Cl}$ );  $\text{R}^1 = \text{R}^2 = \text{R}^3 = \text{H}$ ;  $\text{R}^4 = \text{R}^5 = \text{Et}$ ], with  $\text{MeLi}$  or  $\text{MeMgBr}$  to **24** [ $\text{ML}_n = \text{Co}(\eta^5\text{-Cp}^*)$ ;  $\text{M}'\text{L}'_n = \text{MXX}'(\eta^5\text{-C}_5\text{R}_5)$  ( $\text{M} = \text{Ta}$ ,  $\text{R} = \text{H}$ ,  $\text{X} = \text{X}' = \text{Me}$ );  $\text{R}^1 = \text{R}^2 = \text{R}^3 = \text{H}$ ;  $\text{R}^4 = \text{R}^5 = \text{Et}$ ], with  $\text{Zn}(\text{CH}_2\text{Ph})_2$  to **24** [ $\text{ML}_n = \text{Co}(\eta^5\text{-Cp}^*)$ ;  $\text{M}'\text{L}'_n = \text{MXX}'(\eta^5\text{-C}_5\text{R}_5)$  ( $\text{M} = \text{Ta}$ ,  $\text{R} = \text{H}$ ,  $\text{X} = \text{PhCH}_2$ ,  $\text{X}' = \text{Cl}$ );  $\text{R}^1 = \text{R}^2 = \text{R}^3 = \text{H}$ ;  $\text{R}^4 = \text{R}^5 = \text{Et}$ ], under  $\text{PhCH}_2\text{MgBr}$  to **24** [ $\text{ML}_n = \text{Co}(\eta^5\text{-Cp}^*)$ ;  $\text{M}'\text{L}'_n = \text{MXX}'(\eta^5\text{-C}_5\text{R}_5)$  ( $\text{M} = \text{Ta}$ ,  $\text{R} = \text{H}$ ,  $\text{X} = \text{X}' = \text{PhCH}_2$ );  $\text{R}^1 = \text{R}^2 = \text{R}^3 = \text{H}$ ;  $\text{R}^4 = \text{R}^5 = \text{Et}$ ], with  $\text{Np}_2\text{Mg}$ -dioxane to **24** [ $\text{ML}_n = \text{Co}(\eta^5\text{-Cp}^*)$ ;  $\text{M}'\text{L}'_n = \text{MXX}'(\eta^5\text{-C}_5\text{R}_5)$  ( $\text{M} = \text{Ta}$ ,  $\text{R} = \text{H}$ ,  $\text{X} = \text{Bu}^t\text{CH}_2$ ,  $\text{X}' = \text{Cl}$ );  $\text{R}^1 = \text{R}^2 = \text{R}^3 = \text{H}$ ;  $\text{R}^4 = \text{R}^5 = \text{Et}$ ], and with  $\text{NpLi}$  to **24** [ $\text{ML}_n = \text{Co}(\eta^5\text{-Cp}^*)$ ;  $\text{M}'\text{L}'_n = \text{MXX}'(\eta^5\text{-C}_5\text{R}_5)$  ( $\text{M} = \text{Ta}$ ,  $\text{R} = \text{H}$ ,  $\text{X} = \text{X}' = \text{Bu}^t\text{CH}_2$ ,  $\text{X}' = \text{Cl}$ );  $\text{R}^1 = \text{R}^2 = \text{R}^3 = \text{H}$ ;  $\text{R}^4 = \text{R}^5 = \text{Et}$ ]. Treatment of **24** [ $\text{ML}_n = \text{Co}(\eta^5\text{-Cp}^*)$ ,  $\text{M}'\text{L}'_n = \text{TaCl}_2(\eta^5\text{-Cp})$ ,  $\text{R}^1 = \text{R}^2 = \text{R}^3 = \text{H}$ ;  $\text{R}^4 = \text{R}^5 = \text{Et}$ ] with *N*-bromo- or *N*-iodosuccinimide gives **24** [ $\text{ML}_n = \text{Co}(\eta^5\text{-Cp}^*)$ ;  $\text{M}'\text{L}'_n = \text{TaCl}_2(\eta^5\text{-Cp})$ ;  $\text{R}^1 = \text{R}^2 = \text{R}^3 = \text{Cl}$ ,  $\text{Br}$ ;  $\text{R}^4 = \text{R}^5 = \text{Et}$ ] [<2000OM2200>](#). Reaction of the anionic sandwich **26** [ $\text{ML}_n = \text{Co}(\eta^5\text{-Cp}^*)$ ,  $\text{R}^1 = \text{R}^2 = \text{R}^3 = \text{H}$ ,  $\text{R}^4 = \text{R}^5 = \text{Et}$ ] taken as its lithium salt with  $[(\eta^5\text{-Cp}^*)\text{RuCl}]_4$  gives the triple-decker species **24** [ $\text{ML}_n = \text{Ru}(\eta^5\text{-Cp}^*)$ ,  $\text{M}'\text{L}'_n = \text{Co}(\eta^5\text{-Cp}^*)$ ,  $\text{R}^1 = \text{R}^2 = \text{R}^3 = \text{H}$ ,  $\text{R}^4 = \text{R}^5 = \text{Et}$ ] [<1997JOM\(536\)115>](#). Sandwich *nido*- $[(\eta^5\text{-Cp}^*)\text{Ir}(2,3\text{-Et}_2\text{C}_2\text{B}_3\text{H}_5)]$  enters the reaction of bridge deprotonation with *n*-butyllithium, and further treatment with  $[(\eta^5\text{-Cp}^*)\text{IrCl}_2]_2$  leads to the triple-decker species **24** [ $\text{ML}_n = \text{M}'\text{L}'_n = \text{Ir}(\eta^5\text{-Cp}^*)$ ,  $\text{R}^1 = \text{R}^2 = \text{H}$ ,  $\text{R}^3 = \text{Cl}$ ,  $\text{R}^4 = \text{R}^5 = \text{Et}$ ] [<1996IC7027>](#). The heterobimetallic cobalt-iridium analog **24** [ $\text{ML}_n = \text{Ir}(\eta^5\text{-Cp}^*)$ ,  $\text{M}'\text{L}'_n = \text{Co}(\eta^5\text{-Cp}^*)$ ,  $\text{R}^1 = \text{R}^2 = \text{H}$ ,  $\text{R}^3 = \text{Cl}$ ,  $\text{R}^4 = \text{R}^5 = \text{Et}$ ] derives from the anionic *nido*- $[(\eta^5\text{-Cp}^*)\text{Co}(\text{Et}_2\text{C}_2\text{B}_3\text{H}_4)]^-$  and  $[(\eta^5\text{-Cp}^*)\text{IrCl}_2]_2$ .

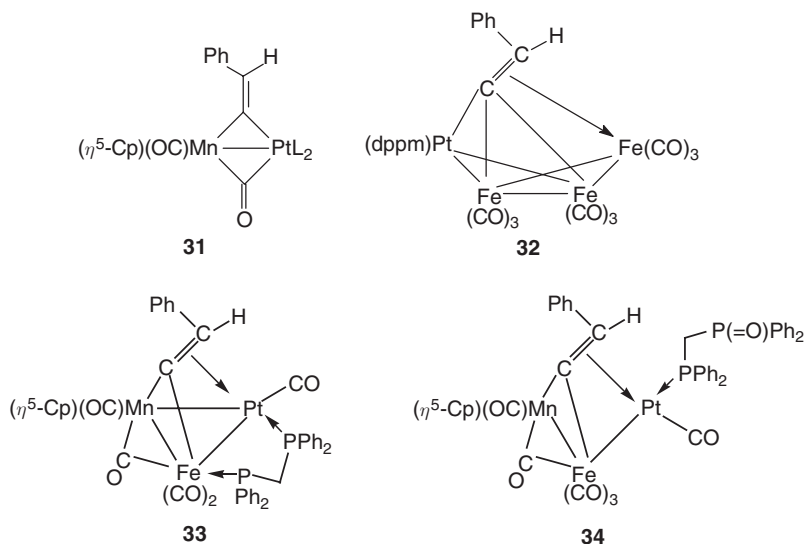


The reaction of  $[\text{M}(\text{CO})_5(\eta^1\text{-DPPM})]$  ( $\text{M} = \text{Cr}, \text{Mo}, \text{W}$ ) with  $[\text{Pt}(\text{CH}_2\text{CH}_2)(\text{PPh}_3)_2]$  leads to the formation of the heterodinuclear complexes  $[(\text{OC})_4\text{M}(\mu\text{-CO})(\mu\text{-DPPM})\text{Pt}(\text{PPh}_3)]$  ( $\text{M} = \text{Cr}, \text{Mo}, \text{W}$ ) [<2003JOM\(684\)216>](#). With  $\text{CF}_3\text{NC}$ ,  $p\text{-MeC}_6\text{H}_4\text{SO}_3\text{CH}_2\text{NC}$ ,  $(\text{PPh}_3\text{CH}_2\text{NC})(\text{PF}_6)$ , the complexes with the bridging isocyanide moiety,  $[(\text{OC})_4\text{M}(\mu\text{-C}=\text{NR})(\mu\text{-DPPM})\text{Pt}(\text{PPh}_3)]$  ( $\text{M} = \text{W}$ ,  $\text{R} = \text{CF}_3$ ;  $\text{M} = \text{Cr}, \text{Mo}, \text{W}$ ,  $\text{R} = \text{CH}_2\text{SO}_2\text{C}_6\text{H}_4\text{Me-}p$ ;  $\text{M} = \text{W}$ ,  $\text{R} = (\text{CH}_2\text{PPh}_3)(\text{PF}_6)$ ). For isocyanides  $\text{PhCH}_2\text{NC}$ ,  $\text{CyNC}$ , and  $(\text{EtO})_2\text{POCH}_2\text{NC}$ , complexes containing terminal isocyanide ligand result  $[(\text{RNC})(\text{OC})_3\text{W}(\mu\text{-CO})(\mu\text{-DPPM})\text{Pt}(\text{PPh}_3)]$  ( $\text{R} = \text{CH}_2\text{Ph}$ ,  $\text{Cy}$ ,  $\text{CH}_2\text{PO}(\text{OEt})_2$ ).

Interaction of  $[\text{M}(\text{CO})_5(\eta^1\text{-(Ph}_2\text{PNHPPH}_2)]$  ( $\text{M} = \text{Mo, W}$ ) gives species **27** ( $\text{M} = \text{Mo, W}$ ) <1999OM248>. The products react with *p*-tosylmethylisonitrile to yield **28** ( $\text{M} = \text{Mo, W}$ ). On protonation using  $\text{HBF}_4$ , the cationic species **29** ( $\text{M} = \text{Mo, W}$ ) evolves. Further interaction of the tungsten complexes with 2,6-xylylisonitrile and benzyliisonitrile gives the substitution products **30** ( $\text{R} = 2,6\text{-xylyl, benzyl}$ ).

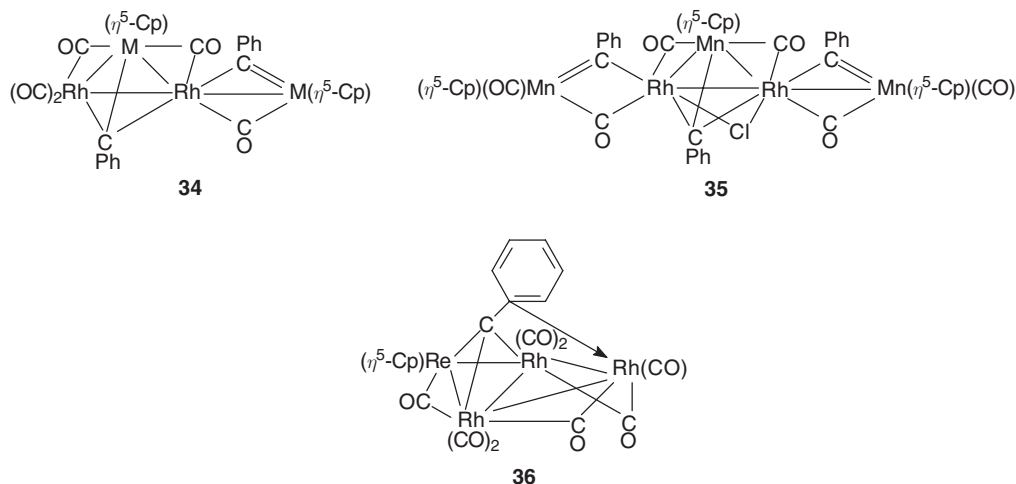


Reaction of  $[(\eta^5\text{-Cp})(\text{Mn}(\text{CO})_2(\text{C}=\text{C}(\text{Ph})\text{H}))]$  with  $[\text{Pt}(\text{PPh}_3)_2]$  gives the mixed metal dinuclear cluster **31** ( $\text{L} = \text{PPh}_3$ ), which can be converted into **32** ( $\text{L}_2 = \text{DPPM}$ ) by a ligand substitution reaction with diphenylphosphinomethane. Interaction of the manganese-platinum cluster with  $[\text{Fe}_2(\text{CO})_9]$  gives rise to the tetranuclear iron-platinum cluster **32** and a couple of trinuclear manganese-iron-platinum clusters, **33** and **34** <1996JOM(524)81, 1998RCB531, 1999JOM(577)238>.

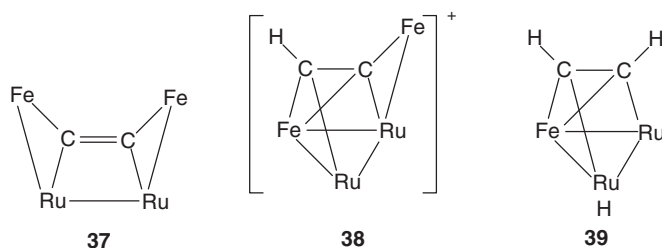


Electrophilic carbyne manganese and rhenium complexes of composition  $[(\eta^5\text{-Cp})(\text{OC})_2\text{M}\equiv\text{CPh}](\text{BBr}_4)$  ( $\text{M} = \text{Mn, Re}$ ) react with  $[\text{Fe}_2(\mu\text{-CO})(\mu\text{-SeBu}^n)(\text{CO})_6]^-$ ,  $[\text{M}_3(\text{CO})_{11}]^{2-}$  ( $\text{M} = \text{Ru, Os}$ ), or  $[\text{Fe}_4(\text{CO})_{13}]^-$  to yield various trimetal bridging carbyne species <2000OM72,

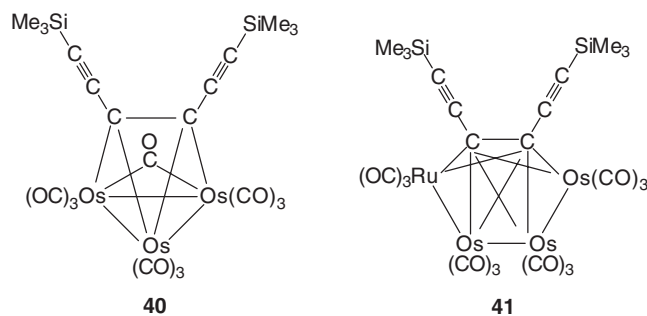
2001OM2226, 2002CCR(231)109, 2002OM2764>. The manganese carbyne complex  $[(\eta^5\text{-Cp})(\text{OC})_2\text{Mn}\equiv\text{CPh}](\text{BBr}_4)$  with  $[(\text{Ph}_3\text{P})_2\text{N}][\text{Rh}(\text{CO})_4]$  gives the tetranuclear and pentanuclear clusters **34** ( $\text{M} = \text{Mn}$ ) and **35** (the presence of the chlorine bridge is due to the contaminants in the rhodium reagent) <2003OM4369, 2004ICA(357)864>. Rhenium analog also forms **34** ( $\text{M} = \text{Re}$ ) but together with a tetranuclear cluster **36** <2003OM4369>.



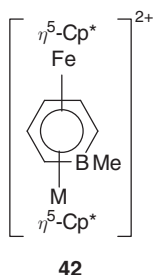
Cluster  $[(\mu_4\text{-C}\equiv\text{C})\text{Fe}_2\text{Ru}_2(\eta^5\text{-Cp}^*)_2(\text{CO})_{10}]$  formally illustrated as **37** reacts with  $\alpha$ -chloropropionic acid via the route of addition to the ruthenium–ruthenium bond to yield the  $\mu$ -hydrido- $\mu$ -carboxylato complex  $[(\mu_4\text{-C}\equiv\text{C})(\mu\text{-H})(\mu\text{-}\kappa^1\text{-MeCHClCOO})\text{Fe}_2\text{Ru}_2(\eta^5\text{-Cp}^*)_2(\text{CO})_8]$  <2003OM3055>. The same starting complex on irradiation with diphenylphosphinomethane and diphenylphosphinoethane gives the products of ligand substitution,  $[(\mu_4\text{-C}\equiv\text{C})\text{Fe}_2\text{Ru}_2(\eta^5\text{-Cp}^*)_2(\text{CO})_8(\mu\text{-Ph}_2\text{P}(\text{CH}_2)_n\text{PPh}_2)]$  ( $n = 1, 2$ ). The product with  $n = 1$  is protonated by  $\text{HBF}_4\cdot\text{OEt}_2$  to yield  $[(\mu_4\text{-CCH})\text{Fe}_2\text{Ru}_2(\eta^5\text{-Cp}^*)_2(\text{CO})_7(\text{DPPM})](\text{BF}_4)$ , which can be schematized in an abbreviated form as **38**. The latter can be reduced using  $\text{NEt}_4\text{BH}_4$ , and the reaction is followed by transformation of the tetranuclear cluster to the trinuclear species  $[(\mu_3\text{-C}\equiv\text{CH})\text{FeRu}_2(\eta^5\text{-Cp}^*)(\text{CO})_5(\text{DPPM})]$ , while the reaction with diphenylsilane gives  $[(\mu_3\text{-HCCH})\text{FeRu}_2(\eta^5\text{-Cp}^*)(\text{CO})_5(\text{DPPM})]$  formally depicted as **39**.



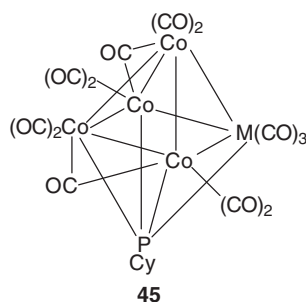
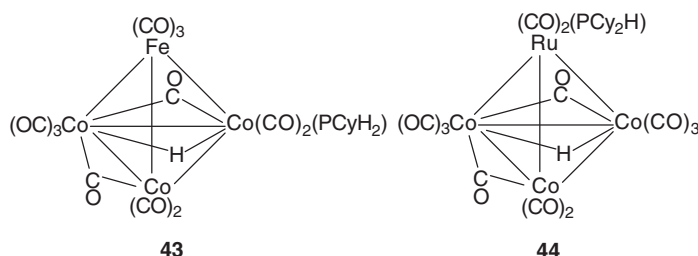
Species **40** considered in the previous chapter further reacts with  $[\text{Ru}_3(\text{CO})_{12}]$  to give the mixed-metal ruthenium–osmium cluster **41** <1999JOM(578)103>.



The lithium salt of  $\text{C}_5\text{H}_5\text{BMe}^-$  with  $[(\eta^5\text{-Cp}^*)\text{Fe}(\text{acac})]_x$  gives  $[(\eta^5\text{-Cp}^*)\text{Fe}(\eta^6\text{-C}_5\text{H}_5\text{BMe})]$  [<1996OM5236>](#) along with  $[\text{Fe}(\eta^5\text{-Cp}^*)_2]$  and  $[\text{Fe}(\eta^6\text{-C}_5\text{H}_5\text{BMe})_2]$ . Further reaction of this sandwich with  $[(\eta^5\text{-Cp}^*)\text{Fe}(\text{AN})_3]$  or  $[(\eta^5\text{-Cp}^*)\text{Ru}(\text{AN})_3](\text{CF}_3\text{SO}_3)$  (AN = acetonitrile) gives the stacking cationic products **42** ( $\text{M} = \text{Fe}, \text{Ru}; n = 1$ ). With  $[(\eta^5\text{-Cp}^*)\text{M}(\text{MeNO}_2)_x]^{2+}$  ( $\text{M} = \text{Rh}, \text{Ir}$ ), **42** ( $\text{M} = \text{Rh}, \text{Ir}; n = 2$ ) is formed. Interaction of  $[(\eta^4\text{-COD})\text{Rh}(\eta^6\text{-C}_5\text{H}_5\text{BMe})]$  with  $[(\eta^4\text{-COD})\text{Rh}(\text{solv})_x]^+$  gives the triple-decker species  $[(\mu\text{-}\eta^6\text{-C}_5\text{H}_5\text{BMe})\{\text{Rh}(\eta^4\text{-COD})\}_2]^+$  (solv =  $\text{CH}_2\text{Cl}_2, \text{MeNO}_2$ ) [<1996OM5236>](#). The scope of the triple-decker species was broadened to  $[(\eta^5\text{-Cp}^*)\text{Fe}(\mu\text{-}\eta^6\text{-C}_5\text{H}_5\text{BMe})\text{ML}_n]^{2+}$  ( $\text{M} = \text{Co}, \text{L}_n = \eta^5\text{-Cp}^*$ ;  $\text{M} = \text{Rh}, \text{Ir}, \text{L}_n = \eta^5\text{-Cp}$ ;  $\text{M} = \text{Ru}, \text{L}_n = \text{C}_6\text{H}_6, 1,3,5\text{-C}_6\text{H}_3\text{Me}_3, \text{C}_6\text{Me}_6$ ) [<2002JOM\(649\)136>](#).

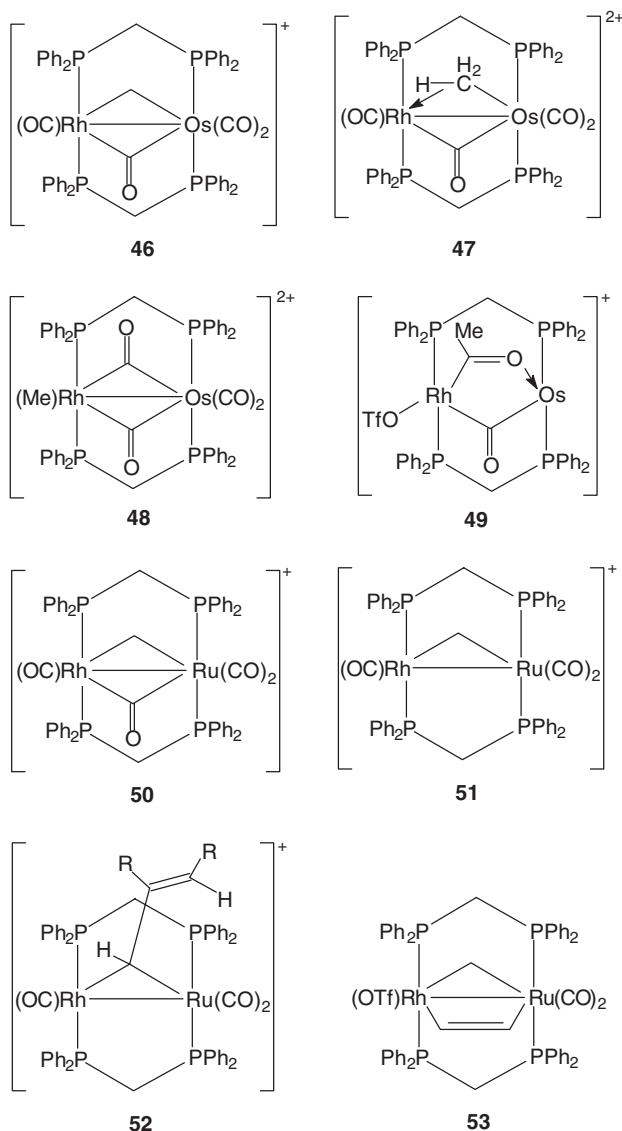


The effect of the presence of two or more different metals in the heteronuclear clusters is attractive in homogeneous catalysis [<1998MI1, 1999MI1>](#). An example is the application of the clusters  $[\text{HMCo}_3(\text{CO})_{12}]$  ( $\text{M} = \text{Fe}, \text{Ru}$ ) [<1996JMRC689>](#) in ligand substitution chemistry by the phosphine ligands. On reaction with cyclohexylphosphine, the iron complex gives **43**, while the ruthenium analog provides **44** [<1999OM4908>](#). They both slowly transform into **45** ( $\text{M} = \text{Fe}, \text{Ru}$ ) along with  $[\text{MCo}_2(\mu_3\text{-PCy})(\text{CO})_9]$  in methylene chloride.

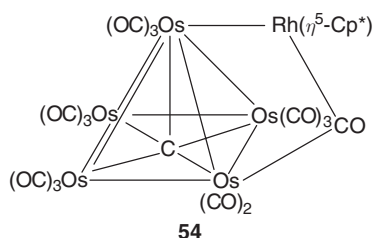


The methylene-bridged species **46** [<1999JA2613>](#) can be protonated by triflic acid at  $-80^\circ\text{C}$  to yield **47**, where the methylene group has been transformed to the methyl moiety strongly bound to osmium but retaining weak bonding to the rhodium site [<2003OM2638>](#). As the temperature is increased to  $-40^\circ\text{C}$ , the dication is transformed to another dicationic species **48** with two bridging carbonyls. Upon warming to room temperature, the latter experiences transformation to a monocationic heterodinuclear complex **49**. The methylene-bridged iridium–ruthenium and rhodium–ruthenium species are of interest in terms of their activity in Fischer–Tropsch catalysis

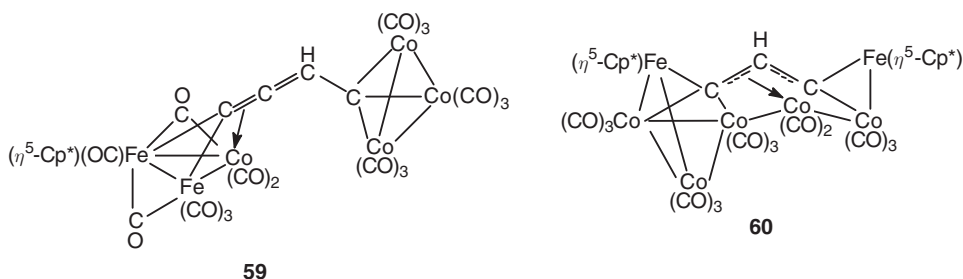
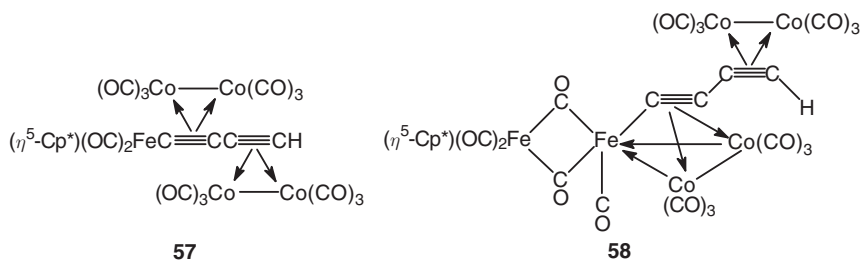
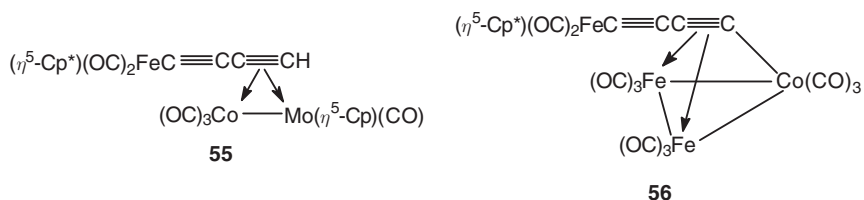
<2001OM88, 2002OM3228>. Thus, the rhodium–ruthenium complex **50** <2002OM3228> undergoes loss of the bridging carbonyl in the presence of trimethylamine *N*-oxide to yield **51** <2003OM2944>. The latter interacts with a number of acetylenes  $\text{RC}\equiv\text{CR}'$  ( $\text{R} = \text{R}' = \text{COOMe}$ ,  $\text{CF}_3$ ,  $\text{COOEt}$ ;  $\text{R} = \text{Me}$ ,  $\text{R}' = \text{CH}(\text{OEt})_2$ ,  $\text{CH}_2\text{OH}$ ) to yield  $[\text{RhRu}(\text{CO})_3\text{-}\{\mu\text{-}\eta^1\text{:}\eta^1\text{-C}(\text{R})=\text{C}(\text{R}')\text{CH}_2\}(\mu\text{-DPPM})_2](\text{CF}_3\text{SO}_3)]$ , of which the one with  $\text{R} = \text{R}' = \text{COOMe}$  was decarbonylated in the same manner to afford **52** ( $\text{R} = \text{COOMe}$ ) <1999OM4134, 2003OM2944>. Complex  $[\text{RhRu}(\text{OTf})(\text{CO})_2\{\mu\text{-}\eta^1\text{:}\eta^1\text{-C}(\text{COOMe})=\text{C}(\text{COOMe})\}(\mu\text{-DPPM})_2]$  enters the reaction with diazomethane to give the mixed-bridged derivative **53** ( $\text{R} = \text{COOMe}$ ) <2003OM2944>.  $[(\text{OC})\text{Rh}(\mu\text{-DPPM})_2\text{Ir}(\text{CO})_2(\text{Me})](\text{CF}_3\text{SO}_3)]$  on reaction with phosphines gives  $[(\text{R}'\text{R}_2\text{P})\text{Rh}(\mu\text{-DPPM})_2(\mu\text{-CO})_2\text{Ir}(\text{CO})(\text{Me})](\text{CF}_3\text{SO}_3)]$  ( $\text{R} = \text{R}' = \text{Me}$ ,  $\text{OPh}$ ;  $\text{R} = \text{Me}$ ,  $\text{R}' = \text{Ph}$ ;  $\text{R} = \text{OMe}$ ,  $\text{R}' = \text{Ph}$ ) <1999OM1629>. Reaction of ethylene with  $[\text{HIrRu}_3(\text{CO})_{12}]$  gives the ethylidyne cluster  $[\text{HIrRu}_4(\text{CO})_{15}(\mu_4\text{-CMe})]$  where the hydrocarbon is coordinated to the four ruthenium atoms via the carbon site <1999ICCC60>.



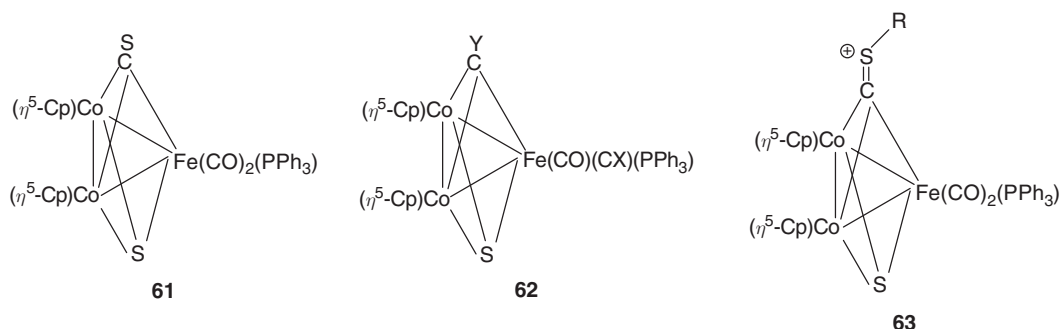
Refluxing  $[\text{Os}_3\text{Rh}(\mu\text{-H})_3(\text{CO})_{12}]$  in toluene in the presence of a hydride acceptor (4-vinylphenol) gives  $[\text{Os}_3\text{Rh}_4(\mu\text{-}\eta^1\text{:}\eta^1\text{:}\eta^1\text{-PhMe})(\text{CO})_{13}]$  <2003AG(E)1935>, a rare coordination mode. The dianionic cluster  $[\text{Os}_5\text{C}(\text{CO})_{14}]^{2-}$  reacts with  $[(\eta^5\text{-Cp}^*)\text{RhRh}(\eta^5\text{-Cp}^*)]^{2+}$  and forms the mixed-metal osmium–rhodium cluster **54** <2003ICC733>. A related cluster is  $[\text{Os}_5\text{PdC}(\text{CO})_{12}\text{-}(\mu\text{-CO})_2(\text{PPh}_3)_2]$  <1998JCLS417>.



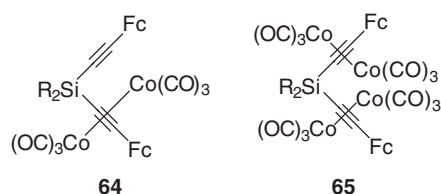
The iron complex  $[(\eta^5\text{-Cp}^*)(\text{OC})_2\text{FeC}\equiv\text{CC}\equiv\text{CH}]$  reacts with  $[(\text{OC})_3\text{CoMo}(\eta^5\text{-Cp})(\text{CO})]$  to yield **55** <1999JCS(CC)101, 1999OM4684, 2003JOM(670)2>. Interaction of the species similar to **55**, where instead of the  $\text{Mo}(\text{CO})(\eta^5\text{-Cp})$  moiety there is the  $\text{Co}(\text{CO})_3$  group, with  $[\text{Fe}_2(\text{CO})_9]$  leads to the elimination of the  $\text{Co}(\text{CO})_4$  moiety and formation of **56**. Cluster **57** with  $[\text{Fe}_2(\text{CO})_9]$  forms a mixture of products **58** and **59** <1998CRV2797>. Thermolysis of **56** after a complicated chain of rearrangements gives cluster **60**. The related example is  $[(\eta^5\text{-Cp}^*)\text{FeCo}_2\text{Ru}(\text{CO})_{10}(\mu_4\text{-C}_2\text{H})]$  <1998JA11071>. Two moles of  $[(\eta^5\text{-Cp})\text{Co}(\text{PPh}_3)_2]$  interact with  $[(\text{OC})_2\text{Fe}(\text{PPh}_3)_2(\eta^2\text{-CSC})]$  to yield the mixed-metal cluster **61** <1998JOM(551)139> and with  $[(\text{OC})_2\text{Fe}(\text{PPh}_3)_2(\eta^2\text{-SCNR})]$  to produce **62** (CX, CY = CO, CNR) <1999JOM(573)109>. Reaction of  $[\text{Fe}_2(\text{CO})_9(\mu\text{-CO})(\mu_3\text{-}\eta^2\text{-C}=\text{C}(\text{C}_6\text{H}_{10}))]$  and  $[\text{Co}_3(\text{CO})_9(\mu_3\text{-CCH}_2(\text{C}_6\text{H}_{10}\text{OH}))]$  with ethynylcyclohexanol leads to the formation of  $[\text{Co}_2\text{Fe}(\text{CO})_6(\mu\text{-CO})(\mu_3\text{-}\eta^7\text{-(C}_6\text{H}_9\text{)CC(H)C(H)C(H)(C}_6\text{H}_{10}))]$  <2001JCS(D)1485>. Clusters  $[(\eta^5\text{-Cp})_3\text{Co}_3(\mu_3\text{-S})(\mu_3\text{-CNR})]$  when treated with  $[\text{Fe}(\text{CO})_2(\text{PPh}_3)_2(\eta^2\text{-SCX})]$  give the heterotrinnuclear products  $[(\eta^5\text{-Cp})\text{Co}_2\text{Fe}(\text{CO})_2(\text{PPh}_3)_2(\mu_3\text{-S})(\mu_3\text{-CX})]$  (X = S, SR<sup>+</sup>, NR; R = Me, Et) <1998JOM(551)139, 1999JOM(573)109>. Cluster **62** interacts with RI or ROTf (R = Me, Et) to produce the cationic species **63** with Y = <sup>+</sup>SR. This reaction can be reverted using R'O<sup>-</sup> (R = H, Me, Et) <2003ICA(354)54>.



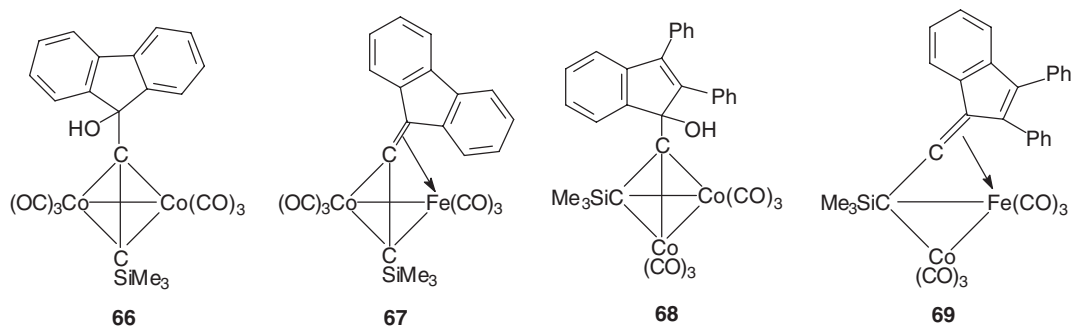




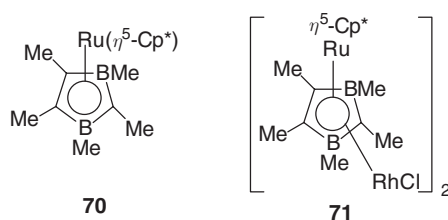
The ferrocenyl derivatives  $R_2Si(C\equiv CFc)_2$  ( $R = Me, Ph$ ) with excess  $[Co_2(CO)_6]$  give species **64** ( $R = Me, Ph$ ) and **65** ( $R = Me, Ph$ ) [<1999JOM\(573\)36>](#), manifesting the role of ferrocenylethynyl complexes as templates for long-range electronic communication [<1996ICA\(247\)99, 1996OM3935, 1997CRV637>](#).

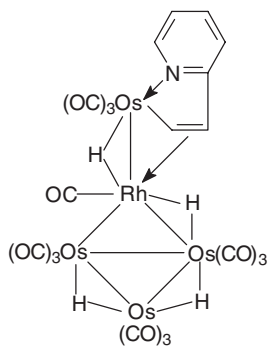


Homogeneous cluster **66**, when reacted with  $[Fe(CO)_5]$  at elevated temperatures in acetone, forms the mixed-metal complex **67** [<1999OM3372>](#). The same type of reaction relates clusters **68** and **69**. The analogous structure  $[CoFe(CO)_6(HC=C=CR_2)]$  is known [<1998OM4992>](#).



Sandwich **70** reacts with  $[(\eta^2-C_2H_4)_2RhCl]$  to give the tetranuclear product **71** formulated as a penta-decker species with two central bridging chlorine atoms [<1999EJI1685>](#). Excess 2-vinylpyridine with  $[Os_3Rh(\mu-H)_3(CO)_{12}]$  gives product **72** [<2003ICC174>](#).



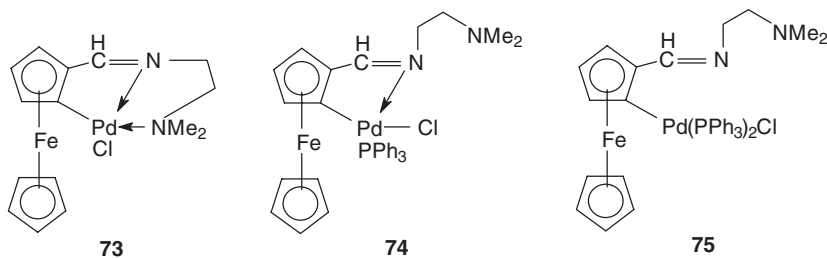


72

The mixed cluster  $[\text{PtRu}_5(\text{CO})_{15}(\mu_6\text{-C})(\mu\text{-CO})]$  [<2000JCS\(CC\)937>](#) enters ligand-substitution reactions [<2003IC3111>](#). With dimethylphenylphosphine, it gives  $[\text{PtRu}_5(\text{CO})_{14}(\text{PMe}_2\text{Ph})(\mu_6\text{-C})(\mu\text{-CO})]$  and  $[\text{PtRu}_5(\text{CO})_{13}(\text{PMe}_2\text{Ph})_2(\mu_6\text{-C})(\mu\text{-CO})]$ , both retaining the structure of an octahedral  $\text{Ru}_5\text{Pt}$  cluster with the carbide site in the center of the base. Trimethylphosphine also gives two substitution products, while with  $\text{Me}_2\text{S}$  only the product of monosubstitution is obtained. A similar structure was observed for  $[\text{PtRu}_5(\text{CO})_{13}(\text{DPPM})(\mu_6\text{-C})(\mu\text{-CO})]$  [<1998OM3020>](#). The cluster  $[\text{PtRu}_5\text{C}(\text{CO})_{16}]$  reacts with methanolic potassium hydroxide to give the dianionic species  $[\text{PtRu}_5\text{C}(\text{CO})_{15}]^{2-}$  [<2003JCS\(D\)2651>](#). The product obtained as the  $(\text{Ph}_4\text{P}^+)_2$  salt, when reacted with  $[\text{Au}(\text{PPh}_3)\text{Cl}]$  in the presence of thallium hexafluorophosphate, leads to  $[\text{PtRu}_5\text{C}(\text{CO})_{15}(\text{AuPPh}_3)_2]$ , similar in structure to that of  $[\text{Ru}_6\text{C}(\text{CO})_{16}(\text{AuPR}_3)_2]$  ( $\text{R}_3 = \text{Ph}_3, \text{MePh}_2$ ) [<1996JOM\(518\)121>](#). With  $[\text{Pt}(\eta^4\text{-COD})\text{Cl}_2]$  in the presence of silica,  $[\text{Pt}_2\text{Ru}_4\text{C}(\text{CO})_{13}(\eta^4\text{-cod})]$  follows [<2003JCS\(D\)2651>](#) with the structural arrangement similar to that in  $[\text{Pt}_2\text{Ru}_{10}\text{C}_2(\text{CO})_{28}]^{2-}$  [<2003EJI1325>](#) and  $[\text{PtRu}_5\text{C}(\text{CO})_{11}(\eta^2\text{-dppe})(\mu_3\text{-}\eta^2, \eta^2, \eta^2\text{-C}_{60})]$ . The  $\text{Ru} = \text{Pt}$  clusters are active catalysts of hydrogenation [<2001AG\(E\)4638>](#).  $[\text{PtRu}_5(\text{CO})_{16}(\mu_6\text{-C})]$  when reacted with  $[\text{Pt}(\text{PBUt}_3)_2]$  and  $[\text{Pd}(\text{PBUt}_3)_2]$  gives  $[\text{PtRu}_3(\text{CO})_6(\mu_6\text{-C})\text{M}(\text{PBUt}_3)_2]$  ( $\text{M} = \text{Pt}, \text{Pd}$ ) and  $[\text{PtRu}_3(\text{CO})_6(\mu_6\text{-C})\text{M}(\text{PBUt}_3)_2]$  ( $\text{M} = \text{Pt}, \text{Pd}$ ) [<2003JOM\(682\)113>](#).

The iron–platinum-bridged  $\text{Ph}_2\text{PNHPPH}_2$  isonitrile complexes have received attention [<1998EJI495>](#), e.g.,  $[(\text{OC})_3\text{Fe}(\mu\text{-CNR})(\mu\text{-dppa})\text{Pt}(\text{PPh}_3)]$ . The mixed-metal complex  $[(\text{OC})_3\text{Fe}(\mu\text{-CO})(\mu\text{-DPPM})\text{Pt}(\text{PPh}_3)]$  reacts with  $\text{PO}(\text{OEt})_2\text{CH}_2\text{NC}$  to give the product with the isocyanide bridge,  $[(\text{OC})_3\text{Fe}(\mu\text{-C}=\text{NCH}_2\text{PO}(\text{OEt})_2)(\mu\text{-DPPM})\text{Pt}(\text{PPh}_3)]$  [<2003JOM\(684\)216>](#).

The ferrocenyl species  $[(\eta^5\text{-Cp})\text{Fe}(\eta^5\text{-C}_5\text{H}_4)\text{CH}=\text{N}(\text{CH}_2)_2\text{NMe}_2]$  reacts with  $\text{Na}_2[\text{PdCl}_4]$  in the presence of sodium acetate trihydrate in methanol to yield the mixed-metal cluster **73** [<1999JOM\(577\)292>](#). With triphenylphosphine in benzene, the latter gives **74**, and with additional triphenylphosphine in deuteriochloroform it gives **75**.

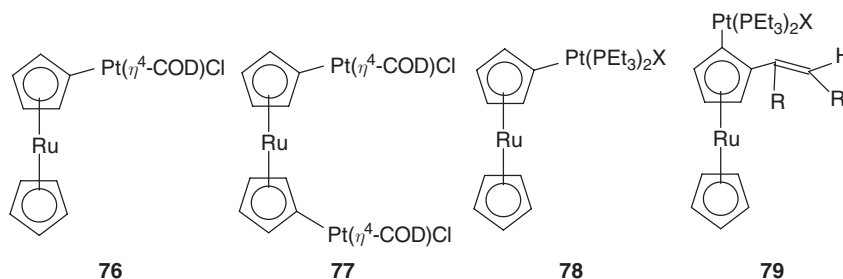


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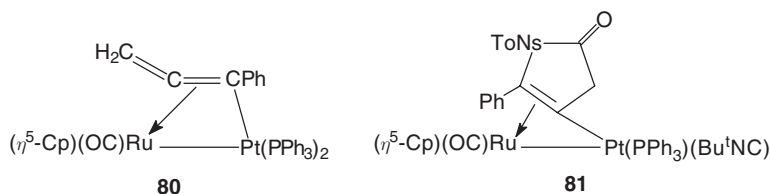
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75

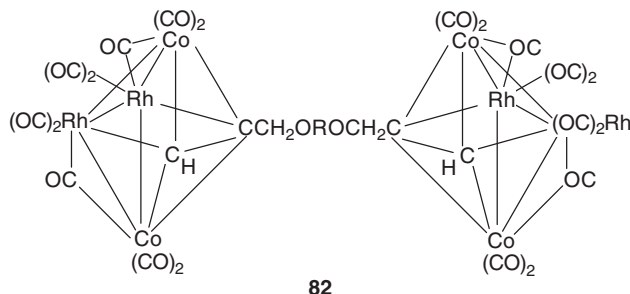
An interesting class of multinuclear complexes results when two different transition metals interact through the cyclopentadienyl ligand in a  $\eta^5:\eta^1$  manner, e.g., ferrocenyl platinum complexes [<1996JOM\(511\)47>](#). Trimethylstannylruthenocene and 1,1'-bis(trimethylstannyl)ruthenocene react with  $[(\eta^4\text{-COD})\text{PtCl}_2]$  in THF to yield **76** and **77**, respectively [<1999JOM\(574\)66>](#). Using ligand-exchange reactions, a series **78** ( $\text{X} = \text{Cl}, \text{Br}, \text{NCS}$ ) was prepared. On reaction with acetylenes,  $\text{RC}\equiv\text{CR}$  ( $\text{R} = \text{COOMe}, \text{COOEt}$ ), some of the species **78** give **79** ( $\text{X} = \text{Cl}, \text{R} = \text{COOMe}; \text{X} = \text{Br}, \text{R} = \text{COOMe}; \text{X} = \text{Cl}, \text{R} = \text{COOEt}$ ).



Reaction of  $[(\eta^5\text{-Cp})(\text{OC})_2\text{RuCH}_2\text{C}\equiv\text{CPh}]$  with  $[\text{Pt}(\text{PPh}_3)_2(\text{C}_2\text{H}_4)]$  gives **80** <2000OM3179, 2002ICC82>. A similar complex  $[(\eta^5\text{-Cp})(\text{OC})_2\text{Ru}(\mu\text{-}\eta^1\text{:}\eta^2\text{-CH=C=CH}_2)\text{Pt}(\text{PPh}_3)_2]$  enters a simple ligand substitution reaction with *t*-butyl isonitrile to yield  $[(\eta^5\text{-Cp})(\text{OC})_2\text{Ru}(\mu\text{-}\eta^1\text{:}\eta^2\text{-CH=C=CH}_2)\text{Pt}(\text{PPh}_3)(\text{Bu}^t\text{NC})]$  <2000JOM(593)465>. Hydration reaction is a nucleophilic process <2000ICA(307)1>. Reaction of  $[(\eta^5\text{-Cp})(\text{OC})_2\text{Ru}(\mu\text{-}\eta^1\text{:}\eta^2\text{-CPh=C=CH}_2)\text{Pt}(\text{PPh}_3)(\text{Bu}^t\text{NC})]$  with the electrophilic agent,  $(p\text{-Tol})\text{SO}_2\text{N=C=O}$ , is a [3 + 2]-cycloaddition reaction affording **81** <2000JOM(593)465>.  $[(\eta^5\text{-Cp})(\text{OC})_2\text{Ru}(\mu\text{-}\eta^1\text{:}\eta^2\text{-CH=C=CH}_2)\text{Pt}(\text{PPh}_3)_2]$  reacts with  $[\text{Au}(\text{PPh}_3)]^+$  (R = Ph, H) and forms the  $\eta^3$ -allyl complexes <2000JCLS233>. The  $\text{Pt}(\text{PPh}_2)_2$  diphenylbutadiyne complex with  $[\text{Fe}(\text{CO})_5]$  or  $[\text{Ru}_3(\text{CO})_{12}]$  gives  $[\text{Pt}_2\text{M}(\text{PhC}_2\text{C}_2\text{Ph})(\text{CO})_5(\text{PPh}_3)_2]$  (M = Fe, Ru) <1998OM775>.

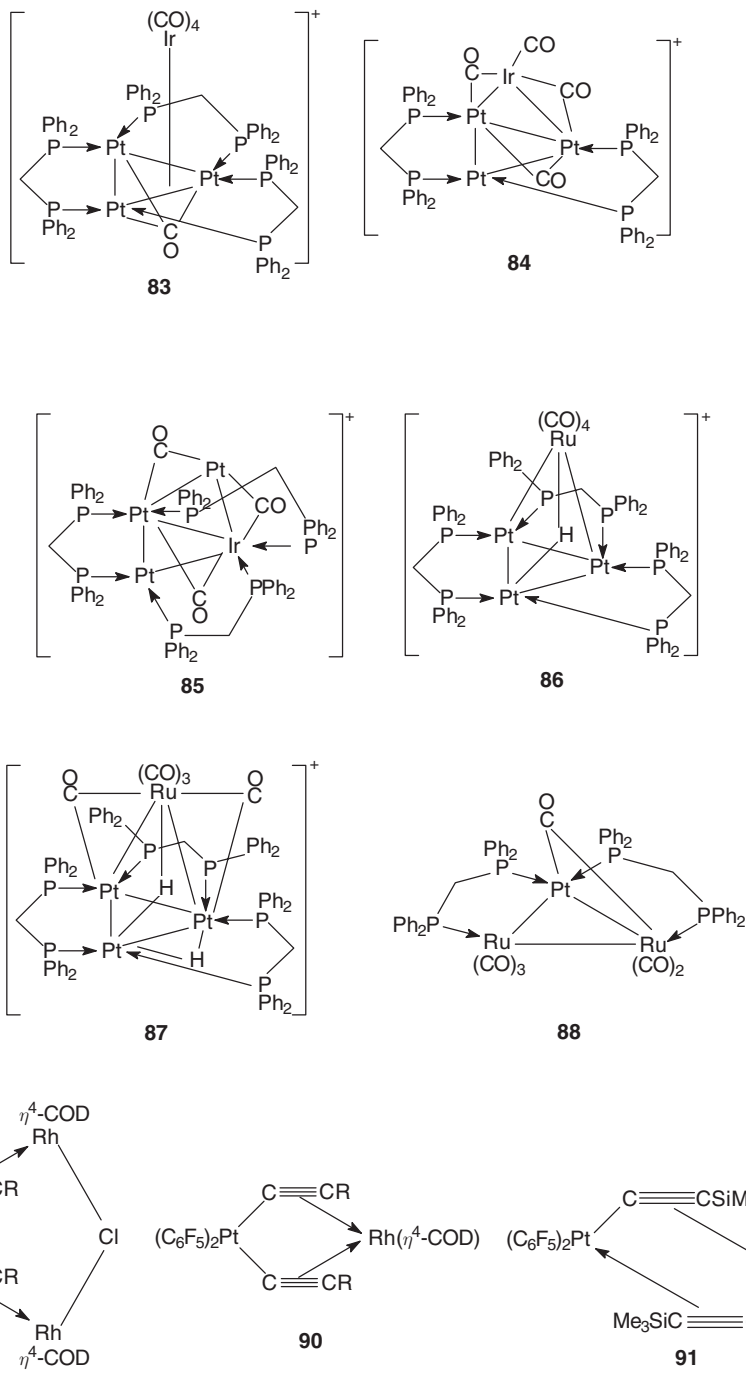


$[\text{Rh}_2\text{Co}_2(\text{CO})_{12}]$  reacts with alkynes to yield  $[\text{Rh}_2\text{Co}_2(\text{CO})_{10}(\mu_4, \eta^2\text{-R}^1\text{C}\equiv\text{CR}^2)]$  <2002JOM(650)181>. The reaction of the same cluster with a series of dialkynes where the alkyne groups are separated,  $\text{HC}\equiv\text{CH}_2\text{O-R-OCH}_2\text{C}\equiv\text{CH}$  (R =  $\text{C}_6\text{H}_4\text{-1,4-(C(O))}_2$ ,  $(\text{C(O)CH}_2)_2$ ,  $(\text{C(O)CH})_2$ ,  $(\text{C(O)})_2\text{CH}_2$ ,  $(\text{C(O)})_2$ ), leads to the linked clusters **82** with the same set of R groups <2003JOM(681)275>. Compounds  $[\text{M}(\text{CO})_4(\eta^2\text{-alkyne})]$  are used to obtain the alkyne-bridged heterometallic species of iron, ruthenium, or osmium and cobalt, rhodium, or iridium <2000OM2766>.  $[\text{RhIr}(\text{CO})_3(\text{DPPM})_2]$  oxidatively adds  $\text{MeOCH}_2\text{I}$  to yield  $[\text{RhIr}(\text{CH}_2\text{OMe})(\text{I})(\text{CO})(\mu\text{-CO})(\text{DPPM})_2]$  <2000OM854>. Methyl triflate causes iodine abstraction and formation of  $[\text{RhIr}(\text{CH}_2\text{OMe})(\text{CO})(\mu\text{-CO})(\text{DPPM})_2](\text{CF}_3\text{SO}_3)$ .

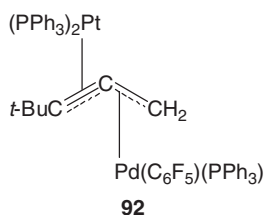


Triplatinum dicationic clusters  $[\text{Pt}_3(\mu_3\text{-CO})(\mu\text{-DPPM})_3](\text{PF}_6)_2$  react with  $[\text{Ir}(\text{CO})_4]^-$  and  $[\text{Re}(\text{CO})_5]^-$  to yield the mixed-metal species, e.g., **83** <1997POL3861, 1998OM2433>. Product **83** decarbonylates to yield **84** and then **85**. Similarly, with  $\text{H}[\text{Ru}(\text{CO})_4]^-$ , cluster **86** is formed, which slowly transforms to **87** <1999OM3737>. The reaction of  $[\text{Pt}(\text{DPPM})_2]\text{Cl}_2$  with  $(\text{PPN})[\text{Ir}(\text{CO})_4]$  gives cluster **88** <1999OM2162>. *o*-Bis(phenylethynyl)benzene with  $[\text{Pt}_2\text{Ru}_4(\text{CO})_{14}(\text{CO})_{18}]$  gives  $[\text{Pt}_2\text{Ru}_4(\text{CO})_{14}(\mu_5\text{-C}_6\text{H}_4(\text{C}_2\text{Ph}_2)_2)]$  with two  $\text{PtRu}_2$  triangles <1999ICC1>.

The rhodium and iridium dimers  $[(\eta^4\text{-COD})\text{M}(\mu\text{-Cl})_2]$  ( $\text{M} = \text{Rh}, \text{Ir}$ ) react with the anionic platinum complexes  $\text{A}[\text{cis-Pt}(\text{C}_6\text{F}_5)_2(\text{C}\equiv\text{CR})_2]$  ( $\text{A} = \text{PPh}_3\text{Me}$ ,  $\text{R} = \text{Ph}$ ;  $\text{A} = \text{N}^t\text{Bu}_4$ ,  $\text{R} = \text{Bu}^t$ ,  $\text{SiMe}_3$ ) to yield **89** ( $\text{R} = \text{Bu}^t$ ,  $\text{SiMe}_3$ ), **90** ( $\text{R} = \text{Ph}$ ,  $\text{Bu}^t$ ,  $\text{SiMe}_3$ ), and **91** [<1999OM4344>](#).

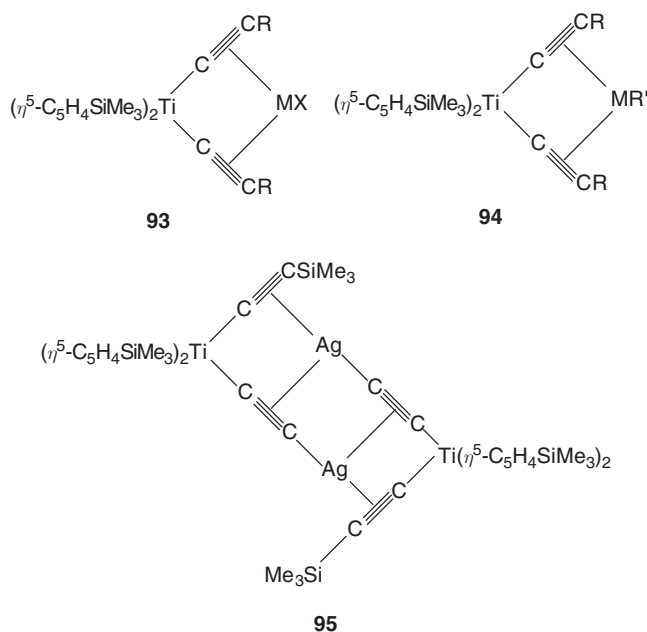


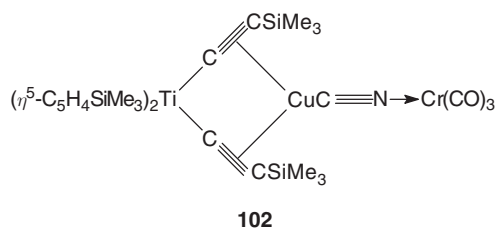
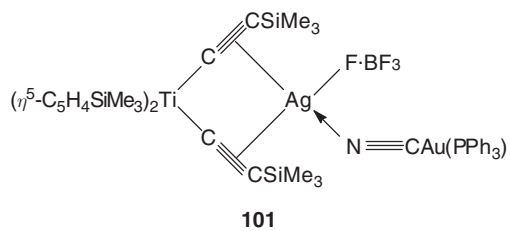
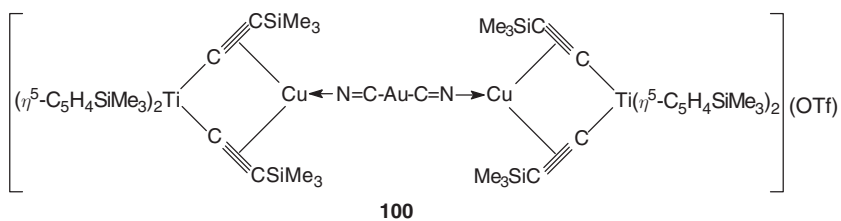
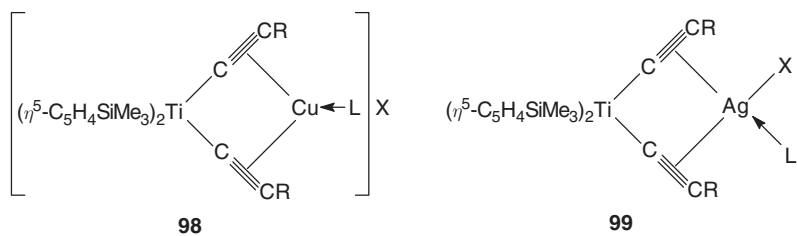
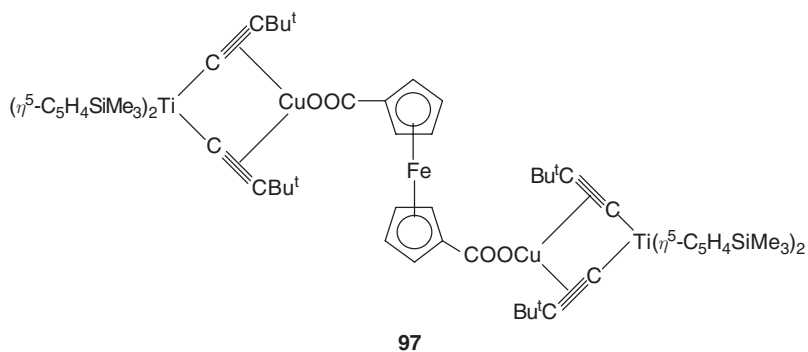
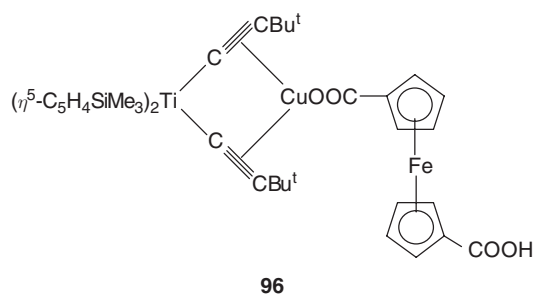
The palladium  $\eta^3$ -allenyl complex  $[(\text{C}_6\text{F}_5)(\text{Ph}_3\text{P})\text{Pd}(\eta^3\text{-(Bu}^t\text{)C}\equiv\text{CH}_2)]$  reacts with  $[\text{Pt}(\text{PPh}_3)_2(\text{C}_2\text{H}_4)]$  to yield the binuclear mixed-metal product **92** [<1998JA1938>](#). Palladium dimer  $[\text{Pd}(\mu\text{-Cl})(\eta^3\text{-C}_3\text{H}_5)]_2$  interacts with  $\text{A}[\text{cis-Pt}(\text{C}_6\text{F}_5)_2(\text{C}\equiv\text{CR})_2]$  ( $\text{A} = \text{PPh}_3\text{Me}$ ,  $\text{R} = \text{Ph}$ ;  $\text{A} = \text{N}^t\text{Bu}_4$ ,  $\text{R} = \text{Bu}^t$ ,  $\text{SiMe}_3$ ) to yield the heterodinuclear cluster  $[\text{cis-Pt}(\text{C}_6\text{F}_5)_2(\mu\text{-C}\equiv\text{CR})_2\text{Pd}(\eta^3\text{-C}_3\text{H}_5)]$  ( $\text{R} = \text{Ph}$ ,  $\text{Bu}^t$ ,  $\text{SiMe}_3$ ) [<1996OM4537>](#). Similar transformations are known [<1997AG\(E\)606, 1998JA6952, 1998OM4578>](#).



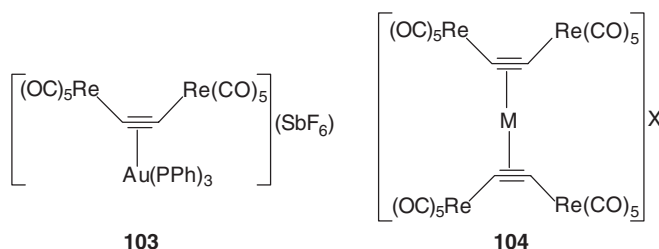
#### 4.16.3.2 A Genuine Transition Metal Linked to a Late Transition, i.e., Group 11 (Cu, Ag, Au) or 12 (Zn, Cd, Hg) Metal

Reaction of  $[(\eta^5\text{-C}_5\text{H}_4\text{SiMe}_3)_2\text{Ti}(\text{C}\equiv\text{CSiMe}_3)_2\text{CuSC}_6\text{H}_4\text{CH}_2\text{NMe}_2\text{-2}]$  with organic nucleophiles (R) gives  $[(\eta^5\text{-C}_5\text{H}_4\text{SiMe}_3)_2\text{Ti}(\text{C}\equiv\text{CSiMe}_3)_2\text{CuR}]$ , where the ethynyl moiety is coordinated to the copper(I) site in an  $\eta^2$  fashion [<1996IC2476, 1996JA4817, 1996SL1>](#). Titanocene  $[(\eta^5\text{-C}_5\text{H}_4\text{SiMe}_3)_2\text{Ti}(\text{C}\equiv\text{CR})_2]$  (R = Bu<sup>t</sup>, SiMe<sub>3</sub>) and MX (M = Cu, X = SCF<sub>3</sub>, SEt, SC<sub>6</sub>H<sub>4</sub>CH<sub>2</sub>NMe<sub>2</sub>-2; M = Ag, X = COOMe, COOPh, NO<sub>3</sub>) give products **93** with the relevant sets of R, M, and X [<1997OM4776, 1999OM598>](#). Products **93** (MX = CuSC<sub>6</sub>H<sub>4</sub>CH<sub>2</sub>NMe<sub>2</sub>-2, R = Bu<sup>t</sup>, SiMe<sub>3</sub>; R = Bu<sup>t</sup>, AgX = AgOCOMe, AgOCOPh, AgONO<sub>2</sub>; R = SiMe<sub>3</sub>, AgX = AgOCOMe, AgOCOPh, AgONO<sub>2</sub>) react with LiR' (R' = Me, C<sub>6</sub>F<sub>5</sub>, C<sub>6</sub>H<sub>2</sub>(CF<sub>3</sub>)<sub>3</sub>-2,4,6) or Mg(C<sub>6</sub>H<sub>2</sub>Ph<sub>3</sub>-2,4,6)Br to produce **93** (R = SiMe<sub>3</sub>, MX = CuC<sub>6</sub>F<sub>5</sub>, CuC<sub>6</sub>H<sub>2</sub>(CF<sub>3</sub>)<sub>3</sub>-2,4,6, CuC<sub>6</sub>H<sub>2</sub>-Ph<sub>3</sub>-2,4,6, AgC<sub>6</sub>H<sub>2</sub>(CF<sub>3</sub>)<sub>3</sub>-2,4,6, AgC<sub>6</sub>H<sub>2</sub>-Ph<sub>3</sub>-2,4,6, AgMe; R = Bu<sup>t</sup>, CuC<sub>6</sub>H<sub>2</sub>-Ph<sub>3</sub>-2,4,6, CuMe, AgMe). Species **94** (R = SiMe<sub>3</sub>, MX = AgMe) tends to lose free silane at -10 °C and form **95**. The arrangement of the silver-containing part of this heterotetranuclear complex is similar to that in  $[\text{AgC}\equiv\text{CR}]_n$  [<1996OM639>](#). Similar examples are described in numerous sources, e.g., [<1996JCS\(CC\)2043, 1996JOM\(514\)219, 1996JOM\(515\)57, 1997OM4970>](#). Species **93** (R = Bu<sup>t</sup>, MX = CuMe) on reaction with  $[(\eta^5\text{-C}_5\text{H}_4\text{COOH})_2\text{Fe}]$  may lose one methane molecule (reactant ratio 1:1) or two such molecules (reactant ratio 2:1) to yield **96** and **97**, respectively [<1999OM5725>](#). Interaction of **93** (R = Me<sub>3</sub>Si, MX = CuMe) with the product **96** gives an analog of **97** where half of the molecule contains *t*-butylethynyl and half trimethylsilylethynyl moieties. Another product formed in this reaction is  $[(\eta^5\text{-C}_5\text{H}_4\text{SiMe}_3)_2\text{Ti}(\text{C}\equiv\text{CSiMe}_3)(\text{C}\equiv\text{CCu})_2]$  [<1999JPRC1>](#). Copper (I) acetate and benzoate species [<1998MI2>](#) are among the related examples. Complexes **93** (M = Cu, Ag; X = OTf, BF<sub>4</sub>, ClO<sub>4</sub>) with Lewis acids, e.g., methyl cyanide, phenyl cyanide, and THF, form complexes of the types **98** and **99** [<1996IC2476>](#). Species **98** (L = NCMe X = BF<sub>4</sub>) with Ph<sub>3</sub>PAuCN gives **100** [<2000OM749>](#). Reaction of **93** (M = Ag, X = BF<sub>4</sub>) with Ph<sub>3</sub>PAuCN leads to the formation of the neutral complex **101**, while reaction of **93** (M = Cu, X = CN) with  $[\text{Cr}(\text{CO})_5(\text{THF})]$  gives **102**.

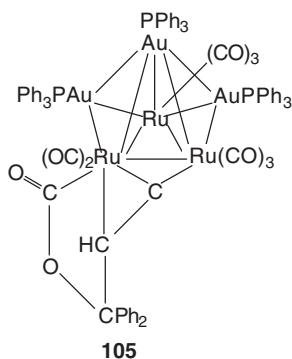




Examples of the trinuclear **103** and pentanuclear **104** ( $M = \text{Cu}$ ,  $X = \text{PF}_6^-$ ;  $M = \text{Ag}$ ,  $X = \text{SbF}_6^-$ ) complexes are remarkable, since these compounds do not contain metal-metal bonds <1999CEJ745, 2003AG(E)1794>. Dianionic cluster  $[\text{Fe}_3(\text{CO})_9(\text{CCO})]^{2-}$  with  $[\text{Re}(\text{CO})_5]^-$  gives  $[\text{Fe}_3(\text{CO})_9\text{CCRe}(\text{CO})_5]^-$  <1996OM3916>.



Reaction of  $[\text{Ru}_3(\mu\text{-H})(\mu_3\text{-C}_2\text{CPh}_2(\text{OH}))(\text{CO})_9]$  with  $\text{K}(\text{BHBu}^s)_3$  and then  $[\text{AuCl}(\text{PPh}_3)]$  gives the heterohexanuclear  $\text{Au}_3\text{Ru}_3$  cluster **105** <1996OM394, 1999ICC453>. Similar cases were analyzed <1997JOM(545)207>.



Heteropolynuclear clusters can be prepared by oxidizing homonuclear species with copper (I), silver (I), and gold (I) salts <1999CCR(193)619>. Thus, the reaction of  $[(\eta^5\text{-Cp})_3\text{Co}_3(\mu\text{-CPh})_2]$  with silver acetate and silver nitrate yields  $[(\eta^5\text{-Cp})_3\text{Co}_3(\mu_3\text{-CPh})_2(\mu\text{-AgX})]$  ( $X = \text{CF}_3\text{COO}$ ,  $\text{NO}_3$ ) <2004JOM(689)146>. When silver tetrafluoroborate or silver hexafluorophosphate in acetonitrile are used, the adduct has the composition  $[(\eta^5\text{-Cp})_3\text{Co}_3(\mu_3\text{-CPh})_2(\mu\text{-Ag(AN)})]^+$ .

Cationic species  $\text{PtAu}^+$  generated from the respective metal alloy dehydrogenates methane to produce the mixed cluster of composition  $[\text{PtAuCH}_2]^+$  <2003JA3676>. The product appeared to be an efficient mediator of the coupling reaction between methane and ammonia to produce hydrogen cyanide and molecular hydrogen.

#### 4.16.3.3 Two Late Transition Metals

No new substantial data are found since the publication of COFGT (1995).

#### 4.16.3.4 A Transition Metal and a Group 13 or 14 Metal

No new substantial data are found since the publication of COFGT (1995).

#### 4.16.3.5 A Transition Metal and Other Metals

No new substantial data are found since the publication of COFGT (1995).



#### 4.16.4 FUNCTIONS CONTAINING AT LEAST ONE GROUP 13 METAL (AND NO GROUP 1, 2, OR TRANSITION METAL)

The titanium–aluminum carbide clusters are stable <2000AG(E)3263, 2001OM3209, 2002JA11486> including  $[(\eta^5\text{-Cp})\text{Ti}(\mu\text{-Me})(\mu\text{-NPMe}_3)(\mu_4\text{-C})(\text{AlMe}_2)_3]$  <2001OM1175>. The reaction mixture consisting of  $[(\eta^5\text{-Cp})_2\text{ZrMe}_2]$ ,  $(\text{CPh}_3)(\text{B}(\text{C}_6\text{F}_5)_4)$ , and excess trimethylaluminum gives the heterodinuclear cationic cluster  $[(\eta^5\text{-Cp})_2\text{Zr}(\mu\text{-Me})_2\text{AlMe}_2]^+$  containing two bridging methyl groups <2000MCP581, 2003JOM(677)10>. The other aluminum-containing anions following from C–H activation are the result of an interaction between trimethylaluminum and  $[(\eta^5\text{-Cp}^*)\text{CrCl}_2]_2$  <2003OM1992>. They have the composition  $\{[(\eta^5\text{-Cp}^*)\text{Cr}]_4(\mu\text{-Cl})_3(\mu\text{-CH}_2)_4\text{-AlMe}\}[(\text{Me}_2\text{Al})(\mu_3\text{-O})(\text{AlCl}_2\text{Me})(\text{AlMe}_2\text{Cl})]$ .

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**Biographical sketch**

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# 4.17

## Functions Incorporating Two Halogens or a Halogen and a Chalcogen

D. J. St. JEAN, Jr. and G. A. MOLANDER  
*University of Pennsylvania, Philadelphia, PA, USA*

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### 4.17.1 DIHALO FUNCTIONS: $R_2C=C(Hal)_2$

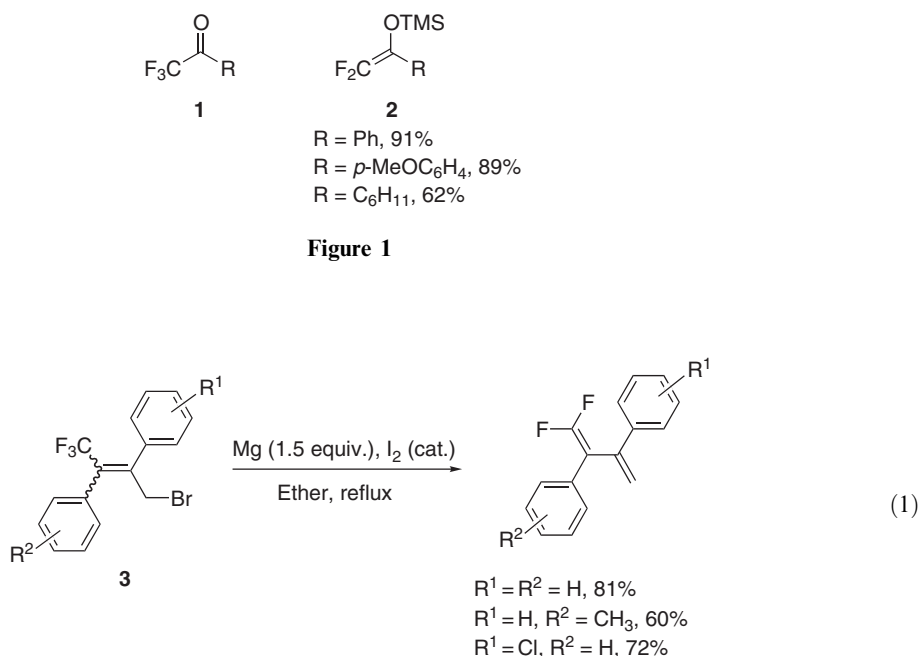
#### 4.17.1.1 Difluoro Alkenes

Difluoroalkenes can be synthesized using a number of well-defined synthetic procedures. These methods have been organized into those involving elimination reactions, the use of organometallics (i.e., additions, substitutions, and Pd-catalyzed cross-couplings), reactions using Wittig-type reagents, thermal reactions, and miscellaneous routes.

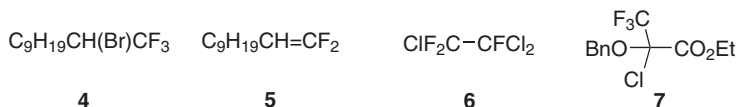
##### 4.17.1.1.1 Elimination reactions

###### (i) Eliminations involving metals in the zero oxidation state

Exposing trifluoromethyl ketones **1** to Mg(0) (with catalytic amounts of  $I_2$ ) results in the formation of an enolate that can be trapped as its trimethylsilyl (TMS) enol ether **2** (see Figure 1) <1999CC1323>. Jeong and co-workers reported that 2,3-diaryl-1,1-difluoro-1,3-butadienes **3** (see Equation (1)) could also be debromofluorinated with Mg(0) to yield difluoro alkenes, presumably through a cyclic transition state <2001SC2261>. Also utilizing Mg(0), 2-bromo-1,1,1-trifluoroundecane **4** was converted to 1,1-difluoroundeca-1-ene **5** <2002JOC8430, 1996TL3223>.



Zinc dust has also been shown to be an efficient reductant for this process. Zinc readily eliminated  $Cl_2$  from **6** (Zn, EtOH, 60 °C, 80%) <2000T3539> and  $ClF$  from **7** (Zn, DMF, 85%) <1995CC1969> (see Figure 2).

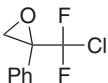
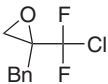
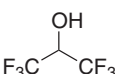
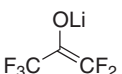


**Figure 2**

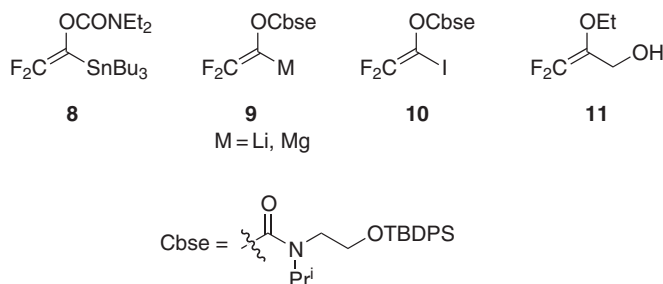
## (ii) Elimination reactions utilizing organometallics

Because of their high basicity, organometallic bases have been extensively used to generate 1,1-difluoroalkenes. Organolithiums, especially *n*-BuLi, are often used to mediate the elimination of HF from trifluoromethylated compounds. Some representative examples of eliminations using *n*-BuLi are shown in Table 1.

**Table 1** Eliminations using Bu<sup>n</sup>Li to produce 1,1-difluoroalkenes

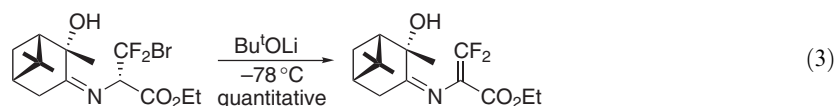
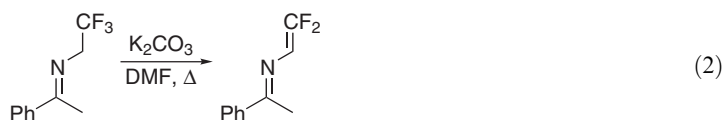
Substrate	Product	Reagents	Yield (%)	References
HOCH <sub>2</sub> CF <sub>3</sub>	PMBOCH=CF <sub>2</sub>	i. NaH, PMBCl ii. Bu <sup>n</sup> Li	32	<2002BMCL2353>
ROCH <sub>2</sub> CF <sub>3</sub> R = (CH <sub>3</sub> )CH=CH <sub>2</sub>	ROCH=CF <sub>2</sub>	Bu <sup>n</sup> Li	100	<2001TL6377>
MEMOCH <sub>2</sub> CF <sub>3</sub>	MEMOC(SnBu <sub>3</sub> )=CF <sub>2</sub>	Bu <sup>n</sup> Li Bu <sub>3</sub> SnCl	70	<1995TL9201>
	MEMOC(TMS)=CF <sub>2</sub>	Bu <sup>n</sup> Li TMSCl	79	<1995TL9201>
	MEMOCH=CF <sub>2</sub>	Bu <sup>n</sup> Li NH <sub>4</sub> Cl	88	<1995TL9201>
(Me <sub>2</sub> N) <sub>2</sub> CHCF <sub>3</sub>	(Me <sub>2</sub> N) <sub>2</sub> C=CF <sub>2</sub>	Bu <sup>n</sup> Li NH <sub>4</sub> Cl		<1997JOC1576>
	HOCH <sub>2</sub> CH(Ph)=CF <sub>2</sub>	Bu <sup>n</sup> Li	70	<1995CC1857>
	HOCH <sub>2</sub> CH(Bn)=CF <sub>2</sub>	Bu <sup>n</sup> Li	75	<1995CC1857>
		Bu <sup>n</sup> Li		<1999OS151>

Lithium diisopropylamine (LDA) has also been used to produce various 1,1-difluoroalkenes. LDA has been used to make stannane **8** <2000SL963, 1996TL5975>, highly reactive organometallics **9** <1999CC2183, 1995T10289>, vinyl iodide **10**, and substituted 1,1-difluoro alkene **11** in high yields <1996SL371, 2000SL963> (see Figure 3). In addition to *n*-BuLi and LDA, Grignard reagents have also been shown to defluorinate allylic acetates <1999IJ193>.

**Figure 3**

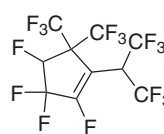
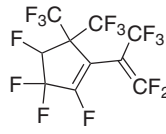
## (iii) Miscellaneous elimination reactions

Certain imines have also been shown to undergo elimination of HX to form difluoroalkenes with either K<sub>2</sub>CO<sub>3</sub> <2002JCS(P2)1033> or *t*-BuOLi <2001TA1303> (Equations (2) and (3)).



A variety of other bases have been shown to promote the formation of 1,1-difluoroalkenes via an elimination pathway. Table 2 provides some stereotypical examples of these elimination reactions.

**Table 2** Miscellaneous eliminations to form 1,1-difluoroalkenes

Substrate	Product	Reagents	Yield (%)	References
$\text{RCF}_2\text{OCF}(\text{CF}_3)\text{C}(\text{O})\text{F}$ $\text{R}=\text{C}(\text{CF}_3)(\text{F})\text{OC}_3\text{F}_7$	$\text{RCF}_2\text{OCF}=\text{CF}_2$	$\text{Na}_2\text{CO}_3$		<2000JFC(106)13>
		$\text{KF}, \Delta$		<2000JFC(104)239>
$\text{CF}_3\text{CH}_2\text{PPh}_2$ $\text{ClF}_2\text{CCHIF}$	$\text{F}_2\text{C}=\text{CHPPh}_2$ $\text{F}_2\text{C}=\text{CIF}$	<i>t</i> -BuOK hydrated lithium dibromoplumbite cat. TBAF	75	<1999JFC(97)109> <1997JFC(83)171>
$(\text{TMSF}_2\text{C})_2$	$\text{F}_2\text{C}=\text{CFTMS}$			<1997JA1572>
$\text{TMSCH}_2\text{CH}(\text{CO}_2\text{Bu}^t)$ $\text{CO}_2\text{Et}$	$\text{TMSCH}_2\text{C}=\text{CF}_2$ $\text{CO}_2\text{Et}$	(i) NaH, $\text{CF}_2\text{Br}_2$ (ii) TFA (iii) NaOH	80	<1996TL5401>
$(\text{BrCF}_2)_2\text{CH}_2$	$\text{BrF}_2\text{CCH}=\text{CF}_2$	KOH, $60^\circ\text{C}$ 35 mmHg	89	<1997S1481>
$\text{TMS}(\text{CH}_2)_2\text{CF}_2\text{Br}$	$\text{TMSCH}_2\text{CH}=\text{CF}_2$	DBU	70	<1995OS225>

#### 4.17.1.1.2 Reactions involving organometallics

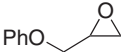
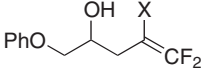

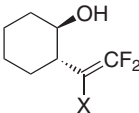
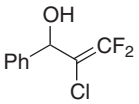
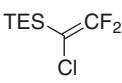

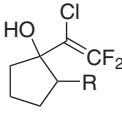
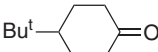
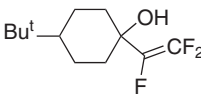
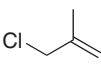
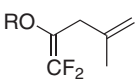
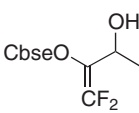
##### (i) Addition reactions

A number of nucleophilic addition reactions involving metallated difluoroethylenes have been reported. Organolithiums, organocuprates, and Grignard reagents have been used in nucleophilic additions involving a wide array of electrophiles (Table 3).

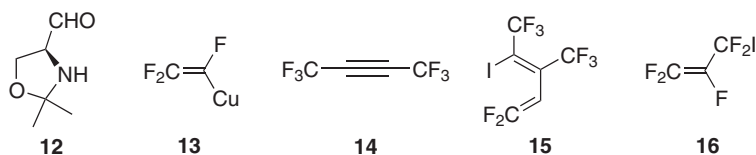
In addition to the organometallics shown in Table 3, Qing and co-workers have shown that  $\text{CF}_3\text{CFBr}_2$  adds to chiral Garner aldehyde **12** in 54% yield with exquisite diastereoselectivity using Zn dust and catalytic amounts of  $\text{AlCl}_3$  <1999JCS(P1)3345>. Cuprate **13** added across bis-trifluoromethylacetylene **14** and, after coupling with  $\text{I}_2$ , yielded fluorinated 1,3-pentadiene **15** in high yield <1995JFC(72)49>. Burton and co-workers also reported that fluorinated allyl iodide **16** reacted with an eclectic variety of electrophiles in good yield using copper metal <1998JOC2887> (see Figure 4).



**Table 3** Addition of organometallics that produce 1,1-difluoroalkenes

Nucleophile	Electrophile	Product	Yield (%)	References
$\text{F}_2\text{C}=\text{C}(\text{X})\text{Li}$ $\text{X} = \text{F}, \text{Cl}$			$\text{X} = \text{F}, 65^{\text{a}}$ $\text{X} = \text{Cl}, 32^{\text{a}}$	<2000JFC(102)43>
$\text{F}_2\text{C}=\text{C}(\text{X})\text{Li}$ $\text{X} = \text{F}, \text{Cl}$			$\text{X} = \text{F}, 69^{\text{a}}$ $\text{X} = \text{Cl}, 76^{\text{a}}$	<1999CC2535>
$\text{F}_2\text{C}=\text{C}(\text{Cl})\text{Li}$	PhCHO		96	<1998JCS(P1)2541>
	TESCl		89	<1998JCS(P1)2541>
	 $\text{R} = (\text{CH}_2)_2\text{CO}_2\text{Et}$		70	<2000CC2339>
$\text{F}_2\text{C}=\text{C}(\text{F})\text{Li}$			100 <sup>b</sup>	<1999JFC(99)127>
$\text{F}_2\text{C}=\text{C}(\text{OR})\text{Cu}$ $\text{R} = \text{CONEt}_2$			76	<1996TL5975>
$\text{F}_2\text{C}=\text{C}(\text{OCbse}^{\text{c}})\text{MgBr}$	CH <sub>3</sub> CHO		87	<1999CC2183>

<sup>a</sup> BF<sub>3</sub>·OEt<sub>2</sub> was also used. <sup>b</sup> Isolated as mixture of diastereomers. <sup>c</sup> Cbse = *N*-[2-(*t*-butyldiphenylsilyloxy)ethyl]-*N*-isopropylcarbamate.

**Figure 4***(ii) Cross-coupling reactions*

Fluorinated organozincs have been proven to be excellent partners in Pd-catalyzed cross-coupling reactions. Zinc reagent **17** (along with derivatives **22** and **23**) has been used in cross-coupling reactions to construct fluorovinylsalicylic acid derivatives (**18** and **19**) <1995JFC(74)67>, difluorostyrene derivatives **20** <1997JOC7758>,  $\alpha$ -bromo- $\beta,\beta$ -difluorostyrenes **21** <1998JOC1714>, and

functionalized protoporphyrins <1999CPB1326, 2000H383, 2000JFC(103)99> in good yields. Burton has developed a convenient one-pot approach to the synthesis of  $\alpha$ -chloro- $\beta,\beta$ -difluorostyrenes <2002TL6979> and  $\alpha,\beta,\beta$ -trifluorostyrenes <2002TL2731> using vinylzinc reagents **22** and **23**. This procedure provides a cost-efficient route to these frameworks and is reported to proceed smoothly at room temperature (rt).

Borane derivatives such as **24** have also been used in cross-coupling reactions, however, only with moderate success <2002CL282, 1997CC1537, 2001BJC971>. Percy and co-workers, while probing the reactivity of difluoroenol carbamates **25** (R = I) with arylboronic acids in Suzuki–Miyaura cross-couplings, have reported that this class of compounds also underwent Stille couplings in good yields to form **26** <2000SL963>.

Finally, both 2,2-difluorovinylzirconocene **27** and *gem*-difluorohomoallenyl bromide **28** have been demonstrated to undergo palladium-catalyzed cross-coupling reactions to form 1,1-difluoroalkenes <1999TL7261, 1996TL8799, 2001OL2213> (see Figure 5).

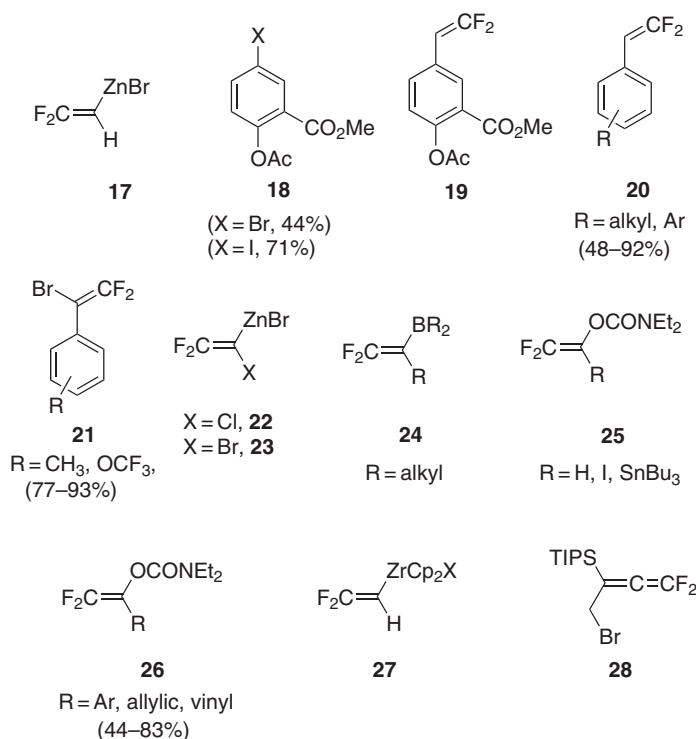


Figure 5

### (iii) Substitution reactions

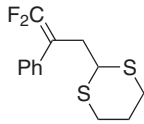
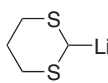
Sodium thiophenoxide cleanly displaces bromide ion in bromodifluoromethyl alkenes ( $\text{BrCF}_2\text{CH}=\text{CHR}$ ) via an  $\text{S}_{\text{N}}2'$  displacement to yield fluorinated allylic sulfides in moderate-to-high yields (52–100%) with good regioselectivities (100:1 to 1:6). <2001JFC(107)89> Other nucleophilic organometallics have been shown to be equally as useful (Table 4).

Of particular synthetic importance is the work by Nemoto and co-workers. This method involved the use of 1-bromo (or acetoxy)-1,1-difluoroallyl derivatives in catalytic  $\pi$ -allyl Pd reactions <2000CPB885, 1995TL6305>.

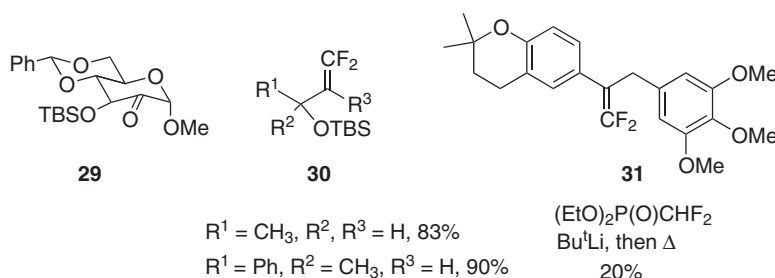
#### 4.17.1.1.3 Wittig-type reactions

In addition to the thorough review of Wittig reactions that form 1,1-difluoroalkenes presented in chapter 4.17.1.2.2 in COFGT (1995) <B-1995COFGT(4)729>, Burton has written a number of reviews concerning the reactivity of fluorinated ylides <1996CRV1641, 1999JFC(100)177>.

**Table 4** Substitution reactions that form 1,1-difluoroalkenes

Substrate	Product	Reagents	Yield (%)	References
$\text{CF}_3\text{C}(\text{CO}_2\text{Et})=\text{NPh}$	$\text{CF}_2=\text{C}(\text{CO}_2\text{Et})\text{NPh}(\text{Et})$	$\text{Et}_2\text{Zn}$	80	<1996TL2045>
$\text{CF}_3(\text{Ph})\text{C}=\text{CH}_2$	$\text{CF}_2=\text{C}(\text{Ph})\text{CH}_2\text{CH}_3$	$\text{CH}_3\text{Li}$	90	<1995TL5003>
$\text{CF}_3(\text{Ph})\text{C}=\text{CH}_2$			90	<1995TL5003>
$\text{CF}_3(\text{Ph})\text{C}=\text{CH}_2$	$\text{CF}_2=\text{C}(\text{Ph})\text{CH}_2\text{N}(i\text{-Pr})_2$	LDA	90	<1996JCS(P1)1409>
$\text{CF}_3\text{C}(\text{F})=\text{C}(\text{H})\text{NMe}_2$	$\text{CF}_2=\text{C}(\text{F})\text{CH}(\text{Ph})(\text{NMe}_2)$	$\text{PhMgBr}$	87	<1999TL2985>
$E\text{-(}n\text{-hex)}\text{CH}=\text{CHCF}_2\text{Br}$	$(n\text{-hex})(n\text{-BuLi})\text{-CHCH}=\text{CF}_2$	$\text{Bu}^n\text{Li}$ , $-20^\circ\text{C}$	96	<1997TL5989>
$E\text{-(}n\text{-hex)}\text{CH}=\text{CHCF}_2\text{Br}$	$(n\text{-hex})(\text{TMS})\text{-CHCH}=\text{CF}_2$	$\text{TMS-Li}$ $\text{CuCN}$	75	
$\text{CH}_2=\text{CHCF}_2\text{Br}$	$(\text{CO}_2\text{Et})_2(\text{CH}_3)\text{C-CH}=\text{CF}_2$	4 mol.% $\text{Pd}^0$ $(\text{CO}_2\text{Et})_2\text{CCH}_3$ Na	97	<2000CPB885>

Serafinowski and co-workers successfully converted a ketone to a 1,1-difluoroalkene using a Wittig reagent generated *in situ* from dibromodifluoromethane ( $\text{CF}_2\text{Br}_2$ ) and hexamethylphosphorus triamide (HMPT) in good overall yield (69–74%) <1996T7929, 2000T333>. Yamazaki and co-workers have also utilized this method to difluoromethylenate 2-keto arabinoside **29** <1997SL669>. Yamazaki and co-workers have also reported that  $\alpha$ -substituted ketones could be difluoromethylated to form difluoroalkenes **30** <2001OL743>. The combination of bromodifluoromethyl[tris(dimethylamino)]phosphonium bromide and zinc using sonication has also been reported <1997S225>. Nicolaou and co-workers have used diethyl(difluoromethyl)phosphonate/ $n\text{-BuLi}$  in dimethoxyethane (DME) to convert an aromatic ketone to the difluoro derivative **31**, albeit in low yield <2000MI972> (see Figure 6).

**Figure 6**

#### 4.17.1.1.4 Thermal methods

McCarthy and co-workers have reported a procedure that involved conversion of a carboxylic acid to sulfoxide **32**. Heating these sulfoxides neat at 160–200 °C resulted in the formation of the desired fluorinated alkenes **33** <1996TL3223>.

Exposure of sodium carboxylates **34** to high temperatures resulted in decarboxylation. The resulting anion then eliminated  $\text{NaF}$  to yield the desired difluoroalkene **35**. Thermally induced extrusion of substituted aromatic carboxylates **36** has also been reported <1998JFC(89)31>. This procedure has been used to make large amounts (>50 g) of difluorinated  $\alpha$ -halovinyl ethers. Shoichet and co-workers have also reported the thermolysis of various trimethylsilyl esters <1997JOC7844>.

Perhaps more synthetically useful is the decarboxylation of  $\alpha,\alpha$ -difluoro- $\beta$ -lactones **38** <1995JOC5378, 1998JFC(88)41>. Exposure of fluorinated hydroxy acids **37**, available from bromodifluoroacetate and various ketones via a Reformatsky reaction, to benzenesulfonyl

chloride followed by careful work-up produced the desired difluoro oxetanones **38**. Heating these lactones neat, or in solvent, yielded the 1,1-difluoroalkenes **39** in near quantitative yields.

Chen and co-workers have shown that the elimination of HBr from bromofluoroalkene **40** produced difluoroalkene **41** in high yield, although the reaction proceeded using harsh conditions (carbon, 300 °C/1 mmHg, 86%) <1997SI481>. Pyrolysis of fluorinated acid fluoride **42** also produced difluoroalkene **43**, but again required very harsh conditions <1999JFC(94)65>. Finally, while elucidating an anomalous elimination of HCl, Dolbier and co-workers also reported that the thermolysis (650 °C) of 2-chloro-1,1-difluoroethane produced relatively small amounts of 1,1-difluoroethylene <2002TL8075> (see Figure 7).

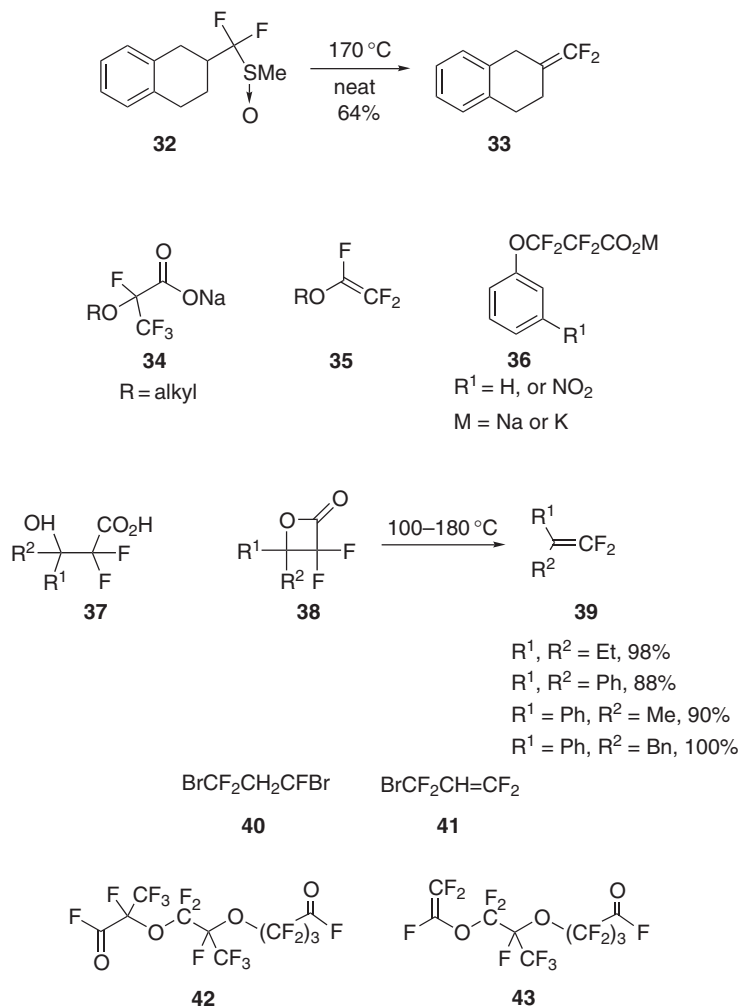


Figure 7

#### 4.17.1.1.5 Miscellaneous methods

A large number of research groups have reported the synthesis of 1-*tert*-butyldimethylsilyloxy-2,2-difluoroethylene derivatives **44**. These methods include the reaction of trifluoromethyltrimethylsilane **45** with TMS-ketone **46** <1999SL432>, electrochemical reduction of trifluoromethyl ketone **47** <1998TL3741>, and nucleophilic addition of *tert*-butyldimethylsilyllithium followed by a subsequent rearrangement <1998JCS(P1)1215>. These reactive silyl enol ethers have been utilized to form fluorinated 1,3-diketones via a Lewis-acid catalyzed aldol <2001JOC4543>.

Shen and co-workers have reported an elegant protocol for the formation of functionalized 1,1-difluoroalkenes <2001JFC(109)141>. In this procedure, 2,2-difluoro-1-tosyloxyvinyl anion **48** reacted with ethoxycarbonylvinylphosphonate **49** to yield a stabilized anion that can react further

with aldehydes to form *gem*-difluoropenta-1,4-dienes **50** in good overall yields (75–96%). Friedel–Crafts addition using  $\text{AlCl}_3$ , *p*-xylene, and 2,3,3-trifluoropropenol **51** has also been reported <1999JOC1366>. Burton and co-workers reported a convenient procedure to access tetrafluoroallene **53** by allowing anion **52** to warm to rt <1995JFC(75)83>. It should be noted that the elimination of  $\text{LiF}$  proceeded smoothly, with only trace amounts (2%) of tetrafluoropropyne **54** being formed under optimized conditions. Finally, Huang and co-workers demonstrated that aryl thiols added to 1,1-difluoroallene **55** to produce 1,1-difluoro substituted sulfides **56** in good yields (61–94%) <1995JFC(70)5> (see Figure 8).

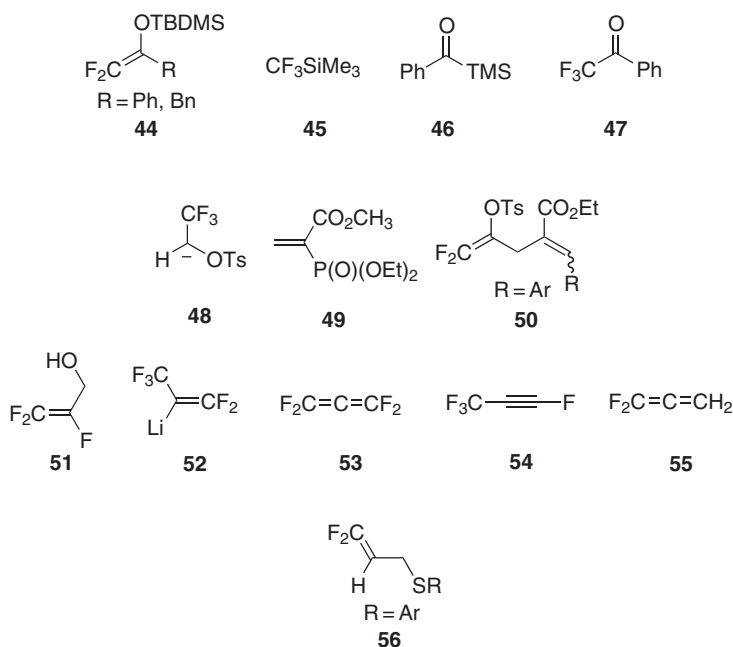


Figure 8

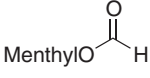
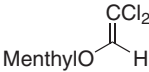
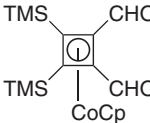
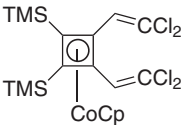
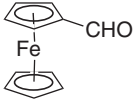
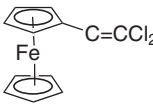
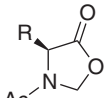
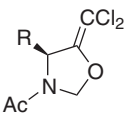
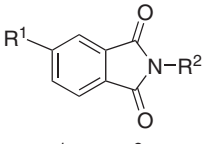
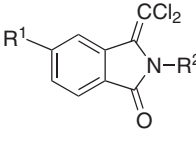
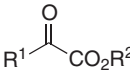
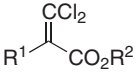
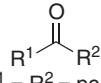

#### 4.17.1.2 Dichloro Alkenes

Because of the structural similarity with difluoroalkenes, a number of similar transformations have been reported to construct 1,1-dichloroalkenes. Also, just as for difluoroalkenes, these transformations can be conveniently grouped into categories that include the Wittig-type reaction of carbonyls using  $\text{PPh}_3$  and  $\text{CCl}_4$ , reactions involving dichlorocarbenes, elimination reactions, and miscellaneous routes.

##### 4.17.1.2.1 Wittig and related reactions

One of the most synthetically useful routes to 1,1-dichloroalkenes is the reaction of carbonyl compounds with a  $\text{PPh}_3/\text{CCl}_4$  mixture. In the late 1990s and early 2000s, a large number of research groups have used this method to form a wide range of dichloroalkenes. As displayed in Table 5, this procedure has been shown to work well for  $\alpha$ -ketoesters, amides, formates, lactones, ketones, and succinimides. Ketones and aldehydes readily underwent the dichloromethylenation at low temperatures ( $\text{CCl}_4$ , rt), whilst amides, lactones, and esters required higher temperatures (refluxing tetrahydrofuran (THF)). In certain cases, however, ketones have required the use of higher temperatures (Table 5, last entry).

**Table 5** Formation of 1,1-dichloroalkenes by reaction of triphenylphosphine and carbon tetrachloride with various carbonyl compounds

Substrate	Product	Conditions	Yield (%)	References
( <i>n</i> -Bu)NTsCHO	( <i>n</i> -Bu)NTsC=CCl <sub>2</sub>	PPh <sub>3</sub> , CCl <sub>4</sub> THF, 60 °C	99	<2000SL1402>
(Ph)NTsCHO	(Ph)NTsC=CCl <sub>2</sub>		81	<2000SL1402>
(Bz)NTsCHO	(Bz)NTsC=CCl <sub>2</sub>		96	<2000SL1402>
RNTsCHO R=CH <sub>2</sub> CH=CH <sub>2</sub>	RNTsC=CCl <sub>2</sub>		97	<2001MI369>
			87	<2000SL1402>
		PPh <sub>3</sub> , CCl <sub>4</sub> Mg	53	<1999JOM(578)144>
		4 equiv. PPh <sub>3</sub> 2 equiv. CCl <sub>4</sub>	85	<2000SC1569>
		PPh <sub>3</sub> , CCl <sub>4</sub> THF, reflux	96 78 75	<1998CL1237> <1998CL1237> <1998CL1237>
R = Bn R = Me R = Pr <sup>i</sup>				
		PPh <sub>3</sub> , CCl <sub>4</sub>	31 39	<1995JHC783> <1995JHC783>
R <sup>1</sup> = H, R <sup>2</sup> = Bn R = H, R <sup>2</sup> = (CH <sub>2</sub> ) <sub>2</sub> p-Tol				
		PPh <sub>3</sub> , CCl <sub>4</sub> , CH <sub>2</sub> Cl <sub>2</sub>	62 65	<2002SC2821> <2002SC2821>
R <sup>1</sup> = Ph, R <sup>2</sup> = Me R <sup>1</sup> = Tol, R <sup>2</sup> = Me				
		PPh <sub>3</sub> , CCl <sub>4</sub> THF, 60 °C	88 89	<2000S109> <2000S109>
R <sup>1</sup> = R <sup>2</sup> = pentyl R <sup>1</sup> = R <sup>2</sup> = fluorenyl				

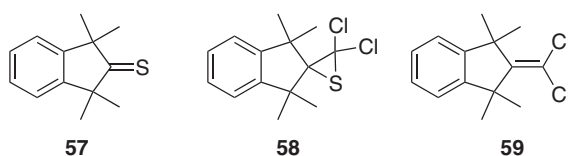
**4.17.1.2.2 Reactions involving dichlorocarbene**

Nenajdenko and co-workers reported a preparation of 1,1-dichloroalkenes from various ketones via the corresponding hydrazones <2002JCS(P1)883>. Exposure of the hydrazone to catalytic amounts of CuCl in CCl<sub>4</sub> led to good yields of chlorinated alkenes (Table 6). The mechanism of this reaction has been thoroughly studied <2000T6557>. Additionally, dichlorocarbene was also added to thioketone **57** to produce 2,2-dichlorothiirane **58**. This compound subsequently underwent desulfurization upon standing to give 1,1-dichloroalkene **59** <1999HCA946> (see Figure 9).

**Table 6** Formation of 1,1-dichloroalkenes using cat. CuCl

$$\begin{array}{c} \text{R}^1 \\ \diagdown \\ \text{C}=\text{NNH}_2 \\ \diagup \\ \text{R}^2 \end{array} \xrightarrow[\text{CuCl (cat.)}]{\text{CCl}_4} \begin{array}{c} \text{CCl}_2 \\ | \\ \text{R}^1-\text{C}=\text{R}^2 \end{array}$$

$R^1$	$R^2$	Yield (%)	References
<i>p</i> -Tol	Me	65	<2002JCS(P1)883>
<i>p</i> -ClC <sub>6</sub> H <sub>4</sub>	Me	82	<2002JCS(P1)883>
Ph	Me	57	<2002JCS(P1)883>
<i>p</i> -MeOC <sub>6</sub> H <sub>4</sub>	Me	70	<2002JCS(P1)883>
<i>p</i> -NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub>	H	84	<2000T6557>

**Figure 9**

#### 4.17.1.2.3 Elimination reactions

Metals in the zero oxidation state have been extensively used to produce 1,1-dichloroalkenes. During their synthesis of lennoxamine, Koseki and Nagasaka used a zinc/AcOH mixture to open trichloromethyl lactone reductively (**60** and **61**) in 90% yield <1995CPB1604>. A variety of 3,3,3-trichloropropyl acetates **62** readily underwent elimination using zinc dust to produce dichloroalkenes **63** in high yields <2000TL4007>. Additionally, Rao and co-workers used zinc metal to synthesize 1,1-dichloro-2,2-difluoroethylene **65** in 80% yield <2000T3539>. Zinc dust has also been shown to form TMS silyl ketene acetal **67** in good yield from trichloromethyl ester **66** <2001TL1313>. Despite the apparent generality of this method, Guirado and co-workers reported that exposing trichloromethylamides **68** to zinc metal did not form the desired dichloroalkene **71**, rather the partial reduction product **69** was formed. This problem was solved by first reacting amides **68** with PCl<sub>5</sub> to yield chlorides **70**, which can be electrochemically reduced to form **71** in good-to-excellent yields <2001T4925> (see Figure 10).

Like zinc, indium readily eliminated Cl-OR from functionalized trichloromethyl carbinols to produce dichloroalkenes. Although the reduction of trichlorocarbinols with indium metal yielded a mixture of products (30% after 18 h at 150 °C), reaction of the corresponding acetate, mesylate, or tosylate produced the chlorinated alkene in excellent yields (Table 7).

CrCl<sub>2</sub> has also been shown to be an efficient reductant <2001CC4925>. Using CrCl<sub>2</sub>, trichloromethyl derivatives **72** has been converted to dichloroalkene **73** in near quantitative yield.

1,1-Dichloroalkenes, like difluoroalkenes, can be constructed by elimination with various bases. Trichloroethyl carbamate **74** reacts with excess lithium diisopropylamide (LDA) to yield dichlorovinyl carbamate **75** in 90% yield <2002OL2193>. Back and Minksztyl reported that allylic selenides **76** could be constructed by elimination of HCl from the trichloromethyl derivatives using *t*-BuOK at -10 °C in excellent yields <1997CC1759>. Lastly, α,α-dichlorocyclobutanones **77** undergo photocycloelimination to yield 1,1-dichloroalkenes **78** in acceptable yields <1999CJC1245> (see Figure 11).

#### 4.17.1.2.4 Miscellaneous reactions

A polychloromethane–titanocene (II) system has been used to construct dichloroalkenes from a variety of ketones. Reaction of titanium complex **79** with ketones in CCl<sub>4</sub> resulted in good yields of the dichloroalkenes **80** <1999T2475>. The Ramberg–Bäcklund rearrangement has also been used to construct 1,1-dichloroalkenes <1998T1901>. Using this rearrangement, Raj and co-workers reported that trichloromethyl sulfones **81** underwent base-induced

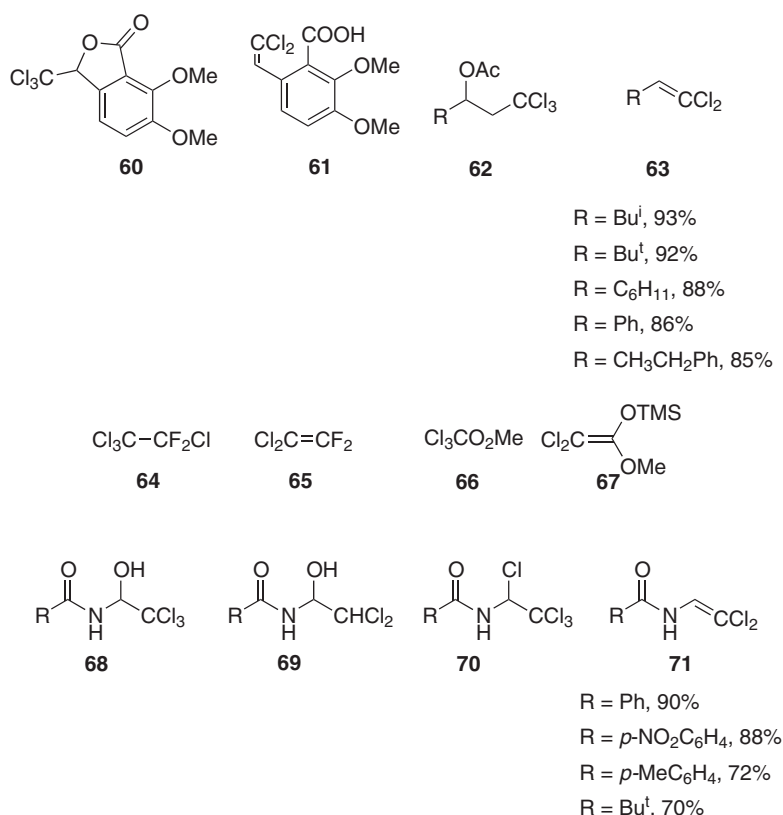


Figure 10

Table 7 Formation of 1,1-dichloroalkenes using indium

$  \begin{array}{c}  \text{R}^2\text{O} \\    \\  \text{R}^1-\text{C}-\text{CCl}_3 \\    \\  \text{H}  \end{array}  \xrightarrow[150-160\text{ }^\circ\text{C}]{\text{In, DMF}}  \begin{array}{c}  \text{CCl}_2 \\    \\  \text{R}^1-\text{C}-\text{H}  \end{array}  $			
R <sup>1</sup>	R <sup>2</sup>	Yield (%)	References
Ph	Ac	76	<2002TL5993>
Ph	Ms	93	<2002TL5993>
Ph	Ts	94	<2002TL5993>
<i>p</i> -MeOC <sub>6</sub> H <sub>4</sub>	Ms	92	<2002TL5993>
<i>p</i> -ClC <sub>6</sub> H <sub>4</sub>	Ts	95	<2002TL5993>

1,5,-diazabicyclo[5.4.0]undec-5-ene (DBU) rearrangement to give 1,1-dichloroalkenes **82** in excellent yields <2000TL1501>. Also, imine **83** reacted with diphenyldiazomethane at 65 °C to yield **84** in 70% yield <1999EJO1541>.

Additionally, while studying the conjugate addition/elimination of unsaturated-TMS esters, Cunico and Zhang reported the synthesis of 3,3-dichloro-1-(trimethylsilyl)-2-propenone **86** by hydrolysis of **85** (MeOH, H<sub>2</sub>O) <1995T9823>. Bis-alkylation of malonate derivatives with **87** has been used to construct symmetrical 1,1-dichloroalkene **88** <2000JOC8532>. Finally, Masuda and co-workers reported the preparation of 1,1-dichloroalkenes from alkynes via hydroboration <1995JCS(P1)2955>. Treatment of the dialkylborane with a copper(II) chloride in the presence of water produced the 1,1-dichloroalkene **89** in excellent yield (see Figure 12).



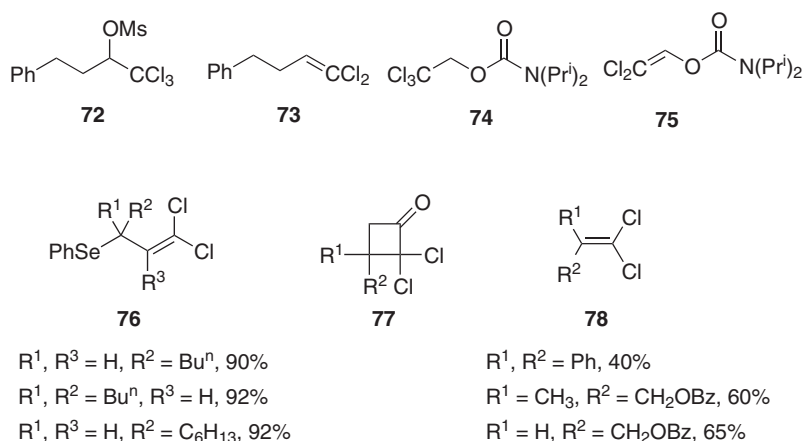


Figure 11

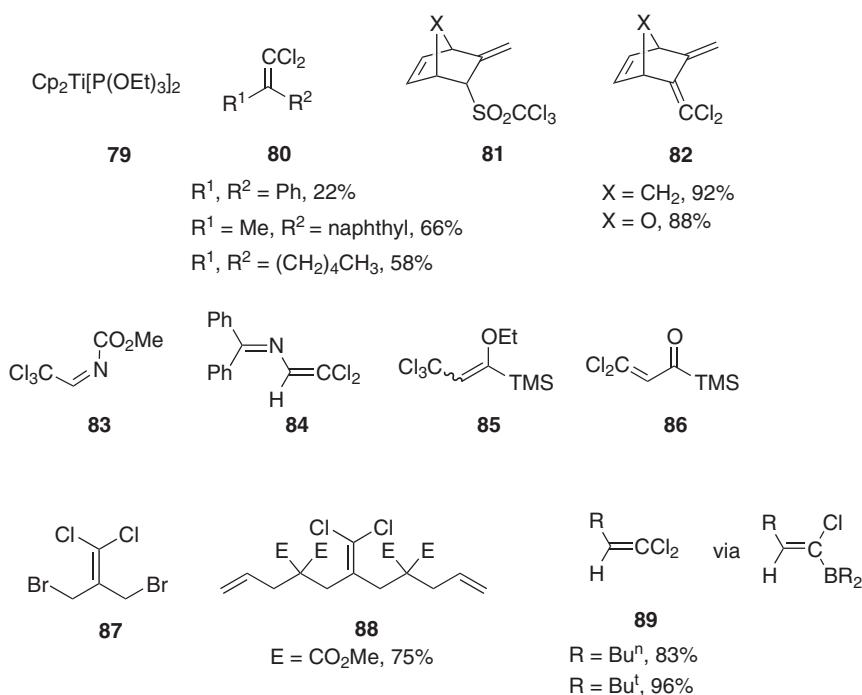


Figure 12

#### 4.17.1.3 Dibromo Alkenes

As expected, methods used to construct other 1,1-dihaloalkenes have been reported to be successful for 1,1-dibromo derivatives as well. The most common method involves the use of  $\text{PPh}_3$  and  $\text{CBr}_4$ . Other miscellaneous methods have also been reported.

##### 4.17.1.3.1 Wittig-type reactions

###### (i) Using $\text{PPh}_3$ and $\text{CBr}_4$

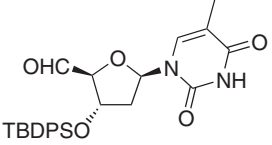
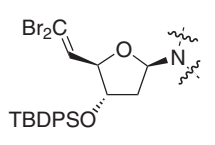
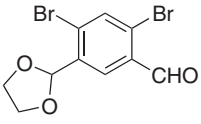
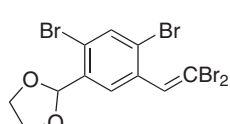
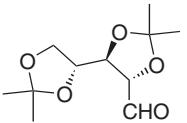
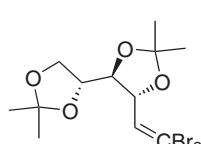
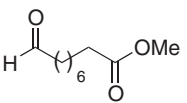
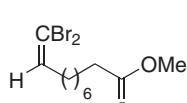
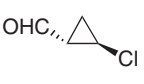
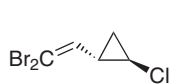
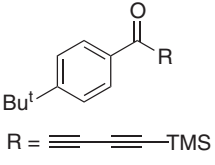
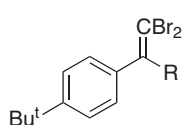
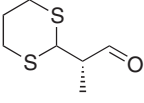
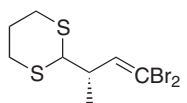
Since the seminal reports of Ramirez and co-workers [<1962JA1745>](#) and Corey and Fuchs [<1972TL3769>](#), the dibromination of carbonyl compounds using  $\text{PPh}_3$  and  $\text{CBr}_4$  has become

a common practice. The high functional group tolerance and typically high yields make this reaction especially amenable to natural product synthesis. Table 8 shows some stereotypical examples of this method, although the list is by no means comprehensive.

**Table 8** Formation of 1,1-dibromoalkenes using triphenylphosphine and carbon tetrabromide with various carbonyl compounds

Substrate	Product	Conditions	Yield (%)	References
		HMPT	95	<1997CL1193>
		25 °C, 15 h	92	<1998S1362>
		CH <sub>2</sub> Cl <sub>2</sub> , 0 °C	87	<1999EJO471>
		CH <sub>2</sub> Cl <sub>2</sub> -10 °C	95	<1999SC3125>
		NEt <sub>3</sub> CH <sub>2</sub> Cl <sub>2</sub>	91	<2000JA9099>
		CH <sub>2</sub> Cl <sub>2</sub> , 60 °C	92	<2000SL1402>
		-	>94	<2001JA4161>
		CH <sub>2</sub> Cl <sub>2</sub> , 0 °C to rt 2.5 h	76	<2001EJO1619>
		NEt <sub>3</sub>	>54	<2001JOC4904>
		CH <sub>2</sub> Cl <sub>2</sub> , -20 °C	92	<2002T2351>

Table 8 (continued)

Substrate	Product	Conditions	Yield (%)	References
		CH <sub>2</sub> Cl <sub>2</sub>	63	<1999SL1124>
		CH <sub>2</sub> Cl <sub>2</sub> , -20 °C	>80	<2002CEJ2116>
		CH <sub>2</sub> Cl <sub>2</sub> , rt	86	<2002T4955>
		CH <sub>2</sub> Cl <sub>2</sub> , 0 °C, 1 h	85	<2002OL2517>
		CH <sub>2</sub> Cl <sub>2</sub> 0 °C, 4 h	80	<2002JA10396>
		CH <sub>2</sub> Cl <sub>2</sub>	>21	<2003JOC1339>
		CH <sub>2</sub> Cl <sub>2</sub>	>92	<1999OL1249>

<sup>a</sup> PMB = *p*-Methoxybenzyl.

Kerr and co-workers reported that aldehyde **90** failed to react under standard conditions. Reacting this aldehyde with excess amounts of these reagents (3.6 equiv. PPh<sub>3</sub> and 1.8 equiv. CBr<sub>4</sub>) produced not only the 1,1-dibromoalkene, but also removed the dioxolane to give ketodibromide **91** <1996T7391>. However, there exists a successful report of the dibromination of this aldehyde without deprotection <1995CC457>.

While investigating the conversion of *p*-methoxybenzyl (PMB) ether to the corresponding alkyl bromides using CBr<sub>4</sub> and PPh<sub>3</sub>, Yadav and Mishra reported that PMB-aldehyde **92** was converted to the bromide **93** using an excess of reagents (4:2 PPh<sub>3</sub>/CBr<sub>4</sub>), with simultaneous removal of the PMB ether. The PMB ether can be removed selectively (2:1 PPh<sub>3</sub>/CBr<sub>4</sub>) <2002TL5419>. In certain cases, PPh<sub>3</sub> can be difficult to remove using standard methods. Sciotti and co-workers reported using polystyrene supported PPh<sub>3</sub> for Wittig-type reactions. This modification to the original procedure allowed for easy separation of the sometimes recalcitrant phosphine, and produced the desired olefin in good yield (**94** and **95**) <2002BMCL2121> (see Figure 13).

Finally, Martin and co-workers have investigated the reaction of simple  $\alpha,\beta$ -epoxy aldehydes with PPh<sub>3</sub> and CBr<sub>4</sub>. They reported that exposing aldehydes **96** to the reaction conditions does not provide the desired 1,1-dibromoalkene **98** directly; rather an intermediate bromohydrin **97** (see Scheme 1) was formed. The formation of this bromohydrin was reported to proceed with complete stereo- and regioselectivity. This bromohydrin could be converted into the desired 1,1-dibromo alkene upon exposure to *n*-Bu<sub>4</sub>NF tetra-*n*-butylammonium fluoride (TBAF) <2001JOC7231>.

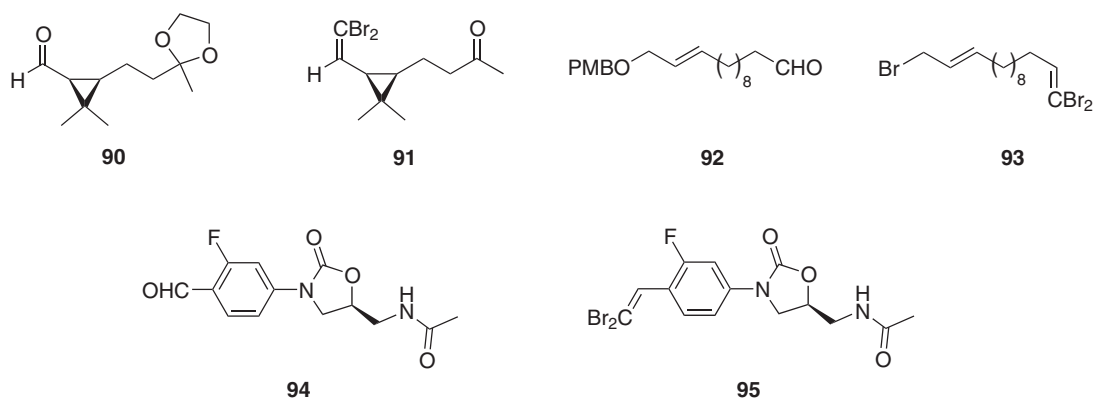
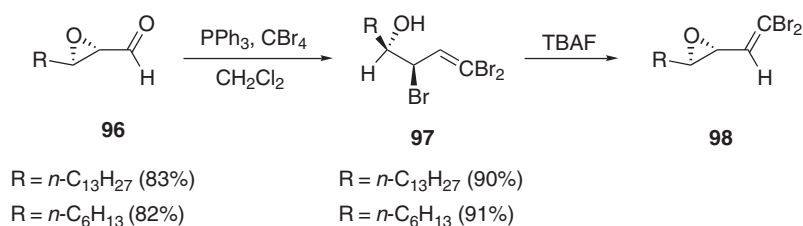


Figure 13



Scheme 1

(ii) Using  $\text{PPh}_3$  and  $\text{CBr}_4$  and Zn metal

Since the original discovery by Corey and Fuchs that the addition of zinc dust removed the requirement for excess amounts of  $\text{Ph}_3\text{P}$ , this reaction has become a valuable addition to the organic chemist's repertoire [\[1972TL3769\]](#). Similar to the  $\text{CBr}_4$  and  $\text{PPh}_3$  system, this mixture exhibits high functional group tolerance and is typically very high yielding.

Parsons and co-workers reported that aldehyde **99** is cleanly converted to 1,1-dibromoalkene **100** [\[1995SL255\]](#). Also,  $\alpha,\beta$ -unsaturated aldehydes undergo dibromination in excellent yield [\[2002JMC2651\]](#). For example, 3,3-dimethylacrolein **101** was converted into *gem*-dibromodiene **102** in high yield [\[2001OL1713, 2002SL743\]](#). Cyclopropanes are also stable under these conditions [\[2001AG\(E\)603\]](#). Cyclopropane **103** was cleanly converted to the *gem*-dibromide **104** in good yield (72%) [\[2002CEJ3195\]](#). Unlike cyclopropanes, epoxides sometimes undergo deleterious side reactions. Rather than delivering the expected product **106**, **105** produced aldehyde **107** (60%), a product derived from rearrangement of the epoxide. Formation of **106** (99% yield) could be achieved using hexamethylphosphorus triamide (HMPT) in place of triphenylphosphine [\[1995JA7379\]](#) (see Figure 14).

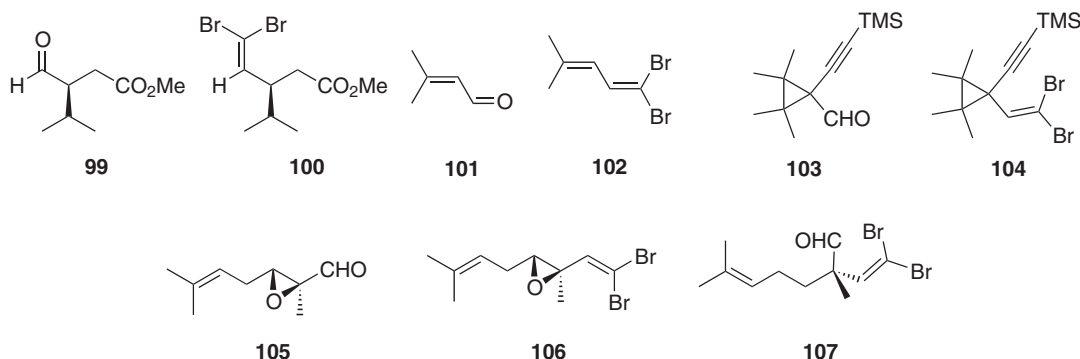
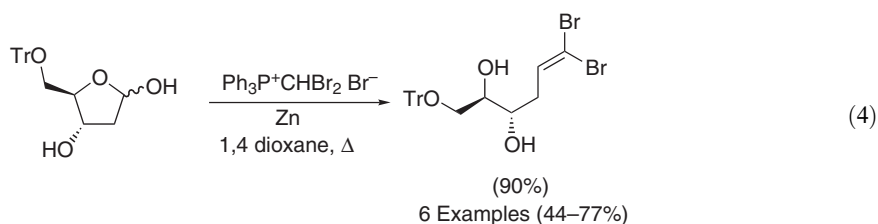


Figure 14

Lièvre and co-workers reported a procedure to dibrominate aldoses. Exposing substituted aldoses to an excess of dibromomethylenetriphenylbromophosphorane (4 equiv.) in hot 1,4-dioxane produced modest-to-good yields of the desired 1,1-dibromoalkene <2002TL1847> (Equation (4)).



This combination of reagents is also compatible with various protection groups. Dioxolanes, as well as methyl acetals, have been shown to be stable to these conditions (108 to 109 and 110 to 111) <2000TA4761, 2002OL3847>. When *t*-butyldimethylsilyl (TBDMS) ether 112 was exposed to a Zn, CBr<sub>4</sub>, and PPh<sub>3</sub> mixture, 113 (see Figure 15) was formed in 83% yield <2001JA765>. Triisopropyl silyl (TIPS) groups are also stable to these conditions <2001TL3175>.

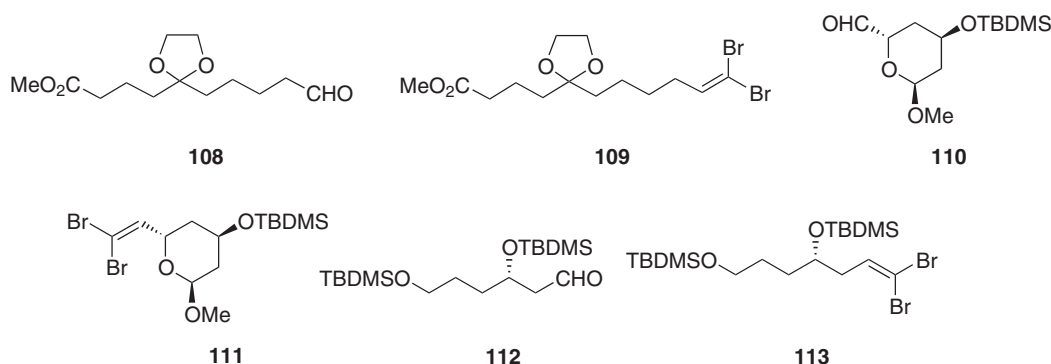


Figure 15

(iii) Using  $Ph_3PCHBr_2$  and *t*-BuOK

Although esters or lactones are not reactive toward the standard CBr<sub>4</sub> and PPh<sub>3</sub> mixture, the combination of bromomethylenetriphenylphosphorane and *t*-BuOK cleanly transformed lactone 114 to the desired 1,1-dibromoalkene 115 in good yield, although the reaction required refluxing THF <2001TL7265>. The mechanism of the reaction has also been studied <2001TL7265>. This combination of reagents is exceedingly reactive toward aldehydes. For example, piperidine 116 was converted to the corresponding 1,1-dibromide 117 (see Figure 16) in high yield at rt in only 10 min <2002OL1955>.

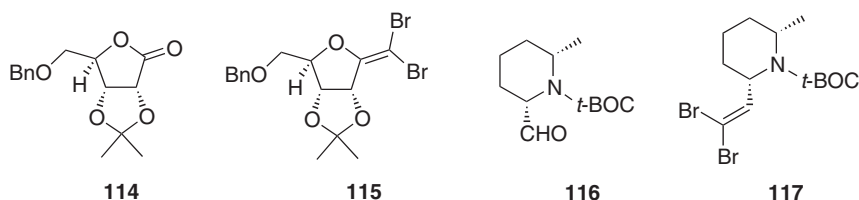
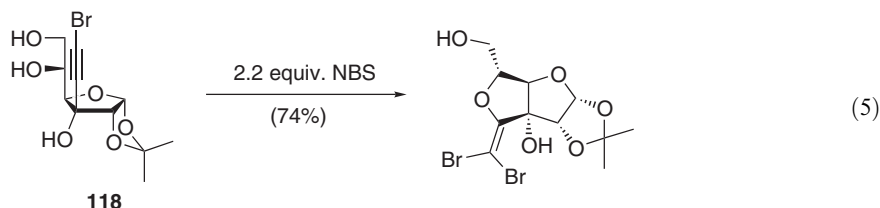


Figure 16

## 4.17.1.3.2 Miscellaneous routes

## (i) Rearrangements

McNelis and co-workers have reported a creative method for the formation of 1,1-dibromoalkenes <2002OL3847, 1996T10267> via the rearrangement of bromoalkynes (Equation (5)). Bromoalkynol derivative **118** has been demonstrated to undergo a rearrangement in the presence of 2.2 equiv. of *N*-bromosuccinimide (NBS) in high yield.



## (ii) Using organometallics

Similar to 1,1-dichloroalkenes, indium metal can also be used to form 1,1-dibromoalkenes (Table 7). Exposing tribromomethyl carbinols **119** to indium metal results in quantitative elimination of Br-OMs to form the desired dibromides **120** <2002TL5993>. Dabdoub and co-workers reported that stannane **121**, produced via hydrosilyrconation of the corresponding tributylstannylacetylene, reacted with NBS to form 1,1-dibromoalkenes **122** in good yields <2001JA9694>. Also, Normant and co-workers demonstrated that bis-metallic species **123** reacted smoothly to give the corresponding *gem*-dibromide <1995TL7451>. Finally,  $\alpha,\alpha$ -bis-indium derivatives, such as **124**, react with NBS to produce 1,1-dibromides in high yields <1999JOC7537> (see Figure 17).

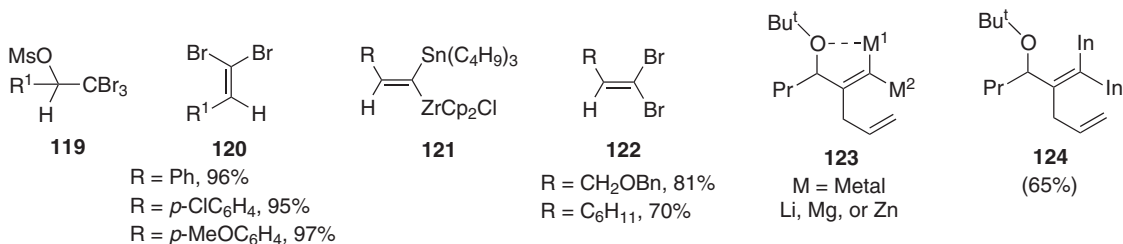
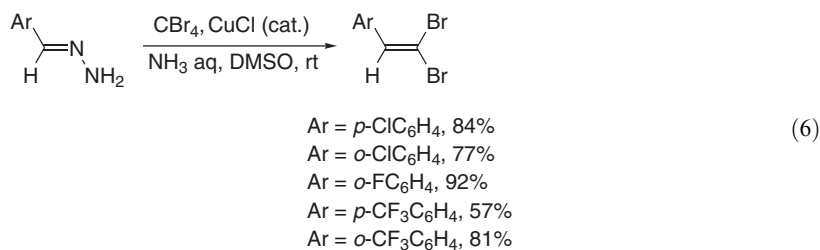


Figure 17

## (iii) Using hydrazones

The synthesis of functionalized  $\beta,\beta$ -dibromostyrenes utilizing catalytic amounts of CuCl and aromatic hydrazones has been reported (Equation (6)) <2001S2081>. This reaction not only produced the desired 1,1-dibromoalkenes in high yield, but it is reported to be air- and moisture-insensitive. The mechanism of this reaction has been studied <2002JCS(P1)883>.



#### 4.17.1.4 Diiodo Alkenes

Unlike other symmetrical 1,1-dihaloalkenes, there exist relatively few examples of this functional group transformation. These relatively few reports can be conveniently grouped into three categories: Wittig and related reactions, reactions using bis-organometallic species, and miscellaneous routes.

##### 4.17.1.4.1 Wittig and related reactions

In the total synthesis of gambierol, Yamamoto and co-workers reported the successful conversion of an advanced intermediate aldehyde into the corresponding 1,1-diiodoalkene using a  $\text{PPh}_3\text{-Cl}_4$  mixture [\[2003JA46\]](#). Not only did this reaction proceed in high yield (>92%), but this example also illustrates the high functional group tolerance associated with this transformation.

The combination of phosphonium salt **125** with base also provides a method for the conversion of aldehyde to 1,1-diiodoalkenes. **126** was shown to react with **125** in the presence of *n*-BuLi (THF, 0°C) to give **127** in 58% yield [\[1999T15071\]](#). Michel and Rassat also reported this reaction worked well with a weaker base (*t*-BuOK) to give the desired products **128** in 80% yield [\[1999TL8579\]](#). It is important to note that **128** was not formed when reacted with the ylide derived from  $\text{Cl}_4$  and  $\text{PPh}_3$  (see [Figure 18](#)).

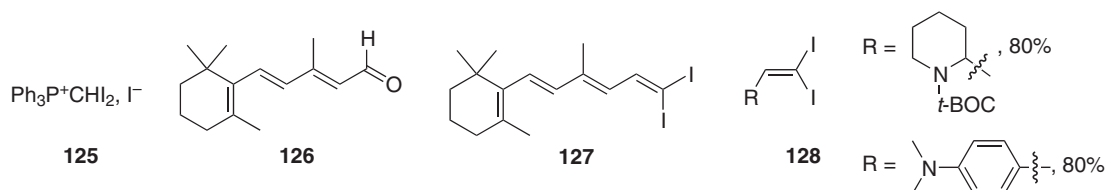


Figure 18

##### 4.17.1.4.2 Reactions involving organometallics

###### (i) Organoindiums

Phenylacetylene reacts cleanly with 1 equiv. of  $(\text{allyl})_3\text{In}_2\text{I}_3$  to form an intermediate  $\alpha, \alpha$ -bis-indium intermediate, **129**. This organometallic can be reacted with either  $\text{I}_2$  or  $\text{LiI}$  (5 equiv., 65–74%) to produce desired diiodide **130** in good yield [\[1999JOC4095, 1997JOC2318\]](#). The mechanism of this transformation has been studied [\[1997JOC2318\]](#). Klaps and Schmid also reported the successful transformation of acetylene derivatives to 1,1-diiodoalkenes **131** (see [Figure 19](#)) using the combination of allyl bromide and indium metal with sonication [\[1999JOC7537\]](#), a method that can also be used to synthesize 1,1-dibromo alkenes (see [Section 4.17.1.3.2](#)).

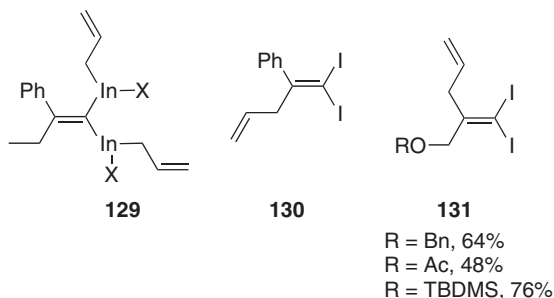
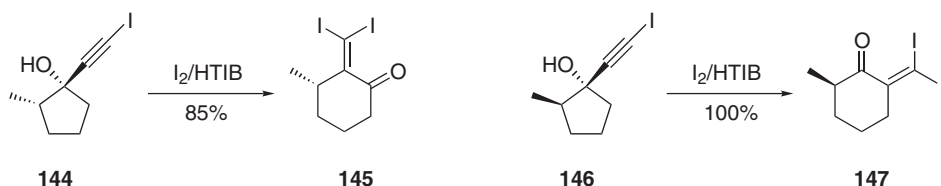


Figure 19







Scheme 2

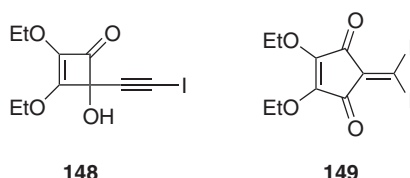


Figure 22

#### 4.17.1.5 Mixed Halo Derivatives

##### 4.17.1.5.1 Fluoro halo alkenes

###### (i) 1,1-Fluoro-chloro alkenes

As expected, transformations that form symmetrical 1,1-dihalo alkenes can be used to construct 1,1-fluorochloroalkenes. For example, Wittig-type reactions have been used to construct unsymmetrical dihaloalkenes. Exposing aldehydes to fluorotribromo-methane in the presence of  $\text{PPh}_3$  and Zn metal cleanly forms the desired alkenes **150** <2000TL827>.

Elimination reactions can also be utilized to form mixed 1,1-dihaloalkenes. The structure **151** readily undergoes a zinc-mediated reduction to give **152** in 75% yield <2000T3539>. This elimination can also be accomplished with KOH in 78% yield ((*E*):(*Z*) = 1.2:1) <1997T17127>. Elimination of HF from **153** with *t*-BuOK produced **154** in 55% yield <2002JFC(115)83> ((*E*):(*Z*) = 4:1). Finally, exposure of 1-chlorotribluoroethylene **155** to phenyllithium results in formation of **156** in 48% yield <2002JFC(113)211> (see Figure 23).

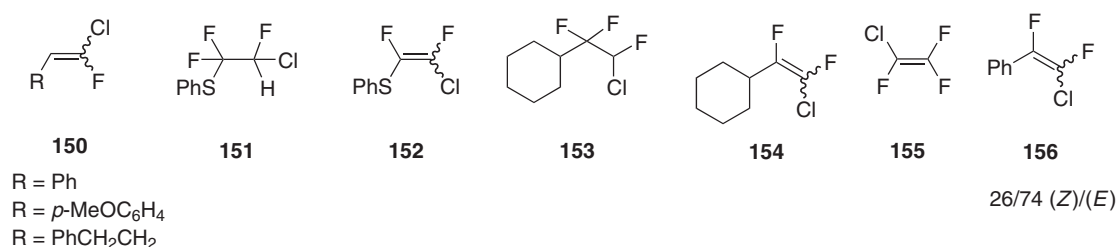
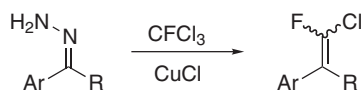


Figure 23

Nenajdenko and co-workers have reported a novel two-step approach to 2-chloro-2-fluorostyrenes from aromatic aldehydes (Equation (7)) <2003EJO302>. After transformation to the corresponding hydrazones, reaction with catalytic amounts of CuCl in the presence of  $\text{CFCl}_3$  provides the desired mixed halo-alkenes in moderate yield.



R = *p*-ClC<sub>6</sub>H<sub>4</sub>, 78%, (*E*)/(*Z*) 2.6/1

R = *p*-BrC<sub>6</sub>H<sub>4</sub>, 68%, (*E*)/(*Z*) 2.4/1

R = *p*-MeOC<sub>6</sub>H<sub>4</sub>, 43%, (*E*)/(*Z*) 4/1

R = Ph, 62%, (*E*)/(*Z*) 2.8/1

R = *p*-IC<sub>6</sub>H<sub>4</sub>, 55%, (*E*)/(*Z*) 2.5/1

(7)

(ii) 1,1-Fluorobromo alkenes

Not surprisingly, many of the same methods used to prepare 1,1-fluorochloroalkenes can be used to construct the 1,1-fluorobromo derivatives. Wittig-type reactions have been used to convert various aldehydes to the desired unsymmetrical 1,1-dihaloalkenes. Simple aromatic aldehydes react with PPh<sub>3</sub>, CFBr<sub>3</sub>, and Zn to produce the desired dihaloalkenes. Benzaldehyde and *p*-nitrobenzaldehyde are converted to the desired alkenes using this protocol, although the latter required the use of cupric sulfate <1999TL827, 2001TL9127>. Using these conditions, when **157** was exposed to (bromofluoromethylene)triphenylphosphorane **158**, bromofluorovinyl derivative **159** was produced in 75% yield <2000JMC1180, 1998JMC3078>. While investigating Pd cross-coupling reactions, Burton and co-workers also reported that aromatic aldehydes **160** formed the desired halogenated alkenes **161** <2002TL2877> using CFBr<sub>3</sub> and PPh<sub>3</sub>. Burton and co-workers also studied the isomerization of these fluorobromoalkenes using various conditions.

Elimination reactions can also be used to construct 1,1-bromofluoroalkenes. Exposing acid **162** to NaHCO<sub>3</sub> (or Bu<sub>4</sub>N<sup>+</sup>OH<sup>−</sup>) resulted in the formation of **163** in near quantitative yield <2001CCC1508, 1997BSF741> (see Figure 24).

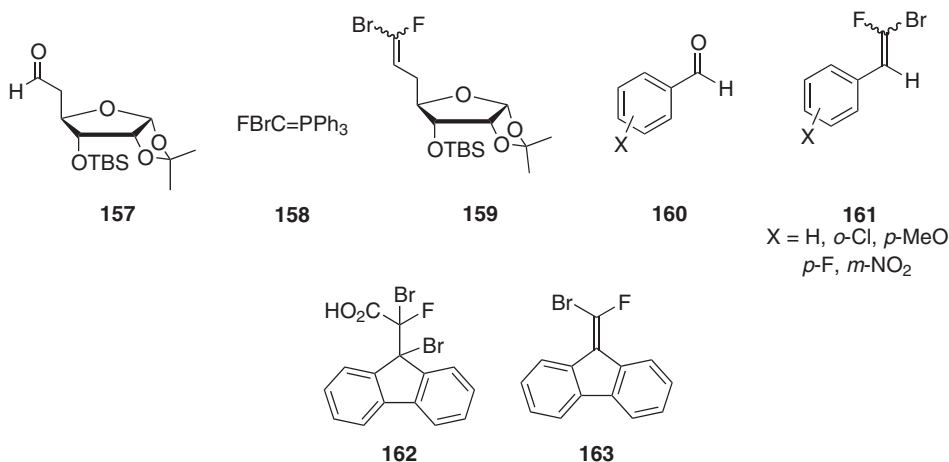
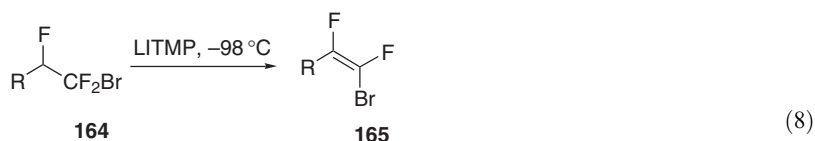


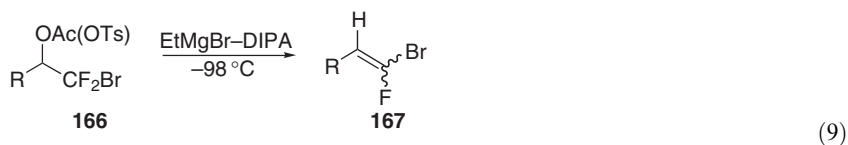
Figure 24

Kuroboshi and co-workers have reported two stereoselective syntheses of (*E*)-1,1-bromofluoro alkenes <1995TL6271, 1998BCJ2903>. When **164** was treated with lithium (2,2,6,6-tetramethyl)piperidide at −98 °C, the (*E*)-isomer **165** was formed with very high selectivity (Equation (8)). Additionally, when acetate (or tosylate) **166** was exposed to the combination of EtMgBr and diisopropylamine (DIPA), the (*E*)-isomer **167** was again preferentially formed (Equation (9)).



R = *p*-MeOC<sub>6</sub>H<sub>4</sub>, 87%, (*E*)/(*Z*) 92/8

R = *p*-Tol, 78%, (*E*)/(*Z*) 91/9



R = naphthyl, 81%, (*E*)/(*Z*) >99/1

R = *p*-NCC<sub>6</sub>H<sub>4</sub>, 89%, (*E*)/(*Z*) 91/9

R = *p*-MeOC<sub>6</sub>H<sub>4</sub>, 84%, (*E*)/(*Z*) >99/1

R = CH<sub>2</sub>CH<sub>2</sub>Ph, 80%, (*E*)/(*Z*) 33/67

Other bases have also been used to produce 1,1-bromofluoroalkenes via an elimination pathway. While studying enantioselective aldol reactions, Iseki and co-workers reported that zinc metal effectively dehydrobrominated **168** in the presence of trimethylsilyl chloride (TMSCl) to form bromofluoroketene silyl acetal **169** <1999T2225>.

Other specialized routes to 1,1-bromofluoroalkenes have been reported. Friedel–Crafts addition using AlCl<sub>3</sub>, *p*-xylene, and allyl bromide **170** yielded **171** in 66% yield as a mixture of (*E*):(*Z*) isomers <1999JOC1366>. Finally, reaction of vinyl stannane **172** with bromine resulted in regioselective bromination to give **173** <1996JFC(52)37> (see Figure 25).

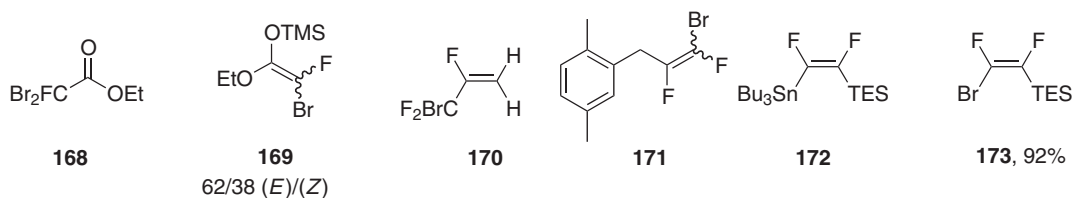
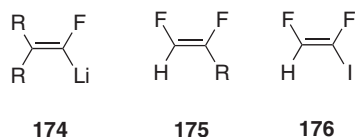


Figure 25

### (iii) 1,1-Fluoroiodo alkenes

Similar transformations used to form 1,1-diiodoalkenes can be adapted to form mixed haloalkenes. Many of the reactions used to construct this functional group involve the formation of the stabilized anion, shown generically as **174**. For example, exposing vinylsilanes **175** to KF in the presence of I<sub>2</sub> resulted in the stereospecific formation of the desired 1,1-fluoroiodo alkene **176** in high yield <2002JFC(113)211, 1996TL7237> (see Figure 26).

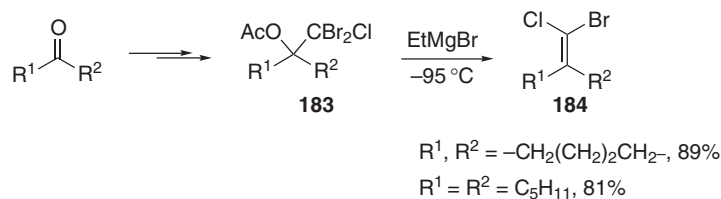


R = SiEt<sub>3</sub>

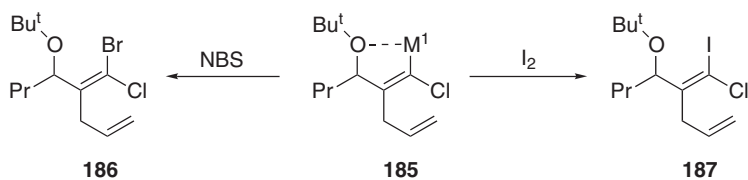
R = SiPhMe<sub>2</sub>

Figure 26

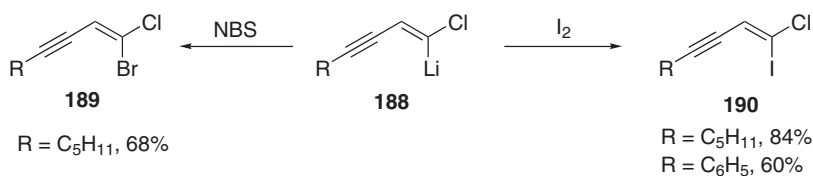




Scheme 3



Scheme 4



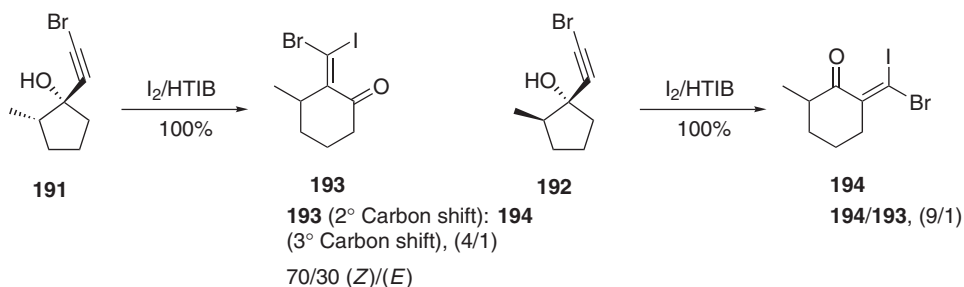
Scheme 5

**Table 10** Formation of dihaloalkenes using hydroboration and copper (II) salts
$$\text{R}^1-\text{C}\equiv\text{C}-\text{X}^1 \xrightarrow[\text{ii. Cu(II)X}_2]{\text{i. HBR}_2} \begin{array}{c} \text{R}^1 \quad \text{X}^1 \\ \diagdown \quad \diagup \\ \text{C}=\text{C} \\ \diagup \quad \diagdown \\ \text{H} \quad \text{X}^2 \end{array}$$

$\text{R}^1$	$\text{X}^1$	Copper salt	Yield (%)	(Z)/(E)
Bu <sup>n</sup>	Br	CuCl <sub>2</sub>	82	100% Z
Bu <sup>n</sup>	I	CuCl <sub>2</sub>	85	99:1
Bu <sup>t</sup>	Cl	CuBr <sub>2</sub>	84	1:99
Bu <sup>t</sup>	Br	CuCl <sub>2</sub>	72	99:1

#### 4.17.1.5.3 Bromo halo alkenes

McNelis and co-workers have reported the rearrangement of bromopropynyl alcohols to form bromoiodo alkenes. Carbinols **191**, **192** (see Scheme 6), and **195** undergo this rearrangement in the presence of I<sub>2</sub> and HTIB ([[(hydroxy)(tosyloxy)iodo]benzene]) to produce **193**, **194**, and **196** (see Figure 28), respectively <1995SC1223, 1996T10267, 1996SC4091>. Marchand and co-workers have also reported a rearrangement of this type <1995T11673>.



Scheme 6

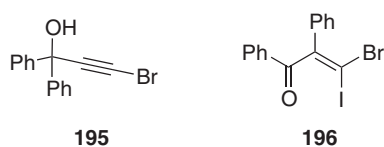


Figure 28

#### 4.17.2 FUNCTIONS INCORPORATING A HALOGEN AND A CHALCOGEN: $\text{R}_2\text{C}=\text{C}(\text{Hal})(\text{Chalc})$

##### 4.17.2.1 Halogen and Oxygen Derivatives

##### 4.17.2.1.1 $\alpha$ -Fluorovinyl ethers

As demonstrated earlier <B-1995COFGT(4)667>, displacement of halogens in alkyl and alkenyl halides remains an effective method for the preparation of  $\alpha$ -fluorovinyl ethers. While investigating the Claisen rearrangement of allyl fluorovinyl ethers, Tellier and co-workers reported that potassium alkoxide **197** reacted quickly at low temperatures with trifluorovinylsilane to give **198** in high yield <1998TL5041>. This alkoxide **197** has also been shown to react with bromotrifluoroethylene **199** by an analogous addition/elimination pathway to produce **200**. The (*E*)-isomer was the major product in all cases <2000EJO1933, 2001TL2665, 1999JFC(94)27>. Unsaturated ketone **201** underwent two addition/elimination reactions with either phenoxide or methoxide to provide olefin **202** <2000JCS(P1)1529> (see Figure 29).

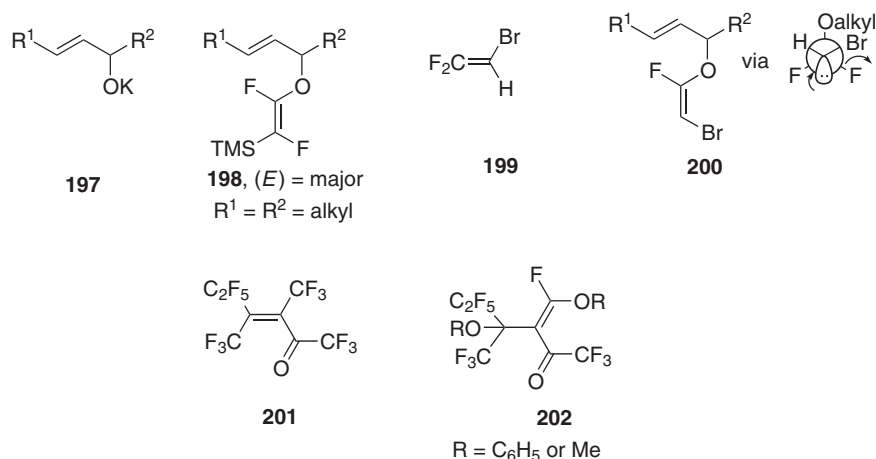
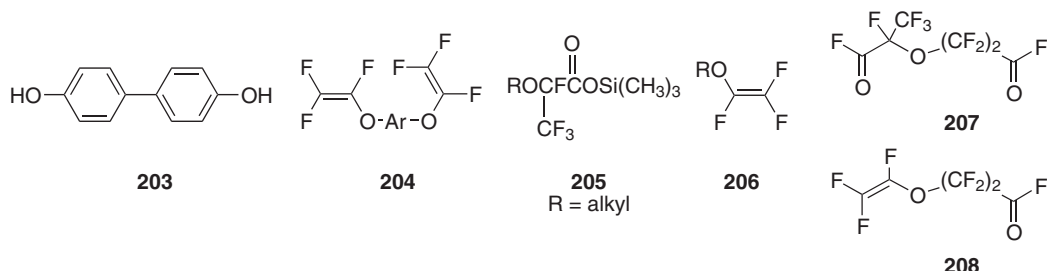


Figure 29

Elimination reactions have also been used to construct  $\alpha$ -fluoroenol ethers. Aromatic diol **203** was dialkylated with  $\text{BrCF}_2\text{CF}_2\text{Br}$ , then subjected to zinc-mediated reduction to produce enol ether **204** in fair yield on relatively large scale <2000JFC(104)109>. Heating acid fluoride **205** resulted in a rearrangement to form alkene **206** <1999JFC(94)65>. Finally, exposure of TMS-carboxylate **207** to high temperature in the presence of KF resulted in extrusion of  $\text{CO}_2$  to form **208** <1997JOC7844> (see Figure 30).

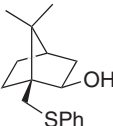
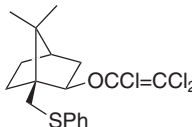
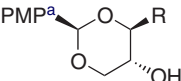
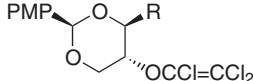
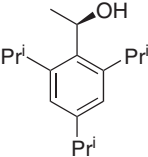
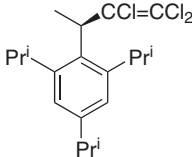


**Figure 30**

#### 4.17.2.1.2 $\alpha$ -Chlorovinyl ethers

Like other  $\alpha$ -halovinyl ethers, the addition of alkoxides to trichloroethylene remains an effective way to construct  $\alpha$ -chlorovinyl ethers. Some stereotypical examples of this method are shown in Table 11.

**Table 11** Displacement reactions involving trichloroethylene

Substrate	Product	Reagents	Yield (%)	References
R—OH	R—OCCl=CCl <sub>2</sub> R = alkyl R = Ar	KH, CHCl=CCl <sub>2</sub>	>59 >57	<2001TL6987> <2001TL6987>
		KH, CHCl=CCl <sub>2</sub>	77	<1998JOC7037>
	 R = CH <sub>2</sub> CH=CH <sub>2</sub> R = CH <sub>2</sub> CH <sub>2</sub> CH=CH <sub>2</sub>	KH, CHCl=CCl <sub>2</sub>	81 87	<2002TL1973> <2002TL1973>
		KH, CHCl=CCl <sub>2</sub>	81	<2000JOC6966>

<sup>a</sup> PMP = *p*-methoxyphenyl.

$\alpha$ -Chlorovinyl ethers can also be formed under phase transfer conditions (PTC). Ketones **209** react smoothly with trichloroethylene (TCI) in aqueous base using PTC to give enol ethers **210** [<2000T6083>](#). Simple alkyl alcohols have also been shown to react with dichloroacetylene under PTC to provide the corresponding  $\alpha$ -chlorovinyl ethers **211** in good yield [<1997BSB809>](#).

Yu and Jin have reported the convenient synthesis of  $\alpha$ -halovinyl ethers from the corresponding alkynes [<2000JA9840>](#). Exposing **212** to TMSCl (0.99 equiv.) and MeOH (0.99 equiv.) resulted in formation of **213** in 97% yield (see [Figure 31](#)). It is important to note that the reaction with TMSCl is not only faster than using commercially available solutions of HCl, but gave better selectivity. Using TMSCl, they were able to carefully monitor the amount of HCl in solution, and since TMSOMe is volatile, neither work-up nor column chromatography was necessary. Direct HCl addition (LiCl/HOAc) to an alkyne has also been demonstrated to produce  $\alpha$ -chlorovinyl ethers [<1998AG\(E\)1253>](#).

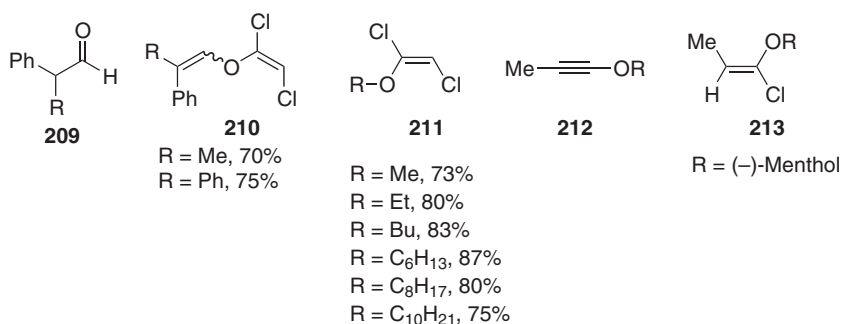


Figure 31

#### 4.17.2.1.3 $\alpha$ -Bromo- and $\alpha$ -iodovinyl ethers

Jin and co-workers have published a convenient preparation of both bromo- and iodo vinyl ethers. Using TMSBr (or TMSI), Yu and Jin were able to form these unstable ethers in quantitative yield, without the need for column chromatography ([Table 12](#)) [<2000JA9840>](#).

Table 12 Formation of  $\alpha$ -halovinylethers using TMS-X

Substrate	Product	Reagents	Yield (%)	References
Me—C≡C—OR	 R = (-)-Menthol R = (-)-Menthol	TMSBr TMSI	99 97	<a href="#">&lt;2000JA9840&gt;</a> <a href="#">&lt;2000JA9840&gt;</a>
	 H Br	TMSBr TMSI	89 91	<a href="#">&lt;2000JA9840&gt;</a> <a href="#">&lt;2000JA9840&gt;</a>
	 H Br R = cyclohexyl	TMSBr TMSI	99 99	<a href="#">&lt;2000JA9840&gt;</a> <a href="#">&lt;2000JA9840&gt;</a>

Additionally, when peroxide **214** was reacted with *N*-iodosuccinimide (NIS),  $\alpha$ -iodovinyl ether **215** was formed in 91% yield [<1999JCS\(P1\)3345>](#) (see [Figure 32](#)).



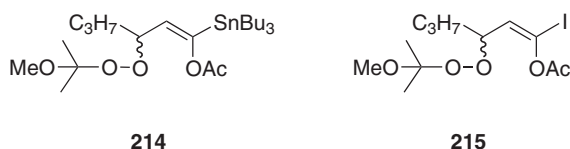
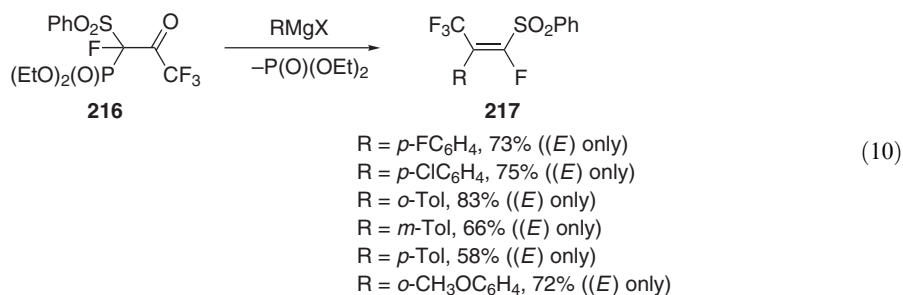


Figure 32

#### 4.17.2.2 Halogen and Sulfur Derivatives

##### 4.17.2.2.1 Fluorovinyl sulfides, sulfoxides, and sulfones

Wittig-type reactions have proven to be an efficient way to construct  $\alpha$ -fluorovinyl sulfoxides and sulfones. Trifluoromethylated phosphonate **216** reacted with Grignard reagents to form fluorovinyl sulfones **217**, after elimination of the phosphoric acid anion (Equation (10)) <2002OL2083>.



Chiral sulfoxide **218** has also been reported to olefinate aldehydes to provide vinylsulfoxides **219** in both good yield and selectivity <2001EJO911> (Equation (11)). Fluorovinyl sulfones can also be synthesized using phosphonate **220**. Phosphonate **220** will also react with both aldehydes and ketones to give the desired sulfones **221** in high yield, albeit with moderate selectivity (see Figure 33).

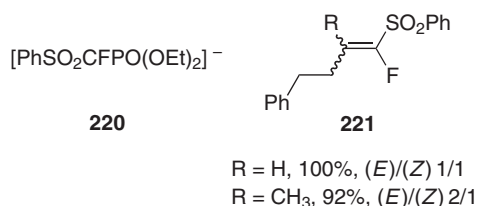
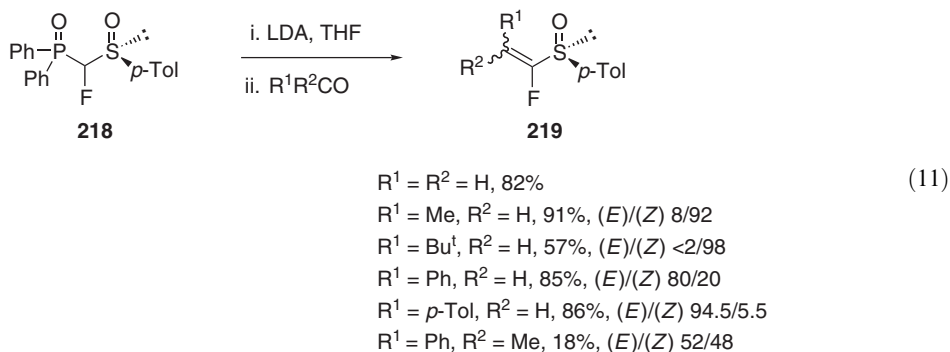


Figure 33

Similar to 1,1-dihaloalkenes, elimination reactions provide a viable route to  $\alpha$ -fluorovinyl sulfides, sulfoxides, and sulfones. Exposing **151** to KOH resulted in dehydrofluorination to form **222**. This sulfide **222** can be oxidized with 3-chloroperoxybenzoic acid (MCPBA) to produce the corresponding vinyl sulfone <2000T3539, 1998TL6529>. Furata and Hiyama reported that **223** reacted with zinc to yield the expected olefin in high yield <1996TL7983>. Carbonate **224** readily eliminated in the presence of NaOH (1.5 equiv.) to form vinyl sulfone **225** in quantitative yield <2001TL4861, 1998BCJ1939>. It is important to note that this elimination failed when sulfide **226** was used, resulting only in decomposition.

Like  $\alpha$ -halovinyl ethers,  $\alpha$ -fluorovinyl sulfides can be prepared by the reaction of metallated thiophenoxides with trifluoroethylene <1997T17127>. Vinyl sulfide **152** was produced via an addition/elimination process when fluorotrichloroethylene was exposed to sodium thiophenoxide (see also Table 11). By an analogous pathway, lithium thiophenoxide reacted with **227** to give vinyl sulfide **228** <1999JFC(97)109>.

Other miscellaneous preparations of this functional group have been reported. Exposure of vinylsilane **229** to CsF resulted in cross-coupling with *S*-phenylbenzenethiosulfonate to afford **230** in excellent yield <2002JFC(118)99>. Lastly, Fuchigami and co-workers have reported the synthesis of allenes **231** by NaOMe-mediated rearrangement of the corresponding alkyne <2001TL3009, 2002T5877> (see Figure 34).

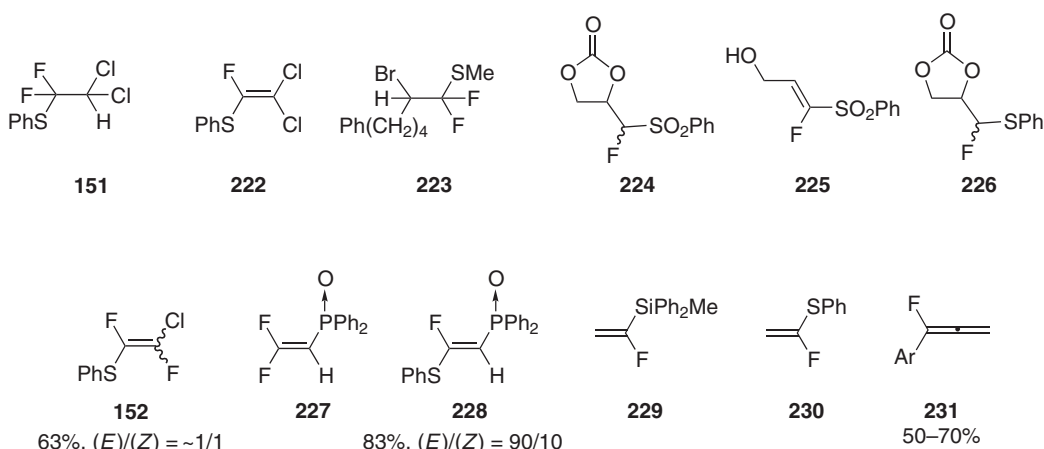


Figure 34

#### 4.17.2.2.2 Chlorovinyl sulfides, sulfoxides, and sulfones

Like the corresponding  $\alpha$ -fluoro derivatives,  $\alpha$ -chlorovinyl sulfoxides can be synthesized using Wittig-type reactions. **232** readily reacted with a variety of aldehydes to provide  $\alpha$ -chlorovinyl sulfoxides **233** in good yields <1996TA3513> (Table 13).

**Table 13** Wittig-type reactions to form  $\alpha$ -chloro vinylsulfoxides

<i>R</i>	Yield (%)	( <i>Z</i> ):( <i>E</i> )
Ph	85	1.2:1
<i>p</i> -BrC <sub>6</sub> H <sub>4</sub>	92	6:1
<i>p</i> -NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub>	78	100:0
Me	63	2.2:1

Phosphine oxide **234** also reacts with a large variety of aldehydes to form  $\alpha$ -chlorovinyl sulfones **235** in good yield with high selectivity <1997T10527> (Table 14).

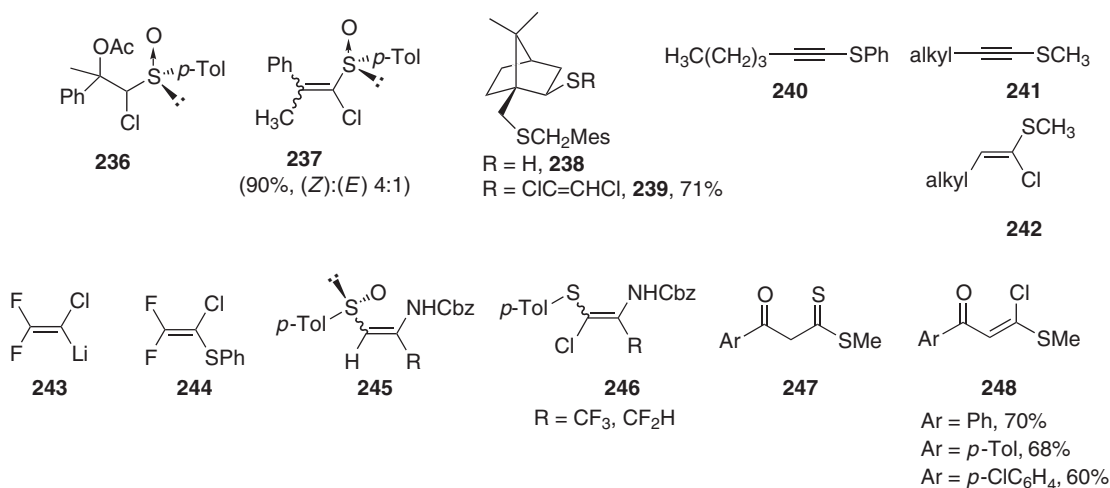
**Table 14** Wittig-type reactions to form  $\alpha$ -chlorovinyl sulfoxides

$  \begin{array}{ccc}  \begin{array}{c} \text{O} \quad \text{O} \\ \parallel \quad \parallel \\ \text{Ph}-\text{P}-\text{C}-\text{S}-\text{R}^1 \\   \quad   \\ \text{Ph} \quad \text{Cl} \end{array} & \xrightarrow[\text{ii. R}_2\text{CHO}]{\text{i. LDA}} & \begin{array}{c} \text{H} \quad \text{O} \\ \diagdown \quad \parallel \\ \text{R}^2-\text{C}=\text{C}-\text{S}-\text{R}^1 \\   \\ \text{Cl} \end{array} \\  \mathbf{234} & & \mathbf{235}  \end{array}  $			
$R^1$	$R^2$	Yield (%)	(Z):(E)
Me	Ph	75	>98:2
Me	<i>p</i> -ClC <sub>6</sub> H <sub>4</sub>	70	>98:2
Me	<i>p</i> -MeOC <sub>6</sub> H <sub>4</sub>	71	>98:2
Me	Bu <sup>n</sup>	63	4.7:1
Ph	H	72	—
Ph	Pr <sup>n</sup>	70	97:3
<i>p</i> -tolyl	Ph	60	>98.2

Elimination reactions also provide a convenient procedure for the preparation of  $\alpha$ -chlorovinyl sulfides and sulfoxides. Reaction of **236** with dimethylsodium resulted in the formation of **237** <2001TL9241, 2000T5113>. Thiol **238** (Mes = 1,3,5-trimethylphenyl) reacted cleanly with trichloroethylene, in the presence of KH, via an addition/elimination pathway to give **239** <2001JOC6400, 1995JOC7690>.

Not only has Jin and co-workers reported a general procedure for the formation of  $\alpha$ -halovinyl ethers using TMS-X (see Sections 4.17.2.1.2 and 4.17.2.1.3), but he also reported a modified procedure for the formation of  $\alpha$ -halovinyl sulfides <2001TL3771>. Acetylenic sulfide **240** reacted cleanly with TMSCl and MeOH to give the expected vinyl sulfide in quantitative yield. HCl gas has also been successfully used to convert a substituted alkyne **241** to the corresponding  $\alpha$ -chlorovinyl sulfide **242** in 82% yield (single isomer) <2001JOC5237>.

Percy and co-workers have reported that organolithium **243** reacted with a variety of electrophiles including *S*-phenyl benzenethiosulfonate, which delivered vinyl sulfide **244** in 93% yield <1998JSC(P1)2541>. Additionally, **245** has been reported to undergo a Pummerer rearrangement in the presence of acetyl chloride to yield **246** <1997JOC8031>. Finally, Suma and Asokan have reported that exposure of **247** to the Vilsmeier reagent (POCl<sub>3</sub>, dimethylformamide (DMF)) resulted in the formation of  $\alpha$ -chlorovinyl sulfides **248** <1996SC847> (see Figure 35).

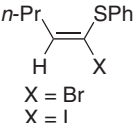
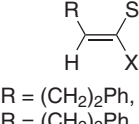
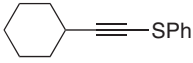
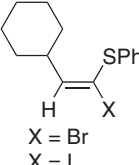


**Figure 35**

4.17.2.2.3  $\alpha$ -Bromo- and  $\alpha$ -iodovinyl sulfides, sulfoxides, and sulfones

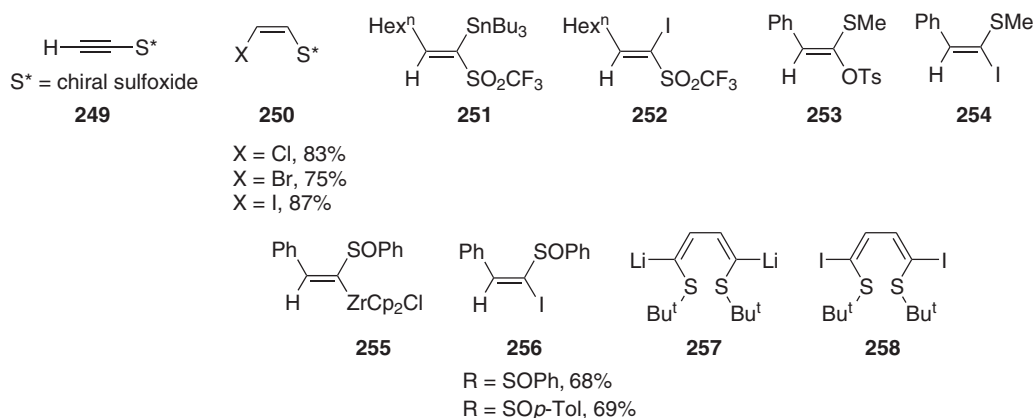
Alkynyl sulfides provide an efficient route to  $\alpha$ -bromo and iodovinyl sulfides. In 2001, Jin and co-workers published a general procedure for the formation of  $\alpha$ -halovinyl sulfides. Jin showed that a variety of acetylenic sulfides react with TMS-X to produce the desired  $\alpha$ -halovinyl sulfides in high yield without the need for purification <2001TL3771> Table 15. Additionally, sulfide **250** was formed in good overall yield when acetylenic sulfide **249** was exposed to  $\text{ZnX}_2$  <1997JOC6326>.

**Table 15** Synthesis of  $\alpha$ -halovinylsulfides using TMS-X

Substrate	Product	Reagents	Yield (%) <sup>a</sup>	References
$n\text{-Pr}\text{---}\text{C}\equiv\text{C}\text{---}\text{SPh}$		TMSBr TMSI	99 <sup>b</sup> 99	<2001TL3771> <2001TL3771>
$\text{R}\text{---}\text{C}\equiv\text{C}\text{---}\text{SPh}$		TMSBr TMSI	99 99	<2001TL3771> <2001TL3771>
		TMSBr TMSI	99 99 <sup>b</sup>	<2001TL3771> <2001TL3771>

<sup>a</sup> All products were isolated as a single isomer unless otherwise indicated. <sup>b</sup> (E)/(Z) 20/1.

The reaction of organometallic species with electrophilic bromine (or iodine) also provides a potential route to these uncommon functional groups. For example, stannane **251** has been shown to react with  $\text{I}_2$  to provide vinylsulfone **252** in 88% yield <1996JA4284>. Also, vinyl tosylate **253** was converted in good yield into the corresponding  $\alpha$ -bromovinyl sulfide upon addition of  $\text{MgBr}_2$  <2001SL371>. Reaction of vinylzirconium species **255** with  $\text{I}_2$  produced vinyl sulfoxide **256** in good overall yield <2000T8921>. Treatment of lithium dianion **257** with  $\text{I}_2$  produced diiodide **258** in 48% yield (see Figure 36). Finally, formation of  $\alpha$ -iodovinyl sulfides can also be accomplished using cuprates <1995TL3605>.

**Figure 36**

The addition of bromine to alkenes or alkynes has also been shown to lead to  $\alpha$ -bromovinyl sulfides and sulfones. Addition of bromine to **259**, followed by exposure to base ( $\text{NEt}_3$ ) resulted in formation of vinyl bromide **260** <1997SL1043, 1995TL3605>. Also, Yoshimatsu and co-workers demonstrated that ethyl enol ether **261** reacted with bromine to give vinyl bromide **262** in high yield <1999CPB1497>. Finally, Braga and co-workers demonstrated that the bromination of acetylenic sulfides could be accomplished using Amberlyst A-26 in its perbromide form **263**, to form  $\alpha$ -bromovinyl sulfides efficiently <2000SC407> (see Figure 37).

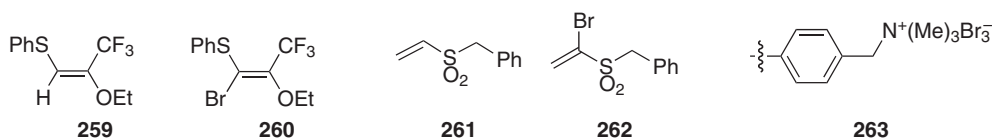


Figure 37

#### 4.17.2.3 Halogen and Selenium or Tellurium Derivatives

The reaction of organometallics with electrophilic halogens provides an efficient method for the preparation of  $\alpha$ -halovinyl chalcogens. Dabdoub and co-workers reported that the hydrozirconation of telluroalkynes produced a vinyl zirconium species that cleanly reacted with  $\text{I}_2$  or NBS to produce telluroalkenes (Table 16) <1998T2371>.

**Table 16** Formation of  $\alpha$ -halovinyl tellurium compounds using vinylzirconium reagents

$\begin{array}{c} \text{R} \\ \text{H} \end{array} \text{C}=\text{C} \begin{array}{c} \text{TeC}_4\text{H}_9 \\ \text{ZrCp}_2\text{Cl} \end{array} \longrightarrow \begin{array}{c} \text{R} \\ \text{H} \end{array} \text{C}=\text{C} \begin{array}{c} \text{TeC}_4\text{H}_9 \\ \text{X} \end{array}$			
<i>R</i>	Reagents	Yield (%)	<i>E:Z</i>
$\text{Pr}^n$	$\text{I}_2$	80	90:10
$\text{Bu}^n$	$\text{I}_2$	77	86:14
$\text{C}_6\text{H}_{13}$	$\text{I}_2$	80	80:20
Ph	$\text{I}_2$	81	95:5
$\text{C}_3\text{H}_7$	NBS	80	55:45
$\text{C}_6\text{H}_{13}$	NBS	77	56:44

Dabdoub and Baroni also reported that stannane **264** reacted with either NBS or  $\text{I}_2$  to give the corresponding iodide **265** <2000JOC54>. It has also been demonstrated that ethynylselanylbenzene **266** undergoes hydrostannation with tributyltin hydride to yield **267**. When exposed to  $\text{I}_2$ , **267** produced iodoalkenes **268** in high yields <1997SC225, 1997SC2407> (see Figure 38).

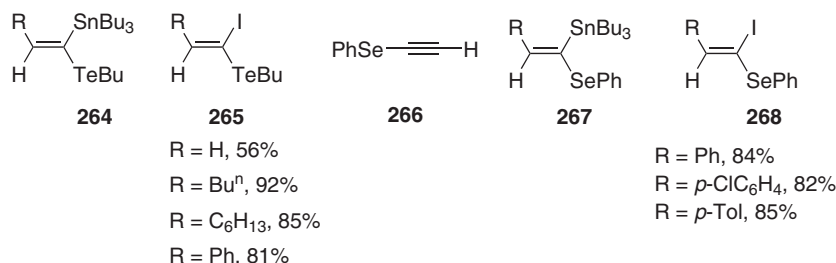


Figure 38

Alkynyl chalcogens have also been converted to the corresponding alkenes by a number of methods. Braga and co-workers have reported that a broad range of acetylenic selenides react with HX to yield 1-halo-1-selenolalkenes (Table 17) <1996T9687>.

**Table 17** Addition of HX to acetylenic selenides

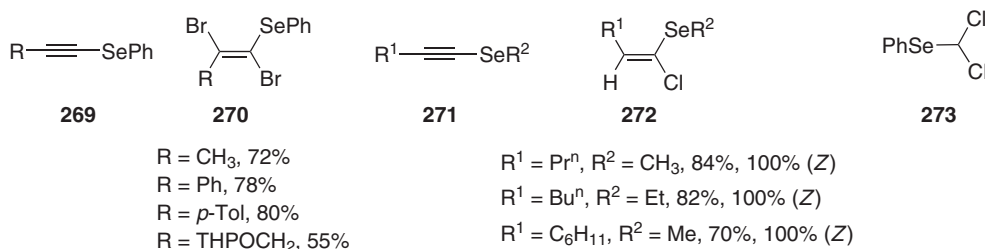
$$\text{Bu}^n\text{—}\equiv\text{—SeMe} \xrightarrow{\text{HX}} \text{Bu}^n\text{—}\text{C}(\text{SeMe})=\text{C}(\text{X})\text{—H}$$

HX	Yield (%)	Z:E
HCl <sup>a</sup>	75	4.2:1
HCl <sup>b</sup>	78	4.1:1
HCl <sup>c</sup>	84	12.8:1
HBr <sup>a</sup>	74	10.8:1
HBr <sup>b</sup>	76	14.1:1
HI <sup>a</sup>	80	2.6:1
HI <sup>b</sup>	85	2.6:1

<sup>a</sup> Reaction performed in benzene/HOAc (3:1)/ aq. HX. <sup>b</sup> Reaction performed in CHCl<sub>3</sub>/aq HX in the presence of catalytic amounts of HgCl<sub>2</sub> (5.0 mol. %). <sup>c</sup> Reaction performed in benzene with saturated, dry HX.

Alkynylseleniums **269** have also been demonstrated to undergo bromination with Br<sub>2</sub> to form **270** in good yield <2001SC3027>. This has also been demonstrated with perbromide resins <2000SC407>. Additionally, **271** was cleanly hydrochlorinated using a mixture of LiCl and HOAc to produce **272** <2000S1819>.

Finally, **273** has been successfully used in Wittig-type reactions with a variety of aldehydes <2001PS(172)173> (see Figure 39).



**Figure 39**

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## Biographical sketch



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## 4.18

# Functions Incorporating a Halogen and Another Group Other Than a Halogen or a Chalcogen

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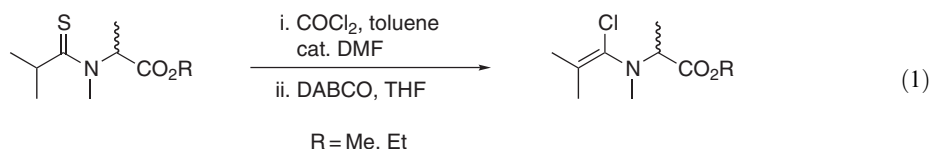
## 4.18.1 HALOGEN AND NITROGEN DERIVATIVES

### 4.18.1.1 *gem*-Amino Halo Alkenes

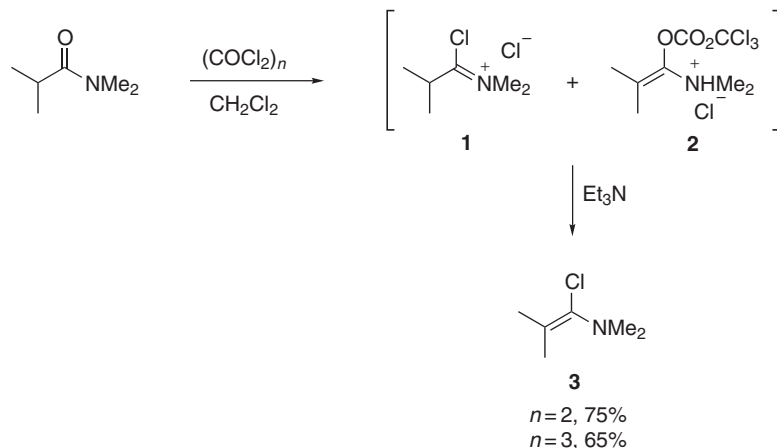
Although Ghosez and Marchand-Brynaert have reviewed the synthesis of  $\alpha$ -haloenamines twice [<B-1976MI418-01, 1988OSC\(6\)282>](#), they did not include those compounds in which the electron pair is involved in further functionality, such as enamides. This chapter focuses on  $\alpha$ -haloenamines as well as compounds bearing further functionalization on nitrogen following the same structure as used by Smith [<1995COFGT\(4\)789>](#). The transformations reviewed by Smith are briefly summarized and further updated concentrating on the period 1995–2003.

#### 4.18.1.1.1 *By addition of halide*

The most common method to synthesize  $\alpha$ -chloroenamines starts from tertiary amides, using phosgene as a chlorination agent and triethylamine as base [<1988OSC\(6\)282>](#). This general method is successfully applied to prepare a wide variety of *N,N*-dialkyl  $\alpha$ -haloenamines. Similarly, Breitenmoser and Heimgartner prepared  $\alpha$ -chloroenamines from the corresponding thioamides using phosgene and DABCO as base (Equation (1)) [<2002HCA885>](#). Compared to the use of the amides directly, treatment of the thioamides with phosgene leads to better yields [<1996HCA527>](#).

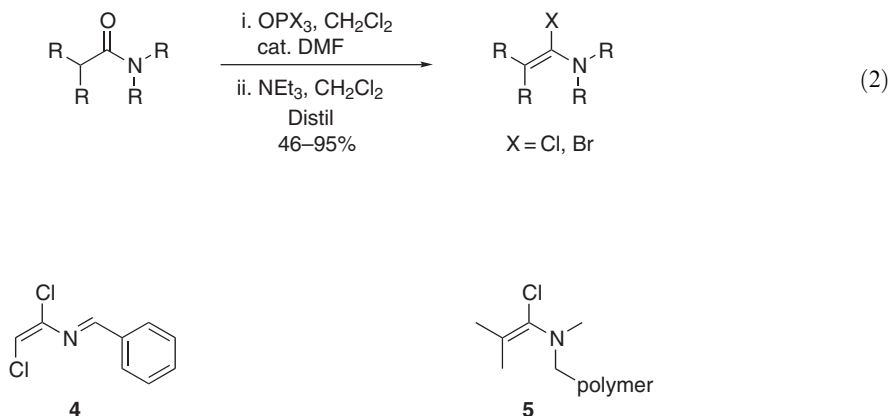


Prompted by the hazards associated with the use of large amounts of phosgene as well as the ban on phosgene in many laboratories, Ghosez and co-workers re-examined the synthesis of  $\beta$ -disubstituted  $\alpha$ -chloroenamines [<1998T9207>](#).  $\alpha$ -Chloroenamine **3** is successfully prepared using di- or triphosgene, which are easier to manipulate and to store (Scheme 1). The best results are obtained with 2 equiv. of diphosgene at room temperature or 3 equiv. of triphosgene in refluxing dichloromethane. In both cases the formation of **1** was accompanied by that of a minor product **2**. However, both compounds lead to enamine **3** upon treatment with base. Holmes and co-workers prepared  $\alpha$ -chloroenamine **3** as well as the corresponding bromo derivative with oxalyl chloride or oxalyl bromide, respectively, followed by treatment with triethylamine [<1997CC1067>](#).

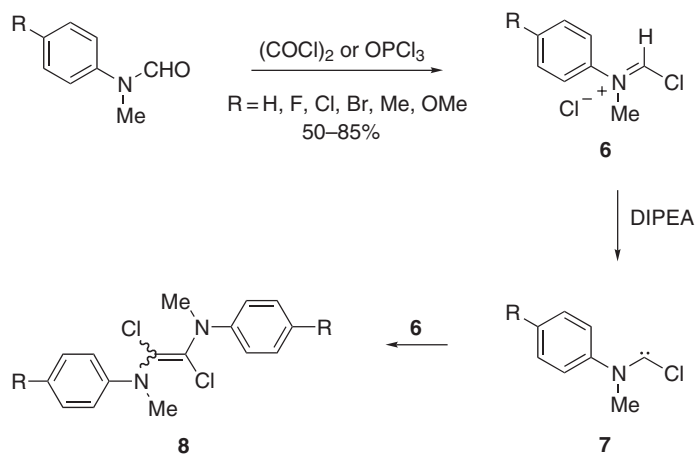


Scheme 1

Using phosphorus oxychloride and phosphorus oxybromide, Ghosez and co-workers successfully prepared a large variety of  $\alpha$ -chloro- and  $\alpha$ -bromo enamines, respectively, which were thermally stable and were purified by distillation (Equation (2)). The bromination reactions take place more rapidly than the corresponding chlorination reactions. Besides, in the presence of a catalytic amount of dimethylformamide (DMF), the chlorination and the bromination is reported to proceed much faster <1998T9207>. Following a similar method using phosphorus pentachloride instead, 2-azabutadiene **4** has been prepared from *N*-benzylidichloroacetamide in 63% yield <2001RJGC143>. This procedure has been extended to the preparation of polymer bounded  $\alpha$ -haloenamines **5** by treating immobilized tertiary amides with phosphorus halide and triethylamine <2003WOP0320684>.

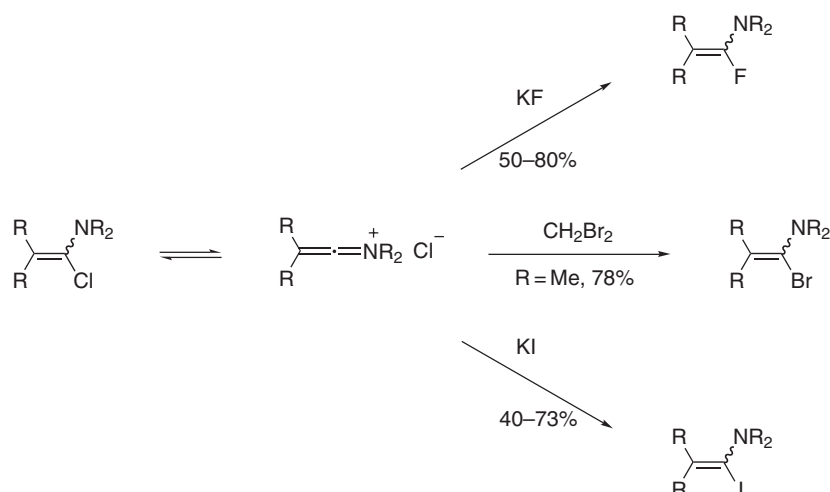


1,2-Dichloro-1,2-diaminoethenes **8** are prepared from Vilsmeier reagent **6** and a bulky base (Scheme 2). Vilsmeier reagent **6**, generated from *N*-methylformanilide and oxalyl chloride or phosphorus oxychloride, is deprotonated leading to the aminochlorocarbene **7**. The carbene subsequently reacts with another molecule of compound **6** yielding the 1,2-dichloro-1,2-diaminoethenes **8**. When *N,N*-diisopropylethylamine (DIPEA) or Hünig's base is used, these dimers are formed optimally. The dimers **8** are unstable compounds that decompose slowly on storage, especially when electron-donating groups are present ( $\text{R} = \text{Me}, \text{MeO}$ ) <1996CC1395, 1998JCS(P1)1619, 2002S2426>.



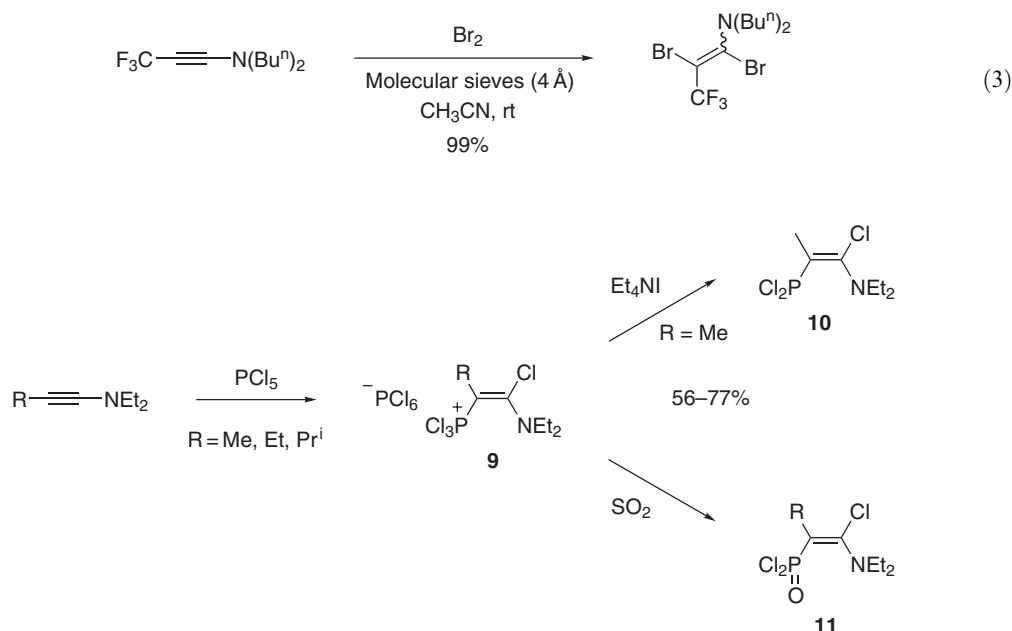
Scheme 2

Due to their mode of reactivity,  $\alpha$ -haloenamines bearing a basic nitrogen atom are usually found in a mixture of (*E*)- and (*Z*)-isomers, equilibrating via the keteniminium halide. This property is used in the preparation of the fluoro, bromo, and iodo derivatives from the readily available chlorides (Scheme 3) <1977NJC369, 1979CC1180>. A fluoro derivative can be alternatively prepared, adding potassium hydrogen difluoride to *N,N*-diethyl-1-propynamine <1977NJC369>. The  $\alpha$ -fluoro enamine is isolated in a 9:1 (*E*):(*Z*) ratio, though slow isomerization shifts the ratio to 10:1 in favor of the (*Z*)-isomer during storage in chloroform.



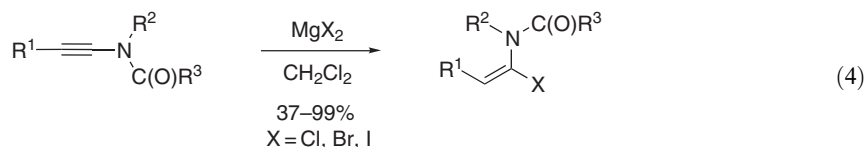
Scheme 3

The direct dihalogenation of ynamines has been described only once. Ishihara and co-workers treated *N,N*-dibutyltrifluoropropynamine with bromine, furnishing the  $\alpha,\beta$ -dibromoenamine quantitatively (Equation (3)). Fluorine NMR analysis showed that the  $\alpha,\beta$ -dibromoenamine was a mixture of two isomers in a ratio of 78:22. The use of other solvents—such as dichloromethane, tetrahydrofuran, diethyl ether, and dioxane—led to similar results, though the ratio of the isomers was slightly varied (78–84:22–16) <2001JFC(108)229>.  $\beta$ -Phosphorylated  $\alpha$ -haloenamines are accessible via the reaction of an ynamine with phosphorus pentachloride. Trostyanskaya and co-workers synthesized compounds **10** and **11** upon treatment of salt **9** with  $\text{Et}_4\text{NI}$  or  $\text{SO}_2$ , respectively (Scheme 4) <1996ZOR1054>. The addition of phosphorus pentachloride is reported to be a stereoselective *anti*-addition solely yielding (*E*)- $\alpha$ -chloroenamines. (*E*)- $\alpha$ -haloenamides have been prepared by hydrohalogenation of ynamides using magnesium halide salts. The reaction is highly regio- and stereoselective when performed in wet dichloromethane. The proposed source of hydrogen halide is its *in situ* generation from the magnesium halide salt and traces of water present in the reaction mixture (Equation (4)) <2003OL1547>.

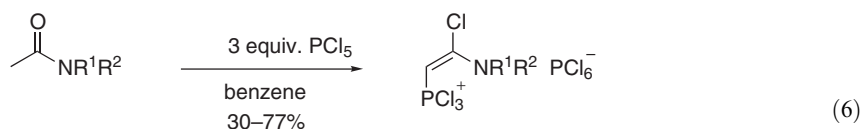
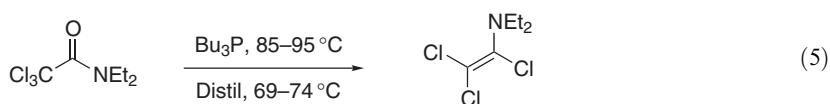


Scheme 4

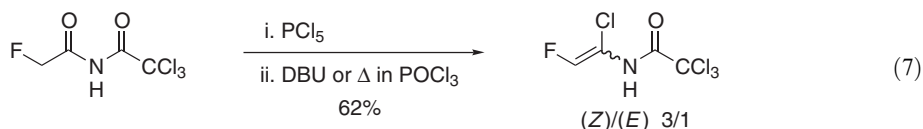




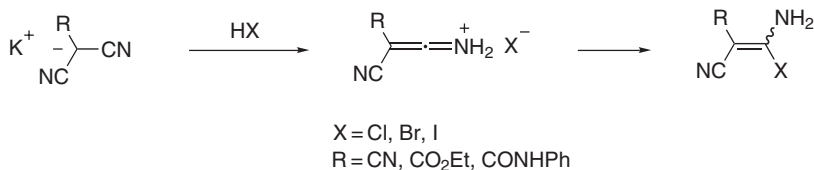
Further functionalization at the  $\beta$ -position can be accomplished employing the appropriate  $\alpha$ -functionalized amide <B-1976MI418-01>. Trichlorovinylamines may be prepared by action of tributylphosphine on trichloroacetamides (Equation (5)) <1960JA903, 1973OSC(5)387>. Alternatively, *N,N*-disubstituted acetamides with the nitrogen atom linked to at least one aromatic substituent yield  $\beta$ -phosphorylated  $\alpha$ -chloroenamines with *cis*(*P*, *N*) configuration when treated with phosphorus pentachloride (Equation (6)) <1999RJGC1377>. Further, reacting *N*-(fluoroacetyl)trichloroacetamide with phosphorus pentachloride leads to the formation of the corresponding acetimidoyl chloride, which upon treatment with 1,5-diazabicyclo[5.4.0]undec-5-ene (DBU) or on heating at elevated temperatures affords the *gem*-chlorovinylenamide (Equation (7)) <2002JFC(117)107>.



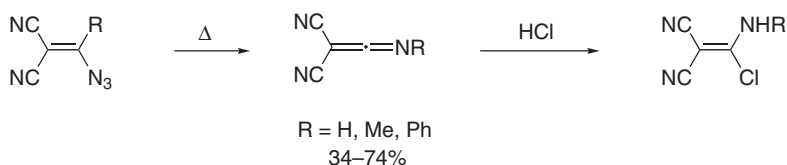
$\text{R}^1 = \text{Ph, 4-CH}_3\text{—C}_6\text{H}_4, 4\text{—NO}_2\text{—C}_6\text{H}_4$   
 $\text{R}^2 = \text{Me, Et, Pr}^i, \text{Ph, Bz, CH}_2\text{CH=CH}_2$



Primary  $\alpha$ -haloenamines have been prepared by addition of hydrogen halides across acetonitrile derivatives bearing electron-withdrawing groups (Scheme 5). Hydrogen chloride, bromide, or iodide successfully adds to the potassium salt of tricyanomethanes in very high yields (93–98%) <1963CB3230>, as does the corresponding addition of hydrogen chloride to dicyanomethane derivatives <1963CB1035, 1970TL1937>. Secondary  $\alpha$ -chloroenamines are prepared by an unusual reaction path involving a thermolysis of 2,2-dicyanovinylazides (Scheme 6) <1967AG(E)959>.



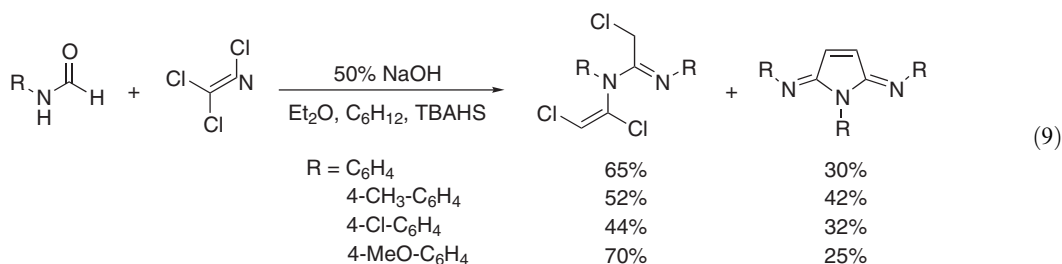
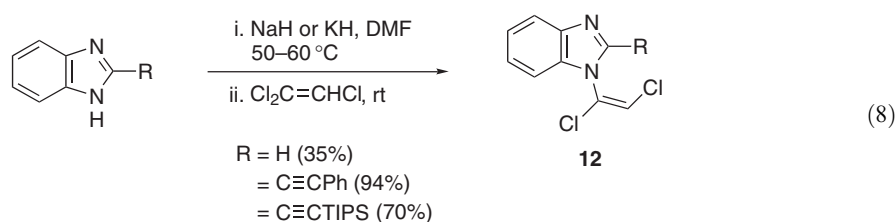
Scheme 5



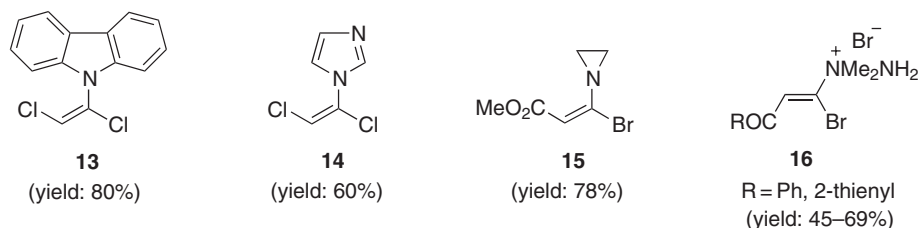
Scheme 6

## 4.18.1.1.2 By amination

The addition of nitrogen nucleophiles to unsaturated halides also leads to the formation of  $\alpha$ -haloenamines. Dimethyl- and diethylamine both add to dichloroalkyne, which is prepared *in situ* from trichloroethene prior to the addition of the amine [<1987S76>](#). In addition, heterocyclic nitrogen nucleophiles add to dichloroalkyne yielding the corresponding  $\alpha$ -chloroenamines as well. The reaction of benzimidazole with trichloroalkene in dimethylformamide furnishes the adduct **12** as the (*E*)-isomer in rather poor yield ([Equation \(8\)](#)). Benzimidazoles bearing an alkyne substituent at the 2-position give better results, although the addition requires more forcing conditions in the case of 2-(2-triisopropylsilylethynyl)benzimidazole [<2002OL4543>](#). Similarly, alkenes **13** and **14** are obtained using carbazole [<1988LA595>](#) and imidazole [<1989BAP123>](#) as nitrogen nucleophiles, respectively. Further, *N*-aryl formamides add to dichloroethyne, which is generated from trichloroethene upon reaction with sodium hydroxide in the presence of tetra-*n*-butylammonium hydrogen sulfate (TBAHS) as a catalyst. The reaction affords a mixture of the  $\alpha$ -chloroenamidine and an azacyclic compound ([Equation \(9\)](#)) [<2002SL1703>](#). Usually, this type of reaction affords the (*E*)-isomer, which is explained by assumption of anti-addition across the triple bond.

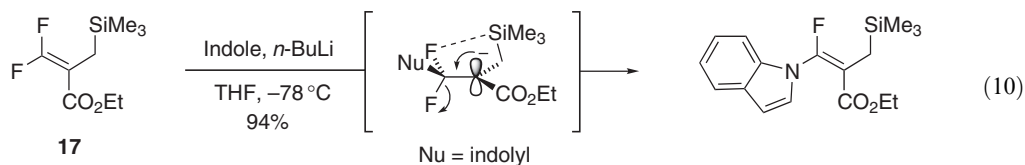


When a functional group capable of stabilizing the developing negative charge is present, monohaloalkynes may also be employed. Aziridine, for example, adds to methyl bromopropiolate in methanol, affording enamine **15** [<1984CHE1231>](#).  $\alpha$ -Bromo enammonium salt **16** is prepared by reaction of  $\beta$ -bromopropynones with *N,N*-dimethylhydrazine in acetonitrile at 20 °C. The structure of the compound was established by X-ray analysis [<1999RCB1516>](#).

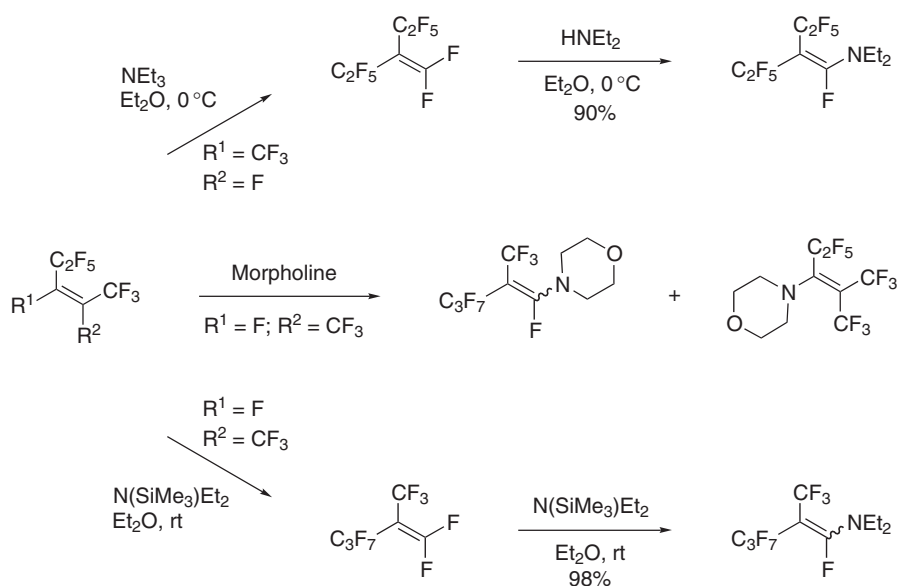


An alternative approach makes use of an addition–elimination reaction of a nitrogen nucleophile with a  $\beta,\beta$ -difluoro  $\alpha,\beta$ -unsaturated ester. Starting from compound **17**, Shi and co-workers isolated the corresponding *gem*-difluoroindolylalkene in excellent yield ([Equation \(10\)](#)). Unlike similar  $\beta,\beta$ -difluoro  $\alpha,\beta$ -unsaturated carbonyl compounds, which lead to exhaustive substitution of two fluorine atoms, only one fluorine is substituted owing to the presence of the electron-donating silyl group. To explain the formation of only the (*Z*)-isomer, Shi and co-workers

proposed an intramolecular coordinative interaction between the silicon and fluorine atom <2000JOC627>.

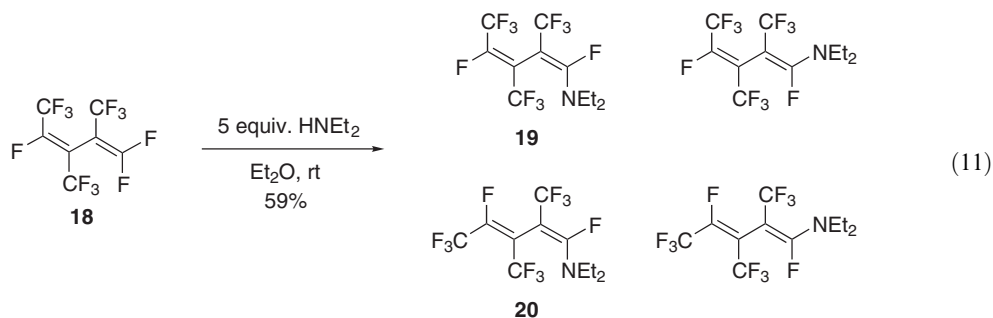


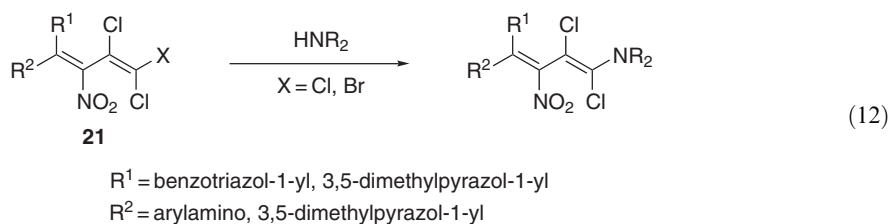
Several perfluorinated alkenes also allow the synthesis of  $\alpha$ -fluoroenamines. Perfluoro-2-methylpent-2-ene <1995JFC(73)267> and perfluoro-3-methylpent-2-ene <1998JFC(88)169> are both found to react in good yield with amines via a fluoride-ion-catalyzed isomerization of the double bond. However, using morpholine or bis(perfluoro-*p*-tolyl)amine, perfluoro-2-methylpent-2-ene affords a mixture of the corresponding  $\alpha$ -fluoroenamine as well as the internal substitution product (Scheme 7) <1996ZPK103>. The  $\alpha$ -fluoroenamines are reported to hydrolyze slowly to the corresponding amide by exposure to the air.



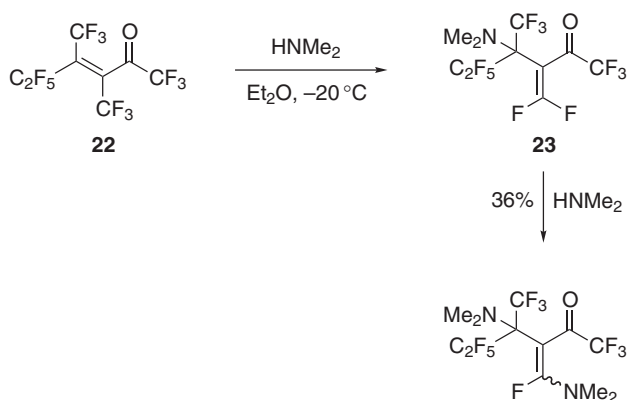
Scheme 7

Furthermore, monosubstitution of *gem*-dihaloalkenes with amines is successfully applied preparing  $\alpha$ -haloenamines. Coe and co-workers allowed diethylamine to react with perfluorinated diene **18**, giving a mixture of the four possible isomers (Equation (11)). Only the major isomers **19** and **20** were isolated and fully characterized <2001JCS(P1)552>. Treatment of polyhalogenated 2-nitro-1,3-butadiene **21** with amines leads to replacement of the terminal chlorine in the trichlorovinyl group or of bromine in the bromodichlorovinyl group (Equation (12)) <1997RJOC1632, 2000RJOC877>.





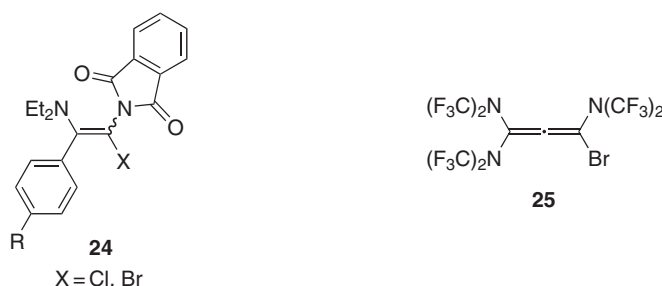
Finally, *gem*-haloaminoalkenes have been prepared using a Michael-type addition followed by a subsequent elimination. Coe and co-workers report the addition of dimethylamine to ketone **22** (Scheme 8) <2000JCS(P1)1529>. The addition product **23** is noted to be more reactive than starting material **22**, so that a second Michael-type addition leads to the corresponding *gem*-haloaminoalkene. Before, Schroth and co-workers isolated *gem*-chloropyrrolidinoalkenes from  $\beta,\beta$ -dichloroalkenylarylketones. According to them,  $\beta$ -keto  $\alpha$ -haloenamines are configurationally unstable. This instability is attributed to a lowering of the barrier to rotation about the double bond by donor–acceptor interactions, rather than to any tendency to form a ketenimine <1982S199>.



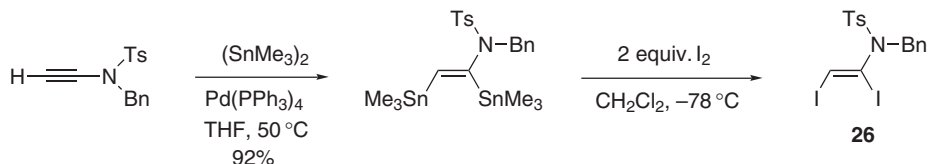
Scheme 8

#### 4.18.1.1.3 By electrophilic attack

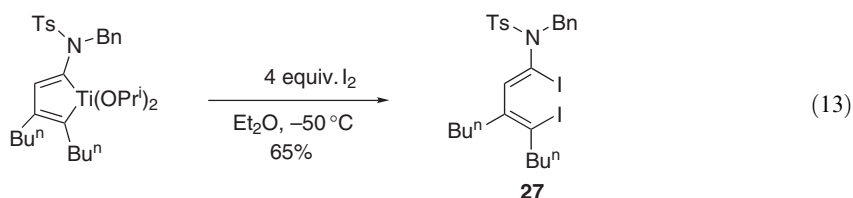
Electrophilic halogenation, in which the multiple bond participates as a nucleophile, is not well documented since enamines direct such substitution into their 2-position. However, halogenation of 1-diethylamino-2-phthalimidostyrenes with chlorine and bromine furnishes  $\alpha$ -haloenamides **24** via a 2-substitution in good yields (68–95%) <1967CB1087>. An unusual example of 1-bromination has been observed with perfluoro-*N*-bromodimethylamine affording the corresponding 3-bromoallene **25** from 1,1,3-tris(hexafluorodimethylamino)propadiene in high yield <1973JCS(P1)1066>.



Minière and Cintrat prepared  $\alpha,\beta$ -diiodoenamide **26** via iododestannylation of the corresponding stannyleneamine with 2 equiv. of iodine (Scheme 9). Compound **26** was reported to be too unstable to be purified, but the purity of the crude compound was reported to be higher than 90% <2001S705>. Employing a titanacycle, Sato and co-workers successfully prepared diiodide **27** by iodolysis in good yield (Equation (13)) <2003OL67>.

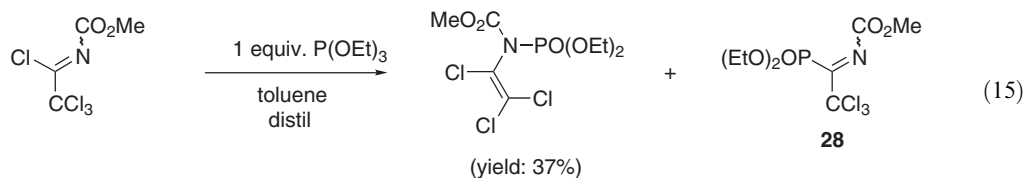
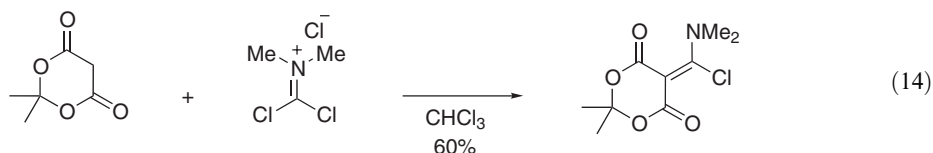


Scheme 9



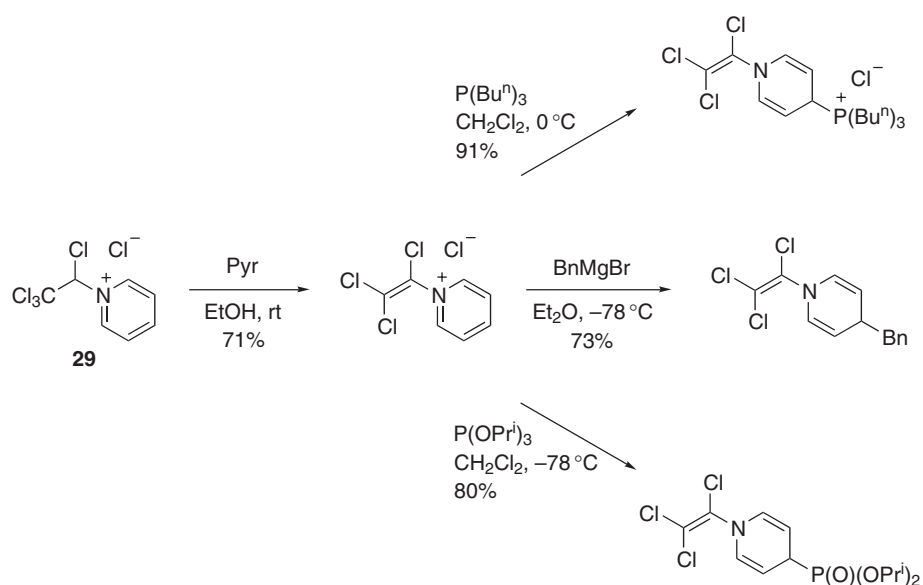
#### 4.18.1.1.4 Other methods of alkene formation

This section covers methods using reactants bearing already the heteroatom functionality. McNab and Morrow treated Meldrum's acid with phosgeniminium chloride affording the corresponding chlorodimethylaminomethylene derivative in satisfactory yield (Equation (14)) <2002MI125>. Trichloroacetimidoyl chlorides react with triethylphosphite yielding a 2:1:1 mixture of compound **28** and the  $\alpha$ -chloroenamide, respectively (Equation (15)). Starting from trifluoroacetimidoyl fluoride, only the corresponding compound **28** and no  $\alpha$ -fluoroenamide is formed <1999RJGC1879>.



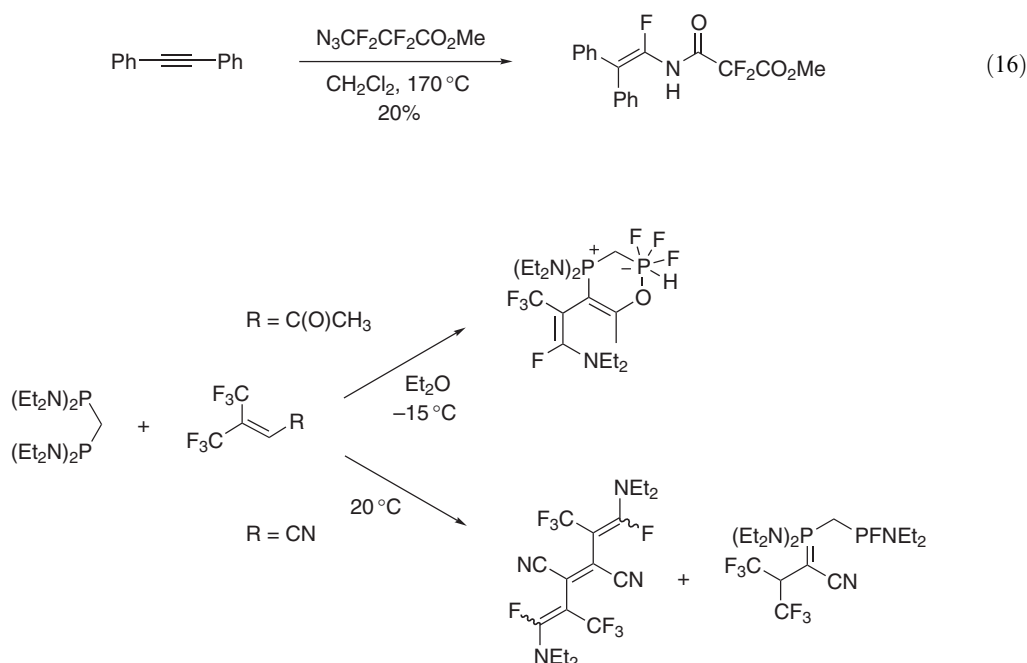
Drach and co-workers have prepared *N*-trichlorovinylbenzimidoyl chloride and -benzylideneamine by 1,2- and 1,4-elimination of hydrogen chloride <1975JOU119, 1976JOU2252, 1980JOU1762>. The elimination method was also implemented by Anders *et al.* (Scheme 10). Pyridinium chloride **29** is prepared from thionyl chloride, trichloroacetaldehyde, and pyridine in acetonitrile in very good yield (80%). The electron-withdrawing trichlorovinyl group of *N*-(trichloroethenyl)pyridinium chloride activates the pyridinium moiety allowing nucleophilic addition. Tributylphosphine, benzylmagnesium bromide, and triisopropylphosphite all add to the C4 position, exclusively <1999JOC3113>.

Diphenylethyne is fluorinated with methyl 3-azidotetrafluoropropionate in a closed vessel and at high temperature, furnishing the corresponding  $\alpha$ -fluoroenamide in poor yield (Equation (16)). The mechanism of the reaction is believed to involve intermediate formation of an *N*-substituted azirine followed by a phenyl and fluoride shift <2002RJGC1289>. Shevchenko and co-workers



Scheme 10

reported an unusual reaction of methylene diphosphine and 5,5,5-trifluoro-4-(trifluoromethyl)pent-3-en-2-one leading to a novel type of zwitterionic compound containing an  $\alpha$ -fluoro enamine functionality (yield: 27%) (Scheme 11). The detailed structure of the enamine was solved by X-ray analysis and is remarkable since it contains two oppositely charged phosphorus atoms with different coordination numbers <2002CC120>. Performing this reaction with the corresponding nitrile, a polyfluorinated triene (yield: 49%) was isolated instead together with a fluorine-substituted ylide in a 1:1 ratio (Scheme 11). In the NMR spectra, a fast interconversion between possible steric isomers has been observed; however, the central double bond always retains its *trans* configuration <2003EJI54>.



Scheme 11

#### 4.18.1.2 *gem*-Halonitroalkenes

Barrett reviewed the preparation and synthetic utility of 1-heterosubstituted nitroalkenes covering ether, thioether, halogen, and nitro substituents <1991CSR95>. Based on the structure used by Smith <1995COFGT(4)789>, this chapter aims to extend and update that work.

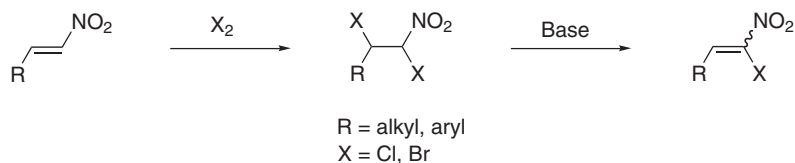
##### 4.18.1.2.1 By halogenation

The reactions outlined in this section are those in which the halogen is added at a nitro-containing compound as an electrophilic species.

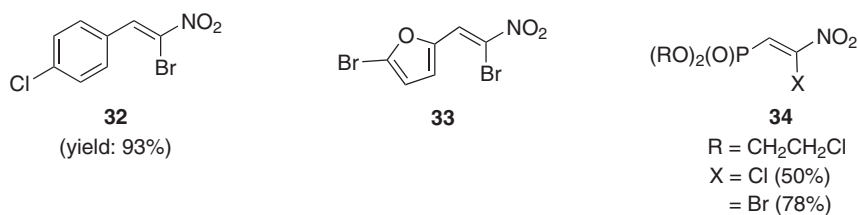
*gem*-Fluoronitroalkenes are very rare in the literature. (*E*)-1,2-difluoro-1,2-dinitroethene **30** has been prepared by fluorination of 1,1,2,2-tetranitroethane and subsequent elimination of dinitrogen tetroxide <1991JOC537>. More general, fluorination of the dianion of 1,1,3,3-tetranitropropane followed by alcohol-induced elimination leads to a series of alkyl  $\beta$ -fluoro- $\beta$ -nitroacrylate esters **31** <1989BAU635>.



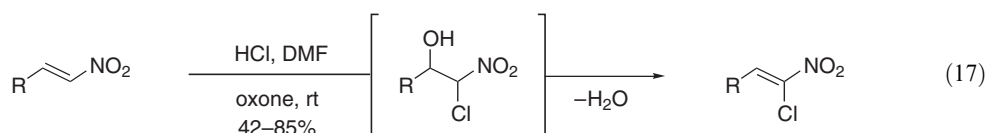
An important method of preparation of  $\alpha$ -bromo- or  $\alpha$ -chloronitroalkenes is from nitroalkenes by dihalogenation and subsequent elimination (Scheme 12). Using this method, Trukhin and co-workers prepared  $\alpha$ -bromonitroalkene **32** in excellent yield <1996RJOC458> and its (*Z*)-configuration was supported by proton NMR and UV spectral data <1998RJOC59>. Bromination of nitroalkene **32** in refluxing chloroform and subsequent treatment of the tribromo compound with potassium hydroxide in ethanol furnishes the corresponding (*E*)- $\alpha,\beta$ -dibromo nitroalkene (yield: 50%) <1998RJOC1061, 1999RJGC803>. *gem*-Bromo nitroalkene **33** was obtained by direct bromination of 2-nitrovinylfuran in the presence of activated carbon, followed by dehydrobromination using pyridine <2000WOP0153283>. Botata and co-workers reported the first preparation of  $\beta$ -phosphorylated *gem*-halonitroethene **34**. Nitrovinylphosphonate is halogenated in glacial acetic acid with bromine or chlorine furnishing the corresponding dihalide that readily undergoes dehydrohalogenation on silica gel or upon storage. Both *gem*-halonitroethenes are isolated as the (*Z*)-configuration, exclusively <1995RJGC141, 1998RJGC384>. *gem*-Halonitroalkenes are reported to be configurationally stable under normal conditions. However, upon irradiation, 2-bromo and 2-chloro-2-nitrostyrene isomerize substantially from the (*Z*)- to the (*E*)-configuration, giving a mixture composed of 60–80% (*E*) for the chloro derivative but only 10–20% (*E*) for the bromo compound <1976JOC2112>.



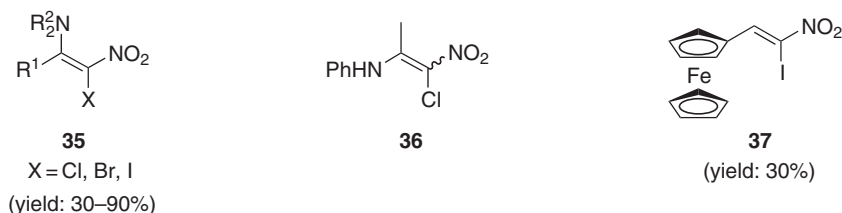
Scheme 12



To synthesize  $\beta$ -chloro- $\beta$ -nitrostyrene derivatives, Kim and co-workers developed an interesting method applying hydrogen chloride in the presence of oxone ( $2\text{KHSO}_5 \cdot \text{KHSO}_4 \cdot \text{K}_2\text{SO}_4$ ) (Equation (17)). The authors tentatively proposed a mechanism involving the addition of hypochlorous acid to the nitroalkene, followed by dehydration of the chloronitroalcohols. Hypochlorous acid is formed *in situ* by oxidation of hydrogen chloride. Due to the reaction of hypochlorous acid with unreacted hydrogen chloride, chlorine is probably generated causing some side reactions such as ring chlorination or addition to the double bond of the produced  $\beta$ -chloro- $\beta$ -nitrostyrenes. *m*-Chloroperbenzoic acid (MCPBA) was also successfully utilized as oxidant, but showed no advantages over oxone in terms of yields and ease of separation. Further, it is notable to report that nitroolefins having a substituent at the  $\beta$ -position such as *p*-chloro- $\beta$ -ethyl- $\beta$ -nitrostyrene decomposed almost quantitatively to *p*-chlorobenzaldehyde <1997SC1885>.

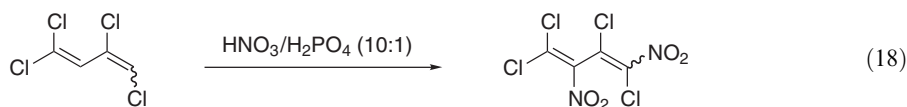


Using *N*-halosuccinimides (NXSs) in benzene-chloroform, the halogenation proceeds directly without the elimination step provided that the alkene is activated by an electron-donating group. Chlorine, bromine, or iodine can be introduced with equal efficiency yielding the 2-halo-2-nitro-enamines **35** <1985JOC1547>. An alternative route to 2-chloro-2-nitroenamine **36** includes the condensation of chlorinated nitroacetone with aniline in the presence of titanium tetrachloride <1977AP(310)30>. Finally, compound **37** has been prepared by addition of iodine to 1-ferrocenyl-2-nitroethene in sodium methoxide <1969BCJ3270>.

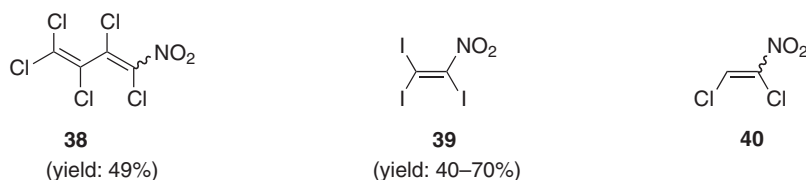


#### 4.18.1.2.2 By nitration

When heavily substituted or polyhalogenated, alkenes have been nitrated with nitric acid or nitrogen oxides. Compound **38** is prepared from 1*H*-perchloro-1,3-butadiene by the action of concentrated nitric acid <1991JOU48>. Nechai and co-workers employed a mixture of nitric and phosphoric acid (10:1) to nitrate 1,1,3,4-tetrachloro-1,3-butadiene in order to synthesize 1,3-dinitro-1,2,4,4-tetrachloro-1,3-butadiene (Equation (18)) <1998MI75>. Treatment of these multifunctional compounds with strongly basic amines results in the substitution of the two terminal chlorine atoms leading to the corresponding dinitrodienediamines <2000RJOC650>.



Dihaloalkynes are also suitable precursors for the preparation of the corresponding *gem*-halonitroalkenes. Nitrotriiodoethene **39** has been prepared from diiodoethyne in variable yield with nitrous acid in an excess of ethereal iodine <1900CB2190>. The addition of nitrogen dioxide to dichloroethyne furnishes compound **40** in unspecified yield and geometry <1943CB88>.

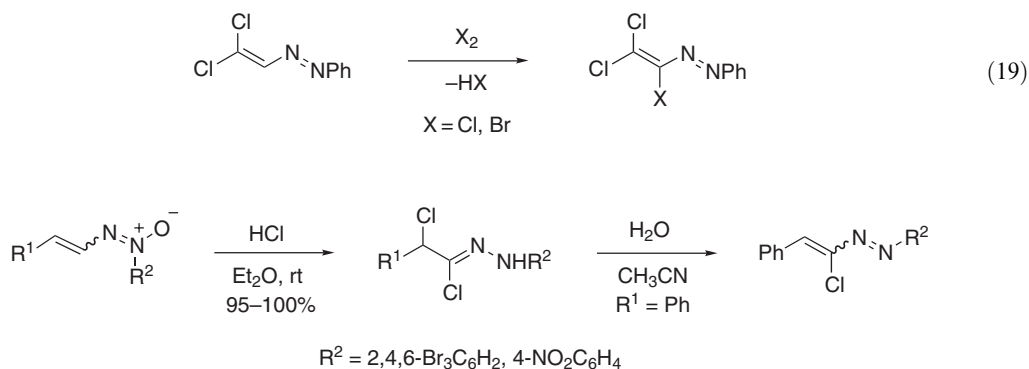




#### 4.18.1.3 Diazonium and Diazo Derivatives

Even though the aryldiazo derivatives of alkenes are stable and isolated as colored solids, the alkyldiazo equivalents are much less stable and are only used as reactive intermediates <1979JCS(P1)249>.

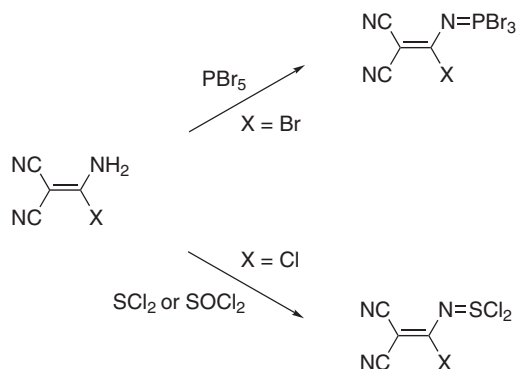
Arylhydrazones of chloral spontaneously lose hydrogen chloride and lead to haloalkenyldiazo compounds upon treatment with bromine or chlorine in unspecified yields (Equation (19)) <1931JCS1088>. More recently, Tyurin and co-workers found that 1-aryl-2-alkenyldiazene oxides furnish the corresponding chlorohydrazones in quantitative yield when treated with hydrogen chloride. Arylhydrazones, obtained from 1-aryl-2-(2-phenylethene)diazene oxides, undergo elimination of hydrogen chloride affording *gem*-chlorodiazoalkene in unspecified yield and in a 1:2 (*E*):(*Z*) ratio (Scheme 13). Heating the mixture of isomers in acetonitrile for 15 h results in the isolation of the (*E*)-isomer only <1994MC220, 1995IZV928, 1995IZV924, 1995IZV917>.



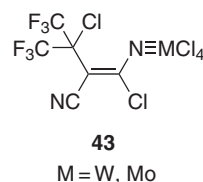
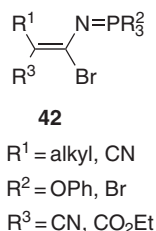
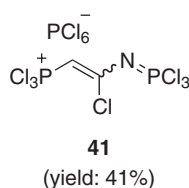
Scheme 13

#### 4.18.1.4 Iminophosphorane, Sulfimide, and Metallonitrene Complexes

A variety of iminophosphoranes <1979JGU1947> and sulfimides <1976JOU782> have been prepared by the reaction of  $\alpha$ -haloenamines with phosphorus or sulfur halides, respectively (Scheme 14). Following an alternative approach, Rozinov and co-workers prepared compound **41** with unspecified configuration by treatment of acetaldoxime with phosphorus pentachloride in benzene <1997RJGC483>. Further, compounds **42** were obtained in high yields by the addition of triphenylphosphite <1972T5149> or phosphorus tribromide <1979JGU1947> across the cyanide triple bond of  $\alpha$ -bromomalononitrile derivatives. Similarly, molybdenum and tungsten chlorides have been added across 1,1-dicyanobis(trifluoromethyl)ethane furnishing compounds **43** <1986CB3150>.



Scheme 14

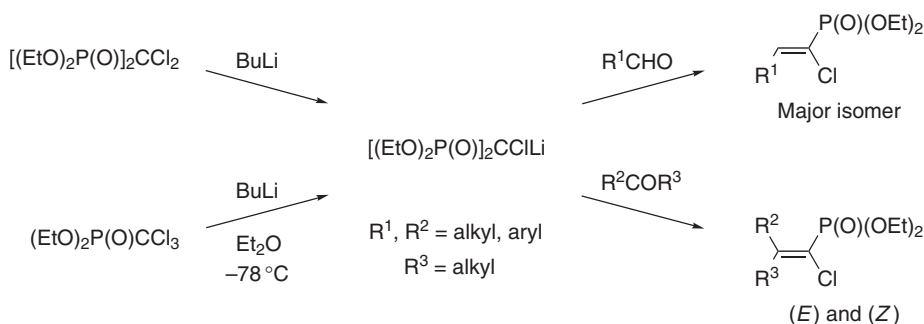


## 4.18.2 DERIVATIVES OF PHOSPHORUS AND OTHER GROUP 15 ELEMENTS

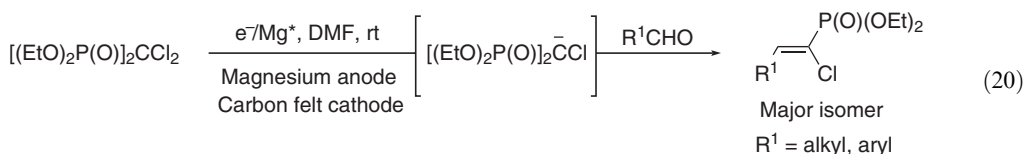
### 4.18.2.1 $\alpha$ -Haloalkenylphosphorus Derivatives

#### 4.18.2.1.1 From carbonyl compounds

Despite the substantial number of reported syntheses of  $\alpha$ -haloalkenylphosphorus species, only a few proceed by direct condensation with carbonyl compounds. The first reaction of this type was described by Seyferth and Marmor, who successfully applied the Wadsworth–Emmons reaction. Treatment of the anion of tetraethyldichloromethanediphosphonate with pivaldehyde or acetone gives high yields of  $\alpha$ -chlorophosphonoalkenes, but fails with benzophenone (Scheme 15) <1973JOM(59)237>. Employing diethyltrichloromethylphosphonate, a one-pot procedure allows the synthesis of  $\alpha$ -chloroalkenylphosphonates via the intermediate formation of lithium tetraethyl chloromethanediphosphonate (Scheme 15) <1994JOC4548, 1997JCS(P2)967>. Feasson and co-workers developed an electrochemically induced Wadsworth–Emmons synthesis of  $\alpha$ -chloro- $\alpha,\beta$ -unsaturated phosphonates with a similar yield and stereoselectivity compared to the ones obtained by the chemical procedure (lithiated base/low temperature) (Equation (20)) <1999S981>.

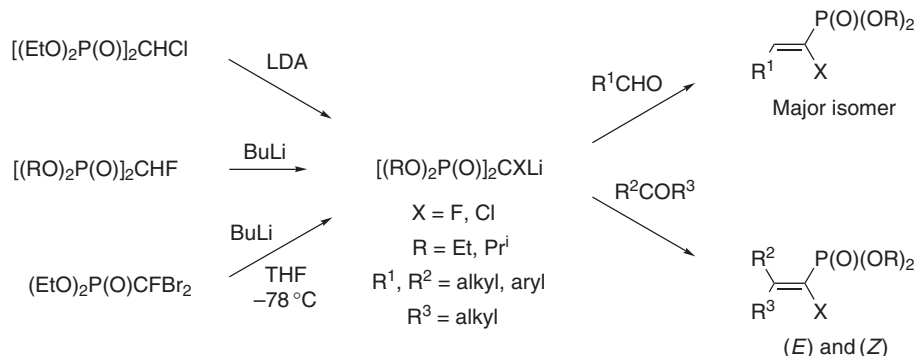


Scheme 15

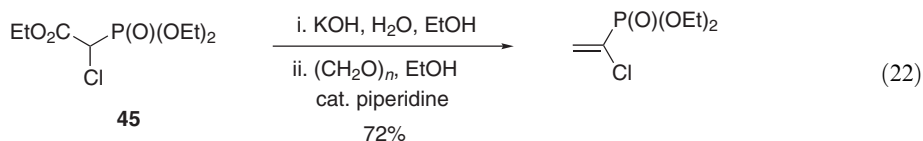
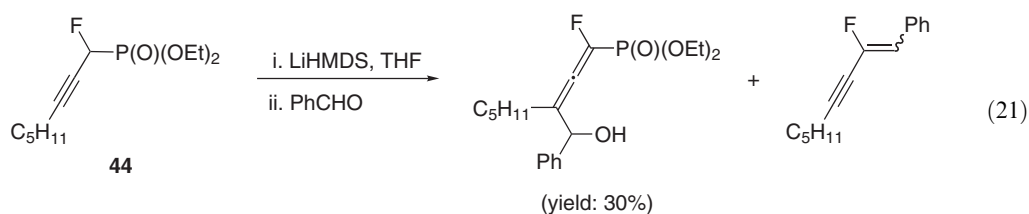


Savignac and co-workers synthesized *gem*-chlorophosphonoalkenes in generally high yields (56–95%) from the anion derived from chloromethanediphosphonate using lithium diisopropylamide (LDA) as a base (Scheme 16) <1986JOM(304)283>. Analogously, *gem*-fluorophosphonoalkenes have been prepared starting from fluoromethanediphosphonates (Scheme 16) <1986JCS(P1)1417, 2003OL2267>. Since the anion of fluoromethanediphosphonate is formed *in situ* when treated with *n*-butyllithium, fluorodibromomethylphosphonate was also successfully

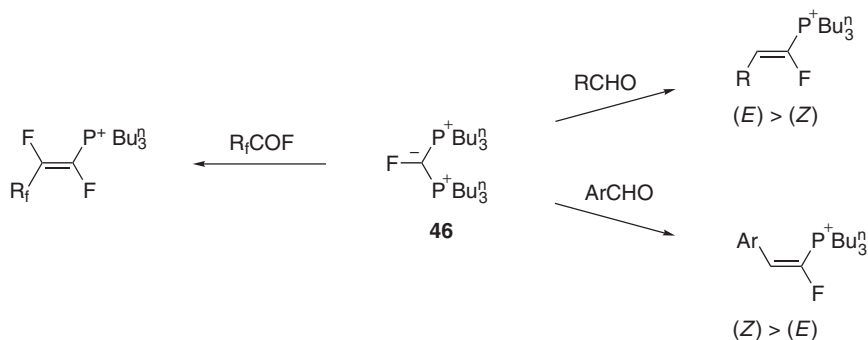
applied to obtain *gem*-fluorophosphonoalkenes (Scheme 16) <1998TL4477>. When treated with lithium bis(trimethylsilyl)amide (LiHMDS) and benzaldehyde at  $-110^{\circ}\text{C}$ , fluorophosphonate **44** furnishes a 1:1 mixture of the *gem*-fluorophosphonoallene and the corresponding Wadsworth–Emmons product (Equation (21), see also Scheme 28) <1998T15541>. Finally, the condensation of chlorinated phosphonoacetate **45** with paraformaldehyde gives *gem*-chloro(phosphono)ethene in good yield (Equation (22)) <2000PJC1123>.



Scheme 16



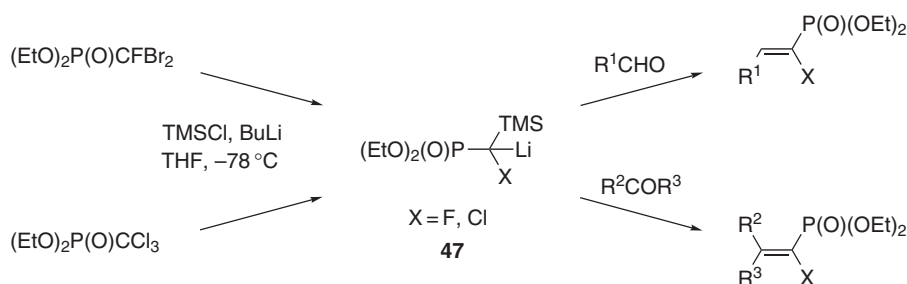
A similar condensation using the Wittig reaction instead is only reported twice. Bisphosphonium ylide **46** undergoes condensation with perfluoro acid fluorides <1983JA650> as well as with alkyl and aryl aldehydes (Scheme 17) <1985JA2811>. When alkyl aldehydes are used, the condensation reaction is (*E*)-selective, but gives alkenes in a (*Z*)-selective manner with aryl aldehydes.



Scheme 17

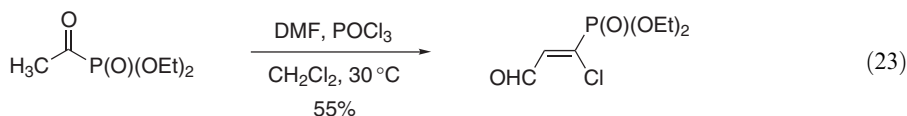
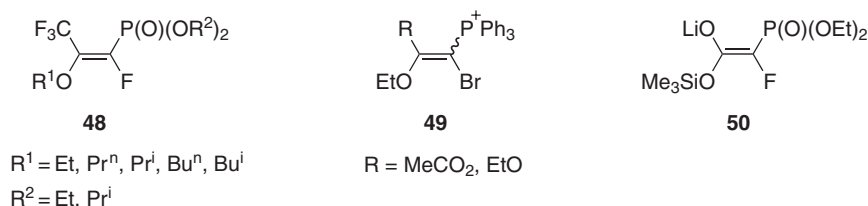
Substituting a phosphonate unit by a trimethylsilyl group, *gem*-halophosphonoalkenes can be formed by the Peterson olefination (Scheme 18). Savignac and co-workers synthesized several

$\alpha$ -fluoroalkenylphosphonates in generally high yields using both aldehydes and ketones. The reaction with aliphatic aldehydes shows no stereochemical control, whereas aromatic and hetero-aromatic aldehydes give rise to the formation of mainly the (*E*)-isomer (up to an 8:2 (*E*):(*Z*) ratio). The reaction with ketones is dependent on steric factors and the corresponding (*Z*)-isomers are produced as main products. Particularly noteworthy is the fact that the condensation with cyclic ketones (2-methylcyclohexanone, (–)-carvone, isophorone, and  $\alpha$ -tetralone) only results in the formation of the (*Z*)-isomer. The influence of different trialkylsilyl groups on the stereoselectivity of the reaction was also examined. Increasing the steric bulk of the trialkylsilyl group, carbonyl compounds leading to mainly the (*E*)-isomer show a decrease in (*E*):(*Z*) ratio. By contrast, the size of the trialkylsilyl group has no influence upon the (*E*):(*Z*) ratio when the (*Z*)-isomer is the main product. Substituting the fluorine atom by a chlorine atom has no effect on the stereochemistry. The authors proposed a closed transition state to explain the results of their study <1996T14199, 1996TL1783, 1996JFC(80)59>.



Scheme 18

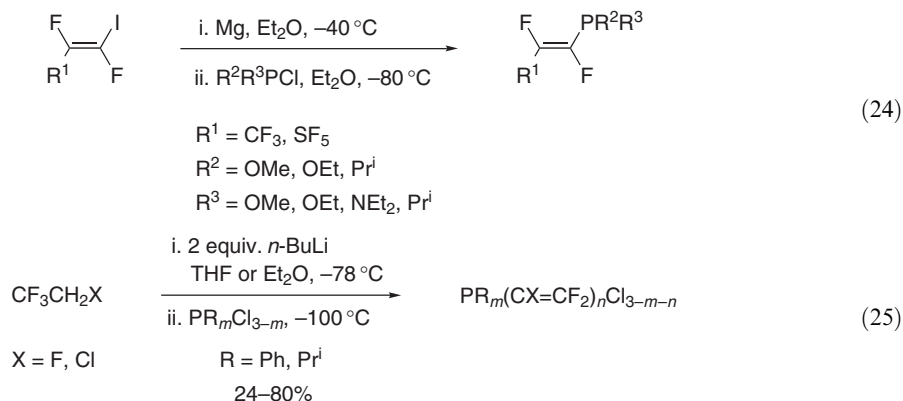
The utility of the Peterson olefination using esters as substrates has been reported only once. Generally, esters are not reactive enough to react with anion **47** (see Scheme 16); however, applying trifluoroacetic esters permits the synthesis of  $\alpha$ -fluoro- $\beta$ -trifluoromethyl- $\beta$ -alkoxyvinylphosphonates **48** with high (*E*)-selectivity (yield: 32–91%) <2001JFC(108)69>. Ylide acylation results in products that exist preferentially or exclusively in the enol form, e.g., enol ether **49** <1993JOC1531>. Treatment of anion **47** with carbon dioxide at  $-60^\circ\text{C}$  gives *gem*-fluorophosphonoalkene **50** in unspecified yield after a [1,3]-migration on warming to room temperature <1997T6391>. A different approach for the synthesis of  $\alpha$ -chloroalkenylphosphonates starts from an acylphosphonate and makes use of the Vilsmeier reagent (DMF/ $\text{POCl}_3$ ). This procedure leads exclusively to the formation of the (*Z*)-isomer in moderate yield (Equation (23)) <2000PS(158)179>.



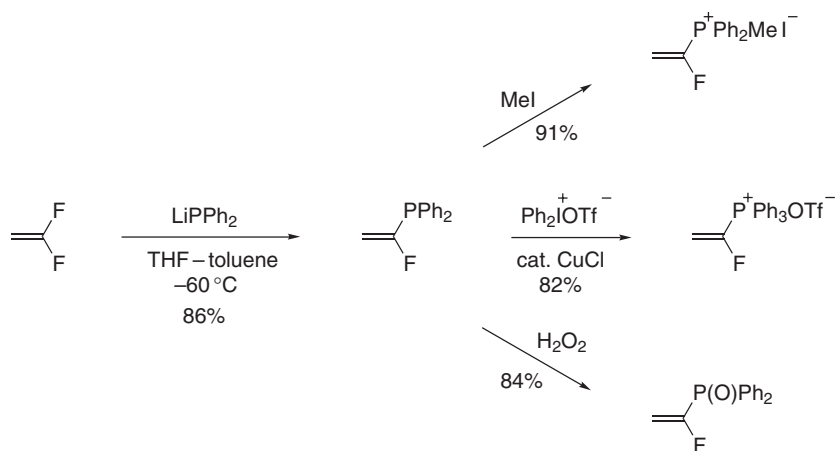
#### 4.18.2.1.2 From fluorinated alkenes

Although the success of these reactions is strongly dependent on experimental conditions, several  $\alpha$ -trifluorovinylphosphorus derivatives have been prepared by action of trifluorovinylolithium or trifluorovinylmagnesium on phosphorus(III) halides <1969JA1934, 1988BAU1686>. Analogously,

several *gem*-difluorophosphonoalkenes have been prepared in unspecified yields from the corresponding  $\alpha$ -fluoroalkenyllithium derivatives (Equation (24)) <1997HAC467>. Brisdon and co-workers significantly improved this method by treating 1,1,1,2-tetrafluoroethane with 2 equiv. of *n*-butyllithium followed by phosphorus(III) chlorides in a one-pot reaction (Equation (25)). Utilizing 1-chloro-2,2,2-trifluoroethane, this procedure was further extended to the formation of 1-chloro-2,2-difluorovinyl-containing phosphines <1999JCS(D)427, 2001JFC(112)35>.

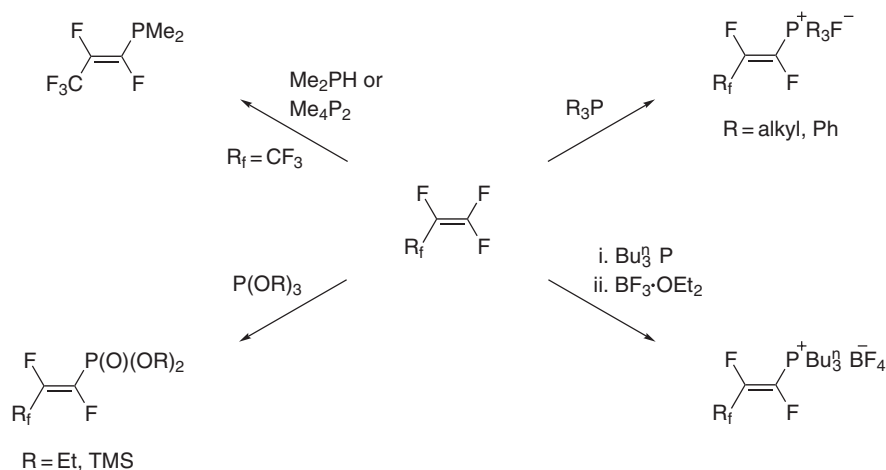


A second route to  $\alpha$ -fluorovinylphosphorus compounds consists of the action of a phosphorus(III) species on a polyfluoroalkene. When treated with triisopropylphosphite, an Arbusov reaction on iodotrifluoroethane furnishes the corresponding 2-iodo-1,2-difluoroethenylphosphonate as the (*E*)-isomer <1981PS(10)127>. In order to prepare the corresponding phosphonium salts and phosphine oxide, Hanamoto and co-workers synthesized  $\alpha$ -fluorovinylidiphenylphosphine by action of lithium diphenylphosphide on 1,1-difluoroethene. Careful temperature control is necessary to avoid the formation of 1,1-bis(diphenylphosphinyl)ethene (Scheme 19) <1999CC151, 2000JCS(P1)103>. Further, a number of phosphorus(III) species have been successfully added to perfluoroalkenes. Dimethylphosphine and tetramethyldiphosphine react with hexafluoropropene in the dark (Scheme 20) <1975JCS(P1)702>. Phosphonium salts are isolated when perfluoroalkenes are treated with tertiary phosphines <1979JA3689, 1996JFC(80)149>, and reaction of perfluoroalkenes with phosphites results in the corresponding phosphonates (Scheme 20) <1988CZ69, 1996JFC(80)149, 2001PS(176)201>.



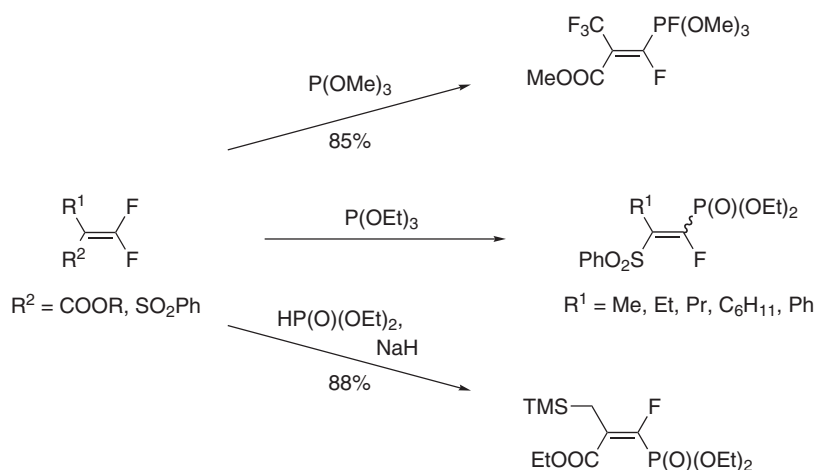
Scheme 19

Michael addition of phosphites to perfluoromethacrylate esters furnishes *gem*-fluorophosphono  $\alpha,\beta$ -unsaturated carbonyl compounds. An Arbusov reaction is not observed; however, the major products being the corresponding *P*-fluorophosphoranes isolated as single, unspecified isomers (Scheme 21) <1976BAU853, 1976BAU873>. Alternatively, treating the  $\beta$ -phenylsulfonyl  $\alpha,\alpha$ -difluoroalkene with triethylphosphite does proceed via an Arbusov reaction, furnishing the



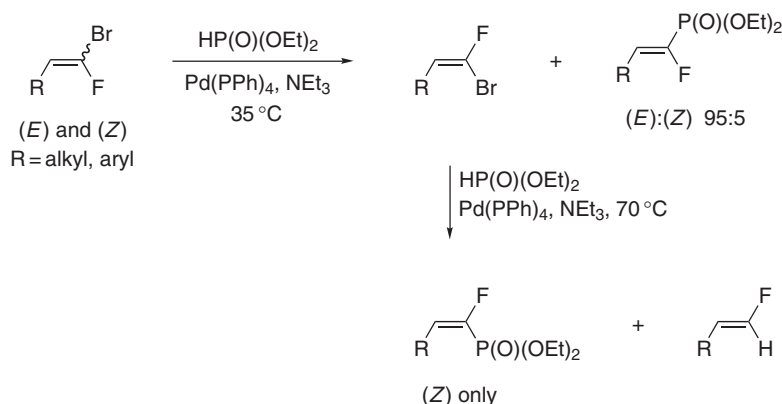
Scheme 20

corresponding  $\alpha$ -fluoroalkenylphosphonate (Scheme 21) <1999MI768>. A similar addition–elimination reaction is observed adding sodium diethylphosphite to 2-[(trimethylsilyl)methyl]-substituted 3,3-difluoropropenoate (Scheme 21). The reaction stops at the stage of the substitution of one fluorine owing to the presence of the electron-donating silyl group. Additionally, an intramolecular coordinative interaction between fluorine and silicon is proposed to control the transition-state conformation leading to the (*E*)-isomer, exclusively (see also Equation (10)) <2000JOC627>.



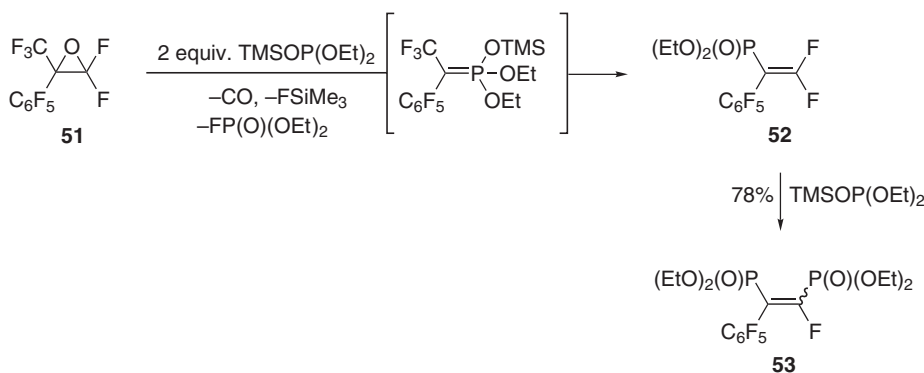
Scheme 21

Although there are several methods to obtain (*E*)- $\alpha$ -fluorovinylphosphonates, there is a paucity of routes for the preparation of (*Z*)- $\alpha$ -fluorovinylphosphonates. A palladium-catalyzed displacement of iodine by diethylphosphite furnishes *gem*-fluorophosphonoalkenes with retention of stereochemistry <1993TL7197>. Utilizing this method, Zhang and Burton developed a kinetic separation method for the stereoselective preparation of 1-fluorovinylphosphonates from (*E*):(*Z*) mixtures of 1-bromo-1-fluoroalkenes (Scheme 22). (*E*)-1-bromo-1-fluoroalkenes react significantly faster than the (*Z*)-isomers, leading to a reaction mixture that contains both 1-fluorovinylphosphonate with a 95:5 (*E*):(*Z*) ratio and pure (*Z*)-isomer of the starting material that could be readily recovered. The isomerically pure (*Z*)-1-fluorovinylphosphonates are prepared via phosphorylation from the (*Z*)-1-bromo-1-fluoroalkenes at higher temperatures. However, at these higher temperatures a competitive reduction becomes significant <2001JFC(112)47>.



Scheme 22

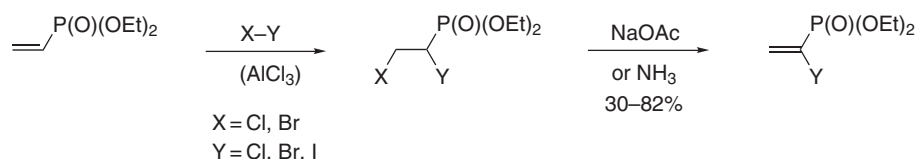
Alkene 1,2-diphosphonates have been prepared as (E):(Z) mixtures by double reaction of phosphites with polyfluoroalkenes <1988BAU1686>. Starting from perfluoroepoxide **51**, a 1:2 (E):(Z) mixture of bisphosphonate **53** is obtained when reacted with diethyl(trimethylsilyl)phosphite (Scheme 23). The reaction proceeds via an ylide, which spontaneously leads to the formation of phosphonate **52** <1997HAC59>.



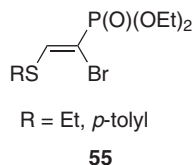
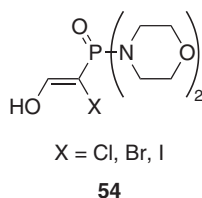
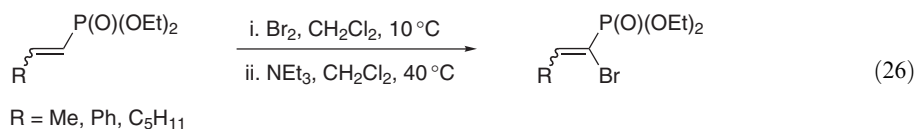
Scheme 23

#### 4.18.2.1.3 By halogenation

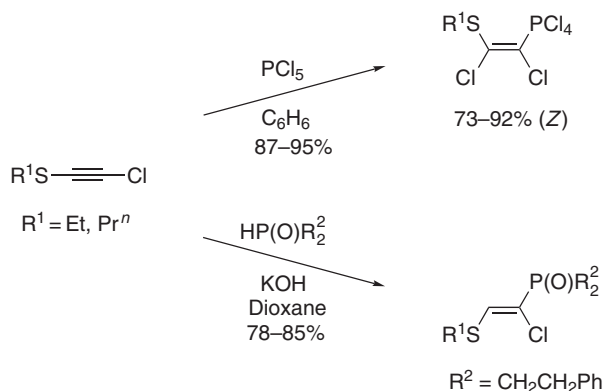
Direct halogenation of vinyl phosphonates followed by elimination is reported to afford  $\alpha$ -haloalkenyl phosphonates. Hägele and Dolhaine performed the halogenation with chlorine, bromine, and their diatomic interhalogen compounds, including those with iodine (Scheme 24). The  $\alpha,\beta$ -dihaloethanes are produced in an anti-Markovnikov fashion, with the more electrophilic halogen geminal to the phosphorus atom. The elimination furnishes the *gem*-halo(phosphono)ethenes in 30–82% yield <1977PS(3)47>. Kobayashi and William successfully extended this method for the synthesis of *gem*-bromophosphonoalkenes bearing a substituent at the  $\beta$ -position (Equation (26)). The *gem*-bromophosphonoalkenes were isolated in good yield and the stereoselectivity was varied from quite high to moderate depending on the  $\beta$ -substituent and the stereochemistry of the substrates <2002OL4241>. The same sequence has also been applied to (Z)-1-propenylphosphonic acid, giving only the (Z)-isomer of 1-bromo-1-propenylphosphonic acid. Starting from (E)-1-propenylphosphonic acid, a mixture of both the (E)- and (Z)-isomer is obtained <1995JOC74>. Proving the generality of this procedure, *gem*-halophosphonamidoaldehydes, predominantly in the (Z)-enol form **54**, were prepared from the corresponding 2-ethoxyvinylphosphonamide <1992JGU1222>. Similarly, 2-(alkylthio)-1-bromovinylphosphonate **55** has been prepared from the corresponding vinyl phosphonate <1987JCS(P1)1275>.



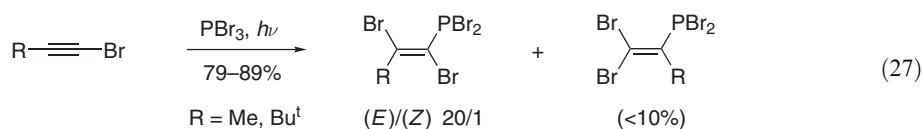
Scheme 24



Addition of phosphorus species has been observed with alkynes and alkenes. Phosphorus pentachloride reacts via an electrophilic attack with (alkylthio)chloroethynes, affording predominantly (*Z*)-( $\alpha$ -chlorovinyl)-tetrachlorophosphoranes (Scheme 25) <1991JGU983>. D'yachkova and co-workers performed the addition of phosphine oxides across (alkylthio)chloroethynes in the presence of potassium hydroxide leading to (*Z*)-1-chloro-2-(alkylthio)vinylphosphine oxides in good yield (Scheme 25) <2001RJGC1717>. Upon irradiation, phosphorus tribromide was added to bromoalkynes leading to 1-dibromophosphino-1,2-dibromoalkenes in a 20:1 (*E*):(*Z*) ratio. The regioselectivity of the addition is not absolute, giving rise to small amounts of the other regioisomer (Equation (27)) <1995RJGC956>.



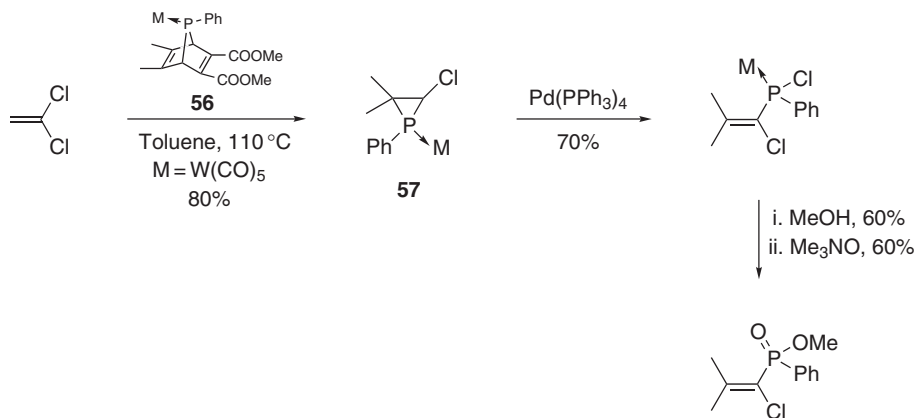
Scheme 25



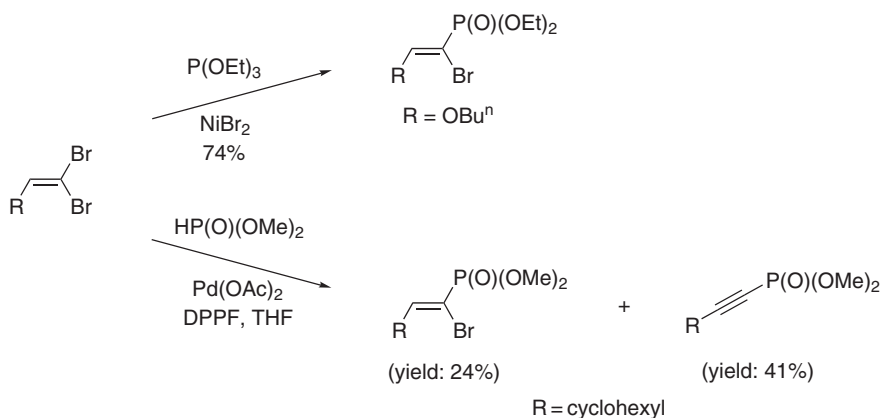
Heating 1,1-dichloroethene in the presence of compound 56, which is a precursor of a terminal phosphinidene complex ( $\text{PhP} \rightarrow \text{M}$ ), results in the formation of phosphirane 57 through a [2 + 1]-cycloaddition. When subjected to a palladium-catalyzed ring opening, a *gem*-chlorophosphinoethene complex is formed that can be oxidized with trimethylamine *N*-oxide (Scheme 26) <2000JOC652>.



Applying a nickel-catalyzed Arbusov reaction, Beletskaya and co-workers obtained 1-bromo-2-butoxyvinylphosphonate from the corresponding dibromide and triethylphosphite (Scheme 27). The phosphonate is initially formed as an isomeric mixture. However, distillation at 120–150 °C leads to isomerization and only the (*Z*)-isomer is isolated <1999TL569>. Utilizing a Pd-catalyst and dimethylphosphite, the *gem*-bromophosphonoalkene is only formed as a side product (Scheme 27) <2000OL3873>.



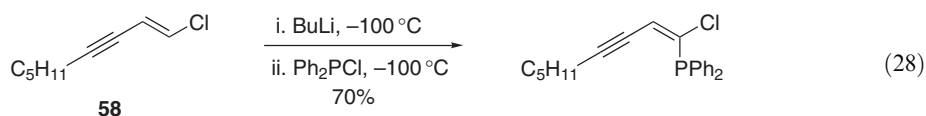
Scheme 26

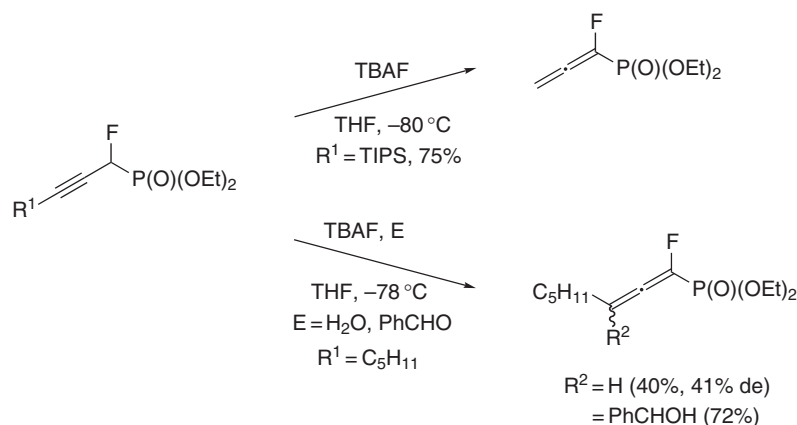


Scheme 27

#### 4.18.2.1.4 Other methods of alkene formation

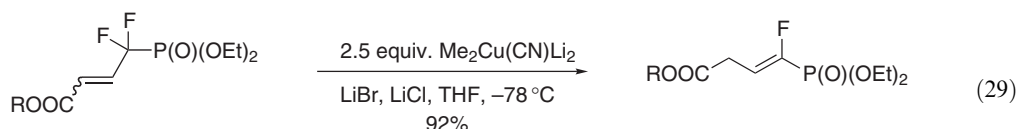
When treated with *n*-butyllithium, (*E*)-chloroenyne **58** reacts with chlorodiphenylphosphine leading to the formation of the (*E*)-isomer of the corresponding *gem*-chlorophosphonoalkene in good yield (Equation (28)). Noteworthy is the fact that under the same conditions, attempted conversions of (*Z*)-chloroenyne and (*E*)-1-chlorohept-1-ene into  $\alpha$ -chlorophosphonoalkenes were unsuccessful <1995TL3687>. Hammond and co-workers prepared *gem*-fluorophosphonoallenes from  $\alpha$ -fluorophosphonoalkynes upon treatment with tetra-*n*-butylammonium fluoride (TBAF) (Scheme 28). The allenes are thermally stable and were easily purified by chromatography <2000JOC227>.



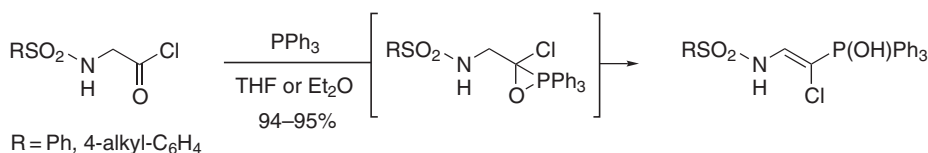
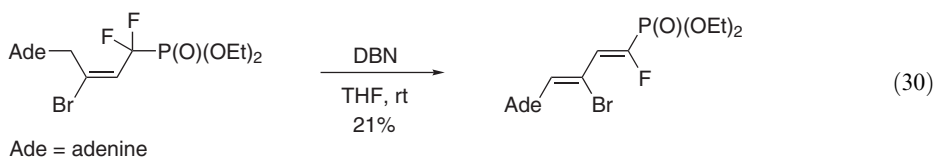


Scheme 28

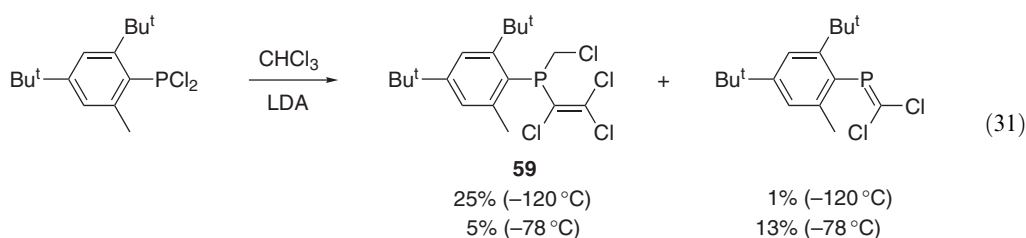
Otaka and co-workers reported the synthesis of  $\alpha$ -fluorophosphonoalkenes via an organocopper-mediated reduction of *gem*-difluorophosphonoalkenes. Although the butylcopper reagent gives the reduction product as well as the Michael adduct (24%), conjugate addition is not detected using methylcopper reagents (Equation (29)) <2000CC1081>. An unsaturated fluoro-analog of adenine has been prepared by elimination of hydrogen fluoride using 1,5-diazabicyclo[4.3.0]-non-5-ene (DBN) as base (Equation (30)) <1997T5389>. Arylsulfonylglycyl chlorides spontaneously lead to *gem*-chloroalkenylphosphorus compounds in excellent yield when treated with triphenylphosphine (Scheme 29). Although the mechanism of the reaction is not established, a cyclic oxaphosphorane has been suggested as an intermediate <2001T9873>. Finally, reacting 2,4-di-*t*-butyl-6-methylphenylphosphonous dichloride with chloroform in the presence of LDA leads to trichlorovinylphosphine **59** in poor yield (Equation (31)). Careful temperature control is necessary to minimize the formation of side product <1996HAC23>.



R = Et, (2*S*)-bornane-[10.2]-sultam

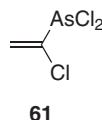
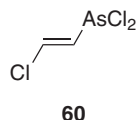


Scheme 29

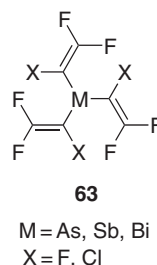
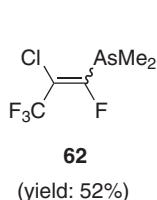


#### 4.18.2.2 $\alpha$ -Haloalkenyl Derivatives of Arsenic, Antimony, and Bismuth

Very little work on the  $\alpha$ -haloalkenyl derivatives of arsenic, and less on those of antimony and bismuth, has been reported. Lewisite **60** is generally a mixture of several compounds with the *trans* isomer being the predominant one. The geminal isomer **61** has been reported by Smith and co-workers <1995MI1541, 1999JPO95> as one of the components of the mixture.



*gem*-Arsinofluoroalkene **62** was prepared by action of dimethylarsine on 2,3-dichlorotetrafluoropropene in good yield <1968JOM(12)133>. In a similar fashion to the phosphorus derivative previously described (see Section 4.18.2.1.2), trifluorovinylmagnesium iodide <1961MI110> and 1-chloro-2,2-difluorovinyl lithium <2000JOM(616)96> react with arsenic, antimony, and bismuth trihalide affording the corresponding tris(trihalovinyl) species **63** in moderate yield.



#### 4.18.3 DERIVATIVES OF SILICON AND OTHER GROUP 14 ELEMENTS

Although silicon and germanium are often classified as metalloids while tin and lead are metals, the synthesis of their covalent derivatives resembles one another so closely that they are conveniently dealt with in one section.

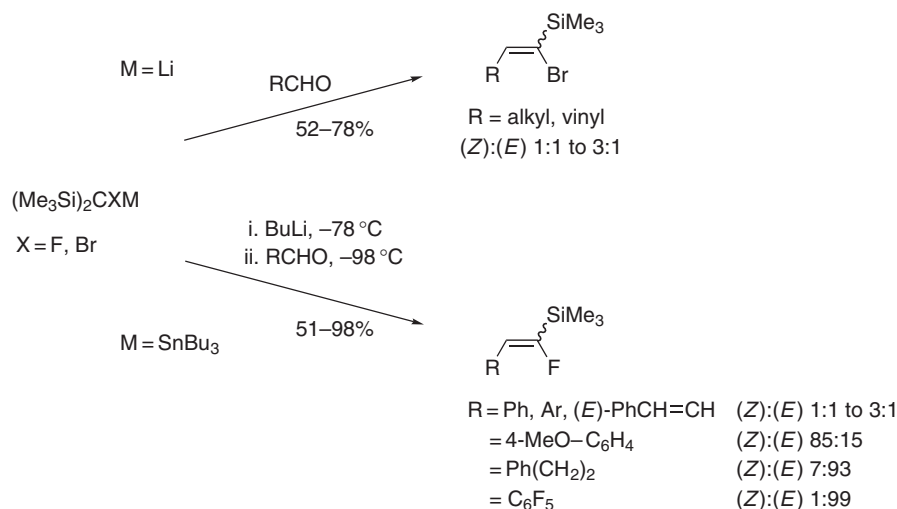
##### 4.18.3.1 $\alpha$ -Haloalkenylsilicon Derivatives

###### 4.18.3.1.1 From carbonyl compounds

The Peterson olefination, commonly encountered in *gem*-fluorophosphonoalkene chemistry, is rarely represented in the synthesis of silylalkenes. Bis(trimethylsilyl)bromomethyl lithium reacts with aldehydes affording *gem*-bromosilylalkenes in good yields, the (*Z*)-isomer being preferred for more bulky alkyl groups (Scheme 30) <1977JOM(142)39>. Analogously, treatment of bis(trimethylsilyl)fluoro(tributylstannyl)methane with *n*-butyllithium followed by addition of an aldehyde furnishes  $\alpha$ -fluoroalkenylsilanes in moderate to good yields. The stereoselectivity of the reaction depends on the substituent R. However, for most aldehydes studied, the (*Z*)-isomer was predominantly formed. Interestingly, 3-phenylpropanal and perfluorobenzaldehyde lead to the (*E*)-isomer instead with high to very high selectivity, respectively (Scheme 30) <1999TL7375, 2000BCJ1685>.

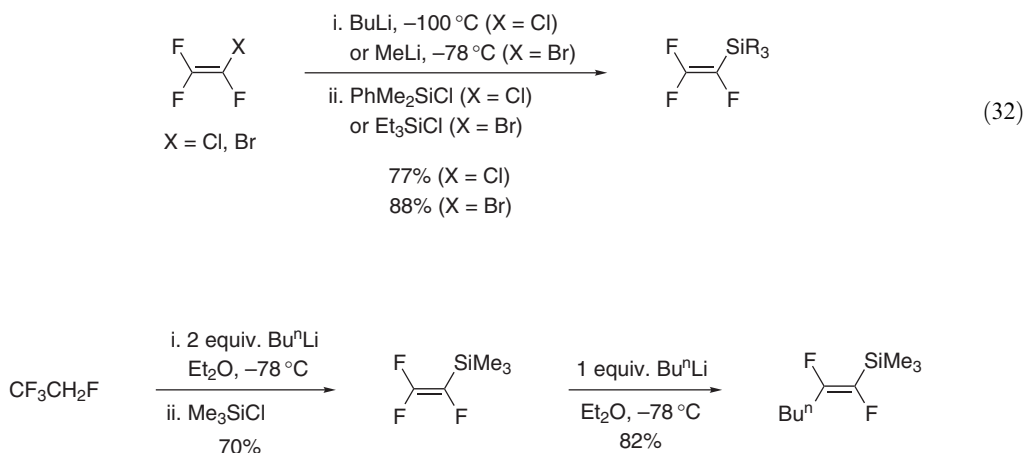
###### 4.18.3.1.2 By silylation of $\alpha$ -haloalkenyllithium and $\alpha$ -haloalkenylmagnesium species

This is the most general method for the preparation of *gem*-fluorosilylalkenes, although it has also been applied to the synthesis of  $\alpha$ -chloro- and  $\alpha$ -bromoalkenes. Only one iodo derivative has been prepared by this method. Seyferth reviewed the use of organomagnesium compounds

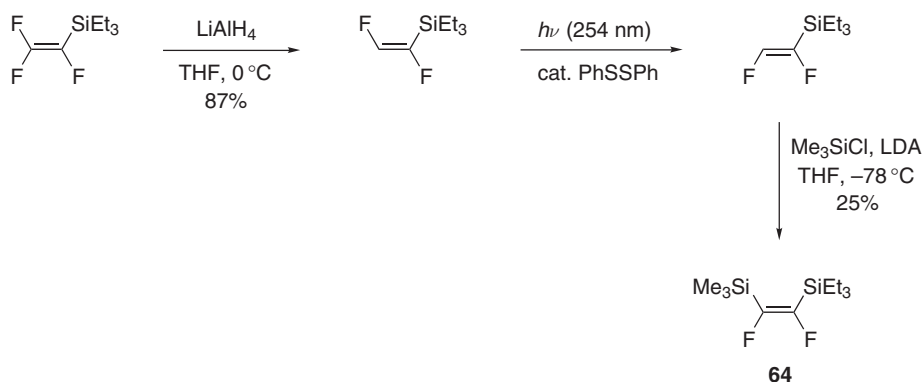


Scheme 30

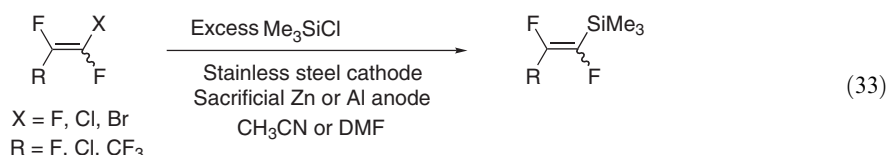
in the preparation of trifluorovinylsilanes <1962MI129> (see also <1968JOC472> and references cited therein). More recently, a lithium derivative, prepared by metal-halogen exchange at low temperature, was used to prepare trifluoroethenylsilane in good yield (Equation (32)) <1996T37, 2002JFC(113)211>. Burton and co-workers <1996CC49> prepared trifluorovinyl silane from 1,1,1,2-tetrafluoroethane via a dehydrofluorination/metallation sequence using trimethylsilyl chloride and 2 equiv. of *n*-butyllithium at low temperature (Scheme 31). Employing 3 equiv. of base, trifluorovinyl silane undergoes further reaction *in situ* with *n*-butyllithium affording the  $\alpha$ -fluorohexenyl silane (Scheme 31) <2000TL971>. To prepare silane **64**, (*E*)-1,2-difluoroethenyl silane was synthesized via reduction of trifluoroethenyl silane and subsequent isomerization of the (*Z*)-isomer by ultraviolet light and a catalytic amount of diphenyl disulfide. Next, (*E*)-1,2-difluoroethenyl silane was treated with LDA and trimethylsilyl chloride furnishing silane **64** in poor yield (Scheme 32) <1996T37>. Stepanov and co-workers developed an electrochemical silylation of fluoroalkenes with an excess of chlorotrimethyl silane. While the vinyl silanes are prepared in good yield from trifluorobromoethene and 1,2-difluoro-1,2-dichloroethene, hexafluoropropene leads to the corresponding *gem*-fluorosilylpropene in only poor yield (Equation (33)) <1998T257, 2000MI190>.



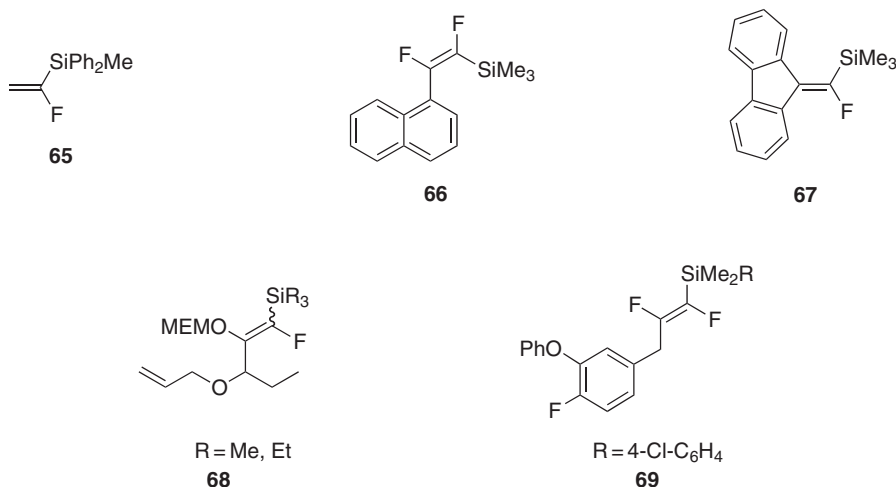
Scheme 31



Scheme 32

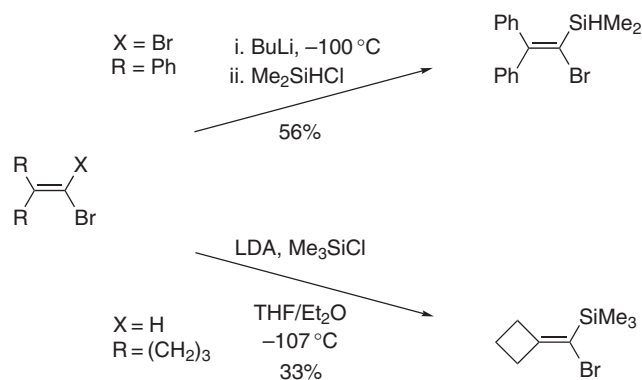


Hanamoto and co-workers prepared vinyl silane **65** from 1,1-difluoroethene upon nucleophilic displacement of fluoride by diphenylmethylsilyllithium (yield: 56%) [<1999CC2397>](#). Sequential lithiation and silylation of (*E*)-1-bromo-1,2-difluoro-2-(1-naphthyl)ethene at  $-130^{\circ}\text{C}$  gives  $\alpha$ -fluoroalkenyl silane **66** with retention of configuration and in excellent yield (96%) [<1995TL6271, 1998BSJ2903>](#) while using a similar sequence, *gem*-fluorosilylalkenes **67** (yield: 40%) [<1995JCS\(P1\)2681, 2001CCC1508>](#), **68** (yield: 60–71%) [<1996TL5183, 1997T14749>](#), and **69** (yield: 51%) are obtained in only moderate yields [<2000USP6159956, 2001USP6207846>](#).

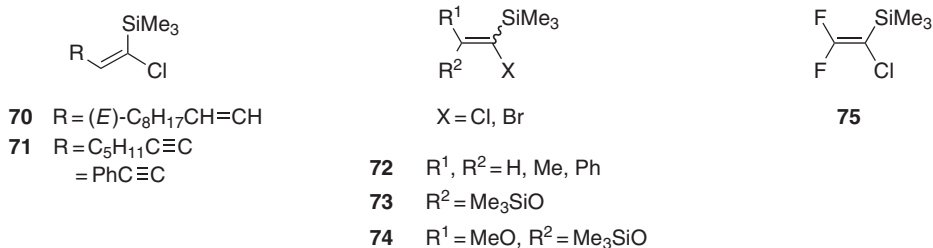


*gem*-Chloro- and *gem*-bromosilylalkenes have also been prepared by metallation and subsequent silylation. Treatment of 1,1-dibromo-2,2-diphenylethene with *n*-butyllithium followed by addition of dimethylsilyl chloride furnishes the  $\alpha$ -bromoalkenylsilane in 56% isolated yield (Scheme 33) [<1995JA3298>](#). Deprotonation of bromomethylenecyclobutane by LDA and trapping the anion with trimethylsilyl chloride leads to the formation of the corresponding *gem*-bromosilylalkene (Scheme 33) [<1999JOC1529>](#). In addition, alkenes **70** [<1999JA7039>](#) and **71** [<1995TL3687>](#) have been prepared with a very high stereoselectivity from the corresponding (*E*)-chloroalkenes using *n*-butyllithium as base at  $-100^{\circ}\text{C}$  (yield: 63–85%). Shimizu and co-workers

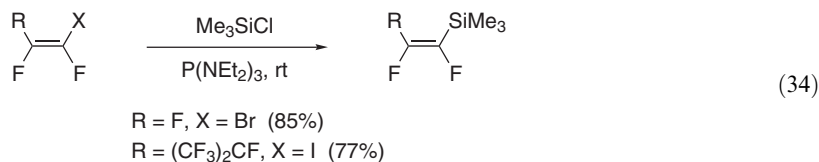
<1987BSJ777> reported a nonstereoselective synthesis of *gem*-bromo- or *gem*-chlorosilylalkene isomers **72**, *gem*-halosilylenoethers **73**, as well as ketene acetals **74** in moderate-to-good yield (23–84%). Similar to the synthesis of trifluorovinylsilane (see [Scheme 31](#)),  $\alpha$ -chloroalkenylsilane **75** has been prepared from 1-chloro-2,2,2-trifluoroethane using only 2 equiv. of *n*-butyllithium (yield: 89%) <1998JCS(P1)2541>.



Scheme 33



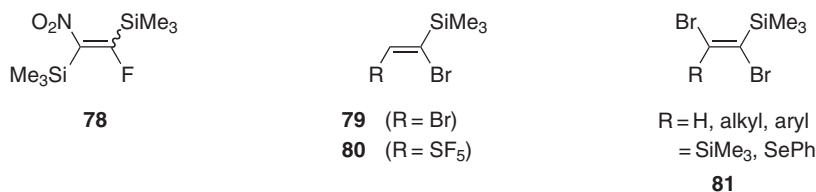
A rare example of the silylation of  $\alpha$ -iodoalkenyllithium species is demonstrated by the synthesis of  $\alpha$ -iodoethenylsilane **76** from iodoethene in poor yield (20%). The best results are obtained with 3 equiv. of LDA as base at  $-100^\circ\text{C}$ . Lithium–iodine exchange from 1,1-diiodoethene gives less satisfying results <1998OM5390>. Although no base is used, the procedure reported by Bardin and co-workers should also be mentioned here. Perfluoroalkenyl silanes are obtained from the corresponding iodides or bromides, applying tris(diethylamino)phosphine as condensing agent at room temperature ([Equation \(34\)](#)). This method is also applicable for the preparation of trichloroethenyl silane **77** from tetrachloroethene in 66% isolated yield <1995SC2425>.



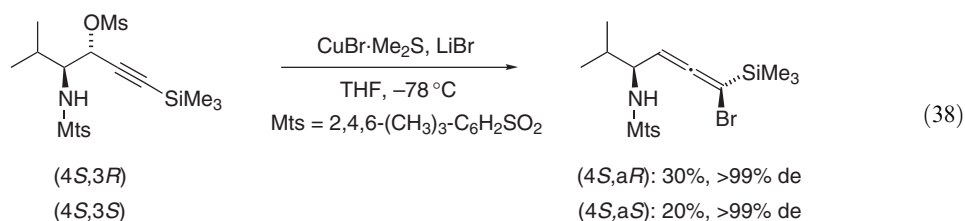
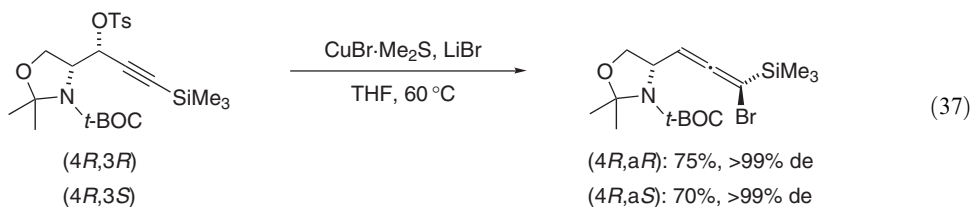
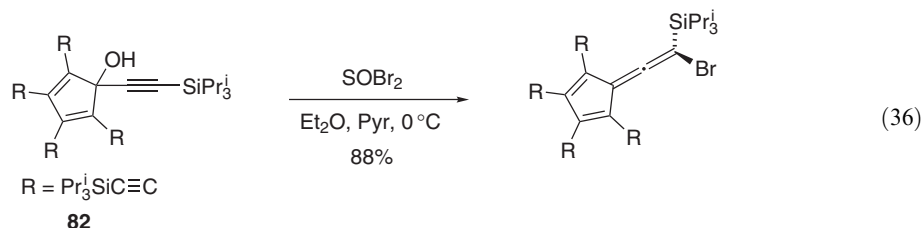
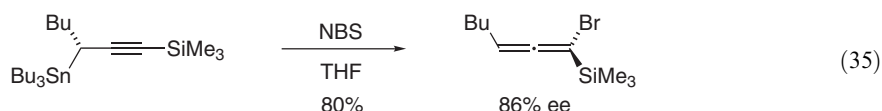
#### 4.18.3.1.3 By halogenation

This section deals with those reactions in which a halogen atom is introduced by electrophilic attack on an unsaturated silane. The introduction of chlorine (reviewed by Seyferth

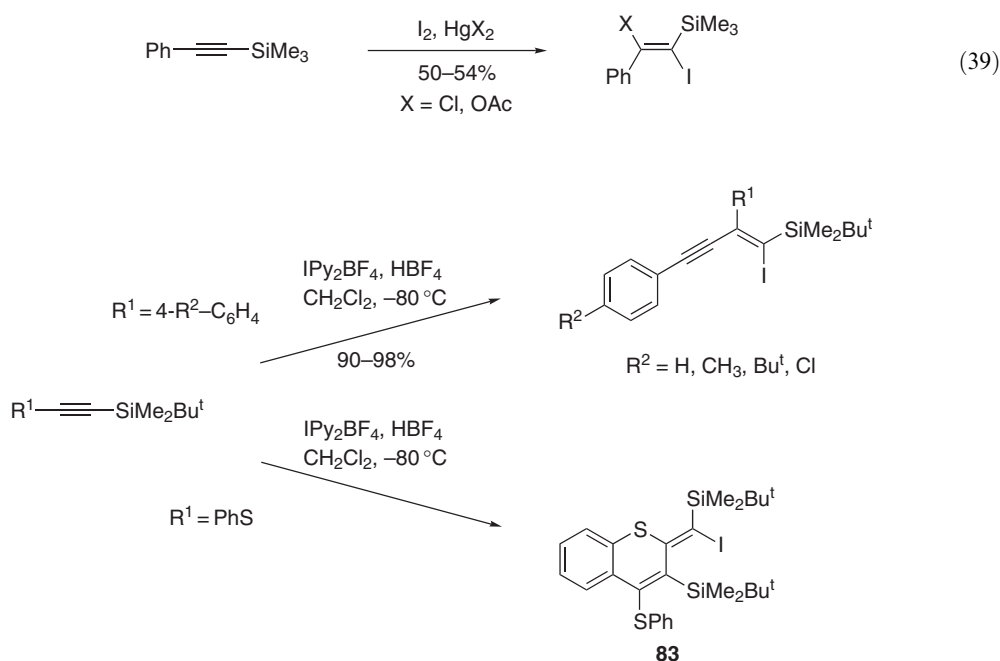
<1962MI129>) and bromine is most abundantly documented, whereas only some examples of iodination have been reported. The single example of fluorination encloses the addition of nitril fluoride to bis(trimethylsilyl)ethyne affording compound **78** in 50% yield <1986S132>. The bromination of vinyl silane followed by elimination has been successfully applied affording  $\alpha$ -bromovinylsilane **79** <1988OSC(6)1033>, while derivative **80** has been prepared in unspecified yield from trimethylsilylethyne by addition of SF<sub>5</sub>Br across the triple bond <2002USP6479645>. Bromination of alkynyl silanes has been shown to afford a range of (*E*)-1,2-dibromosilyl alkenes **81** in generally good yields (42–83%) <1989JOM(372)183, 2001JCS(P1)154, 2001SC3027>. 1,2-Dibromovinylsilane **81** (R = H) has also been isolated in 20% yield from a mixture formed when dibromodifluoromethane is added to trimethylsilyl ethyne in the presence of an equimolar mixture of ammonium persulfate and sodium formate <1998T14189>.



Sato and co-workers prepared a *gem*-bromosilyllallene from the corresponding enantiopure propargylstannane upon treatment with *N*-bromosuccinimide (NBS) as brominating agent (Equation (35)) <2001TL6323>. Further, reacting compound **82** with thionylbromide at 0 °C affords the corresponding *gem*-bromosilyllallene in good yield. It is worth noting that the synthesis of the *gem*-chloro derivative was not successful since applying thionyl chloride leads to substitution of the hydroxyl group by chlorine (Equation (36)) <1996AG(E)1986>. Although not introducing bromine by electrophilic attack, reaction of alkyne tosylates or mesylates with CuBr/LiBr affording *gem*-bromosilylpropadienes is most appropriately listed in this section. The transformation displays a very high stereoselectivity and proceeds, depending on the substrate, in poor-to-good yield (Equations (37) and (38)) <1996JOC9631, 2002JA15255>.

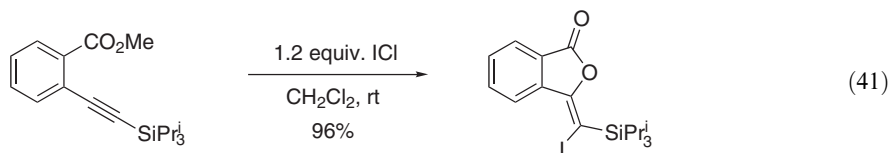
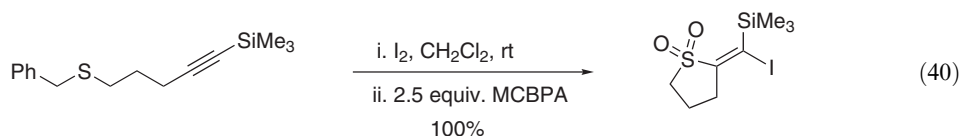


Iodine has been incorporated in a variety of ways. Barluenga and co-workers reported a mercury(II)-catalyzed addition of iodine to phenyl(trimethylsilyl)ethyne affording *gem*-iodosilyl alkenes (Equation (39)) <1987JCS(P1)1017>. Employing bis(pyridyl)iodonium(I)tetrafluoroborate (IPy<sub>2</sub>BF<sub>4</sub>) as iodine source, the same group developed a method for the homocoupling of alkynyl silanes in excellent yield. The reaction only furnishes *gem*-iodosilyl alkenes when, at low temperatures, *t*-butyldimethylsilyl alkynes are applied since trimethylsilyl-protected alkynes lead to iodoalkynes upon reaction with IPy<sub>2</sub>BF<sub>4</sub>/HBF<sub>4</sub>. Related aliphatic alkynyl silanes fail to couple under the same conditions (Scheme 34) <1997JA6933>. Starting from phenylthio(*t*-butyldimethylsilyl)ethyne, this procedure gives rise to the formation of heterocyclic  $\alpha$ -iodoalkenyl silane **83** in unspecified yield (Scheme 34) <1998AG(E)3136>.

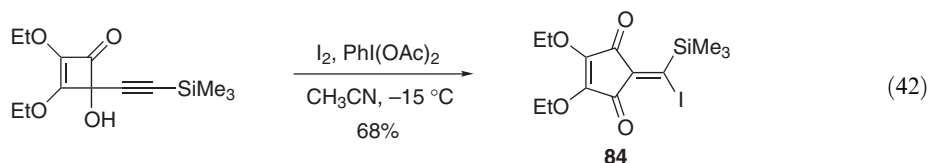


Scheme 34

Finally, several *gem*-iodosilyl alkenes have been successfully prepared via an electrophilic cyclization strategy. Iodocyclization of the 4-pentynyl sulfide followed by an oxidation using 3-chloroperoxybenzoic acid (MCPBA) proceeds cleanly to give the five-membered ring adduct with (*E*)-geometry in quantitative overall yield. Bromocyclization using bromine was not successful (Equation (40)) <1995JOC6468>. Yao and Larock obtained the substituted  $\alpha$ -pyrone in excellent yield of a single isomer treating the trimethylsilyl-substituted 2-(1-alkynyl)benzoate with ICl (Equation (41)) <2003JOC5936>.  $\alpha$ -Iodoalkenyl silane **84** is formed from the corresponding 4-alkynylcyclobutenone via an ionic rearrangement when iodine and iodobenzene diacetate are employed (Equation (42)) <1995TL5539>.



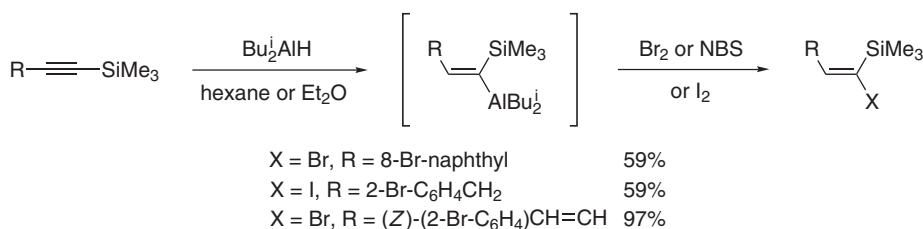




#### 4.18.3.1.4 By halogenation of $\alpha$ -silylalkenyl metal derivatives

This section covers methods for the preparation of mainly *gem*-iodosilylalkenes involving the replacement of a metal atom on an alkenylsilane by an iodine atom. In addition to iodine, bromine and chlorine have also been introduced in this way. However, methods for the incorporation of fluorine are still lacking.

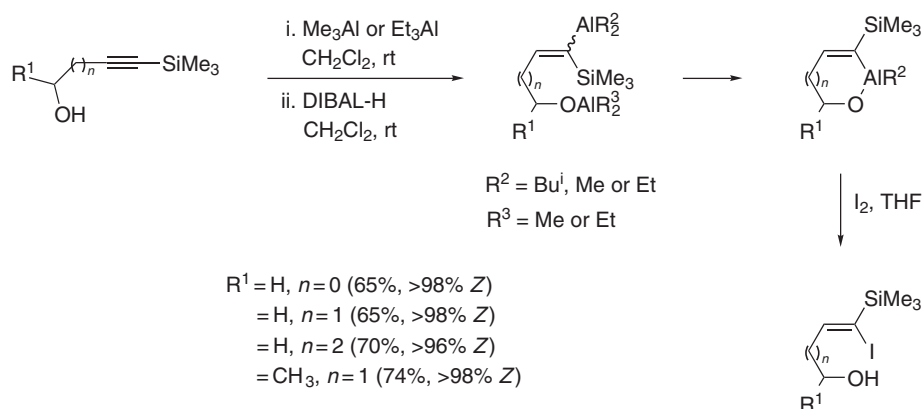
Hydroalumination and subsequent bromination or iodination of alkynylsilanes lead to (*E*)-*gem*-bromosilylalkenes in good yield (Scheme 35) <1999CPB1108, 2001OM2109, 2001CL554>. Using this sequence, (1(*E*),3(*E*))-1-iododienyl silane **85** has been prepared from the corresponding vinyl(trimethylsilyl)ethyne, but undergoes spontaneous isomerization to the (1(*Z*),3(*E*))-isomer on standing (yield: 82%) <1998TL4219>. Similarly, the synthesis of bis( $\alpha$ -bromovinylsilane) **86** has been reported as part of an organic synthesis preparation in good yield (75%) <2002JA9366>. It is worth noting that (*E*)- $\alpha$ -chloro- or bromoalkenylsilanes, and (*E*)- $\alpha$ -iodoalkenylsilanes may be isomerized to their (*Z*)-isomers by reaction with a catalytic amount of bromine under UV irradiation or treatment with *t*-butyllithium (5 mol.%), respectively <1981JOC1292>.



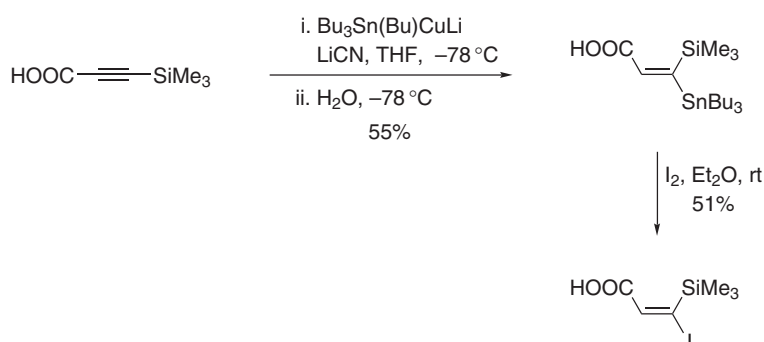
Scheme 35



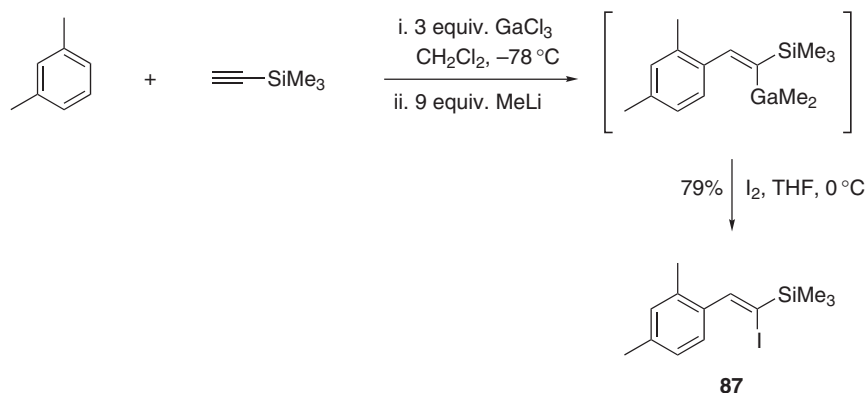
Negishi and co-workers reported a *trans*-hydroalumination of  $\omega$ -trimethylsilyl-substituted alkynyl alcohols by their sequential treatment with Me<sub>3</sub>Al (or Et<sub>3</sub>Al), which acts as a metallating agent for the hydroxy group, and diisobutylaluminum hydride (DIBAL-H). The authors propose a nonstereoselective, though regioselective addition followed by a chelation-controlled stereoisomerization step, which is supported by the fact that the (*E*)- to (*Z*)-isomerization is not observed in the absence of the hydroxy group (Scheme 36) <1997TL3829>. Stannylmetallation of silylated prop-2-ynoic acid furnishes the  $\alpha$ -silylalkenyltin derivative without butyl ligand transfer from the stannylcuprate to the triple bond and with absolute regioselectivity. Subsequent treatment with iodine leads to the (*E*)-3-iodo-3-(trimethylsilyl)prop-2-enoic acid with retention of configuration and in moderate yield (Scheme 37) <1998TL4277>. Analogously, iodinolysis of the corresponding *gem*-silylstannyl alkene has been performed to prepare (*E*)-1-iodo-1-(trimethylsilyl)-1-hexene in 69% yield <2001SL403>. Yamaguchi and co-workers obtained (*Z*)- $\alpha$ -iodoethenyl silane **87** as one stereoisomer by trapping an  $\alpha$ -silylalkenylgallium derivative, which is involved in a Friedel–Crafts  $\beta$ -silylethenylation of aromatic hydrocarbons with trimethylsilylethyne (Scheme 38) <1999BCJ1445>.



Scheme 36

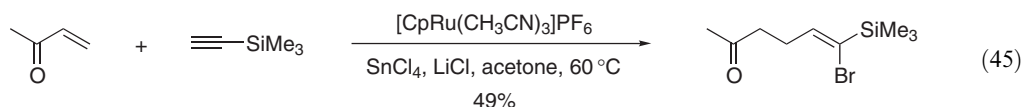
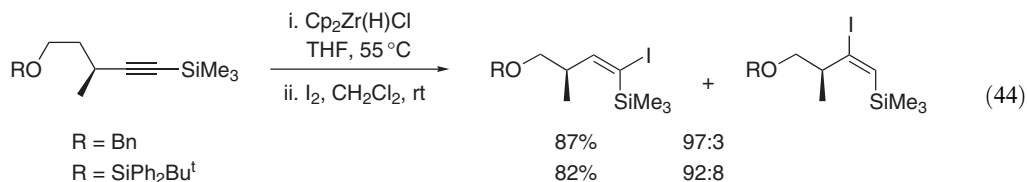
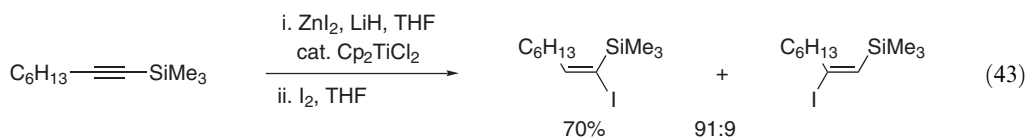


Scheme 37

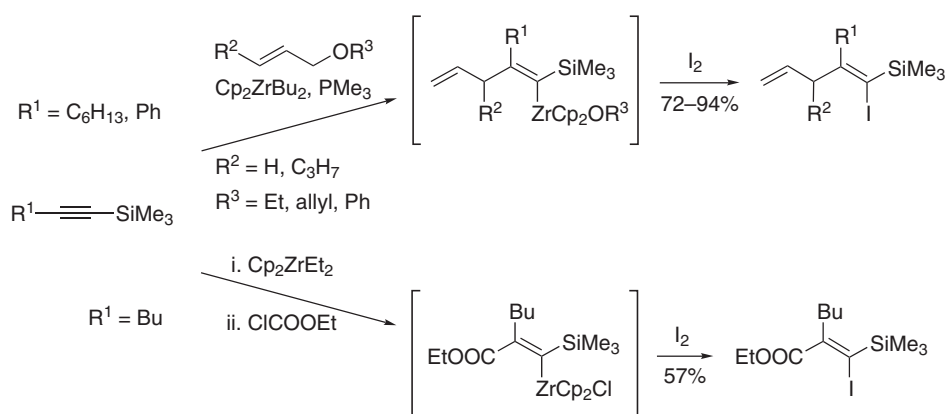
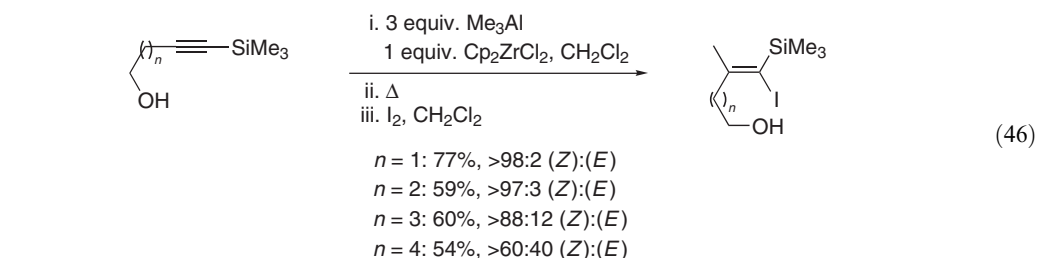


Scheme 38

Titanium-catalyzed hydrozincation of 1-(trimethylsilyl)-1-octyne has been performed with zinc hydride, generated *in situ* from zinc(II) iodide and lithium hydride. Reacting the organozinc compound with iodine affords the (*E*)-*gem*-iodosilyl alkene with good regioselectivity (Equation (43)) <1995JOC290>. Further, electrophilic iodination of the vinylzirconium species, prepared by hydrozirconation using Schwartz reagent ( $\text{Cp}_2\text{Zr(H)Cl}$ ), gives the corresponding  $\alpha$ -iodovinyl silane (Equation (44)) <2001OL3281>. Trost and Pinkerton prepared vinyl halides via a ruthenium-catalyzed three-component coupling. Applying this method on (trimethylsilyl)ethyne and methylvinyl ketone leads to the trisubstituted *gem*-bromosilyl alkene with complete stereoselectivity and in moderate yield (Equation (45)) <2000TL9627, 2002JA7376>.

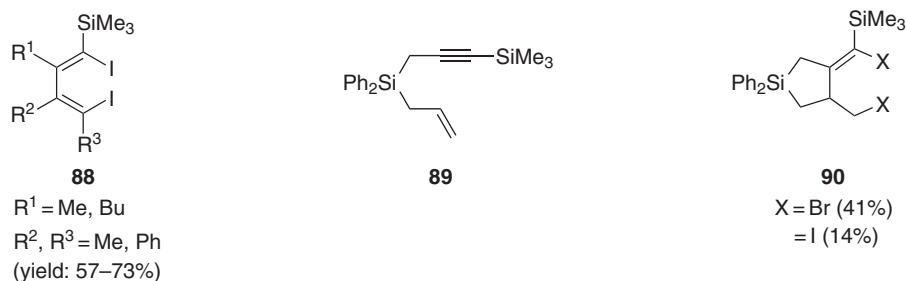


Tetrasubstituted alkenes may be prepared by carbometallation of alkynylsilanes. *trans*-Carboalumination of  $\omega$ -trimethylsilyl-substituted alkynyl alcohols and subsequent iodination furnishes *gem*-iodosilyl alkenes in moderate yield. Initially, the *syn*-carboaluminated alkenes are formed, which are further thermally isomerized via an aluminacycle to give exclusively or predominantly the *anti*-isomers (Equation (46), see also Scheme 36). It is important to note that the hydroxyl group is necessary for the isomerization to occur <1997JOC784>. Takahashi and co-workers reported the carbozirconation of silylated alkynes with allylic compounds <1995T4519> or chloroformate <2000JA3228> followed by iodinolysis affording the corresponding  $\alpha$ -iodoalkenylsilanes in good yield and with high isomeric purity (>96%) (Scheme 39).

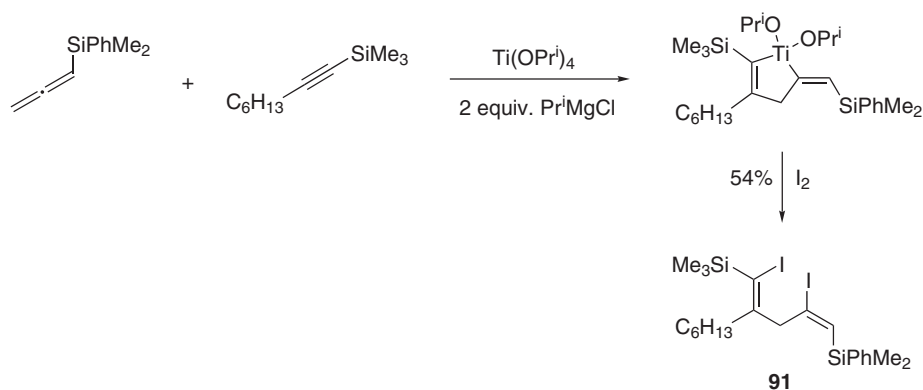


Scheme 39

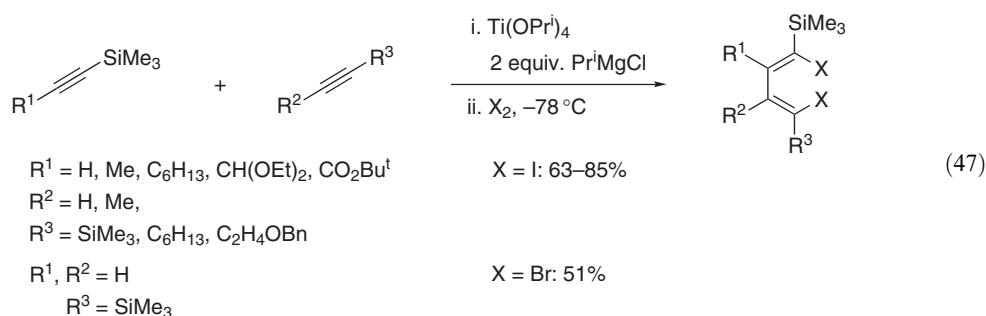
Performing the iodination of the zirconacyclopentadienes in the presence of Cu(I)Cl, the preparation of diiododienes **88** has been improved in terms of preventing the formation of the monoiodinated compounds <1997TL4099>. Carbozirconation–halogenation of 1,6-enyne **89** leads to the (*E*)-configuration (X = I) or to an unspecified mixture of stereoisomers (X = Br) of cyclic *gem*-halosilylalkenes **90** in poor yield <2002JOM(643–644)324>.

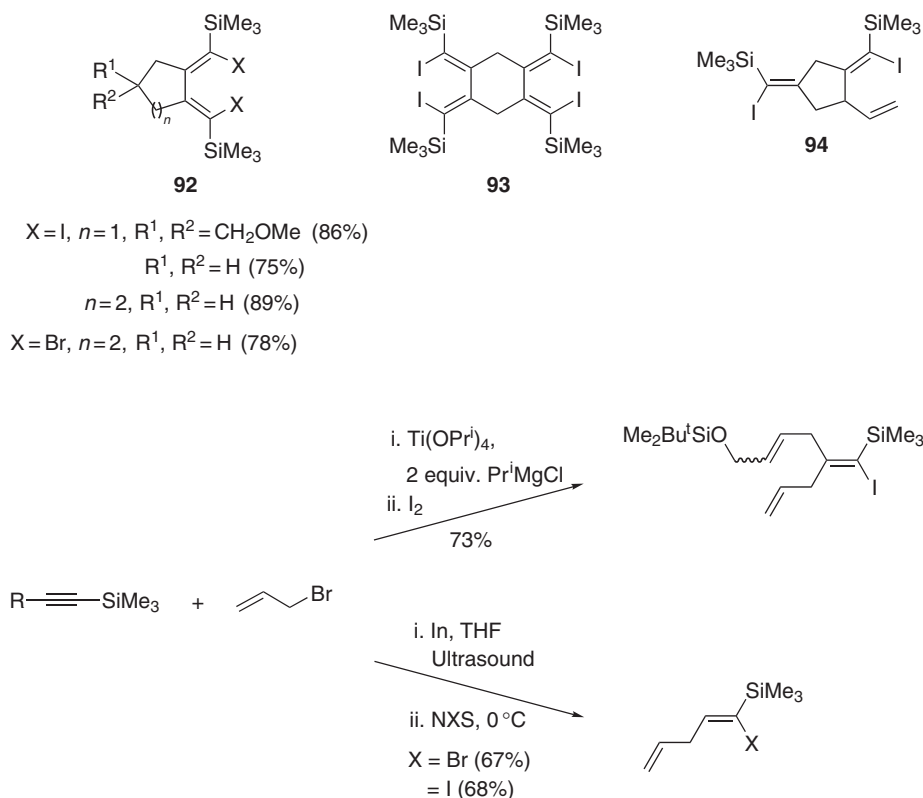


1,4-Diiodopenta-1,4-diene **91** has been prepared as a single regio- and stereoisomer from a monosubstituted allene and 1-(trimethylsilyl)octyne via an intermediate titanacycle (**Scheme 40**) <1998CC271>. Further, halogenation of titanacyclopentadienes, prepared from two alkynes utilizing  $\text{Ti}(\text{OPr}^i)_4/\text{Pr}^i\text{MgCl}$  (1:2) reagent, furnishes 1,4-dihalobuta-1,3-dienes in generally good yields (**Equation (47)**). This procedure does not require any additives such as  $\text{Cu}(\text{I})\text{Cl}$ , which is a notable advantage for the titanacyclopentadiene route in comparison with the zirconacyclopentadiene route <1998JOC10060, 1999AG(E)1604, 2002AG(E)3023>. Employing the same method, but using 1,7-bis(trimethylsilyl)hepta-1,6-diynes instead, affords cyclic diiodo-1,4-dienes **92** <1998JOC10060, 1999JA10420, 1999JAP(K)11246566, 1999CC1543, 2002CEJ4734, 2003OL365>. Homo-coupling product **93** is formed in 65% yield when isopropylmagnesium chloride is added to a mixture of 1,5-bis(trimethylsilyl)penta-1,4-diyne and 2 equiv. of titanium(IV)isopropoxide <2002CC820>. In addition, a mixture of hexenyne and allyl bromide affords the corresponding  $\alpha$ -iodoalkenyl silane when  $\text{Ti}(\text{OPr}^i)_4/\text{Pr}^i\text{MgCl}$  (1:2) reagent is added, followed by iodine (**Scheme 41**) <2000JA11244>. When 1,5-bis(trimethylsilyl)penta-1,4-diyne and 3,4-dichlorobut-1-ene are employed, compound **94** is produced in 64% yield <2001JA4857>. Similarly, an indium-mediated allylation of trimethylsilylethyne followed by quenching with NXS has been reported leading to 1-halo-1-(trimethylsilyl)penta-1,4-dienes in good yield (**Scheme 41**) <1999JOC7537>.



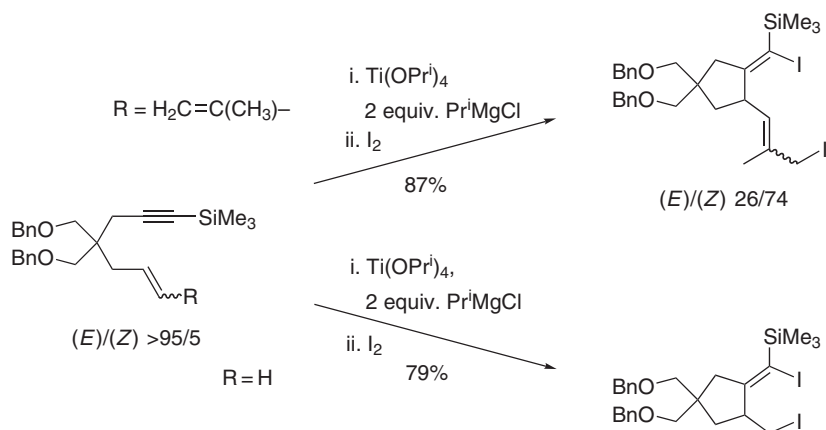
Scheme 40



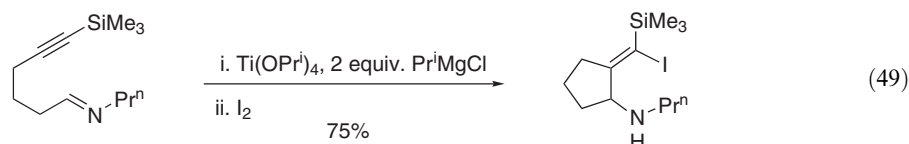
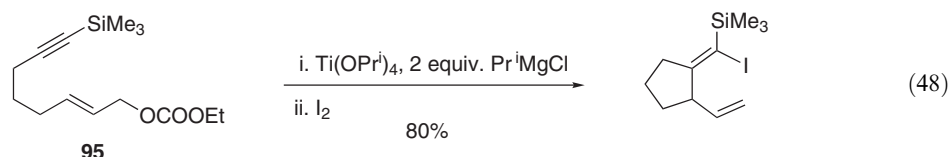


Scheme 41

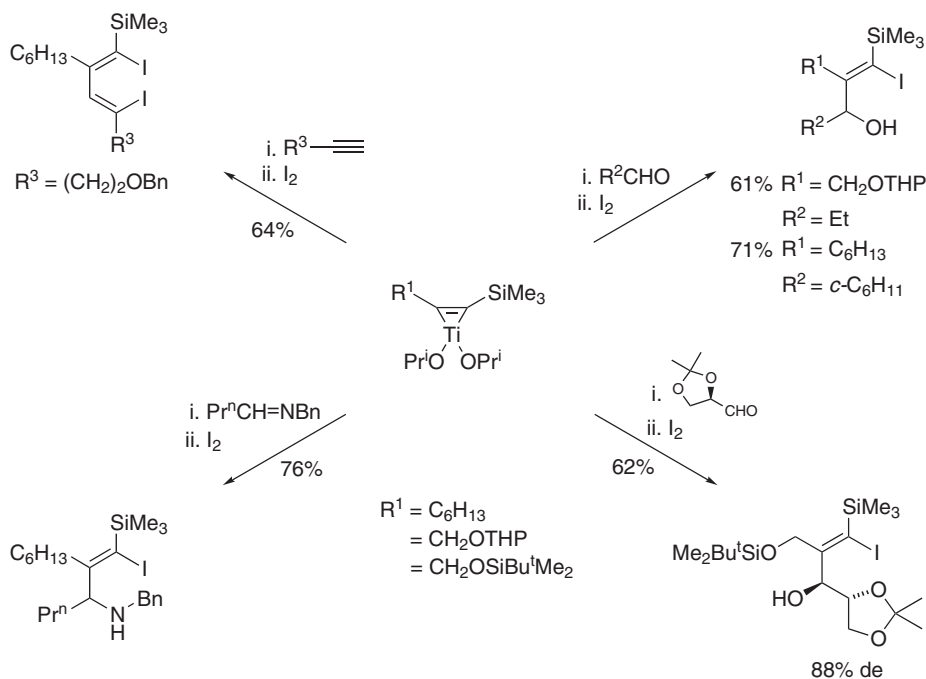
Sato and co-workers [<1995TL4261, 1996TL1253, 2003OL523>](#) reported the cyclization of  $\omega$ -silylated enynes to give the titanacyclopentenes, which, upon addition of iodine, lead to the corresponding  $\alpha$ -iodosilyl alkenes (Scheme 42). Montchamp and Negishi conducted similar cyclizations, though using a trimetallic reagent system ( $\text{Et}_2\text{Zn}/\text{ClTi}(\text{OPr}^i)_3/\text{Pr}^i\text{MgCl}$ ) that is catalytic in titanium [<1998JA5345>](#). Further, carbottitanation–iodination of 2,7-enynylcarbonate **95** and subsequent elimination of ethylcarbonate anion provides the corresponding *gem*-iodosilyl alkene (Equation (48)) [<1997AG\(E\)851>](#). The sequence was successfully extended to an annulation method using *N*-propyl 6-(trimethylsilyl)hex-5-ynalimine instead of an enyne (Equation (49)) [<1996CC533>](#).



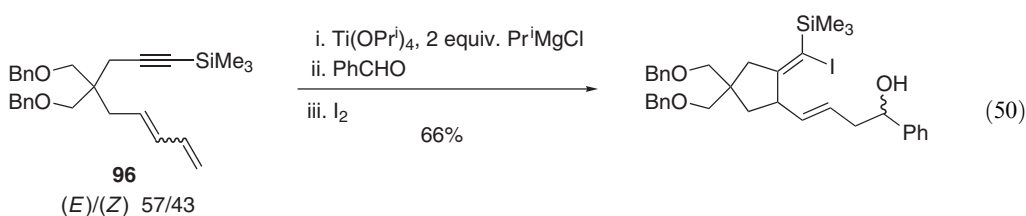
Scheme 42

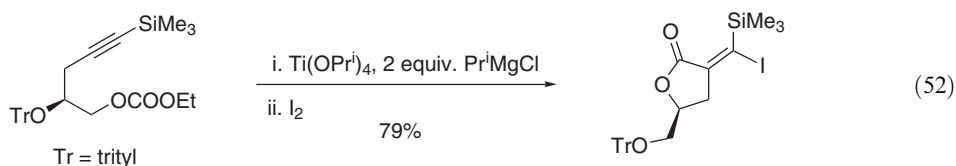
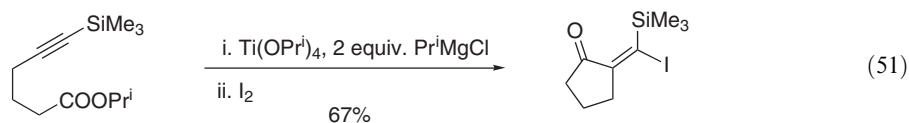


Sato and co-workers also reacted titanacyclopropenes, formed from alkynes upon treatment with  $\text{Ti(OPr}^i\text{)}_4/\text{Pr}^i\text{MgCl}$  (1:2), with alkynes [<1999JA7342>](#), carbonyl compounds [<1995TL3203, 1996TL7275, 1997TL4619>](#), or imines [<1995TL5913, 2003OL2145>](#). Subsequent iodinolysis of the intermediate titanacyclopentenenes furnishes dienes, allyl alcohols or allyl amines, respectively, in good yield ([Scheme 43](#)). Following the same method, diyne **96** has been transformed into the corresponding cyclic  $\alpha$ -iodoalkenylsilane with absolute regioselectivity ([Equation \(50\)](#)) [<1996TL1253>](#). Intramolecular reaction of the titanacyclopropene moiety with an ester and subsequent iodinolysis furnishes the corresponding  $\alpha$ -methylidenecyclopentanone in good yield ([Equation \(51\)](#)) [<1996JA2208>](#). Finally, applying an alkynyl carbonate as carbonyl compound instead, Sato and co-workers [<1998TL7947>](#) synthesized an  $\alpha$ -methylidenelactone in good yield and with retention of absolute stereochemistry ([Equation \(52\)](#)).



Scheme 43

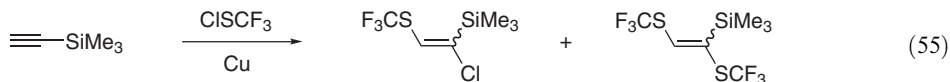
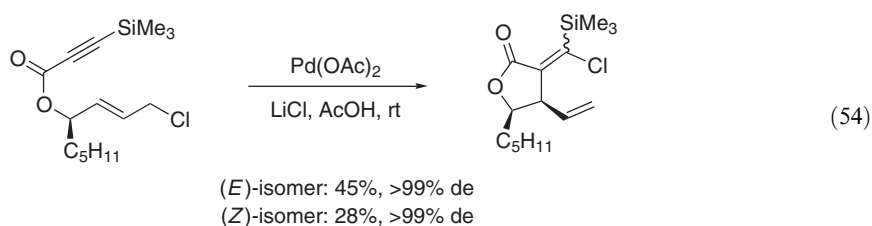
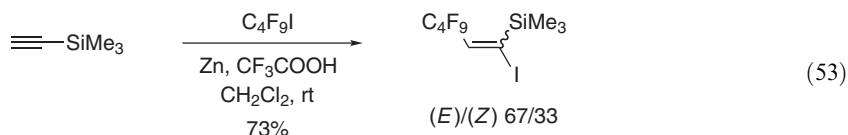




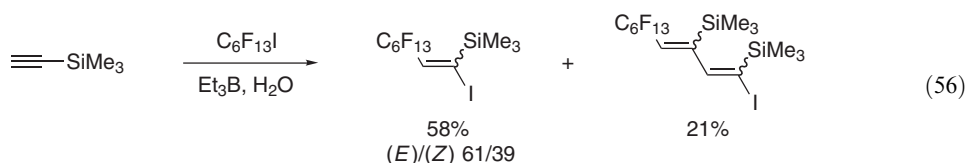
#### 4.18.3.1.5 By addition of alkyl halides to alkynyl silanes

This section covers transition metal-catalyzed and radical-initiated additions of alkyl halides to silylated alkynes. Notable is the consistent reversal of selectivity between perfluoroalkyl transfer (*trans*-selective) and alkyl transfer (*cis*-selective), regardless of the method of catalysis.

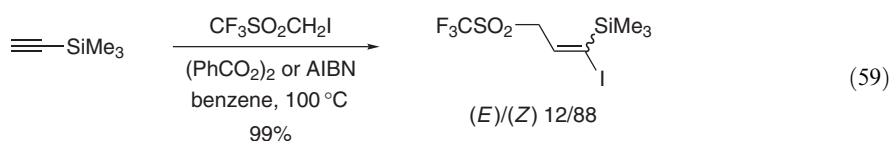
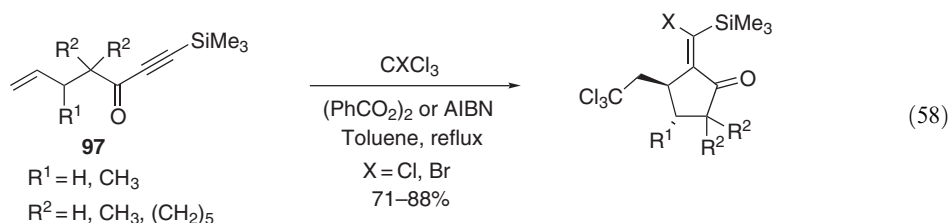
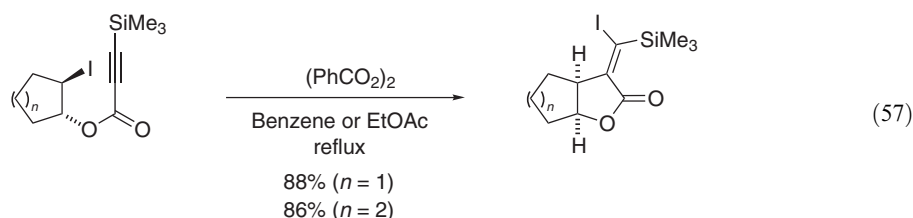
Perfluorobutyl iodide has been added to trimethylsilyl ethyne in the presence of zinc metal as a catalyst via a single electron transfer (SET) mechanism. The reaction affords the *gem*-iodosilyl alkene in good yield and excellent regioselectivity, but only with moderate stereo-selectivity (Equation (53)) <2000JOC8763>. With the aid of a palladium(0) catalyst (Pd(PPh<sub>3</sub>)<sub>4</sub>) <1986CL1895> or iron pentacarbonyl <1984TL303>, perfluoroalkyl groups have been transferred to trimethylsilyl alkynes as well, furnishing (*E*):(*Z*) mixtures of  $\alpha$ -iodoalkenylsilanes in good yields. Zhang and Lu reported the first preparation of a *gem*-chlorosilylalkene via a metal-catalyzed addition. They performed an intramolecular palladium(II)-assisted enyne cyclization reaction providing the corresponding lactone (Equation (54)) <1996TA1923>. Finally, copper-catalyzed trifluoromethylthiolation of trimethylsilyl ethyne gives a mixture containing both isomers of 2-chloro-1-trifluoromethylthio-2-trimethylsilyl ethene (Equation (55)) <1999MI161>.



A catalytic amount of triethylborane in water has been used to initiate radical addition of perfluorohexyliodide to trimethylsilyl ethyne at room temperature. The reaction affords preferentially the (*E*)-isomer of the *gem*-iodosilyl alkene together with a minor dimeric compound (Equation (56)) <1998SL1351>. On the contrary, a (*Z*)-specific addition of alkyl iodides to trimethylsilyl alkynes is observed when a solution of triethylborane in hexane is applied. The (*Z*)-specificity is believed to be due to postaddition isomerization since (*E*)- $\alpha$ -iodoalkenyl silanes are reported to isomerize into the corresponding (*Z*)-isomers when treated with a solution of triethylborane in hexane <1994TA961, 1995BCJ625>.

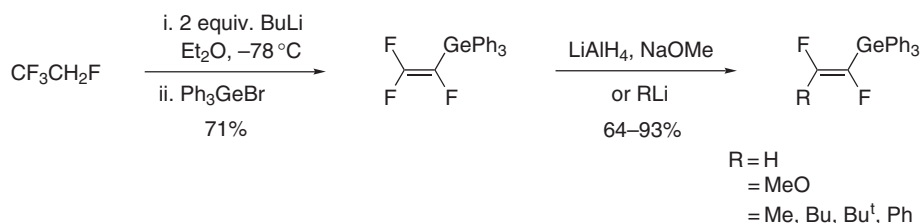


Weavers and co-workers have used and optimized a benzoyl-peroxide-initiated radical cyclization to prepare exocyclic *gem*-iodosilyl alkenes, predominantly as (*E*)-isomers. The authors reported that high concentrations of initiator are required and portionwise addition of initiator is beneficial for the course of the reaction (Equation (57)) <1995T4665, 1995T11257>. Analogously, radical addition of halotrichloromethane to the double bond of compound **97** followed by cyclization leads to the exocyclic *gem*-halosilyl alkene (Equation (58)) <1997TL2919>. Finally, in the presence of benzoyl peroxide or 2,2'-azobisisobutyronitrile (AIBN) and at elevated temperature, iodomethyltrifluoromethanesulfonate adds regioselectively across trimethylsilyl ethyne affording the corresponding *gem*-iodosilylalkenyl sulfone in excellent yield (Equation (59)) <1995JA3272>.



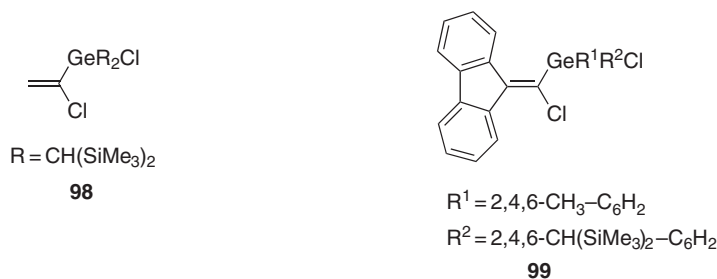
#### 4.18.3.2 $\alpha$ -Haloalkenylgermanium Derivatives

The preparation of *gem*-germylhaloalkenes closely follows that of the corresponding silicon compounds, but far fewer examples are known. Trifluorovinyl lithium reacts with triphenylgermanium bromide, furnishing the corresponding trifluorovinylgermanium derivative. Further  $\beta$ -functionalization by displacement of fluoride has also been reported (Scheme 44) <2002IC4748>. Using tris(dialkylamino)phosphine instead of a lithium base, reaction of iodotrifluoroethene with triethylgermanium chloride leads to trifluorovinyltriethylgermane <1995SC2425>.  $\alpha$ -Chloroalkenylgermanes **98** and **99** have been prepared in very poor yields from the corresponding  $\alpha,\alpha$ -dichloroalkenes upon treatment with divalent germanium compounds (germylenes  $\text{GeR}_2$ ) <1996JOM(521)387, 1997OM5127>.

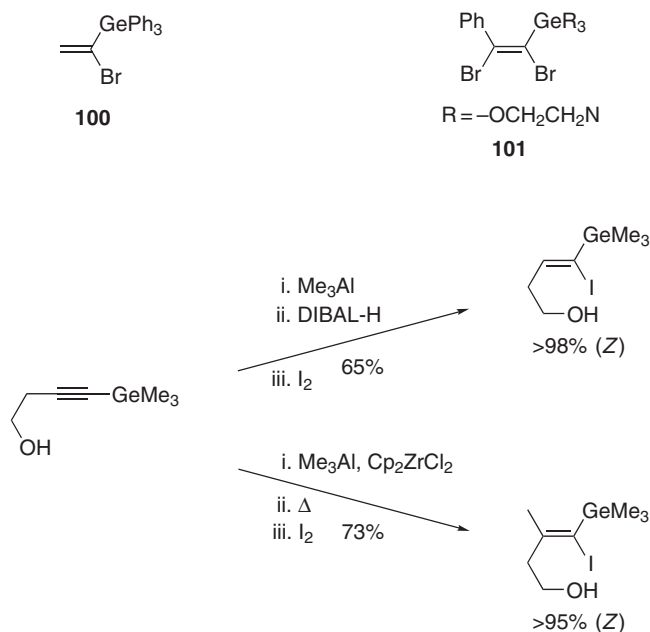


Scheme 44





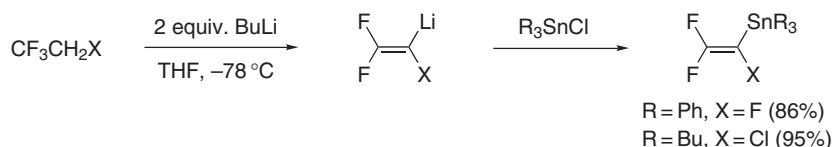
Bromination of vinylgermanes, followed by base-induced elimination, has been used to produce *gem*-bromogermeryl alkenes such as compound **100** <1984TL3221>. Electrophilic bromination of the corresponding germylalkyne affords exclusively the (*Z*)-isomer of *gem*-bromogermeryl alkene **101** (yield: 55%). It was suggested that this rare example of *syn*-addition of bromine across an alkyne is caused by specific stereoelectronic properties of the germyl substituent <2001JOM(627)1>. Negishi and co-workers reported the hydroalumination <1997TL3829> and carboalumination <1997JOC784> of germyl alkynes. Subsequent iodination of the alumina-cycles furnishes the corresponding  $\alpha$ -iodoalkenylgermanes with high stereoselectivity and in good yields (Scheme 45, see also Equation (46) and Scheme 36).



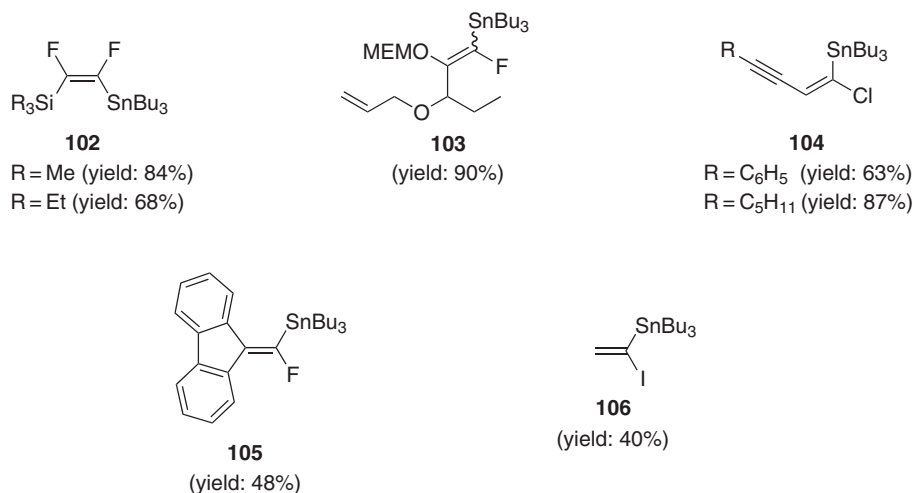
Scheme 45

#### 4.18.3.3 $\alpha$ -Haloalkenyl Derivatives of Tin and Lead

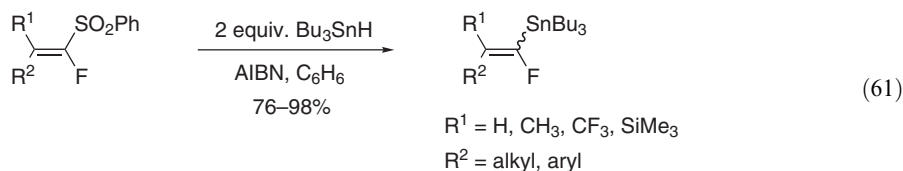
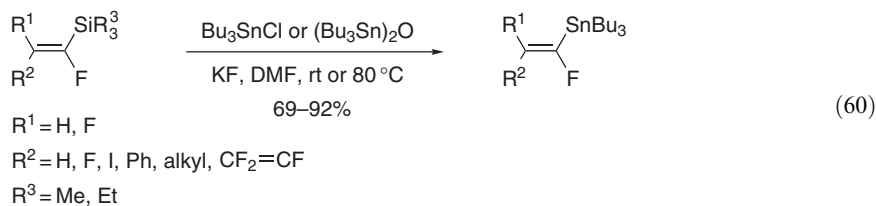
$\alpha$ -Fluorovinyltin compounds have been prepared in high yield by a low-temperature reaction of tin halides with trihalovinyltin, generated from 1,1,1,2-tetrafluoroethane <1996CC49, 1997CC139, 2002IC4748> or 1-chloro-2,2,2-trifluoroethane <1998JCS(P1)2541, 2000JOM(616)96> and 2 equiv. of *n*-butyllithium (Scheme 46). Deprotonation of (*E*)-1,2-difluoro(trialkylsilyl)ethene and subsequent treatment with tributyltin chloride has been used to prepare (*Z*)- $\alpha$ -fluorovinylstannane **102** <1996T37, 2003JFC(119)21>. Starting from (*Z*)-1,2-difluoro(tributylstannyl)ethene instead, the stereoselective synthesis of the corresponding (*E*)-bisstannane is described in 76% yield <2002OL1483>. Similarly, compounds **103** <1996TL5183, 1997T14749>, **104** <1995TL3687>, and **105** <2001CCCC1508> were obtained from the corresponding monohalogenated alkenes in good yields. The preparation of  $\alpha$ -iodoethenylstannane **106** has been reported treating iodoethene with 3 equiv. of LDA followed by tributyltin hydride at  $-100^\circ\text{C}$  <1998OM5390>.



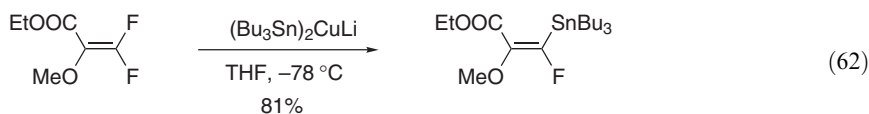
Scheme 46



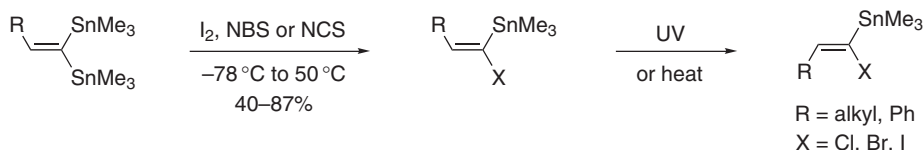
Burton and co-workers reported a stereospecific conversion of a wide range of vinyl silanes to the corresponding vinylstannanes applying tributyltin chloride in the presence of 2 equiv. of potassium fluoride. When bis(tributyltin) oxide is used as electrophile, only catalytic potassium fluoride (5–10%) is needed to complete the conversion (Equation (60)) <1996TL1921, 1997JOC1064, 2002BCJ2497>.  $\alpha$ -Fluoroalkenylphenylsulfones have also been used to prepare  $\alpha$ -fluoroalkenyltin derivatives. Treating 2,2-disubstituted fluorovinylsulfones with 2 equiv. of tributyltin hydride and a radical initiator leads to  $\alpha$ -fluorovinylstannanes with retention of configuration. On the contrary, 2-monosubstituted analogs equilibrate to mixtures of (*E*)- and (*Z*)-isomers (Equation (61)) <1994JOC8034, 1995OS216, 1996T45, 2002OL2083>.



Bis(tributyltin)copper lithium has been added to ethyl 3,3-difluoro-2-methoxyprop-2-enoate via an addition–elimination mechanism affording the corresponding (*E*)-*gem*-fluorostannyl alkene in good yield (Equation (62)) <1995JOC6608>.

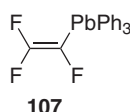


Monohalogenation of *gem*-distannyl alkenes affords  $\alpha$ -fluoroalkenylstannanes by replacement of one stannyl group. Iodine or NBS at low temperatures has been successfully applied, although iodine always gives some *gem*-diiodoalkene. *N*-Chlorosuccinimide (NCS) chlorinates only on heating. Upon UV irradiation or thermolysis, the bromo and iodo compounds both isomerize to the less crowded isomer (Scheme 47) <1983JOM(256)37, 1986OM1991, 1998TL481>.



Scheme 47

Finally, triphenyllead chloride reacts with trifluorovinyl lithium leading to (trifluorovinyl)triphenyllead **107** that was isolated as a solid in 77% yield <2002IC4748>.

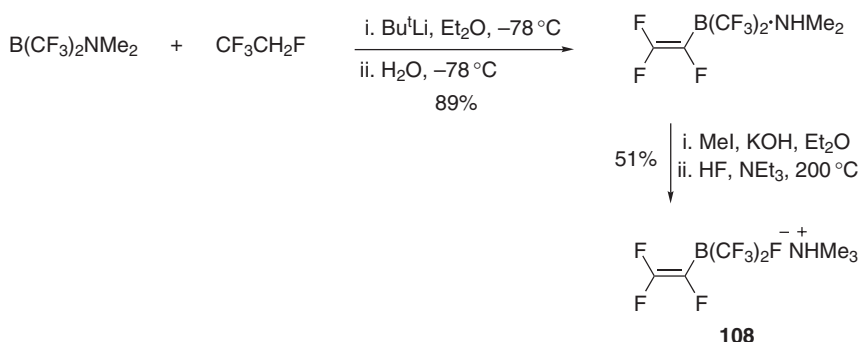


#### 4.18.4 DERIVATIVES OF BORON AND OTHER GROUP 13 ELEMENTS

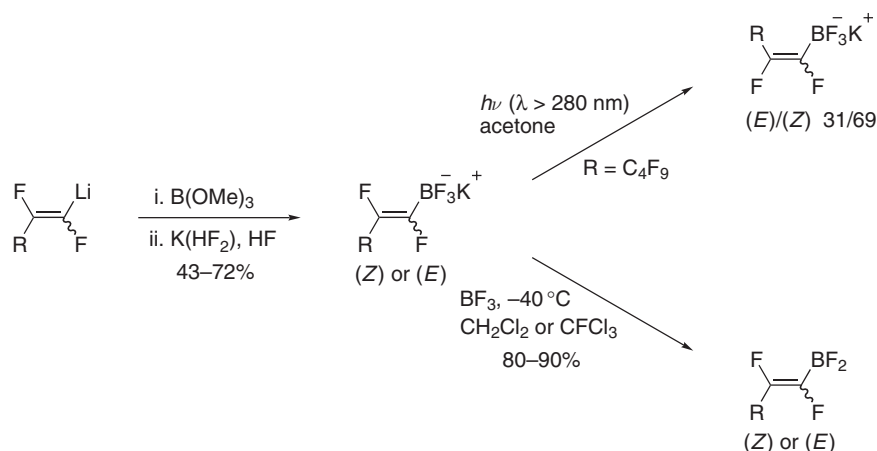
##### 4.18.4.1 $\alpha$ -Haloalkenylboron Derivatives

###### 4.18.4.1.1 By ligand exchange and by halogenation reactions

Generating trifluorovinyl lithium from 1,1,1,2-tetrafluoroethane using *t*-butyllithium as a base, Brauer and Pawelke attached a trifluorovinyl group to dimethylaminobis(trifluoromethyl)borane in quantitative yield. The corresponding trimethylamine borane, which is prepared by alkylation with methyl iodide in the presence of potassium hydroxide, reacts with hydrogen fluoride furnishing fluoroborate **108** (Scheme 48) <2000JOM(604)43>. Analogously, (*E*)- and (*Z*)- $\alpha$ -fluoroalkenylboron derivatives have been prepared with retention of configuration from the corresponding organolithium compounds upon reaction with trimethylborate and subsequent treatment with potassium hydrogen difluoride and hydrogen fluoride in aqueous methanol (Scheme 49) <2001ZAAC(627)2499>. UV irradiation ( $\lambda > 280$  nm) of (*E*)- $\alpha$ -fluoroalkenyltrifluoroborates dissolved in acetone gives rise to partial conversion to the corresponding (*Z*)-isomer (Scheme 49) <2002ZAAC(628)721>. Further, Frohn and Bardin reported the synthesis of difluoroboranes by defluorination of the fluoroborate salts with retention of stereochemistry and in very good yield (Scheme 49) <2001JOM(631)54>.

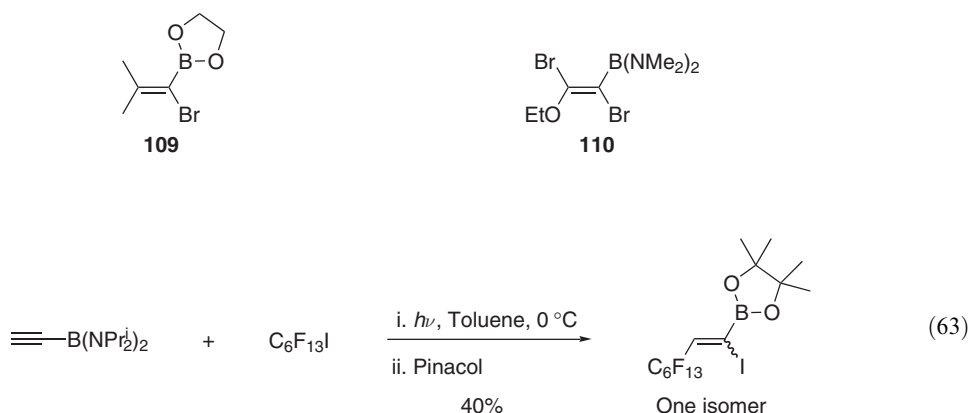


Scheme 48



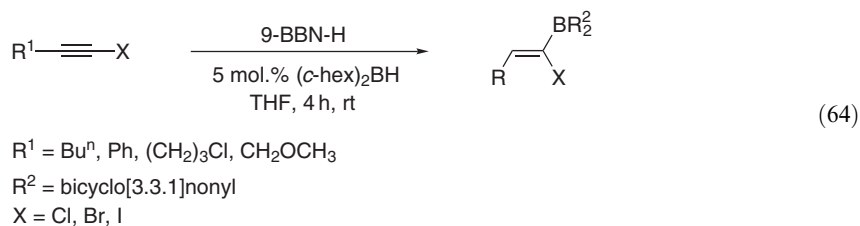
Scheme 49

Because of the relatively good electrofugal-leaving ability of tetracoordinate boron anions compared to protons, halogenation of vinylboronates and subsequent elimination is limited. However, bromination of *gem*-diboroalkene leads to bromodeboronation affording the corresponding *gem*-bromoboroalkene **109** <1974JOM(69)53>. Addition of bromine to an activated alkyne containing a boron atom stabilized by B–N bonds leads to adduct **110** in 57% yield <1989JGU2040>. Finally, radical addition of perfluorohexyliodide to ethynylboronate proceeds regioselectively and furnishes one unspecified isomer of the functionalized  $\alpha$ -iodoalkenylboronate in moderate yield (Equation (63)) <1996SL377>.



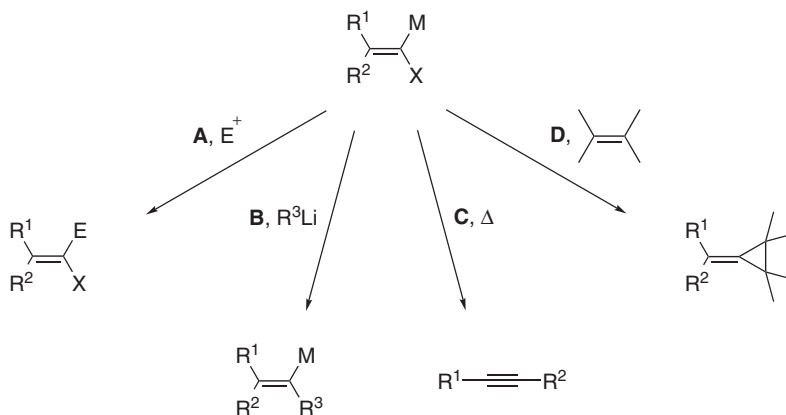
#### 4.18.4.1.2 By hydroboration of haloalkynes

The hydroboration of a wide variety of 1-haloalkynes, substituted with *t*-butyl, cycloalkyl, or *n*-alkyl chains, using dialkylboranes (dicyclohexylborane or 1,1,2-trimethylpropylcyclohexylborane) has been extensively investigated. The products were obtained as (*Z*)-isomers by exclusive *cis*-hydroboration and were described as being relatively stable <1967JA5086, 1972S555>. More recently, a highly regio- and stereoselective (except for R = CH<sub>2</sub>OCH<sub>3</sub>) hydroboration of 1-haloalkynes with 9-BBN-H has been reported. In the presence of 5 mol.% of dicyclohexylborane, the reaction is remarkably accelerated and furnishes the (*Z*)-*gem*-haloboroalkenes in quantitative yields (Equation (64)). The halogen may be chlorine, bromine, or iodine and the reactivity increases in that order. It is also worth mentioning that in contrast with the previously reported procedures, the 1-haloalkynes may also be substituted with a phenyl moiety <1997SC567>.



#### 4.18.5 DERIVATIVES OF LITHIUM AND OTHER GROUP 1 AND GROUP 2 METALS

Derivatives of lithium and other group 1 and group 2 metals, and  $\alpha$ -haloalkenyl metals, in general, exhibit ambiphilic behavior concerning their reactivity and have been described as alkylidene carbenoids (Scheme 50).  $\alpha$ -Metallated vinyl halides readily behave as ordinary organometallic nucleophiles at sufficiently low temperatures demonstrating their carbanionic reactivity (pathway A). Examples of their preparation and nucleophilic behavior are to be found in other sections of this chapter (especially for silicon, see Section 4.18.3.1; for phosphorus, see Section 4.18.2, and for the transition metals, see Section 4.18.6.1). Further, the surprising reaction of metallated vinyl bromides with alkyllithium compounds proves the electrophilic character of the  $\alpha$ -haloalkenyl metals (pathway B) <1993JOC546>. Finally, the intramolecular shift of a  $\beta$ -aryl, cyclopropyl, or hydrogen substituent (known as the Fritsch–Buttenberg–Wiechell rearrangement) of thermolabile  $\alpha$ -lithiated vinyl halides (pathway C) and the cyclopropanation reaction with  $\beta$ -alkyl-substituted  $\alpha$ -haloalkenyl metals (pathway D) are both features of carbene-type reactivity <1952HOU(E19b)85>. Reviews of fluorinated vinyl organometallic species <1994T2993> and  $\alpha$ -heteroatom-substituted 1-alkenyllithium reagents, in general, <1998AG(E)430> have been published.



Scheme 50

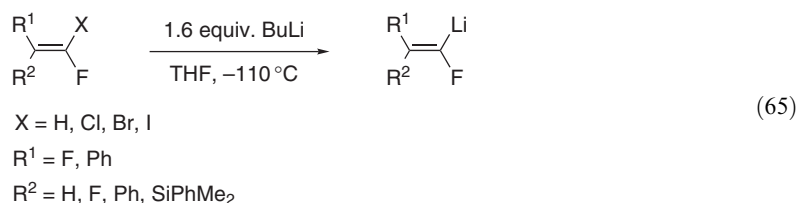
##### 4.18.5.1 $\alpha$ -Haloalkenyllithium Derivatives

$\alpha$ -Haloalkenyllithium derivatives are usually generated quantitatively in solution under inert conditions at low temperatures and allowed to react further without isolation. The greater *s* character of the C—H bond compared with alkanes as well as the presence of a halogen atom increases the acidity of the geminal proton, allowing deprotonation by using alkyllithium reagents (*n*- or *t*-BuLi) or lithium amides (LDA or LITMP). Lithium–halogen exchange and, to a much lesser extent, lithium–metal exchange (see Section 4.18.5.1.1 for example) have also been reported as suitable methods to prepare  $\alpha$ -haloalkenyllithium derivatives. With vinyl fluorides and vinyl chlorides, deprotonation is faster than lithium–halogen exchange, whereas the rate of lithium–halogen exchange increases when going from chlorine to iodine <1993JA5430, 1998AG(E)430>.

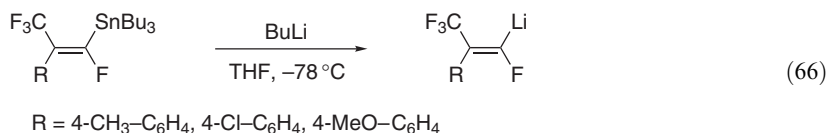
Routes of thermal decomposition are hard to predict but often include elimination of a potential leaving group in the  $\beta$ -position or an intramolecular rearrangement (Fritsch–Buttenberg–Wiechell rearrangement; see [Scheme 50](#), pathway C). These reactions may be suppressed by low temperatures, and  $\beta$ -chloro, fluoro, and alkoxy groups are commonly found in carbenoids [<1993JA5430, 1995JCS\(P1\)2681, 1998AG\(E\)430, 1998OM5390>](#).

#### 4.18.5.1.1 $\alpha$ -Fluoroalkenyllithium compounds

Kvicala and co-workers prepared  $\alpha$ -fluorovinylolithium derivatives employing metallation or lithium–halogen exchange with *n*-butyllithium at  $-100^\circ\text{C}$  ([Equation \(65\)](#)). The influence of several  $\beta$ -substituents on the stability of 1-fluoro-1-lithioalkenes was studied using low-temperature  $^{19}\text{F}$  NMR spectroscopy. It was noticed that a fluorine *cis* to lithium stabilizes the carbanion more than a phenyl group, while hydrogen and silyl groups show no stabilizing effect. This is illustrated by the observation that only products of decomposition of (*E*)-1,2-difluoro-2-(dimethylphenylsilyl)-1-lithioethene are observed, whereas the corresponding (*Z*)-isomer is rather stable even at  $-90^\circ\text{C}$ . Further, it is worth mentioning that lithium–chlorine exchange as well as metallation employed on (*E*):(*Z*) mixtures of  $\beta$ -substituted  $\alpha$ -fluorolithioalkenes proceed with different rates for both isomers [<1995JCS\(P1\)2681, 2001CCC1508, 2002JFC\(113\)211>](#).

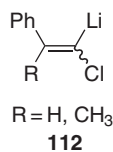
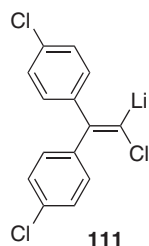


Trifluorovinylolithium has also been prepared from 1,1,1,2-tetrafluoroethane using 2 equiv. of *n*- or *t*-butyllithium as base and is reported to be stable for several hours at  $-78^\circ\text{C}$ . Decomposition in THF is much more rapid than in diethyl ether and the compound is less stable when the concentration is higher. Attempts to prepare  $\alpha$ -fluorovinylolithium derivatives from 1,1,1-trifluoroethane and 1,1,1,3,3,3-hexafluoropropane with *n*-butyllithium were unsuccessful. [<1996CC49, 1999JFC\(99\)127>](#). Finally,  $\alpha$ -fluoroalkenyllithium compounds have been prepared from the corresponding vinylstannanes by lithium–tin exchange ([Equation \(66\)](#)) [<2003S209>](#).



#### 4.18.5.1.2 $\alpha$ -Chloroalkenyllithium compounds

The metallation of 1-chloro-2,2-diarylethenes using *n*-butyllithium at low temperatures has been reviewed [<1990JOM\(400\)19>](#). An X-ray crystal structure analysis of a THF·TMEDA complex of 1-chloro-2,2-bis(4-chlorophenyl)-1-lithioethene **111** reveals that the C–Cl bond is distinctly elongated with respect to that in the nonlithiated compound, while the C–Li bond is shorter than expected. The C–Li bond is bent toward the axis of the alkene C–C bond, whereas the C–Cl bond adopts a position at an angle to the double bond significantly smaller than the  $120^\circ$  angle at  $sp^2$ -hybridized carbon atoms [<1993AG\(E\)1032>](#). Nelson and Brammer performed a computational study of (*E*)- and (*Z*)-1-chloro-1-lithiostyrenes **112** and obtained similar results. The general observation that the most stable carbenoids generally carry the metal atom *cis* to the most bulky group, especially where that group is an aryl ring, has been explained by an agostic bonding between lithium and an *ortho*-proton of the aryl moiety, rather than  $\pi$ -complexation with lithium [<2002HAC263>](#).



The preparation of 1-chloro-2,2-difluorovinyl lithium from 1-chloro-2,2,2-trifluoroethane is analogous to the formation of trifluorovinyl lithium (see Section 4.18.5.1.2). The upper limit for the stability of 1-chloro-2,2-difluorovinyl lithium is reported to be  $-50^\circ\text{C}$  in hexane <1997JFC(85)151, 1998JCS(P1)2541, 1999JFC(99)127>.

#### 4.18.5.1.3 $\alpha$ -Bromoalkenyl lithium compounds

Compared to the corresponding fluoro and chloro species, *gem*-bromolithioalkenes have not been as intensively studied. Metallation of monobromoalkenes with butyllithium may lead to competition from lithium–bromine exchange, affording nonhalogenated products. Lithium amides may provide alternative bases in difficult cases. Hence, Gilbert and co-workers added bromomethylenecyclobutane to a mixture of LDA and trimethylsilyl chloride at  $-107^\circ\text{C}$  (see also Scheme 33) <1999JOC1529>.

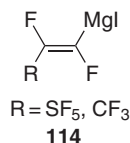
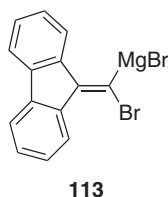
Owing to the high reaction rate, even at low temperatures, lithium–bromine exchange is particularly suitable for generating unstable  $\alpha$ -haloalkenyl lithium derivatives. Jones and co-workers treated 1,1-dibromo-2,2-diphenylethene with 1 equiv. of *n*-butyllithium at  $-100^\circ\text{C}$  to prevent rearrangement (see also Scheme 33) <1995JA3298>.

#### 4.18.5.1.4 $\alpha$ -Iodoalkenyl lithium compounds

Rodriguez and co-workers reported the sole example of the preparation of 1-iodo-1-lithioethene. The best results are obtained employing the metallation method with 3 equiv. of LDA in THF. The solution of 1-iodo-1-lithioethene readily begins to decompose after 5 min at  $-100^\circ\text{C}$  leading to the formation of 1-lithioethyne. However, the anion has been successfully trapped by various electrophiles (see Sections 4.18.3.1.2 and 4.18.3.3 for further details). Applying the lithium–iodine exchange reaction from 1,1-diiodoethene instead, only large amounts of decomposition product were isolated <1998OM5390>.

#### 4.18.5.2 $\alpha$ -Haloalkenylmagnesium Derivatives

Carbenoid **113** has been prepared by Boche and co-workers from 9-(dibromomethylene)fluorene using *n*-octylmagnesium bromide at  $-30^\circ\text{C}$ . The THF complex of compound **113** was isolated as a single crystal and the structure was elucidated by X-ray analysis. Comparable results as for  $\alpha$ -chloroalkenyl lithium **111** (see Section 4.18.5.1.2) were obtained, being characteristic for the carbenoid nature of **113** <1994CC1393>. Further, Grignard reagents **114** have been prepared from the corresponding perfluoroalkenyl iodides in diethyl ether <1997HAC467>.

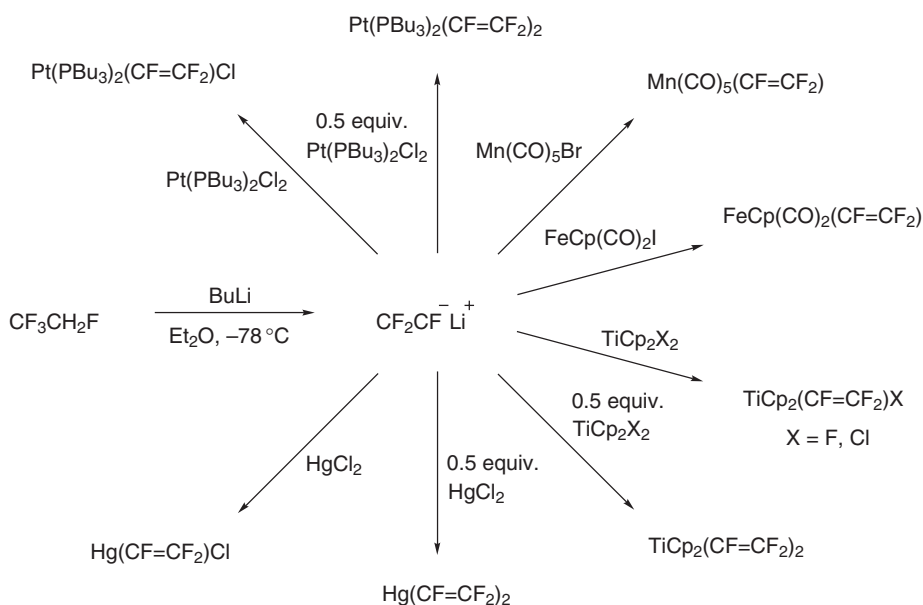
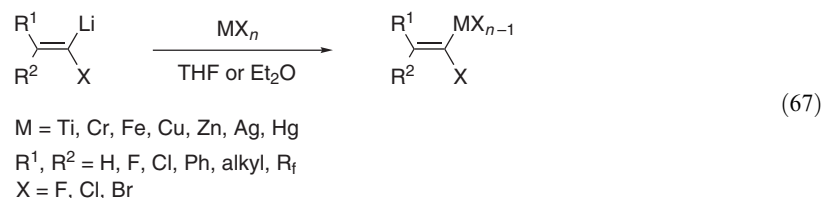


#### 4.18.6 DERIVATIVES OF THE TRANSITION METALS

Many reports of  $\alpha$ -haloalkenyl derivatives of transition elements mainly concentrate on ligand modification. Hence, chemistry of direct relevance to organic synthesis is largely limited to copper and the group 12 elements, especially zinc. There are no reports of  $\alpha$ -haloalkenyl derivatives of the lanthanide and actinide elements. A review of fluorinated vinyl organometallic reagents has been published [<1994T2993>](#).

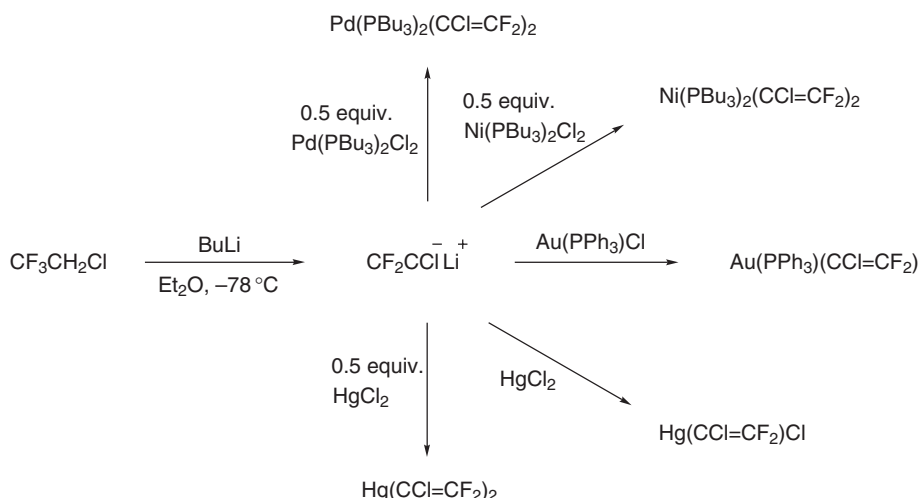
##### 4.18.6.1 By Transmetallation Reactions

Metal exchange between metal salts and lithium carbenoids is the most general route to  $\alpha$ -haloalkenyl transition metals. A variety of  $\alpha$ -chloroalkenyl species have been prepared, some of which were surprisingly stable (Equation (67)) [<1972AG\(E\)473, 1982JFC\(20\)699, 1990JOM\(400\)19>](#). Brisdon and co-workers developed a one-pot synthesis of perfluorovinylmetal derivatives (yield: >90%) reacting the corresponding metal halides with 1,1,1,2-tetrafluoroethane in the presence of *n*-butyllithium at low temperatures (Scheme 51). The majority of these complexes are thermally stable, although decomposition does occur in the presence of water [<1997CC139, 1999JOM\(582\)301, 2001JFC\(112\)35>](#). Analogously, using 1-chloro-2,2,2-trifluoroethane instead, the corresponding *gem*-chlorodifluorovinyl transition metals have been prepared in poor (Ni: 36%)-to-good (Pd, Au, Hg: 60–88%) yields (Scheme 52) [<2000JOM\(616\)96, 2001JFC\(112\)35>](#). Anilkumar and Burton modified this procedure allowing the synthesis of chloro( $\alpha$ -halodifluorovinyl)zinc at room temperature (15–20 °C). Treatment of zinc(II) chloride and 1,1,1,2-tetrafluoroethane [<2002TL2731>](#) or 1-chloro-2,2,2-trifluoroethane [<2002TL6979>](#) with LDA in THF furnishes the corresponding *gem*-fluoro- (yield: 73%) or *gem*-chlorovinylzinc (yield: 91%) derivative, respectively.



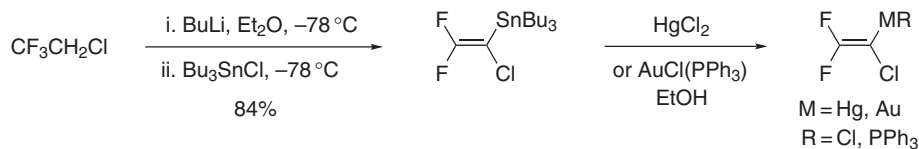
Scheme 51





Scheme 52

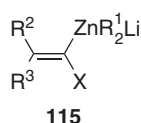
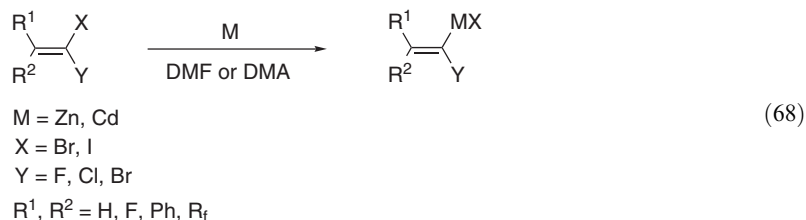
Transmetalation is not restricted to lithium carbenoids only. Brisdon and co-workers prepared chloro(chlorodifluorovinyl)mercury by treatment of mercury(II) chloride with the tin-containing compound acting as transfer reagent of the chlorodifluorovinyl group (Scheme 53) <2000JOM(616)96, 2001JFC(112)35>.



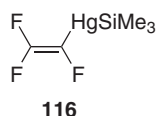
Scheme 53

#### 4.18.6.2 From Alkenyl Halides

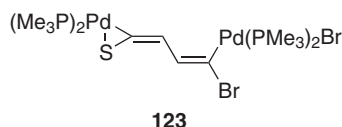
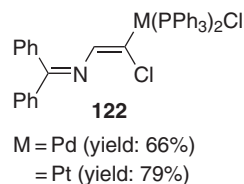
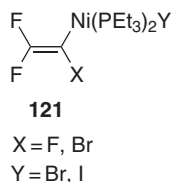
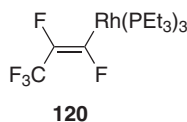
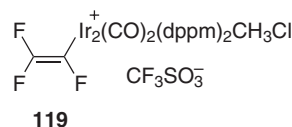
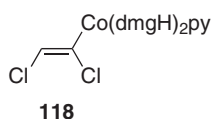
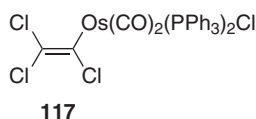
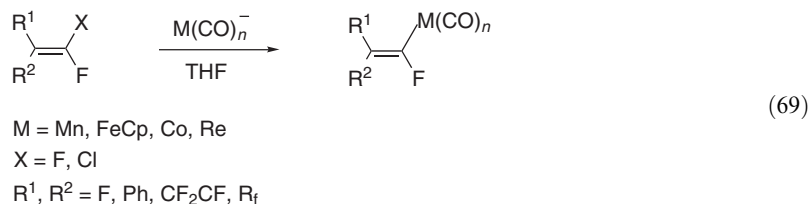
Generally, transmetalation reactions using lithium carbenoids have the disadvantage of requiring low temperatures causing difficulty when carried out on a large scale. To overcome this problem, Burton and co-workers treated a variety of fluorinated alkenylbromides <1993JA5430> and halogenated vinyl iodides <1997JOC9217, 2000TL8045, 2002TL6979> with metallic zinc in polar aprotic solvents (Equation (68)). Further, metal–bromine exchange has been performed utilizing lithium tributylzincate (R<sub>3</sub>ZnLi) <1993JOC4897> or bis(trimethylsilyl)mercury <1971TL1879> affording compounds **115** and **116**, respectively.



R<sup>1</sup> = Bu<sup>n</sup>, Bu<sup>s</sup>, Bu<sup>t</sup>  
R<sup>2</sup>, R<sup>3</sup> = Ph, alkyl  
X = Cl, Br

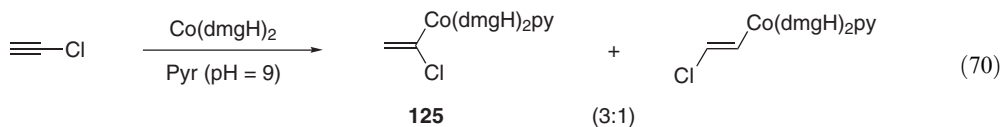
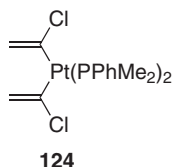


Metal anions react with polyfluoroalkenes by net addition–elimination or by allylic substitution followed by rapid fluoride ion migration producing  $\alpha$ -fluoroalkenyl metal species (Equation (69)) <1989CC1159, 1998RJOC1435>.  $\alpha$ -Chlorovinyl osmium species **117** have been prepared from tetrachloroethene by osmium–chlorine exchange in 71% yield <2000OM4344>. Similarly, chlorovinylcobaloxime complexes **118** (dmgH = dimethylglyoximate) are formed when tetra- or trichloroethene is treated with cobalt(II) acetate or cobalt(II) chloride and dimethylglyoxime (yield: 45%) <2002CC234, 2002IC393>. Starting from chlorotrifluoroethene, Cowie and co-workers synthesized diiridium complex **119** (dppm = 1,2-bis(diphenylphosphino)methane, py = pyridine) as a bright yellow powder in 89% yield <2002OM5172>. As an intermediate of a rhodium-mediated reduction of perfluorinated propene, alkenylrhodium derivative **120** has been isolated in unspecified yield <2002AG(E)2745>. Braun and co-workers <2002JCS(D)2213> obtained fluorovinylnickel complexes **121** from fluorinated vinyl halides upon treatment with bis(1,5-cyclooctadienyl)nickel in the presence of triethylphosphine. The (*Z*)-isomers of palladium and platinum complexes **122** have been successfully prepared when the corresponding *N*-(2,2-dichlorovinyl)imine and phosphino metal complexes are heated in toluene at 50 °C <2003EJI514>. Finally,  $\alpha$ -bromoalkenylpalladium **123** is formed in unspecified yield via cleavage of the C–S bond of 2,5-dibromothiophene. Structure **123** has been confirmed by X-ray crystallography <1999JOM(588)268>.



#### 4.18.6.3 From Alkynes

$\alpha$ -Haloalkenyl metal compounds have been prepared from metalloalkynes or from 1-haloalkynes. The addition of hydrogen chloride to a bis(ethynyl)platinum complex affords *gem*-chlorovinylplatinum compound **124** <1976JA6046>. An example of the second mode of addition is provided by compound **125** formed by reaction of chloroethyne with cobal(I)oxime in unspecified yield (Equation (70)) <2002IC393>.



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### Biographical sketch



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# 4.19

## Functions Bearing Two Chalcogens

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## 4.19.7 FUNCTIONS CONTAINING SELENIUM AND/OR TELLURIUM,

 $R_2^1C=C(SeR^2)_2$ , etc.

828

4.19.7.1 Selenium Derivatives

828

4.19.7.2 Tellurium Derivatives

829

## 4.19.1 INTRODUCTION

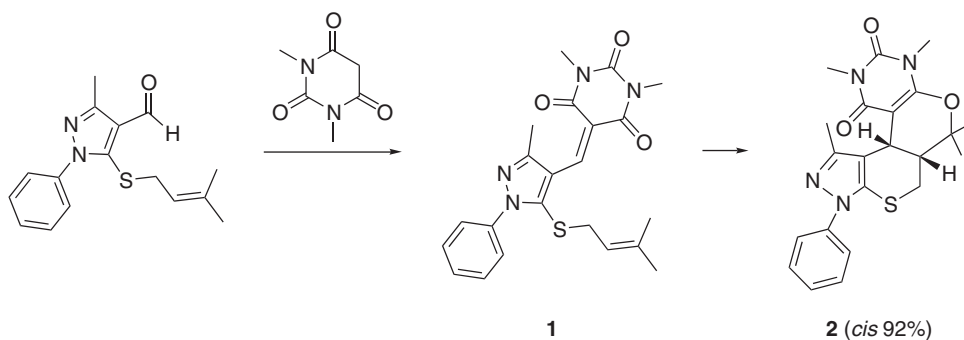
The review covers compounds containing a double bond in which one carbon atom is connected to two chalcogen atoms. Articles published from 1996 through August 2003 were reviewed using Beilstein. Compounds whose chalcogen atoms are part of a heterocycle are generally treated by *Comprehensive Heterocyclic Chemistry* and therefore have been excluded in this review. However, some cases where a synthetic method was considered general are described, especially if one of the reactants bears the double bond and one chalcogen. Also, compounds containing OH, SH, or the chalcogen substructure that display coordination to a metal ion are not included in this review.

4.19.2 FUNCTIONS CONTAINING TWO OXYGEN ATOMS,  $R_2^1C=C(OR^2)_2$ , etc.4.19.2.1 Ketene Acetals,  $R_2^1C=C(OR^2)_2$ 

This section describes compounds in which the two oxygen atoms of the acetal are further connected to carbon atoms.

## 4.19.2.1.1 From carboxylic acids, esters, and chlorides

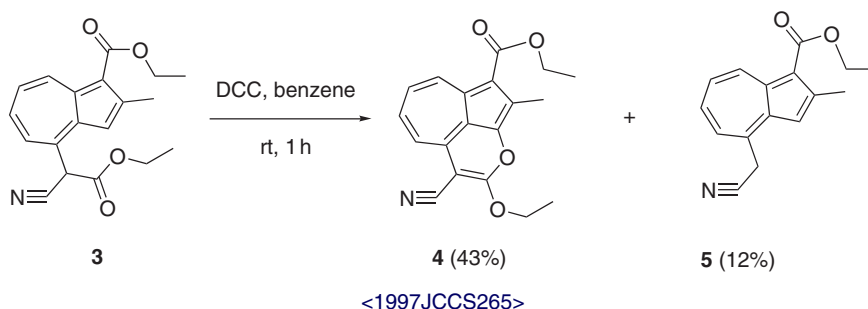
Earlier literature showed that the disadvantage of the formation of ketene acetals from esters is due to the carbon versus oxygen regioselectivity. Intramolecular reactions could occur more successfully when the molecular geometry favors the attack of the carbonyl group to the double bond of a nucleophilic olefin as in the condensation of derivative **1** with dimethyl barbituric acid, when the tetracyclic hetero-Diels–Alder cycloadduct **2** was produced as a single diastereomer *cis* (Scheme 1) <1997SL1155>. A typical example is the reaction of azulene **3** with dicyclohexylcarbodiimide (DCC) in benzene at room temperature for 1 h (Scheme 2). Two reaction products are formed: the benzazulene ketene acetal **4** in 43% yield and the azulene **5** in 12% yield <1997JCCS265>.



&lt;1997SL1155&gt;

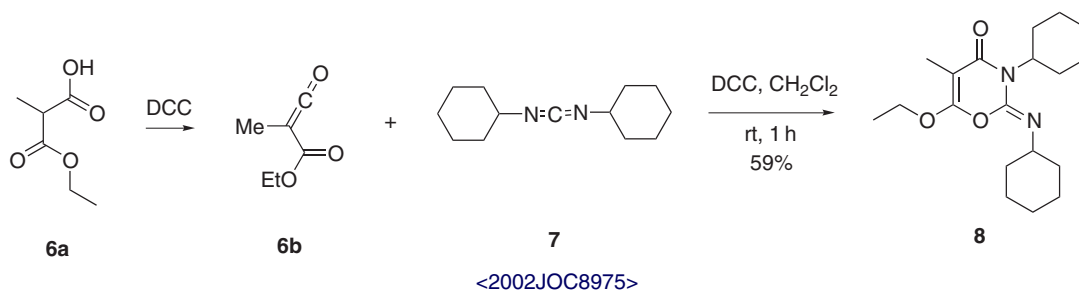
Scheme 1

Acyl ketenes can be obtained *in situ* from carboxylic acids possessing a strong electron-withdrawing group in the  $\alpha$ -position <2002JOC8975>. Methyl malonic monoester **6a** was treated with 1 equiv. of DCC to generate *in situ* acyl ketene **6b**. The reaction was performed in the



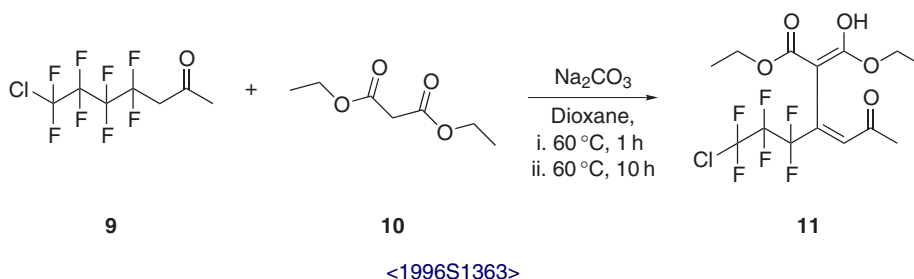
Scheme 2

presence of a large excess of nucleophilic olefins such as cyclopentadiene and ethyl methyl ether, with the idea that a [2+2]-cycloaddition would occur between the acyl ketene formed *in situ* and the olefin to form a cyclobutanone derivative. Ketene acetal **8** was formed instead by a [4+2]-cycloaddition reaction of the acyl ketene with a second DCC molecule **7** (Scheme 3) <2002JOC8975, 2001OL3733>.



Scheme 3

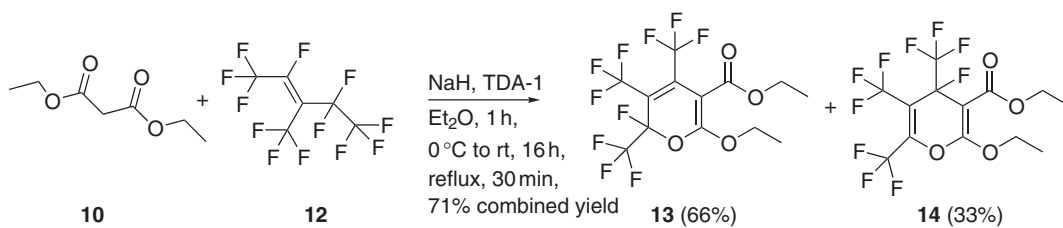
Diethyl malonate **10** was reacted with  $\beta$ -difluoroketones in the presence of sodium carbonate in dioxane at 60 °C to produce the appropriate ketene acetals <1996S1363>. Thus, 7-chloro-4,4,5,5,6,6,7,7-octafluoroheptane-2-one **9** was treated under these conditions to produce derivative **11** with a *trans-trans* stereochemistry (Scheme 4).



Scheme 4

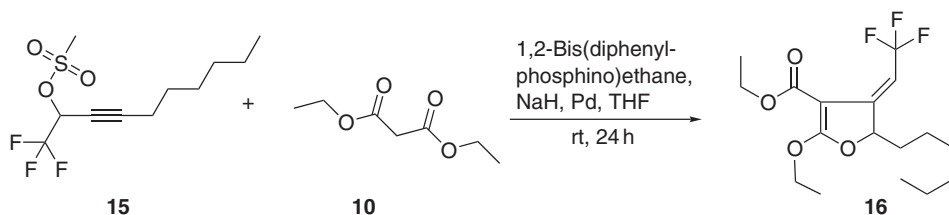
Similarly, perfluoro-3-methylpent-2-ene **12** reacted with 1 equiv. of bidentate nucleophiles such as diethyl malonate **10** in the presence of 2 equiv. of sodium hydride in diethyl ether to produce 2-*F* **13** and 4-*F* **14** pyranes by intermolecular cyclization (Scheme 5) <1998JFC(88)169>.

Diethyl malonate **10** also reacted with the  $\beta$ -alkynylmethanesulfonic acid **15** as shown in Scheme 6, in the presence of 1,2-bis(diphenylphosphino)ethane, sodium hydride, and a palladium catalyst in tetrahydrofuran at room temperature to produce a dihydrofuran derivative **16** <2002CCC1421>.



&lt;1998JFC(88)169&gt;

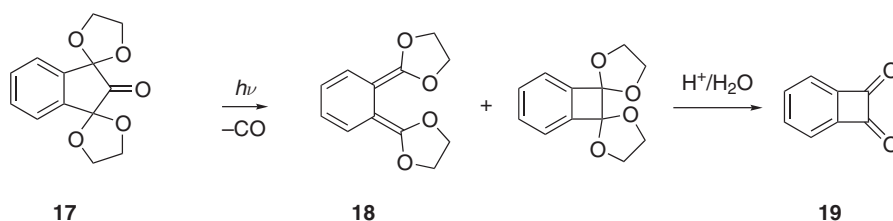
Scheme 5



&lt;2002CCC1421&gt;

Scheme 6

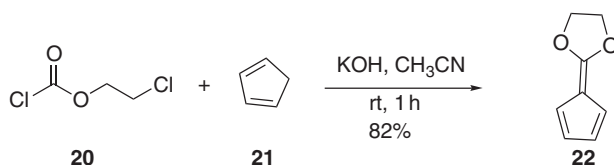
Photodecarbonylation of 1,3-bis(ethylenedioxy)-2-indanone **17** in THF solution led to bisketal **18** in 48% yield (Scheme 7) <2002TL7063>. Benzocyclobutanedione **19** was also formed by irradiation in tetrahydrofuran, while by irradiation in crystal the latter was the only product. Also, Meldrum's acid and analogs reacted with oxygen nucleophiles to give ketene acetals <1996LA1673, 1999H833>.



&lt;2002TL7063&gt;

Scheme 7

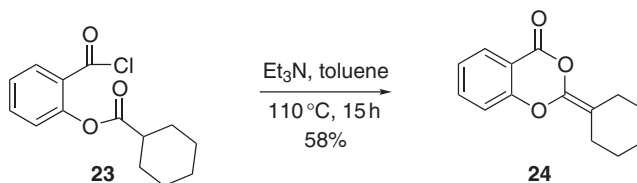
Acid chlorides have also been used as starting material for ketene acetals. Thus, 2-cyclopentadienylden-1,3-dioxolane **22** was prepared as shown in Scheme 8 from cyclopentadiene **21** and 2-chloroethyl chloroformate **20** <1997SC3385>. The reaction was carried out with 2 equiv. of sodium cyclopentadienide and KOH.



&lt;1997SC3385&gt;

Scheme 8

Cyclization of *o*-acyloxy benzoyl chlorides with triethylamine in refluxing toluene led to the preparation of a new class of compounds: 2-alkylidene-benzo-[1,3]dioxin-4-ones <2001TL5231>. For instance, the cyclohexanoic acid derivative **23** produced the acetal **24** in 58% yield, and derivatives with asymmetrical substitution at the ketene acetal double bond were obtained as (*Z*)/(*E*) mixtures (Scheme 9).

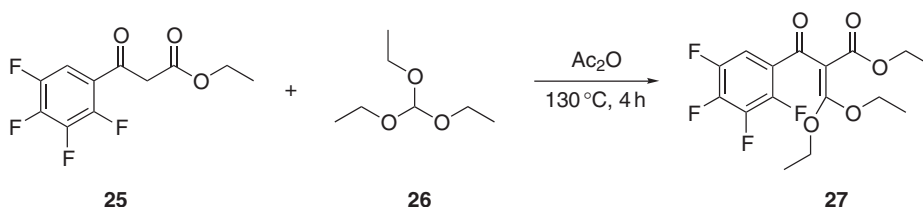


&lt;2001TL5231&gt;

Scheme 9

#### 4.19.2.1.2 From *ortho*-esters and analogs

Earlier literature referred often to this reaction, but only one entry was found in the period reviewed here. Triethoxymethane **26** was reacted with ethyl 2,3,4,5-tetrafluorobenzoylacetate **25** to give the corresponding diethoxyacetylate **27** <1998JMC4273>. The reaction occurred in refluxing acetic anhydride (Scheme 10).

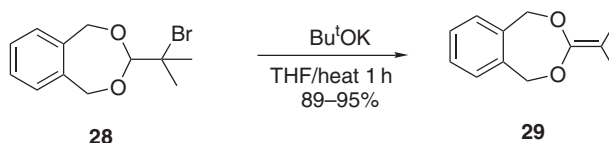


&lt;1998JMC4273&gt;

Scheme 10

#### 4.19.2.1.3 From $\alpha$ -haloacetals and analogs

$\alpha$ -Bromoaldehydes are often protected as 1,2-benzenedimethyloxy acetals because of the facile elimination of the protecting group. Such acetals underwent bromine  $\beta$ -elimination to afford ketene acetals. The bromine elimination in compound **28** was achieved by treatment with potassium *t*-butoxide in THF and subsequent heating for 1 h to obtain product **29** as a solid (Scheme 11) <2001JOC305, 2001TL3183>.



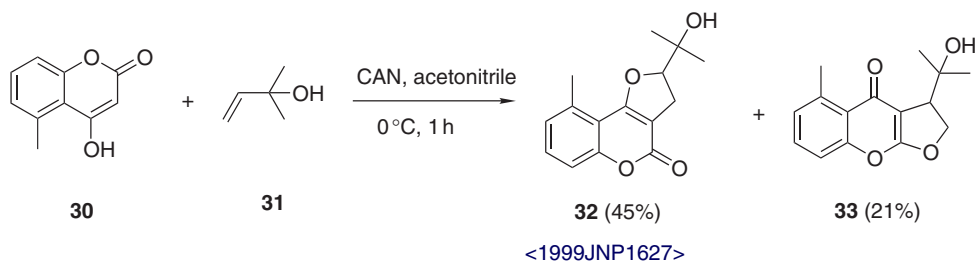
&lt;2001TL3183&gt;

Scheme 11

#### 4.19.2.1.4 From cycloaddition reactions of $\alpha,\beta$ -unsaturated ketones and esters

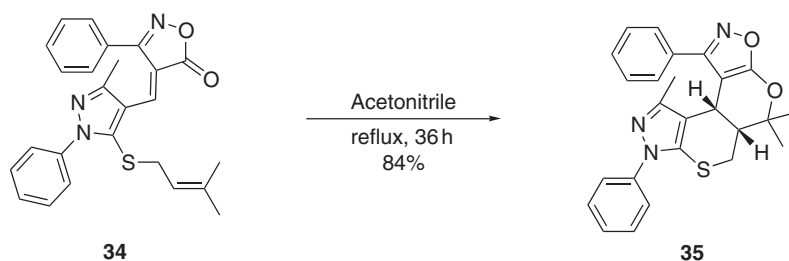
$\alpha,\beta$ -Unsaturated systems react with allylic alcohols to produce ketene acetals. The recent examples refer to the synthesis of some polycycles containing ketene acetal systems. As an example, cumarone **30** treated with 2-methyl-3-buten-2-ol **31**, in the presence of cerium(IV) ammonium

nitrate in acetonitrile at 0 °C, produced the ketene acetal **33** in 21% yield along with the major product **32** (Scheme 12) <1999JNP1627>.



Scheme 12

Intramolecular [2 + 4]-hetero-Diels–Alder cycloaddition of pyrazole **34** produced cycloadduct **35** as a single *cis*-diastereomer in 84% yield. The reaction was carried out in acetonitrile in the presence of ethylene diammonium diacetate (Scheme 13) <1997SL1155>.

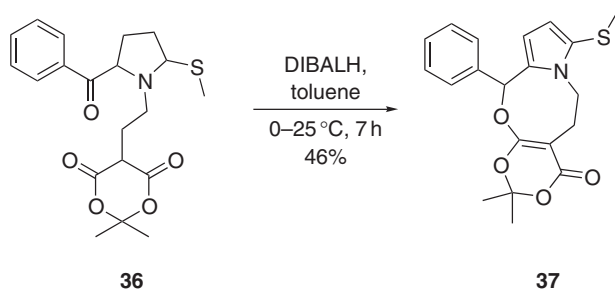


<1997SL1155>

Scheme 13

#### 4.19.2.1.5 By reduction–elimination in $\omega$ -keto esters

Compound **36** (obtained by the condensation of 5-methylthio-2-benzoyl-pyrrole with spiro[2,5]-5,7-dimethyloctane-4,8-dione in the presence of NaH) underwent an acid-catalyzed rearrangement in refluxing toluene/methanol (10:1) to produce tetrahydro-2*H*-oxocine **37** in 46% yield <1999H833>. The same compound was obtained by treatment with DIBALH in toluene at rt for 7 h followed by acidic work-up, which proves indirectly a two-step mechanism to produce the oxocine ring in **37** consisting of reduction of the benzoyl group followed by ring closure under acidic conditions (Scheme 14) <1999H833>.

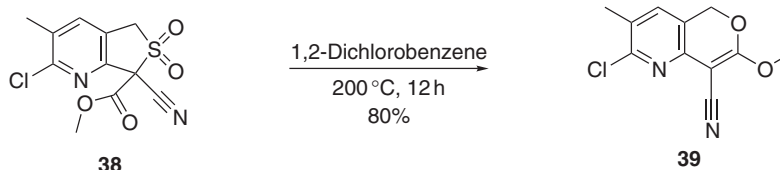


<1999H833>

Scheme 14



In a similar example, the formation of pyrano-pyridine **39** by thermolysis of sulfolene **38** was explained by an electrocyclic ring closure involving the carbonyl function of an ester group <2002T3655>. Sulfolenes of type **38** were converted by thermal extrusion to terminally substituted dienes having either the (*E*)- or (*Z*)-configuration (Scheme 15).

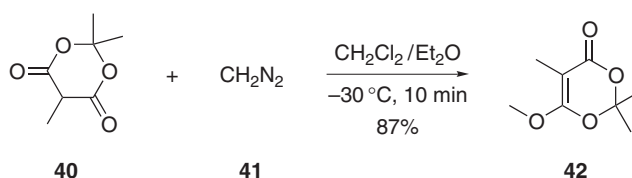


&lt;2002T3655&gt;

Scheme 15

#### 4.19.2.1.6 From diazoalkanes

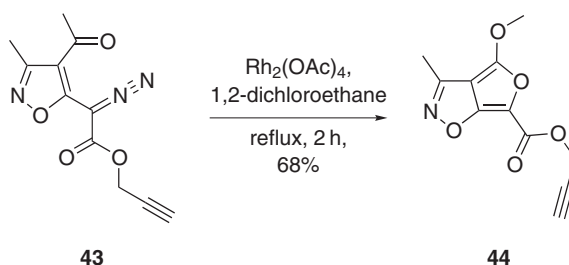
Meldrum's acid derivatives **40** reacted with diazoalkanes **41** in dichloromethane and ether at  $-30^{\circ}\text{C}$  to produce the enolized Meldrum's acid methoxydioxinones **42** (Scheme 16) <1997TL6689>. The compounds underwent [4+2]-cycloreversion at room temperature to the corresponding methoxycarbonyl ketenes and ketones, showing their susceptibility to nucleophilic agents.



&lt;1997TL6689&gt;

Scheme 16

$\beta$ -Carboxyl diazomethanes of type **43** underwent a similar intramolecular reaction to produce methoxyfuro[3,4-*d*]isoxazoles **44** as described in Scheme 17 <1996H1165>. The reaction was performed in the presence of  $\text{Rh}_2(\text{OAc})_4$  by heating in dichloroethane for 2 h.

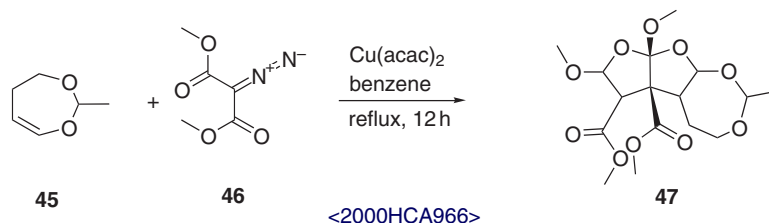


&lt;1996H1165&gt;

Scheme 17

Similarly, dimethyl diazomalonate **46** generated a carbonylcarbene in the presence of bis(acetylacetonato)copper(II) as a catalyst <2000HCA966>. This carbene reacted *in situ* with 1,3-dioxepins **45** to produce polycyclic structures **47**. Treatment of vinyl acetals with dimethyl diazomalonate (dmdm) or ethyl acetodiazooacetate produced 2-alkoxy-substituted dihydrofuranes. Several research groups investigated the reaction of enol ethers with diazodicarbonyl compounds and proposed different mechanisms. The authors have considered the product distribution versus the nature of the diazocarbonyl compound and have established that according to the literature findings ethyl diazoacetate yielded mainly cyclopropanes and rarely rearrangement products, while dmdm

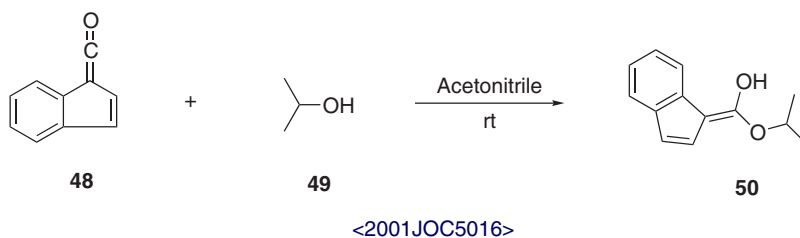
afforded addition–elimination and rearrangement products. Ethyl acetodiazooacetate produced 2-alkoxy-substituted dihydrofuranes and rearrangement products. The rearrangement products occur via structures possessing two chalcogens (Scheme 18) <2000HCA966>.



Scheme 18

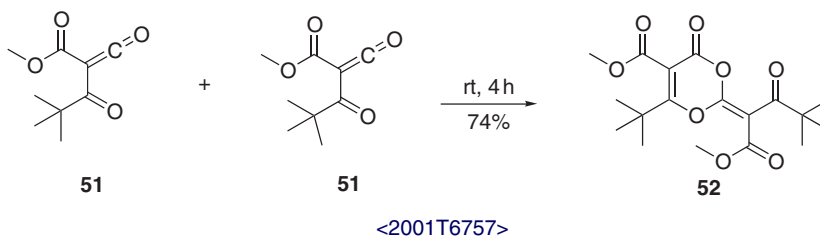
#### 4.19.2.1.7 From ketenes

Ketenes are commonly generated by a photo-Wolff rearrangement from the corresponding diazoketones, and they readily react with various nucleophiles. For instance, by treating ketenes **48** with alcohols such as **49**, ketene acetals such as **50** were produced (Scheme 19) <2001JOC5016>. Similar reactions could also lead to ring closures with the formation of 2-alkoxyfurans <1998AG(E)1540>.



Scheme 19

Carbomethoxypivaloyl ketene **51** (an  $\alpha$ -oxoketene generated by flash vacuum pyrolysis of the corresponding furan-2,3-dione) underwent hetero-Diels–Alder reaction across the ketene carbonyl moiety to produce the [4 + 2]-cycloaddition adduct dioxinone **52** in 87% yield (Scheme 20) <2001T6757>.

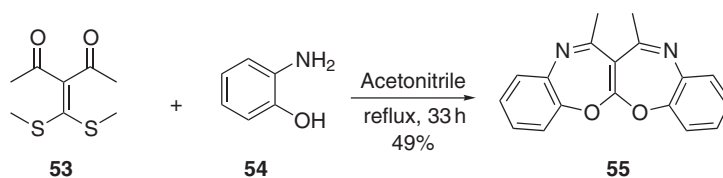


Scheme 20

#### 4.19.2.1.8 From gem-dihalogenoalkenes and analogs

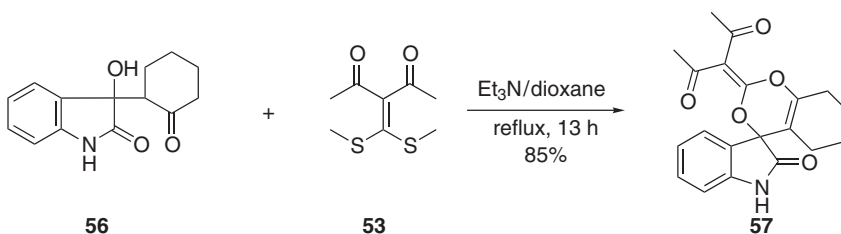
1,1-Dialkylthio alkenes or  $\alpha$ -keto ketene (*S,S*)-acetals **53** were reacted with substituted phenols **54** to produce ketene acetals such as **55** integrated in polycycles (Scheme 21). The reactions were performed in refluxing acetonitrile for 30 min to 1 h <1996SC4289>.

The same substrate **53** was reacted with hydroxyl-indolin-2-ones **56** <2000SC1257>, and spiro-ketene acetals **57** were obtained (Scheme 22).



&lt;1996SC4289&gt;

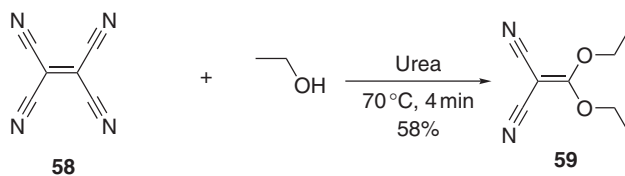
Scheme 21



&lt;2000SC1257&gt;

Scheme 22

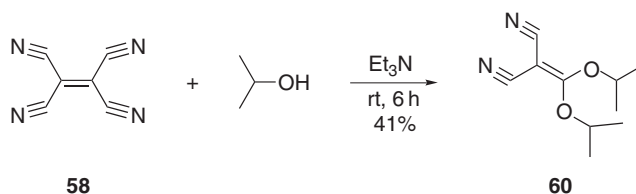
Dienophile tetracyanoethylene **58** was reacted with ethanol under heating at 70 °C for only 4 min in the presence of urea, and diethoxymethylene-malononitrile **59** was produced in 58% yield <2002JCS(D)1687>. This compound and similar structures described within this reference were used as bridging ligands in the preparation of coordination polymers with antiferromagnetic properties (Scheme 23).



&lt;2002JCS(D)1687&gt;

Scheme 23

Dicyanoketene acetal **60** was prepared similarly as **59** (Scheme 24) and was used for copolymerization with styrene, divinylbenzene, or ethylene glycol dimethylacrylate, to produce polymeric dicyanoketene acetals utilized as recyclable  $\pi$ -catalysts in monothioacetalization or C—C bond-forming reactions of acetals <1998TL5799, 2000CPB1010, 1996BCJ195>.

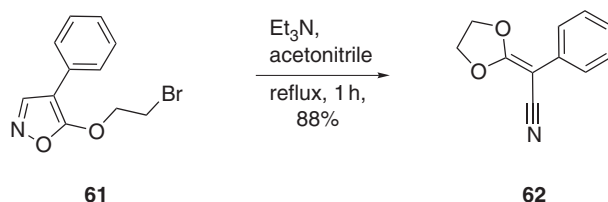


&lt;1996BCJ195&gt;

Scheme 24

#### 4.19.2.1.9 From oxazoles and isoxazoles

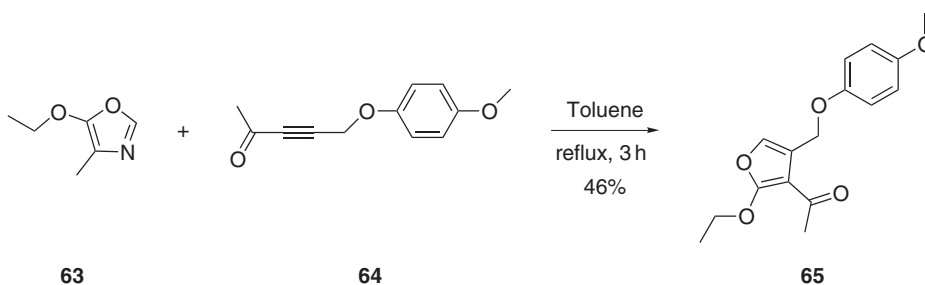
Isoxazole derivatives such as **61** produced ketene acetals of type **62** <1997T10433> (Scheme 25). Derivatives **61** were prepared from 4-aryl-isoxazolin-4-ones and 1,2-bromoethane in acetonitrile in the presence of triethylamine as a catalyst. The *N*-alkylated products were obtained along with derivatives **61**, which generated the corresponding *N,O*-ketene acetals by heating with sodium methoxide in methanol (not shown).



<1997T10433>

Scheme 25

5-Alkoxyoxazole **63** underwent a tandem Diels–Alder–retro-Diels–Alder reaction sequence with the acetylenic dienophile **64** with elimination of acetonitrile to produce 2-alkoxyfuran **65** (Scheme 26) <2000AJC749>.

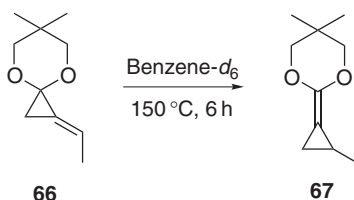


<2000AJC749>

Scheme 26

#### 4.19.2.1.10 By miscellaneous rearrangements and cycloadditions

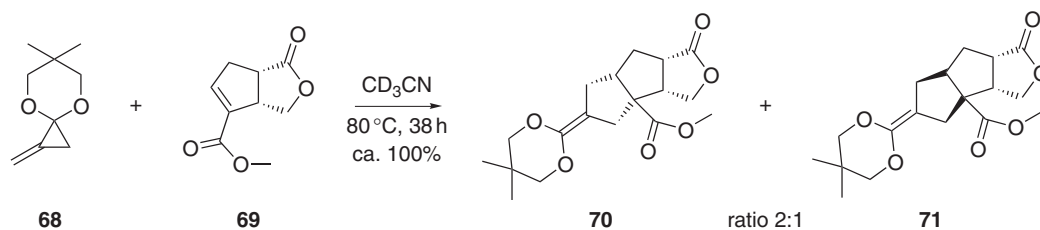
It has been shown earlier that isomerization of 2,2-dialkoxymethylenecyclopropane derivatives of type **66** (Scheme 27) and **68** (Scheme 29) produced dialkyl ketene acetals. Compound **66** isomerized to a dimethylene ketene acetal **67** upon prolonged heating above 120 °C, and further reactions evidenced the high reactivity toward electron-deficient olefins <1996S1380>.



<1996S1380>

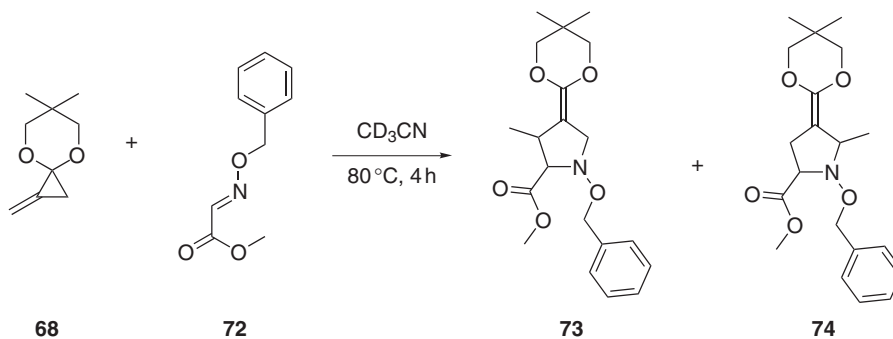
Scheme 27

Methylenecyclopropanone ketal **68** reacted with diquinene **69** (Scheme 28) in acetonitrile at 80 °C following an intermolecular [3+2]-cycloaddition pathway with the formation of two adducts **70** and **71** in a ratio of 2:1 and practically quantitative yield <1998EJO257>. The two



&lt;1998EJO257&gt;

Scheme 28

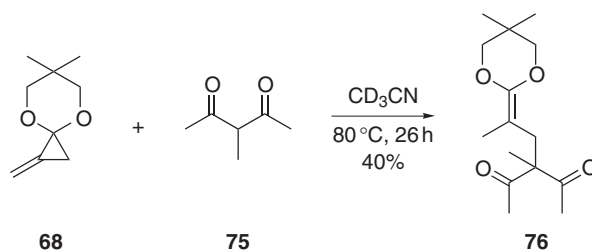


&lt;1998JOC1694&gt;

Scheme 29

acetals hydrolyzed to the corresponding esters while attempting separation on column chromatography. Similar hetero [3+2]-cycloaddition reactions of dipolar trimethylenemethane have also been reported, such as the reaction of ketal **68** with *O*-alkyloxime **72** (Scheme 29) <1998JOC1694>. The reaction occurred similarly in acetonitrile at  $80^\circ\text{C}$  with the formation of both isomers **73** and **74** in a ratio of 30:70 and 81% yield.

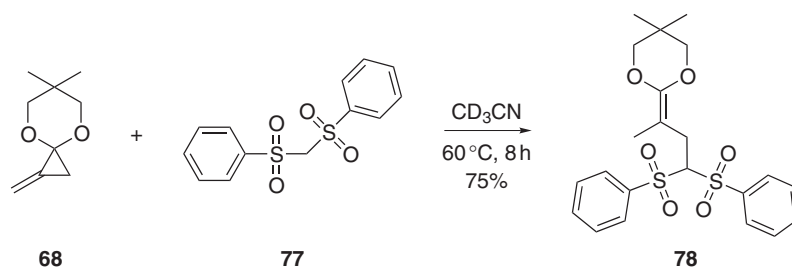
Dipolar trimethylenemethane **68** was also reported to react with active methylene compounds, such as acetylacetone **75**, to produce the end-product **76** (Scheme 30) and with methylene disulfone **77** to produce the end-product **78** (Scheme 31). The reaction proceeds via ionic alkylation of the active methylene substrate under neutral, mild conditions <2001SL(S)1030>.



&lt;2001SL(S)1030&gt;

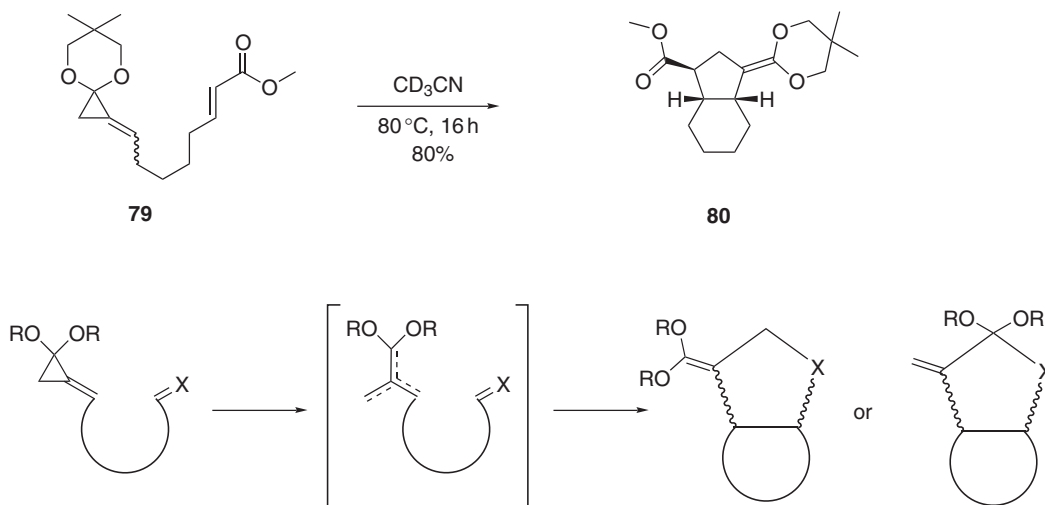
Scheme 30

Alkylidenecyclopropanone acetals such as **79** (Scheme 32) are versatile precursors of dipolar trimethylenemethane (TMM), which was generated by their mild thermolysis. When possessing a terminal diylophile the compounds underwent intramolecular [3+2]-cycloadditions in acetonitrile within 9–32 h <2000CL664>. The regioselectivity and diastereoselectivity of the products were dependent on the electron demand of the terminal diylophile and was not affected by the alkylidenecyclopropanone ring that behaves as a ketene acetal in these reactions. The mechanism does not



&lt;2001SL(S)1030&gt;

Scheme 31

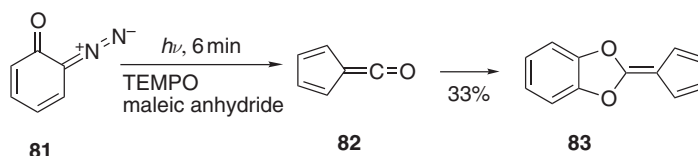


&lt;2000CL664&gt;

Scheme 32

necessarily obey the *endo* rule of cycloaddition, being either concerted, or stepwise single-electron transfer (SET). The concerted pathway was stereochemically more defined and the products obtained were of the type **80**. When exomethylene acetals were obtained instead of structures with two chalcogens, the mechanism was ascribed to a SET intermolecular reaction.

Diazoketone **81** generated fulvenone **82** by mild photolysis via the cyclopentadienyl radical. Two molecules of fulvenone **82** underwent an addition reaction to produce the derivative **83** in 33% yield (Scheme 33) <2001JOC7420>. The reaction was performed in hexanes by photolysis with 300 and 350 nm light for 6 min in the presence of TEMPO and maleic anhydride. Two other dimers were isolated in 4% and 6% yields, respectively (not shown).

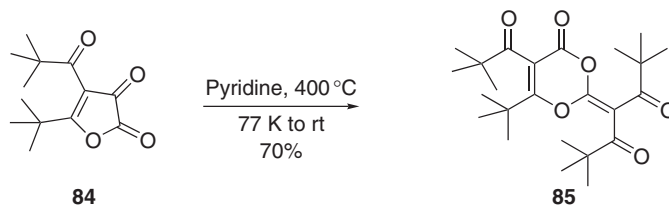


&lt;2001JOC7420&gt;

Scheme 33

Furandione **84** was subjected to flash vacuum pyrolysis at  $400^\circ\text{C}$  and subsequent reaction with pyridine at 40–100 K, followed by heating at room temperature <1996JA12598>. Compound **85**

was then isolated in 70% yield (Scheme 34), proving that dipivaloyl ketene was the intermediate produced by pyrolysis, while pyridine activated the cycloaddition reaction between two molecules of this ketene.

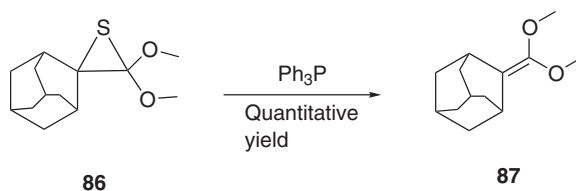


<1996JA12598>

Scheme 34

#### 4.19.2.1.11 By miscellaneous transformations

Adamantylketene dimethyl acetal **87** was prepared quantitatively by desulfurization of 2,2-dimethoxythiirane **86** by treatment with triphenylphosphine (Scheme 35) <2001OL2455>. The stable thiirane **86** was obtained in the reaction of adamantanethione with dimethoxy carbene, which in turn was generated by thermolysis of 1,1-dimethoxy-5,5-dimethyl-oxadiazoline.



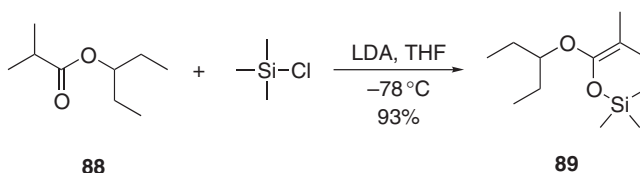
<2001OL2455>

Scheme 35

#### 4.19.2.2 Other Related Ketene Derivatives, $R_2^1C=COR^2OX$ , etc.

##### 4.19.2.2.1 Ketene silyl acetals, $R_2^1C=COR^2OSiR_3^3$

The silylation of ester enolates **88** to give ketene acetals **89** is still widely used in the original Ireland version, although numerous other variations are available. The method entails the deprotonation of an ester with a strong base in hexane/THF at  $-78^\circ\text{C}$  and subsequent trapping of the ester enolate with a silyl derivative, usually with high yields (Scheme 36) <2001JOC7464, 2000CPB1577>.

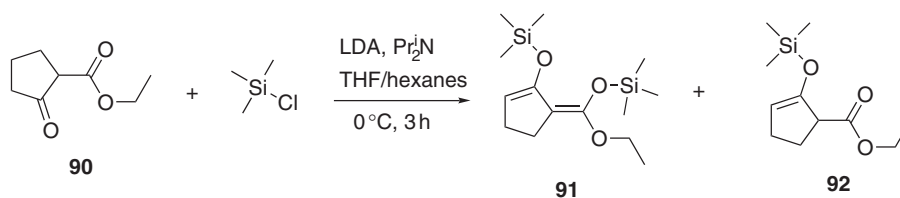


<2000CPB1577>

Scheme 36

When two enolizable groups are present in the molecule, i.e., a 1,3-dicarbonyl system, it was shown that competitive reactions could occur <2001EJO3657>. For example, when ethyl cyclopentanone-2-carboxylate **90** was silylated with trimethylsilyl chloride in the presence of LDA in

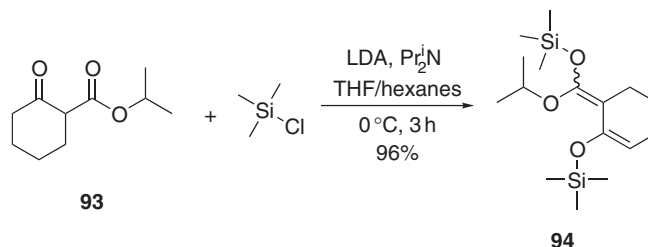
THF, the reaction took place at both carbonyl sites, and two reaction products were formed: the 1,3-bis-(trimethylsiloxy)-1,3-diene **91**, in which both the ester enolate and the keto enolate reacted with the silylating agent, and silyl enol ether **92** where only the ketone group was silylated leaving the ester group intact (Scheme 37).



<2001EJO3657>

Scheme 37

When isopropyl cyclohexanone-2-carboxylate **93** and its 5-substituted analogs were silylated in the same manner, the reaction occurred at both terminal carbon atoms of the 1,3-dicarbonyl system, generating only products of type **94** (Scheme 38). The same outcome was found for cycloheptanoate derivatives. For all compounds in this series yields were reported to be over 90% <2001EJO3657>.



<2001EJO3657>

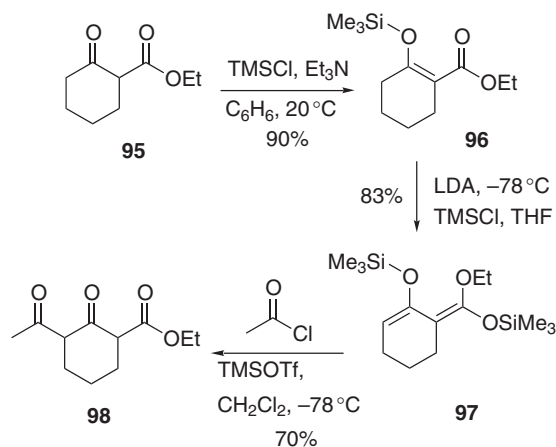
Scheme 38

Cyclohexanone-derived bis-(trimethylsiloxy)-1,3-dienes were regioselectively prepared by using various silylating systems <2000SL497>. Ethyl cyclohexanone-2-carboxylate **95** was treated with triethylamine-TMSCl in benzene at room temperature to produce the thermodynamically favored silyl enol ether **96** (Scheme 39). This compound was treated with LDA for 1 h at  $-78^\circ\text{C}$ , then reacted with TMSCl with warming to rt, whereupon 1,3-bis-(trimethylsiloxy)-1,3-diene **97** as a single stereoisomer was obtained in good yield. Reaction of compound **95** with 2 equiv. of triethylamine-TMSOTf at  $20^\circ\text{C}$  gave silyl enol ether **96** rather than diene **97**. The difference was explained by the base strength of triethylamine, too low for the deprotonation of both the methylene group adjacent to the double bond and the one adjacent to one carbonyl group. The Lewis acid TMSOTf enhances the acidity of a ketone and deprotonation of a neighboring methylene is not possible. Also, the activation described here may not be sufficient for the deprotonation at  $20^\circ\text{C}$  of a methylene group adjacent to a double bond, as in compound **96**. Addition of acetyl chloride to diene **97** in the presence of a catalytic amount of TMSOTf occurred 1,4- at the conjugated system to produce derivative **98**.

$\alpha,\beta$ -Unsaturated esters and acids react with silyl halides to afford silyl dienol ethers. Such an example is the synthesis of compound **100** starting from 1,3-dioxin-4-one **99** (Scheme 40). Compound **99** was treated with a base (LDA or KHMDS) at  $-78^\circ\text{C}$  in THF followed by addition of TMSCl. The isolated yields were in the range of 50–80% <2001JOC3548>.

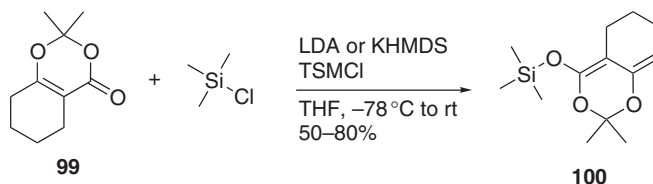
Silyl vinyl ketene acetals **102** obtained from *trans*-but-2-enoic acid (tiglic acid) and its esters **101** were obtained in conditions similar to the ones described above (Scheme 41) <1995TL9465, 2001JOC4293, 2002BMC1249>. The reaction product was isolated as an inseparable mixture of isomers (*Z*) and (*E*) in about 2:1 ratio.





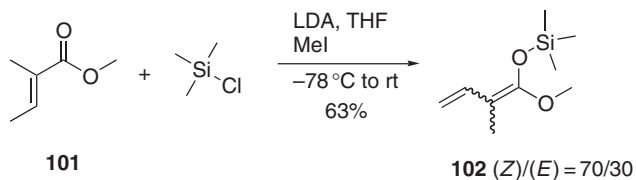
<2000SL497>

Scheme 39



<2001JOC3548>

Scheme 40

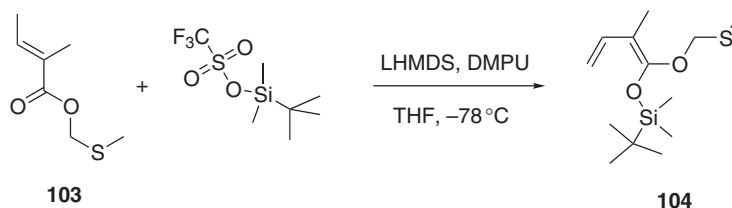


<2001JOC4293>

<1995TL9465>

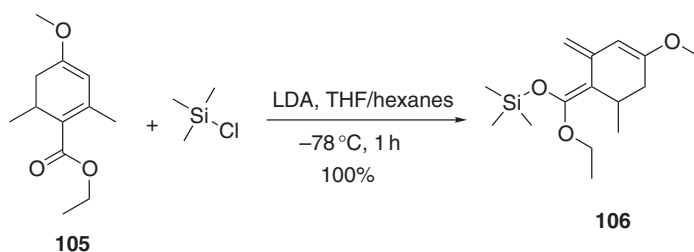
Scheme 41

Esters **103** treated with LHMDS in the presence of 1.3 equiv. of DMPU followed by the addition of *t*-butyldimethylsilyl triflate gave *O,O*-silyl ketene acetals **104** as mixtures of (*Z*) (major) and (*E*) (minor) isomers (Scheme 42) <1998TL3157>. When the 2-butenic system was terminally substituted with a methoxy group, the stereochemistry of the double bond was preserved <1998AJC421>. For cyclohexadiene systems such as **105** (Scheme 43) only the (*Z*)-isomer **106** was formed <2000BMC253>.



<1998TL3157>

Scheme 42



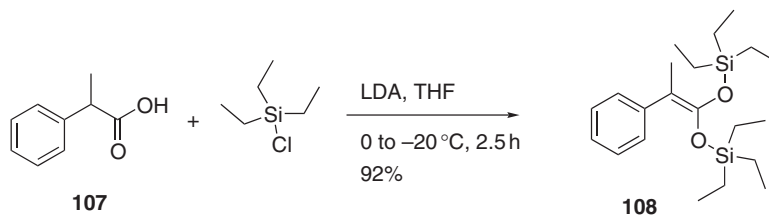
&lt;2000BMC253&gt;

Scheme 43

Other silyl derivatives used besides halides and triflates were: triethyl silane <1997CL1245>, *t*-butyldimethyltrifluoromethanesulfonyloxysilane <1998TL3157>, and *t*-butyldiphenylchlorosilane <1997TL6689>.

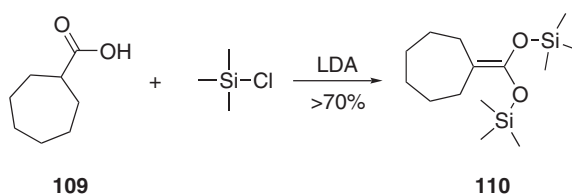
#### 4.19.2.2.2 Ketene silyl acetals, $R_2^1\text{C}=\text{COSiR}_3^2\text{OSiR}_3^3$

Silyl enol ethers are stable and isolable synthetic equivalents of enols and enolates, and they have been often used instead in various reactions, such as enantioselective protonation <2000JA8120>. For this purpose, bis-silylated enol ethers **108** were prepared from 2-arylcarboxylic acids **107** by treatment with LDA and excess triethylchlorosilane in THF at  $0^\circ\text{C}$  with isolated yields of about 90% (Scheme 44). A similar reaction was reported for cycloalkylcarboxylic acid **109** to obtain compound **110** (Scheme 45) <2001JOC7464>.



&lt;2000JA8120&gt;

Scheme 44



&lt;2001JOC7464&gt;

Scheme 45

#### 4.19.2.2.3 Boryloxy derivatives, $R_2^1\text{C}=\text{COR}^2\text{OBR}^3$

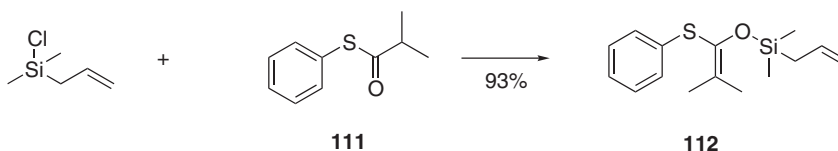
There are no reports on boryloxy derivatives in the time period reviewed, as disclosed by a Beilstein substructure search.

### 4.19.3 FUNCTIONS CONTAINING OXYGEN AND SULFUR, $R_2C=COR^2SR^3$ , etc.

#### 4.19.3.1 Dicoordinated Sulfur Derivatives, $R_2C=COR^2SR^3$

##### 4.19.3.1.1 From monothiocarboxylic acids and esters or thioesters

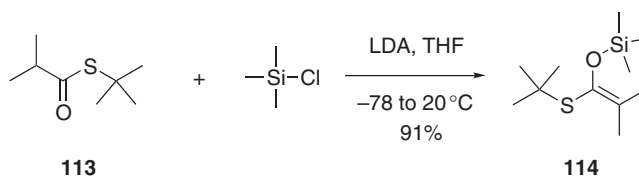
Thiol ester enolates, enethiolates, and thiono esters have been reacted with electrophiles to afford ketene monothioacetals. Ketene-*O*-silyl monothioacetals were prepared from the corresponding thiol esters as their dioxo analogs described above (see Section 4.19.2.2). Thioisobutyric acid *S*-phenyl ester **111** was reacted with allyl-chloro-dimethylsilane to produce the silylketene monothioacetal **112** in over 90% yield (Scheme 46) <1999TL2183>.



<1999TL2183>

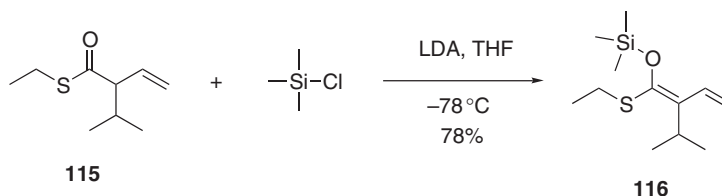
Scheme 46

In a first stage, enethiolization of the thionoester was performed in the presence of a strong base such as LDA at low temperature usually in THF as a solvent, then in a second stage an alkyl or silyl halide was added. Most used in chemical synthesis are the *O*-silylated derivatives. The stereochemistry of the silyl thioketene acetals is determined by the solvent and chelating agents. A series of thioester enolates, e.g., **113**, was treated with trimethylchlorosilane to produce trimethylsilyloxy-thioesters such as **114** (Scheme 47) <2001JOC697>. Similarly, dienolates **116** were obtained from **115** (Scheme 48) as a mixture of isomers (*Z*):(*E*) in a ratio of 1:1 <2001CL1080>.



<2001JOC697>

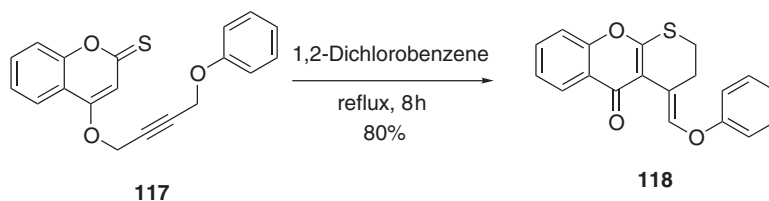
Scheme 47



<2001CL1080>

Scheme 48

Thioesters **117** were refluxed in chlorobenzene for 8 h and thioketene acetal **118** was obtained in 80% yield (Scheme 49) <2001S924>. The reaction was assumed to proceed by a [3,3]-sigmatropic shift followed by a 1,3- $H^+$  shift and enolization. When the coumarin and phenoxy rings were substituted with electron-withdrawing groups, the yields were in the range of 50%, while substitutions with one or two alkyl groups afforded yields of up to 85%.

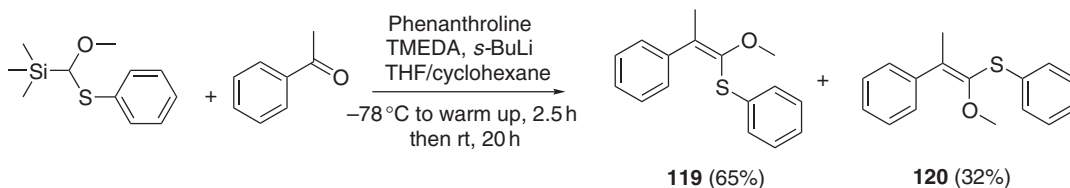


&lt;2001S924&gt;

Scheme 49

#### 4.19.3.1.2 By alkeneation methods

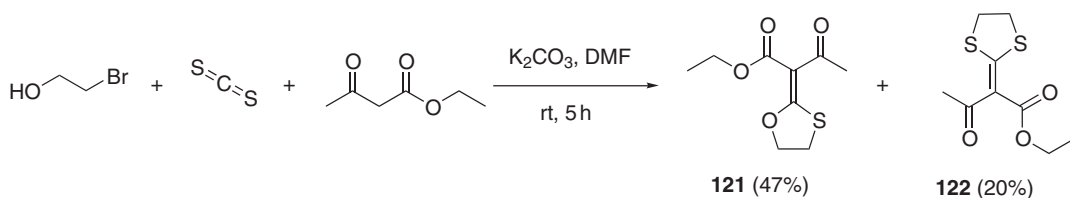
In the time period reviewed here, there is only one report on Peterson alkeneation to convert aldehydes and ketones to the corresponding ketene *O,S*-diacetals <1999CEJ2270>. Aromatic and aliphatic aldehydes and ketones were treated at  $-78^{\circ}\text{C}$  in THF with lithio-phenoxy(phenylthio) (trimethylsilyl)methane (Scheme 50). The ketene-*O,S*-acetals (**119** and **120**) were obtained in almost quantitative yields with poor (*E*) to (*Z*) selectivity for aromatic carbonyl compounds and no selectivity for the aliphatic ones.



&lt;1999CEJ2270&gt;

Scheme 50

There are quite a few reports on alkeneation reactions using carbon disulfide and activated methylene compounds. Thus, carbon disulfide reacted with ethyl acetoacetate and 2-bromoethanol in dimethylformamide in the presence of potassium carbonate at room temperature <2000IJC(B)147>. Both the oxathiolane **121** and the dithiolane **122** were obtained in a ratio of 2.4:1 (Scheme 51).

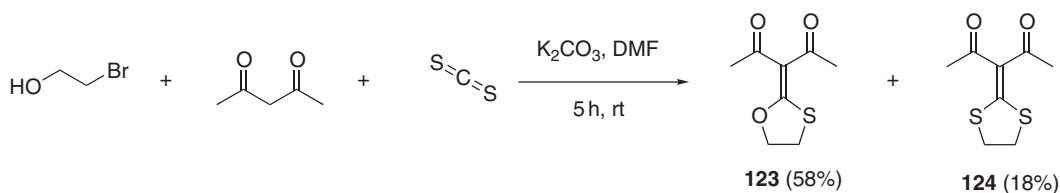


&lt;2000IJC(B)147&gt;

Scheme 51

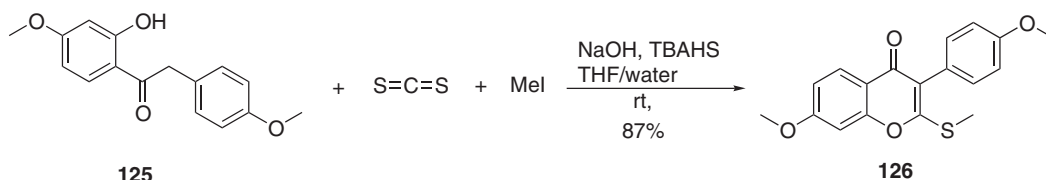
When reacting carbon disulfide and 2-bromoethanol with acetylacetone in the same conditions, the ratio between oxathiolane **123** and dithiolane **124** was about the same (Scheme 52).

Deoxybenzoins **125** reacted similarly with carbon disulfide and methyl iodide to produce 2-(alkylthio)isoflavones in a single step at room temperature <2002TL6113>. The reaction was performed in a THF/water two-phase system by treatment of the three reactants with aqueous sodium hydroxide in the presence of tetrabutylammonium hydrogen sulfate as a catalyst. Isoflavone **126** was obtained in 87% yield (Scheme 53). When allyl and benzyl bromide were used instead of methyl iodide, the yields were over 96%.



&lt;2000JC(B)147&gt;

Scheme 52

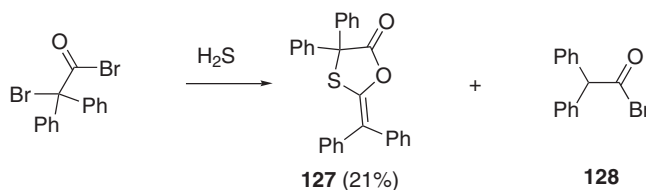


&lt;2002TL6113&gt;

Scheme 53

#### 4.19.3.1.3 By elimination methods

By electroreduction of an  $\alpha$ -haloacyl halide in the presence of sulfide anions generated in the anodic compartment, one can obtain [1,3]oxathiolan-5-one derivatives. When a layer of solid sodium thiosulfate was placed on the diaphragm in the anodic side,  $\text{H}_2\text{S}$  was generated in the anodic compartment, which reacted with electrogenerated bases to give sulfide anions. Anodic elimination of bromine in 2-bromo-2,2-diphenylacetyl bromide led to the formation of oxathiolane 127 in 21% yield (Scheme 54) <1996T1259>, along with 2,2-diphenylacetic acid bromide 128.



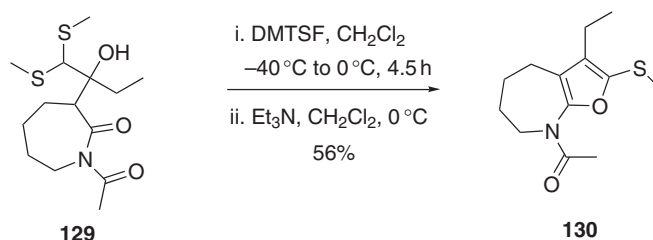
&lt;1996T1259&gt;

Scheme 54

Elimination of methyl sulfide and subsequent cyclization in  $\alpha$ -hydroxy- $\delta$ -oxo-dithioacetals led to the formation of oxathiolane systems <2002JOC1595>. An example is the synthesis of furo-azepine derivative 130 (Scheme 55). It is known that treatment of thioketals with dimethyl(methylthio)sulfonium tetrafluoroborate (DMTSF) causes the carbon-sulfur bond to become labile upon methylthiolation. *N*-Substituted azepan-2-one (lactam) 129 was treated with DMTSF in dichloromethane at low temperatures to afford the cyclic aminofuran 130 in 56% yield. An alkylthiosulfonium salt was first generated, which dissociated into a thionium ion and methyl sulfide. Further, the thionium ion underwent a DMTSF-induced cyclization followed by acetic acid elimination to furnish aminofuran 130.

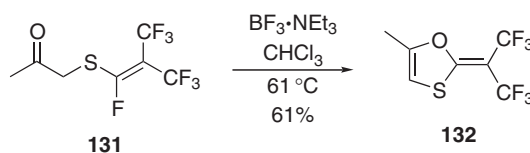
Elimination-cyclization reactions occurred in perfluoro derivatives such as 131 (Scheme 56) <2000RCB1749>. The reaction took place in the presence of  $\text{BF}_3 \cdot \text{NET}_3$  in refluxing chloroform with formation of oxathiole 132.

Sulfonyl chloride 133 was reacted with benzo[1,3]dioxol-5-ol 134 in chloroform, and benzo-xathiole 135 was formed in 85% yield by hydrochloric acid elimination (Scheme 57) <2001RCB1255>.



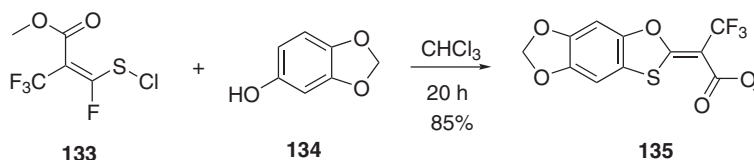
&lt;2002JOC1595&gt;

Scheme 55



&lt;2000RCB1749&gt;

Scheme 56

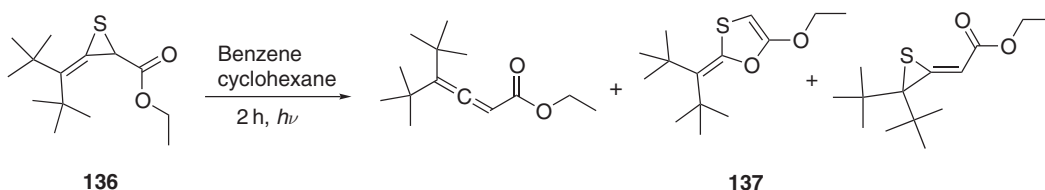


&lt;2001RCB1255&gt;

Scheme 57

#### 4.19.3.1.4 By miscellaneous methods

Thiirane-2-carboxylic ester **136** underwent decomposition by irradiation in benzene/cyclohexane to afford oxathiole **137** among other products (Scheme 58) <1996LA1295>.

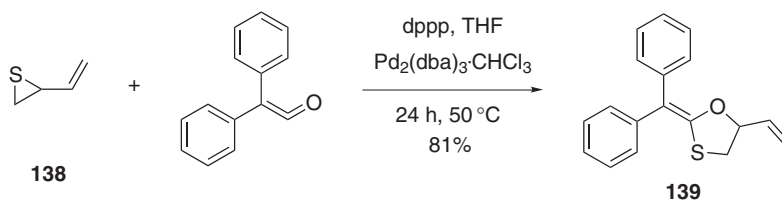


&lt;1996LA1295&gt;

Scheme 58

Vinyl thiirane **138** reacted with heterocumulenes to produce oxathiolanes, dithiolanes, and thiazolidines regio- and enantioselectively by a palladium-catalyzed cyclization reaction performed in THF at 5 psi and 50 °C <2001JOC3502>. When the reaction was performed with ketenes as reactants, oxathiolanes were preferentially obtained. The reaction of vinyl thiirane **138** with diphenyl ketene produced oxythiolane **139** regioselectively, probably because of steric factors (Scheme 59).

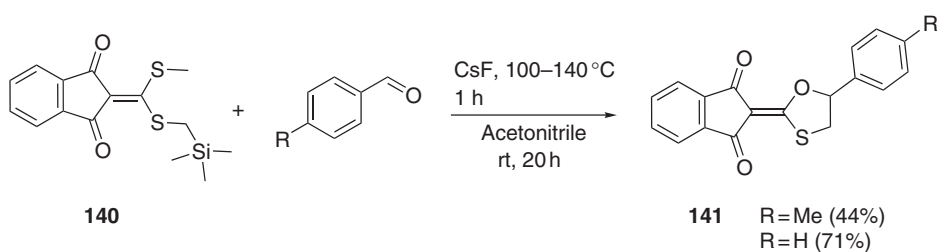
Trimethylsilylmethylthio-1,3-indanthione **140** is a precursor of an alkylidene-thiocarbonyl-ylide that could be generated *in situ* by its treatment with fluorides (CsF, LiF, AgF, or TBAF). The ylide thus formed is a 1,3-dipolar reagent that could react with reactive hetero-dipolarophiles such



&lt;2001JOC3502&gt;

Scheme 59

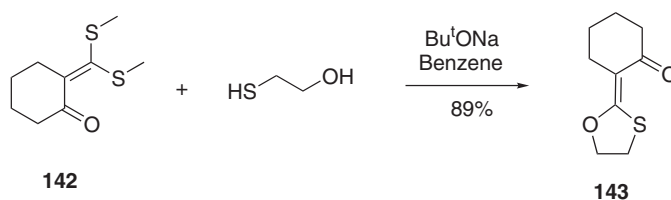
as aldehydes and ketones <1996CPB653>. The reaction showed complete regioselectivity when heterodipolarophiles are aromatic aldehydes. By reacting **140** with tolualdehyde the ketene *O,S*-diacetal **141** was obtained in 44% yield (Scheme 60), while the reaction with benzaldehyde occurred in 71% yield.



&lt;1996CPB653&gt;

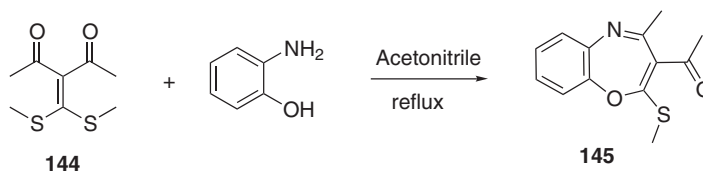
Scheme 60

Ketene dithioacetals were reacted with alcohols and phenols to give oxathiolanes. Compound **142** produced *O,S*-diacetal **143** (Scheme 61) <2000IJC(B)147>, while compound **144** afforded oxepine derivative **145** (Scheme 62) <1996SC4289>.



&lt;2000IJC(B)147&gt;

Scheme 61

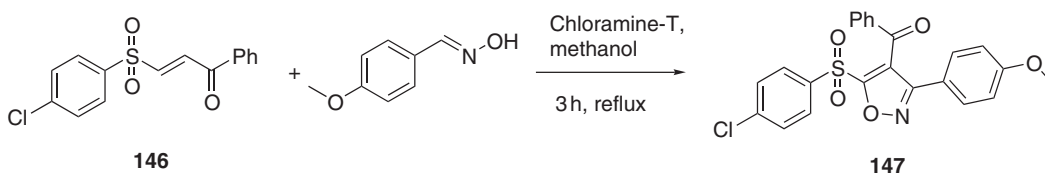


&lt;1996SC4289&gt;

Scheme 62

#### 4.19.3.2 Tricoordinated Sulfur Derivatives, $R_2C=COR^2S(O)R^3$

There is only one report on this class of compounds in the period reviewed <1999JCR(S)610>. A series of compounds of this type were prepared by reacting sulfonyl propenones of the type **146** with aryl hydrazones and aldoximes in refluxing methanol, in the presence of chloramine-T (Scheme 63). When aldoximes were the reagents, 2-isoxazolines of the type **147** were obtained. The reaction is a 1,3-dipolar cycloaddition where the aldoxime acts as a bifunctional olefin.



<1999JCR(S)610>

Scheme 63

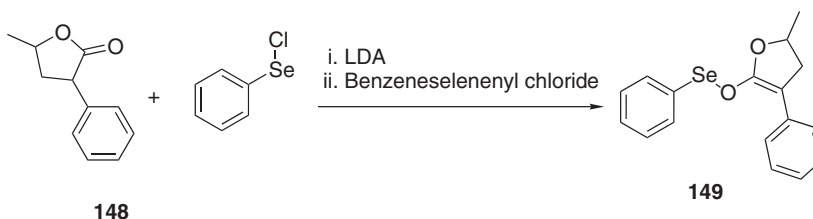
#### 4.19.3.3 Tetracoordinated Sulfur Derivatives, $R_2C=COR^2SO_2R^3$

A Beilstein search for the period 1996 to August 2003 did not reveal any entry in this class.

#### 4.19.4 FUNCTIONS CONTAINING OXYGEN AND EITHER SELENIUM OR TELLURIUM, $R_2C=COR^2SeR^3$ , etc.

One entry was revealed in a Beilstein substructure search.

Benzeneselenenyl chloride reacted with enolized dihydrofuran-2-one **148** and the condensation product thus obtained was derivative **149** (Scheme 64) <2000BMCL1893>.



<2000BMCL1893>

Scheme 64

#### 4.19.5 FUNCTIONS CONTAINING TWO SULFUR ATOMS, $R_2C=C(SR^2)_2$ , etc.

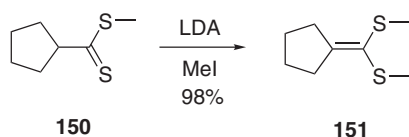
##### 4.19.5.1 Two Dicoordinated Sulfur Atoms, $R_2C=C(SR^2)_2$

###### 4.19.5.1.1 From dithiocarboxylic acids and derivatives

Ketene dithioacetals are usually generated from a dithiocarboxylic acid or ester by  $\alpha$ -deprotonation of the corresponding anion and subsequent addition of an electrophile. The method is similar to the one described in Section 4.19.2.1.1 for ketene diacetals. A typical example is presented in Scheme 65 for the reaction of cyclopentanedithio-carboxylate **150** and iodomethane to produce dithioacetal **151** <1997CC1011>.

Deprotonation could be performed with strong bases such as LDA, LiHMDS, or sodium ethoxide in ethanol. When the dithiocarboxylate is activated by the presence of an  $\alpha$ -oxo group, the deprotonation was performed with potassium carbonate in DMF <2002SC2369>.

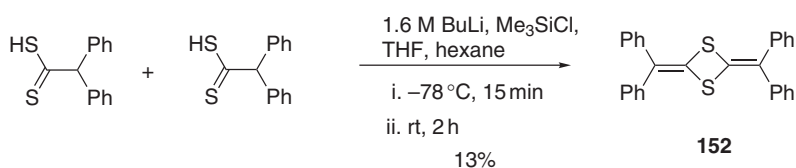




&lt;1997CC1011&gt;

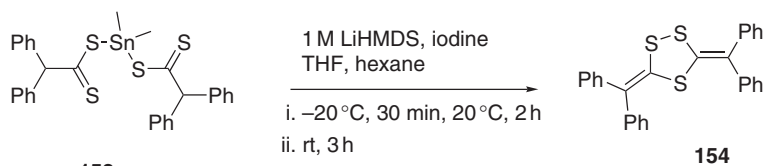
Scheme 65

Compound **152** was prepared in low yield (13%) by disproportionation of diphenylmethyldithio-carboxylic acid. The deprotonation was performed with  $\text{Bu}^n\text{Li}$  in THF at  $-78^\circ\text{C}$ , and was followed by treatment with trimethylchlorosilane at  $20^\circ\text{C}$  (Scheme 66) <1996CB663>. Similarly, by deprotonation of dimethyltin derivative **153** with LiHMDS in THF/hexane at  $-20^\circ\text{C}$  followed by treatment with iodine at room temperature, derivative **154** was obtained (Scheme 67) <1996CB663>.



&lt;1996CB663&gt;

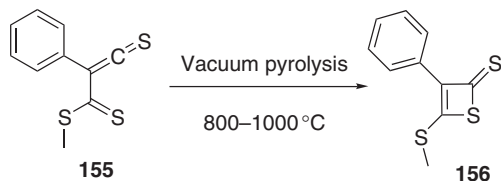
Scheme 66



&lt;1996CB663&gt;

Scheme 67

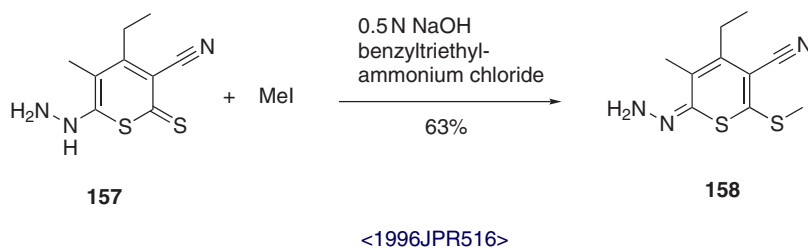
Thioacyl thioketene **155**, subjected to flash vacuum pyrolysis, produced thioacyl thioketene **156** by a 1,3-shift of the phenyl group onto the alkylthio group with a subsequent loss of an *S*-alkyl thiophenol (Scheme 68) <1996TL4805>.



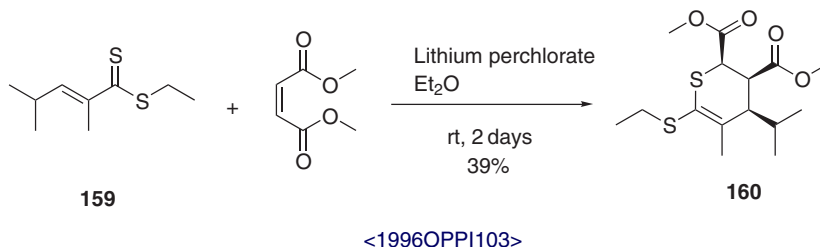
&lt;1996TL4805&gt;

Scheme 68

Cyclic dithiocarboxylic ester **157** was converted with a 63% yield into the corresponding ketene dithioacetal **158** by reaction with 0.5 N sodium hydroxide in the presence of benzyltriethylammonium chloride, followed by treatment with iodomethane (Scheme 69) <1996JPR516>.  $\alpha,\beta$ -Unsaturated dithiocarboxylic ester **159** reacted with maleic acid dimethyl ester in the presence of lithium perchlorate in diethyl ether at room temperature in two days to produce ketene dithioacetal **160** in 39% yield (Scheme 70) <1996OPPI103>.



Scheme 69

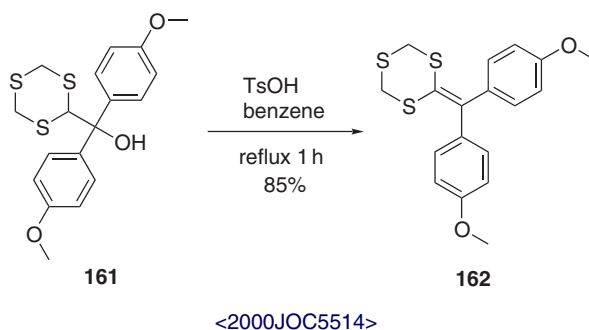


Scheme 70

#### 4.19.5.1.2 By double bond formation via elimination

This section comprises preparations of ketene dithioacetals from compounds containing hydroxyl and halogen groups that allow for the elimination of water and hydrogen halide, respectively.

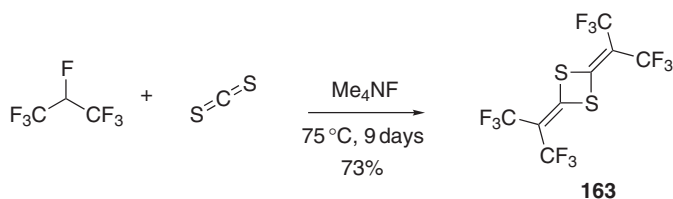
In the case of alcohols, the leaving group is on the thioacetal carbon. Bis(diarylmethylene)-alcohol **161** was converted into thioacetal **162** through TsOH-catalyzed dehydration in 85% yield (Scheme 71) <2000JOC5514>. Elimination of hydrogen halide occurred at the  $\alpha$ -carbon to the dithioacetal carbon. Hydrogen fluoride was eliminated in the reaction of carbon disulfide and tetramethylammonium fluoride with 2-*H*-heptafluoropropane (Scheme 72) <1997JFC(82)29>, and was trapped as fluorodithioformate  $\text{FCS}_2^-$ , which was added to 2-*H*-heptafluoropropane with subsequent dimerization of the addition intermediate. The reaction product thus obtained was bis-dithioacetal **163**.



Scheme 71

#### 4.19.5.1.3 By alkeneation methods

This section refers to the condensation of a carbonyl compound or its equivalent with a dithioacetal anion in particular. Wittig, Horner–Wittig, Horner–Emmons, and Peterson-type reactants are widely used. In this chapter the reaction of carbon disulfide with active methylene compounds was also included.

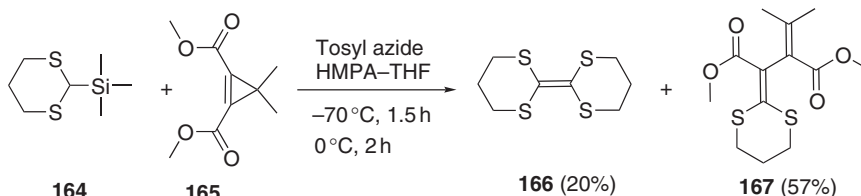


&lt;1997JFC(82)29&gt;

Scheme 72

*(i) Peterson alkeneation*

In the 1990s, the Peterson alkeneation was widely used in the synthesis of ketene dithioacetals <2001JMC4379, 2001NN995, 1998JMC821>. 2-(Trimethylsilyl)-1,3-dithiane **164** is a precursor of dithiane carbene, which was produced by treating lithio- **164** with tosylhydrazide in HMPA–THF solution at  $-70^\circ\text{C}$ . The carbene thus formed was reacted with 3,3-dimethylcyclopropene dicarboxylate derivative **165** at  $-70$  to  $0^\circ\text{C}$  to produce dithianylidene **166** (20% yield) and the dithioacetal adduct of succinic acid derivative **167** (57% yield) (Scheme 73) <1997T9269>.

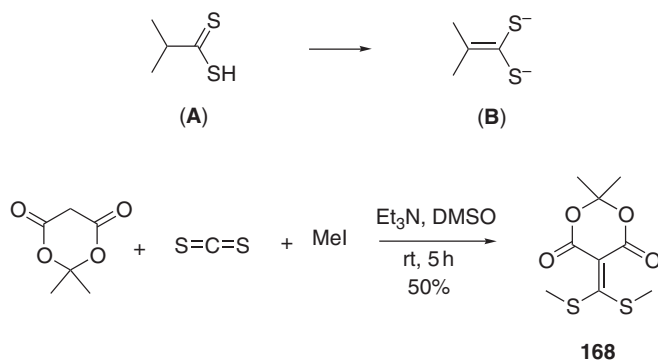


&lt;1997T9269&gt;

Scheme 73

*(ii) The reaction of carbon disulfide with active methylene compounds*

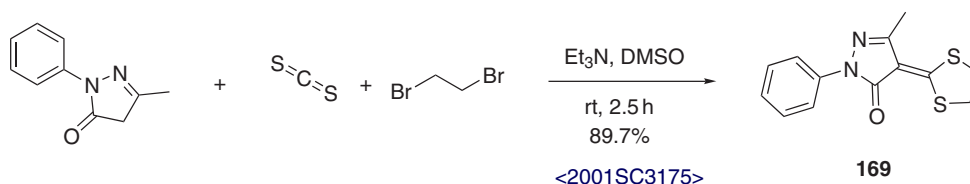
The reaction of active methylene compounds with carbon disulfide and alkyl halides in basic conditions was earlier treated under Section 4.19.5.1.1 as it was considered to involve a dithio-carboxylic acid. Classifying the reaction under an alkeneation reaction would be more suitable, because the alkanedithioic acid **A** (Scheme 74) formed by addition of carbon disulfide to the active methylene group is readily deprotonated by the base to form the corresponding dianion **B**, which could be isolated as a salt <1996CB663>.



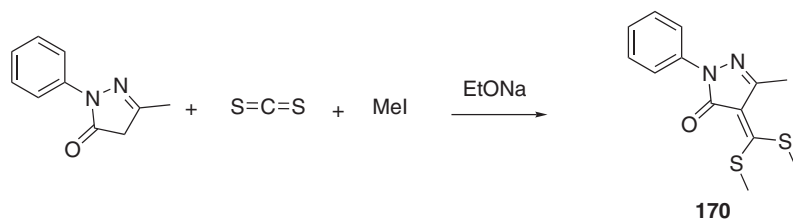
&lt;2001JCS(P2)1534&gt;

Scheme 74

The current reports are focused on replacing strong bases as methanolic potassium hydroxide or alkyllithium derivatives used in earlier reports <1996ZN(B)399, 1996LA953, 1996JST177, 1997S949, 1999MI57> with milder reagents. Among the new methods, the reaction of Meldrum's acid with carbon disulfide and triethylamine followed by alkylation of the thus formed dianion with iodomethane in DMSO produced derivative **168** in 50% yield (Scheme 74) <2001JCS(P2)1534>. 2-Pyrazolin-5-one derivatives were reacted with carbon disulfide and dihalides in a one-pot procedure using triethylamine and DMSO (Scheme 75) <2001SC3175>. The reaction was completed in a shorter time and with improved yields (89.7% for compound **169**) compared to earlier methods. Similar results were obtained in a one-pot procedure when using sodium ethoxide in ethanol (Scheme 76) <1998JCR(S)162>. 2-Pyrazolin-5-ones could also be treated with carbon disulfide and various alkyl bromides or their acetals under phase-transfer catalysis conditions to produce the corresponding ketene dithioacetals **170**. Deprotonation was achieved in a liquid/solid phase combination of benzene and anhydrous potassium carbonate and tetrabutylammonium bromide as a catalyst <1997H451>. 4,4-Dibromo-1-phenyl-pyrazolidine-3,5-dione **171** and malononitrile were reacted in similar one-pot conditions using potassium carbonate, tetrabutylammonium bromide as a catalyst, and dioxane as a solvent to produce dithioacetal **172** (Scheme 77) <2000PS(160)159>.

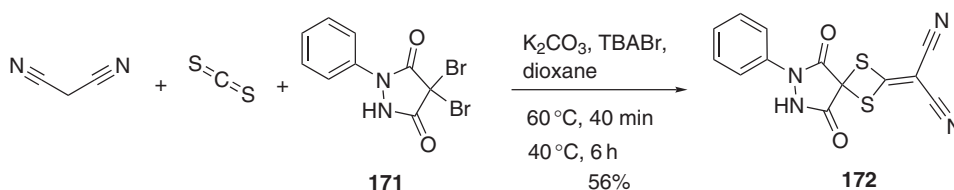


Scheme 75



&lt;1998JCR(S)162&gt;

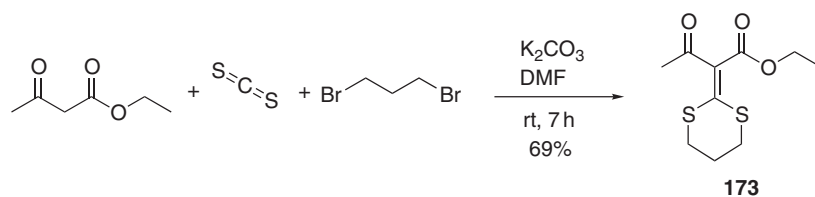
Scheme 76



&lt;2000PS(160)159&gt;

Scheme 77

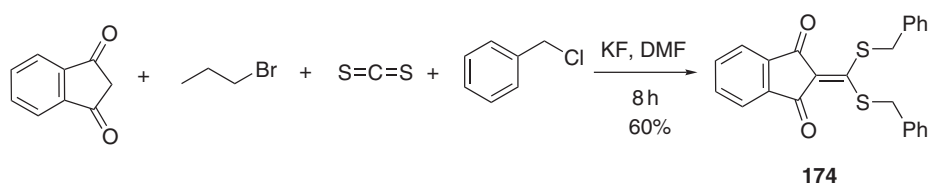
Ketene dithioacetals resulting from acetylacetic acid esters and analogs are important building blocks for heterocyclic synthesis and therefore their preparation was intensively studied. Comparative preparations are reported for ketene dithioacetals **173** of ethyl acetylacacetate <1997T17151>. The reaction presented in Scheme 78 was performed by two methods: (a) in the presence of potassium carbonate in DMF at room temperature, and (b) by absorption of the components on a mixture of alumina and potassium fluoride at room temperature. Method (a) showed higher yields than method (b). Later, it has been shown that potassium fluoride alone, without activation or solid support, could be used to promote these reactions at room



&lt;1997T17151&gt;

Scheme 78

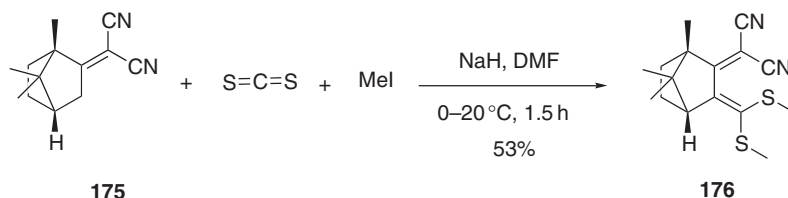
temperature <1999JCR(S)492>. Among the solvents studied, DMF was found to be the solvent of choice in terms of higher conversions after 2 h and better isolated yields, while dioxane, THF, and acetonitrile showed poor conversions even after prolonged contact of the reagents (20 h). Yields were also dependent on the nature of the alkyl halide. As an example, 1,3-indanedione reacted with carbon disulfide and benzyl chloride as shown in Scheme 79 to afford derivative **174** in 60% yield, while when using butyl bromide the reaction product was formed in 79% yield <1999JCR(S)492>.



&lt;1999JCR(S)492&gt;

Scheme 79

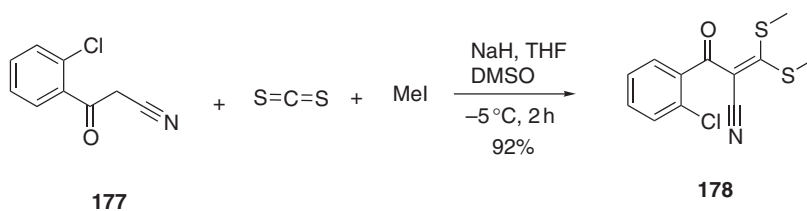
Sodium hydride in DMF was used for the weakly activated malononitrile compound **175** <1999JPR552>. The adduct **176** was obtained in 53% yield (Scheme 80). Similarly, 3-(2-chlorophenyl-3-oxo)-propionitrile **177** was treated with iodomethane and carbon disulfide in the presence of sodium hydride in a mixture of THF and DMSO, to produce bis-methylsulfanyl-acrylonitrile **178** in 92% yield (Scheme 81) <1996F407>. Other weakly activated methylene compounds required stronger reaction conditions. 2-Cyano-thioacetamide (Scheme 82) <1997JCS(P1)3285> and ethyl cyanoacetate (Scheme 83) <1997BMCL651, 1997JCS(P1)3285, 2002SC3509> were reacted with alkyl halides and carbon disulfide using sodium ethoxide as a base to produce compounds **179** and **180**, respectively. Carboxylic acid esters were treated with LDA at  $-78^{\circ}\text{C}$  to generate their lithium enolates in order to react with carbon disulfide to further produce derivative **181** (Scheme 84) <1997JMC2363>, while 2,5-dioxo-*cis*-octahydropentalene **182** required potassium *t*-butoxide in DMSO or DMF at  $0^{\circ}\text{C}$  to produce compound **183** (Scheme 85) <1996PS(113)263>.



&lt;1999JPR552&gt;

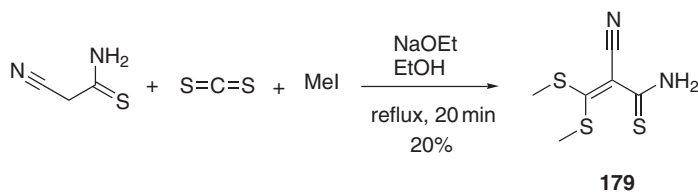
Scheme 80

Dimethyl sulfate has been used as an alkylating agent instead of alkyl halides. The reactions were performed at room temperature in the presence of sodium hydride in acetonitrile and compounds such as **184** were produced with yields in the range of 70–80% (Scheme 86) <1999PS(148)235>.



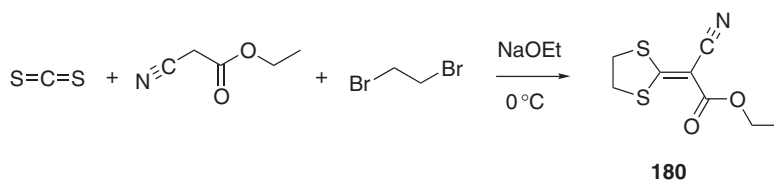
&lt;1996F407&gt;

Scheme 81



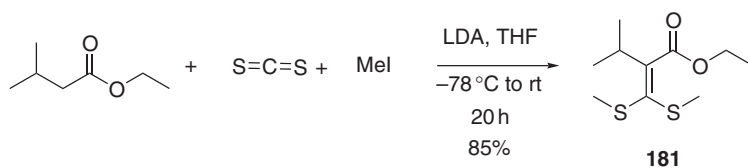
&lt;1997JCS(P1)3285&gt;

Scheme 82



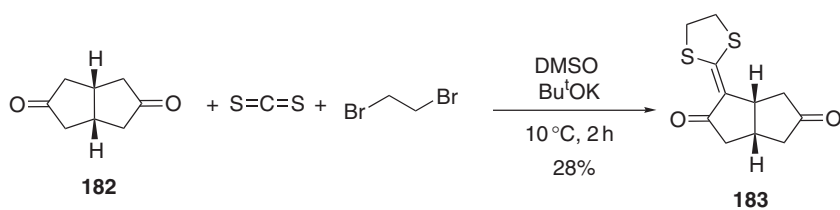
&lt;1997BMCL651&gt;

Scheme 83



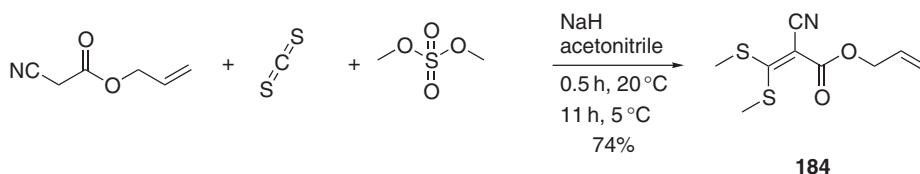
&lt;1997JMC2363&gt;

Scheme 84



&lt;1996PS(113)263&gt;

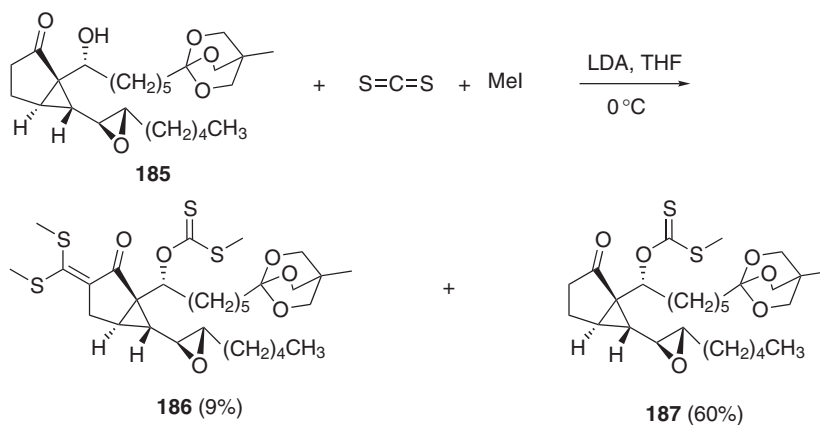
Scheme 85



&lt;1999PS(148)235&gt;

Scheme 86

Competitive C- versus O-alkylation has been reported in a few instances <1996TL809, 1997H451>. Bicyclo[3.1.0]-hexan-2-one **185** gave ketene dithioacetal **186** in only 9% yield, while the major product is the xanthate **187** obtained in 60% yield (Scheme 87) <1996TL809>.

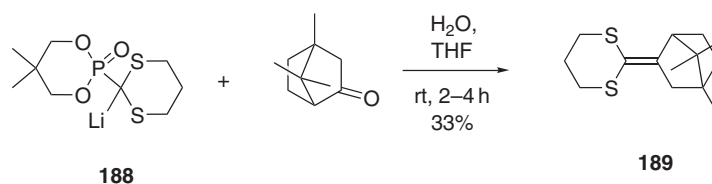


&lt;1996TL809&gt;

Scheme 87

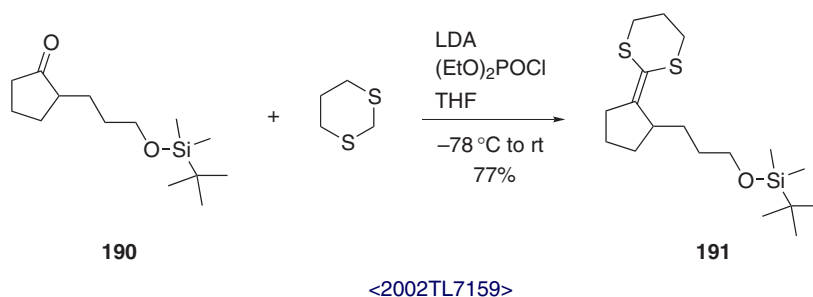
### (iii) Horner–Emmons and Wittig–Horner reactions

There are limited examples of the use of the Horner–Emmons–Wadsworth procedure in the synthesis of ketene dithioacetals <1996S285, 1998JCS(P1)9, 2002TL7159>. Dithianylphosphonates could be readily prepared by condensation of the carbanion obtained from 1,3-dithiane and dialkyl chlorophosphate. Recently, several thioacetals of formylphosphonates **188** were studied and compared, and a one-pot procedure for the preparation of ketene dithioacetals was described <1997BSF891>. Yields were dependent on the nature of the carbonyl compound, being in the range of 90% for products derived from cyclohexanones and cyclooctanone, and 33% for derivative **189** obtained from the more sterically hindered bornan-3-one (Scheme 88). In a typical procedure, a substrate such as ketone **190** was treated with LDA in THF at a low temperature, and the enolate thus formed was treated with 1,3-dithiane and diethyl chlorophosphate to afford derivative **191** in 77% yield (Scheme 89) <2002TL7159>.



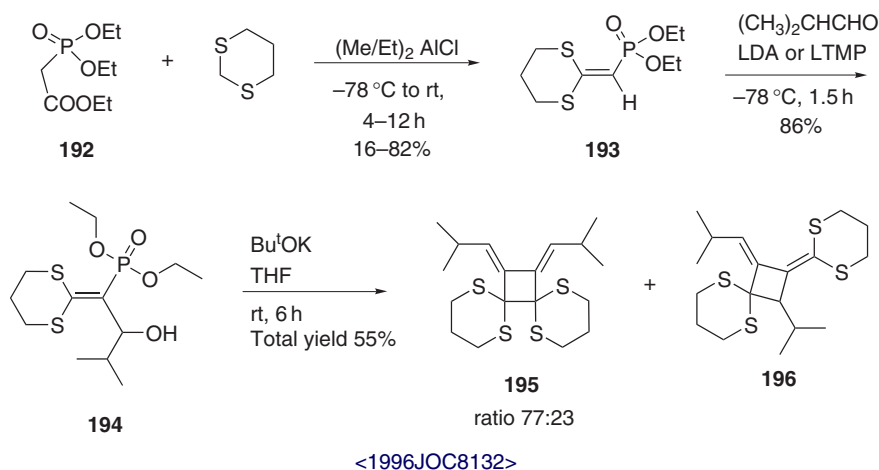
&lt;1997BSF891&gt;

Scheme 88



Scheme 89

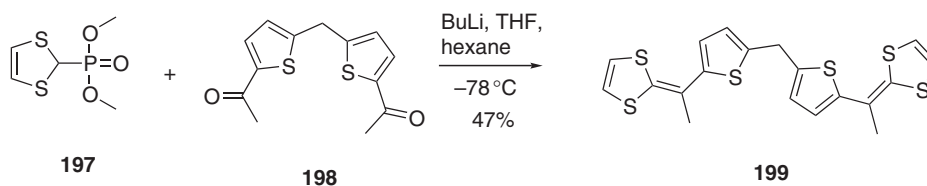
Phosphonoketene dithioacetals such as **193** (Scheme 90) are useful reagents in the synthesis of thioallenes by the Horner–Emmons–Wittig synthesis. As they have no substituent at the  $\alpha$ -position to phosphorus, there are many possibilities for functionalization at this position and the compounds could be widely used in organic syntheses. As an example, compound **193** was prepared by reacting dithiane with triethyl phosphonoacetate **192** in dichloromethane in the presence of dialkylaluminum chloride or ethylaluminum dichloride as catalyst. The former was preferred due to better yields and simplicity of manipulation <1996JOC8132>. The compound was further functionalized by deprotonation with 2,2,6,6-tetramethylpiperidide in THF at  $-78^\circ\text{C}$  followed by treatment with an aldehyde to produce allylic alcohol thioacetal adducts **194**. Treatment of compounds such as **194** with potassium *t*-butoxide in THF at room temperature afforded a mixture of both head-to-head **195** and head-to-tail **196** dimers in a ratio of 77:23 (**195/196**). *t*-Butyl substitution instead of isopropyl  $\alpha$  to the alcohol changed the ratio of the dimers in favor of the head-to-tail dithioacetal derivative.



Scheme 90

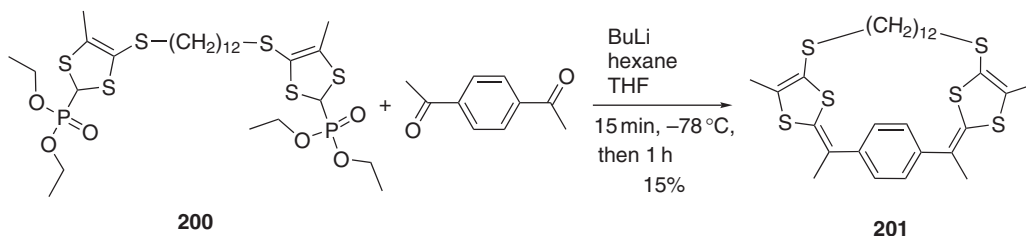
Esters of dithiophosphoric acid are Wittig and Wittig–Horner reagents commonly used in the synthesis of ketene dithioacetals, and preparations are described in several publications <1998JOC1268, 1999TL5997, 2000EJO51, 2001EJO933>. In general, deprotonation of these reagents occur at low temperatures and in the presence of strong bases, especially alkylolithium derivatives. In a typical example (Scheme 91) <1997H263> the dithiophosphoric ester **197** was treated with  $\text{Bu}^n\text{Li}$  at  $-78^\circ\text{C}$  to produce the dithiolylphosphonate anion that underwent further addition to the ketone **198** in moderate-to-high yields to give compound **199**. Cyclophanes **201** obtained by similar olefination using bis-dithiophosphonic ester **200** are interesting for their redox behavior upon oxidation (Scheme 92) <2000JCS(P1)2719>. The Wittig–Horner reaction of ketones with 2-methoxyphosphinyl-1,3-benzodithiole **202** (Schemes 93 <1997CC2325> and 94 <2000CC295, 2001JOC713, 2002M1055>) produced compounds (**203** and **204**) with interesting redox properties. This chemistry is used intensively in the synthesis of sulfur-rich analogs of tetrathiafulvalene derivatives like **204** that have interesting electronic properties including paramagnetic and semiconducting electrical behavior <1996JOC3650, 1997JOC870, 1998JOC1268, 1999TL3271, 1999TL5997, 2000EJO51, 2000EJO1199, 2001EJO933, 2002JACS14227>.





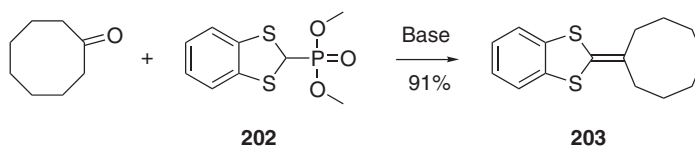
&lt;1997H263&gt;

Scheme 91



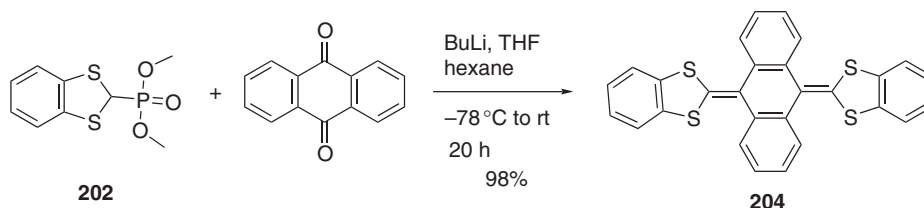
&lt;2000JCS(P1)2719&gt;

Scheme 92



&lt;1997CC2325&gt;

Scheme 93



&lt;2002M1055&gt;

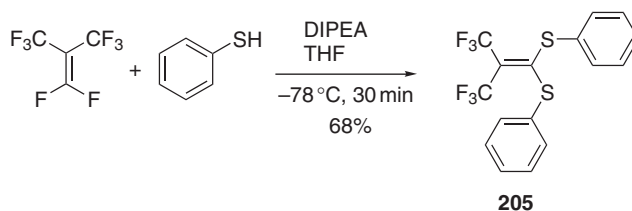
Scheme 94

#### 4.19.5.1.4 From gem-dihalogeno alkenes and analogs

Vinyl halide displacement was reported for the preparation of ketene dithioacetal derivatives of perfluoroisobutene and its 1,1-dichloro analog (Scheme 95) <1999JFC(94)37>. The reaction was performed in THF at  $-78^{\circ}\text{C}$  by mixing excess dihaloalkene with equimolar amounts of aromatic thiol and diethylisopropylamine, affording perfluorinated ketene dithioacetals **205**. Substitution with electron-withdrawing groups in aromatic thiols increased the yields, but 2-aminobenzenethiol gave only a benzothiazole derivative.

#### 4.19.5.1.5 By miscellaneous methods

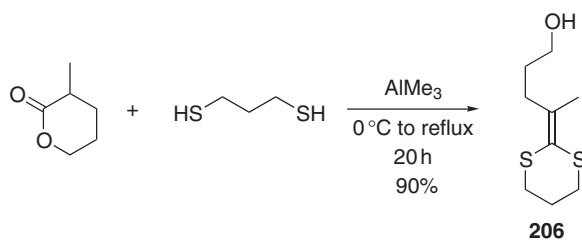
The examples of this section are of more theoretical than preparative interest, and have been reported in connection mainly with mechanistic studies. Ketene dithioacetals of type **206** were



&lt;1999JFC(94)37&gt;

Scheme 95

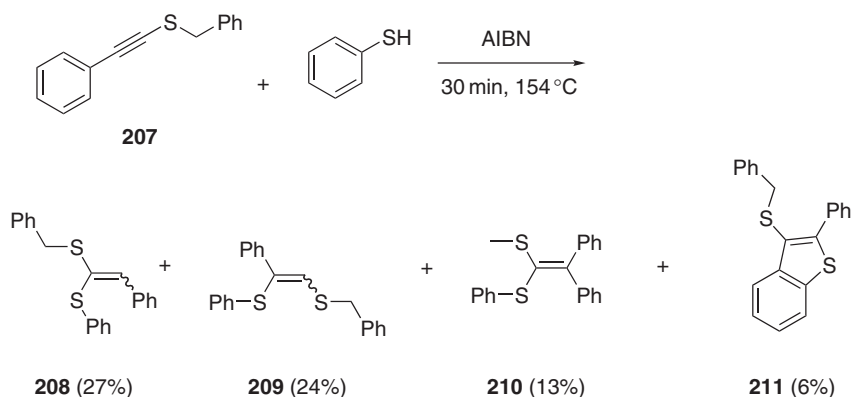
obtained in good yields by reacting lactones with 1,3-dithiols in the presence of trimethylaluminum in dichloromethane at room temperature <2001TL7163, 2002JA10101>. The reaction of 3-methyl-tetrahydropyran-2-one with propane-1,3-dithiol occurred with ring-opening and afforded compound **206** (Scheme 96) <2002JA10101>.



&lt;2002JA10101&gt;

Scheme 96

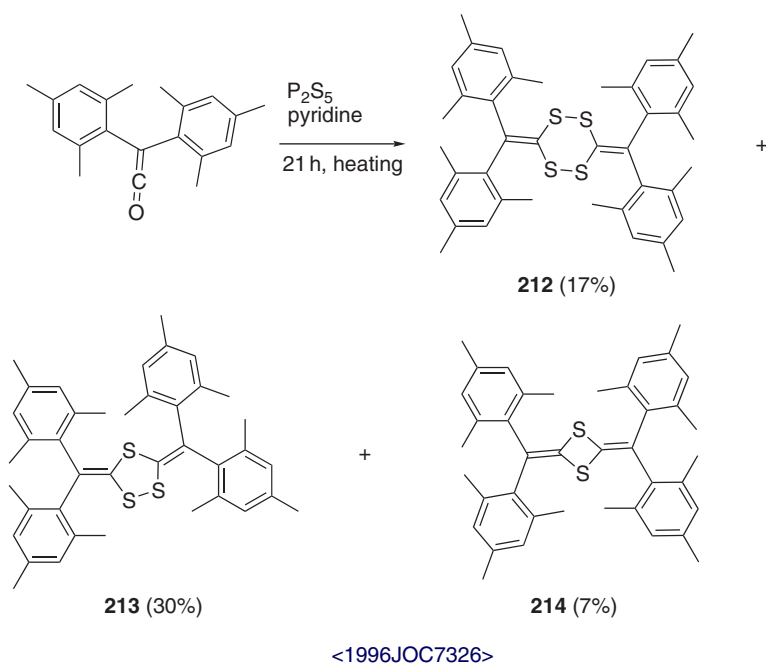
In the reaction of (benzenesulfanyl)phenylacetylene **207** with thiophenol at  $154^{\circ}\text{C}$  in the presence of AIBN, two unsymmetrical ketene dithioacetal species, **208** and **210**, were isolated along with thioderivative **209** and thiophene **211** (Scheme 97) <1999T12227>. The product distribution was considered as the evidence of a mechanism via a vinyl radical followed by hydrogen abstraction in competition with  $\beta$ -fragmentation. The higher yield in product **208** compared to **210** showed that alkanesulfanyl radical addition to the alkyne triple bond was a nonreversible process, whereas arenesulfanyl radicals added under a reversible mechanism.



&lt;1999T12227&gt;

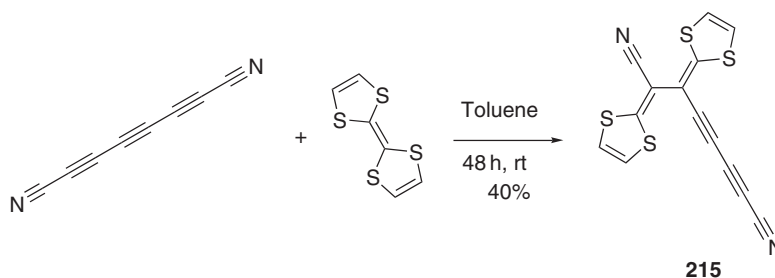
Scheme 97

Diaryl ketenes and  $\text{P}_2\text{S}_5$  in pyridine produced thioketenes as transient species only, and the isolated products were dimers or other heterocycles, such as **214** (Scheme 98) <1996JOC7326>. Compound **213** was separated only as a mixture with compound **212** in a ratio of 7:4 (**213/212**).



Scheme 98

Dicyanohexatriyne and tetrathiafulvalene underwent a [2+2]-cycloaddition with subsequent opening of the cyclobutene ring (Scheme 99) <1999EJO2491>. Initially, a 3,3,4,4-tetrathiasubstituted cyclobutene intermediate was formed by the cycloaddition of one of the terminal triple bonds with the thiafulvalene central double bond. The intermediate was stabilized by subsequent electrocyclic ring opening to generate the butadiene derivative **215**.

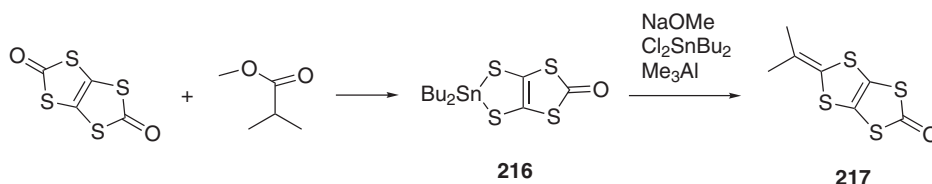


&lt;1999EJO2491&gt;

Scheme 99

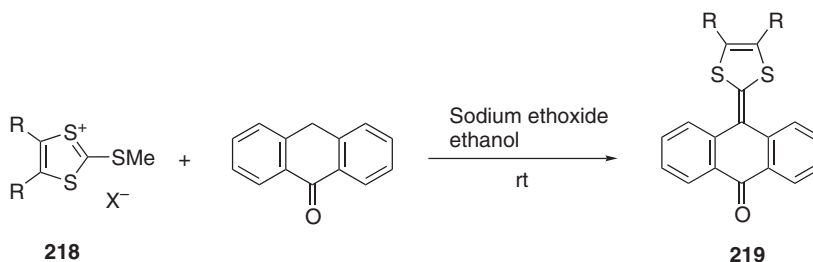
1,3,4,6-Tetrathiapentalene-2,5-diones were reacted with esters of alkyl- and cycloalkyl-carboxylic acids in a multistep preparation (Scheme 100) <1996JOC3987>. The ketone derivative was treated with a Grignard reagent and the intermediate was trapped with an organotin compound such as  $Cl_2SnBu_2$  at  $-78^\circ C$  to produce an organotin thiolate **216**. Without further purification, thiolate **216** was reacted with an ester in a  $Me_3Al$ -promoted coupling synthesis to afford product **217**. Other Lewis acids were also utilized instead of  $Me_3Al$ , and good results were obtained with  $TiCl_4$  and  $Me_2AlCl$ , while with  $BF_3 \cdot OEt_2$  only trace amounts of product **217** were obtained.

Systems of type **219** were synthesized starting from 1,3-dithiolium cation salts **218** and ketones. The trifluoroborate of salt **218** was reacted with anthrone in the presence of sodium ethoxide in ethanol at room temperature (Scheme 101) <1998CEJ2580>. For other cations such as iodine, pyridine in refluxing acetic acid was used.



&lt;1996JOC3987&gt;

Scheme 100

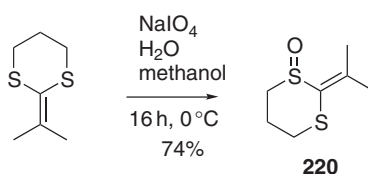


&lt;1998CEJ2580&gt;

Scheme 101

#### 4.19.5.2 One Dicoordinated and One Higher Coordinated Sulfur Derivatives, $\text{R}_2^1\text{C}=\text{SR}^2\text{S}(\text{O})_n\text{R}^3$

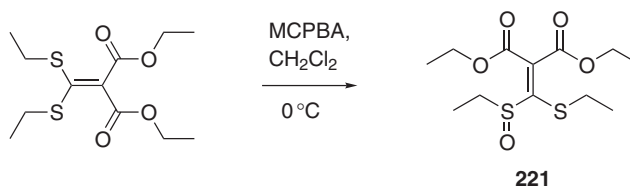
Oxidative methods are widely used for the preparation of higher coordinated sulfur derivatives. Although often mixtures of tri- and tetra-coordinated species are formed, there were reports of highly selective oxidations. For example, vinyl 1,3-dithiane (obtained by treatment of trimethylsilyl-1,3-dithiane with  $\text{Bu}^n\text{Li}$  and acetone as described earlier) underwent oxidation with sodium metaperiodate in methanol/water at  $0^\circ\text{C}$  to produce sulfoxide **220** in 70% yield as a mixture of diastereoisomers in a *syn/anti* ratio of 1:6 (Scheme 102) <1998T14581>.



&lt;1998T14581&gt;

Scheme 102

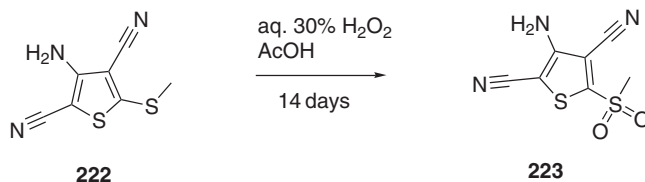
Ketene dithioacetals could also be oxidized to *S*-monoxides by treatment with 1 equiv. of MCPBA, when (*E*)-isomers were preferentially formed <1997CC1011>. The ketene dithioacetal derived from diethyl malonate was reacted with MCPBA in dichloromethane at  $0^\circ\text{C}$  to produce **221** (Scheme 103) in a high yield, but no indication about stereoselectivity was reported <1997JHC1773>.



&lt;1997JHC1773&gt;

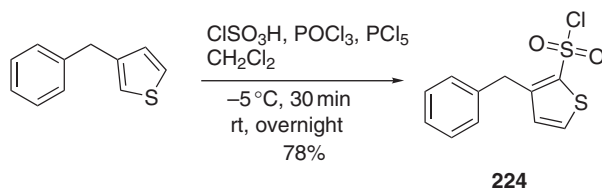
Scheme 103

Tetracoordinated sulfur derivatives are obtained with stronger oxidizing agents than the ones used for tricoordinated ones <2002JMC1176, 1996S285>. In the time frame considered in this review, almost all references with this substructure derive from  $\alpha$ -thiomethyl-substituted thiophenes. Methylsulfonyl derivative **223** was obtained by treatment of thiophene **222** with hydrogen peroxide (Scheme 104) <1999JMC1849>. Thiophenesulfonamides were obtained from thiophenes via thiophene sulfonyl chlorides <1996BMCL2651> in the following reaction sequence: bromothiophenes were treated with  $\text{Bu}^n\text{Li}$ , the anions quenched with sulfur dioxide and further oxidation of the resultant sulfinates with *N*-chlorosuccinimide produced the thiophene sulfonyl chlorides **224** (Scheme 105). Alternative chlorosulfonation using chlorosulfonic acid at low temperature was reported for 3-benzylthiophene only. Treatment of thiophene sulfonyl chlorides with amines produced thiophenesulfonamides.



&lt;1999JMC1849&gt;

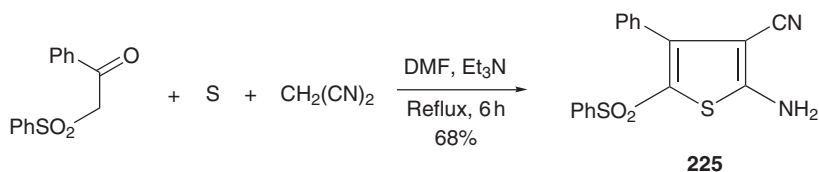
Scheme 104



&lt;1996BMCL2651&gt;

Scheme 105

Phenylsulfonyl-acetophenones reacted with a mixture of elemental sulfur and malononitrile in dry DMF containing a catalytic amount of anhydrous  $\text{Et}_3\text{N}$  to furnish the corresponding 2-amino-4-aryl-5-phenylsulfonylthiophene-3-carbonitriles **225** in good yields (Scheme 106) <1997MC687>.

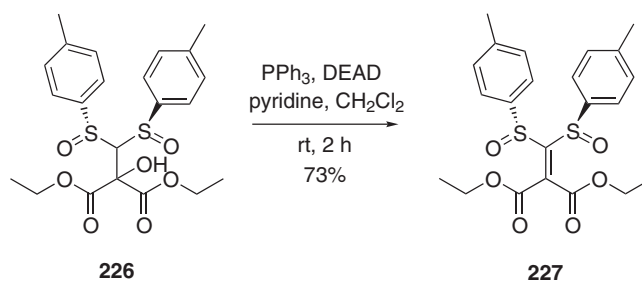


&lt;1997MC687&gt;

Scheme 106

#### 4.19.5.3 Two Tricoordinated Sulfur Atoms, $\text{R}_2\text{C}=\text{C}[\text{S}(\text{O})\text{R}^2]_2$

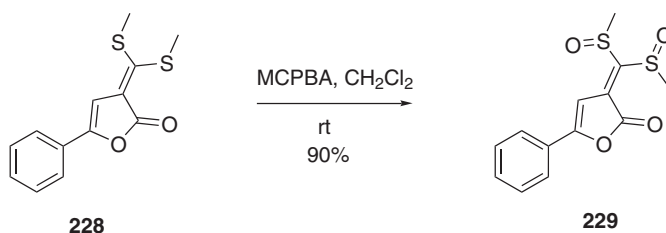
A series of *p*-tolylsulfinyl dienophiles were synthesized and their behavior in Diels–Alder reactions was studied <1997TA409>. Enantiomerically pure dienophile **227** was prepared in two steps from (*S,S*)-bis-*p*-tolylsulfinylmethane **226** with a 73% overall yield by deprotonation of **226** with  $\text{Bu}^n\text{Li}$  in THF and reaction with diethyl oxomalonate at  $-78^\circ\text{C}$ , followed by dehydration of the addition product at room temperature under Mitsunobu conditions (DEAD,  $\text{PPh}_3$  in pyridine/dichloromethane) (Scheme 107).



&lt;1997TA409&gt;

Scheme 107

Oxidation of furan-2-one **228** performed with MCPBA at room temperature in dichloromethane provided the bis-methylsulfinyl derivative **229** in 90% yield (Scheme 108) <2000IJC(B)897>.



&lt;2000IJC(B)897&gt;

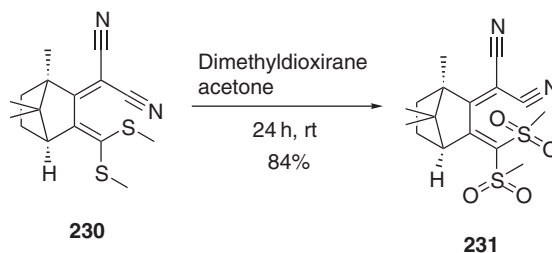
Scheme 108

#### 4.19.5.4 One Tricoordinated and One Tetraordinated Sulfur, $\text{R}_2\text{C}=\text{CS}(\text{O})\text{R}^2\text{S}(\text{O})_2\text{R}^3$

A Beilstein search did not reveal any examples reported in the literature in the period discussed here.

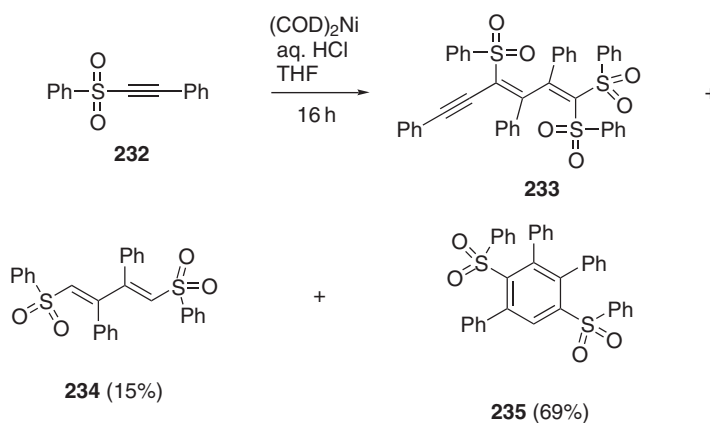
#### 4.19.5.5 Two Tetraordinated Sulfur Atoms, $\text{R}_2\text{C}=\text{C}[\text{S}(\text{O})_2\text{R}^2]_2$

Ketene dithioacetal **230** reacted with dimethyldioxirane in acetone at room temperature to yield 84% of methylsulfonyl derivative **231** (Scheme 109) <1999JPR552>. Trimerization of phenyl phenylethynyl sulfone **232** in the presence of  $(\text{COD})_2\text{Ni}$  is an example of a Diels–Alder reaction with an inverse electron demand. Because of the slowness of the cyclotrimerization step, a nucleophilic dienophile **234** was formed that had time to interact with the nickel adduct of **233** to ultimately produce **235** as the major product (Scheme 110) <1998T1169>. Compound **233** was generated by a 1,4-addition to the conjugated double bond system of Ni–diene **234** followed by reductive elimination of  $\text{Ni}(0)$ .



&lt;1999JPR552&gt;

Scheme 109



&lt;1998T1169&gt;

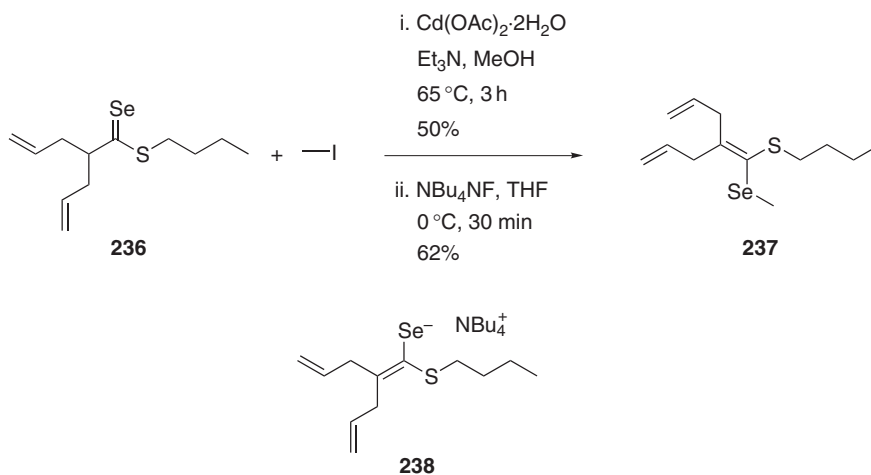
Scheme 110

#### 4.19.6 FUNCTIONS CONTAINING SULFUR AND EITHER SELENIUM OR TELLURIUM, $\text{R}_2\text{C}=\text{CSR}^2\text{SeR}^3$ , etc.

##### 4.19.6.1 Dicoordinated Sulfur Derivatives

##### 4.19.6.1.1 Selenium derivatives

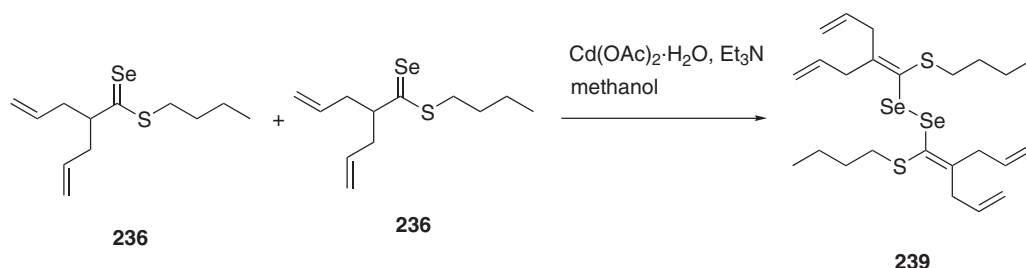
Selenothioic acid *S*-alkyl esters were treated with triethylamine and  $\text{Cd}(\text{OAc})_2 \cdot 2\text{H}_2\text{O}$  in methanol in the presence of alkyl, allyl, and benzyl halides to afford ketene selenothioacetals in moderate yields <1996CL877>. An example is shown in Scheme 111, where selenothioic acid ester **236** was reacted with methyl iodide to afford selenothioacetal **237** in 50% yield. The reactivity of ester **236** toward Zn and Cd is different. When the reaction was performed in the presence of  $\text{Zn}(\text{OAc})_2 \cdot 2\text{H}_2\text{O}$ , the starting ester **236** was recovered in 39% yield along with 18% of compound **237** (Scheme 111). The results were explained by the high affinity of selenocarbonyl compounds toward cadmium salts than other Lewis acids with higher affinity to carbonyl compounds <1996CL877>. In the absence of alkyl halide, only substituted diselenide **239** was obtained (Scheme 112).



&lt;1996CL877&gt;

&lt;2000CL368&gt;

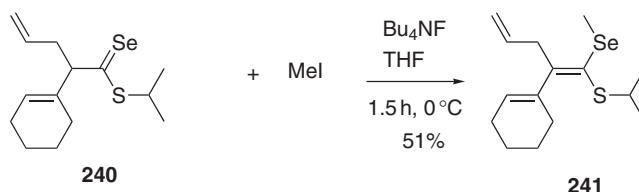
Scheme 111



&lt;1996CL877&gt;

Scheme 112

An alternative method to ketene selenothioacetals was reported later by the same authors <2000CL368>. Ammonium eneselenolates generated ketene selenothioacetals in high yields when reacted with alkyl halides. Selenothioic acid *S*-ester **236** was reacted with tetra-*n*-butylammonium fluoride in THF at room temperature in the presence of methyl iodide. Intermediate selenolate **238** reacted with methyl iodide to produce ketene selenothioacetal **237** in higher yield (Scheme 111). The deprotonation with ammonium fluoride was applied to  $\alpha$ -monosubstituted and unsymmetrically substituted selenothioic acid esters, when both (*E*)- and (*Z*)-isomers were obtained. The lack of stereoselectivity is explained by the fast reaction rates for both the deprotonation and the addition of electrophile. When the alkyl halide was added 30 min after the mixing of selenothioic acid *S*-ester with tetra-*n*-butylammonium fluoride, (*Z*)-isomers were obtained predominantly ((*E*):(*Z*) of 1:6 to 1:19). Similar reactions were described in more recent reports (Scheme 113) <2001JOC8101> showing that exclusive formation of the (*Z*)-isomers depended upon thermodynamic characteristics of the intermediate ammonium selenolates, which were kinetically generated as stereoisomeric mixtures. Only (*Z*)-isomers were obtained when the reaction time to generate selenolates was extended to 1.5–2 h, leaving time for the (*E*) species to convert to the (*Z*)-isomers. Further treatment with alkyl halide provided exclusively the (*Z*)-ketene selenothioacetal **241**.



&lt;2001JOC8101&gt;

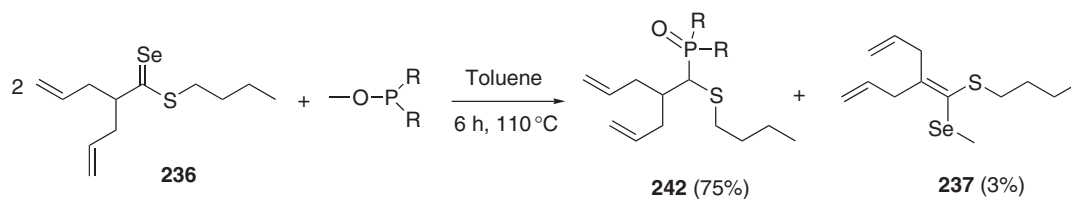
Scheme 113

The reaction of selenothioic acid esters with trialkyl phosphites in toluene at  $85^\circ\text{C}$  was carried out for 10 min and generated ketene acetals along with  $\alpha$ -phosphoryl sulfides <1999CL105>. The product distribution was reported to be strongly dependent on the nature of the ester. For derivative **236** the reaction with trimethyl phosphite generated predominantly  $\alpha$ -phosphoryl sulfide **242** and only small amounts of selenoacetal **237**, while for selenothioacetic acid *S*-butyl ester and triethyl phosphite the products were formed in equimolar amounts (Scheme 114).

Other trivalent phosphorus compounds were used and the product distribution was discussed <2000JCS(P1)917>. It was shown that dimethyl phenylphosphonite and mainly methyl diphenylphosphinite produced the ketene selenoacetals in higher yields, as shown in Scheme 115.

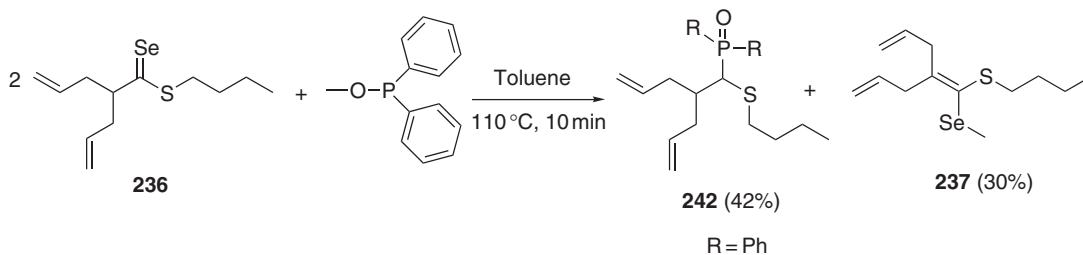
Ketene dithioacetals reacted with activated methylene compounds and freshly prepared sodium selenide to produce selenophenes in moderate-to-good yields <2003SL855>. First, the ketene dithioacetal was heated with freshly prepared sodium selenide at  $50^\circ\text{C}$  in DMF, and then chloroacetyl chloride was added followed by potassium carbonate to produce compound **243** in 32% yield (Scheme 116).





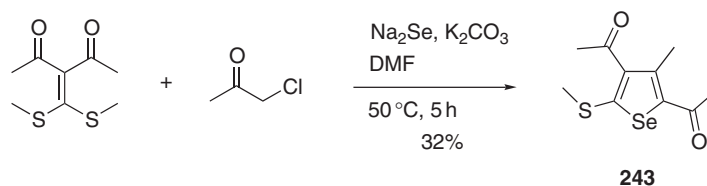
&lt;1999CL105&gt;

Scheme 114



&lt;2000JCS(P1)917&gt;

Scheme 115

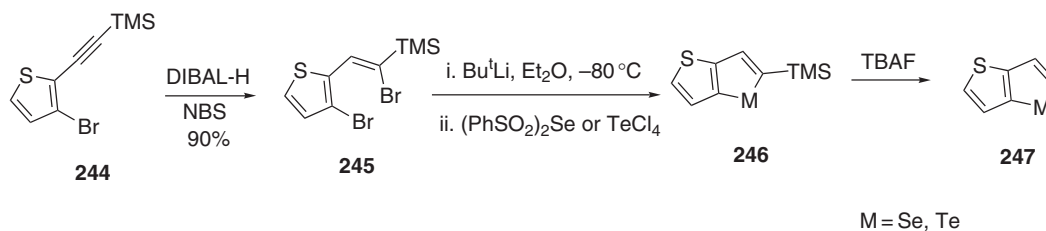


&lt;2003SL855&gt;

Scheme 116

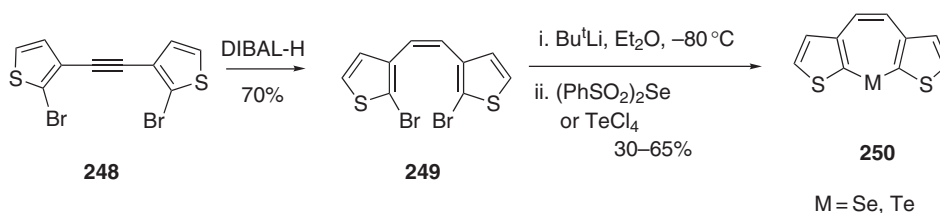
#### 4.19.6.1.2 Tellurium derivatives

The only examples of tellurium derivatives in this class are thienotelluroles <1997H1891> and dithienoheteroepines <1997H1899>. Syntheses are described for thieno[2,3-*b*]-, thieno[3,4-*b*]-, and thieno[3,2-*b*]-telluroles **247** (Scheme 117). Dithienoheteroepines **250** were prepared as displayed in Scheme 118.



&lt;1997H1891&gt;

Scheme 117

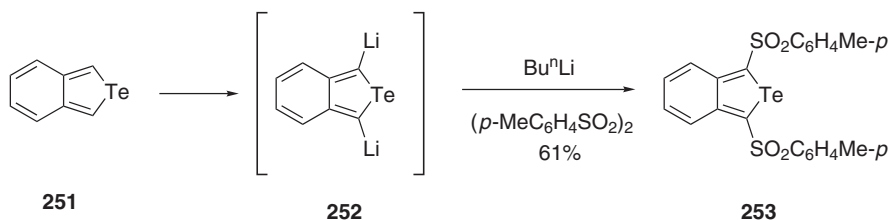


&lt;1997H1899&gt;

Scheme 118

#### 4.19.6.2 Tri- and Tetra-coordinated Sulfur Derivatives

Tellurophene **253** is the only compound belonging to this class <2000JOC5413>. It was obtained from benzo[*c*]-tellurophene **251** via the lithio derivative **252** prepared by treatment with Bu<sup>n</sup>Li at low temperature. Derivative **252** was further treated with toluenesulfonic anhydride to yield tellurophene **253** in 61% yield (Scheme 119).



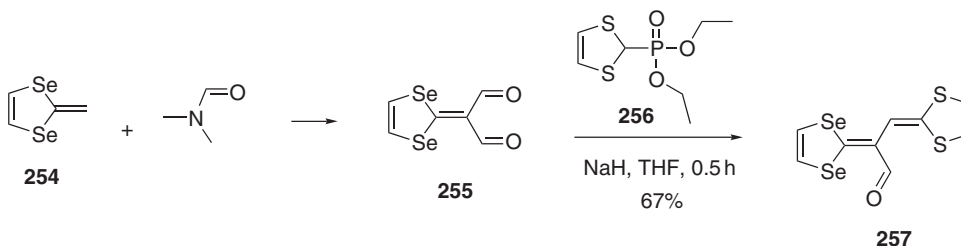
&lt;2000JOC5413&gt;

Scheme 119

#### 4.19.7 FUNCTIONS CONTAINING SELENIUM AND/OR TELLURIUM, R<sub>2</sub>C=C(SeR<sup>2</sup>)<sub>2</sub>, etc.

##### 4.19.7.1 Selenium Derivatives

Dendralenes bearing the 1,3-selenole moiety were prepared as described in Scheme 120 <2001JOC7757>. The selenium-containing template **255** was treated with phosphonate **256** in the presence of NaH in THF at room temperature to produce derivative **257** in 67% yield.

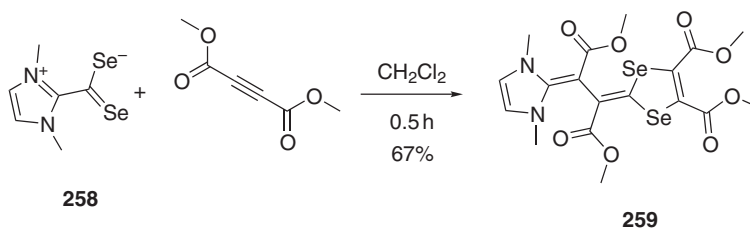


&lt;2001JOC7757&gt;

Scheme 120

Diselenadithiafulvalenes were also obtained as described in Section 4.19.5.1.3 for tetrathiafulvalenes via the Me<sub>3</sub>Al-promoted reactions of organotin selenolates with esters <1996JOC3987>.

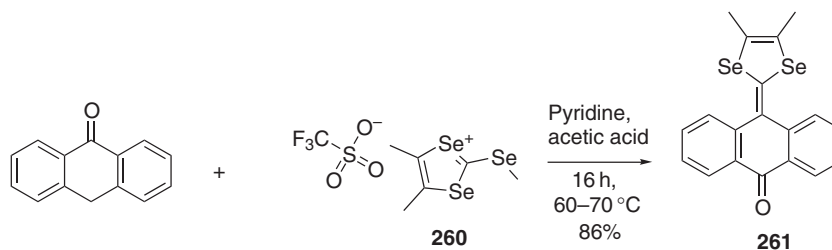
Diselenole derivative **259** was obtained by treating 2 mol. of isolable and stable 2-(1,3-dimethylimidazolidinio)diselenocarboxylate **258** with 1 mol. of diethyl acetylenedicarboxylate (Scheme 121) <2000JA9120>. Even when the ratio between reactants is 1:1, only the bis-adduct **259** was obtained.



<2000JA9120>

Scheme 121

4,5-Dimethyl-2-methylseleno-1,3-diselenolium salts **260** are useful building blocks for diselenols such as **261** (Scheme 122) <1998T13257, 2002JOC4218>. The reaction occurred by heating the reagents in pyridine/acetic acid with a yield of 86%.

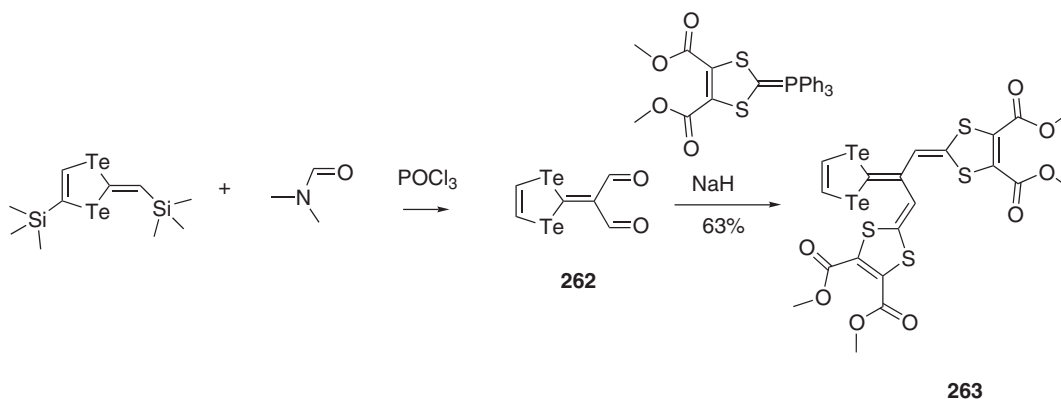


<1998T13257>

Scheme 122

#### 4.19.7.2 Tellurium Derivatives

Tellurole derivatives were synthesized starting from tellurole dialdehyde **262** (Scheme 123) <2002OL2581>. By condensation with malononitrile or with carboxymethyl phosphorane, telluroles were obtained in moderate to high yields (63% for **263**). This compound was used in the synthesis of the first 1,3-ditellurole-containing radialene-type tetrathiafulvalene derivative.



<2002OL2581>

Scheme 123

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## 4.20

# Functions Containing a Chalcogen and Any Group Other Than a Halogen or a Chalcogen

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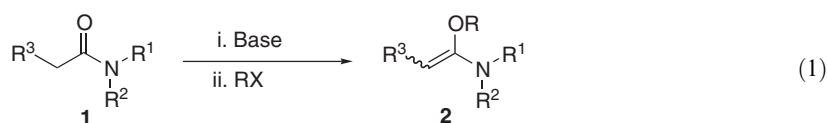
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## 4.20.1 FUNCTIONS CONTAINING A CHALCOGEN AND A NITROGEN FUNCTION

### 4.20.1.1 Functions Bearing Oxygen and Nitrogen

#### 4.20.1.1.1 Ketene hemiaminal derivatives

The main method to synthesize ketene hemiaminals **2** is by *O*-alkylation of amide enolates (Equation (1)):



Neier and co-workers prepared a series of *N*-butadienyl-*O*-silyl hemiaminals by deprotonation of the amides **3** in a mixture of THF/HMPA at  $-78^\circ\text{C}$  (Table 1). Trapping of the resulting enolate with TBDMS-Cl gives the (*Z*)-*N,O*-ketene hemiaminals **4**. <1999CEJ3162, 1996S1239>. The yields, as shown in Table 1, are very high. Although silylation with trimethylsilyl chloride is also feasible, the corresponding acetals are less easily formed and are more sensitive to hydrolytic cleavage.

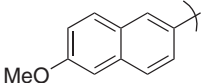
**Table 1** The synthesis of *O*-silyl ketene hemiaminal from amide

$  \begin{array}{ccc}  \begin{array}{c} \text{R}^1 \\   \\ \text{N} \\   \\ \text{C}=\text{O} \\   \\ \text{CH}=\text{CH}-\text{CH}=\text{CH}_2 \\ \mathbf{3} \end{array} & \xrightarrow[\text{-78}^\circ\text{C/TBDMS-Cl}]{\text{LDA/THF-HMPA}} & \begin{array}{c} \text{OTBDMS} \\   \\ \text{C}=\text{C} \\   \\ \text{N}(\text{R}^1) \\   \\ \text{CH}=\text{CH}-\text{CH}=\text{CH}_2 \\ \mathbf{4} \end{array}  \end{array}  $			
$\text{R}^1$	$\text{R}^2$	Yield (%)	References
$\text{Pr}^i$	Me	98	<1996S1239>
$\text{Pr}^i$	Bn	97	<1996S1239>
$\text{Pr}^i$	$\text{CH}=\text{CH}-\text{CH}_3$	98	<1996S1239>
Bn	Et	98	<1996S1239>
$p\text{-BrCH}_2\text{-C}_6\text{H}_4$	Et	96	<1996S1239>
Anthranilylmethyl	Et	70	<1996S1239>
Bz	Me	98	<2000HCA2712>

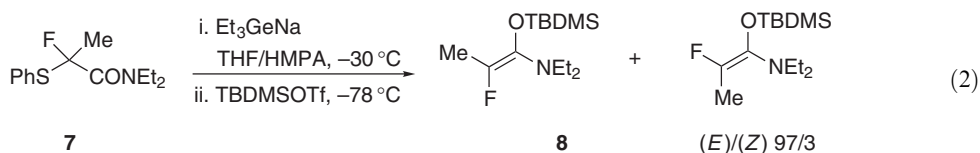
The same reaction can be applied to imides ( $\text{R}^1 = \text{Bz}$ , Table 1), with a similar efficiency <2000HCA2712>.

In studies on the enantioselectivity of enolate formation, Vedejs and co-workers deprotonated a series of arylamides **5** with *s*-butyllithium followed by addition of trimethylsilyl chloride (Table 2). The assignment of the geometry of **6** was based on an upfield shift of the  $\text{SiMe}_3$  protons in the (*Z*)- versus the (*E*)-isomer <2000JA4602, 1995JA891>.

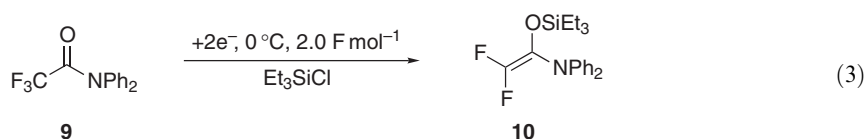
**Table 2** Geometry of *O*-silyl ketene hemiaminal

$  \begin{array}{c} \text{R}^1 \\   \\ \text{Ar}-\text{C}-\text{NR}_2 \\    \\ \text{O} \end{array} \xrightarrow[\text{ii. TMSCl}]{\text{i. Bu}^s\text{Li}} \begin{array}{c} \text{R}^1 \\   \\ \text{Ar}-\text{C}=\text{NR}_2 \\   \\ \text{OTMS} \end{array} + \begin{array}{c} \text{Ar} \\   \\ \text{R}^1-\text{C}=\text{NR}_2 \\   \\ \text{OTMS} \end{array}  $			
<b>5</b>		( <i>Z</i> )- <b>6</b>	( <i>E</i> )- <b>6</b>
<i>Ar</i>	<i>R</i> <sup>1</sup>	<i>R</i>	( <i>Z</i> )/( <i>E</i> )
Ph	Cyclopentyl	Pr <sup>i</sup>	4.7:1
	Me	Me	1:1.6
Ph	Me	Me	2.1:1

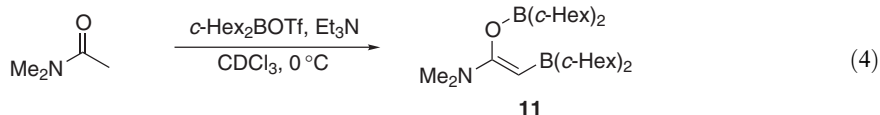
The generation of the amide enolate can also be accomplished using unusual procedures. Thus, deprotonation of the 2-fluoro-2-phenylthiopropionamide **7** by germyl anion followed by quenching with a silyl triflate gives a mixture of *O*-silyl ketene hemiaminal (*E*)/(*Z*)-**8** (Equation (2)) <1998SL37>. Semi-empirical molecular orbital calculations reveal that the (*E*)-enolate is thermodynamically more stable than the (*Z*)-enolate, in accordance with the experimental data.



Another unusual enolate formation is the electroreductive defluorination of trifluoroacetic acid derivatives <1999JOC6717>. Thus, when trifluoroacetamide **9** was electrolyzed in anhydrous acetonitrile at 0 °C using a carbon anode and a lead cathode, in the presence of chlorotriethylsilane, ketene hemiaminal **10** was obtained in 54% yield (Equation (3)).



The enolization of *N,N*-dimethylacetamide with 2.5 equiv. of boron triflate gives the doubly borylated enolate **11** in 98% yield <2002JA10759> (Equation (4)).

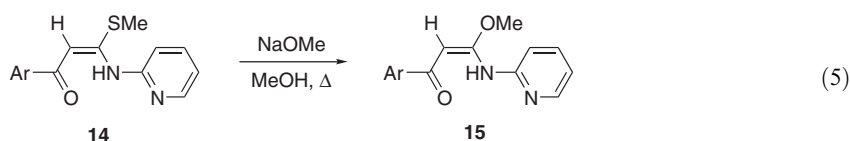


Other methods to access the ketene hemiaminal function **13** do not start from amides. For example, Furukawa and co-workers used  $\beta$ -oxothio ester **12** and amines as starting materials <1999SC599>. This reaction is limited to primary amines (Table 3). When secondary amines are used, reactions are very slow and yields are very low.

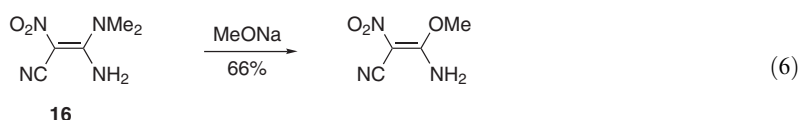
The *N,S*-acetals **14** (obtained from the ketene dithioacetals; see Section 4.20.1.2.1) undergo facile displacement with sodium methoxide in refluxing methanol to afford the corresponding *N,O*-acetals **15** in good yields <2000JOC1583> (Equation (5)).

**Table 3** The synthesis of ketene hemiaminal from  $\beta$ -oxothio ester

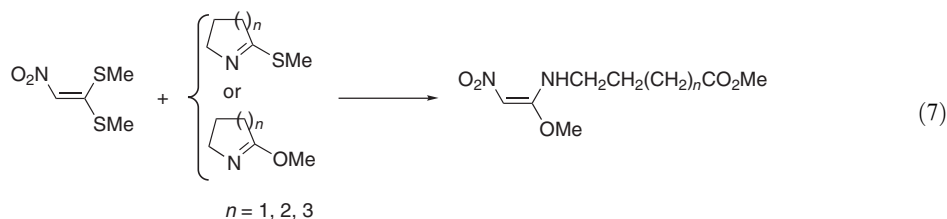
$  \begin{array}{c}  \text{R}^1 \\    \\  \text{CH}=\text{C}(\text{OH})\text{S}(\text{OEt}) \\  \text{12}  \end{array}  + \text{R}^2\text{NH}_2  \xrightarrow[\text{MeCN, rt}]{\text{NEt}_3}  \begin{array}{c}  \text{R}^1 \\    \\  \text{CH}=\text{C}(\text{OEt})\text{NHR}^2 \\  \text{13}  \end{array}  $		
$\text{R}^1$	$\text{R}^2$	Yield (%)
Me	Me	84
Me	Pr	99
Me	Ph	98
Bu <sup>t</sup>	Pr	99
Ph	Me	67
Ph	Pr	99
<i>p</i> -MeOC <sub>6</sub> H <sub>4</sub>	Pr	96



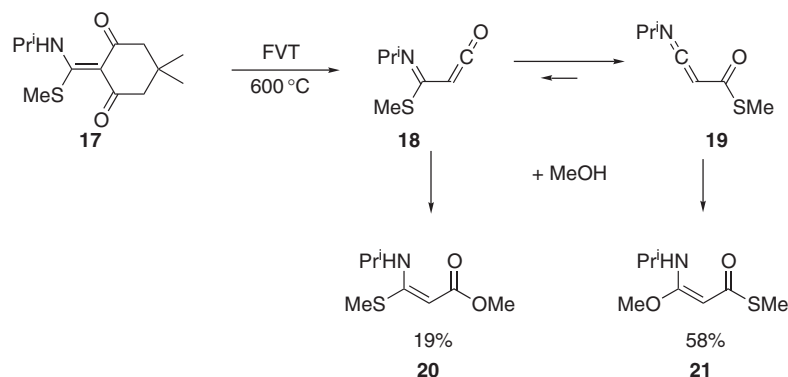
The particular enediamine **16** can also react with sodium methoxide to give the *N,O*-acetal in 66% yield (Equation (6)) <1996KGS699>.



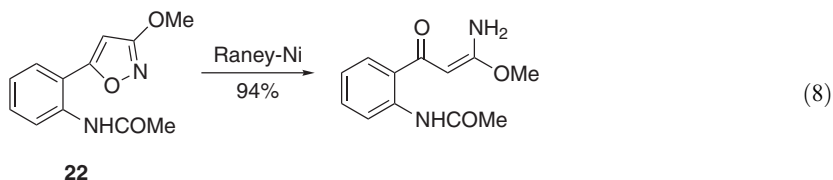
Similarly, lactim ethers or lactim sulfides react with ketene dithioacetals in refluxing methanol for 2 days to afford ring-opened product (Equation (7)) <1997JCS(P1)2421>.



Wentrup and co-workers generated iminopropanedienones by flash vacuum thermolysis (FVT) from substituted Meldrum's acid derivatives <1997JOC4240>. In the case of compound **17**, the generated ketene **18** is in equilibrium with the ketimine **19**. Chemical evidence was obtained by trapping the intermediate with methanol at 77 K giving the *N,S*-acetal **20** and *N,O*-acetal **21** (reaction run on a 1.9 mmol scale, Scheme 1).

**Scheme 1**

The isoxazole ring can be reduced by Raney-Ni to give enamine derivatives. In the case of the 3-methoxyisoxazole **22**, the *N,O*-hemiaminal derivative is obtained in 94% yield (Equation (8)) <1995ACS53>.

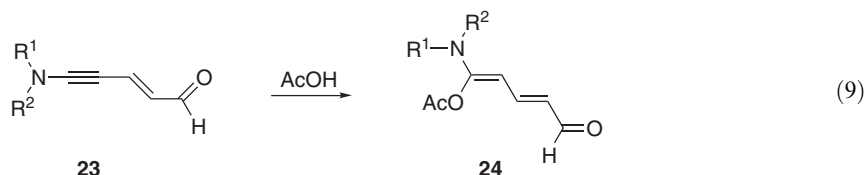


Oxazolidinethione and the acyclic thionocarbamate analogs can lead to *N,O*-hemiaminals after *S*-alkylation followed by sulfur extrusion (Table 4) <2000H827>.

**Table 4** Sulfur extrusion from oxazolidine-2-thione and thionocarbamates

$R^1$		$R^2$	Yield (%)	References
Et		Ph	48	<2000H827>
	CH <sub>2</sub> —CH <sub>2</sub>		52	<2000H827>
			97	<2000H827>

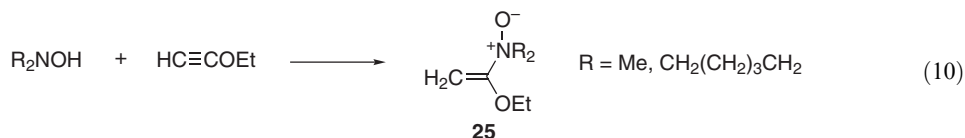
Oxygen nucleophiles can also add to alkynylamines. Thus, acetic acid reacts with the ynamine **23** to give the conjugated *N,O*-hemiaminals **24** (Equation (9)) <1995C72>.



#### 4.20.1.1.2 Other nitrogen derivatives

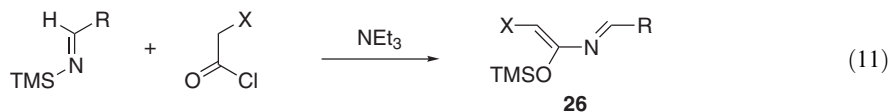
##### (i) *N*-Oxide derivatives

Ciganek and co-workers reported the addition of dimethylhydroxylamine and *N*-hydroxypiperidine to ethoxyacetylene <1995JOC5795>. The *N*-oxide derivatives **25** were obtained in good yields after 3 days at room temperature (Equation (10)).

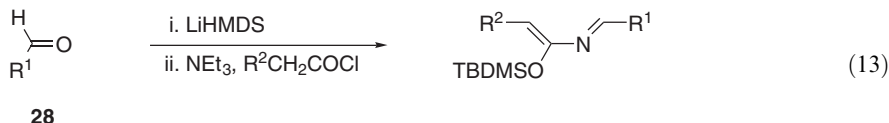
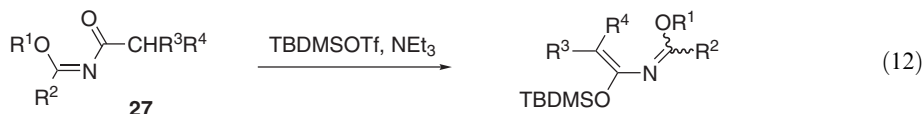


##### (ii) Imino derivatives

Condensation of acid chlorides and *N*-TMS-imine affording the azadiene **26** was reported by Panunzio and co-workers <1997JOC8911, 2000EJO2379, 2000OL1077>. After filtration of the crude reaction mixture over Celite, an aliquot was analyzed by NMR, showing that it contained essentially pure azadiene (Equation (11)). This crude mixture was directly utilized in Diels–Alder cyclization.

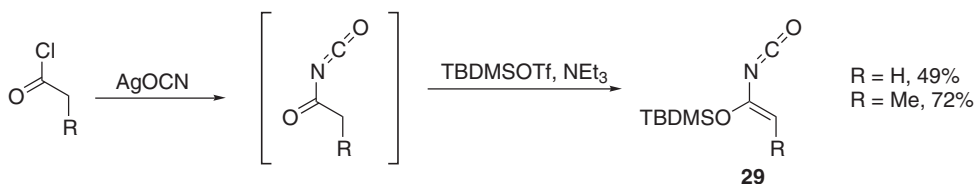


Ghosez and co-workers reported the synthesis of such azadienes from the same starting material as well as from acylimidates **27** (Equation (12)) or directly from aldehydes **28** (Equation (13)) <1995T11021>.



### (iii) Isocyanate derivatives

Ghosez and co-workers also prepared the 1-silyloxy-alkenyl isocyanate **29** by reaction of an acid chloride, silver isocyanate, and *t*-butyldimethylsilyl triflate in the presence of triethylamine (Scheme 2). This one-pot method avoids the isolation and purification of the intermediate acyl isocyanate, a procedure that always leads to extensive decomposition <1997BSF989>.



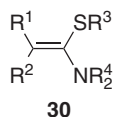
Scheme 2

## 4.20.1.2 Functions Bearing Sulfur and Nitrogen

### 4.20.1.2.1 Dicoordinate sulfur derivatives

#### (i) 1-Amino-1-thioalkenes

These compounds have the general formula **30** and are normally known as ketene *N,S*-acetals.

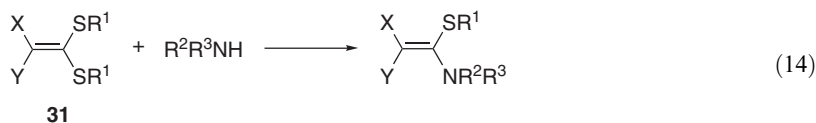


The synthesis of this system is realized according to four main routes:

- (i) displacement of an alkylthio group of a 1,1-bis(alkylthio)alkene;
- (ii) *S*-alkylation of a thioamide;
- (iii) addition of a thiol to nitrile group; and
- (iv) addition of a carbanion to an isothiocyanate

In addition, a number of rather singular and nongeneral methods will be reported under “miscellaneous.”

(a) *Reaction of amines with 1,1-bis(alkylthio)alkenes.* 1,1-Bis(alkylthio)alkene **31**, whose synthesis is discussed in Chapter 4.19, reacts with a wide range of amines (Equation (14)).



As this reaction involves the initial attack at C-1 of the dithioacetal **31** (it is a conjugate addition/elimination on an activated double bond), the ease of reaction will depend on the electron-withdrawing abilities of X and Y. Furthermore, a limited number of dithioacetals **31** are used in this reaction.

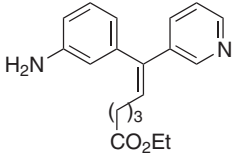
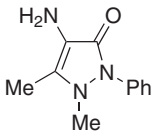
Singh and co-workers have developed an access to 2-oxo-ketene-*N,S*-acetals by condensation of 1 equiv. of the lithium salt of the aromatic amine (either an aniline or a pyridine derivative) on the *S,S*-ketal at room temperature. If 2 equiv. of amines are used, the *N,N*-ketal is obtained (see Chapter 4.21). All the *N,S*-ketals thus obtained exist as a single (*E*)-stereoisomer, based on IR and NMR data. For example, the N–H stretching vibration at 3330–3350 cm<sup>−1</sup> indicates an intramolecularly associated hydrogen <1997JCS(P1)3561, 2003JOC3966>. Representative examples are listed in Table 5.

**Table 5** Displacement of methylthio group by lithio amides

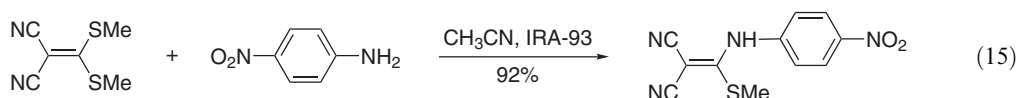
<i>R</i> <sup>1</sup>	<i>R</i> <sup>2</sup>	<i>ArNH</i> <sub>2</sub>	Yield (%)	References
Ph	H	<i>p</i> -ClC <sub>6</sub> H <sub>4</sub> NH <sub>2</sub>	82	<1997JCS(P1)3561>
Ph	H		92	<1997JCS(P1)3561>
<i>p</i> -MeOC <sub>6</sub> H <sub>4</sub>	H		93	<1997JCS(P1)3561>
<i>p</i> -ClC <sub>6</sub> H <sub>4</sub>	H		90	<1997JCS(P1)3561>
2-Furyl	H		88	<1997JCS(P1)3561>
Ph	H		70	<1997JCS(P1)3561>
<i>p</i> -MeOC <sub>6</sub> H <sub>4</sub>	H		70	<1997JCS(P1)3561>
2-Furyl	H		62	<1997JCS(P1)3561>
Ph	H	0.5 equiv. 	68	<2003JOC3966>
Ph	H	0.5 equiv. 	75	<2003JOC3966>
Ph	H	0.5 equiv. 	85	<2003JOC3966>

(Bis-methylthio-methylene)malonitrile **32** is another of the dithioacetals used as precursor of *N,S*-acetals (Table 6). Compound **32** and the appropriate amine are refluxed in an alcoholic solvent (ethanol or isopropanol) for several hours <2003JMC1229, 1999JMC1235, 1997JMC3601>, and sometimes a catalytic amount of piperidine is added <2002SC3509>.

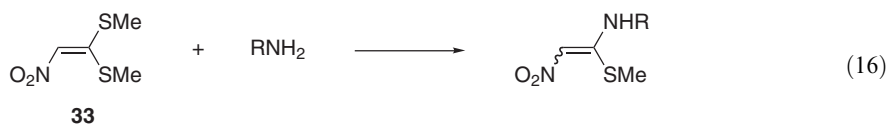
**Table 6** Displacement of methylthio group by amines

$  \begin{array}{c} \text{NC} \quad \text{SMe} \\ \diagdown \quad \diagup \\ \text{C} = \text{C} \\ \diagup \quad \diagdown \\ \text{NC} \quad \text{SMe} \end{array} + \text{RNH}_2 \longrightarrow \begin{array}{c} \text{NC} \quad \text{NHR} \\ \diagdown \quad \diagup \\ \text{C} = \text{C} \\ \diagup \quad \diagdown \\ \text{NC} \quad \text{SMe} \end{array}  $ <p style="text-align: center;"><b>32</b></p>			
Amine	Solvent	Yield (%)	References
4-Methoxyaniline	EtOH	70	<2003JMC1229>
Ethylamine	EtOH	61	<2003JMC1229>
	Pr <sup>i</sup> OH	63	<1999JMC1235>
	EtOH/piperidine(catalytic)	90	<2002SC3509>

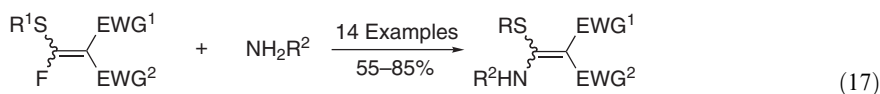
Yang and co-workers have improved the reaction for weakly nucleophilic arylamines (Equation (15)). The best yields are obtained in acetonitrile with a catalytic amount of the ion exchange resin Amberlite IRA-93 <1998SC3965>.



The same reactivity is observed for nitro-activated dithioacetal **33** (Equation (16)). The substitution is realized by reaction with an amine, either neat <1999JMC730>, in ethanol <1998JMC3239>, or in acetonitrile <1996T9509>.



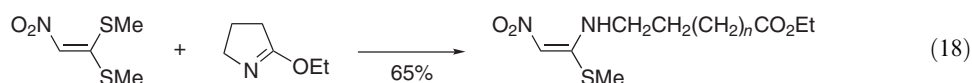
Sizov and co-workers reacted amines with  $\alpha$ -fluoro vinyl sulfides to obtain the product of fluorine substitution (Equation (17)) <2002IZV938>.



EWG = CO<sub>2</sub>Me, CF<sub>3</sub>, CN; R<sup>1</sup> = Bn, Bu; R<sup>2</sup> = aryl

The nitrogen source can also be a lactim ether <1997JCS(P1)2421>. In this case, the reaction was carried out in dioxane/water to give 65% of the product (Equation (18)).



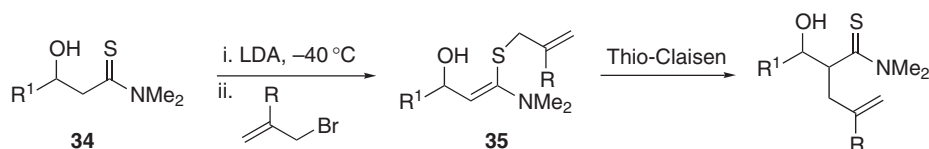


(b) *S*-Alkylation of a thioamide anion. Treatment of a thioamide with a base in the presence of an electrophile produces the *S*-alkylated product (Table 7) <1998HCA1207, 2000PJC1101>.

**Table 7** *S*-Alkylation of a thioamide

$R^1$	$R^2$	$R^3X$	<i>Yield (%)</i>	<i>References</i>
Ph	H	MeI	Quantitative	<1998HCA1207>
Bn	H	MeI	83	<1998HCA1207>
Bn	Bn	MeI	89	<1998HCA1207>
Ph	H	BrCH <sub>2</sub> CH <sub>2</sub> CO <sub>2</sub> Et	41	<2000PJC1101>

The  $\beta$ -hydroxy-*N,N*-dimethylthioamides **34** were deprotonated with LDA at  $-40^{\circ}\text{C}$ , and alkylation of the dianions by allylic halides occurred only at the sulfur atom to give the allylic *N,S*-acetals **35** (Scheme 3) <1997T17253>. Such allylic acetals are prone to thio-Claisen rearrangement and were not isolated, but they were characterized by NMR. Similar thioamides bearing an enantiopure  $\beta$ -sulfinyl group were prepared by the group of Metzner <2001JOC7841>.



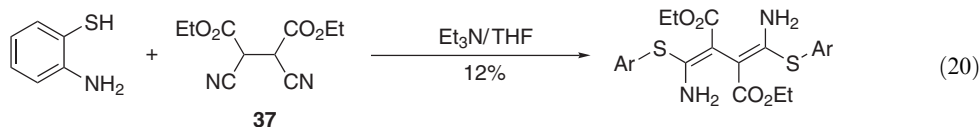
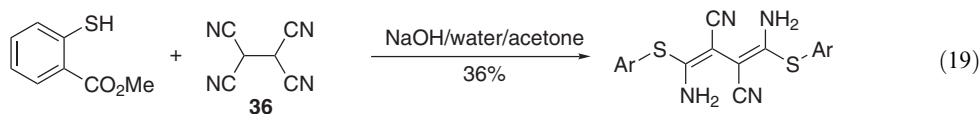
### Scheme 3

(c) *Addition of thiol to a nitrile group.* Addition of a thiol to a nitrile group in the presence of triethylamine leads to the formation of the expected *N,S*-acetals in moderate-to-good yields [<1995S635, 1996S1325>](#). The compounds are obtained as an inseparable mixture of (*Z*)/(*E*) isomers ([Table 8](#)).

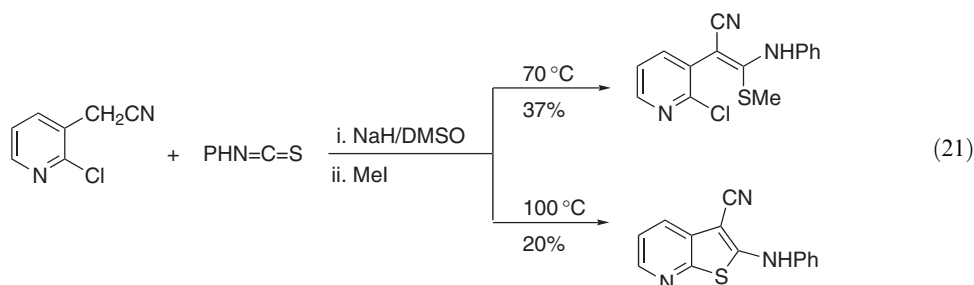
**Table 8** Addition of thiol to nitrile

$R^1$	$R^2$	Yield (%)	References
Me	Et	83	<1995S635>
Bu	Et	72	<1995S635>
Bu	CH <sub>2</sub> CH <sub>2</sub> OAc	60	<1995S635>
Bu	Ph	86	<1995S635>
Bu	Bn	86	<1995S635>
Bu	<i>p</i> -MeOC <sub>6</sub> H <sub>4</sub>	91	<1995S635>
Bu	<i>p</i> -FC <sub>6</sub> H <sub>4</sub>	67	<1995S635>

Duncia and co-workers reacted substituted thiophenols on 1,1,2,2-tetracyanoethylene **36** and 1,2-dicarboethoxy-1,2-dicyanoethane **37** to produce the di-addition product in low yields (Equations (19) and (20)) <1998BMCL2839>.



(d) *Addition of a carbanion to an isothiocyanate.* Bremner and co-workers reacted diversely substituted (*o*-halogeno(cyanomethyl))pyridines with phenyl isothiocyanate in the presence of sodium hydride, followed by quenching with methyl iodide, to obtain the *N,S*-acetals. The latter cyclize to the thienopyridine at rates depending on relative substitution and reaction conditions <1998S1095>. One example is presented in Equation (21).

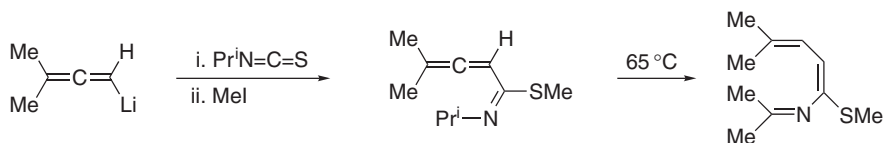


The same method was used by Kirsch and co-workers <2002TL257>, by Papageorgiu and co-workers <1998JMC3530>, and by Rudolf and Uhlig <1995JPR29> to prepare *N,S*-acetals, which are precursors of heterocycles. Wentrup and co-workers used only malononitrile and modified the isothiocyanate (Table 9) <2002JOC1084>.

**Table 9** Addition of activated methylene on isothiocyanate

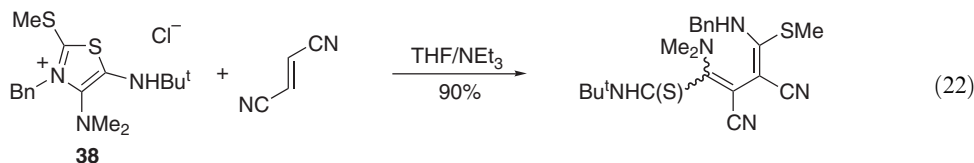
$  \text{R}^1-\text{CH}_2-\text{R}^2 + \text{ArN}=\text{C}=\text{S} \xrightarrow[\text{ii. RX}]{\text{i. Base}} \text{ArHN}-\text{C}(\text{R}^1)=\text{C}(\text{R}^2)-\text{SR}  $					
$R^1$	$R^2$	$Ar$	$RX$	Yield (%)	References
CN	CO <sub>2</sub> Et	( <i>p</i> -CF <sub>3</sub> )Ph	MeI	61	<1998JMC3530>
CN	CO <sub>2</sub> Et	Ph	MeI	87	<2002TL257>
Ac	CO <sub>2</sub> Et	Ph	MeI	97	<2002TL257>
CN	CN	Ph	MeI	91	<2002TL257>
Bz	Bz	Ph	MeI	58	<2002TL257>
CN	CN	Me	MeI	39	<2002JOC1084>
CN	CN	Et	MeI	60	<2002JOC1084>
PhSO	CN	Ph	MeI	61	<1995JPR29>
PhSO	CN	Ph	BnBr	65	<1995JPR29>
<i>p</i> -MePhSO	CN	Ph	BnBr	40	<1995JPR29>
PhS	CN	Ph	MeI	74	<1995JPR29>
PhS	CN	Ph	BnBr	51	<1995JPR29>
PhSO	Bz	Ph	MeI	32	<1995JPR29>
<i>p</i> -MePhSO	Bz	Ph	BnBr	35	<1995JPR29>
<i>p</i> -MePhS	Bz	Ph	MeI	51	<1995JPR29>

Lithiated allenes were also reacted with isopropyl isothiocyanate at  $-100^\circ\text{C}$  to produce, after quenching of the resulting thiolate with methyl iodide, the enamines which rearrange to the fully conjugated compounds upon heating (Scheme 4) <1997TL6905>.

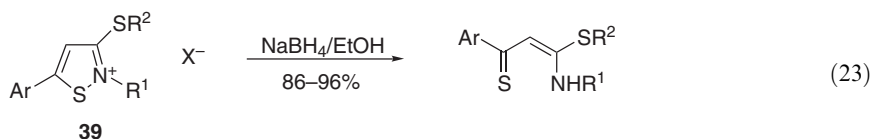


Scheme 4

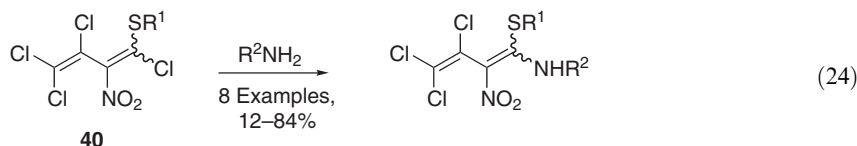
(e) *Miscellaneous preparations of 1-amino-1-thioalkene*. Morel and Berrée reacted 5-aminothiazolium salts **38** with electron-deficient alkenes via 1,3-cycloadditions. Depending on the reaction conditions (solvent, base) and dipolarophiles used, the ketene *N,S*-acetals were obtained in good yields <1995T7019>. One selected example is shown in Equation (22).



Reduction of isothiazolium salts **39** with sodium borohydride gives the *N,S*-acetals in good yields (Equation (23)) <2002JOC5375>.

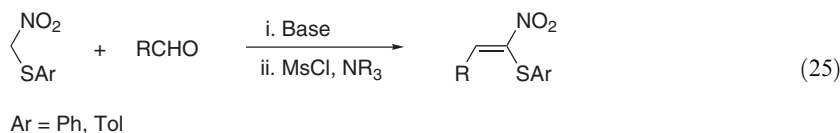


By analogy with the displacement of a methylthio group by an amine in *S,S*-acetals, an amine can substitute the 1-chloro group of diene **40** <2001PS221> (Equation (24)).

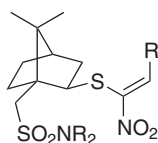


## (ii) 1-Nitro-1-thioalkenes

This class of compounds is mainly obtained by the method of Barrett, via the condensation of alkyl- or arylthionitromethanes with an aldehyde in the presence of a base (Equation (25)). The nitro-alcohols thus obtained are further dehydrated by treatment with methanesulfonyl chloride and a base to give the nitroalkenes <1995JCS(P1)1009, 1995JOC6431, 1999JCS(P1)937, 2002S2296>. In the case of nitro(phenylthio)methane, the base used is potassium *t*-butoxide, whereas for the tolyl derivative, butyllithium is used.

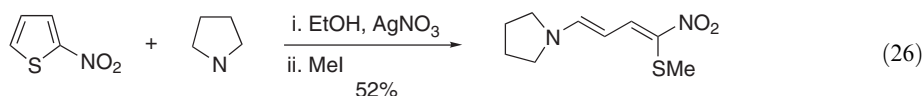


Barrett and co-workers also prepared the chiral, camphor-derived nitroalkenes **41** for asymmetric induction purposes <1999JOC5818>.



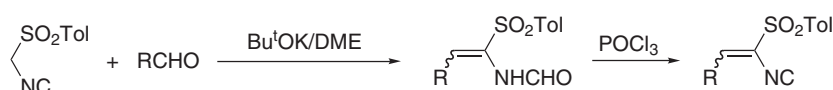
41

The reaction of 2-nitrothiophene with pyrrolidine in ethanol and in the presence of silver nitrate for 10 days at 0 °C gave a salt that was methylated to give nitroalkene in 52% yield (Equation (26)) <1997HCA2329>.



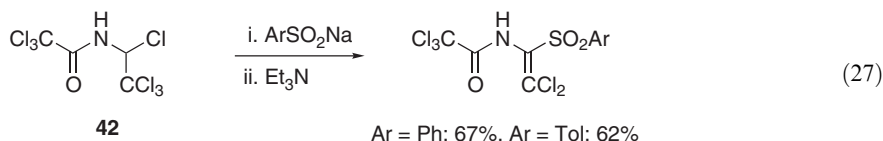
#### 4.20.1.2.2 Tetracoordinate sulfur derivatives

The synthesis of these compounds results mainly from the condensation of tosylmethyl isocyanide (TosMIC) on aldehydes, in DME, using potassium *t*-butoxide as base <1995HCA1837, 1998T9033>. The formamide obtained can be converted to the isonitrile by reaction with POCl<sub>3</sub> (Scheme 5).



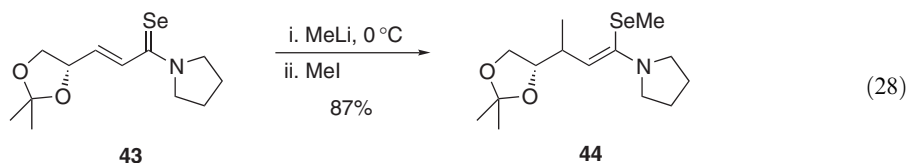
Scheme 5

One example of a sulfone derivative from trichloroacetyl amino compound **42** is reported by a Russian group <1997ZOR1594> (Equation (27)).

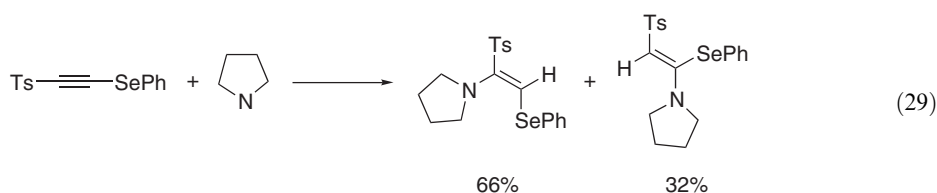


#### 4.20.1.2.3 Functions bearing selenium with nitrogen

There are only two examples of this system. Kato and co-workers alkylated selenoamide **43** with iodomethane to give the ketene (*Z*)-azaselenoacetal **44** in 87% yield (Equation (28)) <1998SL619>. It is noteworthy that when allyl bromide was used as the electrophile, only *C*-alkylation occurred.



Back and co-workers reacted 1-phenylselenoethyne with pyrrolidine to obtain a mixture of 2- and 3-addition products (Equation (29)) <1998JOC7908>.



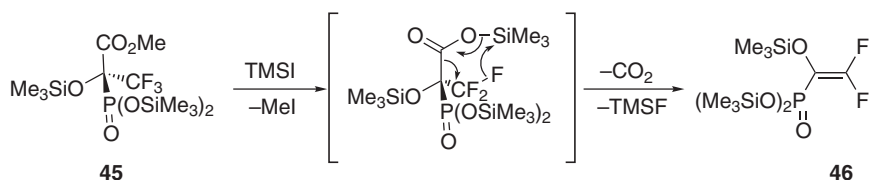
## 4.20.2 FUNCTIONS CONTAINING A CHALCOGEN AND A PHOSPHORUS, ARSENIC, OR ANTIMONY

### 4.20.2.1 Functions Bearing Oxygen

Seven different reactions have been used to produce these systems: elimination reactions, addition to alkynes, addition to ketenes, condensation reactions, enolizations, metal-catalyzed coupling reactions, and cycloaddition.

#### 4.20.2.1.1 Elimination reaction

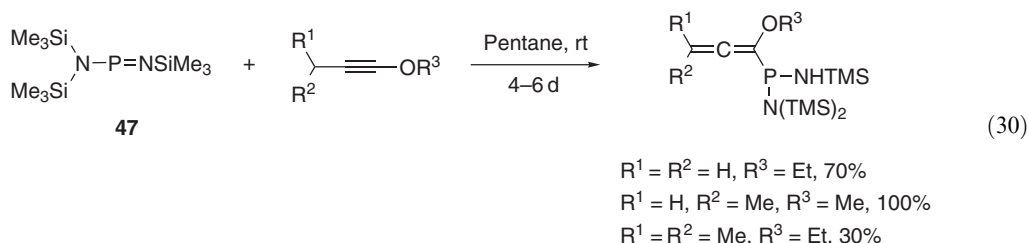
Treatment of compound **45** with iodotrimethylsilane resulted in the formation of methyl iodide, fluorotrimethylsilane, and the unexpected vinylic derivative **46** (Scheme 6) <1997CB279>. The expected trimethylsilyloxycarbonyl derivative was probably formed and decarboxylated together with the loss of fluorotrimethylsilane.



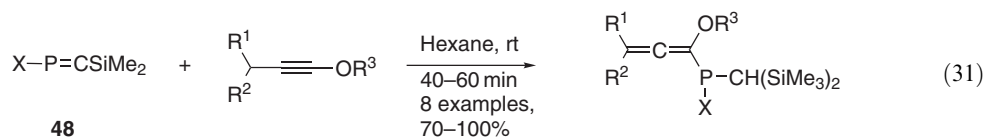
Scheme 6

#### 4.20.2.1.2 Addition to alkynes

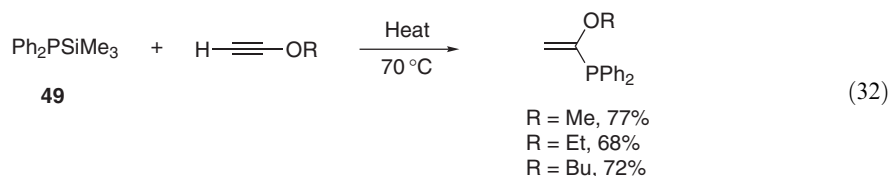
Reaction of amino(imino)phosphines **47** with alkoxyalkynes gives the phosphorus-containing 1-alkoxyallenes in modest-to-good yields (Equation (30)) <1995ZOR488>. The reaction works well in pentane, whereas the yields decrease dramatically when methylene chloride or acetonitrile are used as solvent.



The same group reported the reaction of *P*-halophosphaalkenes **48** with alkoxyalkynes. Similarly, the alkoxyallenes are formed in good yields <2000ZOR1624> (Equation (31)).



Another Russian group reacted silylphosphine **49** with terminal alkoxy acetylenes <1998IZV1792>. Unlike the reaction with internal alkynes (see Section 4.20.3.1.1), the reaction proceeds at room temperature in acetonitrile and gives the  $\alpha$ -alkoxyvinylic phosphine in good yields (Equation (32)).



#### 4.20.2.1.3 Addition to ketenes

Reaction of iron complexes **50** with ketenes afford the adduct **51** in good yields (Table 10) <2000JCS(D)4379, 2000ZAAC1831>. Those compounds are solids and are purified by recrystallization. The antimony derivative with a methyl substituent is thermolabile and is only observed as a mixture by NMR and could not be purified.

Table 10 Addition to ketenes

**50**

E = P, As, Sb

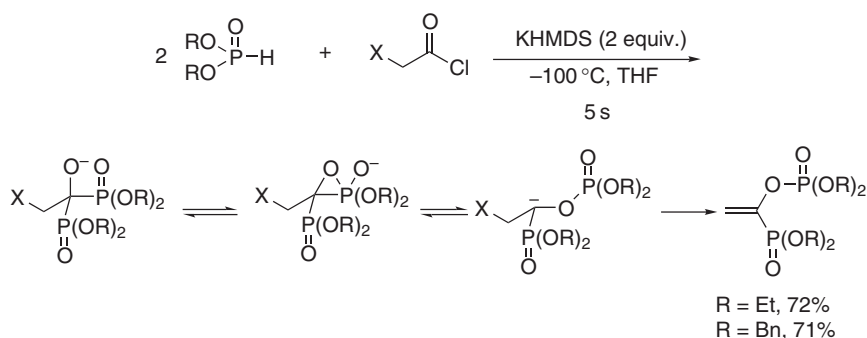
$+$ 
 $\text{R}-\text{C}(\text{O})=\text{C}(\text{O})-\text{Ph}$ 
 $\longrightarrow$

**51**

<i>E</i>	<i>R</i>	Yield (%)	References
P	Ph	89	<2000JCS(D)4379>
As	Ph	73	<2000JCS(D)4379>
Sb	Ph	70	<2000JCS(D)4379>
Sb	Cyclohexyl	76	<2000ZAAC1831>
Sb	Me	Only characterized by NMR	
			<2000ZAAC1831>

#### 4.20.2.1.4 Condensation reaction

Treatment of dialkyl phosphites with 2 equiv. of base in the presence of chloro- or bromoacetyl chloride provides the enol phosphonate in good yield. The reaction was run at  $-100^\circ\text{C}$ , for 5 s <1995JOC5209>. No epoxide resulting from the internal substitution of chloride by the oxoanion was detected (Scheme 7).



Scheme 7

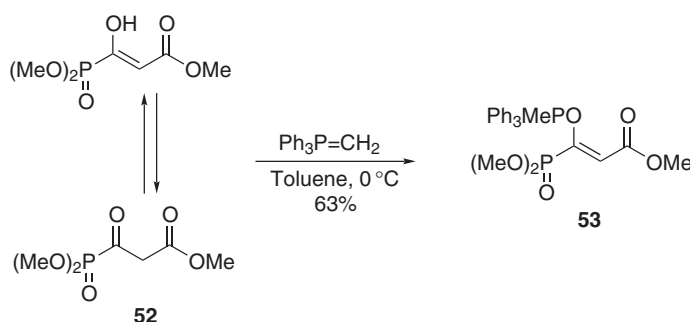
#### 4.20.2.1.5 Enolization of $\alpha$ -carbonylphosphorus compounds

$\alpha$ -Ketophosphonates, obtained by an Arbuzov reaction between an acid chloride and a phosphite, exist partly in the enolized structure. They can also be easily enolized by a base in dichloromethane or THF. The enolate thus obtained can be trapped with acetic anhydride <1997TL1663> or a sulfonyl fluoride <1999TL5337>. If a common triflating agent ( $\text{ Tf}_2\text{O}$ , *N*-phenyltriflimide) is used, the enol triflate is obtained in low yield (0–34%). Results are summarized in Table 11.

**Table 11** Enolization of  $\alpha$ -ketophosphonate

$R^1$	$R^2, R^3$	$R^4X$	Base	Yield (%)	References
Me	H, H	$\text{Ac}_2\text{O}$	$\text{Et}_3\text{N}/\text{rt}$	7	<1997TL1663>
Me	Me, H	$\text{Ac}_2\text{O}$	$\text{Et}_3\text{N}/\text{rt}$	48	<1997TL1663>
Me	Et, H	$\text{Ac}_2\text{O}$	$\text{Et}_3\text{N}/\text{rt}$	55	<1997TL1663>
Me	Ph, H	$\text{Ac}_2\text{O}$	$\text{Et}_3\text{N}/\text{rt}$	74	<1997TL1663>
Me	4-MeOC <sub>6</sub> H <sub>4</sub> , H	$\text{Ac}_2\text{O}$	$\text{Et}_3\text{N}/\text{rt}$	57	<1997TL1663>
Me		$\text{Ac}_2\text{O}$	$\text{Et}_3\text{N}/\text{rt}$	67	<1997TL1663>
Et	H, H	$\text{C}_4\text{F}_9\text{SO}_2\text{-F}$	$\text{DBU}/-45^\circ\text{C}$	82	<1999TL5337>
Et	Ph, H	$\text{C}_4\text{F}_9\text{SO}_2\text{-F}$	$\text{DBU}/-45^\circ\text{C}$	41	<1999TL5337>
Et	Me, Me	$\text{C}_4\text{F}_9\text{SO}_2\text{-F}$	$\text{DBU}/-45^\circ\text{C}$	80	<1999TL5337>
Et	Me, Et	$\text{C}_4\text{F}_9\text{SO}_2\text{-F}$	$\text{DBU}/-45^\circ\text{C}$	72	<1999TL5337>

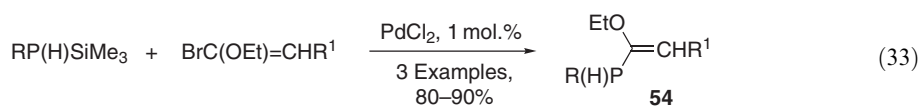
Ketophosphonate **52** exists in the fully enolized form (as determined by NMR) and protonates the methylenephosphorane to give compound **53** as the (*E*)-isomer in 63% yield (Scheme 8) <1999S1056>.



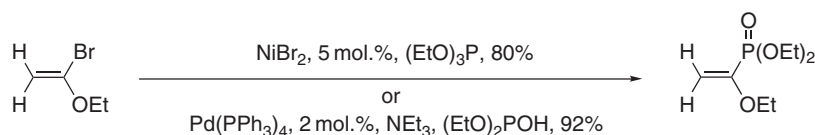
**Scheme 8**

#### 4.20.2.1.6 Metal-catalyzed coupling reaction

Beletskaya and co-workers have prepared  $\alpha$ -alkoxyvinylphosphines <1995TL4121> and  $\alpha$ -alkoxyvinylphosphonates <1999TL569> by nickel- and palladium-catalyzed cross-coupling reactions. Vinyl phosphines **54** are obtained by palladium-catalyzed coupling between a trimethylsilyl phosphine and  $\alpha$ -alkoxyvinyl halide (Equation (33)).



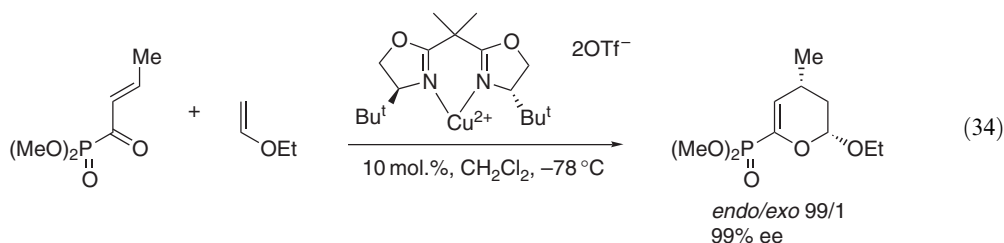
The corresponding vinyl phosphonates are either accessed via nickel-catalyzed cross-coupling of a vinylic halide and a trialkyl phosphite or by palladium-catalyzed cross-coupling of a vinylic halide and a dialkyl phosphite in the presence of a base. The palladium-catalyzed reaction requires milder conditions than the nickel one (temperature in the range 20–100 °C versus 120–160 °C; see Scheme 9).



Scheme 9

#### 4.20.2.1.7 Cycloaddition reactions

Evans and co-workers have used the Diels–Alder reaction to produce  $\alpha$ -phosphonato dihydropyrans <2000JA1635>. The reaction is catalyzed by chiral bis(oxazoline) copper(II) complexes, and gives the dihydropyrans with high regio- and enantioselectivity. One example is displayed in Equation (34).



#### 4.20.2.2 Functions Bearing Sulfur

A smaller range of reactions has been used to produce this system, compared to their oxygenated analogs: condensation reaction, from 1-lithio-1-phosphorylated alkenes and allenes, and from ketene dithioacetals.

##### 4.20.2.2.1 Condensation reaction

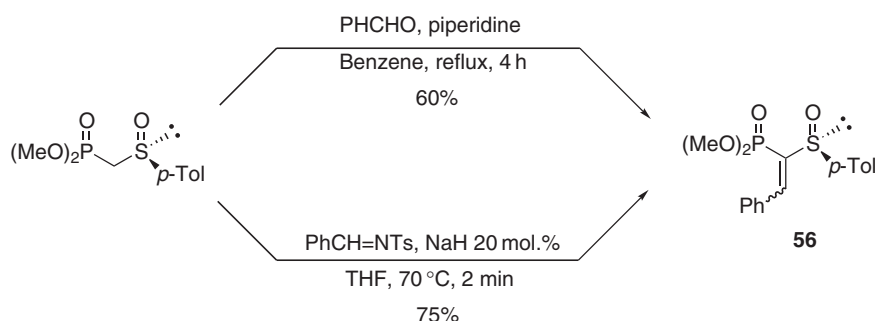
Sheng and Jiang have developed a novel base-catalyzed olefination method <2000S99>. This variation of the Knoevenagel condensation uses *N*-tosyl imine **55** instead of a carbonyl compound (Table 12). The reaction is carried out in THF at 70 °C for 2 min, and the olefins are obtained in good yields as the (*E*)-isomer.

Mikolajczyk and co-workers used this new reaction as well as the classical Knoevenagel condensation to produce vinyl phosphonate **56**, with the advantages of the new reaction (better yield, reaction time considerably reduces) outlined in Scheme 10 <2002TL3061>.



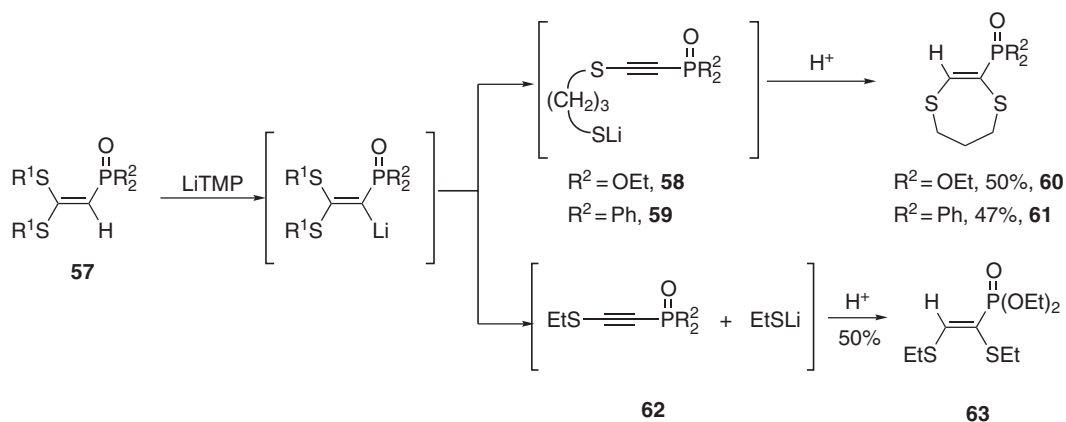
**Table 12** Knoevenagel-type condensation

$  \begin{array}{c} \text{O} \quad \text{O} \\ \parallel \quad \parallel \\ (\text{EtO})_2\text{P}-\text{CH}_2-\text{SPh} \end{array} + \begin{array}{c} \text{NTs} \\   \\ \text{R}-\text{CH}=\end{array} \xrightarrow{\text{NaH 20 mol.}\%} \begin{array}{c} \text{O} \quad \text{O} \\ \parallel \quad \parallel \\ (\text{EtO})_2\text{P}-\text{CH}=\text{CH}-\text{SPh} \\   \\ \text{R} \end{array} + \text{TsNH}_2  $	
<b>55</b>	
<i>R</i>	Yield (%)
Ph	77
4-MeC <sub>6</sub> H <sub>4</sub>	85
4-MeOC <sub>6</sub> H <sub>4</sub>	76
4-ClC <sub>6</sub> H <sub>4</sub>	74
4-FC <sub>6</sub> H <sub>4</sub>	87
2-Furyl	81

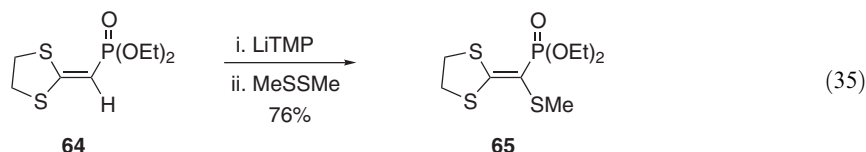

**Scheme 10**

#### 4.20.2.2.2 From 1-lithio-1-phosphorylated alkenes and allenes

Minami and co-workers have treated several phosphonoketene dithioacetals **57** with LiTMP at  $-78^\circ\text{C}$  in THF. The resulting vinyl lithium anion undergoes facile elimination of thiolate to give the thioethynylphosphonates **58** and **62** or the thioethynylphosphine oxide **59**. These are then subjected to nucleophilic attack of the thiolate to induce 1,2-migration of the thio group after hydrolysis (Scheme 11) <1996JOC8132>.


**Scheme 11**

The same group also treated phosphonoketene dithioacetals **64** with LiTMP at  $-78^{\circ}\text{C}$  in THF. In this case, the vinyl anion neither rearranged nor eliminated a thiolate anion as in the case of **58** and **59**. Instead, it could be quenched with various electrophiles, e.g., a disulfide giving **65** (Equation (35)) <1998JOC6239>. It is important to note that elimination of the thiolate anion can be prevented by inverse addition, i.e., by adding LiTMP to a mixture of the phosphonoketene dithioacetal and the electrophile.



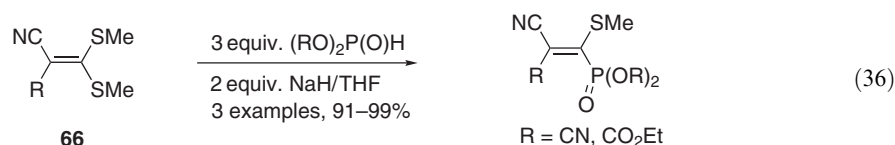
Similarly, phosphorylated allenes can be treated by LDA in THF at  $-78^{\circ}\text{C}$  to furnish the anion that can be condensed with various electrophiles (Table 13) <1998PS1, 2000PS265>.

**Table 13** Condensation with 1-lithio-1-phosphorylated allenes

$  \begin{array}{c} \text{H} \\   \\ \text{R}_2\text{P}=\text{C}=\text{C} \\   \quad   \\ \text{O} \quad \text{R}^1 \end{array}  \xrightarrow[\text{ii. EX, } -78^{\circ}\text{C to rt}]{\text{i. LDA, } -78^{\circ}\text{C}}  \begin{array}{c} \text{E} \\   \\ \text{R}_2\text{P}=\text{C}=\text{C} \\   \quad   \\ \text{O} \quad \text{R}^1 \end{array}  $					
<i>R</i>	<i>R</i> <sup>1</sup>	<i>R</i> <sup>2</sup>	<i>EX</i>	<i>Yield</i> (%)	<i>References</i>
MeO	Me	Me	PhSCl	60	<2000PS265>
Ph	Me	Me	PhSCl	55	<2000PS265>
MeO	–(CH <sub>2</sub> ) <sub>5</sub> –	Me	MeS(O)Cl	59	<2000PS265>
MeO	Me	Me	CCl <sub>3</sub> S(O)Cl	65	<2000PS265>
MeO	Me	Me	Me <sub>3</sub> SiOSO <sub>2</sub> Cl	50	<2000PS265>
Ph	Me	Me	Me <sub>3</sub> SiOSO <sub>2</sub> Cl	48	<2000PS265>
MeO	Me	Me	MeSCl	65	<1998PS1>
MeO	Me	Me	MeS(O)Cl	72	<1998PS1>
MeO	Me	Me	MeS(O) <sub>2</sub> Cl	65–70	<1998PS1>

#### 4.20.2.2.3 From ketene dithioacetals

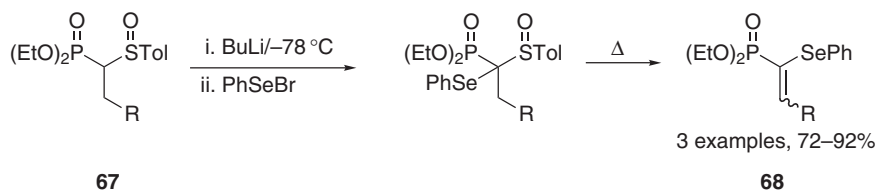
As discussed in Section 4.20.1.2.(i).(a), bis(alkylthio)alkenes **66** bearing electron-withdrawing groups (whose synthesis is discussed in Chapter 4.19) can react with phosphorus nucleophiles to provide the desired products (Equation (36)) <1997TL5201>.



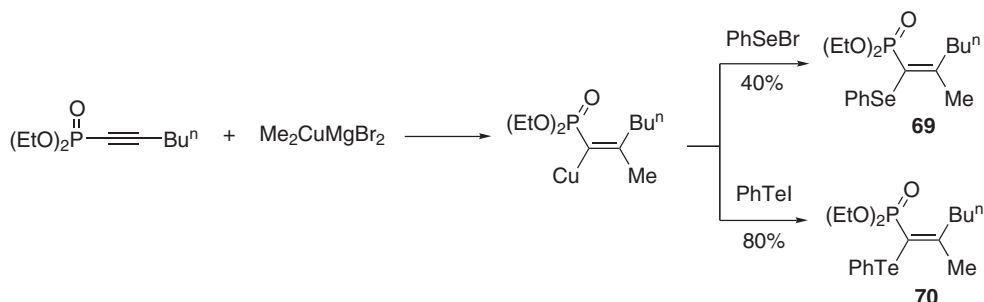
#### 4.20.2.2.4 Functions bearing selenium and tellurium

Midura and Mikolajczyk have synthesized  $\alpha$ -phosphorylvinyl selenide **68** from sulfoxide precursor **67**. Deprotonation of **67** with butyllithium at  $-78^{\circ}\text{C}$  provides an anion that could be captured by phenylselenenyl bromide. Subsequent elimination of sulfenic acid upon heating in benzene at  $80^{\circ}\text{C}$  for 4–5 h affords the selenides in high yields (Scheme 12) <1995TL2871>.

Treatment of alkynylphosphonates with organocuprates and subsequent capture of the intermediate vinylcopper compounds with several electrophiles gives the trisubstituted vinylphosphonates. When phenylselenenyl bromide and phenyltelluranyl iodide were used, the corresponding vinyl selenide **69** and vinyl telluride **70** were obtained (Scheme 13) <1999JOC2950>. In the case of **69**, the 1-bromo-substituted phosphonate was obtained in considerable amount as a side product.

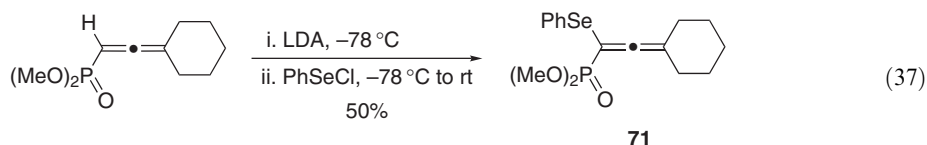


Scheme 12



Scheme 13

As discussed earlier, phosphorylated allenes can be deprotonated with LDA at low temperatures. Quenching of the resulting nucleophile with phenylselenenyl bromide affords vinyl selenide **71** [\(<2000PS265> \(Equation \(37\)\)](#).

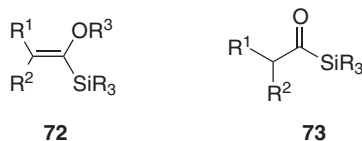


## 4.20.3 FUNCTIONS CONTAINING A CHALCOGEN AND A METALLOID

### 4.20.3.1 Functions Bearing Oxygen

#### 4.20.3.1.1 Oxygen and silicon or germanium

This class of compounds with general formula **72** are formally the enol ethers of the corresponding acyl silanes **73**.

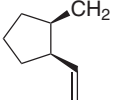
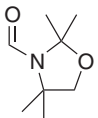
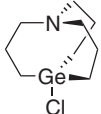



#### (i) Preparation from vinyl ether carbanions

This method is most widely used to generate compounds **74** (Table 14). Nevertheless, access to the vinylic carbanion can be realized starting from different substrates.

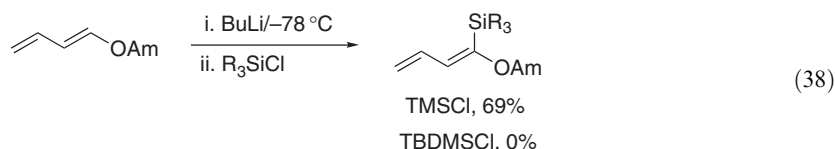
The main method consists of deprotonation of a vinyl ether with an alkyllithium, usually at low temperatures, and subsequent quenching of the resulting anion with a chlorosilane [\(<2002JA10101, 2001JOC2842, 1999HCA561, 1999TL5523>\)](#). Alternatively, hexamethylcyclotri-siloxane can be utilized as demonstrated in the last entry of Table 14 [\(<2000OL3221>\)](#).

**Table 14** Deprotonation of vinyl ethers

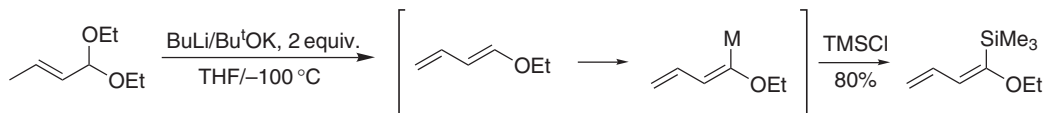
$  \begin{array}{ccc}  R^1 & & OR^2 \\  & \backslash & / \\  & C = C & \\  & / & \backslash \\  H & &   \end{array}  \xrightarrow[\text{ii. } R_3MCl]{\text{i. Base}}  \begin{array}{ccc}  R^1 & & OR^2 \\  & \backslash & / \\  & C = C & \\  & / & \backslash \\  & & MR_3  \end{array}  $					
$R^1$	$R^2$	Base	$R_3MCl$	Yield (%)	References
CH(Bn)(CH <sub>2</sub> CH <sub>2</sub> OH)	Me	Bu <sup>t</sup> Li/0 °C	Me <sub>3</sub> SiCl	72	<2002JA10101>
		Bu <sup>n</sup> Li/(–)-sparteine/0 °C	Me <sub>3</sub> SiCl	84	<2001JOC2842>
CH <sub>2</sub> –CH <sub>2</sub> –CH <sub>2</sub> –	Bu	Bu <sup>t</sup> Li/–78 °C	Pr <sup>i</sup> HSiCl	75	<2000OL3221>
CH <sub>2</sub> –CH <sub>2</sub>		Bu <sup>t</sup> Li/–78 °C	Pr <sup>i</sup> HSiCl	71	<2000OL3221>
H		Bu <sup>t</sup> Li/–78 °C	Pr <sup>i</sup> HSiCl	72	<2000OL3221>
H	Et	Unspecified		86	<1996JOM(508)255>
H	Et	Bu <sup>t</sup> Li/–78 °C	Bu <sup>t</sup> Me <sub>2</sub> SiCl	82	<1999HCA561>
	Me	Bu <sup>n</sup> Li/–40 °C	Me <sub>3</sub> SiCl	62	<1999TL5523>
CH <sub>2</sub> –CH <sub>2</sub> –CH <sub>2</sub> –		Bu <sup>t</sup> Li/–78 °C	(Me <sub>2</sub> SiO) <sub>3</sub>	68	<2000OL3221>

This method has also been used to prepare the only germanium derivative reported <1996JOM(508)255>. These results are summarized in Table 14.

As expected, the size of the chlorosilane is of importance in the silylation of a bulky lithium anion (Equation (38)) <1995T2673>.






The vinyllithium intermediate can also be generated from  $\alpha,\beta$ -unsaturated acetals. Thus, treatment of 1,1-diethoxybut-2-ene with 2 equiv. of Schläpfer's base at –100 °C promotes a 1,4-elimination leading to 1-ethoxybuta-1,3-diene (Scheme 14). Further metallation generates the vinylic anion that reacts with electrophiles <1999S1841>.

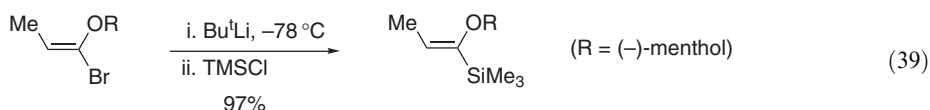
**Scheme 14**

Percy and co-workers <2001TL6377, 1995T10289> and the team of Ishihara and Funabiki <1998JCS(P1)2413> have generated **76** from 2-fluoroethyl ethers **75**. The dehydrofluorination/metallation step is realized by treating **75** with at least 2 equiv. of base in THF at –78 °C and quenching the intermediate vinyllithium with trimethylsilyl chloride. Results are summarized in Table 15.

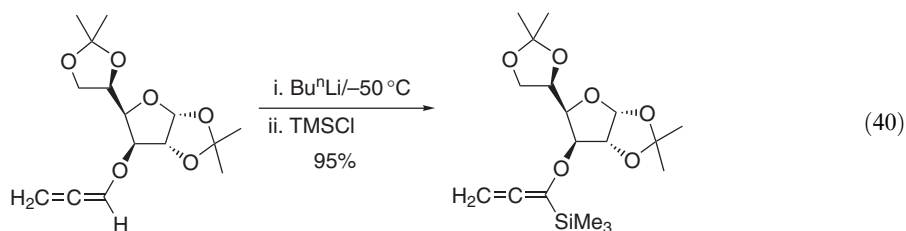
**Table 15** Dehydrofluorination/metallation of 2-fluoroethyl ethers

$  \begin{array}{c}  \text{R}^f\text{F}_2\text{C}-\text{CH}(\text{OR}) \\  \text{75}  \end{array}  \xrightarrow[-78^\circ\text{C}]{\text{Base/THF}}  \begin{array}{c}  \text{R}^f-\text{C}(\text{F})=\text{CH}-\text{OR} \\  \text{Li}  \end{array}  \xrightarrow{\text{TMSCl}}  \begin{array}{c}  \text{R}^f-\text{C}(\text{F})=\text{CH}-\text{OR} \\  \text{SiMe}_3  \end{array}  \text{76}  $				
$\text{R}^f$	$\text{R}$	Base	Yield (%)	References
F	CONEt <sub>2</sub>	LDA	69	<1995T10289>
F		Bu <sup>n</sup> Li	90	<2001TL6377>
F		Bu <sup>n</sup> Li	78	<2001TL6377>
F		Bu <sup>n</sup> Li	90	<2001TL6377>
CHF <sub>2</sub>	Ts	Bu <sup>n</sup> Li/DMPU	79	<1998JCS(P1)2413>
CF <sub>3</sub>	Ts	Bu <sup>n</sup> Li/DMPU	64	<1998JCS(P1)2413>

Halogen–lithium exchange has also been used to generate the vinylic anion that reacts with TMSCl to afford the condensation product in 97% yield (Equation (39)) <2000JA9840>.

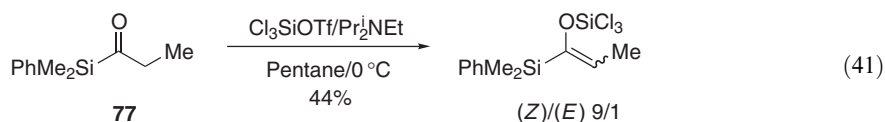


Allenic ethers derived from carbohydrates have also been metallated and the resulting allenyllithium condensed with TMSCl <2001S1377, 2000TA3131>. One example is given in Equation (40).

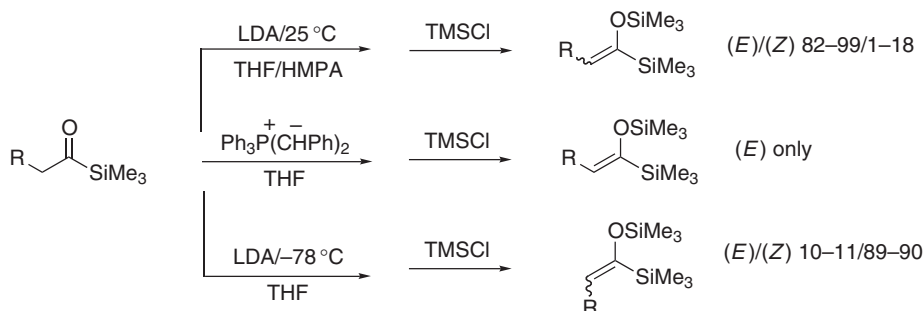


#### (ii) Preparation from acyl silanes

The enolization of acyl silanes has been used by several groups. Treatment of acyl silane **77** by Hünig's base in the presence of trichlorosilyl triflates (Equation (41)) gives a mixture of (*E*) and (*Z*) enolates <1998JOC9517>.

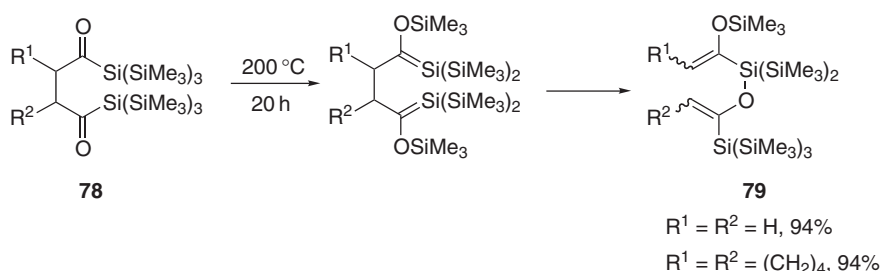


The geometry of the acyl silane silyl enol ether can also be controlled depending on the deprotonation conditions [<2002T6815>](#). Most interesting is the use of the phosphonium diylide prepared from dibenzylidiphenylphosphonium bromide that gives geometrically pure (*E*)-isomers ([Scheme 15](#)).



Scheme 15

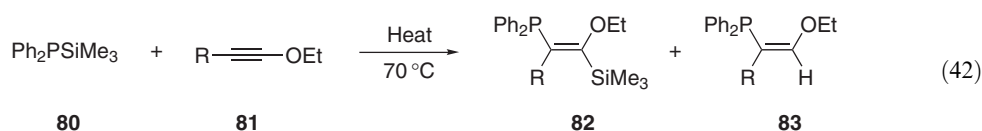
Another Japanese group reports the thermal isomerization of 1,2-bis[tris(trimethylsilyl)silyl-carbonyl]alkanes **78** [<2001JA8400>](#). The formation of **79** is best explained by assuming the formation of an intermediate silene, followed by an oxa-Cope rearrangement ([Scheme 16](#)).



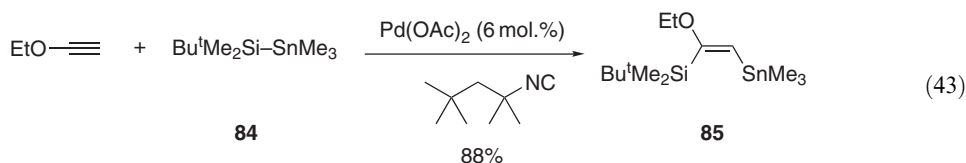
Scheme 16

### (iii) Addition to ynol ethers

Kochetkov and co-workers report the addition of diphenyl(trimethylsilyl)phosphine **80** to alkoxy-acetylenes **81** [<1998IZV1792>](#). Reacting equimolar amounts of **80** and **81** without solvent gives a mixture consisting of (*E*)-(2-alkoxy-2-trimethylsilylalkenyl)phosphine **82**, and (*Z*)-(2-alkoxyalkenyl)-phosphine **83** in a 5/1 ratio. In the presence of solvents, compound **83** becomes the major product ([Equation \(42\)](#)).

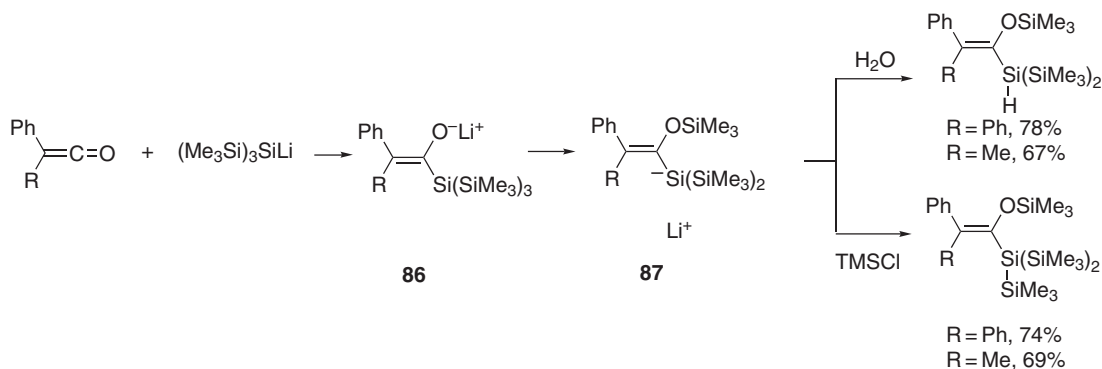


Denmark and Dixon used Ito's silastannylation procedure to generate compound **85**. Thus, palladium-mediated reaction of ethoxy acetylene with silylstannane **84** gives **85** in 88% yield ([Equation \(43\)](#)) [<1998JOC6167>](#).



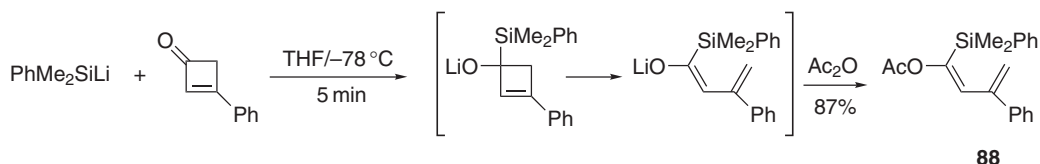
(iv) Addition of silyllithium

Addition of tris(trimethylsilyl)silyllithium to ketenes gives the oxygen anions **86** that rearrange to silicon-based anion **87**. Hydrolysis or quenching with TMSCl gives the corresponding vinyl silanes in good yields (Scheme 17) <1999JOM(574)50>.



Scheme 17

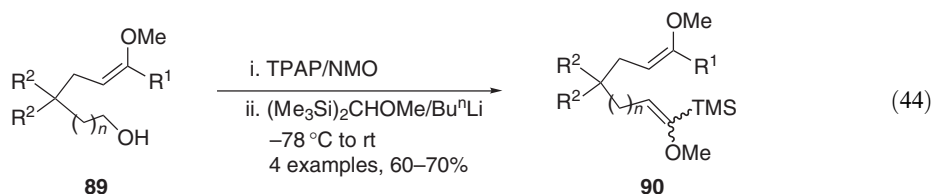
Phenyldimethylsilyllithium adds to cyclobutenone in a 1,2-fashion, followed by immediate ring opening. The resulting lithium enolate was trapped with acetic anhydride to give **88** (Scheme 18) <2001JA6441>.



Scheme 18

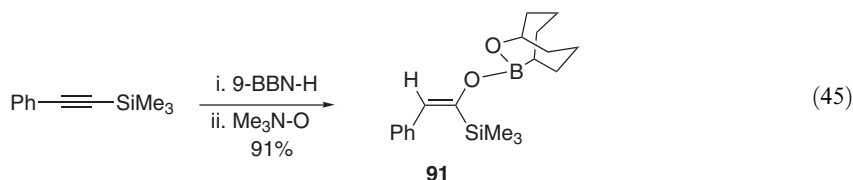
(v) Peterson olefination

Moeller and co-workers used a two-step TPAP oxidation–Peterson olefination to synthesize silylated enol ethers **90** from alcohols **89** (Equation (44)) <2001T5183>.



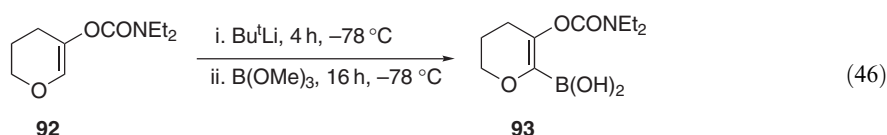
(vi) Oxidation of a C–B bond

Soderquist and León report one example of oxidation of the C–B bond of the hydroboration product of phenyl(trimethylsilyl)alkyne. Oxidation with 2 equiv. of triethylamine *N*-oxide gives styrene derivative **91** in 91% yield (Equation (45)) <1998TL3989>.

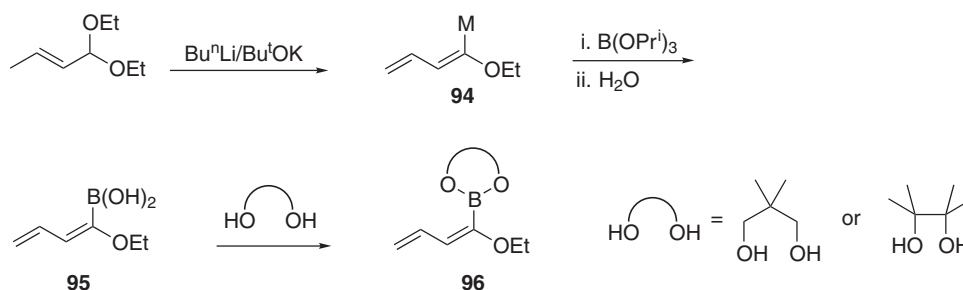


#### 4.20.3.1.2 Oxygen and boron

Few examples of this system appear in the recent literature. Snieckus and co-workers metallated dihydropyran derivative **92** and condensed the resulting vinyl lithium with trimethyl borate. Boronic acid derivative **93** was obtained in 90% yield after hydrolysis and was not purified before use in Suzuki coupling (Equation (46)) <1998JOC1514>.

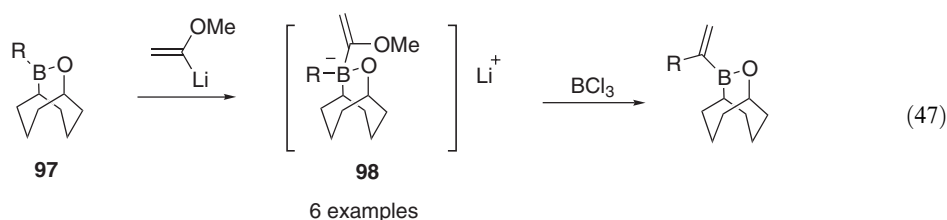


The vinyl lithium anion can also be generated by treatment of an allylic acetal with Schlösser's base. The butadienyllithium **94** thus obtained is condensed with triisopropyl borate to give, after hydrolysis, the boronic acid **95**. Owing to its instability, **95** was isolated as the boronate **96** after esterification with pinacol or 2,2-dimethylpropane-1,3-diol (Scheme 19) <2002OL1275>.



Scheme 19

Finally, one preparation of vinylborinates **98** was reported by Soderquist from *B*-alkyl derivatives of 9-BBN **97**. Thus, reaction of **97** with  $\alpha$ -methoxyvinyl lithium leads to the quantitative formation of stable “ate” complexes **98**, whose reaction with boron trichloride gives rise to the formation of the corresponding neutral vinyl borinates (Equation (47)) <1997TL6639>.



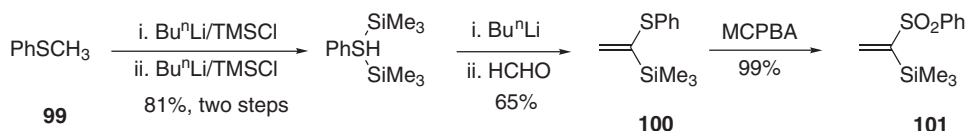


## 4.20.3.2 Functions Bearing Sulfur, Selenium, or Tellurium

## 4.20.3.2.1 Sulfur and silicon or germanium

## (i) Condensation by a Peterson reaction

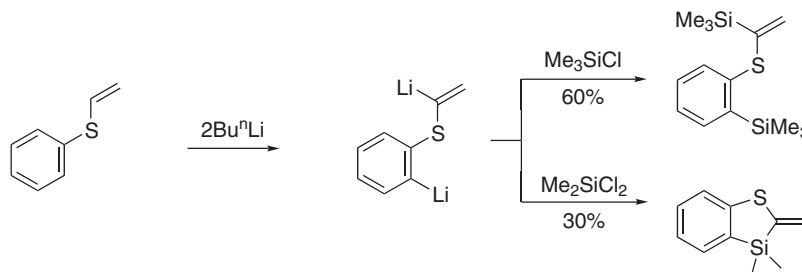
Barton and co-workers prepared the vinylic sulfone **101** by a Peterson olefination <1995AJC407>. Sulfide **99** is dialkylated with TMSCl and treated with BuLi to give the phenyl bis(trimethylsilyl)-methylolithium anion, which reacts with formaldehyde to give vinyl sulfide **100**. Further oxidation with MCPBA gives the corresponding sulfone **101** quantitatively (Scheme 20).



Scheme 20

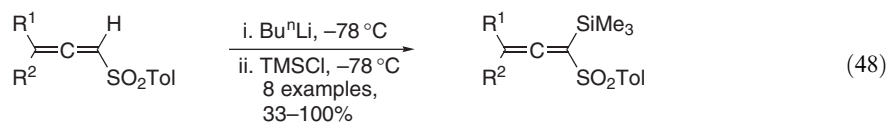
## (ii) Anion reactions

While  $\alpha$ -metallation of aryl thioalkenes is usually best realized using 1 equiv. of Bu<sup>t</sup>Li or LDA in THF at  $-78^\circ\text{C}$ , the group of Cabiddu and Fattuoni employed 2 equiv. of Bu<sup>n</sup>Li at  $0^\circ\text{C}$  to obtain the dimetallated product directly <1998T14095>. Thus, the *ortho, alpha*-dilithiated intermediate is generated, and can be quenched with chlorotrimethylsilane or dichlorodimethylsilane (see Scheme 21).



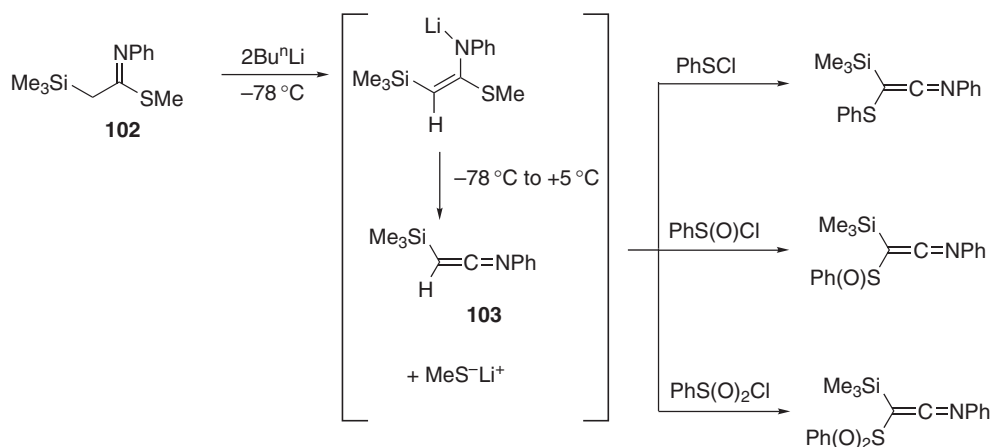
Scheme 21

Allenyl sulfones can similarly be metallated with BuLi at  $-78^\circ\text{C}$  followed by quenching the allenyllithium with TMSCl to give the  $\alpha$ -silylallenyl sulfones (Equation (48)) <1995RTC51>.

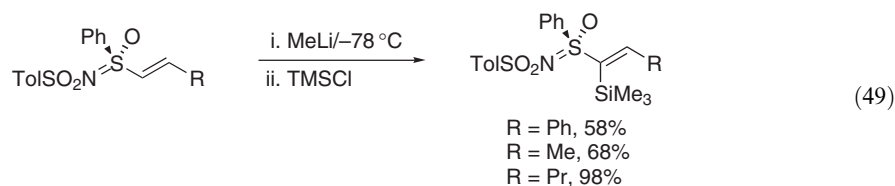


Masson and Fromont obtained silylated keteneimines from *S*-methyl  $\alpha$ -(trimethylsilyl)ethane-imidothioate **102**. Upon lithiation with 2 equiv. of *n*-butyllithium at  $-78^\circ\text{C}$  followed by warming to  $5^\circ\text{C}$ , imidothioester **102** was converted to the silylated ketenimine **103**. Reaction with PhSCl (2 equiv.), PhS(O)Cl (1 equiv.) and the less reactive PhS(O)<sub>2</sub>Cl gave, respectively, the sulfanyl-, sulfinyl-, and sulfonyl ketenimines (Scheme 22) <1999T5405>.

The monolithiation has also been performed using MeLi at  $-78^\circ\text{C}$  to obtain the  $\alpha$ -silyl vinylsulfoximine in good-to-excellent yields (Equation (49)) <1996JCS(P1)1673>.



Scheme 22

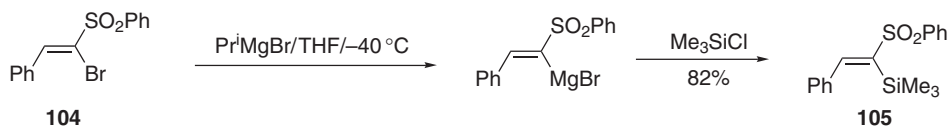


Alternatively,  $\alpha$ -vinyl lithium sulfide or sulfone anion can be obtained by a lithium–halogen exchange reaction. The reaction is realized using either  $\text{Bu}^t\text{Li}$  at  $-78^\circ\text{C}$  <2001TL3771> or  $\text{Bu}^n\text{Li}$  at room temperature <1997SL595>. The results are summarized in Table 16.

Table 16 Lithium–halogen exchange

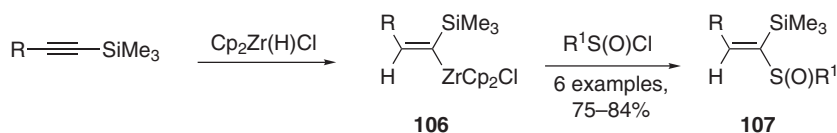
$\text{R}^1-\text{CH}=\text{CH}-\text{SR}^2 \xrightarrow[\text{ii. TMSCl}]{\text{i. RLi}} \text{R}^1-\text{CH}=\text{CH}-\text{SiMe}_3$				
$\text{R}^1$	$\text{R}^2$	$\text{RLi}$	Yield (%)	References
Ph	Me	$\text{Bu}^n\text{Li}/\text{rt}$	60	<1997SL595>
$\text{C}_5\text{H}_{11}$	Me	$\text{Bu}^n\text{Li}/\text{rt}$	71	<1997SL595>
Cyclohexyl	Me	$\text{Bu}^t\text{Li}/-78^\circ\text{C}$	86	<2001TL3771>

Knochel and co-workers realized the lithium–magnesium exchange of  $\alpha$ -bromo vinyl sulfone **104** with  $\text{Pr}^i\text{MgBr}$  in THF at  $-40^\circ\text{C}$ . The vinyl Grignard reagent formed can react with diverse electrophiles, and gives 82% of the silyl derivative **105** (Scheme 23) <2002T4787>.



Scheme 23

Zhong and Guo obtained the zirconocene complex **106** via hydrozirconation of trimethylsilyl acetylene derivatives. The organometallic compounds further react with sulfinyl chloride in THF at  $40^\circ\text{C}$  to afford the vinyl sulfoxides **107** in high yields (Scheme 24) <2001SC615>.

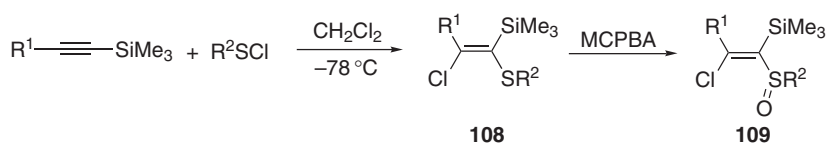


Scheme 24

(iii) Addition to alkynes

One of the simplest ways to access this system involves trimethylsilyl acetylene derivatives as the starting material. Thus addition of alkyl- or arylsulfenyl chloride to the triple bond gives the vinylsulfur compounds **108** <1996JOC1817>, that can be further oxidized to the sulfoxide **109** using MCPBA <2001EJO1643>. The results are summarized in Table 17.

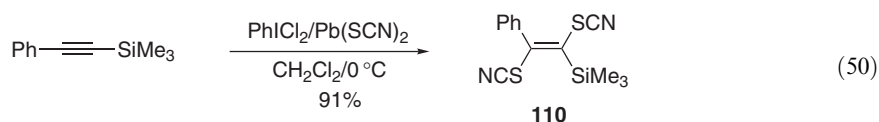
Table 17 Addition of sulfenyl chloride to trimethylsilyl acetylenes



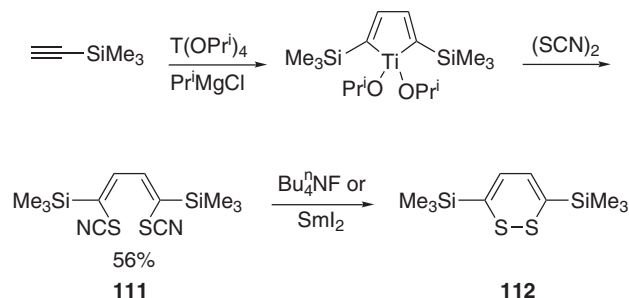
$R^1$	$R^2$	Yield (%)	References
Ph	Ph	86 <sup>a</sup>	<1996JOC1817>
CH <sub>3</sub> (CH <sub>2</sub> ) <sub>5</sub>	Ph	95 <sup>a</sup>	<1996JOC1817>
TMSO(CH <sub>2</sub> ) <sub>3</sub>	Ph	91 <sup>a</sup>	<1996JOC1817>
Ph	TMSCH <sub>2</sub> CH <sub>2</sub>	70 <sup>b</sup>	<2001EJO1643>
Bu <sup>n</sup>	TMSCH <sub>2</sub> CH <sub>2</sub>	62 <sup>b</sup>	<2001EJO1643>
H	TMSCH <sub>2</sub> CH <sub>2</sub>	53 <sup>b</sup>	<2001EJO1643>

<sup>a</sup> Yield of sulfide. <sup>b</sup> Yield after oxidation (two steps).

Moriarty and co-workers investigated the reactivity of the hypervalent iodine reagent PhI(SCN)<sub>2</sub>, prepared *in situ* from PhICl<sub>2</sub> and lead(II) thiocyanate in dichloromethane at 0 °C, with alkynes. In the case of the trimethylsilyl acetylene derivative, the dithiocyanated product **110** was obtained in 91% yield (Equation (50)) <2001TL553>.

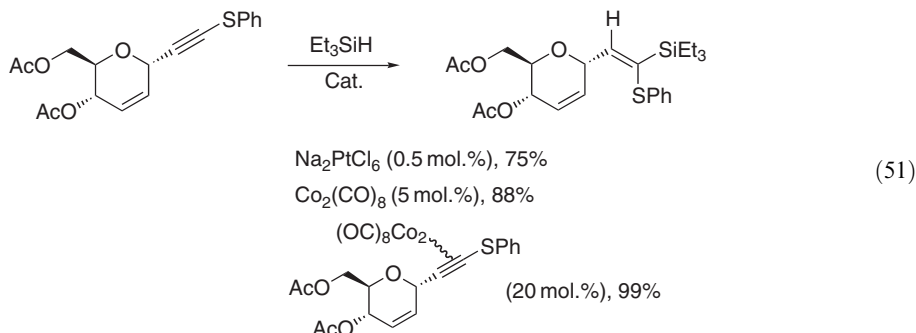


Titanacyclopentadienes, synthesized from alkynes and titanium tetra-isopropoxide, can react with benzene disulfide or other sulfur electrophiles. In the case of trimethylsilyl acetylene, reaction with thiocyanogen affords butadiene **111** in 56% yield, which cyclizes to dithiin **112** upon treatment with Bu<sub>4</sub><sup>n</sup>NF or SmI<sub>2</sub> (Scheme 25) <1999AG(E)1604>.

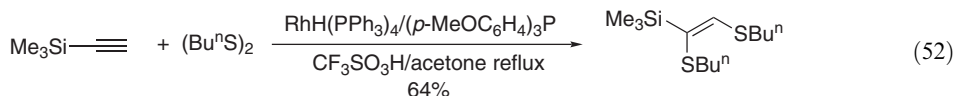


Scheme 25

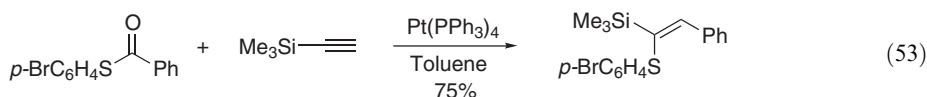
Isobe and co-workers have developed a hydrosilylation of acetylenic compounds in the presence of platinum(II) <1997T5103> or cobalt(III) complexes <1998TL2609, 1999TL6927>. The yield is quantitative with the pre-complexed cobalt derivative. The regioselectivity is extremely high with phenyl thioacetylenes, whereas it is much less selective with other groups (Equation (51)).



Two more examples of the addition of sulfide groups to trimethylsilyl acetylene, catalyzed by transition metal complexes, were reported. The addition of dibutyl disulfide to a terminal alkyne is catalyzed by  $\text{RhH}(\text{PPh}_3)_4$  and trifluoromethanesulfonic acid, no reaction being observed in the absence of either reagent. The addition is stereoselective, giving the (*Z*)-isomer <2001OL763>. Several examples are reported, and in the case of trimethylsilyl acetylene, the addition product is obtained in 64% yield (Equation (52)).

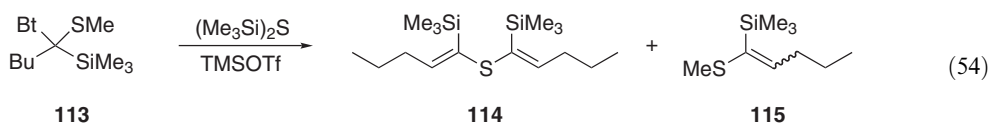


Alkyne can also be carbothiolated with thioesters in the presence of a platinum(0) catalyst. The reaction takes place in toluene, under reflux, with 5 mol.% of platinum tetrakis(triphenylphosphine), whereas no reaction occurs with palladium tetrakis(triphenylphosphine) (Equation (53)) <2001JA5108>.

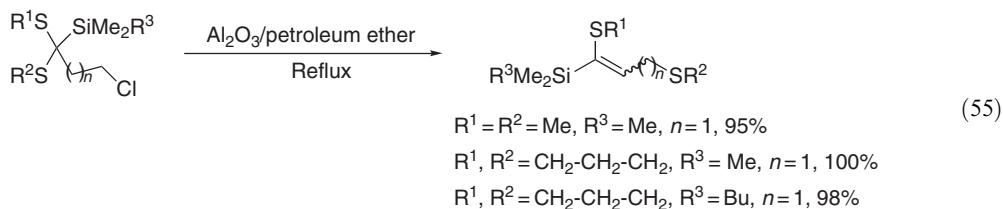


#### (iv) Elimination reactions

Benzotriazole derivative **113** reacts with hexamethyldisilathiane in the presence of TMSOTf or cobalt dichloride to afford the corresponding thioacyl silane. The latter can be trapped with dienes via cycloaddition reactions. In the special case of **113**, use of TMSOTf as a Lewis acid gives a mixture of vinyl sulfides **114** and **115** (Equation (54)) <2000JOC9206>.

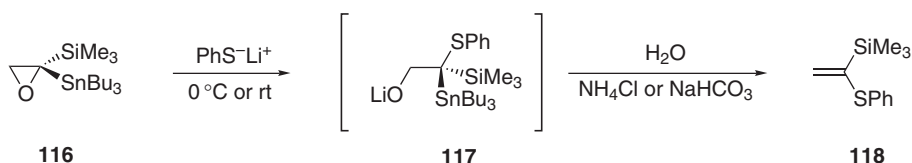


Chloroalkyl dithioketals rearrange to  $\alpha$ -silyl vinyl sulfides when treated with alumina in refluxing petroleum ether (Equation (55)) <2001TL7779>.



(v) From epoxides

$\alpha$ -Silylepoxyastannane **116** is attacked at the  $\alpha$ -position by lithium phenyl sulfide to give the intermediate lithium alkoxide **117**. Surprisingly, instead of undergoing the Peterson elimination to give the  $\alpha$ -stannylated vinyl sulfide, the only product isolated was the  $\alpha$ -silylated vinyl sulfide **118** resulting from elimination of  $\text{HOSnBu}_3$  (Scheme 26) <2001TL8993>.

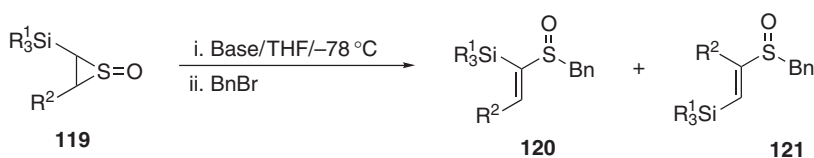


Scheme 26

(vi) From thiirane S-oxide

Schwan and co-workers have shown that thiirane S-oxides **119**, when treated with a base, can lead to the sole formation of elimination products **120** and **121** instead of the possible desulfurization product <1995JA184, 2000SUL111>. Results are summarized in Table 18.

Table 18 Opening of thiiran S-oxide



$\text{R}^1$	$\text{R}^2$	Base	Yield (%)	
			120/121	References
Et	H	LDA	18/49	<1995JA184>
Et	H	$\text{LiN}(\text{TMS})_2$	58/0	<1995JA184>
Et	H	$\text{KN}(\text{TMS})_2$	36/15	<1995JA184>
Ph	H	$\text{LiN}(\text{TMS})_2$	36/0	<1995JA184>
Me	Bu	$\text{LiN}(\text{TMS})_2$	57/0	<1995JA184>
$\text{Me}_2\text{Bu}^\dagger$	Bu	$\text{LiN}(\text{TMS})_2$	54/0	<1995JA184>
Et	H	$\text{MeLi-LiBr}$	46/23	<2000SUL111>

(vii) From acyl silanes

Bonini and co-workers have reported that acyl silanes containing a hydrogen atom  $\alpha$  to the carbonyl can be transformed stereoselectively into (Z)- $\alpha$ -silyl-enethiols. The thionation is performed at low temperatures with hydrogen sulfide and hydrogen chloride, followed by neutralization of the ethereal solution with sodium bicarbonate (Table 19) <1999SL486, 1996T4803, 1996JCS(P1)2803>.

**Table 19** Thionation of acyl silanes

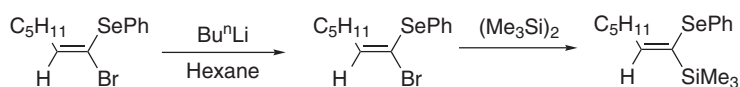
$\text{R}-\text{C}(=\text{O})-\text{SiMe}_2\text{Ph} \xrightarrow[\text{ii. NaHCO}_3]{\text{i. H}_2\text{S / HCl}} \text{R}-\text{C}(\text{SH})=\text{SiMe}_2\text{Ph}$		
<i>R</i>	Yield (%)	References
(CH <sub>2</sub> ) <sub>2</sub> CO <sub>2</sub> H	75	<1999SL486>
(CH <sub>2</sub> ) <sub>4</sub> CO <sub>2</sub> H	86	<1999SL486>
(CH <sub>2</sub> ) <sub>6</sub> CO <sub>2</sub> H	85	<1999SL486>
CH <sub>2</sub> Cl	87	<1996T4803>
(CH <sub>2</sub> ) <sub>2</sub> Cl	100	<1996T4803>
(CH <sub>2</sub> ) <sub>8</sub> Br	100	<1996T4803>
(CH <sub>2</sub> ) <sub>10</sub> Br	96	<1996T4803>

#### 4.20.3.2.2 Selenium or tellurium together with silicon or germanium

The small number of reported syntheses of these compounds can be divided into two main classes: addition to substituted alkynes and reaction of selenium-stabilized anions.

##### (i) Reaction of selenium-stabilized anions

$\alpha$ -Bromo vinyl selenides can be treated with Bu<sup>n</sup>Li at 0 °C to give the intermediate vinyl lithium, which reacts with electrophiles. While the reaction was unsuccessful with TMSCl, (Me<sub>3</sub>Si)<sub>2</sub> reacts at 65 °C (Scheme 27) <1997SL595>.

**Scheme 27**

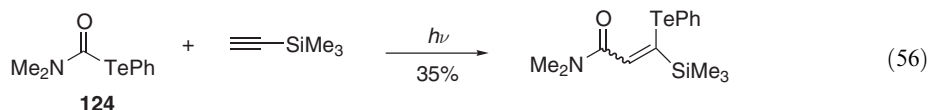
##### (ii) Addition to alkynes

The group of Murai and Kato has studied the reaction of selenoamides **122** with organolithium reagents. While reaction with 2 equiv. of the nucleophile gives the unsymmetrical ketone, reaction with 1 equiv. of trimethylsilyl acetylide gives the conjugated ketone **123** (Table 20) <1998TL4329, 2001OL1993>.

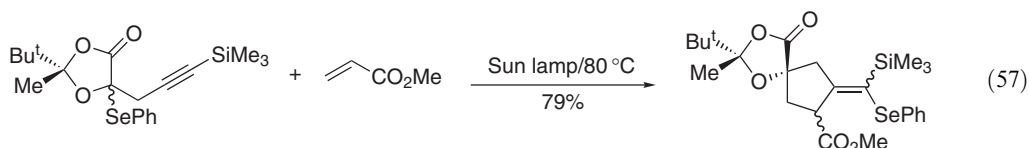
**Table 20** Addition of acetylide to selenoamides

$\text{R}-\text{C}(=\text{Se})-\text{N}(\text{CH}_2)_3 + \text{Me}_3\text{Si}-\text{C}\equiv\text{C}-\text{Li} \longrightarrow \text{R}-\text{C}(=\text{O})-\text{CH}(\text{SeMe})=\text{C}(\text{SiMe}_3)-\text{C}\equiv\text{C}-\text{R}$			
<i>R</i>	Conditions	Yield (%)	References
	i) TMEDA/Et <sub>2</sub> O, 3 h ii) MeI, 3 min	78	<1998TL4329>
4-MeOC <sub>6</sub> H <sub>4</sub>	i) MeOTf, 30 s ii) RLi, 1.5 h	72	<2001OL1993>
4-BrC <sub>6</sub> H <sub>4</sub>	i) MeOTf, 30 s ii) RLi, 1.5 h	64	<2001OL1993>
Bn	i) MeOTf, 30 s ii) RLi, 1.5 h	54	<2001OL1993>

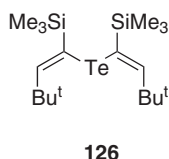
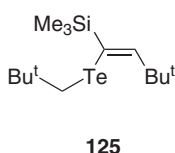
Carbamotelluroate **124** adds to acetylenes under irradiation. The addition proceeds via formation of carbamoyl and PhTe radicals formed by homolytic cleavage of the carbamoyl-C—Te bond. The carbamoyl radical adds to the triple bond and the vinylic radical thus formed is trapped by the tellurium radical (Equation (56)) <2001OL2085>.



Renaud and co-workers have reported examples of radical-mediated [3 + 2] annulation from homopropargylic phenyl selenides. The homolytic cleavage of the C—Se bond is realized by irradiation with a sun lamp. The generated radical reacts with methyl acrylate to give a vinylic radical that couples with the PhSe radical (Equation (57)) <1999EJO477>.

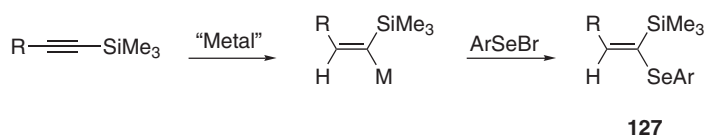


Sonoda and co-workers have shown that the carbottelluration of alkynes could be realized by photoinduced or radical addition of di-alkyl tellurides on triple bonds. When tellurides having one -Bu<sup>t</sup> group are used, the addition is regio- and stereoselective, and gives the vinylic telluride **125** in 62% isolated yield <1998TL5511>. When 2 equiv. of acetylides are used, the divinyl telluride **126** is obtained in 86% yield <1998PS637>.



Trimethylsilyl acetylenes can also undergo hydrozirconation or hydromagnesiation followed by metal–selenium exchange to access this system. Thus hydrozirconation of acetylenes yields the zirconium complexes. Reaction with aryl selenyl bromides at 60 °C gives the vinyl selenides in good yields (Table 21) <1998SC4165>. The same kind of silylated acetylenes are hydromagnesiated with Grignard reagents in the presence of titanium catalyst. The α-silyl vinyl Grignard further reacts with selenyl bromide to afford the α-selenyl vinyl silanes **127** in good yields <2002S1347>.

**Table 21** Hydrometallation followed by metal–selenium exchange



<i>R</i>	“Metal” conditions	<i>Ar</i>	Yield (%)	References
C <sub>6</sub> H <sub>13</sub>	Cp <sub>2</sub> Zr(H)Cl THF, rt	Ph	85	<1998SC4165>
C <sub>6</sub> H <sub>13</sub>	Cp <sub>2</sub> Zr(H)Cl THF, rt	Tolyl	87	<1998SC4165>
CH <sub>3</sub> OCH <sub>2</sub>	Cp <sub>2</sub> Zr(H)Cl THF, rt	Ph	80	<1998SC4165>
Ph	Cp <sub>2</sub> Zr(H)Cl THF, rt	Ph	81	<1998SC4165>
Bu	Bu <sup>t</sup> MgBr/Et <sub>2</sub> O Cp <sub>2</sub> TiCl <sub>2</sub> (5 mol.%)	Ph	81	<2002S1347>
Bu	Bu <sup>t</sup> MgBr/Et <sub>2</sub> O Cp <sub>2</sub> TiCl <sub>2</sub> (5 mol.%)	Tolyl	78	<2002S1347>
Hexyl	Bu <sup>t</sup> MgBr/Et <sub>2</sub> O Cp <sub>2</sub> TiCl <sub>2</sub> (5 mol.%)	Ph	82	<2002S1347>
Bn	Bu <sup>t</sup> MgBr/Et <sub>2</sub> O Cp <sub>2</sub> TiCl <sub>2</sub> (5 mol.%)	Ph	72	<2002S1347>
Bn	Bu <sup>t</sup> MgBr/Et <sub>2</sub> O Cp <sub>2</sub> TiCl <sub>2</sub> (5 mol.%)	Tolyl	68	<2002S1347>

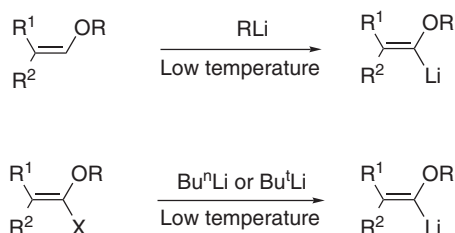
**4.20.4 FUNCTIONS CONTAINING A CHALCOGEN AND A METAL****4.20.4.1 Oxygen Functions**

A wide variety of vinyl ethers bearing a metal at C-1 have been prepared. Some are stable and have been isolated and characterized. Others are reactive intermediates and have the reactivity and stability that can be expected for organometallics. This subject was reviewed in the corresponding section of COFGT (1995), as well as in Friesen's review <2001JCS(P1)1969> dealing with the preparation and reactivity of  $\alpha$ -metallated vinyl ethers, covering the period from 1951 to 1996.

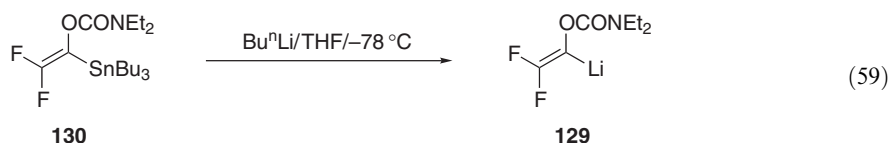
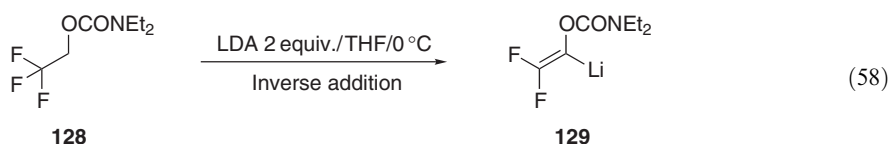
Thus, lithium and tin are the more important metals as described below.

**4.20.4.1.1 Lithium**

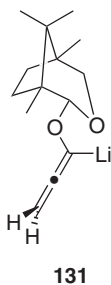
Most of the reactions generating 1-oxyalkenyllithiums have been reported by Kennewell, Westwood and Westwood in COFGT (1995) <1995COFGT(4)879> and involve either the direct metallation of a vinyl ether with a strong base at low temperatures or halogen-metal exchange of  $\alpha$ -halogenovinyl ethers with butyllithium at  $-78^\circ\text{C}$  (Scheme 28).

**Scheme 28**

Nevertheless, a few nonclassical methods are also reported. Percy and co-workers prepared lithium enol carbamate **129** by dehydrofluorination of **128** as well as by tin-lithium exchange of vinylstannane **130** (Equations (58) and (59)) <1996TL8233>.

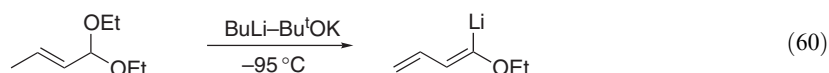


Tius and Harrington prepared lithio allene **131** by deprotonation of the corresponding allene by butyllithium in THF between  $-78^\circ\text{C}$  and  $-30^\circ\text{C}$  <2001JA8509>. This chiral reagent allows high asymmetric induction in the condensation step.





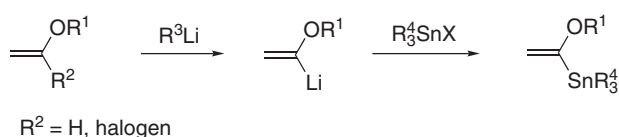
Treatment of crotonaldehyde diethyl acetal with Schläpfer's base at  $-95^{\circ}\text{C}$  readily gives the  $\alpha$ -metallated 1-ethoxy butadiene (Equation (60)) <2002OL1275>.


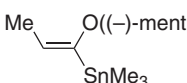
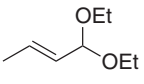
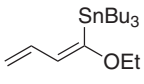
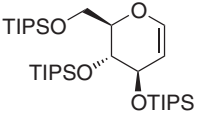
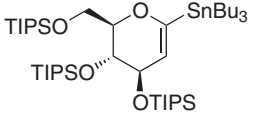
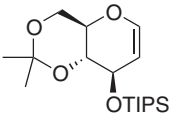
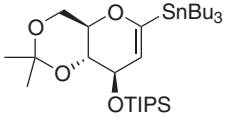
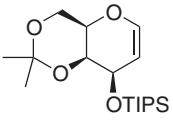
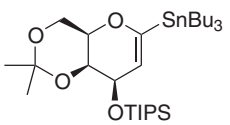


#### 4.20.4.1.2 Tin

The main route to 1-alkoxyvinylstannanes consists of transmetalation with the corresponding lithium compound. The vinyl lithium is obtained by direct metallation or by halogen-lithium exchange (Table 22).

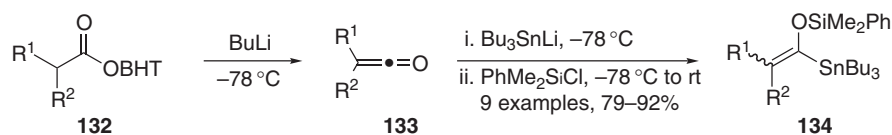
**Table 22** Preparation of 1-trialkylstannyl-1-alkoxyalkanes from vinyl lithium



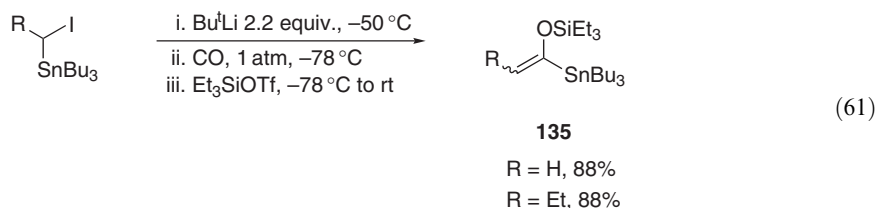
Vinyl ether	$\text{R}^3\text{Li}$	Tin halide	Products	Yield (%)	References
$\text{Me}-\text{CH}=\text{CH}-\text{O}((-)\text{-menthol})$ 	$\text{Bu}^t\text{Li}$	$\text{Me}_3\text{SnCl}$		98	<2000JA9840>
	$\text{Bu}^n\text{Li}$ - $\text{Bu}^t\text{OK}$	$\text{Bu}_3\text{SnCl}$		64	<2001JCS(P1)437>
	$\text{Bu}^t\text{Li}$	$\text{Bu}_3\text{SnCl}$		78	<2001JOM(621)77>
	$\text{Bu}^t\text{Li}$	$\text{Bu}_3\text{SnCl}$		89	<2001JOM(621)77>
	$\text{Bu}^t\text{Li}$	$\text{Bu}_3\text{SnCl}$		33	<2001JOM(624)172>

Other routes to these compounds are less versatile. Barbero and Pulido have added tributylstannyl lithium to the intermediate ketene **133** obtained from the BHT esters **132** (Scheme 29). The enolates are further trapped with phenyldimethylchlorosilane to give the  $\alpha$ -stannylvinyl ethers **134** in good yields <2001SL827>.

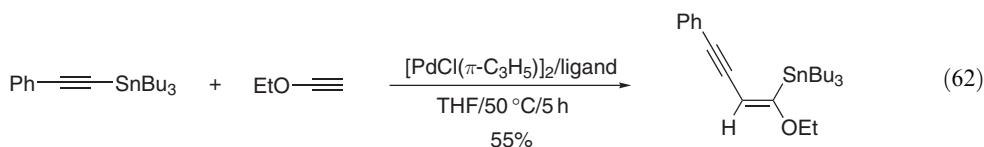
Murai and co-workers have generated stannylmethyl lithium by treatment of the corresponding iodide with  $\text{Bu}^t\text{Li}$  at  $-50^{\circ}\text{C}$  in diethyl ether. Exposure to carbon monoxide, followed by quenching the resulting enolate as a silyl ether resulted in the formation of **135** in good yield (Equation (61)) <1999JOM(574)171>.



Scheme 29



Vinylstannanes could be prepared by noncatalyzed as well as by palladium-catalyzed carbostannylation of alkynes. Shirakawa and Hiyama reported the palladium-catalyzed stannylation of diverse alkynes [\[1999JOM\(576\)169\]](#). In the case of ethoxyacetylene, the reaction is highly regioselective (Equation (62)).

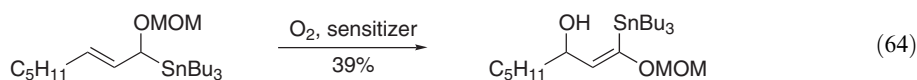
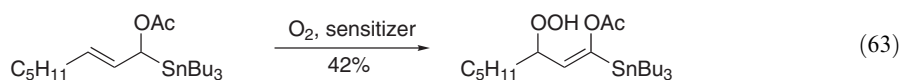


Lébl and co-workers have studied the catalyzed and noncatalyzed carbostannylation of alkynes [\[2001JOM\(625\)86\]](#). As summarized in Table 23, the expected  $\alpha$ -alkoxyvinylstannanes **136** are obtained as the minor products.

Table 23 Carbostannylation of alkoxyalkynes

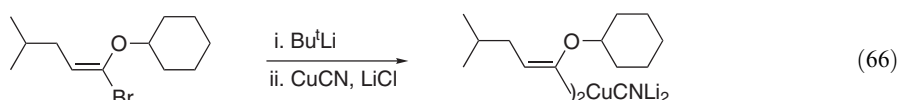
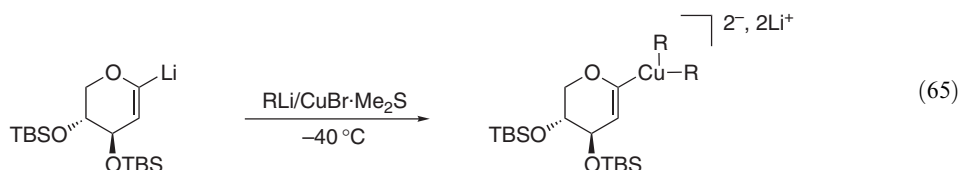
$  \begin{array}{c} \text{R} \\   \\ \text{C}\equiv\text{C} \\   \\ \text{OEt} \end{array} \xrightarrow{\text{Ph}_3\text{SnH}} \begin{array}{c} \text{R} \\   \\ \text{C}=\text{C}-\text{SnPh}_3 \\   \\ \text{OEt} \end{array} + \begin{array}{c} \text{R} \\   \\ \text{C}=\text{C}-\text{SnPh}_3 \\   \\ \text{OEt} \end{array}  $				
		<b>136</b>	<b>137</b>	
<i>R</i>	Catalyst	% ( <b>136</b> )	% ( <b>137</b> )	References
H	None	0	100	<a href="#">[2001JOM(625)86]</a>
Bu	None	3	80	<a href="#">[2001JOM(625)86]</a>
H	$\text{Pd}(\text{PPh}_3)_4$	30	70	<a href="#">[2001JOM(625)86]</a>
Bu	$\text{Pd}(\text{PPh}_3)_4$	54	46	<a href="#">[2001JOM(625)86]</a>

Dussault and co-workers have prepared  $\alpha$ -alkoxyvinylstannane by photooxygenation of allylic  $\alpha$ -alkoxystannanes [\[1999JCS\(P1\)2189\]](#). Instead of the expected dioxolane, the hydroperoxide was generated (Equation (63)). Alternatively, the alcohol could be obtained after reduction (Equation (64)).

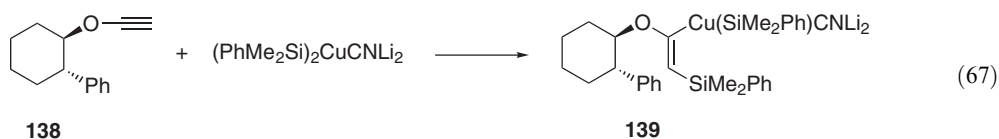


#### 4.20.4.1.3 Copper

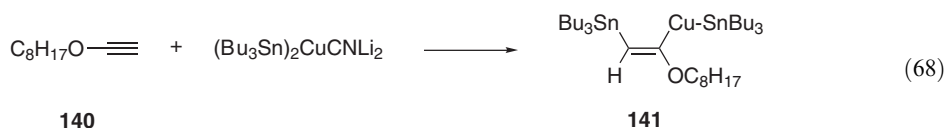
$\alpha$ -Lithiated vinyl ethers can be transmetalated with copper bromide–methyl sulfide complex (Equation (65)) <2002CC426> or copper cyanide (Equation (66)) <2001JA3369> at low temperatures to give the corresponding vinylcopper that further reacts or rearranges.



Alkoxyalkynes can undergo silylcupration. In the case of **138**, the product of  $\beta$ -addition **139** is formed exclusively <1997JA125> (Equation (67)).

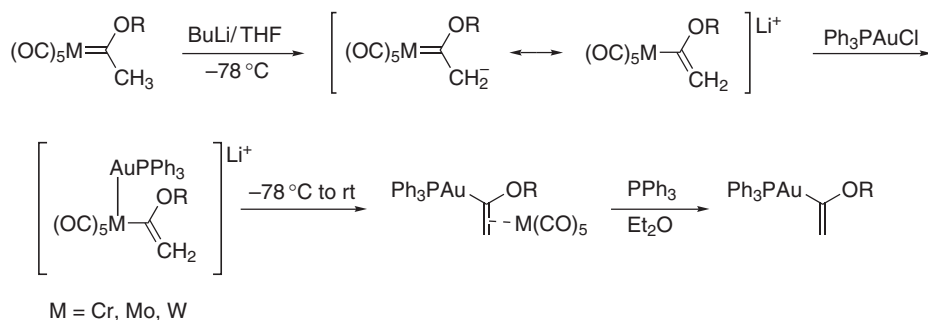


Similarly, stannylcupration of alkoxyalkyne **140** leads to the vinylcuprate **141** (Equation (68)) <1997JA3878>.



#### 4.20.4.1.4 Transition metals

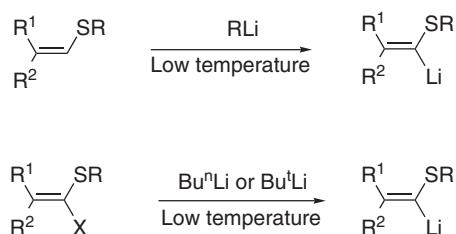
A number of transition metal complexes are known, with diverse access routes and stabilities. Only one example of a gold complex prepared and isolated by Raubenheimer and co-workers is highlighted here (Scheme 30) <2002OM3173>. The Fischer carbene was deprotonated at  $-78^\circ\text{C}$  and the resulting vinyl ether condensed with the  $\text{Ph}_3\text{PAu}^+$  electrophile. The gold complexes can be purified by low temperature ( $-15^\circ\text{C}$ ) column chromatography. In the case of chromium and tungsten, the metal can be decoordinated by treatment with a stronger coordinative ligand such as  $\text{Ph}_3\text{P}$ .



Scheme 30

**4.20.4.2 Sulfur Functions****4.20.4.2.1 Lithium**

As with the oxygen compounds described earlier, most of the methods reported to access these systems have been reviewed in COFGT (1995) <1995COFGT(4)879> and involve either a direct metallation of a vinyl sulfide or a halogen–lithium exchange (Scheme 31). These compounds are only reaction intermediates and are obviously not isolated.

**Scheme 31**

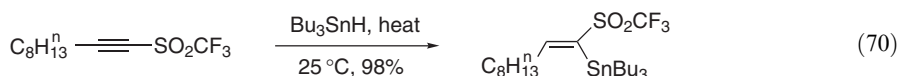
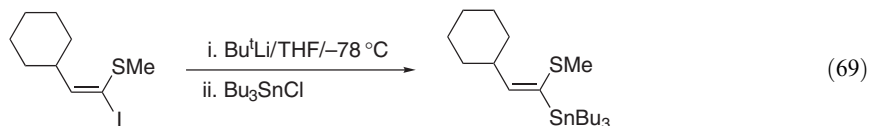
Results are summarized in Table 24.

**Table 24**  $\alpha$ -Lithiation of vinylsulfur compounds

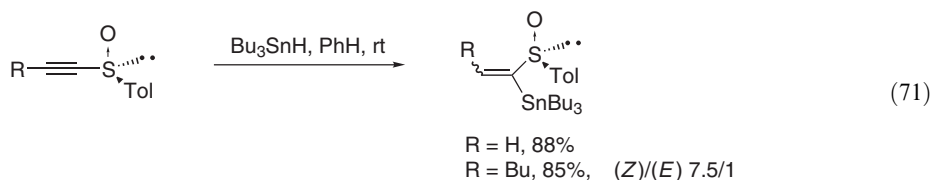
<i>Starting material</i>	<i>Conditions</i>	<i>Product</i>	<i>References</i>
	1.5 BuLi, rt		<1997SL595>
	1.5 BuLi, rt		<1997SL595>
	2 BuLi, 0 °C		<1998T14095>
	2 BuLi, -78 °C		<1999TL5957>
	BuLi-Bu^tOK		<2000JA5052>
	Bu^tLi, -78 °C		<2001TL3771>

## 4.20.4.2.2 Tin

In contrast to the lithium compounds, the tin analogs are stable and isolable compounds. Surprisingly, the most obvious route to this system (reaction of the  $\alpha$ -lithiovinyl sulfides described in the previous section with a stannyl chloride) is seldom used (Equations (69) and (70)) <2001TL3771, 1996JA4284>.



Thus, the main route is the palladium-catalyzed hydrostannylation of alkynes, although non-catalyzed reactions are reported (Equation (71)) <1995TL3605, 1997JOC6326>. The regioselectivity of this noncatalyzed hydrostannylation implies that the reaction proceeds via conjugate addition of the hydride.

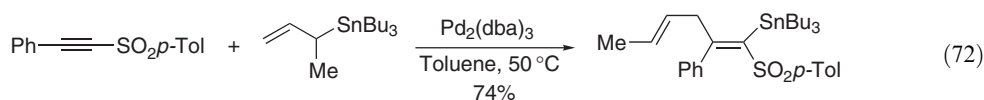


The palladium-catalyzed hydrostannylation is performed in an apolar solvent (benzene, toluene) with palladium tetrakis(triphenylphosphine) as the catalyst. The reaction is generally highly regio- and stereoselective. Results are summarized in Table 25.

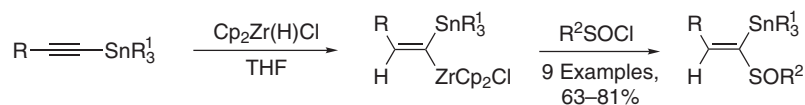
**Table 25** Palladium-catalyzed hydrostannylation of alkynes

$\text{R}^1\text{-C}\equiv\text{C-SR}^2 \xrightarrow{\text{R}^3\text{SnH, [Pd(PPh)}_4\text{]}} \text{R}^1\text{-CH=CH-SR}^2\text{-SnR}^3$					
$\text{R}^1$	$\text{SR}^2$	$\text{R}^3$	(Z)/(E)	Yield (%)	References
	SPh	Bu	0/1		<1998AG(E)1724>
$\text{C}_8\text{H}_{13}^n$	$\text{SO}_2\text{CF}_3$	Bu	1.7/1	80	<1996JA4284>
$\text{C}_8\text{H}_{13}^n$	$\text{SO}_2\text{CF}_3$	Ph	1/1.5	82	<1996JA4284>
		Ph	0/1	35	<2000JA5052>
Bu	Sp-Tol		0/1		<2002JOC8166>

Shirakawa and co-workers have also reported and studied the mechanism of the palladium-catalyzed allylstannylation of alkynes. The reaction is regioselective both in the allylic and alkynic moieties (Equation (72)) <2000OL2209>.



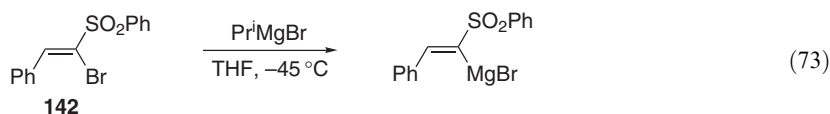
Hydrozirconation of alkynylstannanes followed by reaction with sulfinyl chloride affords (*Z*)- $\alpha$ -stannyl unsaturated sulfoxides in good yields with isomeric purities more than 96% (Scheme 32) <2000JOM(603)249>.



Scheme 32

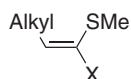
#### 4.20.4.2.3 Magnesium

Knochel and co-workers showed that bromine–magnesium exchange in the vinyl sulfone **142** takes place in THF at  $-45^\circ\text{C}$  in 1 h, affording the Grignard reagent (Equation (73)) <2002T4787>.



#### 4.20.4.2.4 Zinc

Jin and co-workers showed that  $\alpha$ -bromovinyl sulfides **143** could be metallated with *t*-butyllithium to form **144**, followed by transmetalation with anhydrous zinc chloride to give the zinc compounds **145** <2002OL691>.



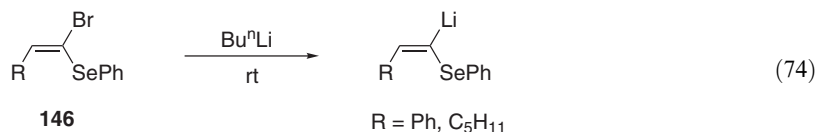
**143** X = Br

**144** X = Li

**145** X = ZnCl

#### 4.20.4.3 Selenium Functions

Metallation of the  $\alpha$ -bromovinyl selenide **146** is realized with *n*-butyllithium at ambient temperature (Equation (74)). The resulting vinyl lithium is further reacted with electrophiles <1997SL595>.



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**Biographical sketch**

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## 4.21

# Functions Containing at Least One Nitrogen and No Halogen or Chalcogen

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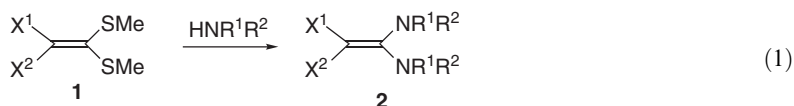
## 4.21.1 FUNCTIONS CONTAINING TWO NITROGENS, $R_2^3C=CNR_2^1NR_2^2$ , etc.

### 4.21.1.1 Ketene Aminals, $R_2^3C=CNR_2^1NR_2^2$

Ketene aminals **2** are tautomeric with amidines but are less stable. Therefore, ketene aminals reported in the literature either contain stabilizing electron-withdrawing groups at the  $\beta$ -position or contain tertiary amino groups that prevent the formation of the amidine tautomer. Ketene aminals of the former type often have low energy barriers to rotation about the formal double bond such that geometrical isomerism is not observed unless other factors such as intramolecular hydrogen bonding are present. A large variety of methods have been reported for the synthesis of ketene aminals <1995COFGT(4)967>. Several of these have continued to be used since the 1990s in particular the use of ketene dithioacetals or ketene N,S-acetals.

#### 4.21.1.1.1 From ketene dithioacetals and ketene N,S-acetals

The reaction of ketene dithioacetals **1** with two or more equivalents of amine remains a popular method for the synthesis of ketene aminals **2** (Equation (1)) <2000MI307, 1994JPR357, 1983EUP0092647, 1997HCA273, 1988EUP0286153>.

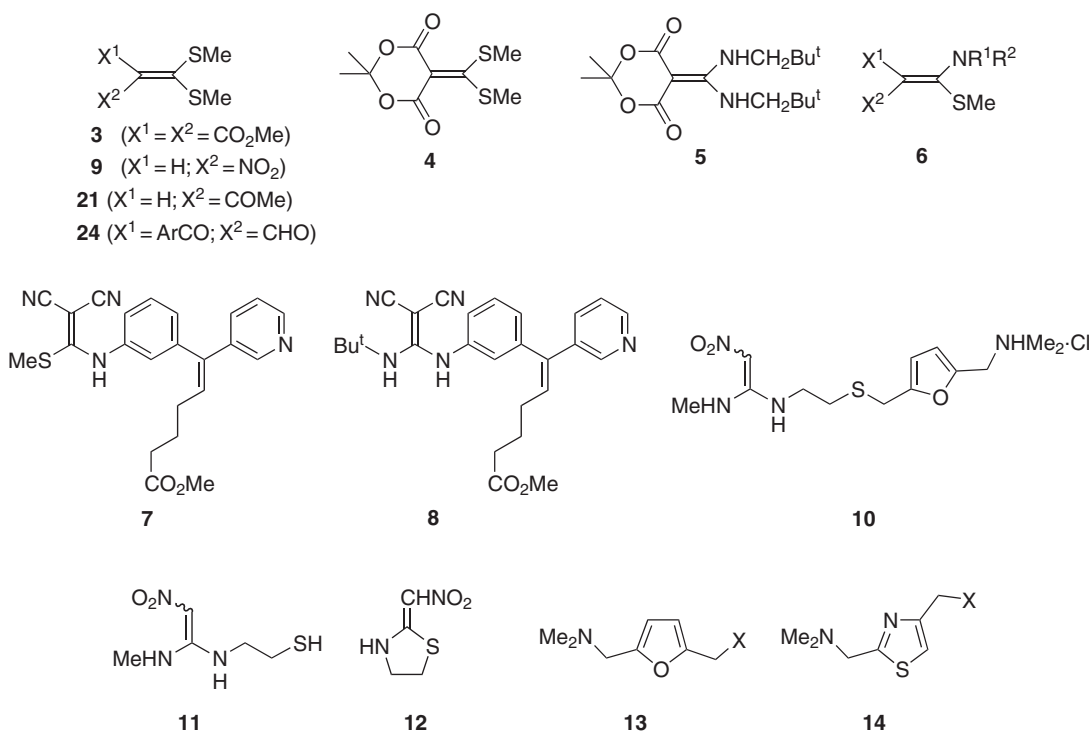


The reaction rate depends on the strength of the electron-withdrawing group(s) at the  $\beta$ -position as well as the strength of the attacking amine. Ketene dithioacetals bearing two ester groups, e.g., **3**, do not normally react with amines. However, the 5-bis(methylthio)methylene derivative of Meldrum's acid **4** reacts with 2 equiv. of 2,2-dimethylpropylamine to give the ketene aminal **5** <2002JOC2619>.

Mixed ketene aminals are obtained by reacting ketene dithioacetals with 1 equiv. of an amine, isolating the intermediate ketene *N,S*-acetal **6**, then substituting the second alkylthio group with a different amine <2003USP6525069, 2002JOC2619, 1999MI93, 1999JMC1235, 1995BMC279, 1997HCA273, 1993EUP547517, 1994EUP591891, 1996USP5521177, 1988EUP0286153, 1992JMC2327>. In certain cases, the second substitution may prove difficult and it is necessary to oxidize the ketene *N,S*-acetal prior to the second substitution <1993EUP547517, 1994EUP591891, 1996USP5521177>. For example, reaction of the ketene *N,S*-acetal **7** with *t*-butylamine proved unsuccessful. Prior oxidation of the ketene *N,S*-acetal with *m*-chloroperbenzoic acid, then reaction with *t*-butylamine was more successful giving the desired ketene aminal **8** in 43% yield <1999JMC1235>. Mercuric oxide and mercuric chloride have also been used in the reaction of a ketene *N,S*-acetal with an amine to aid the second substitution <1997JOC4240>.

Mixed ketene aminals containing a  $\beta$ -nitro group are obtained from the ketene dithioacetal **9** and are of particular interest to the pharmaceutical industry. The histamine antagonist agent ranitidine **10** has been used for many years as an antiulcer agent and can be synthesized by a variety of ways using the ketene dithioacetal **9** (e.g., <1996EUP0697411, 1997USP5696275>). One of these methods involves the intermediate **11** which can in turn be synthesized from **9** <1993PHA143>.

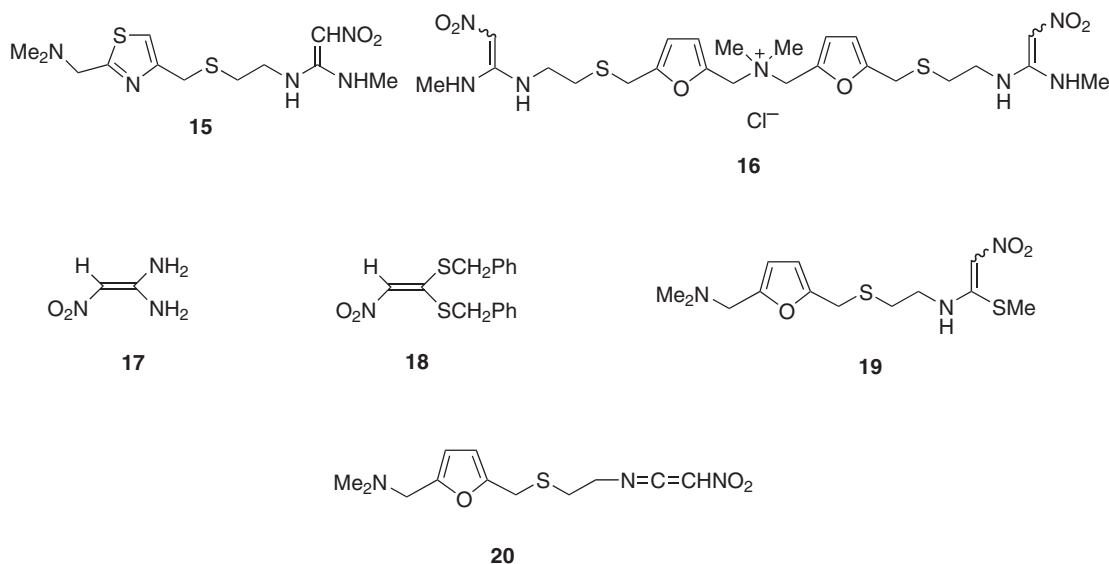
An interesting alternative approach to the synthesis of ranitidine and nizatidine **15** has been the use of the thiazolidine **12**, which can also be viewed as a ketene *N,S*-acetal. Treatment of **12** with methylamine results in the formation of the thiol **11**, which can be alkylated *in situ* with the alkyl halides **13** or **14** to give ranitidine or nizatidine, respectively <1998WOP9811081, 1997USP5672724>.



The ketene dithioacetal route has been used to introduce the  $\beta$ -nitroketene aminal moiety into other structures with a variety of pharmacological activities including histamine antagonists <1998MI187, 1998MI177, 1994AP455, 1996AP87, 1995AP349, 1994MI308, 1994JMC57, 1996USP5541335, 1992CPB2432>, structures having dual histamine H2 and gastrin receptor antagonist activity <1997CPB116>, adrenoceptor antagonists <1994AP661>,  $\beta$ 3 adrenergic receptor agonists <2001BMC379, 2001BRP2356196>, acetylcholinesterase inhibitors <1994JMC689, 1992JMC1102>, structures having potassium ion channel opening activity <1992JMC2327, 1999WOP9958497, 1993BMC999>, analgesics <1993JMC2373>, and insecticides <1997MI7, 1994MI119, 1993MI31, 1993MI41, 1989USP4806553, 1995EUP0649845, 1988EUP0302389>. The ranitidine dimer **16** has also been synthesized <1997BMC3045>.

The ketene dithioacetal **9** has also been treated with ammonia to synthesize the ketene aminal **17** as an important synthetic intermediate for heterocycles. The yield was 45%, but optimization of the reaction conditions improved the yield to 77% by increasing pressure and lowering the temperature of the reaction <1997C280>.

A general disadvantage in using reagent **9** is the fact that the substitution reactions with amines produce volatile and bad smelling methylmercaptans (MeSH). To address this problem, the ketene dithioacetal reagent **18** has been successfully used in the synthesis of ranitidine and ranitidine analogs <1995PHA12>. An alternative method of avoiding the release of methanethiol into the atmosphere has been reported, whereby the ketene *N,S*-acetal **19** was treated with silver nitrate to form the keteneimine **20** with precipitation of silver methylmercaptide. The keteneimine was then treated *in situ* with methylamine to give ranitidine in high yield <1986BRP2169600>.



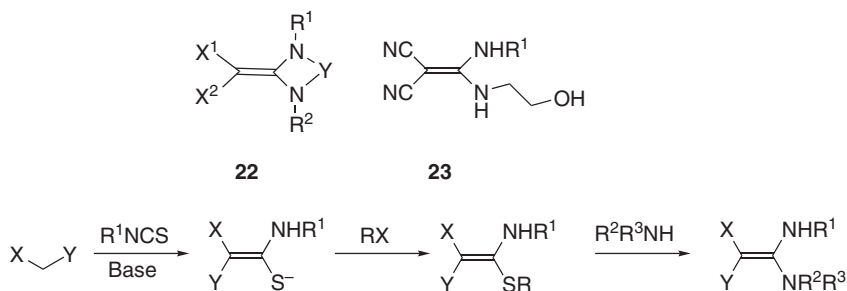
Intermediary ketene *N,S*-acetals can be obtained in better purity and yield using lithiated amino salts without the problem of ketene amins being present as a result of disubstitution <2000JOC1583>. For example, heating the  $\alpha$ -oxoketene dithioacetal **21** with aniline resulted in a mixture of starting material, ketene *N,S*-acetal, and ketene aminal, which was difficult to separate. In contrast, the reaction proceeded in 80–90% yield at room temperature using the lithio salt of aniline. Lithiated amino salts have also proved advantageous in the synthesis of mixed ketene amins from ketene *N,S*-acetals, and in the synthesis of ketene amins **2**. DBU has also been used to advantage in the synthesis of ketene *N,S*-acetals from ketene dithioacetals and amines <1995BMC279>.

Reaction of ketene dithioacetals with diamines gives ketene amins containing a diaza heterocyclic ring **22** <2000MI307, 1995PS87, 1994BMC1107, 1997MI7>. An alternative method of producing such compounds via the mixed ketene aminal **23** has also been described <1995BMC279>.

The reaction of ketene dithioacetals bearing an aldehyde group at the  $\beta$ -position **24** has been studied under various conditions <1995PS87>. The nature of the solvent, the amine, the level of amine present, and the experimental conditions determines the selectivity of the reaction. Reaction at the acetal carbon forms ketene amins or ketene *N,S*-acetals, and is under thermodynamic control, whereas reaction at the aldehyde group to form imines is under kinetic control. In general, more basic nucleophilic aliphatic amines are sufficiently reactive to overcome the

high-energy barrier to acetal attack, especially if the reaction is carried out over long time periods or with a high-enough temperature. With more weakly basic amines such as aromatic amines, the imine is formed, possibly reversibly. However, under vigorous conditions such as refluxing DMF, aromatic amines react at the acetal carbon.

The reaction of isothiocyanates with active methylene compounds, followed by reaction with an alkyl halide, is an alternative method of generating ketene *N,S*-acetals, which can then be converted to ketene aminals on reaction with amines (Scheme 1) <2000WOP027805, 1995EUP760362>.

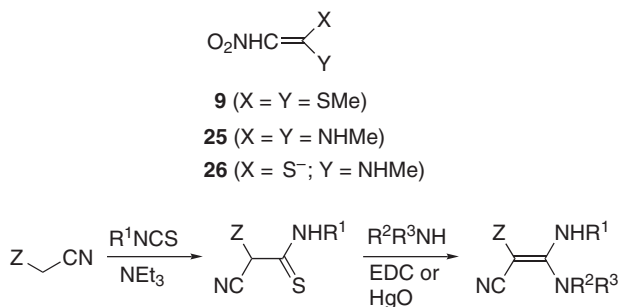


Scheme 1

This procedure has advantages over using a ketene dithioacetal. For example, ketene *N,S*-acetal (**6**;  $X^1 = H$ ,  $X^2 = NO_2$ ,  $NR^1R^2 = NHMe$ ) is an important intermediate in the synthesis of histamine antagonists such as ranitidine and nizatidine. Its synthesis from the ketene dithioacetal **9** results in a product that is contaminated with starting material and the ketene aminal **25**. Better results are obtained via the isothiocyanate route, using methyl isothiocyanate and the carbanion of nitromethane. The reaction has been optimized such that it is suitable for large-scale preparations. The preferred solvent is dimethyl sulfoxide with a co-solvent such as water. A metal alkoxide is preferred as base and the intermediate **26** can be methylated *in situ* with methyl iodide or dimethyl sulfate to give the required ketene *N,S*-acetal **24** in 66% yield <1985BRP2160204>.

#### 4.21.1.1.2 From thioamides, thioureas, and isothioureas

Ketene aminals have been synthesized from isothiocyanates via thioamides (Scheme 2) <1998WOP9850344>. The reaction of the thioamide with amines was carried out in the presence of a desulfurizing agent, for instance mercuric oxide or *N*-ethyl-*N'*-(3-dimethylaminopropyl)carbodiimide hydrochloride (EDC, a water-soluble carbodiimide). This method has also been used in the development of a combinatorial synthesis of ketene aminals (see Section 4.21.1.1.24).

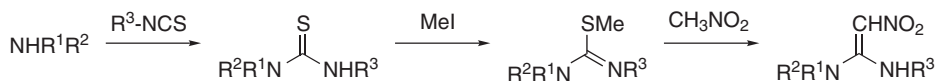


Scheme 2

In the above reaction sequence, an isothiocyanate was reacted with an active methylene compound to give a thioamide that was subsequently treated with the second amine. Alternatively, the isothiocyanate can be treated first with the amine and the active methylene compound added later. Thus, reaction of an isothiocyanate with an amine gives a thiourea, which can then



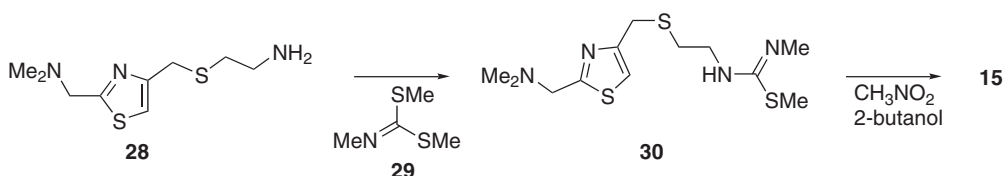
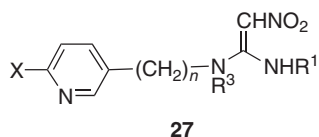
be alkylated to an isothioureia. Reaction of the isothioureia with an active methylene compound such as nitromethane then gives the ketene aminal (Scheme 3) <1988EUP0302389>.



Scheme 3

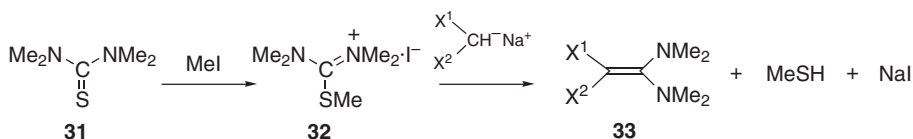
This method has been used in the synthesis of a series of structures **27** having insecticidal activity <1994MI119, 1993MI41, 1993MI31>.

An alternative method of obtaining the required isothioureia intermediate is demonstrated in the synthesis of nizatidine **15** illustrated in Scheme 4 <1984BRP2134521>, whereby the amine **28** is treated with reagent **29** to give the isothioureia **30**.



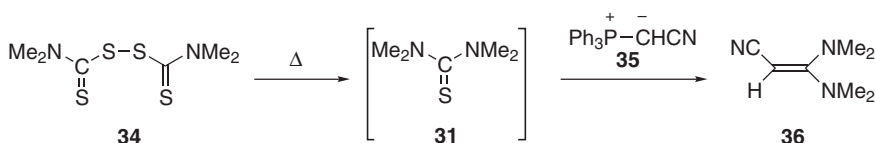
Scheme 4

Treatment of the thiourea **31** with methyl iodide generates *N,N,N',N'*-tetramethylmethylthioformamidinium iodide **32**, which reacts with the carbanions of active methylene compounds to give ketene aminals **33** (Scheme 5) <1995COFGT(4)967>. Similar starting materials have been used for the synthesis of diaza heterocyclic ketene aminals, but despite the fact that these methods were useful in synthesizing ketene aminals containing ester groups at the  $\beta$ -position, they have not been used in the 1990s.



Scheme 5

It has been found that heating tetramethylthiuram disulfide **34** with the ylide **35** resulted in decomposition of the disulfide to form the thiourea **31**, which then reacted with the ylide to form the ketene aminal **36** in 33% yield (Scheme 6) <1993T6411>. However, this reaction was not observed with ylides bearing an ester group.



Scheme 6

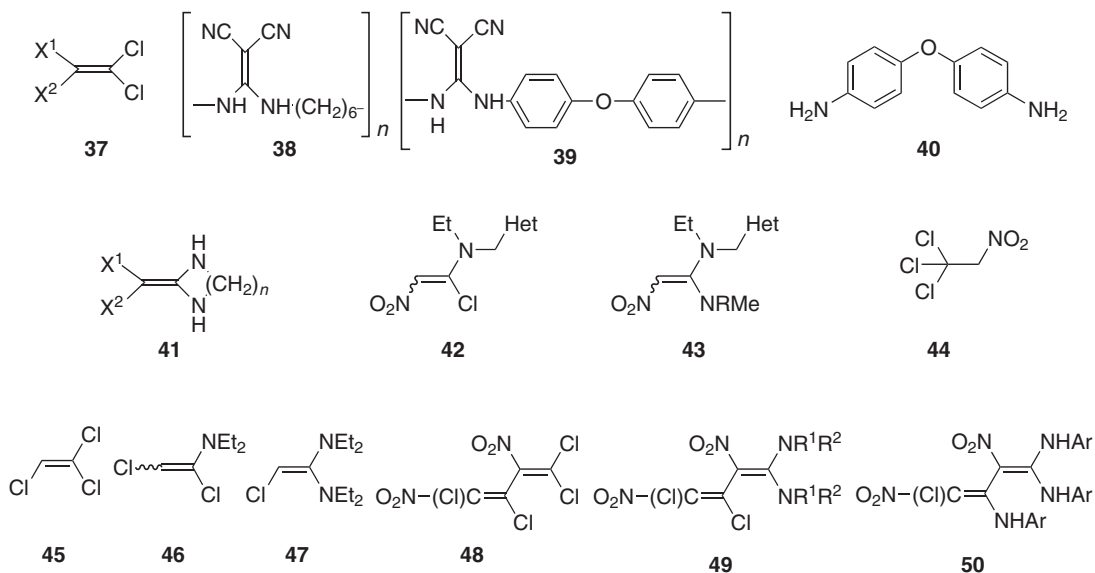
#### 4.21.1.1.3 From vinylidene dihalides, $\alpha,\alpha,\alpha$ -trihaloethanes, and chloro enamines

The reaction of amines with vinylidene dichlorides **37** is another popular method of synthesizing ketene amins [<1995COFGT\(4\)967, 1994CB2013, 1993MM916, 1994JPR29, 1993ZOR885, 1995ZOR1816, 1997ZOR1715, 1999ZOR1809>](#). Vinylidene dihalides have an advantage over ketene dithioacetals in that they are more reactive to amine substitution, allowing the synthesis of ketene amins containing  $\beta$ -substituents that are weakly electron withdrawing. Normally, 4 equiv. of amine are used since 2 equiv. are required to neutralize the 2 equiv. of hydrogen chloride released in the reaction. However, it is possible to use 2 equiv. of the amine if 2 equiv. of a tertiary amine (e.g., triethylamine) are added. Alternatively, sodium hydroxide can be used. Thus, reaction of the vinylidene dichloride **37**;  $X^1 = X^2 = \text{CN}$  with 2 equiv. of hexamethylenediamine in the presence of 2 equiv. of sodium hydroxide successfully resulted in the formation of the first example of an aliphatic poly(enamino nitrile) **38**. Similar attempts to synthesize the polymer **39** were less successful. This was attributed to the weaker nucleophilic nature of the aromatic diamine **40** [<1993MM916>](#).

Reaction of vinylidene dichlorides with diamines gives ketene amins containing a diaza heterocyclic ring **41** [<1995COFGT\(4\)967, 2000ZOR676>](#).

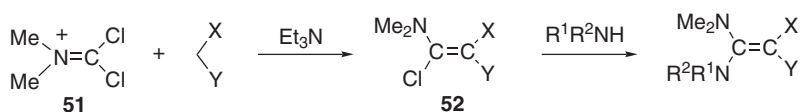
Under carefully controlled conditions, it is possible to synthesize the intermediate chloro enamine intermediate, then react it with a different amine to produce a mixed ketene aminal [<1995COFGT\(4\)967, 1990EUP0381130, 1993MI41>](#). It is possible to carry out this synthesis without isolating the intermediate chloro enamine. For example, 1,1-dichloro-2-nitroethene (**37**;  $X^1 = \text{H}$ ;  $X^2 = \text{NO}_2$ ) was treated with an equivalent of amine in the presence of triethylamine or sodium carbonate to give the chloro enamine **42**. This was then treated *in situ* with an excess of a second amine to give the mixed ketene aminal **43** [<1990EUP0381130>](#). In the same publication, it was shown that identical products could be obtained using 1,1,1-trichloro-2-nitroethane **44** as reagent and generating the vinylidene dichloride *in situ* by dehydrohalogenation with a base. The amines could then be added in either order.

The selectivity of the substitution reaction for the vinylidene dihalide over halides at other positions has been demonstrated [<1997ZOR1715, 1996CJC2331>](#). For example, the reaction of trichloroethylene **45** with lithium diethylamide/diethylamine under mild conditions gave the mono-substituted chloro enamine **46**. Further reaction with excess diethylamine and heating gave the ketene aminal **47** [<1996CJC2331>](#). Reaction of the chlorinated butadiene **48** with aliphatic amines gave the ketene aminal **49** where only the *gem*-vinylidene halides were substituted, while reaction with less basic aromatic amines gave ketene amins **50** [<2000ZOR676>](#). It is known that the  $=\text{CCl}_2$  group is a hard electrophilic center. Thus, hard nucleophiles such as aliphatic amines preferentially attack the  $=\text{CCl}_2$  group while softer nucleophiles such as aromatic amines are capable of reacting at the soft electrophilic center ( $=\text{CCl}-$ ) as well.



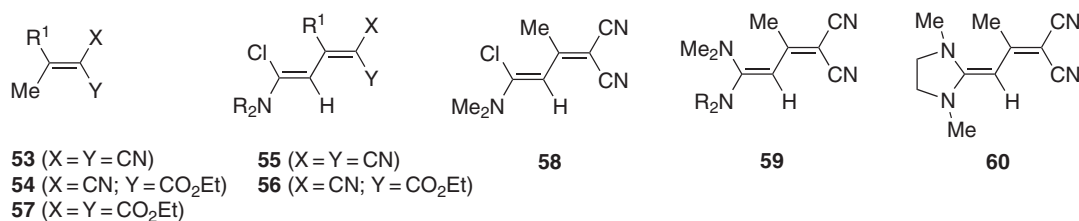
Chloro enamines can be generated from starting materials other than vinylidene dichlorides, then converted to ketene amins. For example, amides can be treated with phosgene to produce chloro enamines, which are subsequently converted to mixed ketene aminsals <1995COFGT(4)967>. This method allows the synthesis of mixed ketene aminsals without electron-withdrawing substituents at the  $\beta$ -position. Other halogenating agents have also been used such as phosphorus pentachloride or thionyl chloride in an aprotic solvent. A base such as pyridine or triethylamine is present to trap the by-product HCl <1988EUP0302389>.

An alternative method of generating chloro enamines is to react activated methylene groups with *N,N*-dimethyldichloromethyleneaminium chloride **51** in the presence of triethylamine. The chloro enamines **52** obtained can then be converted to mixed ketene aminsals where one of the amino functions must be the dimethylamino group (Scheme 7) <1993BSB129, 1993JCS(P2)911>.



Scheme 7

When X and Y are strongly electron withdrawing (e.g., CN), the chloro enamine is formed easily. With weaker electron-withdrawing groups such as esters, the presence of triethylamine is required along with stronger reaction conditions. This also holds true for vinylogous structures. Thus, alkylidenemalononitriles **53** and alkylidencyanoacetates **54** reacted with **51** in the presence of triethylamine to give the (*Z*)-isomer of the  $\alpha$ -chlorodienamines **55** and **56**, respectively, whereas alkylidenemalonates **57** failed to react. Reaction of the  $\alpha$ -chlorodienamine **58** with secondary amines resulted in the formation of “push–pull” dienes **59** with inversion of configuration. Reaction of **58** with 1,2-bis(methylamino)-ethane resulted in substitution of both the chloro and the dimethylamino groups to give the heterocyclic diene **60**.

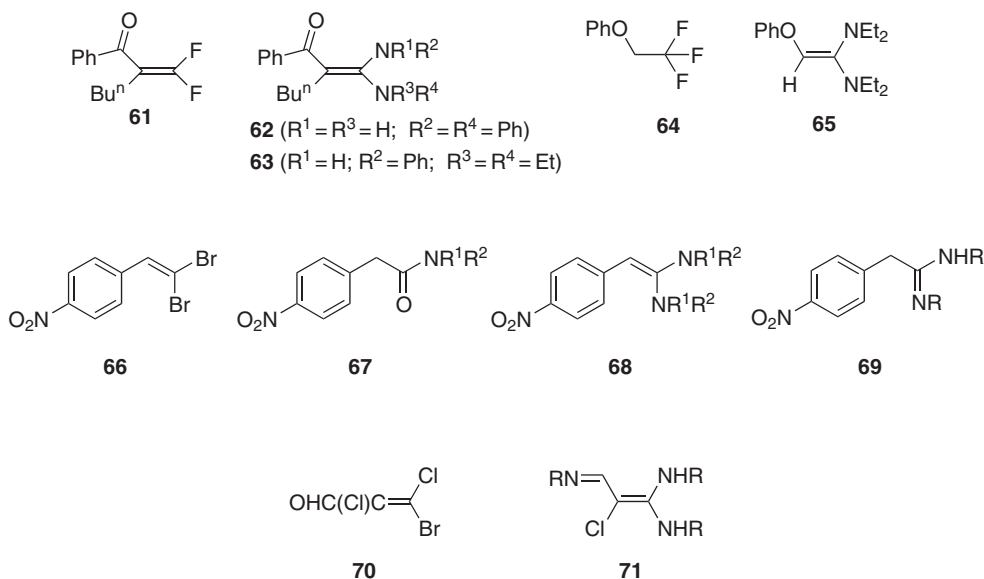


Normally, vinylidene chlorides or chloro enamines are used for the synthesis of ketene aminsals, but other vinylidene dihalides have been reported as starting materials <1995COFGT(4)967>. The reactions of the vinylidene difluoride **61** with various nucleophiles have been studied <1994T11637>. Reaction with 4 equiv. of aniline gave the ketene aminal **62** in 88% yield. The mixed ketene aminal **63** was also prepared by reacting the difluoride with 2 equiv. of diethylamine, then 2 equiv. of aniline. Using 2 equiv. of amine was found to be superior to using 1 equiv. of amine in the presence of a base such as *n*-butyllithium or triethylamine.

It has also been reported that reaction of the phenyl trifluoroethyl ether **64** with 3 equiv. of lithium diethylamide afforded the ketene aminal **65** in 28% yield, presumably via a vinylidene difluoride <1995HAC45>.

Treatment of the vinylidene dibromide **66** with amines using water as a solvent can give amides **67**, ketene aminsals **68**, or amidines **69** depending on the amine used <2002T9925>.

The mixed vinylidene dihalide **70** was treated with 5 equiv. of primary amine to give the ketene aminsals **71** in 53–61% yield <1995ZOR1816>.



#### 4.21.1.1.4 From $\beta$ -amino- $\beta$ -(trihalomethyl)vinyl esters and ketones

Reaction of  $\beta$ -amino- $\beta$ -(trichloromethyl)vinyl esters **72** with primary amines resulted in replacement of the trichloromethyl group to form ketene aminals **73**. Similar results were obtained using the starting materials **74a–74c** <1965JPR239>. The reaction of the vinyl ester **72** with ethylenediamine gave the bis-adduct **75**. In contrast, the reaction of vinyl aliphatic ketones **76** with ethylenediamine led to substitution of both the trichloromethyl and amino groups to give imidazolidines **77** <2000IZV1245, 1999MC206>. The reaction was found to be slow at room temperature with poor-to-moderate yields. However, the experimental conditions were not optimized. In contrast, similar reactions carried out on aliphatic  $\beta$ -amino- $\beta$ -(trifluoromethyl) vinyl ketones **78** gave diazepines **79** or imidazolidines **80** where substitution of the trifluoromethyl group did not take place <1998IZV2305>.

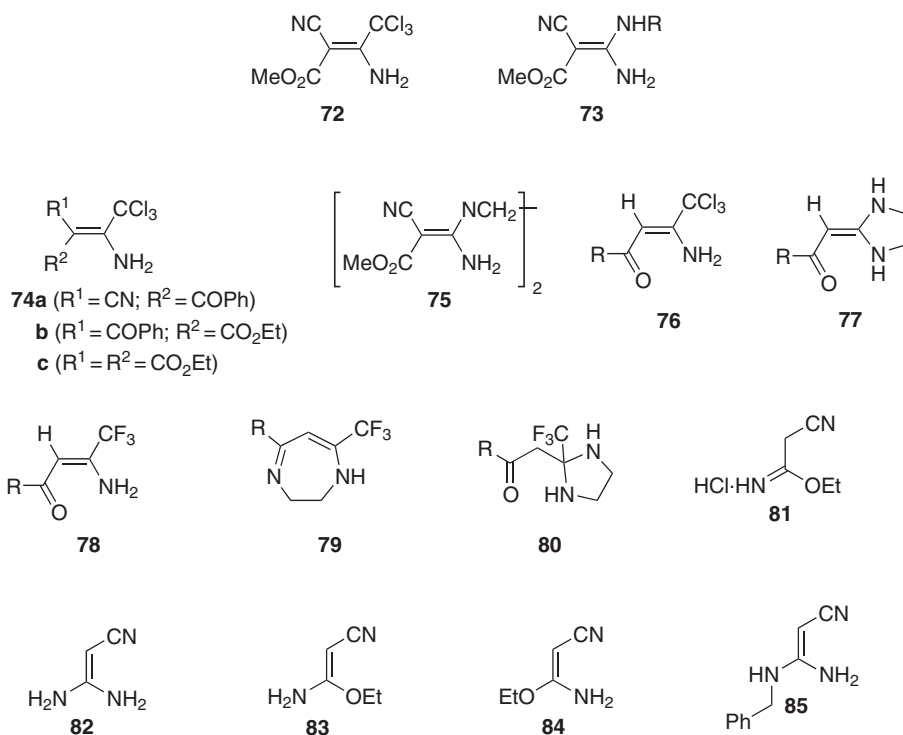
#### 4.21.1.1.5 From ketene acetals

Ketene acetals can be converted to ketene aminals <1995COFGT(4)967>. However, the method offers no advantages over the use of ketene dithioacetals or vinylidene dihalides since the ketene acetals are less reactive. As a result, there have been no reports of ketene acetals being used in the synthesis of ketene aminals since the 1990s.

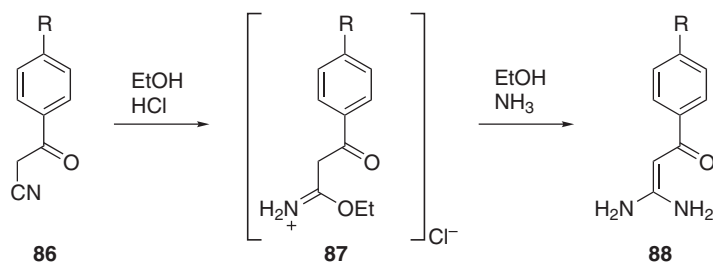
#### 4.21.1.1.6 From imino esters and ketene *N,O*-acetals

Imino esters and their salts are tautomers of ketene *N,O*-acetals and can be converted into ketene aminals <1995COFGT(4)967, 1994MI137>. For example, the imino ester hydrochloride **81** was treated with ammonia or ammonium acetate to generate the ketene aminal **82**, which was further reacted *in situ* to form a range of heterocycles <1999MI313, 1994AP33>.

Imino ester hydrochlorides can be converted to their free bases that exist as the ketene *N,O*-acetal tautomer. These can then be converted to ketene aminals <1995JHC1679>. For example, the imino ester hydrochloride **81** was converted to its ketene *N,O*-acetal tautomer as a mixture of (*Z*)- and (*E*)-isomers, **83** and **84**, then treated with benzylamine to give the ketene aminal **85** as the (*E*)-isomer <1994AP85>.

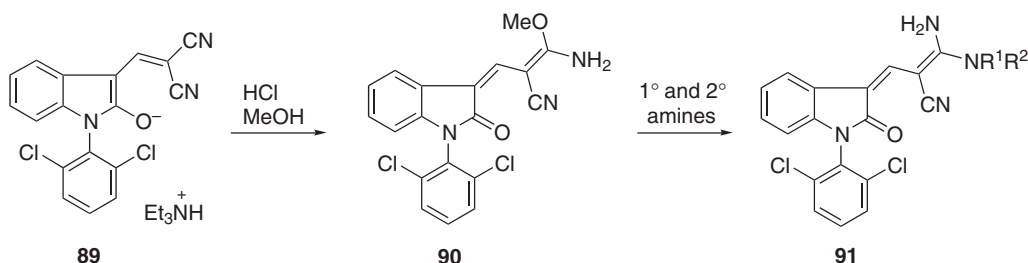


Imino ester hydrochlorides can be obtained from nitriles. Thus, the imino ester hydrochlorides **87** were obtained from nitriles **86** and converted to the ketene amins **88** (Scheme 8) <1994AP225>.



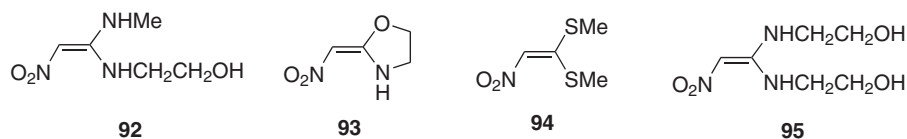
Scheme 8

A series of indolin-2-one ketene amins **91** were synthesized from the hydroxyindole salt **89** via the ketene *N,O*-acetal **90** (Scheme 9) <1998KFZ5>. This was considered a superior route to one that produced similar compounds by reacting an enamine with *N,N*-dimethylacetamide diethyl acetal (see Section 4.2.1.1.7).



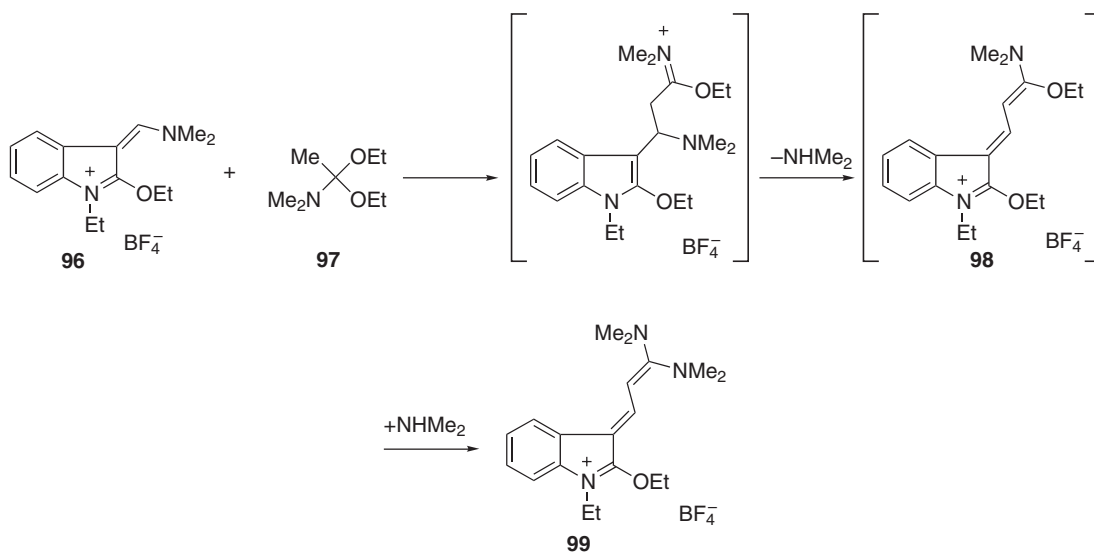
Scheme 9

The ketene aminal **92** was generated in 92% yield from the reaction of methylamine with the ketene *N,O*-acetal. Structure **93** was synthesized in 42% yield from the reaction of ketene dithioacetal **94** with 1 equiv. of ethanolamine in the presence of TsOH. The yield was low since the ketene aminal **95** was also formed in 27% yield <2002MI121>.



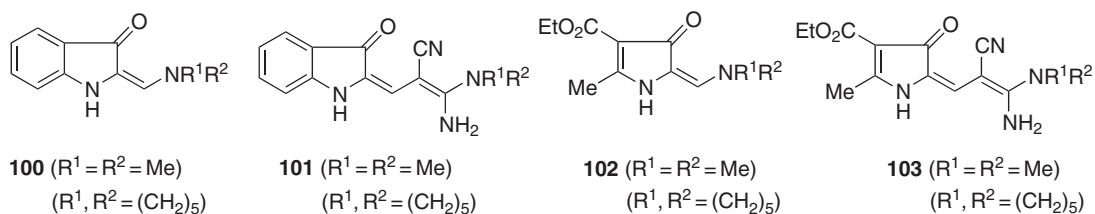
#### 4.21.1.1.7 From enamines

The indole structure **96** was reacted with the diethyl acetal of dimethylacetamide **97** to give the dienediamine **99** as shown in Scheme 10 <1994KFZ48>. The reaction involves the loss of dimethylamine from the indole, and the resulting intermediate then reacts with a ketene *N,O*-acetal intermediate **98** to give the ketene aminal observed.

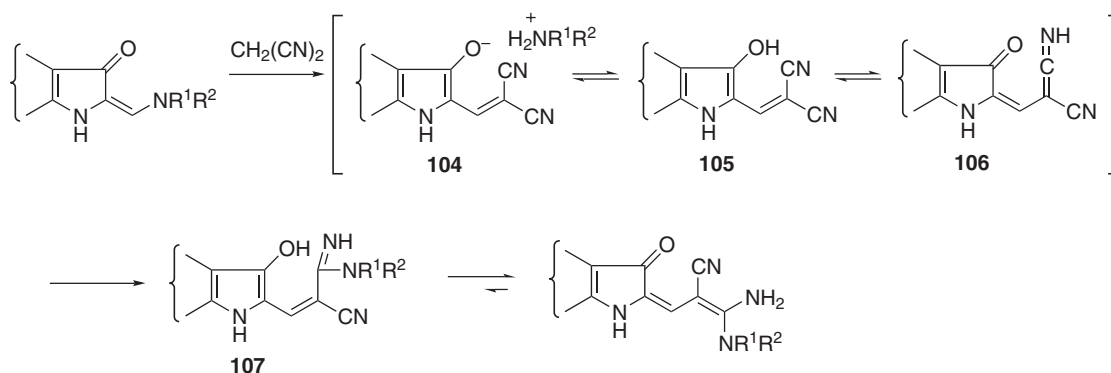


Scheme 10

In a similar manner, the reaction of the indolin-3-ones **100** with malononitrile resulted in the formation of the ketene aminals **101** in 71–75% yield. The same reaction also took place with the pyrrolin-4-ones **102** resulting in the analogous structures **103** in 77–87% yield <1995KFZ22>.



The reaction is thought to occur as shown in Scheme 11. Thus, malononitrile replaces the dialkylamino group to form a salt **104**, which then dissociates to the hydroxy heterocycle **105** and the free amine ( $\text{NHR}^1\text{R}^2$ ). The product of the reaction is achieved when the amine adds to one of the nitrile groups. However, this is not an easy process and usually a nitrile group has to be activated (e.g., by conversion to an imino ester) for amine addition to take place. It is therefore proposed that activation occurs intramolecularly involving the hydroxy group on the heteroaromatic ring to form the ketenimine **106**. The amine then reacts rapidly and irreversibly with the ketenimine to form the amidine **107**, which tautomerizes to the observed product.



Scheme 11

The amino substituent ( $\text{NR}^1\text{R}^2$ ) on the starting material must be tertiary or else this reaction is not observed. When  $\text{R}^1$  or  $\text{R}^2$  is hydrogen, it is thought that intramolecular hydrogen bonding with the carbonyl oxygen stabilizes the molecule. The route illustrated in Scheme 11 is supported by the fact that the salt **104** can be isolated with short-time heating, and then subsequently converted to the ketene aminal by further heating. Acidification of the salt **104** also allows the isolation of the dicyanovinyl structure **105**.

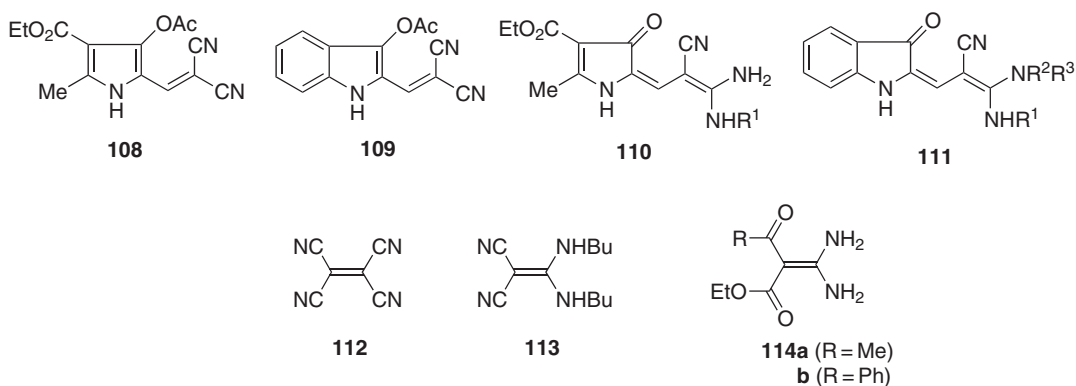
#### 4.21.1.1.8 From nitriles

Ketene aminals are not normally obtained directly from nitriles. However, the reaction is possible if one of the nitrile groups can be activated intramolecularly as described in the previous section. Thus, the vinylidene dinitriles **108** and **109** were treated with a range of primary amines to give the ketene aminals **110** and **111**, respectively. Deacetylation takes place during the reaction to give the hydroxyl group that is necessary for the activation of the nitrile group.

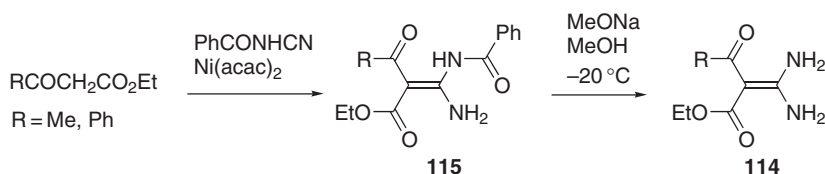
Treatment of tetracyanoethylene **112** with a large excess of *n*-butylamine at room temperature resulted in substitution of two cyano groups and generation of the ketene aminal **113** in 63% yield <1996BCJ195>.

#### 4.21.1.1.9 From cyanamides

Cyanamide and monosubstituted cyanamides react with activated methylene compounds in the presence of nickel acetylacetonate to give ketene aminals <1995COFGT(4)967>. Further work has shown that the reaction of cyanamide with ethyl acetoacetate in the presence of  $\text{Ni}(\text{acac})_2$  (15 mol.%) gives the ketene aminal **114a** in 76% yield while reaction of cyanamide with ethyl benzoylacetate under the same conditions gives the ketene aminal **114b** in 56% yield <1993IZV419>.



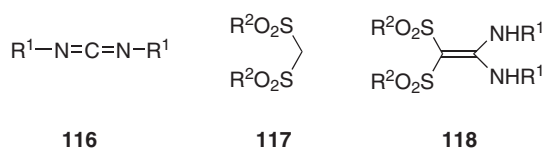
These structures can also be synthesized via the *N*-benzoyl derivatives **115** followed by methanolysis in the presence of sodium methoxide (Scheme 12).



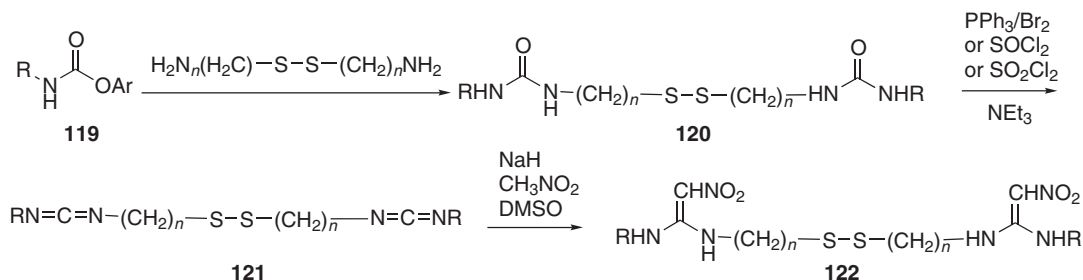
Scheme 12

#### 4.21.1.1.10 From carbodiimides

Ketene aminals have been prepared previously from carbodiimides <1995COFGT(4)967>. The reaction between the carbodiimides **116** and the active methylene compound **117** resulted in formation of the ketene aminals **118** in 63–66% yield <1994S249>.



A synthesis leading to the preparation of the antiulcer agents ranitidine and niperotidine has been reported that involves reaction of the carbamate **119** with a diamine to give the bis-urea **120**. Treatment of **120** with triphenylphosphine/bromine in the presence of a base leads to the bis-carbodiimide **121**, which can be treated with nitromethane in the presence of sodium hydride to give the bis-ketene aminal **122** (Scheme 13) <1992USP5118813>.



Scheme 13



#### 4.21.1.1.11 From halo alkynes

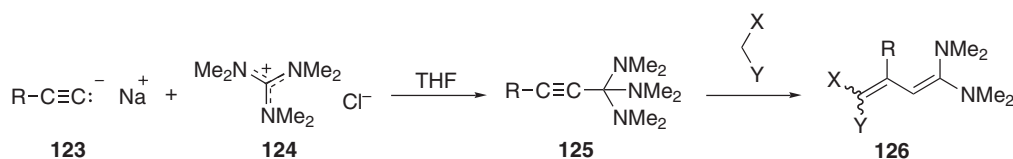
Chloro alkynes containing an electron-withdrawing substituent react with secondary amines to give ketene aminals containing one electron-withdrawing substituent at the  $\beta$ -position and identical tertiary amino groups <1995COFGT(4)967>. As such, the method is quite restricted in its utility and has not been used since the 1990s.

#### 4.21.1.1.12 From ynamines

Ynamines with an electron-withdrawing substituent react mainly with secondary amines to give ketene aminals containing one electron-withdrawing substituent at the  $\beta$ -position, and two tertiary amino groups which may or may not be identical <1995COFGT(4)967>. One of the amino groups is obviously dictated by the ynamine used. The method has not been used since the 1990s.

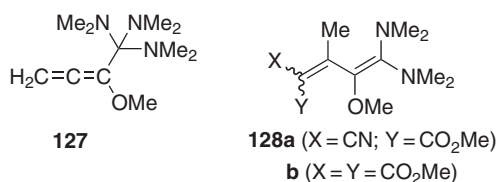
#### 4.21.1.1.13 From acetylides

Reaction of acetylides **123** with the guanidinium salt **124** gave orthoamides **125**, which on treatment with acidic methylene compounds gave the dienes **126** (Scheme 14) <2002ZN(B)399, 1998JPR408>.

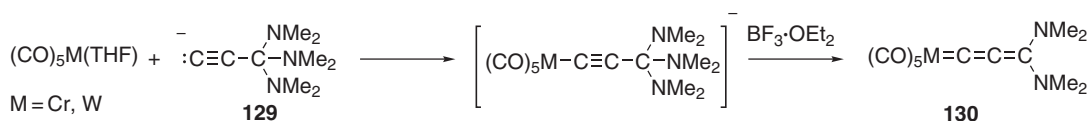


Scheme 14

The orthoamide **127** was obtained in a similar fashion and reacted with acidic methylene compounds to give the dienes **128**.

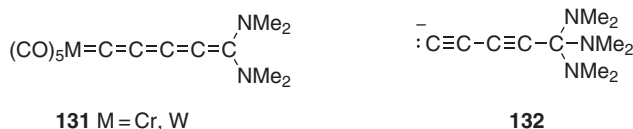


The metal complexes **130** were synthesized in good yield (64–67%) from the reaction of deprotonated tris(dimethylamino)prop-1-yne **129** with metal complexes, followed by abstraction of a dimethylamido group using  $BF_3$  etherate (Scheme 15) <1996OM1139>.



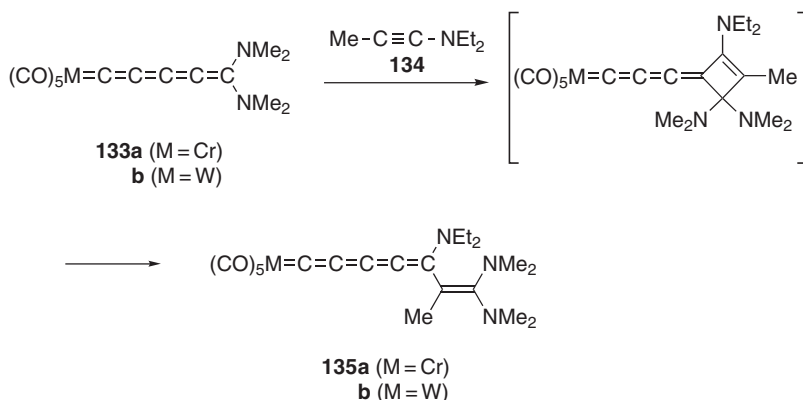
Scheme 15

Metal complexes **131** were synthesized in a similar fashion in 36–42% yield from the acetylide **132**.



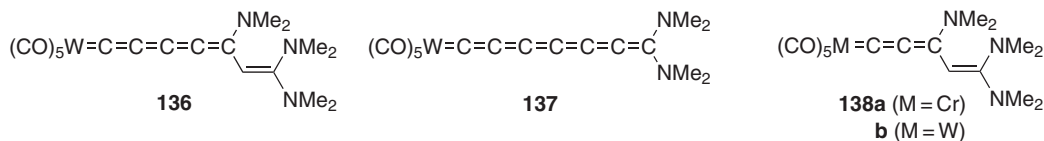
#### 4.21.1.1.14 From enylidene systems

The metal complexes **135** were obtained in good yield from the reaction of the ynamine **134** with metal complexes **133** at room temperature <1998OM1511>. The reaction involves insertion of the electron-rich alkyne into the terminal C=C bond of the metal complex (Scheme 16).



Scheme 16

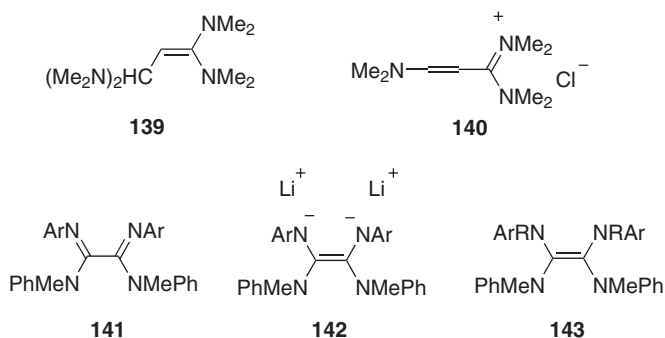
Such compounds are seen as having potential nonlinear optical properties. The related metal complex **136** was synthesized in low yield from the reaction of dimethylamine with the metal complex **137** that was generated *in situ* and could not be isolated. The metal complexes **138** were synthesized by a similar reaction, involving the quantitative addition of dimethylamine to the metal complexes **133** <1996OM1139>.



#### 4.21.1.1.15 From amidines and amidinium salts

The ketene aminal **139** was synthesized in 90% yield from the amidinium salt **140** on reaction with sodium hydride, dimethylamine, and B(OMe)<sub>3</sub> <2000JPR256>.

The amidine **141** has been reduced with lithium using THF as solvent and ultrasound to give the dilithio salt of the tetraaminoethane **142** in quantitative yield. The reaction of **142** with alkyl halides proceeded quantitatively to give the ketene amins **143** <1996CB39, 1998MI183>.



#### 4.21.1.1.16 From tricyanomethanide, dicyanoacetates, dicyanothioacetates, and dicyanoacetamides

The reagents specified react with amines to give ketene amins and have been reported as useful alternatives to using ketene dithioacetals when the ketene aminal to be synthesized bears a primary amino group <1995COFGT(4)967>. However, no reports of their use have been published since the 1990s.

#### 4.21.1.1.17 From amides and other carboxylic acid derivatives

Tertiary amides and other carboxylic acid derivatives can be converted into ketene amins using  $\text{Ti}(\text{NMe}_2)_4$  <1995COFGT(4)967>. Despite the fact that the method seems useful in generating ketene amins without electron-withdrawing substituents at the  $\beta$ -position, there have been no reports of its use since the early 1970s.

#### 4.21.1.1.18 From miscellaneous “head group” synthons

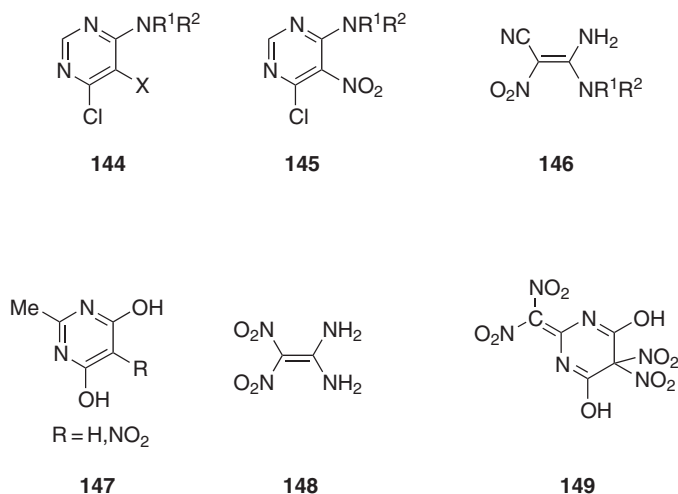
A variety of reagents have been used in the past as “head group” synthons for the synthesis of ketene amins. These include  $N,N,N^1,N^1$ -tetramethylmethylthioformamidinium iodide, alkox-ytris(dimethylamino)methanes <1995COFGT(4)967>, tetramethylurea diisopropyl acetal, tetramethylchloroformamidinium chloride <1995COFGT(4)967>, as well as specific amins, ortho-esters, and amide acetals <1995COFGT(4)967>. However, no reports of these have been given in the 1990s. The lack of interest in “head group” synthons is due presumably to the inevitable restrictions that these methods place on the amino groups which can be added to ketene amins.

#### 4.21.1.1.19 From ring opening of pyrimidines

Pyrimidines **144** bearing an electron-withdrawing substituent at the 5-position and a chloro substituent at the 6-position are prone to nucleophilic attack and ring opening, resulting in ketene amins where one of the amino groups is primary and one of the  $\beta$ -substituents is cyano <1995COFGT(4)967>.

This method has been rarely used for the synthesis of ketene amins. However, a further example of this method has been reported <1996CHE699> involving fission of the pyrimidine rings **145** under acid conditions to give ketene amins **146**. Previously, a dialkylamino substituent was thought necessary for such reactions, but it has been shown that the reaction is possible with aniline substituents.

Nitration of the 2-methyl-4,6-dihydropyrimidines **147** with nitric acid/sulfuric acid, followed by dilution with water, resulted in generation of the ketene aminal **148** in 80% yield. The dihydropyrimidine **149** has been identified as an intermediate <2001ZOR766>.



#### 4.21.1.1.20 From ring opening of imidazoles and imidazolidinediones

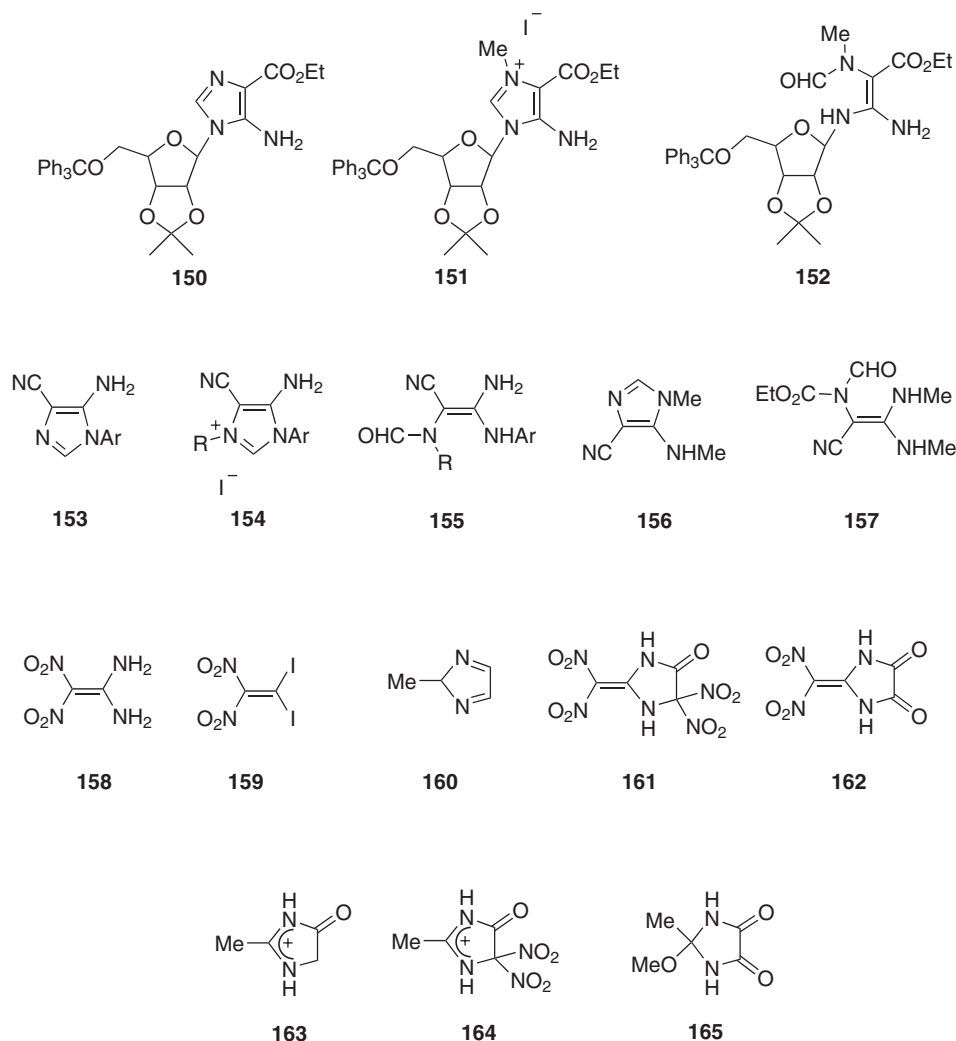
Imidazoles can be quaternized at the *N*-3 position with methyl iodide then ring-opened in the presence of a basic catalyst to give ketene aminals. Thus, the nucleoside **150** was methylated to give the quaternary salt **151** in quantitative yield. Treatment with 1 equiv. of base resulted in the ketene aminal **152** <1995MI367>.

Similar results were obtained when the imidazoles **153** were treated with alkyl iodides to give the quaternary salts **154** in 50–90% yields, then treated with aqueous sodium hydroxide to give the ketene aminals **155** in 55–60% yield <1997MI14>. It has also been reported that the reaction intermediate **157** may be formed during the reaction of the imidazole **156** with ethyl chloroformate in aqueous sodium bicarbonate <1997CPB75> (see also Section 4.21.1.2.1(v)).

1,1-Diamino-2,2-dinitroethylene **158** (also known as FOX-7) is of interest as an explosive. Previous attempts to synthesize this compound from the vinylidene di-iodide **159** were unsuccessful despite the fact that other  $\beta,\beta$ -dinitroketene aminals could be synthesized in this fashion. However, the compound was successfully synthesized from 2-methylimidazole **160**. Nitration of 2-methylimidazole **160** with sulfuric acid and nitric acid resulted in precipitation of the dinitro imidazolidinedione **161**, which on standing at room temperature decomposed with the loss of nitric oxides to the ketene aminal **162** in 15% yield. Addition of **162** to water and neutralization by aqueous ammonia to pH 8–9 resulted in dissolution and ring cleavage to form the insoluble 1,1-diamino-2,2-dinitroethylene **158** in 87% yield <1998T11525>.

It is believed that the mechanism leading to **161** involves oxidation of 2-methylimidazole **160** to give structure **163**, which is then nitrated twice in the ring to give **164**. The electron-withdrawing effects of both the keto and the nitro groups then activate the methyl group to nitration resulting in the formation of **161** <1998T11525>.

The advantage of having electron-withdrawing substituents on the imidazole ring was further demonstrated by the finding that structure **162** can also be obtained in 67% yield from the nitration of the imidazolidinedione **165**. This structure can be synthesized in turn from acetamidine HCl and diethyl oxalate in 64% yield <1998T11525>.



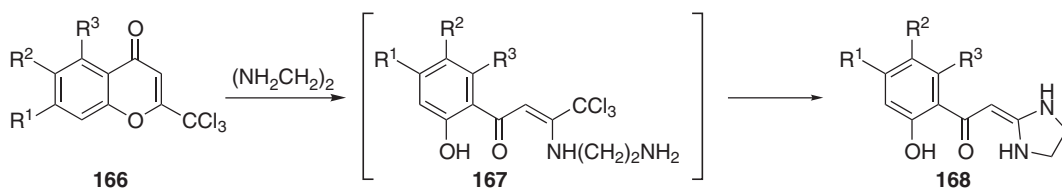
#### 4.21.1.1.21 Miscellaneous syntheses from ring systems

Ketene aminals have been synthesized by the ring opening of various heterocycles [<1995COFGT\(4\)967>](#), but these methods have limited synthetic utility. The following are more recent examples.

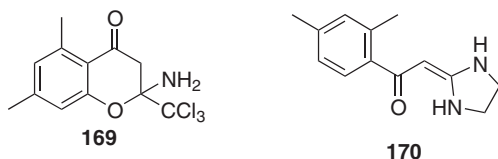
##### (i) From 2-trichloromethylchromones

The reaction of 2-trichloromethylchromones **166** with ethylenediamine at room temperature gave 2-phenacylideneimidazolidines **168** in 63–94% yields. The reaction can be carried out with or without ethanol as solvent. The probable mechanism involves nucleophilic attack on the C(2) atom of the chromone system resulting in pyrone ring opening and formation of an intermediate enamine **167**. Intramolecular replacement of the trichloromethyl group then takes place ([Scheme 17](#)) [<1999MC206>](#). The same products can be obtained by reacting relevant  $\beta$ -amino- $\beta$ -(trihalomethyl) vinyl ketones with amines ([Section 4.21.1.1.4](#)), but the reaction times are longer and the yields are lower (25–40%).

The cyclic system **169** also reacted with ethylenediamine to give the imidazolidine **170**.

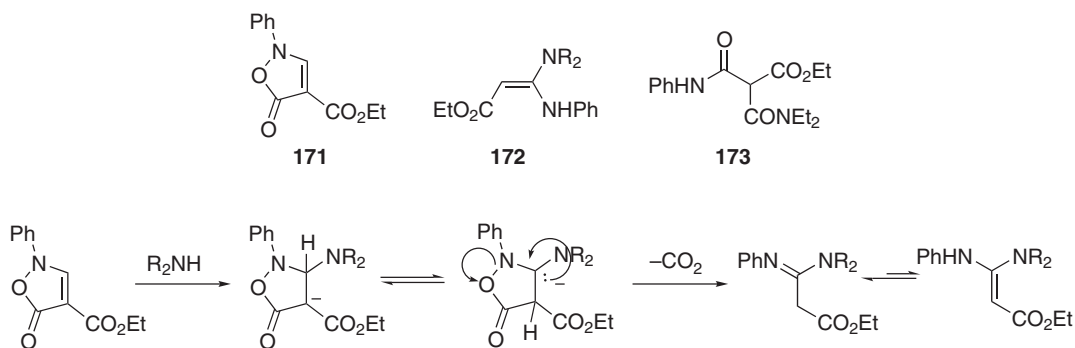


Scheme 17



## (ii) From isoxazolones

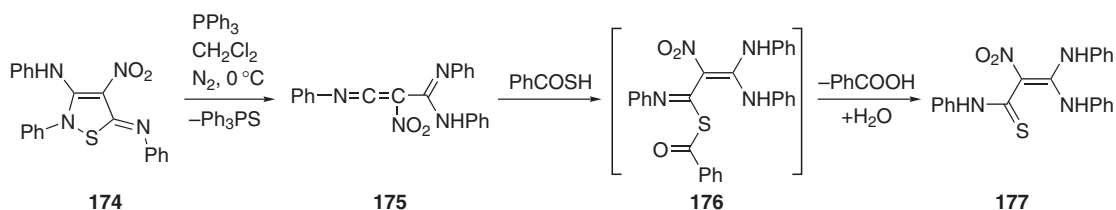
The reaction of 2-phenylisoxazolone **171** with secondary amines resulted in the formation of ketene aminals **172** that exist predominantly as the amidine tautomer [<1992AJC2037>](#). The malonamide **173** was also formed as a product and the ratio of products depended on the solvent, temperature, and nature of the base. With primary amines, only the malonamide product was observed. The ketene aminal product is thought to be formed as shown in [Scheme 18](#).



Scheme 18

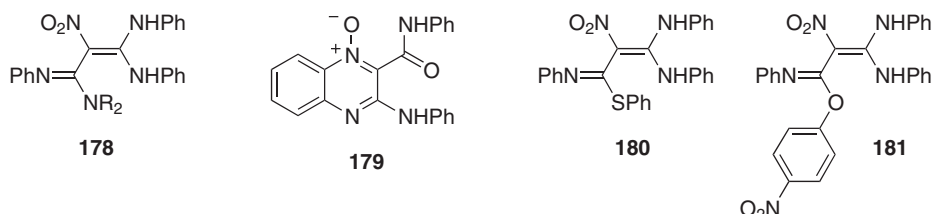
## (iii) From isothiazoles

Desulfurization of the nitroisothiazole structure **174** with triphenylphosphine results in ring opening and the formation of the highly reactive ketene imine intermediate **175**. This was trapped by the addition of thiobenzoic acid to give the adduct **176**, which hydrolyzed on work-up to give the thioamide **177** in 75% yield ([Scheme 19](#)) [<1998HCA2388>](#).



Scheme 19

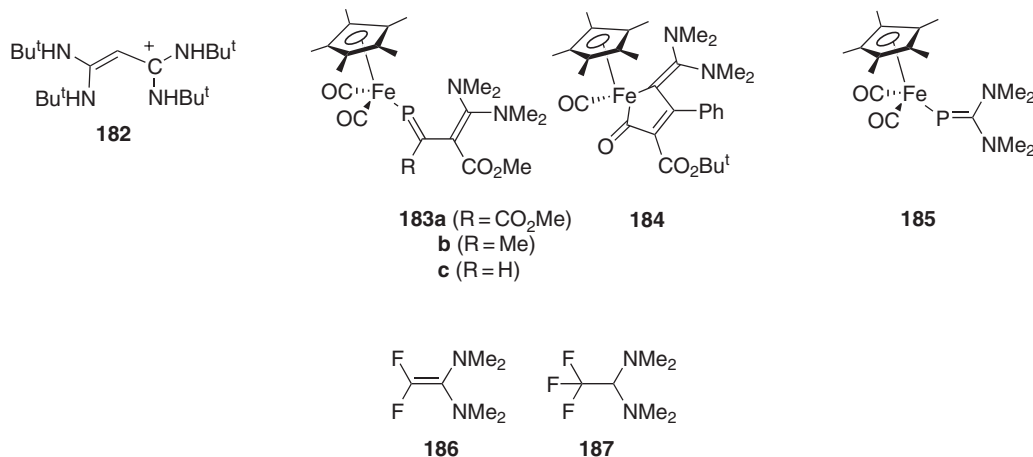
Trapping the intermediate **175** with amines resulted in the formation of ketene aminals **178** in good yields (72–93%). This reaction did not occur in the presence of aniline and 4-methoxyaniline, and the reaction products obtained were those that would be obtained in the absence of an amine (i.e., the quinoxaline *N*-oxide **179**). Addition of thiophenol to the reaction mixture resulted in the formation of the thioimide **180** in 62% yield. However, adding aliphatic thiols failed to trap the intermediate, and only structure **179** was formed along with decomposition products. Addition of 4-nitrophenol was thought to occur in a similar fashion to give **181**. However, this product decomposed on work-up and could not be fully characterized <1998HCA2388>.



#### 4.21.1.1.22 Miscellaneous methods

A variety of procedures has been used for the synthesis of specific ketene aminals. These include the synthesis of the allyl cation **182** from pentachlorocyclopropane <1994CC2517>, and the synthesis of 1-phospha-1,3-butadienes **183** and **184** from the reaction between the metallophosphaalkene **185** and disubstituted alkynes <1996OM123, 1994ZN(B)1693>.

The ketene aminal **186** can be obtained in 90% yield by dehydrofluorinating the saturated diamine **187** with Bu<sup>n</sup>Li in diethyl ether <1997JOC1576>.



#### 4.21.1.1.23 By modification of other ketene aminals

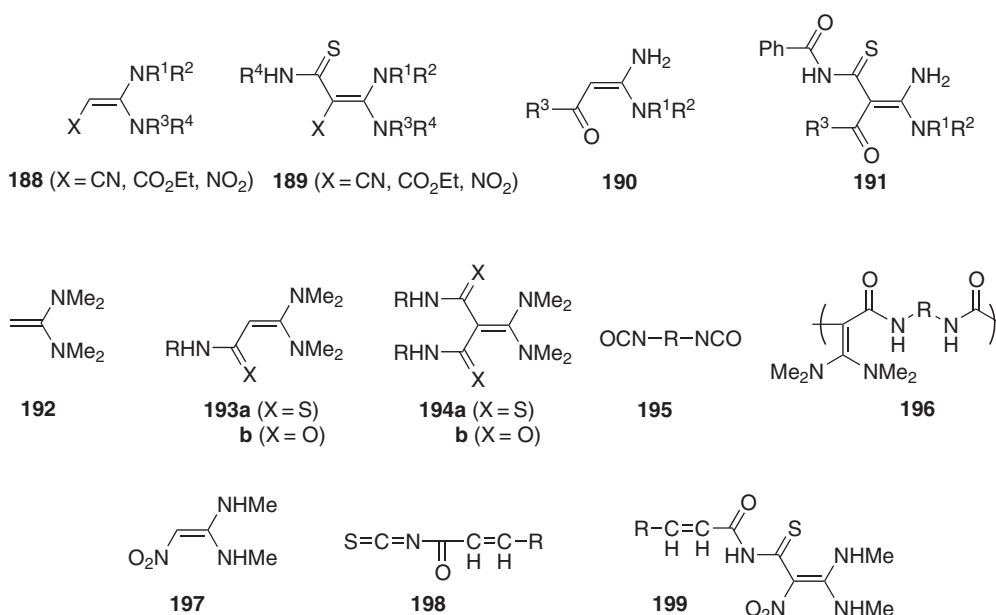
##### (i) Introduction of $\beta$ -substituents

Ketene aminals have nucleophilic properties and can be elaborated to introduce groups at the  $\beta$ -carbon by electrophilic substitution <1995COFGT(4)967>. Both nitrogen groups are generally tertiary and there must necessarily be a hydrogen at the  $\beta$ -position. The other  $\beta$ -substituent is not crucial to the success of the reaction.

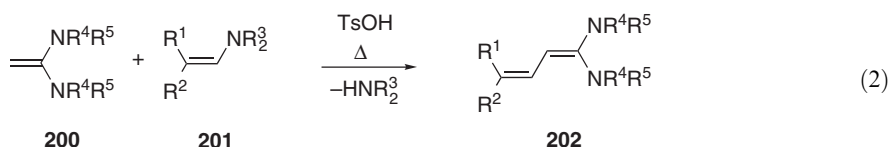
Reaction of ketene aminals **188** with alkyl or aryl isothiocyanates gave keto aminals with  $\beta$ -thioamido substituents **189** <2001MI1763, 1995JHC1679, 1995MI73, 1994MI137, 1997HCA273, 1996SC1187> while reaction of monoacyl ketene aminals **190** with benzoyl isothiocyanate gave the corresponding structures **191**. In these examples, the ketene aminals contained a primary or secondary amino group.

The reaction of the ketene aminal **192** with alkyl or aryl isothiocyanates gave either the monothioamido-substituted ketene aminal **193a** or the disubstituted product **194a** depending on the amount of isothiocyanate used. Similarly the amido-substituted ketene aminals **193b** and **194b** were obtained on reaction of **192** with alkyl or aryl isocyanates. It should be noted that the ketene aminal **192** reacted explosively with phenyl isocyanate in the absence of solvent and that reactions were consequently carried out in THF. The monosubstituted amido ketene aminal **193b** was obtained quantitatively when an equimolar amount of phenyl isocyanate was used, while the disubstituted product **194b** was obtained quantitatively with 2 equiv. of reagent. Treatment of the monosubstituted product **193b** with phenyl isocyanate yielded the disubstituted product **194b** in 98% yield, allowing the possibility of introducing two different amido groups. With less reactive aliphatic isocyanates, longer reaction times and higher reaction temperatures were required to complete the reaction and less selectivity was observed. The reaction of **192** with a bifunctional isocyanate **195** resulted in the formation of the polyamide polymer **196** <1999JPS(A)3079>.

The reaction of the ketene aminal **197** with  $\alpha,\beta$ -unsaturated acyl isothiocyanates **198** has been achieved in acetone to give ketene aminals **199** bearing an acyl thioamide substituent at the  $\beta$ -position <1998HCA718>. Yields varied from 59% to 87%.



The reaction of ketene aminals **200** with enamines **201** allows the synthesis of conjugated ketene aminals **202** bearing a vinylic substituent at the  $\beta$ -position (Equation (2)) <1993BSB645>. The reaction is carried out in the presence of *p*-toluenesulfonic acid in an inert atmosphere and with heating.



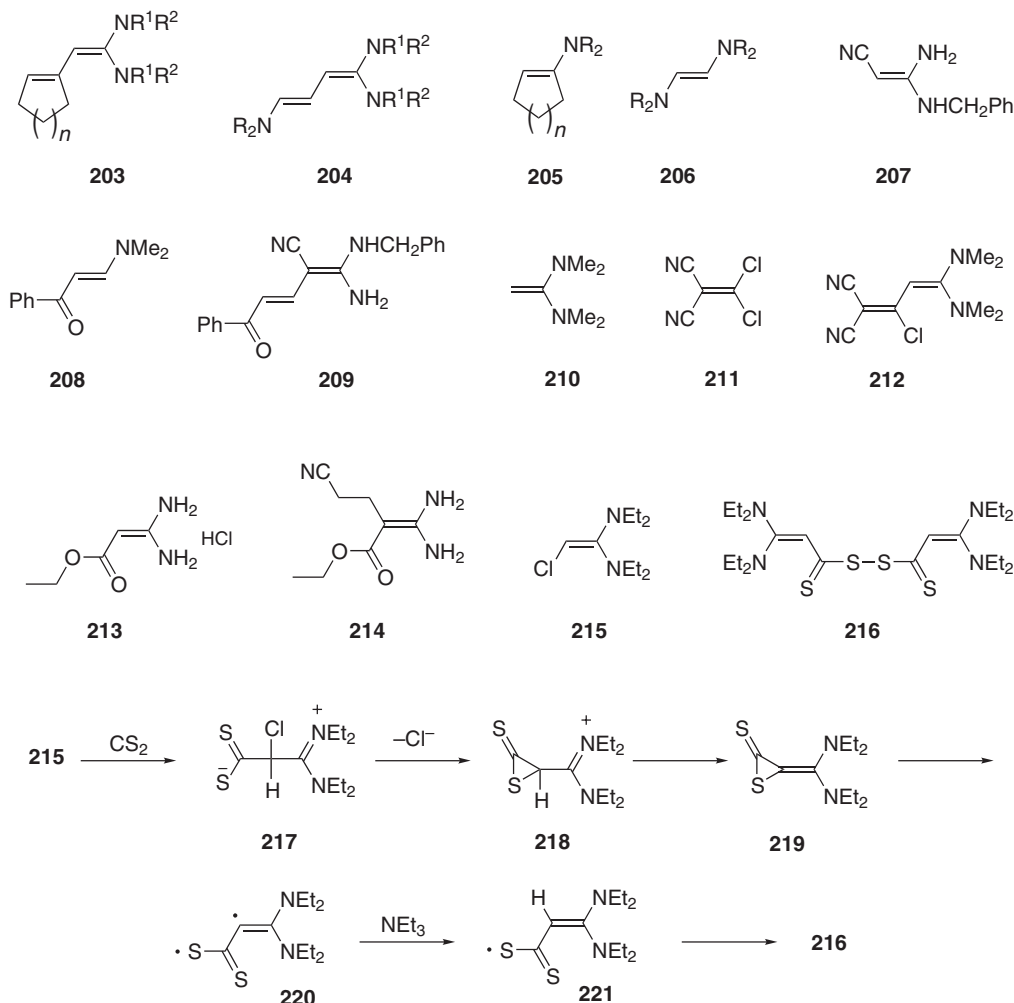
In a similar fashion the conjugated ketene aminals **203** and **204** can be obtained from the reaction of **200** with enamines **205** and **206**, respectively. The reaction of ketene aminal **207** with the enamine **208** gave the diene **209** in 43% yield <1994AP85>.

In the above reactions, vinyl substitution is possible since the amino group can be lost from the enamine moiety. The reaction of the ketene aminal **210** with the vinylidene dichloride **211** can be viewed in a similar light. In the presence of triethylamine, the conjugated ketene aminal **212** is obtained as a result of a chloride ion being lost from the vinylidene dichloride moiety <1993JCS(P2)911, 1993TL1779>.



Michael additions are possible at the  $\beta$ -position of ketene aminals. Thus, the ketene aminal hydrochloride salt **213** reacted with acrylonitrile in THF and triethylamine to give the ketene aminal **214** in 92% yield <1995T7161>.

The  $\beta$ -chloro-substituted ketene aminal **215** reacted with carbon disulfide in the presence of triethylamine to give the disulfide **216** in 30–41% yield <1995SUL73>. The presence of triethylamine is crucial to this reaction and no product is detected in its absence. The proposed mechanism is shown in Scheme 20. Addition of carbon disulfide gives the betaine structure **217**, which cyclizes to give the thiiranthione **218** which in turn undergoes dehydrochlorination to give the dithiolactone **219**. This structure is highly strained and decomposes to give the diradical **220**. Hydrogen abstraction by the more reactive vinyl carbon site, followed by dimerization of the resulting dithiocarboxyl radical **221** gives the final product **216**.



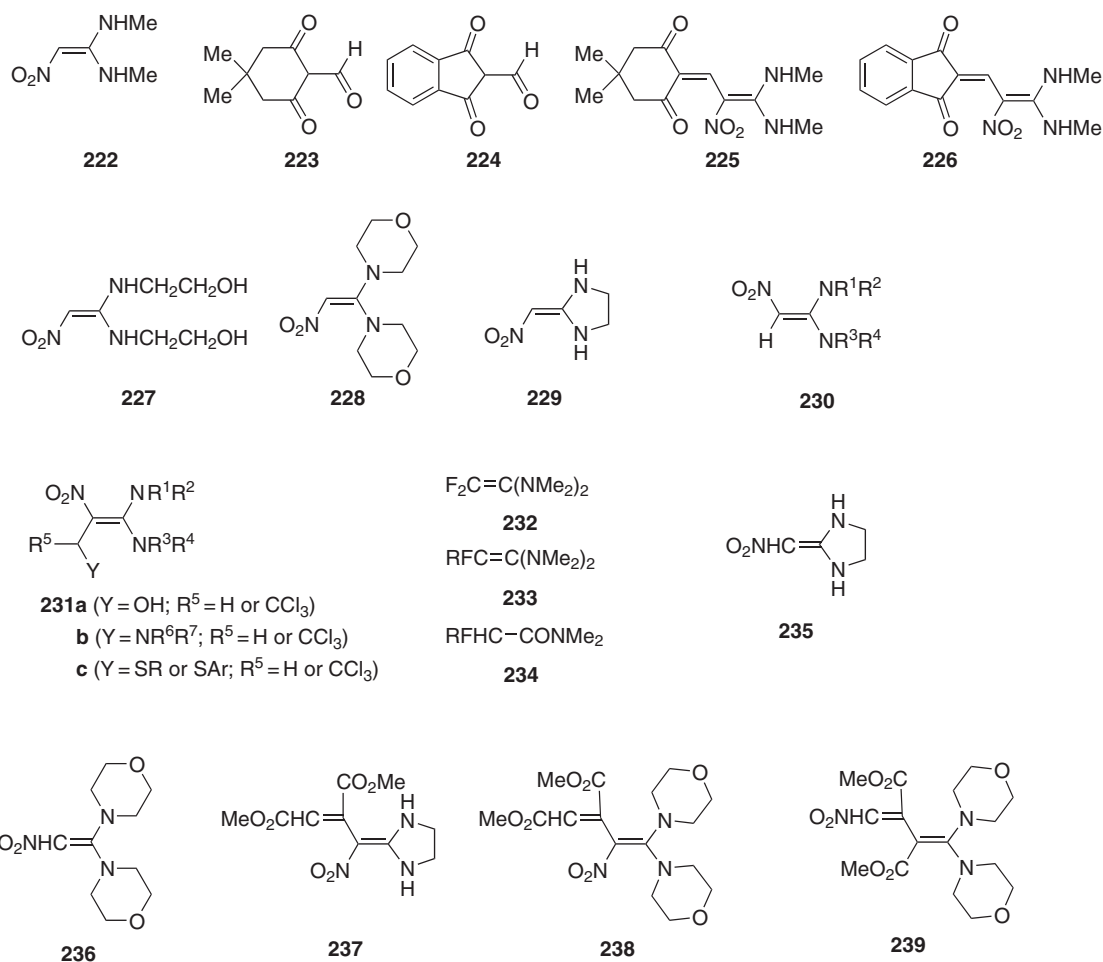
Scheme 20

1,1-Bis(methylamino)-2-nitroethene **222** is strongly polarized due to the influence of the amino groups and the  $\beta$ -nitro group. As a result, it readily undergoes reactions with electrophiles at the  $\beta$ -position. Thus, reaction with the aldehydes **223** and **224** led to the condensation products **225** and **226**, respectively, in 78% and 58% yields. Similar reactions occur using the ketene aminals **227** and **228**. Thus, the ketene aminal **227** reacts with **223** and **224** to give  $\beta$ -substituted ketene aminals in 33% and 70% yields, respectively, while the ketene aminal **228** reacts with the same aldehydes to give  $\beta$ -substituted products in 80% and 46% yields, respectively. The ketene aminal **229** also reacts but the initial condensation products are not isolable and react further to produce heterocyclic structures <1997ZOR1044, 1999CHE286>.

Ketene aminals **230** have been treated with formaldehyde or chloral hydrate in the presence of triethylamine to give the allylic alcohols **231a**. If the reaction is carried out in the presence of a primary or secondary amine instead of triethylamine, allylic amines **231b** are obtained. In a similar fashion, the presence of a thiol in the reaction mixture results in thioethers **231c** <1990EUP0392560>.

The fluorinated ketene aminal **232** reacts with 1 equiv. of an alkyl lithium at room temperature such that one fluorine substituent can be substituted with an alkyl group to give the mono-alkylated products **233**. These structures are converted to  $\alpha$ -fluoroacetamides **234** when a hydrolytic work-up is used <1997JOC1576>.

The reaction of the ketene aminals **235** and **236** with acetylenedicarboxylate in methanol gave the ketene aminals **237** and **238**, respectively, in 29% and 68% yield <1991BCJ2118>. When the reaction was carried out on **236** using acetonitrile as solvent, the ketene aminal **239** was obtained in 62% yield, a reaction which is thought to occur by a [2+2]-cycloaddition followed by ring opening. Apart from structure **235**, ketene aminals bearing an N—H group gave heterocyclic products arising from further cyclization of the initial reaction product.

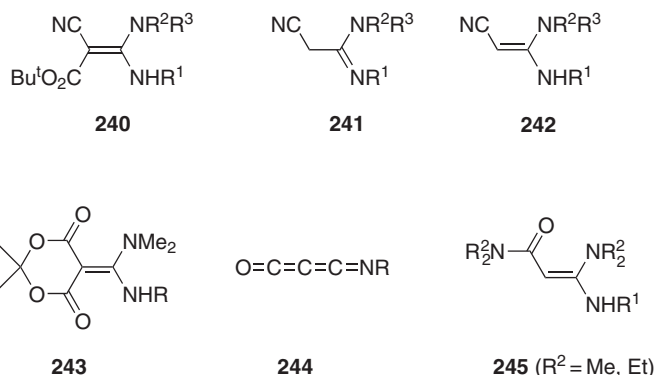


## (ii) Deacylation

$\beta,\beta$ -Diacylketene aminals have been monodeacylated to give  $\beta$ -acylketene aminals using methanol in the presence of  $Co(OAc)_2 \cdot 4H_2O$  <1995COFGT(4)967>. The deacylation of the ketene aminal **240** has also been carried out using trifluoroacetic acid in dichloromethane. The ester group is first hydrolyzed then decarboxylation takes place. The resulting product was the cyanoacetamidine trifluoroacetate **241**, which can be tautomerized by treatment with base or buffer to give the ketene aminal **242** <1998WOP9850344>.

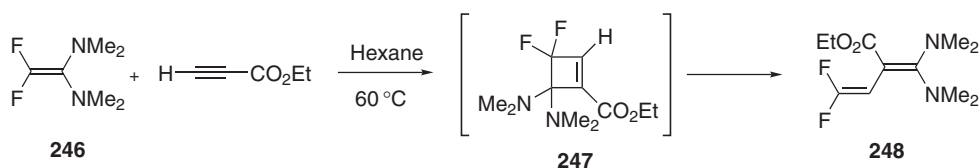
## (iii) From ketene amins via iminopropadienones

The bisaminomethylene derivative of Meldrum's acid **243** can be converted to the iminopropadienone **244** by flash vacuum thermolysis, then treated with secondary amines to give ketene amins bearing a  $\beta$ -amido substituent **245** <2002JOC2619>. The initial addition of the amine is to the C=O group to form an amidoketenimine, which can be detected by NMR and IR spectroscopy. A second molecule of amine then adds more slowly to give the observed products. The products are actually obtained as the amidine tautomers but these tautomerize on distillation to give the ketene amins.



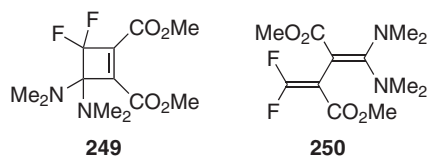
## (iv) From cycloaddition reactions

The  $\beta,\beta$ -difluoroketene aminal **246** undergoes a [2 + 2]-cycloaddition reaction with ethyl propiolate to give a cyclobutene product **247**, which undergoes electrocyclic ring opening to give the ketene aminal **248** in 66% yield (Scheme 21) <1999JOC5599>. The cyclobutene structure is stable at temperatures below  $-15^\circ\text{C}$ .



Scheme 21

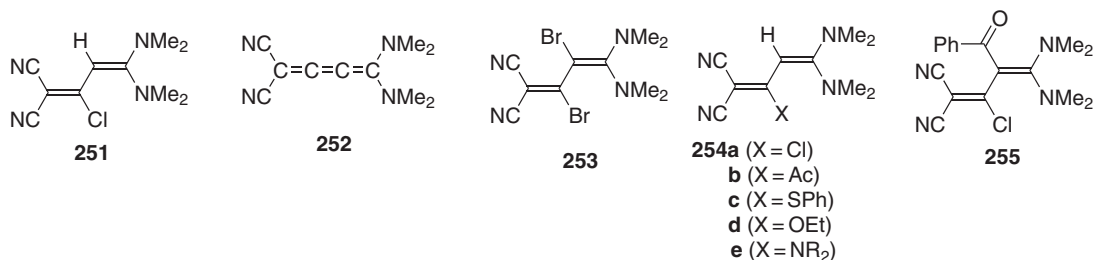
The reaction of **246** with dimethyl acetylene dicarboxylate gives the analogous cyclobutene structure **249** at low temperatures. However, on warming no diene **250** is observed, with polymerization taking place instead.



## (v) Dehydrohalogenation and subsequent reactions

Dehydrohalogenation of the diene structure **251** using DABCO in THF results in the formation of the butatriene **252**, which undergoes polar additions with a variety of electrophilic and nucleophilic compounds leading to ketene aminal derivatives <1993JCS(P2)911, 1993TL1779>. Thus, bromination of **252** gives the dibromo structure **253**. Treatment of **252** with  $\text{HX}$  gives

structures **254a–254c**, treatment with sodium ethoxide in ethanol gives **254d**, treatment with secondary amines gives **254e**, and treatment with benzoyl chloride gives **255**. Attempts to carry out cycloaddition reactions with **252** proved unsuccessful.

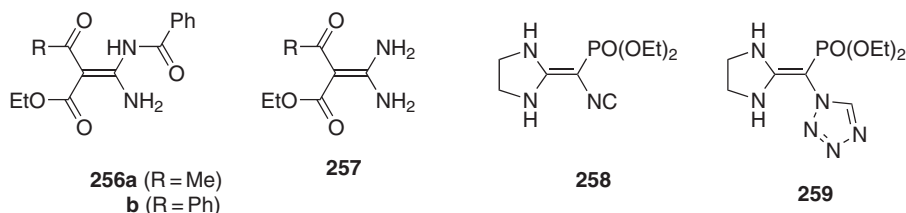


(vi) *Hydrolysis of  $\alpha$ -amido enamines*

The *N*-benzoyl derivatives **256a,b** were treated with sodium methoxide in methanol to generate the ketene aminals **257** <1993IZV419>.

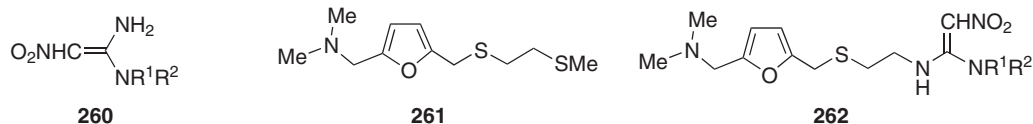
(vii) *Modification of  $\beta$ -isocyano groups*

Treatment of the ketene aminal **258** with hydrazoic acid resulted in the modification of the isocyano group to a tetrazole **259** in 57% yield <1994JPR29>.



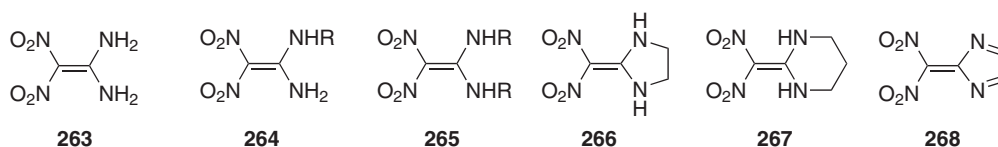
(viii) *Alkylation of amino groups*

Ketene aminals **260** reacted with the thioether **261** when heated at 80 °C, resulting in *N*-alkylation and the formation of the antiulcer agents **262** <1983EUP0092647>.

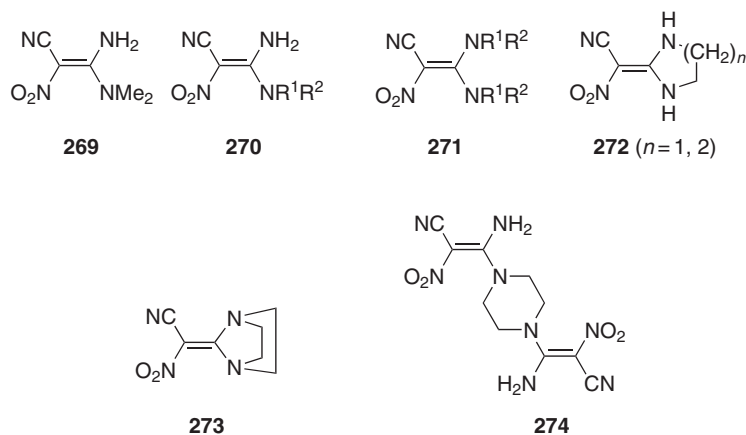


(ix) *Substitution of amino groups*

The explosive 1,1-diamino-2,2-dinitroethene **263** (also known as FOX-7) reacts as a “push–pull” alkene and undergoes transamination reactions via an addition–elimination mechanism when treated with a variety of amines (predominantly primary amines). Either one or both of the amino groups can be replaced to give the mixed ketene aminal **264** and the ketene aminal **265**, respectively. With the diamines 1,2-diaminoethane and 1,3-diaminopropane, it is possible to get the cyclic products **266** and **267**, respectively, when a solvent is used. However, when the reaction is carried out in neat 1,2-diaminoethane, the heterocyclic product **268** is formed instead in 25% yield <2002JCR(S)257>.

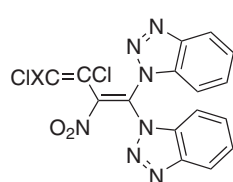
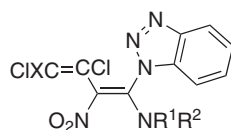
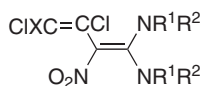
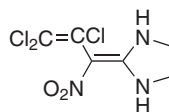
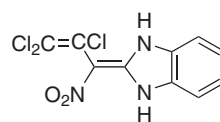
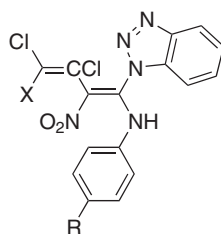
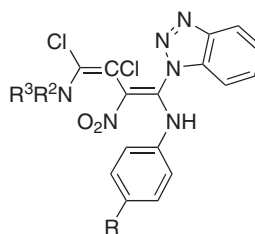


Transamination reactions have also been reported for the ketene aminal **269**. Treatment with 3 equiv. of a strongly basic amine such as ammonia, methylamine, or morpholine in aqueous medium resulted in mono-amination products **270**, which precipitated from solution in low-to-moderate yield. The dimethylamino moiety was selectively replaced. Reaction of **269** with a large excess of amine such as dimethylamine or morpholine, on the other hand, resulted in the bis-amination products **271** in low yield (12–18%). Under these conditions, the mono-aminated product did not precipitate and so reacted further. Reaction of **269** with diamines allowed the formation of ketene aminals containing a diazaheterocyclic ring **272** in reportedly high yields. Reaction of **269** with piperazine resulted in the formation of two products—the diazabicycloheptane derivative **273** obtained in 7% yield, and the bisvinylpiperazine **274** obtained in 32% yield <1996CHE699>.



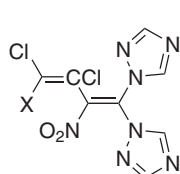
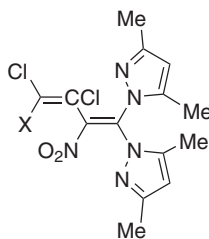
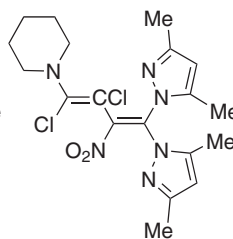
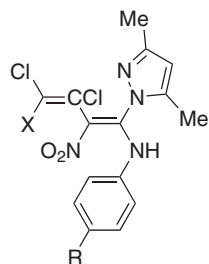
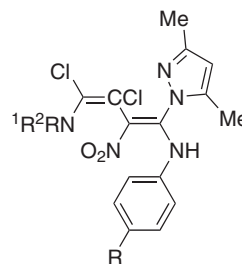
Ketene aminals containing benzotriazolyl groups **275** have been synthesized. The benzotriazolyl group is a good leaving group and the reaction of **275** with 1 equiv. of aromatic, arylaromatic, or heterocyclic amine was investigated and found to result in substitution of one benzotriazolyl residue leading to the mixed ketene aminals **276** in 70–95% yields. The reaction did not proceed satisfactorily with aliphatic amines and tarring took place. Reaction of the mixed ketene aminals **276** with a further equivalent of amine resulted in the substitution of the second benzotriazolyl residue and formation of the ketene aminals **277** in 40–70% yields. The same products were synthesized directly from **275** in 25–50% yields using 2 equiv. of amine. Reaction of **275** ( $X = \text{Cl}$ ) with 1 equiv. of various diamines resulted in the formation of ketene aminals containing diazaheterocyclic rings **278** and **279** in 55% and 75% yields <1997ZOR1541>.

When the amine involved was a *p*-substituted aniline (alkyl or alkoxy substituent), the first substitution took place as described above to give structures **280**. Reaction with various primary and secondary amines then resulted in substitution of one of the terminal chlorines rather than the second benzotriazolyl group to give the substitution products **281** in 47–92% yield. These results were explained by proposing that the C4 atom of the trichlorovinyl fragment is more susceptible to attack by hard bases. In the case of the mixed ketene aminal bearing aniline itself, reaction with another molecule of aniline results in substitution of the second benzotriazolyl group, whereas reaction with the harder base piperidine results in substitution of the chloro substituent <2000ZOR910>.

**275** (X = Br, Cl)**276** (X = Br, Cl)**277** (X = Br, Cl)**278****279****280** (X = Cl or Br;  
R = OR<sup>1</sup> or R<sup>1</sup>)**281**

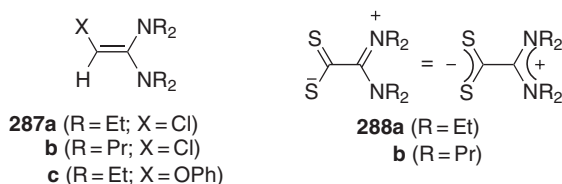
The reaction of the triazolyldienes **282** with 1 equiv. of an aliphatic, heterocyclic, or aromatic amine was also investigated and found to result in transamination of one of the azolyl moieties leading to mixed ketene aminals in high yields (85–95%) [<1997ZOR1715>](#).

Reactions of the bis(pyrazolyl)dienes **283** gave different products depending on the amine used [<1997ZOR1715, 2000ZOR910>](#). Reaction with 1 equiv. of an amine such as diethylamine, morpholine, or *p*-toluidine resulted in mixed ketene aminals, but in lower yields (35–50%) compared to the triazolyldienes. However, reaction with piperidine led to substitution of a terminal chlorine to give structure **284**. With excess amine, the reaction was nonselective and tarring took place. The reaction of **283** with anilines was also investigated. Reaction with 1 equiv. of an aniline resulted in substitution of one of the pyrazole substituents to give the mixed ketene aminals **285**. Reaction of the resulting mixed ketene aminals with diethylamine or piperidine resulted in substitution of a terminal halogen substituent as described above to give products **286** in 63–78% yields, whereas reaction with the less basic anilines resulted in tarring [<2000ZOR910>](#).

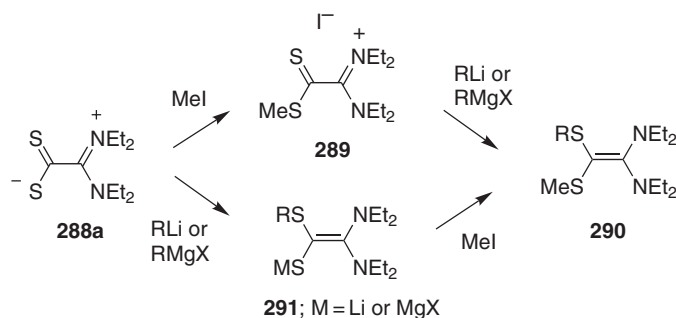
**282****283****284****285****286**

## (x) Ketene aminals via dithiolates

Ketene aminals can be converted to bis(dialkylamino)carbenium dithiocarboxylates, which undergo further reactions to give modified ketene aminals. For example, the ketene aminals **287a–287c** were treated with elemental sulfur in benzene in the presence of triethylamine to give the bis(dialkylamino)carbenium dithiocarboxylates **288a,b** in 70–97% yield <1995HAC45>.



Reaction of the dithioate **288a** with methyl iodide gave the carbenium salt **289**, which reacted at the sulfur atom with a range of soft nucleophiles such as Grignard and organolithium reagents to give the ketene aminals in near-quantitative yield **290** (Scheme 22). The order of the synthetic steps can be reversed, such that the dithioate is first treated with a nucleophile to give the salts **291**, which can then be treated with methyl iodide to give **290** in 84–94% yield. Reactions of **288a** with 1.2 equiv. of Bu<sup>t</sup>Li, followed by treatment with methyl iodide gave a mixture of the ketene aminals **292** and **293** in moderate yield, whereas reaction of **288a** with 2 equiv. of Bu<sup>t</sup>Li followed by methyl iodide gave a 56:44 mixture of **292** and **293** in 89% yield <1998CL321>.



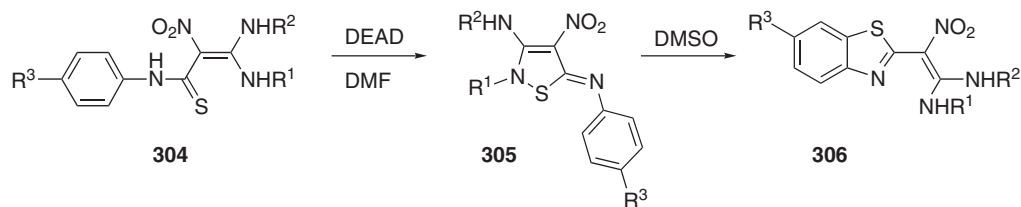
Scheme 22

The mechanism proposed involves a single electron transfer process from Bu<sup>t</sup>Li to **288a** to produce a pair of radicals **294**. Combination of the radical pair and methylation produces **292**, whereas disproportionation of the radical pair produces **295** and isobutene. Structure **295** could then be lithiated to give **296**, which would react twice with methyl iodide to produce the observed product **293**. The ratio of products is dependent on the solvent used and the metal ion. For example, treatment of **288a** with 2 equiv. of Bu<sup>t</sup>MgCl in ether gave only **292** as the product <1998CL321>.

The reaction has been used to synthesize large crystalline water-soluble compounds. Thus, reaction of **288a** with the hexabromide **297**, followed by reaction with 6 equiv. of methyl iodide gave structure **298** bearing 6 ketene aminal moieties in 61% yield <2001CL768>.

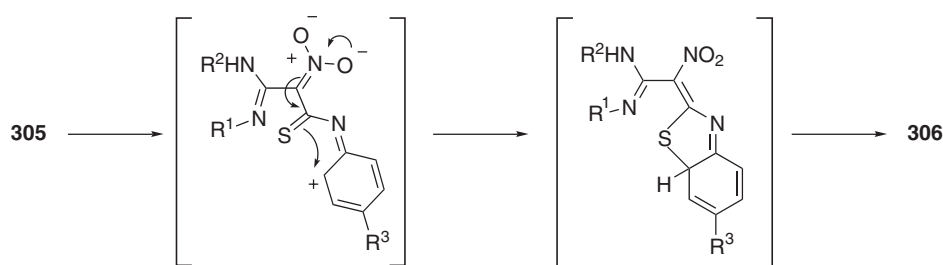






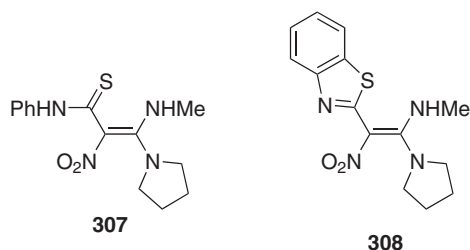
Scheme 23

The isomerization rate was slowed if  $R^3$  was electron withdrawing, or if  $R^1$  and  $R^2$  were aromatic rings with an electron-donating group at the *para* position. A proposed mechanism is shown in [Scheme 24 <1997HCA273>](#).



Scheme 24

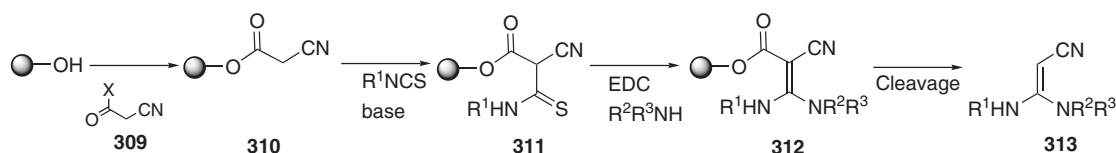
Treatment of the ketene aminal **307** with DEAD led to intractable mixtures. However, treatment with bromine gave the ketene aminal **308** [<1997HCA273>](#).



#### 4.21.1.1.24 By combinatorial synthesis

A combinatorial synthesis of ketene aminals has been reported which involves the reaction of isothiocyanates with active methylene compounds (see also [Section 4.21.1.1.2 <1998WOP9850344>](#)). Various solid supports are reported to be feasible including polystyrene, polyethylene glycol, and polyethylene glycol attached to polystyrene, polyamides, polysaccharides, and silicates. In the case of a polystyrene resin, a Wang or a Rink linker can be used. The reaction sequence involves acylation of hydroxyl groups on the linker with a cyanoacetic acid derivative **309** (preferentially an anhydride generated *in situ*) ([Scheme 25](#)). The resulting resin-bound cyanoacetate **310** is then treated with an excess of an aromatic or aliphatic isothiocyanate in NMP, DMF, or THF in the presence of a base such as diisopropylethylamine or DBU to give a resin-bound thioamide **311**. Treatment with the coupling agent EDC and a primary or secondary amine gives the resin-bound ketene aminal **312**. The use of condensing agents alone or in the presence of a catalyst such as pyridinium tosylate or the salt of a tertiary amine is also reported

for this step. Cleavage conditions depend on the type of resin and linker used in the synthesis. For example, trifluoroacetic acid was used with polystyrene resins having a Wang or a Rink linker. The resulting products were ketene aminals bearing a  $\beta$ -cyano substituent **313**.



Scheme 25

It was also possible to carry out certain modifications on the resin-bound ketene amination before release—such as acylation of an NH group using an activated carboxylic acid derivative, or treatment with isocyanates, isothiocyanates, or sulfonyl chlorides to give carboxamides, ureas, thioureas, or sulfonamides, respectively.

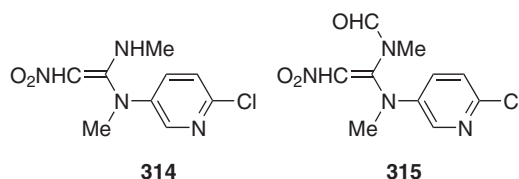
#### 4.21.1.2 Derivatives of Ketene Aminals

##### 4.21.1.2.1 $\alpha$ -Amido enamines, $R_2^4C=C(NR_2^1)(NR^2COR^3)$ , $\alpha$ -formamido enamines, $R_2^3C=C(NR_2^1)(NR^2CHO)$ , and $\alpha$ -thioamido enamines, $R_2^4C=C(NR_2^1)(NR^2CSR^3)$

It is usual to obtain  $\alpha$ -amido enamines by procedures similar to those used for the synthesis of ketene aminals. Starting materials such as ynamines, *N*-acyl ketenimines, isothioureas, and *N*-acylated ketene *N,S* acetals have been described previously <1995COFGT(4)967>.

##### (i) Formylation of ketene aminals

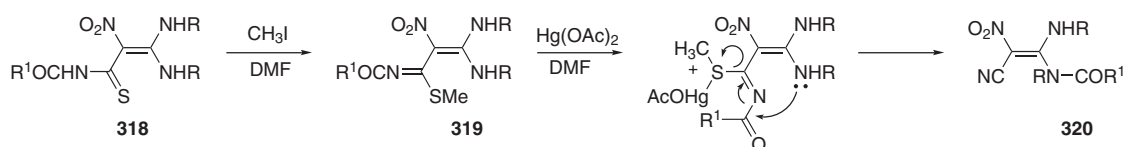
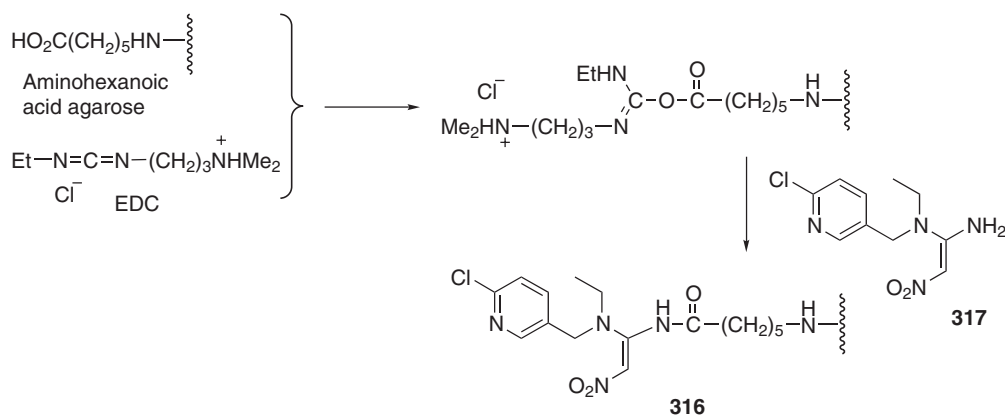
Formylation of ketene aminals has been carried out using sodium hydride to abstract a proton from the ketene amination, then adding formic acetic anhydride to give the *N*-formylated ketene amination <1993MI41>. For example, formylation of the ketene amination **314** was carried out using sodium hydride and formic acetic anhydride to give the *N*-formylated ketene amination **315** in 24% yield <1994MI119>.



##### (ii) Acylation of ketene aminals

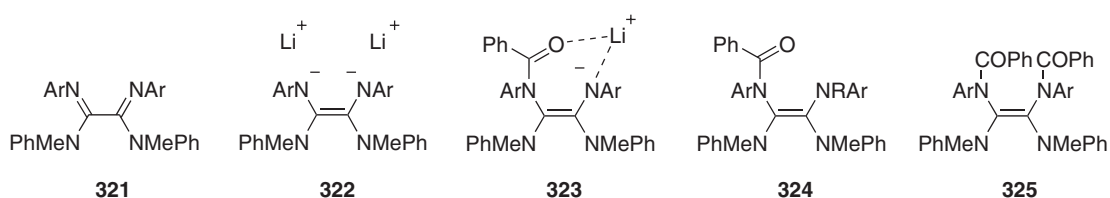
The preparation of a demethylnitenpyram affinity column **316** has been reported, whereby the ketene amination **317** was linked to EDC-activated agarose (Scheme 26) <1996MI1669>.

An intramolecular acylation of ketene aminals has been reported. Reaction of the ketene aminals **318** with methyl iodide in the presence of a base such as silver oxide or potassium carbonate gave the thioimidates **319** in 63–77% yield (Scheme 27). Desulfurization of **319** with mercuric acetate produced an unexpected rearrangement reaction resulting in acylation of one of the amino groups of the ketene amination. The resulting *N*-acylated ketene aminals **320** were obtained in 46–85% yields <1993HCA2817, 1997HCA273>.



(iii) From amidines and formamidines

The persubstituted oxalic amidine **321** was reduced with lithium using THF as solvent and ultrasound to give the dilithio salt of the tetraaminoethane **322** in quantitative yield. Reaction with methyl benzoate gave the monobenzoyleted structure **323**, which was treated *in situ* with an alkyl halide to give structures **324** in 59–61% yield. The dibenzyloyleted structure **325** was obtained in 76% yield by reacting **322** with the stronger electrophile—benzoyl chloride <1998MI183>.

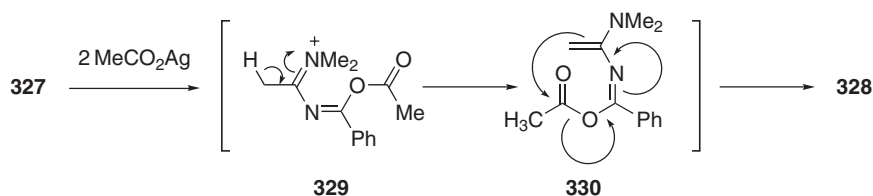


The formamidines **326** were treated with methyl iodide to give the amidinium salts **327** then converted to the  $\alpha$ -amido enamine **328** by reaction with 2 equiv. of silver acetate in dry acetonitrile (Scheme 28) <1999JCS(P1)2821>.



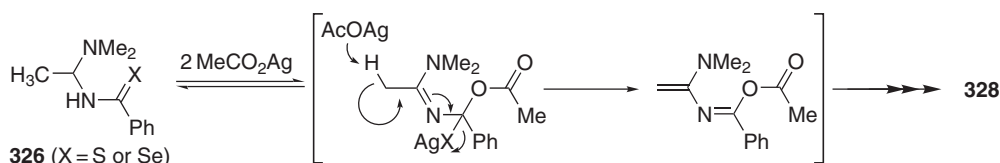
**Scheme 28**

The reaction mechanism is thought to feature formation of an *O*-acylamidinium salt intermediate **329**, followed by acetate-induced deprotonation of the amidinium moiety leading to intermediate **330**, and finally intramolecular capture of the acetyl residue by the enamine moiety previously generated (Scheme 29).



Scheme 29

The nature of the metal counterion and the heteroatom of the incoming nucleophile greatly influences the reaction. For example, the yield is much lower when potassium acetate is used instead of silver acetate. It was also demonstrated that the formamidines **326** could be converted directly to **328** by treatment with silver acetate in dry acetonitrile (Scheme 30).



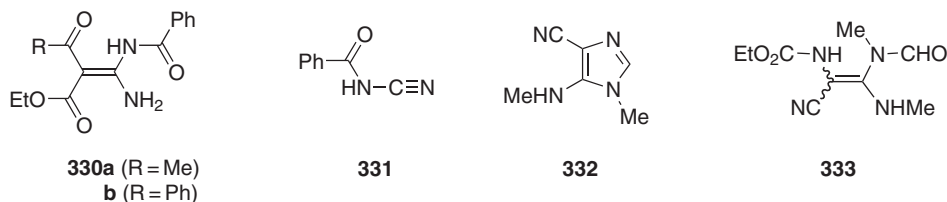
Scheme 30

#### (iv) From cyanamides

The *N*-benzoyl derivatives **330a** and **330b** were synthesized from the reaction of benzoyl cyanamide **331** with ethyl acetoacetate and ethyl benzoylacetate, respectively, in the presence of a Ni(acac)<sub>2</sub> catalyst <1993IZV419>.

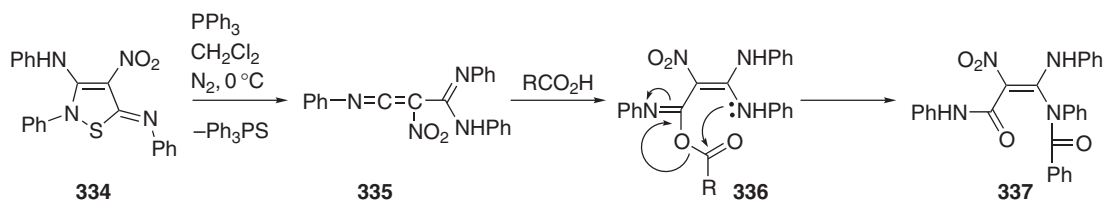
#### (v) From ring opening of imidazoles

Treatment of the imidazole **332** with ethyl chloroformate in aqueous sodium bicarbonate at room temperature resulted in a complex mixture of products, which included the  $\alpha$ -formamido enamine **333**, isolated as a mixture of (*E*)- and (*Z*)-isomers in 20% yield <1997CPB75>.



#### (vi) Ring opening of isothiazoles

Desulfurization of the nitroisothiazole structure **334** with triphenylphosphine resulted in ring opening and the formation of the highly reactive intermediate ketene imine **335**, which was trapped by the addition of benzoic acid to give the unstable adduct **336**. Intramolecular *N*-acylation of **336** as shown in Scheme 31 resulted in the  $\alpha$ -amido enamines **337** in 67% yield <1998HCA2388>.



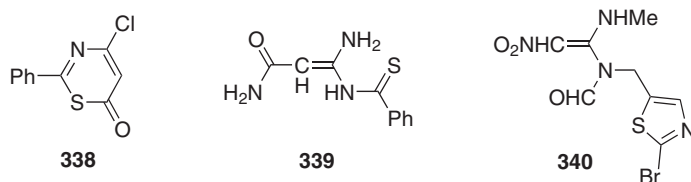
Scheme 31

(vii) Ring opening of thiazines

Reaction of the thiazine **338** with ammonia in dry ether resulted in ring opening and formation of the  $\alpha$ -thioamido enamine **339** <1997ZOB1195>. The nature of the solvent is important and if the reaction is carried out in alcoholic ammonia, a different product is obtained. The reaction is not generally useful in producing  $\alpha$ -thioamido enamines since reaction with primary or secondary amines results in thiazines where the chloro group is substituted by the amine. However, this appears to be the first reported example of  $\alpha$ -thioamido enamines.

(viii) Miscellaneous

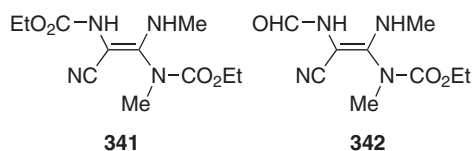
The *N*-formylketene aминаl **340** has been reported, but no details of its synthesis were given <1990EUP0381130>.



4.21.1.2.2  $\alpha$ -Alkoxy carbonylamino enamines,  $R_2C=C(NR^1)(NHCO_2R^2)$

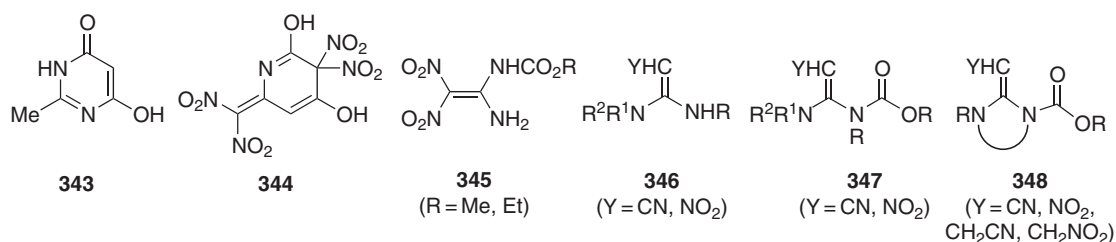
There has only been one reported instance of the synthesis of an  $\alpha$ -alkoxy carbonylamino enamine prior to 1996 <1995COFGT(4)967>. Three other reports have now appeared in the literature.

Compounds of this nature were isolated as by-products arising from ring opening of the imidazole **332** referred to above (Section 4.21.1.2.1). Thus, the  $\alpha$ -alkoxy carbonylamino enamines **341** and **342** were isolated in 2% and 7% yields, respectively <1997CPB75>.



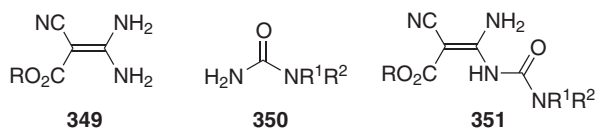
$\alpha$ -Alkoxy carbonylamino enamines have also been prepared by the ring opening of pyrimidines. Thus, pyrimidine **343** was nitrated with nitric acid and sulfuric acid to give the 5,5-dinitrodihydropyrimidine **344** which was heated with anhydrous methanol or ethanol to give the  $\alpha$ -alkoxy carbonylamino enamines **345** in 45% yield <2001ZOR766>.

A more general method for preparing  $\alpha$ -alkoxy carbonylamino enamines has been reported, whereby ketene aминаls **346** are deprotonated with sodium hydride, then acylated with a carbonate to give a range of structures having general formula **347**. Ketene aминаls containing a diazaheterocyclic ring have also been reacted in this way to give structures **348** <2003USP6538013>.



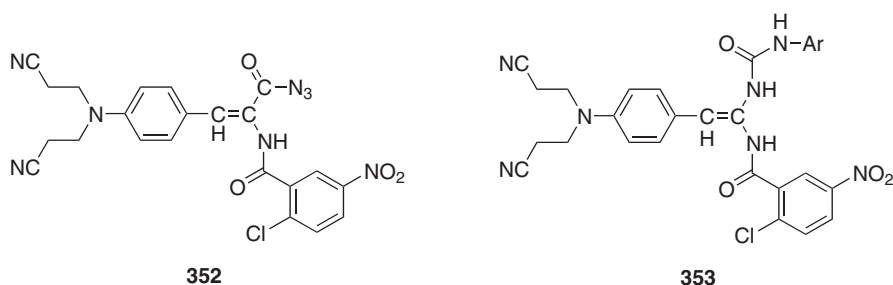
#### 4.21.1.2.3 $\alpha$ -Ureido enamines, $R_2^3C=C(NR_2^1)(NHCONR_2^2)$

$\alpha$ -Ureido enamines have been synthesized from ketene aminals, an oxazin-6-one, and an imino ester <1995COFGT(4)967>. More recently, it has been reported that heating ketene aminals **349** with various disubstituted ureas **350** in DMF gave the  $\alpha$ -ureido enamines **351** in low yield (3–11%) <1999HCO203>. These were shown by X-ray crystallography and NMR to exist as the (*Z*)-isomers, stabilized by intramolecular hydrogen bonding. In contrast, the reaction of (**349** R = Et) with monosubstituted ureas gave  $\alpha$ -ureido enamines which existed as a mixture of (*E*)- and (*Z*)-isomers.



#### 4.21.1.2.4 *N*-Acylated $\alpha$ -ureido enamines

*N*-Acylated  $\alpha$ -ureido enamines have been synthesized by the reaction of an *N*-acylketenimine with carbodiimides, as well as by a Curtius rearrangement of an acyl azide <1995COFGT(4)967>. Further examples of the latter technique have been reported, whereby the acyl azide **352** was treated with aromatic amines to give the *N*-acylated  $\alpha$ -ureido enamines **353** in 22–49% yield <1998MI990>.



#### 4.21.1.2.5 *gem*-Diureido alkenes, $R_2^3C=C(NHCONR_2^1)_2$

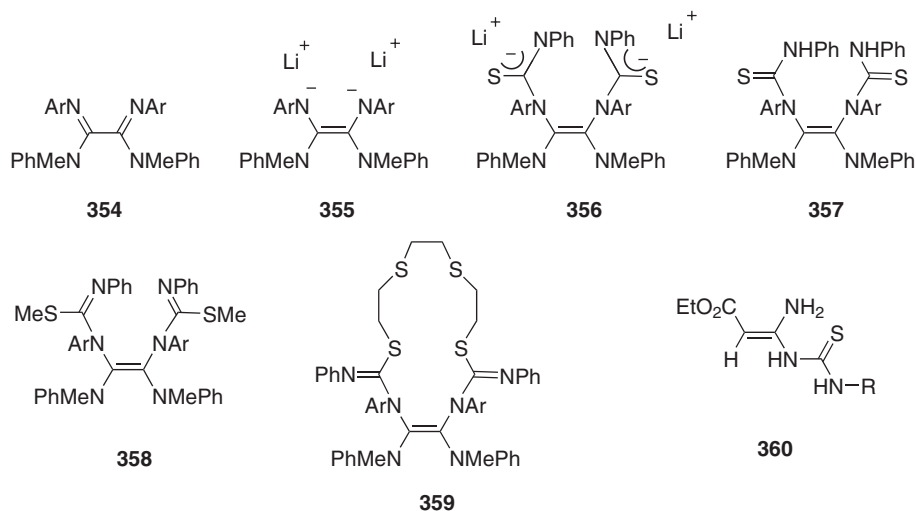
There has only been one instance of a *gem*-diureido alkene synthesis <1995COFGT(4)967> with no syntheses reported in the 1990s.

#### 4.21.1.2.6 $\alpha$ -Thioureido enamines, $R_2^3C=C(NR_2^1)(NHCSNR_2^2)$ , and $\alpha$ -isothioureido enamines, $R_2^3C=C(NR_2^1)(NH(C=NR^2)SR)$

The persubstituted oxalic amidine **354** has been reduced with lithium using THF as solvent and ultrasound to give the dilithio salt of the tetraaminoethane **355** in quantitative yield. Quenching of the dilithio salt with 2 equiv. of phenyl isocyanate gave the dilithium salt **356** which on treatment with methyl iodide gave the isothiurea derivative **358** in 92% yield. Alternatively, treatment of

**356** with methanol gave the thiourea **357** in 95% yield. When methyl isothiocyanate or benzoyl isothiocyanate are used instead of phenyl isothiocyanate, the starting amidine **354** is recovered as the major product after an aqueous work-up. This synthesis has been used to produce a variety of macrocyclic structures such as **359** <1998MI1803>.

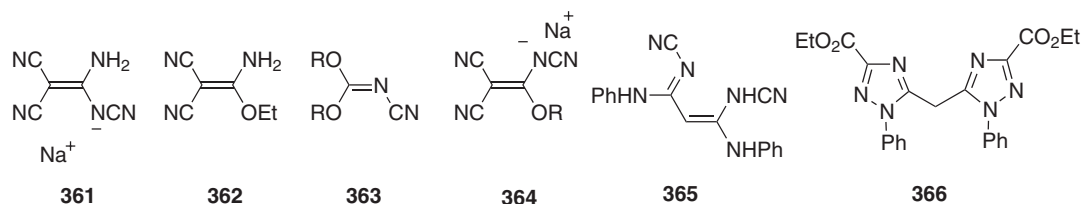
The  $\alpha$ -thioureido enamine **360** has been proposed as a reaction intermediate in the synthesis of a thiouracil from ketene animals and acyl isothiocyanates <1998HCA718>.



#### 4.21.1.2.7 $\alpha$ -Cyanamino enamines, $R_2C=C(NR^1)(NHCN)$

A specific synthesis of the sodium salt of  $\alpha$ -cyanamino enamine **361** has been reported, involving the reaction of malononitrile with sodium dicyanamide at an elevated temperature and in the presence of an aprotic dipolar solvent to give the product in 55–80% yield <1994EUP611751>. This represents an improvement over the previous synthesis which involved the reaction between sodium cyanamide and 1-amino-1-ethoxy-2,2-dicyanoethylene **362** – a reaction which only proceeded in modest yield (28%). Moreover, the previous synthesis required the prior synthesis of the required ketene-*N,O*-acetal, whereas the more recent synthesis involves the use of commercially available reagents. In a later report <1995WOP9503282>, it was revealed that the  $\alpha$ -cyanamino enamine **361** could be prepared by reacting a dialkyl cyanimidocarbonate **363** with an alkali metal salt of malononitrile to give the alkali metal salt of the ketene-*N,O*-acetal **364**. Immediate reaction with ammonia in a polar solvent and with heating furnished **361**. If diethyl (*N*-cyanimido)-carbonate (**363**; R = Et) is used, both reactions can be carried out in the same reaction vessel using ethanol as solvent.

The  $\alpha$ -cyanamino enamine **365** has been reported as a by-product of the decarboxylation reaction of the bis-triazole **366** <1999JOC6756>.



#### 4.21.1.2.8 $\alpha$ -Sulfonylamido enamines, $R_2C=C(NR^1)(NHSO_2R^2)$

$\alpha$ -Sulfonylamido enamines have been synthesized from the ketene dithioacetal **367** (Scheme 32). The ketene dithioacetal was treated directly with a primary cycloalkylamine to give the intermediate ketene *N,S*-acetals **368**. An alternative method was used to introduce isopropylamine, whereby the ketene





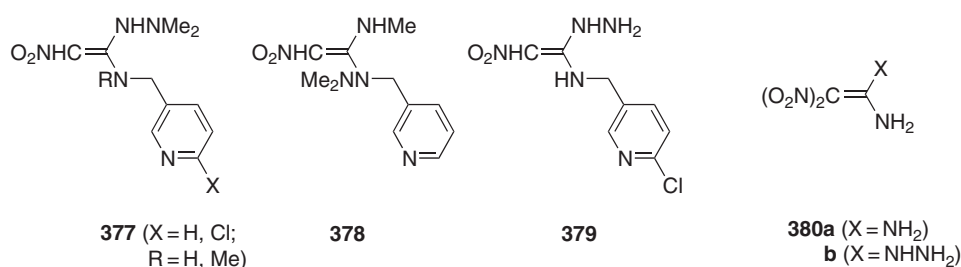
Other examples of the reaction of ketene *N,S*-acetals with hydrazines have been reported <1988EUP0302389>.

(ii) *From vinylidene dihalides*

The  $\alpha$ -hydrazino enamines **377–379** were synthesized from 1,1,1-trihalogeno-2-nitroethanes via vinylidene dihalides <1990EUP0381130>.

(iii) *Transamination of ketene amins*

The reaction between 1,1-diamino-2,2-dinitroethene **380a** and hydrazine is reported to give the  $\alpha$ -hydrazino enamine **381b** by means of a transamination process <2002JCR(S)257>.



#### 4.21.1.3.2 *gem*-Dihydrazino alkenes, $R_2C=C(NR^1NR^2)_2$

Reported syntheses of *gem*-dihydrazino alkenes are rare <1995COFGT(4)967> and there have been no instances since the 1990s.

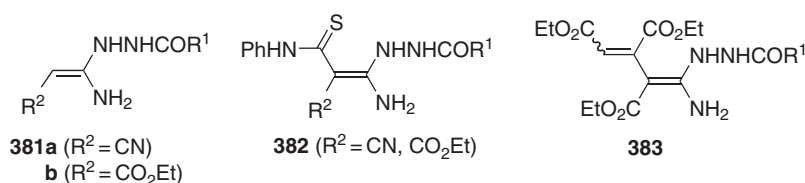
#### 4.21.1.3.3 *Derivatives of $\alpha$ -hydrazino enamines*

(i) *N*-Acylated hydrazino enamines

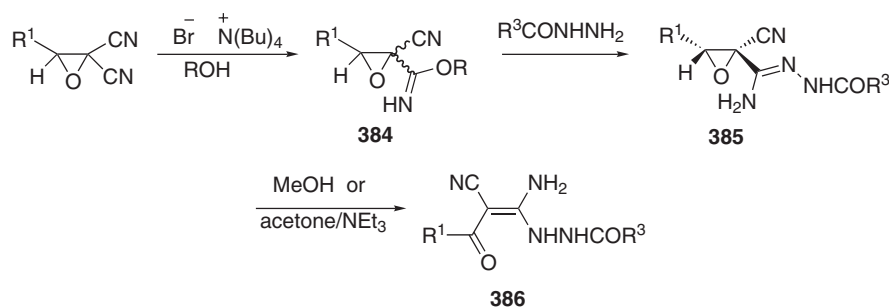
*N*-Acylated hydrazino enamines have been obtained by acylation of the parent  $\alpha$ -hydrazino enamines with acetic anhydride, methyl chloroformate, or methyl isocyanate. They have also been obtained by treating imino esters with arylcarbonylhydrazines <1995COFGT(4)967>.

More recently, it has been shown that it is possible to introduce substituents into the  $\beta$ -position of *N*-acylated hydrazino enamines since the C-2 position is more nucleophilic than the amino groups. Thus, the *N*-acylated hydrazino enamines **381** react with an equimolar amount of phenyl isothiocyanate in dry DMF at room temperature to give the propenethioamides **382** <1999JHC1183>.

Treatment of the *N*-acylated hydrazino enamine **381b** with diethyl acetylenedicarboxylate is thought to involve a Michael-type reaction, whereby the  $\beta$ -carbon of the enamine reacts with the alkyne to give the proposed *N*-acylated hydrazino enamine intermediates **383**. However, these intermediates have not been isolated since they cyclize to heterocycles <1995H1479>.

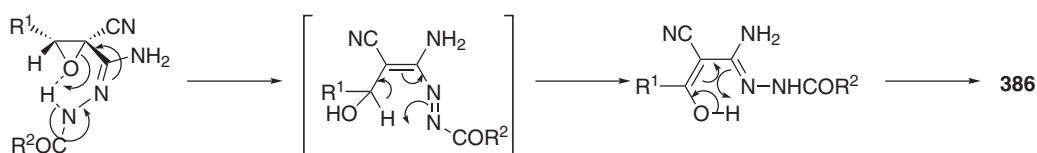


The *trans*-isomer of the epoxy imide **384** reacts with carbazates ( $\text{H}_2\text{NNHCOR}$ ) to give epoxy acylamidrazones **385**, which can then be converted to the *N*-acylated  $\alpha$ -hydrazino enamines **386** by heating in methanol, or by heating in acetone in the presence of triethylamine (Scheme 33) <2001S2435>.



Scheme 33

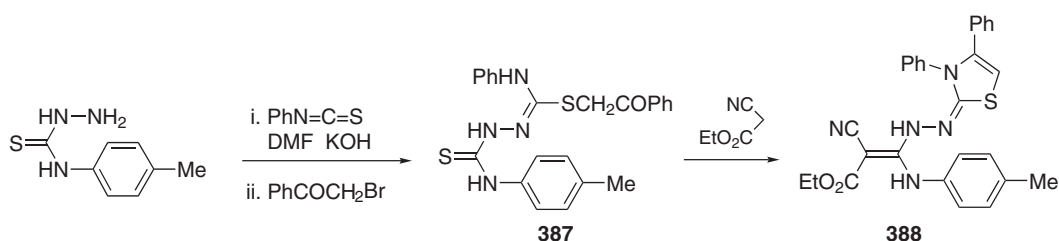
The proposed mechanism involves a rearrangement where the driving force is furnished by the possibility of intramolecular H-bonding between the oxirane and the acylamidrazone substituent (Scheme 34).



Scheme 34

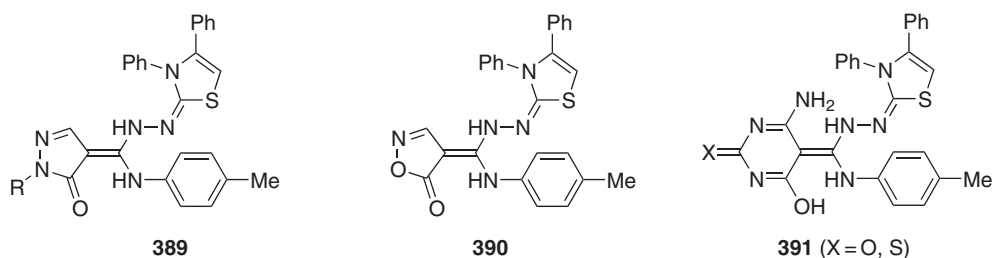
## (ii) Hydrazones of $\alpha$ -hydrazino enamines

Only one synthesis of the hydrazone of an  $\alpha$ -hydrazino enamine has been reported previously <1995COFGT(4)967>. A further example has now been published <1999MI97>. The reaction of ethyl cyanoacetate with the thiourea structure **387**—synthesized as shown in Scheme 35—resulted in the formation of the  $\alpha$ -hydrazino enamine **388** with concurrent formation of a thiazole ring. A yield of 82% was obtained.

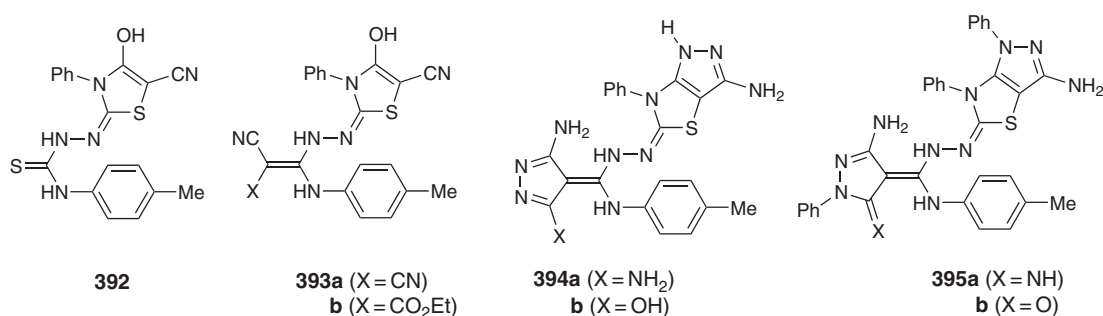


Scheme 35

Structure **388** was further reacted with a range of nitrogen-containing nucleophiles to build different heterocyclic structures at the  $\beta$ -position. Thus, reaction with hydrazines gave the pyrazoles **389**, reaction with hydroxylamine hydrochloride gave the isoxazole-5-one **390**, and reaction with urea or thiourea gave the pyrimidines **391**.



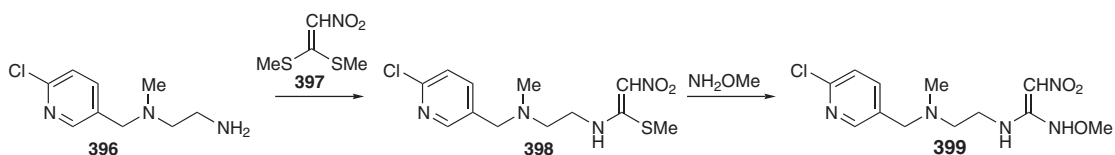
The thiazole derivative **392** was also synthesized and treated with malononitrile and ethyl cyanoacetate to give the condensed products **393a** and **393b**, respectively, in 79–82% yield. These were in turn treated with hydrazine hydrate or phenylhydrazine to give the pyrazolo[3,4-*d*]thiazoles **394** and **395**, respectively.



#### 4.21.1.3.4 $\alpha$ -Hydroxylamino enamines and $\alpha$ -alkoxyamino enamines, $R^3C=C(NR^1_2)(NHOR^2)$

##### (i) From ketene dithioacetals and ketene *N,S*-acetals

The (*E*)-isomer of the  $\alpha$ -alkoxyamino enamine **399** was synthesized by reacting the ketene dithioacetal **397** with a primary amine **396** to give the intermediate ketene *N,S*-acetal **398** in 57% yield, then converting **398** to the final product in 64% yield by reaction with *O*-methylhydroxylamine (Scheme 36) <1989USP4806553>.

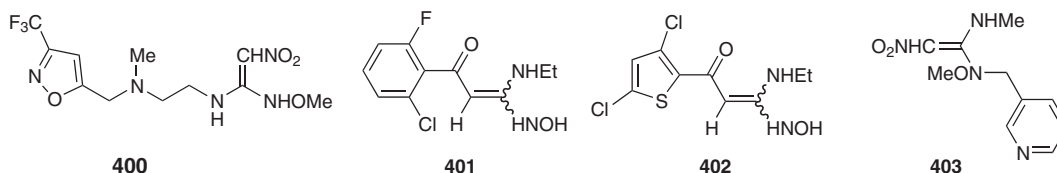


Scheme 36

The  $\alpha$ -alkoxyamino enamine **400** and the  $\alpha$ -hydroxylamino enamines **401** and **402** were similarly prepared <1989USP4806553, 1993EUP563686>.

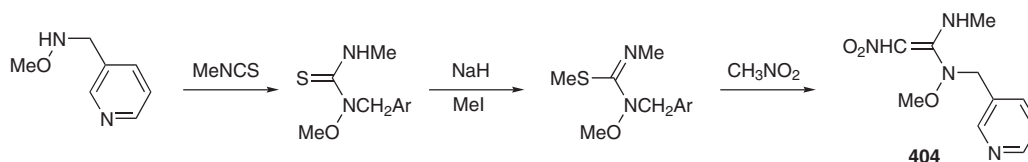
##### (ii) From vinylidene dihalides

It has been reported that the  $\alpha$ -alkoxyamino enamine **403** was synthesized from 1,1,1-trihalo-2-nitroethane via a vinylidene dihalide in a similar manner to ketene amins (Section 4.21.1.1.3) <1990EUP0381130>.



## (iii) From thioureas and isothioureas

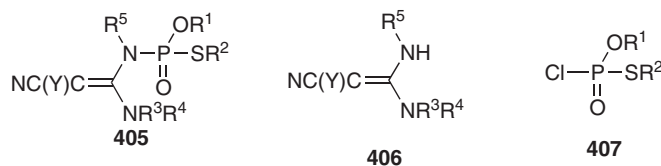
The  $\alpha$ -alkoxyamino enamine **404** was prepared via the thiourea/isothiourea route normally used for the synthesis of ketene amins (Scheme 37) (Section 4.21.1.1.2) <1988EUP0302389>.



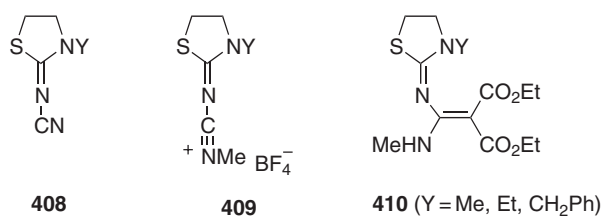
Scheme 37

4.21.1.3.5  $\alpha$ -Thiophosphoramido enamines,  $R_2^5C=C(NR_2^1)(NR_2^2)PO(OR^3)(SR^4)$ 

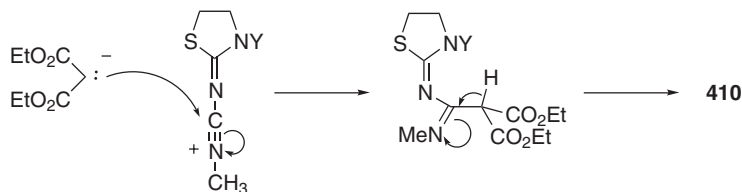
A patent has described the synthesis of  $\alpha$ -thiophosphoramido enamines **405** by treating ketene amins **406** with sodium hydride to deprotonate the secondary amino group, then adding a phosphonochloridethiolate **407** <1995EUP684247>.

4.21.1.4 Derivatives Bearing One NY or NZ Function and One  $NR_2$  Function4.21.1.4.1  $\alpha$ -Alkylideneamino enamines,  $R_2^3C=C(NR_2^1)(N=CR_2^2)$ 

The thiazolidines **408** were methylated with trimethyloxonium tetrafluoroborate to give the nitrilium salts **409**, which were reacted with sodio diethyl malonate to give a mixture of products, one of which was the  $\alpha$ -methyleneamino enamine **410** obtained in low yield (0–11%) <1993H55>. Reaction with sodio ethyl acetoacetate failed to give a similar type of product.



The mechanism proposed for the formation of **410** is shown in Scheme 38. The reaction does not appear to have much synthetic utility. However, it does appear to be the first reported synthesis of an  $\alpha$ -alkylideneamino enamine.



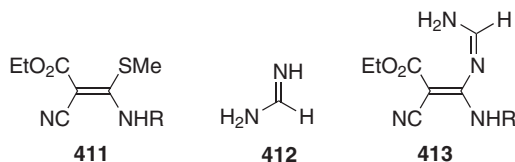
Scheme 38

#### 4.21.1.4.2 $\alpha$ -Aminoalkylideneamino enamines, $R^4C=C(NR^1)(N=CR^2NR^3)$ , $R^3C=C(NR^1)(N=CNR^2)$

$\alpha$ -Aminoalkylideneamino enamines have been synthesized from a variety of starting materials including a ketene aminal, an iminium perchlorate, acetals and enamines, and ketene *N,S*-acetals <1995COFGT(4)967>.

##### (i) From ketene *N,S*-acetals

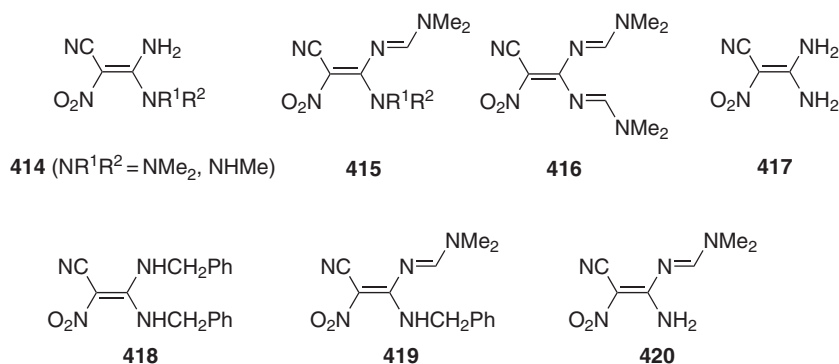
Further examples of the use of ketene *N,S*-acetals have been reported, whereby the ketene *N,S*-acetals **411** were treated with formamidine acetate **412** in the presence of sodium hydroxide and ethanol to give the  $\alpha$ -aminoalkylideneamino enamines **413** in 62–86% yields <1997AF35>.



##### (ii) From ketene aminals

The reaction of ketene aminals **414** with the diethyl acetal of DMF ( $\text{Me}_2\text{NCH}(\text{OEt})_2$ ) led to the mono-amidines **415** in high yield (97–98%) <1996CHE699>. Under the same conditions, the di-amidine **416** was obtained in 97% yield from the ketene aminal **417**.

Treatment of the diamidine **416** with benzylamine resulted in a mixture of transamination products (**418–420**) obtained in low yield. The same reaction carried out on (**415**;  $\text{R}^1 = \text{R}^2 = \text{Me}$ ) gave **418** and **419** <1996CHE699>.



#### 4.21.1.4.3 $\alpha$ -Diaminomethyleneamino enamines, $R^3C=C(NR_2^1)(N=C(NR_2^2)_2)$

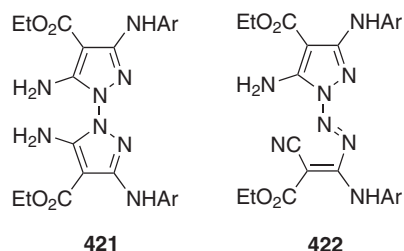
Only one synthesis of an  $\alpha$ -diaminomethyleneamino enamine has been reported <1995COFGT(4)967> and none since the 1990s.

#### 4.21.1.4.4 $\alpha$ -Bis(methylthio)methyleneamino enamines, $R^2C=C(NR_2^1)(N=C(SMe)_2)$

Only one synthesis of an  $\alpha$ -bis(methylthio)methyleneamino enamine has been reported <1995COFGT(4)967> and none since the 1990s.

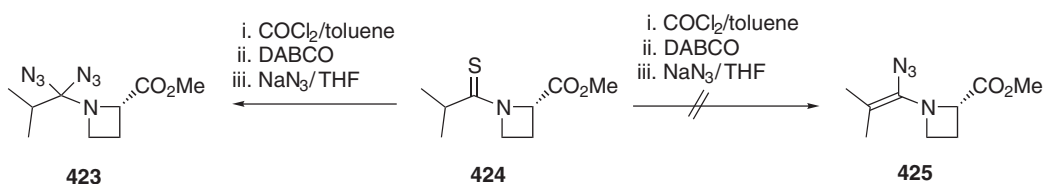
#### 4.21.1.4.5 $\alpha$ -Azo enamines, $R^3C=C(NR_2^1)(N=NR^2)$

$\alpha$ -Azo enamines have been synthesized from a pyrazole ring system and from a dimeric bipyrazole structure <1995COFGT(4)967>. Further examples of the latter synthesis have been reported <1994CB1729>, whereby the dimeric bipyrazoles **421** were treated with  $Pb(OAc)_4$  in methanol to give the azo-substituted enamines **422**.



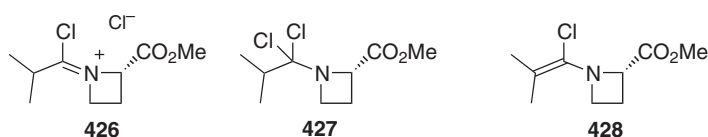
#### 4.21.1.4.6 $\alpha$ -Azido enamines, $R^3C=C(NR_2^1)N_3$

Synthesis of  $\alpha$ -azido enamines has been reported starting from *gem*-diazido alkenes, *N*-alkyl-5-phenylisoxazolium fluoroborates,  $\alpha$ -chloro enamines, and ketene *N,S*-acetals <1995COFGT(4)967>. An attempt to synthesize the azido enamine **425** from the norprolinate **424** proved unsuccessful and gave the geminal diazide **423** instead (Scheme 39) <2002HCA885>.



Scheme 39

This was attributed to the strained nature of the chloriminium chloride intermediate **426**, which prefers to undergo addition of a second chloride ion to relieve the strain of the double bond exocyclic to a four-membered ring and to give the geminal dichloride **427**. Subsequent substitution with azide ions produces the observed product. Thus, the alternative mechanism via the chloro enamine **428** cannot take place.



#### 4.21.1.4.7 $\alpha$ -Isocyano enamines, $R_2C=C(NR_2)NC$

Only one synthesis of an  $\alpha$ -isocyano enamine has been reported <1995COFGT(4)967> and none since the 1990s.

#### 4.21.1.4.8 $\alpha$ -Phosphimino enamines, $R_2C=C(NR_2)(N=PR_3)$

$\alpha$ -Phosphimino enamines have been synthesized from ketene amins, an  $\alpha$ -azido enamine, and a bisphosphimino alkene <1995COFGT(4)967>, but there have been no reports of syntheses since the 1990s.

#### 4.21.1.4.9 $\alpha$ -( $N,N',N'$ -Triphenylphosphorimidic triamido) enamines, $R_2C=C(NHPh)(N=P(NHPh)_3)$

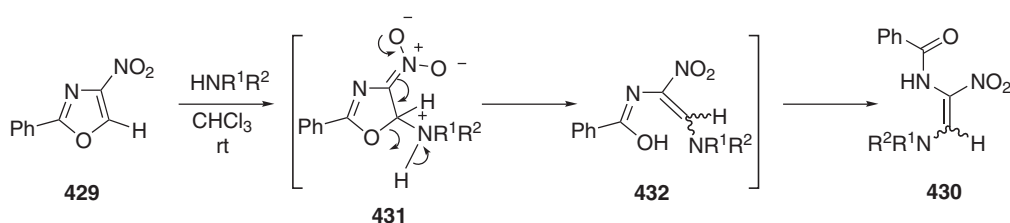
The synthesis of only one  $\alpha$ -( $N,N',N'$ -triphenylphosphorimidic triamido) enamine has been reported <1995COFGT(4)967> with none since the 1990s.

#### 4.21.1.4.10 *gem*-Amido nitro alkenes, $R_2C=C(NR^1COPh)(NO_2)$

Methods for the synthesis of *gem*-amido nitro alkenes have been reported for the first time.

##### (i) From nitrooxazoles

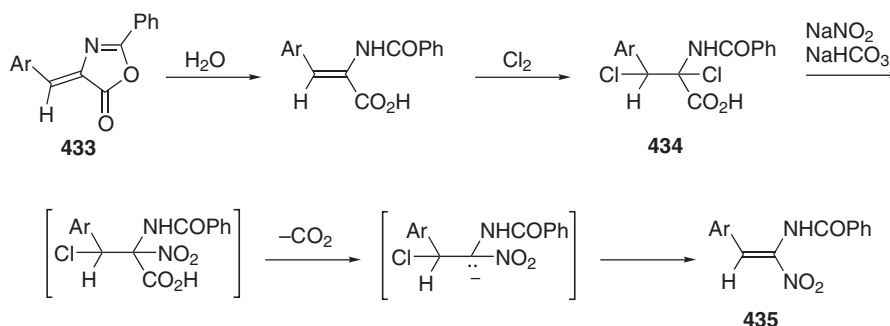
Ring opening of the nitrooxazole **429** with nucleophilic amines affords *gem*-amido nitro alkenes **430** in 70–98% yields (Scheme 40) <1999T13809, 1998JOC6050>. The mechanism involves a three-step hetero-domino process involving the oxazolone **431** and the corresponding ring-opened product **432** as key intermediates. A mixture of isomers is usually obtained.



Scheme 40

##### (ii) From azlactones

Unsaturated azlactones **433** have also been used to synthesize *gem*-amido nitro alkenes. The azlactones are converted in two steps to dichloro  $\alpha$ -acylamino carboxylic acids **434**, which are then reacted with sodium nitrite in the presence of sodium hydrogen carbonate. A chloro group is substituted by a nitro group, then decarboxylation takes place to give the *gem*-amido nitro alkenes **435** in 50–60% yields (Scheme 41) <1997ZOB1046>. The stereochemistry of the products has been determined with the nitro group being *trans* to the aromatic ring.



Scheme 41

#### 4.21.1.4.11 *gem*-Alkoxy carbonylamino nitro alkenes, $R_2^3C=C(NR^1CO_2R^2)(NO_2)$

The carbamate **436** was isolated as a low-yield by-product (5%) from the reaction of nitrostyrene **437** with ethyl [(4-nitrobenzenesulfonyl)oxy]carbamate. The main product was the aziridine **438** <1998T6169>. Although this method is not suitable for the synthesis of *gem*-alkoxy carbonylamino nitro alkenes, this is the first synthetic example of a compound containing this functional group.

### 4.21.1.5 Derivatives Bearing One NY Function and One NRX Function

#### 4.21.1.5.1 *gem*-Acylhydrazino azido alkenes, $R_2^3C=C(NHNHCOR^1)N_3$

*gem*-Acylhydrazino azido alkenes have been involved as intermediates in heterocyclic synthesis but have not so far been isolated <1995COFGT(4)967>.

### 4.21.1.6 Derivatives Bearing Two NY Functions

#### 4.21.1.6.1 *gem*-Alkylideneamino isocyanato alkenes, $R_2^3C=C(NCO)(N=CR_2^1)$

*gem*-Alkylideneamino isocyanato alkenes have been reported on only one occasion and not since the 1990s <1995COFGT(4)967>.

#### 4.21.1.6.2 *gem*-Dithioureido alkenes

Only one example of a *gem*-dithioureido alkene has been reported in the 1970s <1995COFGT(4)967>.

#### 4.21.1.6.3 *gem*-Bisazo alkenes, $R_2^3C=C(N=NR^1)_2$

The syntheses of some *gem*-bisazo alkenes were reported mainly in the late 1970s and early 1980s <1995COFGT(4)967>. Yields were poor and no further syntheses have been reported.

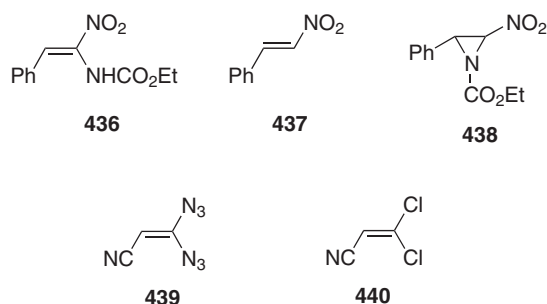
#### 4.21.1.6.4 *gem*-Azido phosphazido alkenes, $R_2^3C=C(N=N-N=PPh_3)N_3$

Only one example of a *gem*-azido phosphazido alkene has been reported in the 1980s <1995COFGT(4)967>.



#### 4.21.1.6.5 *gem*-Diazido alkenes, $R_2C=C(N_3)_2$

*gem*-Diazido alkenes have been synthesized from vinylidene dichlorides by treatment with sodium azide <1995COFGT(4)967>. A further report on the synthesis of the diazide **439** from the vinylidene dichloride **440** has been published <1993JCR(S)162>.

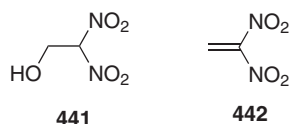


#### 4.21.1.6.6 *gem*-Dinitro alkenes, $R_2C=C(NO_2)_2$

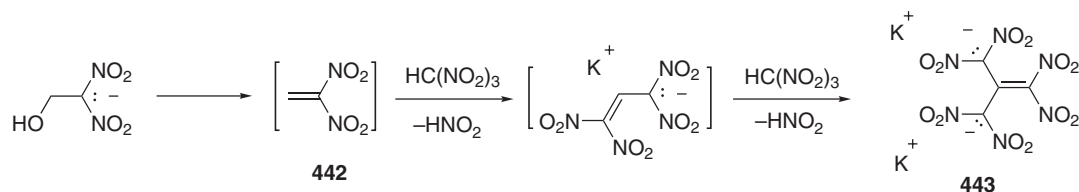
*gem*-Dinitro alkenes have been synthesized by a number of methods, which include the nitration of alkenes and alkanes with nitric acid or dinitrogen tetroxide, thermal extrusion of  $N_2O_4$  from nitro alkanes, thermal or acid/base-catalyzed dehydrations of dinitro alkanols, base-catalyzed extrusions, generation from dinitromethane and from diazo compounds <1995COFGT(4)967>. Further syntheses have been reported since the 1990s.

##### (i) From dinitroalkanols

The acid-catalyzed dehydration of the dinitro alkanol **441** to form the dinitro alkene **442** *in situ* has already been described <1995COFGT(4)967>.



In a similar manner, the potassium salt of **441** was dehydrated to form **442**, which was then reacted *in situ* with trinitromethane to form the hexanitroisobutene anion **443** (Scheme 42) <1999ZOR1581>.

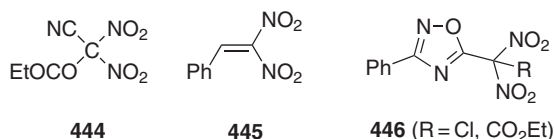


Scheme 42

##### (ii) From diazo compounds

The reaction of diazo compounds with  $Cl(NO_2)_3$  to give dinitroalkenes has been described previously <1995COFGT(4)967>. More recently, the reaction of cyanodinitroethoxycarbonylmethane **444** with phenyldiazomethane resulted in the formation of 1,1-dinitro-2-phenylethene

**445** amongst other products. This contrasts with the reaction of **444** with diazomethane or diazoethane where triazole rings were formed [<1993ZOR61>](#). Treatment of the oxadiazoles **446** with phenyldiazomethane ( $\text{PhCHN}_2$ ) gave a mixture of products, which included the dinitro-alkene **445** obtained in 20–23% yield [<1999ZOR1581>](#).

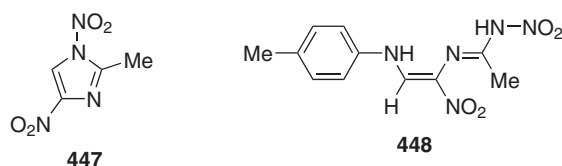


#### 4.21.1.6.7 *gem-Arylazo nitro alkenes*, $\text{R}_2\text{C}=\text{C}(\text{NO}_2)_2(\text{N}=\text{NAr})$

Very few syntheses of alkenes containing *gem*-nitro and arylazo groups have been reported [<1995COFGT\(4\)967>](#) and none since the 1980s.

#### 4.21.1.6.8 *gem-Aminoalkylideneamino nitro alkenes*, $\text{R}_2^3\text{C}=\text{C}(\text{NO}_2)_2(\text{N}=\text{CR}^1\text{NR}_2^2)$

The reaction of the imidazole structure **447** with *p*-toluidine in aqueous methanol resulted in ring opening and formation of the *gem*-imino nitro alkene **448** in 80–90% yield [<1994H1511>](#).



#### 4.21.1.6.9 *gem-Dimethoxazonyl alkenes*, $\text{R}_2\text{C}=\text{C}(\text{NO}=\text{NOMe})_2$

The synthesis of a *gem*-dimethoxazonyl alkene was reported in 1969, with no further examples [<1995COFGT\(4\)967>](#).

#### 4.21.1.6.10 *gem-Imino phosphimino alkenes*, $\text{R}_2^3\text{C}=\text{C}(\text{N}=\text{PR}_3^1)(\text{N}=\text{CR}_2^2)$

The synthesis of two *gem*-imino phosphimino alkenes was reported in 1972, but there have been no further examples [<1995COFGT\(4\)967>](#).

#### 4.21.1.6.11 *gem-Diphosphazido alkenes and gem-diphosphimino alkenes*, $\text{R}_2^3\text{C}=\text{C}(\text{N}=\text{N}=\text{N}=\text{PR}_3^1)_2$ , $\text{R}_2^3\text{C}=\text{C}(\text{N}=\text{PR}_3^1)_2$

There have been no reported syntheses of *gem*-diphosphazido alkenes or *gem*-diphosphimino alkenes since the one reported method published in 1985 [<1995COFGT\(4\)967>](#).

#### 4.21.1.6.12 *gem-Disulfoximido alkenes*, $\text{R}_2^3\text{C}=\text{C}(\text{N}=\text{SOR}_2^1)_2$

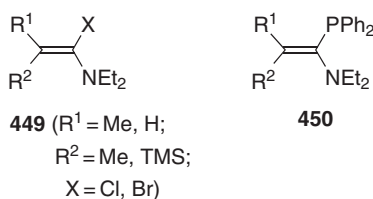
A synthesis of *gem*-disulfoximido alkenes was reported in 1983 [<1995COFGT\(4\)967>](#), but no further syntheses have been published.

## 4.21.2 FUNCTIONS CONTAINING ONE NITROGEN AND ONE PHOSPHORUS, $R^3C=CNR^1_2PO(OR^2)_2$ , $R^3C=CNR^1_2PR^2_2$ , etc.

### 4.21.2.1 Derivatives Bearing a Phosphino Function

#### 4.21.2.1.1 $\alpha$ -Phosphino enamines, $R^2C=C(PPh_2)NHR^1$

$\alpha$ -Phosphino enamines have been synthesized from dihalo alkenes, halo enamines, and ketimines <1995COFGT(4)967>. A further example of the synthesis of these compounds from halo enamines has been reported. Thus, the chloro enamine **449** was treated with diphenylphosphine ( $Ph_2PH$ ) at room temperature in the presence of 5 mol.%  $PdCl_2(PPh_3)_2$  as a catalyst to give the phosphino enamines **450** in 70–84% yield <1999TL573>. Benzene was used as solvent and triethylamine was present as a base. The carbon–halogen bond in **449** is very reactive due to the effect of the  $\alpha$ -dialkylamino group. The reaction can also be carried out using diphenyltrimethylsilylphosphine ( $Ph_2PSiMe_3$ ) with 5 mol.%  $PdCl_2(PPh_3)_2$  as a catalyst to give the same products without the need of additional purification, though prolonged reaction times are required for completion.



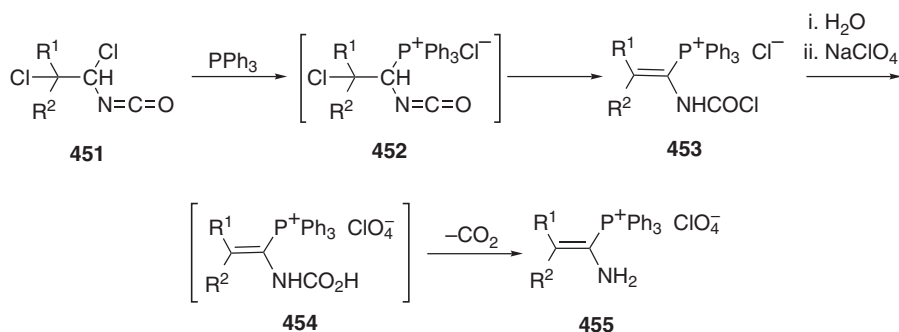
#### 4.21.2.1.2 *gem*-Amido phosphino alkenes, $R^3C=C(NHCOR^1)PR^2_2$

The synthesis of a *gem*-amido phosphino alkene was reported in 1979, but no further examples have been published <1995COFGT(4)967>.

### 4.21.2.2 Derivatives Bearing a Phosphonium Group

#### 4.21.2.2.1 $\alpha$ -Trialkylphosphonio enamines, $R^3C=C(NR^1_2)P^+R^2_3$

$\alpha$ -Trialkylphosphonio enamines have been rarely synthesized with the only example involving an  $\alpha$ -halo enamine as starting material <1995COFGT(4)967>. An alternative method of synthesis has now been reported (Scheme 43) <1993ZOB80>. The reaction of the isocyanate **451** with triphenylphosphine resulted in phosphorylation to give an intermediate **452** that contains a labile hydrogen atom at the  $\alpha$ -position. This favors easy dehydrochlorination to form an alkene. Moreover, the resulting chloride ion reacts with the isocyanate group to form a reactive chloro-carbonylamino ( $NHCOCl$ ) group. The observed products **453** can be isolated in 87–96% yield. Hydrolysis of (**453**;  $R^1 = R^2 = Cl$ ) gave the trialkylphosphonio enamine **455** in 95% yield.



Scheme 43

#### 4.21.2.2.2 *gem*-Carboxyamino phosphonio alkenes and *gem*-chlorocarbonylamino phosphonio alkenes, $R_2C=C(NHCO_2H)P^+Ph_3$ and $R_2C=C(NHCOCl)P^+Ph_3$

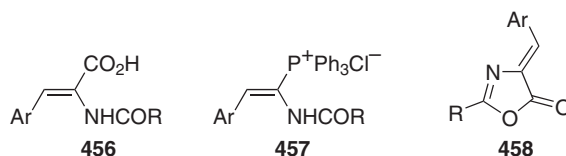
The synthesis of the *gem*-chlorocarbonylamino phosphonio alkene **453** was described in Section 4.21.2.2.1 (Scheme 43). Hydrolysis of **453** resulted in the *gem*-carboxyamino phosphonio alkene **454** as an intermediate which spontaneously decarboxylated to give structure **455**.

#### 4.21.2.2.3 *gem*-Amido phosphonio alkenes, $R_2C=C(NHCOR^I)P^+Ph_3$

*gem*-Amido phosphonio alkenes have been synthesized from *gem*-amido carboxyalkenes, *N*-trichloroethylamides, and *N*-tetrachloroethylamides, and by modification of *gem*-amido phosphonio alkenes <1995COFGT(4)967>.

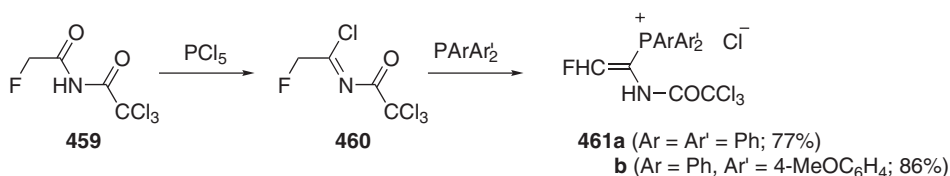
##### (i) From *gem*-amido carboxy alkenes

Further examples of the conversion of *gem*-amido carboxy alkenes **456** to *gem*-amido phosphonio alkenes **457** have been reported <1993ZOB87>. The reaction involves chlorination of the alkene, followed by treatment with triphenylphosphine <1995COFGT(4)967>. The required starting materials are in turn prepared by hydrolysis of unsaturated azlactones **458**.



##### (ii) From *N*-fluoroacetyltrichloroacetamide

Reaction of *N*-fluoroacetyltrichloroacetamide **459** with phosphorus pentachloride gave *N*-trichloroacetylfluoroacetimidoyl chloride **460** in 82% yield, which was treated with an equivalent of an arylphosphine to give the *gem*-amido phosphonio alkenes **461** as a mixture of isomers ((*E*)/(*Z*) 6:1) (Scheme 44) <2002JFC107>.

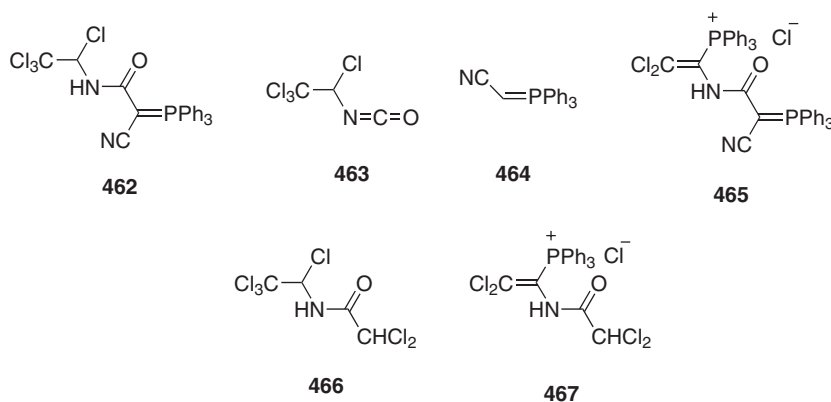


Scheme 44

##### (iii) From *N*-tetrachloroethylamides

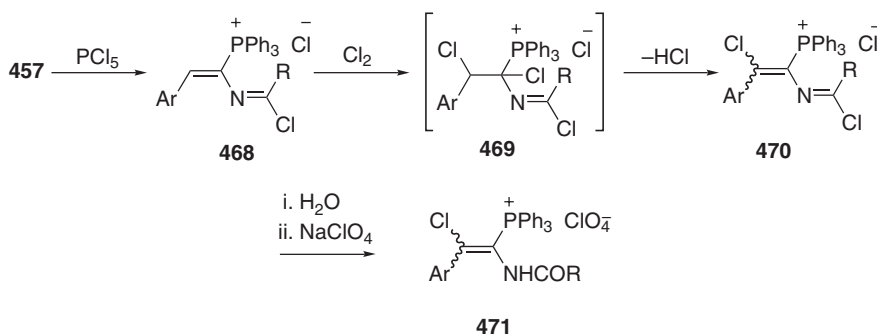
*gem*-Amido phosphonio alkenes have previously been synthesized from *N*-tetrachloroethylamides <1995COFGT(4)967>. A further example has been reported whereby the *N*-tetrachloroethylamide **462** was synthesized in 68% yield by the reaction of the isocyanate **463** with cyanomethylenetriphenylphosphorane **464**, then treated with 1.5 equiv. of triphenylphosphine to give the *gem*-amido phosphonio alkene **465** in 92% yield <1997ZOB391>. The reaction involves nucleophilic substitution by the triphenylphosphine, followed by dehydrochlorination.

Similar treatment of the *N*-tetrachloroethylamide **466** with 1.1 equiv. triphenylphosphine gave the *gem*-amido phosphonio alkene **467** in 85% yield <2002ZOB226>.



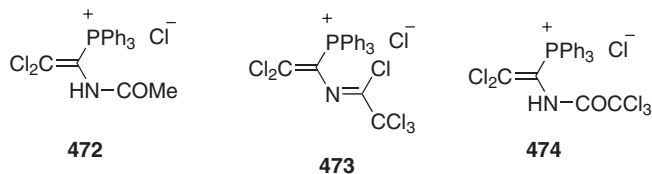
(iv) By modification of *gem*-amido phosphonio alkenes

It is possible to introduce a chlorine substituent into the  $\beta$ -position of structure **457**. However, chlorination of **457** itself does not take place under mild conditions.  $\beta$ -Substitution can be carried out by first converting **457** to the imidoyl chloride **468**. This compound then reacts easily with chlorine to give an intermediate **469** that undergoes dehydrochlorination to give the imidoyl chloride **470**. Subsequent hydrolysis then gives the  $\beta$ -chloro analog **471** (Scheme 45) <1993ZOB87>.



Scheme 45

The *gem*-amido phosphonio alkene **472** was chlorinated by reaction with phosphorus pentachloride to give the hexachlorophosphonium chloride **473** in 95% yield. Hydrolysis gave the *gem*-amido phosphonio alkene **474** in 80% yield <1998ZOB167>.



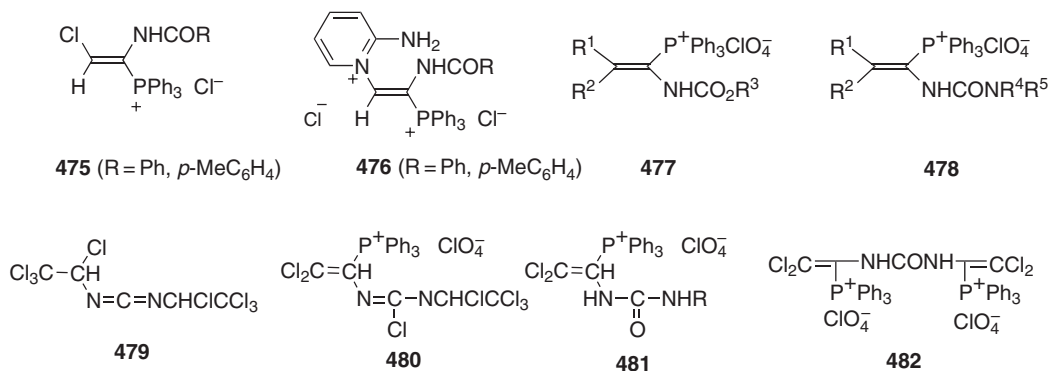
The reaction of the *gem*-amido phosphonio alkene **475** with 2-aminopyridine resulted in substitution of the  $\beta$ -chloro group to give the *gem*-amido phosphonio alkene **476** in 51–63% yield <1993ZOB642>. This is in contrast with the reaction of **475** with benzamidine where 1,3,5-triazines are formed. In the latter case, the greater basicity of benzamidine causes elimination of HCl from **475**, which deactivates the  $\beta$ -carbon to nucleophilic attack and leads to a different reaction.

#### 4.21.2.2.4 *gem*-Alkoxy carbonylamino phosphonio alkenes, $R_2^2C=C(NHCO_2R^1)P^+Ph_3$

Compounds of this nature have been rarely reported <1995COFGT(4)967>. However, it is possible to synthesize such compounds **477** in 80–95% yield by reaction of the chlorocarbonylamino compound **453** with alcohols <1993ZOB80>.

#### 4.21.2.2.5 *gem*-Phosphonio ureido alkenes, $R_2^2C=C(NHCONR_2^1)P^+Ph_3$

In a similar vein, few examples of these structures exist <1995COFGT(4)967>. However, *gem*-phosphonio ureido alkenes **478** are available in 35–96% yield by treating the chlorocarbonylamino compound **453** with ammonia or amines <1993ZOB80>. In the same paper, it was demonstrated that a range of *gem*-phosphonio ureido alkenes could be obtained by the reaction of triphenylphosphine with the carbodiimide **479** to give the reactive intermediate **480**, which was then treated with water, alcohols, or amines to give various *gem*-phosphonio ureido alkenes **481**. Treatment of **480** with triphenylphosphine gave the diphosphorylated urea derivative **482** in 64% yield.



#### 4.21.2.2.6 *gem*-Arylchloromethyleneamino phosphonio alkenes, $R_2^2C=C(N=C(Cl)Ar)P^+R_3^1$

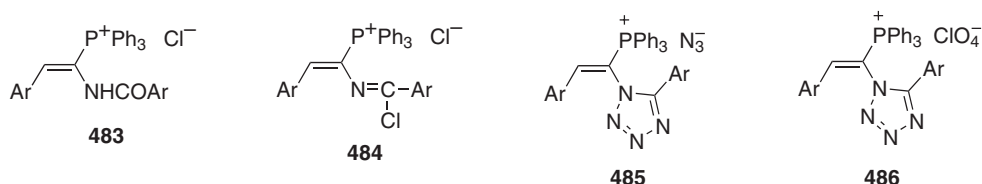
*gem*-Chloroarylideneamino phosphonio alkenes have been previously synthesized by treating the appropriate *gem*-amido phosphonio alkenes with PCl<sub>5</sub>/POCl<sub>3</sub> or with PCl<sub>5</sub> <1995COFGT(4)967>. Further examples have now been reported <1993ZOB87>, whereby *gem*-amido phosphonio alkenes **483** were converted to the *gem*-arylchloromethyleneamino phosphonio alkenes **484** in 86–93% yield on treatment with phosphorus pentachloride. Further reaction with chlorine under mild conditions gives an intermediate that spontaneously loses HCl to give the analogous structures **470** with a β-chloro substituent (Scheme 45). Structure **473** was similarly prepared <1998ZOB167>.

#### 4.21.2.2.7 *gem*-Aminochloromethyleneamino phosphonio alkenes, $R_2^2C=C(N=C(Cl)NR_2^1)P^+R_3^1$

The reaction of triphenylphosphine with the carbodiimide **479** gave the reactive intermediate **480** (Section 4.21.2.2.5) <1993ZOB80>.

#### 4.21.2.2.8 *gem*-Phosphonio tetrazol-1-yl alkenes

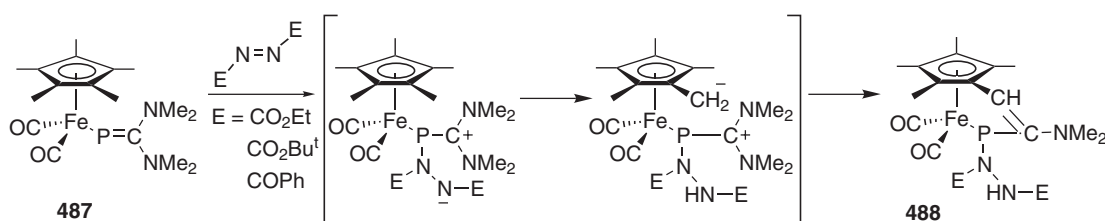
The *gem*-arylchloromethyleneamino phosphonio alkenes **484** were treated with sodium azide to give the phosphonium salts **485** containing a tetrazole ring. These compounds were not characterized but were treated with sodium perchlorate to give the perchlorates **486** in 83–95% overall yield <1995ZOB955>.



#### 4.21.2.3 Derivatives Bearing a Metallophosphino Function

##### 4.21.2.3.1 $\alpha$ -Metallophosphino enamine

Reaction of the metallophosphaphaalkene **487** with azo compounds resulted in the condensation of a ring methyl substituent with the bis(dimethylamino)methylene group to give the metallophosphino enamine **488** (Scheme 46) <1994PS325>.

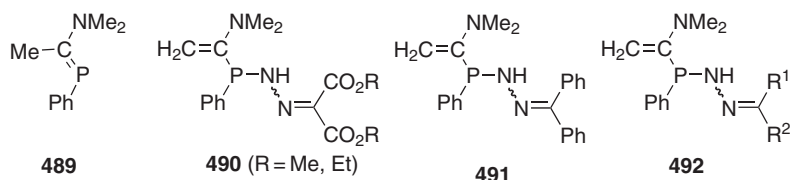


Scheme 46

#### 4.21.2.4 Derivatives Bearing a PPhX Group

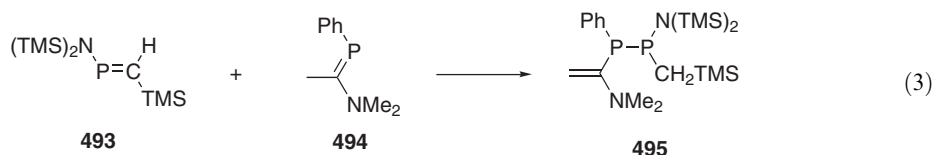
##### 4.21.2.4.1 Enamine derivatives bearing a $PPhNHN=CR_2$ group

The aminophosphaphaalkene **489** reacts with disubstituted diazo compounds at  $-20^\circ\text{C}$  to give the tricoordinated phosphorus compounds (**490–492**) via a Staudinger-type reaction <1993BSB719>. These compounds decompose at room temperature.



##### 4.21.2.4.2 Enamine derivatives bearing a $PR^1PR^2NR_2^3$ group

The reaction of the methylenephosphane **493** with the *C*-amino-substituted ethylenephosphane **494** afforded the unsymmetrical 1,2-diphosphane **495** as a mixture of two diastereomers (due to the formation of two new asymmetric centers at the P atoms) in 64% yield (Equation (3)) <1997JOC7605>. The reaction is the first example of a type II ene reaction between phosphaphaalkenes with different substitution patterns.



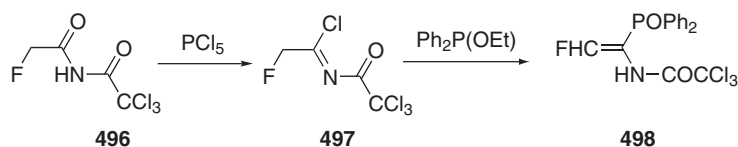
#### 4.21.2.5 Derivatives Bearing a Phosphinoyl or Thiophosphinoyl Group

##### 4.21.2.5.1 $\alpha$ -Phosphinoylenamines, $\text{R}^3\text{C}=\text{C}(\text{NR}^1_2)\text{POR}^2_2$

$\alpha$ -Phosphinoylenamines were reported in 1972 but have not been reported since <1995COFGT(4)967>.

##### 4.21.2.5.2 *gem*-Amido diphenylphosphinoyl alkenes, $\text{R}^2_2\text{C}=\text{C}(\text{NHCOR}^1)\text{POPh}_2$

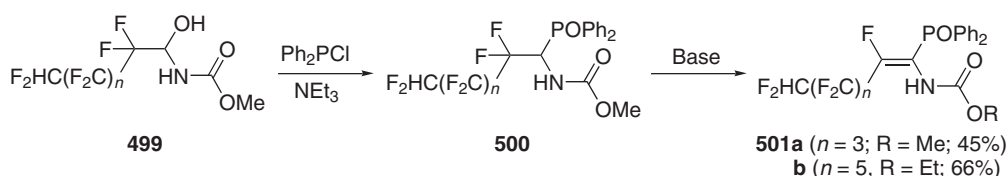
The synthesis of *gem*-amido diphenylphosphinoyl alkenes from *N*-tetrachloroethylamides was reported in the 1970s <1995COFGT(4)967>. A further synthesis has recently been reported. Thus, reaction of *N*-fluoroacetyltrichloroacetamide **496** with phosphorus pentachloride gives *N*-trichloroacetylfluoroacetimidoyl chloride **497** in 82% yield, which reacts with an equivalent of ethyl diphenylphosphinite to give the *gem*-amido diphenylphosphinoyl alkene **498** as a mixture of isomers ((*E*)/(*Z*) 4:1) in 60% yield (Scheme 47) <2002JFC107>.



Scheme 47

##### 4.21.2.5.3 *gem*-Methoxycarbonylamino diphenylphosphinoyl alkenes and *gem*-alkoxycarbonylamino diphenylphosphinoyl alkenes, $\text{R}^2_2\text{C}=\text{C}(\text{NHCO}_2\text{R}^1)\text{POPh}_2$

*gem*-Methoxycarbonylamino diphenylphosphinoyl alkenes were reported in the 1970s <1995COFGT(4)967>. More recently, the fluorinated *gem*-alkoxycarbonylamino diphenylphosphinoylalkenes **501** were synthesized by treating the  $\alpha$ -hydroxy urethane **499** with chlorodiphenylphosphine to give the phosphorylated urethanes **500**. Treatment with base (triethylamine, diazabicyclooctane, or 1 N NaOH) resulted in dehydrofluorination to give the *gem*-alkoxycarbonylamino phosphoryl alkenes **501** (Scheme 48) <1999ZOB1299>. The use of diazabicyclooctane as a base gave better results than triethylamine.



Scheme 48



#### 4.21.2.5.4 *gem*-Diphenylphosphinoyl ureido alkenes, $R_2^2C=C(NHCONR_2^1)POPh_2$

*gem*-Diphenylphosphinoyl ureido alkenes were reported in 1984 but have not been reported since <1995COFGT(4)967>.

#### 4.21.2.5.5 $\alpha$ -Thiophosphinoylenamines, $R_2^3C=C(NR_2^1)P(=S)R_2^2$

$\alpha$ -Thiophosphinoylenamines were reported in 1972 but have not been reported since <1995COFGT(4)967>.

#### 4.21.2.5.6 Derivatives bearing a diphenylphosphinoyl group and an $N=C(X)Ar$ group, $Cl_2C=C(N=C(X)Ar)POPh_2$

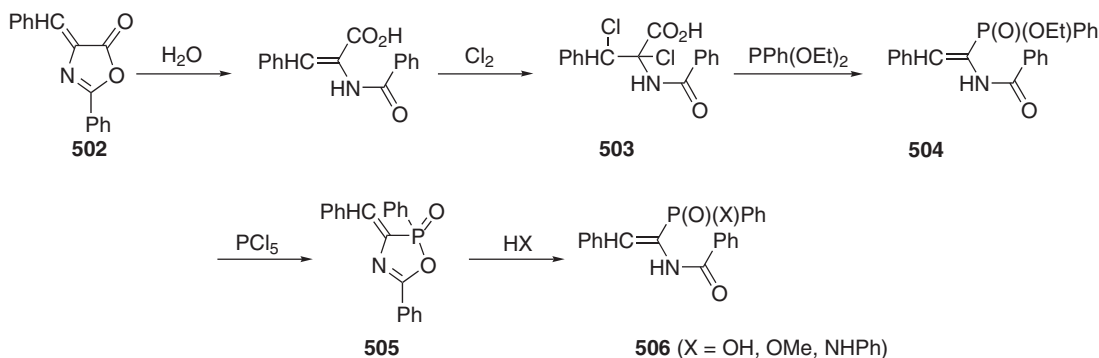
The derivatives described in the title were reported in 1978 but have not been reported since <1995COFGT(4)967>.

### 4.21.2.6 Derivatives Bearing a Phosphonyl Group, POXR

#### 4.21.2.6.1 *gem*-Amido phosphonoyl alkenes, $R_2^3C=C(NHCOR^1)POXR^2$

The synthesis of *gem*-amido phosphonoyl alkenes has been reported, starting from an acylaminophosphinic ester as well as from *N*-tetrachloroethylamides <1995COFGT(4)967>.

Structures of this nature have now been synthesized from the azlactone **502**, which was first hydrolyzed then chlorinated to give the *N*-acylated amino acid **503** (Scheme 49) <1993ZOB1259>. This was then treated with diethyl phenylphosphonate to give the *gem*-amido phosphonoyl alkene **504**. The reaction involves an Arbuzov rearrangement reaction, followed by decarboxylation and elimination of chloride ion. The phosphonoyl alkene **504** undergoes intramolecular cyclization when heated with phosphorus pentachloride to give the cyclic structure **505**. Hydrolysis of this structure with water, methanol, or aniline gives the phosphonoylalkenes **506** in 75–90% yield.



Scheme 49

Various cinnamic acid derivatives **507** obtained by the Erlenmeyer synthesis have been treated in this way to give dichlorinated adducts <1999GEP19801952, 2000PS209, 1998AG(E)2851> in near-quantitative yield. Since the latter were unstable to heat and light, they were treated immediately with different phosphonites ( $R^3P(OR^2)_2$ ) to give the (*E*)-isomers of the phosphonoyl alkenes **508** in 10–35% yield. The corresponding phosphinic acids **509** were prepared from **508** in good yields (over 80%) by transesterification with halogenotrimethyl silane at room temperature followed by saponification of the trimethylsilyl ester.

#### 4.21.2.6.2 *gem*-Phosphonoyl ureido alkenes

A *gem*-phosphonoyl ureido alkene was synthesized in 1984, but no further instances have been reported <1995COFGT(4)967>.

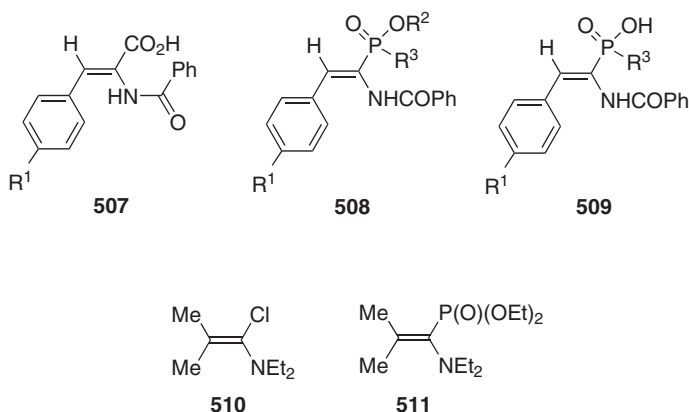
#### 4.21.2.7 Derivatives Containing a Dialkoxy Phosphoryl Group

##### 4.21.2.7.1 $\alpha$ -Phosphorylenamines, $R^3C=C(NR^1_2)PO(OR^2)_2$

$\alpha$ -Phosphorylenamines have previously been synthesized by a variety of methods <1995COFGT(4)967>.

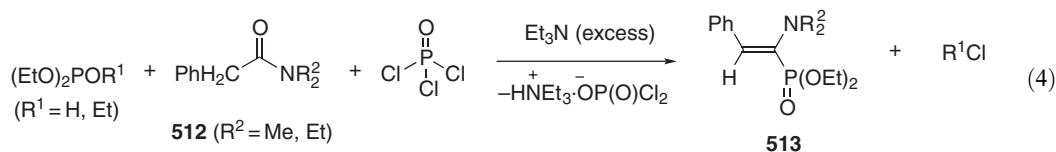
##### (i) From halo enamines

Halo enamines have been treated with triethyl phosphite by the Arbuzov reaction to give  $\alpha$ -phosphorylenamines in good yield <1995COFGT(4)967>. Further work has been reported whereby the chloroenamine **510** reacts with triethyl phosphite without a catalyst to give the product **511** in 15 min in quantitative yield <1999ZOR452, 1999TL569>. The same product was synthesized in 82% yield by a palladium-catalyzed cross-coupling of diethyl hydrogen phosphite with **510** in the presence of 2 mol.% of dichlorobis(triphenylphosphine)palladium and triethylamine.

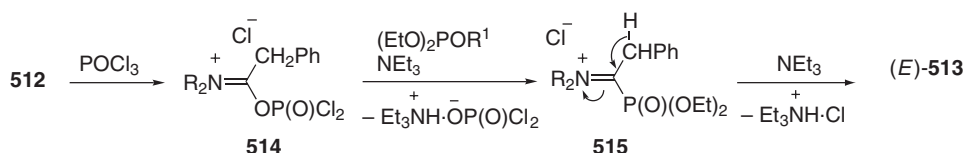


##### (ii) From tertiary amides

Tertiary amides have previously been converted to  $\alpha$ -phosphorylenamines via iminium esters or iminium chlorides <1995COFGT(4)967>. A novel route has now been described which gives a highly stereoselective synthesis of (*E*)-vinylphosphonates and has the advantage of being a short, one-pot reaction <2000HAC512>. Tertiary amides **512** are mixed with phosphorus oxychloride (POCl<sub>3</sub>) to form Vilsmeier reagents, which are reacted with an equimolar amount of the phosphite (EtO)<sub>2</sub>P(O)H to form the vinylphosphonates **513** in 35–50% yield (Equation (4)).



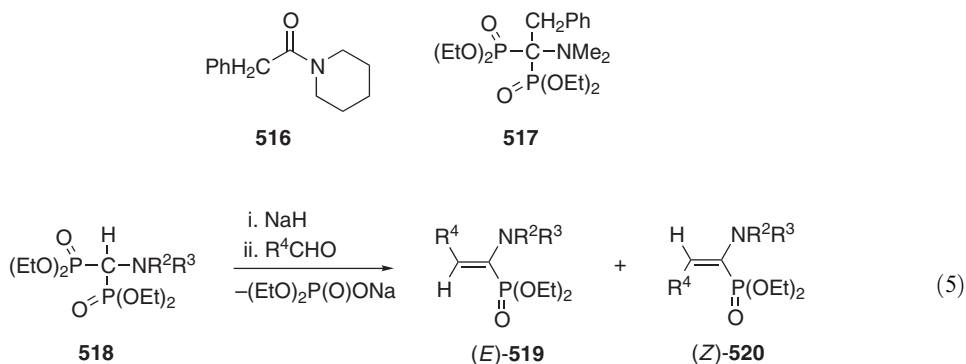
A plausible pathway for this reaction is shown in Scheme 50 where the Vilsmeier reagents act in the form of an iminium chloride **514**. The phosphorus atom of diethyl phosphite then attacks the electrophilic central carbon of **514** with elimination of HOP(O)Cl<sub>2</sub> to give intermediate **515**, which then eliminates HCl to give the product. The observed stereochemistry is thought to arise from a least-crowded, most-stable conformation of the intermediate **515**.



Scheme 50

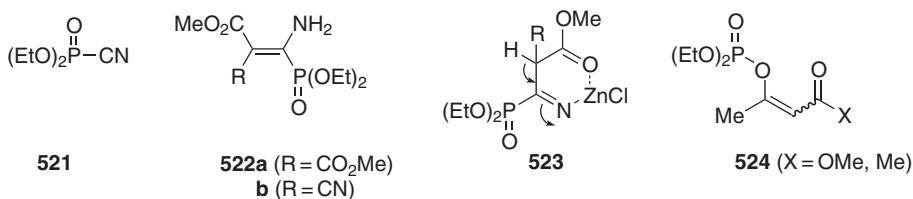
It should be noted that the reaction proceeds in low yield (2–3%) using the amide **516**. The transition state leading to **515** is sterically congested and the presence of four relatively large groups attached to the central carbon atom would make the formation of **515** difficult.

In the absence of triethylamine, the intermediate **515** reacts further with another mole of phosphite to give the corresponding biphosphonate **517**. It is possible to use various tertiary amides to give a range of biphosphonates **518**, which can then be reacted with aldehydes under the conditions of the Wittig–Horner reaction to furnish the vinylphosphonates **519** and **520** in 30–47% yield (Equation (5)) <1999HAC271>. It has also been observed that the (*Z*)-isomer **520** can be converted to the (*E*)-isomer **519** in boiling ethyl acetate.



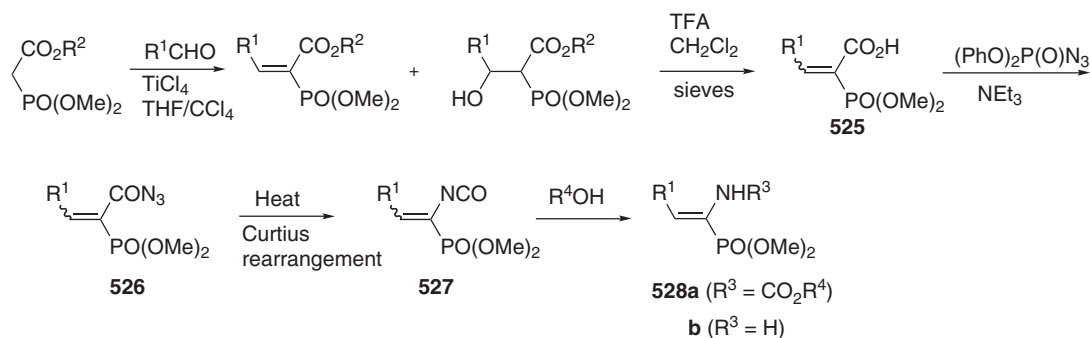
(iii) From active methylene compounds and diethyl phosphorocyanidate

Reaction of diethyl phosphorocyanidate **521** (DEPC) with diethyl malonate and ethyl cyanoacetate in the presence of zinc chloride and triethylamine resulted in selective addition of the active methylene group to the cyano group of DEPC to give the  $\alpha$ -phosphorylenamines **522** <1994CPB1919>. A variety of Lewis acids was used to increase the electrophilicity of the cyano carbon atom, with zinc chloride giving the best results. The addition of molecular sieves to the reaction with diethyl malonate to give **522a** dramatically increases the yield from 22% to 66%. With methyl cyanoacetate, the yield of **522b**—obtained as a single isomer—is lower at 43–49%, and it is believed that this may be due to the Lewis acid being coordinated with the cyano group of the cyanoacetate as well as DEPC. The stereochemistry was confirmed by  $^{13}\text{C}$  NMR with the ester group being (*E*) to the phosphoryl group. This can be rationalized by proposing a reaction intermediate **523** that is fixed by chelation of the zinc metal with the ester carbonyl oxygen atom rather than the nitrile nitrogen atom, followed by a proton shift to give the product. In contrast, treatment of enolizable methyl acetoacetate and acetylacetone with DEPC gave enol phosphates **524** as a result of nucleophilic displacement on the phosphorus atom of DEPC.

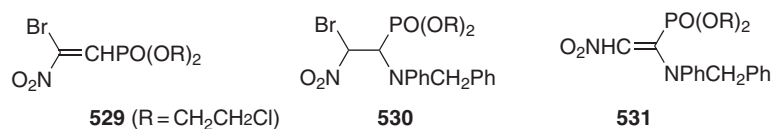


(iv) From  $\alpha$ -phosphoryl- $\alpha,\beta$ -unsaturated carboxylic acids

$\alpha$ -Phosphoryl- $\alpha,\beta$ -unsaturated carboxylic acids **525** were prepared as shown in Scheme 51 as a mixture of isomers, then the mixture was treated with diphenylphosphoryl azide at about 0 °C to give the acyl azide **526** <1994USP5321153>. The acyl azide was diluted with toluene and warmed to 90 °C to effect a Curtius rearrangement. The incipient isocyanate **527** was then trapped *in situ* with an alcohol to produce urethanes **528a**, which on deprotection give the  $\alpha$ -phosphorylenamines **528b**.

(v) From bromonitroethenylphosphonate **529**

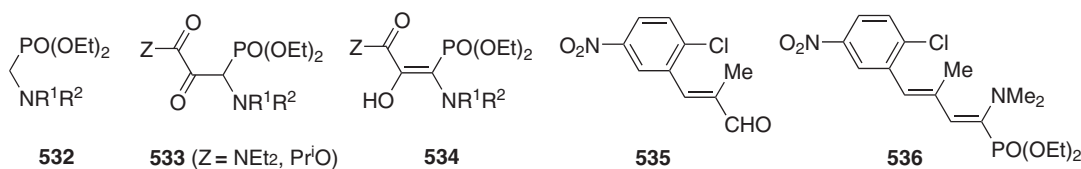
Bromonitroethenylphosphonate **529** reacts with 1 equiv. of benzyaniline to form the adduct **530** in 73% yield, which can be dehydrobrominated in the presence of pyridine to give the  $\alpha$ -phosphorylenamine **531** in 55% yield <1997ZOB160>.



## (vi) From a “head group” synthon

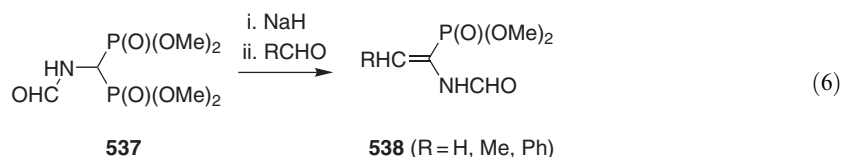
The (dialkylamino)methylphosphonate **532** can be viewed as a head group synthon for the synthesis of  $\alpha$ -phosphorylenamines. Deprotonation using butyllithium, and subsequent reaction with diisopropyl oxalate or ethyl-*N,N*-diethyloxamate resulted in the formation of the 3-(dialkylamino)-3-phosphono pyruvates and pyruvamides **533**. Depending on the nature of the amino substituent, these can primarily exist as the (*E*)-enamine tautomer **534** <1996HCA895>. Thus, when the amino substituent is diethylamino, the  $\alpha$ -phosphorylenamines are formed in 60% and 61% yield for  $Z = \text{NEt}_2$  and  $\text{Pr}^i\text{O}$ , respectively. For other amines, a mixture of the tautomers **533** and **534** are formed, the latter being present both in the (*E*) and (*Z*) configuration.

Related to this, reaction of the aldehyde **535** with **532** gave the  $\alpha$ -phosphorylenamine **536** in 84% yield <1989EUP300387>.



#### 4.21.2.7.2 *gem*-Formamido phosphoryl alkenes, $R^2C=C(NHCHO)PO(OR^1)_2$

*gem*-Formamido phosphoryl alkenes have been synthesized from the reaction of aldehydes with tetraethyl formamidomethylenediphosphonate, as well as from oxazolines <1995COFGT(4)967>. The first of these methods was used more recently to synthesize a range of *gem*-formamido phosphoryl alkenes **538** from tetramethyl formamidomethylenediphosphonate **537** in 42–85% yield (Equation (6)) <1996MI281>. The products (**538**; R = Me, Ph) were obtained as a mixture of (*E*)- and (*Z*)-isomers, which could be separated by chromatography.

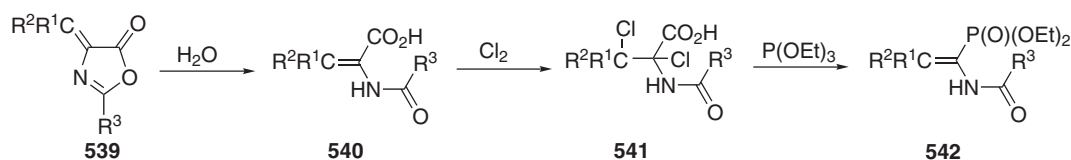


#### 4.21.2.7.3 *gem*-Amido phosphoryl alkenes, $R^2C=C(NHCOR^1)PO(OR^2)_2$

These structures have previously been synthesized from a variety of starting materials such as azlactones, amides and oxophosphonates, *N*-tetrachloroethylamides, and *N*-trichloroethylidene amides <1995COFGT(4)967>.

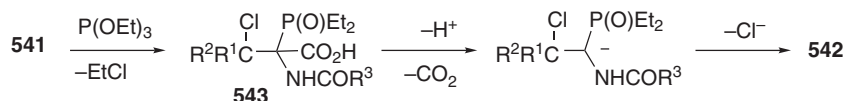
##### (i) From azlactones and cinnamic acids

The synthesis of *gem*-amido phosphoryl alkenes from azlactones has already been described <1995COFGT(4)967>. Further work has been reported on this approach <1993ZOB1259>. Thus, the azlactones **539** were ring-opened by treatment with water to give the  $\alpha,\beta$ -unsaturated carboxylic acids **540** that were then treated with chlorine to give the dichlorinated adducts **541**. Treatment of **541** with triethyl phosphite gave the amido phosphoryl alkenes **542** in 30–90% yield (Scheme 52).



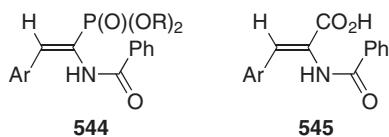
Scheme 52

The reaction with triethyl phosphite is thought to proceed as shown in Scheme 53, whereby an Arbuzov rearrangement reaction takes place to give the first intermediate **543**, which then undergoes decarboxylation and elimination of the chloride ion to give the observed product.

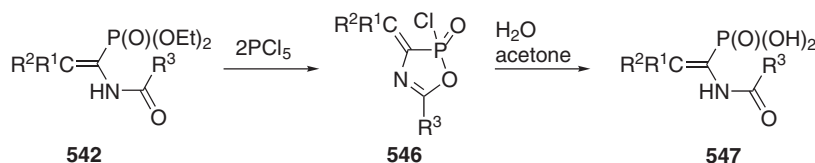


Scheme 53

In general, this route has been used for aromatic derivatives. For example, the (*E*)-phosphoryl alkenes **544** have been obtained from cinnamic acid derivatives **545** <1996GEP19519983, 1998CHIR564, 1996SC777>.



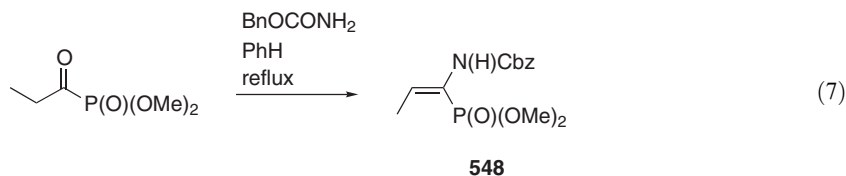
The phosphoryl alkenes **542** can be converted to the corresponding phosphonic acids **547** by treatment with 2 equiv. of phosphorus pentachloride to give the cyclized structures **546**, followed by hydrolysis with excess water in acetone to give the products **547** in 50–84% yield (Scheme 54) <1993ZOB1259>. Attempts to hydrolyze **542** directly in acid solution resulted in a mixture of compounds and proved unsatisfactory.



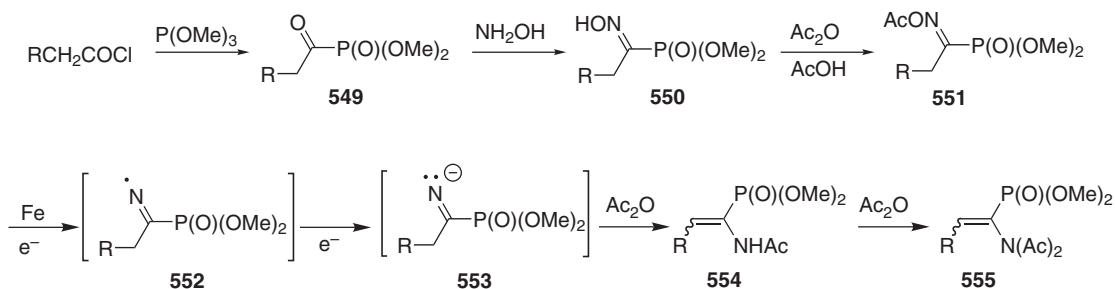
Scheme 54

(ii) From acid chlorides or  $\alpha$ -oxophosphonates

The reaction of primary amides with an  $\alpha$ -oxophosphonate to give *gem*-amido phosphoryl alkenes has already been reported <1995COFGT(4)967>. This procedure has recently been used to synthesize a variety of *gem*-amido phosphoryl alkenes including the (*Z*)-methylenamido phosphonate **548**, the latter being obtained in typically poor yield (11%) <1999OL387> (Equation (7)).



A different method of introducing an amido group has now been described which results in better yields <2002JOM404>. The necessary oxophosphonates **549** are generated from the Arbuzov reaction of acid chlorides with trimethyl phosphite (Scheme 55). These are then converted to the  $\alpha$ -oximinophosphonates **550**. The oximinophosphonates are converted to the oxime acetates **551** that are then reduced *in situ* with metallic iron to cause rupture of the weak N—O bond and formation of an iminyl radical **552**. A second electron transfer leads to the iminyl anion **553** which is captured by acetic anhydride to give the enamides **554** in 71–89% yield from the oximinophosphonate **550**. The substituent R can be alkyl or aromatic. If the reaction is carried out with heating, the imide **555** is obtained. For example the imide (**555**; R = Ph) was obtained in 54% yield in this manner. However, heating also makes side reactions more likely and when R = CH<sub>2</sub>Ph, the main product was 3-phenylpropionitrile isolated in 55% yield—arising from  $\beta$ -scission of the iminyl radical **552**. It was found that carrying out the reduction at a lower temperature of 50–60 °C minimized side reactions and maximized the yield of **554**. The products obtained were a 1:1 mixture of (*E*)- and (*Z*)-isomers, which are thought to be in equilibrium under the mildly acidic conditions used in the reaction. The method has been recommended as a practical and flexible means of accessing *gem*-amido phosphoryl alkenes using cheap and readily available starting materials and reagents, and involving no toxic or hazardous components.

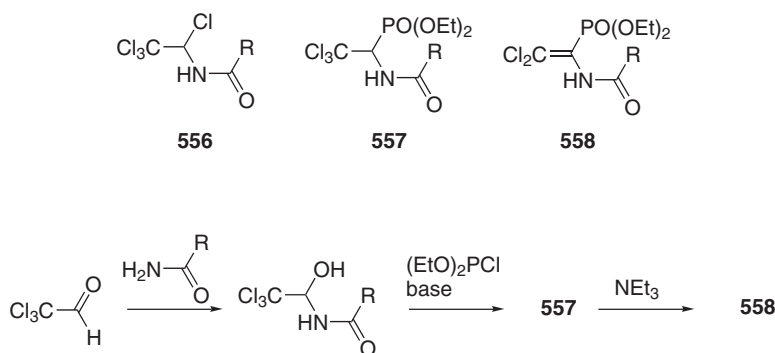


Scheme 55

## (iii) From aldehydes and amides

It has already been recorded that the Arbuzov reaction of the *N*-tetrachloroethylamides **556** with triethyl phosphite gives the phosphonates **557**, which can be dehydrochlorinated in the presence of triethylamine to give the *gem*-amido phosphorylamide **558** <1995COFGT(4)967>.

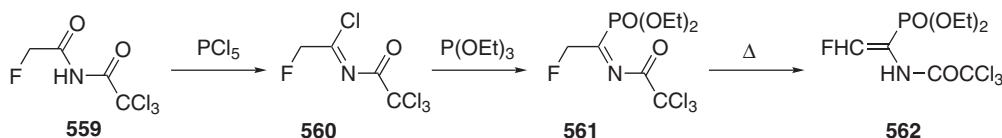
The phosphonate (**557**;  $R = Me$ ) has also been obtained by the route shown in Scheme 56 ( $R = Me$ ) and similarly converted to the *gem*-amido phosphoryl amide (**558**;  $R = Me$ ) in 60% yield in the presence of triethylamine <1998IZV1810>.



Scheme 56

(iv) From *N*-fluoroacetyltrichloroacetamide

Reaction of *N*-fluoroacetyltrichloroacetamide **559** with phosphorus pentachloride gave *N*-trichloroacetylfluoroacetimidoyl chloride **560** in 82% yield, which was then treated with an equivalent of triethyl phosphite to give an equimolar mixture of the *gem*-amido diphenylphosphinoyl alkene **562** and its isomer **561** (Scheme 57). The latter is formed by the Arbuzov reaction and is converted to **562** by an irreversible prototropic isomerization on heating. Thus, vacuum distillation of the mixture led to the complete rearrangement of **561** into **562**, which was obtained as a mixture of isomers (*E*)/(*Z*) 5:1 in 64% yield. The pure (*E*)-isomer of **562** was isolated by fractional crystallization of the isomer mixture <2002JFC107>.

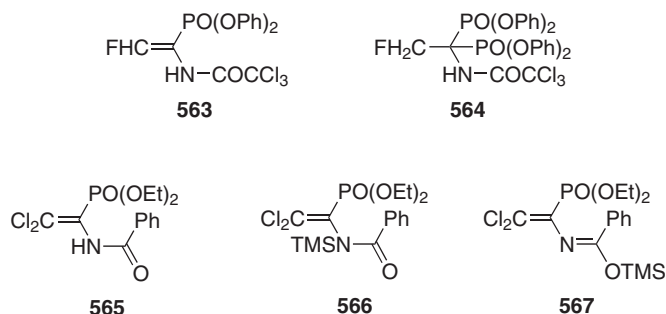


Scheme 57

Reaction of the imidoyl chloride **560** with the hydrophosphoryl compound  $[(\text{EtO})_2\text{P}(\text{O})\text{H}]$  in the presence of triethylamine also resulted in the formation of **562**, which was identified by NMR of the reaction mixture. A similar reaction with diphenyl phosphite resulted in the formation of **563** and the bisphosphonate **564**. The former was identified by NMR of the reaction mixture, while the latter crystallized from the mixture in 35% yield <2002JFC107>.

(v) *Modifications of gem-amido phosphoryl alkenes*

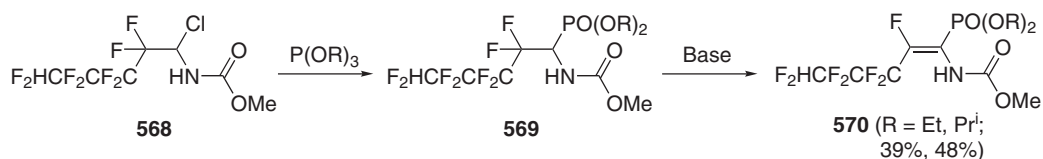
Treatment of the *gem*-amido phosphoryl alkene **565** with chlorotrimethylsilane has been reported to generate the *N*-silylated product **566** in equilibrium with the isomer **567**. Neither of these structures was isolated since they are thermally unstable and distillation results in loss of the TMS group and cyclization to a heterocycle <1998IZV2101>.



4.21.2.7.4 *gem*-Alkoxy carbonylamino phosphoryl alkenes,  $\text{R}_2^3\text{C}=\text{C}(\text{NHCO}_2\text{R}^1)\text{PO}(\text{OR}^2)_2$

*gem*-Alkoxy carbonylamino phosphoryl alkenes were synthesized in the 1980s by the alcoholic hydrolysis of isocyanato or chlorophosphoryl groups <1995COFGT(4)967>. A further synthesis has been reported following the route shown in Scheme 56 ( $\text{R} = \text{OEt}$ ) to give the *gem*-alkoxy carbonylamino phosphoryl alkene (**558**;  $\text{R} = \text{OEt}$ ) <1998IZV1810>.

The fluorinated *gem*-alkoxy carbonylamino phosphoryl alkenes **570** were synthesized by treating the  $\alpha$ -chloro urethane **568** with trialkyl phosphites in an Arbuzov reaction to give the phosphorylated urethanes **569**. Treatment of **569** with base (triethylamine, diazabicyclooctane or 1 N NaOH) resulted in dehydrofluorination to give the *gem*-alkoxy carbonylamino phosphoryl alkenes **570** (Scheme 58) <1999ZOB1299>. The use of diazabicyclooctane as base gave better results than triethylamine.



Scheme 58

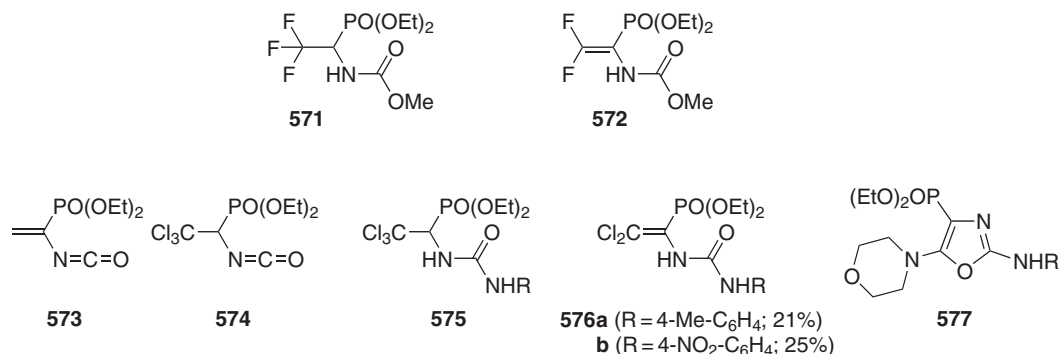
An attempt to dehydrofluorinate the trifluoromethyl analog **571** to give **572** under similar reaction conditions was unsuccessful. Prolonged heating is reported to be successful but no experimental details were given <1999ZOB1299>.

A procedure for synthesizing *gem*-alkoxy carbonylamino phosphoryl alkenes **528a** by means of a Curtius rearrangement has already been described above (Scheme 51) <1994USP5321153>.



#### 4.21.2.7.5 *gem*-Phosphoryl ureido alkenes, $R_2^3C=C(NHCONR^1)PO(OR^2)_2$

Two methods of synthesizing *gem*-phosphoryl ureido alkenes were reported in the 1970s and 1980s <1995COFGT(4)967>. One of these methods involved the reaction of the vinyl isocyanate **573** with aniline. A related method has been reported, whereby the saturated isocyanate **574** is treated with a variety of aliphatic and aromatic amines to give the ureas **575**. Treatment of **575** with morpholine results in dehydrochlorination and the generation of *gem*-phosphoryl ureido alkenes **576**, two of which were isolated and characterized. With longer reaction times, a cyclization reaction takes place to give the heterocyclic structures **577** <1993PS125>.

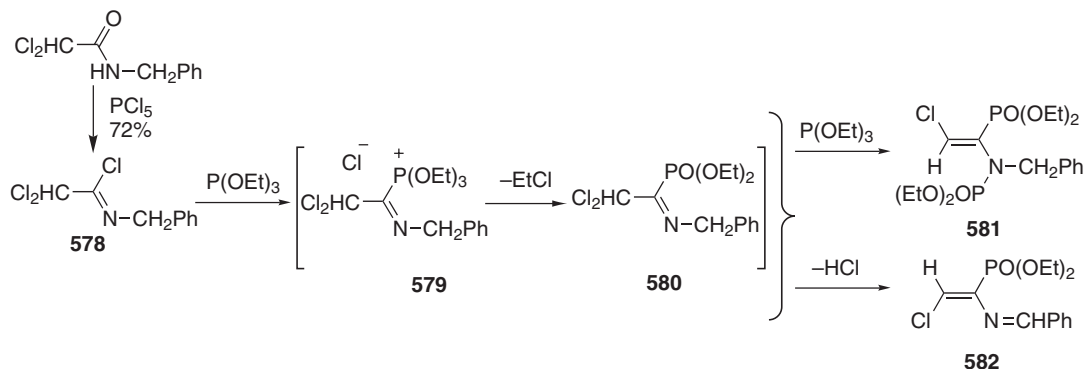


#### 4.21.2.7.6 *gem*-Diphenylphosphinoylamino phosphoryl alkenes, $R_2^3C=C(NHPOPh_2)PO(OR^1)_2$

The only reported synthesis of a *gem*-diphenylphosphinoylamino phosphoryl alkene was in 1988 <1995COFGT(4)967>.

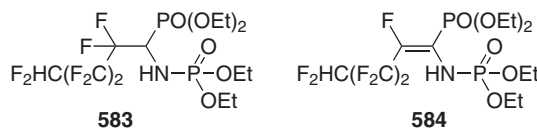
#### 4.21.2.7.7 *gem*-Phosphorylamino phosphoryl alkenes, $R_2^4C=C[NR^2PO(OR^3)_2][PO(OR^1)_2]$

*gem*-Phosphorylamino phosphoryl alkenes have been synthesized from benzoylhydrazones and halotricyanomethanes <1995COFGT(4)967>. Treatment of 2,2,2-trihaloacetimidoyl chlorides with trialkyl phosphites also gave *gem*-phosphorylamino phosphoryl alkenes <1995COFGT(4)967>. In a similar fashion, 2,2-dihaloacetimidoyl chlorides have now been converted to the title compounds. Thus, the imidoyl chloride **578** reacts with 2 equiv. of triethyl phosphite to give the (*Z*)-isomer of the *gem*-phosphorylamino phosphoryl alkene **581** in 35% yield (Scheme 59). The reaction involves an aza-Perkow type mechanism via the reactive intermediates **579** and **580**, and is highly stereoselective. When the reaction is carried out with an equivalent of triethyl phosphite, NMR studies show that the product **581** is still formed along with formation of the phosphorylated azabutadiene **582**, the latter resulting from the dehydrochlorination of intermediates **579** and **580** <2001ZOB157>.



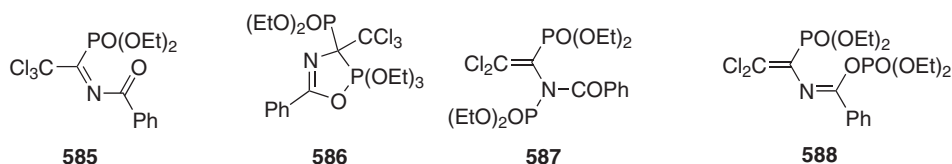
Scheme 59

An attempt to dehydrofluorinate the trifluoromethyl analog **583** to give **584** in the presence of a basic catalyst proved unsuccessful <1999ZOB1299>.

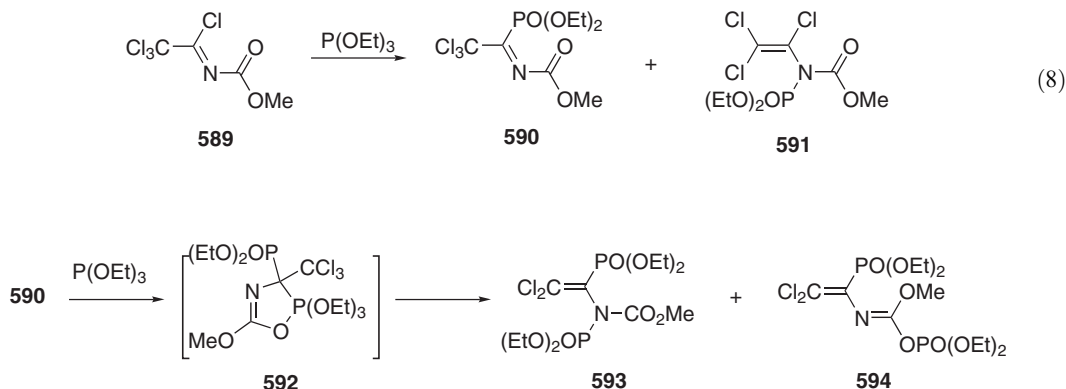


#### 4.21.2.7.8 *gem-N-Phosphorylamido phosphoryl alkenes*, $\text{R}_2^1\text{C}=\text{C}[\text{N}(\text{COR}^1)\text{PO}(\text{OR}^2)_2][\text{PO}(\text{OR}^3)_2]$

The imidoylphosphonate **585** was treated with triethyl phosphite in an Arbuzov reaction to give the heterocyclic compound **586**, which was detected by NMR. This structure is unstable and ring-opens to form the bisphosphorylated enamine **587** and the azadiene **588**, which were also detected by NMR but not isolated. When structure **585** is treated with triethylphosphine or triphenyl phosphite, a different reaction course took place since dealkylation is not possible (see Section 4.21.2.7.10) <1991PS95>.



In a similar fashion, the trichloroacetimidoyl chloride **589** was treated with triethyl phosphite to give the imidoylphosphonate **590** and the trichlorovinylphosphoroamidate **591** in approximately equal amounts (Equation (8)). Reaction of the mixture with a second mole of triethyl phosphite resulted in further reaction of **590** through the unstable phosphorane **592** to give the diphosphorylated isomers **593** and **594** (Scheme 60) <1999ZOB1966>. Fractional distillation resulted in the isolation of **593** in 14% yield. A better method of obtaining **593** was to react the imidoyl chloride **589** with diethyl hydrogen phosphite to isolate structure **590** in 41% yield, then react **590** with triethyl phosphite to give structure **593** in 50% yield <1999ZOB1966>.



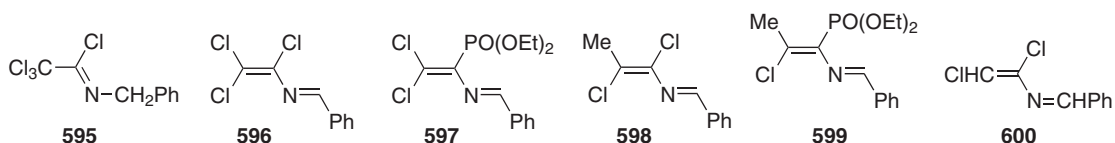
Scheme 60

#### 4.21.2.7.9 *gem-Alkylideneamino phosphoryl alkenes*, $\text{R}_2^1\text{C}=\text{C}(\text{N}=\text{CR}^1)\text{PO}(\text{OR}^2)_2$

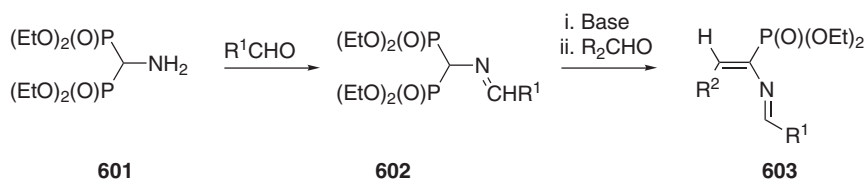
A limited number of *gem*-alkylideneamino phosphoryl alkenes have been synthesized from imidoyl chlorides and from *N*-acylamides. Thus, dehydrochlorination of the 2,2,2-trichloroacetimidoyl chloride **595** with base gave the azadiene **596**, which reacted with triethyl phosphite to give the product **597** in 34% yield <1995COFGT(4)967>. When the azadiene analog **598** is treated

with triethyl phosphite, the reaction is less selective since the electron-donating influence of the methyl group is capable of directing the attack of triethyl phosphite to other electrophilic centers, resulting in a mixture of products. However, analysis of the mixture by NMR indicated the presence of the *gem*-alkylideneamino phosphoryl alkene **599** <2001ZOB159>.

The formation of a *gem*-alkylideneamino phosphoryl alkene **582** was also observed by NMR as one of the products formed when the imidoyl chloride **578** was treated with 1 equiv. of triethyl phosphite (Scheme 59). The same product was synthesized independently by treating the imidoyl chloride **578** with triethylamine to give the dichloroazadiene **600** in 88% yield, then reacting **600** with 2 equiv. of triethyl phosphite. However, the final product could not be obtained in an analytically pure form and contained about 25 mol.% of other unidentified products <2001ZOB157>.



A new synthetic method involves the use of iminebiphosphonates **602** obtained in 40–92% yield from the condensation reaction of aminomethyldiphosphonate **601** with a range of aromatic, heteroaromatic, and  $\alpha,\beta$ -unsaturated aldehydes (Scheme 61) <2000T6319>. The iminebiphosphonates **602** were olefinated by the Wadsworth–Emmons reaction using a range of aliphatic, aromatic, and heteroaromatic aldehydes to give the alkylideneamino phosphoryl alkenes **603** in 30–80% yields.



Scheme 61

A variety of bases can be used in the reaction. However, it was found that the mild base caesium carbonate in THF/ $\text{Pr}^i\text{OH}$  provided good yields when aliphatic, aromatic, or heteroaromatic aldehydes were used. Further advantages included shorter reaction times, the ability to carry out the reaction at room temperature, and an easy work-up procedure. NMR studies demonstrated that the (*E*)-isomers were formed. The conjugated products **604** and **605** were also obtained in good yield using the relevant aldehydes.

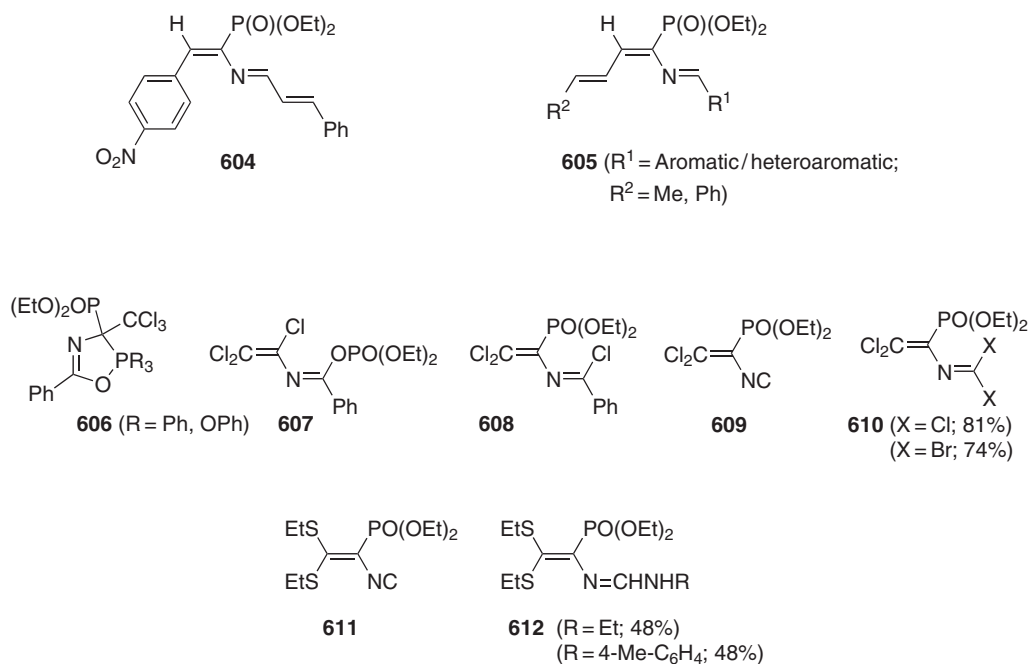
#### 4.21.2.7.10 *gem*-Alkylideneamino phosphoryl alkenes bearing a heteroatom *X* at the vinyl position, $\text{R}_2^3\text{C}=\text{C}(\text{N}=\text{CXR}^1)\text{PO}(\text{OR}^2)_2$ , $\text{R}_2^3\text{C}=\text{C}(\text{N}=\text{CX}_2)\text{PO}(\text{OR}^1)_2$

As mentioned in Section 4.21.2.7.8, the reaction of **585** with triethyl phosphite gives the *gem*-alkylideneamino phosphoryl alkene **588** as one of the products <1998IZV2101>. Treatment of the imidoylphosphonate **585** with triethylphosphine or triphenyl phosphite results in a different reaction course from the one involving triethyl phosphite. An unstable heterocycle **606** is formed as before, but ring opening is accompanied by the loss of  $\text{R}_3\text{PO}$  to form the azadienes **607** and **608**. These were detected by NMR spectroscopy of the reaction solution but were not isolated.

In a similar fashion, reaction of the trichloroacetimidoyl chloride **589** with excess triethyl phosphite resulted in a mixture of compounds that included the diphosphorylated isomer **594**, which was identified by NMR but not isolated (Scheme 60) <1999ZOB1966>.

Treatment of the *gem*-isocyano phosphorylalkene **609** with halogens results in the formation of the dihalogenated products **610** <1994JPR29>.

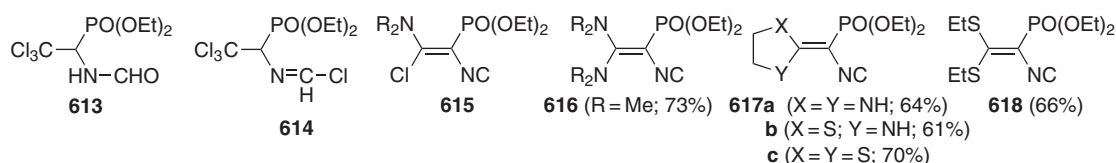
The *gem*-isocyano phosphoryl alkene **611** reacts with primary amines to give the adduct **612** <1994JPR29>.



#### 4.21.2.7.11 *gem*-Isocyano phosphoryl alkenes, $\text{R}_2\text{C}=\text{C}(\text{NC})\text{PO}(\text{OR}^1)_2$

The *gem*-isocyano phosphoryl alkene **609** has been synthesized by the rearrangement of 1-formylimino-2,2,2-trichloroethanephosphonate via a formimide chloride intermediate <1991PS95>. A more convenient method of obtaining this structure is to treat the phosphono trichloroethaneformamide **613** with phosphorus pentachloride to form **614**, which is dehydrohalogenated by the subsequent addition of base. The desired product **609** is obtained in 83% yield <1994JPR29>.

The vinylic chlorides in **609** can be substituted with a variety of nucleophiles. Thus, reaction with secondary amines gives the ketene aminals **616**. It is also possible to isolate the intermediate monoamino derivatives **615** as crude products in high yield. Reaction of **609** with primary amines results in cyclizations and the formation of heterocyclic products. Treatment of **609** with nucleophiles such as ethylenediamine, cysteamine, ethanedithiol, and ethanethiol resulted in the corresponding *gem*-isocyano phosphoryl alkenes (**617a–617c**, **618**). Alternatively, reaction of **609** with propylenediamine led to a cyclic heterocyclic structure <1994JPR29>.



#### 4.21.2.7.12 *gem*-Isocyanato phosphoryl alkenes, $\text{R}_2\text{C}=\text{C}(\text{N}=\text{C}=\text{O})\text{PO}(\text{OR}^1)_2$

A limited number of *gem*-isocyanato phosphoryl alkenes were synthesized in the 1970s and 1980s from various isocyanates <1995COFGT(4)967>. However, no other syntheses have been reported.

#### 4.21.2.8 Derivatives Bearing a PS(OR)<sub>2</sub>, PO(OR<sup>1</sup>)(NR<sub>2</sub><sup>2</sup>), POX<sub>2</sub>, or PO(OR<sup>1</sup>)(SR<sup>2</sup>) Group

##### 4.21.2.8.1 $\alpha$ -Thiophosphorylenamines

An  $\alpha$ -thiophosphorylenamine was synthesized in 1971 from a dialkylthiophosphonate and an ynamine, but no other synthesis has been reported since <1995COFGT(4)967>.

##### 4.21.2.8.2 *gem*-Amido phosphoramidoyl alkenes, $\text{Cl}_2\text{C}=\text{C}(\text{NHCOPh})\text{PO}(\text{OMe})(\text{NR}_2)$

A synthesis of *gem*-amido phosphoramidoyl alkenes from azlactones was reported in 1982, but no further syntheses have been published <1995COFGT(4)967>.

##### 4.21.2.8.3 *gem*-Phosphoramidoyl ureido alkenes, $\text{R}_2^4\text{C}=\text{C}(\text{NHCONR}^1\text{R}^2)\text{PO}(\text{OR}^3)\text{NR}^1\text{R}^2$

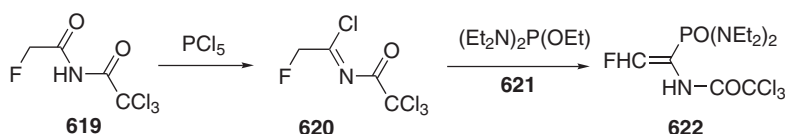
A few *gem*-phosphoramidoyl ureido alkenes were synthesized from isocyanates in the 1980s, but no further syntheses have been reported <1995COFGT(4)967>.

##### 4.21.2.8.4 $\alpha$ -Phosphorodiamidoylenamines, $\text{R}_2^3\text{C}=\text{C}(\text{NR}_2^1)\text{PO}(\text{NR}_2^2)_2$

A synthesis of  $\alpha$ -phosphorodiamidoylenamines from imino chlorides and an alkoxy phosphorus diamine was reported in 1985, but no further reports have appeared in the literature concerning the syntheses of these compounds <1995COFGT(4)967>.

##### 4.21.2.8.5 *gem*-Amido phosphorodiamidoylalkenes, $\text{R}_2^3\text{C}=\text{C}(\text{NRCOR}^1)\text{PO}(\text{NR}_2^2)_2$

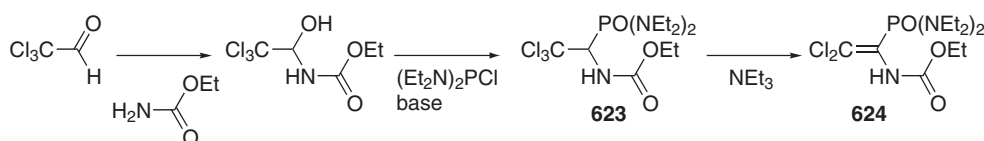
The first example of structures of this type has recently been reported. Reaction of *N*-fluoroacetyltrichloroacetamide **619** with phosphorus pentachloride gave *N*-trichloroacetylfluoroacetimidoyl chloride **620** in 82% yield, which reacted with an equivalent of the diamidophosphite **621** to give the *gem*-amido phosphorodiamidoyl alkene **622** as a mixture of isomers ((*E*)/(*Z*) 3:1) (Scheme 62). Crystallization gave the pure (*E*) isomer in 48% yield <2002JFC107>.



Scheme 62

##### 4.21.2.8.6 *gem*-Alkoxy carbonylamino phosphorodiamidoyl alkenes, $\text{R}_2^4\text{C}=\text{C}(\text{NR}^1\text{CO}_2\text{R}^2)\text{PO}(\text{NR}^3)_2$

The first example **624** of this type of structure was synthesized in 78% yield by the base-catalyzed dehydrochlorination of the trichloromethyl compound **623**. The latter was synthesized from an aldehyde and urethane as shown in Scheme 63 <1998IZV1810>.



Scheme 63

**4.21.2.8.7 *gem*-Phosphorodiamidoyl ureido alkenes,  $R_2C=C(NHCONHAr)PO(NHAr)_2$** 

*gem*-Phosphorodiamidoyl ureido alkenes were synthesized in the 1980s from isocyanato dichlorophosphoryl reagents <1995COFGT(4)967>. No further reports have appeared on their synthesis.

**4.21.2.8.8 *gem*-Aminobenzylideneamino phosphorodiamidoyl alkenes,  $R_2^1C=C(N=C(NR_2^1)Ph)PO(NR_2^1)_2$** 

The synthesis of *gem*-aminobenzylideneamino phosphorodiamidoyl alkenes from dichlorophosphoryl reagents was described in 1982 <1995COFGT(4)967>. No further syntheses have been reported.

**4.21.2.8.9 *gem*-Difluorophosphoryl ureido alkenes**

A *gem*-difluorophosphoryl ureido alkene was synthesized in 1989 from the reaction of a *gem*-difluorophosphoryl isocyanato reagent with aniline <1995COFGT(4)967>. No further examples have been published.

**4.21.2.8.10 *gem*-Arylchloromethyleneamino dichlorophosphoryl alkenes,  $R_2C=C(N=C(Cl)Ar)POCl_2$** 

*gem*-Arylchloromethyleneamino dichlorophosphoryl alkenes were synthesized in 1982 from *gem*-amido phosphoryl alkenes <1995COFGT(4)967>. No further examples have been reported.

**4.21.2.8.11 *gem*-Dihalophosphoryl isocyanato alkenes,  $R_2C=C(NCO)POX^1X^2$** 

A few examples of *gem*-dihalophosphoryl isocyanato alkenes being synthesized from isocyanates were reported in the 1980s <1995COFGT(4)967>. However, no further examples have appeared in the literature.

**4.21.3 FUNCTIONS CONTAINING ONE NITROGEN AND ONE METALLOID,  $R_2^3C=CNR_2^1SiR_3^2$ , etc.****4.21.3.1 Nitrogen and Silicon Derivatives,  $R_2^3C=CNR_2^1SiR_3^2$** **4.21.3.1.1  $\alpha$ -Silylenamines**

A variety of synthetic methods for generating  $\alpha$ -silylenamines have been reported previously <1995COFGT(4)967>, with the most promising approach being the use of cyanohydrins. Further examples have appeared since the 1990s.

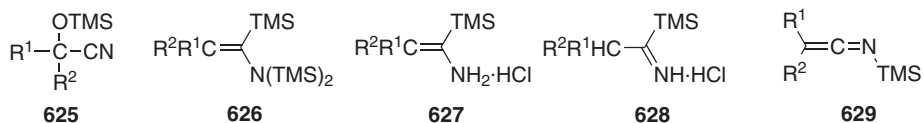
*(i) From cyanohydrins and nitriles*

*N,N*-Bis-silylated  $\alpha$ -silylenamines **626** have been synthesized in 68–82% yield by the reductive silylation of silylated cyanohydrins **625** with lithium and chlorotrimethylsilane at 0 °C, using hexamethylphosphoramide as solvent <1995COFGT(4)967>. The use of HMPA as cosolvent is important to the success of the reaction. Further work has shown that it is possible to carry out this reaction by electroreduction, thus removing the need for lithium and lowering the quantity of HMPA required <1996OM1604>. The reaction can be carried out at room temperature with trimethylsilyl chloride in THF in the presence of 1 equiv. of HMPA (instead of 4 in the chemical process) in an undivided cell equipped with an aluminum-made sacrificial anode. After 4.4 faraday

are passed through the reaction mixture, the enamines **626** are obtained in comparable yields to the chemical route. The products are obtained as mixtures of the (*E*)- and (*Z*)-isomers with the former predominating.

Removal of the *N*-silyl groups can be achieved in quantitative yield by treatment with dry hydrogen chloride in ether, or with chlorotrimethylsilane in methanol to give structure **627**. The enamine obtained slowly isomerizes to the iminium salt **628**.

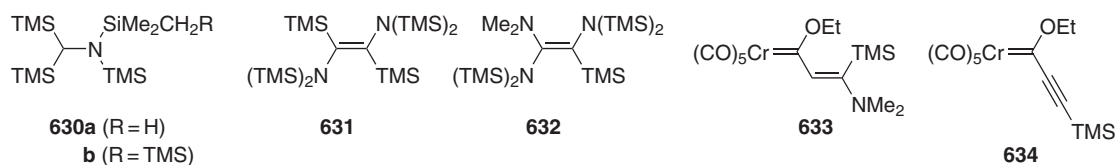
Studies into the electrochemical reductive silylation of nitriles have been carried out <1997MI503>. In the case of nitriles bearing at least one  $\alpha$ -hydrogen ( $RR^1CHCN$ ), a mixture of products is obtained which includes the enamines **626**, presumably formed from an intermediate *N*-silylketenimine **629**. In contrast to the reaction on *O*-silylated cyanohydrins, the major isomer is (*Z*) rather than (*E*).



The reductive silylation of cyanotrimethylsilane in THF with lithium, chlorotrimethylsilane, and HMPA gave principally the saturated products **630a,b** along with trace amounts (5% yield) of the unsaturated product **631** <1993O1378>. The same products were obtained from the electrochemical reductive silylation of cyanotrimethylsilane, with the  $\alpha$ -silylenamine obtained in 8% yield <1994OM3711>. Electrochemical reductive silylation of dimethylcyanamide gave the  $\alpha$ -silylenamine **632** as a by-product in 5% yield.

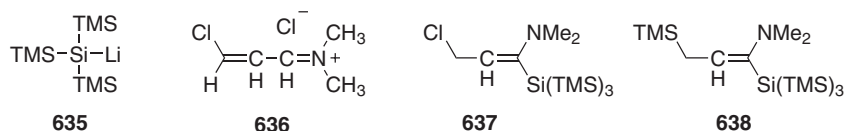
#### (ii) From silylated alkynes

The  $\alpha$ -silylenamine **633** was reported as a minor product (26% yield) in the reaction between the silylated alkyne **634** and dimethylamine <1992CB2051>.



#### (iii) From the iminium salt **636**

Reaction of tris(trimethylsilyl)silyllithium **635** with the iminium salt **636** led to a mixture of the silylenamines **637** and **638** in 50% and 13% yields, respectively <1999EJ121>.

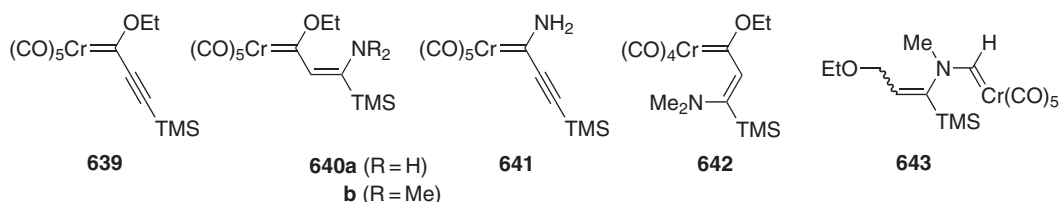


#### (iv) Miscellaneous syntheses

Addition of ammonia to the silylated alkynyl chromium complex **639** in THF generated a mixture of chromium complexes **640a** and **641** with the latter predominating (5% versus 78%) <1993CB2535>. With diethyl ether as solvent, no enamine is formed at all. Reaction of **639** with dimethylamine in diethyl ether gave the enamine **640b** in 27% yield <1993OM2556>. Modification of the reaction conditions allows this compound to be prepared in 52% yield when the reaction is carried out as a one-pot process in pentane <1999AG(E)1285>.



The enamine **640b** was heated in THF at 50–55 °C and converted to a mixture of the chelated tetracarbonylchromium complex **642** and the aminomethylene complex **643** in poor yield (17 and 20% yield, respectively) <1993TL5875>.



#### 4.21.3.1.2 *gem*-Isocyanosilyl alkenes

Only three examples of *gem*-isocyanosilylalkenes have been reported in the literature. All three were synthesized from a vinylidene isocyanide <1995COFGT(4)967>.

#### 4.21.3.1.3 *gem*-Isothiocyanato silyl alkene

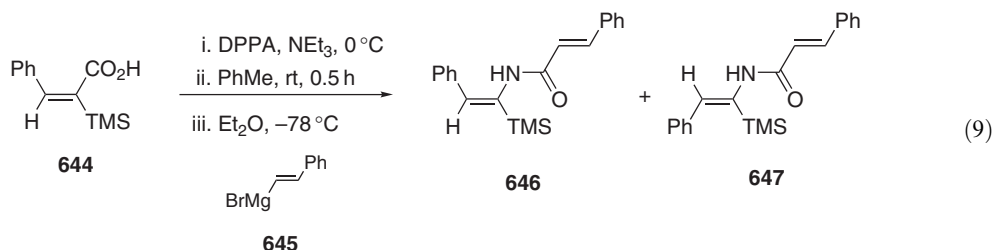
One example of a *gem*-isothiocyanato silyl alkene was synthesized from an isocyanide in 1982 <1995COFGT(4)967>. No further examples have been reported.

#### 4.21.3.1.4 *gem*-Aminoborylamino silyl alkenes, $PrCH=C(TMS)N(R)B(X)NMe_2$

Three examples of *gem*-aminoborylamino silyl alkenes were synthesized in 1982 <1995COFGT(4)967>. No further examples have appeared in the literature.

#### 4.21.3.1.5 *gem*-Amidosilylalkenes, $PhCH=C(TMS)NHCOR$

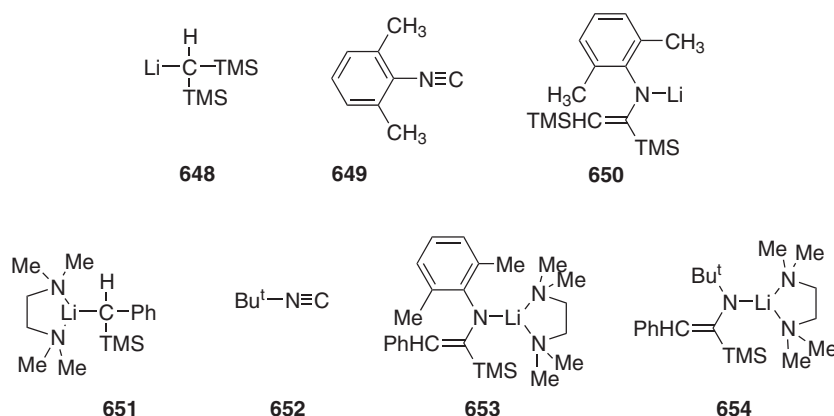
The silyl acid **644** was treated with diphenylphosphoryl azide (DPPA) at 0 °C to give an acyl azide that was converted to a vinyl isocyanate at room temperature. The styryl Grignard reagent **645** was added to give a 1:1 mixture of the vinyl silane **646** and its isomer **647** that could be separated by chromatography (Equation (9)) <2000TL3735>. The yield of each isomer was only 9%.



#### 4.21.3.1.6 *gem*-Lithioamino silyl alkenes, $RCH=C(TMS)NLiAr$

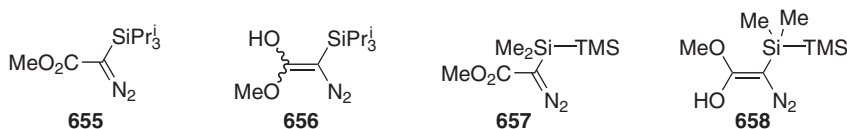
The reaction of the lithium trimethylsilylmethyl compound **648** with the isocyanide **649** resulted in the insertion of the isocyanide into the Li–C bond of **648** to give the lithium 1-azallyls **650** <2001JCS(D)2409, 2000ZAAC1081, 1998CCCC201> in 62% yield. In a similar fashion, the lithio structure **651** was treated with the isocyanides **649** and **652** to give the lithium 1-azallyls **653**, **654**, respectively, in 82% and 70% yields.





#### 4.21.3.1.7 *gem*-Diazonium silyl alkenes, $R_2^2C=C(SiR_3^1)N_2^+$

*gem*-Diazonium silyl alkenes have not been isolated. However, they have been formed in solution and identified by NMR. Thus, protonation of the acetate **655** with superacid  $FSO_3H \cdot SbF_5(1:1)/SO_2$  at less than  $-75^\circ C$  resulted in the formation of five major ions, which included the (*Z*)- and (*E*)-isomers of the *gem*-diazonium silyl alkene **656** <1993JCS(P2)1387>. These ions were also formed when the acetate **655** was treated with the less acidic superacid  $FSO_3H/SO_2$ . The (*Z*) isomer of the diazonium ion **658** was identified by NMR following protonation of the acetate **657** with superacid  $FSO_3H \cdot SbF_5(1:1)/SO_2$  <1993JCS(P2)1387>.



#### 4.21.3.2 Nitrogen and Boron Derivatives, $R_2^3C=CNR_2^1BR_2^2$

Only one synthesis of these structures has been reported involving the addition of trialkylboranes to ynamines <1995COFGT(4)967>.

#### 4.21.4 FUNCTIONS CONTAINING ONE NITROGEN AND ONE METAL, $R_2^2C=CNR_2^1M$ , etc.

##### 4.21.4.1 Group 1 and 2 Metals, $R_2^2C=CNR_2^1Li$ , etc.

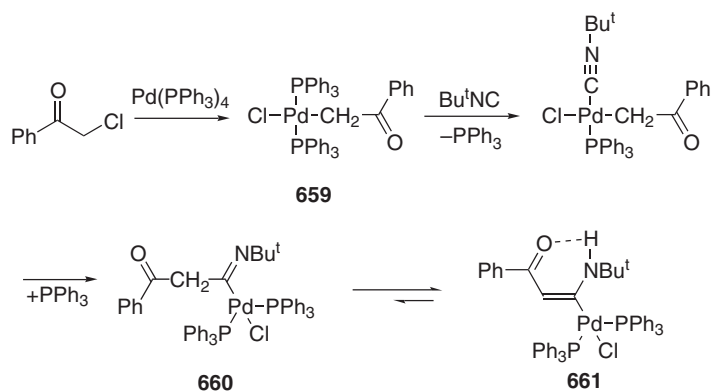
Functions containing one nitrogen along with lithium, sodium, or magnesium were reported previously <1995COFGT(4)967>. However, no further work has been reported.

##### 4.21.4.2 Transition Metals, $R_2^2C=C(NR_2^1)PdX$ , etc.

###### 4.21.4.2.1 Palladium and platinum

Palladio enamines have been synthesized previously from isocyanides <1995COFGT(4)967>. Further work has now appeared on this approach. Thus, the palladium complex **659** synthesized as shown in Scheme 64 was treated with 1 equiv. of *t*-butyl isocyanide, resulting in an insertion–migration reaction of the isonitrile into the  $Pd-C$  bond of **659** to give the palladio imine **660**, which tautomerizes to the palladio enamine—a process driven by the formation of an intramolecular hydrogen bond <1993OM4899>. Structure **659** fails to react with carbon monoxide or ethylene and

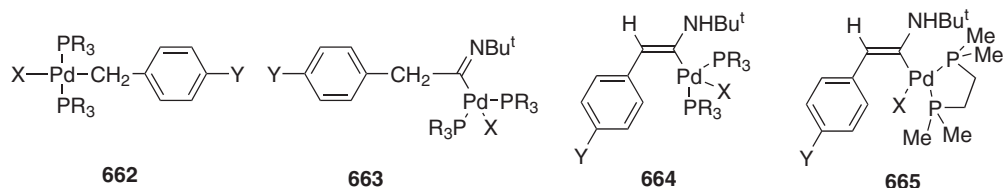
the success of the reaction with the isonitriles is possibly due to the ability of the isocyanide to displace  $\text{PPh}_3$  in the preliminary stage of the insertion in a position *cis* to the  $\text{Pd}-\text{C}$  bond. The yield of **661** is variable (from 30–80%) depending on the solvent used and the concentration of the reagents.



Scheme 64

More recently, it has been reported that the reaction of benzylpalladium complexes **662** with *t*-butyl isocyanide yields imido complexes that exist in solution as equilibrium mixtures of the corresponding imine **663** and enamine **664** tautomers <1999OM5225, 1995OM2151>. The equilibrium constant is markedly affected by the electronic effect exerted by the substituents (Y) on the phenyl ring, but the effect of the metal fragment is less pronounced and is dominated by steric factors. Both tautomeric forms can also be found in the solid state.

Reaction of **664** (X = Cl, Y =  $\text{CF}_3$ , R = Me) with the chelating phosphine 1,2-bis-(dimethylphosphino)ethane afforded the cationic complex **665**, which was found to exist only in the enamine form both in solution and the solid state.



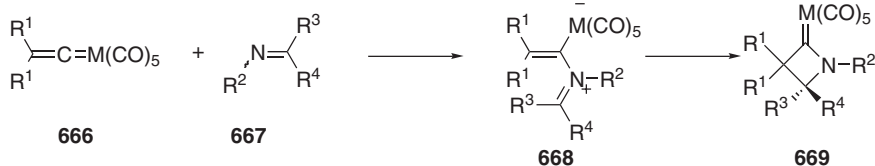
#### 4.21.4.2.2 Copper

A copper-substituted enamine was reported in 1992 <1995COFGT(4)967> but no further reports have been published.

#### 4.21.4.2.3 Chromium, molybdenum, and tungsten

Molybdenum- and tungsten-substituted enamines have been proposed as reaction intermediates while a tungsten-substituted enamine has been isolated from the reaction of a tungsten complex with an ynamine <1995COFGT(4)967>.

The reaction of chromium and tungsten vinylidene complexes **666** with imines **667** has recently been studied (Scheme 65) <2001JOM165>. Analogous studies using iron vinylidene complexes were reported previously <1995COFGT(4)967> and have been used as the first stage of a method to produce  $\beta$ -lactams. It is believed that the imine uses the lone electron pair on nitrogen to form a bond to the  $\alpha$ -carbon of the vinylidene ligand to form the zwitterion **668**. Ring closure may or may not take place resulting in the 2-azetidin-1-ylidene metal complex **669**.



Scheme 65

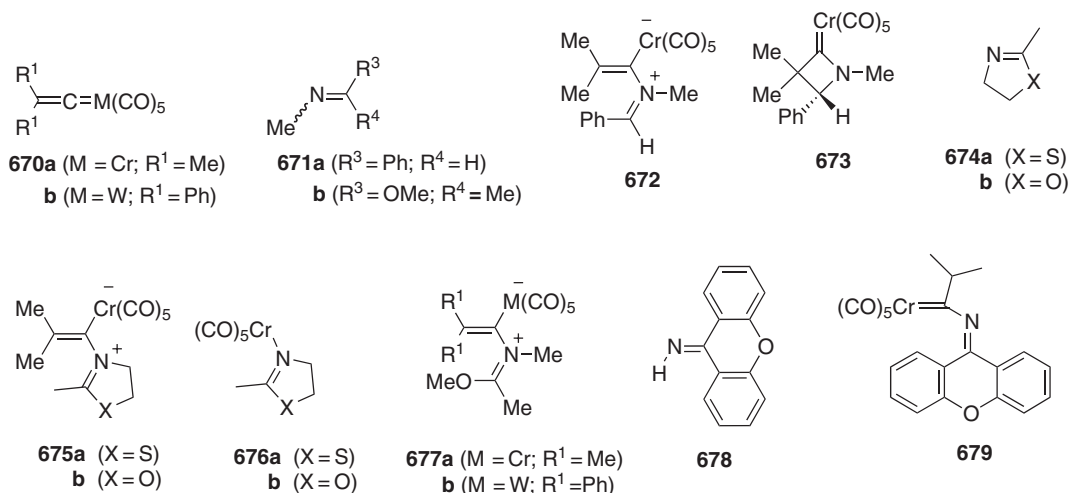
The vinylidene chromium complex **670a** was treated with the imine **671a** to give the zwitterionic chromium complex **672** in 23% yield relative to  $\text{Cr}(\text{CO})_6$ . The complex could be crystallized and was stable in the solid state at room temperature. When dissolved in a nonpolar solvent, the zwitterion cyclized slowly over the period of a week to the 2-azetidin-1-ylidene chromium complex **673**. Cyclization was faster in polar solvents or with heating.

Reaction of the vinylidene chromium complex **670a** with the imines **674** gave the analogous zwitterions **675** in 11% and 21% yields relative to  $\text{Cr}(\text{CO})_6$ , but substitution products **676** were also obtained to a lesser extent (7.5 and 3.4%). These latter compounds were also formed if the zwitterions **675** were heated in solution, rather than the 2-azetidin-1-ylidene chromium complexes.

Reaction of the imine **671b** with the vinylidene chromium complex **670a** or the vinylidene tungsten complex **670b** gave the adducts **677a** and **677b** in 14% (relative to  $\text{Cr}(\text{CO})_6$ ) and 61% yields, respectively, neither of which underwent cyclization.

The mechanism is thought to involve a rapid but reversible addition of the imine to the vinylidene metal complex. Whether the adduct obtained cyclizes to a 2-azetidin-1-ylidene metal complex or not depends on the relative rates of cyclization versus dissociation back to starting materials. Strongly electrophilic vinylidene complexes and strongly nucleophilic imines give rise to adducts such as **672**, which are stable with respect to dissociation and which can undergo cyclization. In contrast, the adducts **675** and **677** dissociate back to starting materials on heating. Decomposition of the vinylidene metal complex takes place with loss of the vinylidene ligand, allowing addition of the imine to form pentacarbonyl(imine)metal complexes such as **676**.

The above reaction was not observed if the imine contained an NH group. For example, the reaction of **670a** with the imine **678** gave mainly the metal complex **679** with no sign of the zwitterion adduct. The reaction of *N*-unsubstituted imines with vinylidene metal complexes is thought to involve the same initial addition reaction as with *N*-substituted imines, but the adduct formed rapidly rearranges by deprotonation/reprotonation.



#### 4.21.4.2.4 Manganese

A manganese-substituted enamine was reported in 1979 <1995COFGT(4)967> but no further reports have been published.

## 4.21.4.2.5 Iron

A few reports of relevant iron complexes were published in the 1970s and 1980s <1995COFGT(4)967> but there have been no subsequent publications.

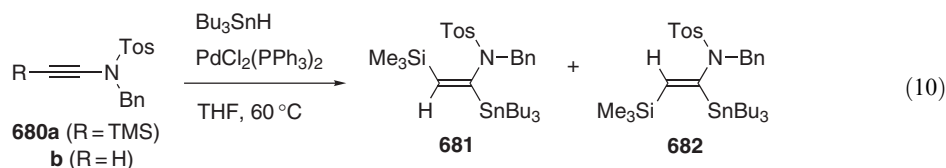
## 4.21.4.2.6 Rhenium

A rhenium-substituted enamine was reported in 1975 <1995COFGT(4)967> but no further reports have been published.

## 4.21.4.3 Other Metals

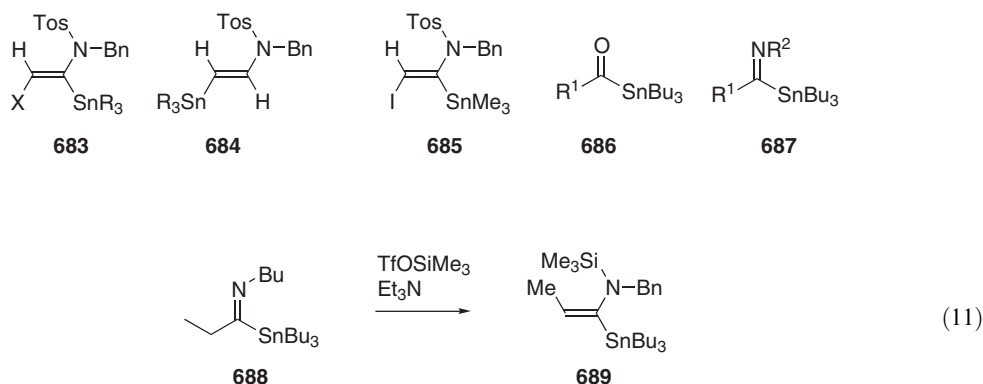
## 4.21.4.3.1 Tin

The synthesis of a stannyleneamine from a diamine has been reported previously <1995COFGT(4)967>. Acyclic stannyleneamines have been reported to be extremely unstable as far as the enamine moiety is concerned. However, a new and efficient synthesis has been reported <2001S705>, which involves the hydrostannation of ynamines. Thus, the ynamine **680a** was reacted with  $\text{Bu}_3\text{SnH}$  in the presence of  $\text{PdCl}_2(\text{PPh}_3)_2$  to give a 71% yield of a mixture of the (*E*)- and (*Z*)-enamines **681** and **682** in an (*E*)/(*Z*) ratio of 3:2 (Equation (10)).



The unprotected ynamine **680b** was also reacted with  $\text{Bu}_3\text{SnSiMe}_3$  in the presence of  $\text{Pd}(\text{PPh}_3)_4$  to give the stannyleneamine **682** as the pure (*Z*)-isomer in 91% yield, making this route complementary to the hydrostannation of the silylated enamine. The ynamine **680b** was treated with a variety of other stannous reagents ( $\text{R}_3\text{SnX}$ ;  $\text{X} = \text{H}, \text{Bu}_3\text{Sn}, \text{Me}_3\text{Sn}$ ) by this method to give other enamines **683** in good yields (65–92%) with exclusively *cis* addition of the stannyl reagents. In the case of the reagent ( $\text{R}_3\text{SnH}$ ), a significant amount of side product **684** was also formed but could be removed by chromatography. Structure **683** ( $\text{X} = \text{Me}_3\text{Sn}, \text{R} = \text{Me}$ ) was iodinated to give the  $\beta$ -iodo enamine **685** in 64% yield.

It has also been reported that the condensation of primary aliphatic and aromatic amines with acylstannanes **686** is a versatile and easy method of synthesizing imidoystannanes **687** <1993S981>. One of these structures **688** was converted to the stannous enamine **689** in 78% yield as shown in Equation (11).



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**Biographical sketch**

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## 4.22

# Functions Containing at Least One Phosphorus, Arsenic, Antimony or Bismuth, and No Halogen, Chalcogen or Nitrogen

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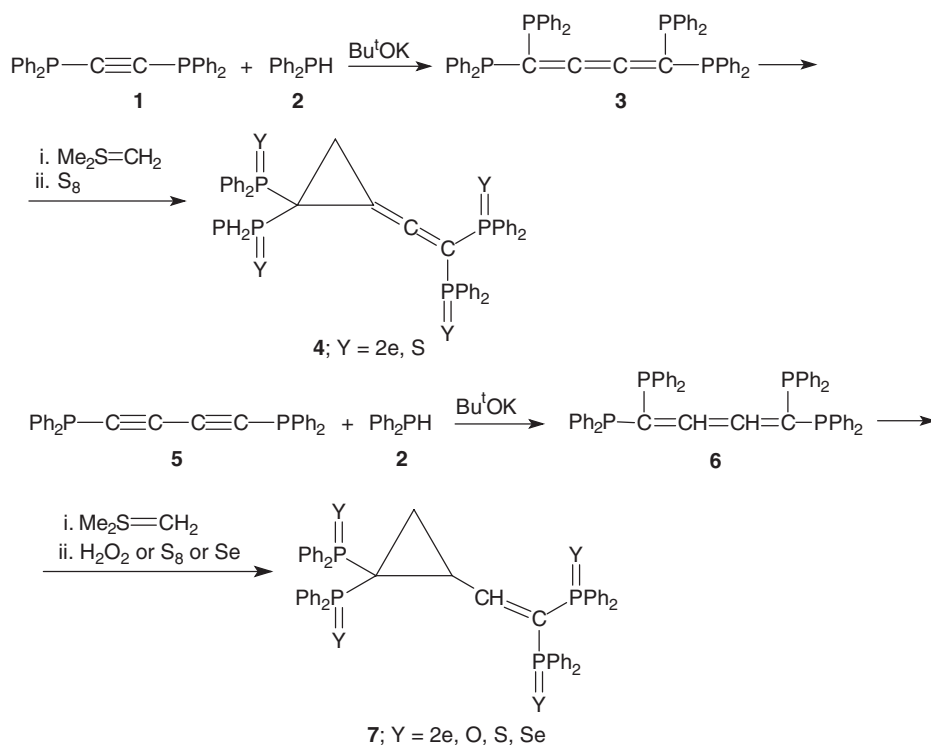
#### 4.22.1 DIPHOSPHORUS FUNCTIONS— $R_3^1C=C(PR_2^2)_2$ , etc.

This class of compounds is subdivided into: (i) acyclic bisphosphino alkenes in which neither phosphorus is included in a ring, (ii) mixed acyclic, cyclic bisphosphino alkenes in which one phosphorus is a part of a ring and the second one is “acyclic,” and (iii) cyclic bisphosphino alkenes in which both phosphorus are included in a ring.

Transition metal complexes of bisphosphino alkenes are metalloorganic compounds with at least one phosphorus atom bound to a metal.

##### 4.22.1.1 Acyclic Bisphosphino Alkenes

Hydrophosphinylation of alkynes and ketenes with diaryl or dialkylphosphines was previously reviewed as one of the general methods for the synthesis of the title compounds via C—P bond formation <1995COFGT(4)1021>. It has been further extended by Schmidbauer and co-workers on alkadiynes and allenes <1995CB365>. Thus, hydrophosphinylation of 1,2-bis(diphenylphosphino)-ethyne **1** and 1,4-bis(diphenylphosphino)butadiyne **5** with diphenylphosphine **2** led to the formation of 1,1,4,4-tetrakis(diphenylphosphino)butatriene **3** in 33% yield and 1,1,4,4-tetrakis(diphenylphosphino)-1,3-butadiene **6** each as the exclusive reaction product, respectively (Scheme 1).

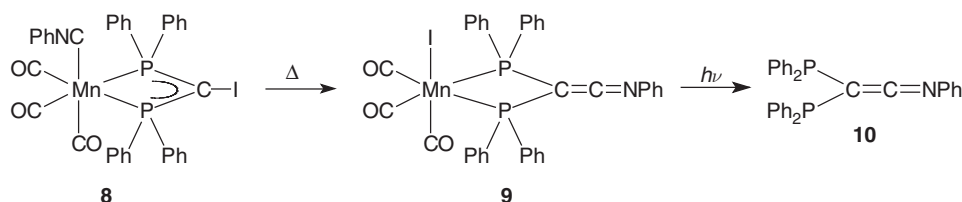


Scheme 1

Both products **3** and **6** were modified on treatment with dimethylsulfonium methylide to give new cyclopropyl derivatives (**4**: Y = 2e) and (**7**: Y = 2e). Further reaction of (**4**: Y = 2e) with elemental sulfur gave the corresponding tetrasulfide (**4**: Y = S) and the reaction of (**7**: Y = 2e) with H<sub>2</sub>O<sub>2</sub>, elemental sulfur and selenium afforded the corresponding tetrachalcogenides **7** [Y = O, S, Se].

In contrast to the potassio derivatives of diphenylphosphines, lithium phosphides were also employed in the reactions with 1,1,2-trichloroethene and perchloroethene to give tris- and tetrakis(diphenylphosphino)ethenes as ligands for platinum group metals <2002MI137>.

The first synthesis of diphosphinoketenimine **10** was formally carried out by the coupling reaction of the transient diphenylphosphino carbene [(Ph<sub>2</sub>P)<sub>2</sub>C:] with phenyl isocyanide to give the manganese (I) complex **8** followed by UV/Vis irradiation to liberate **10** from the metallic fragment **9** <1998OM3835> (Scheme 2).



Scheme 2

The unsymmetrical dimer **11** obtained from the ketenimine **10** as a result of a unique, reversible dimerization involving a new type of [2+3]-cycloaddition reaction <2000AG1891, 2000AG(E)1821> was further selectively oxidized with 1–3 equiv. of H<sub>2</sub>O<sub>2</sub> to give mono- **12**, di- **13** or tri- **14**-oxidized forms <2002CEJ3872> (Scheme 3).

Heating the compounds **12** and **13** in toluene afforded monomeric keteneimines **10** and/or **16** while the fully *P*-oxidized compound **14** decomposed instantaneously to the keteneimine **15** before its isolation. The new keteneimines **10** and **16** behaved as 1,3-dipoles toward a variety of dipolarophiles (alkynes, RNCO, RNCS), allowing the synthesis of five- and six-membered phosphaheterocycles.

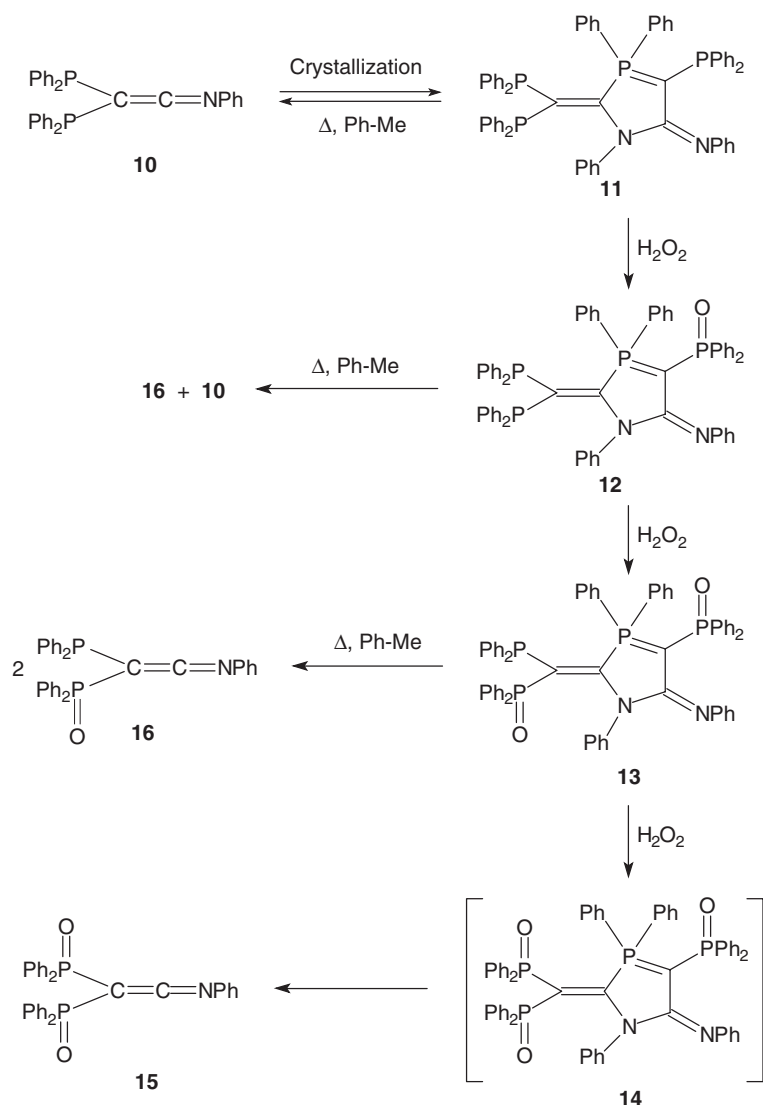
Another class of bisphosphinoalkenes are bis(dichlorophosphino)alkenes represented by **19**. This heterocyclic compound was synthesized by the condensation reaction of the benzene solution of PCl<sub>3</sub> with *N*-(dichlorophosphinomethylene)pyridinium ylide **18** obtained from the pyridinium halide **17** <1996PSS(112)121> (Scheme 4).

Ethylidenebisphosphonates are extremely useful compounds in organic synthesis. Tetraethyl ethylidenebisphosphonate **20** (R = Et) (Scheme 5), synthesized by the method of Degenhardt <1986JOC3488>, was utilized in hydroxylation and epoxidation reactions <1995JOC7080> in Michael addition reactions <2001T1837, 1995PSS(103)125>, as well as in transesterification reactions to tetramethyl ester **20** (R = Me) using trimethoxymethane <1995PSS(103)125> and to tetrakis(trimethylsilyl) ester **20** (R = TMS) using bromotrimethylsilane <1995JOC7080>. A slightly modified version of Degenhardt's protocol was also utilized for the synthesis of **20** R = Et <2002MI1991>. Bromotrimethylsilane itself or with collidine and *p*-toluenesulfonic acid were also used to convert the tetraethyl ester **20** (R = Et) to the corresponding phosphonic tetraacid **20** (R = H) <1995PSS(103)125, 2001T1837, 1995JOC7080, 1998MI687> (Scheme 5). This acid was also obtained by the dehydration reaction under basic conditions (NaOH) of the corresponding 1-hydroxy-1-methylbisphosphonic tetraacid <1998IZV1784>. Tetrabenzyl ethylidenebisphosphonate **20** (R = C<sub>6</sub>H<sub>5</sub>CH<sub>2</sub>) was also synthesized <2002SC211>.

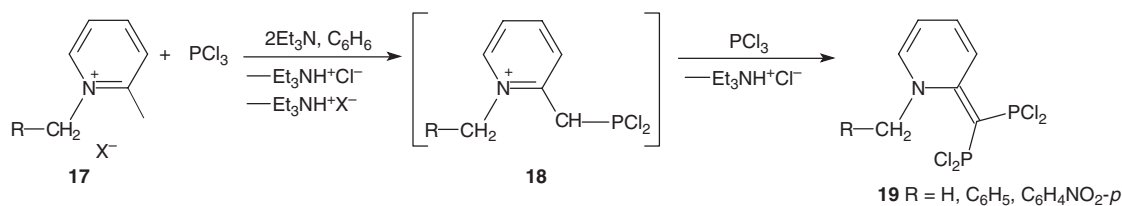
A new methylenebisphosphonic cyclic ester **21** was prepared by condensation of the corresponding unsubstituted cyclic bisphosphonate with formaldehyde in the presence of diethylamine followed by dehydration with Amberlite IR 120 (H<sup>+</sup>) <1998MI1093>.

2-Substituted methylenebisphosphonates and their analogs were also synthesized. For instance, tetraethyl allenebisphosphonate **24** was prepared from diethyl 3-hydroxy-methylbut-1-yne-phosphonate **23** and diethyl chlorophosphite in 77% yield <1996MI171>. Ebetino and co-workers synthesized the bisphosphinic triacid **22** (R = H) from the corresponding triethyl ester **22** (R = Et) upon treatment with bromotrimethylsilane and water (99% yield). The 2-substituted triethyl ester **22** (R = Et) was obtained upon treatment of the corresponding unsubstituted

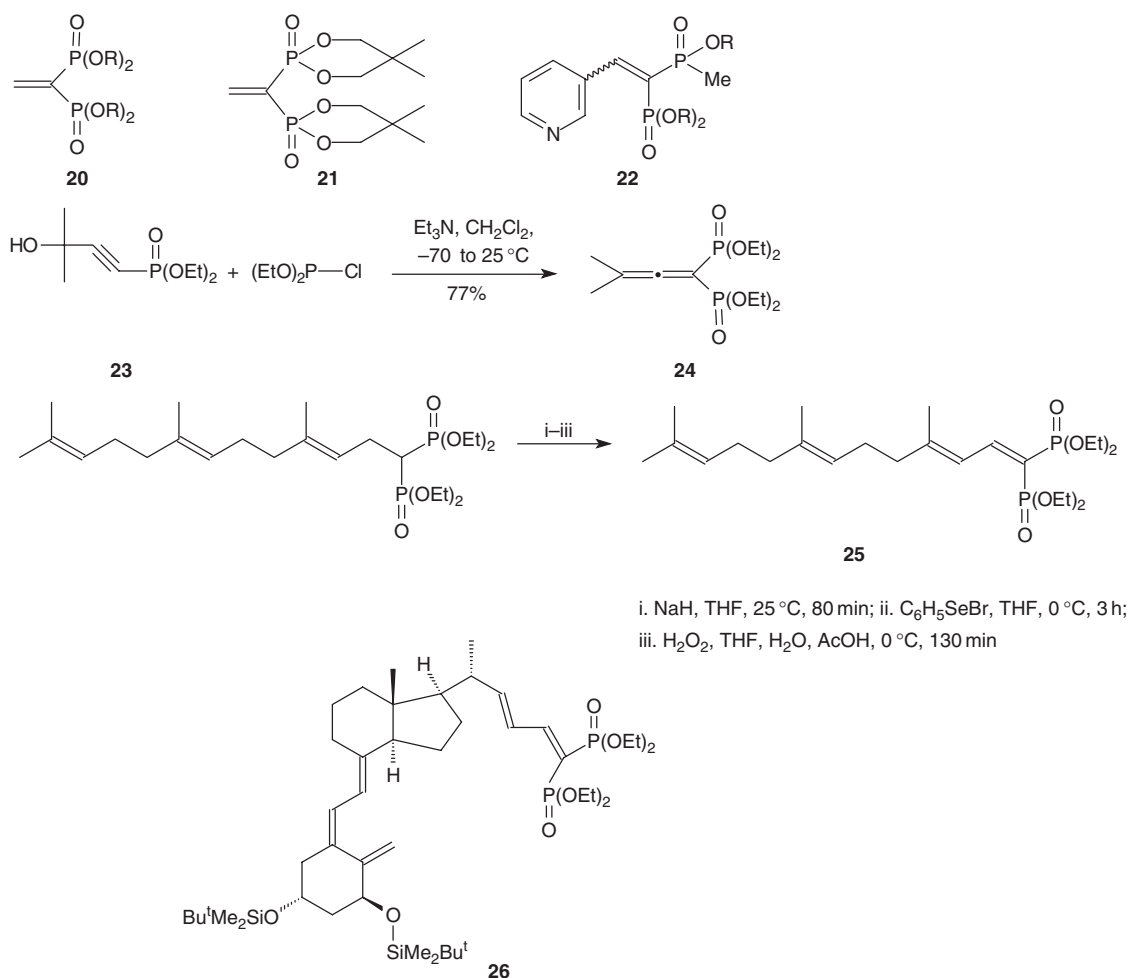
triethyl ester with dimorpholinomethyl-3-pyridine in 41% yield <1996PSS(109)217>. Wiemer and co-workers synthesized the bisphosphonate **25** possessing three isoprenoid units in the phosphonate chain using a classical method involving the selenylation/oxidation elimination sequence for the introduction of the double bond  $\alpha$  to P <1998MI687>. Another 2-substituted bisphosphonate **26** was synthesized in 55.5% yield in the Knoevenagel reaction of the corresponding  $\alpha,\beta$ -unsaturated aldehyde and tetraethyl methylenebisphosphonate in the presence of titanium tetrachloride and *N*-methylmorpholine <2001MI257>.



Scheme 3



Scheme 4

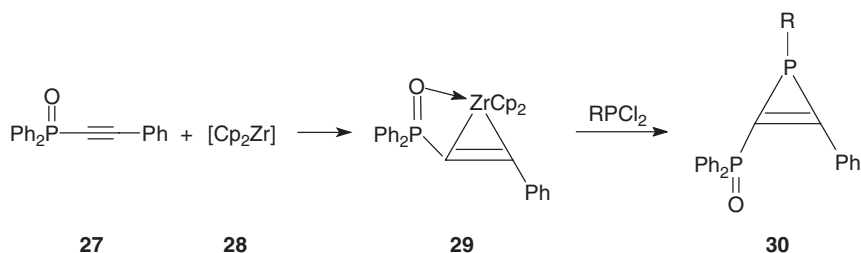


Scheme 5

#### 4.22.1.2 Mixed Acyclic Cyclic (3–6-Membered) Bisphosphino Alkenes

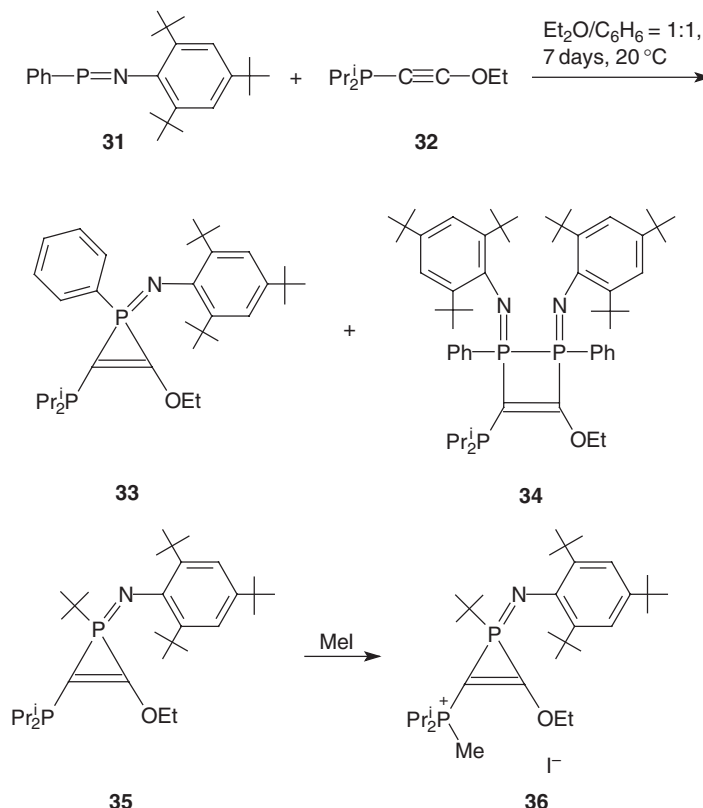
##### 4.22.1.2.1 Three-membered rings

Majoral and co-workers synthesized new three-membered phosphirene systems **30** using zirconium chemistry [<1998CCC1171>](#) (Scheme 6). Thus, treatment of the acetylenic phosphine oxide **27** with the zirconocene [Cp<sub>2</sub>Zr]-**28** followed by reaction with alkyl (R = Me) or aryl (R = Ph) dichlorophosphines gave **30**. It should be emphasized that the phosphoryl group played a key role in stabilization of the intermediate zirconacyclopropene **29** which was fully characterized.



Scheme 6

A mixture of the phosphirene **33** and the 1,2-diphosphete **34** was obtained by treatment of *P*-phenyl-*N*-(2,4,6-tri-*t*-butylphenyl)phosphinimine **31** with 1-ethoxy-2-diisopropylphosphinoethyne **32** in 20% and 28% yields, respectively <1996ZOR443> (Scheme 7).



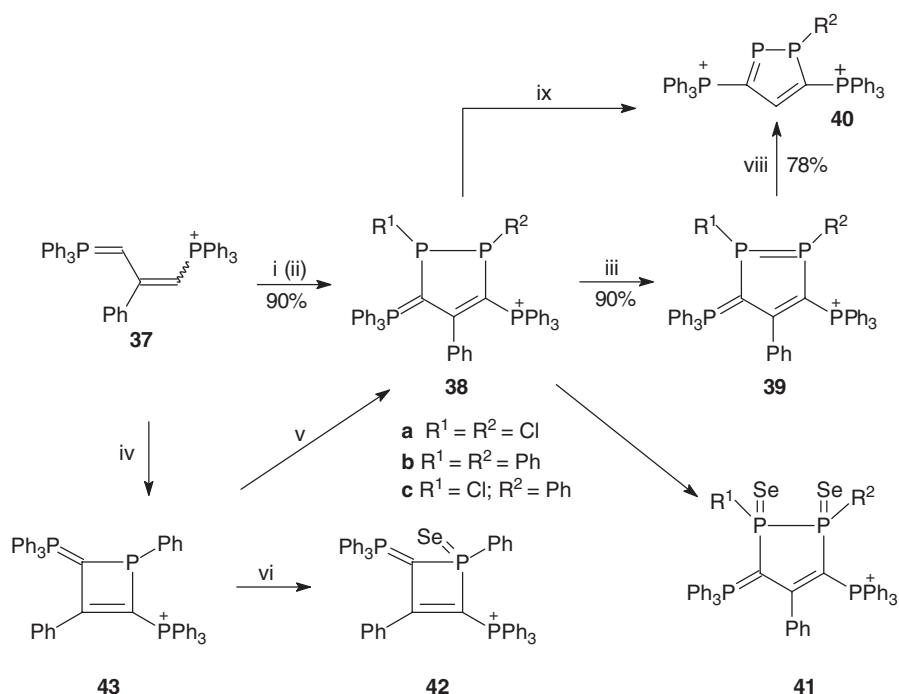
Scheme 7

*P*-*t*-butyl protected phosphirene **35** underwent methylation at the trivalent phosphorus to give the corresponding phosphonium iodide **36** <1995ZOR400>.

#### 4.22.1.2.2 Four-membered rings

Starting from the phosphonium bromide **37**, two basic four- and five-membered frameworks (**38a–38c**) and **43** were synthesized <1996CEJ221> (Scheme 8). Thus, the reaction of **37** with phosphorus trichloride gave the di-*P*-chloro derivative **38a** ( $\text{R}^1 = \text{R}^2 = \text{Cl}$ ), while the reaction of **37** with dichlorophenylphosphine afforded the di-*P*-phenyl derivative **38b** ( $\text{R}^1 = \text{R}^2 = \text{Ph}$ ). Didechlorination of **38a** ( $\text{R}^1 = \text{R}^2 = \text{Cl}$ ) with tri-*n*-butylphosphine afforded the new five-membered system **39**. Replacement of phosphorus trichloride by dichlorophenylphosphine in the reaction of **37** afforded the 4-membered structure **43**, which was converted with the triphenylphosphine/phosphorus trichloride system to the five-membered mono-*P*-chloro derivative **38c**. Addition of elemental selenium to **38b** and **43** gave the corresponding selenides **41** and **42**, respectively. The bis(triflate) and bis(tetrachloroaluminate) of **40** were also synthesized in the methylation reaction of **39** with methyl triflate (pathway viii) and in the reaction of **38c** with aluminum trichloride (pathway ix), respectively <1996CB1083>.





- i.  $\text{PCl}_3$ ,  $\text{PPh}_3$ ,  $\text{Et}_3\text{N}$ ,  $\text{CH}_2\text{Cl}_2$ , 3 days ( $R^1 = R^2 = \text{Cl}$ ); ii.  $\text{PhPCl}_2$ ,  $\text{Ph}_3\text{P}$ ,  $\text{Et}_3\text{N}$ ,  $\text{CH}_2\text{Cl}_2$ , 3 d ( $R^1 = R^2 = \text{Ph}$ );  
 iii.  $\text{Bu}_3\text{P}^+\text{Et}_3\text{N}^-\text{Cl}^-$ , 3 h; iv.  $\text{PhPCl}_2$ ,  $\text{Et}_3\text{N}$ ,  $\text{CH}_2\text{Cl}_2$ , 15 h; v.  $\text{PCl}_3$ ,  $\text{PPh}_3$ ,  $\text{Et}_3\text{N}^+\text{X}^-$ ,  $\text{CH}_2\text{Cl}_2$ , 5 h  
 ( $R^1 = \text{Ph}$ ,  $R^2 = \text{Cl}$ ); vi.  $\text{Se}$ ,  $\text{CH}_2\text{Cl}_2$ , 5 d; vii.  $\text{Se}$ ,  $\text{CH}_2\text{Cl}_2$ , 3 d ( $R^1 = R^2 = \text{Ph}$ ); viii.  $\text{CF}_3\text{SO}_3\text{Me}$  (2 equiv.),  
 $\text{CH}_2\text{Cl}_2$ , 30 min ( $R^2 = \text{Me}$ ); ix.  $\text{AlCl}_3$ ,  $\text{CH}_2\text{Cl}_2$ ,  $-78^\circ\text{C}$ , 10 min ( $R^1 = \text{Cl}$ ,  $R^2 = \text{Ph}$ )

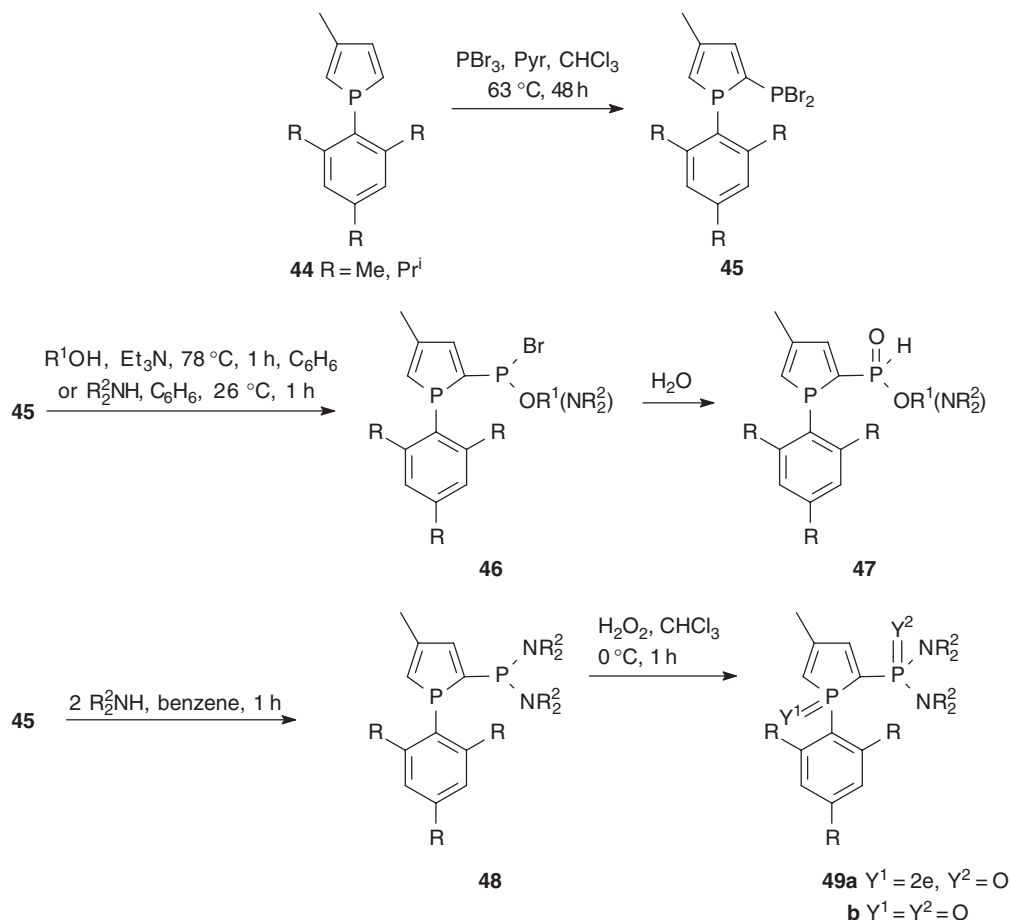
Scheme 8

#### 4.22.1.2.3 Five-membered rings

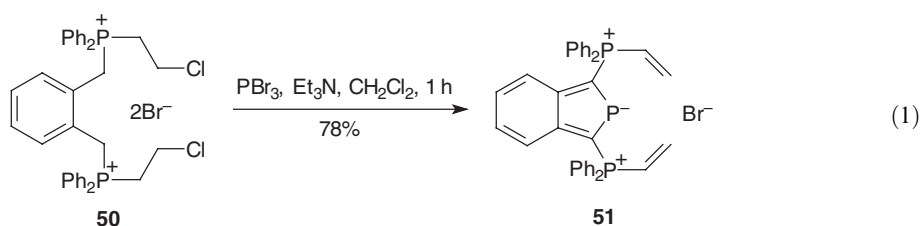
In this section acyclic, cyclic bisphosphino alkenes possessing one or two endo-phosphorus atoms in the five-membered ring in addition to the exocyclic phosphino group will be discussed. The benzophospholide moiety was also used as a five-membered cyclic fragment of bisphosphino alkenes.

1-(Trialkylphenyl)-2-dibromophosphino-4-methylphospholes **45** ( $R = \text{Me}$ ,  $\text{Pr}^i$ ) were synthesized from arylphospholes **44** through the site-phosphorylation reaction with  $\text{PBr}_3$  <2000JCS(P1)1495, 2002JOM(643-644)32> (Scheme 9). One or two P—Br bonds in **45** were further replaced by P—O or P—N bonds in reactions with alcohols (methanol) or secondary amines (diisopropylamine, morpholine) to give, after hydrolysis or oxidation, a variety of organophosphorus compounds such as phosphonic amides, *H*-phosphinic amides, and *H*-phosphinates.

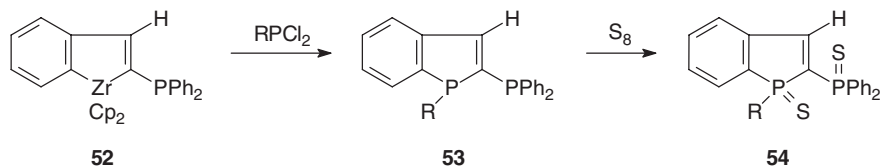
Thus, the substitution reaction of one P—Br bond by either oxygen or nitrogen gave the compounds **46** and **47**, while the substitution of two P—Br bonds by two nitrogen atoms followed by oxidation gave the second set of compounds **48** and **49**. It is noteworthy that the exocyclic *P*-moiety in **48** underwent a selective monooxidation to give **49a** with the phosphole phosphorus atom remaining mostly unoxidized. Oxidation of both P leading to **49b** occurred only in 14% yield. Interestingly, for  $R = \text{Bu}^t$  in **44**, the phosphorylation with  $\text{PBr}_3$  took place at the position 3 of the phosphole moiety. Phosphorus tribromide was also used for cyclization of bisphosphonium dibromide **50** providing the bicyclic derivative **51** in 78% yield <1995BSF280> (Equation (1)).



Scheme 9

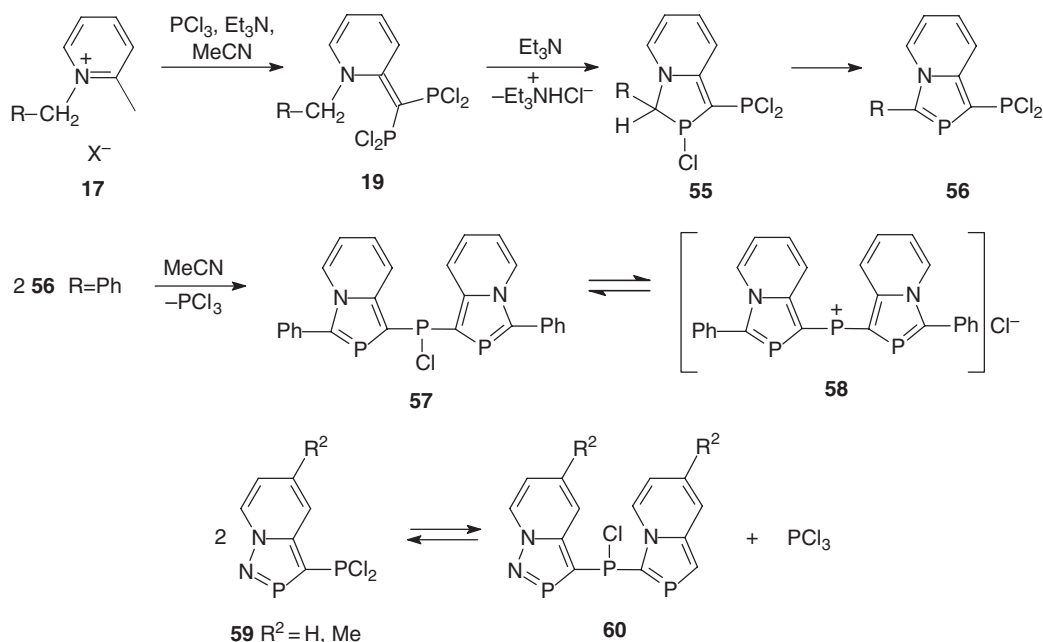


2-Phosphino-1-phosphaindenenes **53** and their disulfides **54** were prepared from the reaction of 2-phosphino-1-zirconaindenenes **52** and dichlorophosphines (R = Ph, Bu<sup>t</sup>) followed by addition of elemental sulfur <1997CC279> (Scheme 10).



Scheme 10

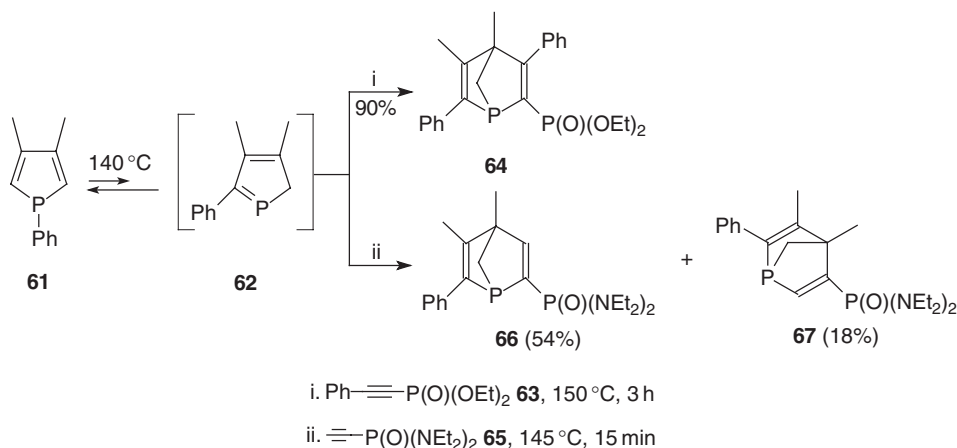
1-Dichlorophosphino-2-phosphaindolizines **56** were synthesized from **17** or directly from **19** via the intermediate **55** from an intramolecular cyclocondensation <1996PSS(112)121> (Scheme 11) in acetonitrile solution.



Scheme 11

In the case of  $\text{R} = \text{Ph}$ , the initially formed **56** underwent disproportionation to form **57**, which exists in equilibrium with **58**. If *N*-alkyl groups in **17** were replaced by the *N*-amino group, moisture-sensitive 1,2,3-diazaphospholo [1,5-*a*] pyridines **59**, being in equilibrium with **60**, were formed in acetonitrile solution upon treatment with 2 equiv. of  $\text{PCl}_3$  and 5 equiv. of  $\text{Et}_3\text{N}$  at  $0-5^\circ\text{C}$  <1995SI173>.

Mathey and co-workers synthesized other acyclic bicyclic structures **64**, **66**, and **67** possessing the exocyclic phosphonate and phosphonamide moieties. They utilized the [4 + 2]-cycloaddition reaction of diethyl ethynylphosphonates and phosphonamides **63** and **65** with transient 2-phenylphosphole **62**, in equilibrium with 1-phenylphosphole **61** at  $140^\circ\text{C}$  <1996JOC3531> (Scheme 12).

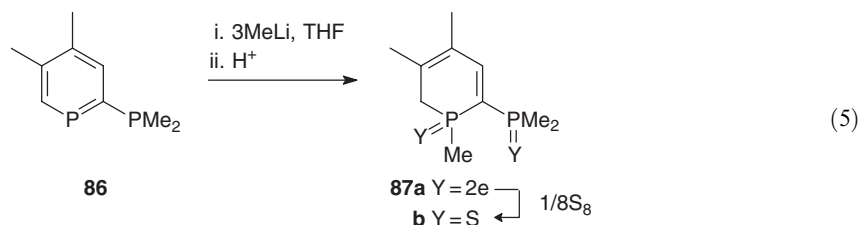


Scheme 12

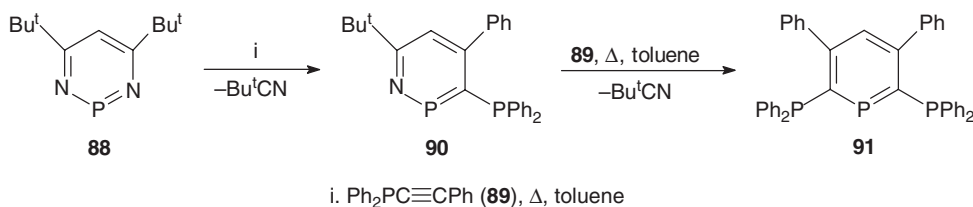
Thus, both diethyl 2-phenylethynylphosphonate **63** and its corresponding phosphonamide gave only one regioisomer **64**, while unsubstituted ethynylphosphonamide **65** afforded two regioisomers **66** and **67**. Dimorpholinyl 2-phenyl-ethynylphosphonamide also gave only one regioisomer.



1,2-Dihydrophosphinine **87a** was obtained on treatment of **86** with excess of methyllithium followed by protonation. Since both substrate and products were air sensitive, the compound **87a** was converted to the stable disulfide **87b** (Equation (5)) <1996OM1597>.

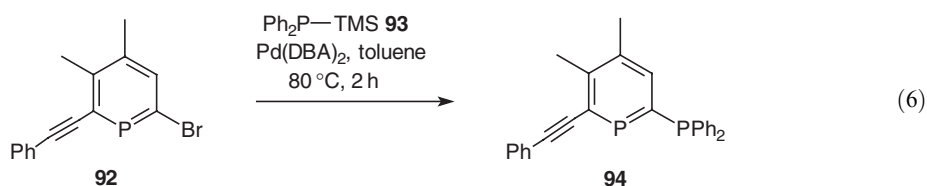


Mathey and co-workers prepared 2,6-diphenylphosphino-phosphinine **91** upon heating the 1,3,2-diazaphosphinine **88** with 2 equiv. of the alkyne **89** <1996JA11978>. This highly regioselective reaction proceeded step by step via the 1,2-azaphosphinine **90** with extrusion of two molecules of *t*-butylnitrile (Scheme 14).

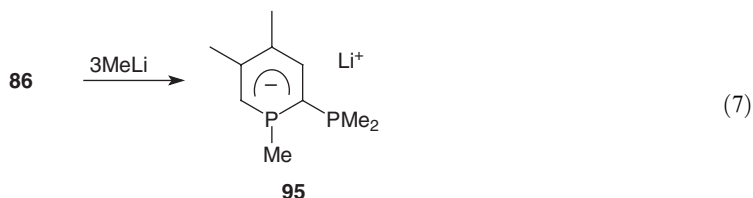


Scheme 14

Another 2-diphenylphosphino-phosphinine **94** was synthesized by Mathey and co-workers via organopalladium insertion into the 2-carbon—bromine bond of the phosphinine **92** followed by reaction with diphenyl(trimethylsilyl)phosphine **93** <1995S717> (Equation (6)).



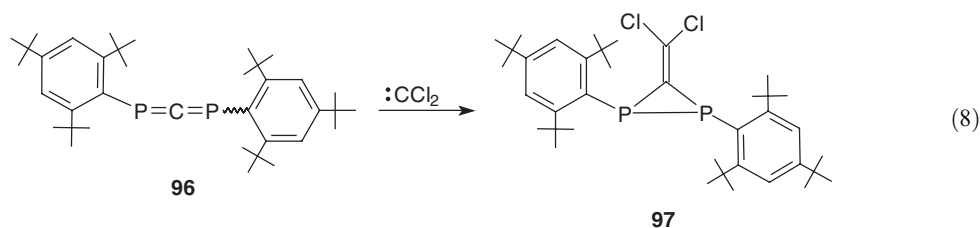
The delocalized carbanion **95** belongs formally to the group of cyclic bisphosphino alkenes and is obtained on treatment of dimethylphosphino-4,5-dimethylphosphinimine **86** with methyllithium (Equation (7)) <1996OM1597>.



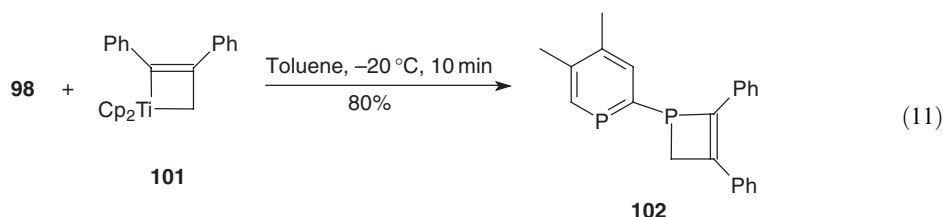
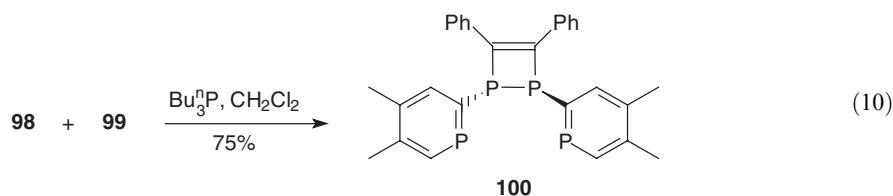
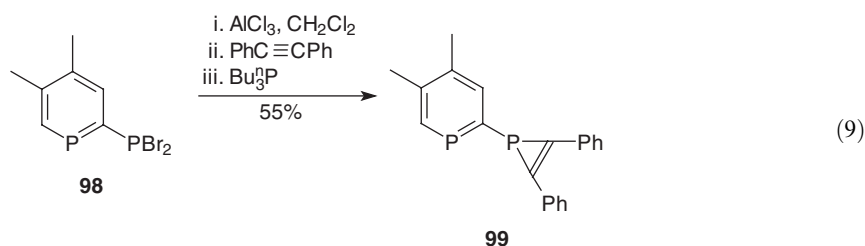
#### 4.22.1.3 Cyclic (3–6-Membered) Bisphosphino Alkenes

In this section syntheses of bisphosphino alkenes containing both the phosphorus atoms in the ring will be discussed. In the review period a very limited number of new methods have been reported. These include syntheses of three-, four-, five-, and six-membered rings and their combinations.

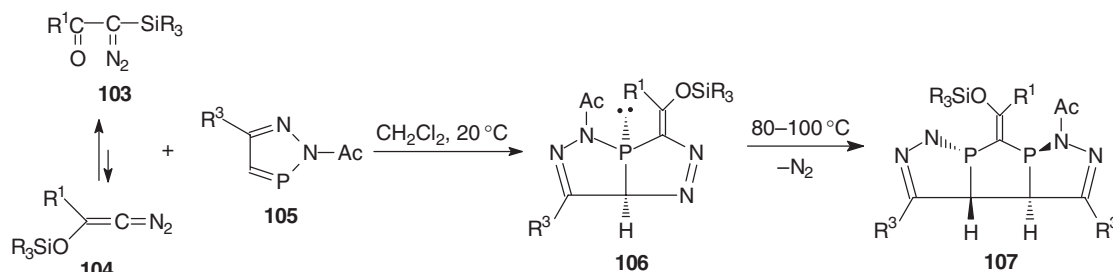
Yoshifuji and Toyota synthesized three-membered methylenediphosphirane **97** from the 1,3-diphosphaallene **96** and dichlorocarbene <1996PSS(109-110)613> (Equation (8)).



Mathey and co-workers synthesized a wide range of 2-phosphinophosphinines **99**, **100**, and **102** by simple conversions of 2-(dibromophosphino)-4,5-dimethylphosphinine **98** <1996OM1597>. The  $\text{PBr}_2$  moiety in **98** was converted to the corresponding  $\text{P}(\text{alkyl, aryl or alkynyl})_2$ ,  $\text{P}(\text{MeO, Bu}^n\text{S or Et}_2\text{N})_2$  and  $\text{PH}_2$  groupings upon reactions with organolithiums, hetero(*O,S,N*)-nucleophiles and  $\text{LiAlH}_4$ , respectively. The reaction of **98** with alkynes gave the phosphirene **99** in 55% yield (Equation (9)). The latter was converted to 1,2-dihydrophosphete **100** in 75% yield upon reaction with the accompanying **98** (Equation (10)). The reaction of **98** with the titanacyclobutene **101** yielded the expected four-membered ring derivative **102** in 80% yield (Equation (11)).

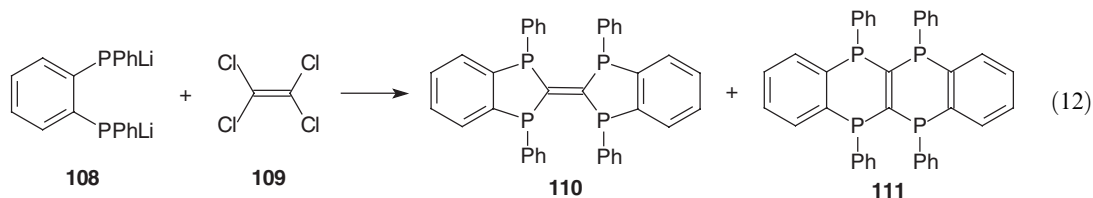


(1-Diazo-2-oxoalkyl)silanes **103** existing in equilibrium with 1-diazo-2-silyloxy-1-alkenes **104**, when treated with 1,2,3( $\lambda^3$ )diazaphospholes **105**, gave [3 + 2]-cycloadducts **106**, which underwent thermolysis in a sealed tube at  $80^\circ\text{C}$  to afford tricyclic *P*-heterocycles **107** with extrusion of nitrogen <1999EJO2633> (Scheme 15).

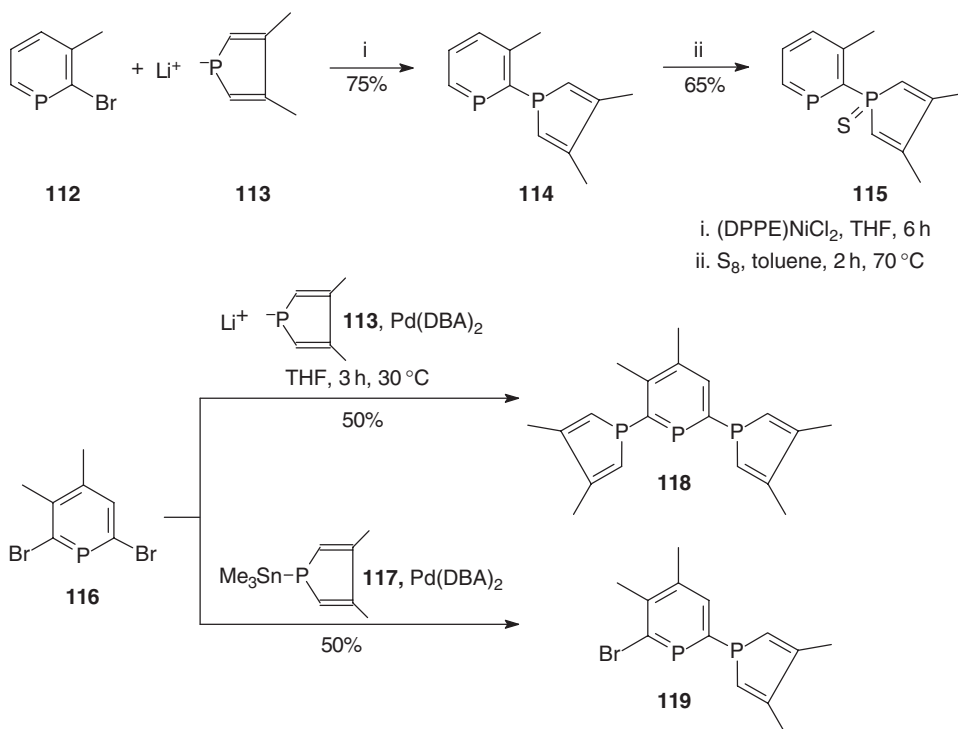


Scheme 15

Starting from 1,2-bis(lithiophenylphosphino) benzene **108** and tetrachloroethylene **109**, both the expected dibenzotetraphosphafulvalene **110** and its strain free six-membered ring isomer **111** were obtained <1997BSF853> (Equation (12)).



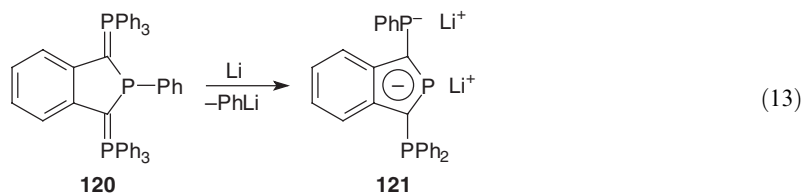
Alkyl-substituted 2-(3,4-dimethyl-phosphol-1-yl)phosphinines such as **114** were synthesized in 75% yield in the condensation reaction of 2-bromo-3-methyl-phosphinine **112** with 3,4-dimethylphospholyllithium **113** in the presence of the nickel complex. Elemental sulfur was added to the phosphole phosphorus in **114** to give the corresponding sulfide **115**. 2,6-Bis-(3,4-dimethyl-phosphol-1-yl)phosphinines, such as **118**, were obtained in the reaction of **113** with 2,6-dibromo-3,4-dimethyl-phosphinine **116** in 50% yield in the presence of palladium complex. Replacement of lithium in **113** by tin in 1-trimethylstannyl-3,4-dimethyl-phosphole **117** gave the monobromo phosphinine **119** in 50% yield <1999BSF910> (Scheme 16).



Scheme 16

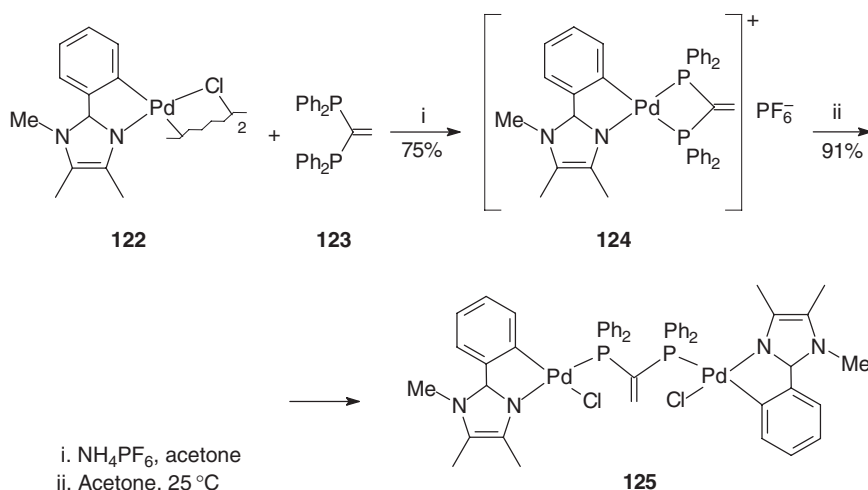
#### 4.22.1.4 Alkali Metal Salts of Bisphosphino Alkenes

Only one product of this type has been reported in the review period. The product **120** underwent reduction with alkali metals (Li, Na) to give the dimetallated species **121** (Equation (13)) <1999EJI1169>.



#### 4.22.1.5 Transition Metal Complexes of Bisphosphino Alkenes

Mononuclear **124** and dinuclear **125** cyclometallated complexes were prepared on treatment of the palladium chloride-bridged complex **122** of 1,3,4,5-trimethyl-2-phenylimidazole with various amounts of 1,1-bis(diphenylphosphino)ethene **123** (Scheme 17) <2000EJ12055>.

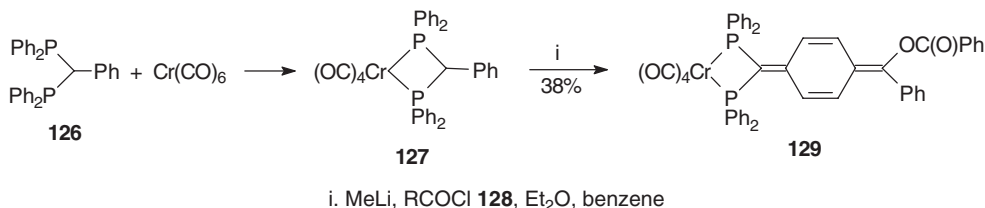


Scheme 17

Thus, treatment of **122** with **123** in a 1:1 molar ratio gave the dinuclear complex **125** while treatment of **122** with **123** in a 1:2 molar ratio in the presence of ammonium hexafluorophosphate afforded the mononuclear complex **124** in 75% yield.

Other mononuclear cyclic palladium complexes of this type with 1,1-bis(diphenylphosphino)ethene were also synthesized <2002NJC1425, 2002OM1304>.

The chromium complex **127**, prepared by treatment of the bisphosphine **126** with chromium hexacarbonyl, was deprotonated with methyl lithium and the resulting carbanion was acylated with acyl chlorides **128** (R = Ph or *p*-tolyl). The intense green color of the chromium complex **129** indicated that the aromatic ring was converted into a quinonoid system (Scheme 18) <1995MI120>.

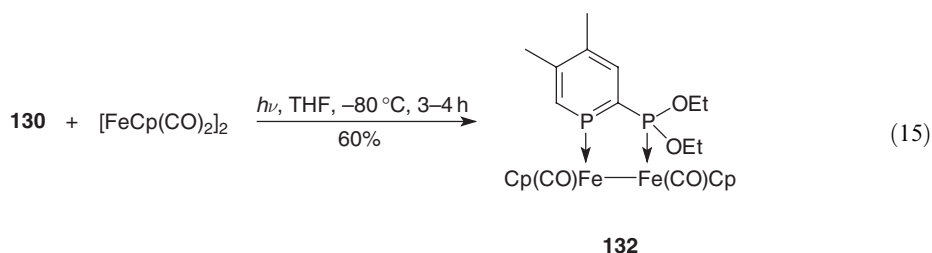
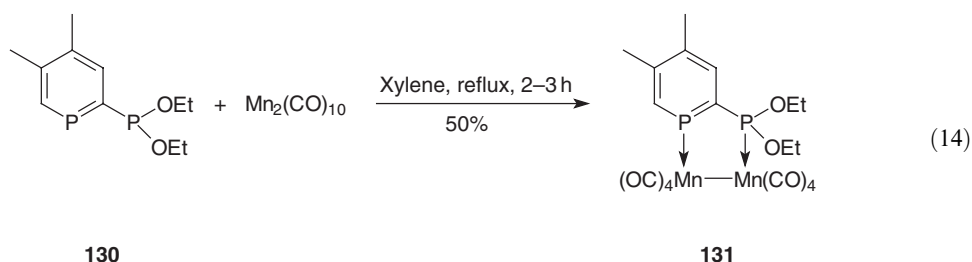


Scheme 18

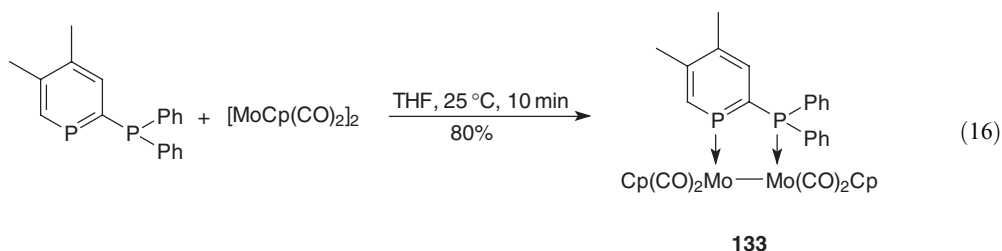


New homo- and heterobimetallic complexes of Ni(II), Pd(II), and Pt(II) with 1,1,2-tris(diphenylphosphino)ethene (3P) and 1,1,2,2-tetrakis(diphenylphosphino)ethene (4P) were synthesized and characterized. The complexes of Pd(II) and Pt(II) showed a square planar geometry while complexes [Ni(3P)Cl<sub>4</sub>] and [NiPt(3P)Cl<sub>4</sub>] had a tetragonal geometry around nickel <2002MI137>.

The stable 1-pentacarbonyltungsten complex of 4,5-dimethyl-2-dichlorophosphinophosphinine **85** was earlier described <1996OM802>. Starting from 2-dibromophosphino-4,5-dimethylphosphinine and ethanol in the presence of triethylamine, Mathey and co-workers prepared the phosphinine derivative **130**, which turned out to be a powerful bridging ligand able to stabilize metal–metal single and triple bonds between low-valent transition metal centers <1997CB(R)843>. Thus, the reaction of **130** with Mn<sub>2</sub>(CO)<sub>10</sub> yielded the corresponding Mn–Mn complex **131** (Equation (14)). Reaction of **130** with [Fe<sub>2</sub>Cp<sub>2</sub>(CO)<sub>4</sub>] under UV irradiation similarly yielded the Fe–Fe-bridged complex **132** (Equation (15)).



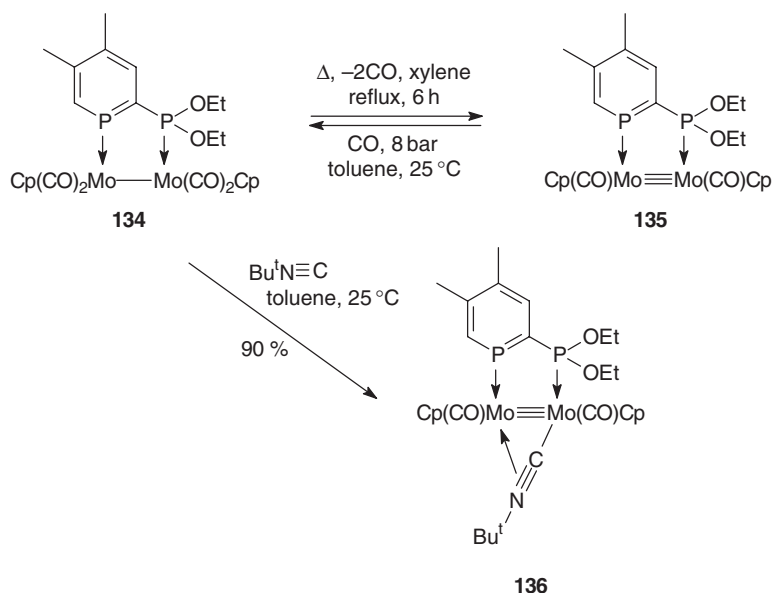
A clean addition of 2-diphenylphosphino-4,5-dimethylphosphinine occurred at the Mo≡Mo triple bond of [Mo<sub>2</sub>Cp<sub>2</sub>(CO)<sub>4</sub>] to give the Mo–Mo single-bonded complex **133** (Equation (16)).



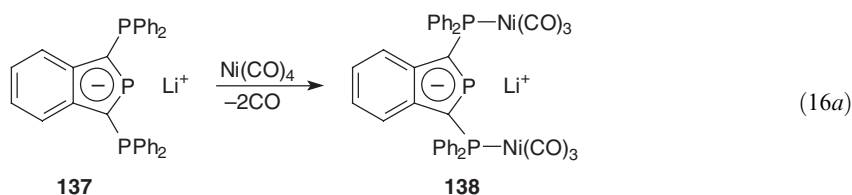
When the phosphino group in **133** was replaced by the P(OEt)<sub>2</sub> group [or P(OAr)<sub>2</sub>], the thermolysis of the resulting **134** occurred to give the Mo<sub>2</sub>Cp<sub>2</sub>(CO)<sub>2</sub> triple-bonded complex **135**.

The Mo≡Mo triple bond of the latter readily added two molecules of CO to reform **134** or one molecule of *t*-butyl isocyanide to give the new complex **136** (Scheme 19).

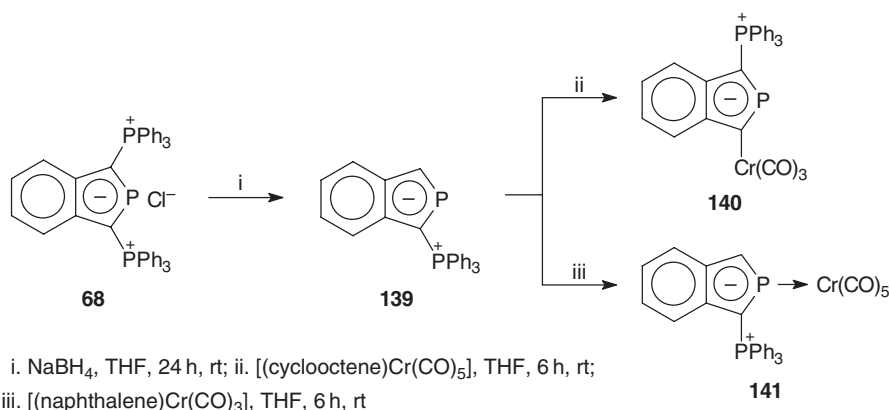
The benzophospholide anion **137**, with an excess of Ni(CO)<sub>4</sub>, formed the complex **138** in 40% yield after recrystallization from THF/diethyl ether <1999EJI1169> (Equation (16a)).



Scheme 19



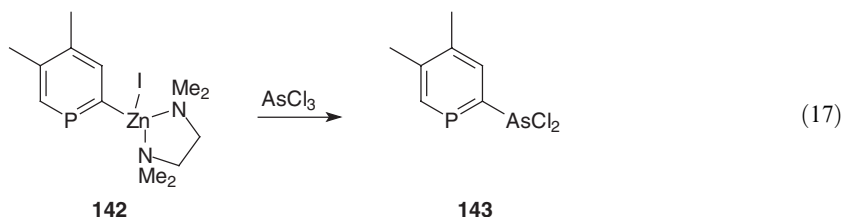
Gudat and co-workers discovered that cationic 1,3-bis-triphenylphosphonio-benzophospholide **68** reacted selectively with an excess of sodium borohydride to give the neutral compound **139** via cleavage of the  $\text{PPh}_3$  moiety [<2000CC1637>](#) (Scheme 20). Treatment of the latter with different chromium carbonyls afforded new complexes **140** and **141**. These reactions showed that **139** behaved like a phosphine-like  $\sigma$ -donor/ $\pi$ -acceptor ligand in  $\sigma(P)$ -complexes and like a phosphaairene ligand in  $\pi$ -complexes.



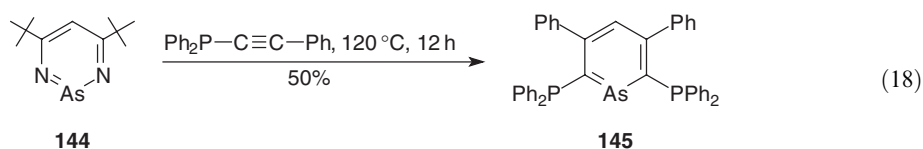
Scheme 20

#### 4.22.2 FUNCTIONS CONTAINING ONE PHOSPHORUS AND EITHER ARSENIC, ANTIMONY OR BISMUTH, $R_2^1C=C(PR_2^2)AsR_3^3$ , etc.

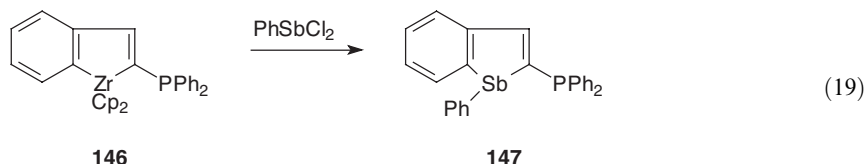
Although no important progress has been made in this area since 1995, it is worth noting that some new products of interest appeared in the literature. The condensation of the organozinc reagent **142** with  $AsCl_3$  gave 2-(dichloroarsino)-4,5-dimethylphosphinine **143** from which the corresponding  $\sigma_P$ -(phosphinine) pentacarbonyltungsten derivative was obtained <1996OM802> (Equation (17)).



The cycloaddition–cycloreversion sequence was utilized by Le Floch and co-workers for the synthesis of the arsinine **145** from the 1,3,2-diazaarsinine **144** and 1-diphenylphosphino-2-phenyl-ethyne <1997OM4089> (Equation (18)).



The 2-phosphinostibole **147** was produced in the reaction of the 2-phosphinozirconaindene **146** with  $PhSbCl_2$  <1997CC279> (Equation (19)).



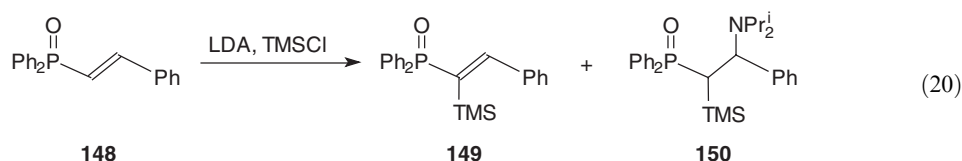
#### 4.22.3 FUNCTIONS CONTAINING ONE PHOSPHORUS AND A METALLOID, $R_2^1C=C(PR_2^2)SiR_3^3$ , etc.

After 1995, many methods leading to this class of compounds possessing one of the three metalloids (Si, Ge, or B) appeared in the literature in contrast to the previous review period in chapter 4.22.3 <1995COFGT(4)1021> where no representative protocol was reported. The majority of methods reviewed here concern the synthesis of compounds with P, Si-functions, three of them concern P, Ge-compounds, and just one deals with the synthesis of a compound with P, B-functions. In all the cyclic P, Si-compounds, the phosphorus is included in the ring while the Si is mostly acyclic. Complexes with metals as well as mono and dianions of the title P, Si-compounds were also reported.

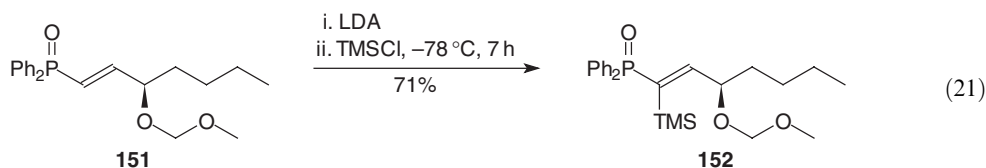
##### 4.22.3.1 Silicon Derivatives

###### 4.22.3.1.1 Acyclic compounds

Treatment of the vinyl phosphine oxide **148** with LDA at low temperatures in the presence of trimethylsilyl chloride afforded a mixture consisting of the silylation product **149** (major) and a minor addition product **150** <1998TL1637> (Equation (20)).

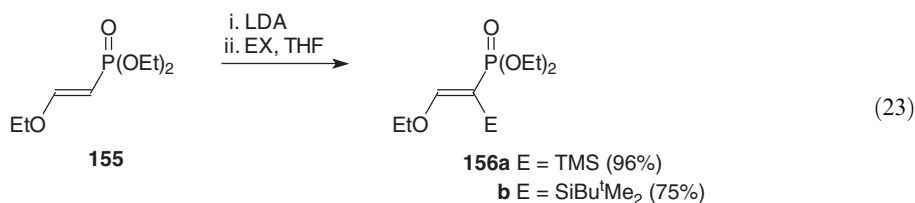
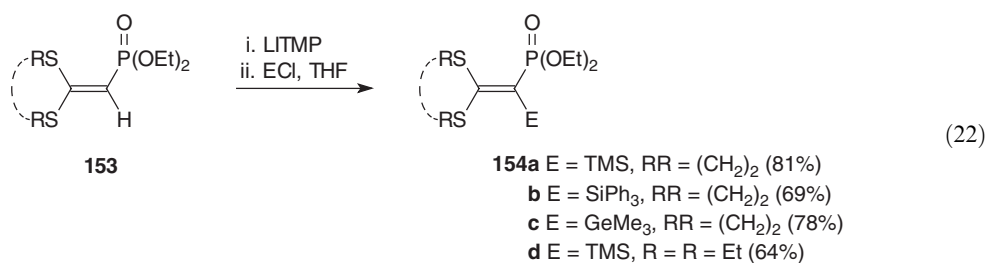


Similarly, the phosphine oxide **151** upon treatment with LDA in the presence of trimethylsilyl chloride gave **152** <1999JCS(P1)1807> (Equation (21)).

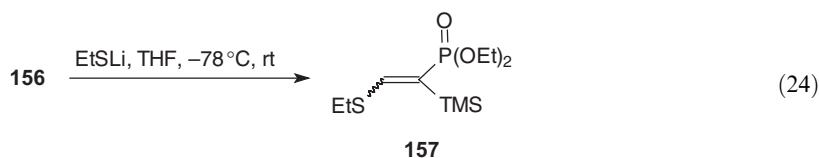


In this case, no addition product of LDA to the double bond was detected. The reaction could be performed at much lower temperature ( $-78^\circ\text{C}$ ) most probably due to a better stabilization of the intermediate vinyllithium by the neighboring acetal oxygen than by the phenyl group in **148**.

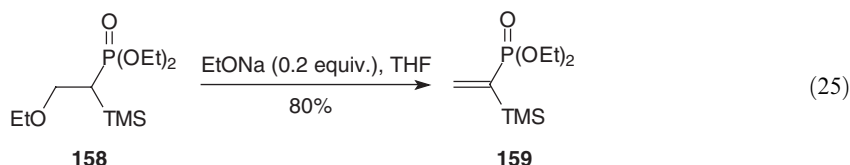
The vinylphosphonates **153** and **155** were also readily lithiated at the  $\alpha$ -position to the phosphorus atom by LDA or LITMP. The resulting 1-lithiovinylphosphonates were trapped with silyl or germyl chlorides to give 1-functionalized phosphonates **154** and **156** <1998JOC6239> (Equations (22) and (23)).



Further transformations at the 2-position of 1-silylated vinylphosphonate **156** were also investigated. Thus, the Michael addition reaction of lithium ethyl mercaptide to **156** gave **157** as a mixture of (*E*)/(*Z*) isomers in a ratio 3.8:1 (Equation (24)).

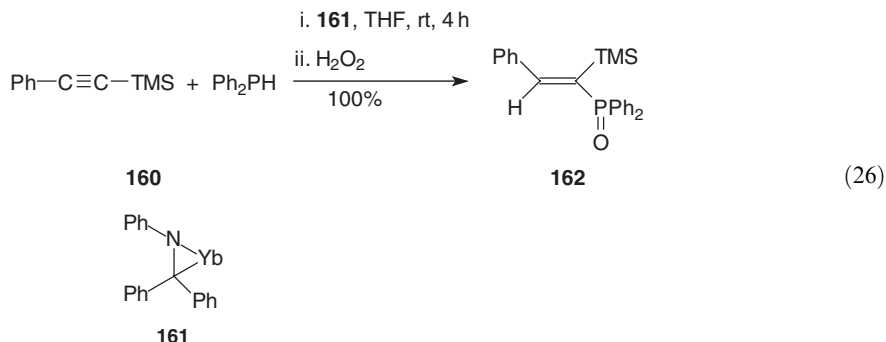


Elimination of ethanol from **158** with catalytic amounts of EtONa in THF afforded the unsubstituted **159** in 80% yield (Equation (25)).

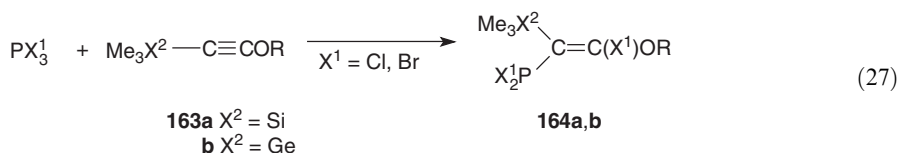


Alkynes and alkynylphosphonates were also employed in the synthesis of the title compounds.

Takaki and co-workers reported hydrophosphination of the alkyne **160** in the presence of catalytic amounts (15 mmol.%) of the ytterbium imine complex **161** to give only one product (*E*)-**162** in quantitative yield <2001TL6357> (Equation (26)).

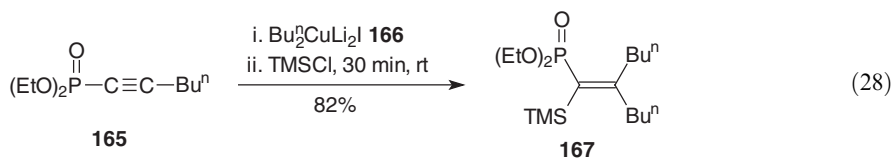


The addition reaction of  $\text{PX}_3^1$  ( $\text{X}^1 = \text{Cl}, \text{Br}$ ) to 1-silylated or 1-germylated alkynes (**163a,b**) afforded 1-silyl- or 1-germyl-1-phosphino alkenes (**164a,b**) <1996ZOB1637> (Equation (27)).



The reactions of  $\text{PCl}_3$  with both types of alkynes (**163a,b**) were performed either neat or in acetonitrile in 5–30 days at 20–50 °C ( $\text{X}^2 = \text{Si}$ ,  $\text{R} = \text{Me}, \text{Et}, \text{Bu}^n$ ) or in 12–72 h at 20 °C ( $\text{X}^2 = \text{Ge}$ ,  $\text{R} = \text{Me}, \text{Et}$ ). The reactions of **163a** with  $\text{PBr}_3$  were carried out in methylene chloride at 20 °C and were completed within 3 h while the reactions of  $\text{PBr}_3$  with **163b** were completed within 10–15 min at 30–40 °C. The addition reaction of  $\text{PBr}_3$  to 1-trimethylsilylethyne was also performed under photochemical conditions (30 min, neat) to give the corresponding addition product in 90% yield, as a mixture of (*E*)/(*Z*) (95:5) isomers <1995ZOB1046>.

Gil and Oh reported addition of the organocopper (I) reagent **166** to 1-alkynyl phosphonate **165** followed by the capture of the resulting 1-phosphonyl-2,2-di-*n*-butylvinylcopper intermediate with trimethylsilyl chloride to give diethyl 1,2,2-trisubstituted vinyl phosphonate **167** with stereoselectivity retained from vinylcopper intermediates <1999JOC2950> (Equation (28)).

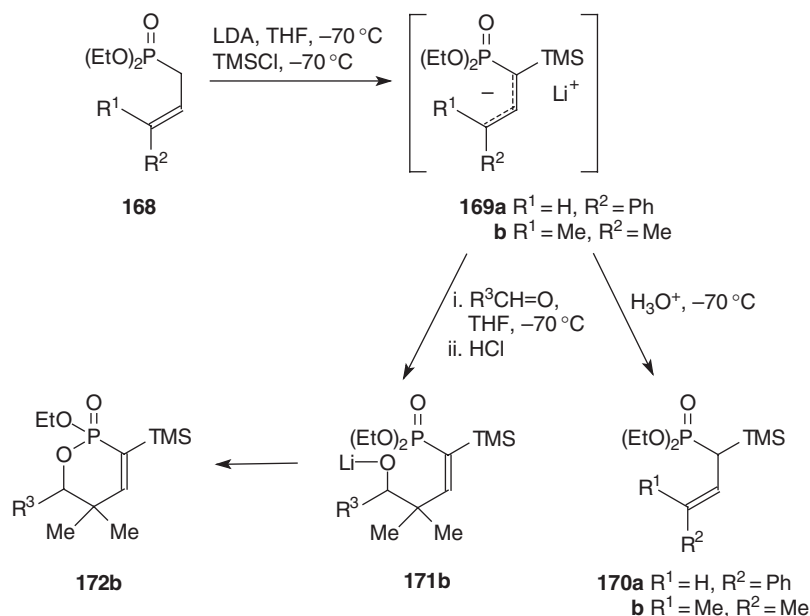


Deprotonation of allylphosphonates **168** upon treatment of an excess of LDA at –70 °C in the presence of trimethylsilyl chloride resulted in the formation of the lithiated intermediates **169**, on acidic hydrolysis gave the corresponding phosphonates **170** in quantitative yields <1996JCS(P1)931> (Scheme 21).

When treated with various aldehydes at –70 °C, the lithio reagent **169b**, surprisingly led to phosphorus analogs of  $\delta$ -lactones **172b** via the intermediate **171b**. Aromatic aldehydes ( $\text{R}^3 = \text{aromatic}$ ) gave exclusively **172b** in 80–92% yields, while aliphatic aldehydes ( $\text{R}^3 = \text{aliphatic}$ ) afforded mixtures of **172b** in 7–30% yield of the Peterson olefination products.

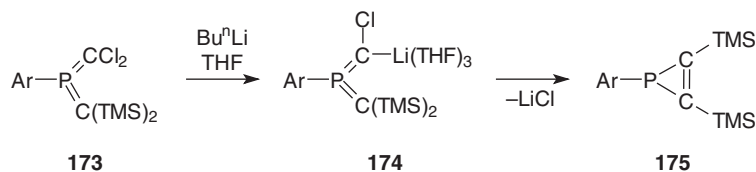
#### 4.22.3.1.2 Acyclic cyclic compounds (3–7 membered)

In this section are described the syntheses of compounds possessing P, Si-functionality with the phosphorus built into three-, four-, five-, six-, and seven-membered rings. Syntheses of trifunctional compounds with P, Si, and metal functions, such as metal complexes and anions, will be discussed in the next section.



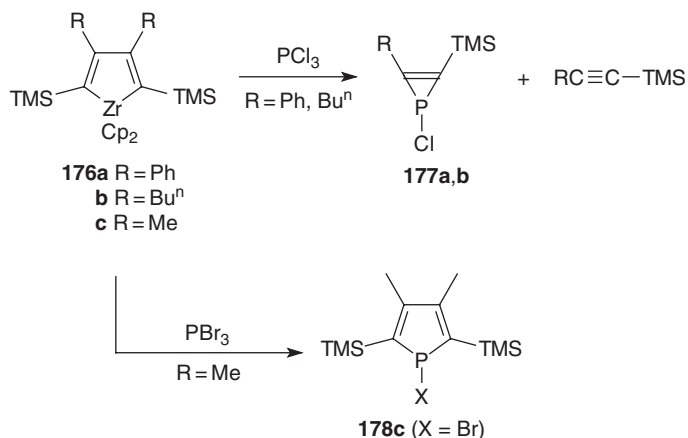
Scheme 21

Silylated aryl-substituted phosphirenes **175** were formed at  $-10^{\circ}\text{C}$  via LiCl elimination from carbenoids **174** obtained from **173** via Cl/Li exchange with *n*-butyllithium <1996PSS(109-110)613> (Scheme 22).



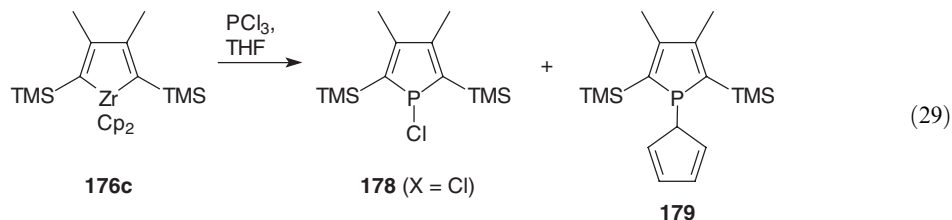
Scheme 22

Zirconacyclopentadienes **176a,b** ( $\text{R} = \text{Ph}, \text{Bu}^n$ ) reacted with  $\text{PCl}_3$  in dichloromethane to give 1-chlorophosphirenes **177a,b** <1999OM4205> (Scheme 23). The latter were also synthesized from the corresponding titanacyclopentadiene complex using a metallacycle transfer reaction <1998OM1677>. In the case of the methyl-substituted derivative **176c** ( $\text{R} = \text{Me}$ ) when  $\text{PBr}_3$  was used as a reagent, the five-membered metathesis reaction product, i.e., 1-bromophosphphole **178c**, was formed within 15 min at  $35^{\circ}\text{C}$  instead of the expected 1-bromophosphirene.



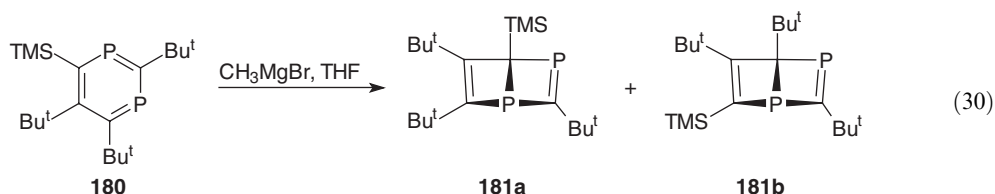
Scheme 23

In contrast, the metathesis reaction of **176c** with  $\text{PCl}_3$  gave a mixture of 1-chloro- **178** and 1-cyclopentadienyl- **179** phospholes, which turned out to be unstable during purification <1999OM2491> (Equation (29)). Analogous chlorostiboles, chlorobismoles, and chloroarsoles were earlier described as thermolabile compounds as well <1988JA2310, 1994JA1880>.

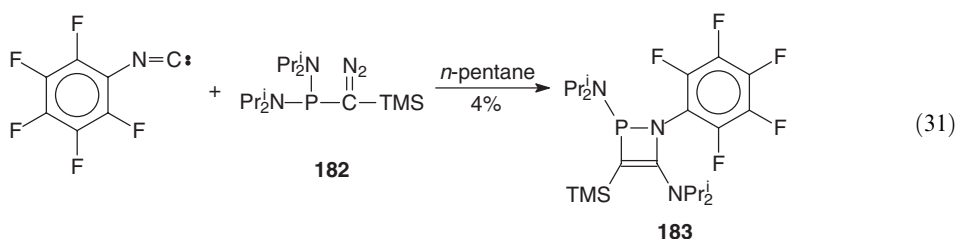


Treatment of a mixture of **178** and **179** with calcium in THF afforded dimeric bis(tetrahydrofuran-O)dicalciumbis[3,4-dimethyl-2,5-bis(trimethylsilyl)-1-phosphacyclopenta-2,4-dienide]-cyclopentadienide chloride, as an example of trifunctional compound containing P-, Si-, and Ca-functions.

While addition reactions of Grignard reagents and organolithium compounds to phosphinines <1967AG(E)87, 1974TL4501, 1977TL407> and 1,3,5-triphosphinines <2003AG(E)1863> are known, the analogous reaction with 1,3-diphosphinines remained unknown until 2003. Regitz and co-workers <2003S1526> discovered that although 1,3-diphosphinines decomposed on treatment with *n*-butyllithium ( $-78^\circ\text{C}$  to room temperature), the reaction with methylmagnesium bromide at  $40^\circ\text{C}$  led to the formation of isomeric Dewar-benzenes **181a** and **181b** in a ratio of 14:1 in 83% yield. When the reaction temperature was raised to  $120^\circ\text{C}$  for 4 days, the same products were obtained in a 5:2 ratio in 20% yield still favoring **181a** (Equation (30)).



The photolysis of pentafluorophenyl isocyanide in the presence of [bis(diisopropylamino)phosphino](trimethylsilyl)diazomethane **182** yielded 3-trimethylsilyl-1,2-azaphosphetene **183** in 4% yield <1989JFC73> (Equation (31)).



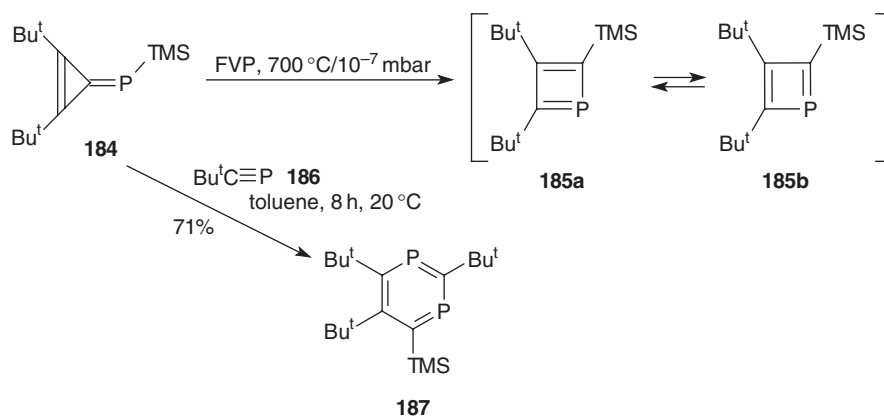
Flash vacuum pyrolysis (FVP) of **184** provided evidence for the existence of equilibrium between the two intermediate phosphacyclobutadienes **185a** and **185b**, which further gave *t*-butylphosphaalkyne **186** and 1-trimethylsilylphosphaalkyne as phosphorus-containing products <2001S463> (Scheme 24). The reaction of **184** with **186** gave 1,3-diphosphinine **187** in 71% yield.

Very rare and thermally rather unstable 2-phosphino-2*H*-phosphirene **188** rearranged after 3 h at room temperature to  $1\lambda^5, 2\lambda^3$ -diphosphete **189**. Photochemical rearrangement of **188** afforded a mixture of **189** (87%), **190** (3%), and **191** (10%).

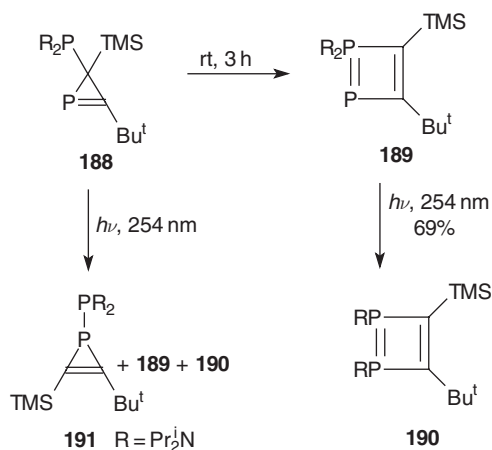
Irradiation of the diphosphete **189** gave the isomeric 1,2-dihydrodiphosphete **190** in 69% yield <1999CEJ274> (Scheme 25).

An attempt to isolate **188** as the more stable thiophosphoranyl derivative or the  $\text{BH}_3$  adduct resulted in the formation of the corresponding new diphosphete derivatives **192** and **193**.

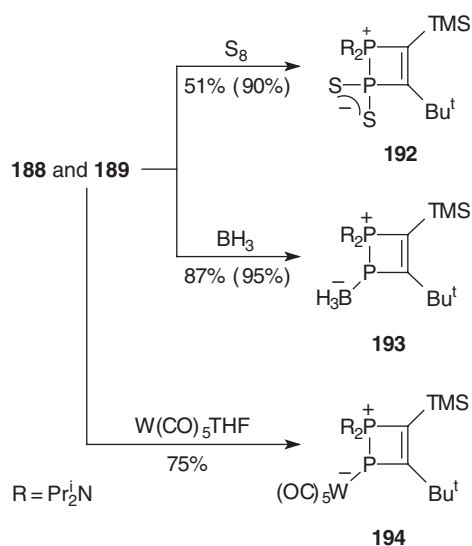
The same adducts were also obtained directly from **189** <2001S463> (Scheme 26).



Scheme 24



Scheme 25

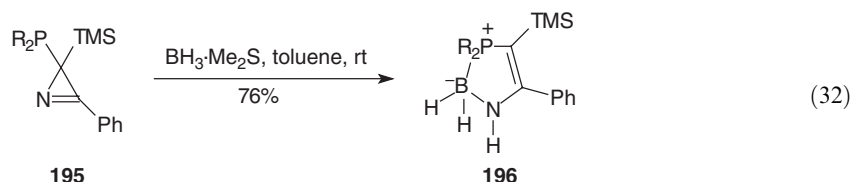


Scheme 26

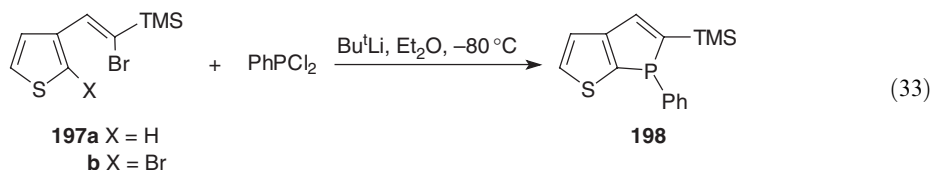


Moreover, **189** reacted at room temperature with pentacarbonyl tungsten to afford the  $\eta^1$ -complex **194** as orange crystals <1995JA10785>. Analogous complexes of **189** with diiron nonacarbonyl were also obtained in 48% yield and further reactions of **189** with MeOTf, Se (1 and 2 equiv.), TMS<sub>2</sub>O<sub>2</sub> (2 equiv.), W(CO)<sub>5</sub>THF/TMS<sub>2</sub>O<sub>2</sub>, 2TCBQ (tetrachloro-*o*-benzoquinone) and MeOTf/TCBQ were also investigated <1996AG2386, 1997JA9720>.

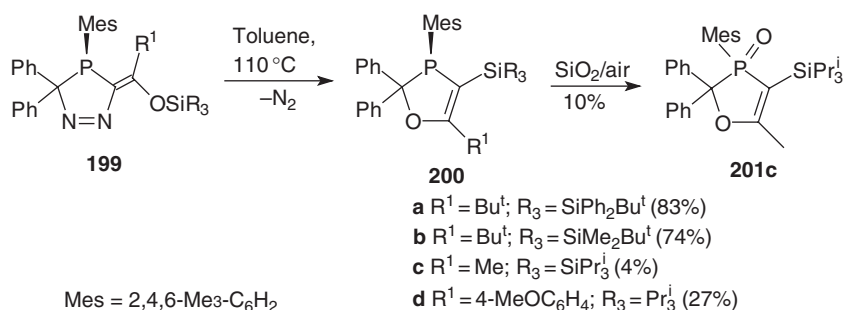
The nitrogen analog of **188**, i.e., the 2-phosphino-2*H*-azirine **195**, showed completely different behavior than its phosphorus counterpart. In the reaction with borane at room temperature the five-membered heterocycle **196** was formed in 76% yield <1997CEJ1757> (Equation (32)) instead of the expected nitrogen analog of **193**.



Deprotonation of both (1-bromo-2-thiophen-3-yl-vinyl)trimethylsilane **197a** (X = H) and its bromo derivative **197b** (X = Br) with *t*-butyllithium followed by the condensation with dichlorophenylphosphine and cyclization afforded the phosphole derivative **198** (Equation (33)). In the analogous reaction [1-bromo-2-(4-bromothiophen-3-yl)vinyl]trimethylsilane was also used <1997H1891>.



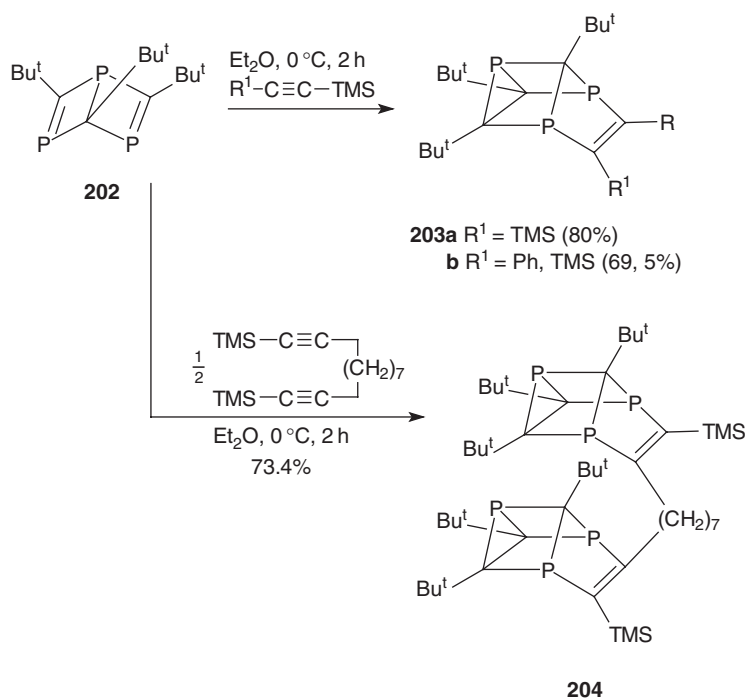
Maas and co-workers described thermal extrusion of nitrogen from the 1,2,4-diaza-phosphole derivative **199** to give 2,3-dihydro-1,3-oxaphospholes **200** in one of the competing reaction pathways <1997CB(R)779> (Scheme 27).



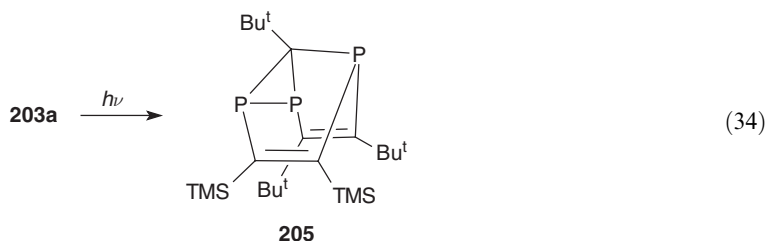
Scheme 27

During chromatographic work-up **200c** was oxidized with the oxygen in air to the cyclic phosphinoid **201c**.

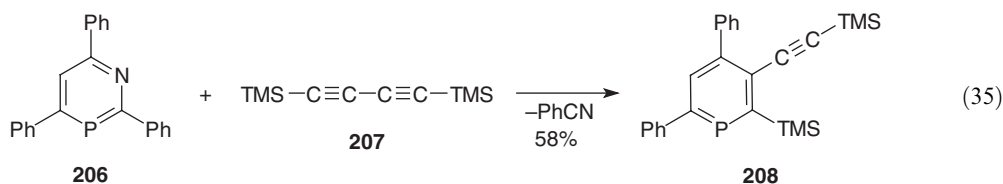
Triphosphabishomoprismanes (**203a** and **b**) and **204** were synthesized by Diels–Alder reaction of 2,4,6-tri-*t*-butyl-1,3,5-triphospha-Dewar-benzene **202** with the corresponding acetylene derivatives (Scheme 28) <1999S1363>. In solution, **203a** slowly rearranged even at room temperature to the corresponding triphosphasenobullvalene **205**. This rearrangement was enhanced by irradiation with the Hg-high-pressure lamp (Equation (34)).



Scheme 28

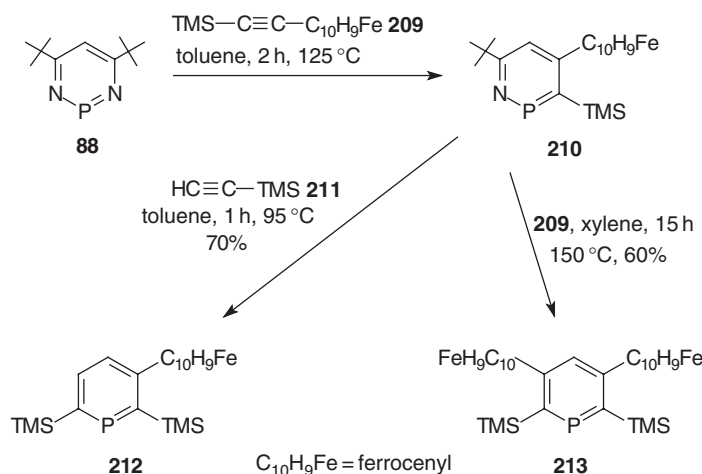


Märkl and Dorsch showed that the 1,3-azaphosphinine **206** underwent the Diels–Alder cycloaddition/cycloreversion reaction sequence with the diacetylene **207** under high pressure (8 kbar) to give the corresponding phosphinine **208** in 58% yield [<1995TL3839>](#) (Equation (35)).

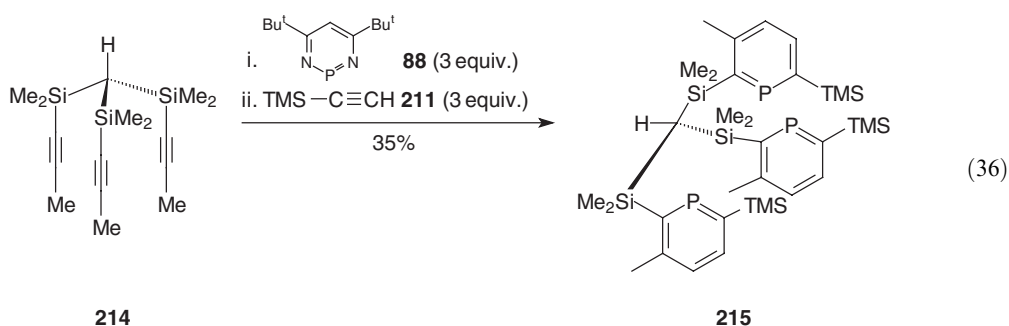


The analogous approach utilizing a  $[4+2]$ -cycloaddition/cycloreversion sequence involving the concomitant loss of one or two nitrile groups and using 1,3,2-diazaphosphinines or 1,2-azaphosphinines under normal pressure was widely developed by the group of Mathey. This approach enabled various syntheses of 2-trimethylsilyl or 2,6-bis(trimethylsilyl)phosphinines as well as silylated tripodal ligands, silacalixphosphinines and other systems. Thus, mono- **210** or bis-silylated phosphinines **212** and **213** were obtained from 1,3,2-diazaphosphinine **88** in one or two  $[4+2]$ -cycloaddition-cycloreversion sequences using 2 equiv. of the same **209** or 1 equiv. each of two different silylated alkynes **209** and **211** [<1997OM4089>](#) (Scheme 29).

These thermally promoted reactions were also utilized in a slightly modified manner for the synthesis of the so far unknown tripodal ligands [<2000EJ12565>](#). One of such new ligands **215**, was synthesized starting from the triyne **214**, 3 equiv. each of 1,3,2-diazaphosphinine **88** and trimethylsilylacetylene **211** (Equation (36)).

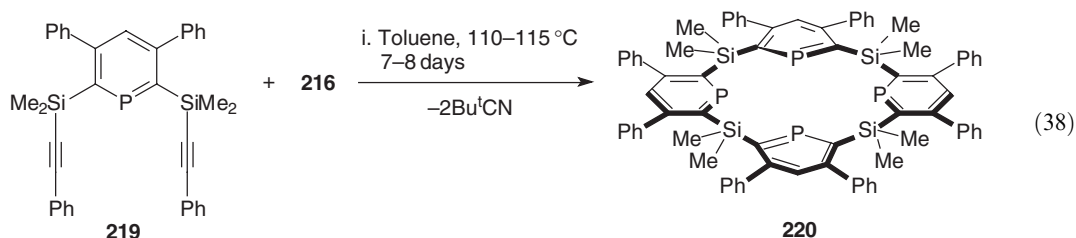
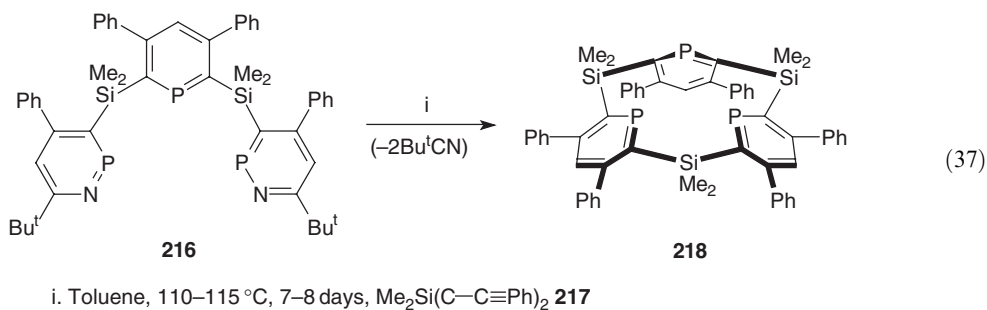


Scheme 29



Some of the tripodal ligands obtained were then complexed with [W(CO)<sub>5</sub>THF] to afford  $\eta^1$ -W(CO)<sub>3</sub> complexes.

The utility of the new process was demonstrated further by the synthesis of silacalix-[*n*]-phosphines [1999CEJ2109](#), [1999PSS\(144-146\)251](#). The best results were obtained when **216** was treated with 1 equiv. of diyne **217** under high-dilution conditions to give **218** (*n* = 3) in 20% yield (Equation (37)). This strategy was also extended to the synthesis of **220** (*n* = 4) (Equation (38)).

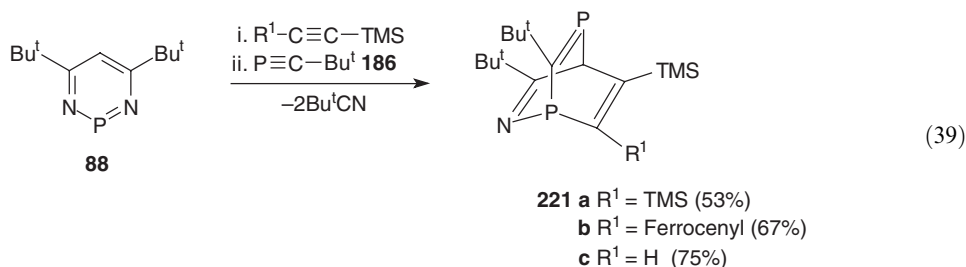


The same method was applied to the synthesis of analogous but more flexible macrocycles having different cavity sizes <2001JOC1054>.

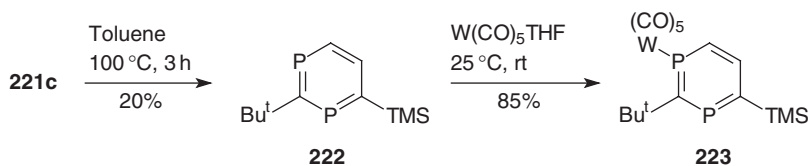
The neutral gold(0) complexes of **220** were obtained and found out to be particularly stable <1999AG(E)3194>. Other silacalix-[3]-phosphinine-based macrocycles with Si—O—Si spacers and their cationic complexes with group 11 metal centers (Cu, Ag, Au) were also synthesized <2002EJI2034>.

Other homogenic 2,6-bis(trimethylsilyl)phosphinines obtained from **88** were also reported <1996JA11978>. Mixed 2-diphenylphosphino-6-trimethylsilylphosphinine was synthesized from **88**, 1,2-bis(diphenylphosphino)acetylene and (trimethylsilyl)acetylene in two [4 + 2]-cycloaddition-cycloreversion steps in 70% yield (toluene, 1 h, 40%) <1997OM4089>. Further examples of reactions involving **88** and bisacetylenes containing a heterocyclic (furan, thiophene, phosphinine, phosphole, phosphaferrrocene) fragment as a central unit were also described <1999OM4205>.

The cycloaddition/cycloconversion sequence was adapted for the combination of the silylated acetylenes and *t*-butylphosphaethyne **186** to afford azadiphosphabarrelenes **221** <1998EJO2039> (Equation (39)).

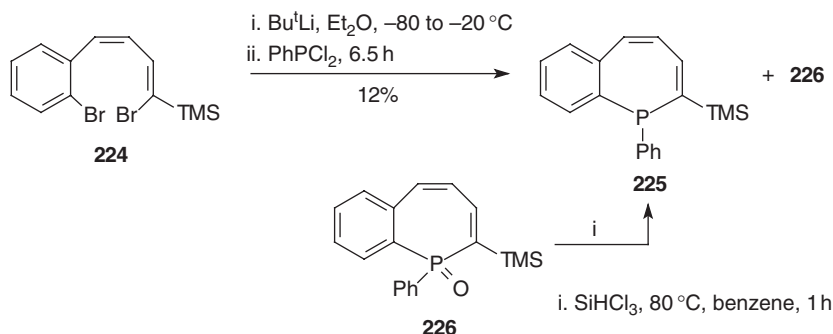


While thermolysis of the barrelenes **221a** and **221b** in refluxing toluene led exclusively to the starting material as the retro-Diels–Alder reaction product, the thermolysis of **221c** under the same reaction conditions furnished the 1,3-diphosphinine **222** unambiguously identified as its tungsten complex **223** (Scheme 30).



Scheme 30

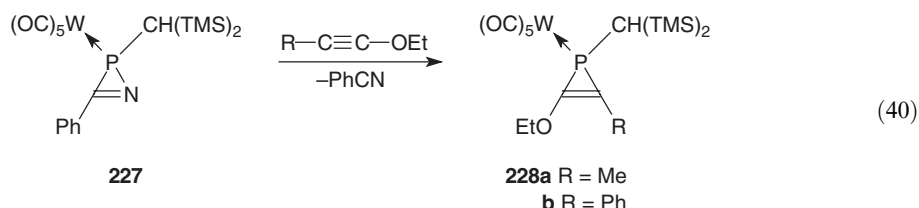
Seven-membered phosphabenzocycloheptenes **225** and **226** were synthesized in a multistage reaction consisting of the metallation of the (*Z*),(*Z*)-butadiene derivative **224**, condensation of the resulting lithium species with dichlorophenylphosphine and finally cyclization, in 12 and 28% overall yield, respectively. The corresponding *P*-oxide **226** was further reduced back to **225** <1999CPB1108> (Scheme 31).



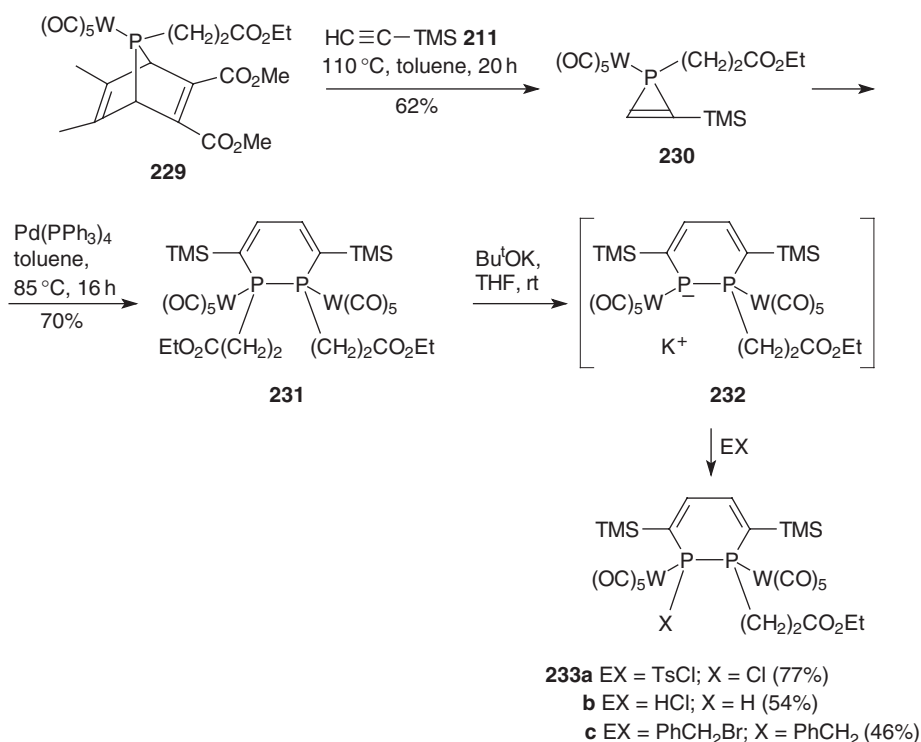
Scheme 31

## 4.22.3.1.3 Acyclic cyclic metal complexes and salts

This section describes syntheses of three-, five-, and six-membered compounds with the *endo*-P and *exo*-Si atoms and possessing various coordination modes to the metal:  $\eta^1(\text{P})$ ,  $\eta^5$  in silylated phosphole anions;  $\eta^5$  in half-sandwich phosphabenzene complexes;  $\eta^5$ ,  $\eta^5$  in 1,1'-diphosphametalloenes;  $\eta^6$ ,  $\eta^6$  in  $\pi$ -sandwich complexes of phosphabenzene as well as ionic compounds such as alkali metal mono-anions and dianions of phosphabenzene derivatives. The tungsten(0) azaphosphirene complex **227** was converted upon heating with silylated acetylenes to phosphirene complexes **228a,b** with a concomitant extrusion of benzonitrile <1999ZAAC102> (Equation (40)).



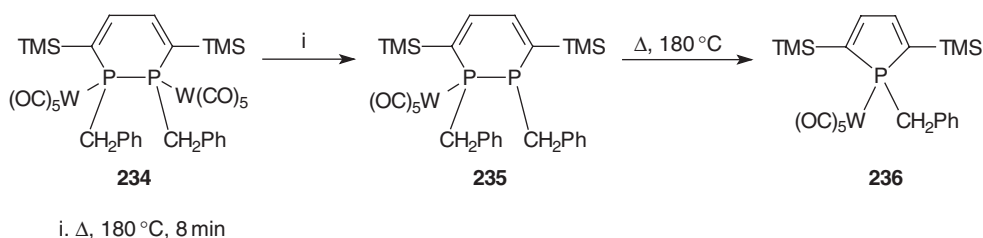
The 7-phosphanorbornadiene derivative **229** with excess of trimethylsilylacetylene **211** gave the silylated phosphirene **230** which dimerized in the presence of Pd(0) catalyst to 1,2-dihydro-1,2-diphosphinine **231** <2000CC1137> (Scheme 32).



Scheme 32

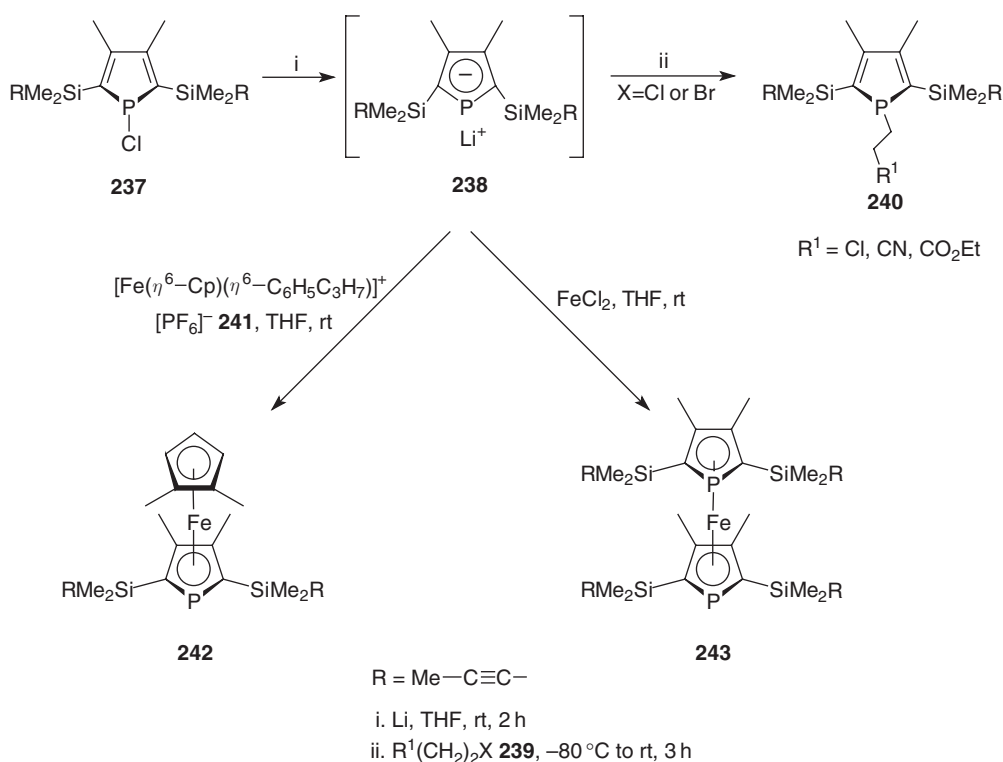
Treatment of **231** with *t*-BuOK in THF induced a clean dealkylation to give the monoanion **232**, which was then transformed to P—Cl, P—H and *P*-alkyl derivatives (**233a–233c**) <2002OM336> (Scheme 32). All transformations were done in the coordination sphere of pentacarbonyl tungsten, which was known to increase the kinetic stability of P=P double bonds.

Finally, an interesting thermal contraction of the ring size was observed in the dibenzyl 6-membered derivative **234**, which on heating to 180 °C, gave the 5-membered phosphole **236** via the transient diphosphinine **235** (Scheme 33).



Scheme 33

The 2,5-disilylated phospholyl anion **238** gave the silylated *P*-functionalized phosphole **240**, phosphaferrrocene **242**, or 1,1'-diphosphaferrrocene **243** upon treatment with halides **239** ( $\text{X} = \text{Cl}$ ,  $\text{Br}$ ), the ionic complex **241** or  $\text{FeCl}_2$ , respectively [<1999OM4205>](#) (Scheme 34). The anion **238** was synthesized from the *P*-chloro derivative **237** with excess lithium in THF.

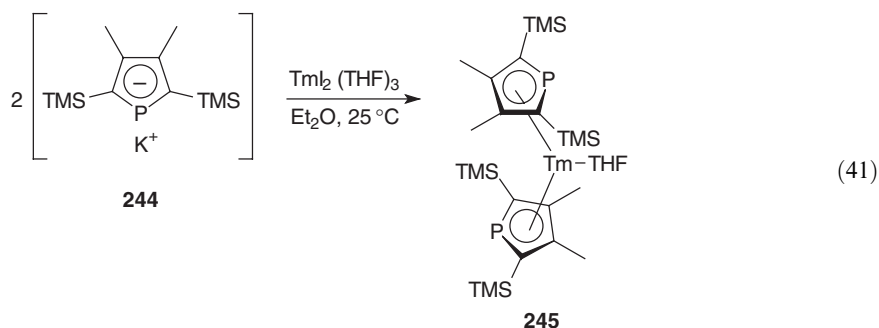


Scheme 34

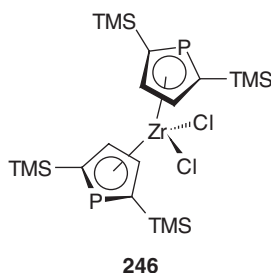
2,2'-Bis(trimethylsilyl)-1,1'-diphosphaferrrocene was obtained in a similar way from 3,4-dimethyl-1-phenyl-2-trimethylsilyl phosphole via the  $\text{P}-\text{Ph}$  bond cleavage with lithium in THF to give the corresponding lithium phospholide followed by the reaction with  $\text{FeCl}_2$  [<1996BSF541>](#).

Similarly, 2,2',5,5'-tetrakis(trimethylsilyl)-3,3',4,4'-tetramethyl-1,1'-diphosphaferrrocene was obtained from 1-phenyl-2,5-bis(trimethylsilyl)-3,4-dimethylphosphole and its dynamic solution behavior was investigated [<1997PSS\(130\)203>](#).

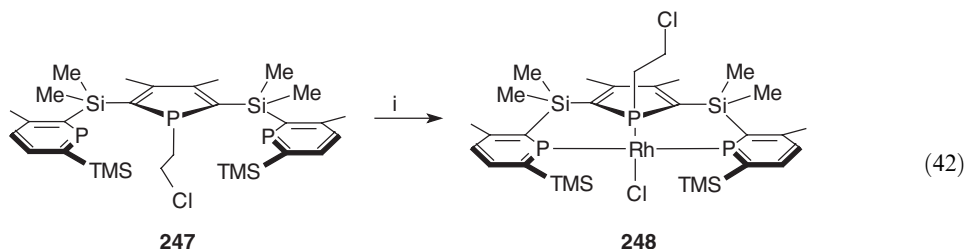
Using the above method involving condensation of the phospholide anion with metal halide, other diphosphametalloenes were obtained. Thus, Nief and co-workers synthesized divalent thulium THF complex **245** using more reactive potassium 2,5-bis(trimethylsilyl)-3,4-dimethylphospholide **244** in the reaction with  $\text{TmI}_2$  [<2002CC1646>](#) (Equation (41)).



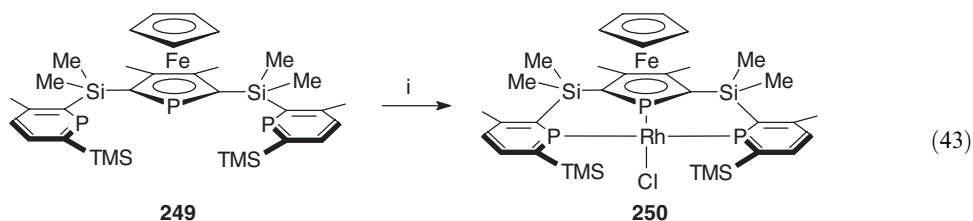
An interesting synthesis of the 1,1'-diphosphazirconocene **246** with bulky TMS substituents, investigated as a co-catalyst in propylene polymerization, was also demonstrated [<1998JMOC155>](#).



Silylated phosphinine-phosphole-based and phosphinine-phosphaferrocene-based tridentate ruthenium complexes **248** and **250** were synthesized from the corresponding precursors **247** and **249**, respectively, and  $[\text{Rh}(\text{COD})\text{Cl}]_2$  [<1999OM4205>](#). The bimetallic (Fe, Rh) complex **250** was notable for its triple  $\eta^1$  (P-Rh) and  $\eta^5$ -ferrocene coordination modes ([Equations \(42\)](#) and [\(43\)](#)).



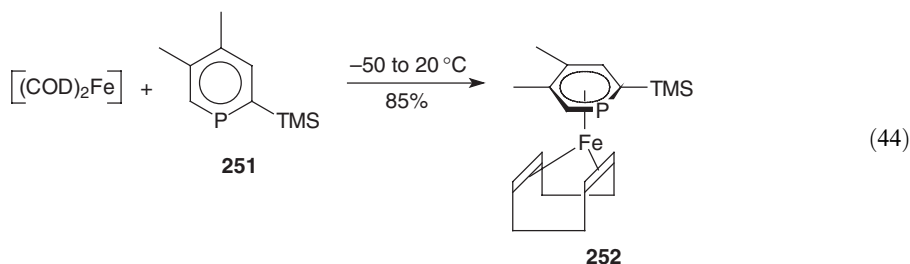
i.  $1/2 [\text{Rh}(\text{COD})\text{Cl}]_2$ ,  $\text{CH}_2\text{Cl}_2$ , 15 min



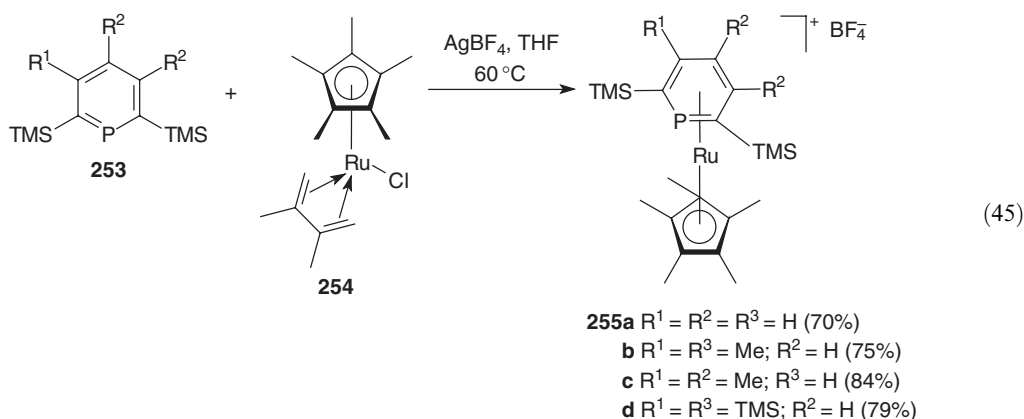
i.  $1/2 [\text{Rh}(\text{COD})\text{Cl}]_2$ ,  $\text{CH}_2\text{Cl}_2$ , 15 min

The phosphinine moieties in both ligands were obtained again utilizing [4 + 2]-cycloaddition–cycloreversion sequence which was discussed in the previous [section \(4.22.3.1.2\)](#).

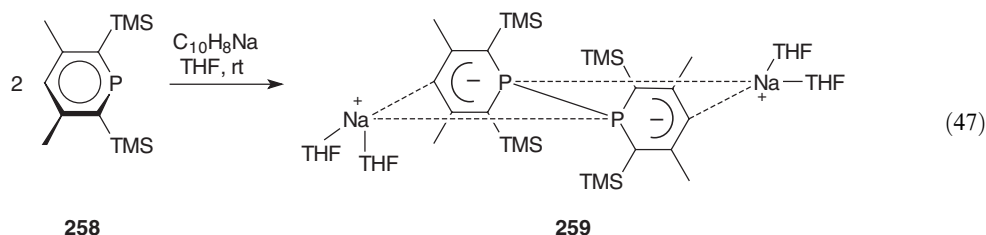
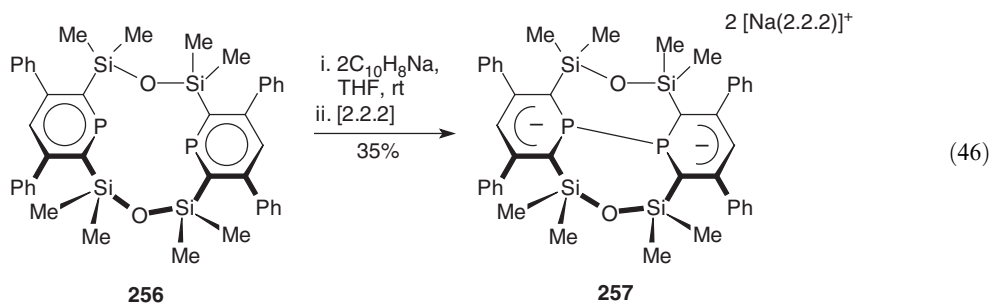
The most effective route to 2-silylated phosphinine iron complexes **252** turned out to be condensation of the  $(\text{COD})_2\text{Fe}$  prepared *in situ* with the phosphinine **251**. The three-component reaction of stoichiometric amounts of  $\text{Fe}_{(\text{g})}$ , COD, and **251** was much less effective (20% yield) [<1996OM2713>](#) ([Equation \(44\)](#)).



The use of bulky 2,6-bis(trimethylsilyl) phosphinines **253** yielded  $\eta^6$ -ionic complexes (**255a–255d**) upon reaction with the ruthenium complex **254** and  $\text{AgBF}_4$  in THF <2001OM3304> (Equation (45)).



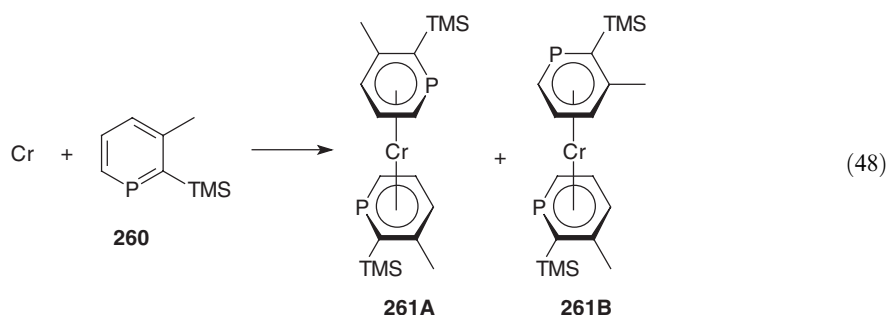
Starting from macrocycles **256** and **258** containing two phosphinine rings, dianions **257** and **259** with P—P bonds were formed as a result of successive one-electron chemical and electrochemical reductions <2001JA6654> (Equations (46) and (47)).



The intermediate radical monoanions were detected by EPR. The dianion **257**, as a cryptand [2.2.2] complex, was obtained from the initially formed THF complex.

The reaction between vapors of chromium and 2-trimethylsilyl-3-methylphosphabenzene **260** using a metal vapor synthesis technique produced an extremely air-sensitive yellow oil containing two nonseparable isomers of bis(2-trimethylsilyl-3-methylphosphabenzene) (**261a** and **261b**) in 40% and 60% yields, respectively <2000MI561> (Equation (48)).





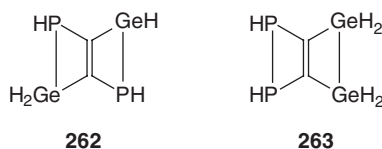
#### 4.22.3.2 Germanium Derivatives

More progress in this field has been recently made in comparison with the previous review period (before 1995) where no examples were reported in the literature.

Thus, the synthesis of a few acyclic compounds with the P, Ge functions has already been mentioned in the previous section (4.22.3.1.1) devoted to the synthesis of analogous P, Si compounds.

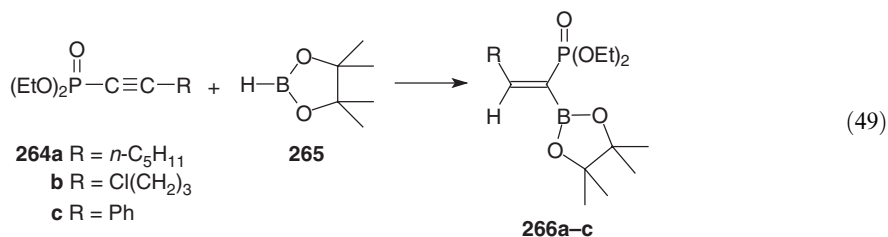
Moreover, bis-(2,5-di-*t*-butyl)-1,1'-diphosphagermanocene was synthesized from the corresponding lithium 2,5-di-*t*-butylphospholide and GeI<sub>2</sub> in an analogous manner to other 1,1'-diphosphametalloenes <1999CC1273>.

It is worthy to note that although bicyclic structures **262** and **263** were not synthesized, their unexpected thermodynamic stability was calculated <1996OM3070>.



#### 4.22.3.3 Boron Derivatives

Only one product of this type, represented by three examples (**266a–266c**), has been reported. Thus, hydroboration of 1-alkynylphosphonates (**264a–264c**) with pinacolborane **265** in methylene chloride gave, after workup, the kinetic products (**266a–266c**) <2001TL8059> (Equation (49)). The latter could be isomerized to place boron at the C2 position (thermodynamic product) by extended heating or by use of PdCl<sub>2</sub> catalyst.



#### 4.22.4 FUNCTIONS CONTAINING PHOSPHORUS AND A METAL, R<sub>2</sub>C=C(PR<sub>2</sub>)M, etc.

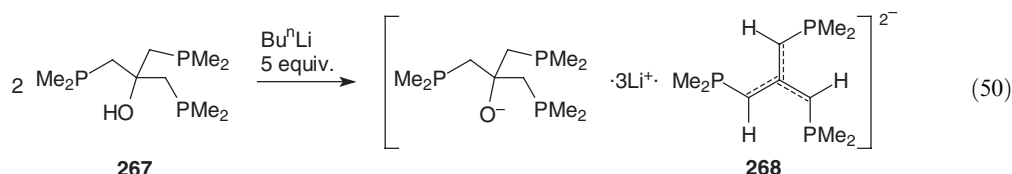
Significant progress in this field has been made since 1995. Many interesting compounds with different metal coordination modes have appeared in the literature and they will be reviewed here. Until 1995, compounds containing an alkali or alkaline earth metal attached to the α-carbon of a phosphino alkene are unknown with the exception of few aromatic compounds, e.g., lithium 2,6-diphenylphospholide <1995COFGT(4)1021>.

## 4.22.4.1 Main Group Metals

## 4.22.4.1.1 Group 1 metals

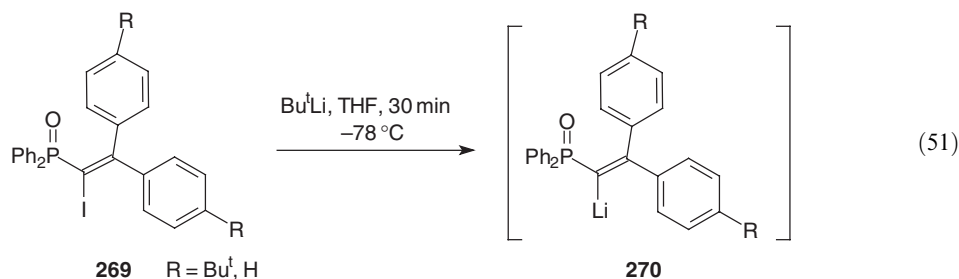
Compounds containing only lithium, sodium, and potassium will be reported below and compounds with heavier members of the family (Rb, Cs) are yet to be synthesized.

Müller and Fenstel reacted the tris(phosphinomethyl)-substituted alcohol **267** with an excess of  $\text{Bu}^n\text{Li}$  in toluene at room temperature to afford the unknown, symmetrically substituted tris(dimethylphosphino)trimethylenemethane dianion **268**, which crystallized with  $[\text{Li}_3\text{OC}(\text{CH}_2\text{PMe}_2)_3]^{2+}$  as a counterion <2001CC1024> (Equation (50)).

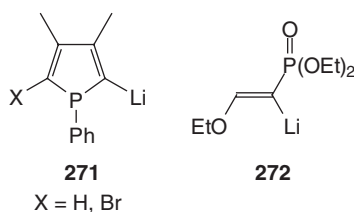


The X-ray structure of the latter showed that each lithium was coordinated to one of the phosphino groups and to a methylene carbanionoid carbon of an adjacent dianion. Thus, the lithium is tetra-coordinate, being bonded to one oxygen, two phosphorus, and one carbon atom.

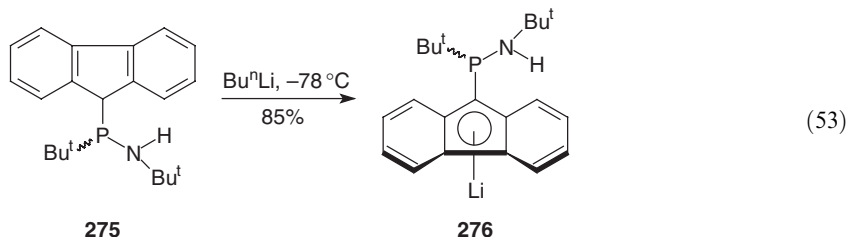
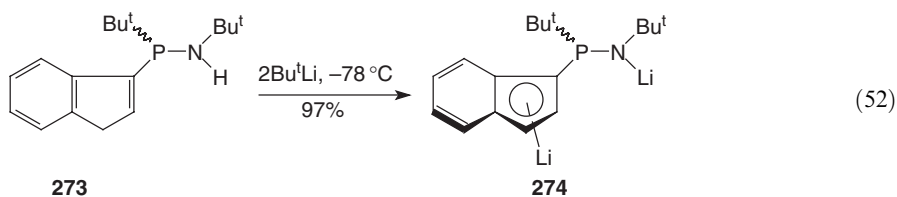
Wang and co-workers synthesized 1-lithioethenylphosphine oxides **270** in the regioselective manner from the corresponding 1-iodoethenyl phosphine oxides **269** and utilized in the alkenylation of aldehydes and ketones <1999JOC1650> (Equation (51)).



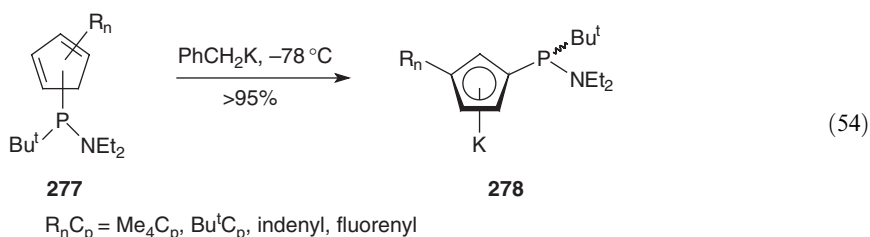
Other lithio derivatives with a defined stereochemistry, i.e., 2-lithio-3,4-dimethylphospholes **271** and diethyl 1-lithio-2-ethoxyethenylphosphonate **272**, were synthesized and reacted with electrophiles <1996BSF33, 2002PSS(177)1953>. Other systems were reviewed earlier in Section 4.22.3.1.1.



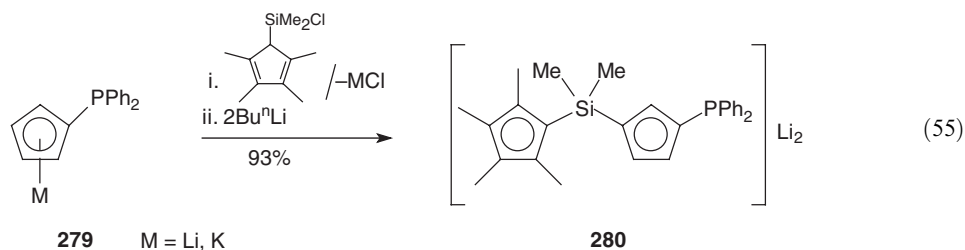
The lithium salts **274** and **276** were prepared on treatment of **273** and **275** with  $\text{Bu}^t\text{Li}$  and  $\text{Bu}^n\text{Li}$ , respectively. Silylation of the resulting fluorenyllithium occurred at the carbon  $\alpha$  to the phosphorus <2002EJI678> (Equations (52) and (53)).



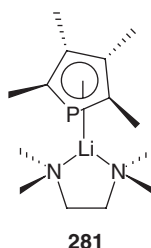
Similarly, cyclopentadienyl, indenyl, and fluorenyl potassium salts **278** were synthesized by deprotonation of **277** with  $\text{PhCH}_2\text{K}$  in yields exceeding 95% (Equation (54)).

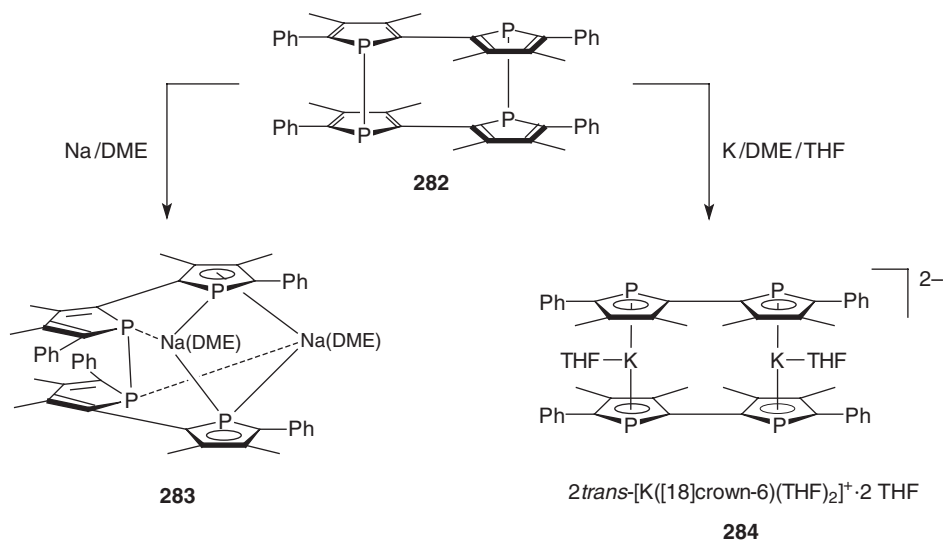


The synthesis of dilithium derivative **280** of asymmetrically substituted cyclopentadienyl *ansa* ligand was also reported in 93% yield starting from lithium or potassium cyclopentadienide **279** <2001OM71> (Equation (55)).



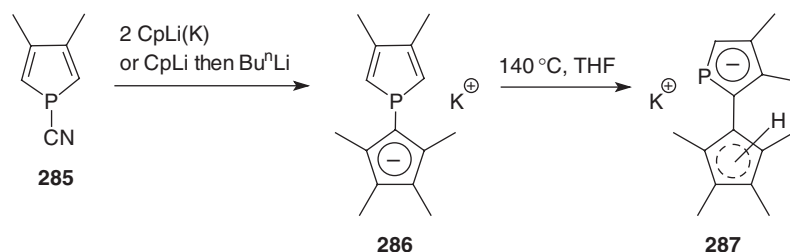
The first crystallographically characterized alkali metal phospholide was lithium tetramethylphospholide **281** obtained from the reaction of the corresponding *P*-chlorophosphole with an excess of lithium and TMEDA in THF at room temperature via the 1,1'-bisphospholyl intermediate <1989AG(E)1367>. This method was applied to the synthesis of sodium **283** and potassium **284** phospholides via the cleavage of one or two P—P bonds of the phosphole tetramer **282** possessing two 1,1'-bisphosphole units <1996AG(E)1125> (Scheme 35).





Scheme 35

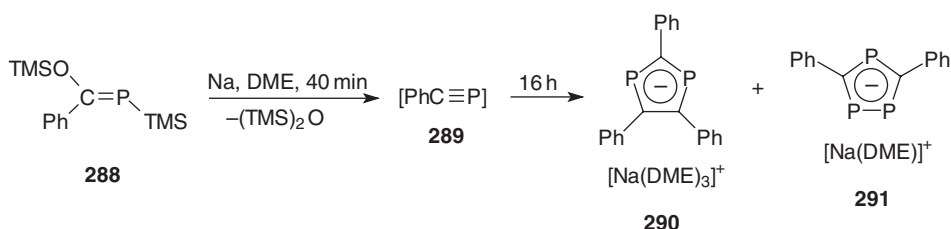
The potassium *P*-cyclopentadienide **286**, obtained from 1-cyano-3,4-dimethylphosphole **285** in 90% yield, underwent the migration of the 2,3,4,5-tetramethyl-1-cyclopentadienylidene substituent from phosphorus to the  $\alpha$ -carbon atom to give three possible isomers of the Cp-substituted phospholide **287** on heating at 140 °C overnight in THF [\[2001OM5513\]](#) (Scheme 36).



Scheme 36

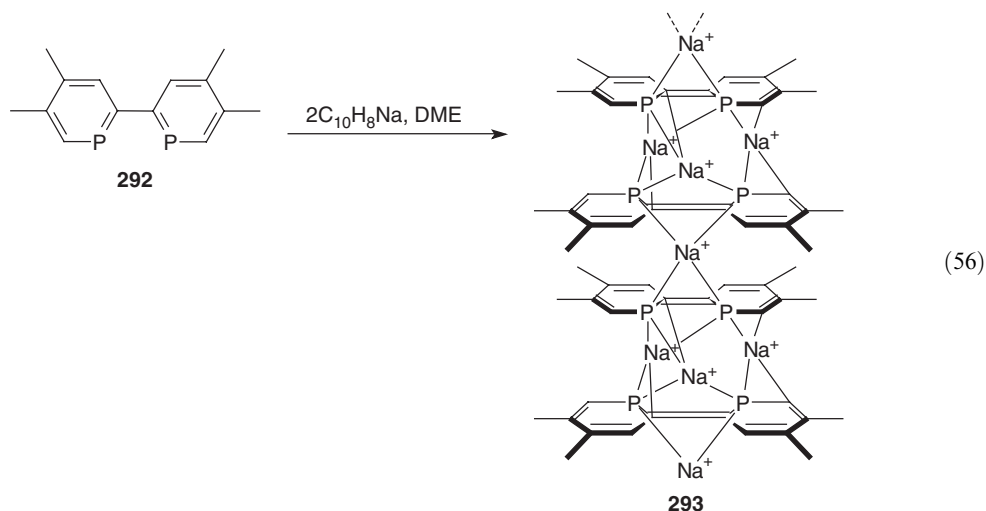
Finally, it is worthwhile to mention the synthesis of some other specific alkali metal phospholides. For instance, a sterically crowded potassium 2,5-di-*t*-butyl-3,4-dimethylphospholide was synthesized from the corresponding Ph-substituted phosphole [\[2002CC1646\]](#), and lithium benzophospholide anion obtained from bis(phosphonio)benzo[*c*]phospholide **68** and lithium naphthalenide [\[1999EJI1169\]](#).

Schmützer and co-workers synthesized sodium phenyl-substituted di- and tri-phospholides **290** and **291** in the reaction of the phosphalkene **288** with an excess of sodium. Phenyl phosphacetylene **289**, detected by <sup>31</sup>P-NMR ( $\delta_{31\text{P}} = -31.8$  ppm) as an intermediate with a half-life of 7 min, gave a 1:1 mixture of **290** and **291** after 16 h [\[1996JOM\(512\)141\]](#) (Scheme 37).

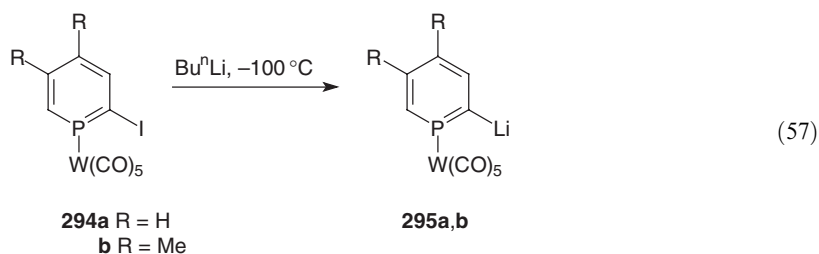


Scheme 37

Six-membered derivatives of phosphinines and group 1 metals are known. An interesting polymeric structure **293** was obtained in the reduction reaction of 4,4',5,5'-tetramethyl-2,2'-biphosphinine **292** with sodium/naphthalene in dimethoxyethane at room temperature <2001AG(E)4476> (Equation (56)). In this structure two sodium cations are bound to the two P atoms of one molecule and in an  $\eta^2$ -fashion to a P—C bond in the second molecule of the ligand. Although the interactions of sodium cations and the reduced ligand are mainly electrostatic in nature, the polymeric structure **293** may be formally qualified to the group of metallophosphinoethenes. The reaction of **292** with the lithium/naphthalene system in the presence of cryptand [2.2.1] yielded only the monomeric complex.



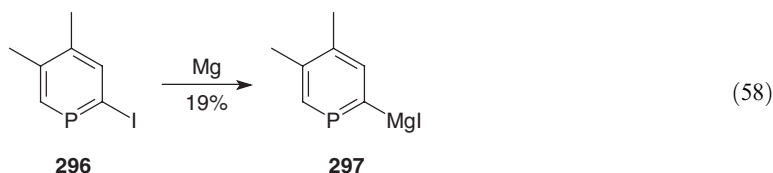
The  $\sigma$ -C-Li bonding was observed in 2-lithio-*P*-pentacarbonyltungsten phosphinines **295a,b** which were obtained via the iodine-lithium exchange from 2-iodo derivatives **294a,b** on treatment with *n*-butyllithium at  $-100^\circ\text{C}$ . The 2-lithio complexes could be detected at this temperature by  $^{31}\text{P}$ -NMR spectroscopy but decomposed thermally at  $-70^\circ\text{C}$ . The lithiation of *P*-uncoordinated 2-iodophosphinines did not occur <1996OM794> (Equation (57)).



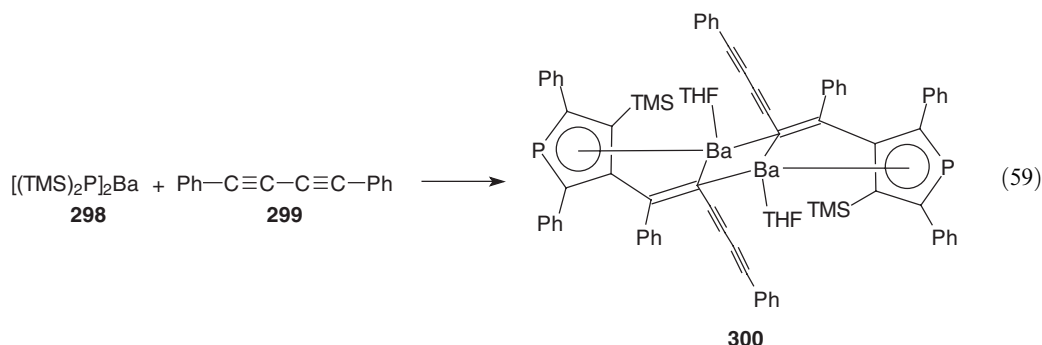
Treatment of dimethylphosphino-4,5-dimethylphosphinine **86** with methyl lithium led to the intermediate delocalised carbanion **95** which was characterized by  $^{31}\text{P}$ -NMR <1996OM1597> (Equation (7)).

#### 4.22.4.1.2 Group 2 metals

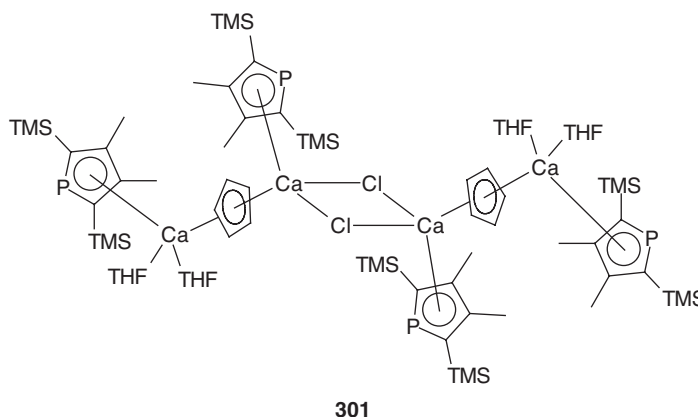
Before 1995 compounds containing the group 2 metals were already known, and more compounds with Mg, Ca and even heavier Ba have since emerged. Based on the limited data, it seems that these compounds are unstable in a monomeric form and tend to adopt more stable dimeric structures. No examples with Be and Sr were reported. Thus, the phosphinine Grignard reagent **297** was synthesized in 19% yield from the corresponding 2-iodo phosphinine **296** as one of the three products identified. It decomposed slowly at room temperature (Equation (58)) <1996OM794>.



The reaction of the barium salt **298** with diphenylbutadiyne **299** yielded the dimeric complex **300** with a unique three-center two-electron Ba—C—Ba bond. The coordination sphere of barium contained phospholide, tetrahydrofuran, and alkenide moieties. The latter bridged two barium atoms with Ba—C bond lengths of 2.881 and 3.071 Å [\[1998JA6722\]](#) (Equation (59)).



The dimeric structure **301** containing the phospholide calcium moieties was also synthesized [\[1999OM2491\]](#).

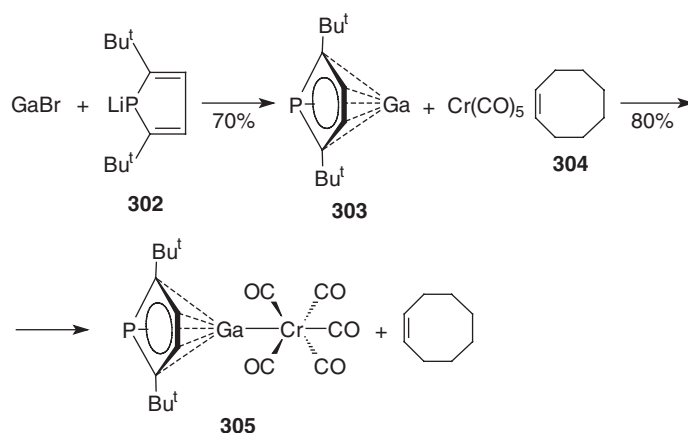


#### 4.22.4.1.3 Group 13 metals

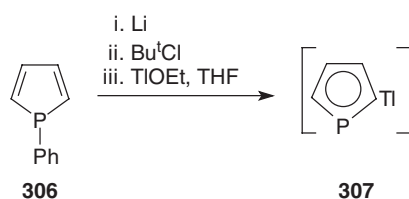
Only Ga- and Tl-containing compounds have been synthesized so far. Compounds of indium are still unknown.

$\eta^5$ -Phospholylgallium **303** was the first synthesized monomeric polyhapto compound between a phospholyl ligand and a main group metal (with the exception of alkali metal complexes) [\[1999AG\(E\)1646\]](#) (Scheme 38). It was obtained in the condensation of gallium(I) bromide with the lithium phospholide **302** at  $-78^\circ\text{C}$  in 70% yield as the main product. Further reaction, with the chromium pentacarbonyl-cyclooctene complex **304**, afforded yellow crystals of the bimetallic complex **305** in 80% yield.

The yellow polymeric structure of the thallium phospholide **307** possessing the thallium  $\eta^5$ -bonded to both sides of the phospholyl ring as revealed by X-ray analysis, was obtained via the lithium cleavage of 1-phenyl phosphole **306** followed by the lithium/thallium exchange with thallos(I) ethoxide [\[2001OM3884\]](#) (Equation (60)).



Scheme 38

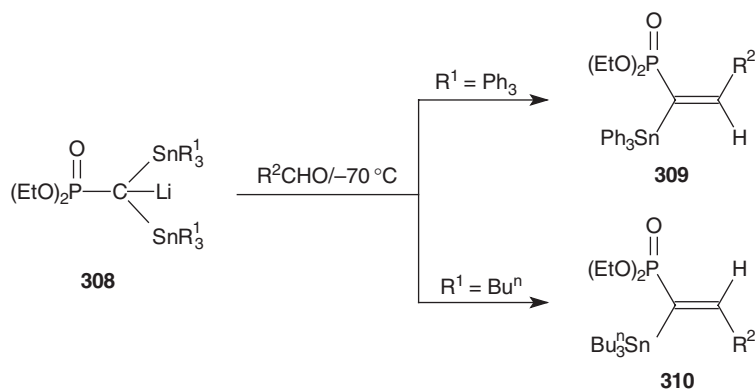


(60)

#### 4.22.4.1.4 Group 14 metals

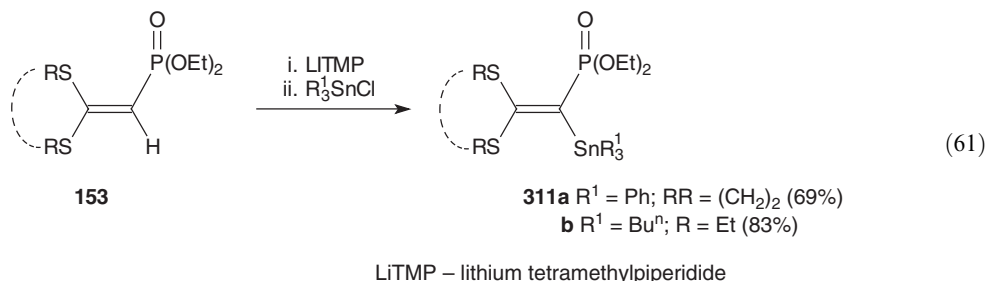
Two representatives (Si, Ge) of the group 14 elements are metalloids and have already been mentioned in Section 4.22.3. Two remaining metallic elements (Sn, Pb) of this group are presented below.

Collignon and co-workers carried out a stereoselective and convenient synthesis of (*E*)-1-triphenylstannyl or (*Z*)-1-tri-*n*-butylstannyl-1-alkenylphosphonates **309** and **310** using a “tin-Peterson-like” reaction <1995SC1921> (Scheme 39). Thus, the key reagent diethyl distannyllithio methylphosphonate **308**, was easily prepared via distannylation of diethyl methylphosphonate with tri-*n*-butyl- or triphenyltin chloride. Subsequent reaction of **308** with aromatic or aliphatic aldehydes at  $-70^{\circ}\text{C}$  showed a regioselectivity depending on the substituent  $\text{R}^1$  in the stannyl group  $\text{SnR}_3^1$ . Actually, with aromatic aldehydes, the triphenylstannyl group led predominantly to the (*E*)-**309** isomer, while in contrast the tri-*n*-butylstannyl group favored the formation of the (*Z*)-**310** isomer.

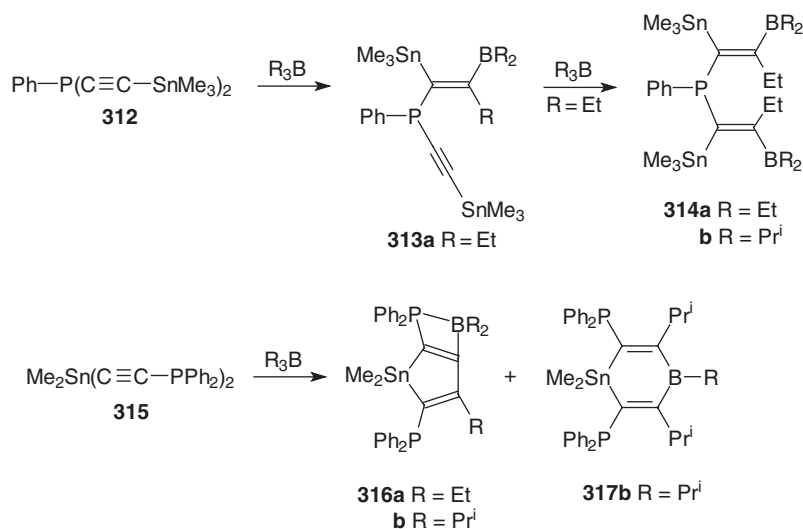


Scheme 39

1-Lithiovinylphosphonates obtained via lithiation of vinylphosphonates **153** with lithium tetramethylpiperide were trapped with stannyl chlorides to give **311** <1998JOC6239> (Equation (61)).



Wrackmeyer and co-workers described 1,1-organoboration of stannylethynylphosphines <1994PSS(91)229>. The reaction of **312** with 1 equiv. of  $\text{Et}_3\text{B}$  gave selectively the (*Z*)-alkene **313a**, and in the presence of excess of  $\text{Et}_3\text{B}$  the bis(alkenyl)phosphine **314a** was formed. Treatment of **312** with bulky  $\text{Pr}^i_3\text{B}$  afforded only **314b** even with a large excess of the borane. The analogous set of reactions was carried out with the alkyne **315**. Thus, the reaction of **315** with an excess of  $\text{Et}_3\text{B}$  gave quantitatively the stannole **316a**, while the reaction with  $\text{Pr}^i_3\text{B}$  gave a 2:1 mixture of the stannole **316b** and the 1-stanna-4-bora-2,5-cyclohexadiene **317b** (Scheme 40).

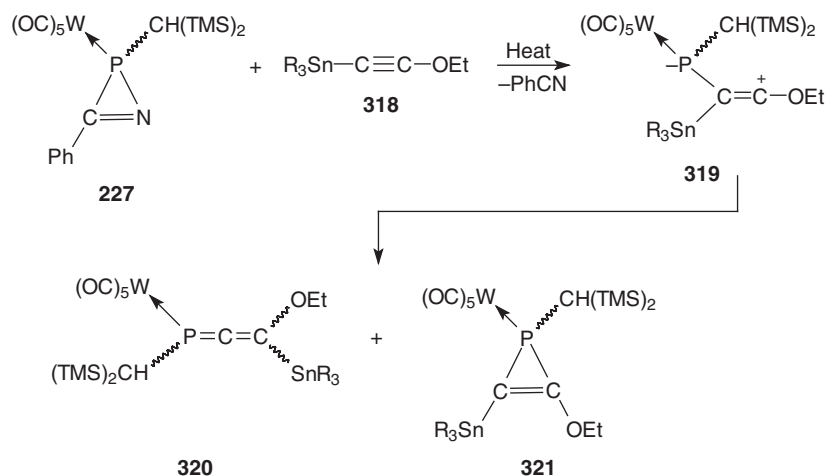


Scheme 40

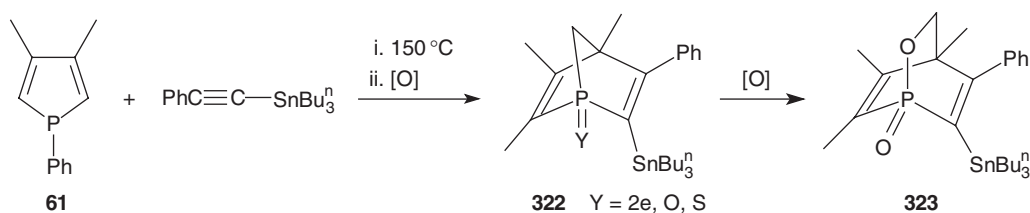
Streubel and co-workers reported the first example of the competitive formation of the tungsten  $\eta^1$ -1-phosphaallene **320** and 1*H*-phosphirene **321** complexes obtained by thermal decomposition of the 2*H*-azaphosphirene complex **227** in the presence of triorganostannyl(ethoxy)acetylenes **318** ( $R = \text{Me}, \text{Ph}$ ). The reaction proceeded via the intermediate formation of the zwitterionic products **319**, which were regarded as common precursors of the final products **320** and **321**. The analogous  $\text{Mo}(\text{CO})_5$  derivatives were also obtained <1998CC1761, 1999ZAAC102> (Scheme 41).

Another use of alkynylstannanes was the reaction of 1-tri-*n*-butylstannyl-2-phenylethyne with 3,4-dimethyl-1-phenylphosphole **61** at 150 °C which afforded 2-stannyl-1-phosphanorbornadiene **322** ( $Y = 2e$ ) in 90% yield. Mild oxidation of the latter gave the corresponding phosphine oxide **322** ( $Y = \text{O}$ ). More drastic oxidation ( $\text{K}_2\text{O}_2$ , 15% in toluene, 80 °C) induced the oxidative cleavage of the  $\text{P}-\text{CH}_2$  bridge and insertion of oxygen to give the strain-released phosphinate derivative **323** <1998EJO2683> (Scheme 42).



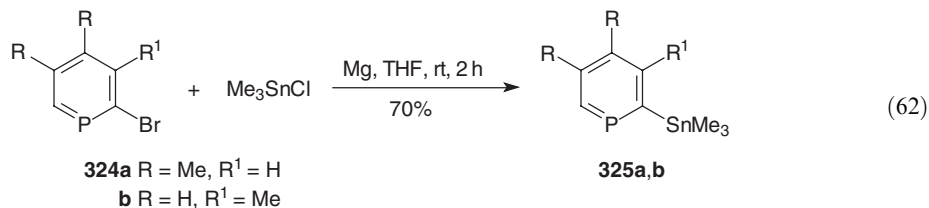


Scheme 41



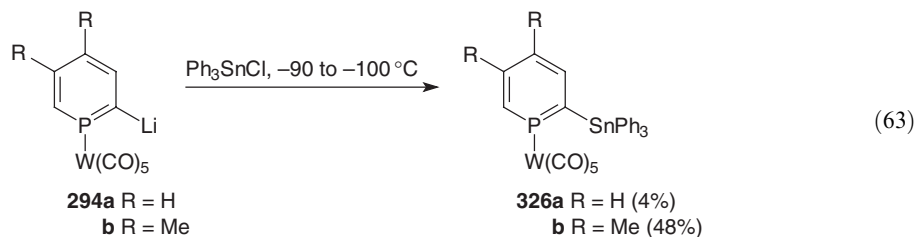
Scheme 42

The synthesis of **322** ( $Y = 2e$ ), its oxidation and sulfurization ( $Y = 2e$  and  $Y = O$ ) are mentioned in the patent literature <1999WOP9947530>. Although some 2-stannylphosphinines have already been described in the literature before 1995, Mathey and co-workers prepared the phosphinines **325a,b** by a variation of the organomagnesium route, used previously for the large scale synthesis of silyl and polysilylphosphines <1995S717, 1992BSF291> (Equation (62)).

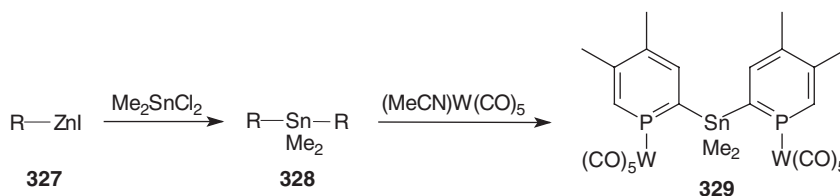


The iodo-Grignard reagent **297** treated with chlorotriphenylstannane also gave the Ph analog of **325a** <1996OM794>.

2-Lithio-1-pentacarbonyltungsten phosphinines **294a,b** were also utilized in Li/Sn transmetalation reactions with chlorotriphenylstannane to give the corresponding 2-stannyl derivatives **326a,b** in 4% and 48% yields, respectively <1996OM794> (Equation (63)). The stannyl compounds were found to be much more stable than their lithio-congeners.



Bickelhaupt and Teunissen used organozinc reagents **327** for the transmetallation reaction with various tin chlorides. The reaction of **327** with chlorotriphenylstannane gave the known phenyl analog **325a** while the reaction with dichlorodimethylstannane gave diphosphinine stannane **328** <1996OM802> (Scheme 43).



Scheme 43

The pentacarbonyltungsten complex **329** was also synthesized from **328** and (acetonitrile)pentacarbonyltungsten.

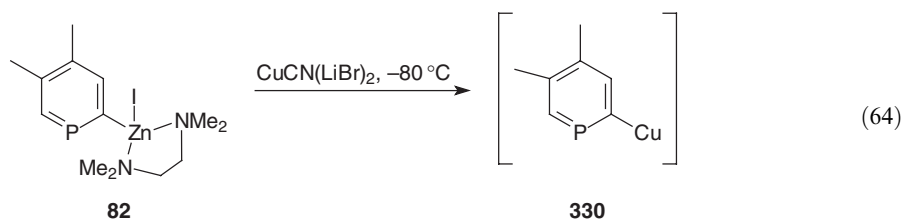
Bis[2,5-di-(*t*-butyl)]-1,1'-diphosphaplumbocene and tinocene were synthesized in a standard way from the corresponding lithium phospholide and  $\text{MX}_2$  ( $\text{M} = \text{Pb}, \text{Sn}$ ) <1999CC1273>.

#### 4.22.4.2 Transitional Metals (Groups 3–12 Metals), $\text{R}_2\text{C}=\text{C}(\text{PR}_2)_2\text{PdX}_2$ , etc.

##### 4.22.4.2.1 $\sigma_{\text{C}=\text{C}}$ -Bonded compounds

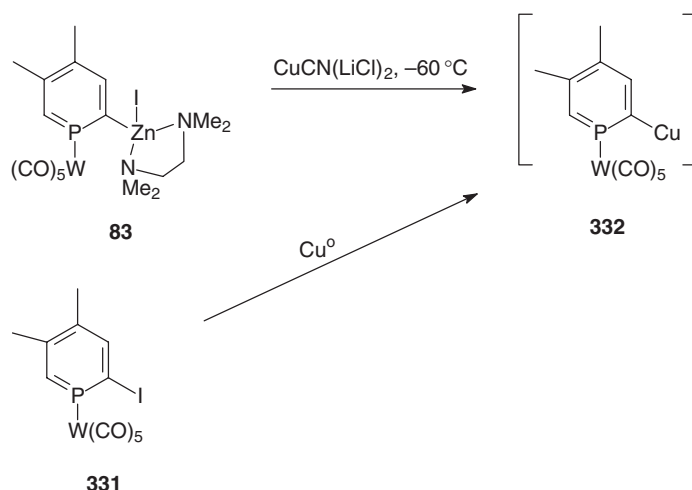
In the case of trifunctional 1-*P*-1-heterosubstituted alkenes involving additional coordination to a transition metal through a double bond, preference will be given to a heteroatom and not to the metal in the discussion below. Thus, for instance, the synthesis of 1,1'-diphosphaferrocene will be discussed in this chapter, while synthesis of the TMS-substituted 1,1'-diphosphaferrocene has already been mentioned in Section 4.22.3.

Organocopper phosphinine **330** and its pentacarbonyltungsten complex **332** were synthesized by Bickelhaupt and Teunissen via transmetallation reactions of the respective phosphinines **82** and **83** with copper(I) salts (Equation (64) and Scheme 44). Both organocopper phosphinines **330** and **332** were obtained at  $-60^\circ\text{C}$  to  $-80^\circ\text{C}$  and found to be unstable at higher temperatures. For instance, the compound **332** decomposed completely at room temperature within 6 h <1996OM802>. In an alternative approach, the complex **332** was obtained by the reaction of **331** with highly reactive metallic copper(0) prepared *in situ* (Scheme 44).

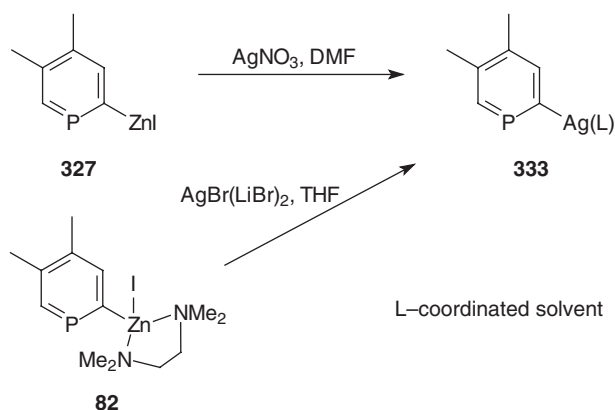


Transmetallation of organozinc phosphinines **327** and **82** with silver salts ( $\text{AgNO}_3$  or THF-soluble  $\text{AgBr} \cdot 2\text{LiBr}$ ) was carried out with limited success since the resulting organosilver derivatives **333** are unstable at room temperature as their Cu analogs <1996OM802> (Scheme 45).

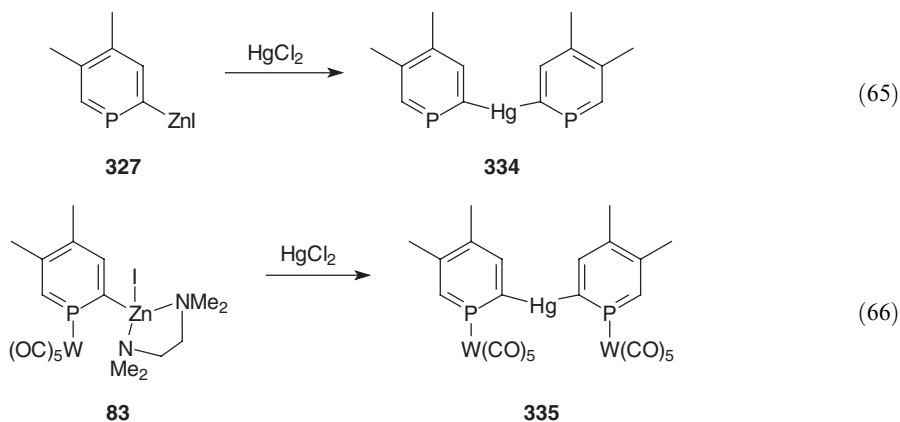
Organomercury phosphinines **334** and **335** were synthesized in a similar manner starting from organozinc phosphinines **327** and **83** via transmetallation of organozinc phosphinines **327** and **83** with  $\text{HgCl}_2$  <1996OM802> (Equations (65) and (66)).



Scheme 44



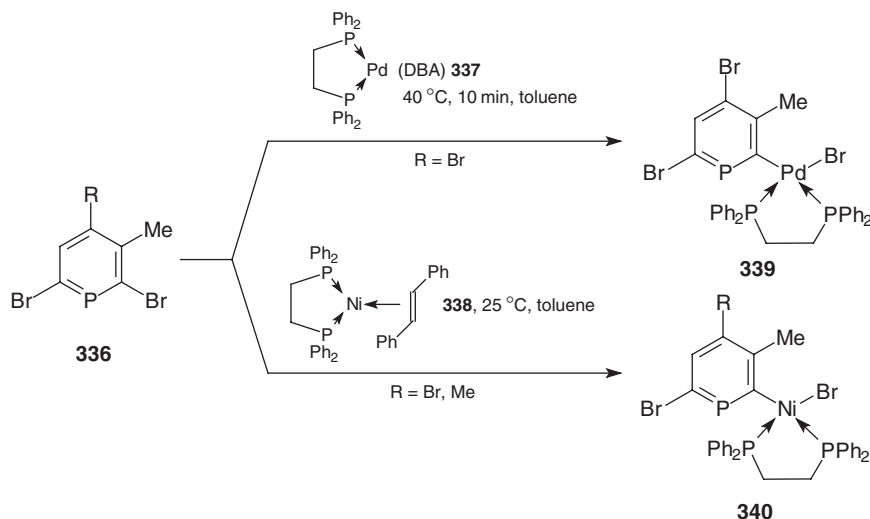
Scheme 45



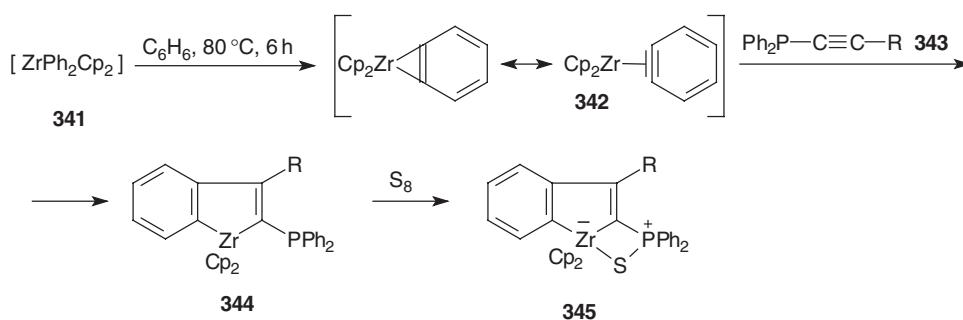
Mathey and co-workers regioselectively inserted palladium(0) and nickel(0) complexes **337** and **338** into the  $\text{C}_\alpha\text{—Br}$  bond of 2,6-dibromophosphenines **336** opening a versatile route to  $\alpha$ -functionalized phosphines **339** and **340**. The new complexes obtained were solids, fully characterized by spectroscopic methods and X-ray analysis <1995S717> (Scheme 46).

Recently, the P/Zr chemistry has been developed intensively by the group of Majoral. For instance, treatment of the alkynylphosphinine **343** with the zirconocene **341** in benzene at  $80^\circ\text{C}$  led to the formation of a phosphinozirconindene **344** as a result of the regioselective insertion of the C—C triple bond into a Zr—C bond of the transient benzene zirconocene **342** <1997CC279>

(Scheme 47). Addition of elemental sulfur to **344** afforded the corresponding sulfide **345** which was analyzed by X-ray diffraction. The insertion reaction mentioned above was also extended to bis(alkynyl)phosphines.



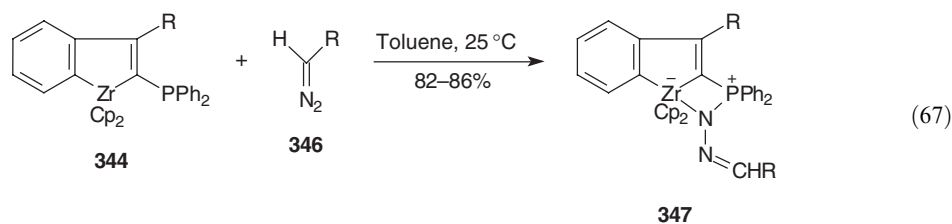
Scheme 46



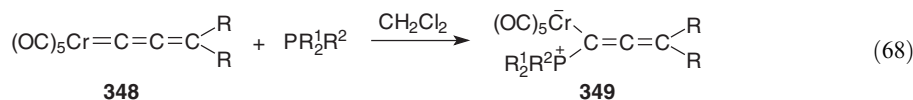
Scheme 47

Many other examples of reactions involving **342** and **344** also came from the group of Majoral and have recently been reviewed [\[2002TCC53\]](#). Various cycloaddition reactions involving 2-phosphinozirconaindene **344** were also described: [3 + 1]-cycloaddition with azides and [3 + 2]-cycloadditions with aldehydes, alkynes, and heterocumulenes (CO<sub>2</sub>, CS<sub>2</sub>, RN=C=NR, RNCO, RNCS) to give 18 electron zirconate complexes of type **345**. Moreover, practical applications of multiple [3 + 2]-cycloadditions involving **344** and dendrimers with terminal or internal aldehyde groups were shown to exemplify the utility of this kind of phosphorus-zirconium chemistry. Finally, syntheses of 2-zirconaphosphinines and  $\eta^2$ -phosphabenzynes-zirconocene dimers were also described.

In 2003 Majoral and co-workers published further examples of the addition of diazoalkanes **346** (R = CO<sub>2</sub>Et, TMS) to **344** to give the corresponding zirconates **347** [\[2003NJC675\]](#) (Equation (67)).

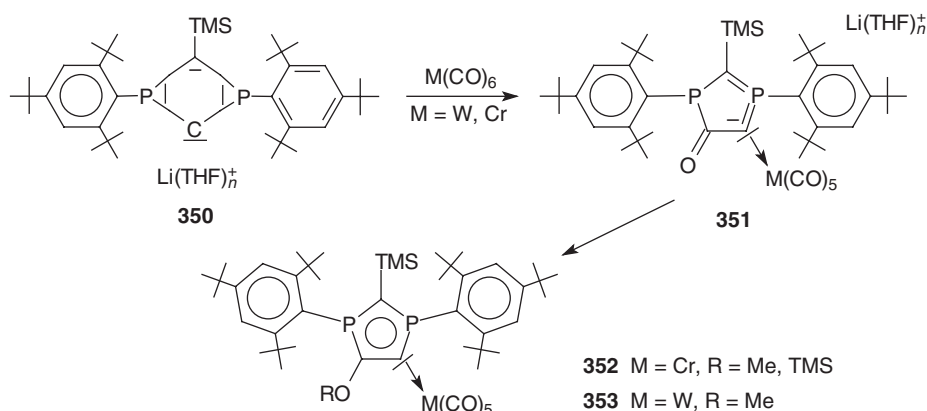


Fischer and co-workers reported the addition of various phosphines to the allenylidene (penta-carbonyl) chromium complexes **348**, which occurred at the  $C_\alpha$  giving the ylide complexes **349** <1995JOM(490)221> (Equation (68)).



The stability of the resulting complexes **349** depended on the nature of substituents. In some cases they could be isolated ( $\text{R} = \text{C}_6\text{H}_4\text{NMe}_2\text{-}p$ ,  $\text{R}^1 = \text{R}^2 = \text{Me}$ , 76% yield). At room temperature they rearranged to the P—Cr allenylphosphine complexes ( $\text{R} = \text{C}_6\text{H}_4\text{NMe}_2\text{-}p$ ,  $\text{R}^1 = \text{R}^2 = \text{H}$ ) followed by isomerization to P—Cr alkynylphosphine complexes ( $\text{R} = \text{C}_6\text{H}_4\text{NMe}_2\text{-}p$ ,  $\text{R}^1 = \text{H}$ ,  $\text{R}^2 = 2,4,6\text{-C}_6\text{H}_2\text{Me}_3$ ) or they underwent [2 + 2]-cycloaddition at the  $C_\beta$  to cyclobutane derivatives.

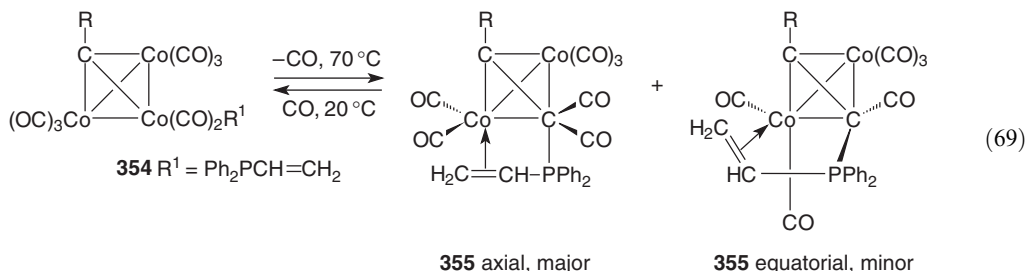
Reaction of the 1,3-diphosphacyclobutane-2,4-diyl-2-ide **350** with chromium or tungsten hexacarbonyl afforded the red anionic complexes **351** ( $\text{M} = \text{W}$ ,  $\text{Cr}$ ) by the formal insertion of CO into the four-membered ring. These complexes further reacted with electrophiles such as  $[\text{Me}_3\text{O}][\text{BF}_4]$  in methylene dichloride or  $\text{TMSCl}$  in THF to afford the neutral complexes **352** and **353** showing almost planar  $\text{P}_2\text{C}_3$  backbone <2002CEJ2188> (Scheme 48).



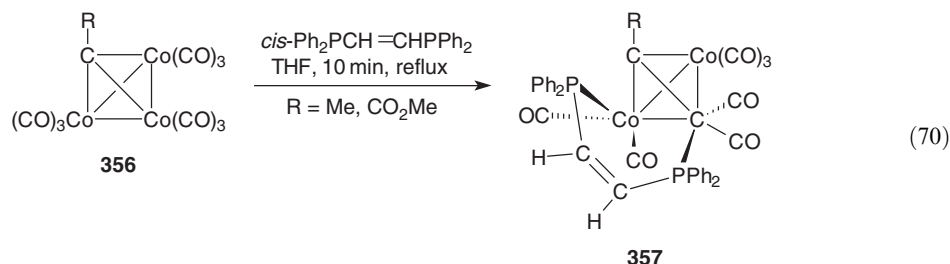
Scheme 48

#### 4.22.4.2.2 $\sigma_{\text{P}-}$ and $\pi_{\text{C}=\text{C}}$ -Bonded compounds

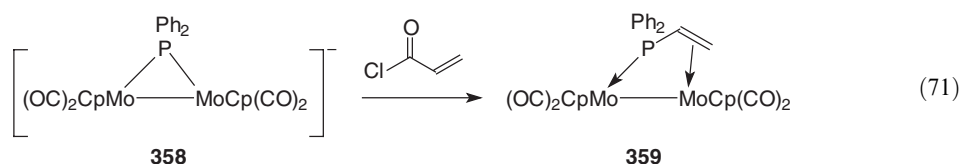
Mays and co-workers reported the thermolysis reaction of the complex **354** ( $\text{R} = \text{Me}$ ,  $\text{CO}_2\text{Me}$ ) in *n*-heptane at  $70^\circ\text{C}$  furnished in each case a mixture of axial and equatorial complexes **355** in a 7:3 ratio <1996JOM(508)137>. The opposite reaction occurred when the reaction mixture containing both isomers **355** was purged with CO at  $20^\circ\text{C}$  (Equation (69)).



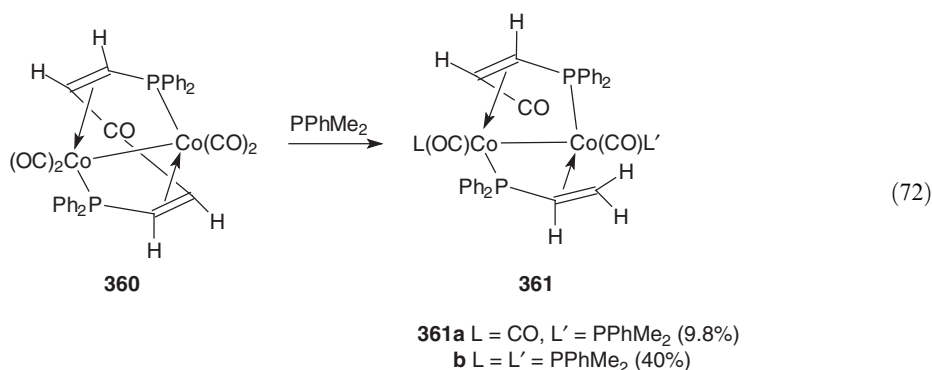
The reaction of **356** ( $\text{R} = \text{Me}$ ,  $\text{CO}_2\text{Me}$ ) with *cis*-1,2-bis(diphenylphosphino)ethene possessing three binding centers (double bond and two P atoms) proceeded in a different way to give the complex **357**, in which coordination to a second phosphorus atom was more favorable than to the double bond as in the compound **355** (Equation (70)).



Mays and co-workers also reported the synthesis of the complex **359** in which the vinyl phosphine acted as a  $\mu\text{-}\eta^1\text{:}\eta^2$  four-electron ligand to a bimetallic fragment [<1999CC2455>](#) (Equation (71)). The complex **359** was obtained as a result of the multistage reaction by treatment of the anionic species **358** with acryloyl chloride.

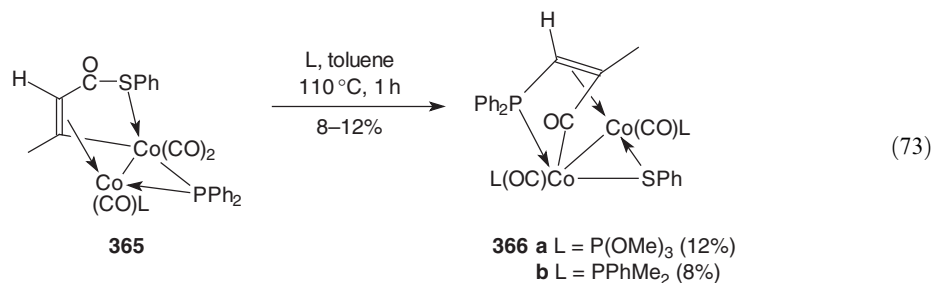


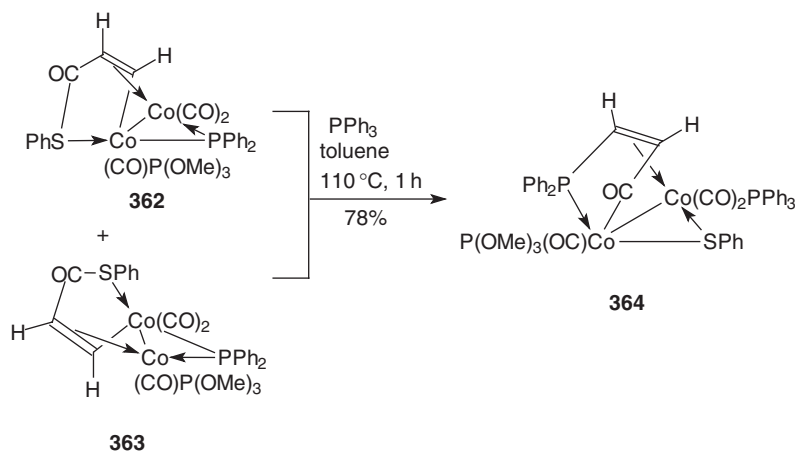
The thermal reactions of diphosphine-substituted dinuclear cobalt carbonyl complex **360** with an excess of the electron donor ligands ( $\text{PPhMe}_2$ ,  $\text{PPh}_2\text{H}$ ,  $\text{P(OMe)}_3$  or  $\text{Bu}^t\text{NC}$ ) in refluxing toluene gave mixtures of mono- and di-substituted complexes of the type **361** in combined yields ranging from 35% to 50%. The mixtures were readily separated by column or thin layer chromatography [<1998ICA186>](#) (Equation (72)). For instance, the reaction of **360** with  $\text{PPhMe}_2$  gave the red-brown complex **361a** ( $\text{L} = \text{CO}$ ,  $\text{L}' = \text{PPhMe}_2$ ) and the dark green complex **361b** ( $\text{L} = \text{L}' = \text{PPhMe}_2$ ) in 9.8% and 40% yield, respectively.



Treatment of an inseparable mixture of two monosubstituted isomeric complexes **362** and **363** with triphenylphosphine in refluxing toluene for 1 h yielded the green complex **364** in 78% yield [<2001JCS\(D\)1269>](#) (Scheme 49).

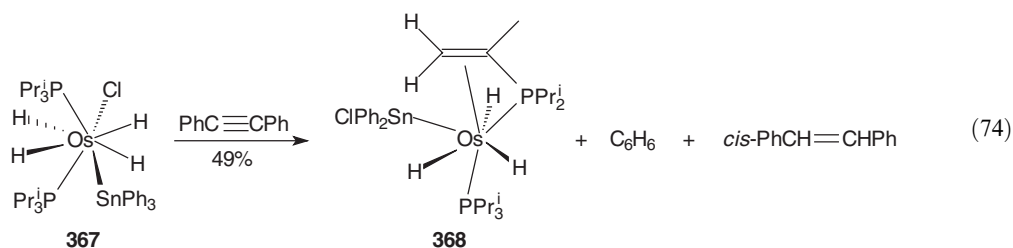
Treatment of **365** with trimethyl phosphite under the same reaction conditions gave a mixture of two compounds of which the minor **366a** was isolated in 12% yield. The analogous reaction was carried out with  $\text{PPhMe}_2$  to give the complex **366b** ( $\text{L} = \text{PPhMe}_2$ ) in 8% yield (Equation (73)).





Scheme 49

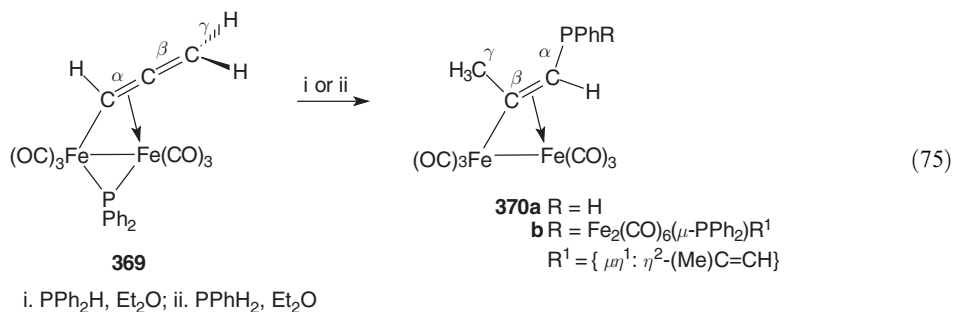
When the osmium complex **367** was reacted with diphenylacetylene in toluene at room temperature, the new yellow complex **368** was formed within 4 h and isolated in 49% yield (Equation (74)).



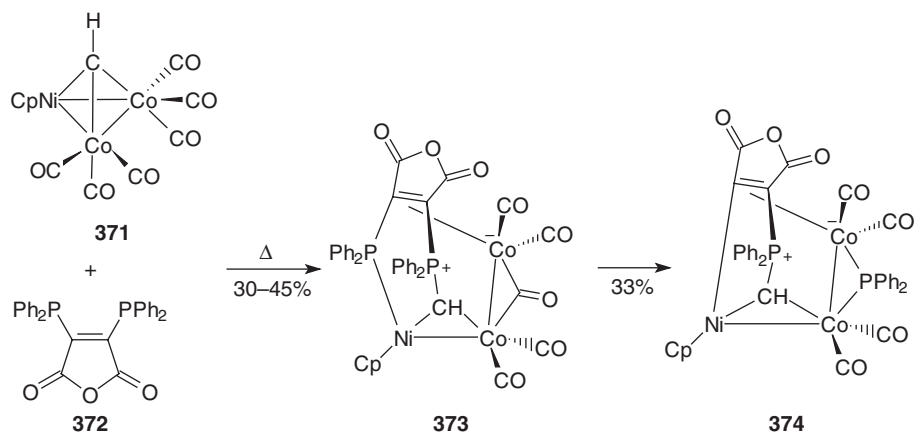
The formation of **368** was a result of multiple complex reactions with the participation of radical-like species as intermediates.

#### 4.22.4.2.3 $\sigma_{\text{C}=\text{C}}$ and $\pi_{\text{C}=\text{C}}$ -Bonded compounds

The binuclear complex **369** reacted with  $\text{PPh}_2\text{H}$  and  $\text{PPhH}_2$  to afford new complexes of the type (**370a,b**) (pathways i and ii) (1996CC1545). The complex **370a** (pathway i) was formed by the 1,3 addition of  $\text{PPh}_2\text{H}$  across the allene fragment while the complex **370b** (pathway ii) was formed via the 1,3-addition of both P—H bonds of  $\text{PPhH}_2$  across 2 equiv. of the allene fragment (Equation (75)).



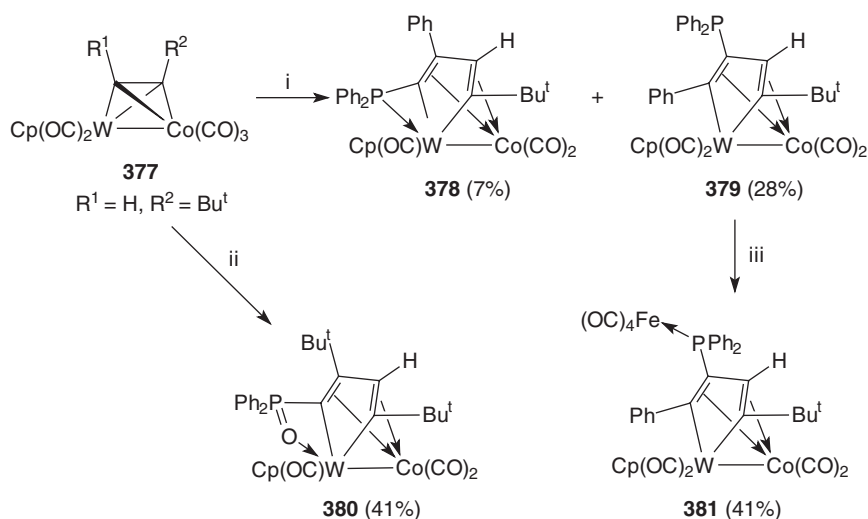
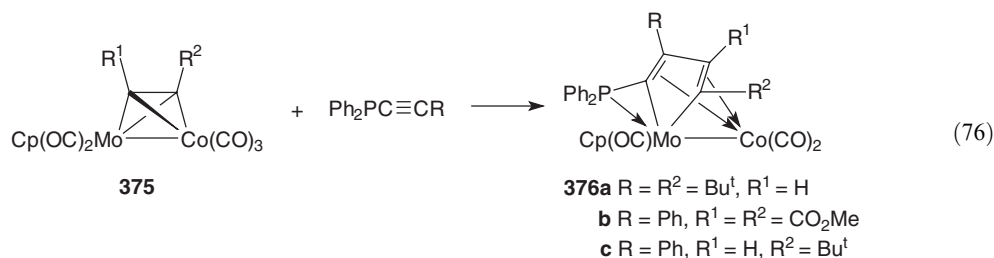
The mixed-metal cluster **371** reacted with the redox-active 2,3-bis(diphenylphosphino)maleic anhydride **372** at  $80^\circ\text{C}$  to afford the new blue-green zwitterionic cluster **373** in 30–45% yield as the initially observed substitution product. This product upon prolonged heating overnight gradually produced the brown-green cluster **374** (2003OM1383) (Scheme 50).



Scheme 50

#### 4.22.4.2.4 $\sigma_P$ , $\sigma_{C=C}$ , and $\pi_{C=C}$ -Bonded compounds

The phosphinoalkyne coupling reaction of the alkyne mixed-metal tungsten–cobalt or molybdenum–cobalt complexes led to the formation of new complexes possessing various combinations of  $\sigma$ - and  $\pi$ -bonding to a double bond and phosphorus (Equation (76) and Scheme 51). Thus, the coupling of the alkyne-bridged Mo–Co complexes **375** with phosphinoalkynes was largely determined by the nature of the substituents of both the reactants and led to the formation of the complexes (**376a–376c**) <2000JCS(D)3331> (Equation (76)).



i.  $\text{Ph}_2\text{PC}\equiv\text{CPh}$ , 110 °C,  $\text{C}_6\text{H}_5\text{Me}$ ; ii.  $\text{Ph}_2\text{PC}\equiv\text{CBu}^t$ , 110 °C,  $\text{C}_6\text{H}_5\text{Me}$ ; iii.  $\text{Fe}_2(\text{CO})_9$ , 60 °C

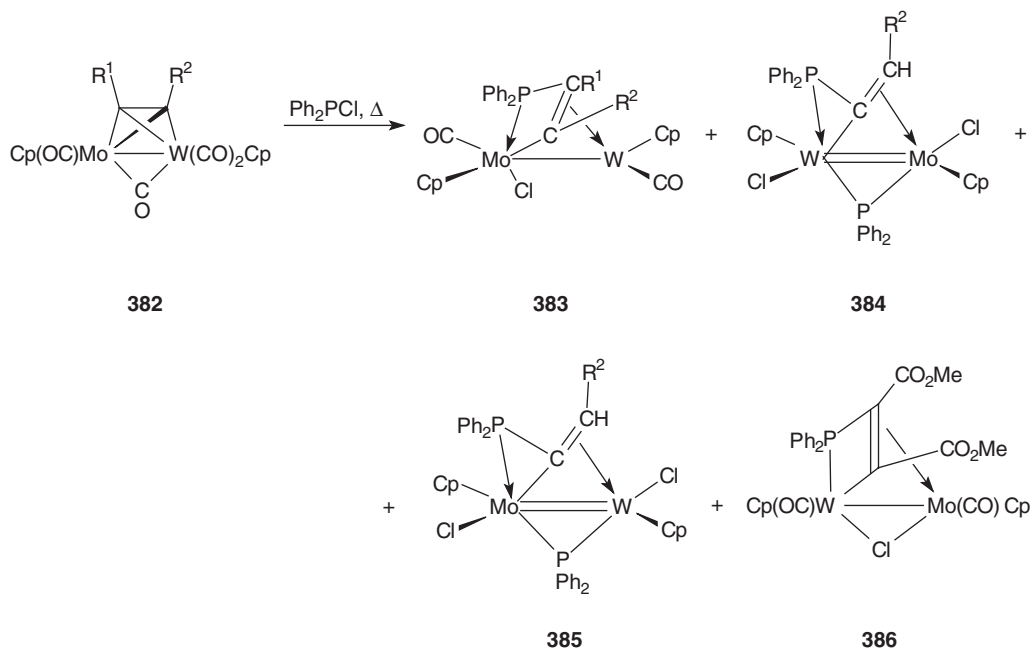
Scheme 51



On the other hand, coupling of the alkyne-bridged W–Co complex **377** with 1-diphenylphosphino-2-phenylethyne afforded a mixture of the regioisomeric complexes **378** and **379** with the C–C double bond coordinated to cobalt. The  $^{31}\text{P}\{-^1\text{H}\}$  NMR spectrum of **378** showed a peak at  $\delta = -56.9$  ppm with satellites due to coupling to  $^{183}\text{W}$  [ $J_{\text{P-W}} = 54$  Hz] indicating that the phosphorus is bound to tungsten rather than to cobalt, while the  $^{31}\text{P}\{-^1\text{H}\}$  NMR spectrum of **379** showed a singlet due to the uncoordinated diphenylphosphino group at  $\delta = -17.1$  ppm.

The reaction of **377** with 1-diphenylphosphino-2-*t*-butylethyne afforded the complex **380**. The source of the oxygen at the P(O) group was uncertain but could either be a carbonyl group, molecular oxygen or water. The anticipated reactivity of the pendant diphenylphosphino group in **379** was realized during its reaction with  $\text{Fe}_2(\text{CO})_9$  in THF to give the complex **381** in 41% yield <2000JCS(D)3331> (Scheme 51).

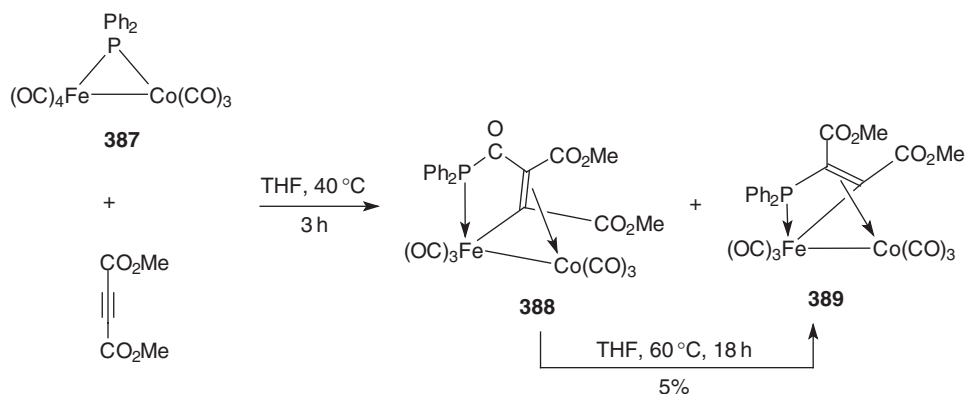
The heterobimetallic complexes **382** underwent a thermal reaction with  $\text{Ph}_2\text{PCl}$  via the initial P–Cl bond cleavage and coupling of the resulting diphenylphosphide unit with an alkyne in one of the four different ways to give the complexes **383** ( $\text{R}^1 = \text{H}$ ,  $\text{R}^2 = \text{Ph}$  or  $\text{R}^1 = \text{R}^2 = \text{H}$  or  $\text{R}^1 = \text{R}^2 = \text{CO}_2\text{Me}$ ), **384** ( $\text{R}^2 = \text{Ph}$  or  $\text{Me}$  or  $\text{H}$ ), **385** ( $\text{R}^2 = \text{Ph}$  or  $\text{Me}$ ), or **386** <1995JCS(D)3049> (Scheme 52).



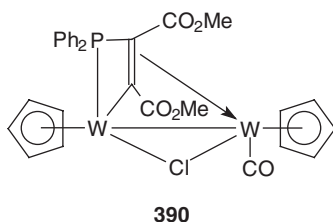
Scheme 52

The iron–cobalt phosphido-bridged complex **387** was subjected to the reaction with symmetrical and unsymmetrical alkynes to give initially the products containing five-membered ferracycle as a result of a regioselective insertion of CO and alkyne into a Co–P bond <2000JOM(601)271>. For instance, treatment of **387** with symmetrical 1,2-bis(methoxycarbonyl)ethyne afforded the five-membered **388** in 27% yield and the decarbonylation product **389** in 24% yield (Scheme 53). The direct conversion of the green-brown complex **388** into the red complex **389** was achieved only in 5% yield.

The new, well-characterized complex **390** is an example of a new class of ditungsten complexes and was obtained under photolytic reaction conditions <1995JCS(D)1597>.

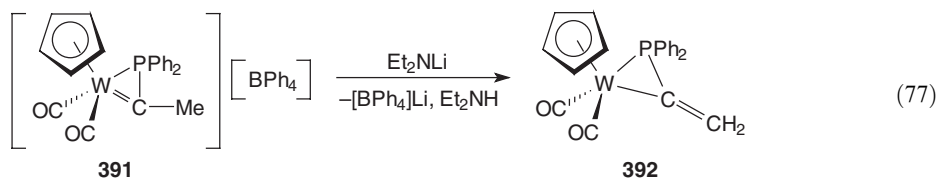


Scheme 53



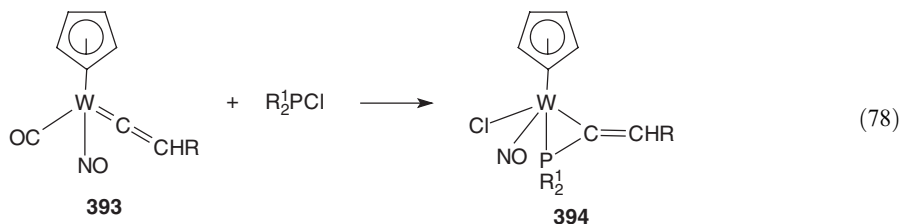
#### 4.22.4.2.5 $\sigma_P$ - and $\sigma_{C=C}$ -Bonded compounds

On treatment of the cationic  $\eta^2$ -complex **391** with Et<sub>2</sub>NLi, the tungsten–carbon double bond migrated into the exo-C–C position to give the new neutral complex **392** <1996JOM(520)59> (Equation (77)).

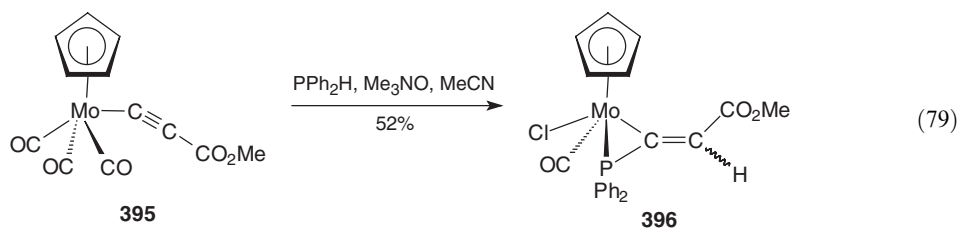


Deprotonation with Et<sub>3</sub>N also gave the same complex <1995JOM(491)283>. In the absence of Na[BPh<sub>4</sub>], a base-induced carbonyl carbene coupling reaction afforded  $\eta^3$ -phosphinoketene complexes <1995CB289>.

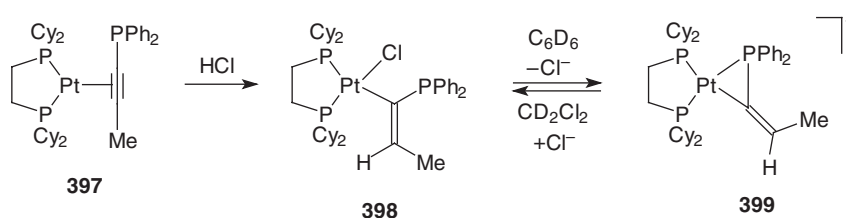
Reaction of the neutral vinylidene complexes **393** (R = H, CH<sub>3</sub>, C<sub>6</sub>H<sub>5</sub>) with chlorodiphenyl phosphine (R<sup>1</sup> = Ph) afforded the neutral complexes **394**. Analogously, the reaction of chloro-di-*t*-butyl phosphine (R<sup>1</sup> = Bu<sup>t</sup>, R = H) with **393** (R = H) gave rise to the bulky complex **394** (R<sup>1</sup> = Bu<sup>t</sup>, R = H). The formation of the metallacyclop propane rings was rationalized by nucleophilic attack of chlorophosphine on the C<sub>α</sub> of the vinylidene followed by chloride–carbon monoxide exchange <2000OM5281> (Equation (78)).



Addition of diphenylphosphine to the molybdenum alkynyl complex **395** afforded a mixture of the (*E*)/(*Z*) addition products **396** in 52% yield <2001JOM(633)125> (Equation (79)).

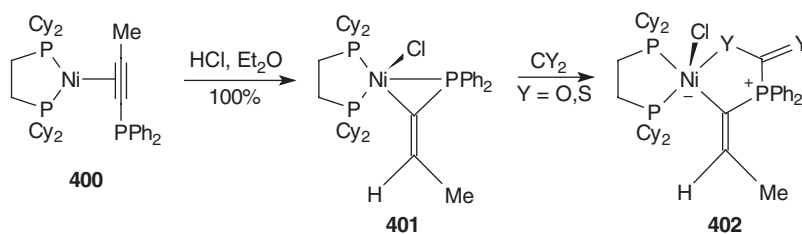


A large number of various platinum complexes differing in structure and metal coordination to the C—C double bond were also prepared based on the  $\eta^2$ -coordinated alkynylphosphine complex **397** <2002JCS(D)226>. The regiospecific addition of hydrogen chloride in benzene formed the tetra-coordinate  $\eta^1$ -vinyl-Pt(II) complex **398** from which the new platinum complex **399** containing a three-membered methylenephosphaplatinacycle fragment was obtained via the reversible dissociation of the chloride ion (Scheme 54).



Scheme 54

On treatment of the  $\eta^2$ -alkynylphosphine complex **400** with HCl (1 equiv.) in diethyl ether, the penta-coordinate nickel(II) complex **401** was prepared as a thermally sensitive red solid <2001OM980> (Scheme 55). Subsequent reactions with carbon dioxide or carbon disulfide gave the corresponding zwitterionic insertion products **402**.

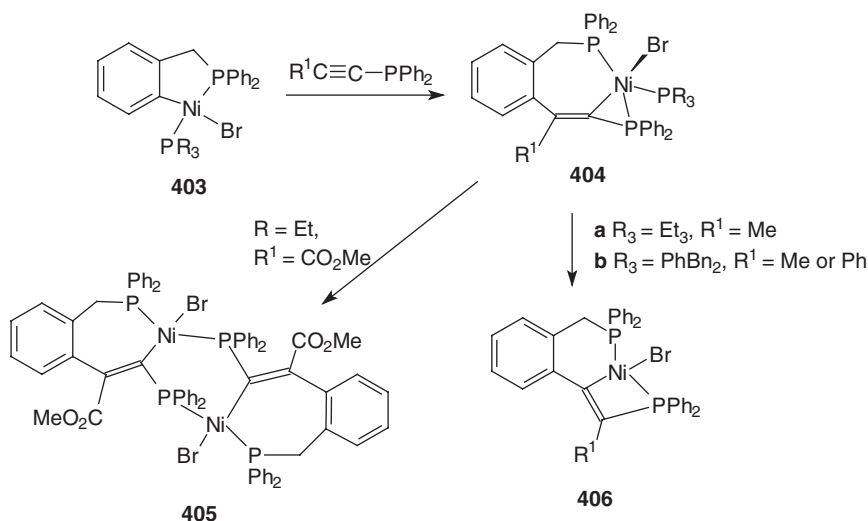


Scheme 55

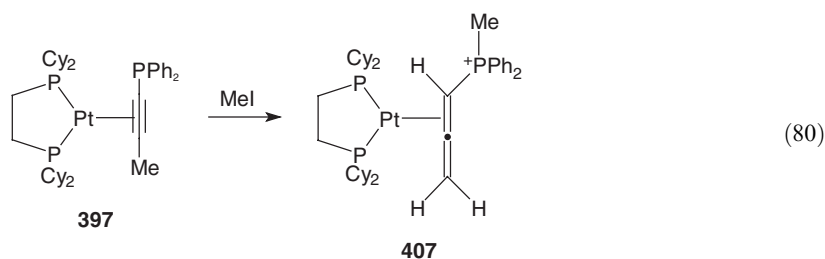
Wenger and co-workers studied regioselective insertion reactions of unsymmetrical phosphinalkynes to the yellow 5-membered phosphanickelacycles **403** ( $R_3 = Et_3$  or  $R_3 = PhBn_2$ ) and obtained new complexes **404** possessing 3-membered alkenylphosphanickelacycles <2001OM2864> (Scheme 56). Depending on substituents R and  $R^1$ , the dimeric structure **405** or four-membered alkenylphosphanickelacycle **406** could be prepared upon further heating of **404**.

#### 4.22.4.2.6 $\pi_{C=C}$ -Bonded compounds

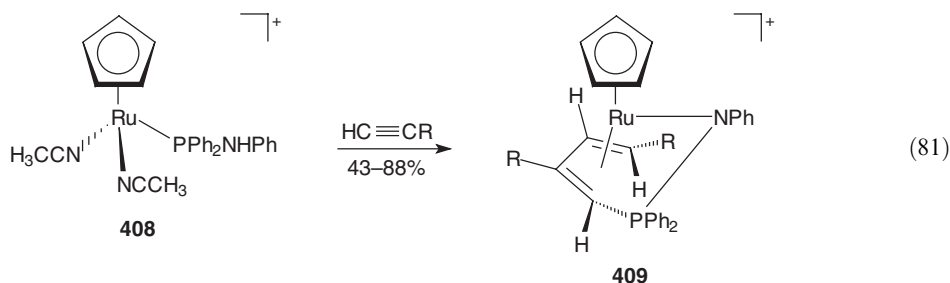
Pure  $\eta^2$ -complexation was observed in the platinum complex of the allenylphosphonium salt **407** prepared from the  $\eta^2$ -coordinated platinum alkynylphosphine complex **397** by methylation with methyl iodide <2001JCS(D)226> (Equation (80)).



Scheme 56

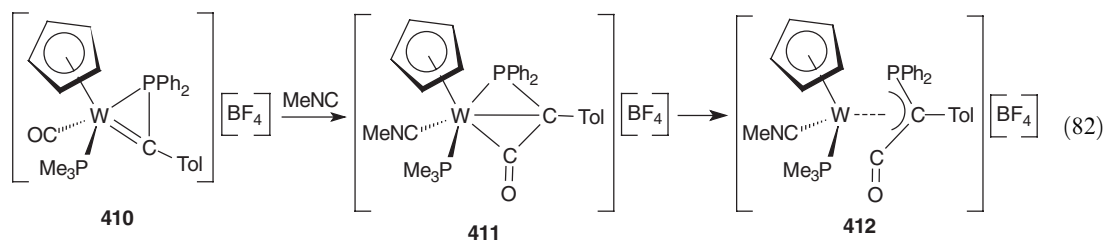


Kirchner and co-workers synthesized  $\eta^4$ -butadiene amido complexes through migration and N—H activation of the  $PPh_2NPh$  ligand. Thus, treatment of the cationic complex **408** with various alkynes ( $R = Ph$ ,  $Bu^n$ ,  $CH_2Ph$ ) resulted in the formation of the corresponding complexes **409** in 43–88% yields [\(Equation \(81\)\)](#). The starting complex **408** was obtained in the reaction of  $[RuCp(CN)_3]PF_6$  with 1 equiv. of  $PPh_2NPh$  at  $100^\circ C$  in 92% yield. In a similar manner cyclic complexes with 1,6-heptadiyne and 1,7-octadiyne were obtained.



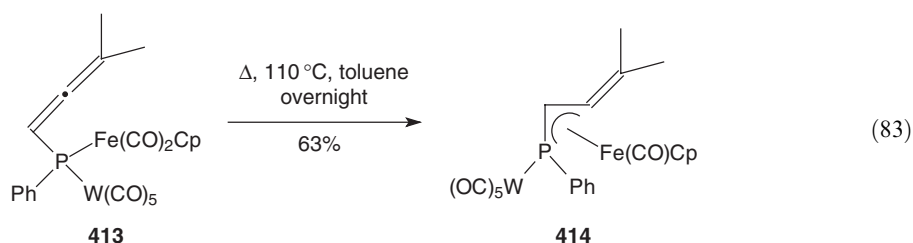
#### 4.22.4.2.7 $\pi_{PCC}$ -Bonded compounds

Cationic  $\eta^2$ -phosphinocarbene complexes **410** reacted at  $-78^\circ C$  with alkyl isocyanides ( $R = Me$ ,  $Bu^t$ ) to provide tungstenaphosphabicyclo[1.1.0]butanone complexes **411**. Besides the description of the complexes as bicyclic systems, the canonical form **412** possessing a planar  $\eta^3$ -allylic arrangement may be considered [\(Equation \(82\)\)](#).



#### 4.22.4.2.8 $\sigma_P$ - and $\pi_{PCC}$ -Bonded compounds

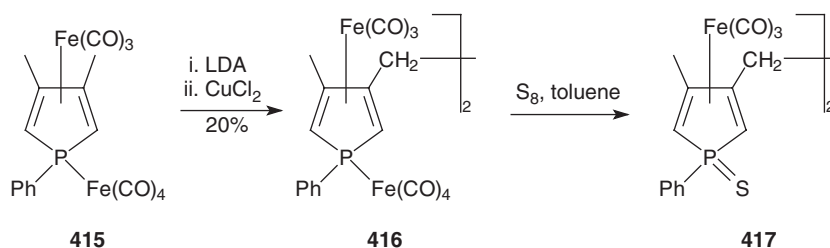
The  $\eta^3$ -1-phosphabutadienyl Fe complex **414** with the phosphorus additionally  $\eta^1$ -bonded to another metal (W) was synthesized by Mathey and co-workers on prolonged heating of the  $\mu$ -phosphido complex **413** in boiling toluene, as the only representative of this new class of compounds till now <2001JOM(617-618)748> (Equation (83)).



#### 4.22.4.2.9 $\pi$ -Half sandwich compounds

##### (i) $\eta^4$ -Phosphole compounds

Mathey and co-workers described functionalization of 1-phenyl-3,4-dimethylphosphole **415** in which the dienic phosphole system and the lone pair of the phosphorus were protected with iron carbonyl groups <2001JOM(624)105> (Scheme 57).

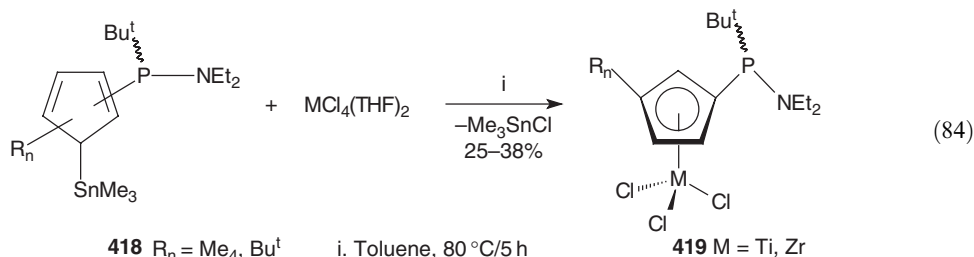


Scheme 57

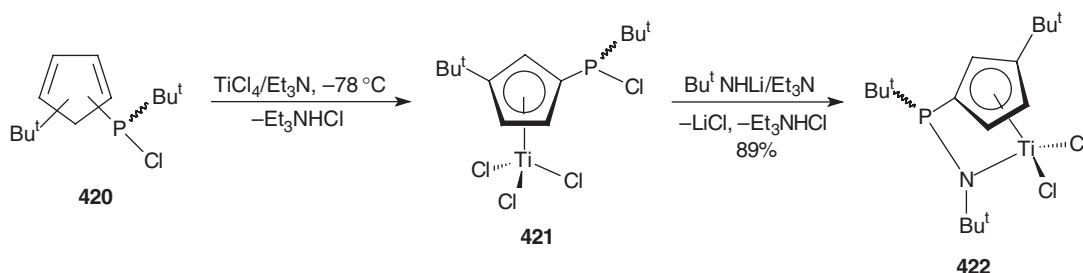
The first stage involved a selective deprotonation of the 3-methyl group in **415** followed by oxidative coupling of the resulting lithium derivative with  $\text{CuCl}_2$  to give the dimer **416**. The  $P$ -protecting iron carbonyl moieties were cleanly removed by treatment with elemental sulfur in refluxing toluene to give **417**. Total decomplexation of the remaining iron carbonyl group  $\text{Fe}(\text{CO})_3$  was achieved with CAN in a dichloromethane/isopropanol mixture. The lithium derivative of **415** also reacted with various electrophiles (MeI, TMSCl, benzophenone,  $p$ -chlorobenzaldehyde, ( $E$ )-cinnamaldehyde) to afford the corresponding expected adducts.

(ii)  $\eta^5$ -Phosphinocyclopentadienyl compounds

Half sandwich titanium and zirconium complexes **419** were prepared in moderate yields through transmetallation reactions starting from trimethyltin derivatives **418** and  $\text{TiCl}_4$  or  $\text{ZrCl}_4$  <2002EJI678> (Equation (84)).



The titanium *P*-chloro complex **421** was prepared via deprotonation of **420** with  $\text{Et}_3\text{N}$  followed by reaction with  $\text{TiCl}_4$  (Scheme 58) <2002EJI678>. This half sandwich complex was further transformed into the constrained complex **422** as a mixture of two diastereoisomers.

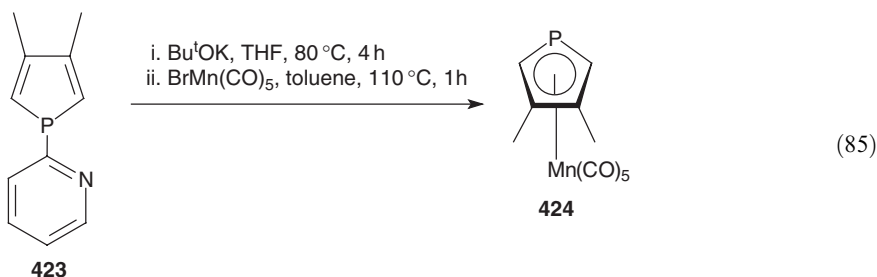


Scheme 58

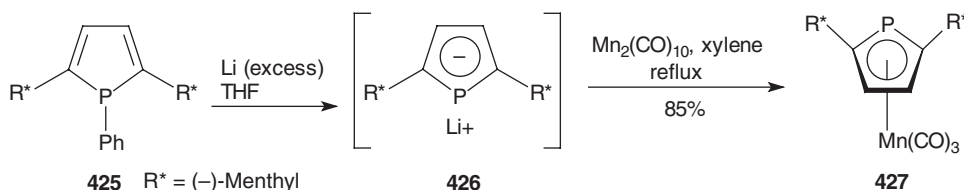
(iii)  $\eta^5$ -Phosphacyclopentadienyl compounds

In this section will be described compounds in which a metal (Mn, Co, Ph, Ir, U) is coordinated to one phosphacyclopentadienyl (phospholide) ring and at the same time either to small molecules [ $\text{CO}$ ,  $\text{BH}_4^-$ ,  $\text{Ph}_3\text{P}$ ,  $(\text{MeO})_3\text{P}$ ] or to the second ring other than cyclopentadienyl (THF, COD, cyclooctatetraenyl, cyclobutadienyl). Accordingly, phosphacymantrenes (metal = Mn) will be mentioned here but metallocenes (a metal coordinated to two cyclopentadienyl rings) will be summarized in the following sections.

Starting from 1-(2'-pyridyl)-3,4-dimethylphosphole **423**, Mathey and co-workers synthesized the phosphacymantrene **424** using the two-step reaction depicted in Equation (85) <1997JOM(548)17>.

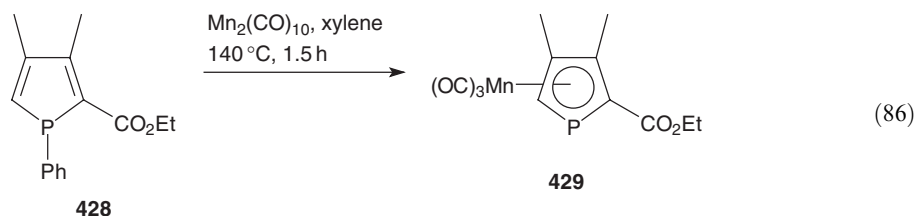


In an approach to chiral phosphacymantrenes, the novel chiral and enantiomerically pure phosphole **425** with two (–)-menthyl groups at the 2- and 5-positions of the phosphole ring was utilized. This compound was submitted to the known reaction with lithium to give the new chiral lithium phospholide **426** followed by the thermal reaction with manganese carbonyl to afford **427** <2001OM1014> (Scheme 59).



Scheme 59

A known approach to unsubstituted phosphacymantrenes was applied by Mathey and co-workers <1999OM5688> to the synthesis of 2-functionalized compounds. Thus, the thermal reaction of 1-phenyl-2-ethoxycarbonyl-3,4-dimethylphosphole **428** with 0.5 equiv. of Mn<sub>2</sub>(CO)<sub>10</sub> gave **429** in 50–70% yield (Equation (86)).

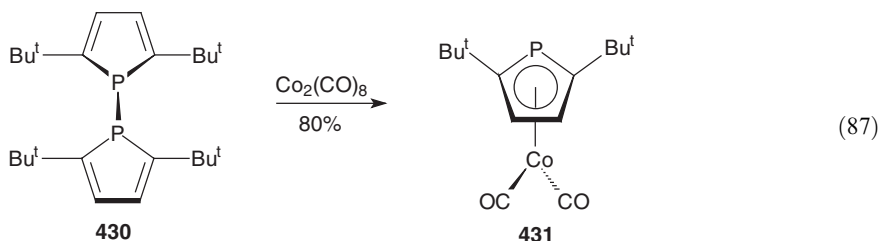


An important finding was that a replacement of one carbonyl group on manganese by triphenylphosphine enhanced the sensitivity of phosphacymantrenes toward electrophilic substitution, for example, the Vilsmeier formylation. Usually, phosphacymantrenes do not undergo the Friedel–Crafts alkylation.

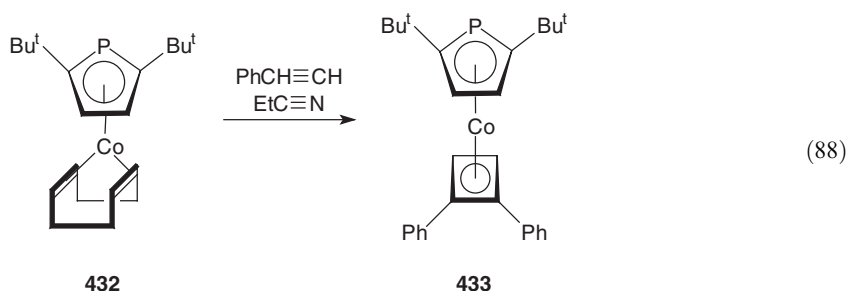
The McMurry coupling (TiCl<sub>4</sub>/3 equiv., Zn/6 equiv., THF, reflux) of 2-acetyl- and 2-benzoyl-3,4-dimethylphosphacymantrenes enabled modification of the side chain of phospholyl rings in bis(phosphacymantrenyl)ethenes <2002OM2635>.

Similarly, Mathey and co-workers <2003OM1340> synthesized phosphacymantrenyl carbenium ion using AlCl<sub>3</sub> in CH<sub>2</sub>Cl<sub>2</sub> at 0 °C which enabled further modification of the pendant 2-phosphole substituents in alkylation of ferrocene as well as alkylation of electron-rich arenes such as anisole and 1,3-dimethoxybenzene.

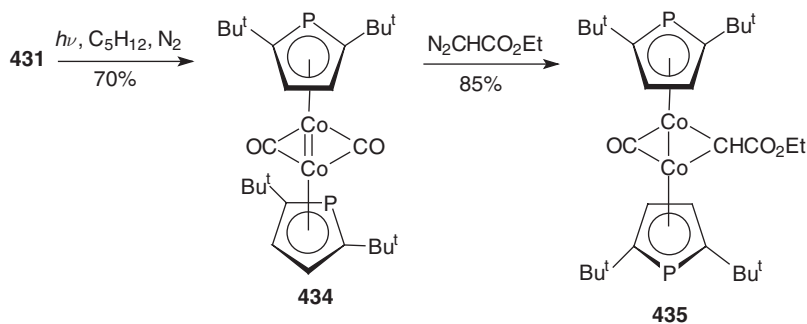
Starting from (2,5-di-*t*-butylphospholyl)dicarbonyl cobalt **431**, Mathey and co-workers obtained a range of cobalt phospholyl complexes <1997OM2049>. The complex **431** was synthesized as a red liquid by thermolysis of the bisphosphole **430** with Co<sub>2</sub>(CO)<sub>8</sub> (7 h, 97 °C, C<sub>7</sub>H<sub>16</sub>) in 80% yield (Equation (87)).



Thermolysis of **431** with trimethyl phosphite resulted in replacement of one CO group in 90% yield. Photolysis of **431** with COD or 1,3-cyclohexadiene afforded orange solids of 2,5-di-*t*-butylphospholyl (COD) cobalt **432** in 90% yield and the analogous 2,5-di-*t*-butyl(1,3-cyclohexadiene) cobalt in 70% yield, respectively. Instead of the expected pyridines, the yellow cyclobutadiene complex **433** was obtained in the thermolysis reaction (3 d, sealed tube, 120 °C) of **432** with a large excess of phenylacetylene in propionitrile (Equation (88)).

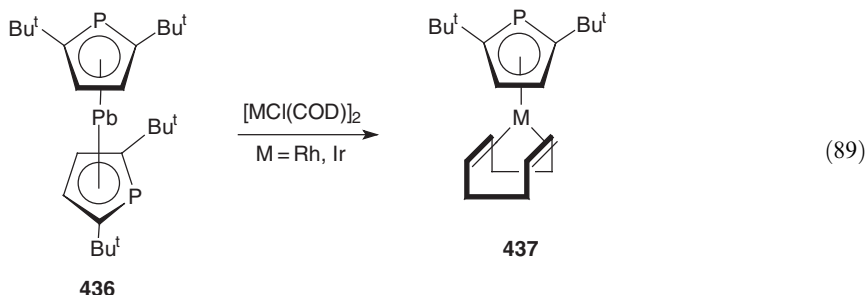


Photolysis of **431** in the absence of donor ligands gave the doubly bonded complex **434** in 70% yield as deep green microcrystals. Ethyl diazoacetate reacted with the latter exclusively at the Co=Co bond to give the carbene complex **435** as a mixture of isomers in 85% yield (Scheme 60).



Scheme 60

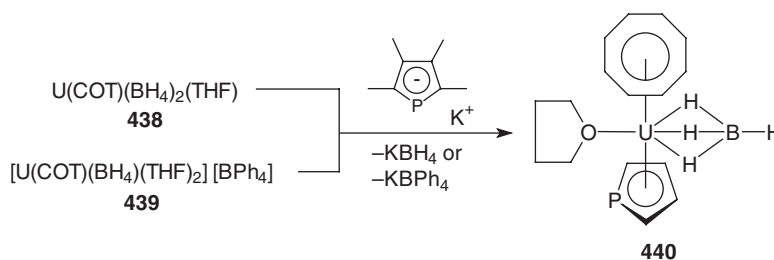
The plumbocene **436** was converted to new rhodium and iridium complexes **437** on treatment with the corresponding metal halides (M = Rh, Ir) complexed to COD [<1999CC1273>](#) (Equation (89)).



Mixed 2,3,4,5-tetramethylphospholyl and 3,4-dimethyl-2,5-bis(trimethylsilyl)phospholyl/cyclooctatetraenyllanthanide (Sm, Nd) complexes were prepared by Visseaux and co-workers by metathesis of the corresponding phospholyl potassium salts with cyclooctatetraenyllanthanide halide precursors.

Treatment of **438** or **439** with potassium phospholide gave the first mixed cyclooctatetraenyl-phospholyl uranium complex **440**, the structure of which was determined by X-ray analysis [<2002JOM\(643/644\)209>](#) (Scheme 61). Other uranium complexes containing the phospholyl moiety were also obtained.

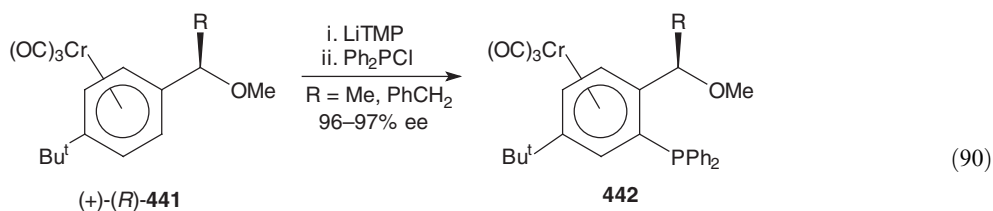




Scheme 61

(iv)  $\eta^6$ -Phosphinobenzene compounds

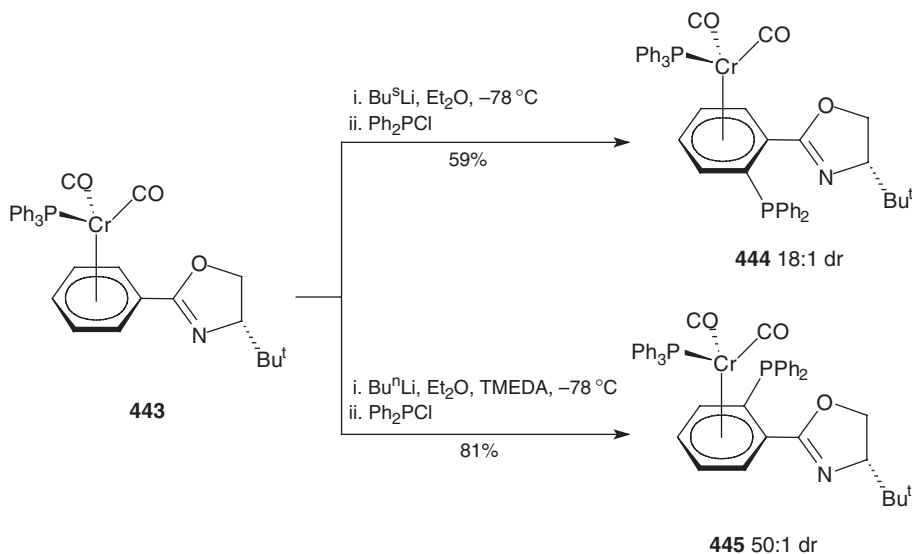
Most compounds of this type constitute di- or tri-carbonyl chromium(0) complexes which were first *ortho*-lithiated and then phosphinylated. For instance, (+)-(*R*)-tricarbonyl chromium(0) complexes **441** were deprotonated with lithium tetramethylpiperidide (LiTMP) at  $-78^\circ\text{C}$  for 1 h. Subsequent reaction with chlorodiphenylphosphine afforded the phosphino modified chromium complexes (**442a,b**) <2002T4617> (Equation (90)).



LiTMP – lithium tetramethylpiperidide

a R = Me, 88% (96% ee)  
b R = PhCH<sub>2</sub>, 91% (97% ee)

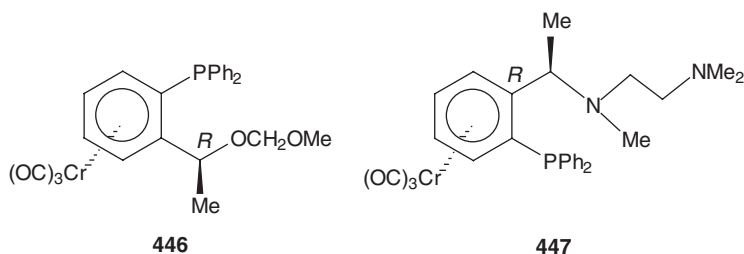
Overman and co-workers reported highly diastereoselective lithiation of the dicarbonyltriphenylphosphinochromium(0) oxazoline complex **443** <2002AG(E)3884> (Scheme 62).



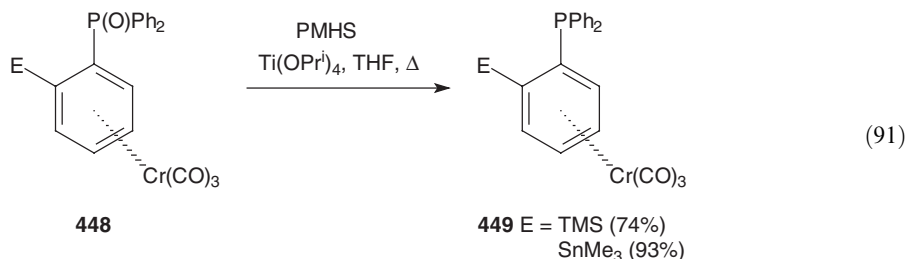
Scheme 62

The lithiation of **443** with *s*-butyllithium at  $-78^\circ\text{C}$  followed by quenching with dichlorophenylphosphine produced diastereoisomers **444** and **445** in an 18:1 ratio, while the use of *n*-butyllithium in the presence of TMEDA at  $-78^\circ\text{C}$  provided **445** and **444** in a 50:1 ratio and in 81% yield.

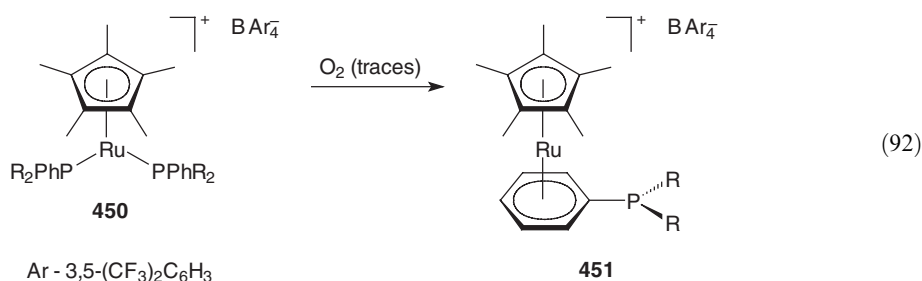
Two other chiral tricarbonyl chromium(0) complexes **446** and **447** were prepared in a similar manner via *ortho*-lithiation with *s*-butyllithium and *t*-butyllithium in Et<sub>2</sub>O in 50% and 25% yields, respectively. One of the three carbonyl groups could be replaced by PPh<sub>3</sub> using the Hg-lamp <1995JOM(503)143>.



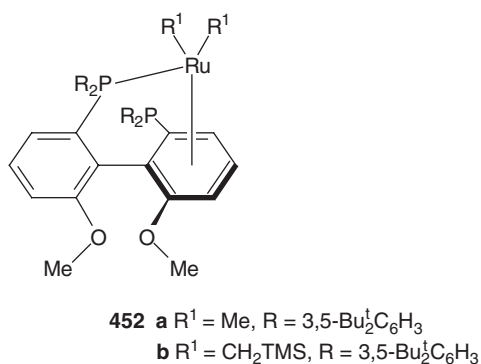
Another method of synthesis of phosphinylated tricarbonyl chromium(0) complexes involves the reduction of the phosphine oxides **448** to phosphines **449** carried out with polymethyl hydrosiloxane (PMHS) in the presence of titanium tetraisopropoxide in THF <1997SL1453> (Equation (91)).



A number of 16e<sup>-</sup> ruthenium complexes were synthesized by Valerga and co-workers <2002OM5334>. It was found that the unstable complexes **450** (R = Ph, Pr<sup>i</sup>) were rearranged to 18e<sup>-</sup> sandwich species **451** on standing in fluorobenzene with trace amounts of oxygen (Equation (92)).

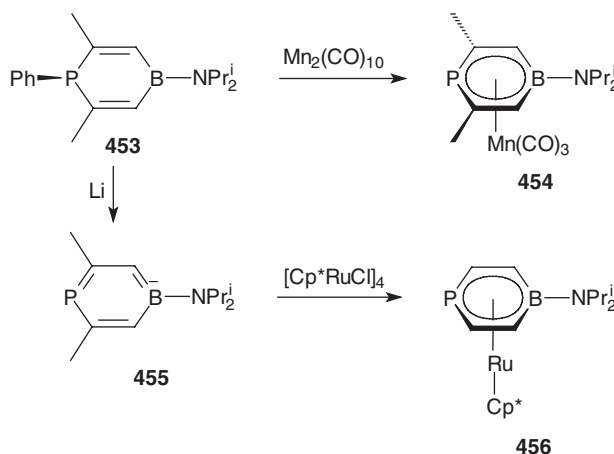


Two other interesting η<sup>6</sup>-ruthenium complexes (**452a,b**), both of yellow color, were synthesized in 91% and 76% yields, respectively, in which only one P was coordinated to an arene η<sup>6</sup>-C<sub>6</sub>H<sub>3</sub> moiety derived from one of the biaryl rings <1997OM3735>.



(v)  $\eta^6$ -Phosphabenzene compounds

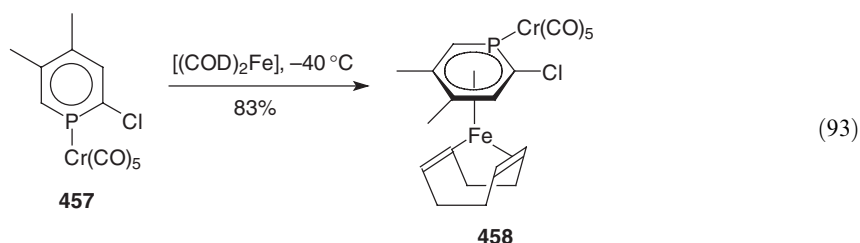
1,4-Phosphaboratabenzenes found to be new and good six- $\pi$ -electron ligands toward transition metals and replacements of Cp groups of metallocenes. The synthesis of these systems was first reported by Nöth and Berger in 1983 <1983JOM(230)33>; however, this coordination chemistry remained unexplored until 2003 when Ashe III and co-workers <2003OM910> synthesized 1,4-dihydro-4-(diisopropylamino)-2,6-dimethyl-1-phenyl-1,4-phosphaborin **453**. The *P*-phenyl group of the latter was easily cleaved and the reaction of **453** with lithium powder in diethyl ether gave a deep red solution of the  $\pi$ -coordinated anion of the 1,4-phosphaboratabenzene **455**. This conversion caused the characteristic downfield shift from  $\delta_{31\text{P}} = -11.5$  ppm **453** to  $\delta_{31\text{P}} = 38.5$  ppm **455**. Further reaction of **455** with  $[\text{Cp}^*\text{RuCl}]_4$  afforded deep yellow crystals of the Ru(II) complex **456**. Similarly the reaction of the 1,4-phosphaborin **453** with  $\text{Mn}_2(\text{CO})_{10}$  in xylene at  $140^\circ\text{C}$  afforded the pale yellow Mn complex **454** (Scheme 63).



Scheme 63

Zenneck and co-workers synthesized the binuclear complex **458** starting from the  $\eta^1$ -pentacarbonyl chromium complex of 2-chloro-4,5-dimethylphosphinine **457**.

Although the yields of the product exceeded 80%, solution of **458** was found to be extremely air sensitive and could be stored only for a few hours at rt even in the absence of oxygen <1996OM2713> (Equation (93)).



## 4.22.4.2.10 Metallocenes

## (i) Phosphino metallocenes

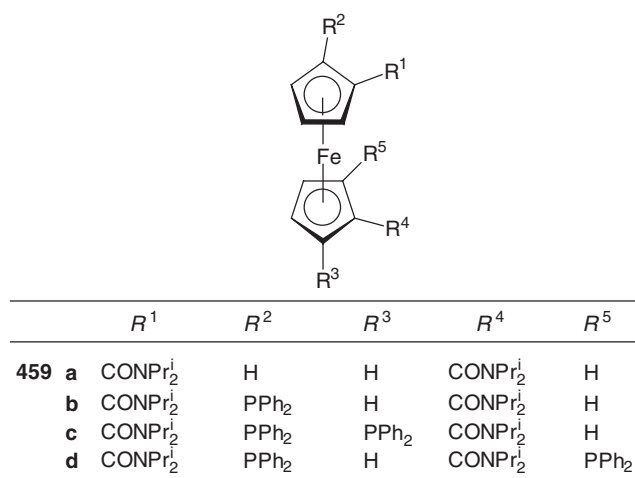
The most widely used method for introduction of a phosphino group to a metallocene still remain lithiation/phosphinylation protocols. Before 1995, lithiation and so called *ortho*-lithiation/phosphinylation procedures were applied only to ferrocene and its derivatives. After 1995 these procedures have been further developed. New modifications, applications to syntheses of other metallocenes (e.g., ruthenocenes and osmocenes) as well as asymmetric lithiations will be briefly mentioned below.

(a) *CH/CLi* exchange. This group of methods includes new *ortho*-lithiation, *ortho*-dilithiation, stepwise lithiation and dilithiation/phosphinylations as well as diastereo- and enantioselective deprotonation reactions.

Most of the new procedures and modifications still concern phosphino ferrocenes. Homochiral compounds of this type can be prepared either via resolution of racemic precursors for instance: <1982ACR395, 1988PAC7, 1992CRV857> or via introduction of chiral “directed metallation group” auxiliaries <1996C86, 1996AG(E)1475> or by asymmetric *ortho*-lithiation. In the latter method, Snieckus and co-workers <1996JA685, 1996JOC1172> used the complex of *n*-BuLi and (–)-sparteine while Uemura and co-workers used the complex of *n*-BuLi and (+)-1(*R*),2(*R*)-bis(dimethylamino)cyclohexane <1996JOC1172>. Jendralla and Paulus <1997SL471> reported a modification of enantioselective deprotonation of the diamido ferrocene **459a** by twofold asymmetric *ortho*-lithiation with the *n*-BuLi/(–)-sparteine complex followed by addition of Ph<sub>2</sub>PCl to afford enantiomerically pure monophosphine **459b** after a single recrystallization. Treatment of the latter with the same complex gave enantiomerically pure C<sub>2</sub>-symmetric diphosphine **459c** with 86–94% de, while the *rac*-**459b** furnished a mixture of **459c** and **459d** in a ratio of 1:1.

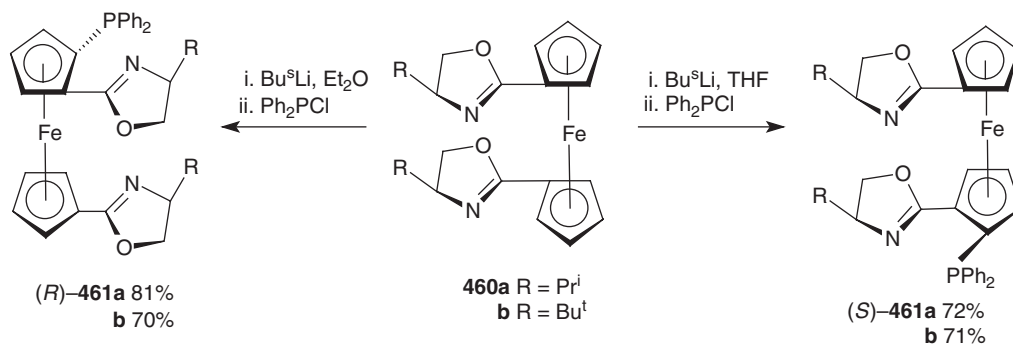
When the *s*-BuLi/(–)-sparteine complex was used, the *meso*-diphosphine **459d** was obtained with 92% de.

The diamides **459b** were also synthesized and used as catalysts by Snieckus and co-workers <2000OL629>.

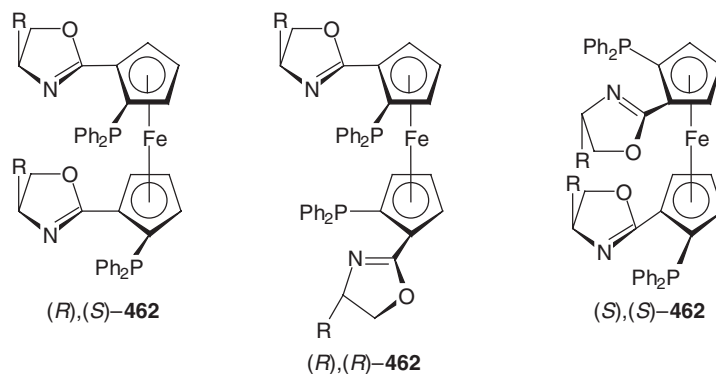


It was reported that the diastereoselectivity of the *ortho*-lithiation of chiral 1,1'-bis(oxazolinyl)ferrocenes (**460a,b**) could be controlled by temperature, solvents, and/or lithiating agents <1996TL6137>.

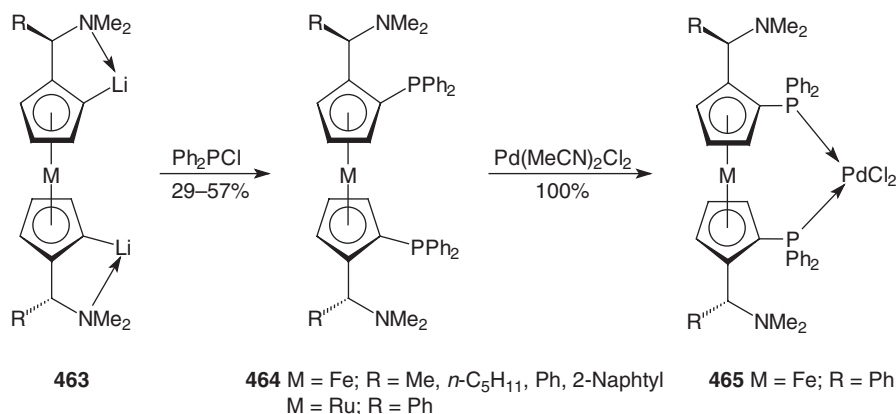
Thus, monolithiation of **460** with butyllithiums (*n*, *s*, *t*) in Et<sub>2</sub>O followed by treatment with Ph<sub>2</sub>PCl favored (*R*)-**461** while the use of THF led to (*S*)-**461** (see Scheme 64 for the use of Bu<sup>s</sup>Li). Dilithiation with *s*-BuLi or *t*-BuLi in Et<sub>2</sub>O led to (*R,S*)-**462**. The step-by-step lithiation at different temperatures with *s*-BuLi in Et<sub>2</sub>O gave (*R,R*)-**462** while *s*-BuLi in THF afforded (*S,S*)-**462** as the major product.



Scheme 64



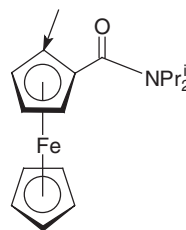
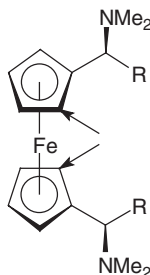
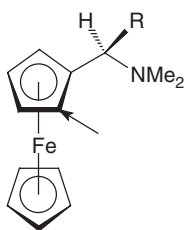
The known diastereoselective *ortho*-metallation was applied in a double fashion by Schwink and Knochel <1998CEJ950> for the  $\alpha$ -(*N,N*-dimethylamino)alkyl ferrocene and ruthenocene to afford the dilithium derivatives **463** (M = Fe, Ru) which were further treated with  $\text{Ph}_2\text{PCl}$  to give **464** (M = Fe, Ru) in moderate chemical yield (29–54%) and with 98% ee. The latter reacted quantitatively with stoichiometric amounts of  $\text{Pd}(\text{MeCN})\text{Cl}_2$  in toluene to give, in the case of ferrocene, the  $\text{C}_2$ -symmetrical complex **465** (R = Ph, M = Fe) and in the other cases (M = Ru), mixtures of less symmetrical coordination isomers (Scheme 65).



Scheme 65

There were also reported other stereoselective *ortho*-lithiation/  $\text{Ph}_2\text{PCl}$  phosphinylation reactions of the following compounds: (*R*) and (*S*)-*N,N*-dimethyl-1-ferroceno(*n*-propyl-*n*-pentyl)amines **466** <2003OM618, 2002TA1687, 1996JOC1172, 1995TA2495>, bis-(dimethylamino)ferrocenes **467** <1996TL25, 1998TL5523>, *N,N*-diisopropyl-ferrocenecarboxamide **468** <1996JA685>, 1,1'-bis[(*S*)-2-(4*R*-oxazolynyl)]ferrocenes **469** <1995TL7263, 1996TL6137>, monooxazolynylferrocenes **470** <1995SL79> and their substituted analogs **471** <1997JOM(545-546)381, 1995SL74>, 4-(methoxymethyl-2-[2-trimethylsilyl,diphenylphosphinyl]-ferrocenyl)-1,3-dioxane **472** <2002OM4552>, *trans*-(2*R*,5*R*)-2,5-dialkyl-1-(ferrocenylmethyl)pyrrolidines **473** <2002JOC4209>, (*R<sub>C</sub>*,*S<sub>P</sub>*)-[ $\eta^5$ -cyclopentadienyl][ $\eta^5$ -4-*N,N*-(dimethylamino)-3-diphenylphosphino]-4,5,6,7-tetrahydro-1*H*-indenyl]iron(II) **474** <2002OM1766>, (*R*)-[amino-*o*-bromophenylmethyl]ferrocene **475** <2002CEJ843>, (*E*)-benzoylferrocene[(*S*)-1-amino-2-methoxymethylpyrrolidine]-hydrazone **476** <2000EJO2839>, 1,2-( $\alpha$ -*exo*-dimethylaminotetramethylene)-ferrocene **477** <2001JOC1560>, (1*S*,2*S*)-*N*-ferrocenylmethyl-*N*-methyl-1-methoxy-1-phenylprop-2-ylamine **478**

<2001JOC8912>, (*S*)-*N*-ferrocenylmethyl-3,5-dihydro-4-*H*-dinaphth[2,1-*c*:1',2'-*e*]azepine **479** <1999TA4369>, (*R*)-(-)-ferrocenyl-*t*-butyl sulfoxide **480** <1998T7301, 2003JOC3679>, (*R*) or (*S*)-ferrocenyl *p*-tolyl sulfoxide **481** <1998JOC3511, 2003JOC3679>, (*S*)-1,1'-(1-*N,N*-dimethylaminopropane-1,3-diyl)ferrocene **482** <1996JOM(508)195>. (Arrows indicate sights of phosphinylation.)



**466a** R = H (49%)

**b** R = Me (93%, 2 steps)

**c** R = Et (59% from *R<sub>C</sub>*  
32% from *S<sub>C</sub>*)

**d** R = Bu<sup>n</sup> (44% from *R*)

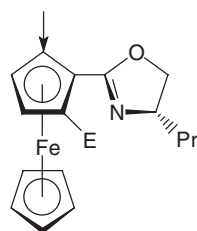
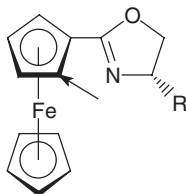
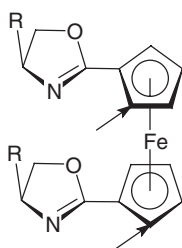
**e** R = Ph

**467a** R = *n*-C<sub>5</sub>H<sub>11</sub> } (55–57%

**b** R = Ph } overall 3 steps)

**c** R = Et (55%)

**468** (82%, 90% ee)



**469a** R = Pr<sup>i</sup> (60%)

**b** R = Bu<sup>t</sup> (43%)

**470a** R = Pr<sup>i</sup> (77%)<sub>s</sub>

**b** R = Bu (58%)

**c** R = Ph (55%)

**d** R = Me (25%)

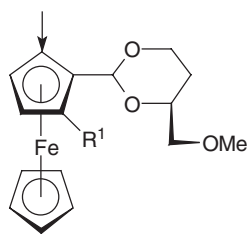
**e** R = PhCH<sub>2</sub> (56%)

**f** R = Bu<sup>t</sup> (51%)

**471a** E = Me (72%)

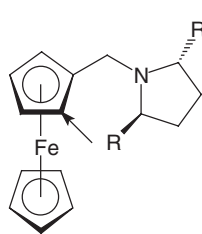
**b** E = PhSe (53%)

**c** E = TMS (75%)



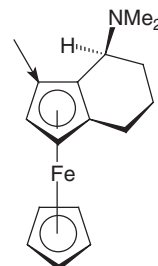
**472a** R<sup>1</sup> = TMS (29%)

**b** R<sup>1</sup> = Ph<sub>2</sub>P (37%)

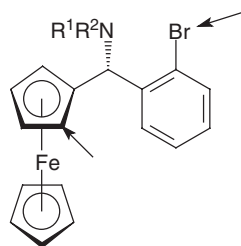


**473a** R = Me (27%)

**b** R = Et (10%)



**474** (71%)



**475a**  $R^1 = R^2 = \text{Me}$  (88%)  
 $R^1 = R^2 = \text{Me}$  [33% for  
 (3,5-xylyl)<sub>2</sub>PCl]

**b**  $R^1 = R^2 = \text{CH}_2\text{CH}_2$  (64%)

**c**  $R^1 = (R)\text{-PhCH(Me)}$ ;  $R^2 = \text{Me}$  (41%)

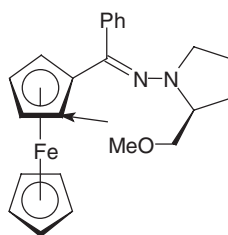
**d**  $R^1 = (S)\text{-PhCH(Me)}$ ;  $R^2 = \text{Me}$  (58%)

**e**  $R^1 = \text{Me}_2\text{NCH}_2\text{CH}_2$ ;  $R^2 = \text{Me}$  (41%)

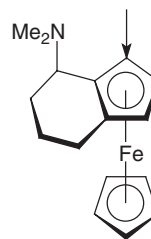
**f**  $R^1 = R^2 = \text{Pr}^n$  (53%)

**g**  $R^1 = R^2 = \text{Bu}^n$  (46%)

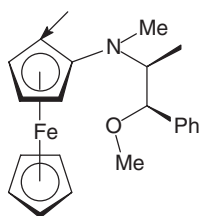
**h**  $R^1 = R^2 = \text{Bu}^i$  (36%)



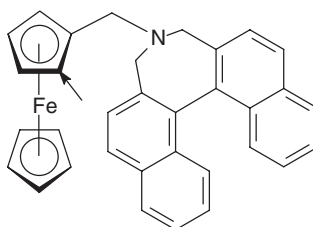
**476** (89%)



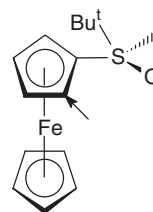
**477** (96%)



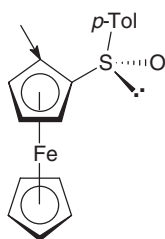
**478** (97%)



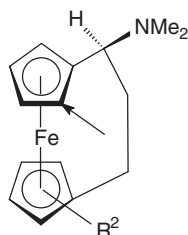
**479** (no yield given)



**480** (82%)

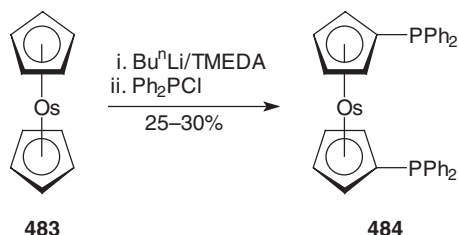


**481** (57%)



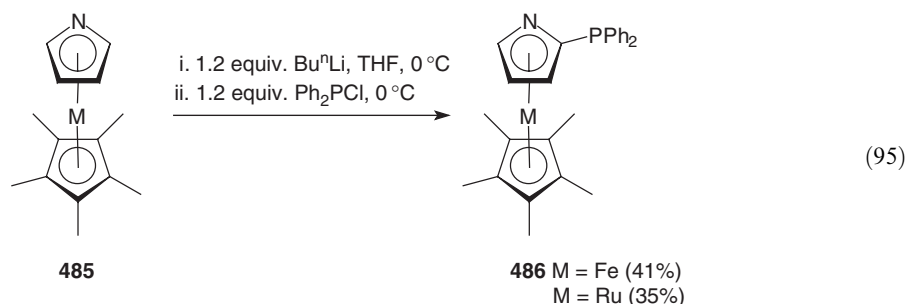
**482a**  $R^1 = \text{PPh}_2$   
**b**  $R^2 = \text{PPh}_2$  (2'-44%, 3'-6%,  
 4'-5%, 5'-7%)

Gusev and co-workers synthesized 1,1'-bis(diphenylphosphino)osmocene **484**, the missing compound along the iron triad (Fe, Ru, Os). It was prepared in 25–30% yield via the double lithiation procedure of the osmocene **483** followed by the reaction with chlorodiphenylphosphine <2003OM913> (Equation (94)).

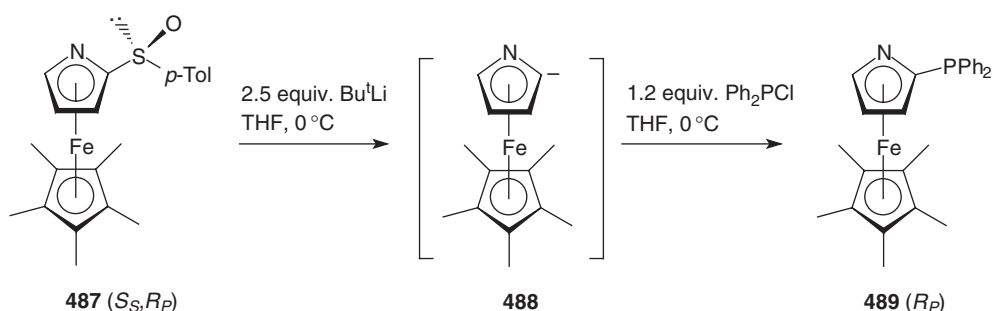


(94)

Hansen and Johannsen described the regioselective *ortho*-lithiation of the azaferrocene **485** (Me = Fe) and the azaruthenocene **485** (M = Ru) with *n*-BuLi at 0 °C <2003JOC1266>. The resulting racemic anions were quenched with chlorodiphenylphosphine to afford new azametallo-cenes **486** (M = Fe, Ru) (Equation (95)).

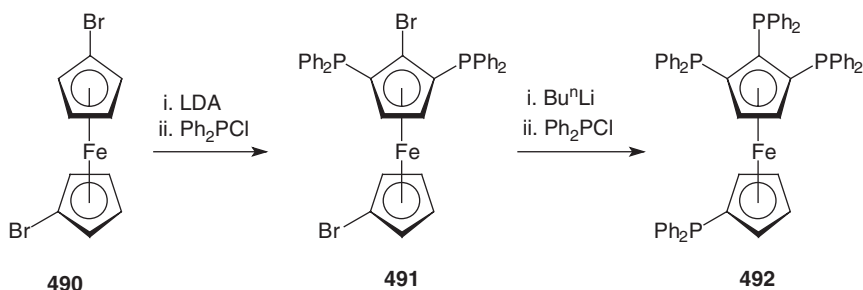


A clean removal of the chiral sulfoxide auxiliary from **487** by treatment with *t*-BuLi generated optically pure anion **488** which was stable at low temperatures and quenched with chlorodiphenylphosphine to give the optically pure azaferrocene **489** (Scheme 66). The same reaction sequence was also performed with the opposite diastereomer (*S<sub>S</sub>*, *S<sub>P</sub>*).



Scheme 66

(b) *C*-Hal/*C*-Li exchange. Various diphenylphosphino-substituted ferrocenes were obtained as a result of a combination of the *ortho*-lithiation (LDA) and/or the Br/Li exchange followed by the reaction with chlorodiphenylphosphine <1999MI576>. For instance, the *ortho*-lithiation of one of the cyclopentadienyl rings in 1,1'-dibromoferrocene **490** gave 1,1'-dibromo-2,5-bis(diphenylphosphino)ferrocene **491** as one of the reaction products. Further reaction of the latter with Bu<sup>n</sup>Li followed by phosphinylation with Ph<sub>2</sub>PCl afforded 1,2,3,1'-tetrakis(diphenylphosphino)ferrocene **492** (Scheme 67).



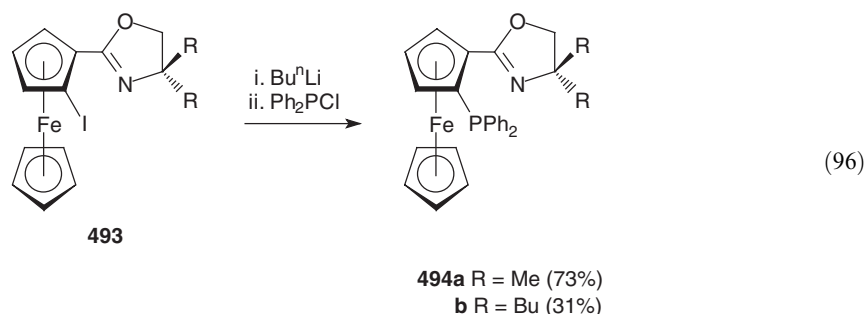
Scheme 67



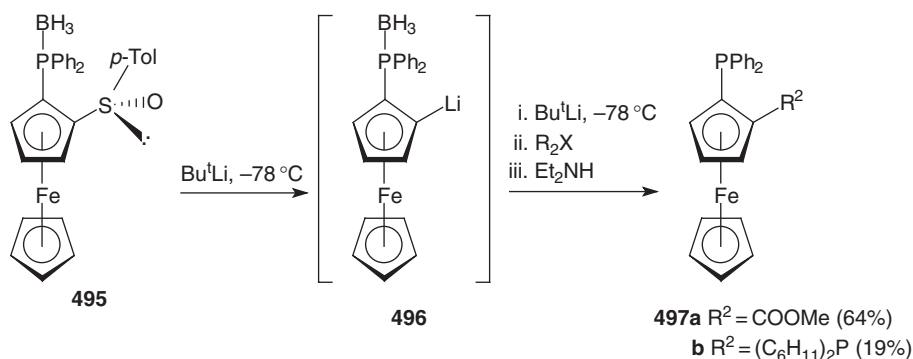
Knochel and co-workers <2002CEJ843> reported another interesting example of the double Br/Li exchange/diphosphinylation reaction facilitated by the presence of the phenyl ring to give products in high chemical yield (91–92%) and with d.r.'s of 95–96/4–5.

The dimethylamino group facilitated the exchange of bromine and iodine for lithium in (*R*)-1-bromo(iodo)-2-(dimethylaminomethyl)ferrocenes. Subsequent reaction of the lithium derivatives formed with  $\text{Ph}_2\text{PCl}$  gave the corresponding (*R*)-products in 80% (I) and 81% (Br) yields <2001JOC8912>. The same lithiation–phosphinylation sequence was also reported for the  $\text{C}_2$ -symmetrical 3,5-dihydro-4*H*-dinaphtho[2,1-*c*:1'2'-*e*]azepine subunit as the chirality inducing fragment <1999TA4369>.

The I/Li exchange enabled by the oxazolinyl ferrocene **493** and leading to **494** was also described (Equation (96)) <2002JOC4684>.



(*c*) *C-p-TolS(O)/C-Li* exchange. Kagan and co-workers <1998JOC3511, 2000EJO2893> synthesized 1,2-disubstituted ferrocenes **497** (ee  $\geq 98\%$ ) starting from the  $\text{BH}_3$ -protected phosphine **495** which in turn was obtained via the LDA *ortho*-lithiation/phosphinylation sequence in 57% yield. Modification of the  $\text{C}_p$ -2 position was achieved in a subsequent step in which *t*-BuLi attacked the sulfinyl sulfur to generate a new chiral 2-lithium species **496**. The latter was further trapped with electrophiles ( $\text{R}^2\text{X} = \text{ClCO}_2\text{Me}$ ,  $\text{Cy}_2\text{PCl}$ ) to give **497** after removal of the borane in refluxing diethylamine (Imamoto method) (Scheme 68).

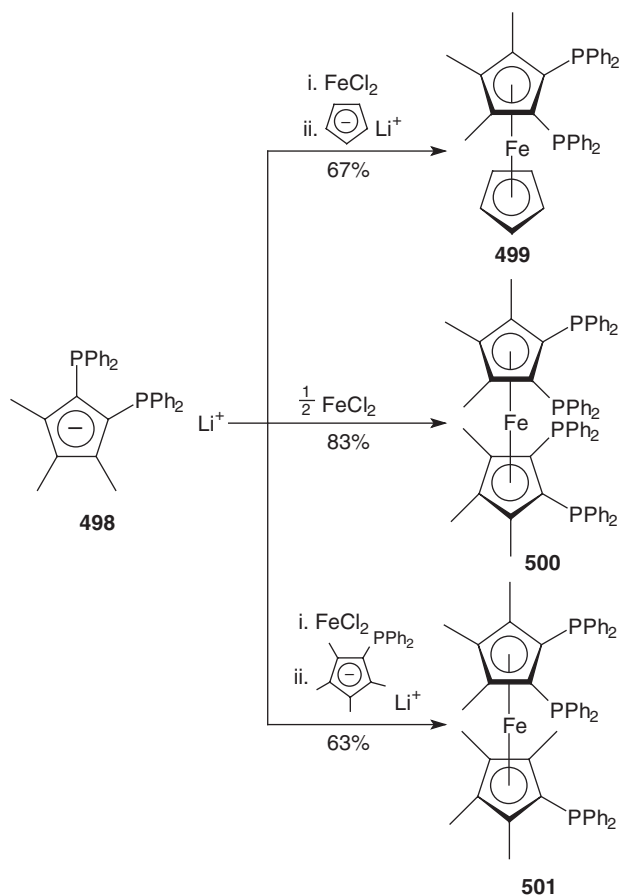


Scheme 68

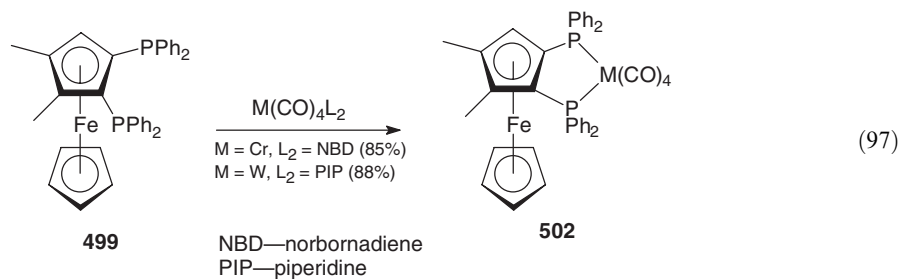
The lithioferrocene **496** was also condensed with  $\text{TMS-Cl}$  at  $-78^\circ\text{C}$  to give the TMS substituted analog of **497** ( $\text{R}^2 = \text{TMS}$ ) <2002JOC7982>. Another example of the *p*-tolylsulfinyl group/Li exchange in the aryl substituted ferrocenes followed by reactions with either  $\text{Ph}_2\text{PCl}$  or  $\text{Ph}_2\text{P(O)Cl}$  in 16–81% yield has recently been reported by Johannsen *et al.* <2003JOC1258>.

(*d*) *Other methods*. Various ferrocenyl polyphosphines (**499**, **500** and **501**), were synthesized by Broussier and co-workers from 1,2-bis(diphenylphosphino)-3,4,5-trimethylcyclopentadienyl-lithium **498** utilizing the classical ferrocene synthesis <1998JOM(561)85> (Scheme 69).

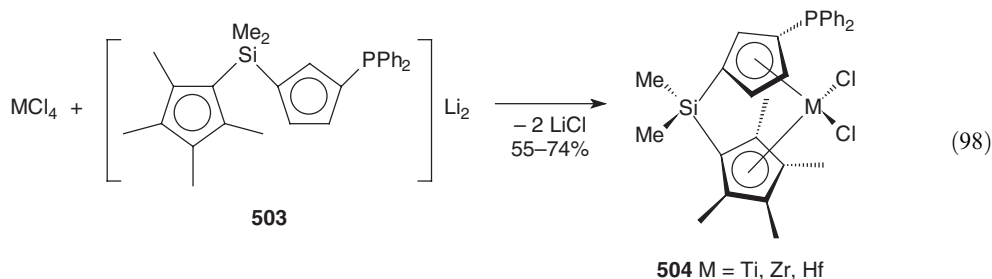
The diphosphine **499** and the tetraphosphine **500** were further oxidized with  $\text{H}_2\text{O}_2$  to the corresponding diphosphinoyl and tetraphosphinoyl ferrocenes. All three polyphosphines (**499**, **500** and **501**), were treated with chromium tetracarbonyl to give complexes of the type **502** possessing two phosphorus bound to Cr (Equation (97)). The tungsten analog of **502** was also obtained.



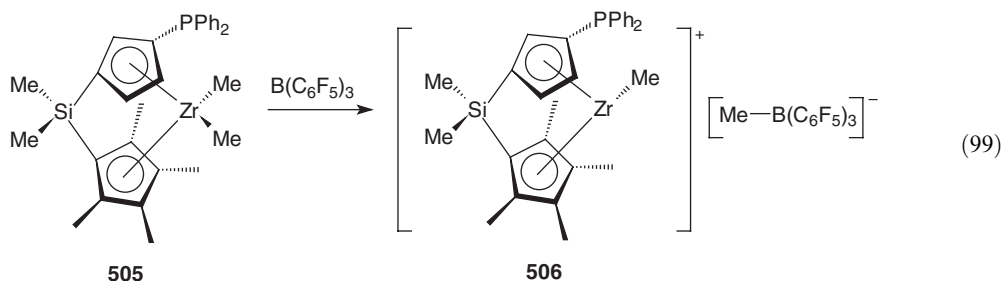
Scheme 69



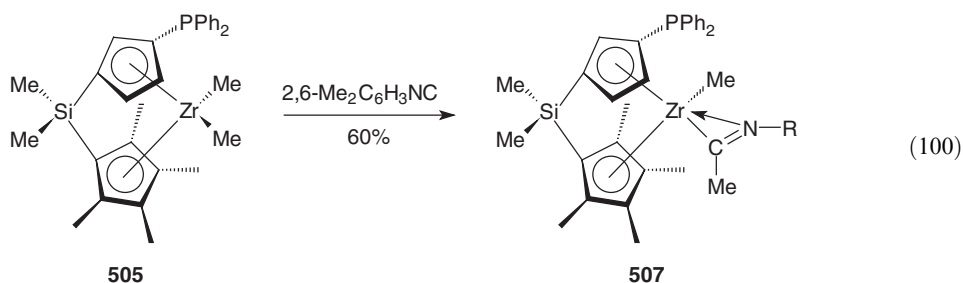
In a similar way, Otero and co-workers prepared the *ansa* complexes **504** in the reaction of  $\text{MCl}_4(\text{THF})_2$  ( $\text{M} = \text{Ti}, \text{Nb}$ ) or  $\text{MCl}_4$  ( $\text{M} = \text{Zr}$  or  $\text{Hf}$ ) and the corresponding dilithiated *ansa* derivative **503** <2002EJI2470, 2002JOM(655)63> (Equation (98)).



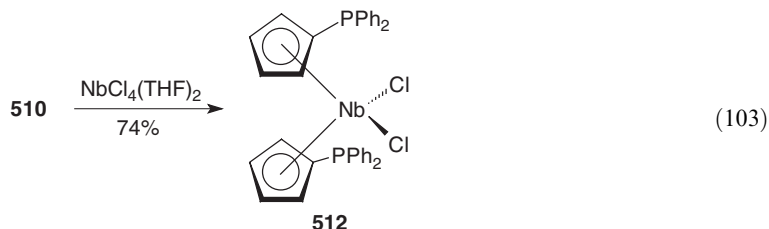
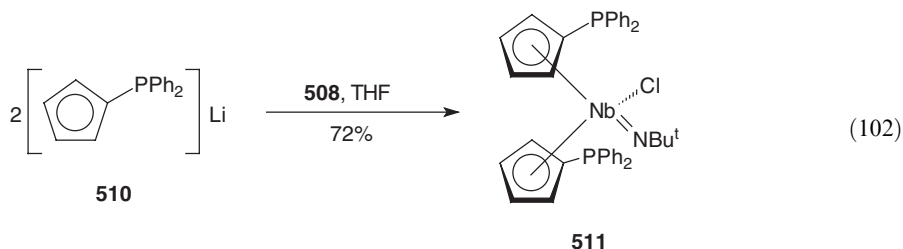
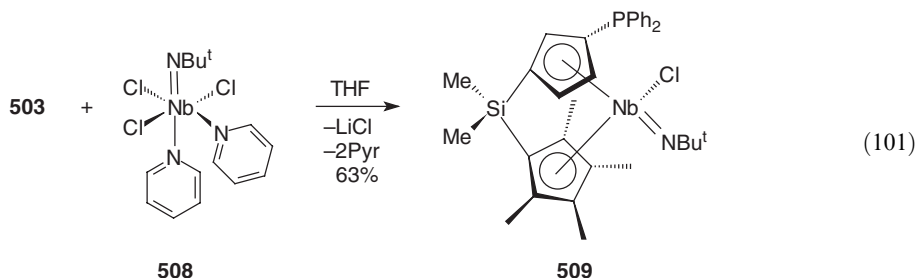
The reaction of the complexes **504** with 2 equiv. of  $\text{MeMgCl}$  led to the replacement of chlorine by methyl to give **505** <2002EJI2470> (Equation (99)).



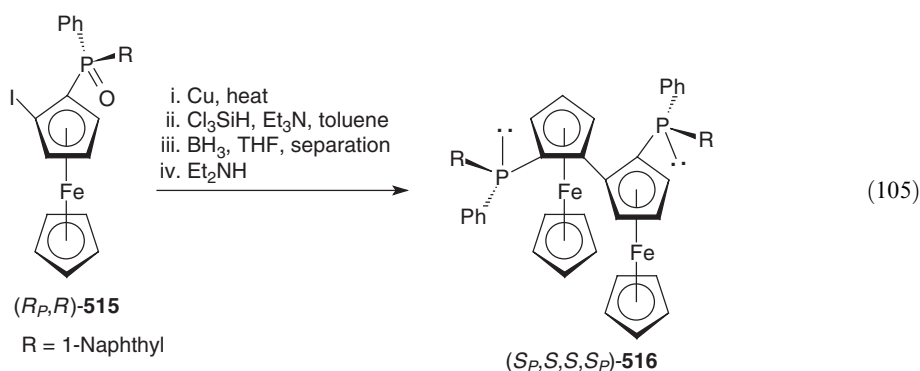
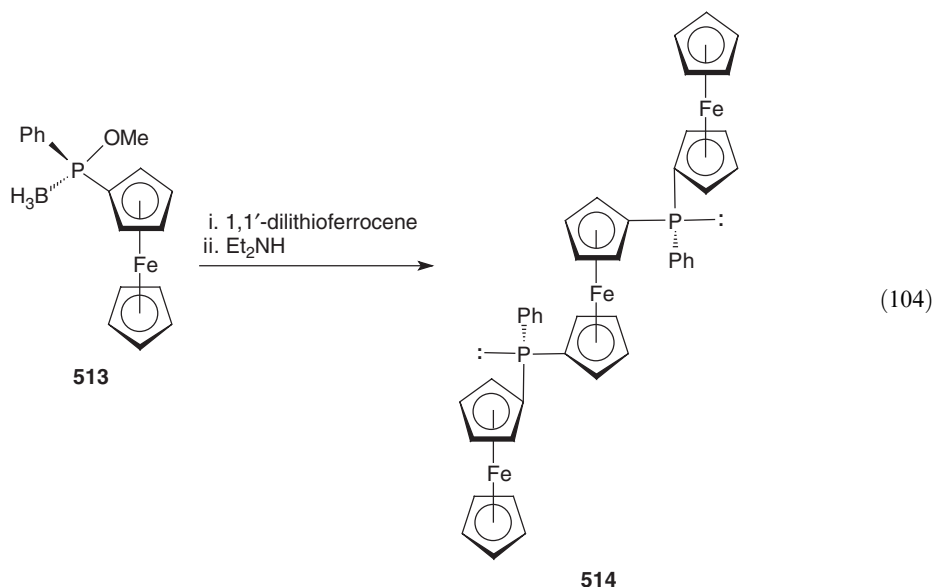
Methyl abstraction from **505** gave the cationic species having the proposed structure **506**. The insertion reaction of the isocyanide unit into the Zr—Me bond of **505** gave the corresponding  $\eta^2$ -iminoacyl complex **507** <2002EJI2470> (Equation (100)).



The two niobocene imides **509**, **511** <2002EJI2470> and the dichloride **512** <2002JOM(655)63> were also prepared (Equation (101)–(103)).

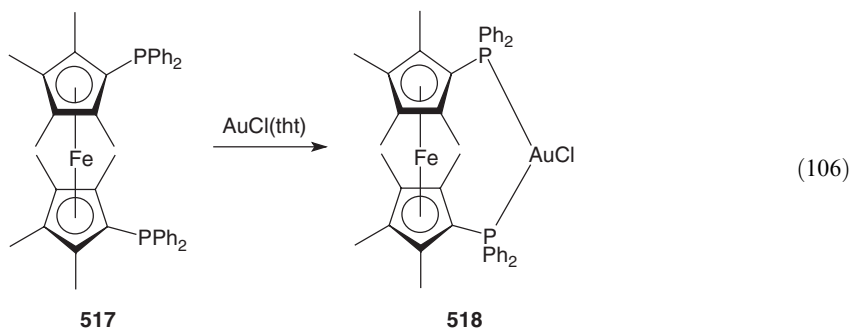


The synthesis of *P*-chiral diphosphines based on ferrocenyl and bisferrocenyl frameworks has recently been reviewed <2001JOC759>. Two novel ligands **514** and **516** were synthesized later and employed in the palladium-catalyzed allylic substitution (Equation (104) and (105)).

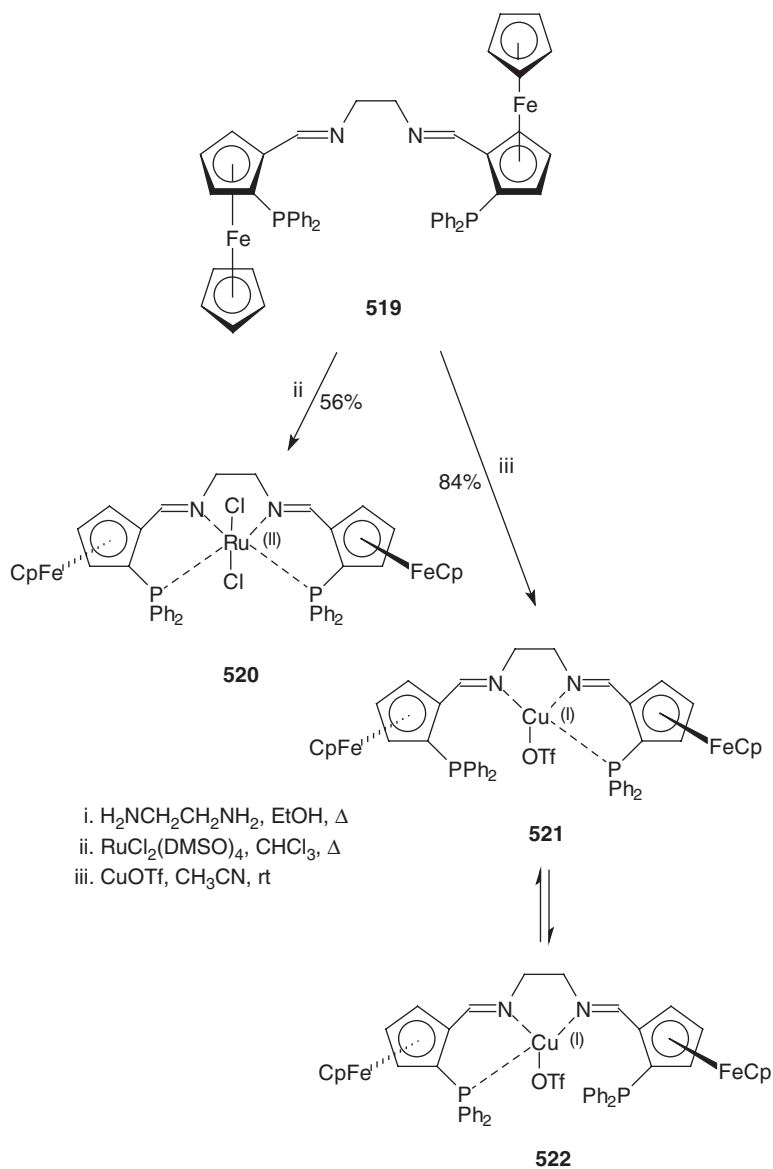


The first (*S,S*)-**514** was obtained via nucleophilic attack of 1,1'-dithioferrocene on the enantiopure methyl phosphinite (*R*)-**513** occurring with inversion of configuration at the phosphorus (Equation (104)). The second bisferrocenyl ligand (*S<sub>P</sub>, S, S, S<sub>P</sub>*)-**516** was synthesized from **515** after the Ullmann coupling in four steps involving reduction of the P(O) group to the corresponding P(III) compound and purification via the bisborane complex (Equation (105)).

(*e*) *Complexes with metals.* 1,1'-Bis(diphenylphosphino)octamethyl ferrocene **517**, when reacted with AuCl(tht) (tht = tetrahydrothiophene) in a 1:2 ratio, afforded the complex in which one AuCl unit was coordinated to each phosphino group <1995IC3465>. The ratio 1:1 led to the tri-coordinate Au(I) monomer complex **518** in which the Au was trigonal planar (Equation (106)).

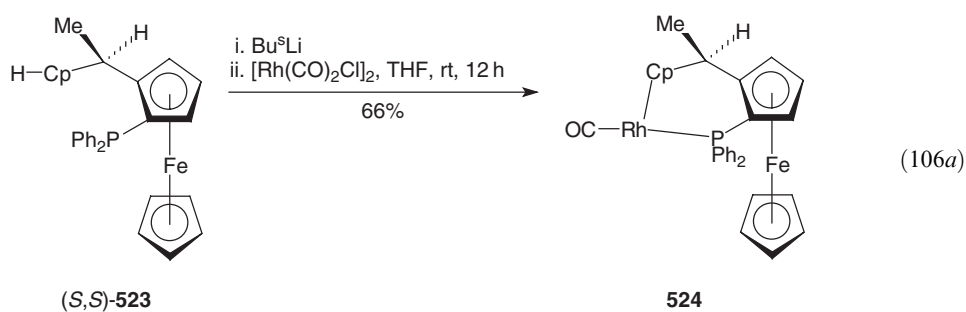


Kagan and co-workers <1996JOM(511)193> reported the asymmetric synthesis of the chiral tetradentate ligand **519** which easily formed with ruthenium(II) dichloride and copper(I) triflate the Ru(II) and Cu(I) complexes (**520**, **521** and **522**), respectively (Scheme 70).

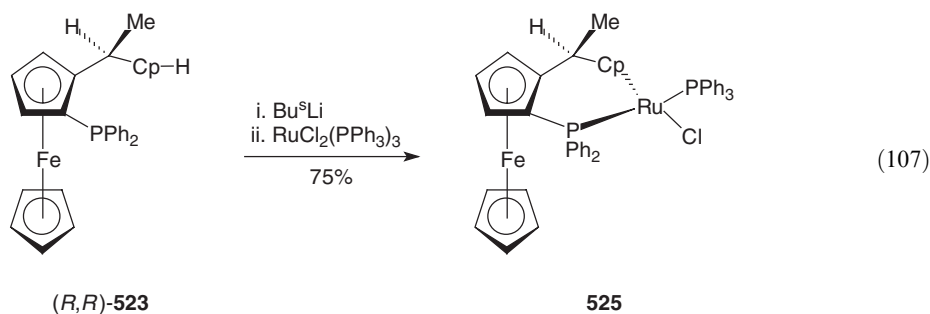


Scheme 70

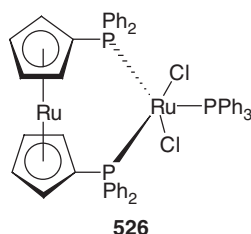
Novel chiral cyclopentadienyl-ferrocenyldiphenylphosphine bidentate ligands **523** were prepared by Hidai and co-workers [\[1997OM3091\]](#). The (*S,S*)-**523** was further deprotonated with *s*-BuLi and then treated with  $[\text{Rh}(\text{CO})_2\text{Cl}]_2$  in a 2:1 ratio in THF to give the rhodium complex **524** (Equation (106a)).



The lithium salt of the diastereomer (*R,R*)-**523** produced with  $[\text{RuCl}_2(\text{PPh}_3)_3]$ , orange crystals of the Ru complex **525** (Equation (107)). Hydrolytic cleavage of the dihydrooxazole ring was utilized by Stepnicka for the synthesis of (*S<sub>P</sub>*)-2-(diphenylphosphino)ferrocenecarboxylic acid in two steps <2002NJC567>. The structures of the corresponding phosphine oxide and ruthenium complexes were studied by X-ray crystallography. The same author described syntheses of *rac*-2-(diphenylphosphino, diphenylphosphinoyl and diphenylthiophosphinoyl) ferrocenyl methanols <2002NJC1389>.



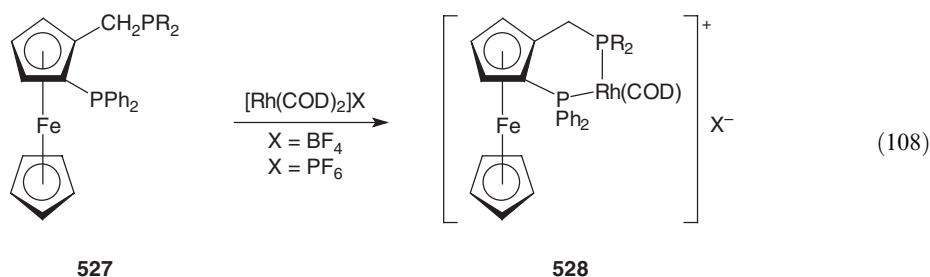
The reaction of  $\text{RuCl}_2(\text{PPh}_3)_3$  with 1,1'-bis(diphenylphosphino)ruthenocene (dppr) in  $\text{CH}_2\text{Cl}_2$  gave dark green crystalline complex **526** in 80% yield <1997JOM(527)133>.



Similarly, the reaction of  $\text{RuCl}(\text{Cp})(\text{PPh}_3)_2$  with dppr in refluxing benzene gave the analogous complex in 91% yield without triphenylphosphine bound to ruthenium <1999JOM(575)171>.

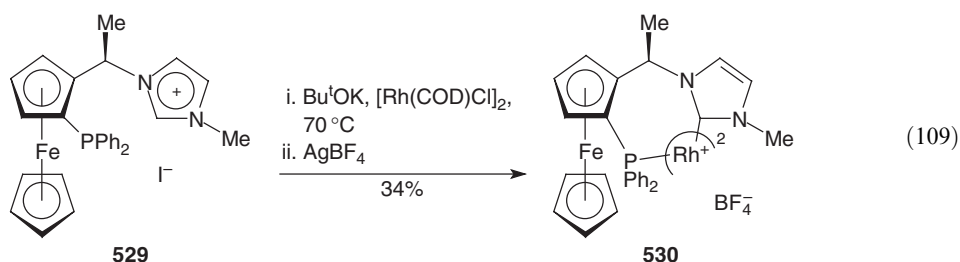
1,2-Ferrocenediylazaphosphinines constitute a completely new family of planar chiral ferrocenes. Their complexes with Mo, W, Re, Pd, and Mn were obtained <2003OM1475>.

Kagan and co-workers synthesized several enantiopure phosphinoferrocenes **527** as substrates for cationic complexes **528** useful in hydrogenation <2000EJO2885, 2001WOP0138336> (Equation (108)).

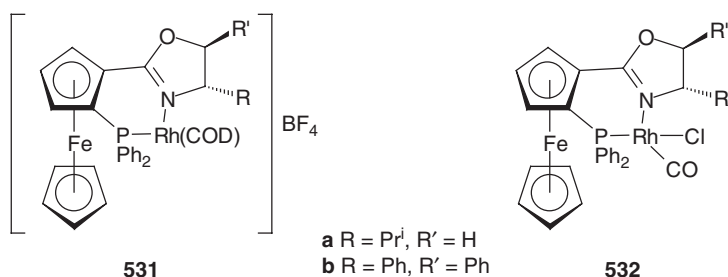


For instance, when  $\text{R} = \text{C}_6\text{H}_{11}$ ,  $\text{X} = \text{PF}_6$ , the corresponding complex **528** was obtained in 80% yield.

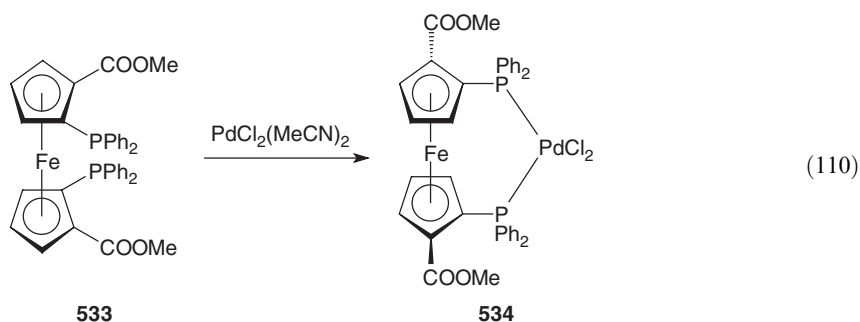
Chung and co-workers <2003OM618> prepared *P*-functionalized chiral imidazolium salt **529** and its rhodium complex **530**. The starting salt **529** was synthesized with retention of configuration via the *ortho*-lithiation/phosphinylation sequence <1970JA5389> of the corresponding chiral ferrocenylamine followed by replacement of the dimethylamino group by 1-methyl imidazole. The reaction of **529** with the dimeric rhodium complex afforded the complex **530** in 34% yield possessing two carbene ligands coordinated to the rhodium center (Equation (109)).



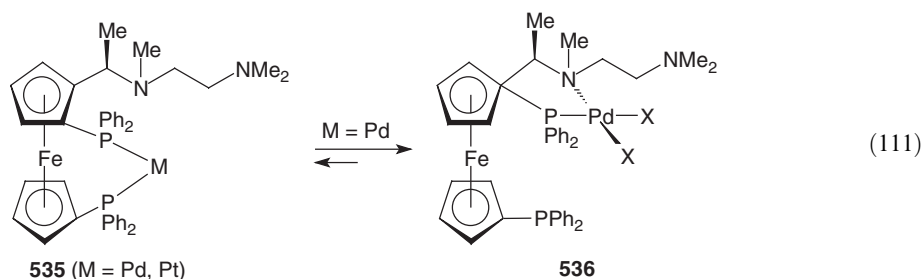
Cationic rhodium complexes (**531a,b**) were also prepared from the corresponding oxazolinyl ferrocenes and  $[\text{Rh}(\text{COD})_2]\text{BF}_4$ , whereas neutral rhodium complexes (**532a,b**) required the use of  $[\text{Rh}(\text{CO})_2\text{Cl}]$  (THF, rt, 14 h, 85% yield) [\[1997JOM\(545-546\)381\]](#).



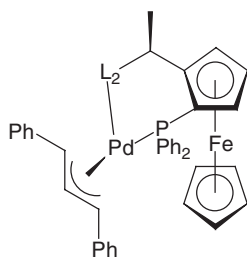
The novel  $C_2$ -symmetric diphosphine ligand **533** containing carboxylic ester groups was obtained by Ikeda and co-workers [\[1996TL7994\]](#) from 1,1'-bis(diphenylphosphino)-2,2'-bis(oxazolinyl)ferrocene. On mixing **533** with 1 equiv. of dichlorobis(acetonitrile)palladium(II), the *P,P*-chelate with Pd(II), **534** was formed in 97% yield ([Equation \(110\)](#)). The orange 1:1 complex of **534** with  $\text{CH}_2\text{Cl}_2$  was formed by crystallization from  $\text{CH}_2\text{Cl}_2/n$ -hexane.



In a similar way, two other phosphino ferrocenes with carboxylic acid-derived functionality were obtained [\[2001JOM\(637-639\)845\]](#). Phosphino bound palladium ( $M = \text{Pd}$ ) and platinum ( $M = \text{Pt}$ ) complexes **535** were prepared based on the reaction of Kumada's ferrocene-based ligand with  $\text{MX}_2$  ( $X = \text{Cl}, \text{Br}$ ) [\[1980BCJ1138\]](#). In the case of palladium they isomerized to the more stable (*P,N*)-complexes **536** ([Equation \(111\)](#)).

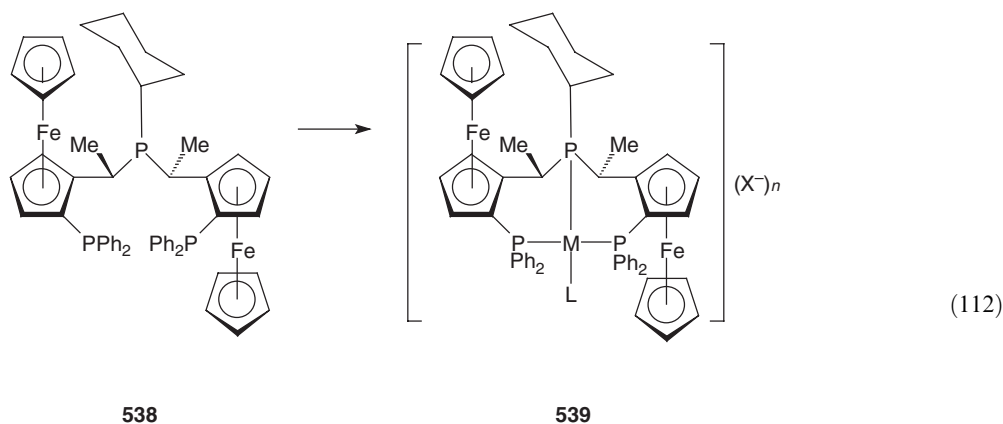


Other examples of stable *P,N*- or transiently formed *P,N*- and *P,S*-ferrocene Pd complexes **537** were also reported <1996JOM(508)209, 2003OM1255>.



**537**  $L_2 = \text{SPh}$ ,  $N = \text{CHPh}$

Togni and Barbaro prepared a new chiral phosphine ligand **538** based on ferrocene <1995OM3570>. It was obtained by the reaction of *N,N*-dimethyl-(*S*)-1-[(*R*)-2-(diphenyl phosphino)ferrocenyl]ethylamine with cyclohexylphosphine in acetic acid in 47% yield. This rare example of tridentate ligand was ideal to form cationic  $d^8$ -metal complexes (**539a–539d**) in which the metal (Pd or Ni) was held in a rigid coordination environment (Equation (112)).



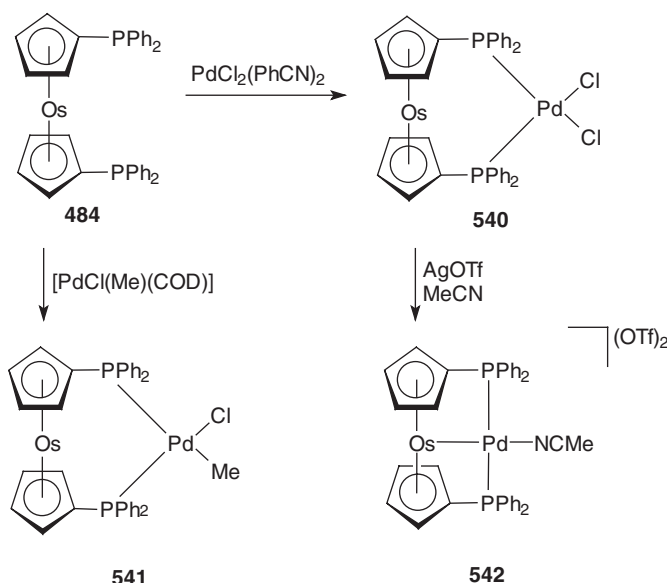
- 539 a**  $M = \text{Pd}$ ,  $L = \text{Cl}$ ,  $(X^-)_n = \text{PF}_6^-$  (64%, orange)  
**b**  $M = \text{Pd}$ ,  $L = \text{MeCN}$ ,  $(X^-)_n = (\text{PF}_6^-)_2$  (62%, purple)  
**c**  $M = \text{Pd}$ ,  $L = \text{MeCN}$ ,  $(X^-)_n = (\text{BF}_4^-)_2$  (82%, purple)  
**d**  $M = \text{Ni}$ ,  $L = \text{MeCN}$ ,  $(X^-)_n = (\text{ClO}_4^-)_2$  (70%, deep purple)

The methoxycarbonylation reaction of ethene catalyzed by bis(aquo)palladium(II) complexes with 1,1'-bis(diphenylphosphino)ferrocene and 1,1-bis(diphenylphosphino)octamethyl ferrocene in the presence of *p*-toluenesulfonic acid was studied using high-pressure NMR <2003OM2409>.

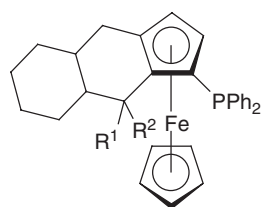
Gusev and co-workers <2003OM913> treated 1,1'-bis(diphenylphosphino)osmocene **484** with  $\text{PdCl}_2(\text{PhCN})_2$  and  $\text{PdCl}(\text{Me})(\text{COD})$  and obtained new Pd complexes **540** and **541**. These complexes were further reacted with halide scavengers ( $\text{AgOTs}$ ,  $\text{AgOTf}$ ,  $\text{NaB}[\text{3,5-(CF}_3)_2\text{C}_6\text{H}_3]_4$ ) to give complexes possessing a new Os—Pd bond. For instance, treatment of **540** with silver triflate in acetonitrile afforded the complex **542**. The X-ray analysis revealed a strong Os—Pd bonding interaction (2.84 Å) and an additional Pd—N interaction (1.885 Å) (Scheme 71).

Novel aminophosphine ligands **543** were prepared based on ferroceno- and *trans*-decalin backbones for enantioselective transition metal (Pd) catalysis <2002M991>.





Scheme 71

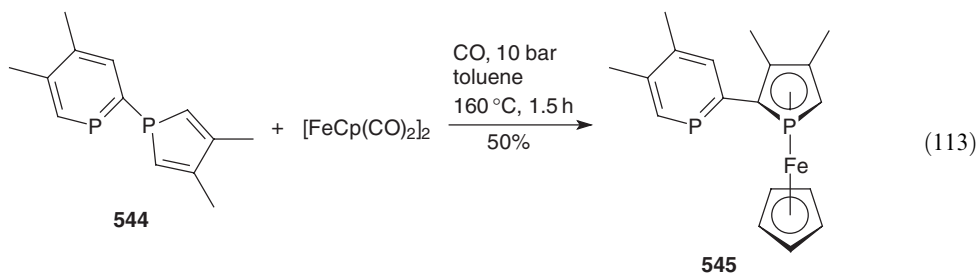
543  $\text{R}^1\text{R}^2=(=\text{O})$ ;  $\text{R}^1 = \text{H}$ ;  $\text{R}^2 = \text{OH}, \text{NMe}_2$ 

Synthesis of homogeneous chiral 1,1'-bis(diphenylphosphino) ferrocene derivatives as well as silica-supported chiral ligands for stereoselective hydrogenation reactions was reported <2000NJC597>.

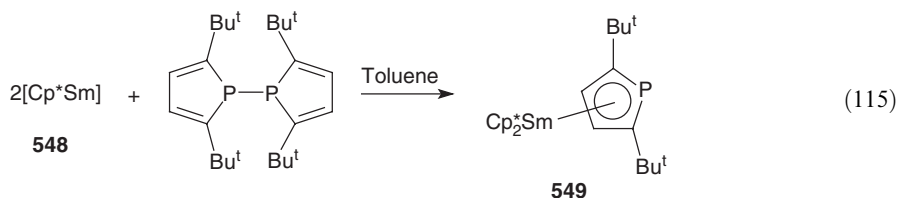
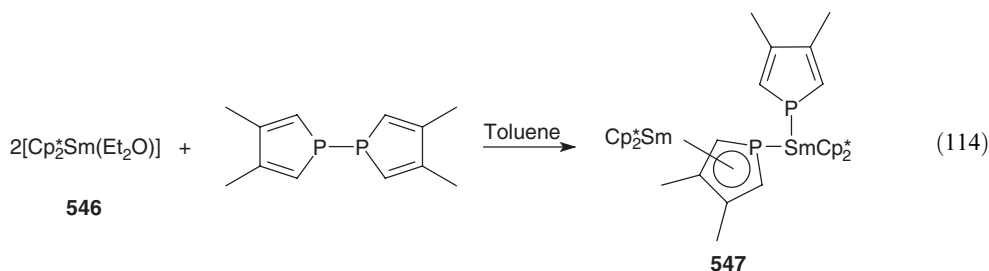
Togni and co-workers synthesized dendrimers containing chiral ferrocenyl diphosphines and applied them to asymmetric catalysis <1998JA10274, 2001CJC1762>. Several patents have also appeared in this field and are dealing with: preparation of silylated ferrocenediphosphine ligands, silica-gel and organic polymeric-bound derivatives and polymeric iridium and rhodium complexes <1996EP729969>, preparation of ferrocenyldiphenylphosphine derivatives as ligands for metal complexes (Pt, Rh, Pd, Ru, Ir) <1997JP09059290>, synthesis of optically active metallocenyl phosphines <1996WOP9616971>.

## (ii) Phosphametallocenes

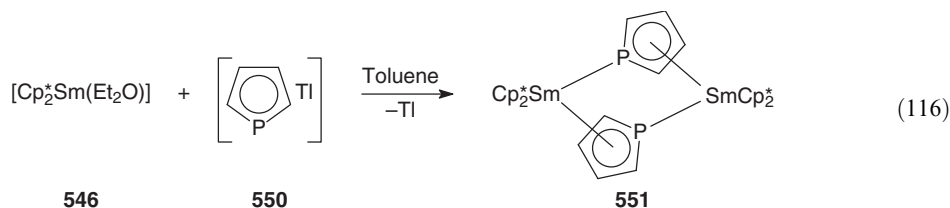
(a) *New methods and modifications.* One of the methods of synthesis of phosphafero-cenes is the reaction of phospholes with dicyclopentadienyltetracarbonyl diiron in boiling xylene. The reported yield remained, however, low and in the range of 20–30%. The performance of such reactions under CO pressure in toluene as in the case of 544 gave the phosphaferrrocene 545 in a slightly better yield of 50% as a result of an accompanying [1,5]-sigmatropic shift of the phosphinine moiety around the phosphole ring <1997CB(R)843> (Equation (113)).



Another method involved the P—P diphosphole precursors which were reacted with penta-methylcyclopentadienylsamariums **546** and **548** to afford new samarium complexes **547** and **549** possessing different coordination modes of samarium to the heterocyclopentadienyl ring (Equations (114) and (115)) <2001OM3884>.



The dimeric structure **551** in which the unsubstituted phospholyl ligands,  $\sigma$ - $\pi$  bonded to the two samarium atoms, were obtained by the condensation of the samarium etherate **546** with the thallium phospholide **550** (Equation (116)).

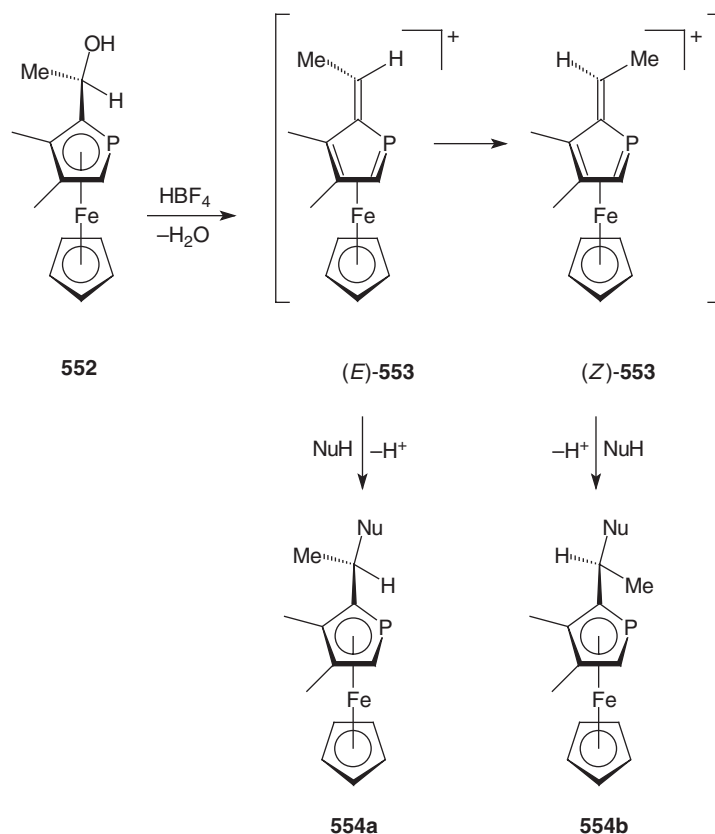


By modification of the side chain of the phospholyl ring, the alcohol **552** could be converted to the cationic fulvene-like species (*E*)-**553**. In the absence of a nucleophile the latter isomerized to the thermodynamically more stable (*Z*)-**553** <1998CEJ2148> (Scheme 72). Both (*E*)- and (*Z*)- forms constitute synthetically valuable intermediates as electrophiles.

Thus, the reaction (*E*)-**553** with nucleophiles (Nu = OH, PPh<sub>2</sub> or P(C<sub>6</sub>H<sub>11</sub>)<sub>2</sub>) yielded the corresponding products **554a** with retention of configuration, while the (*Z*)-**553** gave the products **554b** with inversion of configuration in comparison with the starting alcohol **552**.

### (iii) Enantiopure phosphametalloenes

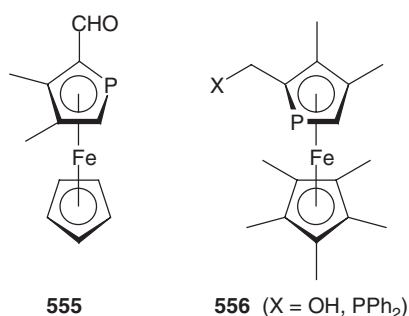
In the review period, interest in the synthesis of chiral phosphametalloenes has increased. Several planar chiral phosphaferrrocenes have been resolved in enantiomerically pure forms <1997TA2607, 1997CB1771, 1997OM2862, 1998EJI1163, 1998OM773, 1998JOC4168, 1999OM5444, 2000OL3695, 2000JA9870, 2001TA533>.



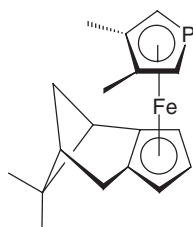
Scheme 72

Ganter and co-workers reported an efficient method (94% yield, >99% ee) for resolution of the racemic **555** via diastereomeric amins formed from **555** and  $(R),(R)$ -1,2-di(*N*-methylamino)-cyclohexane using column chromatography over silica gel <1997TA2607>.

Fu and Qiao synthesized other enantiopure planar chiral phosphoferrocenes **556** ( $\text{X} = \text{OH}$ ,  $\text{PPh}_2$ ) via reduction (LAH) of the corresponding aldehyde to alcohol **556** ( $\text{X} = \text{OH}$ ) and reported its resolution by chiral HPLC followed by one-pot chlorination with  $(\text{COCl})_2$  and condensation with  $\text{Ph}_2\text{PK}$  <1998JOC4168>.

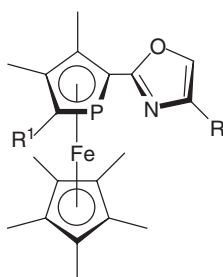


The phosphoferrocene **557** containing the chiral pinene-fused cyclopentadienyl ligand was synthesized from the corresponding dimeric iron carbonyl complex and *P*-*t*-butylphosphole <2000T17>. Introduction of the aldehyde function in the second position to the P was achieved by the Vilsmeier reaction. The diastereomeric aldehydes obtained in a ratio of 2:1 were separated via the respective amins derived from  $(R),(R)$ -1,2-di(*N*-methylamino)cyclohexane.



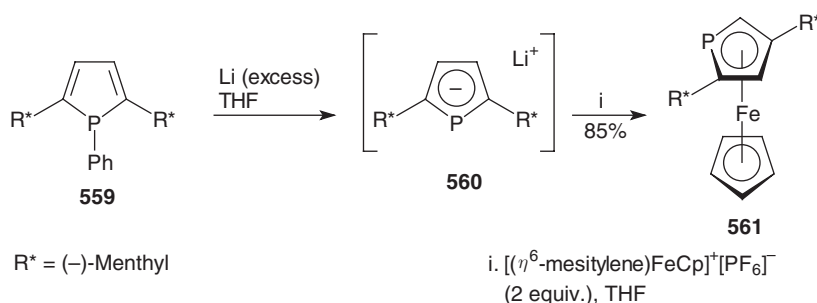
557

Planar-chiral phosphoferrocene-oxazolines **558** ( $R^1 = H$ ) a new class of *P,N*-ligands were synthesized by the reaction of the corresponding trifluoroacetylated monophosphoferrocene with the dianion of the relevant amino alcohol ( $R = Pr^i, Bu^t$ ) followed by separation of diastereomeric oxazolines by column chromatography <2000OL3695>. Phenyl substituted phosphoferrocenes **558** ( $R^1 = Ph$ ) were also obtained in 46% ( $R = Ph$ ) and 47% ( $R = Pr^i$ ) yields <2002OL3699>.



**558**  $R = Pr^i, Bu^t, Ph$   
 $R^1 = H, Ph$

Starting from the novel enantiomerically pure phosphole **559** with two (–)-menthyl groups at the 2- and 5- positions of the phosphole ring, the corresponding chiral monophosphoferrocene **561** was obtained via the chiral lithium phospholide **560** in 84–85% yields, respectively <2001OM1014> (Scheme 73).



Scheme 73

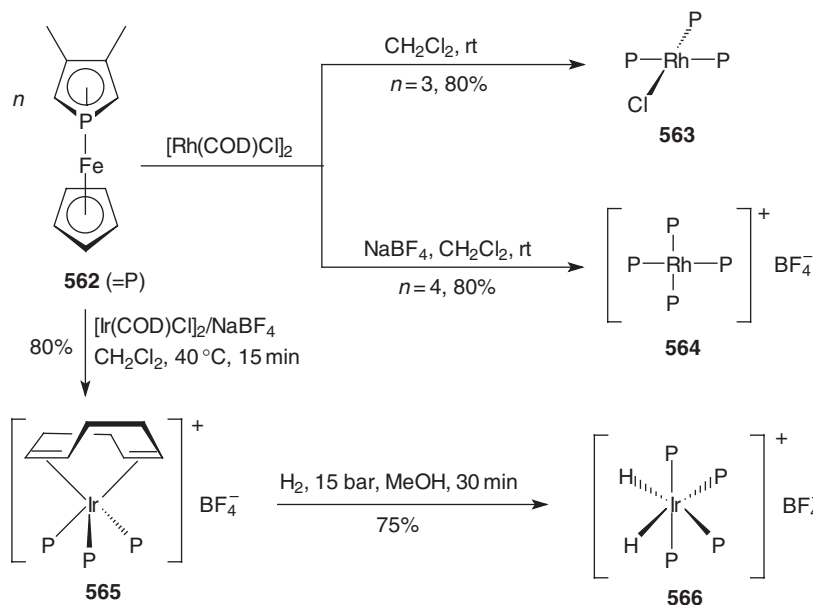
The first NMR studies of two atropisomeric diastereoisomers of monophosphoferrocene with four (–)-menthyl groups have recently been conducted <2003OM1783>.

The latter protocol was applied to synthesis of the 3,4-dimethylphospholyl analog of ferrocifen (a ferrocenyl analog of tamoxifen, a drug used in the treatment of hormone-dependent breast cancers) <2003TL2749>.

The chemistry of other chiral heterometallobenes including enantiomerically pure phosphoferrocenes was reviewed up to 2001 by Ganter <2001JCS(D)3541>.

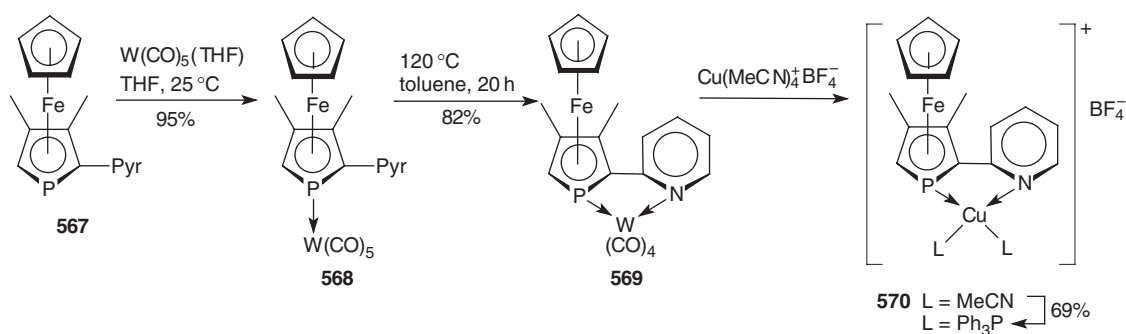
## (iv) Metal complexes

Starting from 3,4-dimethylphosphaferrocene **562**, new neutral and cationic rhodium complexes **563** and **564** as well as iridium complexes **565** and **566** were prepared <1999OM807> (Scheme 74).



Scheme 74

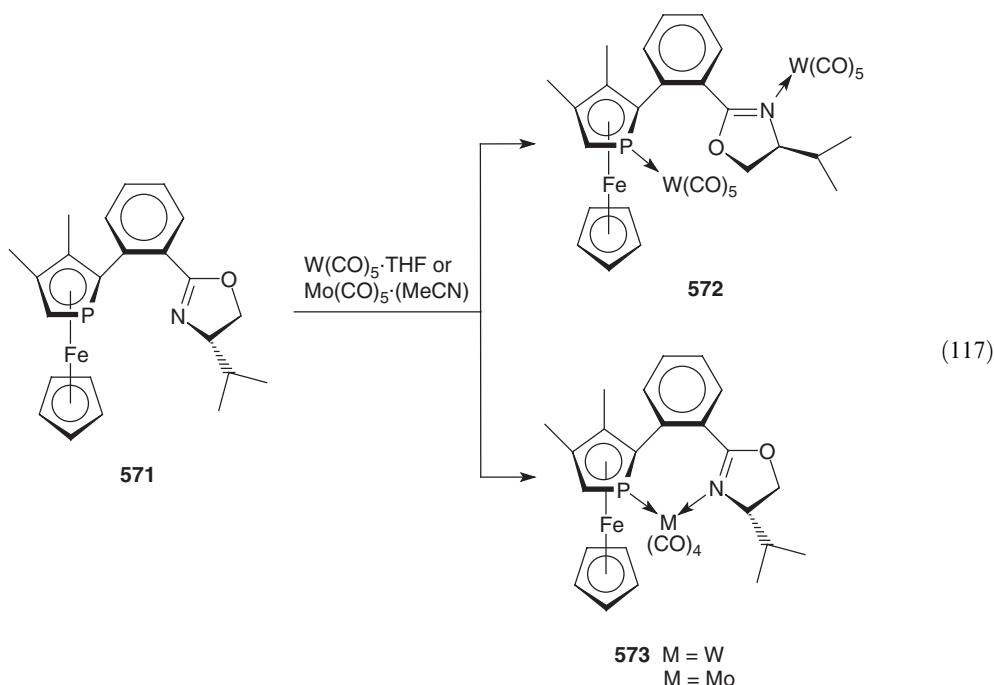
Mathey and co-workers described the *P,N*-chelating properties of the new ligand 2-(2'-pyridyl)phosphaferrocene **567** <1997JOM(548)17>. With soft transition metals they synthesized new neutral tungsten **568** and cationic copper(I) complexes **570** (Scheme 75).



Scheme 75

It was interesting to note that on prolonged heating of the complex **568** in refluxing toluene, it converted to the chelate **569** with loss of one molecule of CO. Both copper(I) complexes possessed a low stability which precluded analysis by means other than NMR.

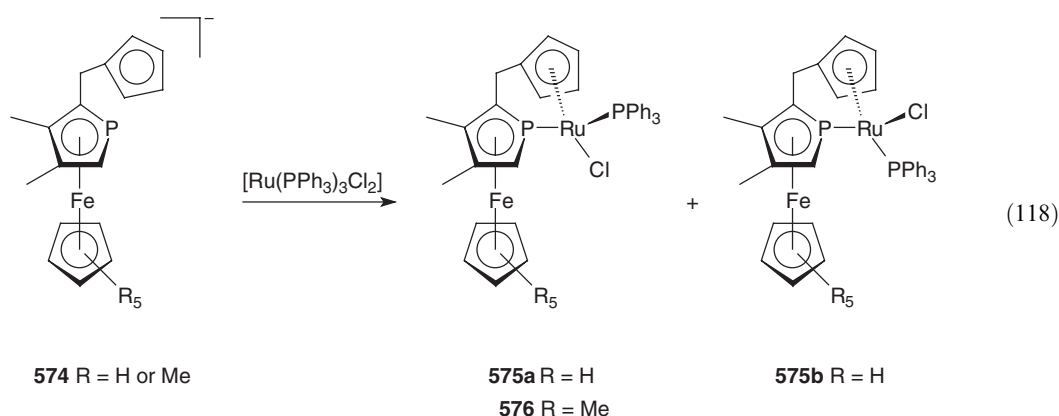
The reaction of the phosphaferrrocene **571** with an excess of the tungsten pentacarbonyl THF complex gave the new bimetallic complex **572** as a mixture of two diastereoisomers, where both P and N atoms are separately complexed by two  $\text{W}(\text{CO})_5$  moieties <2002EJ11657> (Equation (117)).



In this reaction, a minor compound **573** ( $M = W$ ) was also formed as a mixture of two diastereomers. However, the reaction of **571** with the molybdenum complex afforded exclusively the chelate derivative **573** ( $M = Mo$ ).

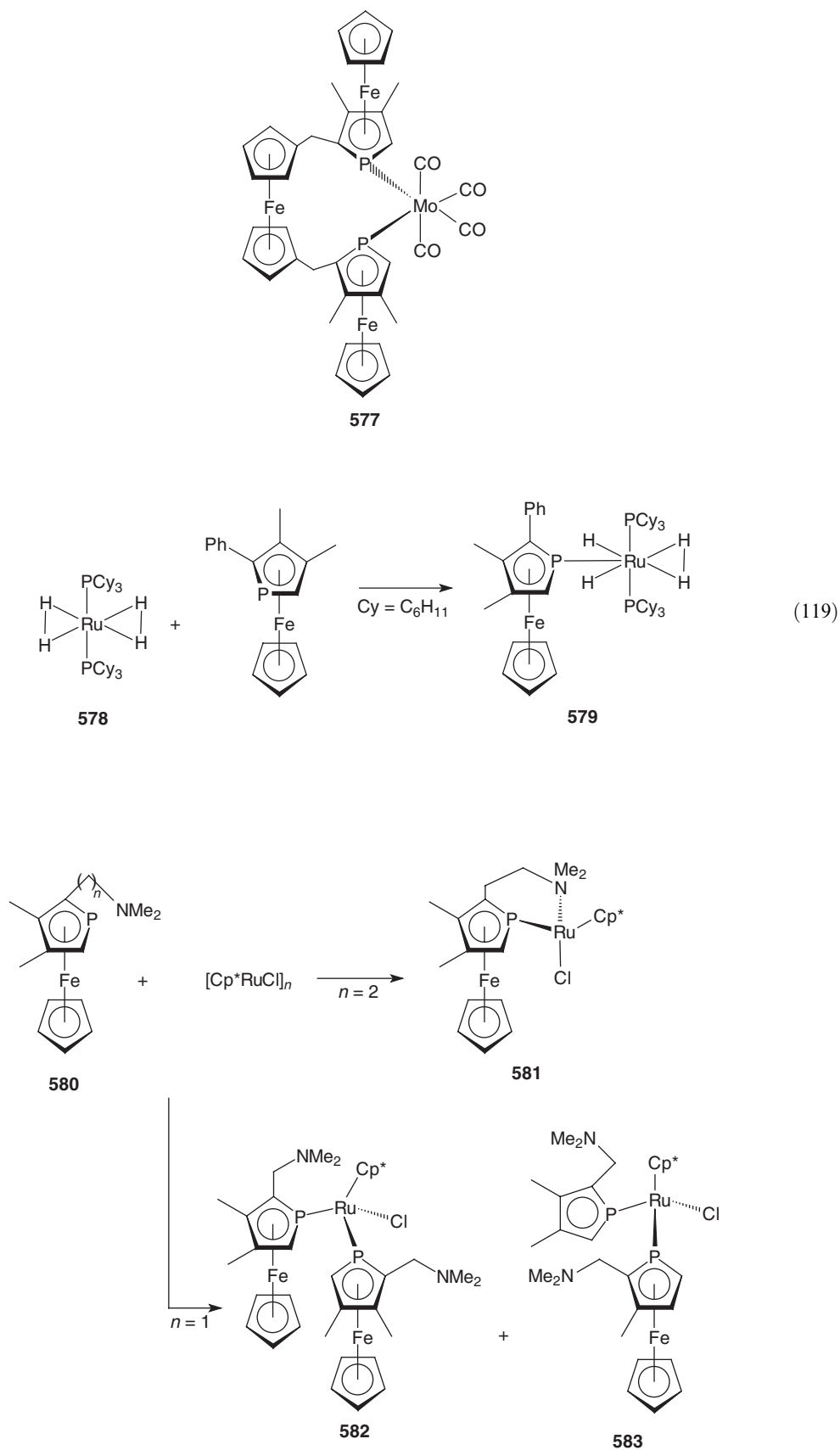
Looking for new *P,P*-chelate ligands, Ganter and co-workers [<1999OM5444>](#) synthesized the cyclopentadienides **574** in the condensation reaction of racemic 3,4-dimethyl-2-formylphosphaferrocenes with cyclopentadiene in the presence of pyrrolidine.

The cyclopentadienide **574** ( $R = H$ ) was further complexed with ruthenium complex  $[Ru(PPh_3)_2Cl_2]$  to give two diastereomeric half-sandwich complexes (**575a,b**) as red crystals in 63% yield and a 95:5 isomer ratio. The diastereomeric purity of the analogous  $Cp^*$  complex **576** exceeded 98% [<2001OM1614>](#) (Equation (118)). From the cyclopentadienide **574a** ( $R = H$ ) and  $FeCl_2$ , the corresponding ferrocene ligand was obtained and further complexed with the molybdenum carbonyl to give the new Mo-complex **577**.



The bis(dihydrogen)ruthenium complex **578**, when treated with 2-phenyl-3,4-dimethylphosphaferrocene, gave the new ruthenium(II) complex **579** in 90% yield [<2001IC3034>](#) (Equation (119)).

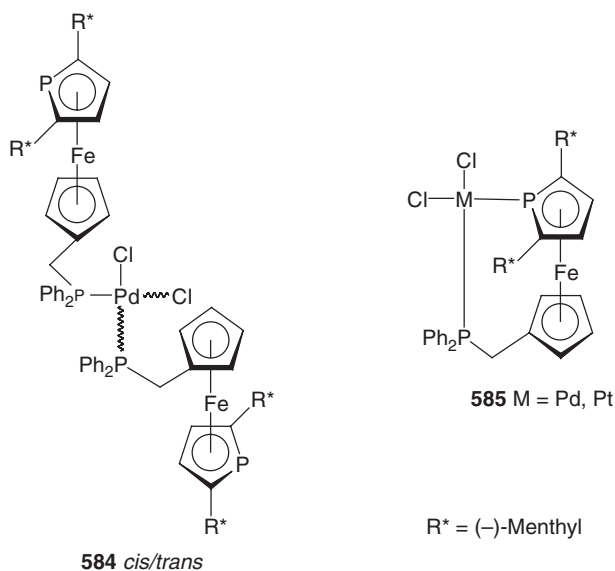
A new concept for *P,N* and *P,P* chelate ligands with planar chirality was presented by Ganter and co-workers [<1997OM2862>](#). They used the phosphapherrocenes **580** ( $n = 1, 2$ ) and reacted them separately with  $[Cp^*RuCl]_4$  (Scheme 76).



Scheme 76

The complexation reaction of **580** ( $n = 2$ ) gave the desired complex **581** as an orange red powder in quantitative yield simply by evaporating the solvent. Completely different results were obtained in the reaction of the ligand **580** ( $n = 1$ ) with the same ruthenium complex and the two isomeric complexes **582** and **583** were obtained. The *P,P* palladium complex with  $(\text{PhCN})_2\text{PdCl}_2$  was also obtained from **580** ( $n = 1$ ) in which  $\text{NMe}_2$  was replaced by  $\text{OPPh}_2$ .

Hayashi and co-workers described the synthesis of a new chiral phosphinomethyl-phosphaferrocene ligand utilizing chiral lithium (–)-2,5-dimethylphospholide [<2001OM3913>](#). The ligand behaved either as a monodentate ligand in the complex **584** (with a free phosphaferrocene) or a bidentate ligand in the complex **585** depending on the ratio of the phosphino-phosphaferrocene/ $\text{MCl}_2(\text{COD})_2$  ( $\text{M} = \text{Pt}, \text{Pd}$ ).



#### (v) Diphosphametalloenes

In the previous review period (until 1995), only 1,1'-diphosphaferrocenes were synthesized as representatives of phosphametalloenes. Both 1,1'-diphosphaferrocenes and monophosphaferrocenes have usually been obtained from phospholes by two different procedures: (i) the lithium induced cleavage of a P-substituent and subsequent reaction of the resulting lithium phospholide with iron(II) halides or arene(cyclopentadienyl) iron derivatives; (ii) thermal sigmatropic shift of the P-substituent followed by the reaction of the resulting intermediate 2*H*-phosphole with iron complexes [<1978JOM\(156\)C33, 1979JCS\(D\)1552, 1984JOM\(263\)55, 1997JOM\(548\)17>](#). The reaction of phospholide anions with various metal halides was also used for the synthesis of other diphosphametalloenes. 1,3-Diphosphaferrocene was also synthesized for the first time.

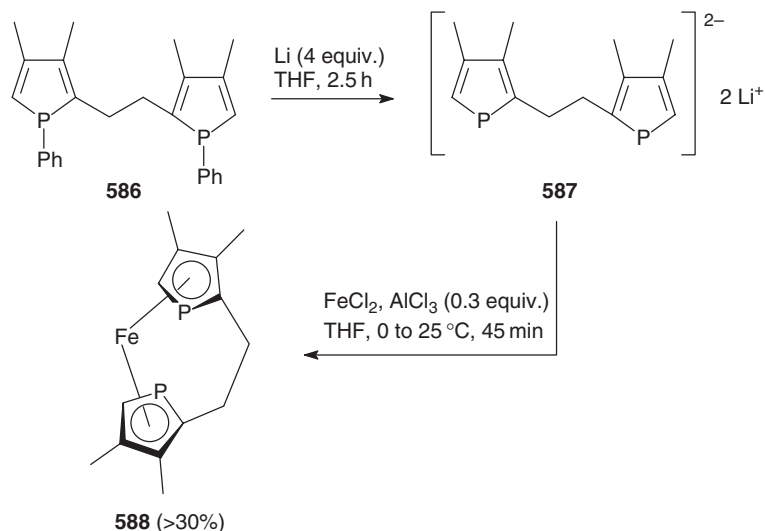
(a) *Modifications and ring functionalizations of 1,1'-diphosphaferrocenes.* 1,1'-Diphospha[2]ferrocenophane **588** with a tilt angle of 20 °C was synthesized as a single isomer by Mathey and co-workers by adaptation of the classical cleavage of the two P–Ph bonds of the diphosphole **586** with lithium (4equiv.) followed by the reaction of the resulting diphospholide **587** with  $\text{FeCl}_2$  [<2001OM1499>](#) (Scheme 77).

Several Si-, S-, and Sn-substituted diphosphaferrocenes were prepared starting from 2-substituted ( $\text{R} = \text{CN}, \text{SMe}, \text{SnMe}_3, \text{TMS}$ ) 1-phenyl-3,4-dimethylphospholes via the usual P–Ph bond cleavage by potassium in DME ( $\text{R} = \text{CN}$ ) or lithium in THF ( $\text{R} = \text{SMe}, \text{SnMe}_3, \text{TMS}$ ) to give the corresponding phospholides followed by the reaction with  $\text{FeCl}_2$  [<1996BSF541>](#).

A mixture of *meso* and *rac* diastereoisomers of diphosphaferrocenes was similarly obtained in 23% yield [<1998OM2996>](#). 1,1'-Diphosphaferrocenes can be easily functionalized via electrophilic substitution reactions. Earlier studies by Mathey and co-workers showed that 1,1'-diphosphaferrocenes underwent an easy functionalization via the Friedel–Crafts acetylation with the acetyl chloride/ $\text{AlCl}_3$  system [<1987NJC585, 1990JOM\(400\)149>](#). Zakrzewski and co-workers [<1998OM5880>](#) showed that diphosphaferrocenes could also be monoacetylated with succinic anhydride and  $\text{AlCl}_3$  (2 h) in dichloromethane in 80% yield. The acetoacetylated



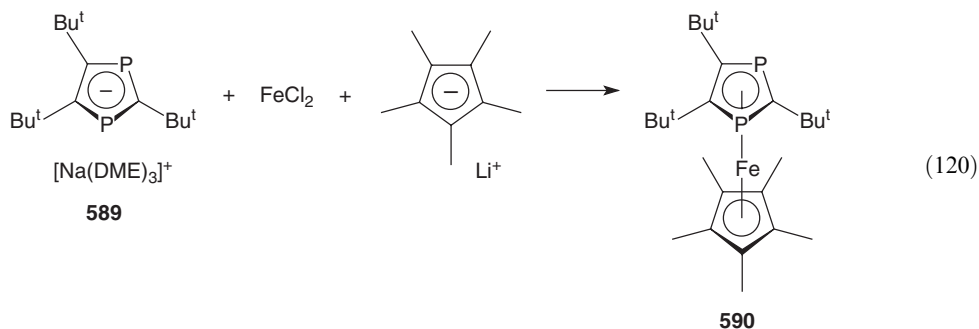
1,1'-diphosphaferrocene was further synthesized by Zakrzewski and co-workers in the Friedel–Crafts-type reaction of 3,3',4,4'-tetramethyl-1,1'-diphosphaferrocene with ketene in the presence of Lewis acids ( $\text{BF}_3$  or  $\text{AlCl}_3$ ) <2001OM4448>.



Scheme 77

Functionalization of the delocalized C—C double bond in 3,3',4,4'-tetramethyl-1,1'-diphosphaferrocene was also achieved by carboxylation with the  $\text{CO}_2$ — $\text{AlCl}_3$  system following a similar procedure applied to ferrocene to give the corresponding 2-carboxylic acid derivative <2002JOM(642)143>.

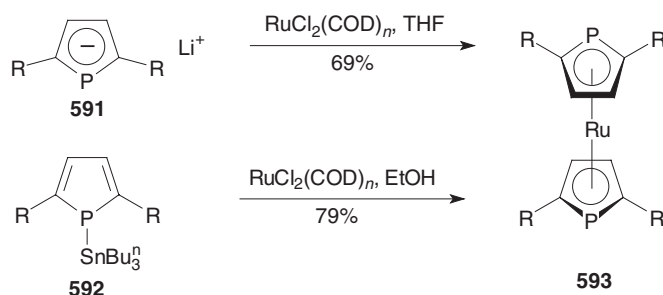
Probably the first example of 1,3-diphosphaferrocene **590** was synthesized on treatment of ferrous chloride with a mixture of the anions  $[\text{C}_3\text{Bu}^t\text{P}_2]^-$  **589**,  $[\text{C}_2\text{Bu}^t\text{P}_3]^-$  and  $[\text{C}_5\text{Me}_5]^-$  by a modified procedure to give a mixture of four cross-products from which pale red crystals of **590** were isolated and analyzed by X-ray <1996JOM(512)141> (Equation (120)).



(vi) 1,1'-Diphosphametalloenes other than 1,1'-diphosphaferrocenes

After 1995, preparations of numerous 1,1'-diphosphametalloenes ( $\text{M} = \text{Ge}, \text{Sn}, \text{Pb}, \text{Ti}, \text{Zr}, \text{Hf}, \text{Tm}, \text{Sm}, \text{Nd}$ ) were reported. Some of them were synthesized according to the usual protocol applied for 1,1'-diphosphaferrocenes. For instance, 2,5-di(*t*-butyl)phospholyl sandwich complexes containing group 14 elements ( $\text{M} = \text{Ge}, \text{Sn}, \text{Pb}$ ) were synthesized by reactions of the corresponding halides  $\text{MX}_2$  ( $\text{M} = \text{Sn}, \text{Pb}, \text{X} = \text{Cl}$ ;  $\text{M} = \text{Ge}, \text{X} = \text{I}$ ) and the THF complex of lithium 2,5-di(*t*-butyl)phospholide <1999CC1273>. Syntheses of other metalloenes utilized the same type of condensation reaction with various modifications of the starting materials. For instance, 2,5-dimethyl and 2,5-dicyclohexyl 1,1'-diphospharuthenocenes **593** [ $\text{R} = (-)\text{-menthyl}, \text{cyclohexyl}$ ] were synthesized by

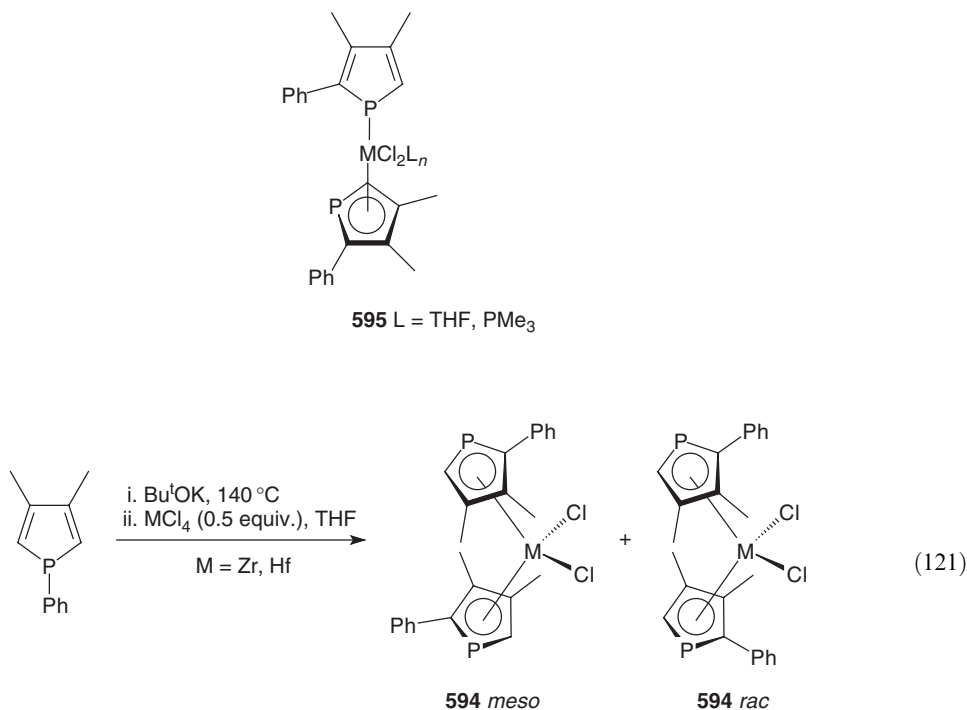
two methods involving the condensation of the COD complexed ruthenium dichloride with: (i) lithium phospholide **591** in THF (69% yield), (ii) *P*-stannylphosphole **592** in EtOH (79% yield) <2002OM3062> (Scheme 78).



Scheme 78

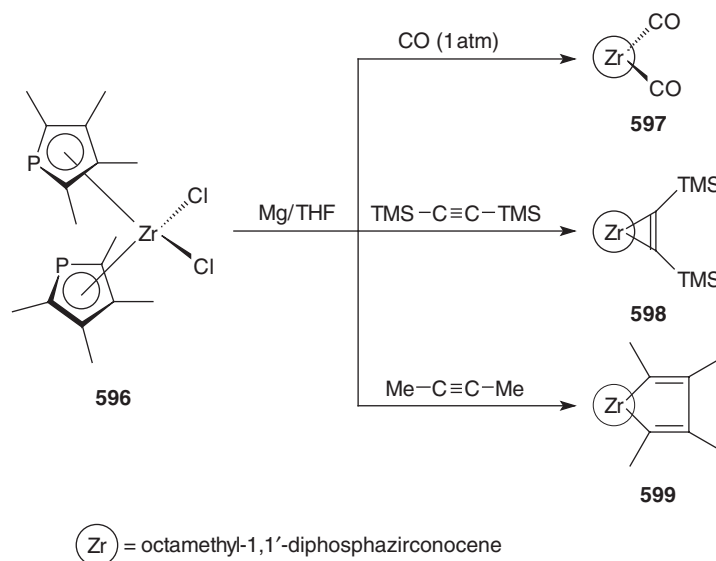
The first NMR studies of two atropoisomeric diastereoisomers of diphospharuthenocene with two (–)-menthyl substituents at each ring have been recently reported <2003OM1783>.

Several  $C_2$ -symmetric bis(phospholyl) adducts of group 4 metals (**594**, M = Ti, Zr, Hf), including the first example of the  $\eta^5$ -phospholyl hafnium complex **594** (M = Hf), were synthesized and structurally characterized. These complexes underwent *rac*/*meso* isomerization in a process that was accelerated by polar Lewis bases. The bases probably facilitated the isomerization by stabilizing ring-slipped intermediates **595** <2001OM3453> (Equation (121)).



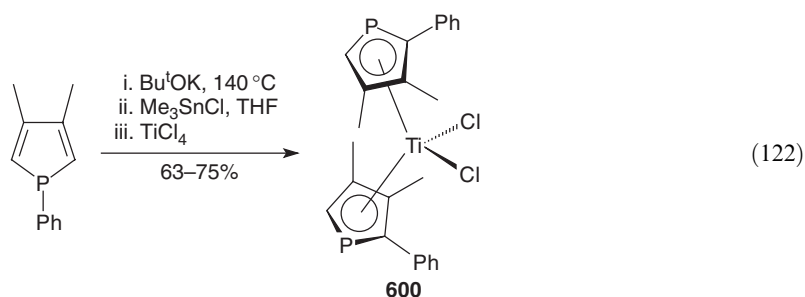
Several other dichlorodiphosphazirconocenes of the structure  $(2,5-R_2C_4H_2P)_2ZrCl_2$  (e.g., R = H, Ph,  $Bu^t$ , TMS) were also synthesized and used as catalysts of propylene polymerization using methylaluminoxane as co-catalyst.

Modification of the metal coordination sphere of the octamethyl-1,1'-diphosphazirconocene dichloride **596** was demonstrated by Mathey and co-workers in syntheses of three new complexes (**597**–**599**) by trapping the transient 14e 1,1'-diphosphazirconocene with CO and alkynes (Scheme 79) <2002OM259>.



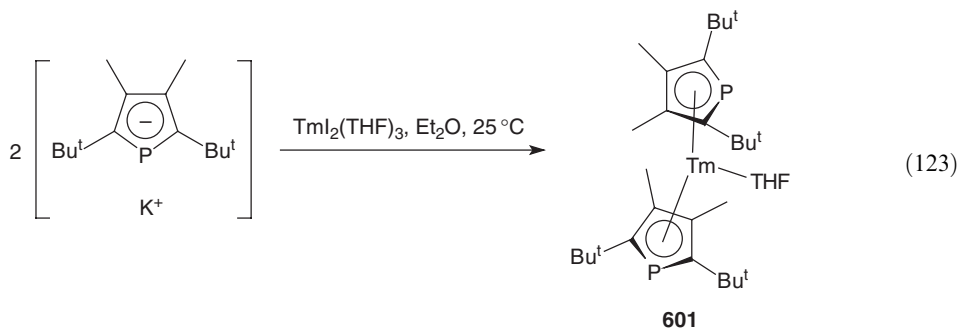
Scheme 79

1,1'-Diphosphatitanocenes were synthesized by Hollis and co-workers according to the modified procedure [<1988CC770>](#) via tin salts outlined in [Equation \(122\)](#) [<2002CC2996>](#). According to this procedure the chiral phosphatitanocene **600** was obtained from 3,4-dimethyl-1-phenylphosphole in a multistep reaction in 63–75% yield.

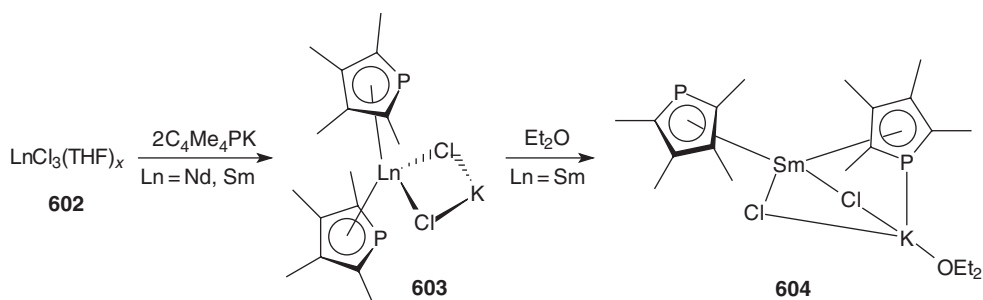


Hollis and co-workers [<2003OM1432>](#) showed further the first example of a low-valent phosphatitanocene, a structural analog of the zirconocene **596**. They applied Mathey's and co-workers' [<2002OM259>](#) reduction conditions using magnesium under an atmosphere of CO at 40 °C to produce the titanocene dicarbonyl analog of **597**.

Condensation of thulium diiodide in THF with two molar excess of the potassium 2,5-di-*t*-butyl-3,4-dimethylphosphole afforded a dark blue-green solid of structure **601** established by X-ray analysis [<2002CC1646>](#) ([Equation \(123\)](#)).



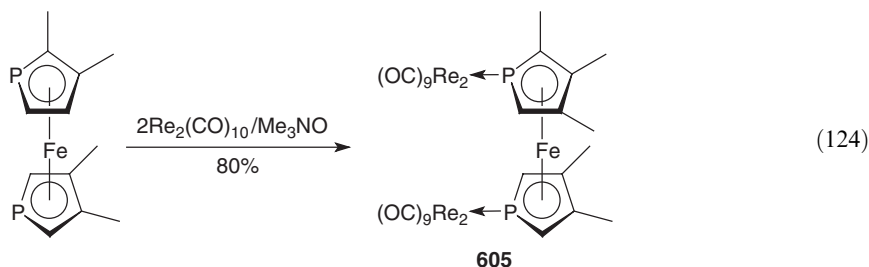
Nief and co-workers synthesized unsolvated bis(phospholyl)neodymium(III) and samarium(III) chlorides **603** (Ln = Nd, Sm) in the reaction of 2,3,4,5-tetramethylphospholyl potassium with the THF solvated neodymium and samarium trichlorides **602** (Ln = Nd, Sm) in 57% and 63% yields, respectively <1999EJI1041> (Scheme 80). Crystallization of the samarium complex **603** (Ln = Sm) from diethyl ether gave a polymeric ether solvate **604** which was characterized by X-ray crystallography. The triply bridging chlorine atoms (between the Sm and K atoms) were responsible for the polymeric chain that linked the organosamarium residues.



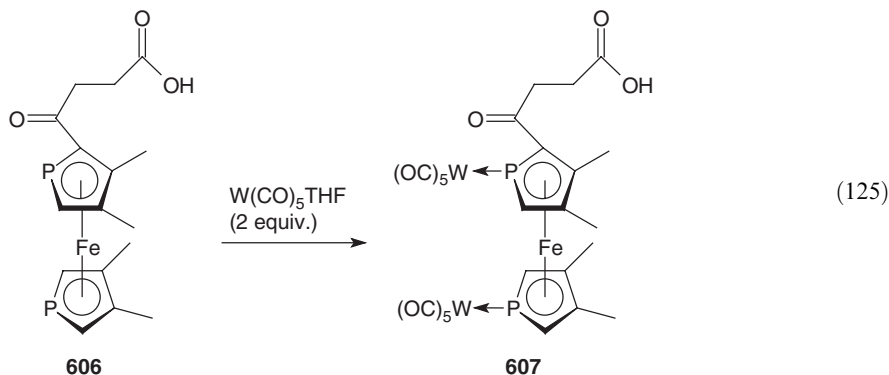
Scheme 80

(vii) Metal complexes

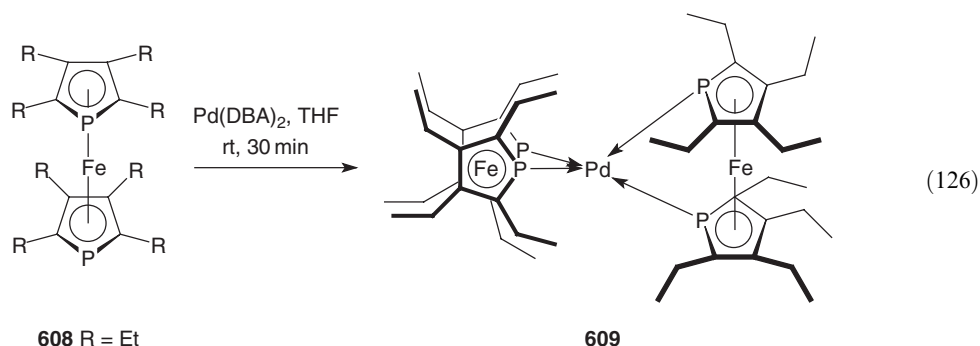
1,1'-Diphosphaferrocene upon treatment with 2 equiv. of rhenium carbonyl/trimethylamine N-oxide afforded the dirhenium complex **605** in 80% yield <2002JOM(645)268> (Equation (124)).



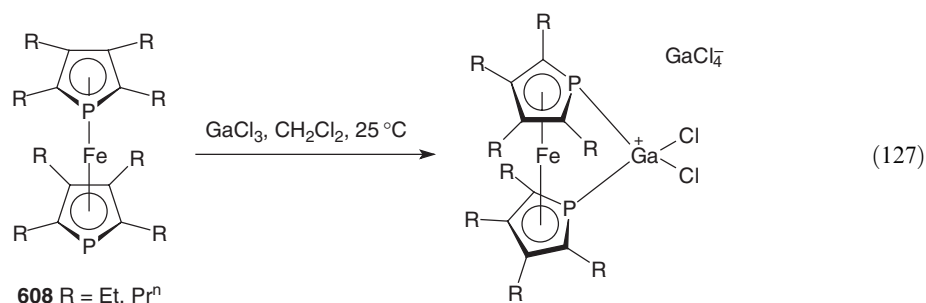
On the other hand, it was shown by Zakrzewski and co-workers <1998OM5880> that the monoacetylated 1,1'-diphosphaferrocene **606**, when treated with 1 equiv. of  $\text{W}(\text{CO})_5\cdot\text{THF}$  under photochemical conditions, gave a mixture of the products in which the  $\text{W}(\text{CO})_5$  moiety was coordinated to either P(1') or P(1) in a 7:1 ratio. With two or more equivalents of  $\text{W}(\text{CO})_5\text{THF}$ , the bis- $\text{W}(\text{CO})_5$  adduct **607** was obtained in 88% yield (Equation (125)).



The reaction of octaethyldiphosphaferrocene **608** with  $\text{Pd}(\text{DBA})_2$  yielded a green complex **609** <200OM4899> (Equation (126)). The reaction of **608** with  $\text{Ni}(\text{COD})_2$  gave the complex of analogous structure which was too oxygen sensitive to be isolated.

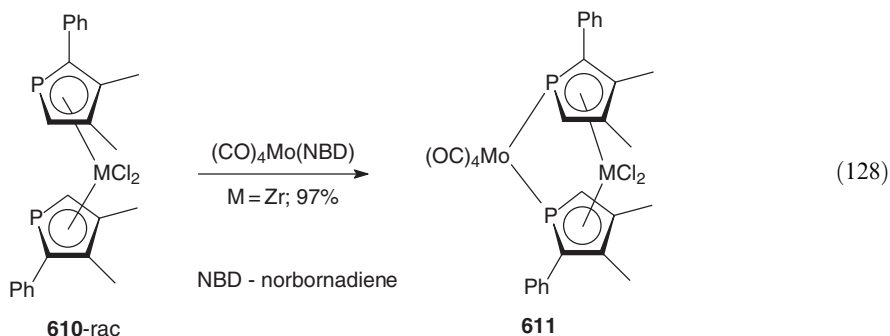


The neutral octaethyl and octapropyldiphosphaferrocene ligand **608** ( $R = \text{Et}, \text{Pr}^n$ ) reacted with gallium chloride at rt to afford cationic gallium complexes [<2002NJC1378>](#) (Equation (127)).



Theoretical studies showed that bonding of the phosphoferrocene ligand to the  $[\text{GaCl}_2]^+$  fragment involved the lone pairs of phosphorus and contribution of the P—Fe bond. The starting ligands **608** ( $R = \text{Et}, \text{Pr}^n$ ) were prepared by condensation of the corresponding lithium phospholides (2 equiv.) with  $\text{FeCl}_2$  (1 equiv.) in THF.

1,1'-Diphosphazirconocene **610** ( $M = \text{Zr}$ ) obtained in 80% yield as a 63:37 mixture of racemic and *meso*-isomers [<2000JA11737>](#) was used for the synthesis of the binap complex with rhodium bound with phospholyl phosphorus. In a similar way  $\text{C}_2$ -symmetric bis(phospholyl)hafnium adduct ( $M = \text{Hf}$ ) was obtained in 25% yield after recrystallization from pentane/ $\text{Et}_2\text{O}$  [<2001OM3453>](#). The bent relationship between the two phospholyl rings in the complex **610-rac** allowed the synthesis of the new bidentate molybdenum complex **611** [<2001OM3453>](#) (Equation (128)).



#### 4.22.5 FUNCTIONS CONTAINING TWO ARSENIC, ANTIMONY OR BISMUTH FUNCTIONS, $\text{R}_2\text{C}=\text{C}(\text{AsR}^2)_2$ , etc.

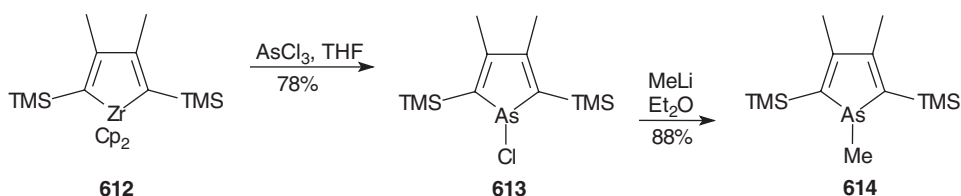
No further advances have occurred in this area since the publication of chapter 4.22.5 in 1995 [<1995COFGT\(4\)1021>](#).

#### 4.22.6 FUNCTIONS CONTAINING TWO DISSIMILAR COMBINATIONS OF ARSENIC, ANTIMONY OR BISMUTH, $R_2^1C=C(AsR_2^2)SbR_4^3$ , etc.

No further advances have occurred in this area since the publication of chapter 4.22.6 in COFGT (1995) <1995COFGT(4)1021>.

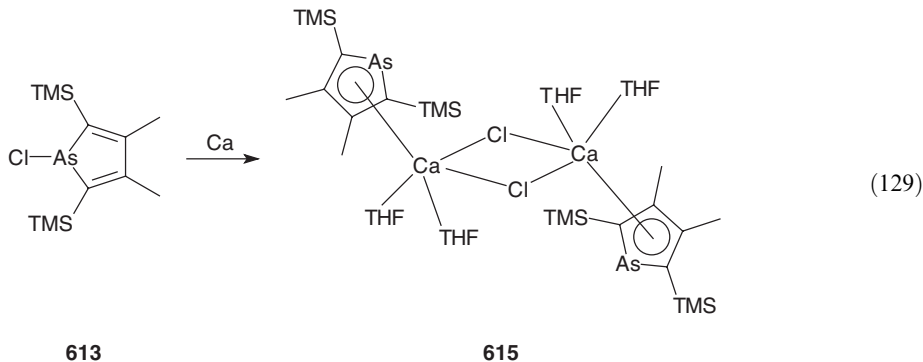
#### 4.22.7 FUNCTIONS CONTAINING ARSENIC, ANTIMONY OR BISMUTH WITH A METALLOID, $R_2^1C=C(AsR_2^2)SiR_3^3$ , etc.

The reaction of zirconocene dichloride with 2 equiv. of *n*-butyllithium and 1-trimethylsilylpropyne yielded a yellow 1,1-bis(cyclopentadienyl)-3,4-dimethyl-2,5-bis(trimethylsilyl)zirconacyclopenta-2,4-diene **612**. The metathesis reaction with  $AsCl_3$  yielded nearly quantitatively 1-chloroarsole **613** without chlorocyclopentadienyl exchange as in the case of the corresponding 1-chlorophospholes <1999OM2491> (Scheme 81).

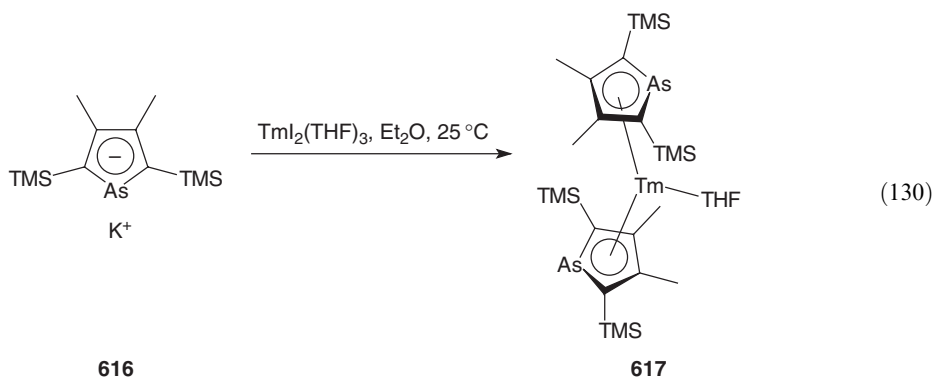


Scheme 81

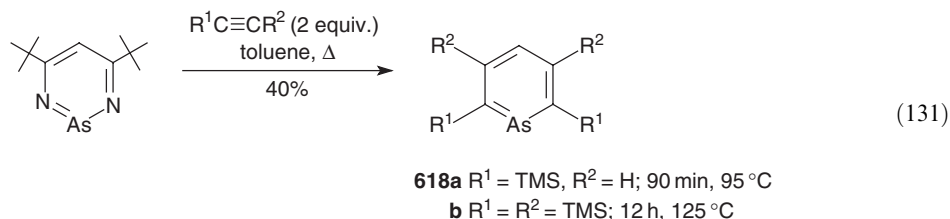
The As—Cl/As—Me conversion of **613** to **614** was carried out with MeLi <2001OM3884>. Earlier, Nief and Mathey reported the instability of chloroarsoles **613** <1993POL19>. The reduction of the latter with distilled calcium gave the dimeric trifunctional (As, Si, Ca) complex **615** (Equation (129)).



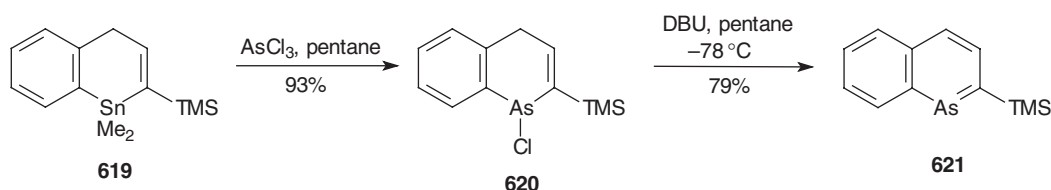
The silylated arsolythulium(II) complex **617** was obtained by Nief and co-workers in the condensation reaction of 2 equiv. of potassium 2,5-bis(trimethylsilyl)-3,4-dimethylarsolide **616** and a THF complex of  $TmI_2$  in diethyl ether <2002CC1646> (Equation (130)).



Silylated arsinines (**618a,b**) were prepared by Le Floch and co-workers from the 1,3,2-diazarsinine and silylated alkynes by the cycloaddition–cycloreversion sequence in 40% yield (Equation (131)) <1997OM4089>.

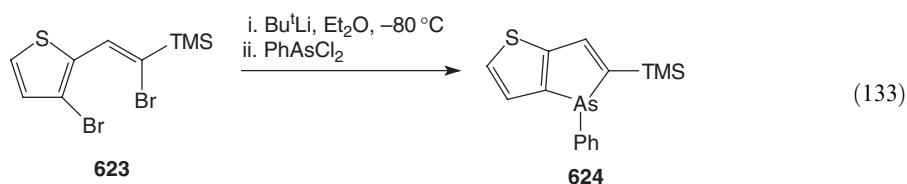
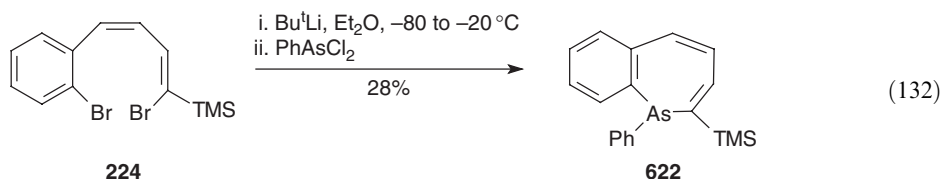


The Sn/As metathesis reaction of the stannacyclohexadiene **619** with  $\text{AsCl}_3$  gave 1-chloroarsacyclohexadiene **620** from which 2-trimethylsilyl-1-arsanaphthalene **621** was prepared (Scheme 82) <2001OM2109>.



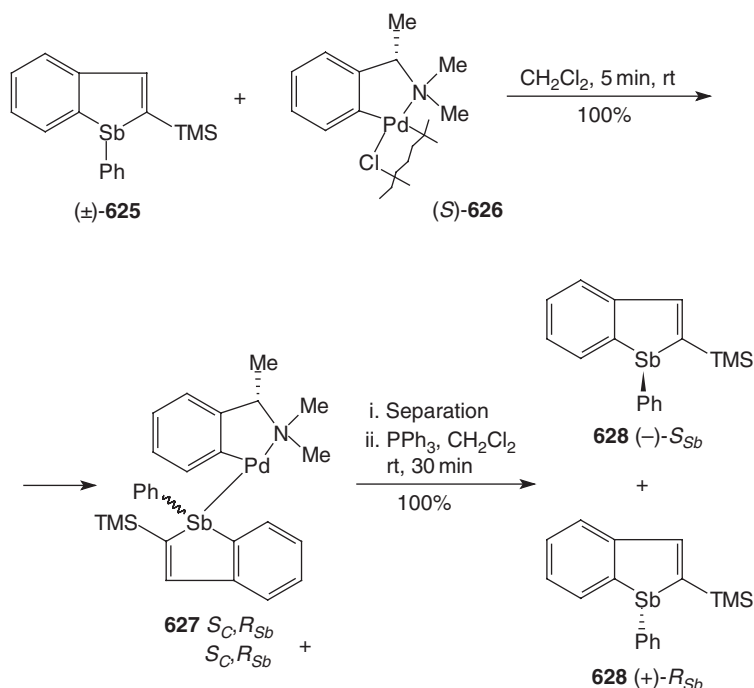
Scheme 82

Condensation of various aromatic acyclic dibromo- or monobromo derivatives with dichlorophenylarsine in the presence of strong and bulky bases led to formation of new 7- and 5-membered rings in bicyclic systems **622** and **624**, respectively, as a result of a multistage reaction consisting of metallation and cyclization. Thus, treatment of (*Z,Z*)-1-(bromophenyl)-4-(2-bromophenyl)-1-trimethylsilyl-1,3-butadiene **224** in the presence of  $\text{Bu}^t\text{Li}$  with dichlorophenylarsine gave 7-membered 5-phenyl-6-trimethylsilyl-5*H*-5-arsabenzocycloheptene **622** <1999CPB1108> (Equation (132)). The reaction of 1-bromo-2-(3-bromothiophen-2-yl)vinyl]trimethylsilane **623** with the same arsine in the presence of  $\text{Bu}^t\text{Li}$  afforded 4-phenyl-5-trimethylsilyl-4*H*-1-thia-4-arsapentalene **624** <1997H1891> (Equation (133)). Analogously, 6-phenyl-5-trimethylsilyl-6*H*-1-thia-6-arsapentalene was prepared from (*Z*)-1-bromo-2-(thiophen-3-yl-vinyl)trimethylsilane or (*Z*)-[1-bromo-2-(2-bromothiophen-3-yl)]trimethylsilane <1997H1891>.



As far as chiral Sb(III) compounds are concerned, only a few examples of Sb-chiral stibafluoranes and triarylstibines with hydroxycarbonyl and amino groups are reported. The first example of a resolution of ( $\pm$ )-1-phenyl-2-trimethylsilylstibindole **625** was presented by Kurita and co-workers <2000CC191>. They separated a mixture of diastereomeric Pd (II) complexes **627** having the bimetallic Pd–Sb bonding, on treatment of racemic **625** with 0.5 equiv. of di- $\mu$ -chlorobis{(*S*)-2-[1-(dimethylamino)ethyl]phenyl-CN}palladium(II) **626** (Scheme 83). It

resulted in a coordination of Sb to Pd to give quantitatively a 1:1 mixture of complexes **627** which were separated chromatographically on silica gel. Decomplexation to give optically pure (–)-**628** and (+)-**628** was carried out with triphenylphosphine.

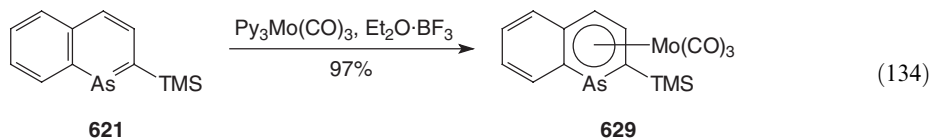


Scheme 83

#### 4.22.8 FUNCTIONS CONTAINING ARSENIC, ANTIMONY OR BISMUTH AND A METAL, $R_2C=C(AsR_2)M$

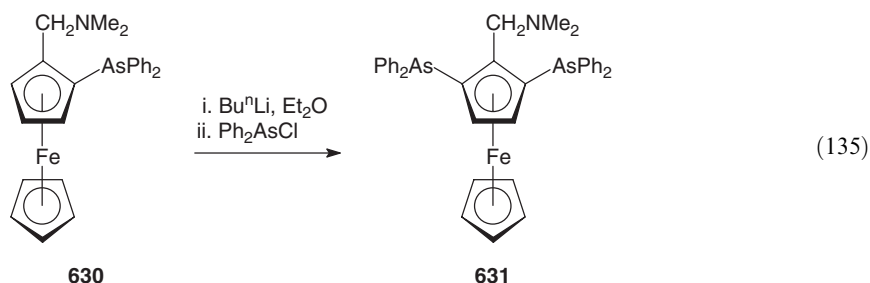
Further progress has been made in the synthesis of new trifunctional compounds containing As, Si, and a metal. Some of these methods have already been reviewed earlier (Section 4.22.7). Thus, dimeric 3,4-dimethyl-2,5-bis(trimethylsilyl)-1-arsacyclopentadienyl-bis(tetrahydrofuran-*O*) calcium chloride **615** was synthesized as the trifunctional (As, Si, Ca) calcium arsolide derivative from 1-chloro-3,4-dimethyl-2,5-bis(trimethylsilyl)arsole (Equation (129)) <1999OM2491>.

2,2',5,5'-Tetra(trimethylsilyl)-3,3',4,4'-tetramethyl-1,1'-diarsathuliumocene **617** was another example of a trifunctional (As, Si, Tm) reagent (Equation (130)) <2002CC1646>. Ashe, III and co-workers synthesized a (As, Si, Mo) trifunctional complex converting 2-trimethylsilyl-1-arsanaphthalene to the dark red tricarbonyl molybdenum compound **629** which in the X-ray analysis showed that the metal was  $\eta^6$ -bound to the  $C_5As$  ring <2001OM2109> (Equation (134)).

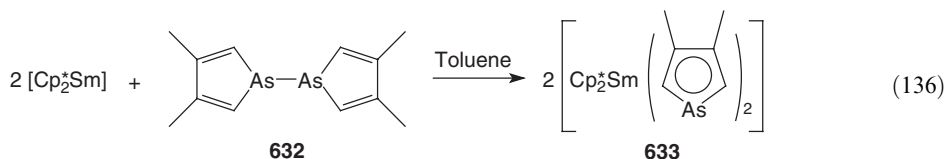


Treatment of 2-(diphenylarsino)-*N,N*-dimethylaminomethylferrocene **630** with *n*-butyllithium in diethyl ether followed by reaction of the resulting monolithium derivative with diphenylchloroarsine gave 2,5-bis(diphenylarsino)-*N,N*-dimethylaminomethylferrocene **631** <2001MI1496> (Equation (135)). The reaction of the dilithio compound derived from **631** with 2 equiv. of diphenylchloroarsine afforded 2,5,1'-tris(diphenylarsino)-*N,N*-dimethylaminomethylferrocene.

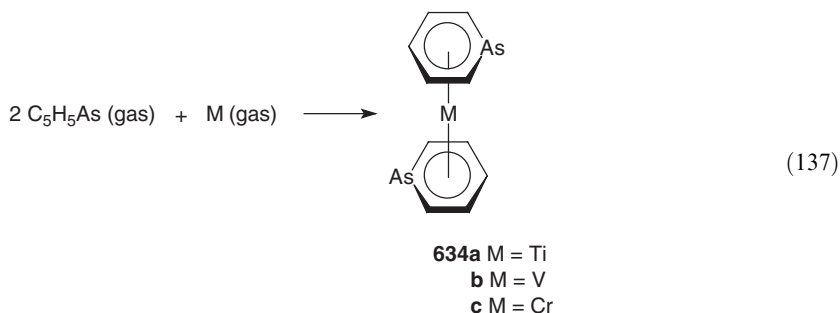




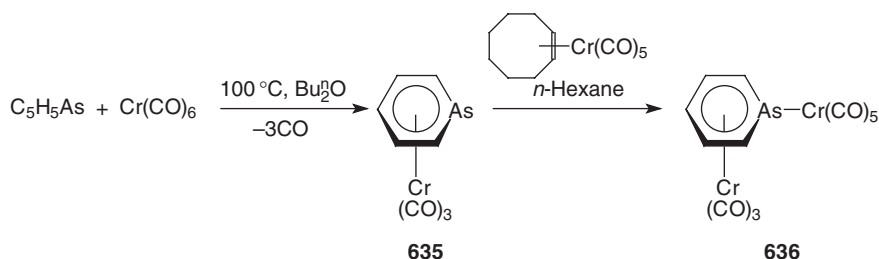
Nief and Ricard synthesized the samarium complex **633** from bis(pentamethylcyclopentadienyl)samarium and the As–As precursor **632** [<2001OM3884>](#) (Equation (136)). In the new complex one arsolyl ring was coordinated to both samarium in a  $\mu:\eta^1, \eta^5$  fashion, whereas the other was only  $\eta^1$ -bonded to one samarium.



Bis( $\eta^6$ -arsenine)titanium **634a** and bis( $\eta^6$ -arsenine) vanadium **634b** in addition to the earlier known bis( $\eta^6$ -arsenine) chromium **634c** were obtained by Elschenbroich and co-workers [<1999OM1495>](#) by means of a metal–ligand vapor co-condensation technique employing an electron beam heated metal evaporation source (Equation (137)).

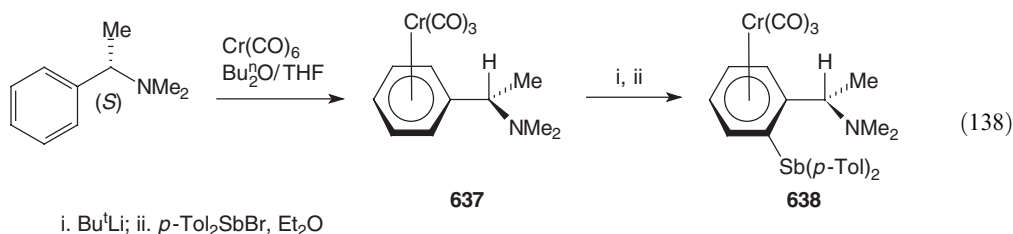


The  $\eta^6$ -As tricarbonylchromium complex **635** and the  $\eta^1$ -As pentacarbonyl complex **636** were also prepared. The  $\text{Cr}(\text{CO})_5$  moiety was easily displaced by THF, demonstrating the lability of the  $\eta^1$  coordination. The competition reaction of the Cr vapor with  $\text{C}_6\text{H}_6$  and  $\text{C}_5\text{H}_5\text{As}$  showed that the  $\eta^6$ -arsenine complexes were strongly favored [<1999OM1495>](#) (Scheme 84).

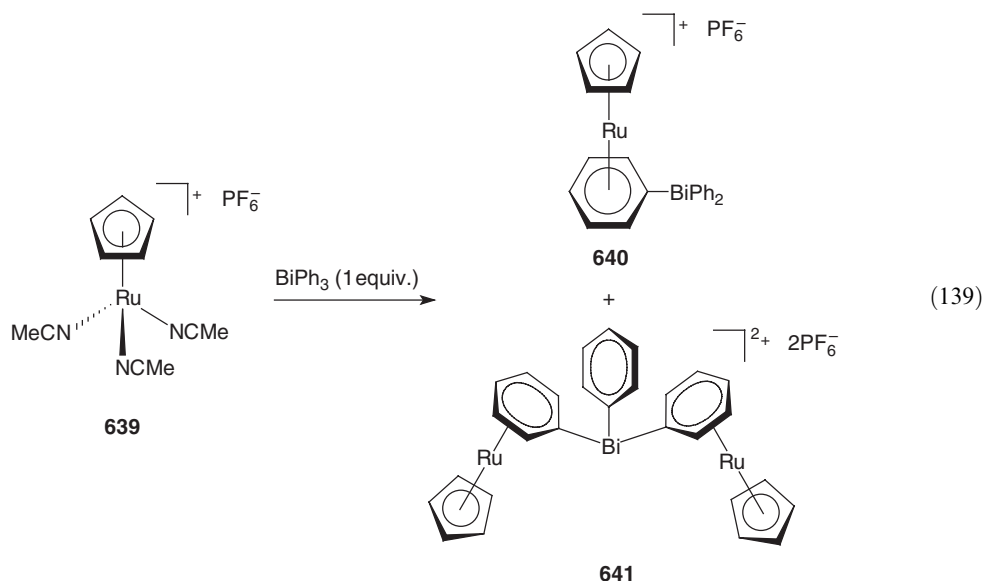


Scheme 84

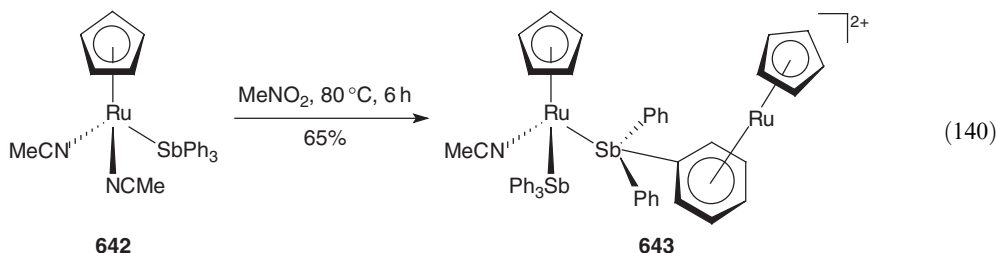
The novel enantiomerically pure organoantimony- $\eta^6$ -arenechromium complex **638** possessing a C-chiral amine moiety was prepared from (*S*)-( $\alpha$ -methylbenzyl)dimethylamine via *ortho*-lithiation of its chromium complex **637** [<2002CPB1404>](#) (Equation (138)).



Kirchner and co-workers investigated reactions of the half-sandwich ruthenium complex **639** with triphenylphosphine, arsine, stibine, and bismuthine [<2002JOM\(649\)55>](#). In the first three cases the Ru—P, Ru—As and Ru—Sb coordination dominated while in the case of bismuthine the competitive  $\eta^6$ -arene coordination was favored due to the weakest Ru—Bi interaction in the series P > As > Sb > Bi. Thus, the reaction of **639** with 1 equiv. of BiPh<sub>3</sub> gave a mixture of two compounds, **640** and **641** (Equation (139)). The compound **640** could not be isolated from the reaction mixture in pure form and **641** was synthesized independently by reaction of **639** and 0.5 equiv. of BiPh<sub>3</sub> in 86% yield.



The same authors [<2002JOM\(649\)55>](#) carried out the thermolysis of the complex **642** in nitromethane at 80 °C for 6 h and isolated the complex **643** in 65% yield (Equation (140)).



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## 4.23

# Functions Containing at Least One Metalloid (Si, Ge, or B) and No Halogen, Chalcogen, or Group 15 Element; Also Functions Containing Two Metals

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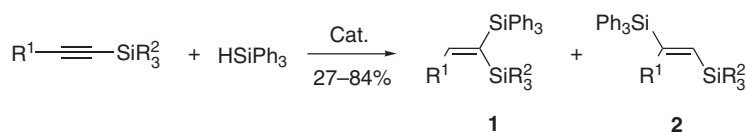
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## 4.23.1 FUNCTIONS CONTAINING TWO METALLOIDS

4.23.1.1 Functions Bearing Two Silicons— $R_2^1C=C(SiR_3^2)_2$ , etc.

1,1-Disilyl alkenes have been studied in detail and many methods for their preparation have been reported. Previously reviewed methods include the hydrosilylation of alkynyl silanes; treatment of silyl alkynes with metallosilyl species; diboration of disilylalkynes; photo chemical rearrangement of alkynyl disilanes; displacement of halogen by a silyl group, via metal–halogen exchange; various reactions of tris(TMS)methyl lithium with electrophiles; base-mediated reactions of dihalodisilyl methanes; cleavage of 1,2-disilabut-3-enes with halogen; various reactions of silirenes; reactions of siliranes with alkynes and the catalytic disilylation of alkynes. 1,1-Disilyl allenes have been prepared through the treatment of silylenynes with Li and TMSCl; silylcupration of silylpropargyl halides; rearrangement of alkynyl disilanes; propargylic deprotonation of silyl alkynes followed by treatment with silyl halides and the polysilylation of butynoic acid with TMSCl and BuLi <1995COFGT(4)1043>.

The hydrosilylation approach has found continued use for the preparation of 1,1-disilyl alkenes, and several different catalysts have proven effective for the regioselective hydrosilylation of silylalkynes, generally favoring 1,1-disilylalkene products **1** over 1,2-disilylalkenes **2** (Scheme 1). For example, organolanthanide and group 3 metallocene complexes have been studied for the hydrosilylation of a wide range of 1-silyl alkynes with  $PhSiH_3$  (Scheme 1) <2002JOM(647)225>. Increasing the steric bulk of the silyl group on the alkyne was found to increase the selectivity of the reaction, but use of a more sterically demanding catalyst required higher reaction temperatures and/or times. Under these more forcing conditions, yields of the required product were lowered due to competing hydrogenation and isomerization reactions. The mechanism of the reaction and the steric and electronic effects of substituents on the alkyne unit have been discussed in some detail, but generally the regioselectivity is controlled by the electronics of the alkynyl silane. Terminal alkynes are incompatible with these catalyst systems due to the acidity of the alkynic proton. The use of Pt on carbon as a catalyst for the addition of a range of silanes has also been reported <2002JOM(645)1>, although formation of products of type **2** was favored over type **1**. With terminal alkynes, 1,2-disilyl alkenes were formed exclusively, and the reaction failed with bis-(TMS)ethyne due to the steric and/or electronic deactivation of the alkyne function by the two TMS groups. Other catalysts including  $(Cp^*)RuH_3(PPh_3)$  <2002OL2825> and  $Pt(CH_2CHSiMe_2)_2O + PBu^t_3$  <2002JOC2645> also catalyze similar hydrosilylations.



$R^1 = n\text{-octyl}, EtCHMeCH_2, C_6H_{11}, Ph, Ph(CH_2)_2;$

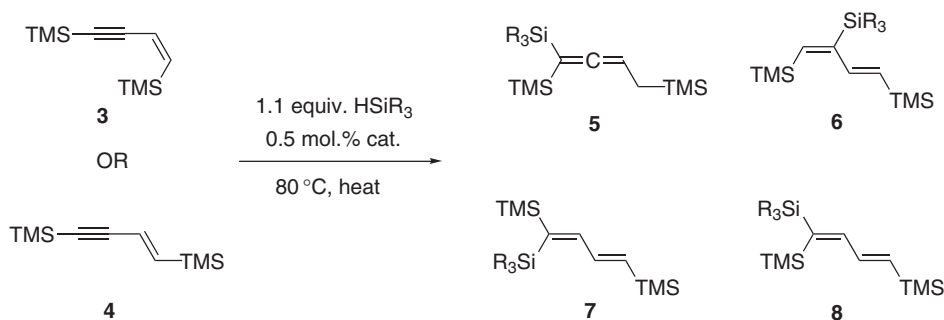
$SiR_3^2 = SiMe_2H, SiPr^i_2H;$

Cat. =  $Cp^*_2YMe\cdot THF$ ,  $[Cp_2^{TMS}YMe]_2$ ;  $[Cp_2^{TMS}LuMe]_2$

Ratio = 1:1 to exclusively **1**

Scheme 1

The effect of different catalysts on the regioselectivity of hydrosilylation of *cis*- and *trans*-1,4-bis(TMS)-3-buten-1-yne **3** and **4** has been studied (Scheme 2). Four kinds of regio- and stereoisomers **5–8** can be obtained with high selectivities with the correct choice of catalyst and **3** or **4**. Some examples are given in Table 1. Other catalysts were also examined and in some cases gave highly selective reactions, although extended reaction times were often required <1997CL623, 2000JOM(609)130>. During studies on the formation of arylchromium complexes of alkynes containing remote phenylsilyl hydride groups, intramolecular hydrosilylation was noted, although the reaction was catalyzed by platinum residues left over from the substrate preparation <1997OM5048>. Chiral 1,1-disilylallenes have been prepared in low to very low yields and very low ee through the hydrosilylation of 1,4-bis(TMS)buta-1,3-diyne with diphenylsilane using chiral nickel complexes <2000JOM(603)116>.

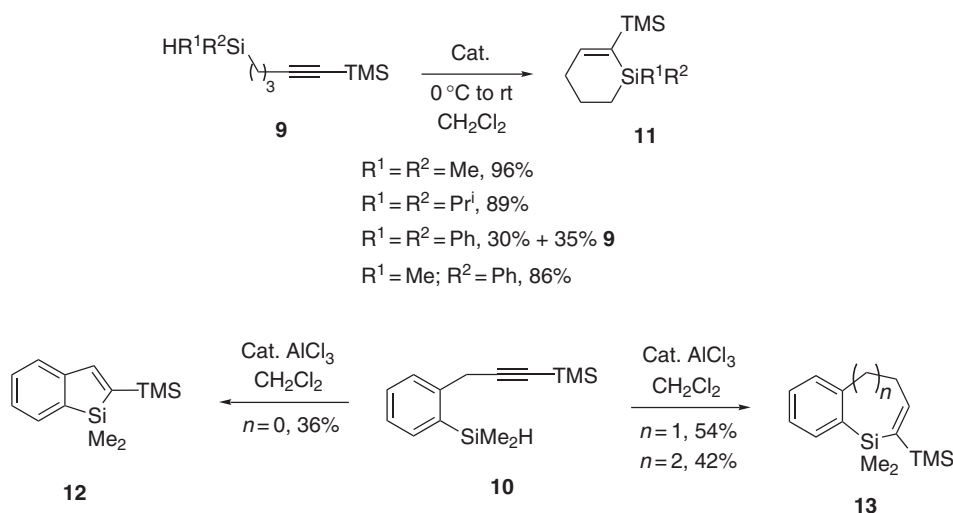


Scheme 2

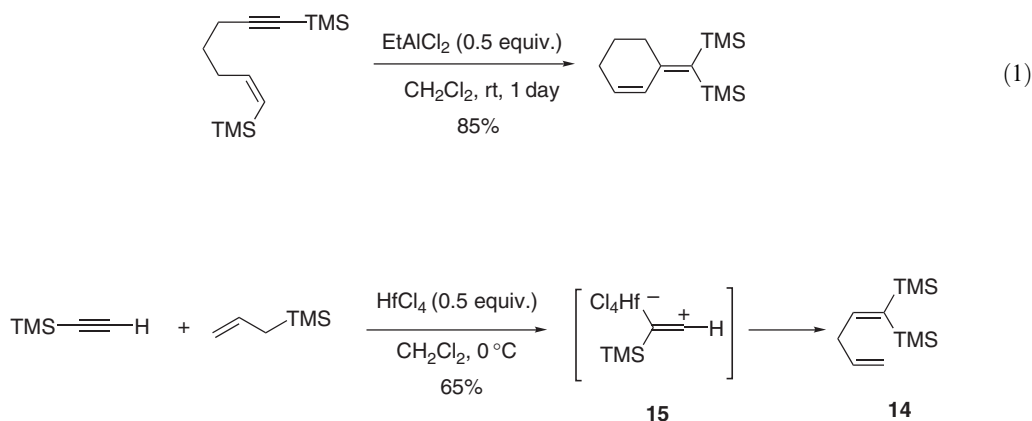
**Table 1** Product ratios from hydrosilylation of (3) and (4)

Ene/yne	$\text{HSiR}_3$	Catalyst	Time	Product ratio				Yield (%)
				5	6	7	8	
3	$\text{HSiMe}_2\text{Ph}$	$\text{H}_2\text{PtCl}_6 \cdot 6\text{H}_2\text{O}$	2 h	96	4	0	0	73
4	$\text{HSiMe}_2\text{Ph}$	$\text{H}_2\text{PtCl}_6 \cdot 6\text{H}_2\text{O}$	3 h	0	93	0	7	100
3	$\text{HSiMe}_2\text{Ph}$	$\text{RhH}(\text{CO})(\text{PPh}_3)_3$	19 h	0	0	95	5	98
4	$\text{HSiMe}_2\text{Ph}$	$\text{RhH}(\text{CO})(\text{PPh}_3)_3$	19 h	10	0	9	81	96
3	$\text{HSiMePh}_2$	$\text{RhH}(\text{CO})(\text{PPh}_3)_3$	24 h	4	0	0	96	99

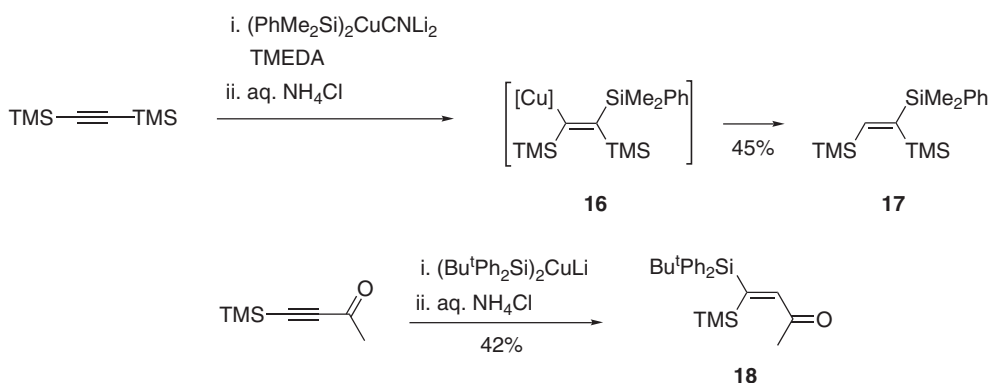
In contrast to intermolecular transition metal-catalyzed hydrosilylation, the Lewis acid-catalyzed intramolecular hydrosilylation of alkynes gives *trans* hydrosilylation products (Scheme 3). Silyl alkynes bearing a tethered silyl hydride function (e.g., **9** and **10**) generally give cyclic disilyl alkenes (e.g., **11–13**) with a range of ring sizes via *endo–trans* addition catalyzed by  $\text{AlCl}_3$  <2000JOC8919>. The intramolecular *trans*-vinylsilylation of a silyl alkyne can also be effected in high yield using  $\text{EtAlCl}_2$  (Equation (1)) <1999JA3797>. Treatment of 1-TMS-ethyne with allyltrimethylsilane in the presence of  $\text{HfCl}_4$  gives the allylsilylation product **14** via the cationic intermediate **15** (Scheme 4) <1997JA6781>. The silylcupration of silyl alkynes provides intermediate 1-silyl-1-cuproalkenes (e.g., **16**) via *syn* addition (Scheme 5). These intermediates can be quenched with electrophiles to give the corresponding alkene derivatives **17** and **18** <2001JOC1961>.



Scheme 3



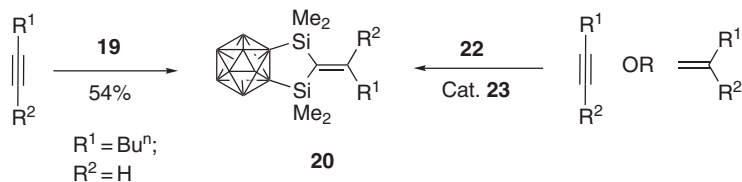
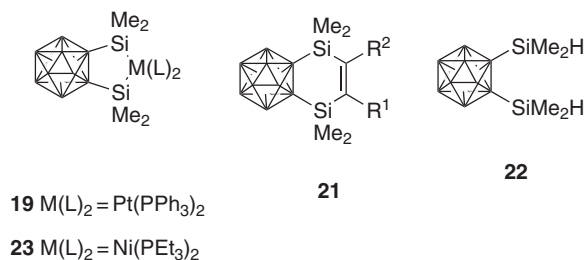
Scheme 4



Scheme 5

The geminal disilylation of alkynes and alkenes has also been used to prepare disilylalkenes. *Ortho*-bis(dimethylsilyl)carborane-bis(triphenylphosphine)platinum complexes **19** react with 1-hexyne to give the 1,1-disilylated product **20** ( $R^1 = \text{Bu}^n$ ,  $R^2 = \text{H}$ ), but 1-phenylethyne gave products of type **21** (Scheme 6) <1999OM1818, 2000OM1216>. Complex **19** was a poor catalyst for the reaction of free *ortho*-bis(dimethylsilyl)carborane **22** with alkynes, due to the strength of the Pt—Si bond, but the related bis(triethylphosphine)nickel carborane complex **23** catalyzed the 1,1-disilylation of both alkynes and monosubstituted alkenes by **22**. In some cases, low levels of 1,2-disilylation products were also observed <2000OM1722>. The mechanisms of the above reactions with alkynes and alkenes have been discussed <2000OM1722>. The nickel-catalyzed intermolecular disilylation of 1,4-bis(TMS)buta-1,3-diyne **24** with tetramethyldisilane gives mixtures of silole **25** and 1,4-disilacyclohexa-2,5-diene **26** (Equation (2)) <1995OM1089>. Furthermore, cyclic disilane **27** reacts with alkynes to give cyclic disilylation products **28** in the presence of Pd catalysts (Scheme 7) <1999OM3792>. When diyne **24** was used, a cyclic tetrasilylbutatriene **29** was obtained (Scheme 7). The Pd(OAc)<sub>2</sub>/1,1,3,3-tetramethylbutylisocyanide-catalyzed high-pressure intramolecular bis-silylation of cyclic silylalkyne **30** ( $M = \text{Si}$ ) gave **31** ( $M = \text{Si}$ ) (Equation (3)) <1995BCJ2981>. However, 1,1,2,2-tetrakis-TMS-ethene could not be prepared through the analogous intermolecular bis-silylation of bis(TMS)ethyne with hexamethyldisilane. The Ru-catalyzed silylation of ethene with bis(disubstituted-silyl)alkenes gives low yields of 1:1 disilyl ethene adducts, along with mixtures of 2:1 adducts and further reduced species <2000OM5750>.





Alkynes:

 $R^1 = Bu^n; R^2 = H$ : 71%

 $R^1 = Ph; R^2 = TMS$ : 62%

 $R^1 = TMS; R^2 = TMS$ : 66%

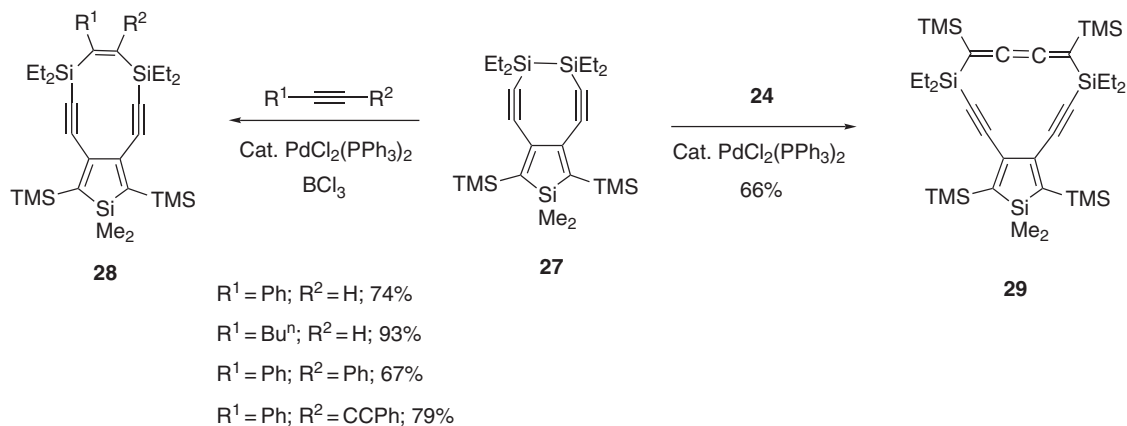
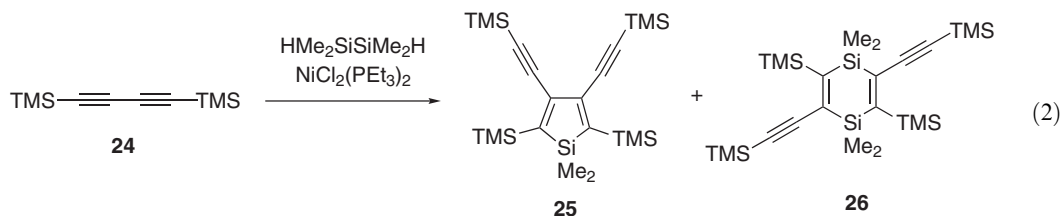
Alkenes:

 $R^1 = p\text{-MeOC}_6\text{H}_4; R^2 = H$ : 52%

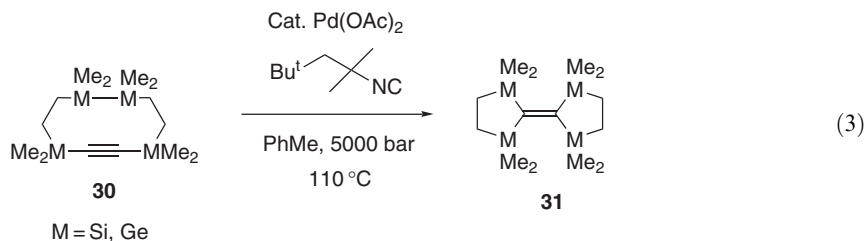
 $R^1 = Me(CH_2)_5; R^2 = H$ : 45%

 $R^1 = Ph; R^2 = H$ : 76% (stoichiometric **23**)

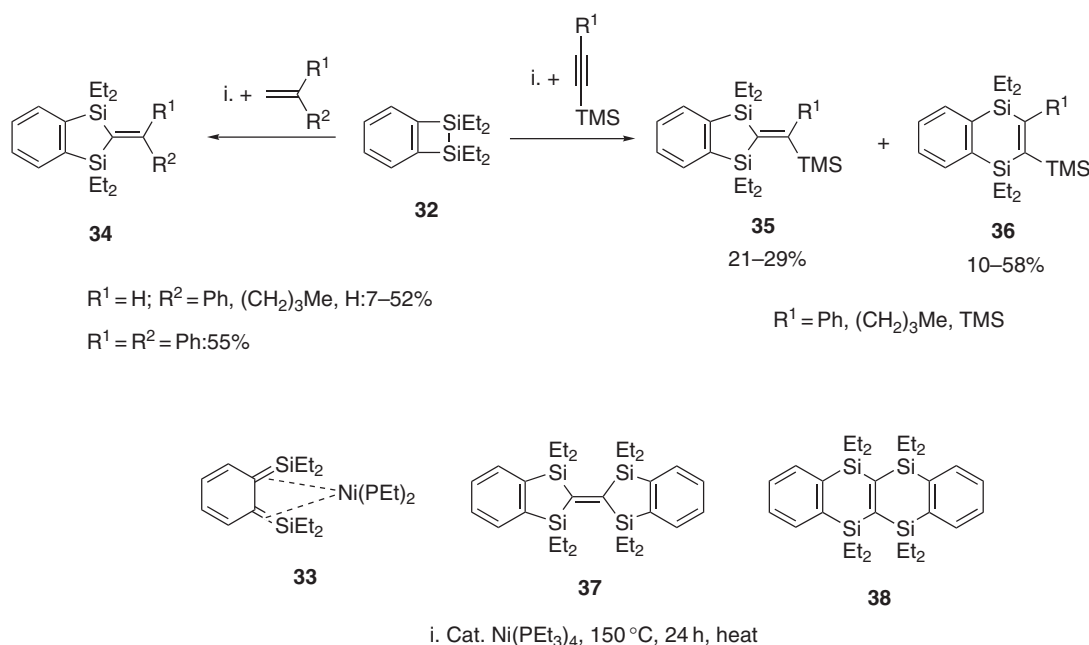
Scheme 6



Scheme 7

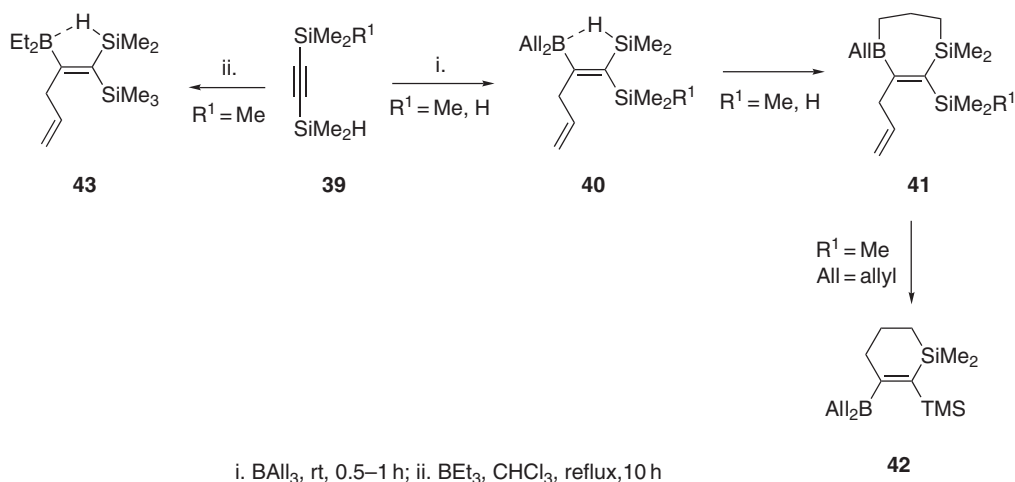


An extension of the above approach involves the reaction of 3,4-benzo-1,1,2,2-tetraethyl-1,2-disilacyclobut-3-ene **32** in the presence of catalytic  $\text{Ni}(\text{PEt}_3)_4$  to give a transient intermediate *o*-quinodisilane-nickel complex **33**. In the presence of terminally unsubstituted alkenes cyclic benzodisilacyclopentenes **34** are formed in low-to-moderate yield, accompanied by a range of by-products, depending upon the alkene used (Scheme 8) <1995OM114>. The reaction of **32** with alkynes gives cyclic benzodisilacyclopentenes **35** and disilacyclohexadiene **36** under similar conditions (Scheme 8) <1995JOM(499)35>. Use of bis(TMS)ethyne led to a more complex reaction mixture, with *trans*-silylation products **37** and **38** accompanying **35** and **36** <1996OM1101>. The mechanisms of the above reactions have been discussed in detail. When some of the above reactions were run in the presence of silyl hydrides, competing hydrosilylation of the alkynes was noted.



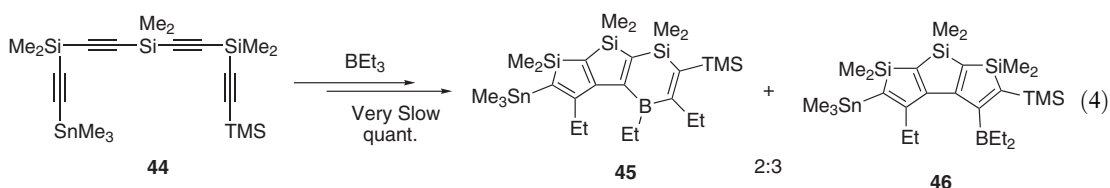
Scheme 8

1,1-Organoboration of 1,2-disilyl alkynes containing one or more hydrosilane units gives 1,1-disilyl-2-boryl alkenes containing novel Si—H—B bridges. The treatment of alkyne **39** (R<sup>1</sup> = Me) with triallylborane gave **40** under mild conditions (Scheme 9) <1999AG(E)124>. Compound **40** contains a novel Si—H—B bridge, confirmed through <sup>1</sup>H, <sup>11</sup>B, and <sup>29</sup>Si NMR and IR, and can undergo further reaction between the SiH moiety and the C=C double bonds of the allyl unit. Thus, **41** can be formed via intramolecular hydrosilylation, which proceeds under remarkably mild conditions in the absence of any catalyst. It is thought that the Si—H—B bridge may be a prerequisite for such a mild reaction. With **41** (R<sup>1</sup> = Me), still further rearrangement occurred during attempts to distil, yielding **42** after a 1,1-deorganoboration–1,1-organoboration sequence, whereas **41** (R<sup>1</sup> = H) did not undergo further reaction. In contrast, much more forcing conditions were required to perform the analogous reaction using BEt<sub>3</sub>, to give **43**.



Scheme 9

When poly(silyl alkynes) such as **44** are treated with triethylborane, 2-silylsilole derivatives such as **45** and polysiloles such as **46** are often isolated after a protracted reaction under somewhat forcing conditions via a series of annulations giving discrete silole intermediates (Equation (4)) <1999JOM(577)82>. The 1,1-hydroboration of 1,2-disilyl alkynes can also give 1,1-disilyl alkenes via a silyl migration; thus, the treatment of 1,2-bis(TMS)ethyne with 6-aza-nido-decaboranes gives 1,1-hydroboration resulting in the corresponding 9-[2,2-bis(TMS)alkenyl]-6-aza-nido-decaboranes in good yields (84–90%) <1995CB947>.

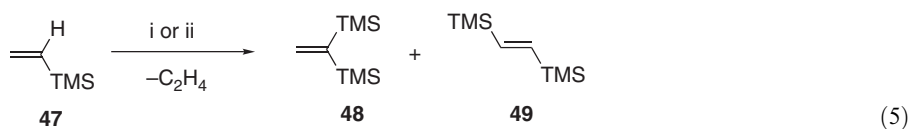


A new approach to 1,1-disilyl alkenes involves a ruthenium-catalyzed ring-closing reaction of  $\alpha,\omega$ -bis(vinylsilyl) compounds and a range of cyclic 1,1-disilylethenes have been prepared in good-to-high yield with excellent regioselectivities using this method (Table 2) <1998CC699>. Only small amounts of intermolecular coupled products were observed, although when the chain length of the aliphatic spacer between the silyl groups was 10 methylene units, the opposite regioselectivity was observed, giving the (*E*)-1,2-disilyl alkene product. Two catalyst precursors, [RuCl(CO)(PPh<sub>3</sub>)<sub>3</sub>(H)] or Werner's hydride, [RuCl(CO)(PPr<sub>3</sub>)<sub>2</sub>(H)], were found to be effective for this transformation, and generally the latter is more active. The mechanism of the reaction is of some note, as it does not proceed via a Grubbs-type ring-closing metathesis, as this would not give the observed 1,1-disilyl alkene. An intramolecular insertion— $\beta$ -elimination mechanism—is thought to operate, resulting in a disproportionation of the  $\alpha,\omega$ -bis(vinylsilyl) species. The intermolecular self-disproportionation of vinyltrimethylsilane **47** has also been studied (Equation (5)), and the regioselectivity of the reaction is often poor, leading to mixtures of **48** and **49**. It is thought that the regioselectivity is controlled by the direction of insertion of the second alkene unit into the Ru—Si bond of the initial Ru—vinylsilane intermediate. In a related reaction, heating of the stable bis( $\eta^2$ -vinyltrimethylsilane)Cp\*Rh complex at 140 °C in the presence of excess vinyltrimethylsilane **47** gave 80% conversion of **47** to **48** (28%) and **49** (72%) after 1 week. Slow degradation of the Rh complex was noted as the reaction proceeded <1999JA4385>.

**Table 2** Cyclic 1,1-disilylalkenes via Ru-catalyzed ring closing of dienes

Starting material	Product	Catalyst <sup>a</sup>	Conditions	Yield (%)
		A	PhMe, 80 °C; 24 h	87 (glc)
		A	THF, 100 °C; 15 h	75 (isolated)
		B	THF, 60 °C; 24 h	83 (isolated)
		A	PhMe, 80 °C; 25 h	97 (glc)
		B	PhMe, 110 °C; 42 h	76 (isolated)

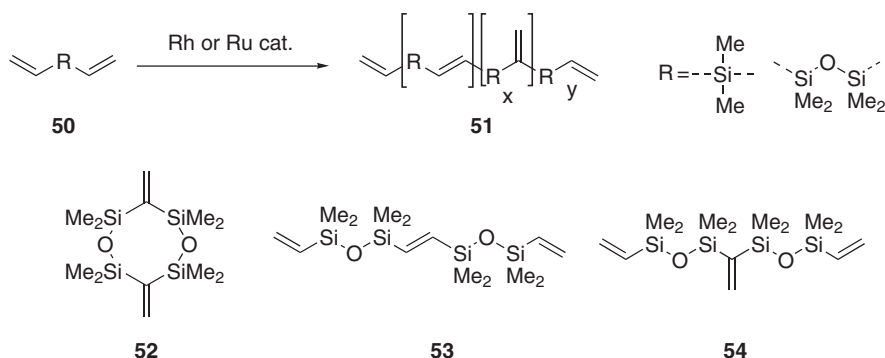
<sup>a</sup> Catalyst A = [RuCl(CO)(PPh<sub>3</sub>)<sub>3</sub>(H)]; catalyst B = [RuCl(CO)(PPr<sup>i</sup>)<sub>3</sub>(H)].



i. Cat. RuCl(CNC<sub>6</sub>H<sub>4</sub>-4-NO<sub>2</sub>)(PPh<sub>3</sub>)<sub>3</sub>(H), PhMe, 100 °C, 20 h. Products: **48**:6%; **49**:42%

ii. Cat. RuCl(CO)(PPh<sub>3</sub>)<sub>3</sub>(H) + MeCN, PhMe, 100 °C, 20 h. Products: **48**:35%; **49**:6%

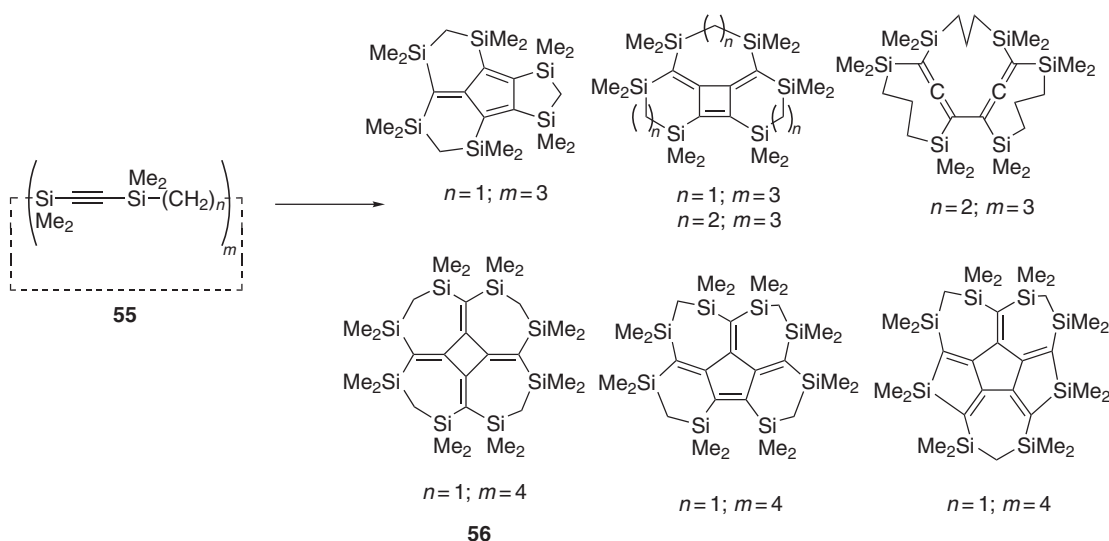
The “acyclic diene polycondensation” (ADPOL) of divinyl-substituted silanes and siloxanes **50** to give poly(silylene-vinylenes) and poly(siloxyene-vinylenes) **51** has been reported (Scheme 10) <1997TL3777>. The process is catalyzed by Ru or Rh complexes and proceeds via splitting of a vinylic CH bond (nonmetathetical conversion), as opposed to cleavage of the C—C double bond (metathesis). In general, cyclic and linear oligomers are initially formed during the ADPOL, but with divinylsiloxanes **50** (R = Me<sub>2</sub>SiOSiMe<sub>2</sub>), dimers **52**, **53**, and **54** can be formed under mild conditions in varying ratios, depending upon the catalyst used (Scheme 10).



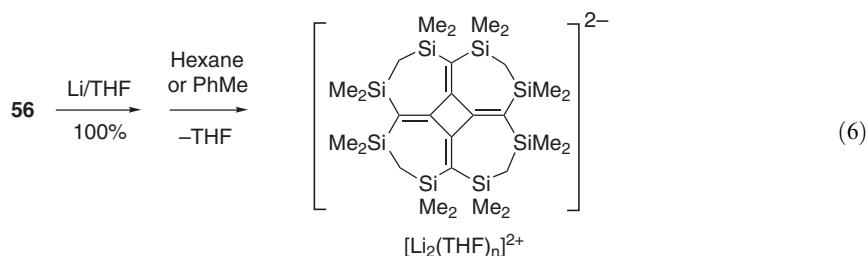
Cat.:  $[\text{RhCl}(\text{COD})]_2$ ;  $[\text{RhH}(\text{CO})(\text{PPh}_3)_3]$ ;  $[\text{RuHCl}(\text{CO})(\text{PPh}_3)_2]$ ;  $[\text{RuCl}_2(\text{PPh}_3)_3]$ ;  $[\text{RuCl}_2(\text{CO})_3]$

Scheme 10

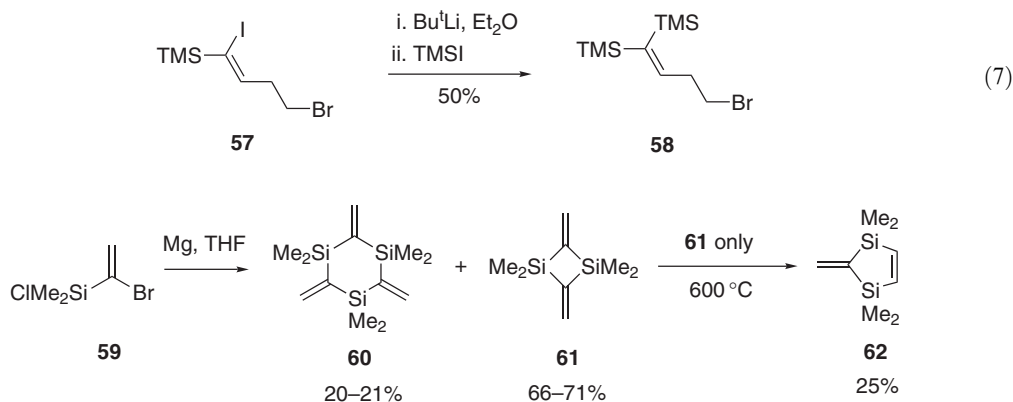
A range of polycyclic 1,1-disilyl alkenes can be prepared through the intramolecular oligomerization of macrocyclic poly(disilyl alkynes) **55** (Scheme 11). The reaction is mediated by transition metal complexes such as  $\text{Co}_2(\text{CO})_8$  and  $(\text{MeCp})\text{Mn}(\text{CO})_3$  and is often performed under photochemical conditions. The nature and ratios of the products formed is dependent on the amount and type of catalyst used and the conditions employed, as well as the structure of the precursor. This method has been applied to a range of poly(disilylalkynes) and examples of some of the products obtained are given in Scheme 11 <1996CL1053, 1998BCJ41, 1998BCJ1705, 2000BCJ2129, 2000BCJ1461>. Many of these compounds, such as **56**, were derivatized to their polyanionic polyolithium, sodium, or potassium salt derivatives (Equation (6)), which were characterized using X-ray crystallography among other techniques.



Scheme 11



The preparation of 1,1-disilyl alkenes from 1-halo-1-silylalkenes has also found synthetic utility <2000JPR(342)804>. Treatment of 1-iodo-1-silyl alkene **57** with Bu<sup>t</sup>Li, and trapping of the resulting vinyl anion with TMSCl gave the 1,1-disilylalkene **58** (Equation (7)). 1-Bromo-1-chlorosilyl alkene **59** was subjected to magnesium–halogen exchange, in an attempt to prepare  $\alpha,\alpha$ -silylenevinylene polymers, but the major products were cyclic 1,1-disilyl alkenes **60** and **61** in a high combined yield (Scheme 12) <1995PP501>. Interestingly, high temperature pyrolysis of **61** in a vertical flow nitrogen system induced rearrangement to give disilacyclopentene **62** in 25% yield (Scheme 12). The mechanism for this rearrangement has been discussed in some detail <1995JA11695>.

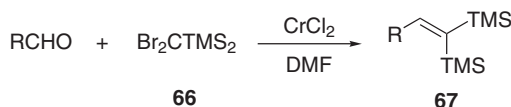


Scheme 12

The base-induced dehydrobromination of 1-bromo-1,1-disilylethanes **63** (prepared from dibromo derivative **64**) gives high yields of the corresponding 1,1-disilylethenes **65** (Scheme 13) <2001CL956, 2002CEJ1730>. 1,1-Bis(TMS)-1,1-dibromomethanes **66** ( $R^1 = R^2 = \text{TMS}$ ) also react with aldehydes in the presence of excess CrCl<sub>2</sub> to give a wide range of 1,1-bis(TMS)alkenes **67** in variable yields (Scheme 14 and Table 3) <1997JCS(P1)2279>. The reaction proceeds under mild conditions and tolerates even enolizable aldehydes. Dichlorodisilylmethanes **68** have been used to prepare a wide range of C-substituted 1,1-disilylalkenes **69** via allylcopper species **70**. The allylcopper species **70** were prepared through an initial lithium halogen exchange, followed by treatment with a vinylmagnesium bromide in the presence of CuCN·2LiCl, as shown in Scheme 15. After formation of **70**, quenching with electrophiles gave  $\gamma$ -adducts **69** exclusively, with no evidence of  $\alpha$ -addition. Suitable electrophiles include alkyl and allyl halides, aldehydes and ketones, acid chlorides and water, and in some cases improved results were obtained by using TMSCl as an additive. Propargyl electrophiles gave the corresponding allenylated product. Selected examples are given in Table 4 <2002TL2399>.

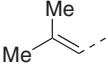



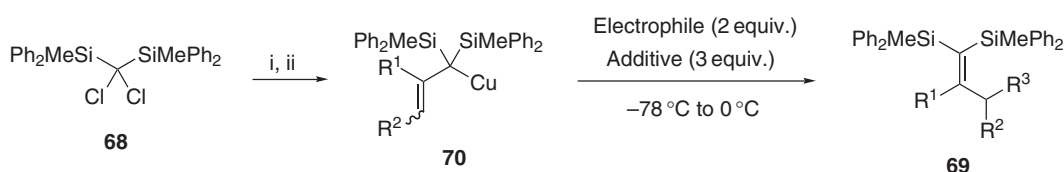
Scheme 13

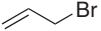

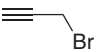

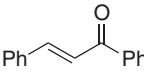
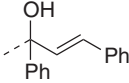
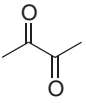
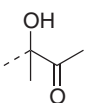




Scheme 14

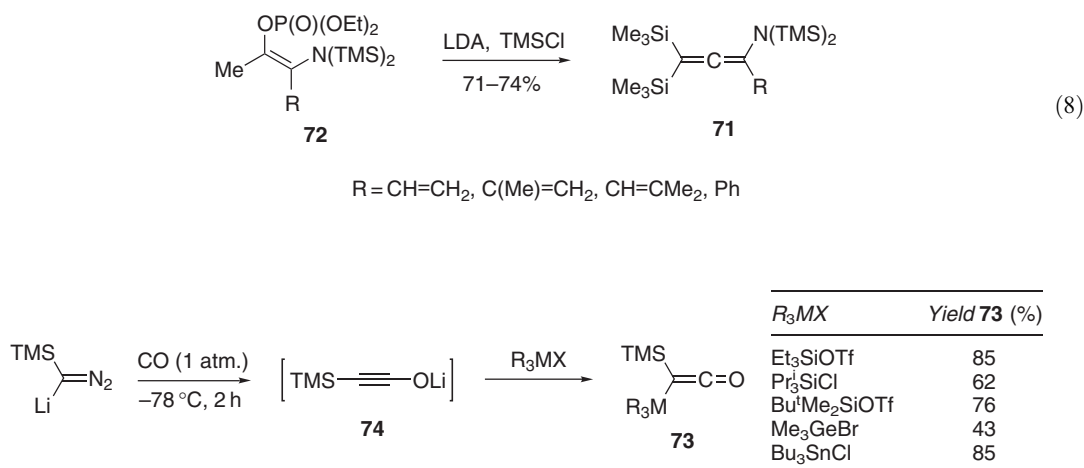
**Table 3** 1,1-Bis(TMS)alkenes via CrCl<sub>2</sub>-mediated reaction of aldehydes with bis(TMS)dibromomethane

<i>R</i>	Yield ( <b>67</b> )(%)	<i>R</i>	Yield <b>67</b> (%)
Ph	84	MeO <sub>2</sub> C(CH <sub>2</sub> ) <sub>4</sub>	64
CH <sub>3</sub> (CH <sub>2</sub> ) <sub>7</sub>	78	NC(CH <sub>2</sub> ) <sub>6</sub>	70
Cy	79	MeCO(CH <sub>2</sub> ) <sub>10</sub>	58
Bu <sup>t</sup>	28	Ph-CH=CH-	84
	73		38
PhCH <sub>2</sub>	39		

i. Bu<sup>n</sup>Li (1 equiv.), THF, -78 °C, 5 min.ii. R<sup>1</sup>CH=CR<sup>2</sup>MgBr (1.1 equiv.), CuCN·2LiCl (1.1 equiv.), -78 °C to 0 °C, 0.5 h**Scheme 15****Table 4** Formation of 1,1-disilylalkenes via allylcopper intermediates

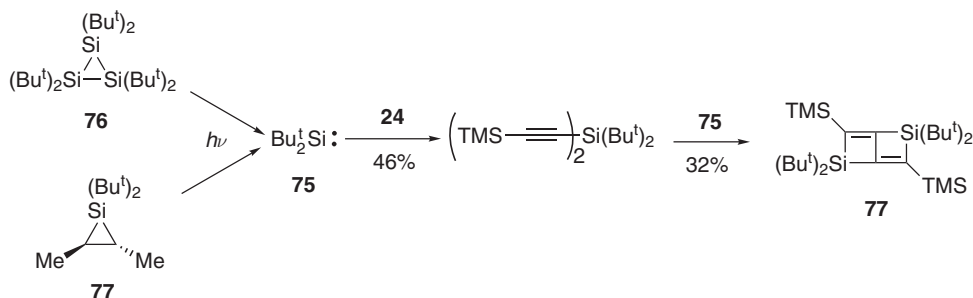
<i>R</i> <sup>1</sup>	<i>R</i> <sup>2</sup>	Electrophile	<i>R</i> <sup>3</sup>	Yield <b>69</b> (%)
H	H	MeI	Me	73
H	H			86
H	H			60
H	H	PhCHO	CH(OH)Ph	69
H	H			53
H	H			64
Ph	H	CH <sub>3</sub> COC(OMe)		73
H	Ph	PhCHO	CH(OH)Ph	83
Me	H	H <sub>3</sub> O <sup>+</sup>	H	78
Me	H	PhCOC(OMe)		73

1,1-Bis-silylated allenes **71** can be synthesized in acceptable yields from phosphonoalkenes **72** through treatment with LDA and quenching with TMSCl (Equation (8)) <1995JOM(487)89>. Disilylketenes **73** have been prepared from quenching of transient lithium ynolates **74** (prepared through carbonylation of lithio TMSdiazomethane with CO) with a silyl halide or pseudohalide (Scheme 16). In no case was reaction observed at the oxygen function <1996JA7634>. Subsequent reaction with organolithium reagents results in attack at the C=O function to give an enolate, which undergoes Peterson type elimination to give silylalkynes <1996SL635>. The treatment of disilylketenes **73** with KOBu<sup>t</sup> in the presence of HMPA results in selective mono-desilylation to regenerate the silylethynolate **74**. When unsymmetrical disilylketenes bearing one TMS group were used, selective removal of the less bulky TMS group was observed. However, when larger silyl groups were present at both positions, the desilylation was less selective. As would be expected, quenching with silyl halides results in reformation of the disilylketenes <2002SL1329>.



Scheme 16

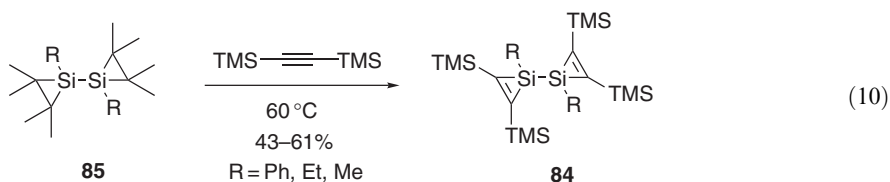
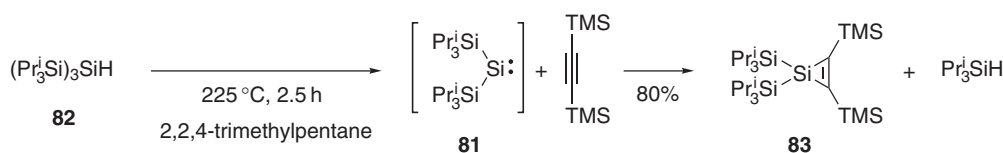
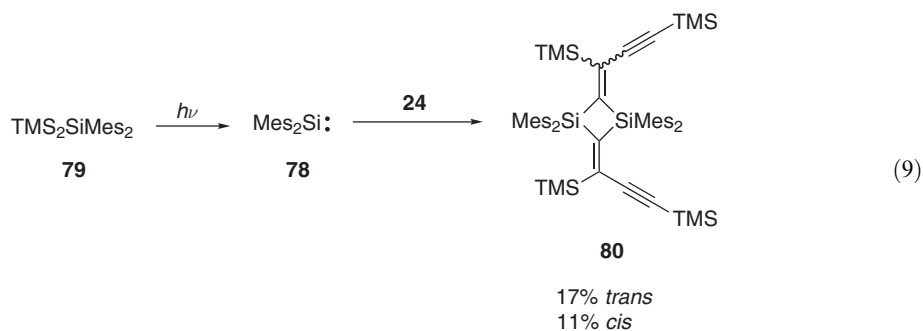
Di-*t*-butylsilylene **75** can be prepared through the photolysis of hexa-*t*-butylcyclotrisilane **76**, or 1,1-di-*t*-butyl-*trans*-2,3-dimethylsilirane **77** (Scheme 17). Excess **75** undergoes a stepwise reaction with bis-TMS-butadiyne **24** to give bicyclic disilyl alkene **77** <1999EJ12301>. In contrast, dimesitylsilylene **78**, prepared from **79**, reacted with **24** to give **80** as a mixture of *cis* and *trans* isomers (Equation (9)). Bis(TIPS)silylene **81**, obtained through pyrolysis of tris(TIPS)silane **82**, inserts into bis(TMS)ethyne to give 1,1-bis(TIPS)-2,3-bis(TMS)-1-silacyclop-2-ene **83** in 80% yield (Scheme 18) <1999OM3921>. Bis(silacyclopropenes) **84** can be prepared through the thermolysis of bis(silacyclopropanes) **85** in the presence of bis-TMS-ethyne at 60 °C (Equation (10)). Heating of **84** resulted in rearrangement to various products, including disilabenzvalenes and



Scheme 17

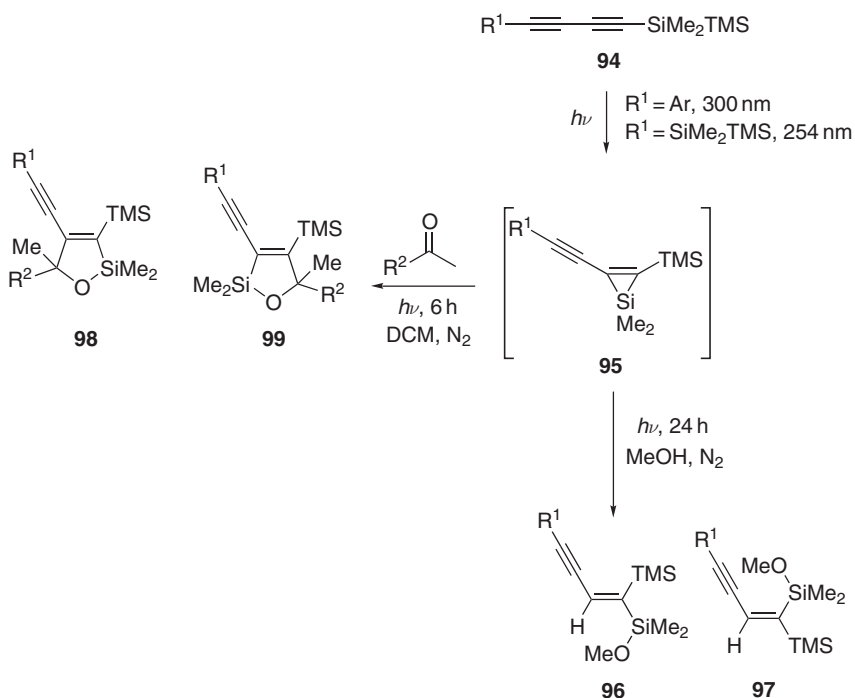


disila(Dewar benzene) depending upon the substituents. Similar products could be obtained through treatment with  $\text{AgBF}_4$  at room temperature <1997JA3629, 2000JA3775>.



Hindered 2-silylsilacycloprenes **86**, which are air stable and can be handled without special precautions, have been prepared through the photorearrangement of alkynyl disilanes **87** (Scheme 19). Interestingly, pyrolysis of **86** ( $\text{R} = \text{Ph}$ ,  $\text{Ar} = 2,6-(\text{MeO})_2\text{C}_6\text{H}_3$ ) in the absence of traps with continuous removal of the eliminated alkyne gave a 3-trimethylsilyl-1,2-disilacyclobutene **88** in 28% yield along with 53% recovered **86** <2003OM2436>. Similarly, irradiation of the aryl alkyne **89** in  $\text{CH}_2\text{Cl}_2$  gives an intermediate silacyclopropene **90**, which can be trapped with acetone to give cyclic 1,1-disilyl alkene **91** (Scheme 20). Running the reaction in benzene in the presence of MeOH gave intramolecular cyclization product **92** in 25% yield, along with other products (Scheme 20) <2001MI1202>. Studies on the thermolysis of several 1-aryl-3-phenyl-1,2-bis(TMS)silacycloprop-2-enes **93** showed that the outcome of the reactions is somewhat dependent upon the nature of the aryl group (Equation (11)). The mechanisms of these transformations have been discussed in some detail. Further studies on the high-temperature pyrolyses of **93** in the presence of alkynes have also been discussed and the reactions of the silacycloprenes with diphenyl methyl silane also gave disilyl alkene derivatives <1995OM1204>. Irradiation of 1-aryl-4-(pentamethyldisilanyl)buta-1,3-diyne **94** ( $\text{R}^1 = \text{Ar}$ ) gives an intermediate excited triplet-state silacyclopropene **95**, which undergoes photoaddition with MeOH to give disilylalkene derivatives **96** and **97**, or with aldehydes or ketones to give dihydrooxasiloles **98** and **99** (Scheme 21) <1995MI988>. The analogous reactions of 1,4-bis(pentamethyldisilanyl)butadiene **94** ( $\text{R}^1 = \text{SiMe}_2\text{TMS}$ ) gave similar results, although 4% of a 2:1 adduct was also obtained in the reaction with methanol <1996OM2182>.

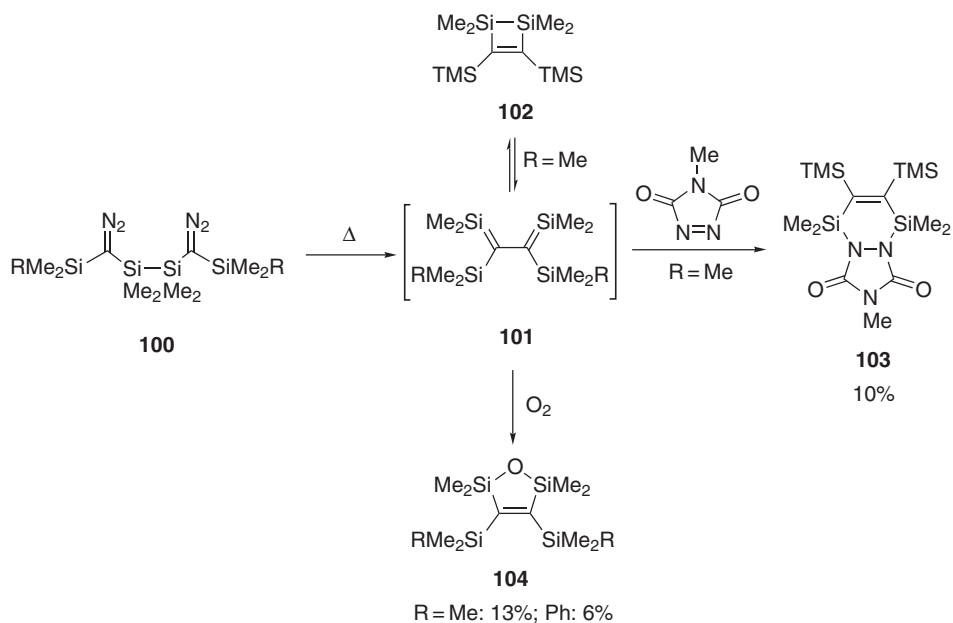




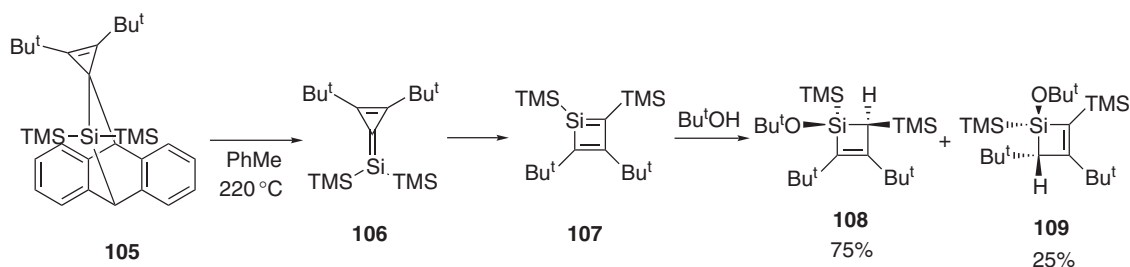
$\text{R}^1$	$\text{R}^2$	Yield <b>98</b> (%)	Yield <b>99</b> (%)
Ph	Me	16	1
<i>p</i> -MeOC <sub>6</sub> H <sub>4</sub>	Me	9	0.5
<i>p</i> -NO <sub>2</sub> C <sub>6</sub> H <sub>4</sub>	Me	35	0
SiMe <sub>2</sub> TMS	Me	48	0
SiMe <sub>2</sub> TMS	H	35	18

$\text{R}^1$	Yield <b>96</b> (%)	Yield <b>97</b> (%)
Ph	13	17
1-naphthyl	25	25
<i>p</i> -MeOC <sub>6</sub> H <sub>4</sub>	13	12
SiMe <sub>2</sub> TMS	12	18

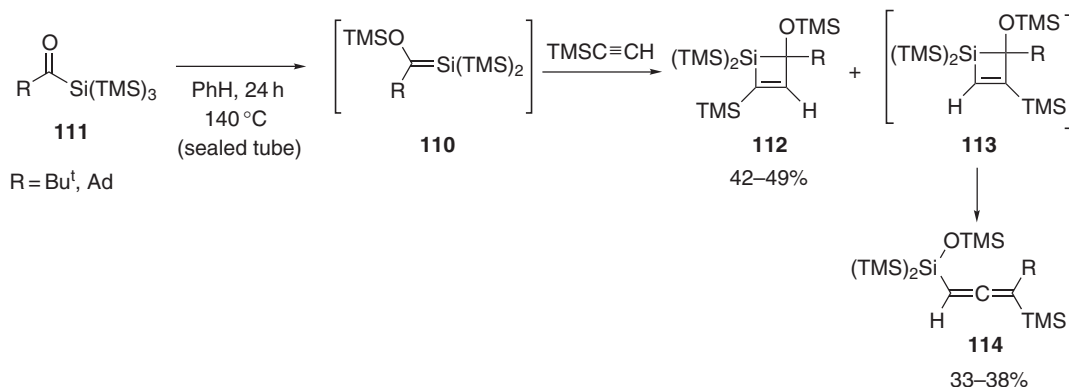
Scheme 21



Scheme 22

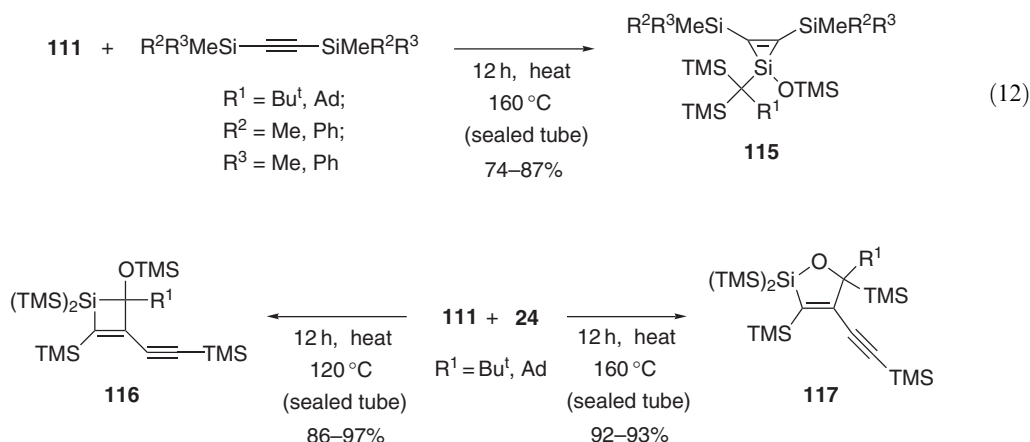


Scheme 23



Scheme 24

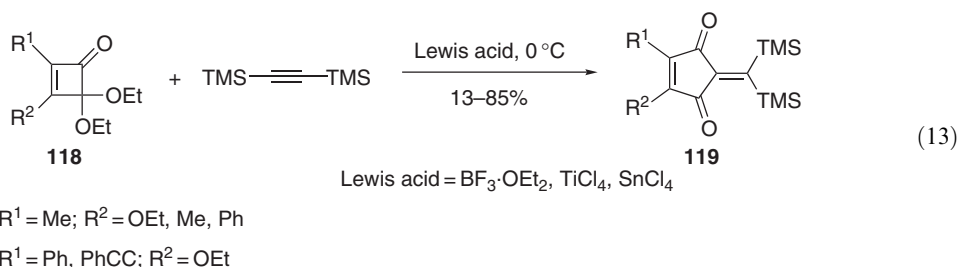
less hindered acyl substituents, no disilyl alkenes are formed [<1996OM5759>](#). Reaction of **111** (R = Bu<sup>t</sup>, Ad) with bis(trialkylsilyl)ethynes gives silylated silacyclopropene derivatives **115** in good yields without the formation of the allenes observed with monosubstituted silyl ethynes ([Equation \(12\)](#)) [<2000OM4921>](#). However, the reactions of **111** (R = Bu<sup>t</sup>, Ad) with diynes **24** give the silene [2 + 2]-cycloadducts **116** at 120 °C, but at 160 °C 2-oxa-1-silacyclopentene derivatives **117** were observed ([Scheme 25](#)). It was later shown that heating of **116** at 160 °C causes rearrangement to **117** in very high yield [<2002CL364>](#).



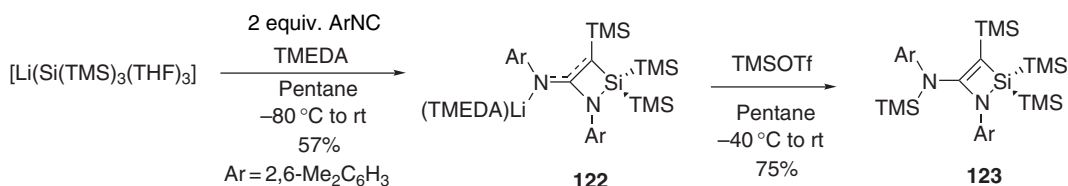
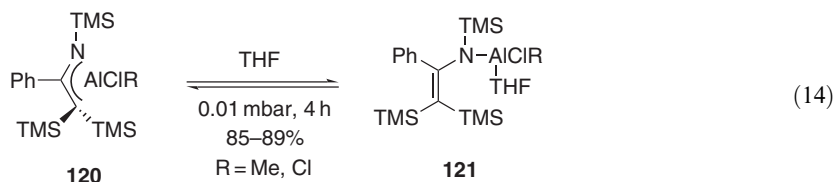
Scheme 25

Cyclobutenedione monoacetals **118** react with excess bis-TMS-ethyne to give 2-[1-(TMS)alkylidene]-4-cyclopentene-1,3-diones **119** in variable yields ([Equation \(13\)](#)). The reaction is catalyzed by Lewis acids and proceeds via a novel cationic 1,2-silyl migrative ring opening and subsequent

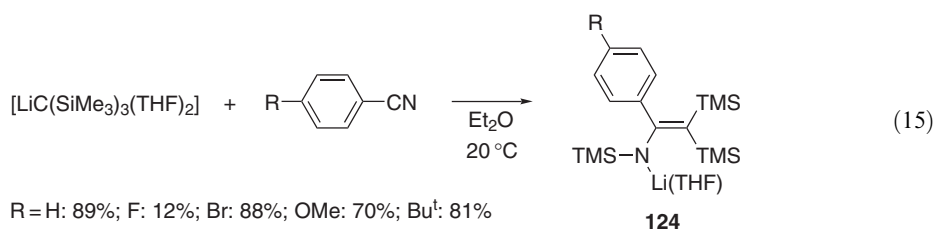
5-*exo-trig* ring closure. Yields varied widely depending upon the substituents on the cyclobutenedione, equivalents of alkyne, and the amount and type of Lewis acid used <1997JOC1292>.

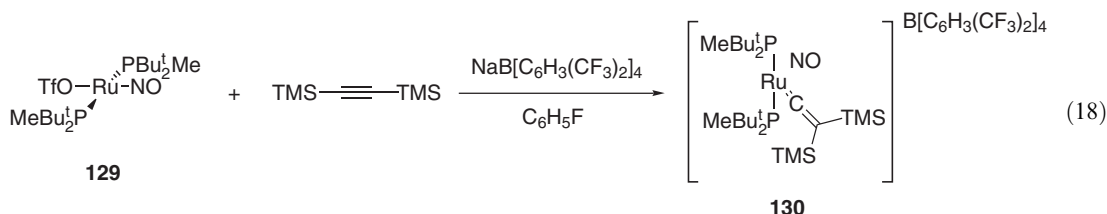
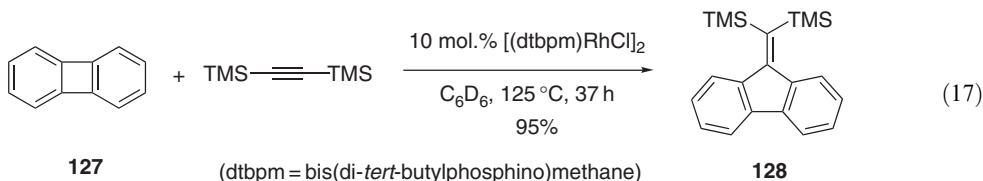
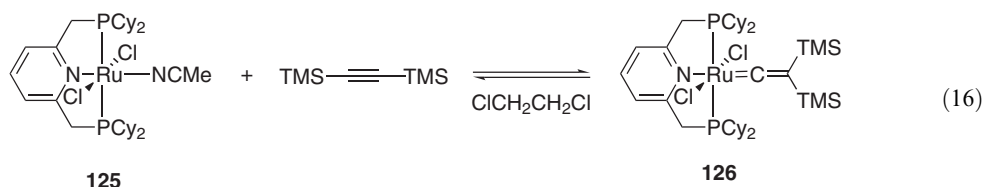


Several isolated syntheses of 1,1-disilyl alkenes or their complexes have been reported and these are briefly mentioned here for completeness. Aluminum 1-aza-allyl complexes **120** form air- and moisture-sensitive adducts **121**, when treated with THF (Equation (14)). The reaction is reversible and removal of the THF ligand at low pressure regenerates complex **120** <1999OM2256>. Treatment of  $[\text{Li}(\text{Si}(\text{TMS})_3(\text{THF})_3)]$  with 2 equiv. of 2,6-dimethylphenylisocyanide in the presence of a slight excess of TMEDA gives the 4-aryl(lithio)amino-1-aza-2-silacyclobut-3-ene derivative **122**, which, when quenched with TMSOTf, gives cyclic 1,1-disilyl alkene **123** (Scheme 26) <1999AG(E)501>. In a related series of reactions,  $\text{LiC}(\text{TMS})_3(\text{THF})_2$  reacts with aryl nitriles to give 1,1-disilyl alkenes **124** (Equation (15)) <1998TL4745>. 1,3,5-Triazine reacts with  $\text{LiC}(\text{TMS})_3(\text{THF})_2$  to give air- and moisture-sensitive 3-lithio-7,7-bis-TMS-1,3,5-triazaheptatriene in 56% yield <1997CC2091>. The pyridyl ruthenium complex **125** reacts with bis-TMSethene to give an equilibrium mixture of **125** and  $\beta$ -silylvinyldiene complex **126** (Equation (16)) <2002OM3285>. Biphenylene **127** undergoes an Rh-catalyzed reaction with bis-TMS-ethene to give 9-(bis(TMS)methylidene)fluorene **128** in high yield (Equation (17)) <2001OM5745>. The thermolysis of tetrakis(TMS)tetrahedrane at  $260^\circ\text{C}$  in tetracosane is reported to yield the 1,1-disilylalkenes tetrakis(TMS)vinylacetylene and tetrakis(TMS)butatriene in varying ratios depending upon reaction time <2002JA13819>. The combination of equimolar amounts of Ru complex **129**,  $\text{NaB}[\text{C}_6\text{H}_3(\text{CF}_3)_2]_4$ , and bis-TMS-ethyne gives a four-coordinate Ru-vinyldiene complex **130** (Equation (18)) <2000OM1967>.



Scheme 26

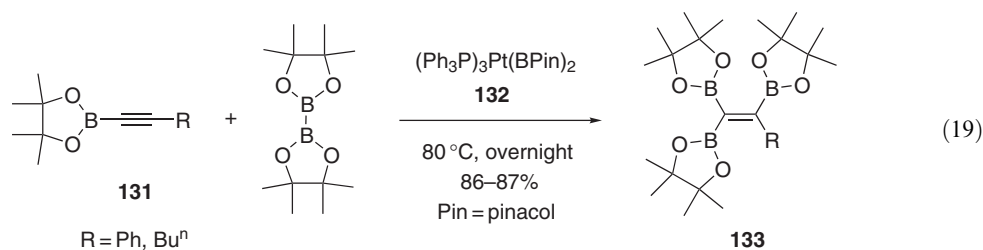


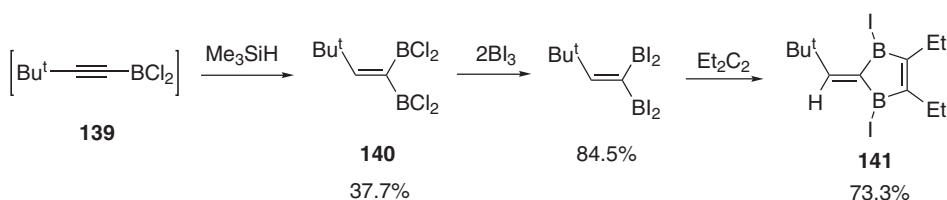
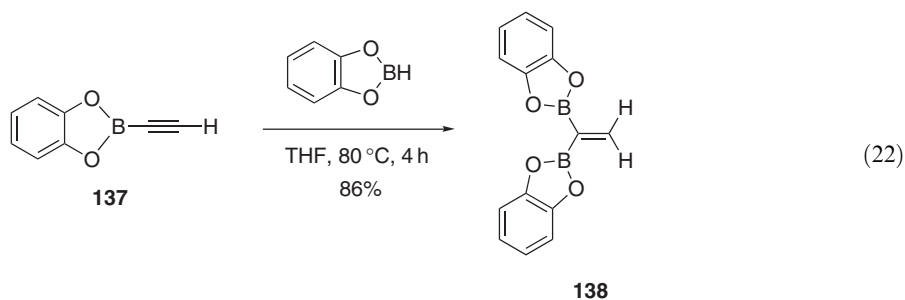
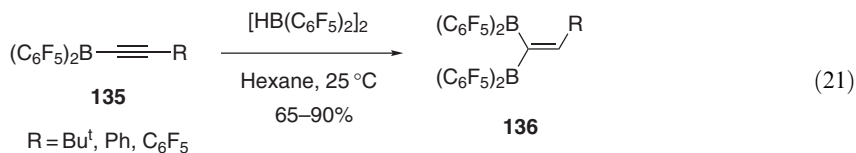
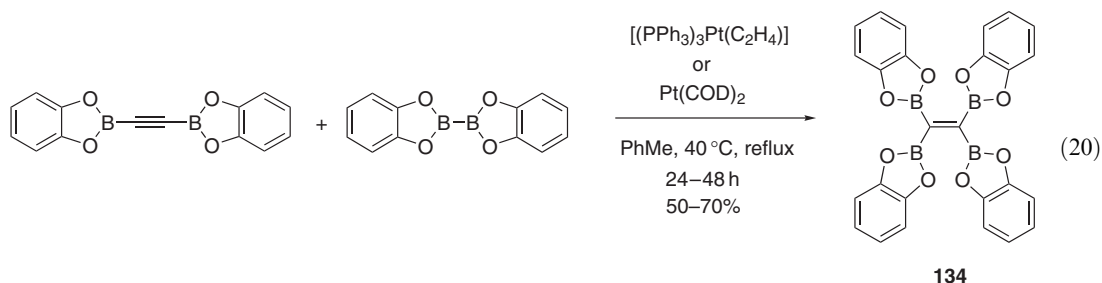


#### 4.23.1.2 Functions Bearing Two Borons— $\text{R}_2\text{C}=\text{C}(\text{BR}_3)_2$ , etc.

The study and preparation of 1,1-diboryl alkenes has been developed significantly since the publication of COFGT (1995), and several new approaches to these systems have been discovered. Previously reported routes to these systems include diboration of alkynes and addition of tris(dialkoxyboryl)methyl lithium to aldehydes and ketones <1995COFGT(4)1043>.

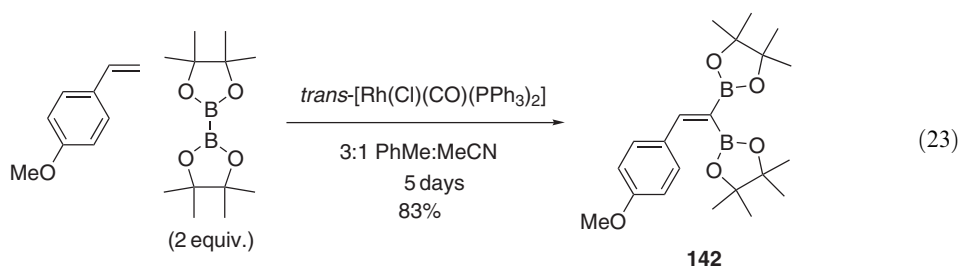
Diboration of alkynes has been further developed and certain transition metal complexes have been found to catalyze the reaction. Thus, the diboration of 1-boryl alkynes **131** using bis(pinacolatoborane) proceeds in high yield in the presence of a Pt catalyst **132** (prepared from  $\text{Pt}(\text{PPh}_3)_4$  and bis(pinacolatoborane)) to give the expected trisboronated alkene **133** (Equation (19)) <2002OM4533>. 1,2-Bis(catecholboryl)ethyne also undergoes diboration in the presence of Pt catalysts, including  $(\text{PPh}_3)_2\text{Pt}(\text{C}_2\text{H}_4)$  <1996AG(E)1501> and  $\text{Pt}(\text{COD})_2$ , <1999EJI1693> to give the tetraboryl alkene **134** (Equation (20)). The hydroboration of boryl alkynes has now also been shown to be an effective approach to 1,1-diborylalkenes. Based on electronic effects, it is predicted that the hydroboration of boryl alkynes should preferably give the geminal-substituted products, and in most cases, this is what is observed. For example, hydroboration of boryl alkynes **135** with bis(pentafluorophenyl)borane gives diboryl alkenes **136** in good yields with high (>95%) regioselectivity (Equation (21)) <1998OM3557>. Similarly, catecholborane performed regioselective hydroboration of boryl alkyne **137** to give 1,1-diboryl alkene **138** with only a small amount of the isomeric 1,2-diboryl alkene observed (Equation (22)) <2001EJI373>. In a related reaction, 1-(dichloroboryl)-4,4-dimethyl butyne **139** (prepared *in situ* from the corresponding lithium acetylide and  $\text{BCl}_3$ ) is hydroborated with  $\text{HBCl}_2$  (prepared *in situ* from  $\text{BCl}_3$  and  $\text{Me}_3\text{SiH}$ ) to give the bis(dichloroboryl)alkene **140**. This could be further elaborated through transhalogenation using  $\text{BI}_3$  followed by reaction with 3-hexyne to yield a 1,3-dihydro-1,3-diborapentafulvene **141** (Scheme 27) <2002ZN(B)1125>.





Scheme 27

Terminal alkenes can also give 1,1-diboryl alkenes through a metal-catalyzed geminal dehydrogenative diborylation reaction. Thus, treatment of vinylanisole with bis(pinacolato)diboron in the presence of 5 mol.% *trans*-[Rh(Cl)(CO)(PPh<sub>3</sub>)<sub>2</sub>] gives the 1,1-diboryl alkene **142** in good yield and high selectivity, although the reaction required 5 days to reach completion (Equation (23)) <2003CC614>. The Rh-catalyzed boration of styrylboronates gives geminal diborylstyrene derivatives <2002JOM(652)77>. 1,1-Bis(diethylboryl)prop-1-ene was observed by <sup>11</sup>B NMR as an intermediate in the complete hydroboration of diethyl(prop-1-ynyl)borane with tetraethyldiborane, ultimately giving carborane products <1995CC1691>. 1,1-Bis(trimethylstannyl)isobutene undergoes tin-boron exchange when treated with bis(1-dichloroboryl)ethyl)chloroborane to give 1,3,5-trichloro-2-isopropylidene-4,6-dimethyl-1,3,5-triboracyclohexane <1995AG(E)681>.



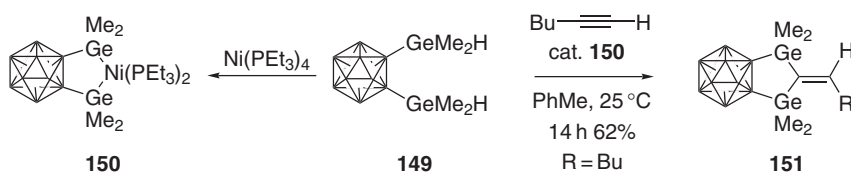




#### 4.23.1.3 Functions Bearing Two Germaniums— $R_2^1C=C(GeR_3^2)_2$ , etc.

The chemistry of 1,1-digermyl alkenes has remained little explored. Previous methods of their preparation include the addition of  $GeCl_4$  to germylalkynyl ethers: eliminations of tris(trialkylgermyl)ethanol or -acetates or reactions of propynoyl chlorides with lithium trialkylgermanium <1995COFGT(4)1043>.

The  $Pd(OAc)_2/1,1,3,3$ -tetramethylbutylisocyanide-catalyzed high-pressure intramolecular bisgermylation of cyclic germyl alkyne **30** ( $M = Ge$ ) gave **31** ( $M = Ge$ ) (Equation (3)). <1995BCJ2981>. *Ortho*-bis(dimethylgermyl)carborane **149** reacts with  $Ni(PEt_3)_4$  to give the 1,3-digermyla-2-nickela-carboranylene **150** (Scheme 29). Compound **150** catalyzes the 1,1-bis(germylation) of 1-hexyne by **149** to give the 1,1-bisgermylalkene **151** ( $R = Bu$ ) in reasonable yield (Scheme 29) <2001CC1730>, although many other alkynes gave 1,2-bisgermylation products <2002OM3922>. Stoichiometric amounts of **150** react with 1-octene to give the 1,1-bisgermylation product **151** ( $R = C_6H_{13}$ ) (Scheme 29) <2002OM3922>.



Scheme 29

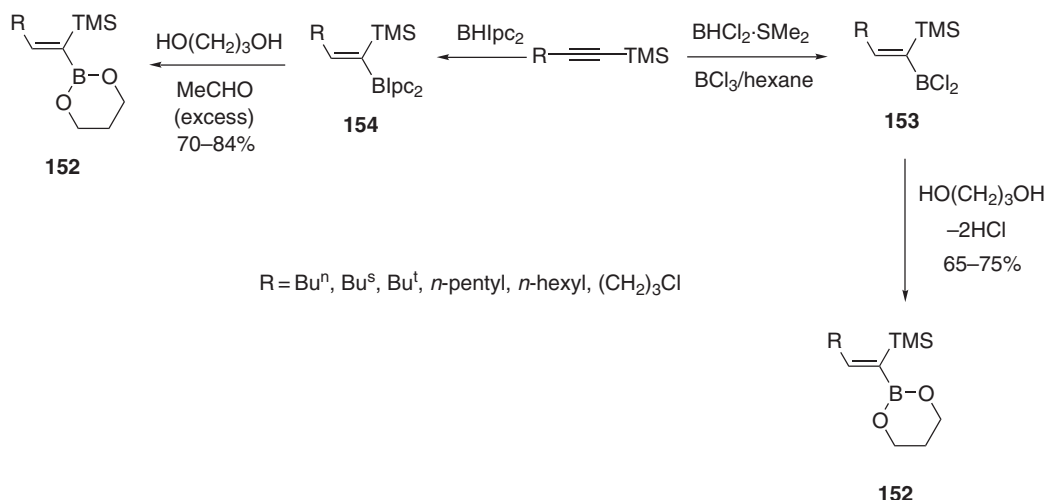
#### 4.23.1.4 Other Functions— $R_2^1C=CSiR_3^2BR_2^3$ , etc.

This section covers those functions containing borylsilyl-, germylsilyl-, and borylgermylalkenes.

##### 4.23.1.4.1 Functions containing one silicon and one boron

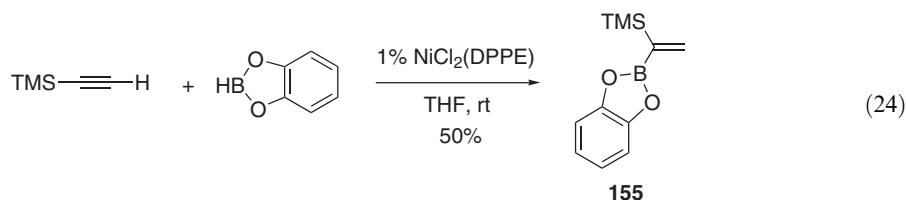
Previously reported routes to these systems include hydroboration and diboration of silyl alkynes and the reaction of geminal vinylsilyllithium species with boron halides. Allene derivatives have been prepared from 3-lithiated-1-silyl propynes and trialkylborates, and ketene derivatives from 1-silyl-2-alkoxyethynes with boron halide derivatives <1995COFGT(4)1043>.

The regiospecific hydroboration of TMS alkynes has continued to be a useful route to 1-boryl-1-silylalkenes. The preparation of (*Z*)-2-(1-TMS-1-alkenyl)-1,3,2-dioxaborinanes **152** from TMS alkynes can be achieved using  $BHCl_2 \cdot Me_2S$  or diisopinocampheylborane to give intermediates **153** or **154** respectively, followed by treatment with propanediol (Scheme 30) <2000TL8027>.

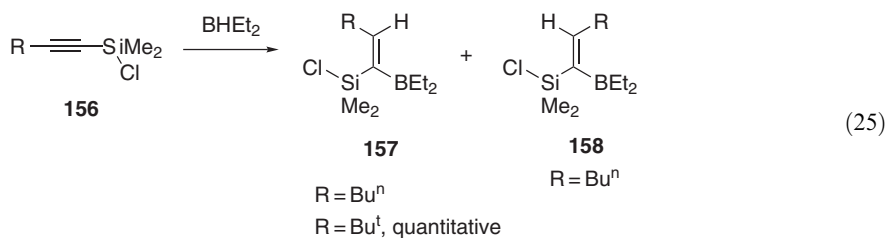


Scheme 30

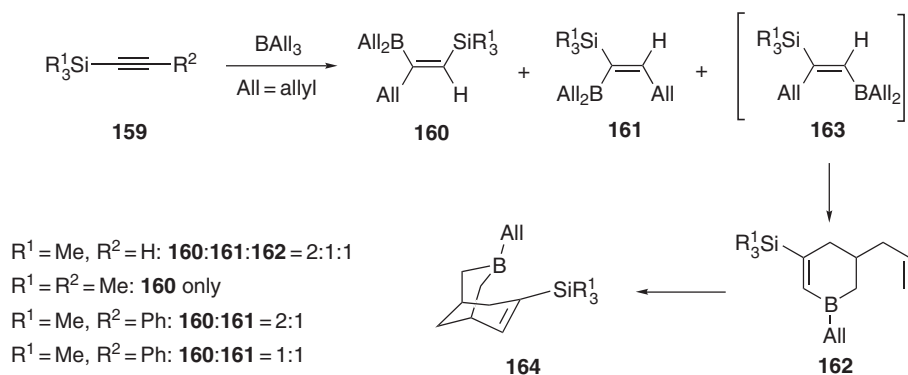
However, use of  $\text{BHBr}_2 \cdot \text{Me}_2\text{S}$  resulted in protodesilylation of the product. Nickel-catalyzed hydroboration of 1-TMS-ethyne with catecholborane gave the 1,1-silylborylalkene **155** with high selectivity (>98%) in moderate yield (Equation (24)). In contrast, the uncatalyzed reaction of neat catecholborane and TMSethyne gave a 1:1 mixture of 1-boryl-1-silylalkene **155** and its 1,2-isomer <2000MI765>.



The hydroboration of 1-alkynylchlorodimethylsilanes **156** with tetraethyldiborane has been studied in some depth. With **156** ( $\text{R} = \text{Bu}^n$ ), both *cis* and *trans* hydroboration adducts **157** and **158** are formed in nonconstant ratios (Equation (25)). However, *trans*-1,2-hydroboration is not mechanistically likely, and it is thought that **158** forms via the twofold hydroboration of **156** ( $\text{R} = \text{Bu}^n$ ) followed by dehydroboration, leading to the observed *cis* and *trans* isomers. Increasing the steric bulk of the R group slows the rate of reaction, and with **156** ( $\text{R} = \text{Bu}^t$ ) forcing conditions are required to achieve hydroboration and only the *cis* product **157** is seen. Subsequent reaction of **157** with a range of *N*- and *C*-lithiated azoles was explored and zwitterionic adducts prepared <1999JOM(584)98, 2000JOM(602)45>. The hydroboration of a range of 1-silyl alkynes with 9-BBN has been studied in some detail <2000JOM(602)45, 2003JOM(669)72>. With alkylsilylalkynes hydroboration was rapid and highly selective, whereas with chlorodialkylsilylalkynes, the reaction required more forcing conditions. With 1-chlorosilyl-2-TMS-ethyne, the regioselectivity of the reaction is low and isomerization of the initial *cis* adducts occurs giving all four *cis* and *trans* 1,1- and 1,2-hydroboration products <2003JOM(669)72>.



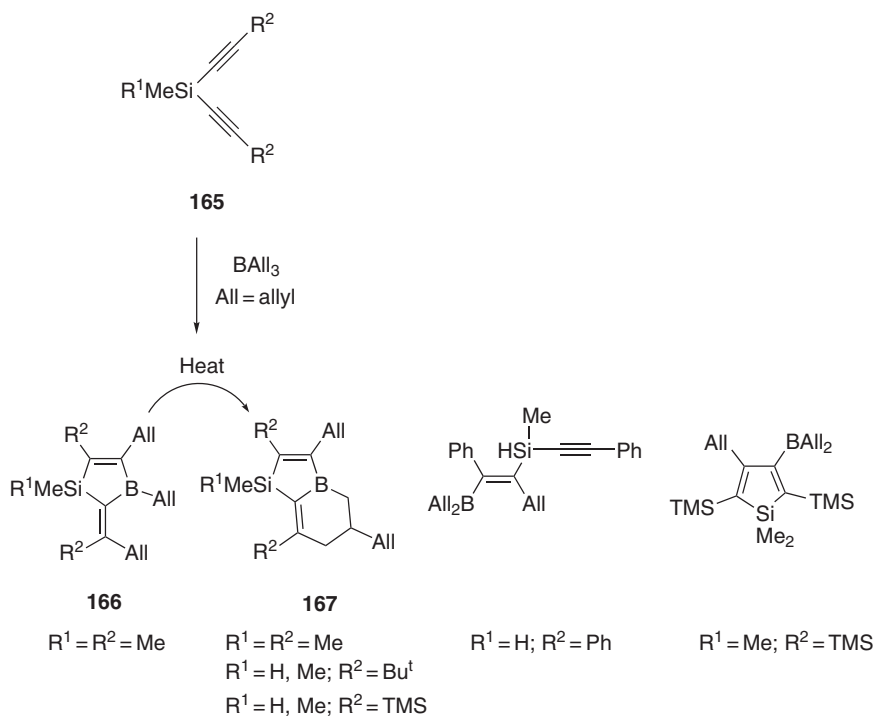
Triallylborane possesses unique reactivity among triorganoboranes due to permanent allylic rearrangement, and it is significantly more reactive than triethylborane in reactions with 1-silyl alkynes. In some cases, 1,2-allylboration competes with 1,1-allylboration, although in most cases the latter is dominant, particularly in polar solvents. For example, **159** ( $\text{R} = \text{H}$ ) gives **160**, **161**, and **162** in a 2:1:1 ratio (Scheme 31). Compound **162** results from the rapid rearrangement of **163**



Scheme 31

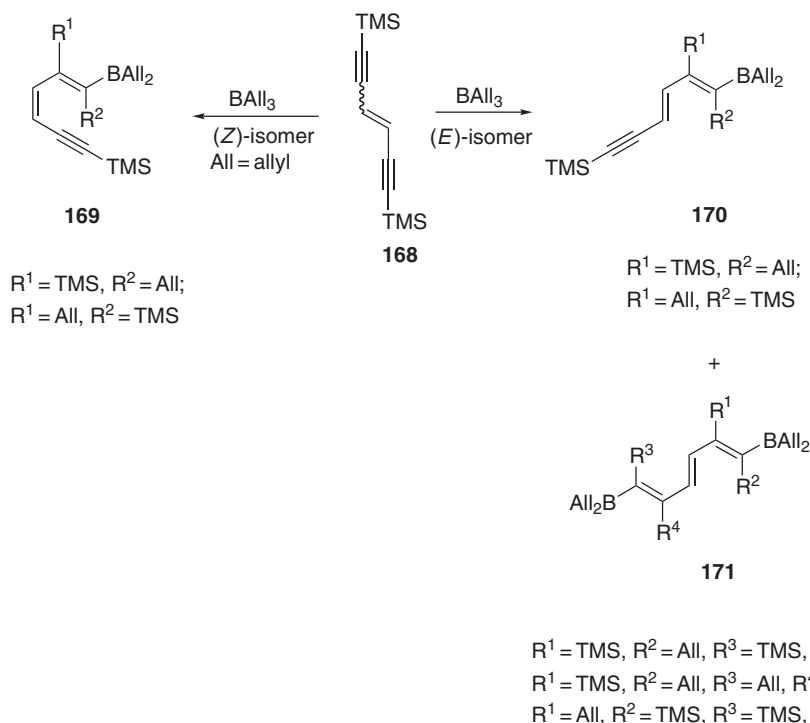
and undergoes further, slow rearrangement to bicycle **164**. With **159** ( $R = \text{Me}$ ), **160** is formed exclusively. Increasing the size of the silane substituents decreases the reactivity of the alkyne, and with **159** ( $R^1 = R^2 = \text{Ph}$ ) no reaction is observed even after prolonged heating <1999JOM(580)234>.

Heterocycles containing the 1-boryl-1-silylalkene unit can also be prepared through reactions of polyalkynyl silanes with triallylborane <2002JOM(657)146>. The outcome of the reactions is somewhat dependent on the nature of the terminal substituent on the alkyne units of **165** as well as the reaction temperature. Examples are given in Scheme 32. As the size of the terminal substituent increases, more forcing conditions are required to achieve reaction. It was also found that **166** underwent thermal rearrangement to **167**. The reactions of more complex polyalkynyl silanes with triallylborane were also studied and bis(TMS-ethynyldimethylsilyl)ethyne and tetrakis(TMS-ethynyl)silane gave similar cyclic 1-boryl-1-silyl alkynes to those in Scheme 32, along with silole derivatives <2002JOM(657)146>. The allylboration of enedynes has also been studied and competition between 1,1 and 1,2-allylboration is observed. The (*Z*)-enediyne **168** gave mainly products of 1:1 reaction with triallylborane, **169** (Scheme 33) <2002CEJ1537>. In contrast, the (*E*)-enediyne **168** reacts with triallyl borane to give all five possible isomeric mono and diallylboration adducts **170** and **171** formed via either 1,1- or 1,2-allylboration or a combination of these modes of addition (Scheme 33).

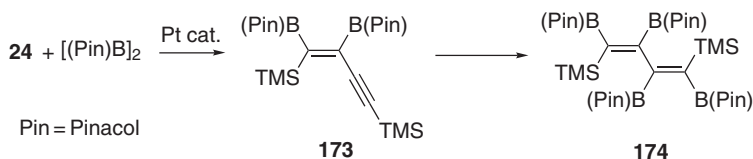
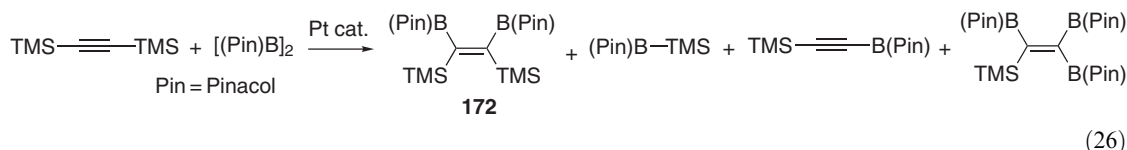


Scheme 32

Platinum-catalyzed diboration of TMS alkynes may also give 1,2-diboryl-1-silylalkenes. For example, treatment of bis-TMS-ethyne with bis(pinacolato)diboron in the presence of  $(\text{Ph}_3\text{P})_2\text{Pt}(\text{C}_2\text{H}_4)$  or  $(\text{Ph}_3\text{P})_2\text{Pt}(\text{boryl})_2$  gives diborated alkene **172** (Equation (26)). However, the reaction is somewhat complicated and metathetical byproducts are observed. The analogous reaction with 1,4-bis-(TMS)butadiyne **24** initially gave the diborated product **173**, which slowly underwent further reaction to give the tetraborated derivative **174** (Scheme 34) <1996OM5137>. Metathetical by-products were also observed. However, when **24** was treated with bis(catechol)-diboron under similar conditions, intermediates of type **173**, were not observed and work-up of the reaction gave a range of products. These and related reactions are discussed in further detail <1996OM5137>.



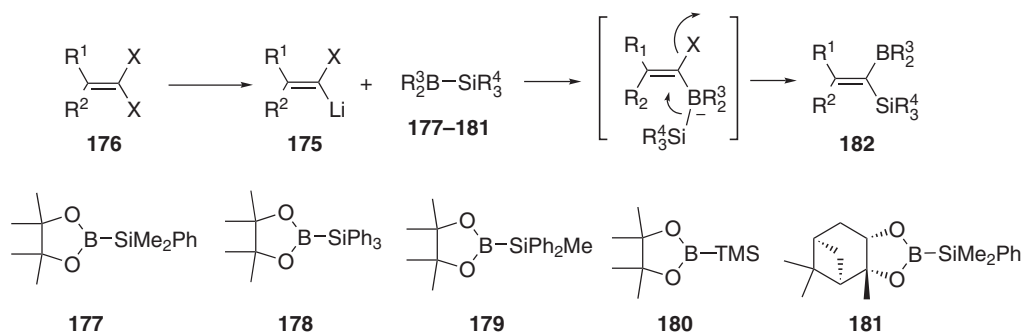
Scheme 33



Scheme 34

1-Halo-1-lithioalkenes **175** (prepared through lithiation of the precursors **176**) react with silylboranes **177–181** to give 1-boryl-1-silylalkenes **182** (Scheme 35) and selected examples are given in Table 6. The reaction proceeds through initial transmetalation of the lithium for the boron species, followed by 1,2-migration of the silyl group. Yields (from dihaloalkene) vary from moderate to good although with sterically demanding silane substituents, reactions with disubstituted carbenoids can be very poor <2001AG(E)790, 2002T6381>.

Using a similar method, 1-boryl-1-silylallenes **183** can be prepared from lithioalkynes **184**, which contain a leaving group  $\alpha$ - to the triple bond (Scheme 36). Selected examples are given in Table 7. The mechanism proceeds through transmetalation of the lithium atom with boron, followed by 1,2-migration of the silyl group from the charged intermediate with elimination of the  $\alpha$ -leaving group. When 3-mesyloxyalkynes **184** ( $\text{X} = \text{OMs}$ ) are used, the

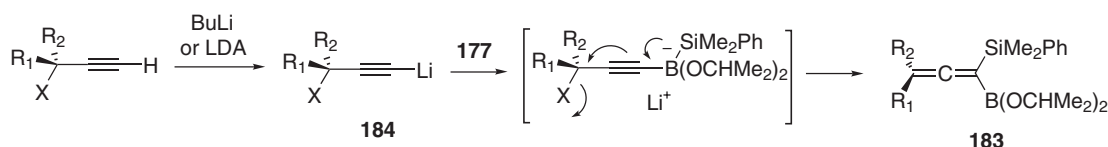


Scheme 35

**Table 6** 1-Boryl-1-silylalkenes from 1-lithio-1-haloalkenes

Precursor <b>176</b>	$R_2^3\text{B}-\text{SiR}_3^4$	Product <b>182</b>	Yield (%)
	<b>177</b>		84
	<b>178</b>		<1
	<b>179</b>		<1
	<b>180</b>		67
	<b>181</b>		78
	<b>177</b>		81
	<b>178</b>		60
	<b>179</b>		62
	<b>180</b>		45
	<b>181</b>		72
	<b>177</b>		75 ( <i>E</i> only)
	<b>177</b>		49 (1/1 <i>E/Z</i> )
		1/1 ( <i>E</i> )/( <i>Z</i> )	
	<b>177</b>		45

reaction can be accelerated and the yield increased through the addition of  $\text{TMSCl}$ , due to coordination of  $\text{TMSCl}$  with the mesyloxy leaving group. Overall yields are moderate. Optically active 3-mesyloxyalkynes **184** ( $\text{X} = \text{OMs}$ ) give enantioenriched allenes, although some racemization is noted <2003OL225>.



Scheme 36

Table 7 Synthesis of 1-boryl-1-silylallenes

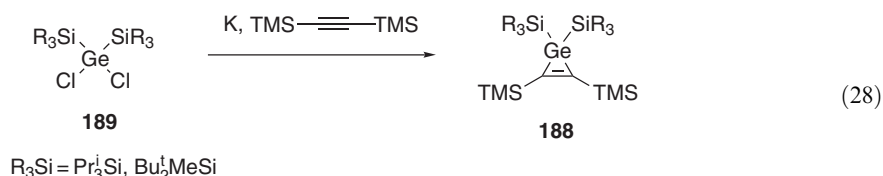
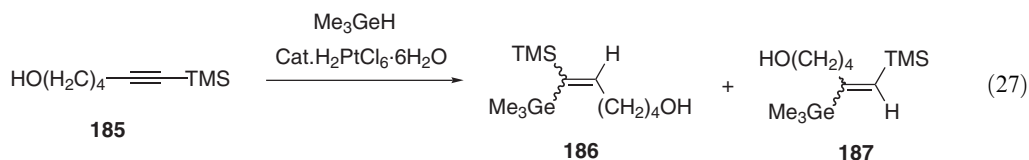
Precursor	Product	Yield (%)
		77
		53–60
		41–52
		51–75
		75 (>74% ee)
		67 (70% ee)

Although strictly outside of the scope of this review, partially reduced 2-silylborabenzene derivatives which contain the 1-silyl-1-borylalkene unit have been prepared through treatment of dihydroboratabenzene with LDA followed by quenching with  $\text{TMSCl}$  [<1997OM926>](#) or through the transmetalation of silylated 1-stannacyclohexa-2,4-dienes with  $\text{BCl}_3$  [<1996OM1315, 1997JOC8286>](#).

#### 4.23.1.4.2 Functions containing one silicon and one germanium

Previously reported routes to 1-germyl-1-silylalkenes include halogermylation of silyl alkynes with germanium tetrachloride, or halosilylation of germyl alkynes with silicon tetrachloride. The insertion of germanium dibromide into 1-bromo-1-silyl alkenes has also proved effective, as has the transmetalation of lithiosilyl alkenes with germyl halides. 1-Germyl-1-silylalkenes have been prepared through the propargylic deprotonation of silyl alkynes followed by quenching with trialkylgermyl chlorides or, conversely, deprotonation of germylalkynes followed by quenching with silyl chlorides [<1995COFGT\(4\)1043>](#). Several alternative routes to 1-germyl-1-silylalkenes have now been reported.

The treatment of 1-bromo-1-germyl-1-silylethane **63** ( $R^1 = \text{SiMePh}_2$ ;  $R^2 = \text{GeEt}_3$ ) with DBU induces dehydrobromination to give 1-germyl-1-silylalkene **65** ( $R^1 = \text{SiMePh}_2$ ;  $R^2 = \text{GeEt}_3$ ) in high yield (Scheme 13) <2002CEJ1730>. The Pt-catalyzed hydrogermylation of 1-TMS-alkynes **185** with trimethylgermane gives ~1:3 ratio of (*Z*)-1-germyl-1-silylalkenes **186** and isomeric (*E*)-1-germyl-2-silylalkenes **187** (Equation (27)) <1995JCS(P1)3>. A new route to silyl-substituted germacyclopropenes has been reported. The 1,1-bis(trialkylsilyl)-1-germacycloprop-2-enes **188** are formed in good yield through reduction of bis(trialkylsilyl)dichlorogermanes **189** with molten potassium in the presence of bis-TMS-ethyne, without solvent (Equation (28)) <2002AG(E)1598>. 1-Germyl-1-silylketenes **73** ( $\text{MR}_3 = \text{GeMe}_3$ ) can be prepared through quenching lithium ynolate **74** with  $\text{Me}_3\text{GeBr}$  (Scheme 16) <1996JA7634>.



#### 4.23.1.4.3 Functions containing one boron and one germanium

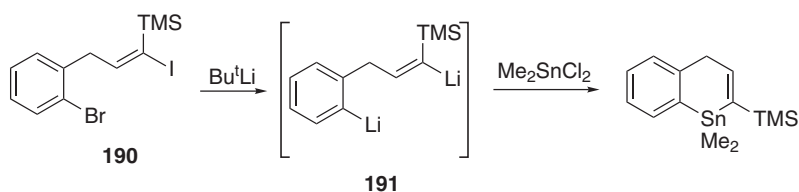
The only route to these species previously reported is the hydroboration of germyl alkynes. No further synthetic approaches have been reported since COFGT (1995).

### 4.23.2 FUNCTIONS CONTAINING A METALLOID AND A METAL

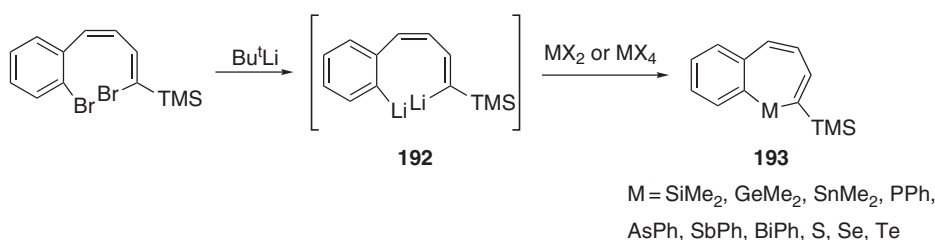
#### 4.23.2.1 Silicon Functions— $\text{R}_2^1\text{C}=\text{CSiR}_3^2\text{M}$

##### 4.23.2.1.1 Functions with one silicon and one group 1 metal

Previously reviewed methods of preparing 1-lithio-1-silylalkenes include the silylcupration of lithioalkynes, lithium–halogen exchange of 1-halo-1-silylalkenes and transmetalation of 1-stannyl-1-silylalkenes. 1-Lithio-1-silylalkenes have been prepared through the lithiation of TMS-propynes <1995COFGT(4)1043>. Of these, only lithium–halogen exchange has found continued use during the 1990s. The synthetic utility of 1-lithio-1-silylalkenes has been demonstrated in the preparation of heavy atom heterocycles <2001OM2109>. For example, lithiation of iodoalkene **190** with  $\text{Bu}^t\text{Li}$  gives **191**, which readily undergoes *cis/trans* isomerization (Scheme 37). Further treatment of **191** with  $\text{Me}_2\text{SnCl}_2$  gives a 1,4-dihydrostannanaphthalene. A wide range of benzoheteroepines was obtained using similar methods, although in this case, a bromine–lithium exchange was employed (Scheme 38) <1999CPB1108>. Quenching of the dilithium species **192** with electrophilic metal reagents gave the corresponding heteroepines **193** <1999CPB1108>.



Scheme 37



Scheme 38

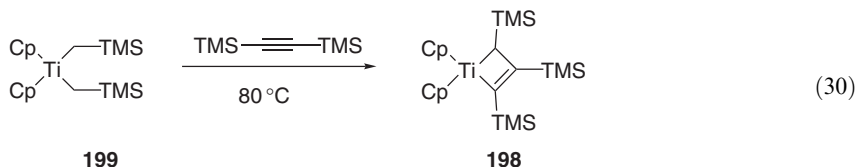
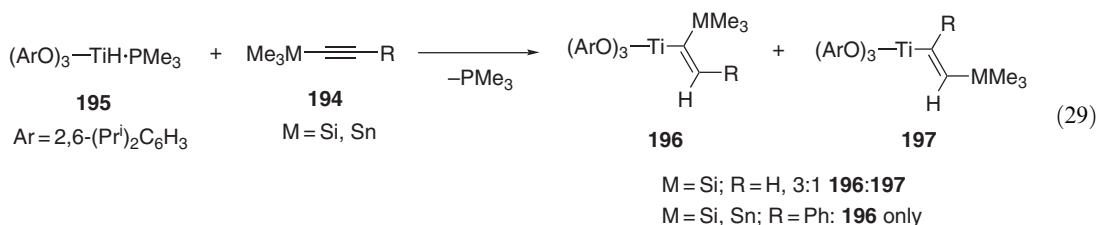
#### 4.23.2.1.2 Functions with one silicon and one group 2 metal

Previously reported routes to these systems include Ni-catalyzed addition of MeMgBr to silyl alkynes: hydromagnesiation or carbomagnesiation of silyl alkynes and transmetalation of 1-silyl-1-bromoalkenes [<1995COFGT\(4\)1043>](#). There have been no significant developments in the preparation of the title compounds.

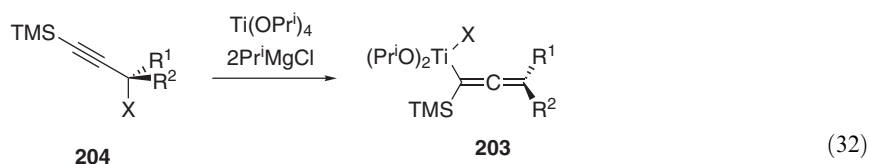
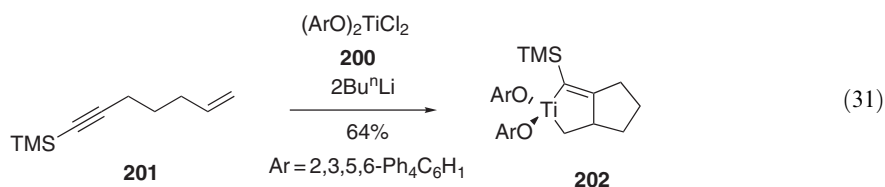
#### 4.23.2.1.3 Functions with one silicon and one transition group metal

##### (i) Functions with one silicon and one group 4 metal

1-Titano-1-silylalkenes have previously been prepared via transmetalation of 1-lithio-1-silylalkenes and carbotitanation of silyl alkynes [<1995COFGT\(4\)1043>](#). However, during the 1990s, the chemistry of group 4 1-metallo-1-silylalkenes including titanium and zirconium species has undergone significant development and new approaches have been discovered. Hydrotitanation of silylalkynes **194** ( $\text{M} = \text{Si}$ ) with tris(aryloxy)titanium (IV) hydrides, stabilized as their  $\text{PMe}_3$  adducts **195**, proceeds via *syn* addition to the triple bond with some degree of stereospecificity giving **196** ( $\text{M} = \text{Si}$ ) and sometimes **197** ( $\text{M} = \text{Si}$ ) (Equation (29)) [<1995OM4601>](#). Tris(TMS)-titanocyclobutene **198** is a mild and effective reagent for the conversion of a wide range of carbonyl groups to alkenyl silanes and it is prepared in high yield through the treatment of bis(TMSmethyl)titanocene **199** with 1,2-bis(TMS)ethyne at  $80^\circ\text{C}$  (Equation (30)) [<1995TL3619>](#). Titanium aryloxy **200** reacts with 1-TMS-6-hepten-2-yne **201** in the presence of 2 equiv. of  $\text{Bu}^n\text{Li}$  to form a bicyclic 1-titano-1-silylalkene **202** (Equation (31)) [<2003CC18>](#). Chiral 1-titano-1-silylallenes **203** can be prepared through treatment of optically active propargyl alcohol derivatives **204** with  $\text{Ti}(\text{OPr}^i)_4$  and 2 equiv. of  $\text{Pr}^i\text{MgCl}$  with an excellent degree of chiral transfer (Equation (32)) [<1998TL4555>](#).



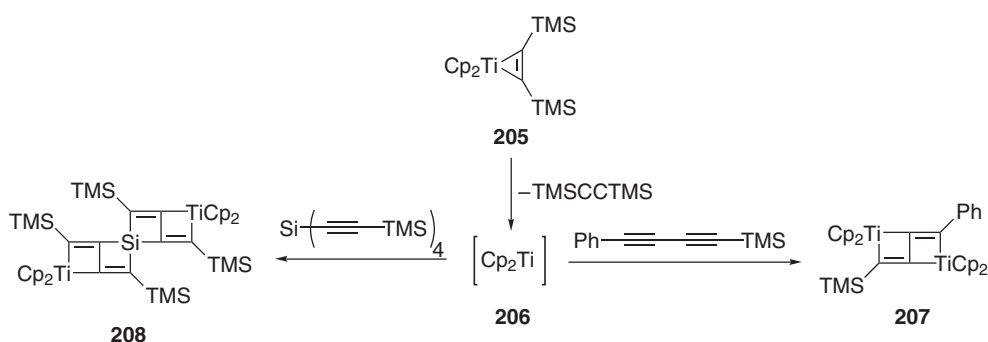




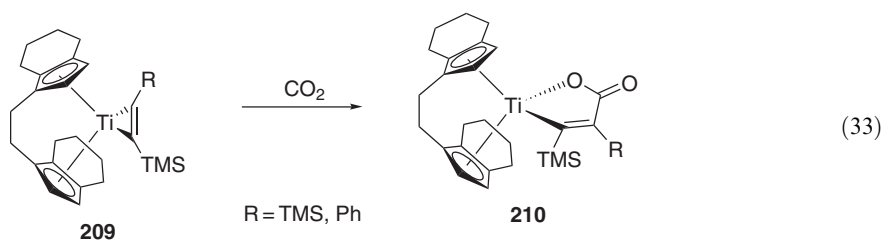
X = OP(O)(OEt)<sub>2</sub>; R<sup>1</sup> = Bu; R<sup>2</sup> = H: **204** = 96.7% ee; **203** = 85% ee

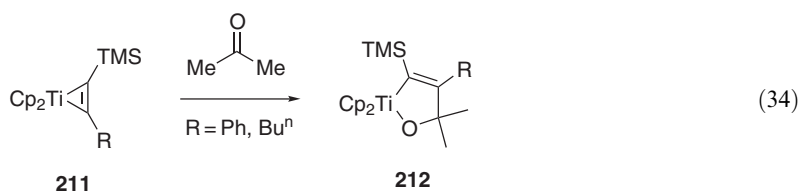
X = OCO<sub>2</sub>Et; R<sup>1</sup> = (CH<sub>2</sub>)<sub>3</sub>CHMe<sub>2</sub>; R<sup>2</sup> = Me: **204** = 97.2% ee; **203** = 85% ee

The  $\eta^2$ -bis(TMS)ethyne complexes of Cp<sub>2</sub>Ti, **205**, offer an excellent route to the unstable free titanocene through elimination of the ethyne ligand. The free metallocene **206** undergoes reaction with 1-TMS-4-phenylbutadiyne to give bimetallic bicycle **207** via an intermediate cyclocumulene (Scheme 39) <1995OM2961>. In a more complex example, reaction of **205** with tetrakis(TMS-alkynyl)silane gave tetracyclic bimetallic species **208** (Scheme 39) <2000OM1198>. The treatment of *meso*-1,2-ethylene-1,1'-bis( $\eta^5$ -tetrahydroindenyl) titanocene- $\eta^2$ -TMS-ethyne complexes **209** with CO<sub>2</sub> can lead to regiospecific insertion reactions to give titanofuranone complexes **210** in good yields, with retention of the 1-titano-1-silylalkene unit (Equation (33)) <1998EJI1495>. However, several related titanocene- $\eta^2$ -TMS-2-phenylethyne complexes containing other modified cyclopentadienyl ligands gave only insertion into the silicon substituted carbon and 1-titano-1-silylalkene derivatives were not obtained. Treatment of **211** with acetone also gave an insertion product, oxatitanacycle **212** (Equation (34)) <1995JOM(501)179>.

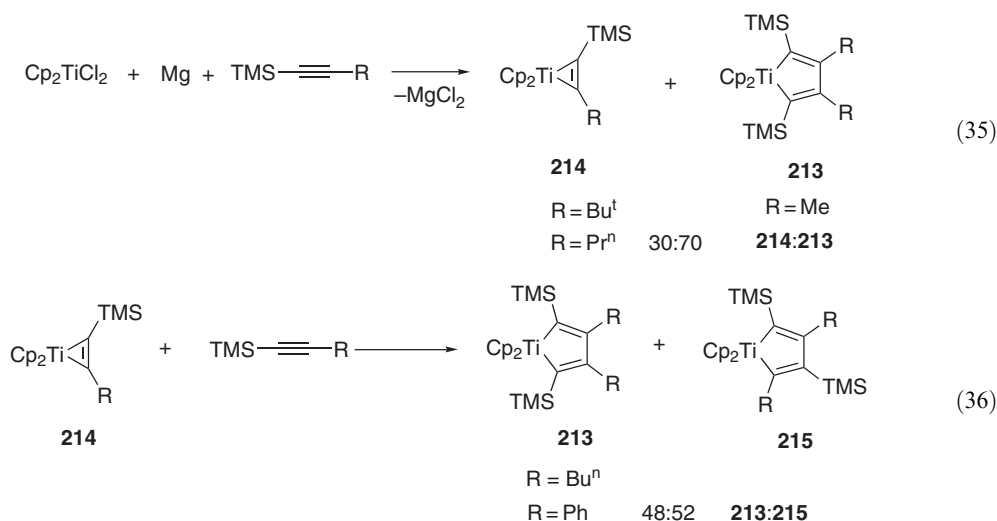


Scheme 39

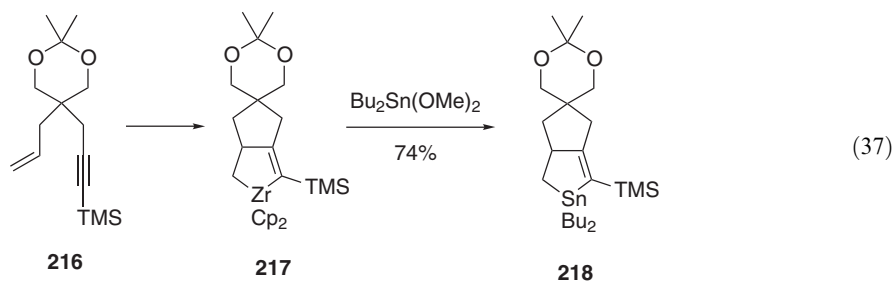


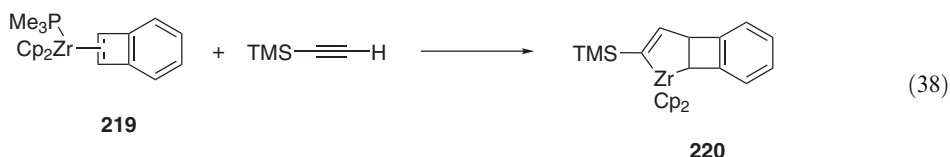


1,5-Disilyl-3,4-dialkyltitanocyclopentadienes (e.g., **213**) can be prepared through the reaction of free titanocene (in this case prepared from  $\text{Cp}_2\text{TiCl}_2$  and Mg) with 2 equiv. of alkyne, although formation of titanocyclopropenes **214** competes as the size of the alkyne substituents increases (Equation (35)) <1995JOM(501)179>. It was also found that **214** undergoes ring expansion with further TMS alkynes to give titanocyclopentadienes **213** and **215** (Equation (36)), although hindered alkyl substituents inhibit the ring expansion. Factors affecting the ratios of isomers such as **213** and **215** have been discussed, and it was found that **215** is the kinetic product of the reaction, with rearrangement to the thermodynamically more stable symmetrical **213** occurring over time <1995JOM(501)179>. Several other 2-silyltitanocyclopentadienes have been prepared under similar conditions <1995JOM(503)221, 1998CEJ1852, 1995CB967>.

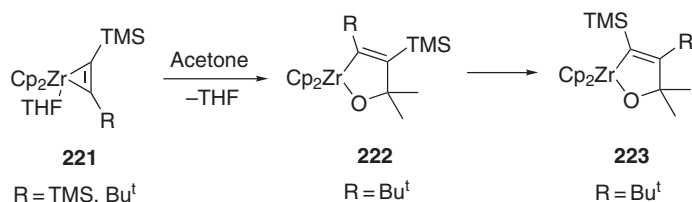


1-Zircona-1-silylalkenes were not discussed in the previous review <1995COFGT(4)1043>, but in recent years there has been much activity in this area and several protocols for the preparation of these species are now available. The main focus has been on the preparation of zirconacyclopentadiene derivatives, although other 1-zircona-1-silylalkenes have been reported. Treatment of eneyne **216** with  $\text{Cp}_2\text{ZrBu}_2$  gave the 2-TMS-zirconacyclopentene **217** (Equation (37)), which was used as an intermediate to the corresponding cyclic stannane derivative **218** <1995TL3725>. Zirconocene alkene complexes are much less robust than the well-known zirconocene-alkyne complexes, and alkene displacement is generally facile. However, complexation with benzocyclobutadiene gives a much more stable system, presumably due to the unfavorable liberation of an antiaromatic compound upon displacement. The zirconium alkene complex **219** reacted with TMS-ethyne gave the tricyclic 1-zircona-1-silylalkene **220** (Equation (38)) <2002OM5685>.

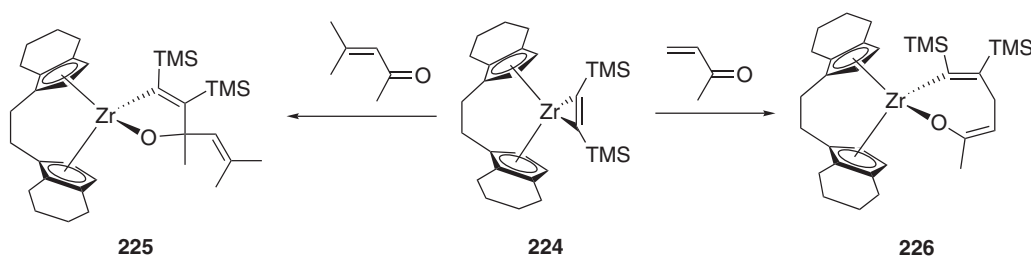




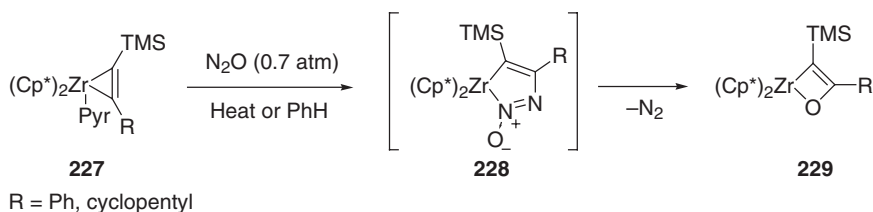
As in the titanium series, reactive-free zirconocene can be generated from stable zirconocene- $\eta^2$ -alkyne complexes. These complexes also undergo a range of insertion reactions to give 1-zircona-1-silylalkene derivatives. When treated with acetone, zirconocene-alkyne complexes **221** initially give zirconadihydrofurans **222**, which rearrange to the thermodynamically more stable isomer **223** (Scheme 40), although with **221** (R = TMS) the product is unstable and prone to the reversion to the starting materials <1995JOM(501)189>. Alkyl vinyl ketones also insert into zirconocene-alkyne complexes, although the outcome is somewhat dependent on both the Cp ligand on the zirconocene and the ketone fragment. Thus, *rac*-1,2-ethylene-1,1'-bis( $\eta^5$ -tetrahydroindenyl)zirconocene complex **224** reacts with methyl vinyl ketone to give the 1,4-insertion product **225** in high yield (Scheme 41), but gives 1,2-insertion complex **226** with mesityl oxide <2002OM3360>. Nitrous oxide inserts into  $\eta^2$ -alkyne-stabilized zirconocenes **227** to give an intermediate azoxy species **228** which eliminates N<sub>2</sub> to give oxazirconacyclobutenes **229** in quantitative yield (Scheme 42) <1998ICA399>. Treatment of **230** with benzoxazole, benzothiazole, thiazole, and dimethylthiazole all give analogous ring-expanded products **231** via insertion of the zirconocene unit into the heterocyclic ring (Equation (39)) <1996CB297>. Benzaldehyde azine inserts into the Zr—C bond of zirconocene-alkyne complexes to give a 1-zircona-2-azacyclopent-4-ene <1998OM4429>.



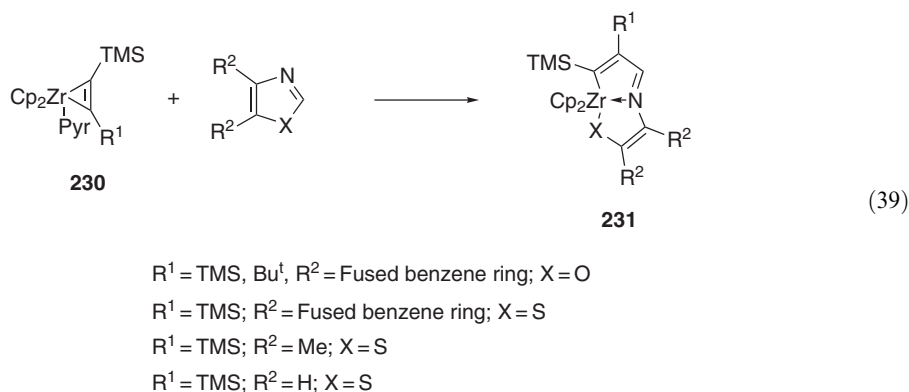
Scheme 40



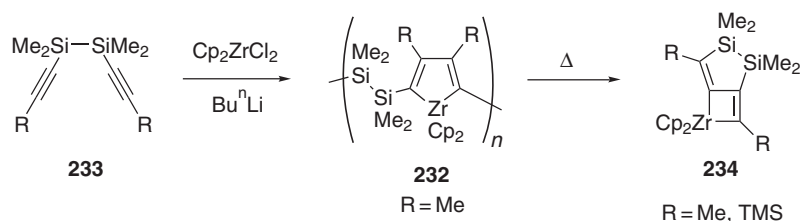
Scheme 41



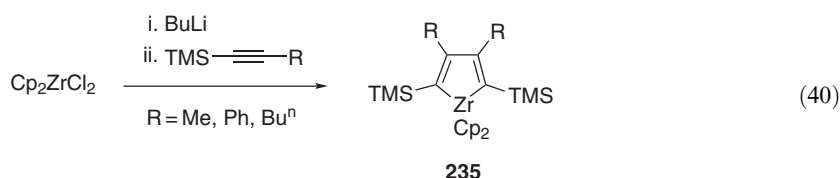
Scheme 42



Zirconacyclopentadienes have attracted much interest in recent times and many examples of 2-silylzirconacyclopentadienes have been reported. Polymeric 2-silylzirconacyclopentadienes **232** have been obtained in quantitative yield through the reaction of free zirconocene (generated *in situ*) with ethynyldisilane **233** ( $R = \text{Me}$ ) (Scheme 43). Heating of the polymer led to depolymerization followed by intramolecular coupling with 1,2-migration of the silyl group, ultimately giving zirconacycle **234**. Use of **233** ( $R = \text{TMS}$ ) led to formation of **234** directly <2000CL1082>. The intermolecular reaction between zirconocene and silyl alkynes has been used in the preparation of symmetrical 2,5-disilylzirconacyclopentadienes **235** (Equation (40)) <1999OM2491, 1999OM4205>. Use of more sterically demanding ligands on the zirconocene unit can promote the formation of the unsymmetrical zirconacyclopentadienes <2002ICA(334)17>. As with titanacyclopentadienes (Equation (36)), the unsymmetrical 2,4-disilyl species are generally the kinetic products, and these rearrange to give the thermodynamically more stable symmetrical 2,5-disilyl species <1998CEJ1852>. The intramolecular cyclization of di(TMS-alkynyl) ether **236** with  $\text{Cp}_2\text{ZrBu}_2$  gives the ring fused zirconacyclopentadienes **237** (Scheme 44) <2002CEJ4734>. Transmetalation with  $\text{CuCl}$  gave the corresponding bis(1-TMS-1-cuproalkene) species **238** which was trapped *in situ* with a divinyl iodide to give cyclooctatetraene derivative **239** (Scheme 44). Use of shorter linkers between the TMS-alkyne units can result in more complex reaction mixtures due to the increased ring strain of any potential fused products <1995T4359>. Zirconacyclopentenes **240** react with bis(butynyl)diphenylsilane to give 1-(diphenylbutynylsilyl)zirconacyclopentadiene **241**, which underwent rearrangement to give **242** upon heating (Scheme 45) <1997JA12842>.



Scheme 43

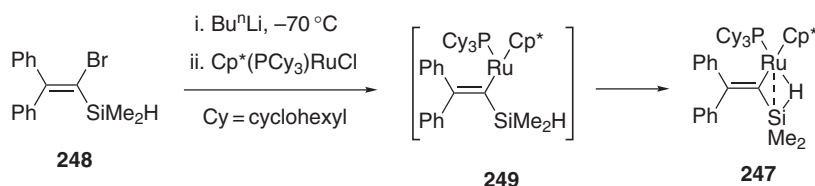
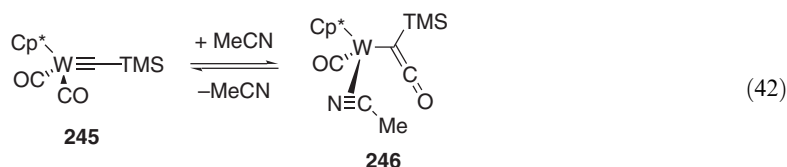


A range of macrocyclic polyzirconacyclopentadienes have been prepared via the cyclooligomerization of bis(silylalkynes) with zirconocene <1995JA7031, 1998JA3271, 1998JOC3673, 2000JA10345, 2001JA2683, 2002CEJ74> (Equation (41)). Due to the reversibility of the zirconocene-alkyne coupling, initially formed oligomeric zirconacyclopentadiene species are converted to the thermodynamic product, which is the smallest strain-free ring that can form. With linear dialkynes, trimers **243** are

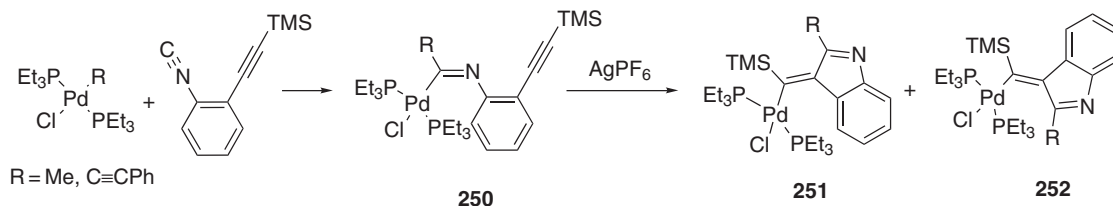


## (ii) Functions with one silicon and one transition metal (not including a group 4 metal)

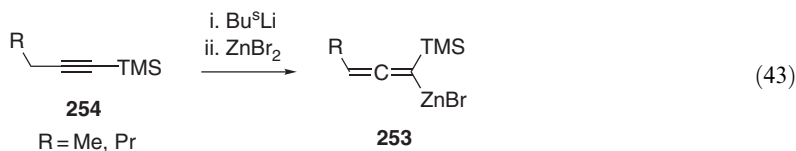
1-Cupro-1-silylalkenes have been prepared from silyl alkynes and organocopper–magnesium halide species and several different transmetalations are also known. 1-Zinco-1-silylalkenes have been prepared through organozincation of silyl alkynes and 1-zinco-1-silylallenes have been prepared through transmetalation of lithium species <1995COFGT(4)1043>. Tungsten carbyne complexes **245** can undergo a carbyne–carbonyl coupling reaction when treated with acetonitrile, to give the 1-tungsto-1-silylketene complex **246**, although the reaction is reversible and **246** can only be obtained pure in the solid state (Equation (42)) <1999JOM(587)233>. 1-Rutheno-1-silylalkene **247** was prepared from 1-bromo-1-silylalkene **248** (presumably via **249**) and can be considered to be an example of a 1-silaallene that is stabilized by both metal ligation and interaction with a metal hydrogen bond (Scheme 46) <1995JA3298>. Alkynes have been found to undergo intramolecular insertion into the Pd–C bond of (iminoacyl)palladium complexes **250**, preferably in the presence of AgPF<sub>6</sub>, to give 1-pallado-1-silylalkenes **251** and **252** (Scheme 47) <1998OM4335>. As reported previously <1995COFGT(4)1043>, 1-zinco-1-silylallenes **253** are accessible via propargylic deprotonation of silyl alkynes **254** and subsequent transmetalation with ZnBr<sub>2</sub> (Equation (43)). The bimetallic reagents thus formed were found to add to  $\alpha$ -chiral imines with high diastereoselectivity <2000JOC6553>. Compound **253** (R = Cl) was obtained through treatment of a mixture of 1-silyl-3-chloropropyne and ZnBr<sub>2</sub> with LDA at low temperature, and its reactions studied <2001EJO3295, 2002EJO1385>. An example of a 1-mercuro-1-silylalkene **255** has been prepared through the carbomercuration of 1-TMS-alkyne **256** using a tethered allylic silane (Equation (44)). The (Z)-alkene **255** was formed exclusively via net *syn* addition of mercuric chloride and the allylic moiety to the alkyne <1997JOC8595>.

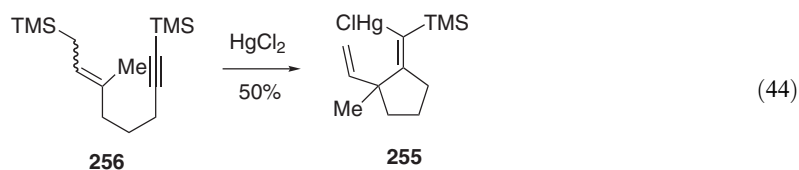


Scheme 46



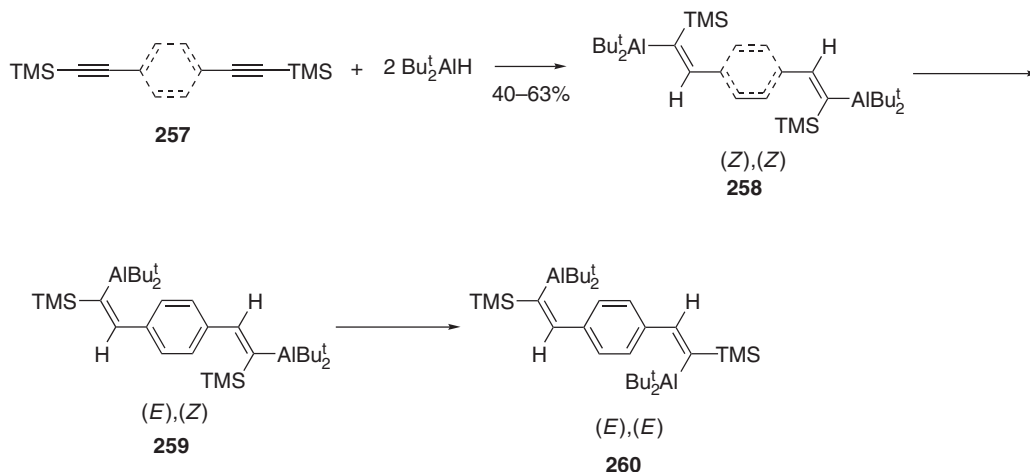
Scheme 47



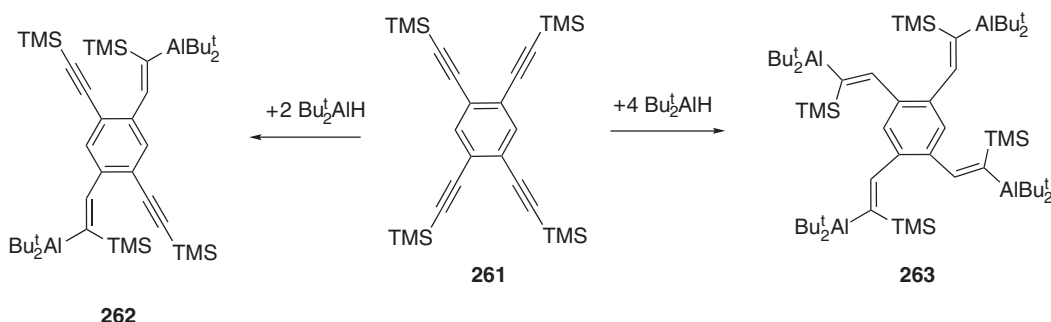


#### 4.23.2.1.4 Functions with one silicon and one group 13 or group 14 metal

Previously reported methods of preparing 1-alumino-1-silylalkenes include the hydroalumination or carboalumination of silyl alkynes <1995COFGT(4)1043>, both of which have found continued use. Hydroalumination of dialkynes **257** (with or without a benzene linker) with di(*t*-butyl)-aluminum hydride offers a facile method for the synthesis of 1-silyl-1-aluminoalkenes. The reaction proceeds via *cis* addition of the aluminum hydride to each alkyne group to give ((*Z*),(*Z*))-dienes **258** (Scheme 48) <2000JOM(608)54>. Heating of **258** gave a stepwise rearrangement when the benzene linker was present to give the thermodynamically more stable ((*E*),(*Z*))-isomer **259**, then ((*E*),(*E*))-isomer **260**, although, in the absence of the benzene linker, only mixtures of uncharacterized products were obtained. Extension of this method to 1,2,4,5-tetrakis(TMS-ethynyl)benzene **261** gave either bis- or tetra-hydroaluminated products **262** and **263**, respectively (Scheme 49), depending on the equivalents of aluminum hydride used <2002JOM(664)110>. Carboalumination of enynes **264** with Et<sub>3</sub>Al in the presence of catalytic Cl<sub>2</sub>ZrCp<sub>2</sub> gives aluminocycles **265** (Equation (45)) <1998TL2503>. 1-TMS-ethyne undergoes a formal insertion into the Al—N bond of dimeric pyrazolatoaluminum dihydride or dichloride, **266** (R = H or Cl) (Scheme 50). With 6 equiv. of TMS-ethyne compound **266** (R = H) gives the

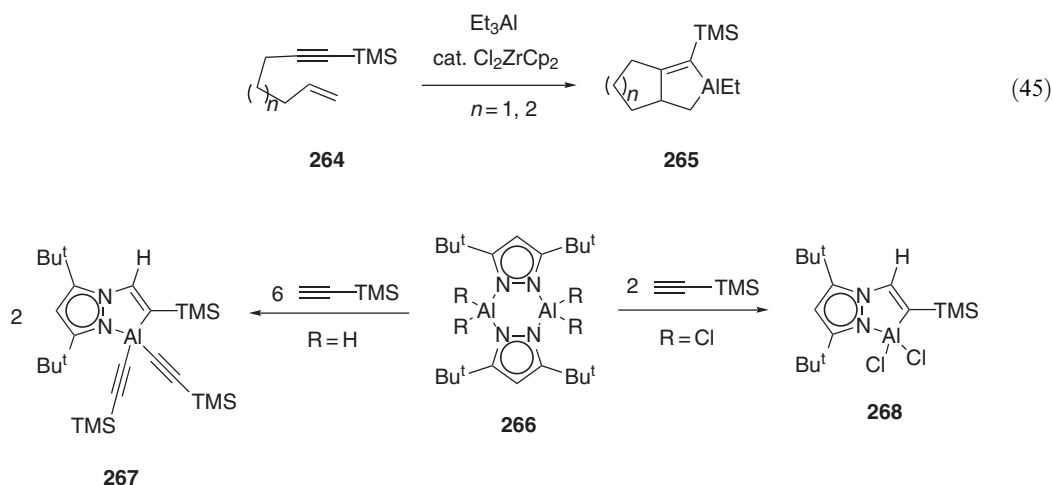


Scheme 48



Scheme 49

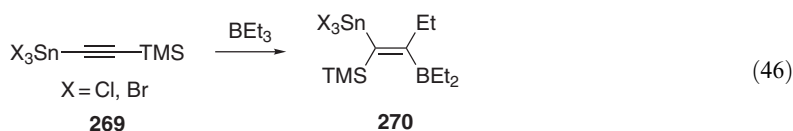
aluminocycle **267** <2000AG(E)3099>, whereas treatment of **266** (R = Cl) with 2 equiv. of TMS-ethyne gives the dichloroaluminum species **268** in high yield <2001OM3299>. The remaining chloride ligands on the aluminum center allow for further elaboration <2002EJI1056>. The reactions are thought to proceed via initial dissociation of the dimeric pyrazolatoaluminum dihydride, **266**, with subsequent reaction with the TMS-alkyne.



Scheme 50

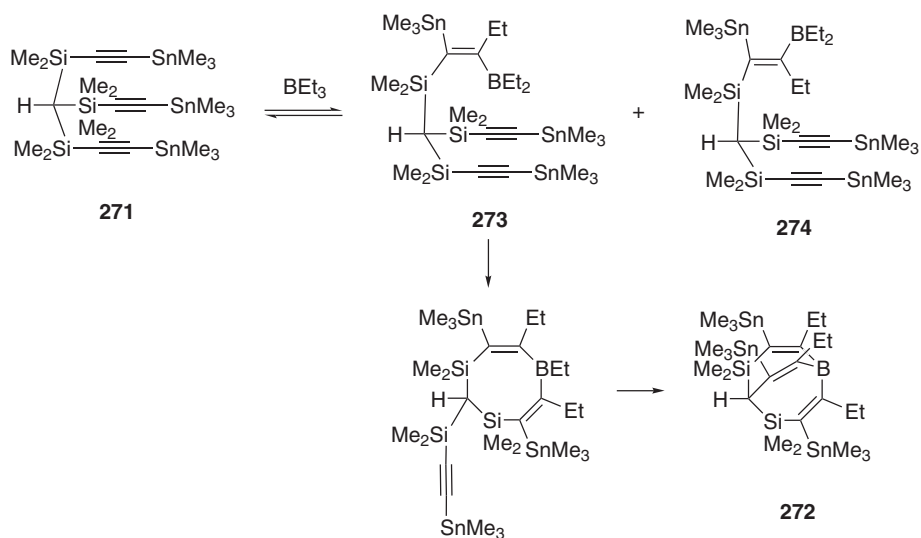
Previously reported methods of preparing 1-stannyl-1-silylalkenes include the hydrostannylation of silyl alkynes or the transmetalation of 1-lithio-, 1-magnesio-, or 1-titano-1-silylalkenes with trialkylstannyl halides. The organoboration of 1-silyl-2-stannylalkynes also gives 1-stannyl-1-silylalkenes via stannyl migration. 1-Silyl-1-stannylallenes were prepared by the BuLi-mediated addition of trialkylstannyl chlorides to terminal alkynes <1995COFGT(4)1043>.

Of these, the organoboration of 1-silyl-2-stannylalkynes has found the most extensive use in recent times. For example, the reaction of 1-trihalostannyl-2-TMS-alkynes **269** with  $\text{BEt}_3$  gives the organoboration products **270** (Equation (46)), although these slowly decompose due to the weak Sn—C bond <2002JOM(646)125>. In a more complex example, treatment of tris(1-silyl-2-stannylalkyne) **271** with  $\text{BEt}_3$  gave **272** in 55% yield, via a series of 1,1-organoboration reactions (Scheme 51) <1995CC399>. The initial organoboration products are (*Z*)- and (*E*)-isomers, **273** and **274**, but due to the reversibility of the organoboration the equilibrium is shifted toward the (*Z*)-isomer **273** by further irreversible organoboration reactions, finally giving **272**.

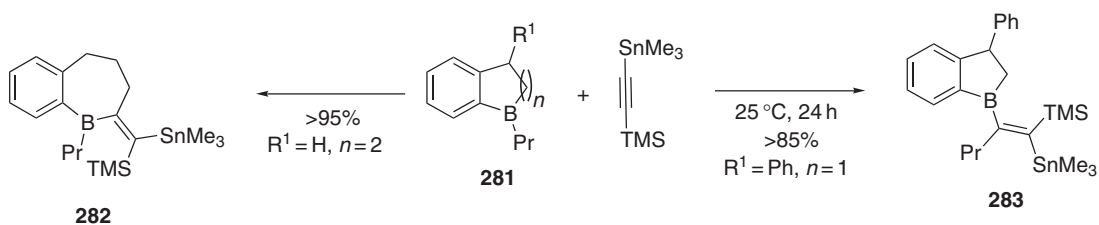
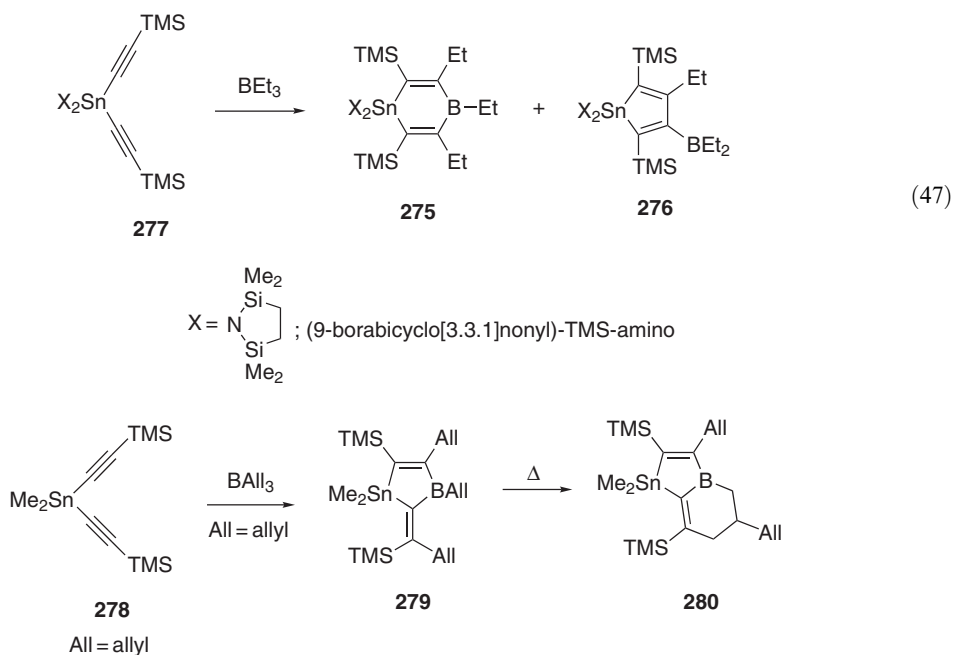


This approach has been used extensively to prepare stannole and silole derivatives, including 2-silylstannoles, 2-stannylsiloles, and fused derivatives <1999ICA(296)26, 1998JOM(562)207, 1999JOM(577)82, 2002JOM(649)232, 1995JOM(503)289>. 2-Plumbylstannoles have also been prepared this way <1995JOM(503)289>. In some cases, other products containing the 1-silyl-1-stannylalkene function have been isolated. For example, 1,4-stannabora-2,5-cyclohexadiene **275** was obtained along with the expected stannole derivative **276** through the treatment of dialkynylstannane **277** with  $\text{BEt}_3$  (Equation (47)) <2002JOM(649)232>. 1-Stannyl-2-silylalkynes also react with triallylborane to give 1-silyl-1-stannylalkenes, although in some cases 2-stannylsiloles were obtained. Thus, treatment of 1,1-bis(TMS-ethynyl)dimethyltin **278** with triallylborane gave an initial reversible 1,1-allylboration, followed by intramolecular 1,2-allylboration to give 1-silyl-1-stannylalkene **279**, which rearranged to **280** upon heating (Scheme 52) <2002JOM(657)146>. In contrast, 1-(TMS-ethynyl)-1-(trimethylstannylethynyl)dimethylsilane gave a 2-stannylsilole derivative. 1-Propyl-1-boratetralins **281** ( $n = 2$ ) react with 1-TMS-2-trimethylstannylethyne to

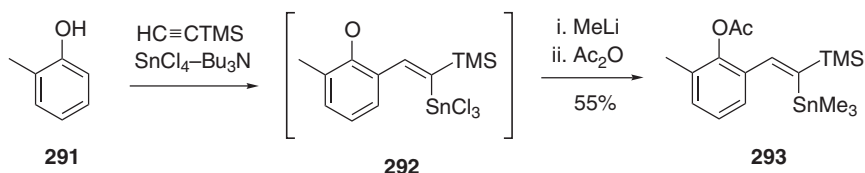




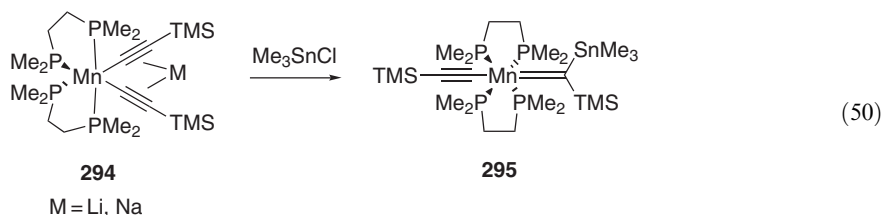
give ring enlarged 1-silyl-1-stannylalkene derivatives **282** with >95% selectivity via a 1,1-organo-boration reaction (Scheme 53) <1996MI215>. The ring expansion is highly selective and gives the (*Z*)-product with the silyl and boryl groups in *cis* positions. However, boraindane **281** ( $n = 1$ ) gave adduct **283**, again via a 1,1-organo-boration (Scheme 53) <1998MI515>.



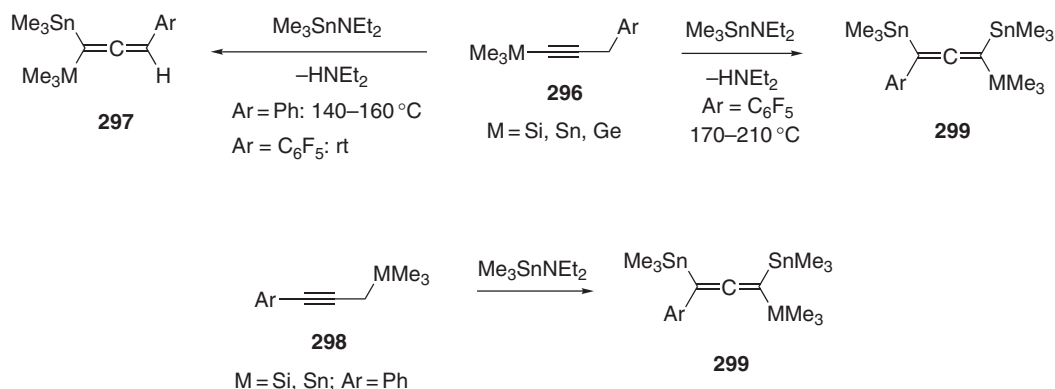




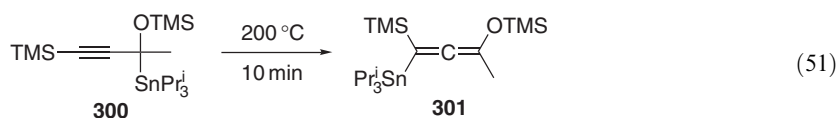
Scheme 55



The treatment of 1-silyl-3-phenylpropynes **296** (M = Si, Ar = Ph) with (trialkylstannyl)dialkylamines at high temperatures (140–160 °C) gives 1-stannyl-1-silyllallenes **297** (M = Si, Ar = Ph) (Scheme 56) <1995MI1369>. With pentafluorophenyl-substituted silyl alkynes **296** (M = Si, Ar = C<sub>6</sub>F<sub>5</sub>), the reaction proceeds at a much lower temperature, due to the significant increase in the acidity of the propargylic methylene protons. With the isomeric 1-phenyl-3-silylpropynes **298** (M = Si, Ar = Ph), even higher temperatures are required to achieve reaction, and bisstannylation occurs to give 1-silyl-1,3-distannylallenes **299** (M = Si, Ar = Ph) (Scheme 56). Increasing the temperature of the reaction **296** (M = Si, Ar = C<sub>6</sub>F<sub>5</sub>) to 170–210 °C also gives 1-silyl-1,3-distannylallenes **299** (M = Si, Ar = C<sub>6</sub>F<sub>5</sub>) (Scheme 56). The thermal isomerization of [α-(silyloxy)-propargyl]stannane **300** was reported to give a good yield of the [γ-(silyloxy)allenyl]stannane **301** via a 1,3-sigmatropic rearrangement (Equation (51)) <1997JOC8955>. 1-Silyl-1-stannylketene **73** (R<sub>3</sub>M = Bu<sub>3</sub>Sn) can be prepared from lithium ynolates **74** through quenching with Bu<sub>3</sub>SnCl (Scheme 16) <1996JA7634>.

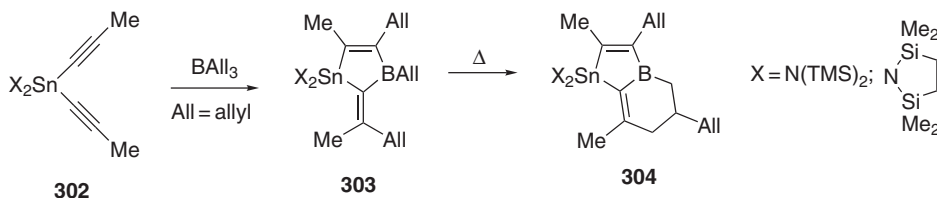


Scheme 56

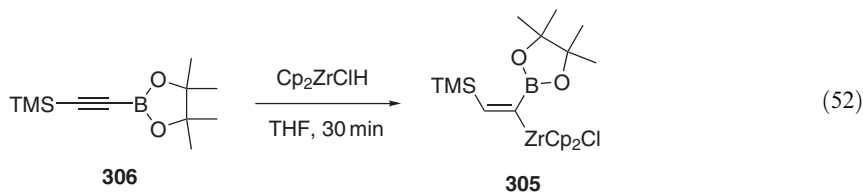


#### 4.23.2.2 Boron Functions— $R_2C=CBR_3M$

The only previously reviewed boron functions are 1-boryl-1-stannylalkenes, and these were prepared through the hydro- and organoboration of stannyl alkynes <1995COFGT(4)1043>. Continuing with this approach, allylboration of bis(alkynyl)stannanes **302** with triallylborane gave heterocycles **303**, via an initial 1,1-allylboration of one of the alkynes, followed by an intramolecular 1,2-allylboration of the second alkyne unit (Scheme 57) <2002JOM(649)232, 2002JOM(657)146>. Rearrangement of **303** to **304** occurred upon heating. 1-Boryl-1-zirconaalkene **305** was prepared through the hydrozirconation of 1-TMS-2-(pinacolboryl)ethyne **306** with  $Cp_2ZrClH$  (Equation (52)), and this was used as an intermediate in a highly stereocontrolled formal synthesis of *rac*-chokol A and G <1996TL2735>.

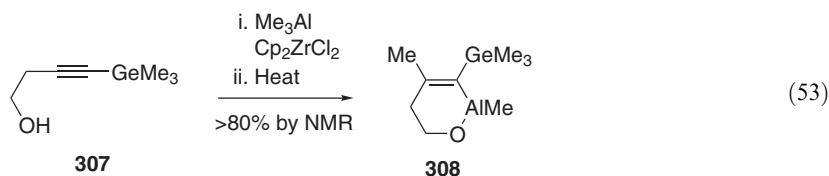


Scheme 57



#### 4.23.2.3 Germanium Functions— $R_2C=CGeR_3M$

This class of compounds was reported as being poorly documented in COFGT (1995). 1-Stannyl- and 1-alumino-1-germylalkenes can be prepared through the hydrostannylation or hydroalumination of 1-germylalkynes. 1-Stannyl- or 1-plumbyl-1-germylalkenes have been prepared through the sequential transmetallation of 1,1-distannyl or diplumbyl alkenes with MeLi, then  $Me_3GeCl$  <1995COFGT(4)1043>. This area of chemistry has remained little explored, although new approaches to 1-alumino- and 1-stannyl-1-germylalkenes have been reported. Trimethylgermyl-substituted homopropargyl alcohol **307** gives cyclic 1-alumino-1-germylalkene **308** when treated with  $AlMe_3$  and  $Cp_2ZrCl_2$  (Equation (53)). *Syn*-methylalumination occurs initially, but reversal of the stereochemistry occurs upon heating to give **308** <1997JOC784>. 1-Germyl-1-stannylallenes have been prepared in direct analogy with 1-silyl-1-stannylallenes (Scheme 56) <1995MI1369>. Thus, the treatment of 1-germyl-3-phenylpropynes **296** (M = Ge, Ar = Ph) with trialkylstannyl-dialkylamines at high temperatures gives 1-stannyl-1-germylallenes **297** (M = Ge, Ar = Ph) (Scheme 56). As before, replacement of the phenyl group of **296** with a pentafluorophenyl moiety allows the transformation to occur at ambient temperature, and increasing the reaction temperature to 170–210 °C gives 1-germyl-1,3-distannylallenes **299** (M = Ge, Ar = C<sub>6</sub>F<sub>5</sub>) <1995MI1369>.



### 4.23.3 FUNCTIONS CONTAINING A GROUP 1 METAL—R<sub>2</sub>C=CLiM

Previously reported methods of preparing 1,1-dilithioalkenes include lithium–halogen exchange of 1,1-diiodoalkenes and transmetallation of 1,1-dimercurioalkenes. Dilithioallenes have been prepared through the treatment of 3-hydroxy-3-TMS-prop-1-ynes with 2 equiv. of alkyllithiums. 1-Lithio-1-stannylalkenes can be prepared through transmetallation of 1,1-distannylalkenes. 1-Plumbyl-1-lithioalkenes can be prepared through the transmetallation of 1-stannyl-1-plumbylalkenes or 1,1-diplumbylalkenes. There have been no significant developments in the preparation of these species since COFGT (1995) <1995COFGT(4)1043>.

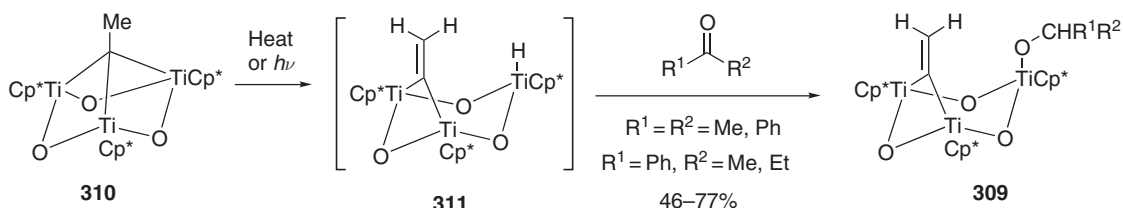
### 4.23.4 FUNCTIONS CONTAINING A GROUP 2 METAL (AND NO GROUP 1 METAL)—R<sub>2</sub>C=CMgXM, etc.

Previously reviewed methods of preparing 1,1-dimagnesioalkenes include the organomagnesiumation of propargylic alcohols. Use of eneynes gives 1,1-dimagnesioallenes. 1-Magnesio-1-stannylalkenes have been prepared through transmetallation of 1-lithio-1-stannylalkenes and through magnesium–halogen exchange of 1-iodo-1-stannylalkenes. 1-Magnesio-1-zincoalkenes have been prepared through treatment of 1-magnesio-propargylic alcohol derivatives with allylzinc reagents <1995COFGT(4)1043>. There have been no significant developments in the preparation of these species since COFGT (1995).

### 4.23.5 FUNCTIONS CONTAINING A TRANSITION METAL (AND NO GROUP 1 OR GROUP 2 METAL)—R<sub>2</sub>C=CTiM, etc.

Several of the title functions have been previously reviewed. 1-Zircono-1-aluminoalkenes and 1-titano-1-aluminoalkenes have been prepared by the treatment of alkynylalanes with either Cp<sub>2</sub>ZrCl(Me) or Cp<sub>2</sub>TiCl(Me). Similarly, cyclic 1-stannyl-1-zirconoalkenes have been prepared from 1-stannylalkynes containing an ω-alkene group and Cp<sub>2</sub>ZrCl<sub>2</sub>. 1,1-Dizincoalkenes have been prepared from an allylzinc bromide and either prop-2-ynol methyl ether or 1-zincoprop-2-ynol as its zinc bromide salt. Dimercuration of alkynes and alkenes gives 1,1-dimercurioalkenes as does treatment of 1,1-diborylalkenes with mercuric chloride <1995COFGT(4)1043>.

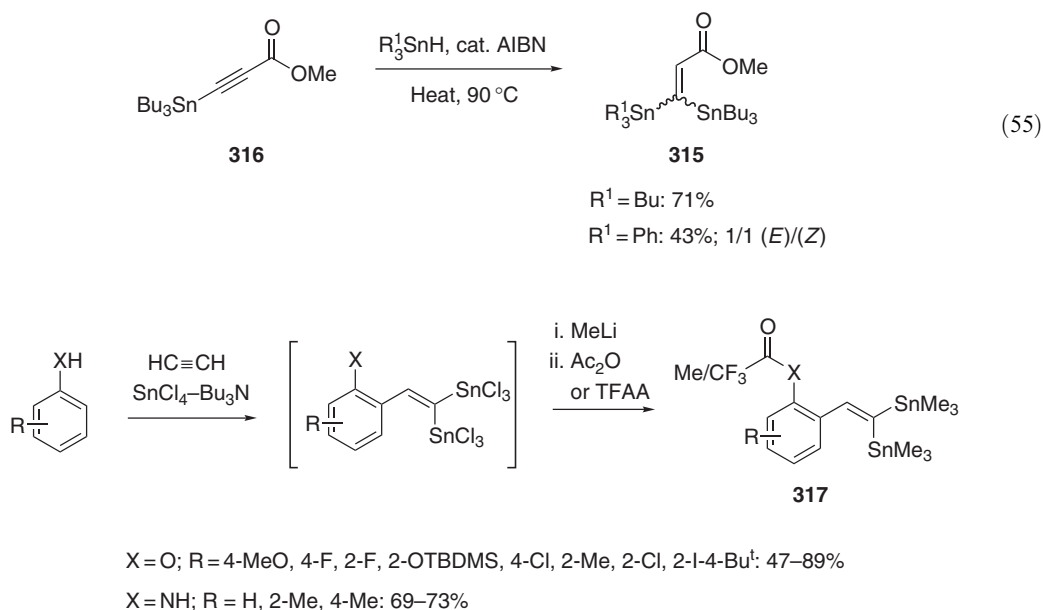
There have been few developments in this field, although some new functionalities have been reported. 1,1-Dititanoethenes **309** have been prepared from organotitanium oxide species **310** and ketones under thermal or photochemical conditions, via a hydride–vinylidene intermediate **311** (Scheme 58) <1998CC691>. Reaction times were significantly longer under photochemical conditions. In direct analogy with the hydrotitanation of silyl alkynes, treatment of 1-trimethylstannyl-2-phenylethyne **194** (M = Sn, R = Ph) with stabilized tris(aryloxy)titanium(IV) hydrides **195**, gives 1-stannyl-1-titanoalkenes **196** (M = Sn, R = Ph) through stereospecific *syn* addition to the triple bond (Equation (29)) <1995OM4601>. 1,1-Dipalladoalkenes have also been reported. The vinylidene complex **312** was prepared through the reaction of [Pd<sub>2</sub>Cl<sub>2</sub>(DPPM)<sub>2</sub>] (DPPM = bis(diphenylphosphinomethane)) with bis(methylthio)ethyne in the presence of HBF<sub>4</sub>·OEt<sub>2</sub> (Equation (54)) or via a stepwise reaction using other Lewis acids <1995OM4257>. A 1,1-dipalladoalkene was also obtained through the double insertion of Pd(PPh<sub>3</sub>)<sub>4</sub> into a vinyl dichloride species **313** (Scheme 59). The product was found to be fluxional in solution due to nondissociative intramolecular flipping of a PPh<sub>3</sub> ligand, but subsequent treatment with DPPM led to derivative **314** <2003EJI514>.



Scheme 58

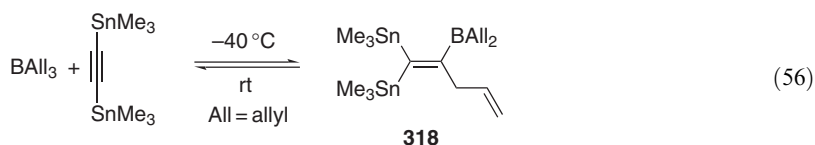


obtained, often in good yields. 2,6-Bis(distannylvinylation) of 4-substituted phenols has also been achieved using modified conditions [<1997CC1663>](#).

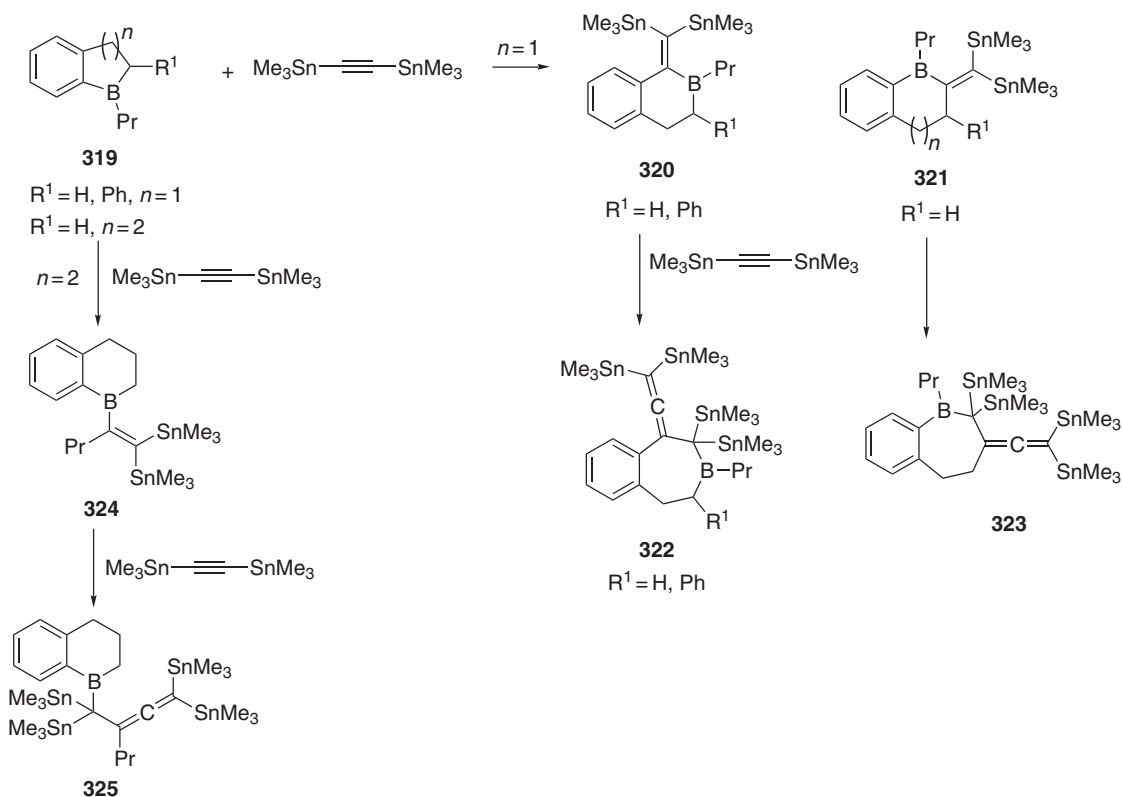


Scheme 60

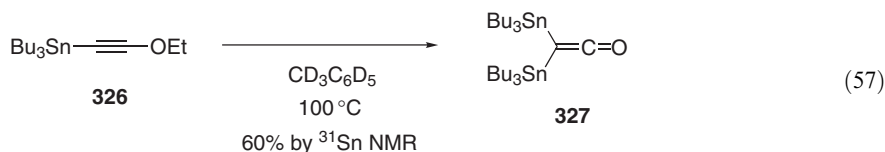
The organoboration of distannyl alkynes has been used extensively to prepare 1,1-distannylalkenes. The treatment of 1,2-distannylalkynes with triallylborane at  $-40^\circ\text{C}$  results in a reversible 1,1-organoboration with migration of a stannyl group to give 1,1-distannylalkenes **318** in quantitative yield (Equation (56)) [<2000ICA169>](#). 1-Propyl-1-boraindane **319** reacts with bis(trimethylstannyl)ethyne to give ring enlarged 1,1-bis(trimethylstannyl)alkene derivatives **320** or both **320** and **321** via a 1,1-organoboration reaction (Scheme 61) [<1996MI215, 1998MI515>](#). Compounds **320** and **321** undergo further ring expansion with excess bis(trimethylstannyl)ethyne to give 1,1-bis(trimethylstannyl)allenes **322** and **323** (Scheme 61). The reaction of 1-propylboratetralin **319** ( $n = 2$ ) with bis(trimethylstannyl)ethyne was originally expected to give a ring expanded product [<1996MI215>](#), but further investigation determined that the product was **324**. Compound **324** reacted with further bis(trimethylstannyl)ethyne to give **325** (Scheme 61) [<1998MI515>](#). Similar reactions were reported with dialkyl- and cycloalkyl(*N*-azoly)boranes and unsymmetrical cycloalkanylboranes [<1997JOM\(541\)97>](#).



1,1-Distannylallenes **297** ( $M = \text{Sn}$ ) and **299** ( $M = \text{Sn}$ ) have also been prepared by stannylation of 1-stannyl-3-arylpropynes **296** ( $M = \text{Sn}$ ) with  $\text{Me}_3\text{SnNEt}_2$  (Scheme 56), in direct analogy with the stannylation of 1-silyl-3-arylpropynes (Section 4.23.2.1.4) [<1995MI1369>](#). The thermal decomposition of ethoxyethynyl(trimethyl)tin **326** was monitored by  $^{31}\text{Sn}$  NMR and the major component was thought to be bis(trimethylstannyl)ketene **327**, along with other by-products (Equation (57)) [<1999ZN\(B\)705>](#). 2-Stannyl- and 2-plumbylstannoles have been prepared from 1-(dialkylchlorostannyl)-2-diethylborylalkenes and trimethylstannyl and trimethylplumbylalkynes [<1995JOM\(503\)289>](#).



Scheme 61



#### 4.23.7 OTHER METAL DERIVATIVES

No examples, not already covered in other sections of this chapter, were found, as was the case in COFGT (1995) <1995COFGT(4)1043>.

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**Biographical sketch**

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## 4.24

# Tri- and Dicoordinated Ions, Radicals, and Carbenes Bearing Two Heteroatoms ( $\text{RX}_2\text{C}^+$ , $\text{RX}_2\text{C}^\cdot$ , $\text{RX}_2\text{C}^-$ , $\text{X}_2\text{C}:$ )

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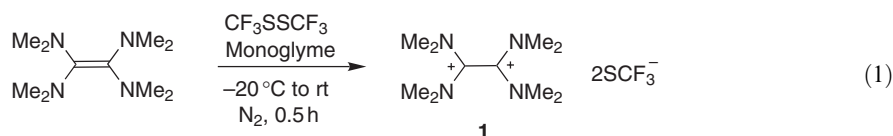
### 4.24.1 INTRODUCTION

In order to continue the article of William M. Horspool in COFGT (1995) <1995COFGT(4)1071>, who gave an early overview of the wide variety of carbon species bearing two heteroatomic substituents, the results in this field are updated for this chapter. Because the understanding of carbene chemistry has advanced dramatically since the 1990s, a special emphasis is placed on the carbene section.

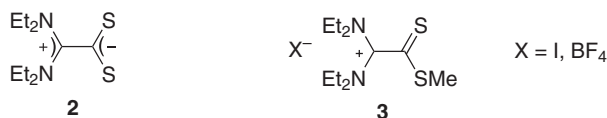
### 4.24.2 CATIONS

#### 4.24.2.1 Cation Centers with Pendant Group 15 Elements

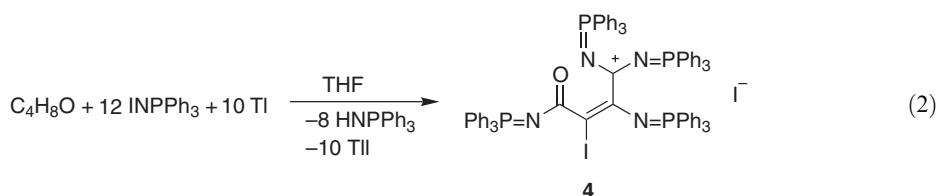
The stable ionic salt **1** was obtained in nearly quantitative yield via reduction of  $\text{CF}_3\text{SSCF}_3$  by two single-electron transfer steps. This salt was found to be stable up to its melting point <2000JCS(P1)2183>.



Bis(diethylamino)carbenium dithiocarboxylate **2** was methylated with methyl iodide to form the carbenium salt **3** quantitatively <1997TL5013>.



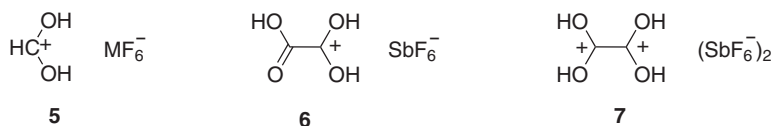
An unexpected cationic product, **4**, was obtained from the reaction of  $\text{INPPh}_3$  with thallium in THF suspension (Equation (2)) <2002ZAAC428>.



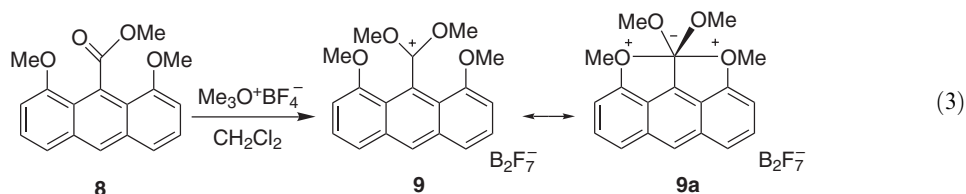
For other examples of carbocations flanked by two nitrogen atoms see Sections 4.24.5.3.1 and 4.24.5.3.4.

#### 4.24.2.2 Cation Centers with Pendant Group 16 Elements

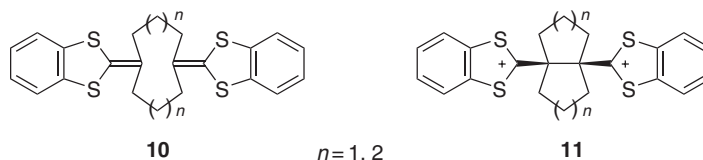
In addition to the fission of C—C bonds, which was reviewed by Horspool <1995COFGT(4)1071>, another method of synthesis of cations flanked by two oxygen atoms, is the protonation of carboxylic acid and their derivatives. For example, the reaction of formic acid in the superacidic system  $\text{HF}/\text{MF}_5$  ( $\text{M} = \text{As}, \text{Sb}$ ) led to dihydroxy carbenium hexafluorometallates **5**. Under inert conditions, they are stable at  $-40^\circ\text{C}$  for some weeks <1996ZAAC1404>. Similarly, the reaction of oxalic acid in  $\text{HF}/\text{SbF}_5$  afforded, dependent on the reaction temperature, different products. At  $-75^\circ\text{C}$ , monoprotonation to  $\text{HO}(\text{O})\text{CC}(\text{OH})_2^+ \text{SbF}_6^-$  **6** occurred, whereas at  $-40^\circ\text{C}$  salt **7** was formed <1999ZAAC1479>.



An ion of the type represented by salt **9** can be prepared by the reaction of **8** with trimethyloxonium tetrafluoroborate ( $\text{Me}_3\text{O}^+\text{BF}_4^-$ ) in dichloromethane under reflux for 20 h (Equation (3)) <1999JA10644>. Akiba and co-workers formulated structure **9** not as an isolated carbocation, but rather as the first example of a structurally characterized 10-C-5 hypervalent carbon **9a**.



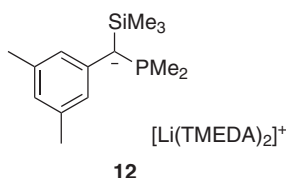
In addition to the methods reviewed by Horspool <1995COFGT(4)1071>, oxidation can also be used as a synthetic approach to the cations bearing two sulfur atoms. Thus, iodine was used to convert **10** into bicyclic dication **11** in almost quantitative yield <1997CC2325>.



#### 4.24.3 ANIONS

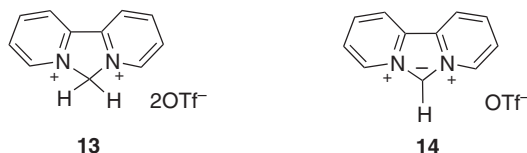
##### 4.24.3.1 Anion Centers with Pendant Group 14 Elements

One example of an anion bearing silicon and phosphorus was reported in 2000. The salt **12** was prepared in 56% yield by the reaction of  $\text{Me}_2\text{P}-\text{CH}(\text{SiMe}_3)-\text{C}_6\text{H}_3-3,5-\text{Me}_2$  and *n*-butyllithium/TMEDA. In the solid state, this salt consists of solvent-separated ion pairs <2000ZN(B)1114>.

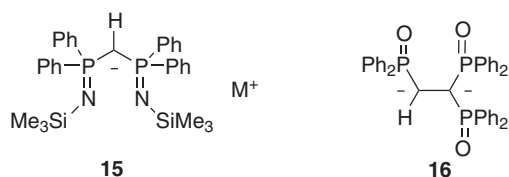


##### 4.24.3.2 Anion Centers with Pendant Group 15 Elements

Weiss and co-workers reported an example of a carbanion bearing two nitrogen atoms. They obtained **14** in 75% yield from the cyclic salt **13** in the presence of 2,2'-bipyridine <1998AG(E)344>.

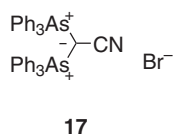


Compound **15** is an example of an anion flanked by two phosphorus atoms. It was obtained by the deprotonation of  $\text{CH}_2(\text{Ph}_2\text{P}=\text{NSiMe}_3)_2$  with  $\text{MN}(\text{SiMe}_3)_2$  ( $\text{M} = \text{Na}, \text{Li}$ ) in toluene <2000IC4981>. Excess *n*-butyllithium was used to deprotonate tris(phosphine oxide),  $\{\text{Ph}_2\text{P}(\text{O})\}_2\text{CHCH}_2\text{P}(\text{O})\text{Ph}_2$ , to give the dianion **16**, the first example of a formal 1,2-dicarbanion stabilized by phosphorus <2002CC2532>.



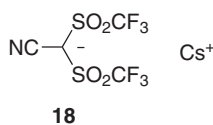
In Section 4.24.3.1 one example of a carbanion flanked by silicon and phosphorus is described.

The asymmetrically substituted iminium salt,  $[\text{Et}_3\text{PNAsPh}_3]\text{Br}$ , reacted in the presence of potassium hydride with acetonitrile to form an anionic center **17** bearing two pendant arsonium cations and a cyano group stabilizing the anionic center <1998ZAAC1341>.



#### 4.24.3.3 Anion Centers with Pendant Group 16 Elements

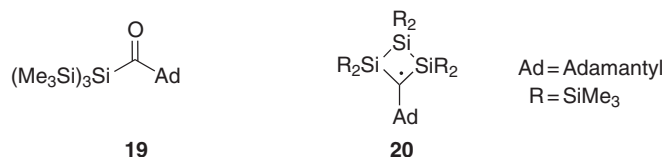
The formation of anions flanked by two sulfur atoms is a common step in many synthetic strategies. Typically, a dithioacetal is treated with a base at low temperature to afford the corresponding anion. As Horspool pointed out, both substitution and changes in the oxidation level of the sulfur do not affect the efficacy of this reaction <1995COFGT(4)1071>. Cyano-substituted anion **18** was prepared by one-pot reaction using stepwise trifluoromethylsulfonation of acetonitrile. Deprotonation of  $\text{CH}_3\text{CN}$  with 3 equiv. of butyllithium followed by the treatment with 2 equiv. of trifluoromethylsulfonyl fluoride afforded the methanide **18**. It was isolated as a caesium salt <1998HAC565>.



#### 4.24.4 RADICALS

##### 4.24.4.1 Radical Centers with Pendant Group 14 Elements

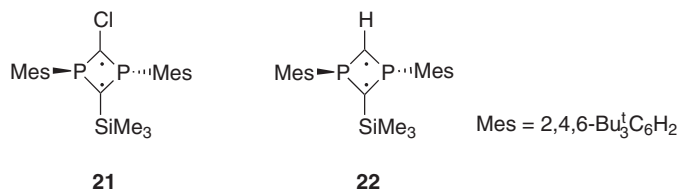
Radical **20** was the first isolated and X-ray characterized alkyl radical bearing two heteroatoms, which was not stabilized by the conjugation with adjacent unsaturated bonds. It was prepared in 15% yield by the reaction of **19** with a twofold excess of  $\text{Et}_3\text{GeLi}$  in THF <1999JA8118>.





#### 4.24.4.2 Radical Centers with Pendant Group 15 Elements

The crystalline 1,3-diphosphacyclobutane-2,4-diyl **22** was readily available from **21** by halogen-metal exchange in the presence of *n*-butyllithium and subsequent *t*-BuOH addition <1999AG(E)3028>.



#### 4.24.5 CARBENES

Since the discovery, in 1991, of stable nucleophilic carbenes, these compounds have become important as ligands in organometallic chemistry and modern homogeneous catalysis. Carbene complexes of late transition metals such as ruthenium and palladium possess the highest catalytic activities in olefin metathesis and Heck-type reactions. These nucleophilic carbenes have developed as catalysts in their own right, even in the absence of transition metals. The chemistry of these nucleophilic carbenes is rapidly growing and forms a convenient framework that can serve to organize this chapter. Adduct formation of nucleophilic carbenes with electrophiles leads to a cation (at least formally) at the former carbene center (e.g., carbenium ions arise from the protonation of carbenes). Similarly, electrophilic carbenes form carbanion centers upon reaction with nucleophiles (e.g., chloride addition to dichlorocarbene produces the trichloromethyl anion) (Scheme 1).



Scheme 1

With cationic electrophiles or anionic nucleophiles, the relationships described above are conceptually simple. A complexity arises in cases where the electrophile or nucleophile is neutral. To overcome this complexity carbene adducts of neutral electrophiles and nucleophiles are viewed as their charge separated zwitterionic structures. For strongly nucleophilic carbenes or strongly electrophilic carbenes this reliance on zwitterionic structures for classification has added validity because the substituents on these carbenes favor charge-separated structures (Scheme 2).



Scheme 2

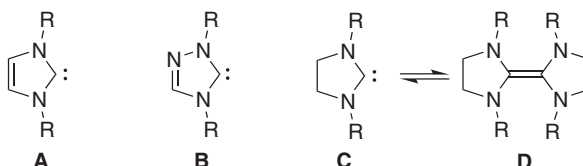
The chemistry described in this section is organized along these conceptual lines. Advances in the chemistry of carbenes are used as entry and reference points for the cationic and anionic carbon centers that conform to the substituent constraints of this chapter. In general, the ease of handling and widespread availability of nucleophilic carbenes has led to greater productivity than from the less stable and difficult to handle electrophilic carbenes.

#### 4.24.5.1 Stable Singlet (Nucleophilic) Carbenes

##### 4.24.5.1.1 Nucleophilic *N,N*-carbenes: general synthetic methods

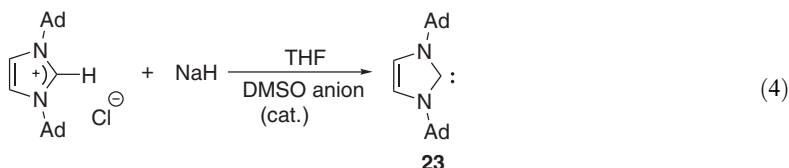
The ylidenes **A** and **B** are monomeric nucleophilic carbenes derived from imidazoles and triazoles. With only one exception (*R* = mesityl), all related C—C saturated (imidazolinylidene) carbenes **C** dimerize to the corresponding diaminocarbene dimer **D**.

The electronic structure of the stable carbene center of an imidazol-2-ylidene **A** or triazol-2-ylidene **B** can be simplified to a strongly bent singlet carbene model ( $^1A_1$ ) in which the carbene carbon is approximately  $sp^2$  hybridized. The two substituents and a lone pair of electrons occupy the three  $sp^2$ -hybrid orbitals, and a formally vacant *p*-orbital remains at carbon.



##### (i) Carbenes from imidazolium and triazolium ions via deprotonation

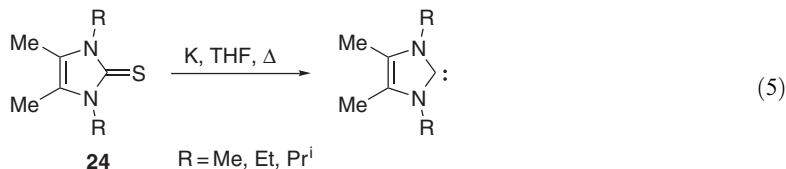
The deprotonation of imidazolium ions with a strong base such as sodium or potassium hydride proceeded smoothly in the presence of catalytic amounts of potassium *t*-butoxide or DMSO (Equation (4)) <1991JA361>. The first isolated imidazol-2-ylidene **23** proved to be remarkably stable both in the solution and in the solid state. Carbene **23** melts at 240 °C without decomposition. A solution of the 1,3-bis(1-adamantyl)imidazol-2-ylidene in THF-*d*<sub>8</sub>, sealed under a few atmospheres of CO, has shown no decomposition or change after 7 years at room temperature <2002UP001>.



Deprotonation with sodium hydride or potassium amide occurred quickly and quantitatively in liquid ammonia providing imidazol-2-ylidenes, but the method is unsuitable for imidazolin-2-ylidenes, which react with ammonia <1996MI1627, 1996MI772>.

##### (ii) Carbenes from imidazolethiones via reduction

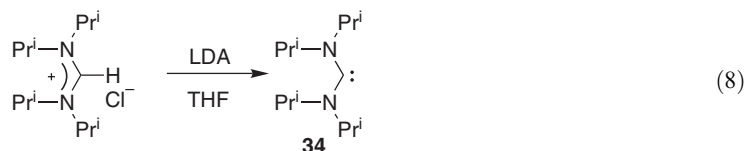
A different approach to the alkyl-substituted nucleophilic carbenes was introduced by Kuhn and co-workers. This original synthetic strategy relied on the reduction of imidazol-2-thiones **24** with potassium in boiling THF (Equation (5)) <1993S561>.



##### (iii) Carbenes via $\alpha$ -elimination

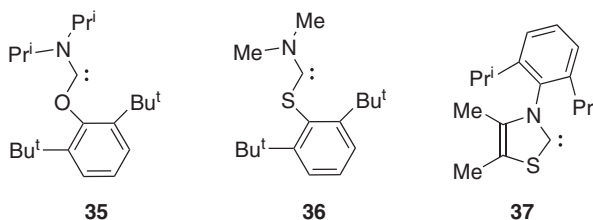
1,2,4-Triazol-5-ylidene **26** was obtained at 80 °C and 0.1 mbar by  $\alpha$ -elimination of methanol from the corresponding 5-methoxytriazole **25** in the solid state (Equation (6)) <1995AG(E)1021>.



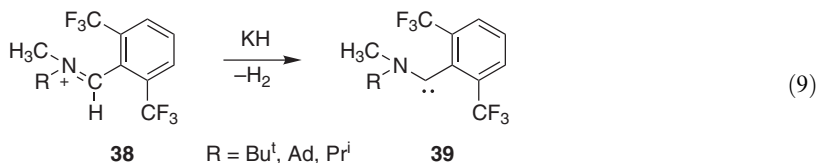


### (iii) Other aminocarbenes

The same synthetic routes described in [Section 4.24.5.1.1](#) were used to prepare a number of stable aminocarbenes containing a weaker  $\pi$ -donor substituent, e.g., aryloxy **35**, arylsulfido **36**, or sulfido **37** groups [<1997LA365, 1998JA11526>](#).

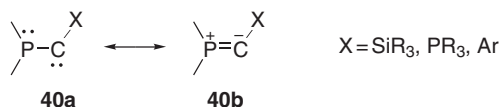


The (amino)(aryl)carbenes **39** were isolated at room temperature in almost quantitative yields by the deprotonation of the corresponding iminium salts **38** [Equation \(9\)](#) [<2001SCI1901>](#).

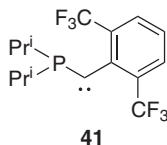


### 4.24.5.1.3 Nucleophilic P,E-carbenes (phosphinocarbenes)

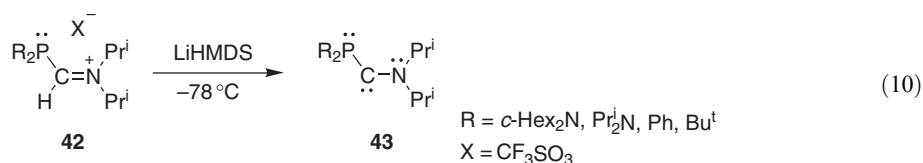
Bertrand and co-workers have used with great success photochemically induced loss of nitrogen from diazo compounds to prepare systems that can be formulated as carbenes where the “carbene” center is flanked by at least one phosphorus **40**.



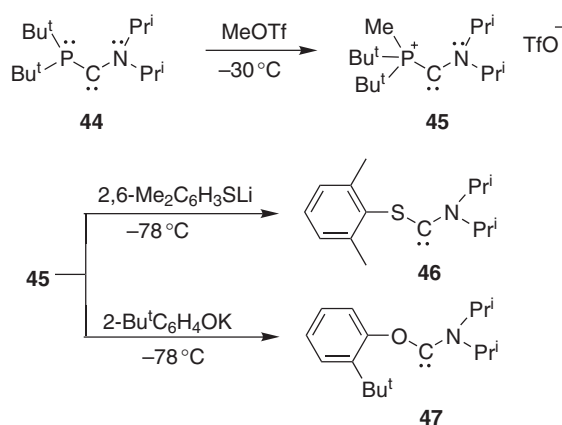
Preparation of (phosphino)(silyl)carbenes was previously reviewed by Horspool in [Section 4.24.5.4.1](#) [<1995COFGT\(4\)1071>](#). A broad range of (phosphino)(alkyl)- and (phosphino)(aryl)-carbenes were prepared by photolysis of their diazo precursors [<2000SCI834, 2002AG\(E\)2835, 2003JA124>](#). The influence of the steric and electronic properties on the structure and stability of these carbenes was studied experimentally and theoretically. Carbene **41** was stable for weeks at room temperature both in the solution and in the solid state [<2000SCI834>](#).



Stable (amino)(phosphino)carbenes **43** were generated cleanly at  $-78^{\circ}\text{C}$  by the deprotonation of the corresponding phosphinoiminium salt **42** with the lithium salt of hexamethyldisilazane (Equation (10)). Their stabilities were dependent on the nature of the substituents at phosphorus. All compounds were stable for days at temperatures below  $-20^{\circ}\text{C}$  <2002JA6806>.



Recently, it was shown that (amino)(phosphino)carbene **44** can be transformed into (amino)(phosphonio)carbene **45**, which undergoes nucleophilic substitution reactions at the carbene center. A variety of carbenes such as **46** and **47** were synthesized starting from a single carbene precursor (Scheme 3) <2003SCI1223>.

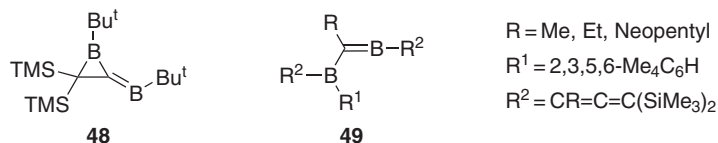


Scheme 3

#### 4.24.5.2 Electrophilic Carbenes

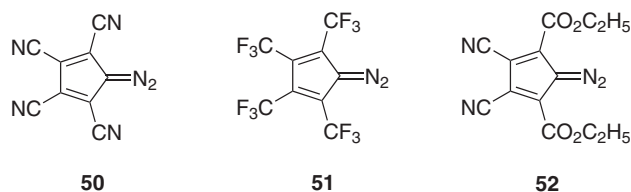
##### 4.24.5.2.1 Electrophilic carbenes with pendant group 13 elements

No diborylcarbene has been isolated yet. However, borylmethyleneboranes **48** <1983AG(E)877> and **49** <1995AG(E)1340> were employed as their synthetic equivalents as experimentally demonstrated by the trapping reactions (see Section 4.24.5.4).



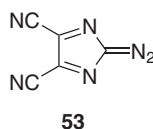
##### 4.24.5.2.2 Electrophilic carbenes with pendant group 14 elements

Diazotetracyanocyclopentadiene **50** <1966JA4055>, diazotetrakis (trifluoromethyl)cyclopentadiene **51** <1983JA3563, 1984TL405>, and diazo(1,4-diethoxycarbonyl-2,3-dicyano)cyclopentadiene **52** <1994JPR145> have been used as thermal precursors to reactive electrophilic carbene intermediates. These carbenes are strongly electrophilic in character and were used to synthesize a variety of ylides (see Section 4.24.5.4).



#### 4.24.5.2.3 Electrophilic carbenes with pendant group 15 elements

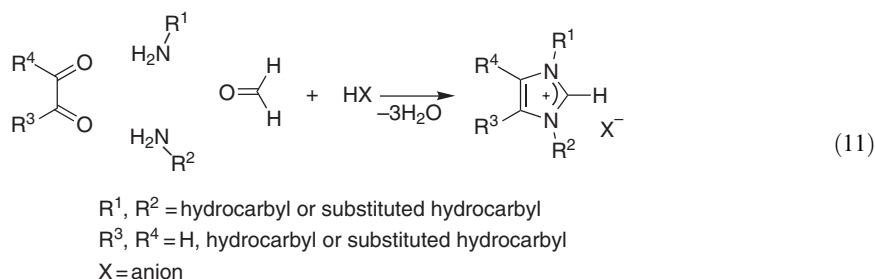
Sheppard and Webster used diazodicyanoimidazole **53** to form a reactive electrophilic carbene that attacked the halogen of arylhalides to form a fairly stable series of chloronium, bromonium, and iodonium ylides [<1973JA2695>](#).



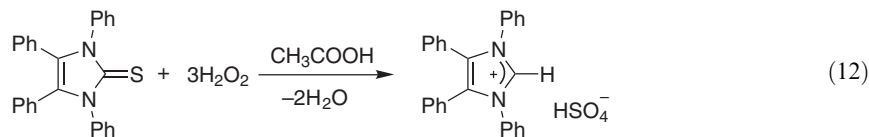
#### 4.24.5.3 Cationic Carbene Adducts

##### 4.24.5.3.1 Carbocations with pendant group 1 elements

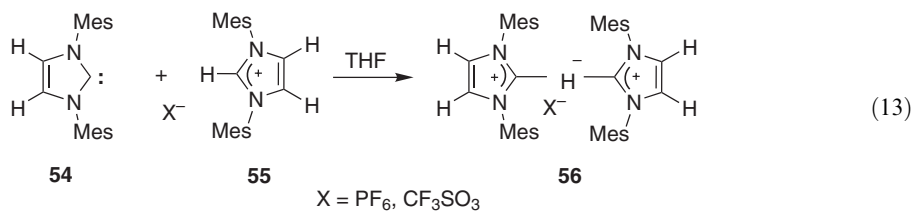
Arduengo developed a one-pot synthesis of imidazolium ions that allows the production of various substituted imidazolium ions that are not accessible by conventional routes ([Equation \(11\)](#)) [<1991USP5077414>](#).



Another source for imidazolium ions was reported from the oxidation of imidazol-2-thiones ([Equation \(12\)](#)) [<1998AG\(E\)1963>](#).

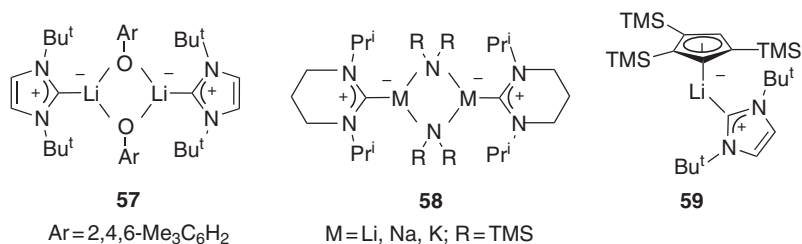


Carbene **54** reacted with 1,3-dimesitylimidazolium salt **55** to form the bis(carbene)proton complex **56**. These complexes were the first structurally characterized species with a C—H—C three-center four-electron interaction ([Equation \(13\)](#)) [<1995JA572>](#).



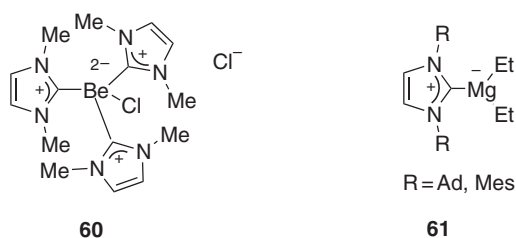
Dimeric nucleophilic carbene-alkali metal adducts were characterized for lithium, sodium, and potassium. Bis(*t*-butyl)imidazol-2-ylidene or tetrahydropyrimid-2-ylidene reacted with alkali metal (2,4,6-trimethyl)phenolates or bis(trimethylsilyl)amides to give the alkoxy-bridged lithium dimer **57** <1996MI001> and amido-bridged dimer **58** <1999CC241>.

A lithium-cyclopentadienyl derivative **59** was reported for an imidazol-2-ylidenes <1999CL1021>.

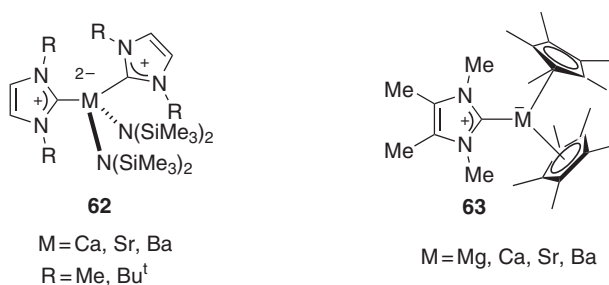


#### 4.24.5.3.2 Carbocations with pendant group 2 elements

Reaction of 1,3-dimethylimidazol-2-ylidene with polymeric BeCl<sub>2</sub> resulted in the formation of the cationic 3:1 adduct **60** <1995JOM(501)C1>. Imidazol-2-ylidenes reacted with diethylmagnesium to afford the corresponding 1:1 adducts **61** <1993JOM(462)13>.



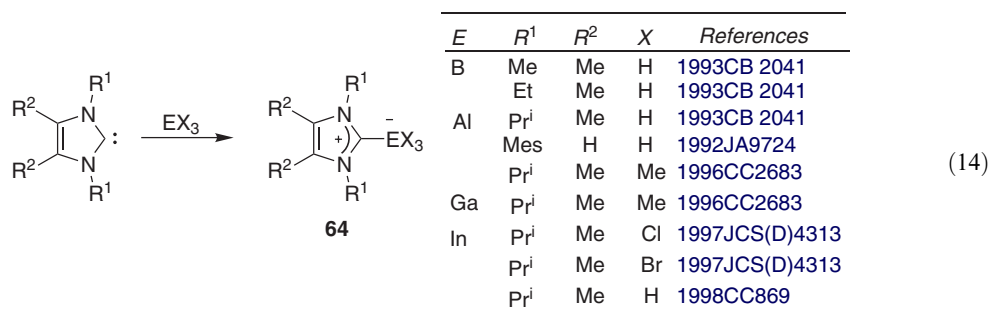
Imidazol-2-ylidenes formed a variety of 2:1 or 1:1 adducts of type **62** <1997MI002> or **63** <1998OM3375> with magnesium, calcium, strontium, and barium.



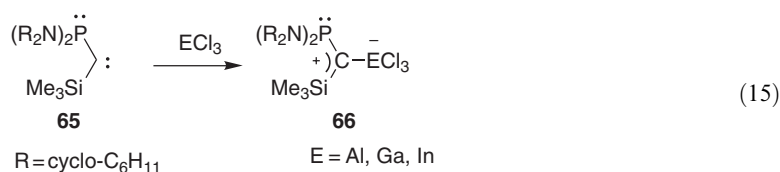
The Cp\* ligands in these complexes bind in different modes depending on the metal. For Ca, Sr, and Ba both C<sub>5</sub>Me<sub>5</sub> rings were η<sup>5</sup>-coordinated to the metal. In the case of magnesium, one cyclopentadienyl ring was η<sup>5</sup>-bound; the other exhibited a “slipped geometry”. The stability of these complexes decreased from calcium to barium.

#### 4.24.5.3.3 Carbocations with pendant group 13 elements

The first nucleophilic carbene group 13 element complex to be isolated was the imidazol-2-ylidene-alane complex **64** (Equation (14)) <1992JA9724>. Since then, a large number of carbene group 13 element complexes were reported and some are summarized in Equation (14). It was suggested that the imidazole fragment in these complexes has an electronic structure that is intermediate between those of the free carbene and imidazolium ion.

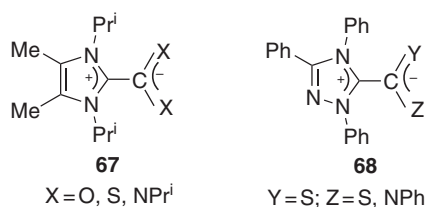


The reaction of phosphinosilyl “carbene” **65** with AlCl<sub>3</sub>, GaCl<sub>3</sub>, or InCl<sub>3</sub> in ethyl ether at 25 °C affords 1:1 adducts **66** (Equation (15)) <1994AG(E)578>. A related adduct was obtained from the reaction of **65** with BEt<sub>3</sub>. This triethylborane adduct is stable in solution for several weeks at –20 °C or for 24 h at room temperature <1993CC1354>.



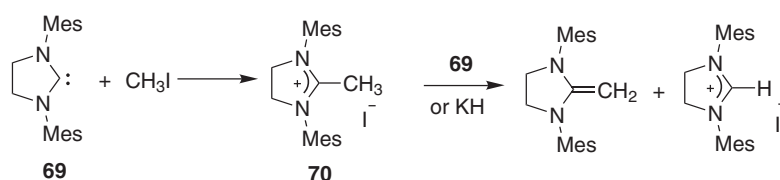
#### 4.24.5.3.4 Carbocations with pendant group 14 elements

There are known adducts of all the elements in this group. Heterocumulenes such as carbon dioxide, carbon disulfide, phenylisothiocyanate, or diisopropylcarbodiimide reacted with imidazol-2-ylidene and 1,2,4-triazol-5-ylidene to give the corresponding zwitterions **67** and **68** in good yields <1999ZN(B)427, 1999ZAAC851, 1999ZN(B)434, 1994ZN(B)1473, 1997CC627>.



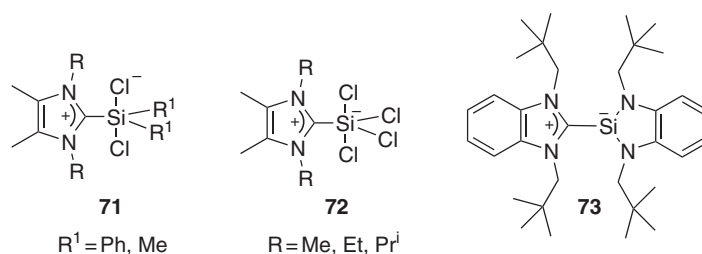
2-Methylimidazolium salt **70** was isolated as an intermediate in the reaction of 1,3-bis(mesityl)-imidazolin-2-ylidene **69** with methyl iodide (Scheme 4) <1997JA12742>.

Carbene adducts with (semi)metals of group 14 are known with main group element in oxidation state II or IV. Pentacoordinate silicon derivatives **71** and **72** formed when imidazol-2-ylidenes were treated with dimethyl- or diphenyldichlorosilane or tetrachlorosilane <1995CB245>. Compound **73** is an example of a tricoordinated silicon derivative <1999CC755>.

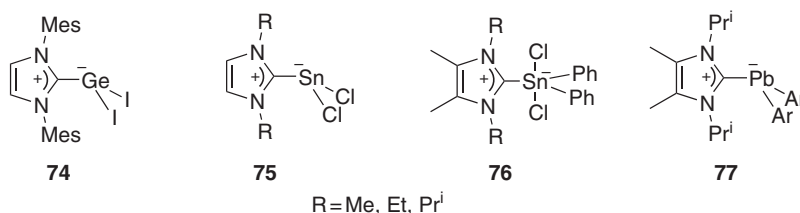


Scheme 4





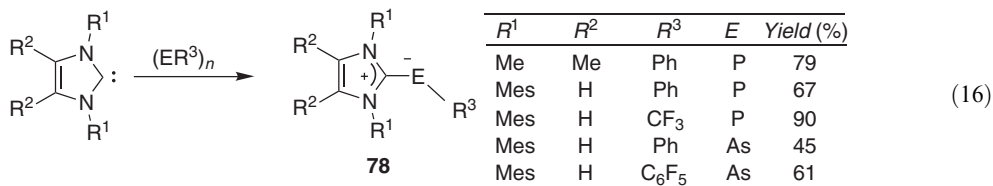
The germanium(II) and tin(II) halides **74** <1993IC1541> and **75** <1995CB245> were obtained starting from imidazol-2-ylidenes and  $\text{GeI}_2$  or  $\text{SnCl}_2$ . A pentacoordinated tin adduct **76** was obtained from imidazol-2-ylidenes and diphenyldichlorostannane <1995CB245>. Plumbene-imidazole carbene complex **77** [ $\text{Ar} = 2,4,6\text{-(Pr}^i)_3\text{C}_6\text{H}_2$ ] was generated in the reaction of an imidazol-2-ylidene with a bis(aryl)-lead(II) compound <1999CC1131>.



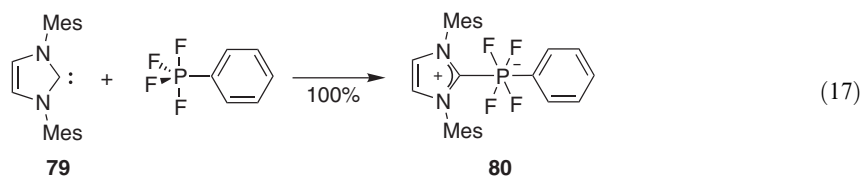
Phosphinosilylcarbenes also react with germanium(II) or tin(II) compounds with putative formation of similar adducts that undergo subsequent rearrangements <1992IC3493>.

#### 4.24.5.3.5 Carbocations with pendant group 15 elements

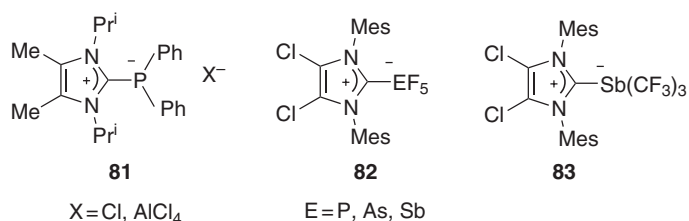
Adducts of imidazol-2-ylidenes with pnictinidenes **78** were generated by the reaction of free carbenes with cyclopolyphosphines  $(\text{PPh})_5$  and  $(\text{PCF}_3)_4$  and cyclopolyarsines  $(\text{AsPh})_6$  and  $(\text{AsC}_6\text{F}_5)_4$  (Equation (16)) <1997CL143, 1997IC2151>.



Phosphorane **80** has been obtained in 100% yield by the reaction of 1,3-bis(mesityl)imidazol-2-ylidene **79** with phenyltetrafluorophosphorane (Equation (17)) <1997JA3381>.

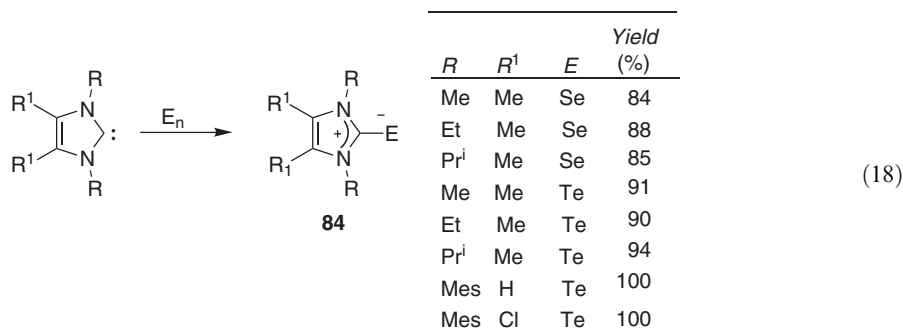


The phosphino-imidazolium salt **81** was the product of the reaction between 1,3-diisopropyl-4,5-dimethylimidazol-2-ylidene and chlorodiphenylphosphine <1999ZAAC729>. Imidazol-2-ylidene **30** reacts with pnictogen pentafluorides ( $\text{EF}_5$ ;  $E = \text{P, As, Sb}$ ) or  $\text{Sb}(\text{CF}_3)_3$  to give the corresponding adducts **82** <2000M251> or **83**, respectively <1999ZAAC1813>.

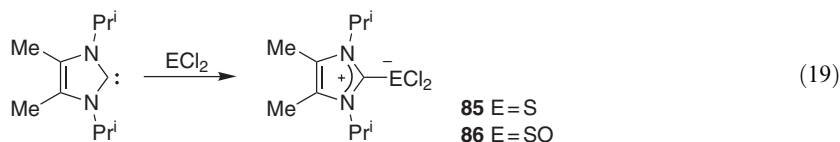


#### 4.24.5.3.6 Carbocations with pendant group 16 elements

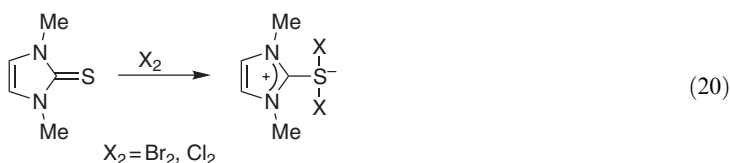
A variety of imidazolium chalcogenides **84** was obtained from imidazol-2-ylidenes and elemental chalcogens (Equation (18)) <1999MI1931, 1993CB2047, 1993ZN(B)973, 1993HAC409>. Similar adducts were reported for 1,2,4-triazol-5-ylidene with oxygen, sulfur, and selenium <1995AG(E)1021>.



By the reaction of 1,3-diisopropyl-4,5-dimethyl-imidazol-2-ylidene with  $\text{SOCl}_2$  and  $\text{SCl}_2$ , hyper-valent sulfur adducts **85** and **86** were formed in 30% and 66% yield, respectively (Equation (19)) <1996CB1579>.

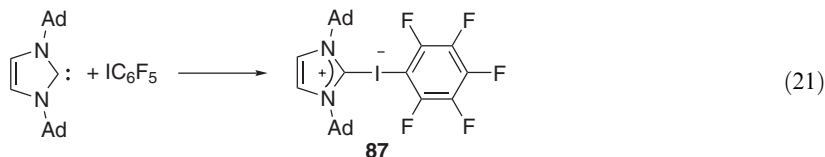


By the oxidation of a 2-telluroimidazoline with iodine, a  $\text{TeI}_2$  adduct of carbene was obtained in 87% yield <1996ZN(B)295>. This latter reaction is analogous to the oxidation of an imidazol-2-thione by bromine or chlorine that was reported by Arduengo and Burgess in 1977 (Equation (20)) <1977JA2376>.

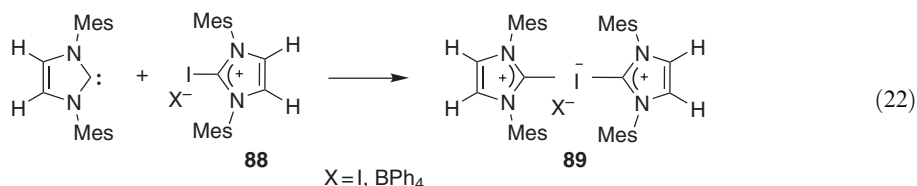


#### 4.24.5.3.7 Carbocations with pendant group 17 elements

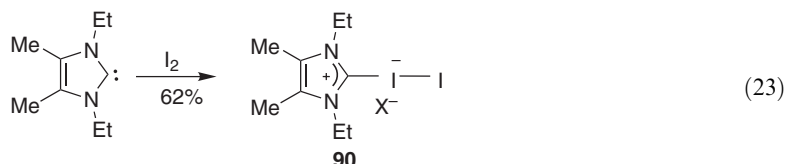
A reverse ylide, **87**, formed from the reaction of a 1,3-di(1-adamantyl)imidazol-2-ylidene with iodopentafluorobenzene (Equation (21)) <1991JA9704>.



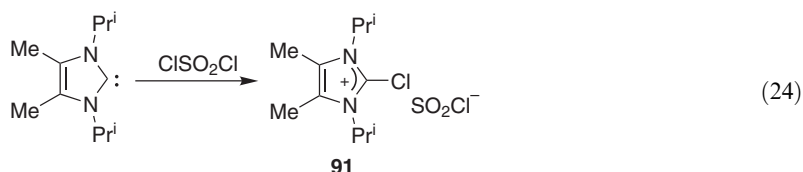
Similarly, 1,3-dimesitylimidazol-2-ylidene reacted with 2-iodoimidazolium salt **88** giving the symmetrical compound **89** in 69% yield (Equation (22)) <1994JA3625>.



A stable adduct **90** was obtained in 62% yield by the reaction of iodine with 1,3-diethyl-4,5-dimethylimidazol-2-ylidene (Equation (23)) <1993CC1778>.

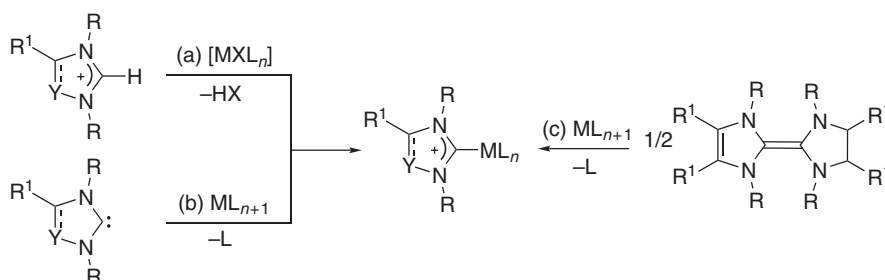


Sulfuryl chloride reacted with 1,3-diisopropyl-4,5-dimethylimidazol-2-ylidene to form chloroimidazolium salt **91** (Equation (24)) <1994CC2283>.



#### 4.24.5.3.8 Carbocations with pendant transition metals

Carbene complexes of many metals of the periodic table are known. Access to these compounds is mainly based on three different synthetic routes: (i) the complexation of the free, pre-isolated carbene; (ii) the *in situ* deprotonation of carbene precursors (carbenium ions); and (iii) the cleavage of electron-rich olefins (Scheme 5). Less general methods, mainly of importance in special cases, will be mentioned at the end of this chapter.

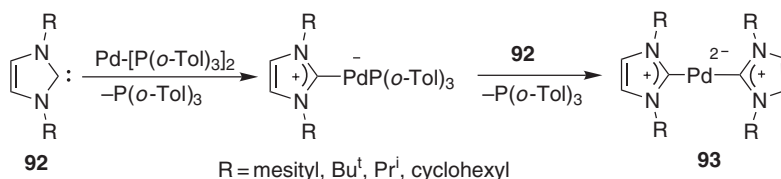


Scheme 5

(i) The use of an isolated carbene has the advantage that a large variety of metal precursors, without special requirements regarding the ligand sphere and the oxidation state, can be used for the preparation of carbene complexes.

Imidazol-2-ylidenes and triazol-2-ylidenes react with a broad variety of organometallic precursors to afford the corresponding complexes after the replacement of a two-electron donor from the metal center. Carbenes can cleave dimeric metal complexes with bridging ligands such as halides, carbon monoxide, or acetonitrile. Metal precursors such as  $[(\eta^4\text{-COD})\text{MCl}]_2$  or  $[\text{Cp}^*\text{MCl}_2]_2$  (M = Rh, Ir) <1996MI1627, 1996MI772, 1977OM2472>,  $[(\eta^6\text{-cymene})\text{RuCl}_2]_2$  <1996MI1627, 1996MI772, 1999OM3760>,  $[\text{Rh}(\text{CO})_2\text{Cl}]_2$  <1996MI772>,  $[\text{Cp}^*\text{RuCl}]_4$  <1999JA2674>, or  $\text{M}[\text{N}(\text{SiMe}_3)_2]_3$  (M = Y, La) <1997OM682> form these kind of complexes.

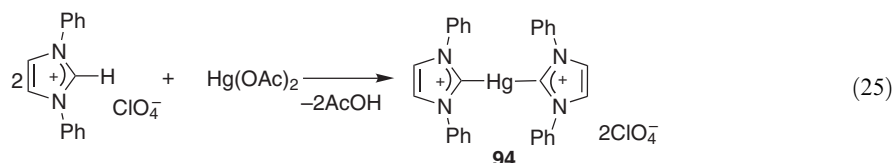
Most phosphine complexes are simple to exchange against carbenes even below room temperature <1999AG(E)2416, 1999JA2674, 1999TL2247, 1998AG(E)2490, 1997OM2209, 1999OM4584>. Starting with bis(tri-*o*-tolylphosphine)palladium(0), the bis(carbene)palladium(0) complex **93** was obtained in quantitative yield (Scheme 6) <2000JOM(595)186>.



Scheme 6

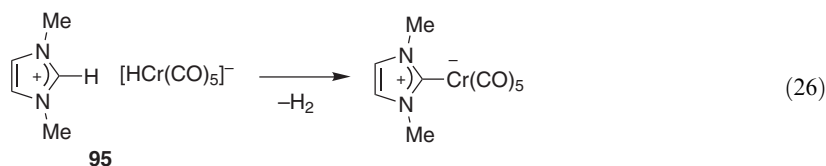
From carbonyl complexes such as [M(CO)<sub>6</sub>] (M = Cr, Mo, W), [Fe(CO)<sub>5</sub>], or [Ni(CO)<sub>4</sub>], one or two molecules of carbon monoxide were easily displaced by carbenes <1996MI1627, 1993JOM(459)177, 1996AG(E)2805, 1994JOM(470)C8>. Exchange of a coordinated solvent such as THF <1994AG(E)1733, 1994JA7927, 1997OM2209, 1999JOM(572)177> or acetonitrile <1993JOM(459)177> afforded other stable carbene–metal complexes. Olefins <1994JA4391>, amines <1994JOM(480)C7>, or other anionic ligands <1999JA2329> were also subject to ligand exchange under certain conditions.

(ii) An advantageous method to prepare carbene–metal complexes employed the *in situ* deprotonation of the ligand precursors. This is the method of choice for carbenes that are not too stable and are difficult to handle. A basic ligand such as hydride <1968JOM(12)42, 1972CB529>, acetate <1995AG(E)2371, 1998JOM(557)93, 1997OM2209, 1999OM4082, 1999JOM(575)80>, or alkoxide <1997JOM(532)261> of a metal precursor can deprotonate the carbenium salt. Wanzlick, for example, used Hg(OCOCH<sub>3</sub>)<sub>2</sub> for the synthesis of a mercury bis-carbene complex **94** (Equation (25)) <1968AG(E)141, 1971AX(B)2276>.



Basic silver(I) oxide <1999OM4325, 1998OM972> or  $\eta^5$ -cyclopentadienyl anions <1999OM529> have also served as the base to deprotonate the imidazolium salts.

Imidazolium **95**, benzimidazolium, triazolium, and tetrazolium salts were deprotonated *in situ* by Brønsted basic metallate anions upon heating (Equation (26)) <1968JOM(12)42, 1970AG(E)739, 1972CB529, 1969AG(E)916, 1976ZN(B)1070>. In these reactions, the metal of the base functioned simultaneously as the carbene acceptor.

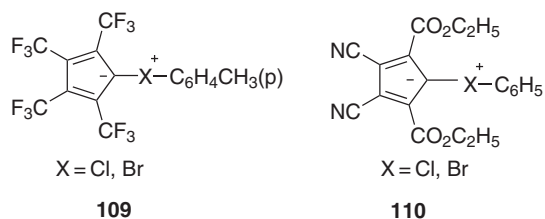


Alternatively, an external base can be used to deprotonate the carbenium salt *in situ*. Triethylamine <1997CB1253>, potassium *t*-butoxide <1996CB1483>, a phosphazene base at 0 °C <1998IC5412>, and *n*-butyllithium <1995JOM(490)149, 1996AG(E)310> were used to generate the desired carbene *in situ*. This method led to different products as compared with the use of metal salts with basic anions.

(iii) Imidazolin-2-ylidene complexes were prepared by the reaction of the corresponding electron-rich olefin dimers with mononuclear or bridged dinuclear organometallic fragments <1988JOM(358)185>. For example, heating tetraaminoethylene **96** in refluxing toluene in the presence of iron pentacarbonyl produced the corresponding bis(carbene)iron complex **97** (Equation (27)).

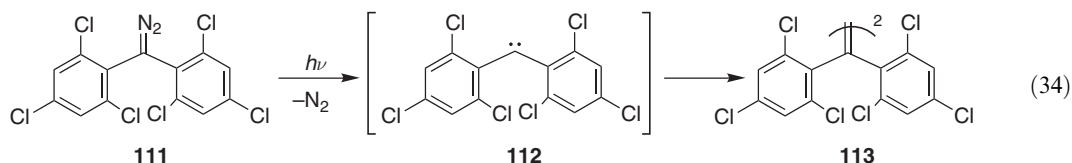




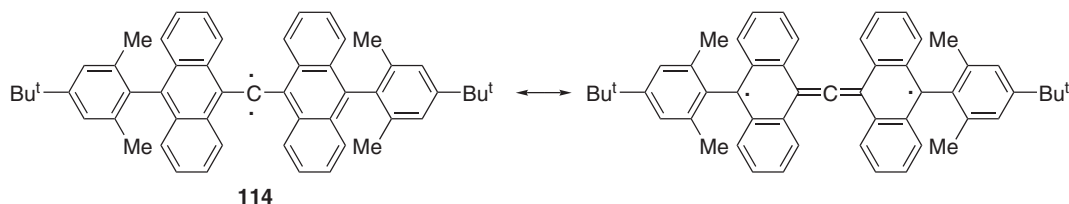


#### 4.24.5.5 Triplet Carbenes (as Analogs for Radicals)

Remarkably stable radicals have been prepared [<1985JA718>](#). Known examples of the most stable carbon centered radicals bear no heteroatoms at the radical center, although remote heteroatomic substitution is critically important. Because there are no direct  $\alpha$ -heteroatoms on these radicals, they do not strictly fall into the subject matter for this chapter and thus will not be discussed in detail. Triplet carbenes can be regarded as a type of geminal diradical. Remarkable strides have been made in the synthesis of stable triplet carbenes. As with the stable carbon radicals, heteroatomic substitution for triplet carbenes has proved important, but again at positions remote to the carbene center. Nonetheless, new stable triplet carbenes in the present context for completeness and continuity will be mentioned briefly. In their attempts to prepare a hindered divalent species completely unreactive toward external reagents, Zimmerman and Paskovich generated triplet diphenylcarbenes [<1964JA2149>](#). These carbenes were not stable enough to be isolated, but they exhibited unusual chemical properties. For example, a solution of hexachloro(diphenyl)carbene **112** at room temperature did not react with the parent diazo compound **111** to give azine, but dimerized to give tetrakis((2,4,6-trichlorophenyl)ethylene) **113** in 70–80% yield (Equation (34)).



Tomioka and co-workers generated stable triplet carbene by using bulky substituents and studied their reactivity (for reviews on persistent triplet carbenes see [<1997ACR315, B-1998MI2005>](#)). The Tomioka group recently generated triplet di{9-[10-(2,6-dimethyl-4-*t*-butylphenyl)-anthryl]} carbene **114** by the photolysis of a precursor diazomethane. The half-life of the carbene is 1 week in the solution at room temperature [<2003JA14664>](#). None of these triplet carbenes bear heteroatoms at the carbene center, but their remarkable stabilities make them worthy of a brief mention in this chapter.



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