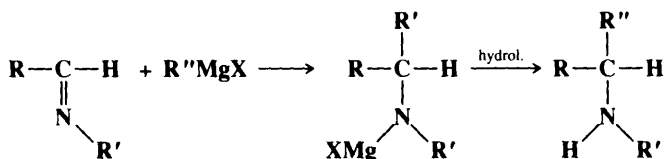


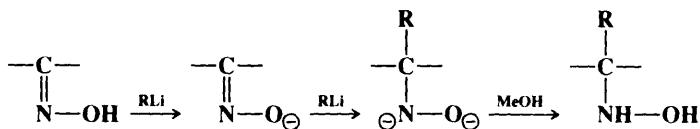
Grignard reagents add to one C=O bond of CO₂ exactly as they do to an aldehyde or a ketone.⁴⁷² Here, of course, the product is the salt of a carboxylic acid. The reaction is usually performed by adding the Grignard reagent to dry ice. Many carboxylic acids have been prepared in this manner, and, along with the sequence 0-101—6-5 and reaction 8-8, this constitutes an important way of increasing a carbon chain by one unit. Since labeled CO₂ is commercially available, this is a good method for the preparation of carboxylic acids labeled in the carboxyl group. Other organometallic compounds have also been used (RLi, RNa, RCaX, etc.), but much less often. The formation of the salt of a carboxylic acid after the addition of CO₂ to a reaction mixture is regarded as a positive test for the presence of a carbanion or of a reactive organometallic intermediate in that reaction mixture (see also 6-43).

OS I, 361, 524; II, 425; III, 413, 553, 555; V, 890, 1043; VI, 845.

6-35 The Addition of Organometallic Compounds to C=N Compounds N-Hydro-C-alkyl-addition



Aldimines can be converted to secondary amines by treatment with Grignard reagents.⁴⁷³ Ketimines generally give reduction instead of addition. However, organolithium compounds give the normal addition product with both aldimines and ketimines.⁴⁷⁴ Other organometallic compounds,⁴⁷⁵ including RCu-BF₃,⁴⁷⁶ allylic boranes⁴⁷⁷ (see 6-29), and allylic stannanes⁴⁷⁸ also add to aldimines in the same manner. The addition of organolithiums has been done enantioselectively, with an optically active amino ether as catalyst.^{478a} Many other C=N systems (phenylhydrazones, oxime ethers, etc.) give normal addition when treated with Grignard reagents; others give reductions; others give miscellaneous reactions. Oximes can be converted to hydroxylamines by treatment with 2 moles of an alkyl lithium reagent, followed by methanol.⁴⁷⁹



⁴⁷²For reviews of the reaction between organometallic compounds and CO₂, see Volpin; Kolomnikov; *Organomet. React.* **1975**, 5, 313-386; Sneed, in Patai *The Chemistry of Carboxylic Acids and Esters*; Wiley: New York, 1969, pp. 137-173; Kharasch; Reinmuth, Ref. 351, pp. 913-948. For a more general review, see Lapidus; *Russ. Chem. Rev.* **1981**, 50, 63-75.

⁴⁷³For reviews of the addition of organometallic reagents to C=N bonds, see Harada, in Patai *The Chemistry of the Carbon-Nitrogen Double Bond*, Ref. 40, pp. 266-272; Kharasch; Reinmuth, Ref. 451, pp. 1204-1227.

⁴⁷⁴Huet *Bull. Soc. Chim. Fr.* **1964**, 952, 960, 967, 973.

⁴⁷⁵For a list of reagents, with references, see Ref. 64, pp. 425-427.

⁴⁷⁶Wada; Sakurai; Akiba *Tetrahedron Lett.* **1984**, 25, 1079.

⁴⁷⁷Yamamoto; Nishii; Maruyama; Komatsu; Ito *J. Am. Chem. Soc.* **1986**, 108, 7778. See also Yamamoto *Acc. Chem. Res.* **1987**, 20, 243-249.

⁴⁷⁸Keck; Enholm *J. Org. Chem.* **1985**, 50, 146.

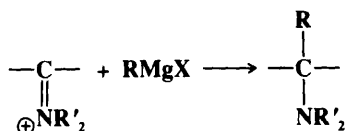
^{478a}Tomioka; Inoue; Shindo; Koga *Tetrahedron Lett.* **1991**, 32, 3095.

⁴⁷⁹Richey; McLane; Phillips *Tetrahedron Lett.* **1976**, 233.

The conjugate bases of nitro compounds (formed by treatment of the nitro compound with BuLi) react with Grignard reagents in the presence of $\text{ClCH}=\text{NMe}_2^+ \text{Cl}^-$ to give oximes: $\text{RCH}=\text{N(O)OLi} + \text{R}'\text{MgX} \rightarrow \text{RR}'\text{C}=\text{NOH}$.⁴⁸⁰

For the addition of an organometallic compound to an imine to give a primary amine, R' in $\text{RCH}=\text{NR}'$ would have to be H, and such compounds are seldom stable (**6-13**). However, the conversion has been done, for $\text{R} = \text{aryl}$, by the use of the masked reagents $(\text{ArCH}=\text{N})_2\text{SO}_2$ [prepared from an aldehyde RCHO and sulfamide $(\text{NH}_2)_2\text{SO}_2$]. Addition of $\text{R}''\text{MgX}$ or $\text{R}''\text{Li}$ to these compounds gives $\text{ArCHR}''\text{NH}_2$ after hydrolysis.⁴⁸¹

Iminium salts³³⁰ give tertiary amines directly, with just R adding:



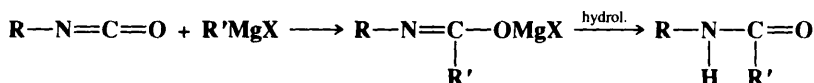
Chloroiminium salts $\text{ClCH}=\text{NR}'_2^+ \text{Cl}^-$ (generated in situ from an amide HCONR'_2 and phosgene COCl_2) react with 2 moles of a Grignard reagent RMgX , one adding to the $\text{C}=\text{N}$ and the other replacing the Cl , to give tertiary amines $\text{R}_2\text{CHNR}'_2$.⁴⁸²

An alkyl group (primary, secondary, or tertiary) can be added to the oxime ether $\text{CH}_2=\text{NOCH}_2\text{Ph}$ by treatment with the appropriate alkyl halide and an equimolar amount of bis(trimethylstannyl)benzopicolinate.⁴⁸³ This reaction, which is a free radical addition, is another way to extend a chain by one carbon.

OS **IV**, 605; **VI**, 64. Also see OS **III**, 329.

6-36 The Addition of Grignard Reagents to Isocyanates

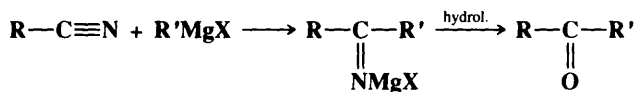
N-Hydro-C-alkyl-addition



The addition of Grignard reagents to isocyanates gives, after hydrolysis, N-substituted amides.⁴⁸⁴ The reaction is written above as involving addition to $\text{C}=\text{O}$, but the ion is a resonance hybrid and the addition might just as well have been shown as occurring on the $\text{C}=\text{N}$. Hydrolysis gives the amide. This is a very good reaction and can be used to prepare derivatives of alkyl and aryl halides. The reaction has also been performed with alkyllithium compounds.⁴⁸⁵ Isothiocyanates give N-substituted thioamides.

6-37 The Addition of Grignard Reagents to Nitriles

Alkyl,oxo-de-nitrilo-tersubstitution (Overall transformation)



⁴⁸⁰Fujisawa; Kurita; Sato *Chem. Lett.* **1983**, 1537.

⁴⁸¹Davis; Giangiodano; Starner *Tetrahedron Lett.* **1986**, 27, 3957.

⁴⁸²Wieland; Simchen *Liebigs Ann. Chem.* **1985**, 2178.

⁴⁸³Hart; Seely *J. Am. Chem. Soc.* **1988**, 110, 1631.

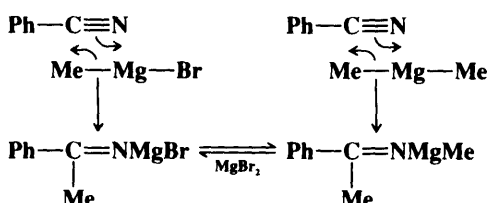
⁴⁸⁴For a review of this and related reactions, see Screttas; Steele *Org. Prep. Proced. Int.* **1990**, 22, 271-314.

⁴⁸⁵LeBel; Cherluck; Curtis *Synthesis* **1973**, 678. For another method, see Einhorn; Luche *Tetrahedron Lett.* **1986**, 27, 501.

Ketones can be prepared by addition of Grignard reagents to nitriles and subsequent hydrolysis. Many ketones have been made in this manner, though when both R groups are alkyl, yields are not high.⁴⁸⁶ Yields can be improved by the use of Cu(I) salts⁴⁸⁷ or by using benzene containing one equivalent of ether as the solvent, rather than ether alone.⁴⁸⁸ The ketimine salt does not in general react with Grignard reagents: hence tertiary alcohols or tertiary alkyl amines are not often side products.⁴⁸⁹ By careful hydrolysis of the salt it is sometimes possible to isolate ketimines $R-\overset{\text{NH}}{\underset{\text{||}}{C}}-R'$,⁴⁹⁰ especially when R and R' = aryl.

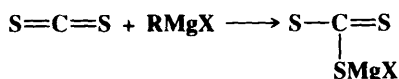
The addition of Grignard reagents to the $C\equiv N$ group is normally slower than to the $C=O$ group, and CN-containing aldehydes add the Grignard reagent without disturbing the CN group.⁴⁹¹ In a similar reaction,⁴⁹² triethylaluminum⁴⁹³ reacts with nitriles (in a 2:1 ratio) to give, after hydrolysis, ethyl ketones.⁴⁹⁴

The following mechanism has been proposed for the reaction of the methyl Grignard reagent with benzonitrile:⁴⁹⁵

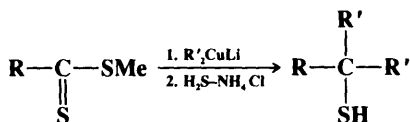


OS III, 26, 562; V, 520.

6-38 The Addition of Organometallic Reagents to the $C=S$ Bond C-Alkyl-S-halomagnesio-addition



Grignard reagents add to CS_2 to give salts of dithiocarboxylic acids (analogous to 6-34).⁴⁹⁶ Two other reactions are worthy of note. (1) Lithium dialkylcopper reagents react with dithiocarboxylic esters to give tertiary thiols⁴⁹⁷ (analogous to 6-32):



⁴⁸⁶For a review, see Kharasch; Reinmuth, Ref. 351, pp. 767-845.

⁴⁸⁷Weiberth; Hall *J. Org. Chem.* **1987**, 52, 3901.

⁴⁸⁸Canonne; Foscolos; Lemay *Tetrahedron Lett.* **1980**, 155.

⁴⁸⁹For examples where tertiary amines have been made the main products, see Alverne; Laurent *Tetrahedron Lett.* **1973**, 1057; Gauthier; Axiotis; Chastrette *J. Organomet. Chem.* **1977**, 140, 245.

⁴⁹⁰Pickard; Tobler *J. Org. Chem.* **1961**, 26, 4886.

⁴⁹¹Cason; Kraus; McLeod *J. Org. Chem.* **1959**, 24, 392.

⁴⁹²For some other reagents, with references, see Ref. 64, p. 701.

⁴⁹³For a review of the reactions of organoaluminum compounds, see Reinheckel; Haage; Jahnke *Organomet. Chem. Rev., Sect. A* **1969**, 4, 47-136.

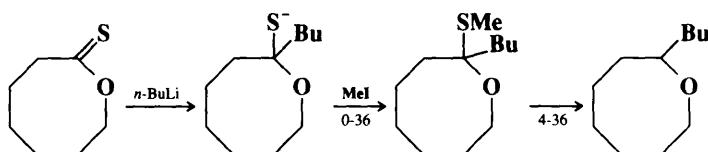
⁴⁹⁴Reinheckel; Jahnke *Chem. Ber.* **1964**, 97, 2661. See also Bagnell; Jeffery; Meisters; Mole *Aust. J. Chem.* **1974**, 27, 2577.

⁴⁹⁵Ashby; Chao; Neumann *J. Am. Chem. Soc.* **1973**, 95, 4896, 5186.

⁴⁹⁶For a review of the addition of Grignard reagents to $C=S$ bonds, see Paquer *Bull. Soc. Chim. Fr.* **1975**, 1439-1449. For a review of the synthesis of dithiocarboxylic acids and esters, see Ramadas; Srinivasan; Ramachandran; Sastry *Synthesis* **1983**, 605-622.

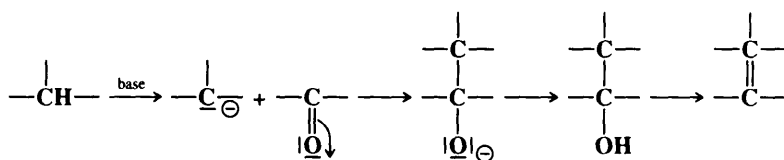
⁴⁹⁷Bertz; Dabagh; Williams *J. Org. Chem.* **1985**, 50, 4414.

(2) Thiono lactones can be converted to cyclic ethers,⁴⁹⁸ e.g.:



This is a valuable procedure because medium and large ring ethers are not easily made, while the corresponding thiono lactones can be prepared from the readily available lactones (see, for example, 0-22) by reaction 6-11.

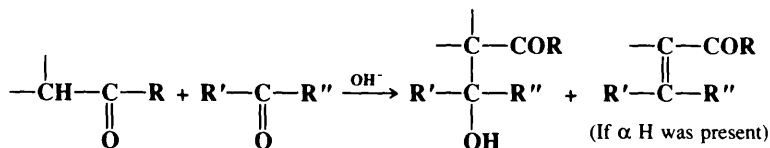
I. Carbon Attack by Active Hydrogen Compounds. Reactions 6-39 through 6-48 are base-catalyzed condensations (though some of them are also catalyzed to acids).⁴⁹⁹ In 6-39 through 6-47, a base removes a C—H proton to give a carbanion, which then adds to a C=O. The oxygen acquires a proton, and the resulting alcohol may or may not be dehydrated, depending on whether an α hydrogen is present and on whether the new double bond would be in conjugation with double bonds already present:



The reactions differ in the nature of the active hydrogen component and the carbonyl component. Table 16.1 illustrates the differences. Reaction 6-48 is an analogous reaction involving addition to $C\equiv N$.

6-39 The Aldol Reaction

O-Hydro-C-(α -acylalkyl)-addition; α -Acylalkylidene-de-oxo-bisubstitution



In the *aldol reaction*⁵⁰⁰ the α carbon of one aldehyde or ketone molecule adds to the carbonyl carbon of another.⁵⁰¹ The base most often used is OH^- , though stronger bases, e.g., alu-

⁴⁹⁸Nicolaou; McGarry; Somers; Veale; Furst *J. Am. Chem. Soc.* **1987**, 109, 2504.

⁴⁹⁹For reviews, see House, Ref. 180, pp. 629-682; Reeves, in Patai, Ref. 2, pp. 567-619. See also Stowell *Carbanions in Organic Synthesis*; Wiley: New York, 1979.

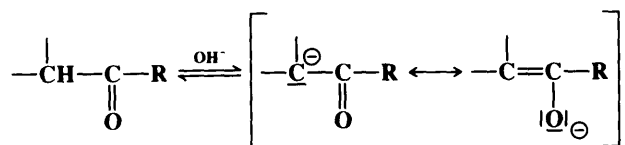
⁵⁰⁰This reaction is also called the *aldol condensation*, though, strictly speaking, this term applies to the formation only of the α,β -unsaturated product, and not the aldol.

⁵⁰¹For reviews, see Thebtaranonth; Thebtaranonth, in Patai, Ref. 252, pt. 1, pp. 199-280, pp. 199-212; Hajos, in Augustine *Carbon-Carbon Bond Formation*, vol. 1; Marcel Dekker: New York, 1979; pp. 1-84; Nielsen; Houlihan, *Org. React.* **1968**, 16, 1-438.

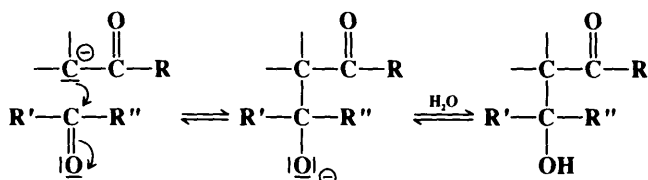
TABLE 16.1 Base-catalyzed condensations showing the active-hydrogen components and the carbonyl components

Reaction	Active-hydrogen component	Carbonyl component	Subsequent reactions
6-39 Aldol reaction	Aldehyde $\begin{array}{c} \\ -\text{CH}-\text{CHO} \end{array}$ Ketone $\begin{array}{c} \\ -\text{CH}-\text{COR} \end{array}$	Aldehyde, ketone	Dehydration may follow
6-40	Ester $\begin{array}{c} \\ -\text{CH}-\text{COOR} \end{array}$	Aldehyde, ketone (usually without α -hydrogens)	Dehydration may follow
6-41 Knoevenagel reaction	$\text{Z}-\text{CH}_2-\text{Z}'$, $\text{Z}-\text{CHR}-\text{Z}'$, and similar molecules	Aldehyde, ketone (usually without α -hydrogens)	Dehydration usually follows
6-42 Peterson reaction	$\text{Me}_3\text{Si}-\begin{array}{c} \\ \text{CH}^- \end{array}$	Aldehyde, ketone	Dehydration may follow
6-43	$\begin{array}{c} \\ -\text{CH}-\text{Z} \end{array}$ $\text{Z} = \text{COR}, \text{COOR}, \text{NO}_2$	CO_2 , CS_2	
6-44 Perkin reaction	Anhydride $\begin{array}{c} \\ -\text{CH}-\text{COOCOR} \end{array}$	Aromatic aldehyde	Dehydration usually follows
6-45 Darzen's reaction	α -Halo ester $\begin{array}{c} \\ \text{XCH}-\text{COOR} \end{array}$	Aldehyde, ketone	Epoxidation (S_N reaction) follows
6-46 Tollens' reaction	Aldehyde $\begin{array}{c} \\ -\text{CH}-\text{CHO} \end{array}$ Ketone $\begin{array}{c} \\ -\text{CH}-\text{COR} \end{array}$	Formaldehyde	Crossed Cannizzaro reaction follows
6-47 Wittig reaction	Phosphorous ylide $\text{Ph}_3\text{P}^+-\begin{array}{c} \\ \text{C}^- \end{array}$	Aldehyde, ketone	"Dehydration" always follows
6-48 Thorpe reaction	Nitrile $\begin{array}{c} \\ -\text{CH}-\text{CN} \end{array}$	Nitrile	

minum *t*-butoxide, are sometimes employed. Hydroxide ion is not a strong enough base to convert substantially all of an aldehyde or ketone molecule to the corresponding enolate

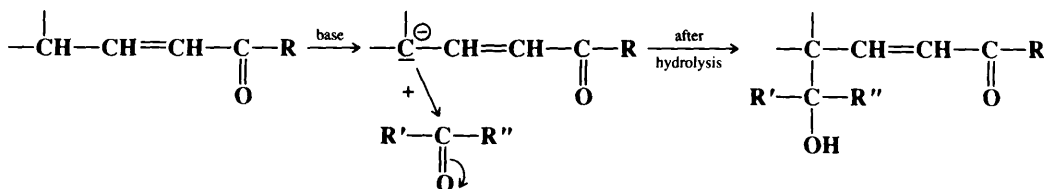


ion, i.e., the equilibrium lies well to the left, for both aldehydes and ketones. Nevertheless, enough enolate ion is present for the reaction to proceed:



The product is a β -hydroxy aldehyde (called an *aldol*) or ketone, which in some cases is dehydrated during the course of the reaction. Even if the dehydration is not spontaneous, it can usually be done easily, since the new double bond is in conjugation with the C=O bond; so that this is a method of preparing α,β -unsaturated aldehydes and ketones as well as β -hydroxy aldehydes and ketones. The entire reaction is an equilibrium (including the dehydration step), and α,β -unsaturated and β -hydroxy aldehydes and ketones can be cleaved by treatment with OH^- (the *retrograde aldol reaction*). There is evidence that an SET mechanism can intervene when the substrate is an aromatic ketone.⁵⁰²

Under the principle of vinylogy, the active hydrogen can be one in the γ position of an α,β -unsaturated carbonyl compound:



The scope of the aldol reaction may be discussed under five headings:

1. Reaction between two molecules of the same aldehyde. The equilibrium lies far to the right,⁵⁰³ and the reaction is quite feasible. Many aldehydes have been converted to aldols and/or their dehydration products in this manner. The most effective catalysts are basic ion-exchange resins. Of course, the aldehyde must possess an α hydrogen.

2. Reaction between two molecules of the same ketone. In this case the equilibrium lies well to the left,⁵⁰⁴ and the reaction is feasible only if the equilibrium can be shifted. This can often be done by allowing the reaction to proceed in a Soxhlet extractor (for example, see OS I, 199). In this method the ketone is refluxed in such a way that the condensate drips into a separate chamber, in which the base is present. In this chamber the reaction proceeds to the small extent permitted by the unfavorable equilibrium. When the chamber is full, the mixture of the ketone and its dimer is siphoned back into the original flask, out of contact with the base. Since the boiling point of the dimer is higher than that of the ketone, only the ketone is volatilized back to the chamber containing the base, where a little more of it is converted to dimer, and the process is repeated until a reasonable yield of dimer is obtained. Two molecules of the same ketone can also be condensed without a

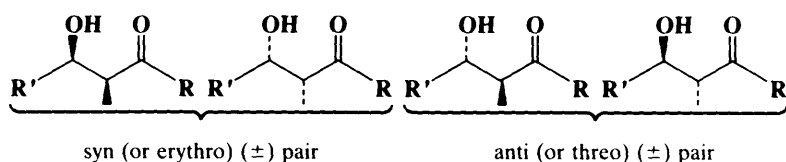
⁵⁰²Ashby; Argyropoulos; Meyer; Goel *J. Am. Chem. Soc.* **1982**, *104*, 6788; Ashby; Argyropoulos *J. Org. Chem.* **1986**, *51*, 472.

⁵⁰³For discussions of equilibrium constants in aldol reactions, see Guthrie; Wang *Can. J. Chem.* **1991**, *69*, 339; Guthrie *J. Am. Chem. Soc.* **1991**, *113*, 7249, and references cited in these papers.

⁵⁰⁴The equilibrium concentration of the product from acetone in pure acetone was determined to be 0.01%: Maple; Allerhand *J. Am. Chem. Soc.* **1987**, *109*, 6609.

dehydes react, but not their acetals, while acetals of ketones react, but not the ketones themselves.⁵¹⁴ Other types of preformed derivatives that react with aldehydes and ketones are enamines (with a Lewis acid catalyst),⁵¹⁵ and enol borinates $R'CH=CR''-OBR_2$ ⁵¹⁶ (which can be synthesized by **5-19**, or directly from an aldehyde or ketone⁵¹⁷). Preformed metallic enolates are also used. For example lithium enolates⁵¹⁸ (prepared by **2-22**) react with the substrate in the presence of $ZnCl_2$,⁵¹⁹ in this case the aldol product is stabilized by chelation of its two oxygen atoms with the zinc ion.⁵²⁰ Among other metallic enolates used for aldol reactions are those of Ti,⁵²¹ Zr,⁵²² and Pd,⁵²³ all of which give products regioselectively. α -Alkoxy ketones react with lithium enolates particularly rapidly.⁵²⁴

The reactions with preformed enol derivatives provide a way to control the stereoselectivity of the aldol reaction.⁵²⁵ As with the Michael reaction (**5-17**), the aldol reaction creates two new chiral centers, and, in the most general case, there are four stereoisomers of the aldol product, which can be represented as



Among the preformed enol derivatives used in this way have been enolates of magnesium, lithium,⁵²⁶ titanium,⁵²⁷ rhodium,⁵²⁸ zirconium,⁵²² and tin,⁵²⁹ silyl enol ethers,⁵³⁰ enol borinates,⁵³¹ and enol borates $R'CH=CR''-OB(OR)_2$.⁵³² In general, metallic *Z* enolates give

⁵¹⁴Sato; Otera; Nozaki *J. Am. Chem. Soc.* **1990**, *112*, 901.

⁵¹⁵Takazawa; Kogami; Hayashi *Bull. Chem. Soc. Jpn.* **1985**, *58*, 2427.

⁵¹⁶Inoue; Mukaiyama *Bull. Chem. Soc. Jpn.* **1980**, *53*, 174; Kuwajima; Kato; Mori *Tetrahedron Lett.* **1980**, *21*, 4291; Wada *Chem. Lett.* **1981**, 153; Hooz; Oudenes; Roberts; Benderly *J. Org. Chem.* **1987**, *52*, 1347; Nozaki; Oshima; Utimoto *Tetrahedron Lett.* **1988**, *29*, 1041. For a review, see Pelter; Smith; Brown, Ref. 361, pp. 324-333.

⁵¹⁷For conversion of ketones to either *Z* or *E* enol borinates, see, for example, Evans; Nelson; Vogel; Taber *J. Am. Chem. Soc.* **1981**, *103*, 3099; Brown; Dhar; Bakshi; Pandiarajan; Singaram *J. Am. Chem. Soc.* **1989**, *111*, 3441.

⁵¹⁸For a complete structure-energy analysis of one such reaction, see Arnett; Fisher; Nichols; Ribeiro *J. Am. Chem. Soc.* **1990**, *112*, 801.

⁵¹⁹House; Crumrine; Teranishi; Olmstead *J. Am. Chem. Soc.* **1973**, *95*, 3310.

⁵²⁰It has been contended that such stabilization is not required: Mulzer; Brüntrup; Finke; Zippel *J. Am. Chem. Soc.* **1979**, *101*, 7723.

⁵²¹Stille; Grubbs *J. Am. Chem. Soc.* **1983**, *105*, 1664.

⁵²²Evans; McGee *Tetrahedron Lett.* **1980**, *21*, 3975; *J. Am. Chem. Soc.* **1981**, *103*, 2876.

⁵²³Nokami; Mandai; Watanabe; Ohya; Tsuji *J. Am. Chem. Soc.* **1989**, *111*, 4126.

⁵²⁴Das; Thornton *J. Am. Chem. Soc.* **1990**, *112*, 5360.

⁵²⁵For reviews, see Heathcock *Aldrichimica Acta* **1990**, *23*, 99-111; *Science* **1981**, *214*, 395-400; Nógrádi, Ref. 294, pp. 193-220; Heathcock, in Morrison, Ref. 294, vol. 3, 1984, pp. 111-212; Heathcock, in Buncl; Durst *Comprehensive Carbanion Chemistry*, pt. B, Elsevier: New York, 1984, pp. 177-237; Evans; Nelson; Taber *Top. Stereochem.* **1982**, *13*, 1-115; Evans *Aldrichimica Acta* **1982**, *15*, 23-32.

⁵²⁶Fellmann; Dubois *Tetrahedron* **1978**, *34*, 1349; Heathcock; Pirrung; Montgomery; Lampe *Tetrahedron* **1981**, *37*, 4087; Masamune; Ellingboe; Choy *J. Am. Chem. Soc.* **1982**, *104*, 5526; Ertas; Seebach *Helv. Chim. Acta* **1985**, *68*, 961.

⁵²⁷Siegel; Thornton *Tetrahedron Lett.* **1986**, *27*, 457; Nerz-Stormes; Thornton *Tetrahedron Lett.* **1986**, 897; Evans; Rieger; Bilodeau; Urpi *J. Am. Chem. Soc.* **1991**, *113*, 1047.

⁵²⁸Slough; Bergman; Heathcock *J. Am. Chem. Soc.* **1989**, *111*, 938.

⁵²⁹Mukaiyama; Iwasawa; Stevens; Haga *Tetrahedron* **1984**, *40*, 1381; Labadie; Stille *Tetrahedron* **1984**, *40*, 2329; Yura; Iwasawa; Mukaiyama *Chem. Lett.* **1986**, 187. See also Nakamura; Kuwajima *Tetrahedron Lett.* **1983**, *24*, 3347.

⁵³⁰Matsuda; Izumi *Tetrahedron Lett.* **1981**, *22*, 1805; Yamamoto; Maruyama; Matsumoto *J. Am. Chem. Soc.* **1983**, *105*, 6963; Sakurai; Sasaki; Hosomi; *Bull. Chem. Soc. Jpn.* **1983**, *56*, 3195; Hagiwara; Kimura; Uda *J. Chem. Soc., Chem. Commun.* **1986**, 860.

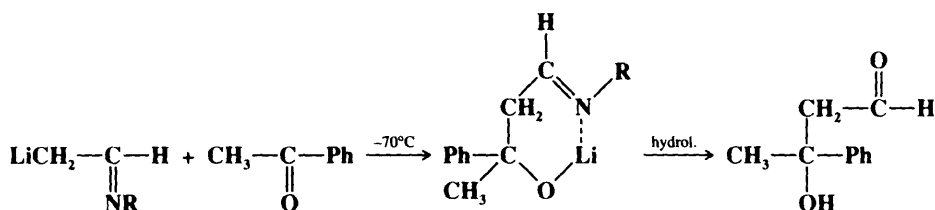
⁵³¹Masamune; Mori; Van Horn; Brooks *Tetrahedron Lett.* **1979**, 1665; Evans et al., Ref. 517; Evans; Bartroli; Shih *J. Am. Chem. Soc.* **1981**, *103*, 2127; Masamune; Choy; Kerdesky; Imperiali *J. Am. Chem. Soc.* **1981**, *103*, 1566; Heathcock; Arseniyadis *Tetrahedron Lett.* **1985**, *26*, 6009; Paterson; Goodman; Lister; Schumann; McClure; Norcross *Tetrahedron* **1990**, *46*, 4663; Walker; Heathcock *J. Org. Chem.* **1991**, *56*, 5747. For reviews, see Paterson *Chem. Ind. (London)* **1988**, 390-394; Pelter; Smith; Brown, Ref. 516.

⁵³²Hoffmann; Ditrch; Fröch *Liebigs Ann. Chem.* **1987**, 977.

the syn (or erythro) pair, and this reaction is highly useful for the diastereoselective synthesis of these products.⁵³³ The *E* isomers generally react nonstereoselectively. However, anti (or threo) stereoselectivity has been achieved in a number of cases, with titanium enolates,⁵³⁴ with germanium enolates,⁵³⁵ with magnesium enolates,^{535a} with certain enol borinates,⁵³⁶ and with lithium enolates at -78°C .⁵³⁷ High diastereoselectivity was also achieved, without a preformed enolate, in the reaction between ethyl ketones and aldehydes, by performing the reaction in the presence of PhBCl_2 and Et_3N .⁵³⁸

These reactions can also be made enantioselective (in which case only one of the four isomers predominates) by using⁵³⁹ chiral enol derivatives,⁵⁴⁰ chiral aldehydes or ketones,⁵⁴¹ or both.⁵⁴² Since both new chiral centers are formed enantioselectively, this kind of process is called *double asymmetric synthesis*.⁵⁴³ A single one of the four stereoisomers has also been produced where both the enolate derivative and substrate were achiral, by carrying out the reaction in the presence of an optically active boron compound⁵⁴⁴ or a diamine coordinated with a tin compound.⁵⁴⁵

It is possible to make the α carbon of the aldehyde add to the carbonyl carbon of the ketone, by using an imine instead of an aldehyde, and $\text{LiN}(\text{iso-Pr})_2$ as the base:⁵⁴⁶



⁵³³For discussion of transition state geometries in this reaction, see Hoffmann; Ditrich; Froech; Cremer *Tetrahedron* **1985**, 41, 5517; Anh; Thanh *Nouv. J. Chim.* **1986**, 10, 681; Li; Paddon-Row; Houk *J. Org. Chem.* **1990**, 55, 481; Denmark; Henke *J. Am. Chem. Soc.* **1991**, 113, 2177.

⁵³⁴See Murphy; Procter; Russell *Tetrahedron Lett.* **1987**, 28, 2037; Shirodkar; Nerz-Stormes; Thornton *Tetrahedron Lett.* **1990**, 31, 4699; Nerz-Stormes; Thornton *J. Org. Chem.* **1991**, 56, 2489.

⁵³⁵Yamamoto; Yamada *J. Chem. Soc., Chem. Commun.* **1988**, 802.

^{535a}Swiss; Choi; Liotta; Abdel-Magid; Maryanoff *J. Org. Chem.* **1991**, 56, 5978.

⁵³⁶Masamune; Sato; Kim; Wollmann *J. Am. Chem. Soc.* **1986**, 108, 8279; Danda; Hansen; Heathcock *J. Org. Chem.* **1990**, 55, 173. See also Corey; Kim *Tetrahedron Lett.* **1990**, 31, 3715.

⁵³⁷Hirama; Noda; Takeishi; Itô *Bull. Chem. Soc. Jpn.* **1988**, 61, 2645; Majewski; Gleave *Tetrahedron Lett.* **1989**, 30, 5681.

⁵³⁸Hamana; Sasakura; Sugawara *Chem. Lett.* **1984**, 1729.

⁵³⁹For reviews, see Klein, in Patai *Supplement A: The Chemistry of Double-bonded Functional Groups*, vol. 2, pt. 1; Wiley: New York, 1989, pp. 567-677; Braun *Angew. Chem. Int. Ed. Engl.* **1987**, 26, 24-37 [*Angew. Chem.* 99, 24-37].

⁵⁴⁰For examples, see Eichenauer; Friedrich; Lutz; Enders *Angew. Chem. Int. Ed. Engl.* **1978**, 17, 206 [*Angew. Chem.* 90, 219]; Meyers; Yamamoto *Tetrahedron* **1984**, 40, 2309; Ando; Shioiri *J. Chem. Soc., Chem. Commun.* **1987**, 1620; Muraoka; Kawasaki; Koga *Tetrahedron Lett.* **1988**, 29, 337; Paterson; Goodman *Tetrahedron Lett.* **1989**, 30, 997; Siegel; Thornton *J. Am. Chem. Soc.* **1989**, 111, 5722; Gennari; Molinari; Cozzi; Oliva *Tetrahedron Lett.* **1989**, 30, 5163; Faunce; Grisso; Mackenzie *J. Am. Chem. Soc.* **1991**, 113, 3418.

⁵⁴¹For example, see Ojima; Yoshida; Inaba *Chem. Lett.* **1977**, 429; Heathcock; Flippin *J. Am. Chem. Soc.* **1983**, 105, 1667; Reetz; Kessler; Jung *Tetrahedron* **1984**, 40, 4327.

⁵⁴²For example, see Heathcock; White; Morrison; VanDerveer *J. Org. Chem.* **1981**, 46, 1296; Short; Masamune *Tetrahedron Lett.* **1987**, 28, 2841.

⁵⁴³For a review, see Masamune; Choy; Petersen; Sita *Angew. Chem. Int. Ed. Engl.* **1985**, 24, 1-30 [*Angew. Chem.* 97, 1-31].

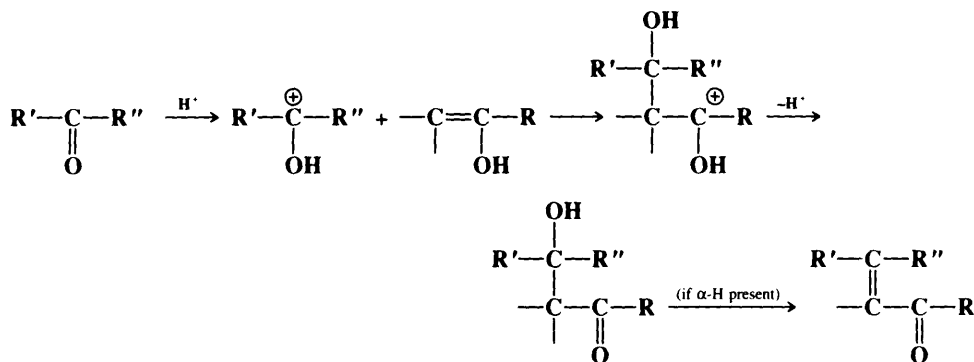
⁵⁴⁴Corey; Imwinkelried; Pikul; Xiang *J. Am. Chem. Soc.* **1989**, 111, 5493; Corey; Kim *J. Am. Chem. Soc.* **1990**, 112, 4976; Furuta; Maruyama; Yamamoto *J. Am. Chem. Soc.* **1991**, 113, 1041; Kiyooka; Kaneko; Komura; Matsuo; Nakano *J. Org. Chem.* **1991**, 56, 2276.

⁵⁴⁵Mukaiyama; Uchiro; Kobayashi *Chem. Lett.* **1990**, 1147.

⁵⁴⁶Wittig; Frommelt; Suchanek *Angew. Chem. Int. Ed. Engl.* **1963**, 2, 683 [*Angew. Chem.* 75, 303]. For reviews, see Mukaiyama *Org. React.* **1982**, 28, 203-331; Wittig *Top. Curr. Chem.* **1976**, 67, 1-14, *Rec. Chem. Prog.* **1967**, 28, 45-60; Wittig; Reiff *Angew. Chem. Int. Ed. Engl.* **1968**, 7, 7-14; [*Angew. Chem.* 80, 8-15]; Reiff *Newer Methods Prep. Org. Chem.* **1971**, 6, 48-66.

This is known as the *directed aldol reaction*. Similar reactions have been performed with α -lithiated dimethylhydrazones of aldehydes or ketones⁵⁴⁷ and with α -lithiated aldoximes.⁵⁴⁸

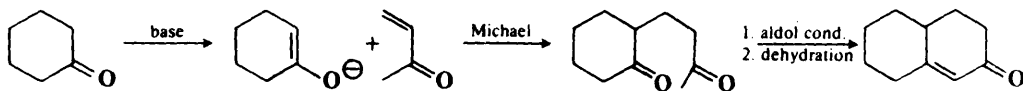
The aldol reaction can also be performed with acid catalysts, in which case dehydration usually follows. Here there is initial protonation of the carbonyl group, which attacks the α carbon of the *enol* form of the other molecule:⁵⁴⁹



With respect to the enol, this mechanism is similar to that of halogenation (2-4).

A side reaction that is sometimes troublesome is further condensation, since the product of an aldol reaction is still an aldehyde or ketone.

Aldol reactions are often used to close five- and six-membered rings. Because of the favorable entropy (p. 211), such ring closures generally take place with ease, even where a ketone condenses with a ketone. An important example is the *Robinson annulation reaction*,⁵⁵⁰ which has often been used in the synthesis of steroids and terpenes. In this reaction a cyclic ketone is converted to another cyclic ketone, with one additional six-membered ring containing a double bond. The substrate is treated with methyl vinyl ketone (or a simple derivative of methyl vinyl ketone) and a base.⁵⁵¹ The enolate ion of the substrate adds to the methyl vinyl ketone in a Michael reaction (5-17) to give a diketone that undergoes or



is made to undergo an internal aldol reaction and subsequent dehydration to give the product.⁵⁵² Because methyl vinyl ketone has a tendency to polymerize, precursors are often used instead, i.e., compounds that will give methyl vinyl ketone when treated with a base. One common example, $\text{MeCOCH}_2\text{CH}_2\text{NEt}_2\text{Me}^+ \text{I}^-$ (see 7-8), is easily prepared by quaternization of $\text{MeCOCH}_2\text{CH}_2\text{NEt}_2$, which itself is prepared by a Mannich reaction (6-16)

⁵⁴⁷Corey; Enders *Tetrahedron Lett.* **1976**, 11. See also Beam; Thomas; Sandifer; Foote; Hauser *Chem. Ind. (London)* **1976**, 487; Sugawara; Toyoda; Sasakura *Synth. Commun.* **1979**, 9, 515; Depezay; Le Merrer *Bull. Soc. Chim. Fr.* **1981**, 11-306.

⁵⁴⁸Hassner; Nümann *Chem. Ber.* **1988**, 121, 1823.

⁵⁴⁹There is evidence (in the self-condensation of acetaldehyde) that a water molecule acts as a base (even in concentrated H_2SO_4) in assisting the addition of the enol to the protonated aldehyde: Baigrie; Cox; Slebocka-Tilk; Tencer; Tidwell *J. Am. Chem. Soc.* **1985**, 107, 3640.

⁵⁵⁰For reviews of this and related reactions, see Gawley *Synthesis* **1976**, 777-794; Jung *Tetrahedron* **1976**, 32, 1-31; Mundy *J. Chem. Educ.* **1973**, 50, 110-113. For a list of references, see Ref. 64, pp. 668-670.

⁵⁵¹Acid catalysis has also been used: see Heathcock; Ellis; McMurry; Coppolino *Tetrahedron Lett.* **1971**, 4995.

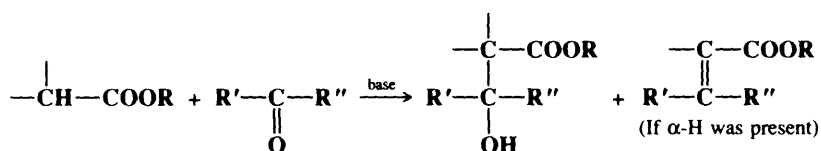
⁵⁵²For improved procedures, see Sato; Wakahara; Otera; Nozaki *Tetrahedron Lett.* **1990**, 31, 1581, and references cited therein.

involving acetone, formaldehyde, and diethylamine. The Robinson annulation reaction has also been carried out with 3-buten-2-one, in which case the new ring of the product contains two double bonds.⁵⁵³ α -Silylated vinyl ketones $\text{RCOC}(\text{SiMe}_3)=\text{CH}_2$ have also been used successfully in annulation reactions.⁵⁵⁴ The SiMe_3 group is easily removed. 1,5-Diketones prepared in other ways are also frequently cyclized by internal aldol reactions. When the ring closure of a 1,5-diketone is catalyzed by the amino acid (*S*)-proline, the product is optically active with high enantiomeric excess.⁵⁵⁵

OS **I**, 77, 78, 81, 199, 283, 341; **II**, 167, 214; **III**, 317, 353, 367, 747, 806, 829; **V**, 486, 869; **VI**, 496, 666, 692, 781, 901; **VII**, 185, 190, 332, 363, 368, 473; **65**, 6, 26; **67**, 121; **68**, 83; **69**, 55, 226. Also see OS **65**, 146.

6-40 Aldol-type Reactions between Carboxylic Esters and Aldehydes or Ketones

O-Hydro-C-(α -alkoxycarbonylalkyl)-addition; α -Alkoxycarbonylalkylidene-de-oxo-bisubstitution



In the presence of a strong base, the α carbon of a carboxylic ester can condense with the carbonyl carbon of an aldehyde or ketone to give a β -hydroxy ester,⁵⁵⁶ which may or may not be dehydrated to the α,β -unsaturated ester. This reaction is sometimes called the Claisen condensation,⁵⁵⁷ an unfortunate usage since that name is more firmly connected to **0-108**. It is also possible for the α carbon of an aldehyde or ketone to add to the carbonyl carbon of a carboxylic ester, but this is a different reaction (**0-109**) involving nucleophilic substitution and not addition to a $\text{C}=\text{O}$ bond. It can, however, be a side reaction if the aldehyde or ketone has an α hydrogen.

Besides ordinary esters (containing an α hydrogen), the reaction can also be carried out with lactones and, as in **6-39**, with the γ position of α,β -unsaturated esters (vinylology).

For most esters, a much stronger base is needed than for aldol reactions; $(i\text{-Pr})_2\text{NLi}$, Ph_3CNa and LiNH_2 are among those employed. However, one type of ester reacts more easily, and such strong bases are not needed: diethyl succinate and its derivatives condense with aldehydes and ketones in the presence of bases such as NaOEt , NaH , or KOCMe_3 . This reaction is called the *Stobbe condensation*.⁵⁵⁸ One of the ester groups (sometimes both) is hydrolyzed in the course of the reaction. The following mechanism accounts for (1) the fact the succinic esters react so much better than others; (2) one ester group is always cleaved; and (3) the alcohol is not the product but the olefin. In addition, intermediate lactones **37** have been isolated from the mixture:⁵⁵⁹

⁵⁵³For example, see Woodward; Singh *J. Am. Chem. Soc.* **1950**, 72, 494.

⁵⁵⁴Stork; Ganem *J. Am. Chem. Soc.* **1973**, 95, 6152; Stork; Singh *J. Am. Chem. Soc.* **1974**, 96, 6181; Boeckman *J. Am. Chem. Soc.* **1974**, 96, 6179.

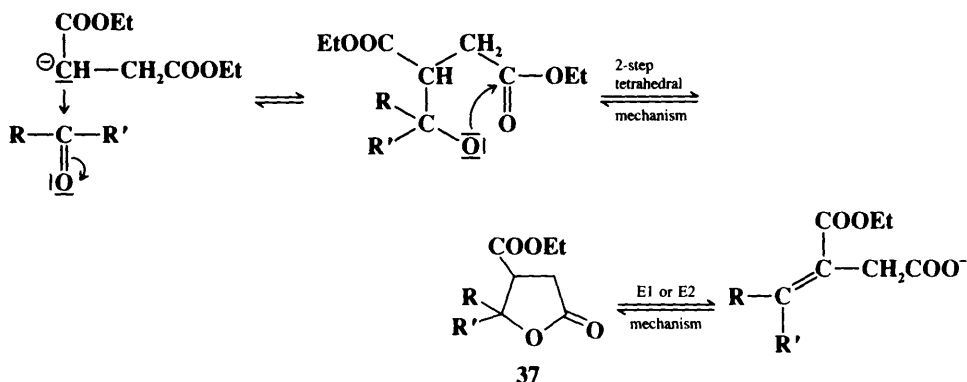
⁵⁵⁵Eder; Sauer; Wiechert *Angew. Chem. Int. Ed. Engl.* **1971**, 10, 496 [*Angew. Chem.* 83, 492]; Hajos; Parrish *J. Org. Chem.* **1974**, 39, 1615. For a review of the mechanism, see Agami *Bull. Soc. Chim. Fr.* **1988**, 499-507.

⁵⁵⁶If the reagent is optically active because of the presence of a chiral sulfoxide group, the reaction can be enantioselective. For a review of such cases, see Solladié *Chimia* **1984**, 38, 233-243.

⁵⁵⁷Because it was discovered by Claisen: *Ber.* **1890**, 23, 977.

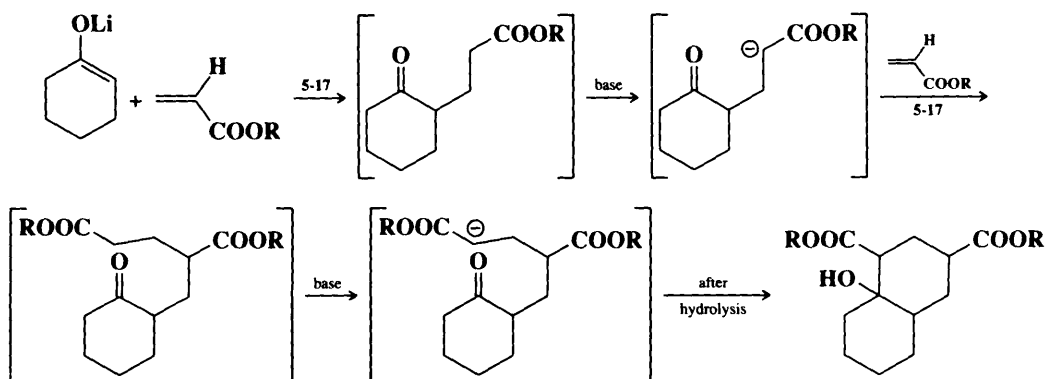
⁵⁵⁸For a review, see Johnson; Daub *Org. React.* **1951**, 6, 1-73.

⁵⁵⁹Robinson; Seijo *J. Chem. Soc.* **1941**, 582.



The Stobbe condensation has been extended to di-*t*-butyl esters of glutaric acid.⁵⁶⁰

This reaction is one step in an annulation sequence that also features two Michael (5-17) steps. An α,β -unsaturated ester is treated with a lithium enolate:

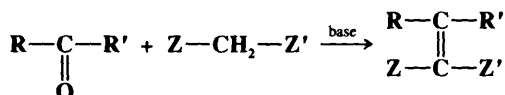


The entire sequence takes place in one laboratory step.⁵⁶¹

OS I, 252; III, 132; V, 80, 564. Also see OS IV, 278, 478; V, 251.

6-41 The Knoevenagel Reaction

Bis(ethoxycarbonyl)methylene-de-oxo-bisubstitution, etc.



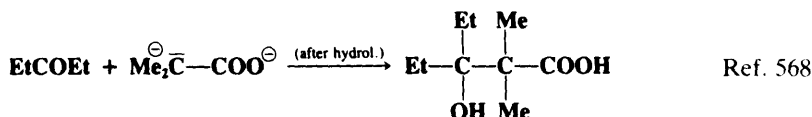
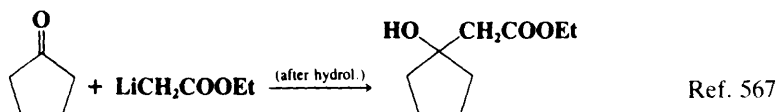
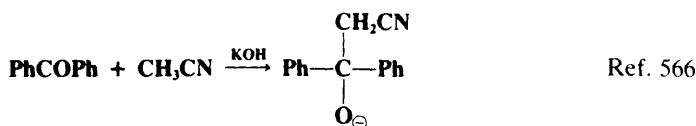
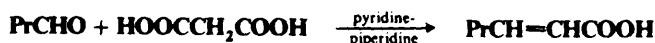
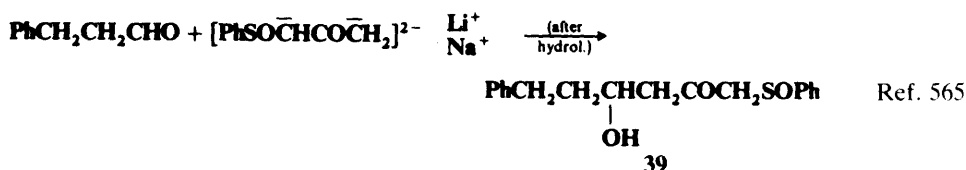
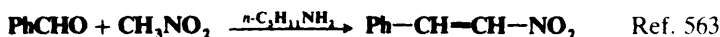
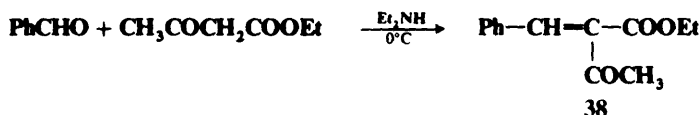
The condensation of aldehydes or ketones, usually not containing an α hydrogen, with compounds of the form $\text{Z}-\text{CH}_2-\text{Z}'$ or $\text{Z}-\text{CHR}-\text{Z}'$ is called the *Knoevenagel reaction*.⁵⁶²

⁵⁶⁰Puterbaugh *J. Org. Chem.* **1962**, 27, 4010. See also El-Newaihy; Salem; Enayat; El-Bassiouny *J. Prakt. Chem.* **1982**, 324, 379.

⁵⁶¹Posner; Lu; Asirvatham; Silversmith; Shulman *J. Am. Chem. Soc.* **1986**, 108, 511. For an extension of this work to the coupling of four components, see Posner; Webb; Asirvatham; Jew; Degl'Innocenti *J. Am. Chem. Soc.* **1988**, 110, 4754.

⁵⁶²For a review, see Jones *Org. React.* **1967**, 15, 204-599.

Z and Z' may be CHO, COR, COOH, COOR, CN, NO₂,⁵⁶³ SOR, SO₂R, SO₂OR, or similar groups. When Z = COOH, decarboxylation of the product often takes place in situ.⁵⁶⁴ If a strong enough base is used, the reaction can be performed on compounds possessing only a single Z, e.g., CH₃Z or RCH₂Z. Other active hydrogen compounds can also be employed, among them CHCl₃, 2-methylpyridines, terminal acetylenes, cyclopentadienes, etc.; in fact any compound that contains a C—H bond the hydrogen of which can be removed by a base. The following examples illustrate the wide scope of the reaction:



⁵⁶³For a review of this reaction with respect to nitroalkanes (often called the *Henry reaction*), see Baer; Urbas, in Feuer, Ref. 180, pp. 76-117. See also Rosini; Ballini; Sorrenti *Synthesis* **1983**, 1014; Matsumoto *Angew. Chem. Int. Ed. Engl.* **1984**, 23, 617 [*Angew. Chem.* 96, 599]; Eyer; Seebach *J. Am. Chem. Soc.* **1985**, 107, 3601. For reviews of the nitroalkenes that are the products of this reaction, see Barrett; Graboski *Chem. Rev.* **1986**, 86, 751-762; Kabalka; Varma *Org. Prep. Proced. Int.* **1987**, 19, 283-328.

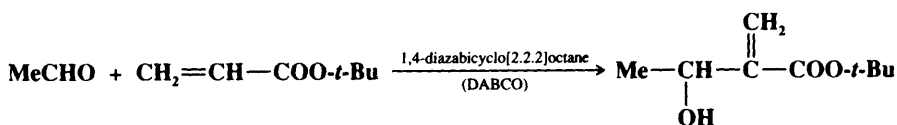
⁵⁶⁴For a discussion of the mechanism when the reaction is accompanied by decarboxylation, see Tanaka; Oota; Hiramatsu; Fujiwara *Bull. Chem. Soc. Jpn.* **1988**, 61, 2473.

⁵⁶⁵Kuwajima; Iwasawa *Tetrahedron Lett.* **1974**, 107. See also Huckin; Weiler *Can. J. Chem.* **1974**, 52, 2157.

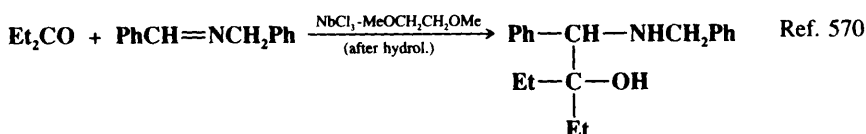
⁵⁶⁶DiBiase; Lipisko; Haag; Wolak; Gokel *J. Org. Chem.* **1979**, 44, 4640. For a review of addition of the conjugate bases of nitriles, see Arseniyadis; Kyler; Watt *Org. React.* **1984**, 31, 1-364.

⁵⁶⁷Rathke *J. Am. Chem. Soc.* **1970**, 92, 3222; van der Veen; Geenevasen; Cerfontain *Can. J. Chem.* **1984**, 62, 2202.

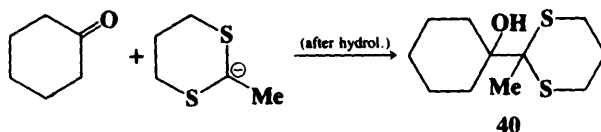
⁵⁶⁸Moersch; Burkett *J. Org. Chem.* **1971**, 36, 1149. See also Cainelli; Cardillo; Contento; Umani-Ronchi *Gazz. Chim. Ital.* **1974**, 104, 625. When the nucleophile is PhCHCOO^- , the reaction is known as the *Ivanov reaction*. For a discussion of the mechanism, see Toullec; Mladenova; Gaudemar-Bardone; Blagoev *J. Org. Chem.* **1985**, 50, 2563.



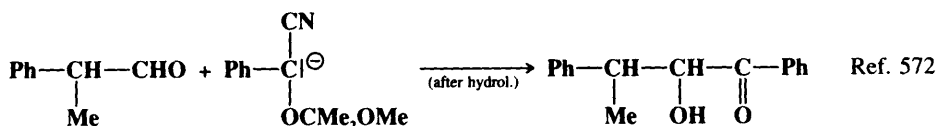
Ref. 569



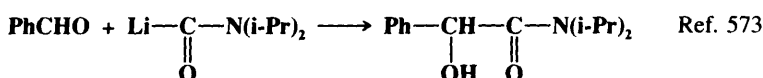
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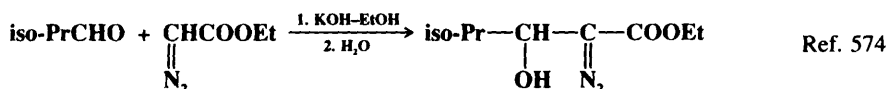
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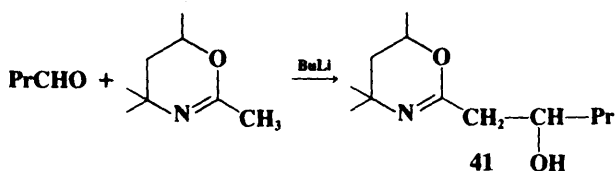
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Ref. 573



Ref. 574



Ref. 575

⁵⁶⁹Hoffmann; Rabe *Angew. Chem. Int. Ed. Engl.* **1983**, 22, 795 [*Angew. Chem.* 95, 795]; Basavaiah; Gowriswari *Tetrahedron Lett.* **1986**, 27, 2031. For a review of reactions of vinylic carbanions with aldehydes, see Drewes; Roos *Tetrahedron* **1988**, 44, 4653-4670.

⁵⁷⁰Roskamp; Pedersen *J. Am. Chem. Soc.* **1987**, 109, 6551.

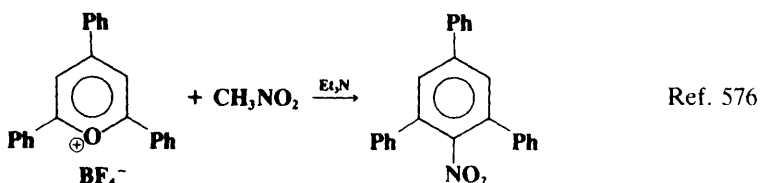
⁵⁷¹Corey; Seebach *Angew. Chem. Int. Ed. Engl.* **1965**, 4, 1075 [*Angew. Chem.* 77, 1134]. For other examples of the addition of 1,3-dithianes and similar reagents to aldehydes, ketones, and compounds containing C=N bonds, see Seebach *Synthesis* **1969**, 17-36, pp. 27-29; Corey; Crouse *J. Org. Chem.* **1968**, 33, 298; Duhamel; Duhamel; Mancelle *Bull. Soc. Chim. Fr.* **1974**, 331; Gröbel; Bürstinghaus; Seebach, *Synthesis* **1976**, 121; Meyers; Tait; Comins *Tetrahedron Lett.* **1978**, 4657; Blatcher; Warren *J. Chem. Soc., Perkin Trans. 1* **1979**, 1074; Ogura *Pure Appl. Chem.* **1987**, 59, 1033.

⁵⁷²Hünig; Marschner *Chem. Ber.* **1989**, 122, 1329.

⁵⁷³Smith; Swaminathan *J. Chem. Soc., Chem. Commun.* **1976**, 387.

⁵⁷⁴Wenkert; McPherson *J. Am. Chem. Soc.* **1972**, 94, 8084. See also Schöllkopf; Bánhidai; Frasnelli; Meyer; Beckhaus *Liebigs Ann. Chem.* **1974**, 1767.

⁵⁷⁵Meyers; Nabeya; Adickes; Fitzpatrick; Malone; Politzer *J. Am. Chem. Soc.* **1969**, 91, 764. For other examples, see Meyers; Temple *J. Am. Chem. Soc.* **1970**, 92, 6644; Meyers; Nabeya; Adickes; Politzer; Malone; Kovelesky; Nolen; Portnoy *J. Org. Chem.* **1973**, 38, 36.



We see from these examples that many of the carbon nucleophiles we encountered in Chapter 10 are also nucleophiles toward aldehydes and ketones (compare reactions **0-94** through **0-98** and **0-100**). As we saw in Chapter 10, the initial products in many of these cases, e.g., **38** through **41**, can be converted by relatively simple procedures (hydrolysis, reduction, decarboxylation, etc.) to various other products. In the reaction with terminal acetylenes,⁵⁷⁷ sodium acetylides are the most common reagents (when they are used, the reaction is often called the *Nef reaction*), but lithium,⁵⁷⁸ magnesium, and other metallic acetylides have also been used. A particularly convenient reagent is lithium acetylide-ethylenediamine complex,⁵⁷⁹ a stable, free-flowing powder that is commercially available. Alternatively, the substrate may be treated with the alkyne itself in the presence of a base, so that the acetylide is generated in situ. This procedure is called the *Favorskii reaction*, not to be confused with the Favorskii rearrangement (**8-7**).⁵⁸⁰ 1,4-Diols can be prepared by the treatment of aldehydes with dimetalloacetylides $\text{MC}\equiv\text{CM}$.⁵⁸¹

With most of these reagents the alcohol is not isolated (only the olefin) if the alcohol has a hydrogen in the proper position.⁵⁸² However, in some cases the alcohol is the major product. With suitable reactants, the Knoevenagel reaction, like the aldol (**6-39**), has been carried out diastereoselectively⁵⁸³ and enantioselectively.⁵⁸⁴ When the reactant is of the form $\text{ZCH}_2\text{Z}'$, aldehydes react much better than ketones and few successful reactions with ketones have been reported. However, it is possible to get good yields of olefin from the condensation of diethyl malonate $\text{CH}_2(\text{COOEt})_2$ with ketones, as well as with aldehydes, if the reaction is run with TiCl_4 and pyridine in THF.⁵⁸⁵ In reactions with $\text{ZCH}_2\text{Z}'$, the catalyst is most often a secondary amine (piperidine is the most common), though many other catalysts have been used. When the catalyst is pyridine (to which piperidine may or may not be added) the reaction is known as the *Doebner modification* of the Knoevenagel reaction. Alkoxides are also common catalysts.

As with **6-39**, these reactions have sometimes been performed with acid catalysts.⁵⁸⁶

⁵⁷⁶Dimroth; Berndt; Reichardt *Org. Synth.* V 1128. See also Dimroth *Angew. Chem.* **1960**, 72, 331-342; Dimroth; Wolf *Newer Methods Prep. Org. Chem.* **1964**, 3, 357-423.

⁵⁷⁷For reviews, see Ziegenbein, in *Viehe Acetylenes*; Marcel Dekker: New York, 1969, pp. 207-241; Ried *Newer Methods Prep. Org. Chem.* **1968**, 4, 95-138.

⁵⁷⁸See Midland *J. Org. Chem.* **1975**, 40, 2250, for the use of amine-free monolithium acetylide.

⁵⁷⁹Beumel; Harris *J. Org. Chem.* **1963**, 28, 2775.

⁵⁸⁰For a discussion of the mechanism of the Favorskii addition reaction, see Kondrat'eva; Potapova; Grigina; Glazunova; Nikitin *J. Org. Chem. USSR* **1976**, 12, 948.

⁵⁸¹Sudweeks; Broadbent *J. Org. Chem.* **1975**, 40, 1131.

⁵⁸²For lists of reagents (with references) that condense with aldehydes and ketones to give olefin products, see Ref. 64, pp. 167-171, 180-184. For those that give the alcohol product, see Ref. 64, pp. 575, 773, 868-871, 875, 878-880, 901, 910-911.

⁵⁸³See, for example, Trost; Florez; Jebaratnam *J. Am. Chem. Soc.* **1987**, 109, 613; Mahler; Devant; Braun *Chem. Ber.* **1988**, 121, 2035; Ronan; Marchalin; Samuel; Kagan *Tetrahedron Lett.* **1988**, 29, 6101; Barrett; Robyr; Spilling *J. Org. Chem.* **1989**, 54, 1233; Pyne; Boche *J. Org. Chem.* **1989**, 54, 2663.

⁵⁸⁴See, for example, Enders; Lotter; Maigrot; Mazaleyrat; Welvert *Nouv. J. Chim.* **1984**, 8, 747; Ito; Sawamura; Hayashi *J. Am. Chem. Soc.* **1986**, 108, 6405; Togni; Pastor *J. Org. Chem.* **1990**, 55, 1649; Pastor; Togni *Tetrahedron Lett.* **1990**, 31, 839; Sakuraba; Ushiki *Tetrahedron Lett.* **1990**, 31, 5349; Niwa; Soai *J. Chem. Soc., Perkin Trans. 1* **1990**, 937.

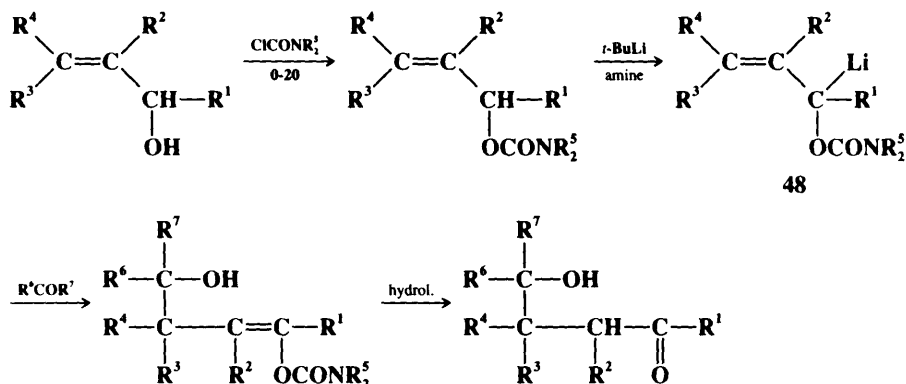
⁵⁸⁵Lehnert *Tetrahedron Lett.* **1970**, 4723, *Tetrahedron* **1972**, 28, 663, **1973**, 29, 635, *Synthesis* **1974**, 667.

⁵⁸⁶For example, see Rappoport; Patai *J. Chem. Soc.* **1962**, 731.

When the reaction is run with potassium *t*-butoxide in THF at -5°C , one obtains (after hydrolysis) the normal Knoevenagel product **45**, except that the isocyano group has been hydrated (**6-65**).⁵⁹² With the same base but with 1,2-dimethoxyethane (DME) as solvent the product is the nitrile **46**.⁵⁹³ When the ketone is treated with **44** and thallium(I) ethoxide in a 4:1 mixture of absolute ethanol and DME at room temperature, the product is a 4-ethoxy-2-oxazoline **47**.⁵⁹⁴ Since **46** can be hydrolyzed⁵⁹⁵ to a carboxylic acid⁵⁹² and **47** to an α -hydroxy aldehyde,⁵⁹⁴ this versatile reaction provides a means for achieving the conversion of RCOR' to $\text{RCHR}'\text{COOH}$, $\text{RCHR}'\text{CN}$, or $\text{RCR}'(\text{OH})\text{CHO}$. The conversions to $\text{RCHR}'\text{COOH}$ and to $\text{RCHR}'\text{CN}$ ⁵⁹⁶ have also been carried out with certain aldehydes ($\text{R}' = \text{H}$).

3. Aldehydes and ketones RCOR' react with α -methoxyvinyl lithium $\text{CH}_2=\text{C}(\text{Li})\text{OMe}$ to give hydroxy enol ethers $\text{RR}'\text{C}(\text{OH})\text{C}(\text{OMe})=\text{CH}_2$, which are easily hydrolyzed to acyloins $\text{RR}'\text{C}(\text{OH})\text{COMe}$.⁵⁹⁷ In this reaction, the $\text{CH}_2=\text{C}(\text{Li})\text{OMe}$ is a synthon for the unavailable $\text{CH}_3-\overset{\ominus}{\text{C}}=\text{O}$ ion.⁵⁹⁸ The reagent also reacts with esters RCOOR' to give $\text{RC}(\text{OH})(\text{COMe}=\text{CH}_2)_2$. A synthon for the $\text{Ph}-\overset{\ominus}{\text{C}}=\text{O}$ ion is $\text{Ph}-\overset{\ominus}{\text{C}}(\text{CN})\text{OSiMe}_3$, which adds to aldehydes and ketones RCOR' to give, after hydrolysis, the α -hydroxy ketones $\text{RR}'\text{C}(\text{OH})\text{COPh}$.⁵⁹⁹

4. Lithiated allylic carbamates (**48**) (prepared as shown) react with aldehydes or ketones ($\text{R}^6\text{COR}'$), in a reaction accompanied by an allylic rearrangement, to give (after hydrolysis) γ -hydroxy aldehydes or ketones.⁶⁰⁰ The reaction is called *the homoaldol reaction*, since the



product is a homolog of the product of **6-39**. The reaction has been performed enantioselectively.⁶⁰¹

⁵⁹²Schöllkopf; Schröder; Blume *Liebigs Ann. Chem.* **1972**, 766, 130; Schöllkopf; Schröder *Angew. Chem. Int. Ed. Engl.* **1972**, 11, 311 [*Angew. Chem.* **84**, 289].

⁵⁹³Oldenziel; van Leusen; van Leusen *J. Org. Chem.* **1977**, 42, 3114.

⁵⁹⁴Oldenziel; van Leusen *Tetrahedron Lett.* **1974**, 163, 167. For conversions to α,β -unsaturated ketones and diketones, see, respectively, Moskal; van Leusen *Tetrahedron Lett.* **1984**, 25, 2585; van Leusen; Oosterwijk; van Echten; van Leusen *Recl. Trav. Chim. Pays-Bas* **1985**, 104, 50.

⁵⁹⁵**45** can also be converted to a nitrile; see **7-38**.

⁵⁹⁶van Leusen; Oomkes *Synth. Commun.* **1980**, 10, 399.

⁵⁹⁷Baldwin; Höfle; Lever *J. Am. Chem. Soc.* **1974**, 96, 7125. For a similar reaction, see Tanaka; Nakai; Ishikawa *Tetrahedron Lett.* **1978**, 4809.

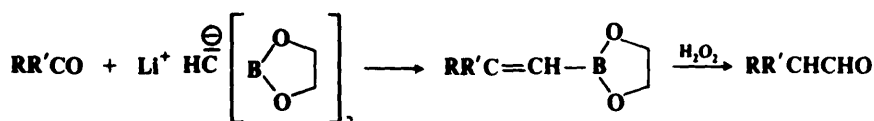
⁵⁹⁸For a synthon for the COCOOEt^- ion, see Reetz; Heimbach; Schwellnus *Tetrahedron Lett.* **1984**, 25, 511.

⁵⁹⁹Hünig; Wehner *Synthesis* **1975**, 391.

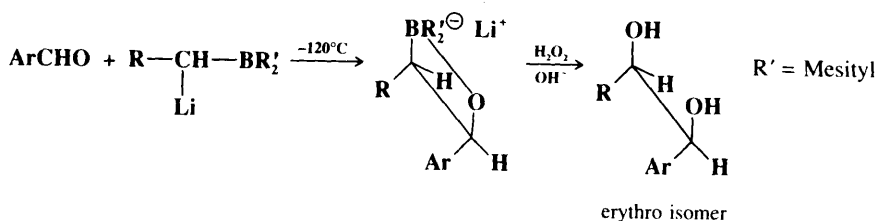
⁶⁰⁰For a review, see Hoppe *Angew. Chem. Int. Ed. Engl.* **1984**, 23, 932-948 [*Angew. Chem.* **96**, 930-946].

⁶⁰¹Krämer; Hoppe *Tetrahedron Lett.* **1987**, 28, 5149.

5. A procedure for converting an aldehyde or ketone $RR'CO$ to the homologous aldehyde $RR'CHCHO$ consists of treating the substrate with lithium bis(ethylenedioxyboryl)methide, followed by oxidation with aqueous H_2O_2 .⁶⁰²

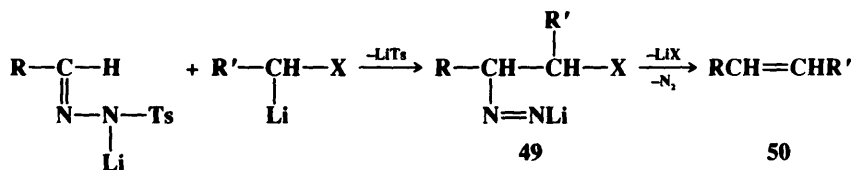


6. A method for the stereoselective synthesis of 1,2-diols consists of treating aromatic aldehydes with carbanions stabilized by an adjacent dimesitylboron group at $-120^\circ C$, followed by oxidation with H_2O_2 .⁶⁰³



The erythro-threo ratio of the product was greater than 9:1.

7. The lithium salt of an active hydrogen compound adds to the lithium salt of the tosylhydrazone of an aldehyde to give product **49**. If $X = CN$, SPh , or SO_2R , **49** spontaneously loses N_2 and LiX to give the alkene **50**. The entire process is done in one reaction



vessel: The active hydrogen compound is mixed with the tosylhydrazone and the mixture is treated with $(i\text{-}Pr)_2NLi$ to form both salts at once.⁶⁰⁴ This process is another alternative to the Wittig reaction for forming double bonds.

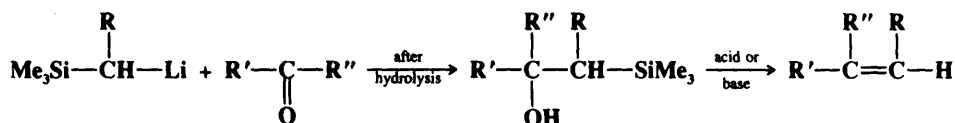
OS I, 181, 290, 413; II, 202; III, 39, 165, 317, 320, 377, 385, 399, 416, 425, 456, 479, 513, 586, 591, 597, 715, 783; IV, 93, 210, 221, 234, 293, 327, 387, 392, 408, 441, 463, 471, 549, 573, 730, 731, 777; V, 130, 381, 572, 585, 627, 833, 1088, 1128; VI, 41, 95, 442, 598, 683; VII, 50, 108, 142, 276, 381, 386, 456; **66**, 220; **67**, 205; **68**, 14, 64; **69**, 19, 31. Also see OS III, 395; V, 450.

⁶⁰²Matteson; Moody *J. Org. Chem.* **1980**, *45*, 1091. For other methods of achieving this conversion, see Corey; Tius *Tetrahedron Lett.* **1980**, *21*, 3535, 1980; Huang; Zhang *Synthesis* **1989**, 42.

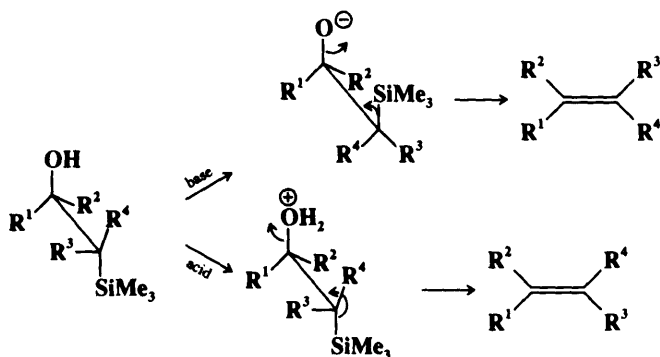
⁶⁰³Pelter; Buss; Pitchford *Tetrahedron Lett.* **1985**, *26*, 5093.

⁶⁰⁴Vedejs; Dolphin; Stolle *J. Am. Chem. Soc.* **1979**, *101*, 249.

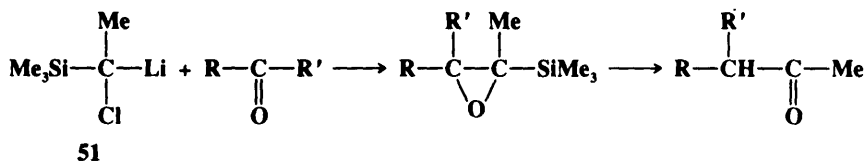
6-42 The Peterson Olefination Reaction Alkylidene-de-oxo-bisubstitution



In the *Peterson olefination reaction*⁶⁰⁵ the lithio (or sometimes magnesio) derivative of a trialkylsilane adds to an aldehyde or ketone to give a β -hydroxysilane, which spontaneously eliminates water, or can be made to do so by treatment with acid or base, to produce an olefin. This reaction is still another alternative to the Wittig reaction, and is sometimes called the *silyl-Wittig reaction*.⁶⁰⁶ R can also be a COOR group, in which case the product is an α,β -unsaturated ester,⁶⁰⁷ or an SO₂Ph group, in which case the product is a vinylic sulfone.⁶⁰⁸ The stereochemistry of the product can often be controlled by whether an acid or a base is used to achieve elimination. Use of a base generally gives syn elimination (Ei mechanism, see p. 1006), while an acid usually results in anti elimination (E2 mechanism, see p. 983).⁶⁰⁹



When aldehydes or ketones are treated with reagents of the form **51**, the product is an epoxy silane (**6-61**), which can be hydrolyzed to a methyl ketone.⁶¹⁰ For aldehydes, this is a method for converting RCHO to a methyl ketone RCH₂COMe.



⁶⁰⁵Peterson *J. Org. Chem.* **1968**, *33*, 780. For reviews, see Ager *Org. React.* **1990**, *38*, 1-223; *Synthesis* **1984**, 384-398; Colvin *Silicon Reagents in Organic Synthesis*; Academic Press: New York, 1988, pp. 63-75; Weber *Silicon Reagents for Organic Synthesis*; Springer: New York, 1983, pp. 58-78; Magnus *Aldrichimica Acta* **1980**, *13*, 43-51; Chan *Acc. Chem. Res.* **1977**, *10*, 442-448. For a list of references, see Ref. 64, pp. 178-180. For books and reviews on silicon reagents in organic synthesis, see Chapter 12, Ref. 286.

⁶⁰⁶For discussions of the mechanism, see Bassindale; Ellis; Lau; Taylor *J. Chem. Soc., Perkin Trans. 2* **1986**, 593; Hudrlík; Agwarambo; Hudrlík *J. Org. Chem.* **1989**, *54*, 5613.

⁶⁰⁷Hartzell; Sullivan; Rathke *Tetrahedron Lett.* **1974**, 1403; Shimoji; Taguchi; Oshima; Yamamoto; Nozaki *J. Am. Chem. Soc.* **1974**, *96*, 1620; Chan; Moreland *Tetrahedron Lett.* **1978**, 515; Strekowski; Visnick; Battiste *Tetrahedron Lett.* **1984**, *25*, 5603.

⁶⁰⁸Craig; Ley; Simpkins; Whitham; Prior *J. Chem. Soc., Perkin Trans. 1* **1985**, 1949.

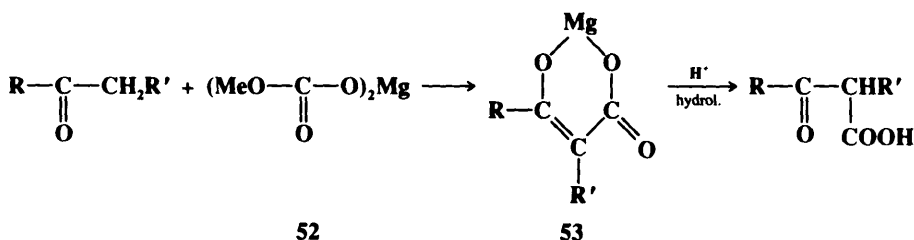
⁶⁰⁹See Colvin, Ref. 605, pp. 65-69.

⁶¹⁰Cooke; Roy; Magnus *Organometallics* **1982**, *1*, 893.

The reagents Me_3SiCHRM ($\text{M} = \text{Li}$ or Mg) are often prepared from $\text{Me}_3\text{SiCHRCI}$ ⁶¹¹ (by **2-38** or **2-39**), but they have also been made by **2-21** and by other procedures.⁶¹²

There are no references in *Organic Syntheses*, but see OS **69**, **89**, for a related reaction.

6-43 The Addition of Active Hydrogen Compounds to CO_2 and CS_2
 α -Acylalkyl-de-methoxy-substitution (overall reaction)



Ketones of the form RCOCH_3 and $\text{RCOCH}_2\text{R}'$ can be carboxylated indirectly by treatment with magnesium methyl carbonate **52**.⁶¹³ Because formation of the chelate **53** provides the driving force of the reaction, carboxylation cannot be achieved at a disubstituted α position. The reaction has also been performed on CH_3NO_2 and compounds of the form RCH_2NO_2 ⁶¹⁴ and on certain lactones.⁶¹⁵ Direct carboxylation has been reported in a number of instances. Ketones have been carboxylated in the α position to give β -keto acids.⁶¹⁶ The base here was lithium 4-methyl-2,6-di-*t*-butylphenoxide.

Ketones $\text{RCOCH}_2\text{R}'$ (as well as other active hydrogen compounds) undergo base-catalyzed addition to CS_2 ⁶¹⁷ to give a dianion intermediate $\text{RCOCHR}'\text{CSS}^-$, which can be dialkylated with a halide $\text{R}''\text{X}$ to produce α -dithiomethylene ketones $\text{RCOCR}'=\text{C}(\text{SR}'')_2$.⁶¹⁸ Compounds of the form $\text{ZCH}_2\text{Z}'$ also react with bases and CS_2 to give analogous dianions.⁶¹⁹

OS VII, 476. See also OS **65**, 17.

6-44 The Perkin Reaction
 α -Carboxyalkylidene-de-oxo-bisubstitution



⁶¹¹For a review of these reagents, see Anderson *Synthesis* **1985**, 717-734.

⁶¹²See, for example, Ager *J. Chem. Soc., Perkin Trans. I* **1986**, 183; Barrett; Flygare *J. Org. Chem.* **1991**, 56, 638.

⁶¹³Stiles *J. Am. Chem. Soc.* **1959**, 81, 2598; Ann. N.Y. Acad. Sci. **1960**, 88, 332; Crombie; Hemesley; Pattenden *Tetrahedron Lett.* **1968**, 3021.

⁶¹⁴Finkbeiner; Stiles *J. Am. Chem. Soc.* **1963**, 85, 616; Finkbeiner; Wagner *J. Org. Chem.* **1963**, 28, 215.

⁶¹⁵Martin; Watts; Johnson *Chem. Commun.* **1970**, 27.

⁶¹⁶Corey; Chen *J. Org. Chem.* **1973**, 38, 4086; Tirpak; Olsen; Rathke *J. Org. Chem.* **1985**, 50, 4877. For an enantioselective version, see Hogeveen; Menge *Tetrahedron Lett.* **1986**, 27, 2767.

⁶¹⁷For reviews of the reactions of CS_2 with carbon nucleophiles, see Ref. 106, pp. 120-225; Yokoyama; Imamoto *Synthesis* **1984**, 797-824, pp. 797-804.

⁶¹⁸See, for example Corey; Chen *Tetrahedron Lett.* **1973**, 3817.

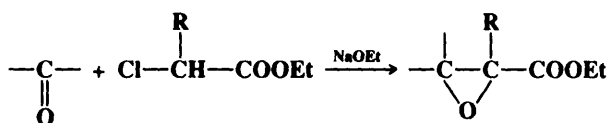
⁶¹⁹Jensen; Dalggaard; Lawesson *Tetrahedron* **1974**, 30, 2413; Konen; Pfeffer; Silbert *Tetrahedron* **1976**, 32, 2507, and references cited in these papers.

The condensation of aromatic aldehydes with anhydrides is called the *Perkin reaction*.⁶²⁰ When the anhydride has two α hydrogens (as shown), dehydration always occurs; the β -hydroxy acid salt is never isolated. In some cases, anhydrides of the form $(R_2CHCO)_2O$ have been used, and then the hydroxy compound is the product since dehydration cannot take place. The base in the Perkin reaction is nearly always the salt of the acid corresponding to the anhydride. Although the Na and K salts have been most frequently used, higher yields and shorter reaction times have been reported for the Cs salt.⁶²¹ Besides aromatic aldehydes, their vinylogs $ArCH=CHCHO$ also give the reaction. Otherwise, the reaction is not suitable for aliphatic aldehydes.⁶²²

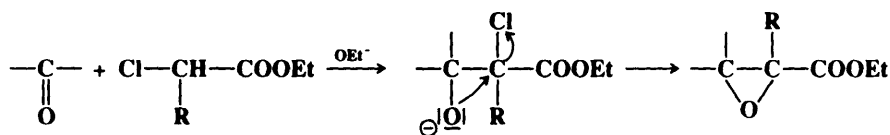
OS I, 398; II, 61, 229; III, 426.

6-45 Darzens Glycidic Ester Condensation

(2 + 1)OC,CC-cyclo- α -Alkoxy-carbonylmethylene-addition



Aldehydes and ketones condense with α -halo esters in the presence of bases to give α,β -epoxy esters, called *glycidic esters*. This is called the *Darzens condensation*.⁶²³ The reaction consists of an initial Knoevenagel-type reaction (6-41), followed by an internal S_N2 reaction (0-13).⁶²⁴



Although the intermediate halo alkoxide is generally not isolated, it has been done, not only with α -fluoro esters (since fluorine is such a poor leaving group in nucleophilic substitutions) but also with α -chloro esters.⁶²⁵ This is only one of several types of evidence that rule out a carbene intermediate.⁶²⁶ Sodium ethoxide is often used as the base, though other bases, including sodium amide, are sometimes used. Aromatic aldehydes and ketones give good yields, but aliphatic aldehydes react poorly. However, the reaction can be made to give good yields (~80%) with simple aliphatic aldehydes as well as with aromatic aldehydes and ketones by treatment of the α -halo ester with the base lithium bis(trimethylsilyl)amide $\text{LiN}(\text{SiMe}_3)_2$ in THF at -78°C (to form the conjugate base of the ester) and addition of the aldehyde or ketone to this solution.⁶²⁷ If a preformed dianion of an α -halo carboxylic

⁶²⁰For a review, see Johnson, *Org. React.* **1942**, *I*, 210-266.

⁶²¹Koepp; *Vögtle Synthesis* **1987**, 177.

⁶²²Crawford; *Little J. Chem. Soc.* **1959**, 722.

⁶²³For a review, see Berti *Top. Stereochem.* **1973**, *7*, 93-251, pp. 210-218.

⁶²⁴For discussions of the mechanism of the reaction, and especially of the stereochemistry, see Roux-Schmitt; Seyden-Penne; Wolfe *Tetrahedron* **1972**, *28*, 4965; Bansal; Sethi *Bull. Chem. Soc. Jpn.* **1980**, *53*, 1197.

⁶²⁵Ballester; Pérez-Blanco *J. Org. Chem.* **1958**, *23*, 652; Martynov; Titov *J. Gen. Chem. USSR* **1960**, *30*, 4072, **1962**, *32*, 716, **1963**, *33*, 1350, **1964**, *34*, 2139; Elkik; Francesch *Bull. Soc. Chim. Fr.* **1973**, 1277, 1281.

⁶²⁶Another, based on the stereochemistry of the products, is described by Zimmerman; Ahramjian *J. Am. Chem. Soc.* **1960**, *82*, 5459.

⁶²⁷Borch *Tetrahedron Lett.* **1972**, 3761.

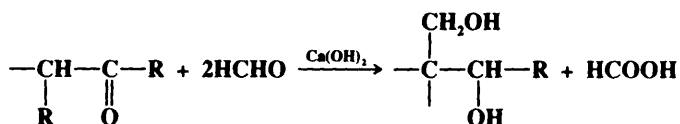
acid $\text{Cl}-\overset{\ominus}{\text{C}}\text{R}-\text{COO}^\ominus$ is used instead, α,β -epoxy acids are produced directly.⁶²⁸ The Darzens reaction has also been carried out on α -halo ketones, α -halo nitriles,⁶²⁹ α -halo sulfoxides⁶³⁰ and sulfones,⁶³¹ α -halo N,N-disubstituted amides,⁶³² α -halo ketimines,⁶³³ and even on allylic⁶³⁴ and benzylic halides. Phase transfer catalysis has been used.⁶³⁵ The Darzens reaction has been performed enantioselectively, by coupling optically active α -bromo- β -hydroxy esters with aldehydes.^{635a}

Glycidic esters can easily be converted to aldehydes (2-40). The reaction has been extended to the formation of analogous aziridines by treatment of an imine with an α -halo ester or an α -halo N,N-disubstituted amide and *t*-BuOK in the solvent 1,2-dimethoxyethane.⁶³⁶ However, yields were not high. Acid-catalyzed Darzens reactions have also been reported.⁶³⁷ See also 6-61.

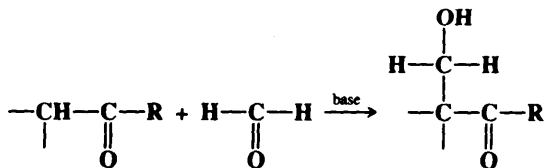
OS III, 727; IV, 459, 649.

6-46 Tollens' Reaction

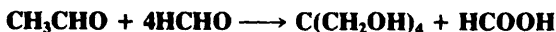
O-Hydro-C-(β -hydroxyalkyl)-addition



In *Tollens' reaction* an aldehyde or ketone containing an α hydrogen is treated with formaldehyde in the presence of Ca(OH)_2 or a similar base. The first step is a mixed aldol reaction (6-39).



The reaction can be stopped at this point, but more often a second mole of formaldehyde is permitted to reduce the newly formed aldol to a 1,3-diol, in a crossed Cannizzaro reaction (9-69). If the aldehyde or ketone has several α hydrogens, they can all be replaced. An important use of the reaction is to prepare pentaerythritol from acetaldehyde:



⁶²⁸Johnson; Bade *J. Org. Chem.* **1982**, 47, 1205.

⁶²⁹See White; Wu *J. Chem. Soc., Chem. Commun.* **1974**, 988.

⁶³⁰Sato; Sugimoto; Itoh; Yamakawa *Tetrahedron Lett.* **1989**, 30, 1083.

⁶³¹Vogt; Tavares *Can. J. Chem.* **1969**, 47, 2875.

⁶³²Tung; Speziale; Frazier *J. Org. Chem.* **1963**, 28, 1514.

⁶³³Mauzé *J. Organomet. Chem.* **1979**, 170, 265.

⁶³⁴Sulmon; De Kimpe; Schamp; Declercq; Tinant *J. Org. Chem.* **1988**, 53, 4457.

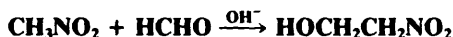
⁶³⁵See Jończyk; Kwast; Makosza *J. Chem. Soc., Chem. Commun.* **1977**, 902; Gladiali; Soccolini *Synth. Commun.* **1982**, 12, 355; Starks; Liotta *Phase Transfer Catalysis*; Academic Press: New York, 1978, pp. 197-198.

^{635a}Corey; Choi *Tetrahedron Lett.* **1991**, 32, 2857.

⁶³⁶Deyrup *J. Org. Chem.* **1969**, 34, 2724.

⁶³⁷Sipos; Schöbel; Balásperi *J. Chem. Soc. C* **1970**, 1154; Sipos; Schöbel; Sirokmán *J. Chem. Soc., Perkin Trans. 2* **1975**, 805.

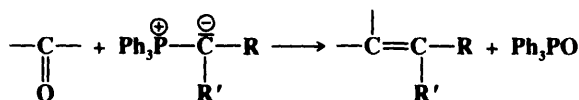
When aliphatic nitro compounds are used instead of aldehydes or ketones, no reduction occurs, and the reaction is essentially a Knoevenagel reaction, though it is usually also called a Tollens' reaction:



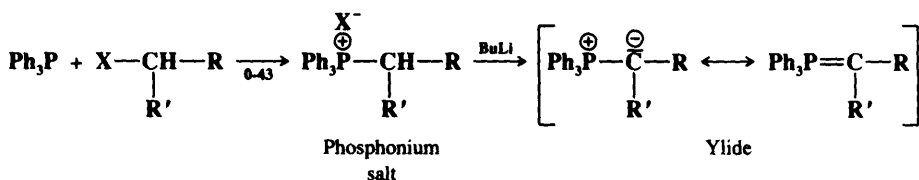
OS I, 425; IV, 907; V, 833.

6-47 The Wittig Reaction

Alkylidene-de-oxo-bisubstitution



In the *Wittig reaction* an aldehyde or ketone is treated with a *phosphorus ylide* (also called a *phosphorane*) to give an olefin.⁶³⁸ Phosphorus ylides are usually prepared by treatment of a phosphonium salt with a base,⁶³⁹ and phosphonium salts are usually prepared from the phosphine and an alkyl halide (0-43):



The overall sequence of three steps may be called the Wittig reaction, or only the final step. Phosphonium salts are also prepared by addition of phosphines to Michael olefins (like 5-7) and in other ways. The phosphonium salts are most often converted to the ylides by treatment with a strong base such as butyllithium, sodium amide,⁶⁴⁰ sodium hydride, or a sodium alkoxide, though weaker bases can be used if the salt is acidic enough. For $(\text{Ph}_3\text{P}^+)_2\text{CH}_2$, sodium carbonate is a strong enough base.⁶⁴¹ When the base used does not contain lithium, the ylide is said to be prepared under "salt-free" conditions.⁶⁴²

⁶³⁸For a general treatise, see Cadogan *Organophosphorus Reagents in Organic Synthesis*; Academic Press: New York, 1979. For a monograph on the Wittig reaction, see Johnson *Ylid Chemistry*; Academic Press: New York, 1966. For reviews, see Maryanoff; Reitz *Chem. Rev.* **1989**, *89*, 863-927; Bestmann; Vostrowsky *Top. Curr. Chem.* **1983**, *109*, 85-164; Pommer; Thieme *Top. Curr. Chem.* **1983**, *109*, 165-188; Pommer *Angew. Chem. Int. Ed. Engl.* **1977**, *16*, 423-429 [*Angew. Chem.* **89**, 437-443]; Maercker *Org. React.* **1965**, *14*, 270-490; House, Ref. 180, pp. 682-709; Lowe *Chem. Ind. (London)* **1970**, 1070-1079; Bergelson; Shemyakin, in Patai, Ref. 472, pp. 295-340. *Newer Methods Prep. Org. Chem.* **1968**, *5*, 154-175. For related reviews, see Tyuleneva; Rokhlin; Knunyants *Russ. Chem. Rev.* **1981**, *50*, 280-290; Starks; Liotta, Ref. 635, pp. 288-297; Weber; Gokel *Phase Transfer Catalysis in Organic Synthesis*; Springer: New York, 1977; pp. 234-241; Zbiral *Synthesis* **1974**, 775-797; Bestmann *Bull. Soc. Chim. Fr.* **1971**, 1619-1634. *Angew. Chem. Int. Ed. Engl.* **1965**, *4*, 583-587, 645-660, 830-838 [*Angew. Chem.* **77**, 609-613, 651-666, 850-858], *Newer Methods Prep. Org. Chem.* **1968**, *5*, 1-60; Horner *Fortschr. Chem. Forsch.* **1966**, *7*, 1-61. For a historical background, see Wittig, *Pure Appl. Chem.* **1964**, *9*, 245-254. For a list of reagents and references for the Wittig and related reactions, see Ref. 64, pp. 173-178.

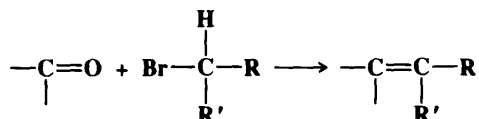
⁶³⁹When phosphonium fluorides are used, no base is necessary, as these react directly with the substrate to give the olefin: Schiemenz; Becker; Stöckigt *Chem. Ber.* **1970**, *103*, 2077.

⁶⁴⁰For a convenient method of doing this that results in high yields, see Schlosser; Schaub *Chimia* **1982**, *36*, 396.

⁶⁴¹Ramirez; Pilot; Desai; Smith; Hansen; McKelvie *J. Am. Chem. Soc.* **1967**, *89*, 6273.

⁶⁴²Bestmann *Angew. Chem. Int. Ed. Engl.* **1965**, *4*, 586 [*Angew. Chem.* **77**, 612].

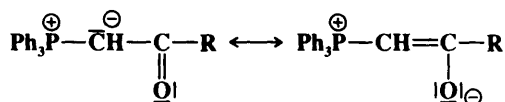
In the overall Wittig reaction, an olefin is formed from the aldehyde or ketone and an alkyl halide in which the halogen-bearing carbon contains at least one hydrogen:



This result is similar to that obtained in the Reformatsky reaction (6-30), but this is more general since no ester or other group is required to be α to the halogen. Another important advantage of the Wittig reaction is that the *position* of the new double bond is always certain, in contrast to the result in the Reformatsky reaction and in most of the base-catalyzed condensations (6-39 to 6-46). Examples of this are given below.

The reaction is very general. The aldehyde or ketone may be aliphatic, alicyclic, or aromatic (including diaryl ketones); it may contain double or triple bonds; it may contain various functional groups, such as OH, OR, NR_2 , aromatic nitro or halo, acetal, or even ester groups.⁶⁴³ Double or triple bonds *conjugated* with the carbonyl also do not interfere, the attack being at the $\text{C}=\text{O}$ carbon.

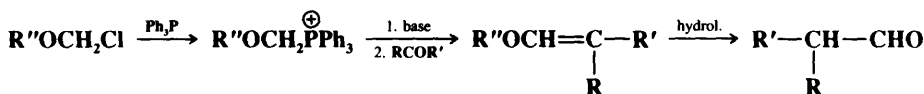
The phosphorus ylide may also contain double or triple bonds and certain functional groups. Simple ylides ($\text{R}, \text{R}' = \text{hydrogen or alkyl}$) are highly reactive, reacting with oxygen, water, hydrohalic acids, and alcohols, as well as carbonyl compounds and carboxylic esters, so the reaction must be run under conditions where these materials are absent. When an electron-withdrawing group, e.g., COR, CN, COOR, CHO, is present in the α position, the ylides are much more stable, because the charge on the carbon is spread by resonance:



These ylides react readily with aldehydes, but slowly or not at all with ketones.⁶⁴⁴ In extreme cases, e.g., **54**, the ylide does not react with ketones *or* aldehydes. Besides these groups,



the ylide may contain one or two α halogens⁶⁴⁵ or an α OR or OAr group. In the latter case the product is an enol ether, which can be hydrolyzed (0-6) to an aldehyde,⁶⁴⁶ so that



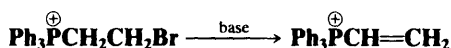
⁶⁴³Although phosphorus ylides also react with esters, that reaction is too slow to interfere: Greenwald; Chaykovsky; Corey *J. Org. Chem.* **1963**, 28, 1128.

⁶⁴⁴For successful reactions of stabilized ylides with ketones, under high pressure, see Isaacs; El-Din *Tetrahedron Lett.* **1987**, 28, 2191. See also Dauben; Takasugi *Tetrahedron Lett.* **1987**, 4377.

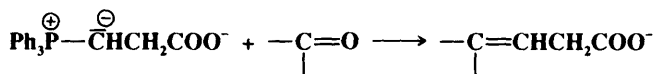
⁶⁴⁵Seyferth; Grim; Read *J. Am. Chem. Soc.* **1960**, 82, 1510, **1961**, 83, 1617; Seyferth; Heeren; Singh; Grim; Hughes *J. Organomet. Chem.* **1966**, 5, 267; Schlosser; Zimmermann *Synthesis* **1969**, 75; Burton; Greenlimb *J. Fluorine Chem.* **1974**, 3, 447; Smithers *J. Org. Chem.* **1978**, 43, 2833; Miyano; Izumi; Fujii; Ohno; Hashimoto *Bull. Chem. Soc. Jpn.* **1979**, 52, 1197; Stork; Zhao *Tetrahedron Lett.* **1989**, 30, 2173.

⁶⁴⁶For references to the use of the Wittig reaction to give enol ethers or enol thioethers, which are then hydrolyzed, see Ref. 64, pp. 715-716, 726.

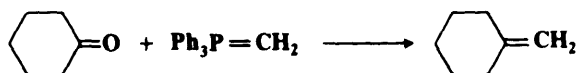
this reaction is a means of achieving the conversion $\text{RCOR}' \rightarrow \text{RR}'\text{CHCHO}$.⁶⁴⁷ However, the ylide may not contain an α nitro group. If the phosphonium salt contains a potential leaving group, such as Br or OMe, in the β position, treatment with a base gives elimination, instead of the ylide:



However, a β COO^- group may be present, and the product is a β,γ -unsaturated acid:⁶⁴⁸



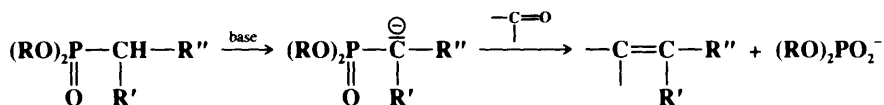
This is the only convenient way to make these compounds, since elimination by any other route gives the thermodynamically more stable α,β -unsaturated isomers. This is an illustration of the utility of the Wittig method for the specific location of a double bond. Another illustration is the conversion of cyclohexanones to olefins containing double bonds, e.g.,⁶⁴⁹



Still another example is the easy formation of anti-Bredt bicycloalkenones⁶⁵⁰ (see p. 160). As indicated above, α,α' -dihalophosphoranes can be used to prepare 1,1-dihaloalkenes. Another way to prepare such compounds⁶⁵¹ is to treat the carbonyl compound with a mixture of CX_4 ($\text{X} = \text{Cl}, \text{Br}, \text{or I}$) and triphenylphosphine, either with or without the addition of zinc dust (which allows less Ph_3P to be used).⁶⁵²

The Wittig reaction has been carried out with polymer-supported ylides⁶⁵³ (see p. 421).

Ylides are usually prepared from triphenylphosphine, but other triarylphosphines,⁶⁵⁴ trialkylphosphines,⁶⁵⁵ and triphenylarsine⁶⁵⁶ have also been used. The Wittig reaction has also been carried out with other types of ylides, the most important being prepared from phosphonates:⁶⁵⁷



⁶⁴⁷For other methods of achieving this conversion via Wittig-type reactions, see Ceruti; Degani; Fochi *Synthesis* **1987**, 79; Moskal; van Leusen *Recl. Trav. Chim. Pays-Bas* **1987**, 106, 137; Doad *J. Chem. Res. (S)* **1987**, 370.

⁶⁴⁸Corey; McCormick; Swensen *J. Am. Chem. Soc.* **1964**, 86, 1884.

⁶⁴⁹Wittig; Schöllkopf *Chem. Ber.* **1954**, 87, 1318.

⁶⁵⁰Bestmann; Schade *Tetrahedron Lett.* **1982**, 23, 3543.

⁶⁵¹For a list of references to the preparation of haloalkenes by Wittig reactions, with references, see Ref. 64, pp. 376-377.

⁶⁵²See, for example, Rabinowitz; Marcus *J. Am. Chem. Soc.* **1962**, 84, 1312; Ramirez; Desai; McKelvie *J. Am. Chem. Soc.* **1962**, 84, 1745; Corey; Fuchs *Tetrahedron Lett.* **1972**, 3769; Posner; Loomis; Sawaya *Tetrahedron Lett.* **1975**, 1373; Suda; Fukushima *Tetrahedron Lett.* **1981**, 22, 759; Gaviña; Luis; Ferrer; Costero; Marco *J. Chem. Soc., Chem. Commun.* **1985**, 296; Li; Alper *J. Org. Chem.* **1986**, 51, 4354.

⁶⁵³Bernard; Ford; Nelson *J. Org. Chem.* **1983**, 48, 3164.

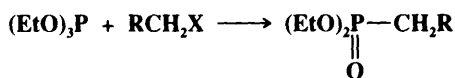
⁶⁵⁴Schiemenz; Thobe *Chem. Ber.* **1966**, 99, 2663.

⁶⁵⁵For example, see Johnson; LaCount *Tetrahedron* **1960**, 9, 130; Bestmann; Kratzer *Chem. Ber.* **1962**, 95, 1894.

⁶⁵⁶An arsenic ylide has been used in a catalytic version of the Wittig reaction; that is, the R_3AsO product is constantly regenerated to produce more arsenic ylide: Shi; Wang; Wang; Huang *J. Org. Chem.* **1989**, 54, 2027.

⁶⁵⁷Horner; Hoffmann; Wippel *Chem. Ber.* **1958**, 91, 61; Horner; Hoffmann; Wippel; Klahre *Chem. Ber.* **1959**, 92, 2499; Wadsworth; Emmons *J. Am. Chem. Soc.* **1961**, 83, 1733.

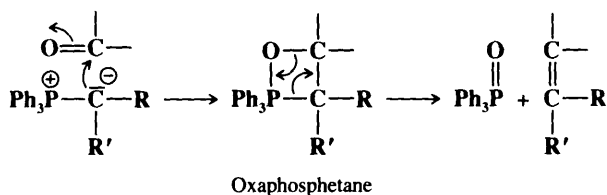
This method, sometimes called the *Horner–Emmons*, *Wadsworth–Emmons*, or *Wittig–Horner reaction*,⁶⁵⁸ has several advantages over the use of phosphoranes.⁶⁵⁹ These ylides are more reactive than the corresponding phosphoranes, and when R' is an electron-withdrawing group, these compounds often react with ketones that are inert to phosphoranes. In addition, the phosphorus product is a phosphate ester and hence soluble in water, unlike Ph₃PO, which makes it easy to separate it from the olefin product. Phosphonates are also cheaper than phosphonium salts and can easily be prepared by the *Arbuzov reaction*.⁶⁶⁰



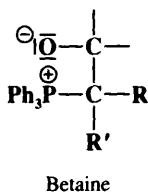
Ylides formed from phosphinoylides $\text{Ar}_2\text{PCHRR}'$, phosphonic acid bisamides

$(\text{R}'_2\text{N})_2\text{POCHRR}'$,⁶⁶¹ and alkyl phosphonothionates $(\text{MeO})_2\text{PSCHRR}'$ ⁶⁶² share some of these advantages. Phosphonates $\text{Ph}_2\text{POCH}_2\text{NR}'_2$ react with aldehydes or ketones R^2COR^3 to give good yields of enamines $\text{R}^2\text{R}^3\text{C}=\text{CHNR}'_2$.⁶⁶³

The mechanism⁶⁶⁴ of the key step of the Wittig reaction is as follows:⁶⁶⁵



For many years it was assumed that a diionic compound, called a *betaine*, is an intermediate on the pathway from the starting compounds to the oxaphosphetane, and in fact it may be



⁶⁵⁸For reviews, see Wadsworth *Org. React.* **1977**, 25, 73-253; Stec *Acc. Chem. Res.* **1983**, 16, 411-417; Walker, in Cadogan, Ref. 638, pp. 156-205; Dombrovskii; Dombrovskii *Russ. Chem. Rev.* **1966**, 35, 733-741; Boutagy; Thomas *Chem. Rev.* **1974**, 74, 87-99.

⁶⁵⁹For a convenient method of carrying out this reaction, see Seguinéau; Villieras *Tetrahedron Lett.* **1988**, 29, 477, and other papers in this series.

⁶⁶⁰Also known as the *Michaelis–Arbuzov rearrangement*. For reviews, see Petrov; Dogadina; Ionin; Garibina; Leonov *Russ. Chem. Rev.* **1983**, 52, 1030-1035; Bhattacharya; Thyagarajan *Chem. Rev.* **1981**, 81, 415-430. For related reviews, see Shokol; Kozhushko *Russ. Chem. Rev.* **1985**, 53, 98-104; Brill; Landon *Chem. Rev.* **1984**, 84, 577-585.

⁶⁶¹Corey; Kwiatkowski *J. Am. Chem. Soc.* **1968**, 90, 6816; Corey; Cane *J. Org. Chem.* **1969**, 34, 3053.

⁶⁶²Corey; Kwiatkowski *J. Am. Chem. Soc.* **1966**, 88, 5654.

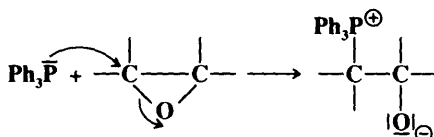
⁶⁶³Broekhof; van der Gen *Recl. Trav. Chim. Pays-Bas* **1984**, 103, 305; Broekhof; van Elburg; Hoff; van der Gen *Recl. Trav. Chim. Pays-Bas* **1984**, 103, 317.

⁶⁶⁴For a review of the mechanism, see Cockerill; Harrison, Ref. 209, pp. 232-240. For a thorough discussion, see Vedejs; Marth *J. Am. Chem. Soc.* **1988**, 110, 3948.

⁶⁶⁵It has been contended that another mechanism, involving single electron transfer, may be taking place in some cases: Olah; Krishnamurthy *J. Am. Chem. Soc.* **1982**, 104, 3987; Yamataka; Nagareda; Hanafusa; Nagase *Tetrahedron Lett.* **1989**, 30, 7187. A diradical mechanism has also been proposed for certain cases: Ward; McEwen *J. Org. Chem.* **1990**, 55, 493.

so, but there is little or no evidence for it,⁶⁶⁶ though many attempts have been made to find it. "Betaine" precipitates have been isolated in certain Wittig reactions,⁶⁶⁷ but these are betaine-lithium halide adducts, and might just as well have been formed from the oxaphosphetane as from a true betaine.⁶⁶⁸ In contrast, there is much evidence for the presence of the oxaphosphetane intermediates, at least with unstable ylides. For example, ³¹P nmr spectra taken of the reaction mixtures at low temperatures⁶⁶⁹ are compatible with an oxaphosphetane structure that persists for some time but not with a tetracoordinated phosphorus species. Since a betaine, an ylide, and a phosphine oxide all have tetracoordinated phosphorus, these species could not be causing the spectra, leading to the conclusion that an oxaphosphetane intermediate is present in the solution. In certain cases oxaphosphetanes have been isolated.⁶⁷⁰ It has even been possible to detect *cis* and *trans* isomers of the intermediate oxaphosphetanes by nmr spectroscopy.⁶⁷¹ According to this mechanism, an optically active phosphonium salt $RR'R''P^{\oplus}CHR_2$ should retain its configuration all the way through the reaction, and it should be preserved in the phosphine oxide $RR'R''PO$. This has been shown to be the case.⁶⁷²

The proposed betaine intermediates can be formed, in a completely different manner, by nucleophilic substitution by a phosphine on an epoxide (**0-49**):



Betaines formed in this way can then be converted to the olefin, and this is one reason why betaine intermediates were long accepted in the Wittig reaction.

Some Wittig reactions give the *Z* olefin; some the *E*, and others give mixtures, and the question of which factors determine the stereoselectivity has been much studied.⁶⁷³ It is generally found that ylides containing stabilizing groups or formed from trialkylphosphines give *E* olefins. However, ylides formed from triarylphosphines and not containing stabilizing groups often give *Z* or a mixture of *Z* and *E* olefins.⁶⁷⁴ One explanation for this⁶⁶⁹ is that the reaction of the ylide with the carbonyl compound is a 2 + 2 cycloaddition, which in order to be concerted must adopt the [π_2 + π_2] pathway. As we have seen earlier (p. 858), this pathway leads to the formation of the more sterically crowded product, in this case the *Z* olefin. If this explanation is correct, it is not easy to explain the predominant formation of *E* products from stable ylides, but *E* compounds are of course generally thermodynamically more stable than the *Z* isomers, and the stereochemistry seems to depend on many factors.

⁶⁶⁶See Vedejs; Marth *J. Am. Chem. Soc.* **1990**, *112*, 3905.

⁶⁶⁷Wittig; Weigmann; Schlosser *Chem. Ber.* **1961**, *94*, 676; Schlosser; Christmann *Liebigs Ann. Chem.* **1967**, *708*, 1.

⁶⁶⁸Maryanoff; Reitz, Ref. 638, p. 865.

⁶⁶⁹Vedejs; Snoble *J. Am. Chem. Soc.* **1973**, *95*, 5778; Vedejs; Meier; Snoble *J. Am. Chem. Soc.* **1981**, *103*, 2823. See also Nesmayanov; Binshtok; Reutov *Doklad. Chem.* **1973**, *210*, 499.

⁶⁷⁰Birum; Matthews *Chem. Commun.* **1967**, 137; Mazhar-Ul-Haque; Caughlan; Ramirez; Pilot; Smith *J. Am. Chem. Soc.* **1971**, *93*, 5229.

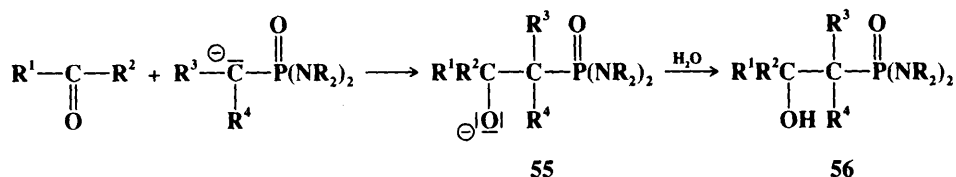
⁶⁷¹Maryanoff; Reitz; Mutter; Inners; Almond; Whittle; Olofson *J. Am. Chem. Soc.* **1986**, *108*, 7664. See also Piskala; Rehan; Schlosser *Coll. Czech. Chem. Commun.* **1983**, *48*, 3539.

⁶⁷²McEwen; Kumli; Bladé-Font; Zanger; VanderWerf *J. Am. Chem. Soc.* **1964**, *86*, 2378.

⁶⁷³For reviews of the stereochemistry of the Wittig reactions, see Maryanoff; Reitz, Ref. 638; Gosney; Rowley, in Cadogan, Ref. 638, pp. 17-153; Reucroft; Sammes *Q. Rev., Chem. Soc.* **1971**, *25*, 135-169, pp. 137-148, 169; Schlosser *Top. Stereochem.* **1970**, *5*, 1-30.

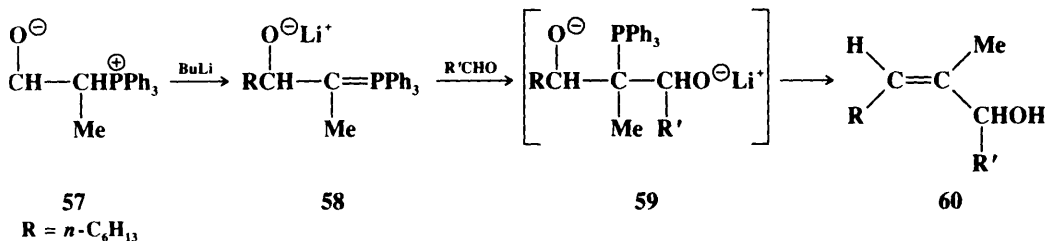
⁶⁷⁴For cases where such an ylide gave *E* olefins, see Maryanoff; Reitz; Duhl-Emswiler *J. Am. Chem. Soc.* **1985**, *107*, 217; Le Bigot; El Gharbi; Delmas; Gaset *Tetrahedron* **1986**, *42*, 3813. For guidance in how to obtain the maximum yields of the *Z* product, see Schlosser; Schaub; de Oliveira-Neto; Jeganathan *Chimia* **1986**, *40*, 244.

The *E:Z* ratio of the product can often be changed by a change in solvent or by the addition of salts.⁶⁷⁵ Another way of controlling the stereochemistry of the product is by use of the aforementioned phosphonic acid bisamides. In this case the betaine (**55**) does form



and when treated with water gives the β -hydroxyphosphonic acid bisamides **56**, which can be crystallized and then cleaved to $\text{R}^1\text{R}^2\text{C}=\text{CR}^3\text{R}^4$ by refluxing in benzene or toluene in the presence of silica gel.⁶⁶¹ **56** are generally formed as mixtures of diastereomers, and these mixtures can be separated by recrystallization. Cleavage of the two diastereomers gives the two isomeric olefins. Optically active phosphonic acid bisamides have been used to give optically active olefins.⁶⁷⁶ Another method of controlling the stereochemistry of the olefin (to obtain either the *Z* or *E* isomer) starting with a phosphine oxide $\text{Ph}_2\text{POCH}_2\text{R}$, has been reported.⁶⁷⁷

In reactions where the betaine–lithium halide intermediate is present, it is possible to extend the chain further if a hydrogen is present α to the phosphorus. For example, reaction of ethylenetriphenylphosphorane with heptanal at -78°C gave **57**, which with butyllithium gave the ylide **58**. Treatment of this with an aldehyde $\text{R}'\text{CHO}$ gave the intermediate **59**,



which after workup gave **60**.⁶⁷⁸ This reaction gives the unsaturated alcohols **60** stereoselectively. **58** also reacts with other electrophiles. For example, treatment of **58** with *N*-chlorosuccinimide or PhICl_2 gives the vinylic chloride $\text{RCH}=\text{CMeCl}$ stereoselectively: *NCS* giving the *cis* and PhICl_2 the *trans* isomer.⁶⁷⁹ The use of Br_2 and FCIO_3 (see **2-4** for the explosive nature of this reagent) gives the corresponding bromides and fluorides, respectively.⁶⁸⁰ Reactions of **58** with electrophiles have been called *scoopy* reactions (α substitution plus carbonyl olefination via β -oxido phosphorus ylides).⁶⁸¹

⁶⁷⁵See, for example, Reitz; Nortey; Jordan; Mutter; Maryanoff *J. Org. Chem.* **1986**, *51*, 3302.

⁶⁷⁶Hanessian; Delorme; Beaudoin; Leblanc *J. Am. Chem. Soc.* **1984**, *106*, 5754.

⁶⁷⁷Buss; Warren *J. Chem. Soc., Perkin Trans. 1* **1985**, 2307; Ayrey; Warren *Tetrahedron Lett.* **1989**, *30*, 4581.

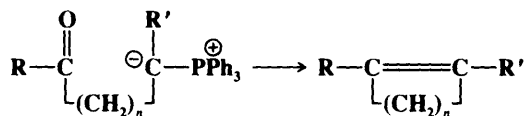
⁶⁷⁸Corey; Yamamoto *J. Am. Chem. Soc.* **1970**, *92*, 226; Schlosser; Christmann; Piskala; Coffinet *Synthesis* **1971**, 29; Schlosser; Coffinet *Synthesis* **1971**, **1972**, 575; Corey; Ulrich; Venkateswarlu *Tetrahedron Lett.* **1977**, 3231; Schlosser; Tuong; Respondek; Schaub *Chimia* **1983**, *37*, 10.

⁶⁷⁹Schlosser; Christmann *Synthesis* **1969**, *38*; Corey; Shulman; Yamamoto *Tetrahedron Lett.* **1970**, 447.

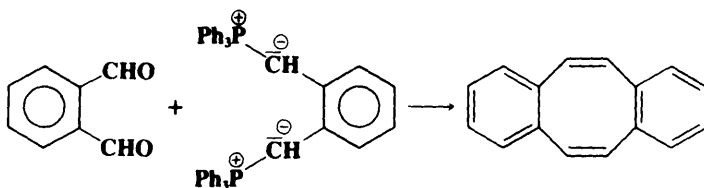
⁶⁸⁰Schlosser; Christmann, Ref. 679.

⁶⁸¹Schlosser, Ref. 673, p. 22.

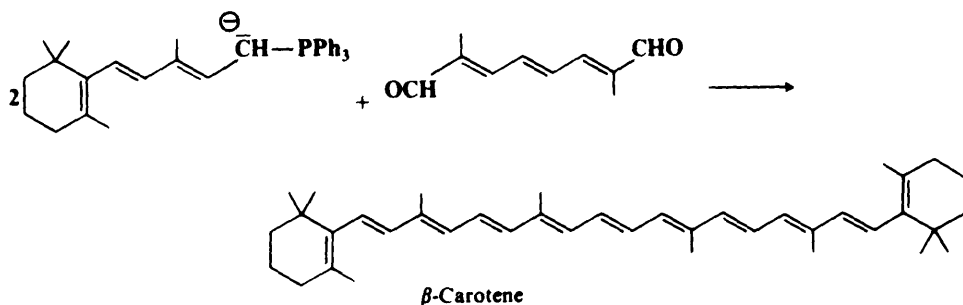
The Wittig reaction has been carried out intramolecularly, to prepare rings containing from 5 to 16 carbons,⁶⁸² both by single ring closure



and double ring closure.⁶⁸³



The Wittig reaction has proved very useful in the synthesis of natural products, some of which are quite difficult to prepare in other ways.⁶⁸⁴ One example out of many is the synthesis of β -carotene.⁶⁸⁵



Phosphorus ylides also react in a similar manner with the C=O bonds of ketenes,⁶⁸⁶ isocyanates,⁶⁸⁷ and certain anhydrides⁶⁸⁸ and imides,⁶⁸⁹ the N=O of nitroso groups, and the C=N of imines.⁶⁹⁰

⁶⁸²For a review, see Becker *Tetrahedron* **1980**, 36, 1717-1745.

⁶⁸³For a review of these double ring closures, see Vollhardt *Synthesis* **1975**, 765-780.

⁶⁸⁴For a review of applications of the Wittig reaction to the synthesis of natural products, see Bestmann; Vostrowsky, Ref. 638.

⁶⁸⁵Wittig; Pommer; German patent **1956**, 954,247, *CA* **1959**, 53, 2279.

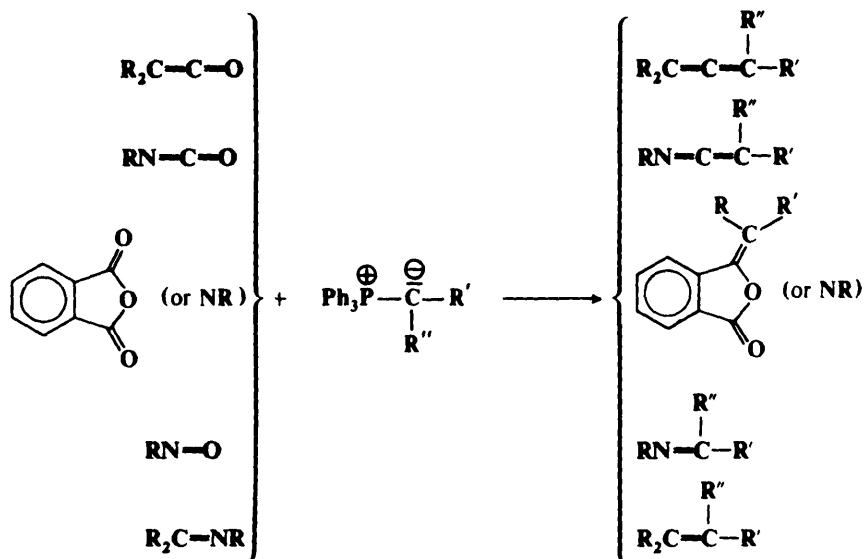
⁶⁸⁶For example, see Aksnes; Frøyen *Acta Chem. Scand.* **1968**, 22, 2347.

⁶⁸⁷For example, see Frøyen *Acta Chem. Scand., Ser. B* **1974**, 28, 586.

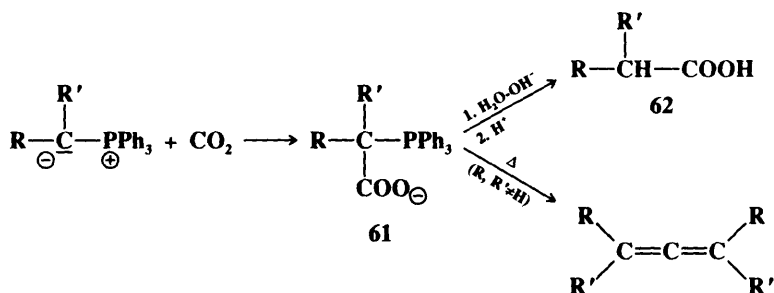
⁶⁸⁸See, for example, Abell; Massy-Westropp *Aust. J. Chem.* **1982**, 35, 2077; Kayser; Breau *Can. J. Chem.* **1989**, 67, 1401. For a study of the mechanism, see Abell; Clark; Robinson *Aust. J. Chem.* **1988**, 41, 1243.

⁶⁸⁹For a review of the reactions with anhydrides and imides (and carboxylic esters, thiol esters, and amides), see Murphy; Brennan *Chem. Soc. Rev.* **1988**, 17, 1-30. For a review with respect to imides, see Flitsch; Schindler *Synthesis* **1975**, 685-700.

⁶⁹⁰Bestmann; Seng *Tetrahedron* **1965**, 21, 1373.



Phosphorus ylides react with carbon dioxide to give the isolable salts **61**,⁶⁹¹ which can be hydrolyzed to the carboxylic acids **62** (thus achieving the conversion $\text{RR}'\text{CHX} \rightarrow$

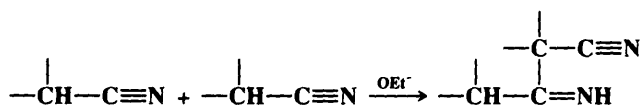


$\text{RR}'\text{CHCOOH}$) or (if neither R nor R' is hydrogen) dimerized to allenes.

OS V, 361, 390, 499, 509, 547, 751, 949, 985; VI, 358; VII, 164, 232; **65**, 119; **66**, 220.

6-48 The Thorpe Reaction

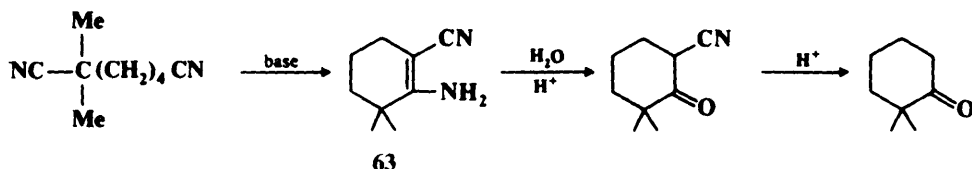
N-Hydro-C-(α-cyanoalkyl)-addition



In the *Thorpe reaction*, the α carbon of one nitrile molecule is added to the CN carbon of another, so this reaction is analogous to the aldol reaction (6-39). The C=NH bond is, of

⁶⁹¹Bestmann; Denzel; Salbaum *Tetrahedron Lett* **1974**, 1275.

course, hydrolyzable (6-2), so β -keto nitriles can be prepared in this manner. The Thorpe reaction can be done internally, in which case it is called the *Thorpe-Ziegler reaction*.⁶⁹² This is a useful method for closing large rings. Yields are high for five- to eight-membered rings, fall off to about zero for rings of nine to thirteen members, but are high again for fourteen-membered and larger rings, if high-dilution techniques are employed. The product

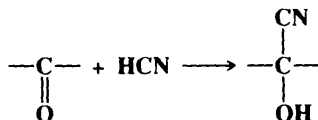


in the Thorpe-Ziegler reaction is not the imine, but the tautomeric enamine, e.g., **63**; if desired this can be hydrolyzed to an α -cyano ketone (6-2), which can in turn be hydrolyzed and decarboxylated (6-5, 2-40). Other active-hydrogen compounds can also be added to nitriles.⁶⁹³

OS VI, 932.

J. Other Carbon Nucleophiles

6-49 The Formation of Cyanohydrins O-Hydro-C-cyano-addition



The addition of HCN to aldehydes or ketones produces cyanohydrins.⁶⁹⁴ This is an equilibrium reaction. For aldehydes and aliphatic ketones the equilibrium lies to the right; therefore the reaction is quite feasible, except with sterically hindered ketones such as diisopropyl ketone. However, ketones ArCOR give poor yields, and the reaction cannot be carried out with ArCOAr since the equilibrium lies too far to the left. With aromatic aldehydes the benzoin condensation (6-54) competes. With α,β -unsaturated aldehydes and ketones, 1,4 addition competes (5-25). Ketones of low reactivity, such as ArCOR, can be converted to cyanohydrins by treatment with diethylaluminum cyanide Et₂AlCN (see OS VI, 307) or, indirectly, with cyanotrimethylsilane Me₃SiCN⁶⁹⁵ in the presence of a Lewis acid or base,^{695a} followed by hydrolysis of the resulting O-trimethylsilyl cyanohydrin **64**. When TiCl₄ is used,

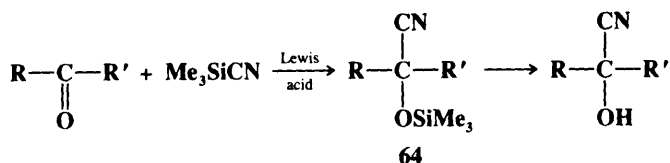
⁶⁹²For a monograph, see Taylor; McKillop *The Chemistry of Cyclic Enaminonitriles and ortho-Amino Nitriles*; Wiley: New York, 1970. For a review, see Schaefer; Bloomfield, *Org. React.* **1967**, 15, 1-203.

⁶⁹³See for example, Josey *J. Org. Chem.* **1964**, 29, 707; Barluenga; Fustero; Rubio; Gotor *Synthesis* **1977**, 780; Hiyama; Kobayashi *Tetrahedron Lett.* **1982**, 23, 1597; Gewald; Bellmann; Jansch *Liebigs Ann. Chem.* **1984**, 1702; Page; van Niel; Westwood *J. Chem. Soc., Perkin Trans. I* **1988**, 269.

⁶⁹⁴For reviews, see Friedrich, in Patai; Rappoport *The Chemistry of Functional Groups, Supplement C*, pt. 2; Wiley: New York, 1983, pp. 1345-1390; Friedrich; Wallenfels, in Rappoport, Ref. 334, pp. 72-77.

⁶⁹⁵For reviews of Me₃SiCN and related compounds, see Rasmussen; Heilmann; Krepski *Adv. Silicon Chem.* **1991**, 1, 65-187; Groutas; Felker *Synthesis* **1980**, 861-868. For procedures using Me₃SiCl and CN⁻ instead of Me₃SiCN, see Yoneda; Santo; Harusawa; Kurihara *Synthesis* **1986**, 1054; Sukata *Bull. Chem. Soc. Jpn.* **1987**, 60, 3820.

^{695a}Kobayashi; Tsuchiya; Mukaiyama *Chem. Lett.* **1991**, 537.



the reaction between Me_3SiCN and aromatic aldehydes or ketones gives α -chloro nitriles $\text{Cl}-\text{CRR}'-\text{CN}$.⁶⁹⁶

Frequently it is the bisulfite addition product that is treated with CN^- . This method is especially useful for aromatic aldehydes, since it avoids competition from the benzoin condensation. If desired, it is possible to hydrolyze the cyanohydrin in situ to the corresponding α -hydroxy acid. This reaction is important in the *Kiliani-Fischer* method of extending the carbon chain of a sugar.

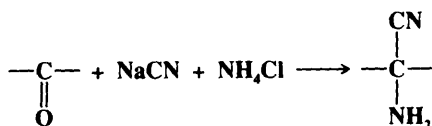
The addition is nucleophilic and the actual nucleophile is CN^- , so the reaction rate is increased by the addition of base.⁶⁹⁷ This was demonstrated by Lapworth in 1903, and consequently this was one of the first organic mechanisms to be known.⁶⁹⁸

The reaction has been carried out enantioselectively: optically active cyanohydrins were prepared with the aid of optically active catalysts.⁶⁹⁹

OS I, 336; II, 7, 29, 387; III, 436; IV, 58, 506; VI, 307; VII, 20, 381, 517, 521. For the reverse reaction, see OS III, 101.

6-50 The Strecker Synthesis

Cyano,amino-de-oxo-bisubstitution



α -Amino nitriles⁷⁰⁰ can be prepared in one step by the treatment of an aldehyde or ketone with NaCN and NH_4Cl . This is called the *Strecker synthesis*;^{700a} it is a special case of the Mannich reaction (6-16). Since the CN is easily hydrolyzed to the acid, this is a convenient method for the preparation of α -amino acids. The reaction has also been carried out with NH_3 + HCN and with NH_4CN . Salts of primary and secondary amines can be used instead of NH_4^+ to obtain N-substituted and N,N-disubstituted α -amino nitriles. Unlike 6-49, the Strecker synthesis is useful for aromatic as well as aliphatic ketones. As in 6-49, the Me_3SiCN method has been used; 64 is converted to the product with ammonia or an amine.⁷⁰¹

OS I, 21, 355; III, 66, 84, 88, 275; IV, 274; V, 437; VI, 334.

⁶⁹⁶Kiyooka; Fujiyama; Kawaguchi *Chem. Lett.* **1984**, 1979.

⁶⁹⁷For a review, see Ogata; Kawasaki, in Zabicky *The Chemistry of the Carbonyl Group*, vol. 2, Wiley: New York, 1970, pp. 21-32. See also Okano; do Amaral; Cordes *J. Am. Chem. Soc.* **1976**, 98, 4201; Ching; Kallen *J. Am. Chem. Soc.* **1978**, 100, 6119.

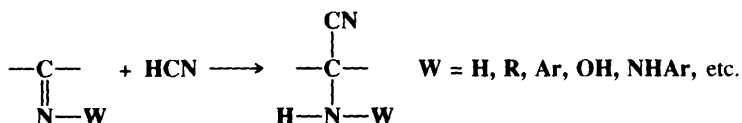
⁶⁹⁸Lapworth *J. Chem. Soc.* **1903**, 83, 998.

⁶⁹⁹See Minamikawa; Hayakawa; Yamada; Iwasawa; Narasaka *Bull. Chem. Soc. Jpn.* **1988**, 61, 4379; Jackson; Jayatilake; Matthews; Wilshire *Aust. J. Chem.* **1988**, 41, 203; Garner; Fernández; Gladysz *Tetrahedron Lett.* **1989**, 30, 3931; Mori; Ikeda; Kinoshita; Inoue *Chem. Lett.* **1989**, 2119; Kobayashi; Tsuchiya; Mukaiyama *Chem. Lett.* **1991**, 541, and references cited in these papers.

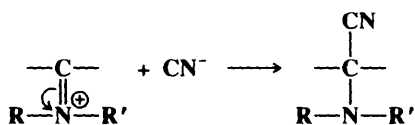
⁷⁰⁰For a review of α -amino nitriles, see Shafran; Bakulev; Mokrushin *Russ. Chem. Rev.* **1989**, 58, 148-162.

^{700a}For a review of asymmetric Strecker syntheses, see Williams *Synthesis of Optically Active α -Amino Acids*; Pergamon: Elmsford, NY, 1989, pp. 208-229.

⁷⁰¹See Mai; Patil *Tetrahedron Lett.* **1984**, 25, 4583; *Synth. Commun.* **1985**, 15, 157.

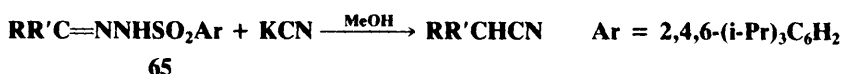
6-51 The Addition of HCN to C=N and C≡N Bonds**N-Hydro-C-cyano-addition**

HCN adds to imines, Schiff bases, hydrazones, oximes, and similar compounds. CN^- can be added to iminium ions.³³⁰

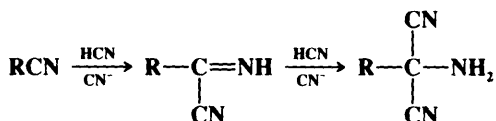


As in **6-48**, the addition to imines has been carried out enantioselectively.⁷⁰²

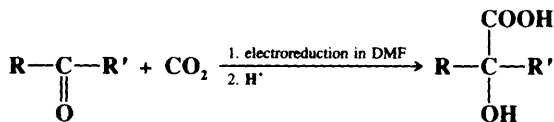
The addition of KCN to triisopropylbenzenesulfonyl hydrazones **65** provides an indirect method for achieving the conversion $\text{RR}'\text{CO} \rightarrow \text{RR}'\text{CHCN}$.⁷⁰³ The reaction is successful for hydrazones of aliphatic aldehydes and ketones.



HCN can also be added to the $\text{C}\equiv\text{N}$ bond to give iminonitriles or α -aminomalononitriles.⁷⁰⁴



OS V, 344. See also OS V, 269.

6-52 The Addition of CO_2 to Aldehydes and Ketones**O-Hydro-C-carboxyl-addition**

⁷⁰²Saito; Harada *Tetrahedron Lett.* **1989**, 30, 4535.

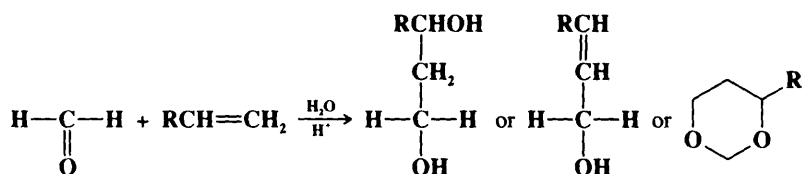
⁷⁰³Jiricny; Ore; Reese *J. Chem. Soc., Perkin Trans. I* **1980**, 1487. For other methods of achieving this conversion, see Ziegler; Wender *J. Org. Chem.* **1977**, 42, 2001; Cacchi; Caglioti; Paolucci *Synthesis* **1975**, 120; Yoneda; Harusawa; Kurihara *Tetrahedron Lett.* **1989**, 30, 3681; Okimoto; Chiba *J. Org. Chem.* **1990**, 55, 1070.

⁷⁰⁴For an example, see Ferris; Sanchez *Org. Synth. V.* 344.

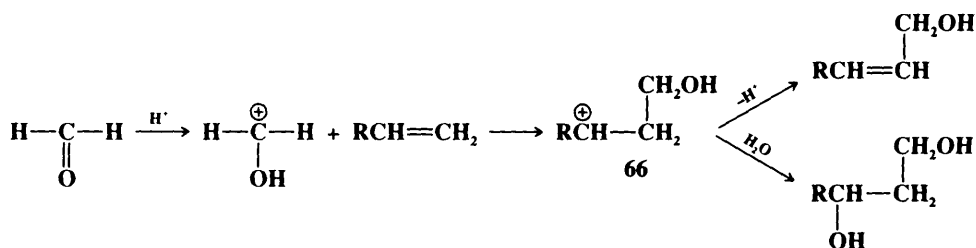
Aromatic aldehydes and ketones have been converted to α -hydroxy acids by electrolysis carried out in the presence of CO_2 in DMF, followed by hydrolysis.⁷⁰⁵ Yields were moderate to high.

Addition of ArH to $\text{C}=\text{O}$, $\text{C}=\text{N}$, and $\text{C}\equiv\text{N}$ bonds is discussed under aromatic substitution: **1-16**, **1-20** to **1-25**, **1-27**, and **1-28**.

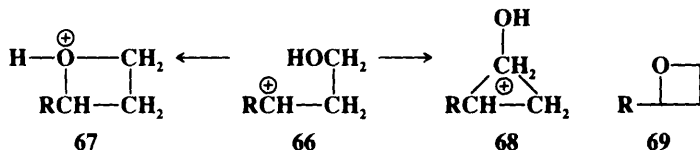
6-53 The Prins Reaction



The addition of an olefin to formaldehyde in the presence of an acid⁷⁰⁶ catalyst is called the *Prins reaction*.⁷⁰⁷ Three main products are possible; which one predominates depends on the olefin and the conditions. When the product is the 1,3-diol or the dioxane,⁷⁰⁸ the reaction involves addition to the $\text{C}=\text{C}$ as well as to the $\text{C}=\text{O}$. The mechanism is one of electrophilic attack on both double bonds. The acid first protonates the $\text{C}=\text{O}$, and the resulting carbocation attacks the $\text{C}=\text{C}$:



66 can undergo loss of H^+ to give the olefin or add water to give the diol.⁷⁰⁹ It has been proposed that **66** is stabilized by neighboring-group attraction, with either the oxygen⁷¹⁰ or



⁷⁰⁵Mcharek; Heintz; Troupel; Perichon *Bull. Soc. Chim. Fr.* **1989**, 95.

⁷⁰⁶The Prins reaction has also been carried out with basic catalysts: Griengl; Sieber *Monatsh. Chem.* **1973**, 104, 1008, 1027.

⁷⁰⁷For reviews, see Adams; Bhatnagar *Synthesis* **1977**, 661-672; Isagulyants; Khaimova; Melikyan; Pokrovskaya *Russ. Chem. Rev.* **1968**, 37, 17-25. For a list of references, see Ref. 64, p. 125.

⁷⁰⁸The reaction to produce dioxanes has also been carried out with equimolar mixtures of formaldehyde and another aldehyde RCHO . The R appears in the dioxane on the carbon between the two oxygens: Safarov; Nigmatullin; Ibatullin; Rafikov *Doklad. Chem.* **1977**, 236, 507.

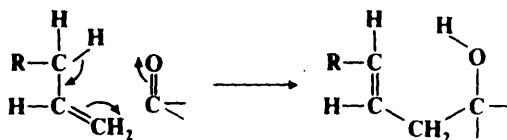
⁷⁰⁹Hellin; Davidson; Coussebant *Bull. Soc. Chim. Fr.* **1966**, 1890, 3217.

⁷¹⁰Blomquist; Wolinsky *J. Am. Chem. Soc.* **1957**, 79, 6025; Schowen; Smissman; Schowen *J. Org. Chem.* **1968**, 33, 1873.

a carbon⁷¹¹ stabilizing the charge (**67** and **68**, respectively). This stabilization is postulated to explain the fact that with 2-butenes⁷¹² and with cyclohexenes the addition is anti. A backside attack of H₂O on the three- or four-membered ring would account for it. Other products are obtained too, which can be explained on the basis of **67** or **68**.^{710,711} Additional evidence for the intermediacy of **67** is the finding that oxetanes (**69**) subjected to the reaction conditions (which would protonate **69** to give **67**) give essentially the same product ratios as the corresponding alkenes.⁷¹³ An argument against the intermediacy of **67** and **68** is that not all alkenes show the anti stereoselectivity mentioned above. Indeed, the stereochemical results are often quite complex, with syn, anti, and nonstereoselective addition reported, depending on the nature of the reactants and the reaction conditions.⁷¹⁴ Since addition to the C=C bond is electrophilic, the reactivity of the olefin increases with alkyl substitution and Markovnikov's rule is followed. The dioxane product may arise from a reaction between the 1,3-diol and formaldehyde⁷¹⁵ (**6-6**) or between **66** and formaldehyde.

Lewis acids such as SnCl₄ also catalyze the reaction, in which case the species that adds to the olefins is H₂C⁺—O[−]—SnCl₄.⁷¹⁶ The reaction can also be catalyzed by peroxides, in which case the mechanism is probably a free-radical one.

A closely related reaction has been performed with other aldehydes and even with ketones; without a catalyst, but with heat.⁷¹⁷ The aldehydes and ketones here are active ones, such as chloral and acetoacetic ester. The product in these cases is a β-hydroxy olefin, and the mechanism is pericyclic:⁷¹⁸



This reaction is reversible and suitable β-hydroxy olefins can be cleaved by heat (**7-43**). There is evidence that the cleavage reaction occurs by a cyclic mechanism (p. 1043), and, by the principle of microscopic reversibility, the addition mechanism should be cyclic too.⁷¹⁹ Note that this reaction is an oxygen analog of the ene synthesis (**5-16**). This reaction can also be done with unactivated aldehydes⁷²⁰ and ketones⁷²¹ if Lewis-acid catalysts such as

⁷¹¹Dolby; Lieske; Rosencrantz; Schwarz *J. Am. Chem. Soc.* **1963**, 85, 47; Dolby; Schwarz *J. Org. Chem.* **1963**, 28, 1456; Safarov; Isagulyants; Nigmatullin *J. Org. Chem. USSR* **1974**, 10, 1378.

⁷¹²Fremaux; Davidson; Hellin; Coussement *Bull. Soc. Chim. Fr.* **1967**, 4250.

⁷¹³Meresz; Leung; Denes *Tetrahedron Lett.* **1972**, 2797.

⁷¹⁴For example, see LeBel; Liesemer; Mehmedbasich *J. Org. Chem.* **1963**, 28, 615; Portoghese; Smissman *J. Org. Chem.* **1962**, 27, 719; Wilkins; Marianelli *Tetrahedron* **1970**, 26, 4131; Karpaty; Hellin; Davidson; Coussement *Bull. Soc. Chim. Fr.* **1971**, 1736; Coryn; Anteunis *Bull. Soc. Chim. Belg.* **1974**, 83, 83.

⁷¹⁵Ref. 709; Isagulyants; Isagulyants; Khairudinov; Rakhmankulov *Bull. Acad. Sci. USSR. Div. Chem. Sci.* **1973**, 22, 1810; Sharf; Kheifets; Freidlin *Bull. Acad. Sci. USSR. Div. Chem. Sci.* **1974**, 23, 1681.

⁷¹⁶Yang; Yang; Ross *J. Am. Chem. Soc.* **1959**, 81, 133.

⁷¹⁷Arnold; Veeravagu *J. Am. Chem. Soc.* **1960**, 82, 5411; Klimova; Abramov; Antonova; Arbuzov *J. Org. Chem. USSR* **1969**, 5, 1308; Klimova; Antonova; Arbuzov *J. Org. Chem. USSR* **1969**, 5, 1312, 1315.

⁷¹⁸See for example, Achmatowicz; Szymoniak *J. Org. Chem.* **1980**, 45, 1228; Ben Salem; Jenner *Tetrahedron Lett.* **1986**, 27, 1575. There is evidence that the mechanism is somewhat more complicated than shown here: Kwart; Brechbiel *J. Org. Chem.* **1982**, 47, 3353.

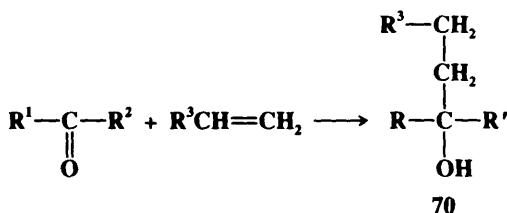
⁷¹⁹For other evidence, see Ref. 718; Papadopoulos; Jenner *Tetrahedron Lett.* **1981**, 22, 2773.

⁷²⁰Snider *Acc. Chem. Res.* **1980**, 13, 426-432; Snider; Phillips *J. Org. Chem.* **1983**, 48, 464; Cartaya-Marin; Jackson; Snider *J. Org. Chem.* **1984**, 49, 2443.

⁷²¹Jackson; Goldman; Snider *J. Org. Chem.* **1984**, 49, 3988.

dimethylaluminum chloride Me_2AlCl or ethylaluminum dichloride EtAlCl_2 are used.⁷²² Lewis acid catalysts also increase rates with activated aldehydes.⁷²³ The use of optically active catalysts has given optically active products with high enantiomeric excesses.⁷²⁴

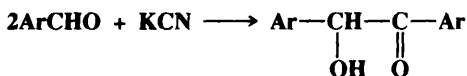
In a related reaction, alkenes can be added to aldehydes and ketones to give reduced alcohols **70**. This has been accomplished by several methods,⁷²⁵ including treatment with



SmI_2 ⁷²⁶ or Zn and Me_3SiCl ,⁷²⁷ and by electrochemical⁷²⁸ and photochemical⁷²⁹ methods. Most of these methods have been used for intramolecular addition and most or all involve free radical intermediates.

OS IV, 786. See also OS VII, 102.

6-54 The Benzoin Condensation Benzoin aldehyde condensation



When certain aldehydes are treated with cyanide ion, *benzoins* are produced in a reaction called the *benzoin condensation*. The condensation can be regarded as involving the addition of one molecule of aldehyde to the $\text{C}=\text{O}$ group of another. The reaction can be accomplished only for aromatic aldehydes, though not for all of them,⁷³⁰ and for glyoxals RCOCHO . The two molecules of aldehyde obviously perform different functions. The one that no longer has a $\text{C}-\text{H}$ bond in the product is called the *donor*, because it has “donated” its hydrogen to the oxygen of the other molecule, the *acceptor*. Some aldehydes can perform only one of these functions and hence cannot be self-condensed, though they can often be condensed with a different aldehyde. For example, *p*-dimethylaminobenzaldehyde is not an acceptor but only a donor. Thus it cannot condense with itself, but it can condense with benzaldehyde, which can perform both functions, but is a better acceptor than it is a donor.

⁷²²For discussions of the mechanism with Lewis-acid catalysts, see Stephenson; Orfanopoulos *J. Org. Chem.* **1981**, *46*, 2200; Kwart; Brechbiel *J. Org. Chem.* **1982**, *47*, 5409; Song; Beak *J. Org. Chem.* **1990**, *112*, 8126.

⁷²³Benner; Gill; Parrott; Wallace *J. Chem. Soc., Perkin Trans. I* **1984**, 291, 315, 331.

⁷²⁴Maruoka; Hoshino; Shirasaka; Yamamoto *Tetrahedron Lett.* **1988**, *29*, 3967; Mikami; Terada; Nakai *J. Am. Chem. Soc.* **1990**, *112*, 3949.

⁷²⁵For references, see Ujikawa; Inanaga; Yamaguchi *Tetrahedron Lett.* **1989**, *30*, 2837; Ref. 64, pp. 575-576.

⁷²⁶Ujikawa et al., Ref. 725.

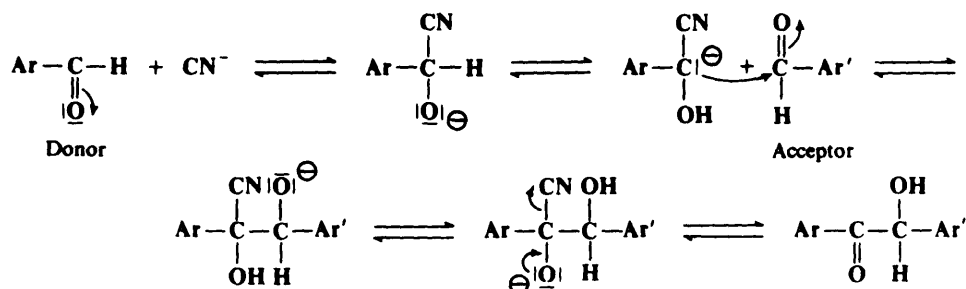
⁷²⁷Corey; Pyne *Tetrahedron Lett.* **1983**, *24*, 2821.

⁷²⁸See Shono; Kashimura; Mori; Hayashi; Soejima; Yamaguchi *J. Org. Chem.* **1989**, *54*, 6001.

⁷²⁹See Belotti; Cossy; Pete; Portella *J. Org. Chem.* **1986**, *51*, 4196.

⁷³⁰For a review, see Ide; Buck *Org. React.* **1948**, *4*, 269-304.

The following is the accepted mechanism,⁷³¹ which was originally proposed by Lapworth in 1903.⁷³²



The reaction is reversible. The key step, the loss of the aldehydic proton, can take place because the acidity of this C—H bond is increased by the electron-withdrawing power of the CN group. Thus, CN^- is a highly specific catalyst for this reaction, because, almost uniquely, it can perform three functions: (1) It acts as a nucleophile; (2) its electron-withdrawing ability permits loss of the aldehydic proton; and (3) having done this, it then acts as a leaving group. Certain thiazolium salts can also catalyze the reaction.⁷³³ In this case aliphatic aldehydes can also be used⁷³⁴ (the products are called *acyloins*), and mixtures of aliphatic and aromatic aldehydes give mixed α -hydroxy ketones.⁷³⁵ The reaction has also been carried out without CN^- , by using the benzoyleted cyanohydrin as one of the components in a phase-transfer catalyzed process. By this means products can be obtained from aldehydes that normally fail to self-condense.⁷³⁶

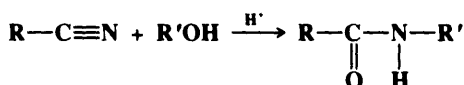
OS I, 94; VII, 95.

Reactions in Which Carbon Adds to the Hetero Atom

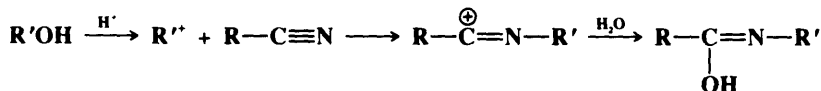
A. Oxygen Adding to the Carbon

6-55 The Ritter Reaction

N-Hydro,*N*-alkyl-C-oxo-biaddition



Alcohols can be added to nitriles in an entirely different manner from that of reaction 6-9. In this reaction, the alcohol is converted by a strong acid to a carbocation, which adds to the negative nitrogen, water adding to the carbon:



⁷³¹For a discussion, See Kuebrich; Schowen; Wang; Lupes *J. Am. Chem. Soc.* **1971**, 93, 1214.

⁷³²Lapworth *J. Chem. Soc.* **1903**, 83, 995, **1904**, 85, 1206.

⁷³³See Ugai; Tanaka; Dokawa *J. Pharm. Soc. Jpn.* **1943**, 63, 296 [CA 45, 5148]; Breslow *J. Am. Chem. Soc.* **1958**, 80, 3719; Breslow; Kool *Tetrahedron Lett.* **1968**, 29, 1635; Castells; López-Calahorra; Domingo *J. Org. Chem.* **1968**, 53, 4433; Diederich; Lutter *J. Am. Chem. Soc.* **1969**, 111, 8438. For another catalyst, see Lappert; Maskell *J. Chem. Soc., Chem. Commun.* **1962**, 580.

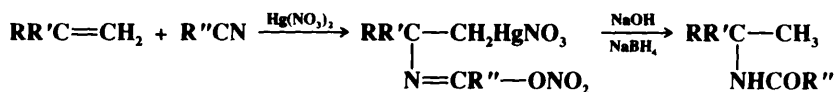
⁷³⁴Stetter; Rämisch; Kuhlmann *Synthesis* **1976**, 733; Stetter; Kuhlmann *Org. Syn. VII*, 95; Matsumoto; Ohishi; Inoue *J. Org. Chem.* **1985**, 50, 603.

⁷³⁵Stetter; Dämbkes *Synthesis* **1977**, 403.

⁷³⁶Rozwadowska *Tetrahedron* **1985**, 41, 3135.

The immediate product tautomerizes to the N-alkyl amide. Only alcohols that give rise to fairly stable carbocations react (secondary, tertiary, benzylic, etc.); primary alcohols do not give the reaction. The carbocation need not be generated from an alcohol but may come from protonation of an olefin or from other sources. In any case, the reaction is called the *Ritter reaction*.⁷³⁷ HCN also gives the reaction, the product being a formamide. Since the amides (especially the formamides) are easily hydrolyzable to amines, the Ritter reaction provides a method for achieving the conversions $R'OH \rightarrow R'NH_2$ (see 0-46) and alkene $\rightarrow R'NH_2$ (see 5-7) in those cases where R' can form a relatively stable carbocation. The reaction is especially useful for the preparation of tertiary alkyl amines because there are few alternate ways of preparing these compounds. The reaction can be extended to primary alcohols by treatment with triflic anhydride⁷³⁸ or $Ph_2CCl^+ SbCl_6^-$ or a similar salt⁷³⁹ in the presence of the nitrile.

Olefins of the form $RCH=CHR'$ and $RR'C=CH_2$ add to nitriles in the presence of mercuric nitrate to give, after treatment with $NaBH_4$, the same amides that would be obtained by the Ritter reaction.⁷⁴⁰ This method has the advantage of avoiding strong acids.

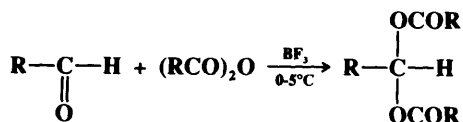


The Ritter reaction can be applied to cyanamides $RNHCN$ to give ureas $RNHCONHR'$.⁷⁴¹

OS V, 73, 471.

6-56 Acylation of Aldehydes and Ketones

O-Acyl-C-acyloxy-addition



Aldehydes can be converted to *acylals* by treatment with an anhydride in the presence of BF_3 , other Lewis acids,⁷⁴² proton acids,⁷⁴³ or PCl_3 .⁷⁴⁴ The reaction cannot normally be applied to ketones, though an exception has been reported when the reagent is trichloroacetic anhydride, which gives acylals with ketones without a catalyst.⁷⁴⁵

OS IV, 489.

⁷³⁷Ritter; Minieri *J. Am. Chem. Soc.* **1948**, 70, 4045. For reviews, see Krimen; Cota *Org. React.* **1969**, 17, 213-325; Beckwith, in Zabicky, Ref. 65, pp. 125-130; Johnson; Madroñero *Adv. Heterocycl. Chem.* **1966**, 6, 95-146.

⁷³⁸Martinez; Alvarez; Vilar; Fraile; Hanack; Subramanian *Tetrahedron Lett.* **1989**, 30, 581.

⁷³⁹Barton; Magnus; Garbarino; Young *J. Chem. Soc., Perkin Trans. 1* **1974**, 2101. See also Top; Jaouen *J. Org. Chem.* **1981**, 46, 78.

⁷⁴⁰Sokolov; Reutov *Bull. Acad. Sci. USSR, Div. Chem. Sci.* **1968**, 225; Brown; Kurek *J. Am. Chem. Soc.* **1969**, 91, 5647; Chow; Robson; Wright *Can. J. Chem.* **1965**, 43, 312; Fry; Simon *J. Org. Chem.* **1982**, 47, 5032.

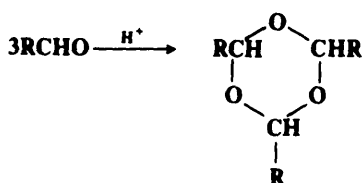
⁷⁴¹Anatol; Berecovechea *Bull. Soc. Chim. Fr.* **1975**, 395, *Synthesis* **1975**, 111.

⁷⁴²For example, $FeCl_3$; Kochhar; Bal; Deshpande; Rajadhyaksha; Pinnick *J. Org. Chem.* **1983**, 48, 1765.

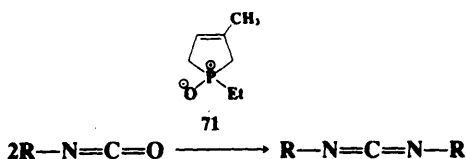
⁷⁴³For example, see Olah; Mehrotra *Synthesis* **1982**, 962.

⁷⁴⁴See Michie; Miller *Synthesis* **1981**, 824.

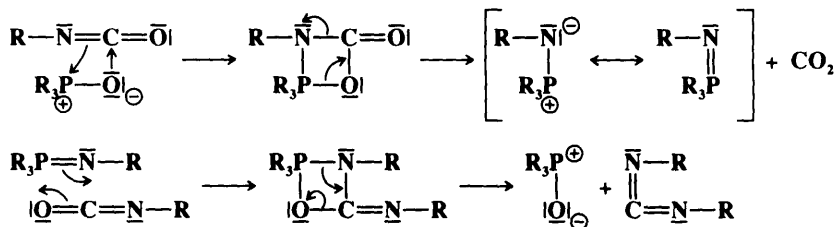
⁷⁴⁵Libman; Sprecher; Mazur *Tetrahedron* **1969**, 25, 1679.

6-57 The Addition of Aldehydes to Aldehydes

When catalyzed by acids, low-molecular-weight aldehydes add to each other to give cyclic acetals, the most common product being the trimer.⁷⁴⁶ The cyclic trimer of formaldehyde is called *trioxane*, and that of acetaldehyde is known as *paraldehyde*. Under certain conditions, it is possible to get tetramers⁷⁴⁷ or dimers. Aldehydes can also polymerize to linear polymers, but here a small amount of water is required to form hemiacetal groups at the ends of the chains. The linear polymer formed from formaldehyde is called *paraformaldehyde*. Since trimers and polymers of aldehydes are acetals, they are stable to bases but can be hydrolyzed by acids. Because formaldehyde and acetaldehyde have low boiling points, it is often convenient to use them in the form of their trimers or polymers.

B. Nitrogen Adding to the Carbon**6-58** The Addition of Isocyanates to Isocyanates
Alkylimino-de-oxo-bisubstitution

The treatment of isocyanates with 3-methyl-1-ethyl-3-phospholene-1-oxide (**71**) is a useful method for the synthesis of carbodiimides⁷⁴⁸ in good yields.⁷⁴⁹ The mechanism does not simply involve the addition of one molecule of isocyanate to another, since the kinetics are first order in isocyanate and first order in catalyst. The following mechanism has been proposed (the catalyst is here represented as $\text{R}_3\text{P}^+-\text{O}^-$):⁷⁵⁰



⁷⁴⁶For a review, see Bevington *Q. Rev., Chem. Soc.* **1952**, 6, 141-156.

⁷⁴⁷Barón; Manderola; Westerkamp *Can. J. Chem.* **1963**, 41, 1893.

⁷⁴⁸For reviews of the chemistry of carbodiimides, see Williams; Ibrahim *Chem. Rev.* **1981**, 81, 589-636; Mikołajczyk; Kiebasinski *Tetrahedron* **1981**, 37, 233-284; Kurzer; Douraghi-Zadeh *Chem. Rev.* **1967**, 67, 107-152.

⁷⁴⁹Campbell; Monagle; Foldi *J. Am. Chem. Soc.* **1962**, 84, 3673.

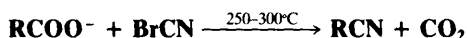
⁷⁵⁰Monagle; Campbell; McShane *J. Am. Chem. Soc.* **1962**, 84, 4288.

According to this mechanism, one molecule of isocyanate undergoes addition to $C=O$, and the other addition to $C=N$. Evidence is that ^{18}O labeling experiments have shown that each molecule of CO_2 produced contains one oxygen atom derived from the isocyanate and one from **71**,⁷⁵¹ precisely what is predicted by this mechanism. Certain other catalysts are also effective.⁷⁵²

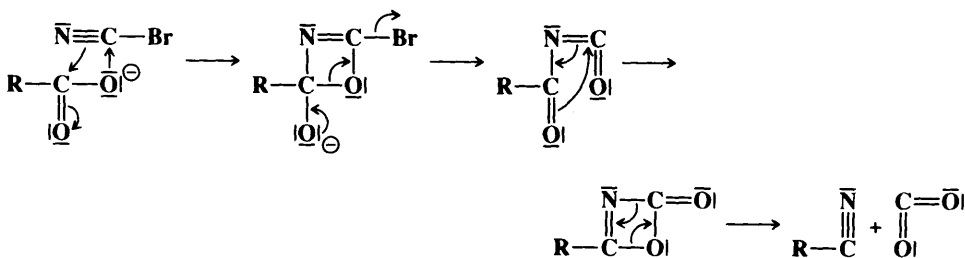
OS V, 501.

6-59 The Conversion of Carboxylic Acid Salts to Nitriles

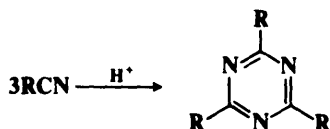
Nitrilo-de-oxido,oxo-tersubstitution



Salts of aliphatic or aromatic carboxylic acids can be converted to the corresponding nitriles by heating with $BrCN$ or $CICN$. Despite appearances, this is not a substitution reaction. When $R^{14}COO^-$ was used, the label appeared in the nitrile, not in the CO_2 ,⁷⁵³ and optical activity in R was retained.⁷⁵⁴ The acyl isocyanate $RCN=C=O$ could be isolated from the reaction mixture; hence the following mechanism was proposed:⁷⁵³



6-60 The Trimerization of Nitriles



Nitriles can be trimerized with various acids, bases, or other catalysts to give triazines.⁷⁵⁵ HCl is most often used, and then the reaction is similar to reaction 6-57. However, most nitriles with an α hydrogen do not give the reaction.

OS III, 71.

C. Carbon Adding to the Carbon. The reactions in this group (6-61 to 6-64) are cycloadditions.

⁷⁵¹Monagle; Mengenhauser *J. Org. Chem.* **1966**, 31, 2321.

⁷⁵²Monagle *J. Org. Chem.* **1962**, 27, 3851; Appleman; DeCarlo *J. Org. Chem.* **1967**, 32, 1505; Ulrich; Tucker; Sayigh *J. Org. Chem.* **1967**, 32, 1360, *Tetrahedron Lett.* **1967**, 1731; Ostrogovich; Kerck; Buzás; Doca *Tetrahedron* **1969**, 25, 1875.

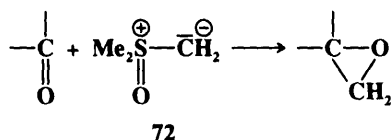
⁷⁵³Douglas; Eccles; Almond *Can. J. Chem.* **1953**, 31, 1127; Douglas; Burditt *Can. J. Chem.* **1958**, 36, 1256.

⁷⁵⁴Barltrop; Day; Bigley *J. Chem. Soc.* **1961**, 3185.

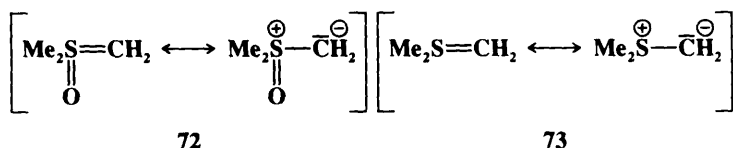
⁷⁵⁵For a review, see Martin; Bauer; Pankratov *Russ. Chem. Rev.* **1978**, 47, 975-990. For a review with respect to cyanamides $RNH-CN$, see Pankratov; Chesnokova *Russ. Chem. Rev.* **1989**, 58, 879-890.

6-61 The Formation of Epoxides from Aldehydes and Ketones

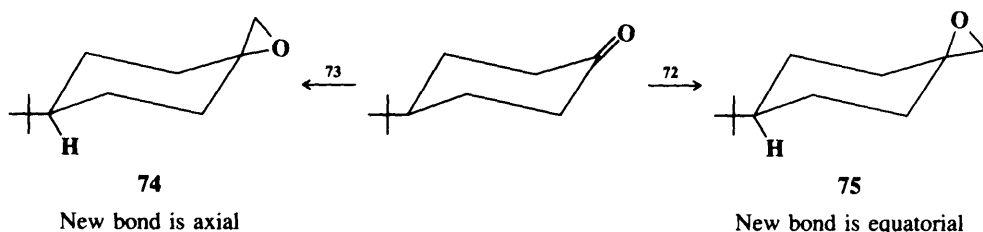
(1 + 2)OC,CC-cyclo-Methylene-addition



Aldehydes and ketones can be converted to epoxides⁷⁵⁶ in good yields with the sulfur ylides dimethyloxosulfonium methylide (**72**) and dimethylsulfonium methylide (**73**).⁷⁵⁷ For most purposes, **72** is the reagent of choice, because **73** is much less stable and ordinarily must be



used as soon as it is formed, while **72** can be stored several days at room temperature. However, when diastereomeric epoxides can be formed, **73** usually attacks from the more hindered and **72** from the less-hindered side. Thus, 4-*t*-butylcyclohexanone, treated with **72** gave exclusively **75** while **73** gave mostly **74**.⁷⁵⁸ Another difference in behavior between the



two reagents is that with α,β -unsaturated ketones, **72** gives only cyclopropanes (reaction 5-50), while **73** gives oxirane formation. Other sulfur ylides have been used in an analogous manner, to transfer CHR or CR₂. Among these are Me₂S=CHCOO⁻,⁷⁵⁹ Me₂S=CHPh,⁷⁶⁰ Me₂S=CH-vinyl,⁷⁶¹ and **111** on p. 872,⁷⁶² which transfer CHCOO⁻, CHPh, CH-vinyl, and CPh₂, respectively. Nitrogen-containing sulfur ylides, such as **112** on p. 872 and Ph(Me₂N)SO=CH₂, as well as carbanions like **114** on p. 872 and sulfonium salts such as trimethylsulfonium bromide Me₃S⁺ Br⁻ (with a phase-transfer catalyst)⁷⁶³ have also been

⁷⁵⁶For reviews, see *Block Reactions of Organosulfur Compounds*; Academic Press: New York, 1978, pp. 101-105; Berti *Top. Stereochem.* **1973**, 7, 93-251, pp. 218-232. For a list of reagents, with references, see Ref. 64, pp. 468-470.

⁷⁵⁷For reviews, see House, Ref. 180, pp. 709-733; Durst *Adv. Org. Chem.* **1969**, 6, 285-388, pp. 321-330; Johnson, Ref. 638, pp. 328-351. For a monograph on sulfur ylides, see Trost; *Melvin Sulfur Ylides*; Academic Press: New York, 1975.

⁷⁵⁸Corey; Chaykovsky *J. Am. Chem. Soc.* **1965**, 87, 1353.

⁷⁵⁹Adams; Hoffman; Trost *J. Org. Chem.* **1970**, 35, 1600.

⁷⁶⁰Yoshimine; Hatch *J. Am. Chem. Soc.* **1967**, 89, 5831.

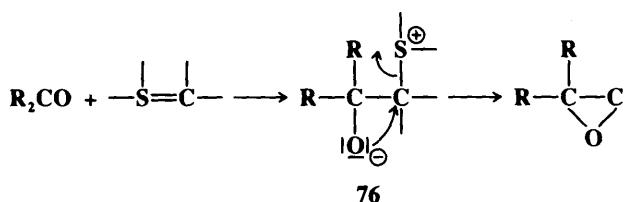
⁷⁶¹Braun; Huber; Kresze *Tetrahedron Lett.* **1973**, 4033.

⁷⁶²Corey; Jautelat; Oppolzer *Tetrahedron Lett.* **1967**, 2325.

⁷⁶³Borredon; Delmas; Gaset *Tetrahedron Lett.* **1982**, 23, 5283, *Tetrahedron* **1987**, 43, 3945, **1988**, 44, 1073; Mosset; Grée *Synth. Commun.* **1985**, 15, 749; Bouda; Borredon; Delmas; Gaset *Synth. Commun.* **1987**, 17, 503.

used.⁷⁶⁴ High yields have been achieved by the use of sulfonium ylides anchored to insoluble polymers under phase transfer conditions.⁷⁶⁵

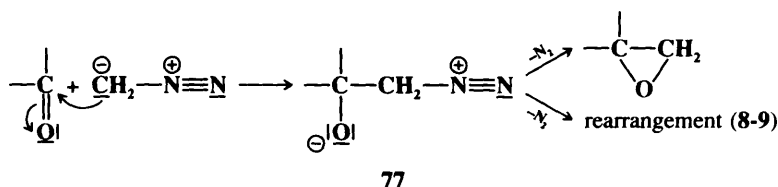
The generally accepted mechanism for the reaction between sulfur ylides and aldehydes or ketone is



which is similar to that of the reaction of sulfur ylides with C=C double bonds (5-50).⁷⁶⁶ The stereochemical difference in the behavior of **72** and **73** has been attributed to formation of the betaine **76** being reversible for **72** but not for the less stable **73**, so that the more-hindered product is the result of kinetic control and the less-hindered of thermodynamic control.⁷⁶⁷

Phosphorus ylides do not give this reaction, but give **6-47** instead.

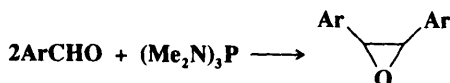
Aldehydes and ketones can also be converted to epoxides by treatment with a diazoalkane,⁷⁶⁸ most commonly diazomethane, but an important side reaction is the formation of an aldehyde or ketone with one more carbon than the starting compound (reaction 8-9). The reaction can be carried out with many aldehydes, ketones, and quinones. A mechanism that accounts for both products is



Compound **77** or nitrogen-containing derivatives of it have sometimes been isolated.

Dihalocarbenes and carbenoids, which readily add to C=C bonds (5-50), do not generally add to the C=O bonds of ordinary aldehydes and ketones.⁷⁶⁹

Symmetrical epoxides can be prepared by treatment of aromatic aldehydes with hexamethylphosphorus triamide.⁷⁷⁰



See also **6-45**.

OS V, 358, 755.

⁷⁶⁴Johnson; Haake; Schroeck *J. Am. Chem. Soc.* **1970**, 92, 6594; Johnson; Janiga *J. Am. Chem. Soc.* **1973**, 95, 7692; Johnson *Acc. Chem. Res.* **1973**, 6, 341-347; Tamura; Matsushima; Ikeda; Sumoto *Synthesis* **1976**, 35.

⁷⁶⁵Farrall; Furst; Fréchet *Tetrahedron Lett.* **1979**, 203.

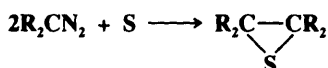
⁷⁶⁶See, for example, Townsend; Sharpless *Tetrahedron Lett.* **1972**, 3313; Johnson; Schroeck; Shanklin *J. Am. Chem. Soc.* **1973**, 95, 7424.

⁷⁶⁷Johnson et al., Ref. 766.

⁷⁶⁸For a review, see Gutsche, *Org. React.* **1954**, 8, 364-429.

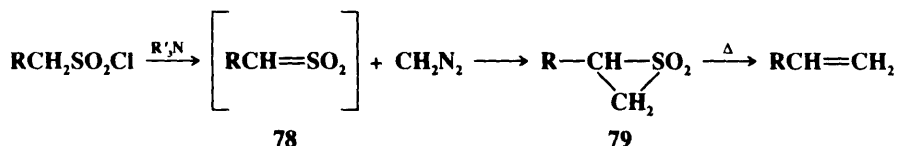
⁷⁶⁹For exceptions, see Greuter; Winkler; Bellu *Helv. Chim. Acta* **1979**, 62, 1275; Sadhu; Matteson *Tetrahedron Lett.* **1986**, 27, 795; Araki; Butsugan *J. Chem. Soc., Chem. Commun.* **1989**, 1286.

⁷⁷⁰Mark *J. Am. Chem. Soc.* **1963**, 85, 1884; *Org. Synth.* V, 358; Newman; Blum *J. Am. Chem. Soc.* **1964**, 86, 5598.

6-62 The Formation of Episulfides and Episulfones⁷⁷¹

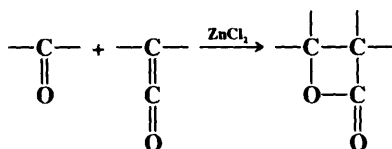
Diazoalkanes, treated with sulfur, give episulfides.⁷⁷² It is likely that $R_2C=S$ is an intermediate, which is attacked by another molecule of diazoalkane, in a process similar to that shown in **6-61**. Thioketones *do* react with diazoalkanes to give episulfides.⁷⁷³ Thioketones have also been converted to episulfides with sulfur ylides.⁷⁵⁸

Alkanesulfonyl chlorides, when treated with diazomethane in the presence of a base (usually a tertiary amine), give episulfones (**79**).⁷⁷⁴ The base removes HCl from the sulfonyl

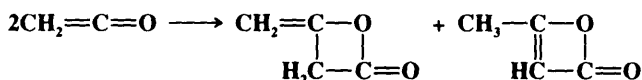


halide to produce the highly reactive sulfene (**78**) (**7-14**), which then adds CH_2 . The episulfone can then be heated to give off SO_2 (**7-25**), making the entire process a method for achieving the conversion $RCH_2SO_2Cl \rightarrow RCH=CH_2$.⁷⁷⁵

OS V, 231, 877.

6-63 The Formation of β -Lactones and Oxetanes
(2 + 2)OC,CC-cyclo-[oxoethylene]-1/2/addition

Aldehydes, ketones, and quinones react with ketenes to give β -lactones, diphenylketene being used most often.⁷⁷⁶ The reaction is catalyzed by Lewis acids, and without them most ketenes do not give adducts because the adducts decompose at the high temperatures necessary when no catalyst is used. When ketene was added to chloral Cl_3CCHO in the presence of the chiral catalyst (+)-quinidine, one enantiomer of the β -lactone was produced in 98% enantiomeric excess.⁷⁷⁷ Other di- and trihalo aldehydes and ketones also give the reaction enantioselectively, with somewhat lower ee values.⁷⁷⁸ Ketene adds to another molecule of itself:



⁷⁷¹For a review, see Muller; Hamer *1,2-Cycloaddition Reactions*; Wiley: New York, 1967, pp. 57-86.

⁷⁷²Schönberg; Frese *Chem. Ber.* **1962**, 95, 2810.

⁷⁷³For example, see Beiner; Lecadet; Paquer; Thuillier *Bull. Soc. Chim. Fr.* **1973**, 1983.

⁷⁷⁴Opitz; Fischer *Angew. Chem. Int. Ed. Engl.* **1965**, 4, 70 [*Angew. Chem.* 77, 41].

⁷⁷⁵For a review of this process, see Fischer *Synthesis* **1970**, 393-404.

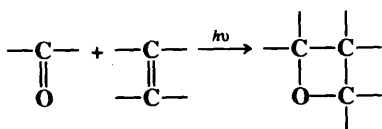
⁷⁷⁶For reviews, see Ref. 771, pp. 139-168; Ulrich *Cycloaddition Reactions of Heterocumulenes*; Academic Press: New York, 1967, pp. 39-45, 64-74.

⁷⁷⁷Wynberg; Staring *J. Am. Chem. Soc.* **1982**, 104, 166, *J. Chem. Soc., Chem. Commun.* **1984**, 1181.

⁷⁷⁸Wynberg; Staring *J. Org. Chem.* **1985**, 50, 1977.

This dimerization is so rapid that ketene does not form β -lactones with aldehydes or ketones, except at low temperatures. Other ketenes dimerize more slowly. In these cases the major dimerization product is not the β -lactone, but a cyclobutenone (see 5-49). However, the proportion of ketene that dimerizes to β -lactone can be increased by the addition of catalysts such as triethylamine or triethyl phosphite.⁷⁷⁹ Ketene acetals $R_2C=C(OR')_2$ add to aldehydes and ketones in the presence of $ZnCl_2$ to give the corresponding oxetanes.⁷⁸⁰

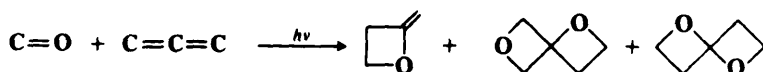
Ordinary aldehydes and ketones can add to olefins, under the influence of uv light, to give oxetanes. This reaction, called the *Paterno-Büchi reaction*,⁷⁸¹ is similar to the photochemical dimerization of olefins discussed at 5-49. In general, the mechanism consists of the



addition of an excited state of the carbonyl compound to the ground state of the olefin. Both singlet (S_1)⁷⁸² and n, π^* triplet⁷⁸³ states have been shown to add to olefins to give

oxetanes. A diradical intermediate⁷⁸⁴ $\dot{O}-\dot{C}-\dot{C}-\dot{C}$ has been detected spectrally.⁷⁸⁵ Yields

in the Paterno-Büchi reaction are variable, ranging from very low to fairly high (90%). There are several side reactions. When the reaction proceeds through a triplet state, it can in general be successful only when the alkene possesses a triplet energy comparable to, or higher than, the carbonyl compound; otherwise energy transfer from the excited carbonyl group to the ground-state alkene can take place (triplet-triplet photosensitization, see p. 241). In most cases quinones react normally with alkenes, giving oxetane products, but other α, β -unsaturated ketones usually give preferential cyclobutane formation (5-49). Aldehydes and ketones also add photochemically to allenes to give the corresponding alkylideneoxetanes and dioxaspiro compounds:⁷⁸⁶



OS III, 508; V, 456. For the reverse reaction, see OS V, 679.

⁷⁷⁹Farnum; Johnson; Hess; Marshall; Webster *J. Am. Chem. Soc.* **1965**, 87, 5191; Elam; *J. Org. Chem.* **1967**, 32, 215.

⁷⁸⁰Aben; Hofstraat; Scheeren *Recl. Trav. Chim. Pays-Bas* **1981**, 100, 355.

⁷⁸¹For reviews, see Ninomiya; Naito *Photochemical Synthesis*; Academic Press: New York, 1989, pp. 138-152; Carless, in *Coyle Photochemistry in Organic Synthesis*; Royal Society of Chemistry: London, 1986, pp. 95-117; Carless, in *Horspool Synthetic Organic Photochemistry*; Plenum: New York, 1984, pp. 425-487; Jones *Org. Photochem.* **1981**, 5, 1-122; Arnold *Adv. Photochem.* **1968**, 6, 301-423; Chapman; Lenz *Org. Photochem.* **1967**, 1, 283-321, pp. 283-294; Ref. 771, pp. 111-139.

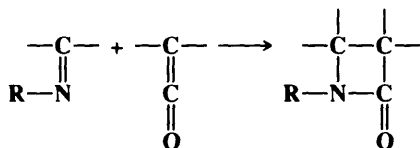
⁷⁸²See, for example, Turro *Pure Appl. Chem.* **1971**, 27, 679-705; Yang; Kimura; Eisenhardt *J. Am. Chem. Soc.* **1973**, 95, 5058; Singer; Davis; Muralidharan *J. Am. Chem. Soc.* **1969**, 91, 897; Barltrop; Carless *J. Am. Chem. Soc.* **1972**, 94, 1951, 8761.

⁷⁸³Arnold; Hinman; Glick *Tetrahedron Lett.* **1964**, 1425; Yang; Nussim; Jorgenson; Murov *Tetrahedron Lett.* **1964**, 3657.

⁷⁸⁴For other evidence for these diradical intermediates, see references cited in Griesbeck; Stadtmüller *J. Am. Chem. Soc.* **1990**, 112, 1281.

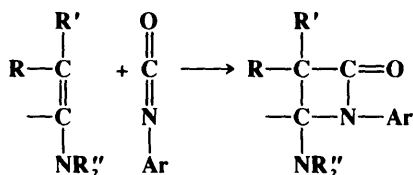
⁷⁸⁵Freilich; Peters *J. Am. Chem. Soc.* **1981**, 103, 6255, **1985**, 107, 3819.

⁷⁸⁶Arnold; Glick *Chem. Commun.* **1966**, 813; Gotthardt; Steinmetz; Hammond *Chem. Commun.* **1967**, 480, *J. Org. Chem.* **1968**, 33, 2774. For a review of the formation of heterocycles by cycloadditions of allenes, see Schuster; Coppola *Allenes in Organic Synthesis*; Wiley: New York, 1984, pp. 317-326.

6-64 The Formation of β -Lactams**(2 + 2)NC,CC-cyclo-[oxoethylene]-1/2/addition**

Ketenes add to imines to give β -lactams.⁷⁸⁷ The reaction is generally carried out with ketenes of the form $\text{R}_2\text{C}=\text{C}=\text{O}$. It has not been successfully applied to $\text{RCH}=\text{C}=\text{O}$, except when these are generated *in situ* by decomposition of a diazo ketone (the Wolff rearrangement, **8-8**) in the presence of the imine. It has been done with ketene, but the more usual course with this reagent is an addition to the enamine tautomer of the substrate. Thioketenes⁷⁸⁸ $\text{R}_2\text{C}=\text{C}=\text{S}$ give β -thiolactams.⁷⁸⁹ Imines also form β -lactams when treated with (1) zinc (or another metal) and an α -bromo ester (Reformatsky conditions—**6-30**),⁷⁹⁰ or (2) the chromium carbene complexes $(\text{CO})_5\text{Cr}=\text{C}(\text{Me})\text{OMe}$.⁷⁹¹ The latter method has been used to prepare optically active β -lactams.⁷⁹² Ketenes have also been added to certain hydrazones (e.g., $\text{PhCH}=\text{NNMe}_2$) to give N-amino β -lactams.⁷⁹³

Like the similar cycloaddition of ketenes to olefins (**5-49**), most of these reactions probably take place by the diionic mechanism *c* (p. 857).⁷⁹⁴ β -Lactams have also been prepared in the opposite manner: by the addition of enamines to isocyanates.⁷⁹⁵



The reactive compound chlorosulfonyl isocyanate⁷⁹⁶ ClSO_2NCO forms β -lactams even with unactivated alkenes,⁷⁹⁷ as well as with allenes,⁷⁹⁸ conjugated dienes,⁷⁹⁹ and cyclopropenes.⁸⁰⁰ OS V, 673; **65**, 135, 140.

⁷⁸⁷For a list of references, see Ref. 64, pp. 961-962. For reviews of the formation of β -lactams, see Brown *Heterocycles* **1989**, 29, 2225-2294; Isaacs *Chem. Soc. Rev.* **1976**, 5, 181-202; Mukerjee; Srivastava *Synthesis* **1973**, 327-346; Ref. 771, pp. 173-206; Ulrich, Ref. 776, pp. 75-83, 135-152; Anselme, in Patai *The Chemistry of the Carbon-Nitrogen Double Bond*, Ref. 40, pp. 305-309. For a review of cycloaddition reactions of imines, see Sandhu; Sain *Heterocycles* **1987**, 26, 777-818.

⁷⁸⁸For a review of thioketenes, see Schaumann *Tetrahedron* **1988**, 44, 1827-1871.

⁷⁸⁹Schaumann *Chem. Ber.* **1976**, 109, 906.

⁷⁹⁰For a review, see Hart; Ha *Chem. Rev.* **1989**, 89, 1447-1465.

⁷⁹¹Hegedus; McGuire; Schultze; Yijun; Anderson *J. Am. Chem. Soc.* **1984**, 106, 2680; Hegedus; McGuire; Schultze *Org. Synth.* 65, 140.

⁷⁹²Hegedus; Imwinkelried; Alarid-Sargent; Dvorak; Satoh *J. Am. Chem. Soc.* **1990**, 112, 1109.

⁷⁹³Sharma; Pandhi *J. Org. Chem.* **1990**, 55, 2196.

⁷⁹⁴See Moore; Hernandez; Chambers *J. Am. Chem. Soc.* **1978**, 100, 2245; Pacansky; Chang; Brown; Schwarz *J. Org. Chem.* **1982**, 47, 2233; Brady; Shieh *J. Org. Chem.* **1983**, 48, 2499.

⁷⁹⁵For example, see Perelman; Mizesak *J. Am. Chem. Soc.* **1962**, 84, 4988; Opitz; Koch *Angew. Chem. Int. Ed. Engl.* **1963**, 2, 152 [*Angew. Chem.* 75, 167].

⁷⁹⁶For reviews of this compound, see Kamal; Sattur *Heterocycles* **1987**, 26, 1051-1076; Szabo *Aldrichimica Acta* **1977**, 10, 23-29; Rasmussen; Hassner *Chem. Rev.* **1976**, 76, 389-408; Graf *Angew. Chem. Int. Ed. Engl.* **1968**, 7, 172-182 [*Angew. Chem.* 80, 179-189].

⁷⁹⁷Graf *Liebigs Ann. Chem.* **1963**, 661, 111; Bestian *Pure Appl. Chem.* **1971**, 27, 611-634. See also Barrett; Betts; Fenwick *J. Org. Chem.* **1985**, 50, 169.

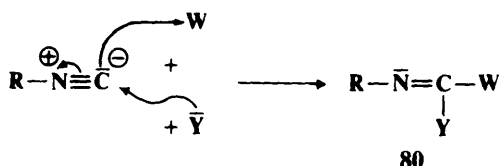
⁷⁹⁸Moriconi; Kelly *J. Am. Chem. Soc.* **1966**, 88, 3657, *J. Org. Chem.* **1968**, 33, 3036. See also Martin; Carter; Chitwood *J. Org. Chem.* **1971**, 36, 2225.

⁷⁹⁹Moriconi; Meyer *J. Org. Chem.* **1971**, 36, 2841; Malpass; Tweddle *J. Chem. Soc. Perkin Trans. I* **1977**, 874.

⁸⁰⁰Moriconi; Kelly; Salomone *J. Org. Chem.* **1968**, 33, 3448.

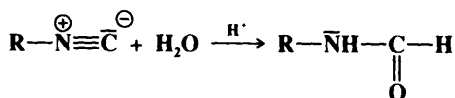
Addition to Isocyanides⁸⁰¹

Addition to $\text{R}-\text{N}^{\oplus}\equiv\text{C}^{\ominus}$ is not a matter of a species with an electron pair adding to one atom and a species without a pair adding to the other, as is addition to the other types of double and triple bonds in this chapter and Chapter 15. In these additions the electrophile and the nucleophile *both add to the carbon*. No species add to the nitrogen, which, however, loses its positive charge by obtaining as an unshared pair one of the triple-bond pairs of electrons:

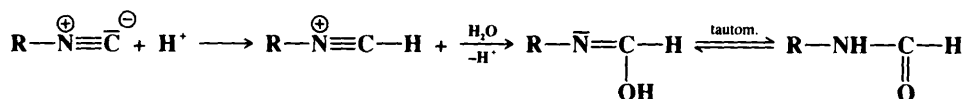


In most of the reactions considered below, **80** undergoes a further reaction, so the product is of the form $\text{R}-\text{NH}-\text{C}(\text{---})_2$. See also 9-30.

6-65 The Addition of Water to Isocyanides 1/N,2/C-Dihydro-2/C-oxo-biaddition



Formamides can be prepared by the acid-catalyzed addition of water to isocyanides. The mechanism is probably⁸⁰²



The reaction has also been carried out under alkaline conditions, with OH^- in aqueous dioxane.⁸⁰³ The mechanism here involves nucleophilic attack by OH^- at the carbon atom.

6-66 The Reduction of Isocyanides 1/N,2,2,2/C-Tetrahydro-biaddition

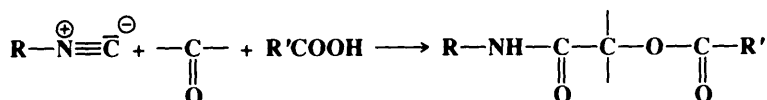


Isocyanides have been reduced to N-methylamines with lithium aluminum hydride as well as with other reducing agents.

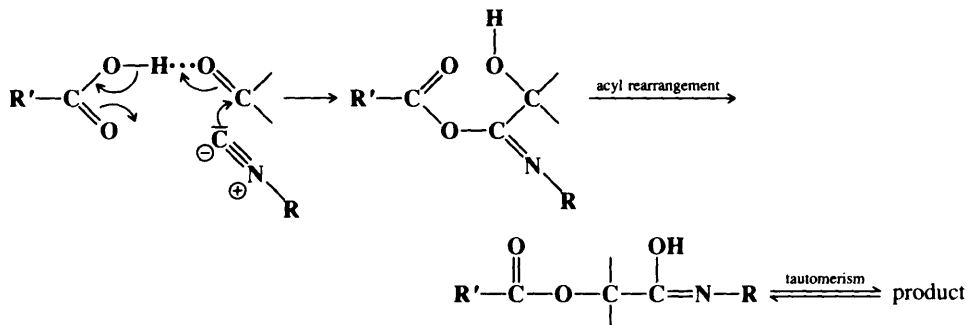
⁸⁰¹For a monograph, see Ugi *Isonitrile Chemistry*; Academic Press: New York, 1971. For reviews, see Walborsky; Periasamy, in Patai; Rappoport, Ref. 694, pt. 2, pp. 835-887; Hoffmann; Marquarding; Kliemann; Ugi, in Rappoport, Ref. 334, pp. 853-883.

⁸⁰²Drenth; *Recl. Trav. Chim. Pays-Bas* **1962**, 81, 319; Lim; *Stein Can. J. Chem.* **1971**, 49, 2455.

⁸⁰³Cunningham; Buist; *Arkle J. Chem. Soc., Perkin Trans. 2* **1991**, 589.

6-67 The Passerini and Ugi Reactions⁸⁰⁴**1/N-Hydro-2/C-(α -acyloxyalkyl),2/C-oxo-biaddition**

When an isocyanide is treated with a carboxylic acid and an aldehyde or ketone, an α -acyloxy amide is prepared. This is called the *Passerini reaction*. The following mechanism has been postulated:

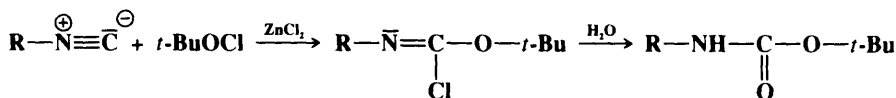
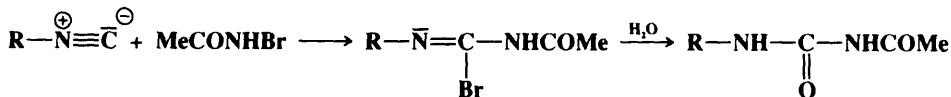


If ammonia or an amine is also added to the mixture (in which case the reaction is known as the *Ugi reaction*, or the *Ugi four-component condensation*, abbreviated 4 CC),

the product is the corresponding bisamide $\text{R}'-\text{C}(=\text{O})-\text{NH}-\text{C}(\text{OR}')-\text{C}(=\text{O})-\text{NH}-\text{R}$ (from NH_3) or

$\text{R}'-\text{C}(=\text{O})-\text{NR}''-\text{C}(\text{OR}')-\text{C}(=\text{O})-\text{NH}-\text{R}$ (from a primary amine $\text{R}''\text{NH}_2$). This product probably arises

from a reaction between the carboxylic acid, the isocyanide, and the *imine* formed from the aldehyde or ketone and ammonia or the primary amine. The use of an N-protected amino acid or peptide as the carboxylic acid component and/or the use of an isocyanide containing a C-protected carboxyl group allows the reaction to be used for peptide synthesis.⁸⁰⁵

6-68 The Addition of O- and N-Halides to Isocyanides**1/N-Hydro-2/C-butoxy,2/C-oxo-biaddition****1/N-Hydro-2/C-acylamino,2/C-oxo-biaddition**

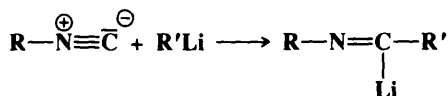
⁸⁰⁴For reviews, see Ugi *Angew. Chem. Int. Ed. Engl.* **1982**, 21, 810-819 [*Angew. Chem.* 94, 826-836]; Marquarding; Gokel; Hoffmann; Ugi, in Ugi, Ref. 801, pp. 133-143; Gokel; Lüdke; Ugi, in Ugi, Ref. 801, pp. 145-199, 252-254.

⁸⁰⁵For reviews, see Ugi, in Gross; Meienhofer *The Peptides*, vol. 2; Academic Press: New York, 1980, pp. 365-381, *Intra-Sci. Chem. Rep.* **1971**, 5, 229-261, *Rec. Chem. Prog.* **1969**, 30, 289-311; Gokel; Hoffmann; Kleimann; Klusacek; Lüdke; Marquarding; Ugi, in Ugi, Ref. 801, pp. 201-215. See also Kunz; Pfengle *J. Am. Chem. Soc.* **1988**, 110, 651.

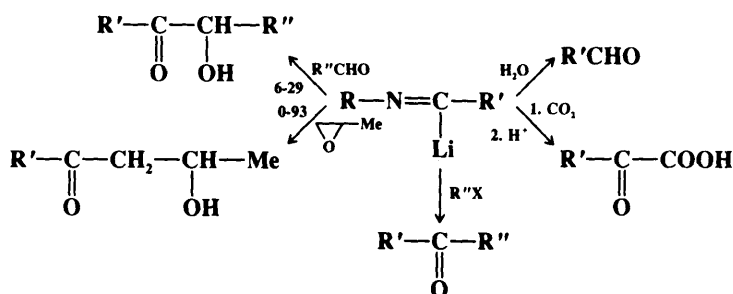
Alkyl hypochlorites and N-halo amides add to isocyanides to give, after hydrolysis, carbamates and N-acylureas (ureides), respectively.⁸⁰⁶

6-69 The Formation of Metalated Aldimines

1/1/Lithio-alkyl-addition



Isocyanides that do not contain an α hydrogen react with alkyllithium compounds,⁸⁰⁷ as well as with Grignard reagents, to give lithium (or magnesium) aldimines.⁸⁰⁸ These metalated aldimines are versatile nucleophiles and react with various substrates as follows (see also 8-25):



The reaction therefore constitutes a method for converting an organometallic compound $\text{R}'\text{M}$ to an aldehyde $\text{R}'\text{CHO}$ (see also 2-32), an α -keto acid,⁸⁰⁹ a ketone $\text{R}'\text{COR}$ (see also 2-32), an α -hydroxy ketone, or a β -hydroxy ketone. In each case the $\text{C}=\text{N}$ bond is hydrolyzed to a $\text{C}=\text{O}$ bond (6-2).

In a related reaction, isocyanides can be converted to aromatic aldimines by treatment with an iron complex followed by irradiation in benzene solution: $\text{RNC} + \text{C}_6\text{H}_6 \rightarrow \text{PhCH}=\text{NR}$.⁸¹⁰

OS VI, 751.

⁸⁰⁶Okano; Ito; Shono; Oda *Bull. Chem. Soc. Jpn.* **1963**, 36, 1314. See also Yamada; Wada; Tanimoto; Okano *Bull. Chem. Soc. Jpn.* **1982**, 55, 2480.

⁸⁰⁷For a review of other metallation reactions of isocyanides, see Ito; Murakami *Synlett* **1990**, 245-250.

⁸⁰⁸Niznik; Morrison; Walborsky *J. Org. Chem.* **1974**, 39, 600; Marks; Walborsky *J. Org. Chem.* **1981**, 46, 5405, **1982**, 47, 52. See also Walborsky; Ronman *J. Org. Chem.* **1978**, 43, 731. For the formation of zinc aldimines, see Murakami; Ito; Ito *J. Org. Chem.* **1988**, 53, 4158.

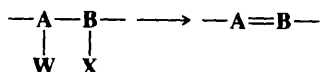
⁸⁰⁹For a review of the synthesis and properties of α -keto acids, see Cooper; Ginos; Meister *Chem. Rev.* **1983**, 83, 321-358.

⁸¹⁰Jones; Foster; Putinas *J. Am. Chem. Soc.* **1987**, 109, 5047.

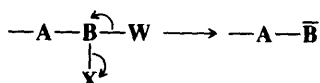
17

ELIMINATIONS

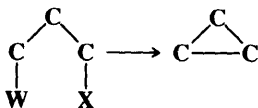
When two groups are lost from adjacent atoms so that a new double (or triple) bond is



formed the reaction is called β *elimination*; one atom is the α , the other the β atom. In an α elimination both groups are lost from the same atom to give a carbene (or a nitrene):



In a γ elimination, a three-membered ring is formed:



Some of these processes were discussed in Chapter 10. Another type of elimination involves the expulsion of a fragment from within a chain or ring ($\text{X---Y---Z} \rightarrow \text{X---Z} + \text{Y}$). Such reactions are called *extrusion reactions*. This chapter discusses β elimination and (beginning on p. 1045) extrusion reactions; however, β elimination in which both X and W are hydrogens are oxidation reactions and are treated in Chapter 19.

MECHANISMS AND ORIENTATION

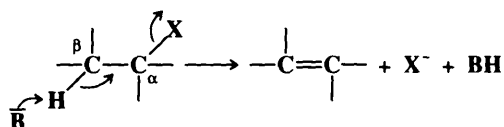
β elimination reactions may be divided into two types; one type taking place largely in solution, the other (pyrolytic eliminations) mostly in the gas phase. In the reactions in solution one group leaves with its electrons and the other without, the latter most often being hydrogen. In these cases we refer to the former as the leaving group or nucleofuge. For pyrolytic eliminations there are two principal mechanisms, one pericyclic and the other a free-radical pathway. A few photochemical eliminations are also known (the most important is Norrish type II cleavage of ketones, p. 243), but these are not generally of synthetic importance¹ and will not be discussed further. In most β eliminations the new bonds are

¹For synthetically useful examples of Norrish type II cleavage, see Neckers; Kellogg; Prins; Schoustra *J. Org. Chem.* **1971**, *36*, 1838.

$C=C$ or $C\equiv C$; our discussion of mechanisms is largely confined to these cases.² Mechanisms in solution (E2, E1, E1cB) are discussed first.

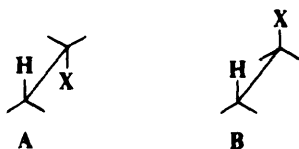
The E2 Mechanism

In the E2 mechanism (elimination, bimolecular), the two groups depart simultaneously, with the proton being pulled off by a base:



The mechanism thus takes place in one step and kinetically is second order: first order in substrate and first order in base. The IUPAC designation is $A_{\text{XH}}D_{\text{H}}D_{\text{N}}$, or more generally (to include cases where the electrofuge is not hydrogen), $A_{\text{N}}D_{\text{E}}D_{\text{N}}$. It is analogous to the $S_{\text{N}}2$ mechanism (p. 294) and often competes with it. With respect to the substrate, the difference between the two pathways is whether the species with the unshared pair attacks the carbon (and thus acts as a nucleophile) or the hydrogen (and thus acts as a base). As in the case of the $S_{\text{N}}2$ mechanism, the leaving group may be positive or neutral and the base may be negatively charged or neutral.

Among the evidence for the existence of the E2 mechanism are: (1) the reaction displays the proper second-order kinetics; (2) when the hydrogen is replaced by deuterium in second-order eliminations, there is an isotope effect of from 3 to 8, consistent with breaking of this bond in the rate-determining step.³ However, neither of these results alone could prove an E2 mechanism, since both are compatible with other mechanisms also (e.g., see E1cB p. 991). The most compelling evidence for the E2 mechanism is found in stereochemical studies.⁴ As will be illustrated in the examples below, the E2 mechanism is stereospecific: the five atoms involved (including the base) in the transition state must be in one plane. There are two ways for this to happen. The H and X may be trans to one another (A) with a dihedral angle of 180° , or they may be cis (B) with a dihedral angle of 0° .⁵ Conformation



²For a monograph on elimination mechanisms, see Saunders: Cockerill *Mechanisms of Elimination Reactions*; Wiley: New York, 1973. For reviews, see Gandler, in Patai *Supplement A: The Chemistry of Double-bonded Functional Groups*, vol. 2, pt. 1; Wiley: New York, 1989, pp. 733-797; Aleskerov; Yufit; Kucherov *Russ. Chem. Rev.* **1978**, *47*, 134-147; Cockerill; Harrison, in Patai *The Chemistry of Functional Groups, Supplement A*, pt. 1; Wiley: New York, 1977, pp. 153-221; Willi *Chimia* **1977**, *31*, 93-101; More O'Ferrall, in Patai *The Chemistry of the Carbon-Halogen Bond*, pt. 2; Wiley: New York, 1973, pp. 609-675; Cockerill, in Bamford; Tipper *Comprehensive Chemical Kinetics*, vol. 9; Elsevier: New York, 1973, pp. 163-372; Saunders *Acc. Chem. Res.* **1976**, *9*, 19-25; Stirling *Essays Chem.* **1973**, *5*, 123-149; Bordwell *Acc. Chem. Res.* **1972**, *5*, 374-381; Fry *Chem. Soc. Rev.* **1972**, *1*, 163-210; LeBel *Adv. Alicyclic Chem.* **1971**, *3*, 195-290; Bunnett *Surv. Prog. Chem.* **1969**, *5*, 53-93; in Patai *The Chemistry of Alkenes*, vol. 1; Wiley: New York, 1964, the articles by Saunders, pp. 149-201 (eliminations in solution); and by Maccoll, pp. 203-240 (pyrolytic eliminations); Köbrich *Angew. Chem. Int. Ed. Engl.* **1965**, *4*, 49-68, pp. 59-63 [*Angew. Chem.* *77*, 75-94] (for the formation of triple bonds).

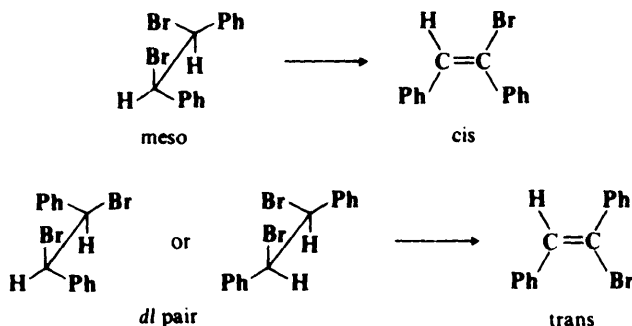
³See, for example, Saunders; Edison *J. Am. Chem. Soc.* **1960**, *82*, 138; Shiner; Smith *J. Am. Chem. Soc.* **1958**, *80*, 4095, **1961**, *83*, 593. For a review of isotope effects in elimination reactions, see Fry, Ref. 2.

⁴For reviews, see Bartsch; Závada *Chem. Rev.* **1980**, *80*, 453-494; Coke *Sel. Org. Transform.* **1972**, *2*, 269-307; Sicher *Angew. Chem. Int. Ed. Engl.* **1972**, *11*, 200-214 [*Angew. Chem.* *84*, 177-191]; *Pure Appl. Chem.* **1971**, *25*, 655-666; Saunders; Cockerill, Ref. 2, pp. 105-163; Cockerill, Ref. 2, pp. 217-235; More O'Ferrall, Ref. 2, pp. 630-640.

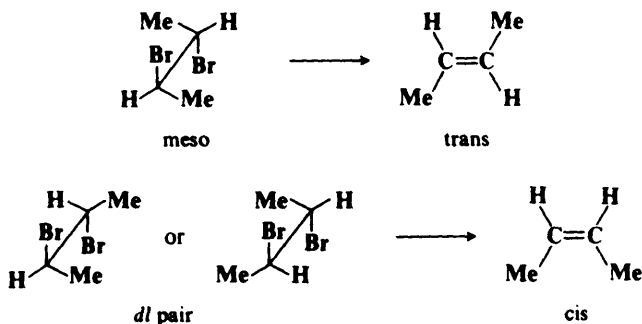
⁵DePuy; Morris; Smith; Smat *J. Am. Chem. Soc.* **1965**, *87*, 2421.

A is called *anti-periplanar*, and this type of elimination, in which H and X depart in opposite directions, is called *anti elimination*. Conformation **B** is *syn-periplanar*, and this type of elimination, with H and X leaving in the same direction, is called *syn elimination*. Many examples of both kinds have been discovered. In the absence of special effects (discussed below) anti elimination is usually greatly favored over syn elimination, probably because **A** is a staggered conformation (p. 139) and the molecule requires less energy to reach this transition state than it does to reach the eclipsed transition state **B**. A few of the many known examples of predominant or exclusive anti elimination follow.

1. Elimination of HBr from *meso*-1,2-dibromo-1,2-diphenylethane gave *cis*-2-bromostilbene, while the (+) or (−) isomer gave the *trans* olefin. This stereospecific result, which



was obtained in 1904,⁶ demonstrates that in this case elimination is anti. Many similar examples have been discovered since. Obviously, this type of experiment need not be restricted to compounds that have a *meso* form. Anti elimination requires that an *erythro dl* pair (or either isomer) give the *cis* olefin, and the *threo dl* pair (or either isomer) give the *trans* isomer, and this has been found many times. Anti elimination has also been demonstrated in cases where the electrofuge is not hydrogen. In the reaction of 2,3-dibromobutane with iodide ion, the two bromines are removed (7-29). In this case the *meso* compound gave the *trans* olefin and the *dl* pair the *cis*:⁷

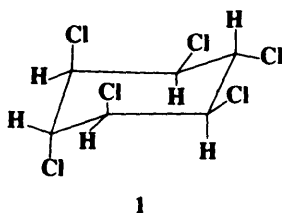


2. In open-chain compounds the molecule can usually adopt that conformation in which H and X are anti-periplanar. However, in cyclic systems this is not always the case. There

⁶Pfeiffer Z. Phys. Chem. 1904, 48, 40.

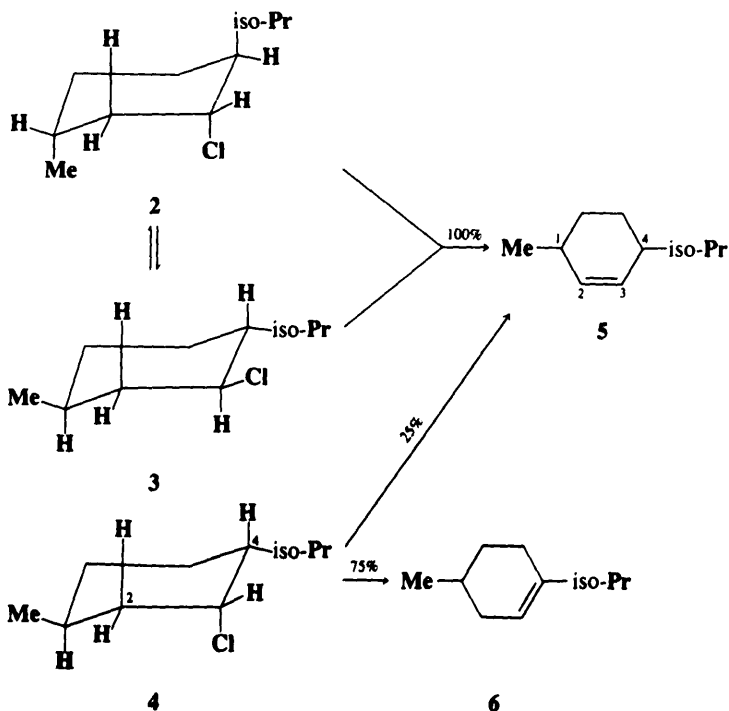
⁷Winstein; Pressman; Young J. Am. Chem. Soc. 1939, 61, 1645.

are nine stereoisomers of 1,2,3,4,5,6-hexachlorocyclohexane: seven meso forms and a *dl* pair (see p. 131). Four of the meso compounds and the *dl* pair (all that were then known) were subjected to elimination of HCl. Only one of these (**1**) has no Cl trans to an H. Of



the other isomers, the fastest elimination rate was about three times as fast as the slowest, but the rate for **1** was 7000 times slower than that of the slowest of the other isomers.⁸ This result demonstrates that with these compounds anti elimination is greatly favored over syn elimination, though the latter must be taking place on **1**, very slowly, to be sure.

3. The preceding result shows that elimination of HCl in a six-membered ring proceeds best when the H and X are trans to each other. However, there is an additional restriction. Adjacent trans groups on a six-membered ring can be diaxial or diequatorial (p. 144) and the molecule is generally free to adopt either conformation, though one may have a higher energy than the other. Anti-periplanarity of the leaving groups requires that they be diaxial, even if this is the conformation of higher energy. The results with menthyl and neomenthyl chlorides are easily interpretable on this basis. Menthyl chloride has two chair conformations,



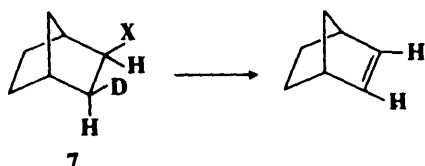
⁸Cristol *J. Am. Chem. Soc.* **1947**, *69*, 338; Cristol; Hause; Meek *J. Am. Chem. Soc.* **1951**, *73*, 674.

2 and **3**. **3**, in which the three substituents are all equatorial, is the more stable. The more stable chair conformation of neomenthyl chloride is **4**, in which the chlorine is axial; there are axial hydrogens on both C-2 and C-4. The results are: neomenthyl chloride gives rapid E2 elimination and the olefin produced is predominantly **6** (6/5 ratio is about 3:1) in accord with Zaitsev's rule (p. 998). Since an axial hydrogen is available on both sides, this factor does not control the direction of elimination and Zaitsev's rule is free to operate. However, for menthyl chloride, elimination is much slower and the product is entirely the anti-Zaitsev **5**. It is slow because the unfavorable conformation **2** has to be achieved before elimination can take place, and the product is **5** because only on this side is there an axial hydrogen.⁹

4. That anti elimination also occurs in the formation of triple bonds is shown by elimination from *cis*- and *trans*-HOOC—CH=CCl—COOH. In this case the product in both cases is HOOC≡CCOOH, but the *trans* isomer reacts about 50 times faster than the *cis* compound.¹⁰

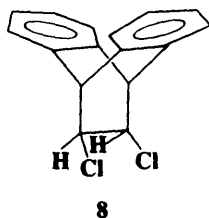
Some examples of syn elimination have been found in molecules where H and X could not achieve an anti-periplanar conformation.

1. The deuterated norbornyl bromide (**7**, X = Br) gave 94% of the product containing no deuterium.¹¹ Similar results were obtained with other leaving groups and with bicy-



clo[2.2.2] compounds.¹² In these cases the exo X group cannot achieve a dihedral angle of 180° with the endo β hydrogen because of the rigid structure of the molecule. The dihedral angle here is about 120°. These leaving groups prefer syn elimination with a dihedral angle of about 0° to anti elimination with an angle of about 120°.

2. The molecule **8** is a particularly graphic example of the need for a planar transition state. In **8** each Cl has an adjacent hydrogen trans to it, and if planarity of leaving groups



were not required, anti elimination could easily take place. However, the crowding of the rest of the molecule forces the dihedral angle to be about 120°, and elimination of HCl from

⁹Hughes; Ingold; Rose *J. Chem. Soc.* **1953**, 3839.

¹⁰Michael *J. Prakt. Chem.* **1895**, 52, 308. See also Marchese; Naso; Modena *J. Chem. Soc. B* **1968**, 958.

¹¹Kwart; Takeshita; Nyce *J. Am. Chem. Soc.* **1964**, 86, 2606.

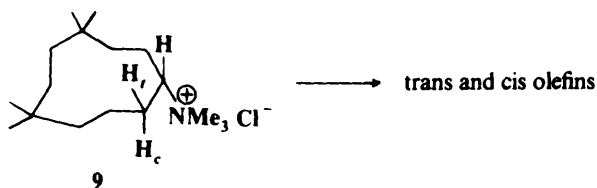
¹²For example, see Bird; Cookson; Hudec; Williams *J. Chem. Soc.* **1963**, 410; Stille; Sonnenberg; Kinstle *J. Am. Chem. Soc.* **1966**, 88, 4922; Coke; Cooke *J. Am. Chem. Soc.* **1967**, 89, 6701; DePuy; Naylor; Beckman *J. Org. Chem.* **1970**, 35, 2750; Brown; Liu *J. Am. Chem. Soc.* **1970**, 92, 200; Sicher; Pánkova; Závada; Kniežo; Orahovats *Collect. Czech. Chem. Commun.* **1971**, 36, 3128; Bartsch; Lee *J. Org. Chem.* **1991**, 56, 212, 2579.

8 is much slower than from corresponding nonbridged compounds.¹³ (Note that syn elimination from **8** is even less likely than anti elimination.) Syn elimination can take place from the *trans* isomer of **8** (dihedral angle about 0°); this isomer reacted about eight times faster than **8**.¹³

The examples so far given illustrate two points. (1) Anti elimination *requires* a dihedral angle of 180°. When this angle cannot be achieved, anti elimination is greatly slowed or prevented entirely. (2) For the simple systems so far discussed syn elimination is not found to any significant extent unless anti elimination is greatly diminished by failure to achieve the 180° angle.

As noted in Chapter 4 (p. 156), six-membered rings are the only ones among rings of four to thirteen members in which strain-free anti-periplanar conformations can be achieved. It is not surprising, therefore, that syn elimination is least common in six-membered rings. Cooke and Coke subjected cycloalkyltrimethylammonium hydroxides to elimination (**7-6**) and found the following percentages of syn elimination with ring size: four-membered, 90%; five-membered, 46%; six-membered, 4% seven-membered, 31 to 37%.¹⁴ It should be noted that the NMe₃⁺ group has a greater tendency to syn elimination than do other common leaving groups such as OTs, Cl, and Br.

Other examples of syn elimination have been found in medium-ring compounds, where both *cis* and *trans* olefins are possible (p. 128). As an illustration, we can look at experiments performed by Závada, Svoboda, and Sicher.¹⁵ These workers subjected 1,1,4,4-tetramethyl-7-cyclodecyltrimethylammonium chloride (**9**) to elimination and obtained mostly *trans*- but



also some *cis*-tetramethylcyclodecenes as products. (Note that *trans*-cyclodecenes, though stable, are less stable than the *cis* isomers). In order to determine the stereochemistry of the reaction, they repeated the elimination, this time using deuterated substrates. They found that when **9** was deuterated in the *trans* position ($H_i = D$), there was a substantial isotope effect in the formation of *both* *cis* and *trans* olefins, but when **9** was deuterated in the *cis* position ($H_c = D$), there was *no* isotope effect in the formation of either olefin. Since an isotope effect is expected for an E2 mechanism,¹⁶ these results indicated that *only* the *trans* hydrogen (H_i) was lost, whether the product was the *cis* or the *trans* isomer.¹⁷ This in turn means that the *cis* isomer must have been formed by anti elimination and the *trans* isomer by syn elimination. (Anti elimination could take place from approximately the conformation shown, but for syn elimination the molecule must twist into a conformation in which the C—H_i and C—NMe₃⁺ bonds are syn-periplanar.) This remarkable result, called the *syn-anti dichotomy*, has also been demonstrated by other types of evidence.¹⁸ The fact

¹³Cristol; Hause *J. Am. Chem. Soc.* **1952**, 74, 2193.

¹⁴Cooke; Coke *J. Am. Chem. Soc.* **1968**, 90, 5556. See also Coke; Smith; Britton *J. Am. Chem. Soc.* **1975**, 97, 4323.

¹⁵Závada; Svoboda; Sicher *Tetrahedron Lett.* **1966**, 1627, *Collect. Czech. Chem. Commun.* **1968**, 33, 4027.

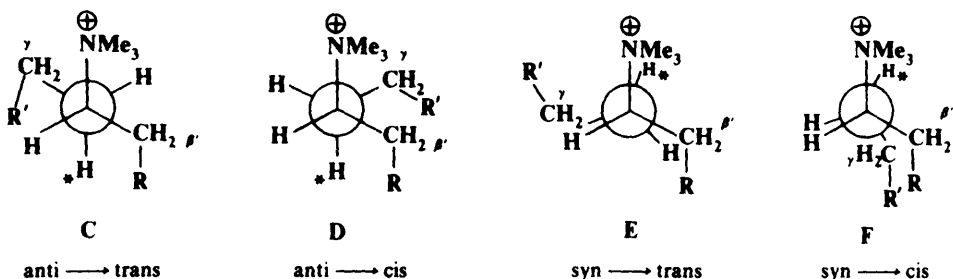
¹⁶Other possible mechanisms, such as E1cB (p. 991) or α' , β elimination (p. 1018), were ruled out in all these cases by other evidence.

¹⁷This conclusion has been challenged by Coke, Ref. 4.

¹⁸Sicher; Závada; Krupička *Tetrahedron Lett.* **1966**, 1619; Sicher; Závada *Collect. Czech. Chem. Commun.* **1967**, 32, 2122; Závada; Sicher *Collect. Czech. Chem. Commun.* **1967**, 32, 3701. For a review, see Bartsch; Závada, Ref. 4.

that syn elimination in this case predominates over anti (as indicated by the formation of trans isomer in greater amounts than cis) has been explained by conformational factors.¹⁹ The syn-anti dichotomy has also been found in other medium-ring systems (8- to 12-membered),²⁰ though the effect is greatest for 10-membered rings. With leaving groups,²¹ the extent of this behavior decreases in the order $\text{NMe}_3^+ > \text{OTs} > \text{Br} > \text{Cl}$, which parallels steric requirements. When the leaving group is uncharged, syn elimination is favored by strong bases and by weakly ionizing solvents.²²

Syn elimination and the syn-anti dichotomy have also been found in open-chain systems, though to a lesser extent than in medium-ring compounds. For example, in the conversion of 3-hexyl-4-*d*-trimethylammonium ion to 3-hexene with potassium *sec*-butoxide, about 67% of the reaction followed the syn-anti dichotomy.²³ In general syn elimination in open-chain systems is only important in cases where certain types of steric effect are present. One such type is compounds in which substituents are found on both the β' and the γ carbons (the unprimed letter refers to the branch in which the elimination takes place). The factors that cause these results are not completely understood, but the following conformational effects have been proposed as a partial explanation.²⁴ The two anti- and two syn-periplanar conformations are, for a quaternary ammonium salt:



In order for an E2 mechanism to take place a base must approach the proton marked *. In **C** this proton is shielded on both sides by R and R'. In **D** the shielding is on only one side. Therefore, when anti elimination does take place in such systems, it should give more cis product than trans. Also, when the normal anti elimination pathway is hindered sufficiently to allow the syn pathway to compete, the anti \rightarrow trans route should be diminished more than the anti \rightarrow cis route. When syn elimination begins to appear, it seems clear that **E**, which is less eclipsed than **F**, should be the favored pathway and syn elimination should generally give the trans isomer. In general, deviations from the syn-anti dichotomy are greater on the trans side than on the cis. Thus, trans olefins are formed partly or mainly by syn elimination, but cis olefins are formed entirely by anti elimination. Predominant syn

¹⁹For discussions, see Ref. 4.

²⁰For example, see Coke; Mourning *J. Am. Chem. Soc.* **1968**, *90*, 5561, where the experiment was performed on cyclooctyltrimethylammonium hydroxide, and *trans*-cyclooctene was formed by a 100% syn mechanism, and *cis*-cyclooctene by a 51% syn and 49% anti mechanism.

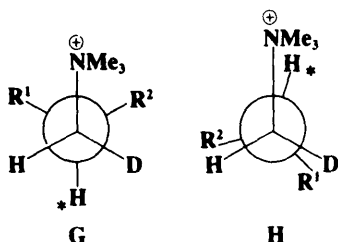
²¹For examples with other leaving groups, see Závada; Krupička; Sicher *Chem. Commun.* **1967**, *66*, Collect. Czech. Chem. Commun. **1968**, *33*, 1393; Sicher; Jan; Schlosser *Angew. Chem. Int. Ed. Engl.* **1971**, *10*, 926 [*Angew. Chem.* **83**, 1012]; Závada; Pánková *Collect. Czech. Chem. Commun.* **1980**, *45*, 2171.

²²See, for example, Sicher; Závada *Collect. Czech. Chem. Commun.* **1968**, *33*, 1278.

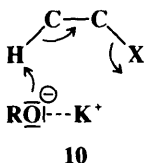
²³Bailey; Saunders *Chem. Commun.* **1968**, 1598, *J. Am. Chem. Soc.* **1970**, *92*, 6904. For other examples of syn elimination and the syn-anti dichotomy in open-chain systems, see Pánková; Sicher; Závada *Chem. Commun.* **1967**, 394; Pánková; Vítek; Vašíčková; Řeřicha; Závada *Collect. Czech. Chem. Commun.* **1972**, *37*, 3456; Schlosser; An *Helv. Chim. Acta* **1979**, *62*, 1194; Sugita; Nakagawa; Nishimoto; Kasai; Ichikawa *Bull. Chem. Soc. Jpn.* **1979**, *52*, 871; Pánková; Kocián; Krupička; Závada *Collect. Czech. Chem. Commun.* **1983**, *48*, 2944.

²⁴Bailey; Saunders, Ref. 23; Chiao; Saunders *J. Am. Chem. Soc.* **1977**, *99*, 6699.

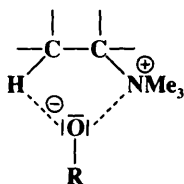
elimination has also been found in compounds of the form $R^1R^2CHCHDNMe_3^+$, where R^1 and R^2 are both bulky.²⁵ In this case also the conformation leading to syn elimination (**H**) is less strained than **G**, which gives anti elimination. **G** has three bulky groups (including NMe_3^+) in the gauche position to each other.



It was mentioned above that weakly ionizing solvents promote syn elimination when the leaving group is uncharged. This is probably caused by ion pairing, which is greatest in nonpolar solvents.²⁶ Ion pairing can cause syn elimination with an uncharged leaving group by means of the transition state shown in **10**. This effect was graphically illustrated by



elimination from 1,1,4,4-tetramethyl-7-cyclodecyl bromide.²⁷ The ratio of syn to anti elimination when this compound was treated with *t*-BuOK in the nonpolar benzene was 55.0. But when the crown ether dicyclohexano-18-crown-6 was added (this compound selectively removes K^+ from the $t\text{-BuO}^- K^+$ ion pair and thus leaves $t\text{-BuO}^-$ as a free ion), the syn/anti ratio decreased to 0.12. Large decreases in the syn/anti ratio on addition of the crown ether were also found with the corresponding tosylate and with other nonpolar solvents.²⁸ However, with positively charged leaving groups the effect is reversed. Here, ion pairing *increases* the amount of anti elimination.²⁹ In this case a relatively free base (e.g., PhO^-) can be attracted to the leaving group, putting it in a favorable position for attack on the syn β hydrogen, while ion pairing would reduce this attraction.



²⁵Tao; Saunders *J. Am. Chem. Soc.* **1983**, *105*, 3183; Dohner; Saunders *J. Am. Chem. Soc.* **1986**, *108*, 245.

²⁶For reviews of ion pairing in this reaction, see Bartsch; Závada, Ref. 4; Bartsch *Acc. Chem. Res.* **1975**, *8*, 239-245.

²⁷Svoboda; Hapala; Závada *Tetrahedron Lett.* **1972**, 265.

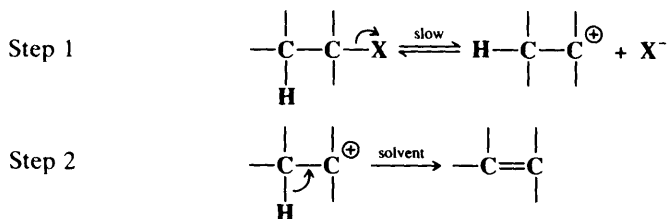
²⁸For other examples of the effect of ion pairing, see Bayne; Snyder *Tetrahedron Lett.* **1971**, 571; Bartsch; Wiegers *Tetrahedron Lett.* **1972**, 3819; Fiandanese; Marchese; Naso; Sciacovelli *J. Chem. Soc., Perkin Trans. 2* **1973**, 1336; Borchardt; Swanson; Saunders *J. Am. Chem. Soc.* **1974**, *96*, 3918; Mano; Sera; Maruyama *Bull. Chem. Soc. Jpn.* **1974**, *47*, 1758; Závada; Pánková; Svoboda *Collect. Czech. Chem. Commun.* **1976**, *41*, 3778; Baciocchi; Ruzziconi; Sebastiani *J. Org. Chem.* **1979**, *44*, 3718; Croft; Bartsch *Tetrahedron Lett.* **1983**, *24*, 2737; Kwart; Gaffney; Wilk *J. Chem. Soc., Perkin Trans. 2* **1984**, 565.

²⁹Borchardt; Saunders *J. Am. Chem. Soc.* **1974**, *96*, 3912.

We can conclude that anti elimination is generally favored in the E2 mechanism, but that steric (inability to form the anti-periplanar transition state), conformational, ion-pairing, and other factors cause syn elimination to intervene (and even predominate) in some cases.

The E1 Mechanism

The E1 mechanism is a two-step process in which the rate-determining step is ionization of the substrate to give a carbocation that rapidly loses a β proton to a base, usually the solvent:

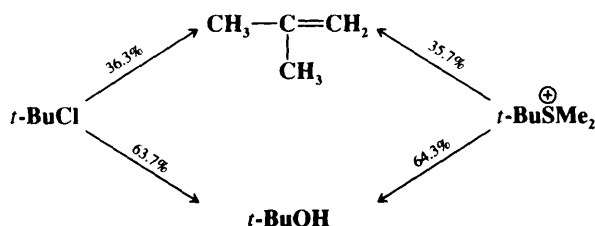


The IUPAC designation is $\text{D}_\text{N} + \text{D}_\text{E}$ (or $\text{D}_\text{N} + \text{D}_\text{H}$). This mechanism normally operates without an *added* base. Just as the E2 mechanism is analogous to and competes with the $\text{S}_\text{N}2$, so is the E1 mechanism related to the $\text{S}_\text{N}1$. In fact, the first step of the E1 is exactly the same as that of the $\text{S}_\text{N}1$ mechanism. The second step differs in that the solvent pulls a proton from the β carbon of the carbocation rather than attacking it at the positively charged carbon, as in the $\text{S}_\text{N}1$ process. In a pure E1 reaction (i.e., without ion pairs, etc.) the product should be completely nonstereospecific, since the carbocation is free to adopt its most stable conformation before giving up the proton.

Some of the evidence for the E1 mechanism is as follows:

1. The reaction exhibits first-order kinetics (in substrate) as expected. Of course the solvent is not expected to appear in the rate equation, even if it were involved in the rate-determining step (p. 222), but this point can be easily checked by adding a small amount of the conjugate base of the solvent. It is generally found that such an addition does not increase the rate of the reaction. If this more powerful base does not enter into the rate-determining step, it is unlikely that the solvent does. An example of an E1 mechanism with a rate-determining second step (proton transfer) has been reported.³⁰

2. If the reaction is performed on two molecules that differ only in the leaving group (for example, *t*-BuCl and *t*-BuSM₂⁺), the rates should obviously be different, since they depend on the ionizing ability of the molecule. However, once the carbocation is formed, if the solvent and the temperature are the same, it should suffer the same fate in both cases, since the nature of the leaving group does not affect the second step. This means that *the ratio of elimination to substitution should be the same*. The compounds mentioned in the example were solvolyzed at 65.3°C in 80% aqueous ethanol with the following results:³¹



³⁰Bacocchi; Clementi; Sebastiani; Ruzziconi *J. Org. Chem.* **1979**, *44*, 32.

³¹Cooper; Hughes; Ingold; MacNulty *J. Chem. Soc.* **1948**, 2038.

Although the rates were greatly different (as expected with such different leaving groups), the product ratios were the same, within 1%. If this had taken place by a second-order mechanism, the nucleophile would not be expected to have the same ratio of preference for attack at the β hydrogen compared to attack at a *neutral* chloride as for attack at the β hydrogen compared to attack at a *positive* SMe_2 group.

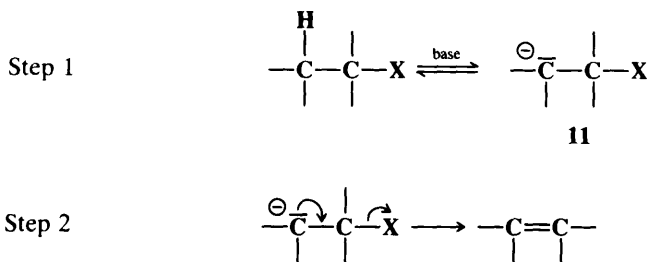
3. Many reactions carried out under first-order conditions on systems where E2 elimination is anti proceed quite readily to give olefins where a *cis* hydrogen must be removed, often in preference to the removal of a *trans* hydrogen. For example, menthyl chloride (**2**, p. 985), which by the E2 mechanism gave only **5**, under E1 conditions gave 68% **6** and 32% **5**, since the steric nature of the hydrogen is no longer a factor here, and the more stable olefin (Zaitsev's rule, p. 998) is predominantly formed.

4. If carbocations are intermediates, we should expect rearrangements with suitable substrates. These have often been found in elimination reactions performed under E1 conditions.

E1 reactions can involve ion pairs, just as is true for $\text{S}_{\text{N}}1$ reactions (p. 302).³² This effect is naturally greatest for nondissociating solvents: it is least in water, greater in ethanol, and greater still in acetic acid. It has been proposed that the ion-pair mechanism (p. 305) extends to elimination reactions too, and that the $\text{S}_{\text{N}}1$, $\text{S}_{\text{N}}2$, E1, and E2 mechanisms possess in common an ion-pair intermediate, at least occasionally.³³

The E1cB Mechanism³⁴

In the E1 mechanism, X leaves first and then H. In the E2 mechanism the two groups leave at the same time. There is a third possibility: the H leaves first and then the X. This is a two-step process, called the *E1cB mechanism*, or the *carbanion mechanism*, since the intermediate is a carbanion:



The name E1cB comes from the fact that it is the conjugate base of the substrate that is giving up the leaving group (see the $\text{S}_{\text{N}}1\text{cB}$ mechanism, p. 356). The IUPAC designation is $\text{A}_{\text{N}}\text{D}_{\text{E}} + \text{D}_{\text{N}}$ or $\text{A}_{\text{XH}}\text{D}_{\text{H}} + \text{D}_{\text{N}}$ (see p. 290). We can distinguish three limiting cases: (1) The carbanion returns to starting material faster than it forms product: step 1 is reversible;

³²Cocivera; Winstein *J. Am. Chem. Soc.* **1963**, *85*, 1702; Smith; Goon *J. Org. Chem.* **1969**, *34*, 3127; Bunnett; Eck *J. Org. Chem.* **1971**, *36*, 897; Sridharan; Vitullo *J. Am. Chem. Soc.* **1977**, *99*, 8093; Seib; Shiner; Sendjarević; Humski *J. Am. Chem. Soc.* **1978**, *100*, 8133; Jansen; Koshy; Mangru; Tidwell *J. Am. Chem. Soc.* **1981**, *103*, 3863; Coxon; Simpson; Steel; Whiting *Tetrahedron* **1984**, *40*, 3503; Thibblin *J. Am. Chem. Soc.* **1987**, *109*, 2071, *J. Phys. Org. Chem.* **1989**, *2*, 15.

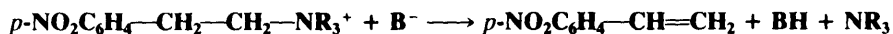
³³Sneen; Robbins *J. Am. Chem. Soc.* **1969**, *91*, 3100, Sneen *Acc. Chem. Res.* **1973**, *6*, 46-53. See, however, McLennan *J. Chem. Soc., Perkin Trans. 2* **1972**, 1577.

³⁴For reviews, see Cockerill; Harrison, *Ref. 2*, pp. 158-178; Hunter *Intra-Sci. Chem. Rep.* **1973**, *7*(3), 19-26; McLennan *Q. Rev., Chem. Soc.* **1967**, *21*, 490-506. For a general discussion, see Koch *Acc. Chem. Res.* **1984**, *17*, 137-144.

step 2 is slow. (2) Step 1 is the slow step, and formation of product is faster than return of the carbanion to starting material. In this case step 1 is essentially irreversible. (3) Step 1 is rapid, and the carbanion goes slowly to product. This case occurs only with the most stable carbanions. Here, too, step 1 is essentially irreversible. These cases have been given the designations: (1) $(\text{E1cB})_{\text{R}}$, (2) $(\text{E1cB})_{\text{I}}$ (or E1cB_{irr}), and (3) $(\text{E1})_{\text{anion}}$. Their characteristics are listed in Table 17.1.³⁵ Investigations of the reaction order are generally not very useful (except for case 3 which is first order), because cases 1 and 2 are second order and thus difficult or impossible to distinguish from the E2 mechanism by this procedure.³⁶ We would expect the greatest likelihood of finding the E1cB mechanism in substrates that have (a) a poor nucleofuge and (b) an acidic hydrogen, and most investigations have concerned such substrates. The following is some of the evidence in support of the E1cB mechanism.

1. The first step of the $(\text{E1cB})_{\text{R}}$ mechanism involves a reversible exchange of protons between the substrate and the base. In that case, if deuterium is present in the base, recovered starting material should contain deuterium. This was found to be the case in the treatment of $\text{Cl}_2\text{C}=\text{CHCl}$ with NaOD to give $\text{ClC}\equiv\text{CCl}$. When the reaction was stopped before completion, there was deuterium in the recovered olefin.³⁷ A similar result was found for pentahaloethanes.³⁸ These substrates are relatively acidic. In both cases the electron-withdrawing halogens increase the acidity of the hydrogen, and in the case of trichloroethylene there is the additional factor that a hydrogen on an sp^2 carbon is more acidic than one on an sp^3 carbon (p. 269). Thus, the E1cB mechanism is more likely to be found in eliminations yielding triple bonds than in those giving double bonds. Another likely place for the E1cB mechanism should be in reaction of a substrate like $\text{PhCH}_2\text{CH}_2\text{Br}$, since the carbanion is stabilized by resonance with the phenyl group. Nevertheless, no deuterium exchange was found here.³⁹ If this type of evidence is a guide, then it may be inferred that the $(\text{E1cB})_{\text{R}}$ mechanism is quite rare, at least for eliminations with common leaving groups such as Br, Cl, or OTs, which yield $\text{C}=\text{C}$ double bonds.

2. When the reaction



was carried out in water containing acetohydroxamate buffers, a plot of the rate against the buffer concentration was curved and the rate leveled off at high buffer concentrations, indicating a change in rate-determining step.⁴⁰ This rules out an E2 mechanism, which has only one step. When D_2O was used instead of H_2O as solvent, there was an initial inverse solvent isotope effect of 7.7 (the highest inverse solvent isotope effect yet reported). That is, the reaction took place faster in D_2O than in H_2O . This is compatible only with an E1cB mechanism in which the proton-transfer step is not entirely rate-determining. The isotope effect arises from a partitioning of the carbanion intermediate **11**. This intermediate either can go to product or it can revert to starting compound, which requires taking a proton from the solvent. In D_2O the latter process is slower (because the O—D bond of D_2O cleaves less easily than the O—H bond of H_2O), reducing the rate at which **11** returns to

³⁵This table, which appears in Cockerill; Harrison, Ref. 2, p. 161, was adapted from a longer one in Bordwell, Ref. 2, p. 375.

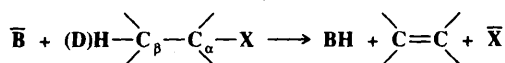
³⁶ $(\text{E1cB})_{\text{I}}$ cannot be distinguished from E2 by this means, because it has the identical rate law: $\text{Rate} = k[\text{substrate}][\text{B}^-]$. The rate law for $(\text{E1cB})_{\text{R}}$ is different: $\text{Rate} = k[\text{substrate}][\text{B}^-]/[\text{BH}]$, but this is often not useful because the only difference is that the rate is also dependent (inversely) on the concentration of the conjugate acid of the base, and this is usually the solvent, so that changes in its concentration cannot be measured.

³⁷Houser; Bernstein; Miekka; Angus *J. Am. Chem. Soc.* **1955**, *77*, 6201.

³⁸Hine; Wiesboeck; Ghirardelli *J. Am. Chem. Soc.* **1961**, *83*, 1219; Hine; Wiesboeck; Ramsay *J. Am. Chem. Soc.* **1961**, *83*, 1222.

³⁹Skell; Hauser *J. Am. Chem. Soc.* **1945**, *67*, 1661.

⁴⁰Keeffe; Jencks *J. Am. Chem. Soc.* **1963**, *105*, 265.

TABLE 17.1 Kinetic predictions for base-induced β -eliminations³⁵

Mechanism	Kinetic ^a order	β -hydrogen exchange faster than elimination	General or specific base catalysis	$k_{\text{H}}/k_{\text{D}}$	Electron withdrawal at C_{β} ^d	Electron release at C_{α} ^d	Leaving- group isotope effect or element effect
(E1) _{anion}	1	Yes	General ^c	1.0	Rate decrease	Rate increase	Substantial
(E1cB) _R	2	Yes	Specific	1.0	Small rate increase	Small rate increase	Substantial
(E1cB) _{ip}	2	No	General ^c	1.0 \rightarrow 1.2	Small rate increase	Small rate increase	Substantial
(E1cB) _I	2	No	General	2 \rightarrow 8	Rate increase	Little effect	Small to negligible
E2 ^b	2	No	General	2 \rightarrow 8	Rate increase	Small rate increase	Small

^aAll mechanisms exhibit first-order kinetics in substrate.

^bOnly transition states with considerable carbanion character considered in this table.

^cSpecific base catalysis predicted if extent of substrate ionization reduced from almost complete.

^dEffect on rate assuming no change in mechanism is caused; steric factors upon substitution at C_{α} and C_{β} have not been considered. The rate predictions are geared to substituent effects such as those giving rise to Hammett reaction constants on β - and α -aryl substitution.

^eDepends on whether ion pair assists in removal of leaving group.

starting compound. With the return reaction competing less effectively, the rate of conversion of **11** to product is increased.

3. We have predicted that the E1cB mechanism would be most likely to be found with substrates containing acidic hydrogens and poor leaving groups. Compounds of the type $\text{ZCH}_2\text{CH}_2\text{OPh}$, where Z is an electron-withdrawing group (e.g., NO_2 , SMe_2^+ , ArSO_2 , CN , COOR , etc.), belong to this category, because OPh is a very poor leaving group (p. 352). There is much evidence to show that the mechanism here is indeed E1cB.⁴¹ Isotope effects,

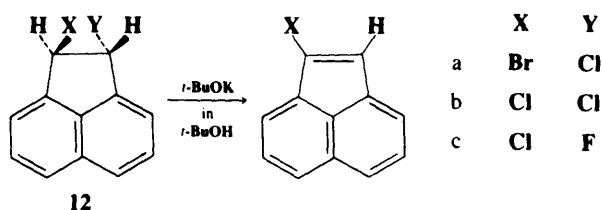
measured for $\text{MeSODCD}_2\text{CH}_2\text{OPh}$ and $\text{Me}_2\text{SCD}_2\text{CH}_2\text{OPh}$ with NaOD in D_2O , are about 0.7. This is compatible with an (E1cB)_R mechanism, but not with an E2 mechanism for which an isotope effect of perhaps 5 might be expected (of course, an E1 mechanism is precluded by the extremely poor nucleofugal ability of OPh). The fact that $k_{\text{H}}/k_{\text{D}}$ is less than the expected value of 1 is attributable to solvent and secondary isotope effects. Among other evidence for an E1cB mechanism in these systems is that changes in the identity of Z had a dramatic effect on the relative rates: a span of 10^{11} between NO_2 and COO^- . Note that elimination from substrates of the type $\text{RCOCH}_2\text{CH}_2\text{Y}$ is the reverse of Michael-type addition to $\text{C}=\text{C}$ bonds. We have seen (p. 741) that such addition involves initial attack by a nucleophile Y and subsequent attack by a proton. Thus the initial loss of a proton from substrates of this type (i.e., an E1cB mechanism) is in accord with the principle of microscopic reversibility.⁴² It may also be recalled that benzyne formation (p. 647) can occur by such a

⁴¹Crosby; Stirling *J. Chem. Soc. B* **1970**, 671, 679; Redman; Stirling *Chem. Commun.* **1970**, 633; Cann; Stirling *J. Chem. Soc., Perkin Trans. 2* **1974**, 820. For other examples; see Fedor *J. Am. Chem. Soc.* **1969**, 91, 908; More O'Ferrall; Slac *J. Chem. Soc. B* **1970**, 260; Kurzawa; Lefek *Can. J. Chem.* **1977**, 55, 1696.

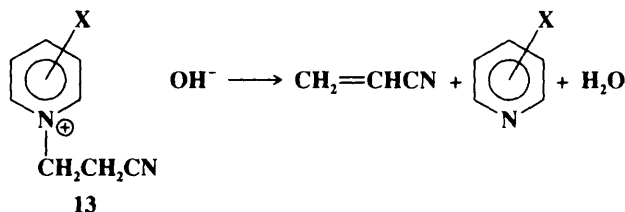
⁴²Patai; Weinstein; Rappoport *J. Chem. Soc.* **1962**, 1741. See also Hilbert; Fedor *J. Org. Chem.* **1978**, 43, 452.

process. It has been suggested that all base-initiated eliminations wherein the proton is activated by a strong electron-withdrawing group are E1cB reactions,⁴³ but there is evidence that this is not the case—that when there is a good nucleofuge, the mechanism is E2 even when strong electron-withdrawing groups are present.⁴⁴ On the other hand, Cl⁻ has been found to be a leaving group in an E1cB reaction.⁴⁵

Of the three cases of the E1cB mechanism, the one most difficult to distinguish from E2 is (E1cB)₁. One way to make this distinction is to study the effect of a change in leaving group. This was done in the case of the three acenaphthylenes **12**, where it was found that (1) the three rates were fairly similar, the largest being only about four times that of the



smallest, and (2) in compound c (X = Cl, Y = F), the only product contained Cl and no F, i.e., only the poorer nucleofuge F departed while Cl remained.⁴⁶ Result (1) rules out all the E1cB mechanisms except (E1cB)₁, because the others should all have considerable leaving group effects (Table 17.1). An ordinary E2 mechanism should also have a large leaving group effect, but an E2 mechanism with substantial carbanionic character (see the next section) might not. However, no E2 mechanism can explain result (2), which can be explained by the fact that an α Cl is more effective than an α F in stabilizing the planar carbanion that remains when the proton is lost. Thus (as in the somewhat similar case of aromatic nucleophilic substitution, see p. 653), when X⁻ leaves in the second step, the one that leaves is not determined by which is the better nucleofuge, but by which has had its β hydrogen removed.⁴⁷ Additional evidence for the existence of the (E1cB)₁ mechanism was the observation of a change in the rate-determining step in the elimination reaction of N-(2-cyanoethyl)pyridinium ions **13**, treated with base, when X was changed.⁴⁸ Once again,



the demonstration that two steps are involved precludes the one-step E2 mechanism.

⁴³Bordwell; Vestling; Yee *J. Am. Chem. Soc.* **1970**, 92, 5950; Bordwell, Ref. 2.

⁴⁴Marshall; Thomas; Stirling *J. Chem. Soc., Perkin Trans. 2* **1977**, 1898, 1914; Fishbein; Jencks *J. Am. Chem. Soc.* **1988**, 110, 5075, 5087; Banait; Jencks *J. Am. Chem. Soc.* **1990**, 112, 6950.

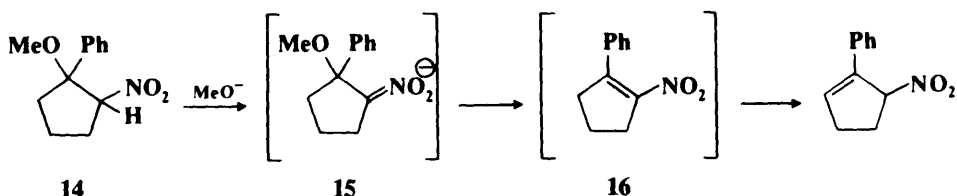
⁴⁵Ölwegård; McEwen; Thibblin; Ahlberg *J. Am. Chem. Soc.* **1985**, 107, 7494.

⁴⁶Baclocchi; Ruzziconi; Sebastiani *J. Org. Chem.* **1982**, 47, 3237.

⁴⁷For other evidence for the existence of the (E1cB)₁ mechanism, see Bordwell; Vestling; Yee, Ref. 43; Fedor; Glave *J. Am. Chem. Soc.* **1971**, 93, 985; Redman; Thomas; Stirling *J. Chem. Soc., Perkin Trans. 2* **1978**, 1135; Thibblin *Chem. Scr.* **1980**, 15, 121; Carey; More O'Ferrall; Vernon *J. Chem. Soc., Perkin Trans. 2* **1982**, 1581; Baclocchi; Ruzziconi *J. Org. Chem.* **1984**, 49, 3395; Jarczewski; Waligorska; Leffek *Can. J. Chem.* **1985**, 63, 1194; Gula; Vitale; Dostal; Trometer; Spencer *J. Am. Chem. Soc.* **1988**, 110, 4400; Garay; Cabaleiro *J. Chem. Res. (S)* **1988**, 388; Gandler; Storer; Ohlberg *J. Am. Chem. Soc.* **1990**, 112, 7756.

⁴⁸Bunting; Toth; Heo; Moors *J. Am. Chem. Soc.* **1990**, 112, 8878. See also Bunting; Kanter *J. Am. Chem. Soc.* **1991**, 113, 6950.

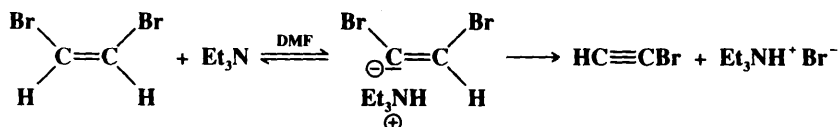
4. An example of an (E1)_{anion} mechanism has been found with the substrate **14**, which when treated with methoxide ion undergoes elimination to **16**, which is unstable under the



reaction conditions and rearranges as shown.⁴⁹ Among the evidence for the proposed mechanism in this case were kinetic and isotope-effect results, as well as the spectral detection of **15**.⁵⁰

5. In many eliminations to form C=O and C≡N bonds the initial step is loss of a positive group (normally a proton) from the oxygen or nitrogen. These may also be regarded as E1cB processes.

There is evidence that some E1cB mechanisms can involve carbanion ion pairs, e.g.,⁵¹



This case is designated (E1cB)_{ip}; its characteristics are shown in Table 17.1.

The E1–E2–E1cB Spectrum

In the three mechanisms so far considered the similarities are greater than the differences. In each case there is a leaving group that comes off with its pair of electrons and another group (usually hydrogen) that comes off without them. The only difference is in the order of the steps. It is now generally accepted that there is a spectrum of mechanisms ranging from one extreme, in which the leaving group departs well before the proton (pure E1), to the other extreme, in which the proton comes off first and then, after some time, the leaving group follows (pure E1cB). The *pure* E2 case would be somewhere in the middle, with both groups leaving simultaneously. However, most E2 reactions are not exactly in the middle, but somewhere to one side or the other. For example, the nucleofuge might depart just before the proton. This case may be described as an E2 reaction with a small amount of E1 character. The concept can be expressed by the question: In the transition state, which bond (C—H or C—X) has undergone more cleavage?⁵²

⁴⁹Bordwell; Yee; Knipe *J. Am. Chem. Soc.* **1970**, *92*, 5945.

⁵⁰For other examples of this mechanism, see Rappoport *Tetrahedron Lett.* **1968**, 3601; Berndt *Angew. Chem. Int. Ed. Engl.* **1969**, *8*, 613 [*Angew. Chem.* *81*, 567]; Albeck; Hoz; Rappoport *J. Chem. Soc., Perkin Trans. 2* **1972**, 1248, **1975**, 628.

⁵¹Kwok; Lee; Miller *J. Am. Chem. Soc.* **1969**, *91*, 468. See also Lord; Naan; Hall *J. Chem. Soc. B* **1971**, 220; Rappoport; Shohamy *J. Chem. Soc. B* **1971**, 2060; Fiandanes; Marchese; Naso *J. Chem. Soc., Chem. Commun.* **1972**, 250; Koch; Dahlberg; Toczko; Solsky *J. Am. Chem. Soc.* **1973**, *95*, 2029; Hunter; Shearing *J. Am. Chem. Soc.* **1973**, *95*, 8333; Thibblin; Ahlberg *J. Am. Chem. Soc.* **1977**, *99*, 7926, **1979**, *101*, 7311; Thibblin; Bengtsson; Ahlberg *J. Chem. Soc., Perkin Trans. 2* **1977**, 1569; Petrillo; Novi; Garbarino; Dell'Erba; Mugnoli *J. Chem. Soc., Perkin Trans. 2* **1985**, 1291.

⁵²For discussions, see Cockerill; Harrison, Ref. 2, pp. 178-189; Saunders *Acc. Chem. Res.*, Ref. 2; Bunnett, Ref. 2; Saunders; Cockerill, Ref. 2, pp. 47-104; Bordwell, Ref. 2.

One way to determine just where a given reaction stands on the E1-E2-E1cB spectrum is to study isotope effects, which ought to tell something about the behavior of bonds in the transition state.⁵³ For example, $\text{CH}_3\text{CH}_2\text{NMe}_3^+$ showed a nitrogen isotope effect (k^{14}/k^{15}) of 1.017, while $\text{PhCH}_2\text{CH}_2\text{NMe}_3^+$ gave a corresponding value of 1.009.⁵⁴ It would be expected that the phenyl group would move the reaction toward the E1cB side of the line, which means that for this compound the C—N bond is not as greatly broken in the transition state as it is for the unsubstituted one. The isotope effect bears this out, for it shows that in the phenyl compound, the mass of the nitrogen has less effect on the reaction rate than it does in the unsubstituted compound. Similar results have been obtained with SR_2^+ leaving groups by the use of $^{32}\text{S}/^{34}\text{S}$ isotope effects⁵⁵ and with Cl ($^{35}\text{Cl}/^{37}\text{Cl}$).⁵⁶ The position of reactions along the spectrum has also been studied from the other side of the newly forming double bond by the use of H/D and H/T isotope effects,⁵⁷ though interpretation of these results is clouded by the fact that β hydrogen isotope effects are expected to change smoothly from small to large to small again as the degree of transfer of the β hydrogen from the β carbon to the base increases⁵⁸ (recall—p. 227—that isotope effects are greatest when the proton is half-transferred in the transition state), by the possibility of secondary isotope effects (e.g., the presence of a β deuterium or tritium may cause the leaving group to depart more slowly), and by the possibility of tunneling⁵⁹ (see footnote 55 in Chapter 6). Other isotope-effect studies have involved labeled α or β carbon, labeled α hydrogen, or labeled base.⁵³

Another way to study the position of a given reaction on the spectrum involves the use of β aryl substitution. Since a positive Hammett ρ value is an indication of a negatively charged transition state, the ρ value for substituted β aryl groups should increase as a reaction moves from E1-like to E1cB-like along the spectrum. This has been shown to be the case in a number of studies;⁶⁰ e.g., ρ values of $\text{ArCH}_2\text{CH}_2\text{X}$ increase as the leaving-group ability of X decreases. A typical set of ρ values was: X = I, 2.07; Br, 2.14; Cl, 2.61; SMe_2^+ , 2.75; F, 3.12.⁶¹ As we have seen, decreasing leaving-group ability correlates with increasing E1cB character.

Still another method measures volumes of activation.⁶² These are negative for E2 and positive for E1cB mechanisms. Measurement of the activation volume therefore provides a continuous scale for deciding just where a reaction lies on the spectrum.

⁵³For a review, see Fry, Ref. 2. See also Hasan; Sims; Fry, *J. Am. Chem. Soc.* **1983**, 105, 3967; Pulay; Fry *Tetrahedron Lett.* **1986**, 27, 5055.

⁵⁴Ayrey; Bourns; Vyas *Can. J. Chem.* **1963**, 41, 1759. Also see Simon; Müllhofer *Chem. Ber.* **1963**, 96, 3167, **1964**, 97, 2202; *Pure Appl. Chem.* **1964**, 8, 379, 536; Smith; Bourns *Can. J. Chem.* **1970**, 48, 125.

⁵⁵Saunders; Zimmerman *J. Am. Chem. Soc.* **1964**, 86, 3789; Wu; Hargreaves; Saunders *J. Org. Chem.* **1985**, 50, 2392.

⁵⁶Grout; McLennan; Spackman *J. Chem. Soc., Perkin Trans. 2* **1977**, 1758.

⁵⁷For example, see Saunders; Edison *J. Am. Chem. Soc.* **1960**, 82, 138; Hodnett; Sparapany *Pure Appl. Chem.* **1964**, 8, 385, 537; Finley; Saunders *J. Am. Chem. Soc.* **1967**, 89, 898; Ghanbarpour; Willi *Liebigs Ann. Chem.* **1975**, 1295; Simon; Müllhofer, Ref. 54; Thibblin *J. Am. Chem. Soc.* **1988**, 110, 4582; Smith; Amin *Can. J. Chem.* **1989**, 67, 1457.

⁵⁸There is controversy as to whether such an effect has been established in this reaction: See Cockerill *J. Chem. Soc. B* **1967**, 964; Blackwell *J. Chem. Soc., Perkin Trans. 2* **1976**, 488.

⁵⁹For examples of tunneling in elimination reactions, see Miller; Saunders *J. Org. Chem.* **1981**, 46, 4247 and previous papers in this series. See also Shiner; Smith, Ref. 3; McLennan *J. Chem. Soc., Perkin Trans. 2* **1977**, 1753; Fouad; Farrell *Tetrahedron Lett.* **1978**, 4735; Koth; McLennan; Koch; Tumas; Dobson; Koch *J. Am. Chem. Soc.* **1983**, 105, 1930; Kwart; Wilk *J. Org. Chem.* **1985**, 50, 817; Amin; Price; Saunders *J. Am. Chem. Soc.* **1990**, 112, 4467.

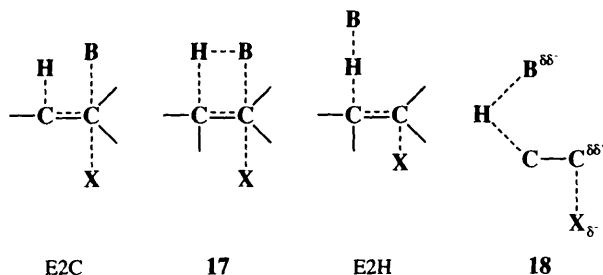
⁶⁰Saunders; Bushman; Cockerill *J. Am. Chem. Soc.* **1968**, 90, 1775; Oac; Yano *Tetrahedron* **1968**, 24, 5721; Yano; Oac *Tetrahedron* **1970**, 26, 27, 67; Blackwell; Buckley; Jolley; MacGibbon *J. Chem. Soc., Perkin Trans. 2* **1973**, 169; Smith; Tsui *J. Am. Chem. Soc.* **1973**, 95, 4760; *Can. J. Chem.* **1974**, 52, 749.

⁶¹DePuy; Froemsdorf *J. Am. Chem. Soc.* **1957**, 79, 3710; DePuy; Bishop *J. Am. Chem. Soc.* **1960**, 82, 2532, 2535.

⁶²Brower; Muhsin; Brower *J. Am. Chem. Soc.* **1976**, 98, 779. For a review, see van Eldik; Asano; le Noble *Chem. Rev.* **1989**, 89, 549-688.

The E2C Mechanism⁶³

Certain alkyl halides and tosylates undergo E2 eliminations faster when treated with such weak bases as Cl^- in polar aprotic solvents or PhS^- than with the usual E2 strong bases such as RO^- in ROH .⁶⁴ In order to explain these results Parker and co-workers proposed⁶⁵ that there is a spectrum⁶⁶ of E2 transition states in which the base can interact in the transition state with the α carbon as well as with the β hydrogen. At one end of this spectrum is a mechanism (called E2C) in which, in the transition state, the base interacts mainly with the



carbon. The E2C mechanism is characterized by strong nucleophiles that are weak bases. At the other extreme is the normal E2 mechanism, here called E2H to distinguish it from E2C, characterized by strong bases. **17** represents a transition state between these extremes. Additional evidence⁶⁷ for the E2C mechanism is derived from Brønsted equation considerations (p. 258), from substrate effects, from isotope effects, and from the effects of solvents on rates.

However, the E2C mechanism has been criticized, and it has been contended that all the experimental results can be explained by the normal E2 mechanism.⁶⁸ McLennan has suggested that the transition state is that shown as **18**.⁶⁹ An ion-pair mechanism has also been proposed.⁷⁰ Although the actual mechanisms involved may be a matter of controversy, there is no doubt that a class of elimination reactions exists that is characterized by second-order attack by weak bases.⁷¹ These reactions also have the following general characteris-

⁶³For reviews, see McLennan *Tetrahedron* **1975**, *31*, 2999-3010; Ford *Acc. Chem. Res.* **1973**, *6*, 410-415; Parker *CHEMTECH* **1971**, 297-303.

⁶⁴For example, see Winstein; Darwish; Holness *J. Am. Chem. Soc.* **1956**, *78*, 2915; de la Mare; Vernon *J. Chem. Soc.* **1956**, 41; Eliel; Ro *Tetrahedron* **1958**, *2*, 353; Bunnett; Davis; Tanida *J. Am. Chem. Soc.* **1962**, *84*, 1606; McLennan *J. Chem. Soc. B* **1966**, 705, 709; Hayami; Ono; Kaji *Bull. Chem. Soc. Jpn.* **1971**, *44*, 1628.

⁶⁵Parker; Ruane; Biale; Winstein *Tetrahedron Lett.* **1968**, 2113.

⁶⁶This is apart from the E1-E2-E1cB spectrum.

⁶⁷Lloyd; Parker *Tetrahedron Lett.* **1968**, 5183. **1970**, 5029; Cook; Parker; Ruane *Tetrahedron Lett.* **1968**, 5715; Alexander; Ko; Parker; Broxton *J. Am. Chem. Soc.* **1968**, *90*, 5049; Ko; Parker *J. Am. Chem. Soc.* **1968**, *90*, 6447; Parker; Ruane; Palmer; Winstein *J. Am. Chem. Soc.* **1972**, *94*, 2228; Biale; Parker; Stevens; Takahashi; Winstein *J. Am. Chem. Soc.* **1972**, *94*, 2235; Cook; Hutchinson; Parker *J. Org. Chem.* **1974**, *39*, 3029; Cook; Hutchinson; MacLeod; Parker *J. Org. Chem.* **1974**, *39*, 534; Cook *J. Org. Chem.* **1976**, *41*, 2173; Muir; Parker *Aust. J. Chem.* **1983**, *36*, 1667; Kwart; Wilk *J. Org. Chem.* **1985**, *50*, 3038.

⁶⁸Anderson; Ang; England; McCann; McLennan *Aust. J. Chem.* **1969**, *22*, 1427; Bunnett; Baciocchi *J. Org. Chem.* **1967**, *32*, 11. **1970**, *35*, 76; Jackson; McLennan; Short; Wong *J. Chem. Soc., Perkin Trans. 2* **1972**, 2308; McLennan; Wong *Tetrahedron Lett.* **1970**, 881; *J. Chem. Soc., Perkin Trans. 2* **1972**, 279. **1974**, 1818; Bunnett; Eck *J. Am. Chem. Soc.* **1973**, *95*, 1897, 1900; Ford; Pietsek *J. Am. Chem. Soc.* **1975**, *97*, 2194; Loupy *Bull. Soc. Chim. Fr.* **1975**, 2662; Miller; Saunders *J. Am. Chem. Soc.* **1979**, *101*, 6749; Bunnett; Sridharan; Cavin *J. Org. Chem.* **1979**, *44*, 1463; Bordwell; Mroczek *J. Org. Chem.* **1982**, *47*, 4813; Bunnett; Migdal *J. Org. Chem.* **1989**, *54*, 3037, 3041.

⁶⁹McLennan, Ref. 63, *J. Chem. Soc., Perkin Trans. 2* **1977**, 293, 298; McLennan; Lim *Aust. J. Chem.* **1983**, *36*, 1821. For an opposing view, see Kwart; Gaffney *J. Org. Chem.* **1983**, *48*, 4502.

⁷⁰Ford, Ref. 63.

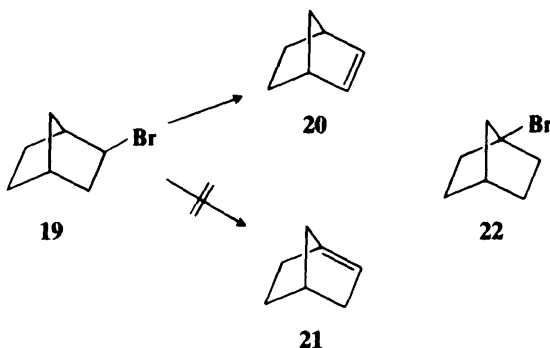
⁷¹For convenience, we will refer to this class of reactions as E2C reactions, though the actual mechanism is in dispute.

tics:⁷² (1) they are favored by good leaving groups; (2) they are favored by polar aprotic solvents; (3) the reactivity order is tertiary > secondary > primary, the opposite of the normal E2 order (p. 1003); (4) the elimination is always anti (syn elimination is not found), but in cyclohexyl systems, a diequatorial anti elimination is about as favorable as a diaxial anti elimination (unlike the normal E2 reaction, p. 985); (5) they follow Zaitsev's rule (see below), where this does not conflict with the requirement for anti elimination.

Orientation of the Double Bond

With some substrates, a β hydrogen is present on only one carbon and (barring rearrangements) there is no doubt as to the identity of the product. For example, $\text{PhCH}_2\text{CH}_2\text{Br}$ can give only $\text{PhCH}=\text{CH}_2$. However, in many other cases two or three olefinic products are possible. In the simplest such case, a *sec*-butyl compound can give either 1-butene or 2-butene. There are a number of rules that enable us to predict, in many instances, which product will predominantly form.⁷³

1. No matter what the mechanism, a double bond does not go to a bridgehead carbon unless the ring sizes are large enough (Bredt's rule, see p. 160). This means, for example, not only that **19** gives only **20** and not **21** (indeed **21** is not a known compound), but also that **22** does not undergo elimination.



2. No matter what the mechanism, if there is a double bond ($\text{C}=\text{C}$ or $\text{C}=\text{O}$) or an aromatic ring already in the molecule that can be in conjugation with the new double bond, the conjugated product usually predominates, sometimes even when the stereochemistry is unfavorable (for an exception, see p. 1001).

3. In the E1 mechanism the leaving group is gone before the choice is made as to which direction the new double bond takes. Therefore the direction is determined almost entirely by the relative stabilities of the two (or three) possible olefins. In such cases Zaitsev's rule⁷⁴ operates. This rule states that *the double bond goes mainly toward the most highly substituted carbon*. That is, a *sec*-butyl compound gives more 2-butene than 1-butene, and 3-bromo-

⁷²Biale; Parker; Smith; Stevens; Winstein *J. Am. Chem. Soc.* **1970**, 92, 115; Lloyd; Muir; Parker *Tetrahedron Lett.* **1971**, 3015; Beltrame; Biale; Lloyd; Parker; Ruane; Winstein *J. Am. Chem. Soc.* **1972**, 94, 2240; Beltrame; Cecon; Winstein *J. Am. Chem. Soc.* **1972**, 94, 2315.

⁷³For a review of orientation in cycloalkyl systems, see Hückel; Hanack *Angew. Chem. Int. Ed. Engl.* **1967**, 6, 534-544 [*Angew. Chem.* 79, 555-565].

⁷⁴Often given the German spelling: Saytzeff.

2,3-dimethylpentane gives more 2,3-dimethyl-2-pentene than either 3,4-dimethyl-2-pentene or 2-ethyl-3-methyl-1-butene. Thus Zaitsev's rule predicts that the olefin predominantly formed will be the one with the largest possible number of alkyl groups on the C=C carbons, and in most cases this is what is found. From heat of combustion data (see p. 23) it is known that olefin stability increases with alkyl substitution, though just why this should be is a matter of conjecture. The most common explanation is hyperconjugation. For E1 eliminations Zaitsev's rule governs the orientation whether the leaving group is neutral or positive, since, as already mentioned, the leaving group is not present when the choice of direction is made. This statement does not hold for E2 eliminations, and it may be mentioned here, for contrast with later results, that E1 elimination of $\text{Me}_2\text{CHCHMeSMe}_2^+$ gave 91% of the Zaitsev product and 9% of the other.⁷⁵ However, there *are* cases in which the leaving group affects the direction of the double bond in E1 eliminations.⁷⁶ This may be attributed to ion pairs; that is, the leaving group is not completely gone when the hydrogen departs. Zaitsev's rule breaks down in cases where the non-Zaitsev product is more stable for steric reasons. For example, E1 or E1-like eliminations of 1,2-diphenyl-2-X-propanes $\text{PhMeCXCH}_2\text{Ph}$ were reported to give about 50% $\text{CH}_2=\text{CPhCH}_2\text{Ph}$, despite the fact that the double bond of the Zaitsev product ($\text{PhMeC}=\text{CHPh}$) is conjugated with two benzene rings.⁷⁷

4. For the anti E2 mechanism a trans β proton is necessary; if this is available in only one direction, that is the way the double bond will form. Because of the free rotation in acyclic systems (except where steric hindrance is great), this is a factor only in cyclic systems. Where trans β hydrogens are available on two or three carbons, two types of behavior are found, depending on substrate structure and the nature of the leaving group. Some compounds follow Zaitsev's rule and give predominant formation of the most highly substituted olefin, but others follow *Hofmann's rule: the double bond goes mainly toward the least highly substituted carbon*. Though many exceptions are known, the following general statements can be made: In most cases, compounds containing uncharged nucleofuges (those that come off as negative ions) follow Zaitsev's rule, just as they do in E1 elimination, no matter what the structure of the substrate. However, elimination from compounds with charged nucleofuges, e.g., NR_3^+ , SR_2^+ (those that come off as neutral molecules), follow Hofmann's rule if the substrate is acyclic,⁷⁸ but Zaitsev's rule if the leaving group is attached to a six-membered ring.⁷⁹

Much work has been devoted to searching for the reasons for the differences in orientation. Since Zaitsev orientation almost always gives the thermodynamically more stable isomer, what needs to be explained is why in some cases the less stable Hofmann product predominates. Three explanations have been offered for the change in orientation in acyclic systems with a change from uncharged to charged nucleofuges. The first of these, by Hughes and Ingold,⁸⁰ is that Hofmann orientation is caused by the fact that the acidity of the β hydrogen is decreased by the presence of the electron-donating alkyl groups. For example, under E2 conditions $\text{Me}_2\text{CHCHMeSMe}_2^+$ gives more of the Hofmann product; it is the more acidic hydrogen that is removed by the base.

⁷⁵de la Mare *Prog. Stereochem.* **1954**, *1*, 112.

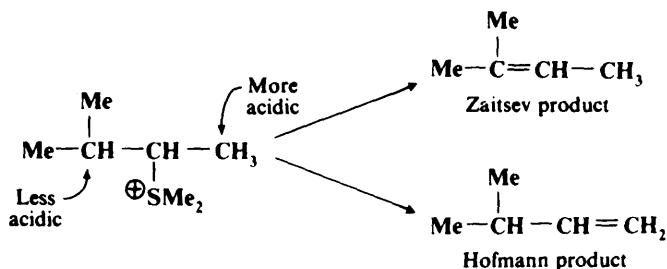
⁷⁶Cram; Sahyun *J. Am. Chem. Soc.* **1963**, *85*, 1257; Silver *J. Am. Chem. Soc.* **1961**, *83*, 3482.

⁷⁷Ho; Smith *Tetrahedron* **1970**, *26*, 4277.

⁷⁸An example of an acyclic quaternary ammonium salt that follows Zaitsev's rule is found in Feit; Saunders *J. Am. Chem. Soc.* **1970**, *92*, 5615.

⁷⁹For examples where Zaitsev's rule is followed with charged leaving groups in cyclohexyl systems, see Gent; McKenna *J. Chem. Soc.* **1959**, 137; Hughes; Wilby *J. Chem. Soc.* **1960**, 4094; Brownlee; Saunders *Proc. Chem. Soc.* **1961**, 314; Booth; Franklin; Gidley *J. Chem. Soc. C* **1968**, 1891. For a discussion of the possible reasons for this, see Saunders; Cockerill, *Ref. 2*, pp. 192-193.

⁸⁰For summaries of this position, see Ingold *Proc. Chem. Soc.* **1962**, 265-274; Banthorpe; Hughes; Ingold *J. Chem. Soc.* **1960**, 4054.



Of course, the CH_3 hydrogens would still be more acidic than the Me_2CH hydrogen even if a neutral leaving group were present, but the explanation of Hughes and Ingold is that acidity matters with charged and not with neutral leaving groups, because the charged groups exert a strong electron-withdrawing effect, making differences in acidity greater than they are with the less electron-withdrawing neutral groups.⁸⁰ The explanation of Bunnett⁸¹ is similar. According to this, the change to a positive leaving group causes the mechanism to shift toward the E1cB end of the spectrum, where there is more $\text{C}-\text{H}$ bond breaking in the rate-determining step and where, consequently, acidity is more important. In this view, when there is a neutral leaving group, the mechanism is more E1 -like, $\text{C}-\text{X}$ bond breaking is more important, and olefin stability determines the direction of the new double bond. The third explanation, by H. C. Brown, is completely different. In this picture, field effects are unimportant, and the difference in orientation is largely a steric effect caused by the fact that charged groups are usually larger than neutral ones. A CH_3 group is more open to attack than a CH_2R group and a CHR_2 group is still less easily attacked. Of course, these considerations also apply when the leaving group is neutral, but, according to Brown, they are much less important here because the neutral groups are smaller and do not block access to the hydrogens as much. Brown showed that Hofmann elimination increases with the size of the leaving group. Thus the percentage of 1-ene obtained from $\text{CH}_3\text{CH}_2\text{CH}_2\text{CHXCH}_3$ was as follows (X listed in order of increasing size): Br, 31%; I, 30%; OTs, 48%; SMe_2^+ , 87%; SO_2Me , 89%; NMe_3^+ , 98%.⁸² Hofmann elimination was also shown to increase with increase in bulk of the substrate.⁸³ With large enough compounds, Hofmann orientation can be obtained even with halides, e.g., *t*-amyl bromide gave 89% of the Hofmann product. Even those who believe in the acidity explanations concede that these steric factors operate in extreme cases.⁸⁴

There is one series of results incompatible with the steric explanation— E2 elimination from the four 2-halopentanes gave the following percentages of 1-pentene: F, 83%; Cl, 37%; Br, 25%; I, 20%.⁸⁵ The same order was found for the four 2-halohexanes.⁸⁶ Although there is some doubt about the relative steric requirements of Br, Cl, and I, there is no doubt that F is the smallest of the halogens, and if the steric explanation were the only valid one, the fluoroalkanes could not give predominant Hofmann orientation. Another result that argues against the steric explanation is the effect of changing the nature of the base. An experiment in which the effective size of the base was kept constant while its basicity was increased (by

⁸¹Bunnett, Ref. 2.

⁸²Brown; Wheeler *J. Am. Chem. Soc.* **1956**, 78, 2199.

⁸³Brown; Moritani; Nakagawa *J. Am. Chem. Soc.* **1956**, 78, 2190; Brown; Moritani *J. Am. Chem. Soc.* **1956**, 78, 2203; Bartsch *J. Org. Chem.* **1970**, 35, 1334. See also Charton *J. Am. Chem. Soc.* **1975**, 97, 6159.

⁸⁴For example, see Banthorpe; Hughes; Ingold *J. Chem. Soc.* **1960**, 4054.

⁸⁵Saunders; Fahrenholtz; Caress; Lowe; Schreiber *J. Am. Chem. Soc.* **1965**, 87, 3401. Similar results were obtained by Brown; Klimisch *J. Am. Chem. Soc.* **1966**, 88, 1425.

⁸⁶Bartsch; Bunnett *J. Am. Chem. Soc.* **1968**, 90, 408.

using as bases a series of $\text{XC}_6\text{H}_4\text{O}^-$ ions) showed that the percentage of Hofmann elimination increased with increasing base strength, though the size of the base did not change.⁸⁷ These results are in accord with the explanation of Bunnett, since an increase in base strength moves an E2 reaction closer to the E1cB end of the spectrum. In further experiments, a large series of bases of different kinds was shown to obey linear free-energy relationships between basicity and percentage of Hofmann elimination,⁸⁸ though certain very large bases (e.g., 2,6-di-*t*-butyl-phenoxide) did not obey the relationships, steric effects becoming important in these cases. How large the base must be before steric effects are observed depends on the pattern of alkyl substitution in the substrate, but not on the nucleofuge.⁸⁹ One further result may be noted. In the gas phase, elimination of H and BrH^+ or H and ClH^+ using Me_3N as the base predominantly followed Hofmann's rule,⁹⁰ although BrH^+ and ClH^+ are not very large.

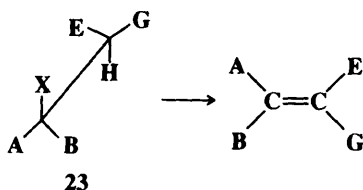
5. Only a few investigations on the orientation of syn E2 eliminations have been carried out, but these show that Hofmann orientation is greatly favored over Zaitsev.⁹¹

6. In the E1cB mechanism the question of orientation seldom arises because the mechanism is generally found only where there is an electron-withdrawing group in the β position, and that is where the double bond goes.

7. As already mentioned, E2C reactions show a strong preference for Zaitsev orientation.⁹² In some cases this can be put to preparative use. For example, the compound $\text{PhCH}_2\text{CHOTsCHMe}_2$ gave about 98% PhCH=CHCHMe_2 under the usual E2 reaction conditions (*t*-BuOK in *t*-BuOH). In this case the double bond goes to the side with more hydrogens because on that side it will be able to conjugate with the benzene ring. However, with the weak base $\text{Bu}_4\text{N}^+ \text{Br}^-$ in acetone the Zaitsev product $\text{PhCH}_2\text{CH=CMe}_2$ was formed in 90% yield.⁹³

Steric Orientation of the Double Bond

When elimination takes place on a compound of the form $\text{CH}_3\text{—CABX}$ or CHAB—CGGX , the new olefin does not have cis-trans isomerism, but for compounds of the form CHEG—CABX (E and G not H) (**23**) and $\text{CH}_2\text{E—CABX}$ (**24**), cis and trans isomers are possible. When the anti E2 mechanism is in operation, **23** gives the isomer arising from



⁸⁷Froemdsdorf; Robbins *J. Am. Chem. Soc.* **1967**, *89*, 1737. See also Froemdsdorf; Dowd; Leimer *J. Am. Chem. Soc.* **1966**, *88*, 2345; Bartsch; Kelly; Pruss *Tetrahedron Lett.* **1970**, 3795; Feit; Breger; Capobianco; Cooke; Gitlin *J. Am. Chem. Soc.* **1975**, *97*, 2477; Ref. 78.

⁸⁸Bartsch; Pruss; Bushaw; Wiegiers *J. Am. Chem. Soc.* **1973**, *95*, 3405; Bartsch; Roberts; Cho *J. Org. Chem.* **1979**, *44*, 4105.

⁸⁹Bartsch; Read; Larsen; Roberts; Scott; Cho *J. Am. Chem. Soc.* **1979**, *101*, 1176.

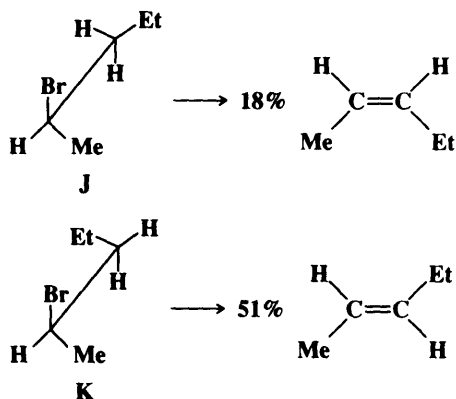
⁹⁰Angelini; Lilla; Speranza *J. Am. Chem. Soc.* **1989**, *111*, 7393.

⁹¹Sicher; Svoboda; Pánková; Závada *Collect. Czech. Chem. Commun.* **1971**, *36*, 3633; Bailey; Saunders *J. Am. Chem. Soc.* **1970**, *92*, 6904.

⁹²For example; see Ono *Bull. Chem. Soc. Jpn.* **1971**, *44*, 1369; Bailey; Saunders *J. Org. Chem.* **1973**, *38*, 3363; Muir; Parker *J. Org. Chem.* **1976**, *41*, 3201.

⁹³Lloyd; Muir; Parker, Ref. 72.

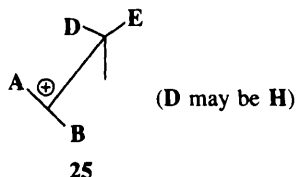
trans orientation of X and H and, as we have seen before (p. 984), an erythro compound gives the cis olefin and a threo compound the trans. For **24** two conformations are possible for the transition state; these lead to different isomers and often both are obtained. However, the one that predominates is often determined by an eclipsing effect.⁹⁴ For example, Zaitsev elimination from 2-bromopentane can occur as follows:



In conformation **J** the ethyl group is between Br and Me, while in **K** it is between Br and H. This means that **K** is more stable, and most of the elimination should occur from this conformation. This is indeed what happens, and 51% of the trans isomer is formed (with KOEt) compared to 18% of the cis (the rest is the Hofmann product).⁹⁵ These effects become larger with increasing size of A, B, and E.

However, eclipsing effects are not the only factors that affect the cis/trans ratio in anti E2 eliminations. Other factors are the nature of the leaving group, the base, the solvent, and the substrate. Not all these effects are completely understood.⁹⁶

For E1 eliminations, if there is a free carbocation (**25**), it is free to rotate, and no matter



what the geometry of the original compound, the more stable situation is the one where the larger of the D-E pair is opposite the smaller of the A-B pair and the corresponding olefin should form. If the carbocation is not completely free, then to that extent, E2-type products are formed. Similar considerations apply in E1cB eliminations.⁹⁷

⁹⁴See Cram; Greene; DePuy *J. Am. Chem. Soc.* **1956**, 78, 790; Cram, in *Newman Steric Effects in Organic Chemistry*; Wiley: New York, 1956, pp. 338-345.

⁹⁵Brown; Wheeler *J. Am. Chem. Soc.* **1956**, 78 2199.

⁹⁶For discussions, see Bartsch; Bunnett *J. Am. Chem. Soc.* **1969**, 91, 1376, 1382; Feit; Saunders *J. Am. Chem. Soc.* **1970**, 92, 1630, 5615; Alunni; Baciocchi *J. Chem. Soc., Perkin Trans. 2* **1976**, 877; Saunders; Cockerill, *Ref. 2*, pp. 165-193.

⁹⁷See, for example, Redman; Thomas; Stirling *J. Chem. Soc., Chem. Commun.* **1978**, 43.

REACTIVITY

In this section we examine the effects of changes in the substrate, base, leaving group, and medium on (1) overall reactivity, (2) E1 vs. E2 vs. E1cB,⁹⁸ and (3) elimination vs. substitution.

Effect of Substrate Structure

1. Effect on reactivity. We refer to the carbon containing the nucleofuge (X) as the α carbon and to the carbon that loses the positive species as the β carbon. Groups attached to the α or β carbons can exert at least four kinds of influence:

- a. They can stabilize or destabilize the incipient double bond (both α and β groups).
- b. They can stabilize or destabilize an incipient negative charge, affecting the acidity of the proton (β groups only).
- c. They can stabilize or destabilize an incipient positive charge (α groups only).
- d. They can exert steric effects (e.g., eclipsing effects) (both α and β groups).

Effects a and d can apply in all three mechanisms, though steric effects are greatest for the E2 mechanism. Effect b does not apply in the E1 mechanism, and effect c does not apply in the E1cB mechanism. Groups such as Ar and C=C increase the rate by any mechanism, whether they are α or β (effect a). Electron-withdrawing groups increase the acidity when in the β position, but have little effect in the α position unless they also conjugate with the double bond. Thus Br, Cl, CN, Ts, NO₂, CN, and SR in the β position all increase the rate of E2 eliminations.

2. Effect on E1 vs. E2 vs. E1cB. α alkyl and α aryl groups stabilize the carbocation character of the transition state, shifting the spectrum toward the E1 end. β alkyl groups also shift the mechanism toward E1, since they *decrease* the acidity of the hydrogen. However, β aryl groups shift the mechanism the other way (toward E1cB) by stabilizing the carbanion. Indeed, as we have seen (p. 993), all electron-withdrawing groups in the β position shift the mechanism toward E1cB.⁹⁹ α alkyl groups also increase the extent of elimination with weak bases (E2C reactions).

3. Effect on elimination vs. substitution. Under second-order conditions α branching increases elimination, to the point where tertiary substrates undergo few S_N2 reactions, as we saw in Chapter 10. For example, Table 17.2 shows results on some simple alkyl bromides. Similar results were obtained with SMe₂⁺ as the leaving group.¹⁰⁰ Two reasons can be presented for this trend. One is statistical: as α branching increases, there are usually more hydrogens for the base to attack. The other is that α branching presents steric hindrance to attack of the base at the carbon. Under first-order conditions, increased α branching also increases the amount of elimination (E1 vs. S_N1), though not so much, and usually the substitution product predominates. For example, solvolysis of *t*-butyl bromide gave only 19% elimination¹⁰¹ (compare with Table 17.2). β branching also increases the amount of E2 elimination with respect to S_N2 substitution (Table 17.2), not because elimination is faster but because the S_N2 mechanism is so greatly slowed (p. 339). Under first-order conditions too, β branching favors elimination over substitution, probably for steric reasons.¹⁰² However, E2 eliminations from compounds with charged leaving groups are slowed

⁹⁸For discussions, see Cockerill; Harrison, Ref. 2, pp. 178-189.

⁹⁹For a review of eliminations with COOH, COOR, CONH₂, and CN groups in the β position, see Butskus; Denis *Russ. Chem. Rev.* **1966**, 35, 839-850.

¹⁰⁰Hughes; Ingold; Maw *J. Chem. Soc.* **1948**, 2072; Hughes; Ingold; Woolf *J. Chem. Soc.* **1948**, 2084.

¹⁰¹Hughes; Ingold; Maw *J. Chem. Soc.* **1948**, 2065.

¹⁰²Brown; Berneis *J. Am. Chem. Soc.* **1953**, 75, 10.

TABLE 17.2 The effect of α and β branching on the rate of E2 elimination and the amount of olefin formed

The reactions were between the alkyl bromide and OEt^- . The rate for isopropyl bromide was actually greater than that for ethyl bromide, if the temperature difference is considered. Neopentyl bromide, the next compound in the β -branching series, cannot be compared because it has no β -hydrogen and cannot give an elimination product without rearrangement.

Substrate	Temperature, °C	Olefin, %	Rate $\times 10^5$ of E2 reaction	Reference
$\text{CH}_3\text{CH}_2\text{Br}$	55	0.9	1.6	103
$(\text{CH}_3)_2\text{CHBr}$	25	80.3	0.237	104
$(\text{CH}_3)_3\text{CBr}$	25	97	4.17	101
$\text{CH}_3\text{CH}_2\text{CH}_2\text{Br}$	55	8.9	5.3	103
$\text{CH}_3\text{CHCH}_2\text{Br}$ CH_3	55	59.5	8.5	103

by β branching. This is related to Hofmann's rule (p. 999). Electron-withdrawing groups in the β position not only increase the rate of E2 eliminations and shift the mechanisms toward the E1cB end of the spectrum but also increase the extent of elimination as opposed to substitution.

Effect of the Attacking Base

1. *Effect on E1 vs. E2 vs. E1cB.* In the E1 mechanism, an external base is generally not required; The solvent acts as the base. Hence, when external bases are added, the mechanism is shifted toward E2. Stronger bases and higher base concentrations cause the mechanism to move toward the E1cB end of the E1–E2–E1cB spectrum.¹⁰⁵ However, weak bases in polar aprotic solvents can also be effective in elimination reactions with certain substrates (the E2C reaction). Normal E2 elimination has been accomplished with the following bases:¹⁰⁶ H_2O , NR_3 , OH^- , OAc^- , OR^- , OAr^- , NH_2^- , CO_3^{2-} , LiAlH_4 , I^- , CN^- , and organic bases. However, the only bases of preparative importance in the normal E2 reaction are OH^- , OR^- , and NH_2^- , usually in the conjugate acid as solvent, and certain amines. Weak bases effective in the E2C reaction are Cl^- , Br^- , F^- , OAc^- , and RS^- . These bases are often used in the form of their R_4N^+ salts.

2. *Effect on elimination vs. substitution.* Strong bases not only benefit E2 as against E1, but also benefit elimination as against substitution. With a high concentration of strong base in a nonionizing solvent, bimolecular mechanisms are favored and E2 predominates over $\text{S}_{\text{N}}2$. At low base concentrations, or in the absence of base altogether, in ionizing solvents, unimolecular mechanisms are favored, and the $\text{S}_{\text{N}}1$ mechanism predominates over the E1. In Chapter 10, it was pointed out that some species are strong nucleophiles though weak bases (p. 349). The use of these obviously favors substitution, except that, as we have seen, elimination can predominate if polar aprotic solvents are used. It has been shown for the

¹⁰³Dhar; Hughes; Ingold; Masterman *J. Chem. Soc.* **1948**, 2055.

¹⁰⁴Dhar; Hughes; Ingold *J. Chem. Soc.* **1948**, 2058.

¹⁰⁵For a review, see Baciocchi *Acc. Chem. Res.* **1979**, 12, 430-436. See also Baciocchi; Ruzziconi; Sebastiani *J. Org. Chem.* **1980**, 45, 827.

¹⁰⁶This list is from Banthorpe *Elimination Reactions*; Elsevier: New York, 1963, p. 4.

base CN^- that in polar aprotic solvents, the less the base is encumbered by its counterion in an ion pair (i.e., the freer the base), the more substitution is favored at the expense of elimination.¹⁰⁷

Effect of the Leaving Group

1. Effect on reactivity. The leaving groups in elimination reactions are similar to those in nucleophilic substitution. E2 eliminations have been performed with the following groups: NR_3^+ , PR_3^+ , SR_2^+ , OHR^+ , SO_2R , OSO_2R , OCOR , OOH OOR , NO_2 ,¹⁰⁸ F, Cl, Br, I, and CN (not OH_2^+). E1 eliminations have been carried out with: NR_3^+ , SR_2^+ , OH_2^+ , OHR^+ , OSO_2R , OCOR , Cl, Br, I, and N_2^+ .¹⁰⁹ However, the major leaving groups for preparative purposes are OH_2^+ (always by E1) and Cl, Br, I, and NR_3^+ (usually by E2).

2. Effect on E1 vs. E2 vs. E1cB. Better leaving groups shift the mechanism toward the E1 end of the spectrum, since they make ionization easier. This effect has been studied in various ways. One way already mentioned was a study of ρ values (p. 996). Poor leaving groups and positively charged leaving groups shift the mechanism toward the E1cB end of the spectrum because the strong electron-withdrawing field effects increase the acidity of the β hydrogen.¹¹⁰ The E2C reaction is favored by good leaving groups.

3. Effect on elimination vs. substitution. As we have already seen (p. 990), for first-order reactions the leaving group has nothing to do with the competition between elimination and substitution, since it is gone before the decision is made as to which path to take. However, where ion pairs are involved, this is not true, and results have been found where the nature of the leaving group does affect the product.¹¹¹ In second-order reactions, the elimination/substitution ratio is not greatly dependent on a halide leaving group, though there is a slight increase in elimination in the order $\text{I} > \text{Br} > \text{Cl}$. When OTs is the leaving group, there is usually much more substitution. For example, $n\text{-C}_{18}\text{H}_{37}\text{Br}$ treated with *t*-BuOK gave 85% elimination, while $n\text{-C}_{18}\text{H}_{37}\text{OTs}$ gave, under the same conditions, 99% substitution.¹¹² On the other hand, positively charged leaving groups increase the amount of elimination.

Effect of the Medium

1. Effect of solvent on E1 vs. E2 vs. E1cB. With any reaction a more polar environment enhances the rate of mechanisms that involve ionic intermediates. For neutral leaving groups, it is expected that E1 and E1cB mechanisms will be aided by increasing polarity of solvent and by increasing ionic strength. With certain substrates, polar aprotic solvents promote elimination with weak bases (the E2C reaction).

2. Effect of solvent on elimination vs. substitution. Increasing polarity of solvent favors $\text{S}_{\text{N}}2$ reactions at the expense of E2. In the classical example, alcoholic KOH is used to effect elimination, while the more polar aqueous KOH is used for substitution. Charge-dispersal discussions, similar to those on p. 358,¹¹³ only partially explain this. In most solvents $\text{S}_{\text{N}}1$

¹⁰⁷Loupy; Seyden-Penne *Bull. Soc. Chim. Fr.* **1971**, 2306.

¹⁰⁸For a review of eliminations in which NO_2 is a leaving group, see Ono, in Feuer; Nielsen *Nitro Compounds; Recent Advances in Synthesis and Chemistry*; VCH: New York, 1990, pp. 1-135, pp. 86-126.

¹⁰⁹These lists are from Banthorpe, Ref. 106, pp. 4, 7.

¹¹⁰For a discussion of leaving-group ability, see Stirling *Acc. Chem. Res.* **1979**, *12*, 198-203. See also Varma; Stirling *J. Chem. Soc., Chem. Commun.* **1981**, 553.

¹¹¹For example, see Skell; Hall *J. Am. Chem. Soc.* **1963**, *85* 2851; Cocivera; Winstein, Ref. 32; Feit; Wright *J. Chem. Soc., Chem. Commun.* **1975**, 776. See, however, Cavazza *Tetrahedron Lett.* **1975**, 1031.

¹¹²Veeravagu; Arnold; Eigenmann *J. Am. Chem. Soc.* **1964**, *86*, 3072.

¹¹³Cooper; Dhar; Hughes; Ingold; MacNulty; Woolf *J. Chem. Soc.* **1948**, 2043.

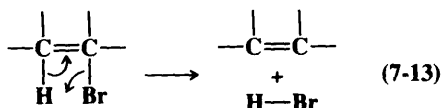
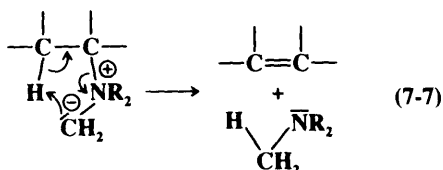
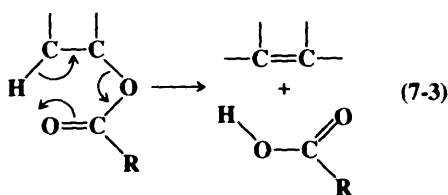
reactions are favored over E1. E1 reactions compete best in polar solvents that are poor nucleophiles, especially dipolar aprotic solvents.¹¹⁴ A study made in the gas phase, where there is no solvent, has shown that when 1-bromopropane reacts with MeO^- only elimination takes place—no substitution—even with this primary substrate.¹¹⁵

3. *Effect of temperature.* Elimination is favored over substitution by increasing temperature, whether the mechanism is first or second order.¹¹⁶ The reason is that the activation energies of eliminations are higher than those of substitutions (because eliminations have greater changes in bonding).

MECHANISMS AND ORIENTATION IN PYROLYTIC ELIMINATIONS

Mechanisms¹¹⁷

Several types of compound undergo elimination on heating, with no other reagent present. Reactions of this type are often run in the gas phase. The mechanisms are obviously different from those already discussed, since all those require a base (which may be the solvent) in one of the steps, and there is no base or solvent present in pyrolytic elimination. Two mechanisms have been found to operate. One involves a cyclic transition state, which may be four-, five-, or six-membered. Examples of each size are:



In this mechanism the two groups leave at about the same time and bond to each other as they are doing so. The designation is E_i in the Ingold terminology and cyclo- $\text{D}_\text{E}\text{D}_\text{N}\text{A}_\text{n}$ in the IUPAC system. The elimination must be syn and, for the four- and five-membered transition states, the four or five atoms making up the ring must be coplanar. Coplanarity

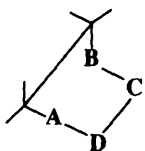
¹¹⁴Aksnes; Stensland *Acta Chem. Scand.* **1989**, *43*, 893, and references cited therein.

¹¹⁵Jones; Ellison *J. Am. Chem. Soc.* **1989**, *111*, 1645. For a different result with other reactants, see Lum; Grabowski *J. Am. Chem. Soc.* **1988**, *110*, 8568.

¹¹⁶Cooper; Hughes; Ingold; Maw; MacNulty *J. Chem. Soc.* **1948**, 2049.

¹¹⁷For reviews, see Taylor, in Patai *The Chemistry of Functional Groups, Supplement B*, pt. 2; Wiley: New York, 1979, pp. 860-914; Smith; Kelly *Prog. Phys. Org. Chem.* **1971**, *8*, 75-234, pp. 76-143, 207-234; in Bamford; Tipper, Ref. 2, vol. 5, 1972, the articles by Swinbourne, pp. 149-233 (pp. 158-188), and by Richardson; O'Neal, pp. 381-565 (pp. 381-446); Maccoll, Ref. 2, *Adv. Phys. Org. Chem.* **1965**, *3*, 91-122. For reviews of mechanisms in pyrolytic eliminations of halides, see Egger; Cocks; in Patai *The Chemistry of the Carbon-Halogen Bond*, pt. 2; Wiley: New York, 1973, pp. 677-745; Maccoll *Chem. Rev.* **1969**, *69*, 33-60.

is not required for the six-membered transition state, since there is room for the outside atoms when the leaving atoms are staggered.

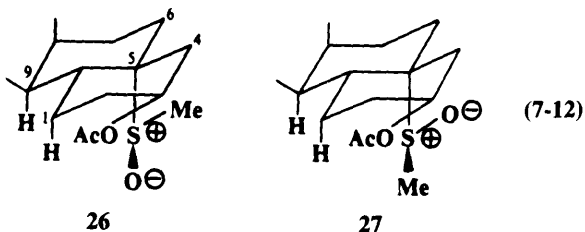


As in the E2 mechanism, it is not necessary that the C—H and C—X bond be equally broken in the transition state. In fact, there is also a spectrum of mechanisms here, ranging from a mechanism in which C—X bond breaking is a good deal more advanced than C—H bond breaking to one in which the extent of bond breaking is virtually identical for the two bonds. Evidence for the existence of the E_i mechanism is:

1. The kinetics are first order, so only one molecule of the substrate is involved in the reaction (that is, if one molecule attacked another, the kinetics would be second order in substrate).¹¹⁸

2. Free-radical inhibitors do not slow the reactions, so no free-radical mechanism is involved.¹¹⁹

3. The mechanism predicts exclusive syn elimination, and this behavior has been found in many cases.¹²⁰ The evidence is inverse to that for the anti E2 mechanism and generally involves the following facts: (1) an erythro isomer gives a trans olefin and a threo isomer gives a cis olefin; (2) the reaction takes place only when a cis β hydrogen is available; (3) if, in a cyclic compound, a cis hydrogen is available on only one side, the elimination goes in that direction. Another piece of evidence involves a pair of steroid molecules. In 3β-acetoxy-(R)-5α-methylsulfinylcholestane (**26** shows rings A and B of this compound) and in 3β-acetoxy-(S)-5α-methylsulfinylcholestane (**27**; rings A and B), the *only* difference is the



configuration of oxygen and methyl about the sulfur. Yet pyrolysis of **26** gave only elimination to the 4-side (86% 4-ene), while **27** gave predominant elimination to the 6-side (65% 5-ene and 20% 4-ene).¹²¹ Models show that interference from the 1- and 9-hydrogens causes the two groups on the sulfur to lie *in front of it* with respect to the rings, rather than behind it. Since the sulfur is chiral, this means that in **26** the oxygen is near the 4-hydrogen, while in **27** it is near the 6 hydrogen. This experiment is compatible only with syn elimination.¹²²

4. ¹⁴C isotope effects for the Cope elimination (7-8) show that both the C—H and C—N bonds have been extensively broken in the transition state.¹²³

¹¹⁸O'Connor; Nace *J. Am. Chem. Soc.* **1953**, 75, 2118.

¹¹⁹Barton; Head; Williams *J. Chem. Soc.* **1953**, 1715.

¹²⁰In a few instances anti or nonstereoselective elimination has been found; this behavior is generally ascribed to the intervention of other mechanisms. For example, see Bordwell; Landis *J. Am. Chem. Soc.* **1958**, 80, 2450, 6383; Briggs; Djerassi *J. Org. Chem.* **1968**, 33, 1625; Smisson; Li; Creese *J. Org. Chem.* **1970**, 35, 1352.

¹²¹Jones; Saeed *Proc. Chem. Soc.* **1964**, 81. See also Goldberg; Sahli *J. Org. Chem.* **1967**, 32, 2059.

¹²²For other evidence for syn elimination, see Curtin; Kellom *J. Am. Chem. Soc.* **1953**, 75, 6011; Skell; Hall *J. Am. Chem. Soc.* **1964**, 86, 1557; Bailey; Bird *J. Org. Chem.* **1977**, 42, 3895.

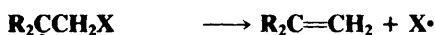
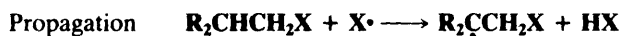
¹²³Wright; Sims; Fry *J. Am. Chem. Soc.* **1983**, 105, 3714.

5. Some of these reactions have been shown to exhibit negative entropies of activation, indicating that the molecules are more restricted in geometry in the transition state than they are in the starting compound.

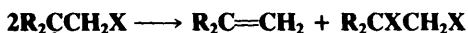
Where a pyrolytic elimination lies on the mechanistic spectrum seems to depend mostly on the leaving group. When this is halogen, all available evidence suggests that in the transition state the C—X bond is cleaved to a much greater extent than the C—H bond, i.e., there is a considerable amount of carbocation character in the transition state. This is in accord with the fact that a completely nonpolar four-membered cyclic transition state violates the Woodward–Hoffmann rules (see the similar case of 5-49). Evidence for the carbocation-like character of the transition state when halide is the leaving group is that relative rates are in the order $I > Br > Cl$ ¹²⁴ (see p. 352), and that the effects of substituents on reaction rates are in accord with such a transition state.¹²⁵ Rate ratios for pyrolysis of some alkyl bromides at 320°C were: ethyl bromide, 1; isopropyl bromide, 280; *t*-butyl bromide, 78,000. Also, α -phenylethyl bromide had about the same rate as *t*-butyl bromide. On the other hand, β -phenylethyl bromide was only slightly faster than ethyl bromide.¹²⁶ This indicates that C—Br cleavage was much more important in the transition state than C—H cleavage, since the incipient carbocation was stabilized by α alkyl and α aryl substitution, while there was no incipient carbanion to be stabilized by β aryl substitution. These substituent effects, as well as those for other groups, are very similar to the effects found for the S_N1 mechanism and thus in very good accord with a carbocation-like transition state.

For carboxylic esters, the rate ratios were much smaller,¹²⁷ though still in the same order, so that this reaction is closer to a pure E_i mechanism, though the transition state still has some carbocationic character. Other evidence for a greater initial C—O cleavage with carboxylic esters is that a series of 1-arylethyl acetates followed σ^+ rather than σ , showing carbocationic character at the 1 position.¹²⁸ The extent of $E1$ character in the transition state increases in the following order of ester types: acetate < phenylacetate < benzoate < carbamate < carbonate.¹²⁹ Cleavage of xanthates (7-4), cleavage of sulfoxides (7-12), the Cope reaction (7-8), and reaction 7-7 are probably very close to straight E_i mechanisms.¹³⁰

The second type of pyrolysis mechanism is completely different and involves free radicals. Initiation occurs by pyrolytic homolytic cleavage. The remaining steps may vary, and a few are shown:



Termination (disproportionation)



¹²⁴Maccoll, Ref. 2, pp. 215-216.

¹²⁵For reviews of such studies, see Maccoll, Ref. 117.

¹²⁶For rate studies of pyrolysis of some β -alkyl substituted ethyl bromides, see Chuchani; Rotinov; Dominguez; Martin *Int. J. Chem. Kinet.* **1987**, 19, 781.

¹²⁷For example, see Scheer; Kooymann; Sixma *Recl. Trav. Chim. Pays-Bas* **1963**, 82, 1123. See also Louw; Vermeeren; Vogelzang *J. Chem. Soc., Perkin Trans. 2* **1983**, 1875.

¹²⁸Taylor; Smith; Wetzel *J. Am. Chem. Soc.* **1962**, 84, 4817; Smith; Jones; Brown *J. Org. Chem.* **1963**, 28, 403; Taylor *J. Chem. Soc., Perkin Trans. 2* **1978**, 1255. See also Ottenbrite; Brockington *J. Org. Chem.* **1974**, 39, 2463; Jordan; Thorne *J. Chem. Soc., Perkin Trans. 2* **1984**, 647; August; McEwen; Taylor *J. Chem. Soc., Perkin Trans. 2* **1987**, 1683, and other papers in this series; Al-Awadi *J. Chem. Soc., Perkin Trans. 2* **1990**, 2187.

¹²⁹Taylor *J. Chem. Soc., Perkin Trans. 2* **1975**, 1025.

¹³⁰For a review of the mechanisms of 7-12, 7-8, and the pyrolysis of sulfilimines, see Oae; Furukawa *Tetrahedron* **1977**, 33, 2359-2367.

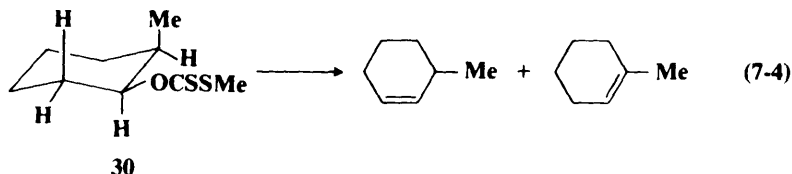
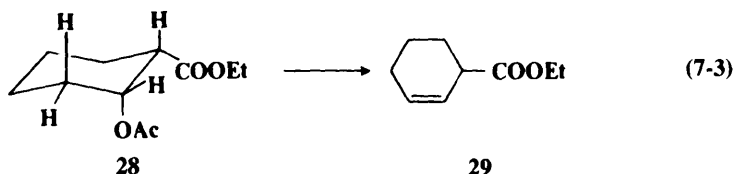
Free-radical mechanisms are mostly found in pyrolyses of polyhalides and of primary monohalides,¹³¹ though they also have been postulated in pyrolysis of certain carboxylic esters.¹³² Much less is known about these mechanisms and we shall not consider them further. Free-radical eliminations in solution are also known but are rare.¹³³

Orientation in Pyrolytic Eliminations

As in the E1-E2-E1cB mechanistic spectrum, Bredt's rule applies; and if a double bond is present, a conjugated system will be preferred, if sterically possible. Apart from these considerations, the following statements can be made for Ei eliminations:

1. In the absence of considerations mentioned below, orientation is statistical and is determined by the number of β hydrogens available (therefore *Hofmann's rule* is followed). For example, *sec*-butyl acetate gives 55 to 62% 1-butene and 38 to 45% 2-butene,¹³⁴ which is close to the 3:2 distribution predicted by the number of hydrogens available.¹³⁵

2. A *cis* β hydrogen is required. Therefore in cyclic systems, if there is a *cis* hydrogen on only one side, the double bond will go that way. However, when there is a six-membered transition state, this does not necessarily mean that the leaving groups must be *cis* to each other, since such transition states need not be completely coplanar. If the leaving group is axial, then the hydrogen obviously must be equatorial (and consequently *cis* to the leaving group), since the transition state cannot be realized when the groups are both axial. But if the leaving group is equatorial, it can form a transition state with a β hydrogen that is either axial (hence, *cis*) or equatorial (hence, *trans*). Thus **28**, in which the leaving group is most likely axial, does not form a double bond in the direction of the carbethoxyl group, even though that would be conjugated, because there is no equatorial hydrogen on that side. Instead it gives 100% **29**.¹³⁶ On the other hand, **30**, with an equatorial leaving group, gives



¹³¹For example, see Barton; Howlett *J. Chem. Soc.* **1949**, 155, 165.

¹³²For example, see Rummens *Recl. Trav. Chim. Pays-Bas* **1964**, 83, 901; Louw; Kooyman *Recl. Trav. Chim. Pays-Bas* **1965**, 84, 1511.

¹³³For examples; see Kampmeier; Geer; Meskin; D'Silva *J. Am. Chem. Soc.* **1966**, 88, 1257; Kochi; Singleton; Andrews *Tetrahedron* **1968**, 24, 3503; Boothe; Greene; Shevlin *J. Org. Chem.* **1980**, 45, 794; Stark; Nelson; Jensen *J. Org. Chem.* **1980**, 45, 420; Kochi *Organic Mechanisms and Catalysis*; Academic Press: New York, 1978, pp. 346-349; Kamimura; Ono *J. Chem. Soc., Chem. Commun.* **1988**, 1278.

¹³⁴Froemsdorf; Collins; Hammond; DePuy *J. Am. Chem. Soc.* **1959**, 81, 643; Haag; Pines *J. Org. Chem.* **1959**, 24, 877.

¹³⁵DePuy; King *Chem. Rev.* **1960**, 60, 431-445, have tables showing the product distribution for many cases.

¹³⁶Bailey; Baylouny *J. Am. Chem. Soc.* **1959**, 81, 2126.

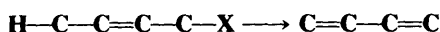
about 50% of each olefin, even though, for elimination to the 1-ene, the leaving group must go off with a trans hydrogen.¹³⁷

3. In some cases, especially with cyclic compounds, the more stable olefin forms and Zaitsev's rule applies. For example, menthyl acetate gives 35% of the Hofmann product and 65% of the Zaitsev, even though a cis β hydrogen is present on both sides and the statistical distribution is the other way. A similar result was found for the pyrolysis of menthyl chloride.¹³⁸

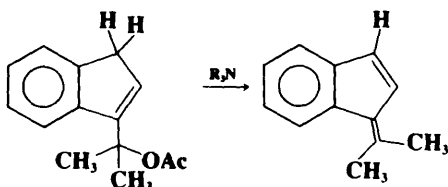
4. There are also steric effects. In some cases the direction of elimination is determined by the need to minimize steric interactions in the transition state or to relieve steric interactions in the ground state.

1,4 Conjugate Eliminations

1,4 eliminations of the type



are much rarer than conjugate additions (Chapter 15), but some examples are known.¹⁴⁰ One such is¹⁴¹



REACTIONS

First we consider reactions in which a $\text{C}=\text{C}$ or a $\text{C}\equiv\text{C}$ bond is formed. From a synthetic point of view, the most important reactions for the formation of double bonds are 7-1 (usually by an E1 mechanism), 7-6, 7-13, and 7-29 (usually by an E2 mechanism), and 7-3, 7-4, and 7-8 (usually by an Ei mechanism). The only synthetically important method for the formation of triple bonds is 7-13.¹⁴² In the second section we treat reactions in which $\text{C}\equiv\text{N}$ bonds and $\text{C}=\text{N}$ bonds are formed, and then eliminations that give $\text{C}=\text{O}$ bonds and diazoalkanes. Finally, we discuss extrusion reactions.

Reactions in Which $\text{C}=\text{C}$ and $\text{C}\equiv\text{C}$ Bonds are Formed

A. Reactions in Which Hydrogen is Removed from One Side. In 7-1 to 7-5 the other leaving atom is oxygen. In 7-6 to 7-10 it is nitrogen. For reactions in which hydrogen is removed from both sides, see 9-1 to 9-6.

¹³⁷Botteron; Shulman *J. Org. Chem.* **1962**, 27, 2007.

¹³⁸Barton; Head; Williams *J. Chem. Soc.* **1952**, 453; Bamkole; Maccoll *J. Chem. Soc. B* **1970**, 1159.

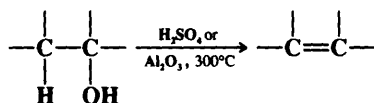
¹³⁹Taylor. Ref. 117, pp. 885-890; Smith; Mutter; Todd *J. Org. Chem.* **1977**, 42, 44; Chuchani; Dominguez *Int. J. Chem. Kinet.* **1981**, 13, 577; Hernández A.; Chuchani *Int. J. Chem. Kinet* **1983**, 15, 205.

¹⁴⁰For a review of certain types of 1,4 and 1,6 eliminations, see Wakselman *Nouv. J. Chem.* **1983**, 7, 439-447.

¹⁴¹Thibblin; Onyido; Ahlberg *Chem. Scr.* **1982**, 19, 145; Thibblin *J. Chem. Soc., Perkin Trans. 2* **1986**, 321; Ölwegård; Ahlberg *Acta Chem. Scand.* **1990**, 44, 642. For studies of the stereochemistry of 1,4 eliminations, see Hill; Bock *J. Am. Chem. Soc.* **1978**, 100, 637; Moss; Rickborn *J. Org. Chem.* **1986**, 51, 1992; Ölwegård; Ahlberg *J. Chem. Soc., Chem. Commun.* **1989**, 1279.

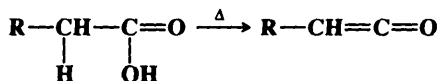
¹⁴²For reviews of methods for preparing alkynes, see Friedrich, in Patai; Rappoport *The Chemistry of Functional Groups, Supplement C*, pt. 2; Wiley: New York, 1983; pp. 1376-1384; Ben-Efraim, in Patai *The Chemistry of the Carbon-Carbon Triple Bond*, pt. 2; Wiley: New York, 1978, pp. 755-790. For a comparative study of various methods, see Mesnard; Bernadou; Miginiac *J. Chem. Res. (S)* **1981**, 270, and other papers in this series.

7-1 Dehydration of Alcohols

Hydro-hydroxy-elimination

Dehydration of alcohols can be accomplished in several ways. H_2SO_4 and H_3PO_4 are common reagents, but in many cases these lead to rearrangement products and to ether formation (0-16). If the alcohol can be evaporated, vapor-phase elimination over Al_2O_3 is an excellent method since side reactions are greatly reduced. This method has even been applied to such high-molecular-weight alcohols as 1-dodecanol.¹⁴³ Other metallic oxides (e.g., Cr_2O_3 , TiO_2 , WO_3) have also been used, as have been sulfides, other metallic salts, and zeolites. Another method of avoiding side reactions is the conversion of alcohols to esters, and the pyrolysis of these (7-3 to 7-5). The ease of dehydration increases with α branching, and tertiary alcohols are dehydrated so easily with only a trace of acid that it sometimes happens even when the investigator desires otherwise. It may also be recalled that the initial alcohol products of many base-catalyzed condensations dehydrate spontaneously (Chapter 16) because the new double bond can be in conjugation with one already there. Many other dehydrating agents¹⁴⁴ have been used on occasion: P_2O_5 , I_2 , ZnCl_2 , BF_3 -etherate, dimethyl sulfoxide, KHSO_4 , anhydrous CuSO_4 , and phthalic anhydride, among others. Secondary and tertiary alcohols can also be dehydrated, without rearrangements, simply on refluxing in HMPA.¹⁴⁵ With nearly all reagents, dehydration follows Zaitsev's rule. An exception involves the passage of hot alcohol vapors over thorium oxide at 350 to 450°C, under which conditions Hofmann's rule is followed,¹⁴⁶ and the mechanism is probably different.

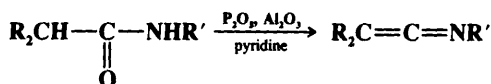
Carboxylic acids can be dehydrated by pyrolysis, the product being a ketene:



Ketene itself is commercially prepared in this manner. In a similar reaction, carbon suboxide is produced by heating malonic acid with P_2O_5 :



Carboxylic acids have also been converted to ketenes by treatment with certain reagents, among them TsCl ,¹⁴⁷ dicyclohexylcarbodiimide,¹⁴⁸ and 1-methyl-2-chloropyridinium iodide (*Mukaiyama's reagent*).¹⁴⁹ Analogously, amides can be dehydrated with P_2O_5 , pyridine, and Al_2O_3 to give ketenimines:¹⁵⁰



¹⁴³For example, see Spitzin; Michailenko; Pirogova *J. Prakt. Chem.* **1964**, [4] 25, 160; Bertsch; Greiner; Kretzschmar; Falk *J. Prakt. Chem.* **1964**, [4] 25, 184.

¹⁴⁴For a list of reagents, with references, see Larock *Comprehensive Organic Transformations*; VCH: New York, 1989, pp. 151-152.

¹⁴⁵Monson *Tetrahedron Lett.* **1971**, 567; Monson; Priest *J. Org. Chem.* **1971**, 36, 3826; Lomas; Sagatys; Dubois *Tetrahedron Lett.* **1972**, 165.

¹⁴⁶Lundeen; Van Hoozer *J. Am. Chem. Soc.* **1963**, 85, 2180; *J. Org. Chem.* **1967**, 32, 3386. See also Davis *J. Org. Chem.* **1982**, 47, 900; Iimori; Ohtsuka; Oishi *Tetrahedron Lett.* **1991**, 32, 1209.

¹⁴⁷Brady; Marchand; Giang; Wu *Synthesis* **1987**, 395; *J. Org. Chem.* **1987**, 52, 3457.

¹⁴⁸Olah; Wu; Farooq *Synthesis* **1989**, 568.

¹⁴⁹Ref. 147; Funk; Abelman; Jellison *Synlett* **1989**, 36.

¹⁵⁰Stevens; Singhal *J. Org. Chem.* **1964**, 29, 34.

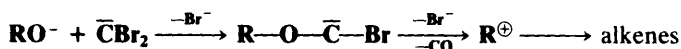
There is no way in which dehydration of alcohols can be used to prepare triple bonds: *gem*-diols and vinylic alcohols are not normally stable compounds and *vic*-diols¹⁵¹ give either conjugated dienes or lose only 1 mole of water to give an aldehyde or ketone.

When proton acids catalyze alcohol dehydration, the mechanism is E1.¹⁵² The principal process involves conversion of ROH to ROH₂⁺ and cleavage of the latter to R⁺ and H₂O, though with some acids a secondary process probably involves conversion of the alcohol to an inorganic ester and ionization of *this* (illustrated for H₂SO₄):



Note that these mechanisms are the reverse of those involved in the acid-catalyzed hydration of double bonds (5-2), in accord with the principle of microscopic reversibility. With anhydrides (e.g., P₂O₅, phthalic anhydride) as well as with some other reagents such as HMPA,¹⁵³ it is likely that an ester is formed, and the leaving group is the conjugate base of the corresponding acid. In these cases the mechanism can be E1 or E2. The mechanism with Al₂O₃ and other solid catalysts has been studied extensively but is poorly understood.¹⁵⁴

Dehydration of alcohols has also been accomplished by treating the *alkoxide* form of the alcohol with bromoform.¹⁵⁵ This reaction is called *deoxidation*. It is known that bromoform in basic solution gives rise to dibromocarbene, and the following mechanism is likely:

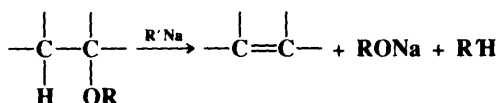


Note that the cleavage of the intermediate ROCCBr is analogous to cleavage of RN₂⁺ (p. 355) and the product distribution is similar.¹⁵⁶ Magnesium alkoxides (formed by ROH + Me₂Mg → ROMgMe) have been decomposed thermally, by heating at 195–340°C to give the alkene, CH₄, and MgO.¹⁵⁷ Syn elimination is found and an Ei mechanism is likely. Similar decomposition of aluminum and zinc alkoxides has also been accomplished.¹⁵⁸

OS I, 15, 183, 226, 280, 345, 430, 473, 475; II, 12, 368, 408, 606; III, 22, 204, 237, 312, 313, 353, 560, 729, 786; IV, 130, 444, 771; V, 294; VI, 307, 901; VII, 210, 241, 363, 368, 396; 65, 12, 98. See also OS VII, 63; 67, 125; 69, 199. No attempt has been made to list olefin-forming dehydrations accompanying condensations or rearrangements.

7-2 Cleavage of Ethers to Olefins

Hydro-alkoxy-elimination



¹⁵¹For a review on the dehydration of 1,2 and 1,3 diols, see Bartók; Molnár, in Patai *The Chemistry of Functional Groups, Supplement E*, pt. 2; Wiley: New York, 1980, pp. 721–760.

¹⁵²For reviews of dehydration mechanisms, see Vinnik; Obraztsov *Russ. Chem. Rev.* **1990**, 59, 63–77; Saunders; Cockerill, *Ref. 2*, pp. 221–274, 317–331; Knözinger, in Patai *The Chemistry of the Hydroxyl Group*, pt. 2; Wiley: New York, 1971, pp. 641–718.

¹⁵³See, for example, Kawanisi; Arimatsu; Yamaguchi; Kimoto *Chem. Lett.* **1972**, 881.

¹⁵⁴For reviews, see Beránek; Kraus; in Bamford; Tipper, *Ref. 2*, vol. 20, 1978, pp. 274–295; Pines *Intra-Sci. Chem. Rep.* **1972**, 6(2), 1–42, pp. 17–21; Noller; Andréu; Hunger *Angew. Chem. Int. Ed. Engl.* **1971**, 10, 172–181 [*Angew. Chem.* 83, 185–194]; Knözinger *Angew. Chem. Int. Ed. Engl.* **1968**, 7, 791–805 [*Angew. Chem.* 80, 778–792]; Pines; Manassen *Adv. Catal.* **1966**, 16, 49–93; *Ref. 152*. See also Berteau; Ruwet; Delmon *Bull. Soc. Chim. Belg.* **1985**, 94, 859.

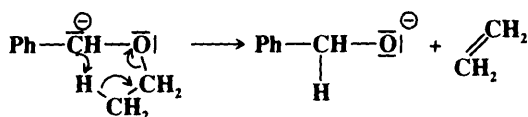
¹⁵⁵Skell; Starer *J. Am. Chem. Soc.* **1959**, 81, 4117.

¹⁵⁶See, for example, Lee; Hahn *Can J. Chem.* **1967**, 45, 2129.

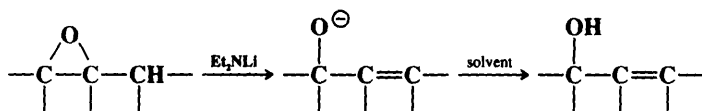
¹⁵⁷Ashby; Willard; Goel *J. Org. Chem.* **1979**, 44, 1221.

¹⁵⁸*Ref. 157*; Brieger; Watson; Barar; Shene *J. Org. Chem.* **1979**, 44, 1340.

Olefins can be formed by the treatment of ethers with very strong bases, such as alkylsodium or alkyllithium compounds or sodium amide,¹⁵⁹ though there are usually side reactions too. The reaction is aided by electron-withdrawing groups in the β position, and, for example, $\text{EtOCH}_2\text{CH}(\text{COOEt})_2$ can be converted to $\text{CH}_2=\text{C}(\text{COOEt})_2$ without any base at all, but simply on heating.¹⁶⁰ *t*-Butyl ethers are cleaved more easily than others. Several mechanisms are possible. In many cases the mechanism is probably E1cB or on the E1cB side of the mechanistic spectrum,¹⁶¹ since the base required is so strong, but it has been shown (by the use of PhCD_2OEt) that PhCH_2OEt reacts by the five-membered Ei mechanism:¹⁶²

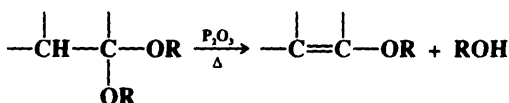


Epoxides can be converted to allylic alcohols¹⁶³ by treatment with several reagents, including lithium diethylamide,¹⁶⁴ *t*-butyldimethylsilyl iodide,¹⁶⁵ methylmagnesium N-cy-



clohexylisopropylamide,¹⁶⁶ $i\text{-Pr}_2\text{NLi-t-BuOK}$ (the *LIDAKOR* reagent),¹⁶⁷ and a diethylaluminum dialkylamide R_2NAlEt ¹⁶⁸ (an alternative procedure is given in 7-12). When an optically active reagent is used, optically active allylic alcohols can be produced from achiral epoxides.¹⁶⁹

Ethers have also been converted to olefins and alcohols by passing vapors over hot P_2O_5 or Al_2O_3 (this method is similar to 7-1), but this is not a general reaction. However, acetals can be converted to enol ethers in this manner:



This can also be done at room temperature by treatment with trimethylsilyl triflate and a tertiary amine¹⁷⁰ or with Me_3SiI in the presence of hexamethyldisilazane.¹⁷¹

¹⁵⁹For a review, see Maercker *Angew. Chem. Int. Ed. Engl.* **1967**, 26, 972-989 [*Angew. Chem.* 99, 1002-1019].

¹⁶⁰Feely; Boekelheide *Org. Synth.* IV, 298.

¹⁶¹For an investigation in the gas phase, see DePuy; Bierbaum *J. Am. Chem. Soc.* **1961**, 103, 5034.

¹⁶²Letsinger; Pollart *J. Am. Chem. Soc.* **1956**, 78, 6079.

¹⁶³For reviews, see Smith *Synthesis* **1984**, 629-656, pp. 637-642; Crandall; Appar *Org. React.* **1983**, 29, 345-443.

For a list of reagents, with references, see Ref. 144, pp. 117-118.

¹⁶⁴See, for example, Cope; Brown; Lee *J. Am. Chem. Soc.* **1958**, 80, 2855; Kissel; Rickborn *J. Org. Chem.* **1972**, 37, 2060; Crandall; Crawley *Org. Synth.* VI, 948.

¹⁶⁵Detty *J. Org. Chem.* **1980**, 45, 924. For another silyl reagent, see Murata; Suzuki; Noyori *J. Am. Chem. Soc.* **1979**, 101, 2738.

¹⁶⁶Mosset; Manna; Viala; Falck *Tetrahedron Lett.* **1986**, 27, 299.

¹⁶⁷Mordini; Ben Rayana; Margot; Schlosser *Tetrahedron* **1990**, 46, 2401.

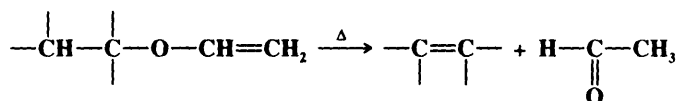
¹⁶⁸For a review, see Yamamoto; Nozaki *Angew. Chem. Int. Ed. Engl.* **1978**, 17, 169-175 [*Angew. Chem.* 90, 180-186]. See also Yasuda; Tanaka; Yamamoto; Nozaki *Bull. Chem. Soc. Jpn.* **1979**, 52, 1752.

¹⁶⁹Su; Walder; Zhang; Scheffold *Helv. Chim. Acta* **1988**, 71, 1073, and references cited therein.

¹⁷⁰Gassman; Burns *J. Org. Chem.* **1968**, 33, 5574.

¹⁷¹Miller; McKean *Tetrahedron Lett.* **1982**, 23, 323. For another method, see Marsi; Gladysz *Organometallics* **1982**, 1, 1467.

Enol ethers can be pyrolyzed to olefins and aldehydes in a manner similar to that of 7-3:

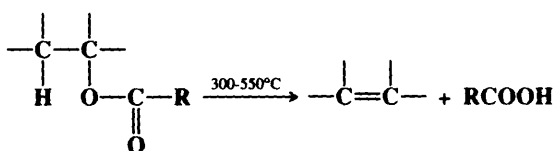


The rate of this reaction for $\text{R}-\text{O}-\text{CH}=\text{CH}_2$ increased in the order $\text{Et} < i\text{-Pr} < t\text{-Bu}$.¹⁷² The mechanism is similar to that of 7-3.

OS IV, 298, 404; V, 25, 642, 859, 1145; VI, 491, 564, 584, 606, 683, 948; 65, 98.

7-3 Pyrolysis of Esters of Carboxylic Acids

Hydro-acyloxy-elimination



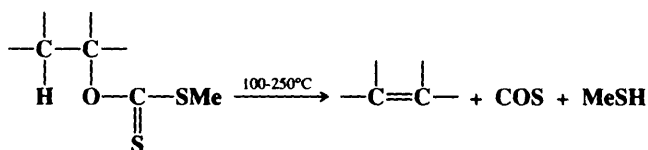
Carboxylic esters in which the alkyl group has a β hydrogen can be pyrolyzed, most often in the gas phase, to give the corresponding acid and an olefin.¹⁷³ No solvent is required. Since rearrangement and other side reactions are few, the reaction is synthetically very useful and is often carried out as an indirect method of accomplishing 7-1. The yields are excellent and the workup is easy. Many olefins have been prepared in this manner. For higher olefins (above about C_{10}) a better method is to pyrolyze the alcohol in the presence of acetic anhydride.¹⁷⁴

The mechanism is Ei (see p. 1006). Lactones can be pyrolyzed to give unsaturated acids, provided that the six-membered transition state required for Ei reactions is available (it is not available for five- and six-membered lactones, but it is for larger rings¹⁷⁵). Amides give a similar reaction but require higher temperatures.

Allylic acetates give dienes when heated with certain palladium¹⁷⁶ or molybdenum¹⁷⁷ compounds.

OS III, 30; IV, 746; V, 235.

7-4 The Chugaev Reaction



¹⁷²McEwen; Taylor *J. Chem. Soc., Perkin Trans. 2* **1982**, 1179. See also Taylor *J. Chem. Soc., Perkin Trans. 2* **1988**, 737.

¹⁷³For a review, see DePuy; King, Ref. 135, pp. 432-444. For some procedures, see Jenneskens; Hoefs; Wiersum *J. Org. Chem.* **1989**, 54, 5811, and references cited therein.

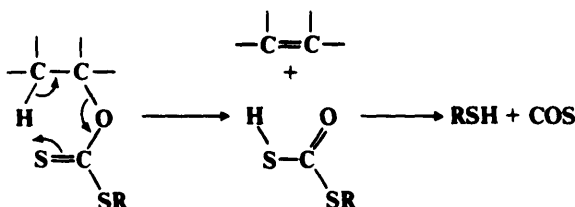
¹⁷⁴Aubrey; Barnatt; Gerrard *Chem. Ind. (London)* **1965**, 681.

¹⁷⁵See, for example, Bailey; Bird, Ref. 122.

¹⁷⁶For a review, see Heck *Palladium Reagents in Organic Synthesis*; Academic Press: New York, 1985, pp. 172-178.

¹⁷⁷Trost; Lautens; Peterson *Tetrahedron Lett.* **1983**, 24, 4525.

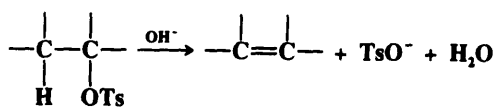
Methyl xanthates are prepared by treatment of alcohols with NaOH and CS₂ to give RO—CS—SNa, followed by treatment of this with methyl iodide.¹⁷⁸ Pyrolysis of the xanthate to give the olefin, COS, and the thiol is called the *Chugaev reaction*.¹⁷⁹ The reaction is thus, like 7-3, an indirect method of accomplishing 7-1. The temperatures required with xanthates are lower than with ordinary esters, which is advantageous because possible isomerization of the resulting olefin is minimized. The mechanism is Ei, similar to that of 7-3. For a time there was doubt as to which sulfur atom closed the ring, but now there is much evidence, including the study of ³⁴S and ¹³C isotope effects, to show that it is the C=S sulfur.¹⁸⁰



The mechanism is thus exactly analogous to that of 7-3.
OS VII, 139.

7-5 Decomposition of Other Esters

Hydro-tosyloxy-elimination

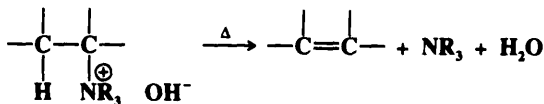


Several types of inorganic ester can be cleaved to olefins by treatment with bases. Esters of sulfuric, sulfurous, and other acids undergo elimination in solution by E1 or E2 mechanisms, as do tosylates and other esters of sulfonic acids.¹⁸¹ It has been shown that bis(tetra-*n*-butylammonium) oxalate (Bu₄N⁺)₂ (COO⁻)₂ is an excellent reagent for inducing tosylates to undergo elimination rather than substitution.¹⁸² Aryl sulfonates have also been cleaved without a base. Esters of 2-pyridinesulfonic acid and 8-quinolinesulfonic acid gave olefins in high yields simply on heating, without a solvent.¹⁸³ Esters of PhSO₂OH and TsOH behaved similarly when heated in a dipolar aprotic solvent such as Me₂SO or HMPA.¹⁸⁴

OS, VI, 837; VII, 117.

7-6 Cleavage of Quaternary Ammonium Hydroxides

Hydro-trialkylammonio-elimination



¹⁷⁸For a method of preparing xanthates from alcohols in one laboratory step, see Lee; Chan; Wong; Wong *Synth. Commun.* **1989**, 19, 547.

¹⁷⁹For reviews, see DePuy; King, Ref. 135, pp. 444-448; Nace *Org. React.* **1962**, 12, 57-100.

¹⁸⁰Bader; Bourns *Can. J. Chem.* **1961**, 39, 348.

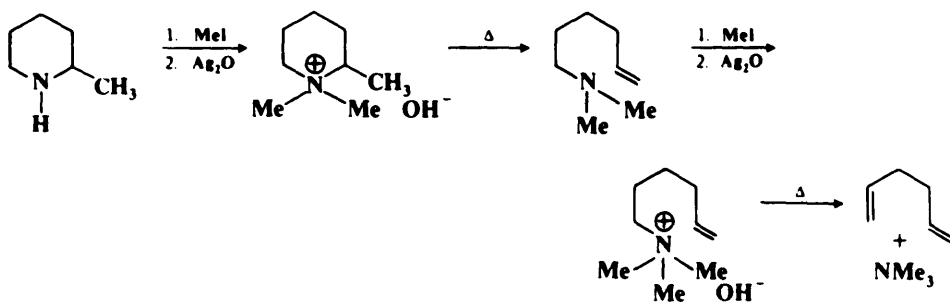
¹⁸¹For a list of reagents used for sulfonate cleavages, with references, see Ref. 144, pp. 153-154.

¹⁸²Corey; Terashima *Tetrahedron Lett.* **1972**, 111.

¹⁸³Corey; Posner; Atkinson; Wingard; Halloran; Radzik; Nash *J. Org. Chem.* **1989**, 54, 389.

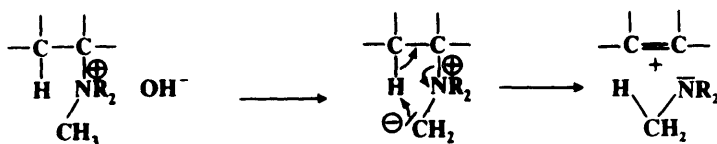
¹⁸⁴Nace *J. Am. Chem. Soc.* **1959**, 81, 5428.

Cleavage of quaternary ammonium hydroxides is the final step of the process known as *Hofmann exhaustive methylation* or *Hofmann degradation*.¹⁸⁵ In the first step, a primary, secondary, or tertiary amine is treated with enough methyl iodide to convert it to the quaternary ammonium iodide (**0-43**). In the second step, the iodide is converted to the hydroxide by treatment with silver oxide. In the cleavage step an aqueous or alcoholic solution of the hydroxide is distilled, often under reduced pressure. The decomposition generally takes place at a temperature between 100 and 200°C. Alternatively, the solution can be concentrated to a syrup by distillation or freeze-drying.¹⁸⁶ When the syrup is heated at low pressures, the cleavage reaction takes place at lower temperatures than are required for the reaction in the ordinary solution, probably because the base (OH^- or RO^-) is less solvated.¹⁸⁷ The reaction has never been an important synthetic tool, but in the 19th century and the first part of the 20th century it saw much use in the determination of the structure of unknown amines, especially alkaloids. In many of these compounds the nitrogen is in a ring, or even at a ring junction, and in such cases the olefin still contains nitrogen. Repetitions of the process are required to remove the nitrogen completely, e.g.,



A side reaction involving nucleophilic substitution to give an alcohol ($\text{R}_4\text{N}^+ \text{OH}^- \rightarrow \text{ROH} + \text{R}_3\text{N}$) generally accompanies the normal elimination reaction¹⁸⁸ but seldom causes trouble. However, when none of the four groups on the nitrogen has a β hydrogen, substitution is the only reaction possible. On heating $\text{Me}_4\text{N}^+ \text{OH}^-$ in water, methanol is obtained, though without a solvent the product is not methanol but dimethyl ether.¹⁸⁹

The mechanism is usually E2. Hofmann's rule is generally obeyed by acyclic and Zaitsev's rule by cyclohexyl substrates (p. 999). In certain cases, where the molecule is highly hindered, a five-membered E_i mechanism, similar to that in 7-7, has been shown to operate. That is, the OH^- in these cases does not attract the β hydrogen, but instead removes one of the methyl hydrogens:



¹⁸⁵For reviews, see Bentley, in Bentley; Kirby *Elucidation of Organic Structures by Physical and Chemical Methods*, 2nd ed. (vol. 4 of Weissberger *Techniques of Chemistry*), pt. 2; Wiley: New York, 1973, pp. 255-289; White; Woodcock, in Patai *The Chemistry of the Amino Group*; Wiley: New York, 1968, pp. 409-416; Cope; Trumbull *Org. React.* **1960**, *11*, 317-493.

¹⁸⁶Archer *J. Chem. Soc. C* **1971**, 1327.

¹⁸⁷Saunders; Cockerill, Ref. 2, pp. 4-5.

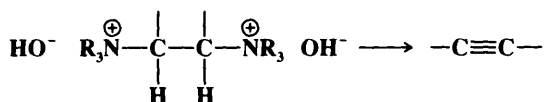
¹⁸⁸Baumgarten *J. Chem. Educ.* **1968**, *45*, 122.

¹⁸⁹Musker *J. Am. Chem. Soc.* **1964**, *86*, 960; *J. Chem. Educ.* **1968**, *45*, 200; Musker; Stevens *J. Am. Chem. Soc.* **1968**, *90*, 3515; Tanaka; Dunning; Carter *J. Org. Chem.* **1966**, *31*, 3431.

The obvious way to distinguish between this mechanism and the ordinary E2 mechanism is by the use of deuterium labeling. For example, if the reaction is carried out on a quaternary hydroxide deuterated on the β carbon ($R_2CDCH_2NMe_3^+ OH^-$), the fate of the deuterium indicates the mechanism. If the E2 mechanism is in operation, the trimethylamine produced would contain no deuterium (which would be found only in the water). But if the mechanism is Ei, the amine would contain deuterium. In the case of the highly hindered compound $(Me_3C)_2CDCH_2NMe_3^+ OH^-$, the deuterium did appear in the amine, demonstrating an Ei mechanism for this case.¹⁹⁰ With simpler compounds, the mechanism is E2, since here the amine was deuterium-free.¹⁹¹

When the nitrogen bears more than one group possessing a β hydrogen, which group cleaves? The Hofmann rule says that *within* a group the hydrogen on the least alkylated carbon cleaves. This tendency is also carried over to the choice of which group cleaves: thus ethyl with three β hydrogens cleaves more readily than any longer n -alkyl group, all of which have two β hydrogens. "The β hydrogen is removed most readily if it is located on a methyl group, next from RCH_2 , and least readily from R_2CH ."¹⁹² In fact, the Hofmann rule as first stated¹⁹³ in 1851 applied only to which group cleaved, not to the orientation within a group; the latter could not have been specified in 1851, since the structural theory of organic compounds was not formulated until 1857-1860. Of course, the Hofmann rule (applied to which group cleaves *or* to orientation within a group) is superseded by conjugation possibilities. Thus $PhCH_2CH_2NMe_2Et^+ OH^-$ gives mostly styrene instead of ethylene.

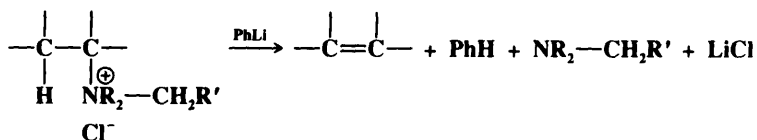
Triple bonds have been prepared by pyrolysis of 1,2-bis salts.¹⁹⁴



OS IV, 980; V, 315, 608; VI, 552. Also see OS V, 621, 883; VI, 75.

7-7 Cleavage of Quaternary Ammonium Salts with Strong Bases

Hydro-trialkylammonio-elimination



When quaternary ammonium halides are treated with strong bases (e.g., $PhLi$, KNH_2 in liquid NH_3 ¹⁹⁵), an elimination can occur that is similar in products, though not in mechanism,

¹⁹⁰Cope; Mehta *J. Am. Chem. Soc.* **1963**, 85, 1949. See also Baldwin; Banthorpe; Loudon; Waller *J. Chem. Soc. B* **1967**, 509.

¹⁹¹Cope; LeBel; Moore; Moore *J. Am. Chem. Soc.* **1961**, 83, 3861.

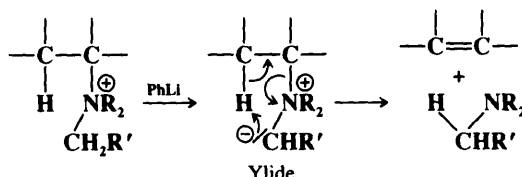
¹⁹²Cope; Trumbull. Ref. 185, p. 348.

¹⁹³Hofmann *Liebigs Ann. Chem.* **1851**, 78, 253.

¹⁹⁴For a review, see Franke; Ziegenbein; Meister *Angew. Chem.* **1960**, 72, 391-400, pp. 397-398.

¹⁹⁵Bach; Andrzejewski *J. Am. Chem. Soc.* **1971**, 93, 7118; Bach; Bair; Andrzejewski *J. Am. Chem. Soc.* **1972**, 94, 8608. *J. Chem. Soc., Chem. Commun.* **1974**, 819.

to **7-6**. This is an alternative to **7-6** and is done on the quaternary ammonium halide, so that it is not necessary to convert this to the hydroxide. The mechanism is Ei:

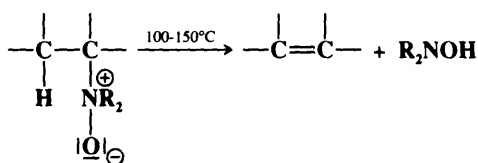


An α' hydrogen is obviously necessary in order for the ylide to be formed. This type of mechanism is called α',β elimination, since a β hydrogen is removed by the α' carbon. The mechanism has been confirmed by labeling experiments similar to those described at **7-6**,¹⁹⁶ and by isolation of the intermediate ylides.¹⁹⁷ An important synthetic difference between this and most instances of **7-6** is that syn elimination is observed here and anti elimination in **7-6**, so products of opposite configuration are formed when the olefin exhibits cis-trans isomerism.

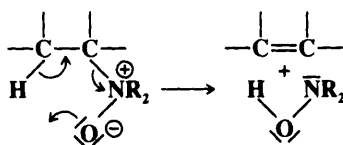
An alternative procedure that avoids the use of a very strong base is heating the salt with KOH in polyethylene glycol monomethyl ether.¹⁹⁸

7-8 Cleavage of Amine Oxides

Hydro-(Dialkyloxidoammonio)-elimination



Cleavage of amine oxides to produce an alkene and a hydroxylamine is called the *Cope reaction* (not to be confused with the *Cope rearrangement*, **8-34**). It is an alternative to **7-6** and **7-7**.¹⁹⁹ The reaction is usually performed with a mixture of amine and oxidizing agent (see **9-28**) without isolation of the amine oxide. Because of the mild conditions side reactions are few, and the olefins do not usually rearrange. The reaction is thus very useful for the preparation of many olefins. A limitation is that it does not open 6-membered rings containing hetero nitrogen, though it does open rings of 5 and 7 to 10 members.²⁰⁰ Rates of the reaction increase with increasing size of α and β substituents.²⁰¹ The reaction can be carried out at room temperature in dry Me_2SO or THF.²⁰² The elimination is a stereoselective syn process,²⁰³ and the five-membered Ei mechanism operates:



¹⁹⁶Weygand; Daniel; Simon *Chem. Ber.* **1958**, 91, 1691; Bach; Andrzejewski; Bair *J. Chem. Soc., Chem. Commun.* **1974**, 820; Bach; Knight *Tetrahedron Lett.* **1979**, 3815.

¹⁹⁷Wittig; Polster *Liebigs Ann. Chem.* **1958**, 612, 102; Wittig; Burger *Liebigs Ann. Chem.* **1960**, 632, 85.

¹⁹⁸Hünig; Öller; Wehner *Liebigs Ann. Chem.* **1979**, 1925.

¹⁹⁹For reviews, see Cope; Trumbull, Ref. 185, pp. 361-370; DePuy; King, Ref. 135, pp. 448-451.

²⁰⁰Cope; LeBel *J. Am. Chem. Soc.* **1960**, 82, 4656; Ciganek; Howell; Schweizer *J. Am. Chem. Soc.* **1960**, 82, 4663.

²⁰¹Závada; Pánková; Svoboda *Collect. Czech. Chem. Commun.* **1973**, 38, 2102.

²⁰²Cram; Sahyun; Knox *J. Am. Chem. Soc.* **1962**, 84, 1734.

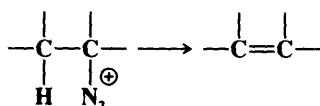
²⁰³See, for example, Bach; Andrzejewski; Dusold *J. Org. Chem.* **1973**, 38, 1742.

Almost all evidence indicates that the transition state must be planar. Deviations from planarity as in 7-3 (see p. 1006) are not found here, and indeed this is why six-membered heterocyclic nitrogen compounds do not react. Because of the stereoselectivity of this reaction and the lack of rearrangement of the products, it is useful for the formation of trans cycloolefins (eight-membered and higher).

OS IV, 612.

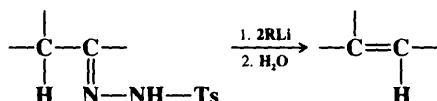
7-9 Olefins from Aliphatic Diazonium Salts

Hydro-diazonio-elimination

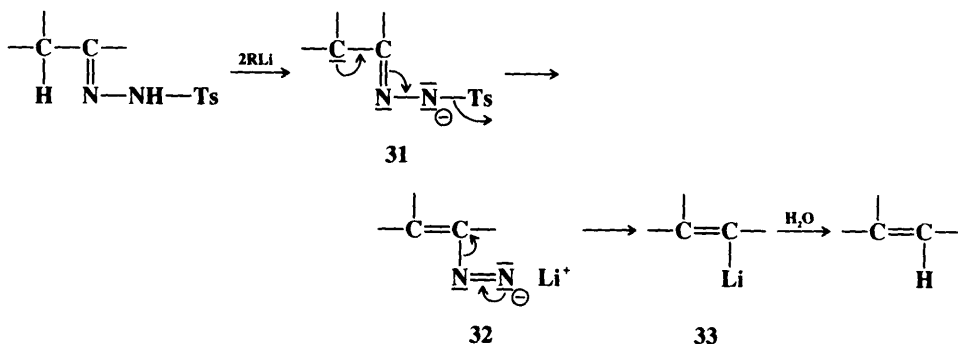


The treatment of aliphatic amines with nitrous acid is not a useful method for the preparation of olefins any more than it is for the preparation of alcohols (p. 355), though some olefin is usually formed in such reactions.

7-10 Decomposition of Toluene-*p*-sulfonylhydrazones



Treatment of the tosylhydrazone of an aldehyde or a ketone with a strong base leads to the formation of an olefin, the reaction being formally an elimination accompanied by a hydrogen shift.²⁰⁴ The reaction (called the *Shapiro reaction*) has been applied to tosylhydrazones of many aldehydes and ketones. The most useful method synthetically involves treatment of the substrate with at least two equivalents of an organolithium compound²⁰⁵ (usually MeLi) in ether, hexane, or tetramethylenediamine.²⁰⁶ This procedure gives good yields of alkenes without side reactions and, where a choice is possible, predominantly gives the less highly substituted olefin. Tosylhydrazones of α,β -unsaturated ketones give conjugated dienes.²⁰⁷ The mechanism²⁰⁸ has been formulated as:



²⁰⁴For reviews, see Adlington; Barrett *Acc. Chem. Res.* **1983**, *16*, 55-59; Shapiro *Org. React.* **1976**, *23*, 405-507.

²⁰⁵Shapiro; Heath *J. Am. Chem. Soc.* **1967**, *89*, 5734; Kaufman; Cook; Shechter; Bayless; Friedman *J. Am. Chem. Soc.* **1967**, *89*, 5736; Shapiro *Tetrahedron Lett.* **1968**, 345; Meinwald; Uno *J. Am. Chem. Soc.* **1968**, *90*, 800.

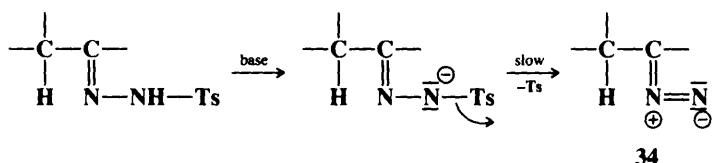
²⁰⁶Stemke; Bond *Tetrahedron Lett.* **1975**, 1815.

²⁰⁷See Dauben; Rivers; Zimmerman *J. Am. Chem. Soc.* **1977**, *99*, 3414.

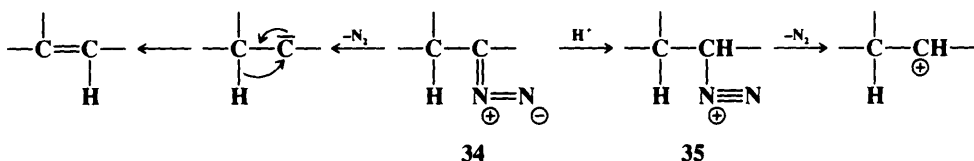
²⁰⁸For a review of the mechanism, see Casanova; Waegell *Bull. Soc. Chim. Fr.* **1975**, 922-932.

Evidence for this mechanism is: (1) two equivalents of RLi are required; (2) the hydrogen in the product comes from the water and not from the adjacent carbon, as shown by deuterium labeling;²⁰⁹ and (3) the intermediates **31-33** have been trapped.²¹⁰ This reaction, when performed in tetramethylenediamine, can be a synthetically useful method²¹¹ of generating vinylic lithium compounds (**33**), which can be trapped by various electrophiles such as D₂O (to give deuterated alkenes), CO₂ (to give α,β -unsaturated carboxylic acids—**6-34**), or DMF (to give α,β -unsaturated aldehydes—**0-105**).

The reaction also takes place with other bases (e.g., LiH,²¹³ Na in ethylene glycol, NaH, NaNH₂) or with smaller amounts of RLi, but in these cases side reactions are common and the orientation of the double bond is in the other direction (to give the more highly substituted olefin). The reaction with Na in ethylene glycol is called the *Bamford-Stevens reaction*.²¹⁴ For these reactions two mechanisms are possible—a carbenoid and a carbocation mechanism.²¹⁵ The side reactions found are those expected of carbenes and carbocations. In general, the carbocation mechanism is chiefly found in protic solvents and the carbenoid mechanism in aprotic solvents. Both routes involve formation of a diazo compound (**34**) which in some cases can be isolated.



In fact, this reaction has been used as a synthetic method for the preparation of diazo compounds.²¹⁶ In the absence of protic solvents **34** loses N₂, and hydrogen migrates, to give the olefin product. The migration of hydrogen may immediately follow, or be simultaneous with, the loss of N₂. In a protic solvent, **34** becomes protonated to give the diazonium ion **35** which loses N₂ to give the corresponding carbocation which may then undergo elimination



(7-9) or give other reactions characteristic of carbocations. A diazo compound is an intermediate in the formation of olefins by treatment of N-nitrosoamides with a rhodium(II) catalyst.²¹⁷

²⁰⁹Ref. 205; Shapiro; Hornaman *J. Org. Chem.* **1974**, 39, 2302.

²¹⁰Shapiro; Lipton; Kolonko; Buswell; Capuano *Tetrahedron Lett.* **1975**, 1811, Ref. 206; Lipton; Shapiro *J. Org. Chem.* **1978**, 43, 1409.

²¹¹See Traas; Boelens; Takken *Tetrahedron Lett.* **1976**, 2287; Stemke; Chamberlin; Bond *Tetrahedron Lett.* **1976**, 2947.

²¹²For a review, see Chamberlin; Bloom *Org. React.* **1990**, *39*, 1-83.

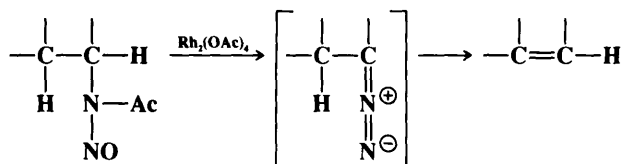
²¹³Biellmann; Pète *Bull. Soc. Chim. Fr.* **1967**, 675.

²¹⁴Bamford; Stevens *J. Chem. Soc.* **1952**, 4735.

²⁵Powell; Whiting *Tetrahedron* **1959**, 7, 305, **1961**, 12 168; DePuy; Froemdsdorf *J. Am. Chem. Soc.* **1960**, 82, 634; Bayless; Friedman; Cook; Shechter *J. Am. Chem. Soc.* **1968**, 90, 531; Nickon; Werstiuk *J. Am. Chem. Soc.* **1972**, 94, 7081.

²¹⁶For a review, see Regitz; Maas *Diazo Compounds*; Academic Press: New York, 1986, pp. 257-295. For an improved procedure, see Wulfman; Yousefian; *White Synth. Commun.* **1988**, *18*, 2349.

²¹⁷Godfrey; Ganem *J. Am. Chem. Soc.* **1990**, *112*, 3717.

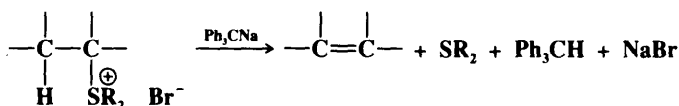
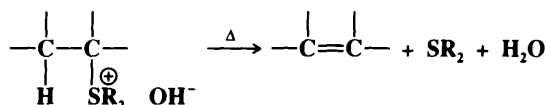


See also 7-28.

OS VI, 172; VII, 77. For the preparation of a diazo compound, see OS VII, 438.

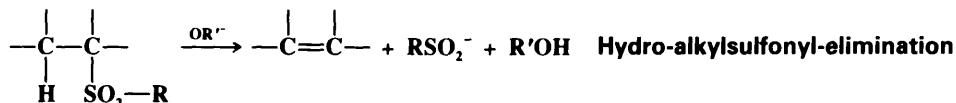
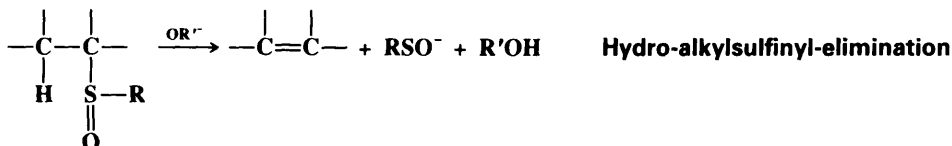
7-11 Cleavage of Sulfonium Compounds

Hydro-dialkylsulfonio-elimination



Sulfonium compounds undergo elimination similar to that of their ammonium counterparts (7-6 and 7-7) in scope and mechanism. The decomposition by heat of sulfonium hydroxides has been known for many years.²¹⁸ The ylide reaction was discovered more recently.²¹⁹ Neither is important synthetically.

7-12 Cleavage of Sulfoxides, Selenoxides, and Sulfones



Sulfones and sulfoxides with a β hydrogen undergo elimination on treatment with an alkoxide or, for sulfones,²²⁰ even with OH^- .²²¹ In mechanism, these reactions belong on the E1-E2-E1cB spectrum.²²² Although the leaving groups are uncharged, the orientation follows Hofmann's rule, not Zaitsev's. Sulfoxides (but not sulfones) also undergo elimination on pyrolysis

²¹⁸For a discussion, see Knipe, in Stirling *The Chemistry of the Sulphonium Group*, pt. 1; Wiley: New York, 1981, pp. 334-347.

²¹⁹Franzen; Mertz *Chem. Ber.* **1960**, 93, 2819. For a review, see Block *Reactions of Organosulfur Compounds*; Academic Press: New York, 1978, pp. 112-117.

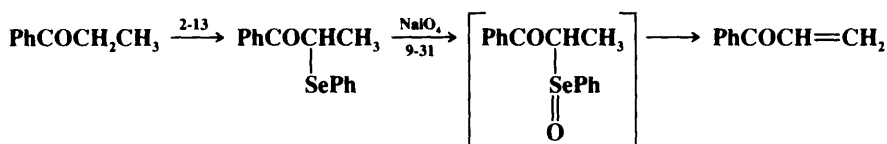
²²⁰Certain sulfones undergo elimination with 5% HCl in THF; Yoshida; Saito *Chem. Lett.* **1982**, 165.

²²¹Hofmann; Wallace; Argabright; Schriesheim *Chem. Ind. (London)* **1963**, 1234.

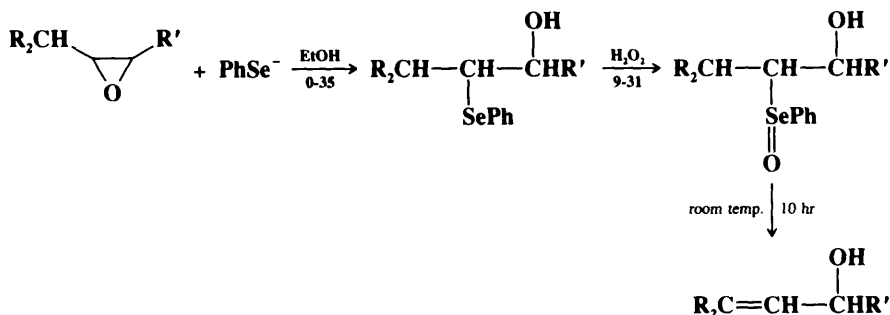
²²²Hofmann; Wallace; Schriesheim *J. Am. Chem. Soc.* **1964**, 86, 1561.

at about 80°C in a manner analogous to 7-8. The mechanism is also analogous, being the five-membered Ei mechanism with syn elimination.²²³ Selenoxides²²⁴ and sulfinate esters $R_2CH-CHR-SO-OMe$ ²²⁵ also undergo elimination by the Ei mechanism, the selenoxide reaction taking place at room temperature. The reaction with selenoxides has been extended to the formation of triple bonds.²²⁶

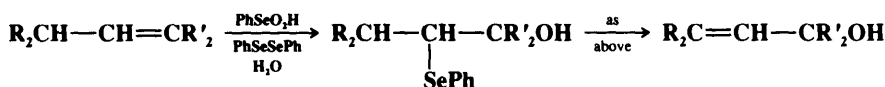
Both the selenoxide²²⁷ and sulfoxide²²⁸ reactions have been used in a method for the conversion of ketones, aldehydes, and carboxylic esters to their α,β -unsaturated derivatives (illustrated for the selenoxide).



Because of the mildness of the procedure, this is probably the best means of accomplishing this conversion. The selenoxide reaction has been used in a procedure for the conversion of epoxides to allylic alcohols.²²⁹



In another process, an olefin is converted to a rearranged allylic alcohol.²³⁰



²²³Kingsbury; Cram *J. Am. Chem. Soc.* **1960**, 82, 1810; Walling; Bollyky *J. Org. Chem.* **1964**, 29, 2699; Entwistle; Johnstone *Chem. Commun.* **1965**, 29; Yoshimura; Tsukurimichi; Iizuka; Mizuno; Isaji; Shimasaki *Bull. Chem. Soc. Jpn.* **1969**, 62, 1891.

²²⁴For reviews, see Back, in Patai *The Chemistry of Organic Selenium and Tellurium Compounds*, vol. 2; Wiley: New York, 1987, pp. 91-213, pp. 95-109; Paulmier *Selenium Reagents and Intermediates in Organic Synthesis*; Pergamon: Elmsford, NY, 1986, pp. 132-143; Reich *Acc. Chem. Res.* **1979**, 12, 22-30, in Trahanovsky *Oxidation in Organic Chemistry*, pt. C; Academic Press: New York, 1978, pp. 15-101; Sharpless; Gordon; Lauer; Patrick; Singer; Young *Chem. Scr.* **1975**, 8A, 9-13. See also Liotta *Organoselenium Chemistry*; Wiley: New York, 1987.

²²⁵Jones; Higgins *J. Chem. Soc. C* **1970**, 81.

²²⁶Reich; Willis *J. Am. Chem. Soc.* **1980**, 102, 5967.

²²⁷Clive *J. Chem. Soc., Chem. Commun.* **1973**, 695; Reich; Reich; Renga *J. Am. Chem. Soc.* **1973**, 95, 5813; Reich; Renga; Reich *J. Org. Chem.* **1974**, 39, 2133, *J. Am. Chem. Soc.* **1975**, 97, 5434; Sharpless; Lauer; Teranishi *J. Am. Chem. Soc.* **1973**, 95, 6137; Grieco; Miyashita *J. Org. Chem.* **1974**, 39, 120. For lists of reagents, with references, see Ref. 144, pp. 149-150.

²²⁸Trost; Salzmann; Hiroi *J. Am. Chem. Soc.* **1976**, 98, 4887. For a review of this and related methods, see Trost *Acc. Chem. Res.* **1978**, 11, 453-461.

²²⁹Sharpless; Lauer *J. Am. Chem. Soc.* **1973**, 95, 2697.

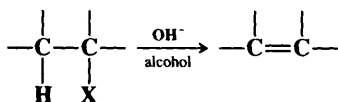
²³⁰Hori; Sharpless *J. Org. Chem.* **1978**, 43, 1689; Reich; Wollowitz; Trend; Chow; Wendelborn *J. Org. Chem.* **1978**, 43, 1697. See also Reich *J. Org. Chem.* **1974**, 39, 428; Clive *J. Chem. Soc., Chem. Commun.* **1974**, 100; Sharpless; Lauer *J. Org. Chem.* **1974**, 39, 429.

See p. 473 for another application of the selenoxide reaction. Allylic sulfoxides undergo 1,4 elimination to give dienes.²³¹

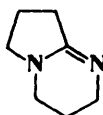
OS VI, 23, 737; 67, 157.

7-13 Dehydrohalogenation of Alkyl Halides

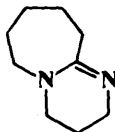
Hydro-halo-elimination



The elimination of HX from an alkyl halide is a very general reaction and can be accomplished with chlorides, fluorides, bromides, and iodides.²³² Hot alcoholic KOH is the most frequently used base, though stronger bases (OR⁻, NH₂⁻, etc.) or weaker ones (e.g., amines) are used where warranted.²³⁴ The bicyclic amidines 1,5-diazabicyclo[3.4.0]nonene-5 (DBN)²³⁵ and 1,8-diazabicyclo[5.4.0]undecene-7 (DBU)²³⁶ are good reagents for difficult cases.²³⁷



DBN



DBU

Dehydrohalogenation with the non-ionic base (Me₂N)₃P=N—P(NMe₂)₂=NMe is even faster.²³⁸ Phase transfer catalysis has been used with OH⁻ as base.²³⁹ As previously mentioned (p. 997), certain weak bases in dipolar aprotic solvents are effective reagents for dehydrohalogenation. Among those most often used for synthetic purposes are LiCl or LiBr—LiCO₃ in DMF.²⁴⁰ Dehydrohalogenation has also been effected by heating of the alkyl halide in HMPA with no other reagent present.²⁴¹ As in nucleophilic substitution (p. 352), the order of leaving group reactivity is I > Br > Cl > F.²⁴²

²³¹de Groot; Jansen; Reuvers; Tedjo *Tetrahedron Lett.* **1981**, 22, 4137.

²³²For a review of eliminations involving the carbon-halogen bond, see Baciocchi, in Patai: Rappoport *The Chemistry of Functional Groups, Supplement D*, pt. 2; Wiley: New York, 1983, pp. 1173-1227.

²³³Triphenylmethylpotassium rapidly dehydrohalogenates secondary alkyl bromides and iodides, in over 90% yields, at 0°C: Anton; Crabtree *Tetrahedron Lett.* **1983**, 24, 2449.

²³⁴For a list of reagents, with references, see Ref. 144, pp. 131-133.

²³⁵Truscheit; Eiter *Liebigs Ann. Chem.* **1962**, 658, 65; Oediger; Kabbe; Möller; Eiter *Chem. Ber.* **1966**, 99, 2012; Vogel; Klärner *Angew. Chem. Int. Ed. Engl.* **1968**, 7, 374 [*Angew. Chem.* **80**, 402].

²³⁶Oediger; Möller *Angew. Chem. Int. Ed. Engl.* **1967**, 6, 76 [*Angew. Chem.* **79**, 53]; Wolkoff *J. Org. Chem.* **1982**, 47, 1944.

²³⁷For a review of these reagents, see Oediger; Möller; Eiter *Synthesis* **1972**, 591.

²³⁸Schwesinger; Schlemper *Angew. Chem. Int. Ed. Engl.* **1987**, 26, 1167 [*Angew. Chem.* **99**, 1212].

²³⁹Kimura; Regen *J. Org. Chem.* **1983**, 48, 195; Halpern; Zahalka; Sasson; Rabinovitz *J. Org. Chem.* **1985**, 50, 5088. See also Barry; Bram; Decodts; Loupy; Pigeon; Sansoulet *J. Org. Chem.* **1984**, 49, 1138.

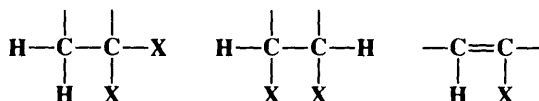
²⁴⁰For a discussion, see Fieser; *Fieser Reagents for Organic Syntheses*, vol. 1; Wiley: New York, 1967, pp. 606-609. For a review of alkali-metal fluorides in this reaction, see Yakobson; Akhmetova *Synthesis* **1983**, 169-184, pp. 170-173.

²⁴¹Hanna *Tetrahedron Lett.* **1968**, 2105; Monson *Chem. Commun.* **1971**, 113; Hutchins; Hutchins; Milewski *J. Org. Chem.* **1972**, 37, 4190.

²⁴²Matsubara; Matsuda; Hamatani; Schlosser *Tetrahedron* **1988**, 44, 2855.

Tertiary halides undergo elimination most easily. Eliminations of chlorides, bromides, and iodides follow Zaitsev's rule, except for a few cases where steric effects are important (for an example, see p. 1000). Eliminations of fluorides follow Hofmann's rule (p. 1000).

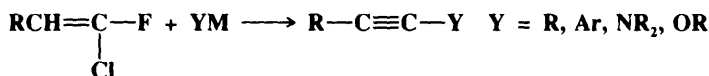
This reaction is by far the most important way of introducing a triple bond into a molecule.²⁴³ This can be accomplished with substrates of the types:²⁴⁴



When the base is NaNH_2 1-alkynes predominate (where possible), because this base is strong enough to form the salt of the alkyne, shifting any equilibrium between 1- and 2-alkynes. When the base is OH^- or OR^- , the equilibrium tends to be shifted to the internal alkyne, which is thermodynamically more stable. If another hydrogen is suitably located (e.g., $\text{---CRH---CX}_2\text{---CH}_2\text{---}$), allene formation can compete, though alkynes are usually more stable.

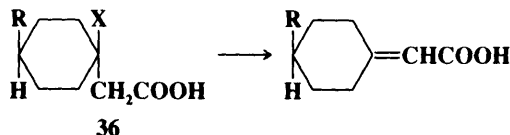
Dehydrohalogenation is generally carried out in solution, with a base, and the mechanism is usually E2, though the E1 mechanism has been demonstrated in some cases. However, elimination of HX can be accomplished by pyrolysis of the halide, in which case the mechanism is Ei (p. 1006) or, in some instances, the free-radical mechanism (p. 1008). Pyrolysis is normally performed without a catalyst at about 400°C . The pyrolysis reaction is not generally useful synthetically, because of its reversibility. Less work has been done on pyrolysis with a catalyst²⁴⁵ (usually a metallic oxide or salt), but the mechanisms here are probably E1 or E2.

A combination elimination and substitution reaction has been used to synthesize alkynes. In this reaction a compound RCH=CFCl is treated with YM , where M is a metal and Y may be alkyl, aryl, NR_2 , or OR :



Alkynes, ynamines,²⁴⁶ and acetylenic ethers²⁴⁷ can be prepared in this manner.²⁴⁸

In the special case of the prochiral carboxylic acids **36**, dehydrohalogenation with an



optically active lithium amide gave an optically active product with enantiomeric excesses as high as 82%.²⁴⁹

²⁴³For reviews, see Ben-Efraim, Ref. 142; Köbrich; Buck, in *Viehe Acetylenes*; Marcel Dekker: New York, 1969, pp. 100-134; Ref. 194, pp. 391-397; Köbrich, Ref. 2, pp. 50-53.

²⁴⁴For a list of reagents, with references, see Ref. 144, pp. 289-291.

²⁴⁵For a review, see Noller; Andréu; Hunger, Ref. 154.

²⁴⁶For a review of methods for the synthesis of ynamines, see Collard-Motte; Janousek *Top. Curr. Chem.* **1986**, 130, 89-131.

²⁴⁷For a review of acetylenic ethers, see Radchenko; Petrov *Russ. Chem. Rev.* **1989**, 58, 948-966.

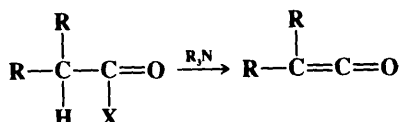
²⁴⁸*Viehe Angew. Chem. Int. Ed. Engl.* **1963**, 2, 477 [*Angew. Chem.* 75, 638]. For reviews of ynamines, see Ficini *Tetrahedron* **1976**, 32, 1448-1486; Viehe, in *Viehe*, Ref. 243, pp. 861-912.

²⁴⁹Duhamel; Ravard; Plaquevent; Plé; Davoust *Bull. Soc. Chim. Fr.* **1990**, 787.

OS I, 191, 205, 209, 438; II, 10, 17, 515; III, 125, 209, 270, 350, 506, 623, 731, 785; IV, 128, 162, 398, 404, 555, 608, 616, 683, 711, 727, 748, 755, 763, 851, 969; V, 285, 467, 514; VI, 87, 210, 327, 361, 368, 427, 462, 505, 564, 862, 883, 893, 954, 991, 1037; VII, 126, 319, 453, 491; 65, 32, 68, 90; 69, 238. Also see OS VI, 968.

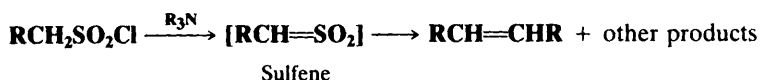
7-14 Dehydrohalogenation of Acyl Halides and Sulfonyl Halides

Hydro-halo-elimination



Ketenes can be prepared by treatment of acyl halides with tertiary amines. The scope is broad, and most acyl halides possessing an α hydrogen give the reaction, but if at least one R is hydrogen, only the ketene dimer, not the ketene, is isolated. However, if it is desired to use a reactive ketene in a reaction with a given compound, the ketene can be generated in situ in the presence of the given compound.²⁵⁰

Closely related is the reaction of tertiary amines with sulfonyl halides that contain an α hydrogen. In this case the initial product is the highly reactive sulfene, which cannot be

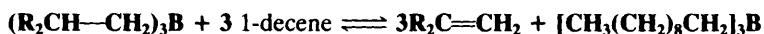


isolated but reacts further to give products, one of which may be the alkene that is the dimer of RCH.²⁵¹ Reactions of sulfenes in situ are also common (for example, see 6-62).

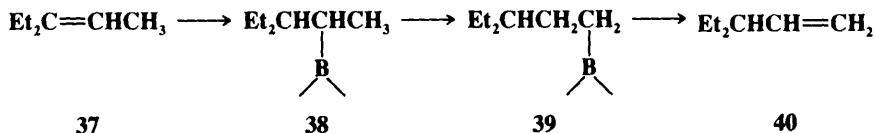
OS IV, 560; V, 294, 877; VI, 549, 1037; VII, 232; 68, 32.

7-15 Elimination of Boranes

Hydro-boranetriyl-elimination



Trialkylboranes are formed from an olefin and BH_3 (5-12). When the resulting borane is treated with another olefin, an exchange reaction occurs.²⁵² This is an equilibrium process that can be shifted by using a large excess of olefin, by using an unusually reactive olefin, or by using an olefin with a higher boiling point than the displaced olefin and removing the latter by distillation. The reaction is useful for shifting a double bond in the direction opposite to that resulting from normal isomerization methods (2-2). This cannot be accomplished simply by treatment of a borane such as 38 with an olefin, because elimination in this reaction follows Zaitsev's rule: It is in the direction of the most stable olefin, and the product would be 37, not 40. However, if it is desired to convert 37 to 40, this can be accomplished by converting 37 to 38, isomerizing 38 to 39 (8-11) and then subjecting 39 to the exchange



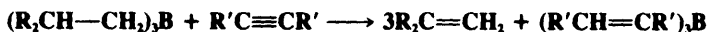
²⁵⁰For a review of this procedure, see Luknitskii; Vovsi *Russ. Chem. Rev.* **1969**, 38, 487-494.

²⁵¹For reviews of sulfenes, see Ref. 1729 in Chapter 10.

²⁵²Brown; Bhatt; Munkata; Zweifel *J. Am. Chem. Soc.* **1967**, 89, 567; Taniguchi *Bull. Chem. Soc. Jpn.* **1979**, 52, 2942.

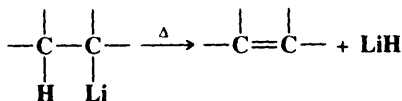
reaction with a higher-boiling olefin, e.g., 1-decene, whereupon **40** is produced. In the usual isomerizations (**2-2**), **40** could be isomerized to **37**, but not the other way around. The reactions **38** \rightarrow **39** and **39** \rightarrow **40** proceed essentially without rearrangement. The mechanism is probably the reverse of borane addition (**5-12**).

A similar reaction, but irreversible, has been demonstrated for alkynes.²⁵³



7-16 Pyrolysis of Alkali-Metal Organometallic Compounds

Hydro-metallo-elimination

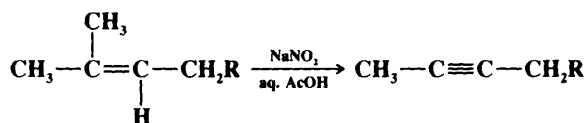


Solid lithium hydride and an olefin can be obtained by heating alkyl lithium compounds containing a β hydrogen.²⁵⁴ The reaction has also been applied to alkylsodium and alkylpotassium compounds.²⁵⁵ Grignard reagents gave olefins when thermally decomposed in nonsolvating solvents, e.g., cumene.²⁵⁶ Alkenes have also been obtained from RLi and RMgX in solution, by treatment with ethylene and NiCl₂ or with certain other reagents.²⁵⁷ Nitroalkenes have been obtained by cleavage of H and HgCl from β -nitro mercuric halides²⁵⁸ (prepared by nitromercuration—see **5-7**). The mechanism is generally believed to be a four-centered pericyclic one (Ei).²⁵⁹

OS **68**, 148.

7-17 Conversion of Alkenes to Alkynes

Hydro-methyl-elimination



Alkenes of the form shown lose the elements of methane when treated with sodium nitrite in acetic acid and water, to form alkynes in moderate-to-high yields.²⁶⁰ The R may contain additional unsaturation as well as OH, OR, OAc, C=O, and other groups, but the Me₂C=CHCH₂— portion of the substrate is necessary for the reaction to take place. The mechanism is complex, beginning with a nitration that takes place with allylic rearrangement [Me₂C=CHCH₂R \rightarrow H₂C=CMeCH(NO₂)CH₂R], and involving several additional intermediates.²⁶¹ The CH₃ lost from the substrate appears as CO₂, as demonstrated by the trapping of this gas.²⁶¹

²⁵³Hubert *J. Chem. Soc.* **1965**, 6669.

²⁵⁴Ziegler; Gellert *Liebigs Ann. Chem.* **1950**, 567, 179.

²⁵⁵For example, see Finnegan *Chem. Ind. (London)* **1962**, 895; *Tetrahedron Lett.* **1963**, 851.

²⁵⁶Zakharkin; Okhlobystin; Strunin *J. Organomet. Chem.* **1965**, 4, 349; Lefrançois; Gault *J. Organomet. Chem.* **1969**, 16, 7; Dymova; Grazhulene; Kuchinskii; Kuznetsov *Bull. Acad. Sci. USSR; Div. Chem. Sci.* **1971**, 20, 1532.

²⁵⁷Reetz; Stephan *Liebigs Ann. Chem.* **1980**, 171, and previous papers in this series. See also Laycock; Baird *Tetrahedron Lett.* **1978**, 3307; Baudin; Julia; Rolando; Verpeaux *Tetrahedron Lett.* **1984**, 25, 3203.

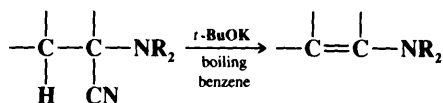
²⁵⁸Corey; Estreicher *J. Am. Chem. Soc.* **1978**, 100, 6294.

²⁵⁹See, for example, Li; San Filippo *Organometallics* **1983**, 2, 554.

²⁶⁰Abidi *Tetrahedron Lett.* **1986**, 27, 267; *J. Org. Chem.* **1986**, 51, 2687.

²⁶¹Corey; Seibel; Kappos *Tetrahedron Lett.* **1987**, 28, 4921.

7-18 Dehydrocyanation
Hydro-cyano-elimination



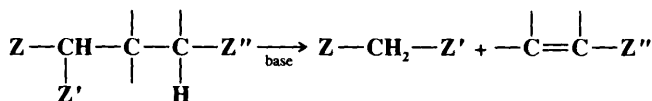
Enamines can be prepared from α -cyano tertiary amines by treatment with KOH or *t*-BuOK in boiling benzene or toluene, or in *t*-butyl methyl ether at room temperature.²⁶²

7-19 Decarbonylation of Acyl Halides
Hydro-chloroformyl-elimination



Acyl chlorides containing an α hydrogen are smoothly converted to olefins, with loss of HCl and CO, on heating with chlorotris(triphenylphosphine)rhodium, with metallic platinum, or with certain other catalysts.²⁶³ The mechanism probably involves conversion of $\text{RCH}_2\text{CH}_2\text{COCl}$ to $\text{RCH}_2\text{CH}_2\text{—RhCO}(\text{Ph}_3\text{P})_2\text{Cl}_2$ followed by a concerted syn elimination of Rh and H.²⁶⁴ See also 4-41 and 9-13.

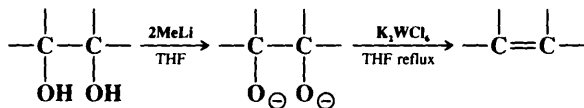
7-20 Reversal of the Michael Reaction
Hydro-bis(ethoxycarbonyl)methyl-elimination, etc.



Olefins can be formed on base cleavage of Michael adducts. (See 5-17. Z is defined on p. 741) In some cases cleavage occurs simply on heating, without basic catalysis.

B. Reactions in Which Neither Leaving Atom is Hydrogen

7-21 Deoxygenation of Vicinal Diols
Dihydroxy-elimination



vic-Diols can be deoxygenated by treatment of the dilithium dialkoxide with the tungsten halide K_2WCl_6 , or with certain other tungsten reagents, in refluxing THF.²⁶⁵ Tetrasubstituted diols react most rapidly. The elimination is largely, but not entirely, syn. Several other

²⁶²Ahlbrecht; Raab; Vonderheid *Synthesis* **1979**, 127; Ahlbrecht; Raab *Synthesis* **1980**, 320.

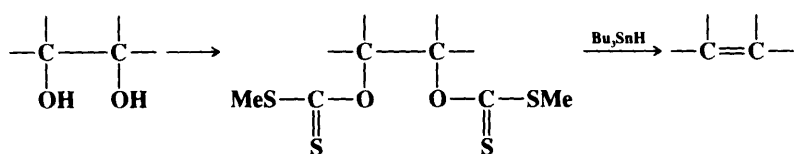
²⁶³Tsuiji; Ohno *J. Am. Chem. Soc.* **1966**, 88, 3452, **1968**, 90, 94; Ohno; Tsuiji *J. Am. Chem. Soc.* **1968**, 90, 99. For a review, see Tsuiji; Ohno *Synthesis* **1969**, 157-169. For extensions to certain other acid derivatives, see Minami; Nisar; Yuhara; Shimizu; Tsuiji *Synthesis* **1987**, 992.

²⁶⁴Lau; Becker; Huang; Baenziger; Stille *J. Am. Chem. Soc.* **1977**, 99, 5664.

²⁶⁵Sharpless; Flood *J. Chem. Soc., Chem. Commun.* **1972**, 370; Sharpless; Umbreit; Nieh; Flood *J. Am. Chem. Soc.* **1972**, 94, 6538.

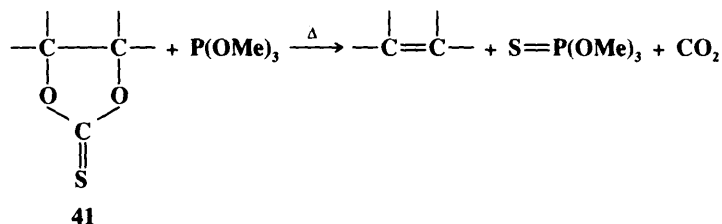
methods have been reported,²⁶⁶ in which the diol is deoxygenated directly, without conversion to the dialkoxide. These include treatment with titanium metal,²⁶⁷ with TsOH–NaI,²⁶⁸ with Ph₂PCI–imidazole–I₂ in toluene,²⁶⁹ and with PBr₃–CuBr–ether at low temperatures, followed by zinc powder.²⁷⁰

vic-Diols can also be deoxygenated indirectly, through sulfonate ester derivatives. For example, *vic*-dimesylates and *vic*-ditosylates have been converted to alkenes by treatment, respectively, with naphthalene–sodium²⁷¹ and with NaI in dimethylformamide.²⁷² In another procedure, the diols are converted to bisdithiocarbonates (bis xanthates), which undergo

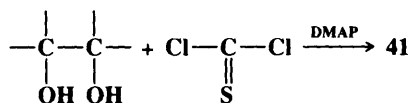


elimination (probably by a free-radical mechanism) when treated with tri-*n*-butylstannane in toluene or benzene.²⁷³ *vic*-Diols can also be deoxygenated through cyclic derivatives (7-22).

7-22 Cleavage of Cyclic Thionocarbonates



Cyclic thionocarbonates (41) can be cleaved to olefins (the *Corey–Winter reaction*)²⁷⁴ by heating with trimethyl phosphite²⁷⁵ or other trivalent phosphorus compounds²⁷⁶ or by treatment with bis(1,5-cyclooctadiene)nickel.²⁷⁷ The thionocarbonates can be prepared by treatment of 1,2-diols with thiophosgene and 4-dimethylaminopyridine (DMAP):²⁷⁸



²⁶⁶For a list of reagents, with references, see Ref. 144, pp. 155-156.

²⁶⁷McMurry; Fleming *J. Org. Chem.* **1976**, *41*, 896; McMurry *Acc. Chem. Res.* **1983**, *16*, 405-411.

²⁶⁸Sarma; Sharma *Chem. Ind. (London)* **1987**, 96.

²⁶⁹Liu; Classon; Samuelsson *J. Org. Chem.* **1990**, *55*, 4273.

²⁷⁰Tanaka; Yasuda; Yamamoto; Nozaki *J. Am. Chem. Soc.* **1975**, *97*, 3252.

²⁷¹Carnahan; Closson *Tetrahedron Lett.* **1972**, 3447.

²⁷²Dafaye *Bull. Soc. Chim. Fr.* **1968**, 2099.

²⁷³Barrett; Barton; Bielski *J. Chem. Soc., Perkin Trans. 1* **1979**, 2378.

²⁷⁴For reviews, see Block *Org. React.* **1984**, *30*, 457-566; Sonnet *Tetrahedron* **1980**, *36*, 557-604, pp. 593-598; Mackie, in Cadogan *Organophosphorus Reagents in Organic Synthesis*; Academic Press: New York, 1979, pp. 354-359; Block, *Ref.* 219, pp. 229-235.

²⁷⁵Corey; Winter *J. Am. Chem. Soc.* **1963**, *85*, 2677.

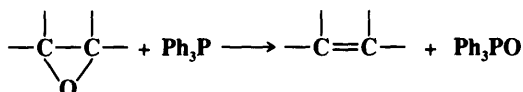
²⁷⁶Corey *Pure Appl. Chem.* **1967**, *14*, 19-37, pp. 32-33.

²⁷⁷Semmelhack; Stauffer *Tetrahedron Lett.* **1973**, 2667. For another method, see Vedejs; Wu *J. Org. Chem.* **1974**, *39*, 3641.

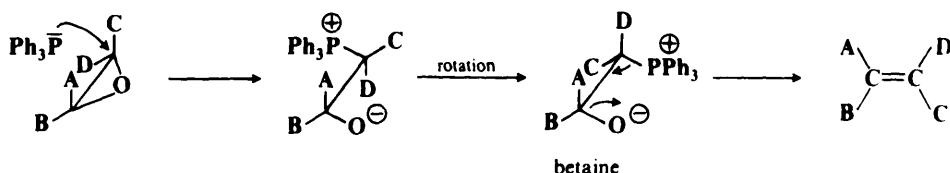
²⁷⁸Corey; Hopkins *Tetrahedron Lett.* **1982**, *23*, 1979.

The elimination is of course syn, so the product is sterically controlled. Olefins that are not sterically favored can be made this way in high yield, e.g., *cis*-PhCH₂CH=CHCH₂Ph.²⁷⁹ Certain other 5-membered cyclic derivatives of 1,2-diols can also be converted to alkenes.²⁸⁰

7-23 The Conversion of Epoxides to Olefins *epi*-Oxy-elimination



Epoxides can be converted to olefins²⁸¹ by treatment with triphenylphosphine²⁸² or triethyl phosphite P(OEt)₃.²⁸³ The first step of the mechanism is nucleophilic substitution (0-49), followed by a four-center elimination. Since inversion accompanies the substitution, the overall elimination is anti, i.e., if two groups A and C are *cis* in the epoxide, they will be *trans* in the olefin:



Alternatively, the epoxide can be treated with lithium diphenylphosphide Ph₂PLi, and the product quaternized with methyl iodide.²⁸⁴ Olefins have also been obtained from epoxides by reaction with a large number of reagents,²⁸⁵ among them Li in THF,²⁸⁶ TsOH and NaI,²⁸⁷ trimethylsilyl iodide,²⁸⁸ dimethyl diazomalonate,²⁸⁹ PI₃,²⁹⁰ P₂I₄,²⁹¹ AlI₃,²⁹² Mg-I₂-Et₂O,²⁹³ F₃COOH-NaI,²⁹⁴ 9-diazo fluorene and uv light,²⁹⁵ SmI₂,²⁹⁶ titanocene dichloride-Mg,²⁹⁷

²⁷⁹Corey; Carey; Winter *J. Am. Chem. Soc.* **1965**, 87, 934.

²⁸⁰See Hines; Peagram; Whitham; Wright *Chem. Commun.* **1968**, 1593; Josan; Eastwood *Aust. J. Chem.* **1968**, 21, 2013; Hiyama; Nozaki *Bull. Chem. Soc. Jpn.* **1973**, 46, 2248; Marshall; Lewellyn *J. Org. Chem.* **1977**, 42, 1311; Breuer; Bannet *Tetrahedron* **1978**, 34, 997; Hanessian; Bargiotti; LaRue *Tetrahedron Lett.* **1978**, 737; Hatanaka; Tanimoto; Oida; Okano *Tetrahedron Lett.* **1981**, 22, 5195; Ando; Ohhara; Takase *Chem. Lett.* **1986**, 879; King; Posner; Mak; Yang *Tetrahedron Lett.* **1987**, 28, 3919; Beels; Coleman; Taylor *Synlett* **1990**, 479.

²⁸¹For reviews, see Wong; Fok; Wong *Heterocycles* **1987**, 26, 1345-1382; Sonnet, Ref. 274, pp. 576-586.

²⁸²Wittig; Haag *Chem. Ber.* **1955**, 88, 1654.

²⁸³Scott *J. Org. Chem.* **1957**, 22, 1118.

²⁸⁴Vedejs; Fuchs *J. Am. Chem. Soc.* **1971**, 93, 4070, **1973**, 95, 822.

²⁸⁵For a list of reagents, with references, see Ref. 144, pp. 140-142.

²⁸⁶Gurudutt; Ravindranath *Tetrahedron Lett.* **1980**, 21, 1173.

²⁸⁷Baruah; Sharma; Baruah *Chem. Ind. (London)* **1983**, 524.

²⁸⁸Denis; Magnane; Van Eenoo; Krief *Nouv. J. Chim.* **1979**, 3, 705. For other silyl reagents, see Reetz; Plachky *Synthesis* **1976**, 199; Dervan; Shippey *J. Am. Chem. Soc.* **1976**, 98, 1265; Caputo; Mangoni; Neri; Palumbo *Tetrahedron Lett.* **1981**, 22, 3551.

²⁸⁹Martin; Ganem *Tetrahedron Lett.* **1984**, 25, 251.

²⁹⁰Denis, et al., Ref. 288.

²⁹¹Suzuki; Fuchita; Iwasa; Mishina *Synthesis* **1978**, 905; Ref. 290.

²⁹²Sarmah; Barua *Tetrahedron Lett.* **1988**, 29, 5815.

²⁹³Chowdhury *J. Chem. Res. (S)* **1990**, 192.

²⁹⁴Sarma; Sharma *Chem. Ind. (London)* **1984**, 712.

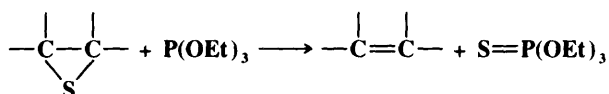
²⁹⁵Shields; Schuster *Tetrahedron Lett.* **1987**, 28, 853.

²⁹⁶Girard; Namy; Kagan *J. Am. Chem. Soc.* **1980**, 102, 2693; Matsukawa; Tabuchi; Inanaga; Yamaguchi *Chem. Lett.* **1987**, 2101.

²⁹⁷Schobert *Angew. Chem. Int. Ed. Engl.* **1988**, 27, 855 [*Angew. Chem.* 100, 869]. See also Yadav; Shekharam; Gadgil *J. Chem. Soc., Chem. Commun.* **1990**, 843.

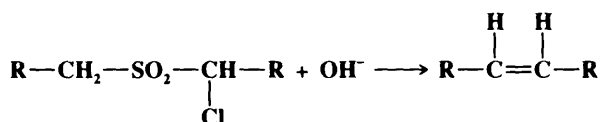
$\text{Fe}(\text{CO})_5$,²⁹⁸ $\text{TiCl}_3\text{-LiAlH}_4$,²⁹⁹ $\text{FeCl}_3\text{-BuLi}$,³⁰⁰ the tungsten reagents mentioned in 7-21,²⁶⁵ and NaI-NaOAc-Zn-AcOH .³⁰¹ The last-mentioned method is actually a variation of 7-31, since iodohydrins are intermediates. Some of these methods give syn elimination.

7-24 The Conversion of Episulfides to Olefins **epi-Thio-elimination**

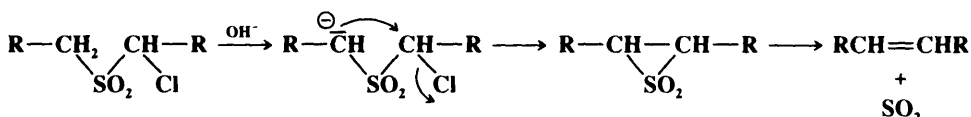


Episulfides³⁰² can be converted to olefins in a reaction similar in appearance to 7-23.³⁰³ However, in this case the elimination is syn, so the mechanism cannot be the same as that of 7-23. The phosphite attacks not the carbon, but the sulfur. Among other reagents that convert episulfides to olefins are Bu_3SnH ,³⁰⁴ P_2I_4 ,³⁰⁴ certain rhodium complexes,³⁰⁵ LiAlH_4 ,³⁰⁶ (this compound behaves quite differently with epoxides, see 0-80), and methyl iodide.³⁰⁷ Episulfides can be converted to olefins and sulfur monoxide simply by heating.³⁰⁸

7-25 The Ramberg-Bäcklund Reaction **Ramberg-Bäcklund halosulfone transformation**



The reaction of an α -halo sulfone with a base to give an olefin is called the *Ramberg-Bäcklund reaction*.³⁰⁹ The reaction is quite general for α -halo sulfones with an α' hydrogen, despite the unreactivity of α -halo sulfones in normal $\text{S}_\text{N}2$ reactions (p. 344). Halogen reactivity is in the order $\text{I} > \text{Br} \gg \text{Cl}$. Phase transfer catalysis has been used.³¹⁰ In general, mixtures of cis and trans isomers are obtained, but usually the less stable cis isomer predominates. The mechanism involves formation of an episulfone and then elimination of



²⁹⁸Alper; Des Roches *Tetrahedron Lett.* **1977**, 4155.

²⁹⁹McMurry; Silvestri; Fleming; Hoz; Grayston *J. Org. Chem.* **1978**, 43, 3249.

³⁰⁰Fujisawa; Sugimoto; Ohta *Chem. Lett.* **1975**, 883.

³⁰¹Cornforth; Cornforth; Mathew *J. Chem. Soc.* **1959**, 112. See also Yamada; Goto; Nagase; Kyotani; Hirata *J. Org. Chem.* **1978**, 43, 2076; Sonnet *Synthesis* **1980**, 828.

³⁰²For a review of this reaction, see Sonnet, Ref. 274, pp. 587-590. For a review of episulfides, see Goodman; Reist, in Kharasch; Meyers *The Chemistry of Organic Sulfur Compounds*, vol. 2; Pergamon: Elmsford, NY, 1966, pp. 93-113.

³⁰³Neureiter; Bordwell *J. Am. Chem. Soc.* **1959**, 81, 578; Davis *J. Org. Chem.* **1957**, 23, 1767.

³⁰⁴Schauder; Denis; Krief *Tetrahedron Lett.* **1983**, 24, 1657.

³⁰⁵Calet; Alper *Tetrahedron Lett.* **1986**, 27, 3573.

³⁰⁶Lightner; Djerassi *Chem. Ind. (London)* **1962**, 1236; Latif; Mishriky; Zeid *J. Prakt. Chem.* **1970**, 312, 421.

³⁰⁷Culvenor; Davies; Heath *J. Chem. Soc.* **1949**, 282; Helmkamp; Pettitt *J. Org. Chem.* **1964**, 29, 3258.

³⁰⁸Hartzell; Paige *J. Am. Chem. Soc.* **1966**, 88, 2616; *J. Org. Chem.* **1967**, 32, 459; Aalbersberg; Vollhardt *J. Am. Chem. Soc.* **1977**, 99, 2792.

³⁰⁹For reviews, see Paquette *Org. React.* **1977**, 25, 1-71, *Mech. Mol. Migr.* **1968**, 1, 121-156, *Acc. Chem. Res.* **1968**, 1, 209-216; Meyers; Matthews; Ho; Kolb; Parady, in *Smith Catalysis in Organic Synthesis*; Academic Press: New York, 1977, pp. 197-278; Rappe, in Patai *The Chemistry of the Carbon-Halogen Bond*, Ref. 2, pt. 2, pp. 1105-1110; Bordwell *Acc. Chem. Res.* **1970**, 3, 281-290, pp. 285-286; in Janssen *Organosulfur Chemistry*; Wiley: New York, 1967, pp. 271-284.

³¹⁰Hartman; Hartman *Synthesis* **1982**, 504.

SO₂. There is much evidence for this mechanism,³¹¹ including the isolation of the episulfone intermediate,³¹² and the preparation of episulfones in other ways and the demonstration that they give olefins under the reaction conditions faster than the corresponding α-halo sulfones.³¹³ Episulfones synthesized in other ways (e.g., **6-62**) are reasonably stable compounds but eliminate SO₂ to give olefins when heated or treated with base.

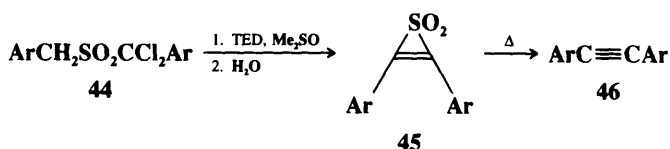
If the reaction is run on the unsaturated bromo sulfones RCH₂CH=CHSO₂CH₂Br (prepared by reaction of BrCH₂SO₂Br with RCH₂CH=CH₂ followed by treatment with Et₃N), the dienes RCH=CHCH=CH₂ are produced in moderate-to-good yields.³¹⁴ The compound mesyltriflone CF₃SO₂CH₂SO₂CH₃ can be used as a synthon for the tetraion ²⁻C=C²⁻. Successive alkylation (**0-94**) converts it to CF₃SO₂CR¹R²SO₂CHR³R⁴ (anywhere from one to four alkyl groups can be put in), which, when treated with base, gives R¹R²C=CR³R⁴.³¹⁵ The nucleofuge here is the CF₃SO₂⁻ ion.

2,5-Dihydrothiophene-1,1-dioxides (**42**) and 2,7-dihydrothiepin-1,1-dioxides (**43**)



undergo analogous 1,4 and 1,6 eliminations, respectively (see also **7-48**). These are concerted reactions and, as predicted by the orbital-symmetry rules (p. 846), the former³¹⁶ is a suprafacial process and the latter³¹⁷ an antarafacial process. The rules also predict that elimination of SO₂ from episulfones cannot take place by a concerted mechanism (except antarafacially, which is unlikely for such a small ring), and the evidence shows that this reaction occurs by a nonconcerted pathway.³¹⁸ The eliminations of SO₂ from **42** and **43** are examples of *cheletropic reactions*,³¹⁹ which are defined as reactions in which two σ bonds that terminate at a single atom (in this case the sulfur atom) are made or broken in concert.³²⁰

α,α-Dichlorobenzyl sulfones (**44**) react with an excess of the base triethylenediamine in



dimethyl sulfoxide at room temperature to give 2,3-diarylthiiren-1,1-dioxides (**45**), which can be isolated.³²¹ Thermal decomposition of **45** gives the alkynes **46**.³²²

³¹¹See, for example, Bordwell; Cooper *J. Am. Chem. Soc.* **1951**, 73, 5187; Paquette *J. Am. Chem. Soc.* **1964**, 86, 4089; Neureiter *J. Am. Chem. Soc.* **1966**, 88, 558; Bordwell; Wolfinger *J. Org. Chem.* **1974**, 39, 2521; Bordwell; Doomes *J. Org. Chem.* **1974**, 39, 2526, 2531.

³¹²Sutherland; Taylor *Tetrahedron Lett.* **1989**, 30, 3267.

³¹³Bordwell; Williams; Hoyt; Jarvis *J. Am. Chem. Soc.* **1968**, 90, 429; Bordwell; Williams *J. Am. Chem. Soc.* **1968**, 90, 435.

³¹⁴Block; Aslam; Eswarakrishnan; Gebreyes; Hutchinson; Iyer; Laffitte; Wall *J. Am. Chem. Soc.* **1986**, 108, 4568.

³¹⁵Hendrickson; Boudreaux; Palumbo *J. Am. Chem. Soc.* **1986**, 108, 2358.

³¹⁶Mock *J. Am. Chem. Soc.* **1966**, 88, 2857; McGregor; Lemal *J. Am. Chem. Soc.* **1966**, 88, 2858.

³¹⁷Mock *J. Am. Chem. Soc.* **1969**, 91, 5682.

³¹⁸Ref. 313. See also Vilsmaier; Tropitzsch; Vostrowsky *Tetrahedron Lett.* **1974**, 3987.

³¹⁹For a review, see Mock, in Marchand; Lehr *Pericyclic Reactions*, vol. 2; Academic Press: New York, 1977, pp. 141-179.

³²⁰Woodward; Hoffmann *The Conservation of Orbital Symmetry*; Academic Press: New York, 1970, pp. 152-163.

³²¹Philips; Swisher; Haidukewych; Morales *Chem. Commun.* **1971**, 22.

³²²Carpino; McAdams; Rynbrandt; Spiewak *J. Am. Chem. Soc.* **1971**, 93, 476; Philips; Morales *J. Chem. Soc., Chem. Commun.* **1977**, 713.

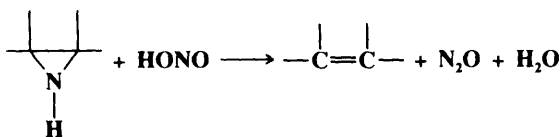
A Ramberg-Bäcklund-type reaction has been carried out on the α -halo sulfides $\text{ArCHClSCH}_2\text{Ar}$, which react with *t*-BuOK and PPh_3 in refluxing THF to give the alkenes ArCH=CHAr .³²³

The Ramberg-Bäcklund reaction can be regarded as a type of extrusion reaction (see p. 1045).

OS V, 877; VI, 454, 555; 65, 90.

7-26 The Conversion of Aziridines to Olefins

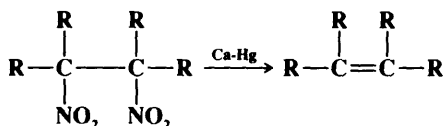
epi-Imino-elimination



Aziridines not substituted on the nitrogen atom react with nitrous acid to produce olefins.³²⁴ An N-nitroso compound is an intermediate (2-51); other reagents that produce such intermediates also give olefins. The reaction is stereospecific: cis aziridines give cis olefins and trans aziridines give trans olefins.³²⁵ Aziridines carrying N-alkyl substituents can be converted to olefins by treatment with ferrous iodide³²⁶ or with *m*-chloroperbenzoic acid.³²⁷ An N-oxide intermediate (9-28) is presumably involved in the latter case.

7-27 Conversion of Vicinal Dinitro Compounds to Olefins

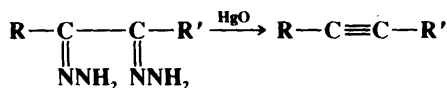
Dinitro-elimination



Tetrasubstituted *vic*-dinitro compounds have been converted to olefins by treatment with amalgamated calcium.³²⁸ Various functional groups, such as CN and COOR, did not affect the reaction. Other reagents that have been used include sodium sulfide in DMF,³²⁹ nickel boride and ultrasound,³³⁰ Bu_3SnH ,³³¹ and SnCl_2 .³³² Radical-ion mechanisms are likely in all these cases.

7-28 The Conversion of Dihydrazones to Alkynes

Dihydrazono-bielimination



³²³Mitchell *Tetrahedron Lett.* **1973**, 4395. For a similar reaction without base treatment, see Pommelet; Nyns; Lahousse; Merényi; Viehe *Angew. Chem. Int. Ed. Engl.* **1981**, 20, 585 [*Angew. Chem.* 93, 594].

³²⁴For reviews, see Sonnet, Ref. 274, pp. 591-592; Dermer; Ham *Ethylenimine and other Aziridines*; Academic Press: New York, 1969, pp. 293-295.

³²⁵Clark; Helmkamp *J. Org. Chem.* **1964**, 29, 1316; Carlson; Lee *Tetrahedron Lett.* **1969**, 4001.

³²⁶Imamoto; Yukawa *Chem. Lett.* **1974**, 165.

³²⁷Heine; Myers; Peltzer *Angew. Chem. Int. Ed. Engl.* **1970**, 9, 374 [*Angew. Chem.* 82, 395].

³²⁸Kornblum; Cheng *J. Org. Chem.* **1977**, 42, 2944.

³²⁹Kornblum; Boyd; Pinnick; Smith *J. Am. Chem. Soc.* **1971**, 93, 4316.

³³⁰Madjadbadi; Beugelmans; Lechavallier *Synth. Commun.* **1989**, 19, 1631.

³³¹Ono; Miyake; Tamura; Hamamoto; Kaji *Chem. Lett.* **1981**, 1139.

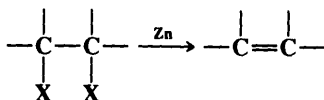
³³²Fukunaga; Kimura *Bull. Chem. Soc. Jpn.* **1979**, 52, 1107.

1,2-Dihydrazones can be made to lose two moles of nitrogen to give alkynes by treatment with HgO , Ag_2O , $\text{CuCl}_2\text{-O}_2$ -pyridine, or certain other reagents.³³³ R and R' may be alkyl or aryl. Highly strained seven- and eight-membered cycloalkynes (see p. 159), as well as large cycloalkynes, have been obtained by this reaction.³³⁴

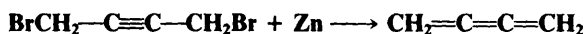
OS IV, 377. See also OS VI, 791.

7-29 Dehalogenation of Vicinal Dihalides

Dihalo-elimination



Dehalogenation has been accomplished with many reagents, the most common being zinc, magnesium, and iodide ion.³³⁵ Among reagents used less frequently have been phenyllithium, phenylhydrazine, CrCl_2 , naphthalene-sodium,³³⁶ Na-NH_3 ,³³⁷ Na_2S in DMF,³³⁸ Na_2Te ,³³⁹ and LiAlH_4 .³⁴⁰ Electrochemical reduction has also been used.³⁴¹ Though the reaction usually gives good yields, it is not very useful because the best way to prepare *vic*-dihalides is by the addition of halogen to a double bond (5-26). One useful feature of this reaction is that there is no doubt about the *position* of the new double bond, so that it can be used to give double bonds exactly where they are wanted. For example, allenes, which are not easily prepared by other methods, can be prepared from $\text{X-C-CX}_2\text{-C-X}$ or X-C-CX=C-C systems.³⁴² Cumulenes have been obtained from 1,4 elimination:



Triple bonds can be prepared from $\text{X-C}\equiv\text{C-X}$ or $\text{X}_2\text{C-CX}_2$ systems,³⁴³ but availability considerations are even more extreme here. 1,4 Elimination of $\text{BrC-C}\equiv\text{C-CBr}$ has been used to prepare conjugated dienes $\text{C}=\text{C-C}=\text{C}$.³⁴⁴

The reaction can be carried out for any combination of halogens, except where one is fluorine. Mechanisms are often complex and depend on the reagent and reaction conditions.³⁴⁵ For different reagents, mechanisms involving carbocations, carbanions, and free-radical intermediates, as well as concerted mechanisms, have been proposed. When the reagent is zinc, anti stereospecificity has been observed in some cases,³⁴⁶ but not in others.³⁴⁷

³³³For a list of reagents, with references, see Ref. 144, p. 293.

³³⁴For example, see Blomquist; Liu *J. Am. Chem. Soc.* **1953**, *75*, 2153; Krebs; Kimling *Tetrahedron Lett.* **1970**, 761; Tsuji; Kezuka; Toshida; Takayanagi; Yamamoto *Tetrahedron* **1983**, *39*, 3279.

³³⁵For a review of this reaction, see Baciocchi, in Patai; Rappoport, Ref. 232; pt. 1, pp. 161-201.

³³⁶Scouten; Barton; Burgess; Story; Garst *Chem. Commun.* **1969**, 78; Garst; Pacifici; Singleton; Ezzel; Morris *J. Am. Chem. Soc.* **1975**, *97*, 5242.

³³⁷Allred; Beck; Voorhees *J. Org. Chem.* **1974**, *39*, 1426.

³³⁸Fukunaga; Yamaguchi *Synthesis* **1981**, 879. See also Nakayama; Machida; Hoshino *Tetrahedron Lett.* **1983**, *24* 3001; Landini; Milesi; Quadri; Rolla *J. Org. Chem.* **1984**, *49*, 152.

³³⁹Suzuki; Inouye *Chem. Lett.* **1985**, 225. See also Huang; Hou *Synth. Commun.* **1988**, *18*, 2201.

³⁴⁰For a lists of reagents, with references, see Ref. 144, pp. 133-135.

³⁴¹See Shono *Electroorganic Chemistry as a New Tool in Organic Synthesis*; Springer: New York, 1984, pp. 145-147; Fry *Synthetic Organic Electrochemistry*, 2nd ed.; Wiley: New York, 1989, pp. 151-154.

³⁴²For reviews of allene formation, see Schuster; Coppola *Allenes in Organic Synthesis*; Wiley: New York, 1984, pp. 9-56; Landor, in Landor *The Chemistry of the Allenes*, vol. 1; Academic Press: New York, 1982; pp. 19-233; Taylor *Chem. Rev.* **1967**, *67*, 317-359.

³⁴³For a review, see Köbrich; Buck; in Viehe, Ref. 243, pp. 134-138.

³⁴⁴Engman; Byström *J. Org. Chem.* **1985**, *50*, 3170.

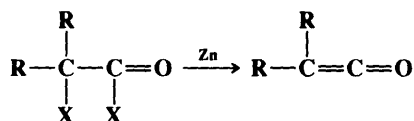
³⁴⁵For discussion, see Saunders; Cockerill, Ref. 2, pp. 332-368; Ref. 335.

³⁴⁶For example, see House; Ro *J. Am. Chem. Soc.* **1958**, *80*, 182; Gordon; Hay *J. Org. Chem.* **1968**, *33*, 427.

³⁴⁷For example, see Stevens; Valicenti *J. Am. Chem. Soc.* **1965**, *87*, 838; Sicher; Havel; Svoboda *Tetrahedron Lett.* **1968**, 4269.

OS **III**, 526, 531; **IV**, 195, 268; **V**, 22, 255, 393, 901; **VI**, 310, **VII**, 241. Also see OS **IV**, 877, 914, 964.

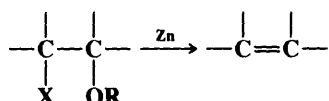
7-30 Dehalogenation of α -Halo Acyl Halides
Dihalo-elimination



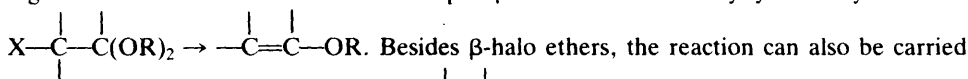
Ketenes can be prepared by dehalogenation of α -halo acyl halides with zinc or with triphenylphosphine.³⁴⁸ The reaction generally gives good results when the two R groups are aryl or alkyl, but not when either one is hydrogen.³⁴⁹

OS **IV**, 348; **68**, 41.

7-31 Elimination of a Halogen and a Hetero Group
Alkoxy-halo-elimination



The elimination of OR and halogen from β -halo ethers is called the *Boord reaction*. It can be carried out with zinc, magnesium, sodium, or certain other reagents.³⁵⁰ The yields are high and the reaction is of broad scope. β -Halo acetals readily yield vinylic ethers



Besides β -halo ethers, the reaction can also be carried out on compounds of the formula $\begin{array}{c} | \quad | \\ \text{X}-\text{C}-\text{C}-\text{Z} \\ | \end{array}$, where X is halogen and Z is OCOR,

OTs,³⁵¹ NR₂,³⁵² or SR.³⁵³ Z may also be OH, but then X is limited Br and I. Like **7-29**, this method ensures that the new double bond will be in a specific position. The fact that magnesium causes elimination in these cases limits the preparation of Grignard reagents from these compounds. It has been shown that treatment of β -halo ethers and esters with zinc gives nonstereospecific elimination,³⁵⁴ so the mechanism was not E2. An E1cB mechanism was postulated because of the poor leaving-group ability of OR and OCOR. Bromohydrins can be converted to olefins (elimination of Br, OH) in high yields by treatment with LiAlH₄-TiCl₃.³⁵⁵

OS **III**, 698, **IV**, 748; **VI**, 675.

³⁴⁸Darling; Kidwell *J. Org. Chem.* **1968**, 33, 3974.

³⁴⁹For a procedure that gives 60 to 65% yields when one R = H, see McCarney; Ward *J. Chem. Soc., Perkin Trans. 1* **1975**, 1600. See also Masters; Sorensen; Ziegler *J. Org. Chem.* **1986**, 51, 3558.

³⁵⁰See Ref. 144, pp. 136-139, for reagents that produce olefins from β -halo ethers and esters, and from halohydrins.

³⁵¹Cristol; Rademacher *J. Am. Chem. Soc.* **1959**, 81, 1600; Reeve; Brown; Steckel *J. Am. Chem. Soc.* **1971**, 93, 4607.

³⁵²Gurien *J. Org. Chem.* **1963**, 28, 878.

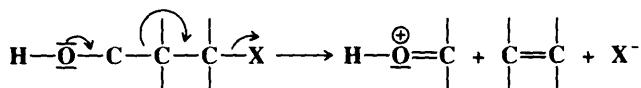
³⁵³Amstutz *J. Org. Chem.* **1944**, 9, 310.

³⁵⁴House; Ro, Ref. 346.

³⁵⁵McMurry; Hoz *J. Org. Chem.* **1975**, 40, 3797.

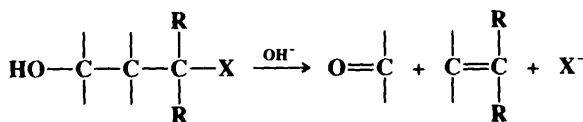
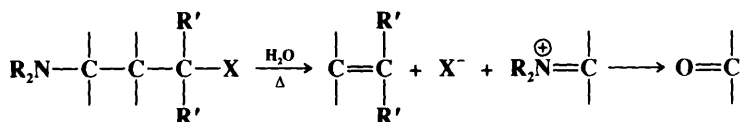
Fragmentations

When carbon is the positive leaving group (the electrofuge) in an elimination, the reaction is called *fragmentation*.³⁵⁶ These processes occur on substrates of the form $W-C-C-X$, where X is a normal nucleofuge (e.g., halogen, OH_2^+ , OTs, NR_3^+ , etc.) and W is a positive-carbon electrofuge. In most of the cases W is $HO-C-$ or R_2N-C- , so that the positive charge on the carbon atom is stabilized by the unshared pair of the oxygen or nitrogen, e.g.,

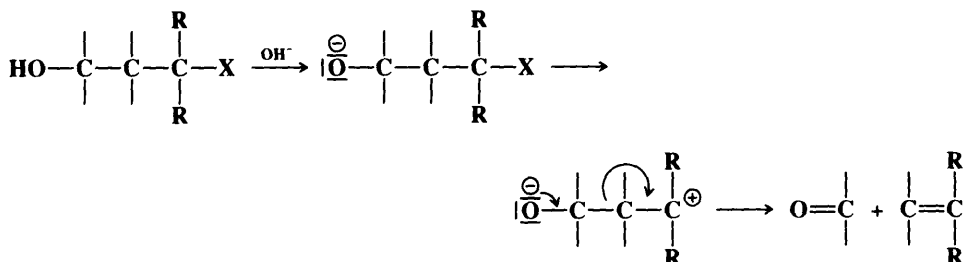


The mechanisms are mostly E1 or E2. We shall discuss only a few fragmentations, since many are possible and not much work has been done on most of them. Reactions 7-32 to 7-36 and 7-38 may be considered fragmentations. See also 9-13 and 9-14.

7-32 Fragmentation of γ -Amino and γ -Hydroxy Halides Dialkylaminoalkyl-halo-elimination, etc.



γ -Dialkylamino halides undergo fragmentation when heated with water to give an olefin and an iminium salt, which under the reaction conditions is hydrolyzed to an aldehyde or ketone (6-2).³⁵⁷ γ -Hydroxy halides and tosylates are fragmented with base. In this instance the base does not play its usual role in elimination reactions but instead serves to remove a proton from the OH group, which enables the carbon leaving group to come off more easily:



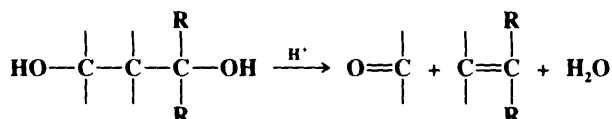
³⁵⁶For reviews, see Becker; Grob, in Patai, *The Chemistry of Functional Groups, Supplement A*, Ref. 2, pt. 2, pp. 653-723; Grob *Angew. Chem. Int. Ed. Engl.* **1969**, 8, 535-546 [*Angew. Chem.* 81, 543-554]; Grob; Schiess *Angew. Chem. Int. Ed. Engl.* **1967**, 6, 1-15 [*Angew. Chem.* 79, 1-14].

³⁵⁷Grob; Ostermayer; Raudenbusch *Helv. Chim. Acta* **1962**, 45, 1672.

The mechanism of these reactions is often E1. However, in at least some cases, an E2 mechanism operates.³⁵⁸ It has been shown that stereoisomers of cyclic γ -amino halides and tosylates in which the two leaving groups can assume an anti-periplanar conformation react by the E2 mechanism, while those isomers in which the groups cannot assume such a conformation either fragment by the E1 mechanism or do not undergo fragmentation at all, but in either case give rise to side products characteristic of carbocations.³⁵⁹

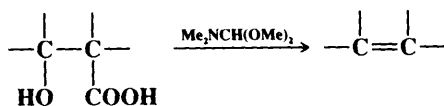
γ -Dialkylamino alcohols do not give fragmentation, since for ionization the OH group must be converted to OH_2^+ and this would convert NR_2 to NR_2H^+ , which does not have the unshared pair necessary to form the double bond with the carbon.³⁶⁰

7-33 Fragmentation of 1,3-Diols Hydroxyalkyl-hydroxy-elimination

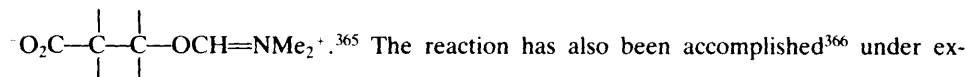


1,3-Diols in which at least one OH group is tertiary or is located on a carbon with aryl substituents can be cleaved by acid treatment.³⁶¹ The reaction is most useful synthetically when at least one of the OH groups is on a ring.³⁶²

7-34 Decarboxylation of β -Hydroxy Carboxylic Acids and of β -Lactones Carboxy-hydroxy-elimination



An OH and a COOH group can be eliminated from β -hydroxy carboxylic acids by refluxing with excess dimethylformamide dimethyl acetal.³⁶³ Mono-, di-, tri-, and tetrasubstituted olefins have been prepared by this method in good yields.³⁶⁴ There is evidence that the mechanism involves E1 or E2 elimination from the zwitterionic intermediate



The reaction has also been accomplished³⁶⁶ under extremely mild conditions (a few seconds at 0°C) with PPh_3 and diethyl azodicarboxylate $\text{EtOOC}-\text{N}=\text{N}-\text{COOEt}$.³⁶⁷ In a related procedure, β -lactones undergo thermal decar-

³⁵⁸Grob; Schwarz *Helv. Chim. Acta* **1964**, 47, 1870; Fischer; Grob *Helv. Chim. Acta* **1978**, 61, 2336.

³⁵⁹Bottini; Grob; Schumacher; Zergenyi *Helv. Chim. Acta* **1966**, 49, 2516; Burckhardt; Grob; Kiefer *Helv. Chim. Acta* **1967**, 50, 231; Grob; Kiefer; Lutz; Wilkens *Helv. Chim. Acta* **1967**, 50, 416; Geisel; Grob; Wohl *Helv. Chim. Acta* **1969**, 52, 2206.

³⁶⁰Grob; Hoegerle; Ohta *Helv. Chim. Acta* **1962**, 45, 1823.

³⁶¹Zimmerman; English *J. Am. Chem. Soc.* **1954**, 76, 2285, 2291, 2294.

³⁶²For a review of such cases, see Caine *Org. Prep. Proced. Int.* **1988**, 20, 1-51.

³⁶³Hara; Taguchi; Yamamoto; Nozaki *Tetrahedron Lett.* **1975**, 1545.

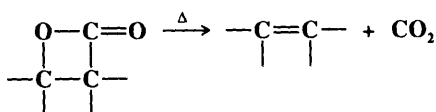
³⁶⁴For a 1,4 example of this reaction, see Rüttimann; Wick; Eschenmoser *Helv. Chim. Acta* **1975**, 58, 1450.

³⁶⁵Mulzer; Brüntrup *Tetrahedron Lett.* **1979**, 1909.

³⁶⁶For another method, see Tanzawa; Schwartz *Organometallics* **1990**, 9, 3026.

³⁶⁷Mulzer; Brüntrup *Angew. Chem. Int. Ed. Engl.* **1977**, 16, 255 [*Angew. Chem.* 89, 265]; Mulzer; Lammer *Angew. Chem. Int. Ed. Engl.* **1983**, 22, 628 [*Angew. Chem.* 95, 629].

boxylation to give olefins in high yields. The reaction has been shown to be a stereospecific

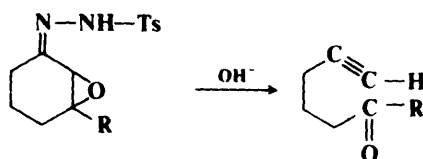


syn elimination.³⁶⁸ There is evidence that this reaction also involves a zwitterionic intermediate.³⁶⁹

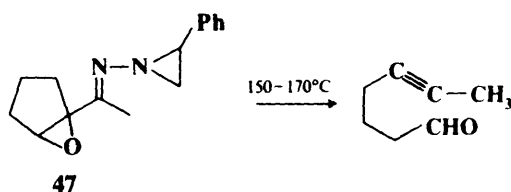
There are no OS references, but see OS VII, 172, for a related reaction.

7-35 Fragmentation of α,β -Epoxy Hydrazones

Eschenmoser–Tanabe ring cleavage



Cyclic α,β -unsaturated ketones³⁷⁰ can be cleaved by treatment with base of their epoxy tosylhydrazone derivatives to give acetylenic ketones.³⁷¹ The reaction can be applied to the formation of acetylenic aldehydes ($R = H$) by using the corresponding, 2,4-dinitrotosylhydrazones derivatives.³⁷² Hydrazones (e.g., **47**) prepared from epoxy ketones and ring-sub-

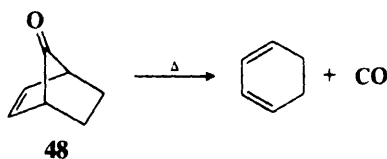


stituted N-aminoaziridines undergo similar fragmentation when heated.³⁷³

OS VI, 679.

7-36 Elimination of CO and CO₂ from Bridged Bicyclic Compounds

seco-Carbonyl-1/4/elimination



³⁶⁸Noyce; Banitt *J. Org. Chem.* **1966**, 31, 4043; Adam; Baeza; Liu *J. Am. Chem. Soc.* **1972**, 94, 2000; Krapcho; Jahngen *J. Org. Chem.* **1974**, 39, 1322, 1650; Mageswaran; Sultanbawa *J. Chem. Soc., Perkin Trans. 1* **1976**, 884; Adam; Martinez; Thompson; Yany *J. Org. Chem.* **1981**, 46, 3359.

³⁶⁹Mulzer; Zippel; Brüntrup *Angew. Chem. Int. Ed. Engl.* **1980**, 19, 465 [*Angew. Chem.* 92, 469]; Mulzer; Zippel *Tetrahedron Lett.* **1980**, 21, 751. See also Moyano; Pericaas; Valenti *J. Org. Chem.* **1989**, 573.

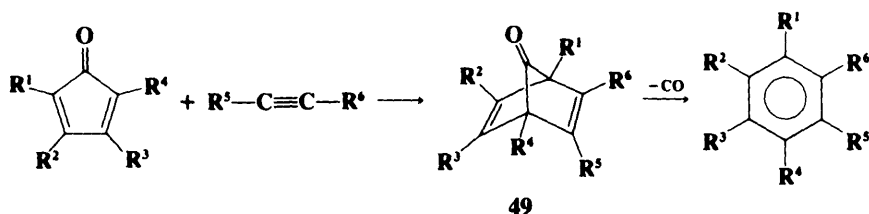
³⁷⁰For other methods of fragmentation of α,β -epoxy ketone derivatives, see MacAlpine; Warkentin *Can. J. Chem.* **1978**, 56, 308, and references cited therein.

³⁷¹Eschenmoser; Felix; Ohloff *Helv. Chim. Acta* **1967**, 50, 708; Tanabe; Crowe; Dehn; Detre *Tetrahedron Lett.* **1967**, 3739; Tanabe; Crowe; Dehn *Tetrahedron Lett.* **1967**, 3943.

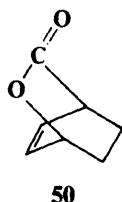
³⁷²Corey; Sachdev *J. Org. Chem.* **1975**, 40, 579.

³⁷³Felix; Müller; Horn; Joos; Schreiber; Eschenmoser *Helv. Chim. Acta* **1972**, 55, 1276.

On heating, bicyclo[2.2.1]hept-2,3-en-7-ones (**48**) usually lose CO to give cyclohexadienes,³⁷⁴ in a type of reverse Diels–Alder reaction. Bicyclo[2.2.1]heptadienones (**49**) undergo the



reaction so readily (because of the stability of the benzene ring produced) that they cannot generally be isolated. The parent **49** has been obtained at 10–15 K in an Ar matrix, where its spectrum could be studied.³⁷⁵ **48** and **49** can be prepared by Diels–Alder reactions between a cyclopentadienone and an alkyne or olefin, so that this reaction is a useful method for the preparation of specifically substituted benzene rings and cyclohexadienes.³⁷⁶ Unsaturated bicyclic lactones of the type **50** can also undergo the reaction, losing CO₂. See also 7-47.

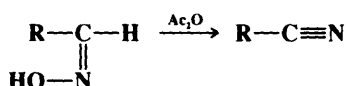


OS III, 807; V, 604, 1037.

Reversal of the Diels–Alder reaction may be considered a fragmentation. See 5-47.

Reactions in Which C≡N or C=N Bonds Are Formed

7-37 Dehydration of Aldoximes and Similar Compounds C-Hydro-*N*-hydroxy-elimination



Aldoximes can be dehydrated to nitriles³⁷⁷ by many dehydrating agents, of which acetic anhydride is the most common. Among reagents that are effective under mild conditions³⁷⁸

³⁷⁴For a review, see Stark; Duke, Ref. 444, pp. 16-46.

³⁷⁵Birney; Berson *J. Am. Chem. Soc.* **1985**, 107, 4553; *Tetrahedron* **1986**, 42, 1561; LeBlanc; Sheridan *J. Am. Chem. Soc.* **1985**, 107, 4554; Birney; Wiberg; Berson *J. Am. Chem. Soc.* **1988**, 110, 6631.

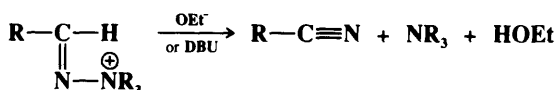
³⁷⁶For a review with many examples, see Ogliaruso; Romanelli; Becker *Chem. Rev.* **1965**, 65, 261-367, pp. 300-348. For references to this and related reactions, see Ref. 144, pp. 101-103.

³⁷⁷For reviews, see Friedrich, in Patai; Rappoport, Ref. 142, pt. 2, pp. 1345-1390; Friedrich; Wallenfels in Rappoport *The Chemistry of the Cyano Group*; Wiley: New York, 1970, pp. 92-96. For a review of methods of synthesizing nitriles, see Fatiadi, in Patai; Rappoport, Ref. 142, pt. 2, pp. 1057-1303.

³⁷⁸For lists of some other reagents, with references, see Molina; Alajarin; Vilaplana *Synthesis* **1982**, 1016; Aizpurua; Palomo *Nouv. J. Chim.* **1983**, 7, 465; Attanasi; Palma; Serra-Zanetti *Synthesis* **1983**, 741; Juršić *Synth. Commun.* **1989**, 19, 689.

(room temperature) are ethyl orthoformate and H^+ ,³⁷⁹ $\text{Ph}_3\text{P}-\text{CCl}_4$,³⁸⁰ trichloromethyl chloroformate ClCOOCCl_3 ,³⁸¹ methyl (or ethyl) cyanoformate ROCOCN ,³⁸² trifluoromethane sulfonic anhydride,³⁸³ P_2I_4 ,²⁹¹ SeO_2 ,³⁸⁴ CS_2 under phase transfer conditions,³⁸⁵ $\text{Cl}_3\text{COCl}-\text{Et}_3\text{N}$,³⁸⁶ and chloromethylene dimethylammonium chloride $\text{Me}_2\text{N}=\text{CHCl}^+ \text{Cl}^-$.³⁸⁷ Electrochemical synthesis has also been used.³⁸⁸ The reaction is most successful when the H and OH are anti. Various alkyl and acyl derivatives of aldoximes, for example, $\text{RCH}=\text{NOR}$, $\text{RCH}=\text{NOCOR}$, $\text{RCH}=\text{NOSO}_2\text{Ar}$, etc., also give nitriles, as do chlorimines $\text{RCH}=\text{NCl}$ (the latter with base treatment).³⁸⁹ N,N-dichloro derivatives of primary amines give nitriles on pyrolysis: $\text{RCH}_2\text{NCl}_2 \rightarrow \text{RCN}$.³⁹⁰

Quaternary hydrazonium salts (derived from aldehydes) give nitriles when treated with OEt^- ³⁹¹ or DBU (p. 1023):³⁹²

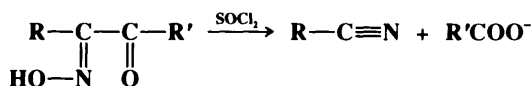


as do dimethylhydrazones $\text{RCH}=\text{NNMe}_2$ when treated with Et_2NLi and HMPA.³⁹³ All these are methods of converting aldehyde derivatives to nitriles. For the conversion of aldehydes directly to nitriles, without isolation of intermediates, see 6-22.

OS II, 622; III, 690.

7-38 The Conversion of Ketoximes to Nitriles

C-Acyl-N-hydroxy-elimination



Certain ketoximes can be converted to nitriles by the action of proton or Lewis acids.³⁹⁴ Among these are oximes of α -diketones (illustrated above), α -keto acids, α -dialkylamino ketones, α -hydroxy ketones, β -keto ethers, and similar compounds.³⁹⁵ These are fragmen-

³⁷⁹Rogić; Van Peppen; Klein; Demmin *J. Org. Chem.* **1974**, 39, 3424.

³⁸⁰Kim; Chung; Ryu *Synth. Commun.* **1990**, 20, 2785.

³⁸¹Mai; Patil *Synthesis* **1986**, 1037.

³⁸²Thomas; Greyn *Synthesis* **1990**, 129.

³⁸³Hendrickson; Blair; Kechen; *Tetrahedron Lett.* **1976**, 603.

³⁸⁴Sosnovsky; Krogh *Synthesis* **1978**, 703.

³⁸⁵Shinozaki; Imaizumi; Tajima *Chem. Lett.* **1983**, 929.

³⁸⁶Saednya *Synthesis* **1983**, 748.

³⁸⁷Dulcere *Tetrahedron Lett.* **1981**, 22, 1599.

³⁸⁸See Shono; Matsumura; Tsubata; Kamada; Kishi *J. Org. Chem.* **1989**, 54, 2249.

³⁸⁹Hauser; Le Maistre; Rainsford *J. Am. Chem. Soc.* **1935**, 57, 1056.

³⁹⁰Roberts; Rittberg; Kovacic *J. Org. Chem.* **1981**, 46, 4111.

³⁹¹Smith; Walker *J. Org. Chem.* **1962**, 27, 4372; Grandberg *J. Gen. Chem. USSR* **1964**, 34, 570; Grundon; Scott *J. Chem. Soc.* **1964**, 5674; Ioffe; Zelenina *J. Org. Chem. USSR* **1968**, 4, 1496.

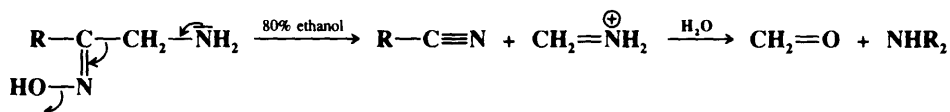
³⁹²Moore; Stupp *J. Org. Chem.* **1990**, 55, 3374.

³⁹³Cuvigny; Le Borgne; Larchevêque; Normant *Synthesis* **1976**, 237.

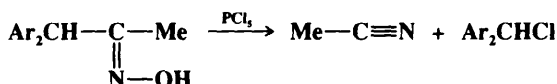
³⁹⁴For reviews, see Gawley *Org. React.* **1988**, 35, 1-420; Conley; Ghosh *Mech. Mol. Migr.* **1971**, 4, 197-308, pp. 197-251; McCarty; in *Patai The Chemistry of the Carbon-Nitrogen Double Bond*; Wiley: New York, 1970, pp. 416-439; Casanova; in Rappoport, Ref. 377, pp. 915-932.

³⁹⁵For more complete lists with references, see Olah; Vankar; Berrier *Synthesis* **1980**, 45; Conley; Ghosh, Ref. 394.

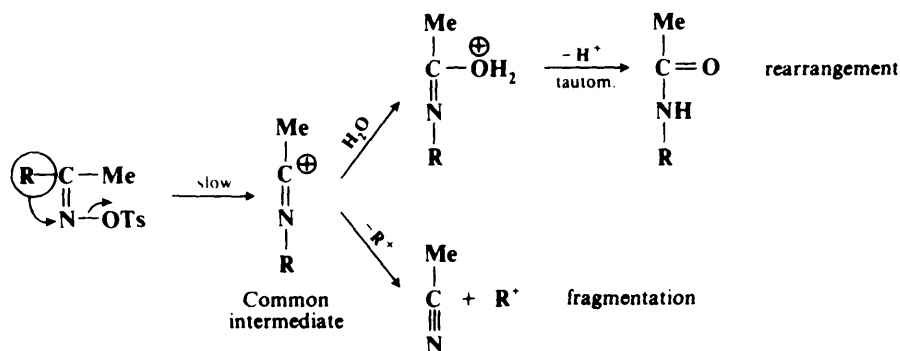
tation reactions, analogous to 7-32 and 7-33. For example, α -dialkylamino ketoximes also give amines and aldehydes or ketones besides nitriles:³⁹⁶



The reaction that normally occurs on treatment of a ketoxime with a Lewis or proton acid is the Beckmann rearrangement (8-18); fragmentations are considered side reactions, often called "abnormal" or "second-order" Beckmann rearrangements.³⁹⁷ Obviously, the substrates mentioned are much more susceptible to fragmentation than are ordinary ketoximes, since in each case an unshared pair is available to assist in removal of the group cleaving from the carbon. However, fragmentation is a side reaction even with ordinary ketoximes³⁹⁸ and, in cases where a particularly stable carbocation can be cleaved, may be the main reaction:³⁹⁹



There are indications that the mechanism at least in some cases first involves a rearrangement and then cleavage. The ratio of fragmentation to Beckmann rearrangement of a series of oxime tosylates $\text{RC}(=\text{NOTs})\text{Me}$ was not related to the solvolysis rate but was related to the stability of R^+ (as determined by the solvolysis rate of the corresponding RCl), which showed that fragmentation did not take place in the rate-determining step.⁴⁰⁰ It may be postulated then that the first step in the fragmentation and in the rearrangement is the same and that this is the rate-determining step. The product is determined in the second step:



However, in other cases the simple E1 or E2 mechanisms operate.⁴⁰¹

³⁹⁶Fischer; Grob; Renk *Helv. Chim. Acta* **1962**, *45*, 2539; Fischer; Grob *Helv. Chim. Acta* **1963**, *46*, 936.

³⁹⁷See the discussion in Ferris *J. Org. Chem.* **1960**, *25*, 12.

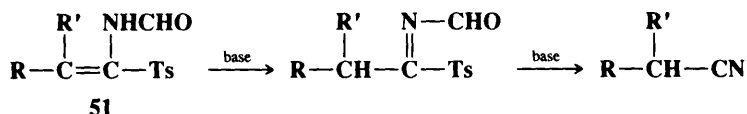
³⁹⁸See, for example, Hill; Conley *J. Am. Chem. Soc.* **1960**, *82*, 645.

³⁹⁹Hassner; Nash *Tetrahedron Lett.* **1965**, 525.

⁴⁰⁰Grob; Fischer; Raudenbusch; Zergenyi *Helv. Chim. Acta* **1964**, *47*, 1003.

⁴⁰¹Ahmad; Spenser *Can. J. Chem.* **1961**, *39*, 1340; Ferris; Johnson; Gould *J. Org. Chem.* **1960**, *25*, 1813; Grob; Sieber *Helv. Chim. Acta* **1967**, *50*, 2520; Green; Pearson *J. Chem. Soc. B* **1969**, 593.

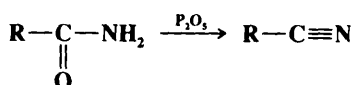
The fragmentation of N-(1-tosyl-1-alkenyl)formamides (**51**) by refluxing with NaOMe in MeOH is a step in the conversion of a ketone to a nitrile,⁴⁰² since **51** can be prepared by



treatment of ketones with TsCH₂NC (p. 949). The overall conversion is RR'C=O to RR'CHCN.

OS V, 266.

7-39 Dehydration of Unsubstituted Amides N,N-Dihydro-C-oxo-bielimination



Unsubstituted amides can be dehydrated to nitriles.⁴⁰³ Phosphorous pentoxide is the most common dehydrating agent for this reaction, but many others, including POCl₃, PCl₅, CCl₄-Ph₃P,⁴⁰⁴ TiCl₄-base,⁴⁰⁵ HMPA,⁴⁰⁶ Cl₃COCl-Et₃N,⁴⁰⁷ MeOOCNSO₂[⊖]NEt₃[⊕] (the Burgess reagent),⁴⁰⁸ nitrilium salts,⁴⁰⁹ cyanuric chloride,⁴¹⁰ Me₂N=CHCl[⊖] Cl[⊕],⁴¹¹ trimethylsilyl polyphosphate,⁴¹² and SOCl₂ have also been used.⁴¹³ It is possible to convert an acid to the nitrile, without isolation of the amide, by heating its ammonium salt with the dehydrating agent,⁴¹⁴ or by other methods.⁴¹⁵ Acyl halides can also be directly converted to nitriles by heating with sulfamide (NH₂)₂SO₂.⁴¹⁶ The reaction may be formally looked on as a β elimination from the enol form of the amide RC(OH)=NH, in which case it is like **7-37**, except that H and OH have changed places. In some cases, for example, with SOCl₂, the mechanism probably is through the enol form, with the dehydrating agent forming an ester with the OH group, for example, RC(OSOCl)=NH, which undergoes elimination by the E1 or E2 mechanism.⁴¹⁷ N,N-Disubstituted ureas give cyanamides (R₂N-CO-NH₂ → R₂N-CN) when dehydrated with CHCl₃-NaOH under phase transfer conditions.⁴¹⁸

⁴⁰²Schöllkopf; Schröder *Angew. Chem. Int. Ed. Engl.* **1973**, 12, 407 [*Angew. Chem.* 85, 402].

⁴⁰³For reviews, see Bieron; Dinan; in Zabicky *The Chemistry of Amides*; Wiley: New York, 1970, pp. 274-283; Friedrich; Wallenfels, Ref. 377, pp. 96-103; Friedrich, Ref. 377.

⁴⁰⁴Yamato; Sugawara *Tetrahedron Lett.* **1970**, 4383; Appel; Kleinstück; Ziehn *Chem. Ber.* **1971**, 104, 1030; Harrison; Hodge; Rogers *Synthesis* **1977**, 41.

⁴⁰⁵Lehnert *Tetrahedron Lett.* **1971**, 1501.

⁴⁰⁶Monson; Priest *Can. J. Chem.* **1971**, 49, 2897.

⁴⁰⁷Saednya *Synthesis* **1985**, 184.

⁴⁰⁸Claremon; Phillips *Tetrahedron Lett.* **1988**, 29, 2155.

⁴⁰⁹Jochims; Glocker *Chem. Ber.* **1990**, 123, 1537.

⁴¹⁰Olah; Narang; Fung; Gupta *Synthesis* **1980**, 657.

⁴¹¹Barger; Riley *Synth. Commun.* **1980**, 10, 479.

⁴¹²Yokoyama; Yoshida; Imamoto *Synthesis* **1982**, 591. See also Rao; Rambabu; Srinivasan *Synth. Commun.* **1989**, 19, 1431.

⁴¹³For a list of reagents, with references, see Ref. 144, pp. 991-992.

⁴¹⁴See, for example, Imamoto; Takaoka; Yokoyama *Synthesis* **1983**, 142.

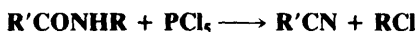
⁴¹⁵For a list of methods, with references, see Ref. 144, pp. 976-977.

⁴¹⁶Hulkenberg; Troost *Tetrahedron Lett.* **1982**, 23, 1505.

⁴¹⁷Rickborn; Jensen *J. Org. Chem.* **1962**, 27, 4608.

⁴¹⁸Schroth; Kluge; Frach; Hodek; Schädler *J. Prakt. Chem.* **1983**, 325, 787.

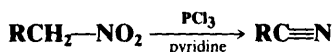
N-Alkyl-substituted amides can be converted to nitriles and alkyl chlorides by treatment with PCl_5 . This is called the *von Braun reaction* (not to be confused with the other von



Braun reaction, 0-73). In a similar reaction, treatment of N-alkyl-substituted amides with chlorotris(triphenylphosphine)rhodium $\text{RhCl}(\text{PPh}_3)_3$ or certain other catalysts give nitriles and the corresponding alcohols.⁴¹⁹

OS I, 428; II, 379; III, 493, 535, 584, 646, 768; IV, 62, 144, 166, 172, 436, 486, 706; VI, 304, 465.

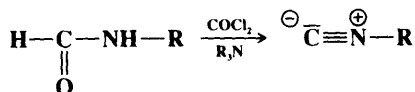
7-40 Conversion of Primary Nitro Compounds to Nitriles



Nitriles can be obtained in one step by treatment of primary nitro compounds with PCl_3 and pyridine.⁴²⁰ R may be alkyl or aryl and may contain $\text{C}=\text{C}$ double bonds or various functional groups. Yields are moderate to good. The reaction has also been carried out with $\text{Me}_3\text{N—SO}_2$ and with HMPA.⁴²¹ Primary azides RCH_2N_3 have been converted to nitriles RCN with Pd metal.⁴²² Primary nitro compounds RCH_2NO_2 were converted to nitrile oxides $\text{RCN}^+\text{—}\overset{\ominus}{\text{O}}$ by treatment with ClCOOEt or PhSO_2Cl in the presence of Et_3N .⁴²³

7-41 Conversion of N-Alkylformamides to Isocyanides

CN-Dihydro-C-oxo-bielimination



Isocyanides can be prepared by elimination of water from N-alkylformamides with phosgene and a tertiary amine.⁴²⁴ Other reagents, among them TsCl in quinoline, POCl_3 and a tertiary amine,⁴²⁵ $\text{Me}_2\text{N}=\text{CHCl}^+\text{Cl}^-$,⁴²⁶ di-2-pyridyl sulfite,⁴²⁷ triflic anhydride- $(i\text{-Pr})_2\text{NEt}$,⁴²⁸ $\text{Ph}_3\text{P—CCl}_4\text{—Et}_3\text{N}$,⁴²⁹ and $\text{Ph}_3\text{PBr}_2\text{—Et}_3\text{N}$ ⁴³⁰ have also been employed.

OS V, 300, 772; VI, 620, 751, 987. See also OS VII, 27.

⁴¹⁹Blum; Fisher; Greener *Tetrahedron* **1973**, 29, 1073.

⁴²⁰Wehrli; Schaefer *J. Org. Chem.* **1977**, 42, 3956.

⁴²¹Olah; Vankar; Gupta *Synthesis*; **1979**, 36. For another method, see Urpi; Vilarrasa *Tetrahedron Lett.* **1990**, 31, 7497.

⁴²²Hayashi; Ohno; Oka *Bull. Chem. Soc. Jpn.* **1976**, 49, 506. See also Jarvis; Nicholas *J. Org. Chem.* **1979**, 44, 2951.

⁴²³Shimizu; Hayashi; Shibafuchi; Teramura *Bull. Chem. Soc. Jpn.* **1986**, 59, 2827.

⁴²⁴For reviews, see Hoffmann; Gokel; Marquarding; Ugi, in *Ugi Isonitrile Chemistry*; Academic Press: New York, 1971, pp. 10-17; Ugi; Fetzer; Eholzer; Knupfer; Offermann *Angew. Chem. Int. Ed. Engl.* **1965**, 4, 472-484 [*Angew. Chem.* 77, 492-504], *Newer Methods Prep. Org. Chem.* **1968**, 4, 37-66.

⁴²⁵See Obrecht; Herrmann; Ugi *Synthesis* **1985**, 400.

⁴²⁶Walborsky; Niznik *J. Org. Chem.* **1972**, 37, 187.

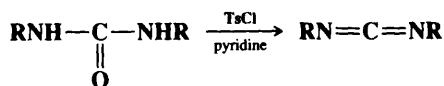
⁴²⁷Kim; Yi *Tetrahedron Lett.* **1986**, 27, 1925.

⁴²⁸Baldwin; O'Neil *Synlett* **1991**, 603.

⁴²⁹Appel; Kleinstück; Zichn *Angew. Chem. Int. Ed. Engl.* **1971**, 10, 132 [*Angew. Chem.* 83, 143].

⁴³⁰Bestmann; Lienert; Mott *Liebigs Ann. Chem.* **1968**, 718, 24.

7-42 Dehydration of N,N'-Disubstituted Ureas and Thioureas
1/N,3/N-Dihydro-2/C-oxo-bielimination



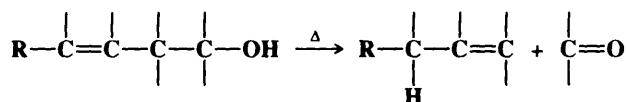
Carbodiimides⁴³¹ can be prepared by the dehydration of N,N'-disubstituted ureas with various dehydrating agents,⁴³² among which are TsCl in pyridine, POCl₃, PCl₅, P₂O₅-pyridine, TsCl (with phase-transfer catalysis),⁴³³ and Ph₃PBr₂-Et₃N.⁴³⁰ H₂S can be removed from the corresponding thioureas by treatment with HgO, NaOCl, phosgene,⁴³⁴ or diethyl azodicarboxylate-triphenylphosphine.⁴³⁵

OS V, 555; VI, 951.

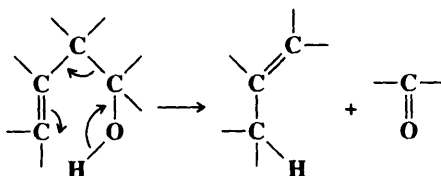
Reactions in Which C=O Bonds Are Formed

Many elimination reactions in which C=O bonds are formed were considered in Chapter 16, along with their more important reverse reactions. Also see 2-40 and 2-41.

7-43 Pyrolysis of β-Hydroxy Olefins
O-Hydro-C-allyl-elimination



When pyrolyzed, β-hydroxy olefins cleave to give olefins and aldehydes or ketones.⁴³⁶ Olefins produced this way are quite pure, since there are no side reactions. The mechanism has



been shown to be pericyclic, primarily by observations that the kinetics are first order⁴³⁷ and that, for ROD, the deuterium appeared in the allylic position of the new olefin.⁴³⁸ This

⁴³¹For a review of the reactions in this section, see Bocharov *Russ. Chem. Rev.* **1965**, 34, 212-219. For a review of carbodiimide chemistry; see Williams; Ibrahim *Chem. Rev.* **1981**, 81, 589-636.

⁴³²For some others not mentioned here, see Sakai; Fujinami; Otani; Aizawa *Chem. Lett.* **1976**, 811; Shibamura; Shiono; Mukaiyama *Chem. Lett.* **1977**, 575; Kim; Yi *J. Org. Chem.* **1986**, 51, 2613. Ref. 427.

⁴³³Jászay; Petneházy; Tóke; Szajáni *Synthesis* **1987**, 520.

⁴³⁴Ulrich; Sayigh *Angew. Chem. Int. Ed. Engl.* **1966**, 5, 704-712 [*Angew. Chem.* 78, 761-769], *Newer Methods Prep. Org. Chem.* **1971**, 6, 223-242.

⁴³⁵Mitsunobu; Kato; Tomari *Tetrahedron* **1970**, 26, 5731.

⁴³⁶Arnold; Smolinsky *J. Am. Chem. Soc.* **1959**, 81, 6643. For a review, see Marvell; Whalley, in Patai, Ref. 152, pt. 2, pp. 729-734.

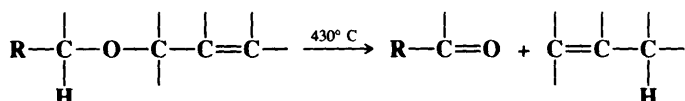
⁴³⁷Smith; Yates *J. Chem. Soc.* **1965**, 7242; Voorhees; Smith *J. Org. Chem.* **1971**, 36, 1755.

⁴³⁸Arnold; Smolinsky *J. Org. Chem.* **1960**, 25, 128; Smith; Taylor *Chem. Ind. (London)* **1961**, 949.

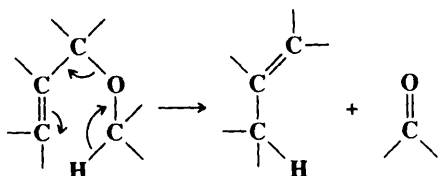
mechanism is the reverse of that for the oxygen analog of the ene synthesis (6-53). β -Hydroxyacetylenes react similarly to give the corresponding allenes and carbonyl compounds.⁴³⁹ The mechanism is the same despite the linear geometry of the triple bonds.

7-44 Pyrolysis of Allylic Ethers

C-Hydro-O-allyl-elimination



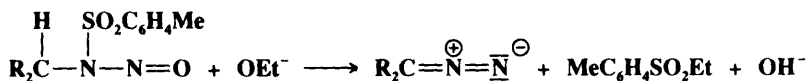
Pyrolysis of allylic ethers that contain at least one α hydrogen gives olefins and aldehydes or ketones. The reaction is closely related to 7-43, and the mechanism is also pericyclic⁴⁴⁰



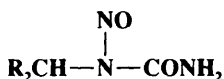
Reactions in Which N=N Bonds Are Formed

7-45 Eliminations to Give Diazoalkanes

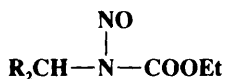
N-Nitrosoamine-diazoalkane transformation



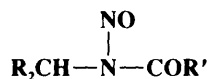
Various N-nitroso-N-alkyl compounds undergo elimination to give diazoalkanes.⁴⁴¹ One of the most convenient methods for the preparation of diazomethane involves base treatment of N-nitroso-N-methyl-*p*-toluenesulfonamide (illustrated above, with R = H).⁴⁴² However, other compounds commonly used are (base treatment is required in all cases):



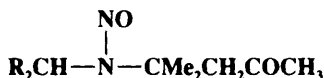
N-nitroso-N-alkylureas



N-nitroso-N-alkylcarbamates



N-nitroso-N-alkyl amides



N-nitroso-N-alkyl-4-amino-4-methyl-2-pentanones

⁴³⁹Viola; MacMillan; Proverb; Yates *J. Am. Chem. Soc.* **1971**, 93, 6967; Viola; Proverb; Yates; Larrahondo *J. Am. Chem. Soc.* **1973**, 95, 3609.

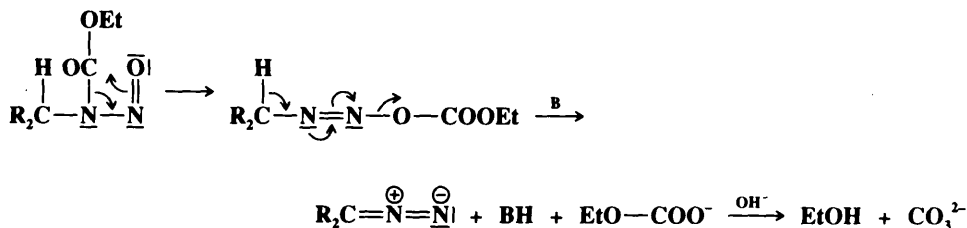
⁴⁴⁰Cookson; Wallis *J. Chem. Soc. B.* **1966**, 1245; Kwart; Slutsky; Sarner *J. Am. Chem. Soc.* **1973**, 95, 5242; Egger; Vitins *Int. J. Chem. Kinet.* **1974**, 6, 429.

⁴⁴¹For a review, see Regitz; Maas *Diazo Compounds*; Academic Press: New York, 1986, pp. 296-325. For a review of the preparation and reactions of diazomethane, see Black *Aldrichimica Acta* **1983**, 16, 3-10. For discussions, see Cowell; Ledwith *Q. Rev., Chem. Soc.* **1970**, 24, 119-167, pp. 126-131; Smith *Open-chain Nitrogen Compounds*; W. A. Benjamin: New York, 1966, especially pp. 257-258, 474-475, in vol. 2.

⁴⁴²de Boer; Backer *Org. Synth. IV* 225, 250; Hudlicky *J. Org. Chem.* **1980**, 45, 5377.

All these compounds can be used to prepare diazomethane, though the sulfonamide, which is commercially available, is most satisfactory. (N-Nitroso-N-methylcarbamate and N-nitroso-N-methylurea give good yields, but are highly irritating and carcinogenic.⁴⁴³) For higher diazoalkanes the preferred substrates are nitrosoalkylcarbamates.

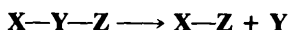
Most of these reactions probably begin with a 1,3 nitrogen-to-oxygen rearrangement, followed by the actual elimination (illustrated for the carbamate):



OS II, 165; III, 119, 244; IV, 225, 250; V, 351; VI, 981.

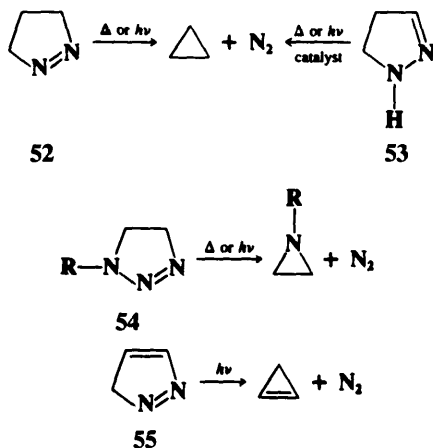
Extrusion Reactions

We consider an *extrusion reaction*⁴⁴⁴ to be one in which an atom or group Y connected to two other atoms X and Z is lost from a molecule, leading to a product in which X is bonded directly to Z.



Reactions **4-41** and **7-25** also fit this definition. Reaction **7-36** does not fit the definition, but is often also classified as an extrusion reaction. An extrusibility scale has been developed, showing that the ease of extrusion of the common Y groups is in the order: $-\text{N}=\text{N}- > -\text{COO}- > -\text{SO}_2- > -\text{CO}-$.⁴⁴⁵

7-46 Extrusion of N₂ from Pyrazolines, Pyrazoles, and Triazolines

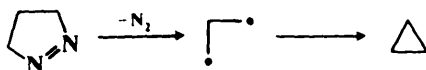
⁴³Searle *Chem. Br.* **1970**, 6, 5-10.

⁴⁴For a monograph, see Stark; Duke *Extrusion Reactions*; Pergamon: Elmsford, NY, 1967. For a review of extrusions that are photochemically induced, see Givens *Org. Photochem.* **1981**, 5, 227-346.

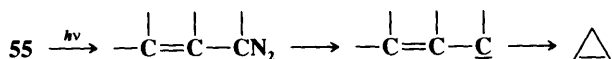
⁴⁴⁵Paine; Warkentin *Can. J. Chem.* **1981**, *59*, 491.

1-Pyrazolines (**52**) can be converted to cyclopropane and N_2 on photolysis⁴⁴⁶ or pyrolysis.⁴⁴⁷ The tautomeric 2-pyrazolines (**53**), which are more stable than **52**, also give the reaction, but in this case an acidic or basic catalyst is required, the function of which is to convert **53** to **52**.⁴⁴⁸ In the absence of such catalysts, **53** do not react.⁴⁴⁹ In a similar manner, triazolines (**54**) are converted to aziridines.⁴⁵⁰ Side reactions are frequent with both **52** and **54**, and some substrates do not give the reaction at all. However, the reaction has proved synthetically useful in many cases. In general, photolysis gives better yields and fewer side reactions than pyrolysis with both **52** and **54**. 3*H*-Pyrazoles⁴⁵¹ (**55**) are stable to heat, but in some cases can be converted to cyclopropenes on photolysis,⁴⁵² though in other cases other types of products are obtained.

There is much evidence that the mechanism⁴⁵³ of the 1-pyrazoline reactions generally involves diradicals, though the mode of formation and detailed structure (e.g., singlet vs.

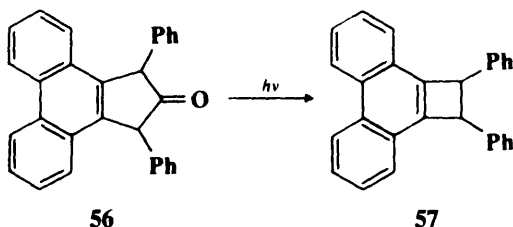


triplet) of these radicals may vary with the substrate and reaction conditions. The reactions of the 3*H*-pyrazoles have been postulated to proceed through a diazo compound that loses N_2 to give a vinylic carbene.⁴⁵⁴



OS V, 96, 929. See also OS **66**, 142.

7-47 Extrusion of CO or CO₂ Carbonyl-extrusion



⁴⁴⁶Van Auker; Rinehart *J. Am. Chem. Soc.* **1962**, *84*, 3736.

⁴⁴⁷For reviews of the reactions in this section, see Adam; De Lucchi *Angew. Chem. Int. Ed. Engl.* **1980**, *19*, 762-779 [*Angew. Chem.* *92*, 815-832]; Meier; Zeller *Angew. Chem. Int. Ed. Engl.* **1977**, *16*, 835-851 [*Angew. Chem.* *89*, 876-890]; Stark; Duke, Ref. 444, pp. 116-151. For a review of the formation and fragmentation of cyclic azo compounds, see Mackenzie; in Patai *The Chemistry of the Hydrazo, Azo, and Azoxy Groups*, pt. 1; Wiley: New York, 1975, pp. 329-442.

⁴⁴⁸For example, see Jones; Sanderfer; Baarda *J. Org. Chem.* **1967**, *32*, 1367.

⁴⁴⁹McGreer; Wai; Carmichael *Can. J. Chem.* **1960**, *38*, 2410; Kocsis; Ferrini; Arigoni; Jeger *Helv. Chim. Acta* **1960**, *43*, 2178.

⁴⁵⁰For a review, see Scheiner *Sel. Org. Transform.* **1970**, *1*, 327-362.

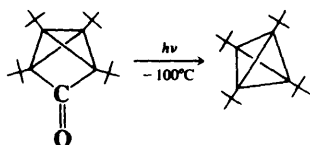
⁴⁵¹For a review of 3*H*-pyrazoles, see Sammes; Katritzky *Adv. Heterocycl. Chem.* **1983**, *34*, 2-52.

⁴⁵²Closs; Böll *J. Am. Chem. Soc.* **1963**, *85*, 3904, *Angew. Chem. Int. Ed. Engl.* **1963**, *2*, 399 [*Angew. Chem.* *75*, 640]; Ege *Tetrahedron Lett.* **1963**, 1667; Closs; Böll; Heyn; Dev *J. Am. Chem. Soc.* **1968**, *90*, 173; Franck-Neumann; Buchecker *Tetrahedron Lett.* **1969**, 15; Pincock; Morchat; Arnold *J. Am. Chem. Soc.* **1973**, *95*, 7536.

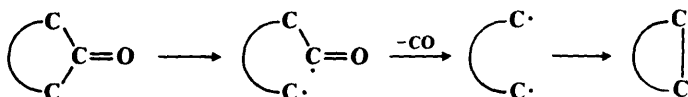
⁴⁵³For a review of the mechanism; see Engel *Chem. Rev.* **1980**, *80*, 99-150. See also Engel; Nalepa *Pure Appl. Chem.* **1980**, *52*, 2621; Engel; Gerth *J. Am. Chem. Soc.* **1983**, *105*, 6849; Reedich; Sheridan *J. Am. Chem. Soc.* **1988**, *110*, 3697.

⁴⁵⁴Closs; Böll; Heyn; Dev, Ref. 452; Pincock; Morchat; Arnold, Ref. 452.

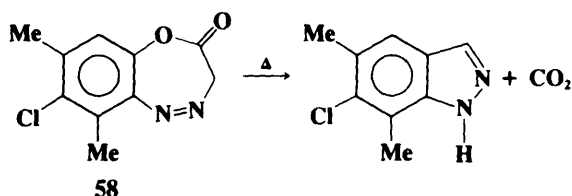
Though the reaction is not general, certain cyclic ketones can be photolyzed to give ring-contracted products.⁴⁵⁵ In the example above, the tetracyclic ketone **56** was photolyzed to give **57**.⁴⁵⁶ This reaction was used to synthesize tetra-*t*-butyltetrahydrene:⁴⁵⁷



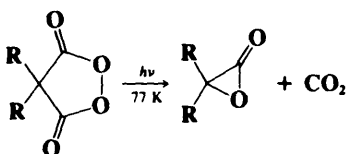
The mechanism probably involves a Norrish type I cleavage (p. 243), loss of CO from the resulting radical, and recombination of the radical fragments.



Certain lactones extrude CO₂ on heating or on irradiation, examples being pyrolysis of **58**,⁴⁵⁸



and the formation of α-lactones by photolysis of 1,2-dioxolane-3,5-diones.⁴⁵⁹



Decarboxylation of β-lactones (see 7-34) may be regarded as a degenerate example of this reaction. Unsymmetrical diacyl peroxides RCO—OO—COR' lose two molecules of CO₂ when photolyzed in the solid state to give the product RR'.⁴⁶⁰ Electrolysis was also used, but yields were lower. This is an alternative to the Kolbe reaction (4-38). See also 7-36 and 7-51.

There are no OS references, but see OS VI, 418, for a related reaction.

⁴⁵⁵For reviews of the reactions in this section, see Redmore; Gutsche *Adv. Alicyclic Chem.* **1971**, 3, 1-138, pp. 91-107; Stark; Duke, Ref. 444, pp. 47-71.

⁴⁵⁶Cava; Mangold *Tetrahedron Lett.* **1964**, 1751.

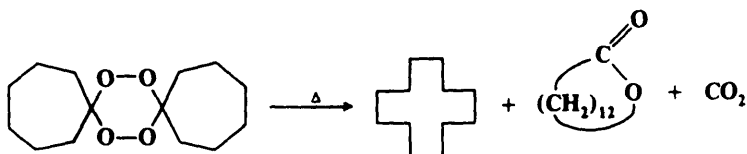
⁴⁵⁷Maier; Pfriem; Schäfer; Matusch *Angew. Chem. Int. Ed. Engl.* **1978**, 17, 520 [*Angew. Chem.* 90, 552].

⁴⁵⁸Ried; Dietrich *Angew. Chem. Int. Ed. Engl.* **1963**, 2, 323 [*Angew. Chem.* 75, 476]; Ried; Wagner *Liebigs Ann. Chem.* **1965**, 681, 45.

⁴⁵⁹Chapman; Wojtkowski; Adam; Rodriquez; Rucktäschel *J. Am. Chem. Soc.* **1972**, 94, 1365.

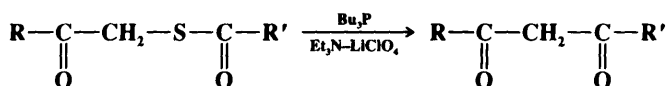
⁴⁶⁰Feldhues; Schäfer *Tetrahedron* **1985**, 41, 4195, 4213, **1986**, 42, 1285; Lomölder; Schäfer *Angew. Chem. Int. Ed. Engl.* **1987**, 26, 1253 [*Angew. Chem.* 99, 1282].

cycloalkylidene peroxides, in which case the cycloalkane and lactone products result from loss of two molecules and one molecule of CO_2 , respectively, e.g.,



Both dimeric and trimeric cycloalkylidene peroxides can be synthesized⁴⁶⁷ by treatment of the corresponding cyclic ketones with H_2O_2 in acid solution.⁴⁶⁸ The trimeric peroxide is formed first and is subsequently converted to the dimeric compound.⁴⁶⁹

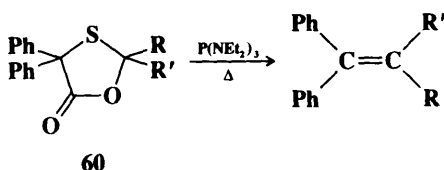
7-50 Formation of β -Dicarbonyl Compounds by Extrusion of Sulfur Thio-extrusion



Thioesters containing a β keto group in the alkyl portion can be converted to β -diketones by treatment with a tertiary phosphine under basic conditions.⁴⁷⁰ The starting thioesters can be prepared by the reaction between a thiol acid and an α -halo ketone (similar to 0-24).

OS VI, 776.

7-51 Olefin Synthesis by Twofold Extrusion Carbon dioxide,thio-extrusion



4,4-Diphenyloxathiolan-5-ones (60) give good yields of the corresponding olefins when heated with tris(diethylamino)phosphine.⁴⁷¹ This reaction is an example of a general type:

⁴⁶⁷For synthesis of mixed trimeric peroxides (e.g., 59), see Sanderson; Zeiler *Synthesis* **1975**, 388; Paul; Story; Busch; Sanderson *J. Org. Chem.* **1976**, 41, 1283.

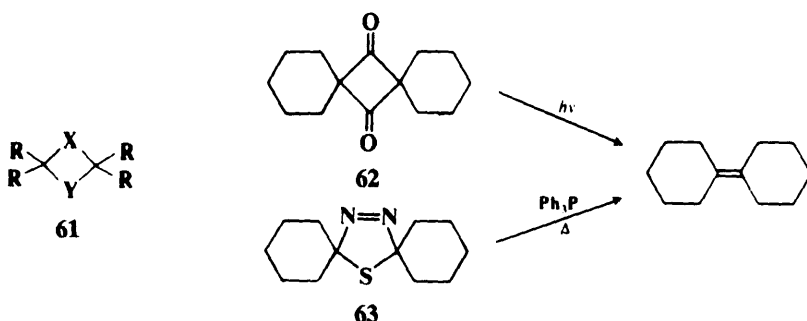
⁴⁶⁸Kharasch; Sosnovsky *J. Org. Chem.* **1958**, 23, 1322; Ledaal *Acta Chem. Scand.* **1967**, 21, 1656. For another method, see Sanderson; Zeiler *Synthesis* **1975**, 125.

⁴⁶⁹Story; Lee; Bishop; Denson; Busch *J. Org. Chem.* **1970**, 35, 3059. See also Sanderson; Wilterdink; Zeiler *Synthesis* **1976**, 479.

⁴⁷⁰Roth; Dubs; Götschi; Eschenmoser *Helv. Chim. Acta* **1971**, 54, 710. For a review of thio-extrusion, see Williams; Harpp *Sulfur Rep.* **1990**, 10, 103-191.

⁴⁷¹Barton; Willis *J. Chem. Soc., Perkin Trans. 1* **1972**, 305.

olefin synthesis by twofold extrusion of X and Y from a molecule of the type **61**.⁴⁷² Other examples are photolysis of 1,4-diones⁴⁷³ (e.g., **62**) and treatment with Ph_3P of the azo sulfide



63.⁴⁷⁴ **60** can be prepared by the condensation of thiobenzilic acid $\text{Ph}_2\text{C}(\text{SH})\text{COOH}$ with aldehydes or ketones.

OS V, 297.

⁴⁷²For a review of those in which X or Y contains S, Se, or Te, see Guziec; SanFilippo, Ref. 462.

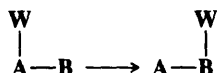
⁴⁷³Turro; Leermakers; Wilson; Neckers; Byers; Vesley *J. Am. Chem. Soc.* **1965**, 87, 2613.

⁴⁷⁴Barton; Smith; Willis *Chem. Commun.* **1970**, 1226; Barton; Guziec; Shahak *J. Chem. Soc., Perkin Trans. 1* **1974**, 1794. See also Bee; Beeby; Everett; Garratt *J. Org. Chem.* **1975**, 40, 2212; Back; Barton; Britten-Kelly; Guziec *J. Chem. Soc., Perkin Trans. 1* **1976**, 2079; Guziec; Moustakis *J. Chem. Soc., Chem. Commun.* **1984**, 63.

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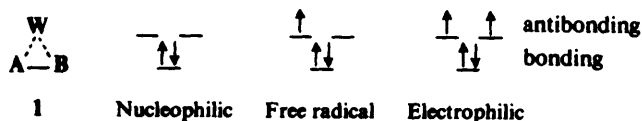
REARRANGEMENTS

In a rearrangement reaction a group moves from one atom to another in the same molecule.¹ Most are migrations from an atom to an adjacent one (called 1,2 shifts), but some are over



longer distances. The migrating group (W) may move with its electron pair (these can be called *nucleophilic* or *anionotropic* rearrangements; the migrating group can be regarded as a nucleophile), without its electron pair (*electrophilic* or *cationotropic* rearrangements; in the case of migrating hydrogen, *prototropic* rearrangements), or with just one electron (free-radical rearrangements). The atom A is called the *migration origin* and B is the *migration terminus*. However, there are some rearrangements that do not lend themselves to neat categorization in this manner. Among these are those with cyclic transition states (8-29 to 8-38).

As we shall see, nucleophilic 1,2 shifts are much more common than electrophilic or free-radical 1,2 shifts. The reason for this can be seen by a consideration of the transition states (or in some cases intermediates) involved. We represent the transition state or intermediate for all three cases by **1**, in which the two-electron A—W bond overlaps with the



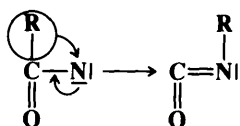
orbital on atom B, which contains zero, one, and two electrons, in the case of nucleophilic, free-radical, and electrophilic migration, respectively. The overlap of these orbitals gives rise to three new orbitals, which have an energy relationship similar to those on p. 52 (one bonding and two degenerate antibonding orbitals). In a nucleophilic migration, where only two electrons are involved, both can go into the bonding orbital and **1** is a low-energy transition state; but in a free-radical or electrophilic migration, there are, respectively, three or four electrons that must be accommodated, and antibonding orbitals must be occupied. It is not surprising therefore that, when 1,2-electrophilic or free-radical shifts are found, the migrating group W is usually aryl or some other group that can accommodate the extra one or two electrons and thus effectively remove them from the three-membered transition state or intermediate (see 37 on p. 1065).

In any rearrangement we can in principle distinguish between two possible modes of reaction: In one of these the group W becomes completely detached from A and may end

¹For books, see Mayo *Rearrangements in Ground and Excited States*, 3 vols.; Academic Press: New York, 1980; Stevens; Watts *Selected Molecular Rearrangements*; Van Nostrand-Reinhold: Princeton, 1973. For a review of many of these rearrangements, see Collins; Eastham, in Patai *The Chemistry of the Carbonyl Group*, vol. 1; Wiley: New York, 1966, pp. 761-821. See also the series *Mechanisms of Molecular Migrations*.

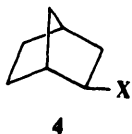
After the migration has taken place, the atom at the migration origin (A) must necessarily have an open sextet. In the third step this atom acquires an octet. In the case of carbocations, the most common third steps are combinations with a nucleophile (rearrangement with substitution) and loss of H^+ (rearrangement with elimination).

Though we have presented this mechanism as taking place in three steps, and some reactions do take place in this way, in many cases two or all three steps are simultaneous. For instance, in the nitrene example above, as the R migrates, an electron pair from the nitrene moves into the C—N bond to give a stable isocyanate:



In this example, the second and third steps are simultaneous. It is also possible for the second and third steps to be simultaneous even when the “third” step involves more than just a simple motion of a pair of electrons. Similarly, there are many reactions in which the first two steps are simultaneous; that is, there is no actual formation of a species such as **2** or **3**. In these instances it may be said that R assists in the removal of the leaving group, with migration of R and the removal of the leaving group taking place simultaneously. Many investigations have been carried out in attempts to determine, in various reactions, whether such intermediates as **2** or **3** actually form, or whether the steps are simultaneous (see, for example, the discussions on pp. 1055, 1090), but the difference between the two possibilities is often subtle, and the question is not always easily answered.⁴

Evidence for this mechanism is that rearrangements of this sort occur under conditions where we have previously encountered carbocations: SN_1 conditions, Friedel–Crafts alkylation, etc. Solvolysis of neopentyl bromide leads to rearrangement products, and the rate increases with increasing ionizing power of the solvent but is unaffected by concentration of base,⁵ so that the first step is carbocation formation. The same compound under SN_2 conditions gave no rearrangement, but only ordinary substitution, though slowly. Thus with neopentyl bromide, formation of a carbocation leads only to rearrangement. Carbocations usually rearrange to more stable carbocations. Thus the direction of rearrangement is usually primary \rightarrow secondary \rightarrow tertiary. Neopentyl (Me_3CCH_2), neophyl ($PhCMe_2CH_2$), and norbornyl (e.g., **4**) type systems are especially prone to carbocation rearrangement reactions.



It has been shown that the rate of migration increases with the degree of electron deficiency at the migration terminus.⁶

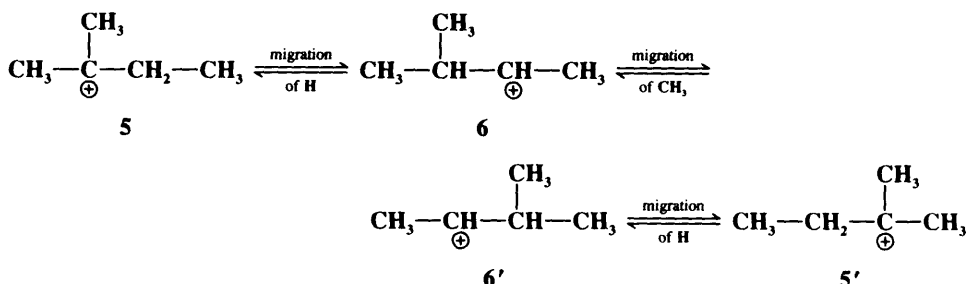
We have previously mentioned (p. 166) that stable tertiary carbocations can be obtained, in solution, at very low temperatures. Nmr studies have shown that when these solutions are warmed, rapid migrations of hydride and of alkyl groups take place, resulting in an

⁴The IUPAC designations depend on the nature of the steps. For the rules, see Guthrie *Pure Appl. Chem.* **1989**, 61, 23-56, pp. 44-45.

⁵Dostrovsky; Hughes *J. Chem. Soc.* **1946**, 166.

⁶Borodkin; Shakirov; Shubin; Koptiug *J. Org. Chem. USSR* **1976**, 12, 1293, 1298, **1978**, 14, 290, 924.

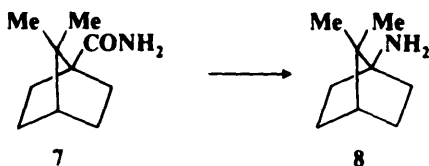
equilibrium mixture of structures.⁷ For example, the *t*-pentyl cation (**5**)⁸ equilibrates as follows:



Carbocations that rearrange to give products of identical structure (e.g., $\mathbf{5} \rightleftharpoons \mathbf{5'}$, $\mathbf{6} \rightleftharpoons \mathbf{6'}$) are called *degenerate carbocations* and such rearrangements are *degenerate rearrangements*. Many examples are known.⁹

The Actual Nature of the Migration

Most nucleophilic 1,2 shifts are intramolecular. W does not become free but always remains connected in some way to the substrate. Apart from the evidence from crossover experiments, the strongest evidence is that when the group W is chiral, the configuration is *retained* in the product. For example, (+)-PhCHMeCOOH was converted to (–)-PhCHMeNH₂ by the Curtius (8-15), Hofmann (8-14), Lossen (8-16), and Schmidt (8-17) reactions.¹⁰ In these reactions the extent of retention varied from 95.8 to 99.6%. Retention of configuration in the migrating group has been shown many times since.¹¹ Another experiment demonstrating



retention was the easy conversion of **7** to **8**.¹¹ Neither inversion nor racemization could take place at a bridgehead. There is much other evidence that retention of configuration usually occurs in W, and inversion never.¹³ However, this is not the state of affairs at A and B. In

⁷For reviews, see Brouwer; Hogeveen *Prog. Phys. Org. Chem.* **1972**, *9*, 179-240, pp. 203-237; Olah; Olah, in Olah; Schleyer *Carbonium Ions*, vol. 2; Wiley: New York, 1970, pp. 751-760, 766-778. For a discussion of the rates of these reactions, see Sorensen *Acc. Chem. Res.* **1976**, *9*, 257-265.

⁸Brouwer *Recl. Trav. Chim. Pays-Bas* **1968**, *87*, 210; Saunders; Hagen *J. Am. Chem. Soc.* **1968**, *90*, 2436.

⁹For reviews, see Ahlberg; Jonsäll; Engdahl *Adv. Phys. Org. Chem.* **1983**, *19*, 223-379; Leone; Barborak; Schleyer, in Olah; Schleyer, Ref. 7, vol. 4, pp. 1837-1939; Leone; Schleyer *Angew. Chem. Int. Ed. Engl.* **1970**, *9*, 860-890 [*Angew. Chem.* **82**, 889-919].

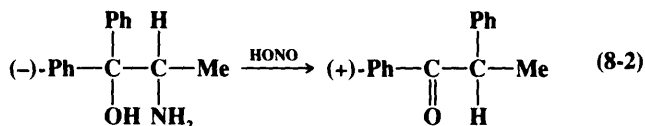
¹⁰Arcus; Kenyon *J. Chem. Soc.* **1939**, 916; Kenyon; Young *J. Chem. Soc.* **1941**, 263; Campbell; Kenyon *J. Chem. Soc.* **1946**, 25.

¹¹For retention of migrating group configuration in the Wagner–Meerwein and pinacol rearrangements, see Beggs; Meyers *J. Chem. Soc. B* **1970**, 930; Kirmse; Gruber; Knist *Chem. Ber.* **1973**, *106*, 1376; Shono; Fujita; Kumai *Tetrahedron Lett.* **1973**, 3123; Borodkin; Panova; Shakirov; Shubin *J. Chem. Soc., Chem. Commun.* **1979**, 354, *J. Org. Chem. USSR* **1983**, *19*, 103.

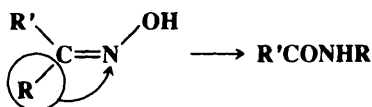
¹²Barlett; Knox *J. Am. Chem. Soc.* **1939**, *61*, 3184.

¹³See Cram, in Newman *Steric Effects in Organic Chemistry*; Wiley: New York, 1956; pp. 251-254; Wheland *Advanced Organic Chemistry*, 3rd ed.; Wiley: New York, 1960, pp. 597-604.

many reactions, of course, the structure of W—A—B is such that the product has only one steric possibility at A or B or both, and in most of these cases nothing can be learned. But in cases where the steric nature of A or B can be investigated, the results are mixed. It has been shown that either inversion or racemization can occur at A or B. Thus the following conversion proceeded with inversion at B:¹⁴



and inversion at A has been shown in other cases.¹⁵ However, in many other cases, racemization occurs at A or B or both.¹⁶ It is not always necessary for the product to have two steric possibilities in order to investigate the stereochemistry at A or B. Thus, in most Beckmann rearrangements (8-18), only the group trans (usually called *anti*) to the hydroxyl group migrates:

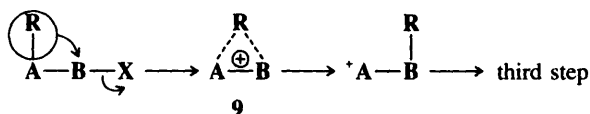


showing inversion at B.

This information tells us about the degree of concertedness of the three steps of the rearrangement. First consider the migration terminus B. If racemization is found at B, it is probable that the first step takes place before the second and that a positively charged carbon (or other sextet atom) is present at B:



With respect to B this is an S_N1-type process. If inversion occurs at B, it is likely that the first two steps are concerted, that a carbocation is *not* an intermediate, and that the process is S_N2-like:



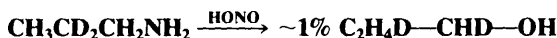
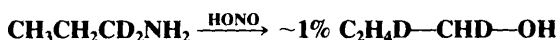
In this case participation by R assists in removal of X in the same way that neighboring groups do (p. 309). Indeed, R is a neighboring group here. The only difference is that, in the case of the neighboring-group mechanism of nucleophilic substitution, R never becomes detached from A, while in a rearrangement the bond between R and A is broken. In either

¹⁴Bernstein; Whitmore *J. Am. Chem. Soc.* **1939**, 61, 1324. For other examples, see Tsuchihashi; Tomooka; Suzuki *Tetrahedron Lett.* **1984**, 25, 4253.

¹⁵See Meerwein; van Emster *Ber.* **1920**, 53, 1815, **1922**, 55, 2500; Meerwein; Gérard *Liebigs Ann. Chem.* **1923**, 435, 174.

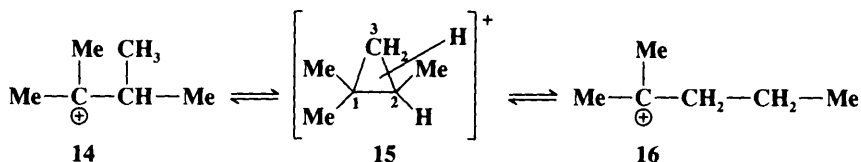
¹⁶For example, see Winstein; Morse *J. Am. Chem. Soc.* **1952**, 74, 1133.

Though the bulk of the products are not formed from protonated cyclopropane intermediates, there is considerable evidence that at least in 1-propyl systems, a small part of the product can in fact arise from such intermediates.²³ Among this evidence is the isolation of 10 to 15% cyclopropanes (mentioned on p. 325). Additional evidence comes from propyl cations generated by diazotization of labeled amines ($\text{CH}_3\text{CH}_2\text{CD}_2^+$, $\text{CH}_3\text{CD}_2\text{CH}_2^+$, $\text{CH}_3\text{CH}_2^{14}\text{CH}_2^+$), where isotopic distribution in the products indicated that a small amount (about 5%) of the product had to be formed from protonated cyclopropane intermediates, e.g.,²⁴



Even more scrambling was found in trifluoroacetolysis of 1-propyl-1-¹⁴C-mercuric perchlorate.²⁵ However, protonated cyclopropane intermediates accounted for less than 1% of the products from diazotization of labeled isobutylamine²⁶ and from formolysis of labeled 1-propyl tosylate.²⁷

It is likely that protonated cyclopropane transition states or intermediates are also responsible for certain non-1,2 rearrangements. For example, in super-acid solution, the ions **14** and **16** are in equilibrium. It is not possible for these to interconvert solely by 1,2 alkyl



or hydride shifts unless primary carbocations (which are highly unlikely) are intermediates. However, the reaction can be explained²⁸ by postulating that (in the forward reaction) it is the 1,2 bond of the intermediate or transition state **15** that opens up rather than the 2,3 bond, which is the one that would open if the reaction were a normal 1,2 shift of a methyl group. In this case opening of the 1,2 bond produces a tertiary cation, while opening of the 2,3 bond would give a secondary cation. (In the reaction **16** \rightarrow **14**, it is of course the 1,3 bond that opens).

3. There has been much discussion of H as migrating group. There is no conclusive evidence for the viewpoint that **9** in this case is or is not a true intermediate, though both positions have been argued (see p. 325).

²³For reviews, see Saunders; Vogel; Hagen; Rosenfeld *Acc. Chem. Res.* **1973**, *6*, 53-59; Lee *Prog. Phys. Org. Chem.* **1970**, *7*, 129-187; Collins *Chem. Rev.* **1969**, *69*, 543-550. See also Cooper; Jenner; Perry; Russell-Kling; Storresund; Whiting *J. Chem. Soc., Perkin Trans. 2* **1982**, 605.

²⁴Lee; Kruger; Wong *J. Am. Chem. Soc.* **1965**, *87*, 3985; Lee; Kruger *J. Am. Chem. Soc.* **1965**, *87*, 3986, *Tetrahedron* **1967**, *23*, 2539; Karabatsos; Orzech; Meyerson *J. Am. Chem. Soc.* **1965**, *87*, 4394; Lee; Wan *J. Am. Chem. Soc.* **1969**, *91*, 6416; Karabatsos; Orzech; Fry; Meyerson *J. Am. Chem. Soc.* **1970**, *92*, 606.

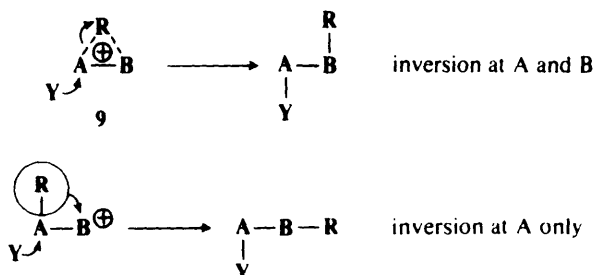
²⁵Lee; Cessna; Ko; Vassie *J. Am. Chem. Soc.* **1973**, *95*, 5688. See also Lee; Chwang *Can. J. Chem.* **1970**, *48*, 1025; Lee; Law *Can. J. Chem.* **1971**, *49*, 2746; Lee; Reichle *J. Org. Chem.* **1977**, *42*, 2058.

²⁴Karabatsos; Hsi; Meyerson *J. Am. Chem. Soc.* **1970**, *92*, 621. See also Karabatsos; Anand; Rickter; Meyerson *J. Am. Chem. Soc.* **1970**, *92*, 1254.

²⁷Lee; Kruger *Can. J. Chem.* **1966**, *44*, 2343; Shatkina; Lovtsova; Reutov *Bull. Acad. Sci. USSR, Div. Chem. Sci.* **1967**, 2616; Karabatsos; Fry; Meyerson *J. Am. Chem. Soc.* **1970**, *92*, 614. See also Lee; Zohdi *Can. J. Chem.* **1983**, *61*, 2092.

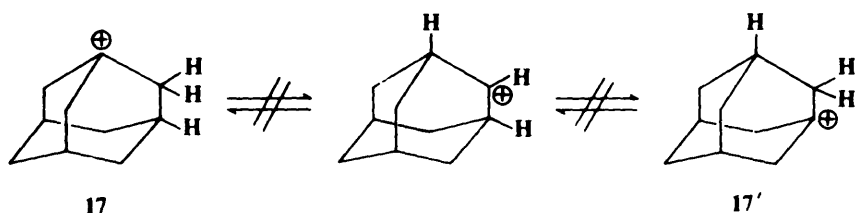
²Brouwer; Oelderik *Recl. Trav. Chim. Pays-Bas* **1968**, 87, 721; Saunders; Jaffe; Vogel *J. Am. Chem. Soc.* **1971**, 93, 2558; Saunders; Vogel *J. Am. Chem. Soc.* **1971**, 93, 2559, 2561; Kirmse; Loosen; Prolingheuer *Chem. Ber.* **1980**, 113, 129.

The stereochemistry at the migration origin A is less often involved, since in most cases it does not end up as a tetrahedral atom; but when there is inversion here, there is an S_N2 -type process at the beginning of the migration. This may or may not be accompanied by an S_N2 process at the migration terminus B:



In some cases it has been found that, when H is the migrating species, the configuration at A may be *retained*.²⁹

There is evidence that the configuration of the molecule may be important even where the leaving group is gone long before migration takes place. For example, the 1-adamantyl cation (**17**) does not equilibrate intramolecularly, even at temperatures up to 130°C,³⁰ though open-chain (e.g., **5** \rightleftharpoons **5'**) and cyclic tertiary carbocations undergo such equilibration at 0°C



or below. On the basis of this and other evidence it has been concluded that for a 1,2 shift of hydrogen or methyl to proceed as smoothly as possible, the vacant p orbital of the carbon bearing the positive charge and the sp^3 orbital carrying the migrating group must be coplanar,³⁰ which is not possible for **17**.

Migratory Aptitudes³¹

In many reactions there is no question about which group migrates. For example, in the Hofmann, Curtius, and similar reactions there is only one possible migrating group in each molecule, and one can measure migratory aptitudes only by comparing the relative rearrangement rates of different compounds. In other instances there are two or more potential migrating groups, but which migrates is settled by the geometry of the molecule. The Beckmann rearrangement (**8-18**) provides an example. As we have seen, only the group

²⁹Winstein; Holness *J. Am. Chem. Soc.* **1955**, *77*, 5562; Cram; Tadanier *J. Am. Chem. Soc.* **1959**, *81*, 2737; Bundel'; Pankratova; Gordin; Reutov *Doklad. Chem.* **1971**, *199*, 700; Kirmse; Arold *Chem. Ber.* **1971**, *104*, 1800; Kirmse; Ratajczak; Rauleder *Chem. Ber.* **1977**, *110*, 2290.

³⁰Brouwer; Hogeveen *Recl. Trav. Chim. Pays-Bas* **1970**, *89*, 211; Majerski; Schleyer; Wolf *J. Am. Chem. Soc.* **1970**, *92*, 5731.

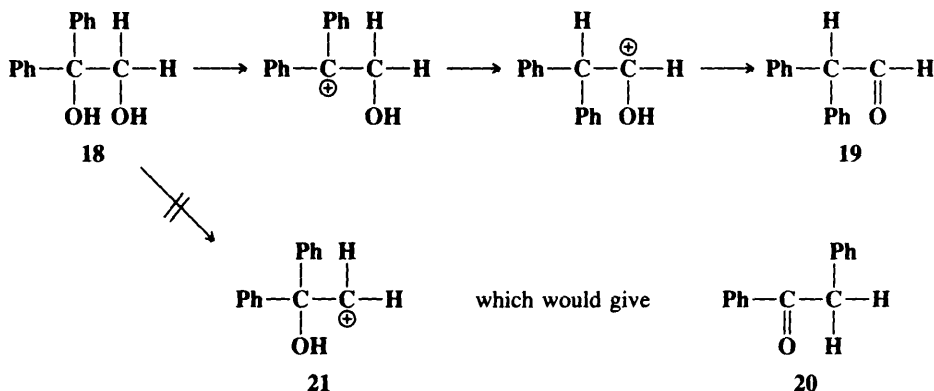
³¹For discussions, see Koptug; Shubin *J. Org. Chem. USSR* **1980**, *16*, 1685-1714; Wheland, Ref. 13, pp. 573-597.

trans to the OH migrates. In compounds whose geometry is not restricted in this manner, there still may be eclipsing effects (see p. 1002), so that the choice of migrating group is largely determined by which group is in the right place in the most stable conformation of the molecule.³² However, in some reactions, especially the Wagner–Meerwein (8-1) and the pinacol (8-2) rearrangements, the molecule may contain several groups that, geometrically at least, have approximately equal chances of migrating, and these reactions have often been used for the direct study of relative migratory aptitudes. In the pinacol rearrangement there is the additional question of which OH group leaves and which does not, since a group can migrate only if the OH group on the *other* carbon is lost.

We deal with the second question first. To study this question, the best type of substrate to use is one of the form $R_2C(OH)-C(OH)R_2$, since the only thing that determines migratory aptitude



is which OH group comes off. Once the OH group is gone, the migrating group is determined. As might be expected, the OH that leaves is the one whose loss gives rise to the more stable carbocation. Thus 1,1-diphenylethanediol (18) gives diphenylacetaldehyde (19), not phen-



ylacetophenone (20). Obviously, it does not matter in this case whether phenyl has a greater inherent migratory aptitude than hydrogen or not. Only the hydrogen can migrate because 21 is not formed. As we know, carbocation stability is enhanced by groups in the order aryl > alkyl > hydrogen, and this normally determines which side loses the OH group. However, exceptions are known, and which group is lost may depend on the reaction conditions (for an example, see the reaction of 41, p. 1073).

In order to answer the question about inherent migratory aptitudes, the obvious type of substrate to use (in the pinacol rearrangement) is $RR'C(OH)-C(OH)R'R'$, since the same carbocation

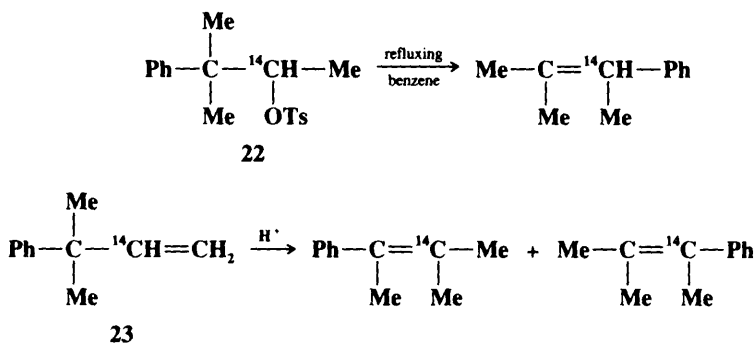


is formed no matter which OH leaves, and it would seem that a direct comparison of the migratory tendencies of R and R' is possible. On closer inspection, however, we can see that several factors are operating. Apart from the question of possible conformational effects, already mentioned, there is also the fact that whether the group R or R' migrates is determined not only by the relative inherent migrating abilities of R and R' but also by whether the group that does *not* migrate is better at stabilizing the positive charge that will now be found at the migration origin.³³ Thus, migration of R gives rise to the cation

³²For a discussion, see Cram, Ref. 13, pp. 270-276. For an interesting example, see Nickon; Weglein *J. Am. Chem. Soc.* **1975**, 97, 1271.

³³For example, see Howells; Warren *J. Chem. Soc., Perkin Trans. 2* **1973**, 1645; McCall; Townsend; Bonner *J. Am. Chem. Soc.* **1975**, 97, 2743; Brownbridge; Hodgson; Shepherd; Warren *J. Chem. Soc., Perkin Trans. 1* **1976**, 2024.

$R'\overset{\oplus}{C}(OH)CR_2R'$, while migration of R' gives the cation $RC(OH)CRR_2'$ and these cations have different stabilities. It is possible that in a given case R might be found to migrate less than R' , not because it actually has a lower inherent migrating tendency, but because it is much better at stabilizing the positive charge. In addition to this factor, migrating ability of a group is also related to its capacity to render anchimeric assistance to the departure of the nucleofuge. An example of this effect is the finding that in the decomposition of the tosylate **22** only the phenyl group migrates, while in acid treatment of the corresponding



alkene **23**, there is competitive migration of both methyl and phenyl (in these reactions ^{14}C labeling is necessary to determine which group has migrated).³⁴ **22** and **23** give the same carbocation; the differing results must be caused by the fact that in **22** the phenyl group can assist the leaving group, while no such process is possible for **23**. This example clearly illustrates the difference between migration to a relatively free terminus and one that proceeds with the migrating group lending anchimeric assistance.³⁵

It is not surprising therefore that clear-cut answers as to relative migrating tendencies are not available. More often than not migratory aptitudes are in the order aryl > alkyl, but exceptions are known, and the position of hydrogen in this series is often unpredictable. In some cases migration of hydrogen is preferred to aryl migration; in other cases migration of alkyl is preferred to that of hydrogen. Mixtures are often found, and the isomer that predominates often depends on conditions. For example, the comparison between methyl and ethyl has been made many times in various systems, and in some cases methyl migration and in others ethyl migration has been found to predominate.³⁶ However, it can be said that among aryl migrating groups, electron-donating substituents in the para and meta positions increase the migratory aptitudes, while the same substituents in the ortho positions decrease them. Electron-withdrawing groups decrease migrating ability in all positions. The following are a few of the relative migratory aptitudes determined for aryl groups by Bachmann and Ferguson:³⁷ *p*-anisyl, 500; *p*-tolyl, 15.7; *m*-tolyl, 1.95; phenyl, 1.00; *p*-chlorophenyl, 0.7; *o*-anisyl, 0.3. For the *o*-anisyl group, the poor migrating ability probably has a

³⁴Grimaud; Laurent *Bull. Soc. Chim. Fr.* **1967**, 3599.

³⁵A number of studies of migratory aptitudes in the dienone-phenol rearrangement (**8-5**) are in accord with the above. For a discussion, see Fischer; Henderson *J. Chem. Soc., Chem. Commun.* **1979**, 279, and references cited therein. See also Palmer; Waring *J. Chem. Soc., Perkin Trans. 2* **1979**, 1089; Marx; Hahn *J. Org. Chem.* **1988**, 53, 2866.

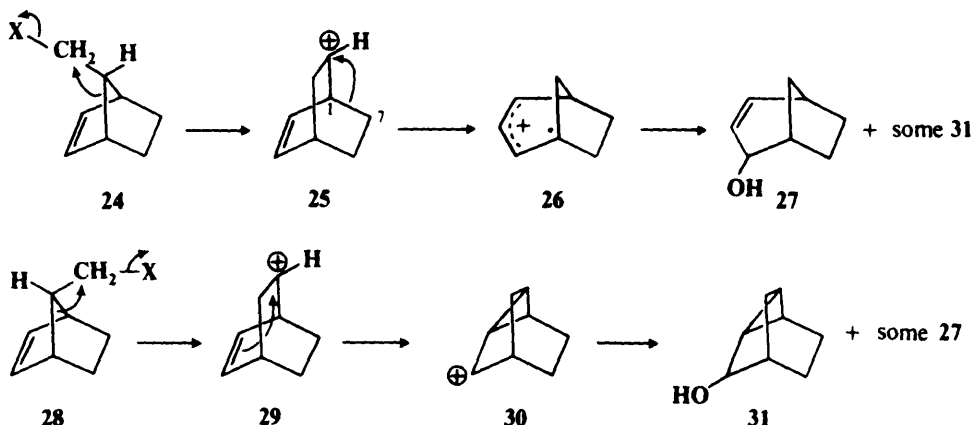
³⁶For examples, see Cram; Knight *J. Am. Chem. Soc.* **1952**, 74, 5839; Stiles; Mayer *J. Am. Chem. Soc.* **1959**, 81, 1497; Heidke; Saunders *J. Am. Chem. Soc.* **1966**, 88, 5816; Dubois; Bauer *J. Am. Chem. Soc.* **1968**, 90, 4510, 4511; Bundel'; Levina; Reutov *J. Org. Chem. USSR* **1970**, 6, 1; Pilkington; Waring *J. Chem. Soc., Perkin Trans. 2* **1976**, 1349; Korchagina; Derendyaev; Shubin; Koptyug *J. Org. Chem. USSR* **1976**, 12, 378; Wistuba; Rüchardt *Tetrahedron Lett.* **1981**, 22, 4069; Jost; Laali; Sommer *Nouv. J. Chim.* **1983**, 7, 79.

³⁷Bachmann; Ferguson *J. Am. Chem. Soc.* **1934**, 56, 2081.

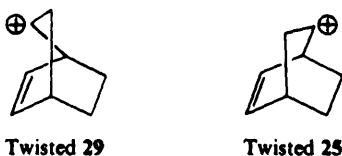
steric cause, while for the others there is a fair correlation with activation or deactivation of electrophilic aromatic substitution, which is what the process is with respect to the benzene ring. It has been reported that at least in certain systems acyl groups have a greater migratory aptitude than alkyl groups.³⁸

Memory Effects³⁹

Solvolysis of the endo bicyclic compound **24** ($X = \text{ONs}$, p. 353, or Br) gave mostly the bicyclic allylic alcohol **27**, along with a smaller amount of the tricyclic alcohol **31**, while



solvolysis of the exo isomers **28** gave mostly **31**, with smaller amounts of **27**.⁴⁰ Thus the two isomers gave entirely different ratios of products, though the carbocation initially formed (**25** or **29**) seems to be the same for each. In the case of **25**, a second rearrangement (a shift of the 1,7 bond) follows, while with **29** what follows is an intramolecular addition of the positive carbon to the double bond. It seems as if **25** and **29** “remember” how they were formed before they go on to give the second step. Such effects are called *memory effects* and other such cases are known.⁴¹ The causes of these effects are not well understood, though there has been much discussion. One possible cause is differential solvation of the apparently identical ions **25** and **29**. Other possibilities are: (1) that the ions have geometrical structures that are twisted in opposite senses (e.g., a twisted **29** might have its positive carbon



³⁸Le Drian; Vogel *Helv. Chim. Acta* **1987**, 70, 1703, *Tetrahedron Lett.* **1987**, 28, 1523.

³⁹For a review, see Berson *Angew. Chem. Int. Ed. Engl.* **1968**, 7, 779-791 [*Angew. Chem.* **80**, 765-777].

⁴⁰Berson; Poonian; Libbey *J. Am. Chem. Soc.* **1969**, 91, 5567; Berson; Donald; Libbey *J. Am. Chem. Soc.* **1969**, 91, 5580; Berson; Wege; Clarke; Bergman *J. Am. Chem. Soc.* **1969**, 91, 5594, 5601.

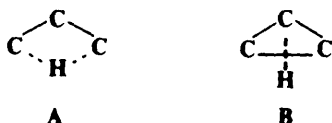
⁴¹For examples of memory effects in other systems, see Berson; Gajewski; Donald *J. Am. Chem. Soc.*, **1969**, 91, 5550; Berson; Luibrand; Kundu; Morris *J. Am. Chem. Soc.* **1971**, 93, 3075; Collins *Acc. Chem. Res.* **1971**, 4, 315-322; Collins; Glover; Eckart; Raaen; Benjamin; Benjaminov *J. Am. Chem. Soc.* **1972**, 94, 899; Svensson *Chem. Scr.* **1974**, 6, 22.

closer to the double bond than a twisted **25**); (2) that ion pairing is responsible;⁴² and (3) that nonclassical carbocations are involved.⁴³ One possibility that has been ruled out is that the steps **24** → **25** → **26** and **28** → **29** → **30** are concerted, so that **25** and **29** never exist at all. This possibility has been excluded by several kinds of evidence, including the fact that **24** gives not only **27**, but also some **31**; and **28** gives some **27** along with **31**. This means that some of the **25** and **29** ions interconvert, a phenomenon known as *leakage*.

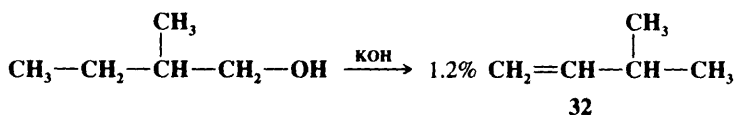
Longer Nucleophilic Rearrangements

The question as to whether a group can migrate with its electron pair from A to C in W—A—B—C or over longer distances has been much debated. Although claims have been made that alkyl groups can migrate in this way, the evidence is that such migration is extremely rare, if it occurs at all. One experiment that demonstrated this was the generation of the 3,3-dimethyl-1-butyl cation $\text{Me}_3\text{CCH}_2\text{CH}_2^+$. If 1,3 methyl migrations are possible, this cation would appear to be a favorable substrate, since such a migration would convert a primary cation into the tertiary 2-methyl-2-pentyl cation $\text{Me}_2\overset{+}{\text{C}}\text{CH}_2\text{CH}_2\text{CH}_3$, while the only possible 1,2 migration (of hydride) would give only a secondary cation. However, no products arising from the 2-methyl-2-pentyl cation were found, the only rearranged products being those formed by the 1,2 hydride migration.⁴⁴ 1,3 Migration of bromine has been reported.⁴⁵

However, most of the debate over the possibility of 1,3 migrations has concerned not methyl or bromine but 1,3 hydride shifts.⁴⁶ There is no doubt that *apparent* 1,3 hydride shifts take place (many instances have been found), but the question is whether they are truly direct hydride shifts or whether they occur by another mechanism. There are at least two ways in which indirect 1,3 hydride shifts can take place: (1) by successive 1,2 shifts or (2) through the intervention of protonated cyclopropanes (see p. 1057). A direct 1,3 shift would have the transition state **A**, while the transition state for a 1,3 shift involving a



protonated cyclopropane intermediate would resemble **B**. The evidence is that most reported 1,3 hydride shifts are actually the result of successive 1,2 migrations,⁴⁷ but that in some cases small amounts of products cannot be accounted for in this way. For example, the reaction of 2-methyl-1-butanol with KOH and bromoform gave a mixture of olefins, nearly all of which could have arisen from simple elimination or 1,2 shifts of hydride or alkyl. However, 1.2% of the product was **32**:⁴⁸



⁴²See Collins *Chem. Soc. Rev.* **1975**, 4, 251-262.

⁴³See, for example, Seybold; Vogel; Saunders; Wiberg *J. Am. Chem. Soc.* **1973**, 95, 2045; Kirmse; Günther *J. Am. Chem. Soc.* **1978**, 100, 3619.

⁴⁴Skell; Reichenbacher *J. Am. Chem. Soc.* **1968**, 90, 2309.

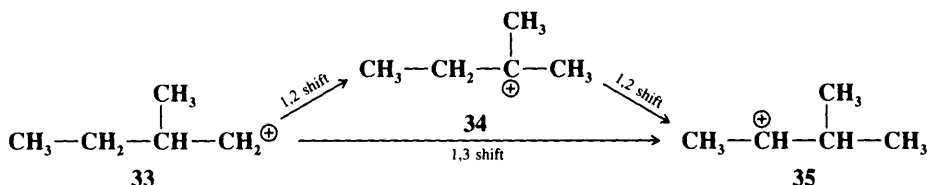
⁴⁵Reineke; McCarthy *J. Am. Chem. Soc.* **1970**, 92, 6376; Smolina; Gopius; Gruzdnova; Reutov *Doklad. Chem.* **1973**, 209, 280.

⁴⁶For a review, see Fry; Karabatsos, in Olah; Schleyer, Ref. 7, vol. 2, pp. 527-566.

⁴⁷For example, see Bundel; Levina; Krzhizhevskii; Reutov *Doklad. Chem.* **1968**, 181, 583; Fărcașiu; Kascheres; Schwartz *J. Am. Chem. Soc.* **1972**, 94, 180; Kirmse; Knist; Ratajczak *Chem. Ber.* **1976**, 109, 2296.

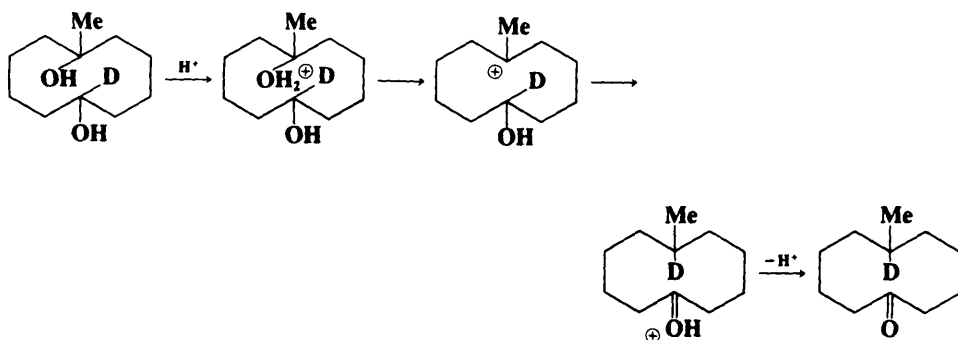
⁴⁸Skell; Maxwell *J. Am. Chem. Soc.* **1962**, 84, 3963. See also Skell; Starer *J. Am. Chem. Soc.* **1962**, 84, 3962.

Hypothetically, **32** could have arisen from a 1,3 shift (direct or through a protonated cyclopropane) or from two successive 1,2 shifts:



However, the same reaction applied to 2-methyl-2-butanol gave no **32**, which demonstrated that **35** was not formed from **34**. The conclusion was thus made that **35** was formed directly from **33**. This experiment does not answer the question as to whether **35** was formed by a direct shift or through a protonated cyclopropane, but from other evidence⁴⁹ it appears that 1,3 hydride shifts that do not result from successive 1,2 migrations usually take place through protonated cyclopropane intermediates (which, as we saw on p. 1056, account for only a small percentage of the product in any case). However, there is evidence that direct 1,3 hydride shifts by way of **A** may take place in super-acid solutions.⁵⁰

Although direct nucleophilic rearrangements over distances greater than 1,2 are rare (or perhaps nonexistent) when the migrating atom or group must move along a chain, this is not so for a shift across a ring of 8 to 11 members. Many such transannular rearrangements are known.⁵¹ Several examples are given on p. 157. This is the mechanism of one of these:⁵²



It is noteworthy that the *methyl* group does not migrate in this system. It is generally true that alkyl groups do not undergo transannular migration.⁵³ In most cases it is hydride that undergoes this type of migration, though a small amount of phenyl migration has also been shown.⁵⁴

⁴⁹For example, see Brouwer; van Doorn *Recl. Trav. Chim. Pays-Bas* **1969**, 8, 573; Dupuy; Goldsmith; Hudson *J. Chem. Soc., Perkin Trans. 2* **1973**, 74; Hudson; Koplick; Poulton *Tetrahedron Lett.* **1975**, 1449; Fry; Karabatsos, *Ref. 46*.

⁵⁰Saunders; Stofko *J. Am. Chem. Soc.* **1973**, 95, 252.

⁵¹For reviews, see Cope; Martin; McKervey *Q. Rev. Chem. Soc.* **1966**, 20, 119-152. For many references, see Blomquist; Buck *J. Am. Chem. Soc.* **1951**, 81, 672.

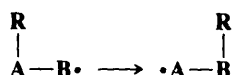
⁵²Prelog; Kung *Helv. Chim. Acta* **1956**, 39, 1394.

⁵³For an apparent exception, see Fărcașiu; Seppo; Kizirian; Ledlie; Sevin *J. Am. Chem. Soc.* **1989**, 111, 8466.

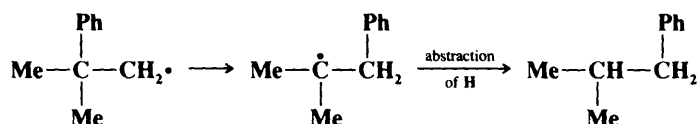
⁵⁴Cope; Burton; Caspar *J. Am. Chem. Soc.* **1962**, 84, 4855.

Free-Radical Rearrangements⁵⁵

1,2-Free-radical rearrangements are much less common than the nucleophilic type previously considered, for the reasons mentioned on p. 1051. Where they do occur, the general pattern is similar. There must first be generation of a free radical, and then the actual migration in which the migrating group moves with one electron:



Finally, the new free radical must stabilize itself by a further reaction. The order of radical stability leads us to predict that here too, as with carbocation rearrangements, any migrations should be in the order primary \rightarrow secondary \rightarrow tertiary, and that the logical place to look for them should be in neopentyl and neophyl systems. The most common way of generating free radicals for the purpose of detection of rearrangements is by decarbonylation of aldehydes (4-41). In this manner it was found that neophyl radicals *do* undergo rearrangement. Thus, $\text{PhCMe}_2\text{CH}_2\text{CHO}$ treated with di-*t*-butyl peroxide gave about equal amounts of the normal product $\text{PhCMe}_2\text{CH}_3$ and the product arising from migration of phenyl:⁵⁶



Many other cases of free-radical migration of aryl groups have been found.⁵⁷

It is noteworthy that the extent of migration is much less than with corresponding carbocations: thus in the example given, there was only about 50% migration, whereas the carbocation would have given much more. Also noteworthy is that there was no migration of the methyl group. In general it may be said that free-radical migration of alkyl groups does not occur at ordinary temperatures. Many attempts have been made to detect such migration on the traditional neopentyl and bornyl types of substrates. However, alkyl migration is not observed, even in substrates where the corresponding carbocations undergo facile rearrangement.⁵⁸ Another type of migration that is very common for carbocations, but not observed for free radicals, is 1,2 migration of hydrogen. We confine ourselves to a few examples of the lack of migration of alkyl groups and hydrogen:

1. 3,3-Dimethylpentanal ($\text{EtCMe}_2\text{CH}_2\text{CHO}$) gave no rearranged products on decarbonylation.⁵⁹

⁵⁵For reviews, see Beckwith; Ingold, in Mayo, Ref. 1, vol. 1, pp. 161-310; Wilt, in Kochi *Free Radicals*, vol. 1; Wiley: New York, 1973, pp. 333-501; Stepukhovich; Babayan *Russ. Chem. Rev.* **1972**, *41*, 750; Nonhebel; Walton *Free-Radical Chemistry*; Cambridge University Press: London, 1974, pp. 498-552; Huyser *Free-Radical Chain Reactions*; Wiley: New York, 1970, pp. 235-255; Freidlina *Adv. Free-Radical Chem.* **1965**, *1*, 211-278; Pryor *Free Radicals*; McGraw-Hill: New York, 1966, pp. 266-284.

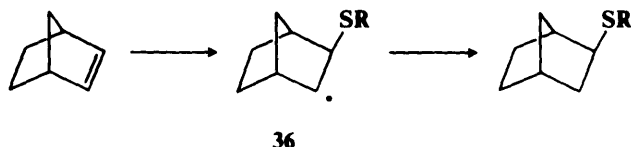
⁵⁶Winstein; Seubold *J. Am. Chem. Soc.* **1947**, *69*, 2916; Seubold *J. Am. Chem. Soc.* **1953**, *75*, 2532. For the observation of this rearrangement by esr, see Hamilton; Fischer *Helv. Chim. Acta* **1973**, *56*, 795.

⁵⁷For example, see Curtin; Hurwitz *J. Am. Chem. Soc.* **1952**, *74*, 5381; Wilt; Philip *J. Org. Chem.* **1959**, *24*, 441, **1960**, *25*, 891; Pines; Goetschel *J. Am. Chem. Soc.* **1964**, *87*, 4207; Goerner; Cote; Vittimberga *J. Org. Chem.* **1977**, *42*, 19; Collins; Roark; Raaen; Benjamin *J. Am. Chem. Soc.* **1979**, *101*, 1877; Walter; McBride *J. Am. Chem. Soc.* **1981**, *103*, 7069, 7074.

⁵⁸For a summary of unsuccessful attempts, see Slaugh; Magoon; Guinn *J. Org. Chem.* **1963**, *28*, 2643.

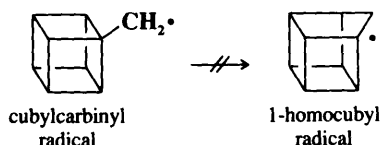
⁵⁹Seubold *J. Am. Chem. Soc.* **1954**, *76*, 3732.

2. Addition of RSH to norbornene gave only *exo*-norbornyl sulfides, though **36** is an



intermediate, and the corresponding carbocation cannot be formed without rearrangement.⁶⁰

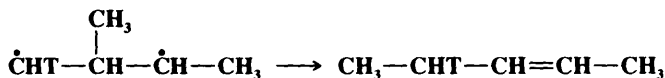
3. The cubylcarbiny radical did not rearrange to the 1-homocubyl radical, though doing



so would result in a considerable decrease in strain.^{60a}

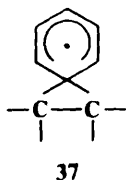
4. It was shown⁶¹ that no rearrangement of isobutyl radical to *t*-butyl radical (which would involve the formation of a more stable radical by a hydrogen shift) took place during the chlorination of isobutane.

However, 1,2 migration of alkyl groups has been shown to occur in certain *diradicals*.⁶² For example, the following rearrangement has been established by tritium labeling.⁶³



In this case the fact that migration of the methyl group leads directly to a compound in which all electrons are paired undoubtedly contributes to the driving force of the reaction.

The fact that aryl groups migrate, but alkyl groups and hydrogen generally do not, leads to the proposition that **37**, in which the odd electron is not found in the three-membered



ring, may be an intermediate. There has been much controversy on this point, but the bulk of the evidence indicates that **37** is a transition state, not an intermediate.⁶⁴ Among the

⁶⁰Cristol; Brindell *J. Am. Chem. Soc.* **1954**, 76, 5699.

^{60a}Eaton; Yip *J. Am. Chem. Soc.* **1991**, 113, 7692.

⁶¹Brown; Russell *J. Am. Chem. Soc.* **1952**, 74, 3995. See also Desai; Nechvtal; Tedder *J. Chem. Soc. B.* **1970**, 386.

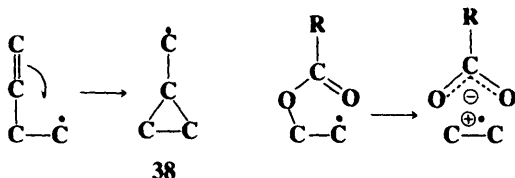
⁶²For a review, see Freidlina; Terent'ev *Russ. Chem. Rev.* **1974**, 43, 129-139.

⁶³McKnight; Rowland *J. Am. Chem. Soc.* **1966**, 88, 3179. For other examples, see Greene; Adam; Knudsen *J. Org. Chem.* **1966**, 31, 2087; Gajewski; Burka *J. Am. Chem. Soc.* **1972**, 94, 8857, 8860, 8865; Adam; Aponte *J. Am. Chem. Soc.* **1971**, 93, 4300.

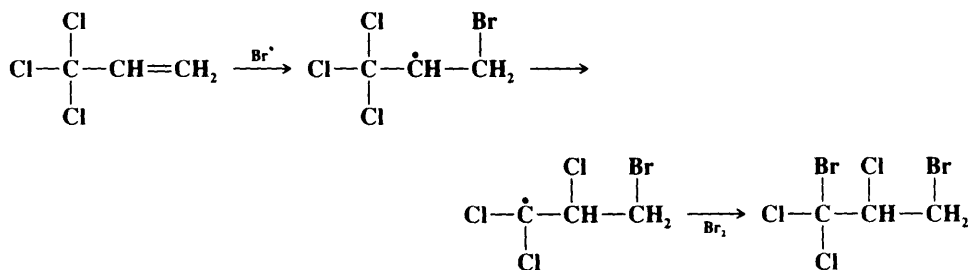
⁶⁴For molecular orbital calculations indicating that **37** is an intermediate, see Yamabe *Chem. Lett.* **1989**, 1523.

evidence is the failure to observe **37** either by esr⁶⁵ or CIDNP.⁶⁶ Both of these techniques can detect free radicals with extremely short lifetimes (pp. 186-187).⁶⁷

Besides aryl, vinylic⁶⁸ and acetoxy groups⁶⁹ also migrate. Vinylic groups migrate by way of a cyclopropylcarbinyl radical intermediate,⁷⁰ while the migration of acetoxy groups may involve the charge-separated structure shown.⁷¹ In addition, migration has been observed



for chloro (and to a much lesser extent bromo) groups. For example, in the reaction of $\text{Cl}_3\text{CCH}=\text{CH}_2$ with bromine under the influence of peroxides, the products were 47% $\text{Cl}_3\text{CCHBrCH}_2\text{Br}$ (the normal addition product) and 53% $\text{BrCCl}_2\text{CHClCH}_2\text{Br}$, which arose by rearrangement:



In this particular case the driving force for the rearrangement is the particular stability of dichloroalkyl free radicals. Nesmeyanov, Freidlina, and co-workers have extensively studied reactions of this sort.⁷² It has been shown that the 1,2 migration of Cl readily occurs if the migration origin is tertiary and the migration terminus primary.⁷³ Migration of Cl and Br could take place by a transition state in which the odd electron is accommodated in a vacant *d* orbital of the halogen.

⁶⁵Kochi; Krusic *J. Am. Chem. Soc.* **1969**, *91*, 3940; Edge; Kochi *J. Am. Chem. Soc.* **1972**, *94*, 7695.

⁶⁶Shevlin; Hansen *J. Org. Chem.* **1977**, *42*, 3011; Olah; Krishnamurthy; Singh; Iyer *J. Org. Chem.* **1983**, *48*, 955. **37** has been detected as an intermediate in a different reaction: Effio; Griller; Ingold; Scaiano; Sheng *J. Am. Chem. Soc.* **1980**, *102*, 6063; Leardini; Nanni; Pedulli; Tundo; Zanardi; Foresti; Palmieri *J. Am. Chem. Soc.* **1989**, *111*, 7723.

⁶⁷For other evidence, see Martin *J. Am. Chem. Soc.* **1962**, *84*, 1986; Rüchardt; Hecht *Tetrahedron Lett.* **1962**, 957; *Chem. Ber.* **1965**, *98*, 2460, 2471; Rüchardt; Trautwein *Chem. Ber.* **1965**, *98*, 2478.

⁶⁸For example, see Slauch; Mullineaux; Raley *J. Am. Chem. Soc.* **1963**, *85*, 3180; Slauch *J. Am. Chem. Soc.* **1965**, *87*, 1522; Newcomb; Glenn; Williams *J. Org. Chem.* **1969**, *34*, 2675.

⁶⁹Surzur; Teissier *C. R. Acad. Sci., Ser. C* **1967**, *264*, 1981; *Bull. Soc. Chim. Fr.* **1970**, 3060; Tanner; Law *J. Am. Chem. Soc.* **1969**, *91*, 7535; Julia; Lorne *C. R. Acad. Sci., Ser. C* **1971**, *273*, 174; Lewis; Miller; Winstein *J. Org. Chem.* **1972**, *37*, 1478.

⁷⁰For evidence for this species, see Montgomery; Matt; Webster *J. Am. Chem. Soc.* **1967**, *89*, 923; Montgomery; Matt *J. Am. Chem. Soc.* **1967**, *89*, 934, 6556; Giese; Heinrich; Horler; Koch; Schwarz *Chem. Ber.* **1986**, *119*, 3528.

⁷¹Beckwith; Tindal *Aust. J. Chem.* **1971**, *24*, 2099; Beckwith; Thomas *J. Chem. Soc., Perkin Trans. 2* **1973**, 861; Barclay; Lusztzyk; Ingold *J. Am. Chem. Soc.* **1984**, *106*, 1793.

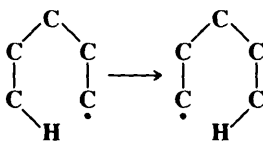
⁷²For reviews, see Freidlina; Terent'ev *Russ. Chem. Rev.* **1979**, *48*, 828-839; Freidlina, Ref. 55, pp. 231-249.

⁷³See, for example, Skell; Pavlis; Lewis; Shea *J. Am. Chem. Soc.* **1973**, *95*, 6735; Chen; Tang; Montgomery; Kochi *J. Am. Chem. Soc.* **1974**, *96*, 2201.

Migratory aptitudes have been measured for the phenyl and vinyl groups, and for three other groups, using the system $\text{RCMe}_2\text{CH}_2^\bullet \rightarrow \text{Me}_2\dot{\text{C}}\text{CH}_2\text{R}$. These were found to be in the order $\text{R} = \text{H}_2\text{C}=\text{CH}_2 > \text{Me}_3\text{CC}=\text{O} > \text{Ph} > \text{Me}_3\text{C}\equiv\text{C} > \text{CN}$.⁷⁴

In summary then, 1,2 free-radical migrations are much less prevalent than the analogous carbocation processes, and are important only for aryl, vinylic, acetoxy, and halogen migrating groups. The direction of migration is normally toward the more stable radical, but "wrong-way" rearrangements are also known.⁷⁵

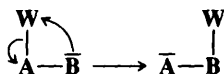
Despite the fact that hydrogen atoms do not migrate 1,2, longer free-radical migrations of hydrogen are known.⁷⁶ The most common are 1,5 shifts, but 1,6 and longer shifts have also been found. The possibility of 1,3 hydrogen shifts has been much investigated, but it is not certain if any actually occur. If they do they are rare, presumably because the most favorable geometry for $\text{C}-\text{H}-\text{C}$ in the transition state is linear and this geometry cannot be achieved in a 1,3 shift. 1,4 shifts are definitely known, but are still not very common. These long shifts are best regarded as internal abstractions of hydrogen (for reactions involving them, see 4-8 and 8-42):



Transannular shifts of hydrogen atoms have also been observed.⁷⁷

Electrophilic Rearrangements⁷⁸

Rearrangements in which a group migrates without its electrons are much rarer than the two kinds previously considered, but the general principles are the same. A carbanion (or other negative ion) is created first, and the actual rearrangement step involves migration of a group without its electrons:



The product of the rearrangement may be stable or may react further, depending on its nature (see also p. 1072).

⁷⁴Lindsay; Luszytk; Ingold *J. Am. Chem. Soc.* **1984**, 106, 7087.

⁷⁵Slaugh; Raley *J. Am. Chem. Soc.* **1960**, 82, 1259; Bonner; Mango *J. Org. Chem.* **1964**, 29, 29; Dannenberg; Dill *Tetrahedron Lett.* **1972**, 1571.

⁷⁶For a discussion, see Freidlina; Terent'ev. *Acc. Chem. Res.* **1977**, 10, 9-15.

⁷⁷Heusler; Kalvoda *Tetrahedron Lett.* **1963**, 1001; Cope; Bly; Martin; Petterson *J. Am. Chem. Soc.* **1965**, 87, 3111; Fisch; Ourisson *Chem. Commun.* **1965**, 407; Traynham; Couvillon *J. Am. Chem. Soc.* **1967**, 89, 3205.

⁷⁸For reviews, see Hunter; Stothers; Warnhoff, in Mayo, Ref. 1, vol. 1, pp. 391-470; Grovenstein *Angew. Chem. Int. Ed. Engl.* **1978**, 17, 313-332 [*Angew. Chem.* **90**, 317-336], *Adv. Organomet. Chem.* **1977**, 16, 167-193; Jensen; Rickborn *Electrophilic Substitution of Organomercurials*; McGraw-Hill: New York, 1968, pp. 21-30; Cram *Fundamentals of Carbanion Chemistry*; Academic Press: New York, 1965, pp. 223-243.

REACTIONS

The reactions in this chapter are classified into three main groups. 1,2 shifts are considered first. Within this group, reactions are classified according to (1) the identity of the substrate atoms A and B and (2) the nature of the migrating group W. In the second group are the cyclic rearrangements. The third group consists of rearrangements that cannot be fitted into either of the first two categories.

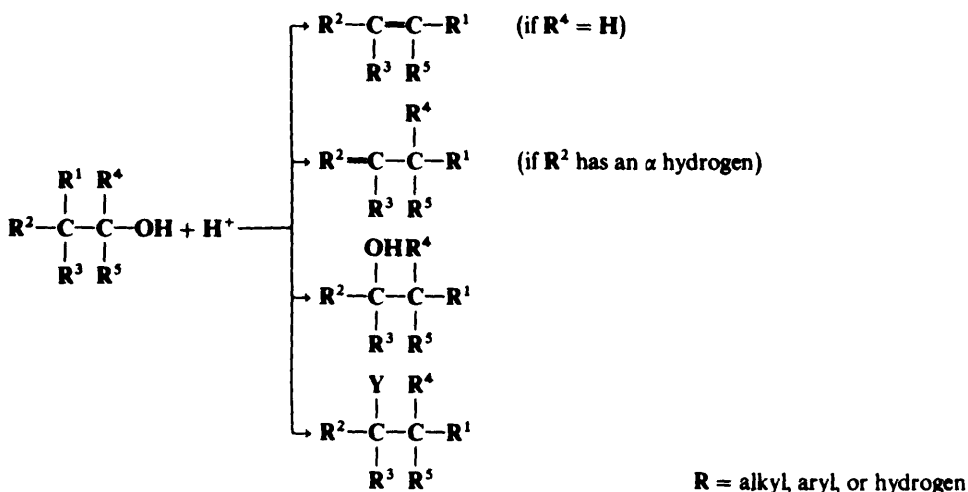
Reactions in which the migration terminus is on an aromatic ring have been treated under aromatic substitution. These are **1-30** to **1-36**, **1-40**, **3-25** to **3-28**, and, partially, **1-37**, **1-41**, and **1-42**. Double-bond shifts have also been treated in other chapters, though they may be considered rearrangements (p. 327, p. 577, and 2-2). Other reactions that may be regarded as rearrangements are the Pummerer (**9-71**) and Willgerodt (**9-72**) reactions.

1,2 Rearrangements

A. Carbon-to-Carbon Migrations of R, H, and Ar

8-1 Wagner–Meerwein and Related Reactions

1/Hydro,1/hydroxy-(2/→1/alkyl)-migr-o-elimination, etc.

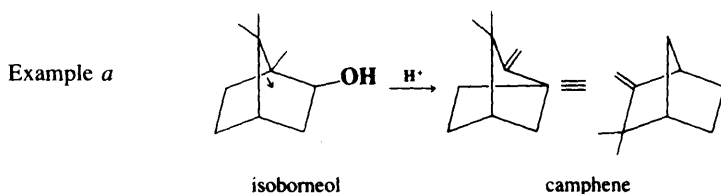


When alcohols are treated with acids, simple substitution (e.g., **0-67**) or elimination (**7-1**) usually accounts for most or all of the products. But in many cases, especially where two or three alkyl or aryl groups are on the β carbon, some or all of the product is rearranged. These rearrangements are called *Wagner–Meerwein rearrangements*. As pointed out previously, the carbocation that is a direct product of the rearrangement must stabilize itself, and most often it does this by the loss of a hydrogen β to it, so the rearrangement product is usually an olefin.⁷⁹ The proton lost may be R^4 (if this is a hydrogen) or an α proton from R^2 (if it has one). If there is a choice of protons, Zaitsev's rule (p. 998) governs the direction, as we might expect. Sometimes a different positive group is lost instead of a proton. Less

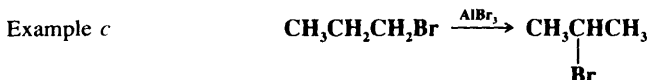
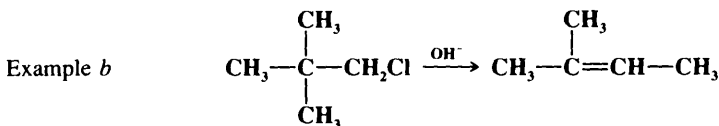
⁷⁹For a review of such rearrangements, see Kaupp *Top. Curr. Chem.* **1988**, *146*, 57-98.

often, the new carbocation stabilizes itself by combining with a nucleophile instead of losing a proton. The nucleophile may be the water which is the original leaving group, so that the product is a rearranged alcohol, or it may be some other species present, which we have called Y. Rearrangement is usually predominant in neopentyl and neophyl types of substrates, and with these types normal nucleophilic substitution is difficult (normal elimination is of course impossible). Under S_N2 conditions, substitution is extremely slow;⁸⁰ under S_N1 conditions, carbocations are formed that rapidly rearrange. However, free-radical substitution, unaccompanied by rearrangement, can be carried out on neopentyl systems, though, as we have seen (p. 1064), neophyl systems undergo rearrangement as well as substitution.

Wagner–Meerwein rearrangements were first discovered in the bicyclic terpenes, and most of the early development of this reaction was with these compounds.⁸¹ An example is

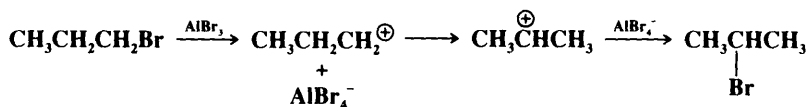


Examples in simpler systems are:



These examples illustrate the following points:

1. Hydride ion can migrate. In example *c*, it was hydride that shifted, not bromine:



2. The leaving group does not have to be H_2O , but can be any departing species whose loss creates a carbocation, including N_2 from aliphatic diazonium ions⁸² (see the section on leaving groups in nucleophilic substitution, p. 352). Also, rearrangement may follow when the carbocation is created by addition of a proton or other positive species to a double bond. Even alkanes give rearrangements when heated with Lewis acids, provided some species is initially present to form a carbocation from the alkane.

⁸⁰See, however, Ref. 248 in Chapter 10.

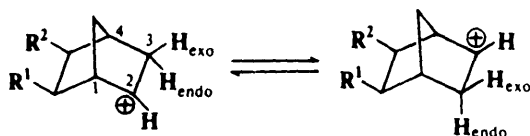
⁸¹For a review of rearrangements in bicyclic systems, see Hogeveen; van Kruchten *Top. Curr. Chem.* **1979**, *80*, 89-124. For reviews concerning caranes and pinanes see, respectively, Arbuzov; Isaeva *Russ. Chem. Rev.* **1976**, *45*, 673-683; Banthorpe; Whittaker *Q. Rev. Chem. Soc.* **1966**, *20*, 373-387.

⁸²For reviews of rearrangements arising from diazotization of aliphatic amines, see, in Patai *The Chemistry of the Amino Group*; Wiley: New York, 1968, the articles by White; Woodcock, pp. 407-497 (pp. 473-483) and by Banthorpe, pp. 585-667 (pp. 586-612).

3. Example *c* illustrates that the last step can be substitution instead of elimination.

4. Example *b* illustrates that the new double bond is formed in accord with Zaitsev's rule.

2-Norbornyl cations, besides displaying the 1,2 shifts of a CH₂ group previously illustrated for the isoborneol → camphene conversion, are also prone to rapid hydride shifts from the 3 to the 2 position (known as 3,2 shifts). These 3,2 shifts usually take place from the exo

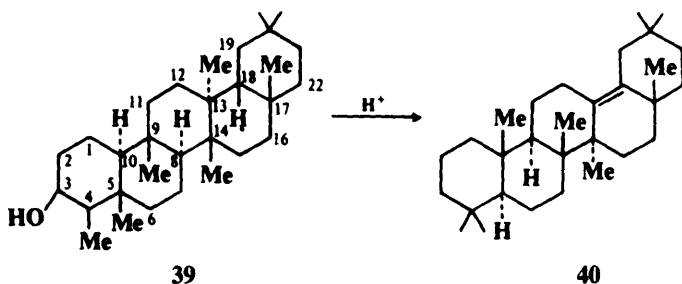


side;⁸³ that is, the 3-exo hydrogen migrates to the 2-exo position.⁸⁴ This stereoselectivity is analogous to the behavior we have previously seen for norbornyl systems, namely, that nucleophiles attack norbornyl cations from the exo side (p. 321) and that addition to norbornenes is also usually from the exo direction (p. 753).

The direction of rearrangement is usually towards the most stable carbocation (or radical), which is tertiary > secondary > primary, but rearrangements in the other direction have also been found,⁸⁵ and often the product is a mixture corresponding to an equilibrium mixture of the possible carbocations.

The term "Wagner-Meerwein rearrangement" is not precise. Some use it to refer to all the rearrangements in this section and in 8-2. Others use it only when an alcohol is converted to a rearranged olefin. Terpene chemists call the migration of a methyl group the *Nametkin rearrangement*. The term *retropinacol rearrangement* is often applied to some or all of these. Fortunately, this disparity in nomenclature does not seem to cause much confusion.

Sometimes several of these rearrangements occur in one molecule, either simultaneously or in rapid succession. A spectacular example is found in the triterpene series. Friedelin is a triterpenoid ketone found in cork. Reduction gives 3β-friedelanol (**39**). When this compound is treated with acid, 13(18)-oleanene (**40**) is formed.⁸⁶ In this case *seven* 1,2 shifts take place. On removal of H₂O from position 3 to leave a positive charge, the following



shifts occur: hydride from 4 to 3; methyl from 5 to 4; hydride from 10 to 5; methyl from 9 to 10; hydride from 8 to 9; methyl from 14 to 8; and methyl from 13 to 14. This leaves a

⁸³For example, see Kleinfelter; Schleyer *J. Am. Chem. Soc.* **1961**, 83, 2329; Collins; Cheema; Werth; Benjamin *J. Am. Chem. Soc.* **1964**, 86, 4913; Berson; Hammons; McRowe; Bergman; Remanick; Houston *J. Am. Chem. Soc.* **1967**, 89, 2590.

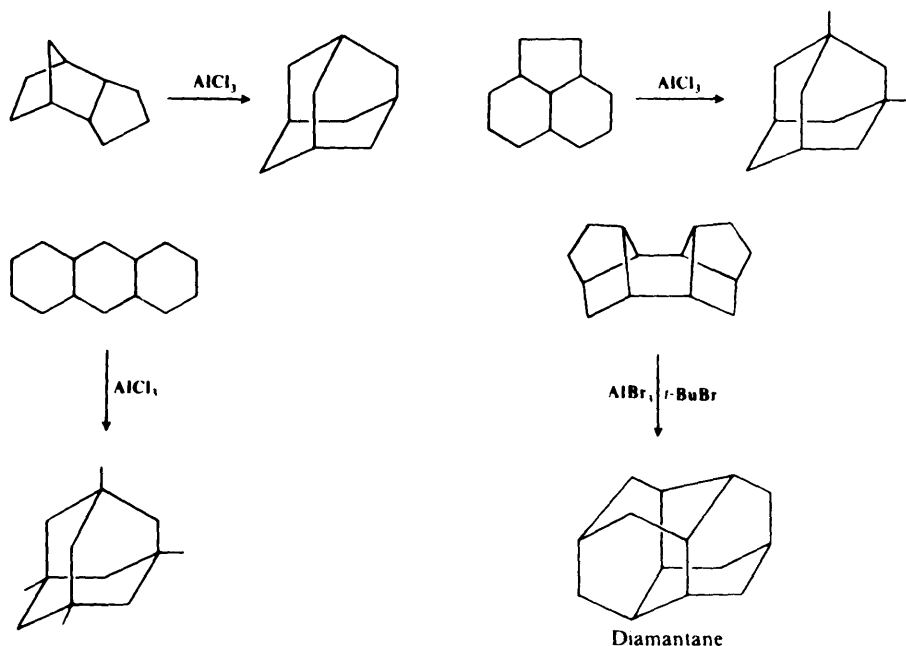
⁸⁴For examples of 3,2 endo shifts, see Bushell; Wilder *J. Am. Chem. Soc.* **1967**, 89, 5721; Wilder; Hsieh *J. Org. Chem.* **1971**, 36, 2552.

⁸⁵See, for example, Cooper et al., Ref. 23.

⁸⁶Corey; Ursprung *J. Am. Chem. Soc.* **1956**, 78, 5041.

positive charge at position 13, which is stabilized by loss of the proton at the 18 position to give **40**. All these shifts are stereospecific, the group always migrating on the side of the ring system on which it is located; that is, a group above the "plane" of the ring system (indicated by a solid line in **39**) moves above the plane, and a group below the plane (dashed line) moves below it. It is probable that the seven shifts are not all concerted, though some of them may be, for intermediate products can be isolated.⁸⁷ As an illustration of point 2 (p. 1069), it may be mentioned that friedelene, derived from dehydration of **39**, also gives **40** on treatment with acid.⁸⁸

It was mentioned above that even alkanes undergo Wagner–Meerwein rearrangements if treated with Lewis acids and a small amount of initiator. An interesting application of this reaction is the conversion of tricyclic molecules to adamantane and its derivatives.⁸⁹ It has been found that *all* tricyclic alkanes containing 10 carbons are converted to adamantane by treatment with a Lewis acid such as AlCl_3 . If the substrate contains more than 10 carbons, alkyl-substituted adamantanes are produced. The IUPAC name for these reactions is **Schleyer adamantization**. Some examples are



If 14 or more carbons are present, the product may be diamantane or a substituted diamantane.⁹⁰ These reactions are successful because of the high thermodynamic stability of adamantane, diamantane, and similar diamond-like molecules. The most stable of a set of C_nH_m isomers (called the *stabilomer*) will be the end product if the reaction reaches equi-

⁸⁷For a discussion, see Whitlock; Olson *J. Am. Chem. Soc.* **1970**, 92, 5383.

⁸⁸Dutler; Jeger; Ruzicka *Helv. Chim. Acta* **1955**, 38, 1268; Brownlie; Spring; Stevenson; Strachan *J. Chem. Soc.* **1956**, 2419; Coates *Tetrahedron Lett.* **1967**, 4143.

⁸⁹For reviews, see McKervey; Rooney, in *Olah Cage Hydrocarbons*; Wiley: New York, 1990, pp. 39-64; McKervey *Tetrahedron* **1980**, 36, 971-992; *Chem. Soc. Rev.* **1974**, 3, 479-512; Greenberg; Liebman *Strained Organic Molecules*; Academic Press: New York, 1978, pp. 178-202; Bingham; Schleyer, *Fortschr. Chem. Forsch.* **1971**, 18, 1-102, pp. 3-23.

⁹⁰See Gund; Osawa; Williams; Schleyer *J. Org. Chem.* **1974**, 39, 2979.

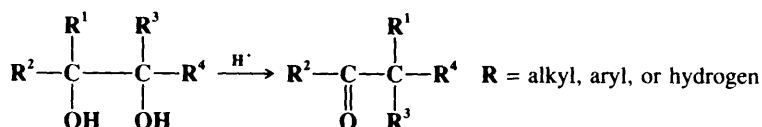
librium.⁹¹ Best yields are obtained by the use of "sludge" catalysts⁹² (i.e., a mixture of AlX_3 and *t*-butyl bromide or *sec*-butyl bromide).⁹³ Though it is certain that these adamantane-forming reactions take place by nucleophilic 1,2 shifts, the exact pathways are not easy to unravel because of their complexity.⁹⁴ Treatment of adamantane-2- ^{14}C with AlCl_3 results in total carbon scrambling on a statistical basis.⁹⁵

As already indicated, the mechanism of the Wagner–Meerwein rearrangement is usually nucleophilic. Free-radical rearrangements are also known (see the mechanism section of this chapter), though virtually only with aryl migration. However, carbanion mechanisms (electrophilic) have also been found.⁷⁸ Thus $\text{Ph}_3\text{CCH}_2\text{Cl}$ treated with sodium gave $\text{Ph}_2\text{CHCH}_2\text{Ph}$ along with unrearranged products.⁹⁶ This is called the *Grovenstein–Zimmerman rearrangement*. The intermediate is $\text{Ph}_3\text{C}\bar{\text{C}}\text{H}_2^-$, and the phenyl moves without its electron pair. Only aryl and vinylic,⁹⁷ and not alkyl, groups migrate by the electrophilic mechanism (p. 1051) and transition states or intermediates analogous to **37** and **38** are likely.⁹⁸

OS V, 16, 194; VI, 378, 845.

8-2 The Pinacol Rearrangement

1/O-Hydro,3/hydroxy-(2/→3/alkyl)-migr-o-elimination



When *vic*-diols (glycols) are treated with acids, they can be rearranged to give aldehydes or ketones, though elimination without rearrangement can also be accomplished. This reaction is called the *pinacol rearrangement*; the reaction gets its name from the typical compound pinacol $\text{Me}_2\text{COHCOHMe}_2$, which is rearranged to pinacolone $\text{Me}_3\text{CCOCH}_3$.⁹⁹ The reaction has been accomplished many times, with alkyl, aryl, hydrogen, and even ethoxycarbonyl (COOEt)¹⁰⁰ as migrating groups. In most cases each carbon has at least one alkyl or aryl group, and the reaction is most often carried out with tri- and tetrasubstituted glycols. As mentioned earlier, glycols in which the four R groups are not identical can give rise to more than one product, depending on which group migrates (see p. 1058 for a discussion of migratory aptitudes). Mixtures are often produced, and which group preferentially migrates

⁹¹For a method for the prediction of stabilomers, see Godleski; Schleyer; Ōsawa; Wipke *Prog. Phys. Org. Chem.* **1981**, 13, 63-117.

⁹²Schneider; Warren; Janoski *J. Org. Chem.* **1966**, 31, 1617; Williams; Schleyer; Gleicher; Rodewald *J. Am. Chem. Soc.* **1966**, 88, 3862; Robinson; Tarratt *Tetrahedron Lett.* **1968**, 5.

⁹³For other methods, see Johnston; McKerver; Rooney *J. Am. Chem. Soc.* **1971**, 93, 2798; Olah; Wu; Farooq; Prakash *J. Org. Chem.* **1989**, 54, 1450.

⁹⁴See, for example, Engler; Farcasiu; Sevin; Cense; Schleyer *J. Am. Chem. Soc.* **1973**, 95, 5769; Klester; Ganter *Helv. Chim. Acta* **1983**, 66, 1200, **1985**, 68, 734.

⁹⁵Majerski; Liggero; Schleyer; Wolf *Chem. Commun.* **1970**, 1596.

⁹⁶Grovenstein *J. Am. Chem. Soc.* **1957**, 79, 4985; Zimmerman; Smentowski *J. Am. Chem. Soc.* **1957**, 79, 5455; Grovenstein; Williams *J. Am. Chem. Soc.* **1961**, 83, 412; Zimmerman; Zweig *J. Am. Chem. Soc.* **1961**, 83, 1196. See also Crimmins; Murphy; Hauser *J. Org. Chem.* **1966**, 31, 4273; Grovenstein; Cheng *J. Am. Chem. Soc.* **1972**, 94, 4971.

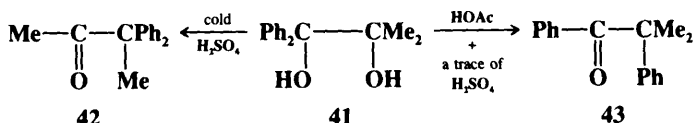
⁹⁷See Grovenstein; Black; Goel; Hughes; Northrop; Streeter; VanDerveer *J. Org. Chem.* **1989**, 54, 1671, and references cited therein.

⁹⁸Grovenstein; Wentworth *J. Am. Chem. Soc.* **1967**, 89, 2348; Bertrand; Grovenstein; Lu; VanDerveer *J. Am. Chem. Soc.* **1976**, 98, 7835.

⁹⁹For reviews, see Bartók; Molnár, in Patai *The Chemistry of Functional Groups, Supplement E*; Wiley: New York, 1980, pp. 722-732; Collins; Eastham, Ref. 1, pp. 762-771.

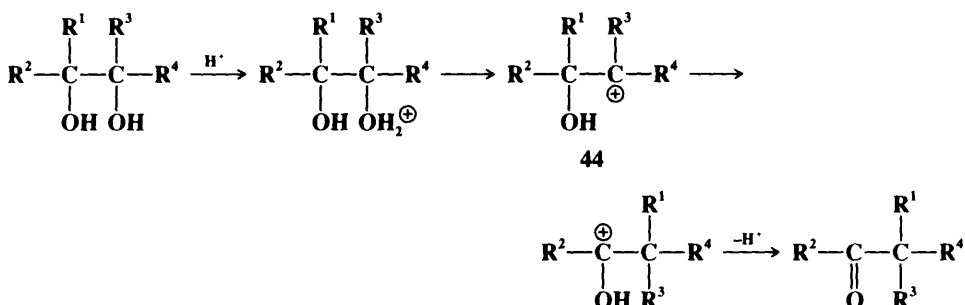
¹⁰⁰Kagan; Agdeppa; Mayers; Singh; Walters; Wintermute *J. Org. Chem.* **1976**, 41, 2355. COOH has been found to migrate in a Wagner–Meerwein reaction: Berner; Cox; Dahn *J. Am. Chem. Soc.* **1982**, 104, 2631.

may depend on the reaction conditions as well as on the nature of the substrate. Thus the action of cold, concentrated sulfuric acid on **41** produces mainly the ketone **42** (methyl



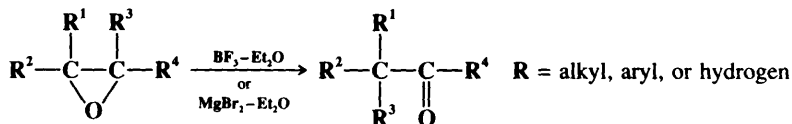
migration), while treatment of **41** with acetic acid containing a trace of sulfuric acid gives mostly **43** (phenyl migration).¹⁰¹ If at least one R is hydrogen, aldehydes can be produced as well as ketones. Generally, aldehyde formation is favored by the use of mild conditions (lower temperatures, weaker acids), because under more drastic conditions the aldehydes may be converted to ketones (**8-4**). The reaction has been carried out in the solid state, by treating solid substrates with HCl gas or with an organic solid acid.¹⁰²

The mechanism involves a simple 1,2 shift. The ion **44** (where all four R groups are Me)



has been trapped by the addition of tetrahydrothiophene.¹⁰³ It may seem odd that a migration takes place when the positive charge is already at a tertiary position, but carbocations stabilized by an oxygen atom are even more stable than tertiary alkyl cations (p. 170). There is also the driving force supplied by the fact that the new carbocation can immediately stabilize itself by losing a proton.

It is obvious that other compounds in which a positive charge can be placed on a carbon α to one bearing an OH group can also give this rearrangement. This is true for β -amino alcohols, which rearrange on treatment with nitrous acid (this is called the *semipinacol* rearrangement), iodohydrins, for which the reagent is mercuric oxide or silver nitrate, β -hydroxyalkyl selenides $\text{R}^1\text{R}^2\text{C}(\text{OH})\text{C}(\text{SeR}^5)\text{R}^3\text{R}^4$,¹⁰⁴ and allylic alcohols, which can rearrange on treatment with a strong acid that protonates the double bond. A similar rearrangement is given by epoxides, when treated with acidic¹⁰⁵ reagents such as BF_3 -etherate or MgBr_2 -etherate, or sometimes by heat alone.¹⁰⁶ It has been shown that epoxides are



¹⁰¹Ramart-Lucas; Salmon-Legagneur *C. R. Acad. Sci.* **1928**, 188, 1301.

¹⁰²Toda; Shigemasa *J. Chem. Soc., Perkin Trans. I* **1969**, 209.

¹⁰³Bosshard; Baumann; Schetty *Helv. Chim. Acta* **1970**, 53, 1271.

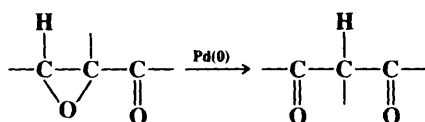
¹⁰⁴For a review, see Krief; Laboureur; Dumont; Labar *Bull. Soc. Chim. Fr.* **1990**, 681-696.

¹⁰⁵Epoxides can also be rearranged with basic catalysts, though the products are usually different. For a review, see Yandovskii; Ershov *Russ. Chem. Rev.* **1972**, 41, 403, 410.

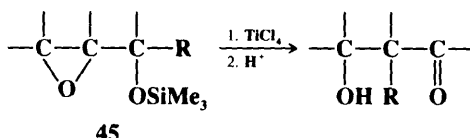
¹⁰⁶For a list of reagents that accomplish this transformation, with references, see Larock *Comprehensive Organic Transformations*; VCH: New York, 1989, p. 628.

intermediates in the pinacol rearrangements of certain glycols.¹⁰⁷ Among the evidence for the mechanism given is that $\text{Me}_2\text{COHCOHMe}_2$, $\text{Me}_2\text{COHCNH}_2\text{Me}_2$, and $\text{Me}_2\text{COHCClMe}_2$ gave the reaction at different rates (as expected) but yielded the *same mixture* of two products—pinacol and pinacolone—indicating a common intermediate.¹⁰⁸

Epoxides can also be rearranged to aldehydes or ketones on treatment with certain metallic catalysts.¹⁰⁹ A good way to prepare β -diketones consists of heating α,β -epoxy ketones at 80–140°C in toluene with small amounts of $(\text{Ph}_3\text{P})_4\text{Pd}$ and 1,2-bis(diphenylphosphino)ethane.¹¹⁰



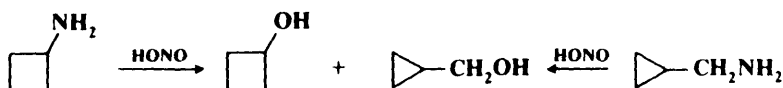
β -Hydroxy ketones can be prepared by treating the silyl ethers (45) of α,β -epoxy alcohols with TiCl_4 .¹¹¹



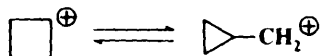
OS I, 462; II, 73, 408; III, 312; IV, 375, 957; V, 326, 647; VI, 39, 320; VII, 129. See also OS VII, 456.

8-3 Expansion and Contraction of Rings

Demyanov ring contraction; Demyanov ring expansion



When a positive charge is formed on an alicyclic carbon, migration of an alkyl group can take place to give ring contraction, producing a ring that is one carbon smaller than the original



Note that this change involves conversion of a secondary to a primary carbocation. In a similar manner, when a positive charge is placed on a carbon α to an alicyclic ring, ring

¹⁰⁷See, for example, Matsumoto *Tetrahedron* **1968**, 24, 6851; Pocker; Ronald *J. Am. Chem. Soc.* **1970**, 92, 3385. *J. Org. Chem.* **1970**, 35, 3362; Tamura; Moriyoshi *Bull. Chem. Soc. Jpn.* **1974**, 47, 2942.

¹⁰⁸Pocker *Chem. Ind. (London)* **1959**, 332. See also Herlihy *Aust. J. Chem.* **1981**, 34, 107.

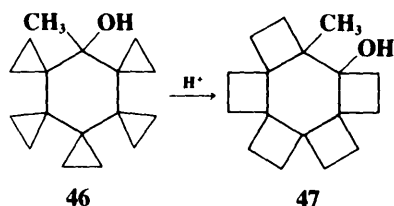
¹⁰⁹For example, see Alper; Des Roches; Durst; Legault *J. Org. Chem.* **1976**, 41, 3611; Milstein; Buchman; Blum *J. Org. Chem.* **1977**, 42, 2299; Prandi; Namy; Menoret; Kagan *J. Organomet. Chem.* **1985**, 285, 449; Miyashita; Shimada; Sugawara; Nohira *Chem. Lett.* **1986**, 1323; Maruoka; Nagahara; Ooi; Yamamoto *Tetrahedron Lett.* **1989**, 30, 5607.

¹¹⁰Suzuki; Watanabe; Noyori *J. Am. Chem. Soc.* **1980**, 102, 2095.

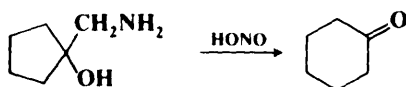
¹¹¹Maruoka; Hasegawa; Yamamoto; Suzuki; Shimazaki; Tsuchihashi *J. Am. Chem. Soc.* **1986**, 108, 3827. For a different rearrangement of 45, see Maruoka; Ooi; Yamamoto *J. Am. Chem. Soc.* **1989**, 111, 6431.

expansion can take place.¹¹² The new carbocation, and the old one, can then give products by combination with a nucleophile (e.g., the alcohols shown above), or by elimination, so that this reaction is a special case of **8-1**. Often, both rearranged and unrearranged products are formed, so that, for example, cyclobutylamine and cyclopropylmethylamine give similar mixtures of the two alcohols shown above on treatment with nitrous acid (a small amount of 3-buten-1-ol is also produced). When the carbocation is formed by diazotization of an amine, the reaction is called the *Demyanov rearrangement*,¹¹³ but of course similar products are formed when the carbocation is generated in other ways. The expansion reaction has been performed on rings of C₃ to C₈,¹¹⁴ but yields are best with the smaller rings, where relief of small-angle strain provides a driving force for the reaction. The contraction reaction has been applied to four-membered rings and to rings of C₆ to C₈, but contraction of a cyclopentyl cation to a cyclobutylmethyl system is generally not feasible because of the additional strain involved. Strain is apparently much less of a factor in the cyclobutyl-cyclopropylmethyl interconversion (for a discussion of this interconversion, see p. 323).

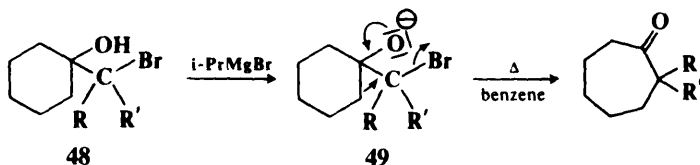
An interesting example of a cascade of ring expansions, similar to the friedelin example described in **8-1**, is the conversion of 16-methylpentaspiro[2.0.2.0.2.0.2.1]hexadecan-16-ol (**46**) to 2-methylhexacyclo[12.2.0.0.2.5.0^{5,8}.0^{8,11}.0^{11,14}]hexadecan-1-ol (**47**) on treatment



with *p*-toluenesulfonic acid in acetone–water.¹¹⁵ The student may wish to write out the mechanism as an exercise. Ring expansions of certain hydroxyamines, e.g.,



are analogous to the semipinacol rearrangement (**8-2**). This reaction is called the *Tiffeneau–Demyanov ring expansion*. These have been performed on rings of C₄ to C₈ and the yields are better than for the simple Demyanov ring expansion. A similar reaction has been used



¹¹²For monographs on ring expansions, see Hesse *Ring Enlargement in Organic Chemistry*; VCH: New York, 1991; Gutsche; Redmore *Carbocyclic Ring Expansion Reactions*; Academic Press: New York, 1968. For a review of ring contractions, see Redmore; Gutsche *Adv. Alicyclic Chem.* **1971**, 3, 1-138. For reviews of ring expansions in certain systems, see Baldwin; Adlington; Robertson *Tetrahedron* **1989**, 45, 909-922; Stach; Hesse *Tetrahedron* **1988**, 44, 1573-1590; Dolbier *Mech. Mol. Migr.* **1971**, 3, 1-66. For reviews of expansions and contractions of three- and four-membered rings, see Salaün, in Rappoport *The Chemistry of the Cyclopropyl Group*, pt. 2; Wiley: New York, 1987, pp. 809-878; Conia; Robson *Angew. Chem. Int. Ed. Engl.* **1975**, 14, 473-485 [*Angew. Chem.* 87, 505-516]. For a list of ring expansions and contractions, with references, see Ref. 106, pp. 630-637.

¹¹³For a review, see Smith; Baer *Org. React.* **1960**, 11, 157-188.

¹¹⁴For a review concerning three-membered rings, see Wong; Hon; Tse; Yip; Tanko; Hudlicky *Chem. Rev.* **1989**, 89, 165-198, pp. 182-186. For a review concerning three- and four-membered rings, see Breslow, in Mayo *Molecular Rearrangements*, vol. 1; Wiley: New York, 1963, pp. 233-294.

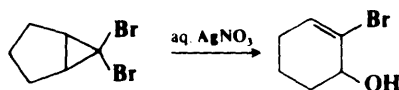
¹¹⁵Fitjer; Wehle; Noltemeyer; Egert; Sheldrick *Chem. Ber.* **1984**, 117, 203. For similar cascade rearrangements, see Giersig; Wehle; Fitjer; Schormann; Clegg *Chem. Ber.* **1988**, 121, 525, and other papers in this series.

to expand rings of from five to eight members.¹¹⁶ In this case, a cyclic bromohydrin of the form **48** is treated with a Grignard reagent which, acting as a base, removes the OH proton to give the alkoxide **49**. Refluxing of **49** brings about the ring enlargement. The reaction has been accomplished for **48** in which at least one R group is phenyl or methyl,¹¹⁷ but fails when both R groups are hydrogen.¹¹⁸

A positive charge generated on a three-membered ring gives "contraction" to an allylic cation.¹¹⁹

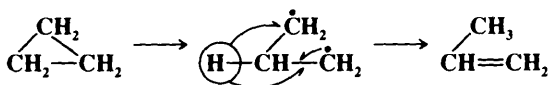


We have previously seen (p. 345) that this is the reason nucleophilic substitutions are not feasible at a cyclopropyl substrate. The reaction is often used to convert cyclopropyl halides and tosylates to allylic products, especially for the purpose of ring expansion, an example being¹²⁰



The stereochemistry of these cyclopropyl cleavages is governed by the principle of orbital symmetry conservation (for a discussion, see p. 1119).

Three-membered rings can also be cleaved to unsaturated products in at least two other ways. (1) On pyrolysis, cyclopropanes can undergo "contraction" to propenes.¹²¹ In the simplest case, cyclopropane gives propene when heated to 400 to 500°C. The mechanism is generally regarded¹²² as involving a diradical intermediate¹²³ (recall that free-radical 1,2



migration is possible for diradicals, p. 1065). (2) The generation of a carbene or carbenoid carbon in a three-membered ring can lead to allenes, and allenes are often prepared in this

¹¹⁶Sisti *Tetrahedron Lett.* **1967**, 5327; *J. Org. Chem.* **1968**, 33, 453. See also Sisti; Vitale *J. Org. Chem.* **1972**, 37, 4090.

¹¹⁷Sisti *J. Org. Chem.* **1970**, 35, 2670; *Tetrahedron Lett.* **1970**, 3305; Sisti; Meyers *J. Org. Chem.* **1973**, 38, 4431; Sisti; Rusch *J. Org. Chem.* **1974**, 39, 1182.

¹¹⁸Sisti *J. Org. Chem.* **1968**, 33, 3953.

¹¹⁹For reviews, see Marvel, Ref. 365, pp. 23-53; Sorensen; Rauk, in Marchand; Lehr *Pericyclic Reactions*, vol. 2; Academic Press: New York, 1977, pp. 1-78.

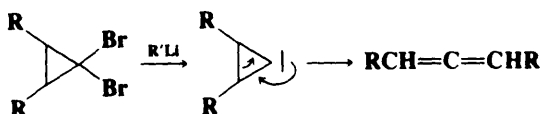
¹²⁰Skell; Sandler *J. Am. Chem. Soc.* **1958**, 80, 2024.

¹²¹For reviews, see Berson, in Mayo, Ref. 1, vol. 1, pp. 324-352, *Ann. Rev. Phys. Chem.* **1977**, 28, 111-132; Bergman, in Kochi, Ref. 55, vol. 1, pp. 191-237; Frey *Adv. Phys. Org. Chem.* **1966**, 4, 147-193, pp. 148-170.

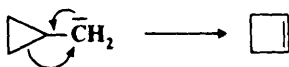
¹²²For evidence that diradical intermediates may not be involved, at least in some cases, see Fields; Haszeldine; Peter *Chem. Commun.* **1967**, 1081; Parry; Robinson *Chem. Commun.* **1967**, 1083; Clifford; Holbrook *J. Chem. Soc., Perkin Trans. 2* **1972**, 1972; Baldwin; Grayston *J. Am. Chem. Soc.* **1974**, 96, 1629, 1630.

¹²³We have seen before that such diradicals can close up to give cyclopropanes (**7-46**). Therefore, pyrolysis of cyclopropanes can produce not only propenes but also isomerized (cis → trans or optically active → inactive) cyclopropanes. See, for example, Berson; Balquist *J. Am. Chem. Soc.* **1968**, 90, 7343; Bergman; Carter *J. Am. Chem. Soc.* **1969**, 91, 7411.

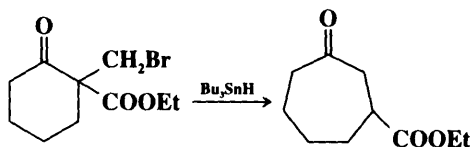
way.¹²⁴ One way to generate such a species is treatment of a 1,1-dihalocyclopropane with an alkyl lithium compound (2-39).¹²⁵ In contrast, the generation of a carbene or carbenoid



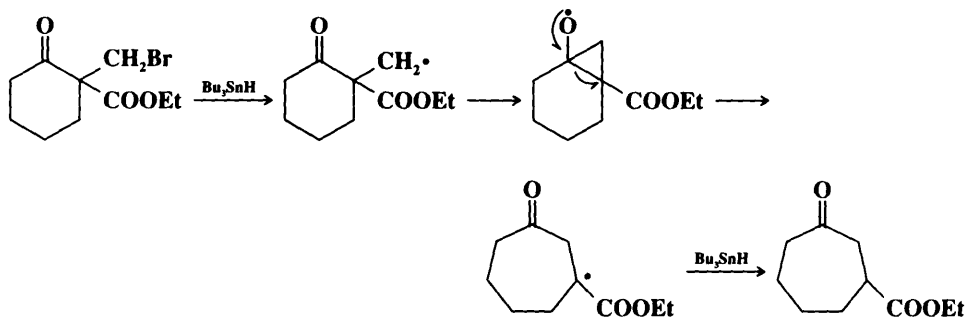
at a cyclopropylmethyl carbon gives ring expansion.¹²⁶



Some free-radical ring enlargements are also known, an example being:¹²⁷



This reaction has been used to make rings of 6, 7, 8, and 13 members. A possible mechanism is:



This reaction has been extended to the expansion of rings by 3 or 4 carbons, by the use of a substrate containing $(\text{CH}_2)_n\text{X}$ ($n = 3$ or 4) instead of CH_2Br .¹²⁸ By this means, 5-, 6-, and 7-membered rings were enlarged to 8- to 11-membered rings.

OS III, 276; IV, 221, 957; V, 306, 320; VI, 142, 187; VII, 12, 114, 117, 129, 135; 65, 17; 67, 210; 68, 220; 69, 220.

¹²⁴For reviews, see Schuster; Coppola *Allenenes in Organic Synthesis*; Wiley: New York, 1984, pp. 20-23; Kirmse *Carbene Chemistry*, 2nd ed.; Academic Press: New York, 1971, pp. 462-467.

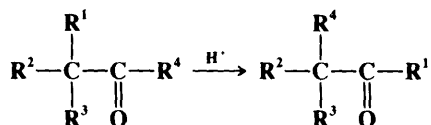
¹²⁵See Baird; Baxter *J. Chem. Soc., Perkin Trans. I* **1979**, 2317, and references cited therein.

¹²⁶For a review, see Gutsche; Redmore, Ref. 112, pp. 111-117.

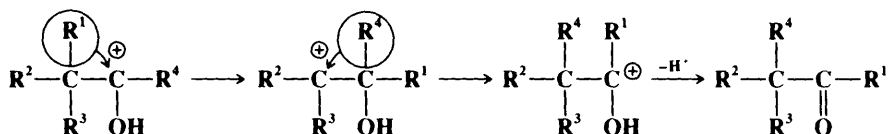
¹²⁷Dowd; Choi *J. Am. Chem. Soc.* **1987**, 109, 3493, *Tetrahedron Lett.* **1991**, 32, 565, *Tetrahedron* **1991**, 47, 4847. For a related ring expansion, see Baldwin; Adlington; Robertson *J. Chem. Soc., Chem. Commun.* **1988**, 1404.

¹²⁸Dowd; Choi *J. Am. Chem. Soc.* **1987**, 109, 6548, *Tetrahedron Lett.* **1991**, 32, 565.

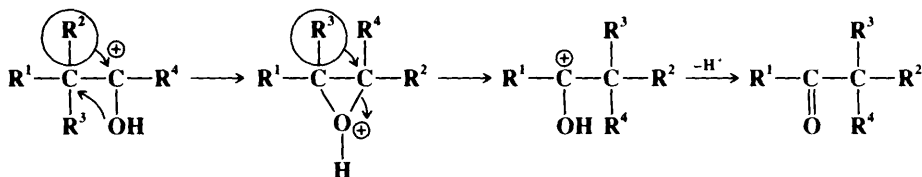
8-4 Acid-Catalyzed Rearrangements of Aldehydes and Ketones 1/Alkyl,2/alkyl-interchange, etc.



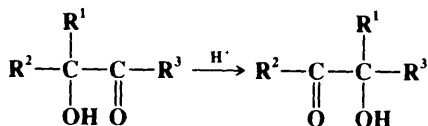
Rearrangements of this type, where a group α to a carbonyl "changes places" with a group attached to the carbonyl carbon, occur when migratory aptitudes are favorable.¹²⁹ R^2 , R^3 , and R^4 may be alkyl or hydrogen. Certain aldehydes have been converted to ketones, and ketones to other ketones (though more drastic conditions are required for the latter), but no rearrangement of a ketone to an aldehyde ($\text{R}^1 = \text{H}$) has so far been reported. There are two mechanisms,¹³⁰ each beginning with protonation of the oxygen and each involving two migrations. In one pathway, the migrations are in opposite directions:¹³¹



In the other pathway the migrations are in the same direction. The actual mechanism of this pathway is not certain, but an epoxide (protonated) intermediate¹³² is one possibility:¹³³



If the reaction is carried out with ketone labeled in the $\text{C}=\text{O}$ group with ^{14}C , the first pathway predicts that the product will contain all the ^{14}C in the $\text{C}=\text{O}$ carbon, while in the second pathway the label will be in the α carbon (demonstrating migration of oxygen). The results of such experiments¹³⁴ have shown that in some cases only the $\text{C}=\text{O}$ carbon was labeled, in other cases only the α carbon, while in still others both carbons bore the label, indicating that in these cases both pathways were in operation. With α -hydroxy aldehydes and ketones, the process may stop after only one migration (this is called the α -ketol rearrangement).



¹²⁹For reviews, see Fry *Mech. Mol. Migr.* **1971**, *4*, 113-196; Collins; Eastham, in Patai, Ref. 1, pp. 771-790.

¹³⁰Favorskii; Chilingaren C. R. *Acad. Sci.* **1926**, 182, 221.

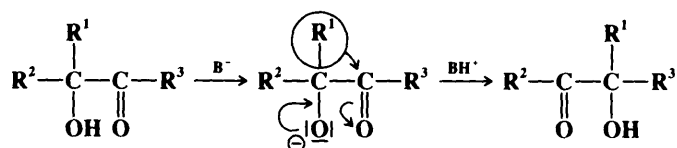
¹³¹Raaen; Collins *J. Am. Chem. Soc.* **1958**, *80*, 1409; Kendrick; Benjamin; Collins *J. Am. Chem. Soc.* **1958**, *80*, 4057; Rothrock; Fry *J. Am. Chem. Soc.* **1958**, *80*, 4349; Collins; Bowman *J. Am. Chem. Soc.* **1959**, *81*, 3614.

¹³²Zook; Smith; Greene *J. Am. Chem. Soc.* **1957**, *79*, 4436.

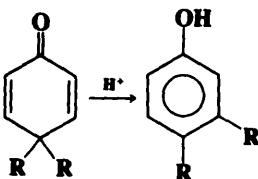
¹³³Some such pathway is necessary to account for the migration of oxygen that is found. It may involve a protonated epoxide, a 1,2-diol, or simply a 1,2 shift of an OH group.

¹³⁴See, for example, Barton; Porter *J. Chem. Soc.* **1956**, 2483; Fry; Carrick; Adams *J. Am. Chem. Soc.* **1958**, *80*, 4743; Zaleskaya; Remizova *J. Gen. Chem. USSR* **1965**, *35*, 29; Fry; Oka *J. Am. Chem. Soc.* **1979**, *101*, 6353.

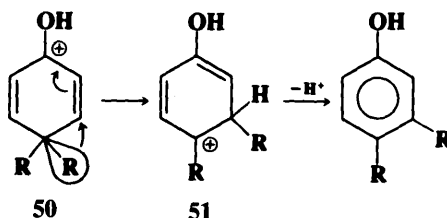
The α -ketol rearrangement can also be brought about by base catalysis, but only if the alcohol is tertiary, since if R^1 or R^2 = hydrogen, enolization of the substrate is more favored than rearrangement.



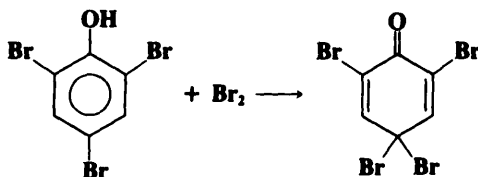
8-5 The Dienone-Phenol Rearrangement 2/C→5/O-Hydro, 1/C→2/C-alkyl-bis-migration



Compounds in which a cyclohexadienone has two alkyl groups in the 4 position undergo, on acid treatment,¹³⁵ 1,2 migration of one of these groups:



The driving force in the overall reaction (the *dienone-phenol rearrangement*) is of course creation of an aromatic system.¹³⁶ It may be noted that **50** and **51** are arenium ions (p. 502), the same as those generated by attack of an electrophile on a phenol.¹³⁷ Sometimes, in the reaction of a phenol with an electrophile, a kind of reverse rearrangement (called the *phenol-dienone rearrangement*) takes place, though without an actual migration.¹³⁸ An example is



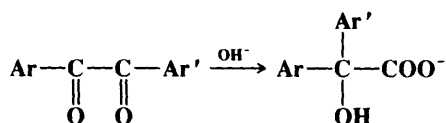
¹³⁵For a reagent that greatly accelerates this reaction, see Chalais; Laszlo; Mathy *Tetrahedron Lett.* **1986**, 27, 2627.

¹³⁶For reviews, see Perkins; Ward *Mech. Mol. Migr.* **1971**, 4, 55-112, pp. 90-103; Miller *Mech. Mol. Migr.* **1968**, 1, 247-313; Shine *Aromatic Rearrangements*; Elsevier: New York, 1967, pp. 55-68; Waring *Adv. Alicyclic Chem.* **1966**, 1, 129-256, pp. 207-223. For a review of other rearrangements of cyclohexadienones, see Miller *Acc. Chem. Res.* **1975**, 8, 245-256.

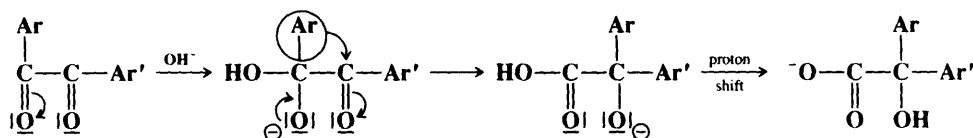
¹³⁷For evidence that these ions are indeed intermediates in this rearrangement, see Vitullo *J. Org. Chem.* **1969**, 34, 224; *J. Org. Chem.* **1970**, 35, 3976; Vitullo; Grossman *J. Am. Chem. Soc.* **1972**, 94, 3844; Planas; Tomás; Bonet *Tetrahedron Lett.* **1987**, 28, 471.

¹³⁸For a review, see Ershov; Volod'kin; Bogdanov *Russ. Chem. Rev.* **1963**, 32, 75-93.

8-6 The Benzil-Benzilic Acid Rearrangement

1/*O*-Hydro,3/oxido-(1→2/aryl)-*migro*-addition

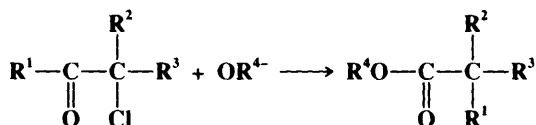
When treated with base, α -diketones rearrange to give the salts of α -hydroxy acids, a reaction known as the *benzil-benzilic acid rearrangement* (benzil is PhCOCOPh ; benzilic acid is $\text{Ph}_2\text{COHCOOH}$).¹³⁹ Though the reaction is usually illustrated with aryl groups, it can also be applied to aliphatic diketones¹⁴⁰ and to α -keto aldehydes. The use of alkoxide ion instead of OH^- gives the corresponding ester directly,¹⁴¹ though alkoxide ions that are readily oxidized (such as OEt^- or OCHMe_2^-) are not useful here, since they reduce the benzil to a benzoin. The mechanism is similar to the rearrangements in 8-1 to 8-4, but there is a difference: The migrating group does not move to a carbon with an open sextet. The carbon makes room for the migrating group by releasing a pair of π electrons from the $\text{C}=\text{O}$ bond to the oxygen. The first step is attack of the base at the carbonyl group, the same as the first step of the tetrahedral mechanism of nucleophilic substitution (p. 331) and of many additions to the $\text{C}=\text{O}$ bond (Chapter 16):



The mechanism has been intensely studied,¹³⁹ and there is much evidence for it.¹⁴² The reaction is irreversible.

OS I, 89.

8-7 The Favorskii Rearrangement

2/*Alkoxy-de-chloro*(2→1/*alkyl*)-*migro*-substitution

The reaction of α -halo ketones (chloro, bromo, or iodo) with alkoxide ions¹⁴³ to give rearranged esters is called the *Favorskii rearrangement*.¹⁴⁴ The use of hydroxide ions or amines

¹³⁹For a review, see Selman; Eastham *Q. Rev. Chem. Soc.* **1960**, *14*, 221-235.

¹⁴⁰For an example, see Schaltegger; Bigler *Helv. Chim. Acta* **1986**, *69*, 1666.

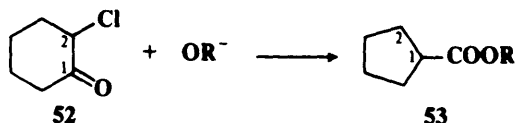
¹⁴¹Doering; Urban *J. Am. Chem. Soc.* **1956**, *78*, 5938.

¹⁴²However, some evidence for an SET pathway has been reported: Screttas; Micha-Screttas; Cazianis *Tetrahedron Lett.* **1983**, *24*, 3287.

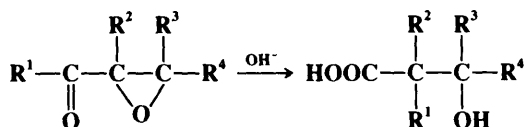
¹⁴³The reaction has also been reported to take place with $\text{BF}_3\text{-MeOH}$ and Ag^+ : Giordano; Castaldi; Casagrande; Abis *Tetrahedron Lett.* **1982**, *23*, 1385.

¹⁴⁴For reviews, see Hunter; Stothers; Warnhoff, in Mayo, Ref. 1, vol. 1, pp. 437-461; Chenier *J. Chem. Educ.* **1978**, *55*, 286-291; Rappe, in Patai *The Chemistry of the Carbon-Halogen Bond*, pt. 2; Wiley: New York, 1973, pp. 1084-1101; Redmore; Gutsche, Ref. 112, pp. 46-69; Akhrem; Ustynyuk; Titov *Russ. Chem. Rev.* **1970**, *39*, 732-746.

as bases leads to the free carboxylic acid (salt) or amide, respectively, instead of the ester. Cyclic α -halo ketones give ring contraction:

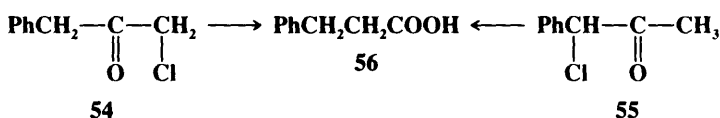


The reaction has also been carried out on α -hydroxy ketones¹⁴⁵ and on α,β -epoxy ketones:¹⁴⁶



The fact that an epoxide gives a reaction analogous to a halide indicates that the oxygen and halogen are leaving groups in a nucleophilic substitution step.

Through the years, the mechanism¹⁴⁷ of the Favorskii rearrangement has been the subject of much investigation; at least five different mechanisms have been proposed. However, the finding¹⁴⁸ that **54** and **55** both give **56** (this behavior is typical) shows that any mechanism



where the halogen leaves and R^1 takes its place is invalid, since in such a case **54** would be expected to give **56** (with PhCH_2 migrating), but **55** should give PhCHMeCOOH (with CH_3 migrating). That is, in the case of **55**, it was PhCH that migrated and not methyl. Another important result was determined by radioactive labeling. **52**, in which C-1 and C-2 were equally labeled with ^{14}C , was converted to **53**. The product was found to contain 50% of the label on the carbonyl carbon, 25% on C-1, and 25% on C-2.¹⁴⁹ Now the carbonyl carbon, which originally carried half of the radioactivity, still had this much, so the rearrangement did not directly affect it. However, if the C-6 carbon had migrated to C-2, the other half of the radioactivity would be only on C-1 of the product:



On the other hand, if the migration had gone the other way—if the C-2 carbon had migrated to C-6—then this half of the radioactivity would be found solely on C-2 of the product:



¹⁴⁵Craig; Dinner; Mulligan *J. Org. Chem.* **1972**, 37, 3539.

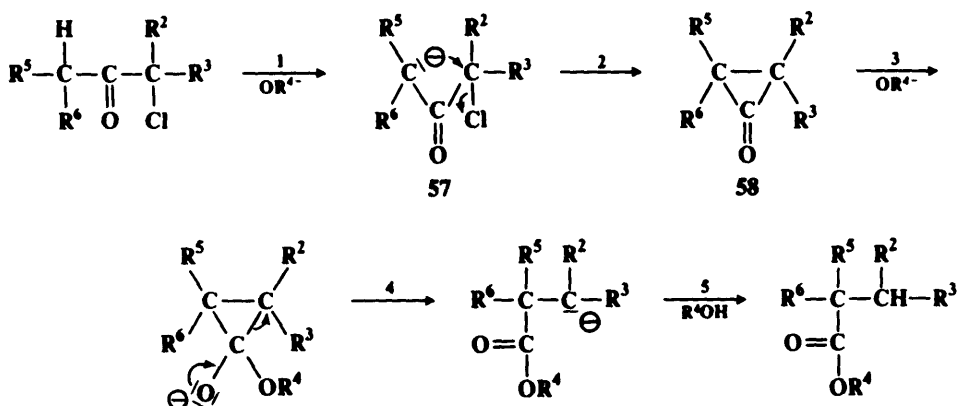
¹⁴⁶See, for example, House; Gilmore *J. Am. Chem. Soc.* **1961**, 83, 3972; Mouk; Patel; Reusch *Tetrahedron* **1975**, 31, 13.

¹⁴⁷For a review of the mechanism, see Baretta; Waegell *React. Intermed. (Plenum)* **1982**, 2, 527-585.

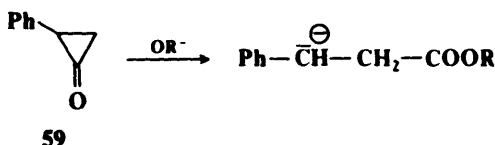
¹⁴⁸McPhee; Klingsberg *J. Am. Chem. Soc.* **1944**, 66, 1132; Bordwell; Scamehorn; Springer *J. Am. Chem. Soc.* **1969**, 91, 2087.

¹⁴⁹Lofthfield *J. Am. Chem. Soc.* **1951**, 73, 4707.

The fact that C-1 and C-2 were found to be equally labeled showed that *both migrations occurred*, with equal probability. Since C-2 and C-6 of **52** are not equivalent, this means that there must be a symmetrical intermediate.¹⁵⁰ The type of intermediate that best fits the circumstances is a cyclopropanone,¹⁵¹ and the mechanism (for the general case) is formulated (replacing R¹ of our former symbolism with CHR⁵R⁶, since it is obvious that for this mechanism an α hydrogen is required on the nonhalogenated side of the carbonyl):



The intermediate corresponding to **58** in the case of **52** is a symmetrical compound, and the three-membered ring can be opened with equal probability on either side of the carbonyl, accounting for the results with ¹⁴C. In the general case, **58** is not symmetrical and should open on the side that gives the more stable carbanion.¹⁵² This accounts for the fact that **54** and **55** give the same product. The intermediate in both cases is **59**, which always opens to



give the carbanion stabilized by resonance. The cyclopropanone intermediate (**58**) has been isolated in the case where R² = R⁵ = *t*-Bu and R³ = R⁶ = H,¹⁵³ and it has also been trapped.¹⁵⁴ Also, cyclopropanones synthesized by other methods have been shown to give Favorskii products on treatment with NaOMe or other bases.¹⁵⁵

The mechanism discussed is in accord with all the facts when the halo ketone contains an α hydrogen on the other side of the carbonyl group. However, ketones that do not have

¹⁵⁰ A preliminary migration of the chlorine from C-2 to C-6 was ruled out by the fact that recovered **52** had the same isotopic distribution as the starting **52**.

¹⁵¹ Although cyclopropanones are very reactive compounds, several of them have been isolated. For reviews of cyclopropanone chemistry, see Wasserman; Clark; Turley *Top. Curr. Chem.* **1974**, 47, 73-156; Turro *Acc. Chem. Res.* **1969**, 2, 25-32.

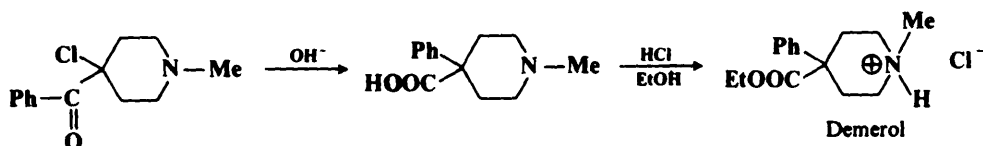
¹⁵² Factors other than carbanion stability (including steric factors) may also be important in determining which side of an unsymmetrical **58** is preferentially opened. See, for example, Rappe; Knutsson *Acta Chem. Scand.* **1967**, 21, 2205; Rappe; Knutsson; Turro; Gagosian *J. Am. Chem. Soc.* **1970**, 92, 2032.

¹⁵³ Pazos; Pacifici; Pierson; Sclove; Greene *J. Org. Chem.* **1974**, 39, 1990.

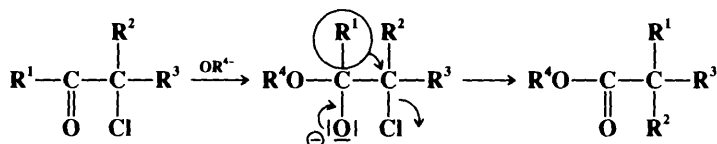
¹⁵⁴ Fort *J. Am. Chem. Soc.* **1962**, 84, 4979; Cookson; Nye *Proc. Chem. Soc.* **1963**, 129; Breslow; Posner; Krebs *J. Am. Chem. Soc.* **1963**, 85, 234; Baldwin; Cardellina *Chem. Commun.* **1968**, 558.

¹⁵⁵ Turro; Hammond *J. Am. Chem. Soc.* **1965**, 87, 3258; Crandall; Machleder *J. Org. Chem.* **1968**, 90, 7347; Turro; Gagosian; Rappe; Knutsson *Chem. Commun.* **1969**, 270; Wharton; Fritzberg *J. Org. Chem.* **1972**, 37, 1899.

a hydrogen there also rearrange to give the same type of product. This is usually called the *quasi-Favorskii rearrangement*. An example is found in the preparation of Demerol:¹⁵⁶



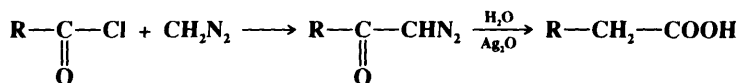
The quasi-Favorskii rearrangement obviously cannot take place by the cyclopropanone mechanism. The mechanism that is generally accepted (called the *semibenzilic mechanism*)¹⁵⁷



is a base-catalyzed pinacol rearrangement-type mechanism similar to that of 8-6. This mechanism requires inversion at the migration terminus and this has been found.¹⁵⁸ It has been shown that even where there is an appropriately situated α hydrogen, the semibenzilic mechanism may still operate.¹⁵⁹

OS IV, 594; VI, 368, 711.

8-8 The Arndt-Eistert Synthesis



In the *Arndt-Eistert synthesis* an acyl halide is converted to a carboxylic acid with one additional carbon.¹⁶⁰ The first step of this process is reaction 0-112. The actual rearrangement occurs in the second step on treatment of the diazo ketone with water and silver oxide or with silver benzoate and triethylamine. This rearrangement is called the *Wolff rearrangement*. It is the best method of increasing a carbon chain by one if a *carboxylic acid* is available (0-101 and 6-34 begin with alkyl halides). If an alcohol $\text{R}'\text{OH}$ is used instead of water, the ester $\text{RCH}_2\text{COOR}'$ is isolated directly. Similarly, ammonia gives the amide. Other catalysts are sometimes used, e.g., colloidal platinum, copper, etc., but occasionally the diazo ketone is simply heated or photolyzed in the presence of water, an alcohol, or ammonia, with no catalyst at all.¹⁶¹ The photolysis method¹⁶² often gives better results than the silver catalysis

¹⁵⁶Smismman; Hite *J. Am. Chem. Soc.* **1959**, *81*, 1201.

¹⁵⁷Tchoubar; Sackur *C. R. Acad. Sci.* **1939**, 208, 1020.

¹⁵⁸Baudry; Bégue; Charpentier-Morize *Bull. Soc. Chim. Fr.* **1971**, 1416, *Tetrahedron Lett.* **1970**, 2147.

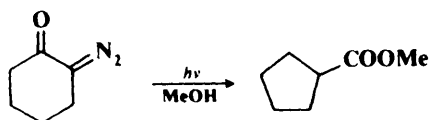
¹⁵⁹For example, see Conia; Salaun *Tetrahedron Lett.* **1963**, 1175, *Bull. Soc. Chim. Fr.* **1964**, 1957; Salaun; Garnier; Conia *Tetrahedron* **1973**, *29*, 2895; Rappe; Knutsson *Acta Chem. Scand.* **1967**, *21*, 163; Warnhoff; Wong; Tai *J. Am. Chem. Soc.* **1968**, *90*, 514.

¹⁶⁰For reviews, see Meier; Zeller *Angew. Chem. Int. Ed. Engl.* **1975**, *14*, 32-43 [*Angew. Chem.* **87**, 52-63]; Kirmse, Ref. 124, pp. 475-493; Rodina; Korobitsyna *Russ. Chem. Rev.* **1967**, *36*, 260-272; For a review of rearrangements of diazo and diazonium compounds, see Whittaker, in Patai *The Chemistry of Diazonium and Diazo Compounds*, pt. 2; Wiley: New York, 1978, pp. 593-644.

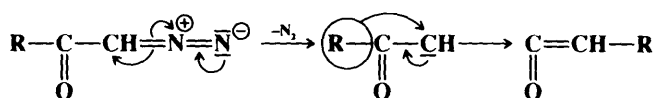
¹⁶¹For a list of methods, with references, see Ref. 106, p. 933.

¹⁶²For reviews of the photolysis method, see Regitz; Maas *Diazo Compounds*; Academic Press: New York, 1986, pp. 185-195; Ando, in Patai, Ref. 160, pp. 458-475.

method. Of course, diazo ketones prepared in any other way also give the rearrangement.¹⁶³ The reaction is of wide scope. R may be alkyl or aryl and may contain many functional groups including unsaturation, but not including groups acidic enough to react with CH_2N_2 or diazo ketones (e.g., **0-5** and **0-26**). Sometimes the reaction is performed with other diazoalkanes (that is, $\text{R}'\text{CHN}_2$) to give $\text{RCHR}'\text{COOH}$. The reaction has often been used for ring contraction of cyclic diazo ketones,¹⁶⁴ e.g.,¹⁶⁵

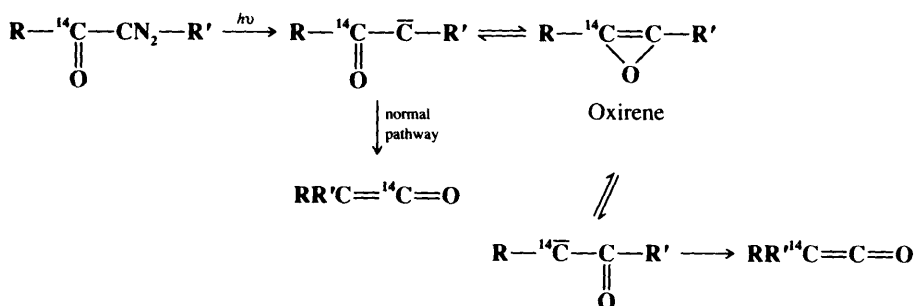


The mechanism is generally regarded as involving formation of a carbene. It is the divalent carbon that has the open sextet and to which the migrating group brings its electron pair:



The actual product of the reaction is thus the ketene, which then reacts with water (**5-2**), an alcohol (**5-4**), or ammonia or an amine (**5-7**). Particularly stable ketenes (e.g., $\text{Ph}_2\text{C}=\text{C}=\text{O}$) have been isolated and others have been trapped in other ways (e.g., as β -lactams,¹⁶⁶ **6-64**). The purpose of the catalyst is not well understood, though many suggestions have been made. This mechanism is strictly analogous to that of the Curtius rearrangement (**8-15**). Although the mechanism as shown above involves a free carbene and there is much evidence to support this,¹⁶⁷ it is also possible that at least in some cases the two steps are concerted and a free carbene is absent.

When the Wolff rearrangement is carried out photochemically, the mechanism is basically the same,¹⁶² but another pathway can intervene. Some of the ketocarbene originally formed can undergo a carbene-carbene rearrangement, through an oxirene intermediate.¹⁶⁸ This was shown by ^{14}C labeling experiments, where diazo ketones labeled in the carbonyl group



¹⁶²For a method of conducting the reaction with trimethylsilyldiazomethane instead of CH_2N_2 , see Aoyama; Shioiri *Tetrahedron Lett.* **1980**, 21, 4461.

¹⁶³For a review, see Redmore; Gutsche, Ref. 112, pp. 125-136.

¹⁶⁴Korobitsyna; Rodina; Sushko *J. Org. Chem. USSR* **1968**, 4, 165; Jones; Ando *J. Am. Chem. Soc.* **1968**, 90, 2200.

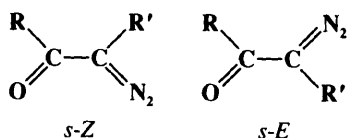
¹⁶⁵Kirmse; Horner *Chem. Ber.* **1956**, 89, 2759; also see Horner; Spietschka *Chem. Ber.* **1956**, 89, 2765.

¹⁶⁷For a summary of evidence on both sides of the question, see Kirmse, Ref. 124, pp. 476-480. See also Torres; Ribo; Clement; Strausz *Can J. Chem.* **1983**, 61, 996; Tomoika; Hayashi; Asano; Izawa *Bull. Chem. Soc. Jpn.* **1983**, 56, 758.

¹⁶⁸For a review of oxirenes, see Lewars *Chem. Rev.* **1983**, 83, 519-534.

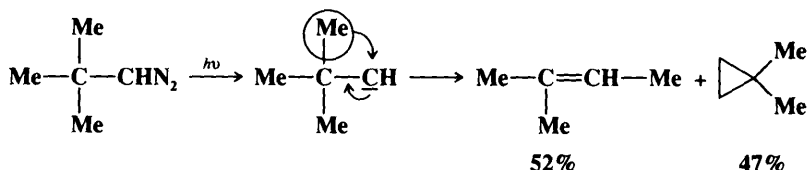
gave rise to ketenes that bore the label at both C=C carbons.¹⁶⁹ In general, the smallest degree of scrambling (and thus of the oxirene pathway) was found when R' = H. An intermediate believed to be an oxirene has been detected by laser spectroscopy.¹⁷⁰ The oxirene pathway is not found in the thermal Wolff rearrangement. It is likely that an excited singlet state of the carbene is necessary for the oxirene pathway to intervene.¹⁷¹ In the photochemical process, ketocarbene intermediates, in the triplet state, have been isolated in an Ar matrix at 10–15 K, where they have been identified by uv-visible, ir, and esr spectra.¹⁷² These intermediates went on to give the rearrangement via the normal pathway, with no evidence for oxirene intermediates.

The diazo ketone can exist in two conformations, called *s-E* and *s-Z*. Studies have shown



that Wolff rearrangement takes place preferentially from the *s-Z* conformation.¹⁷³

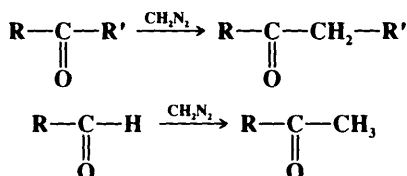
Other 1,2 alkyl migrations to a carbene or carbenoid terminus are also known,¹⁷⁴ e.g.,¹⁷⁵



OS III, 356; VI, 613, 840.

8-9 Homologation of Aldehydes and Ketones

Methylene-insertion



Aldehydes and ketones¹⁷⁶ can be converted to their homologs¹⁷⁷ with diazomethane.¹⁷⁸ Formation of the epoxide (6-61) is a side reaction. Although this reaction appears super-

¹⁶⁹Csizmadia; Font; Strausz *J. Am. Chem. Soc.* **1968**, *90*, 7360; Fenwick; Frater; Ogi; Strausz *J. Am. Chem. Soc.* **1973**, *95*, 124; Zeller *Chem. Ber.* **1978**, *112*, 678. See also Thornton; Gosavi; Strausz *J. Am. Chem. Soc.* **1970**, *92*, 1768; Russell; Rowland *J. Am. Chem. Soc.* **1970**, *92*, 7508; Majerski; Redvanly *J. Chem. Soc. Chem. Commun.* **1972**, 694.

¹⁷⁰Tanigaki; Ebbesen *J. Am. Chem. Soc.* **1987**, *109*, 5883. See also Bachmann; N'Guessan; Debû; Monnier; Pourcin; Aycard; Bodot *J. Am. Chem. Soc.* **1990**, *112*, 7488.

¹⁷¹Csizmadia; Gunning; Gosavi; Strausz *J. Am. Chem. Soc.* **1973**, *95*, 133.

¹⁷²McMahon; Chapman; Hayes; Hess; Krimmer *J. Am. Chem. Soc.* **1985**, *107*, 7597.

¹⁷³Kaplan; Mitchell *Tetrahedron Lett.* **1979**, 759; Tomioka; Okuno; Izawa *J. Org. Chem.* **1980**, *45*, 5278.

¹⁷⁴For a review, see Kirmse, Ref. 124, pp. 457-462.

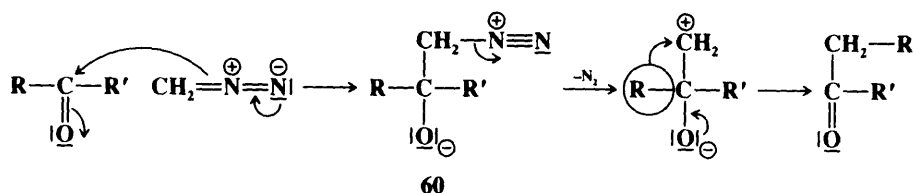
¹⁷⁵Kirmse; Horn *Chem. Ber.* **1967**, *100*, 2698.

¹⁷⁶For a homologation of carboxylic esters RCOOEt → RCH₂COOEt, which goes by an entirely different pathway, see Kowalski; Haque; Fields *J. Am. Chem. Soc.* **1985**, *107*, 1429.

¹⁷⁷Other homologation reagents have also reported: See Taylor; Chiang; McKillop *Tetrahedron Lett.* **1977**, 1827; Villieras; Perriot; Normant *Synthesis* **1979**, 968; Hashimoto; Aoyama; Shioiri *Tetrahedron Lett.* **1980**, *21*, 4619; Aoyama; Shioiri *Synthesis* **1988**, 228.

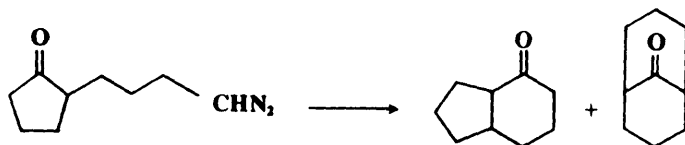
¹⁷⁸For a review, see Gutsche, *Org. React.* **1954**, *8*, 364-429.

ficially to be similar to the insertion of carbenes into C—H bonds, **2-20** (and IUPAC names it as an insertion), the mechanism is quite different. This is a true rearrangement and no free carbene is involved. The first step is an addition to the C=O bond:

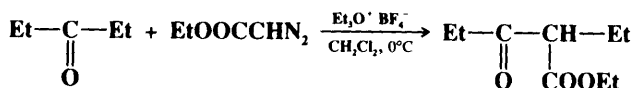


The betaine **60** can sometimes be isolated. As shown in **6-61**, **60** can also go to the epoxide. The evidence for this mechanism is summarized in the review by Gutsche.¹⁷⁸ It may be noted that this mechanism is essentially the same as in the apparent “insertions” of oxygen (**8-20**) and nitrogen (**8-17**) into ketones.

Aldehydes give fairly good yields of methyl ketones; that is, hydrogen migrates in preference to alkyl. The most abundant side product is not the homologous aldehyde, but the epoxide. However, the yield of aldehyde at the expense of methyl ketone can be increased by the addition of methanol. If the aldehyde contains electron-withdrawing groups, the yield of epoxides is increased and the ketone is formed in smaller amounts, if at all. Ketones give poorer yields of homologous ketones. Epoxides are usually the predominant product here, especially when one or both R groups contain an electron-withdrawing group. The yield of ketones also decreases with increasing length of the chain. The use of BF_3 ¹⁷⁹ or AlCl_3 ¹⁸⁰ increases the yield of ketone.¹⁸¹ Cyclic ketones,¹⁸² three-membered¹⁸³ and larger, behave particularly well and give good yields of ketones with the ring expanded by one.¹⁸⁴ Aliphatic diazo compounds (RCHN_2 and R_2CN_2) are sometimes used instead of diazomethane, with the expected results.¹⁸⁵ An interesting example is the preparation of bicyclic compounds from alicyclic compounds with a diazo group in the side chain, e.g.,¹⁸⁶



Ethyl diazoacetate can be used analogously, in the presence of a Lewis acid or of triethyloxonium fluoroborate,¹⁸⁷ e.g.,



¹⁷⁹House; Grubbs; Gannon *J. Am. Chem. Soc.* **1960**, 82, 4099.

¹⁸⁰Müller; Heischkeil *Tetrahedron Lett.* **1964**, 2809.

¹⁸¹For a review of homologations catalyzed by Lewis acids, see Müller; Kessler; Zeeh *Fortschr. Chem. Forsch.* **1966**, 7, 128-171, pp. 137-150.

¹⁸²For other methods for the ring enlargement of cyclic ketones, see Krief; Laboureur *Tetrahedron Lett.* **1987**, 28, 1545; Krief; Laboureur; Dumont *Tetrahedron Lett.* **1987**, 28, 1549; Abraham; Bhupathy; Cohen *Tetrahedron Lett.* **1987**, 28, 2203; Trost; Mikhail *J. Am. Chem. Soc.* **1987**, 109, 4124.

¹⁸³For example, see Turro; Gagosian *J. Am. Chem. Soc.* **1970**, 92, 2036.

¹⁸⁴For a review, see Gutsche; Redmore, Ref. 112, pp. 81-98. For a review pertaining to bridged bicyclic ketones, see Krow *Tetrahedron* **1987**, 43, 3-38.

¹⁸⁵For example, see Smith *J. Org. Chem.* **1960**, 25, 453; Warner; Walsh; Smith *J. Chem. Soc.* **1962**, 1232; Loeschorn; Nakajima; Anselme *Bull. Soc. Chim. Belg.* **1981**, 90, 985.

¹⁸⁶Gutsche; Bailey *J. Org. Chem.* **1963**, 28, 607; Gutsche; Zandstra *J. Org. Chem.* **1974**, 39, 324.

¹⁸⁷Mock; Hartman *J. Org. Chem.* **1977**, 42, 459, 466; Baldwin; Landmesser *Synth. Commun.* **1978**, 8, 413.

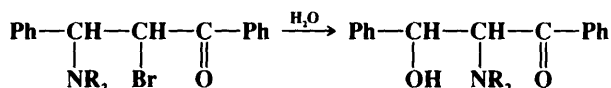
When unsymmetrical ketones were used in this reaction (with BF_3 as catalyst), the less highly substituted carbon preferentially migrated.¹⁸⁸ The reaction can be made regioselective by applying this method to the α -halo ketone, in which case only the other carbon migrates.¹⁸⁹ The ethyl diazoacetate procedure has also been applied to the acetals or ketals of α,β -unsaturated aldehydes and ketones.¹⁹⁰

OS IV, 225, 780.

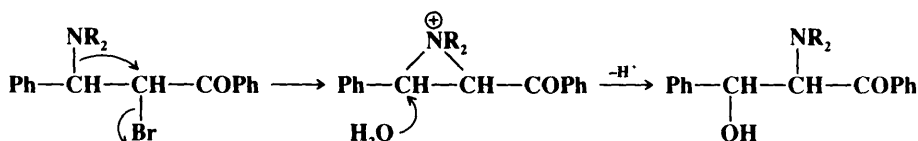
B. Carbon-to-Carbon Migrations of Other Groups

8-10 Migrations of Halogen, Hydroxyl, Amino, etc.

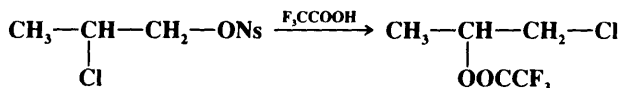
Hydroxy-de-bromo-*cis*-substitution, etc.



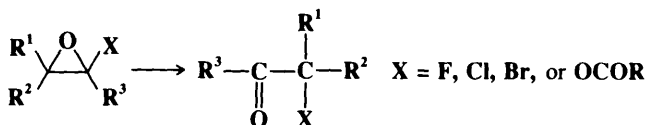
When a nucleophilic substitution is carried out on a substrate that has a neighboring group (p. 309) on the adjacent carbon, if the cyclic intermediate is opened on the opposite side, the result is migration of the neighboring group. In the example shown above (NR_2 = morpholino),¹⁹¹ the reaction took place as follows:



Another example is¹⁹² (ONs = nosylate, see p. 353):



α -Halo and α -acyloxy epoxides undergo ready rearrangement to α -halo and α -acyloxy ketones, respectively.¹⁹³ These substrates are very prone to rearrange, and often do so on



¹⁸⁸Liu; Majumdar *Synth. Commun.* **1975**, 5, 125.

¹⁸⁹Dave; Warnhoff *J. Org. Chem.* **1983**, 48, 2590.

¹⁹⁰Doyle; Trudell; Terpstra *J. Org. Chem.* **1983**, 48, 5146.

¹⁹¹Southwick; Walsh *J. Am. Chem. Soc.* **1955**, 77, 405. See also Suzuki; Okano; Nakai; Terao; Sekiya *Synthesis* **1983**, 723.

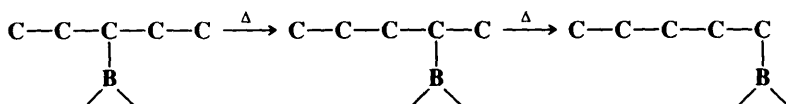
¹⁹²For a review of Cl migrations, see Peterson, *Acc. Chem. Res.* **1971**, 4, 407-413. See also Loktev; Korchagina; Shubin; Koptuyg *J. Org. Chem. USSR* **1977**, 13, 201; Dobronravov; Shteingarts *J. Org. Chem. USSR* **1977**, 13, 420. For examples of Br migration, see Gudkova; Uteniyazov; Reutov *Doklad. Chem.* **1974**, 214, 70; Brusova; Gopius; Smolina; Reutov *Doklad. Chem.* **1980**, 253, 334. For a review of F migration (by several mechanisms) see Kobrina; Kovtonyuk *Russ. Chem. Rev.* **1988**, 57, 62-71. For an example OH migration, see Cathcart; Bovenkamp; Moir; Bannard; Casselman *Can. J. Chem.* **1977**, 55, 3774. For a review of migrations of ArS and $\text{Ar}_2\text{P}(\text{O})$, see Warren *Acc. Chem. Res.* **1978**, 11, 403-406. See also Aggarwal; Warren *J. Chem. Soc., Perkin Trans. I* **1987**, 2579.

¹⁹³For a review, see McDonald *Mech. Mol. Migr.* **1971**, 3, 67-107.

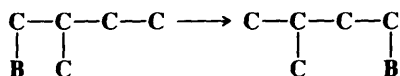
standing without a catalyst, though in some cases an acid catalyst is necessary. The reaction is essentially the same as the rearrangement of epoxides shown in 8-2, except that in this case halogen or acyloxy is the migrating group (as shown above; however, it is also possible for one of the R groups—alkyl, aryl, or hydrogen—to migrate instead, and mixtures are sometimes obtained).

8-11 Migration of Boron

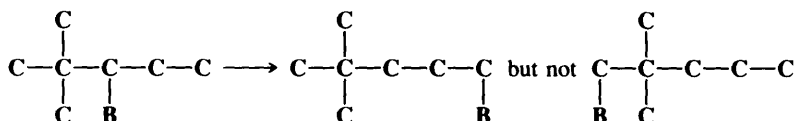
Hydro,dialkylboro-interchange, etc.



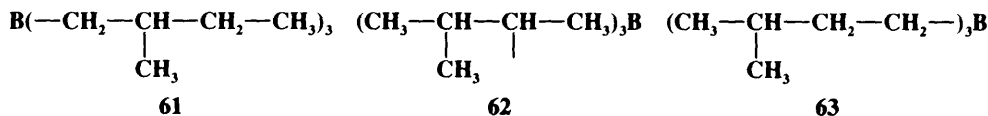
When a nonterminal borane is heated at temperatures ranging from 100 to 200°C, the boron moves toward the end of the chain.¹⁹⁴ The reaction is catalyzed by small amounts of borane or other species containing B—H bonds. The boron can move past a branch, e.g.,



but not past a double branch, e.g.,



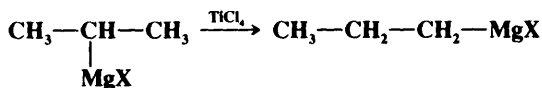
The reaction is an equilibrium: **61**, **62**, and **63** each gave a mixture containing about 40% **61**, 1% **62**, and 59% **63**. The migration can go quite a long distance. Thus



(C₁₁H₂₃CHC₁₁H₂₃)₃B was completely converted to (C₂₃H₄₇)₃B, involving a migration of 11 positions.¹⁹⁵ If the boron is on a cycloalkyl ring, it can move around the ring; if any alkyl chain is also on the ring, the boron may move from the ring to the chain, ending up at the end of the chain.¹⁹⁶ The reaction is useful for the migration of double bonds in a controlled way (see 2-2). The mechanism may involve a π complex, at least partially.¹⁹⁷

8-12 Rearrangement of Grignard Reagents

Hydro,magnesio-interchange



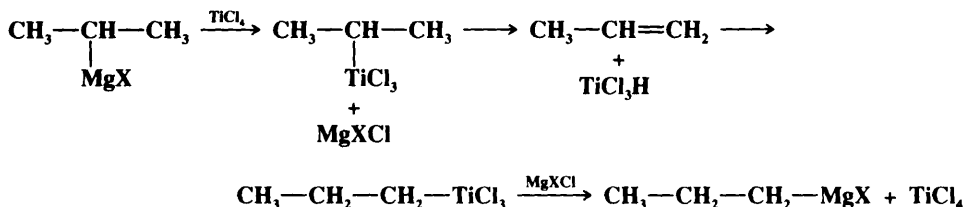
¹⁹⁴Brown *Hydroboration*; W. A. Benjamin: New York, 1962, pp. 136-149, Brown; Zweifel *J. Am. Chem. Soc.* **1966**, *88*, 1433. See also Brown; Racherla *J. Organomet. Chem.* **1982**, *241*, C37.

¹⁹⁵Logan *J. Org. Chem.* **1961**, *26*, 3657.

¹⁹⁶Brown; Zweifel *J. Am. Chem. Soc.* **1967**, *89*, 561.

¹⁹⁷See Wood; Rickborn *J. Org. Chem.* **1983**, *48*, 555; Field; Gallagher *Tetrahedron Lett.* **1985**, *26*, 6125.

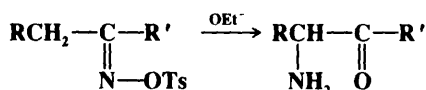
The MgX of Grignard reagents¹⁹⁸ can migrate to terminal positions in the presence of small amounts of TiCl_4 .¹⁹⁹ The proposed mechanism consists of metal exchange (2-35), elimination-addition, and metal exchange:



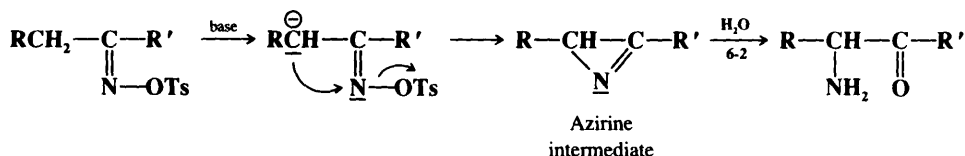
The addition step is similar to 5-12 or 5-13 and follows Markovnikov's rule, so the positive titanium goes to the terminal carbon.

8-13 The Neber Rearrangement

Neber oxime tosylate-amino ketone rearrangement



α -Amino ketones can be prepared by treatment of ketoxime tosylates with a base such as ethoxide ion or pyridine.²⁰⁰ This is called the *Neber rearrangement*. R is usually aryl, though the reaction has been carried out with R = alkyl or hydrogen. R' may be alkyl or aryl but not hydrogen. The Beckmann rearrangement (8-18) and the abnormal Beckmann reaction (elimination to the nitrile, 7-38) may be side reactions, though these generally occur in acid media. A similar rearrangement is given by N,N-dichloroamines of the type $\text{RCH}_2\text{CH}(\text{NCl}_2)\text{R}'$, where the product is also $\text{RCH}(\text{NH}_2)\text{COR}'$.²⁰¹ The mechanism of the Neber rearrangement is as follows:²⁰²



The best evidence for this mechanism is that the azirine intermediate has been isolated.²⁰³ In contrast to the Beckmann rearrangement, this one is sterically indiscriminate.²⁰⁴ Both a syn and an anti ketoxime give the same product. The mechanism as shown above consists of three steps. However, it is possible that the first two steps are concerted, and it is also possible that what is shown as the second step is actually two steps: loss of OTs to give a nitrene, and formation of the azirine. In the case of the dichloroamines, HCl is first lost to

¹⁹⁸For reviews of rearrangements in organomagnesium chemistry, see Hill *Adv. Organomet. Chem.* **1977**, *16*, 131-165; *J. Organomet. Chem.* **1975**, *91*, 123-271.

¹⁹⁹Cooper; Finkbeiner *J. Org. Chem.* **1962**, *27*, 1493; Fell; Asinger; Sulzbach *Chem. Ber.* **1970**, *103*, 3830. See also Ashby; Ainslie *J. Organomet. Chem.* **1983**, *250*, 1.

²⁰⁰For a review, see Conley; Ghosh *Mech. Mol. Migr.* **1971**, *4*, 197-308, pp. 289-304.

²⁰¹Baumgarten; Petersen *J. Am. Chem. Soc.* **1960**, *82*, 459, and references cited therein.

²⁰²Cram; Hatch *J. Am. Chem. Soc.* **1953**, *75*, 33; Hatch; Cram *J. Am. Chem. Soc.* **1953**, *75*, 38.

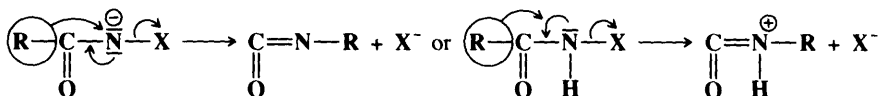
²⁰³Neber; Burgard *Liebigs Ann. Chem.* **1932**, *493*, 281; Parcell *Chem. Ind. (London)* **1963**, 1396; Ref. 202.

²⁰⁴House; Berkowitz *J. Org. Chem.* **1963**, *28*, 2271.

give $\text{RCH}_2\text{C}(=\text{NCl})\text{R}'$, which then behaves analogously.²⁰⁵ N-Chloroimines prepared in other ways also give the reaction.²⁰⁶

OS V, 909; VII, 149.

C. Carbon-to-Nitrogen Migrations of R and Ar. The reactions in this group are nucleophilic migrations from a carbon to a nitrogen atom. In each case the nitrogen atom either has six electrons in its outer shell (and thus invites the migration of a group carrying an electron pair) or else loses a nucleofuge concurrently with the migration (p. 1053). Reactions 8-14 to 8-17 are used to prepare amines from acid derivatives. Reactions 8-17 and 8-18 are used to prepare amines from ketones. The mechanisms of 8-14, 8-15, 8-16, and 8-17 (with carboxylic acids) are very similar and follow one of two patterns:

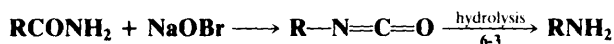


Some of the evidence²⁰⁷ is: (1) configuration is retained in R (p. 1054); (2) the kinetics are first order; (3) intramolecular rearrangement is shown by labeling; and (4) no rearrangement occurs *within* the migrating group, e.g., a neopentyl group on the carbon of the starting material is still a neopentyl group on the nitrogen of the product.

In many cases it is not certain whether the nucleofuge X is lost first, creating an intermediate nitrene²⁰⁸ or nitrenium ion, or whether migration and loss of the nucleofuge are simultaneous, as shown above.²⁰⁹ It is likely that both possibilities can exist, depending on the substrate and reaction conditions.

8-14 The Hofmann Rearrangement

Bishydrogen-(2/→1/N-alkyl)-migro-detachment (formation of isocyanate)



In the *Hofmann rearrangement*, an unsubstituted amide is treated with sodium hypobromite (or sodium hydroxide and bromine, which is essentially the same thing) to give a primary amine that has one carbon fewer than the starting amide.²¹⁰ The actual product is the isocyanate, but this compound is seldom isolated²¹¹ since it is usually hydrolyzed under the reaction conditions (6-3). R may be alkyl or aryl, but if it is an alkyl group of more than about six or seven carbons, low yields are obtained unless Br_2 and NaOMe are used instead of Br_2 and NaOH.²¹² Under these conditions the product of addition to the isocyanate is the carbamate RNHCOOMe (6-8), which is easily isolated or can be hydrolyzed to the amine. Side reactions when NaOH is the base are formation of ureas RNHCONHR and acylureas RCONHCONHR by addition, respectively, of RNH_2 and RCONH_2 to RNCO (6-17). If acylureas are desired, they can be made the main products by using only half the

²⁰⁵For example, see Oae; Furukawa *Bull. Chem. Soc. Jpn.* **1965**, 38, 62; Nakai; Furukawa; Oae *Bull. Chem. Soc. Jpn.* **1969**, 42, 2917.

²⁰⁶Baumgarten; Petersen; Wolf *J. Org. Chem.* **1963**, 28, 2369.

²⁰⁷For a discussion of this mechanism and the evidence for it, see Smith, in Mayo, Ref. 114, vol. 1, pp. 258-550.

²⁰⁸For a review of rearrangements involving nitrene intermediates, see Boyer *Mech. Mol. Migr.* **1969**, 2, 267-318. See also Ref. 221.

²⁰⁹The question is discussed by Lwowski, in Lwowski *Nitrenes*; Wiley: New York, 1970, pp. 217-221.

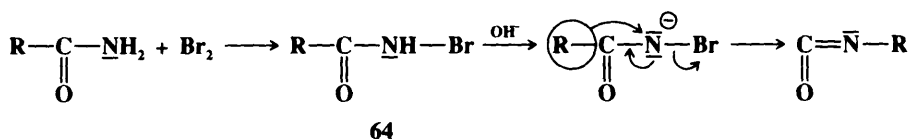
²¹⁰For a review, see Wallis; Lane *Org. React.* **1946**, 3, 267-306.

²¹¹If desired, the isocyanate can be isolated by the use of phase transfer conditions; see Sy and Raksis *Tetrahedron Lett.* **1980**, 21, 2223.

²¹²For an example of the use of this method at low temperatures, see Radlick; Brown *Synthesis* **1974**, 290.

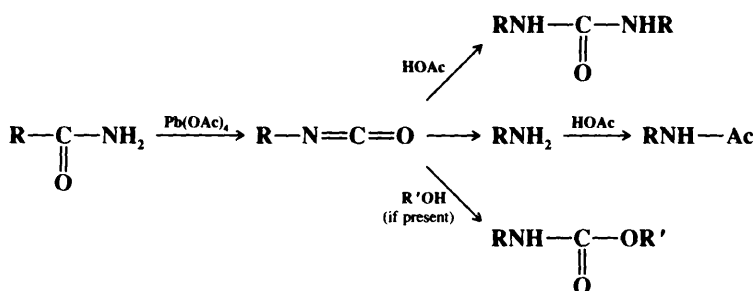
usual quantities of Br_2 and NaOH . Another side product, though only from primary R , is the nitrile derived from oxidation of RNH_2 (9-5). Imides react to give amino acids, e.g., phthalimide gives *o*-aminobenzoic acid. α -Hydroxy and α -halo amides give aldehydes and ketones by way of the unstable α -hydroxy- or α -haloamines. However, a side product with an α -halo amide is a *gem*-dihalide. Ureas analogously give hydrazines.

The mechanism follows the pattern outlined on p. 1090.



The first step is an example of 2-54 and intermediate N-halo amides (64) have been isolated. In the second step, 64 lose a proton to the base. 64 are acidic because of the presence of two electron-withdrawing groups (acyl and halo) on the nitrogen. It is possible that the third step is actually two steps: loss of bromide to form a nitrene, followed by the actual migration, but most of the available evidence favors the concerted reaction.²¹³

A similar reaction can be effected by the treatment of amides with lead tetraacetate.²¹⁴ In this case the initial isocyanate and the amine formed from it react with the acetic acid liberated from the lead tetraacetate to give, respectively, ureas and amides. If the reaction is carried out in the presence of an alcohol, carbamates are formed (6-8).



Among other reagents that convert RCONH_2 to RNH_2 (R = alkyl, but not aryl) are phenyliodosyl bis(trifluoroacetate) $\text{PhI}(\text{OCOCF}_3)_2$ ²¹⁵ and hydroxy(tosyloxy)iodobenzene $\text{PhI}(\text{OH})\text{OTs}$.²¹⁶ A mixture of *N*-bromosuccinimide, $\text{Hg}(\text{OAc})_2$, and $\text{R}'\text{OH}$ is one of several reagent mixtures that convert an amide RCONH_2 to the carbamate $\text{RNHCOOR}'$ (R = primary, secondary, or tertiary alkyl or aryl) in high yield.²¹⁷

OS II, 19, 44, 462; IV, 45; 65, 173; 66, 132.

8-15 The Curtius Rearrangement

Dinitrogen-(2/→1/*N*-alkyl)-migr-detachment



²¹³See, for example, Imamoto; Tsuno; Yukawa *Bull. Chem. Soc. Jpn.* **1971**, *44*, 1632, 1639, 1644; Imamoto; Kim; Tsuno; Yukawa *Bull. Chem. Soc. Jpn.* **1971**, *44*, 2776.

²¹⁴Acott; Beckwith *Chem. Commun.* **1965**, 161; Baumgarten; Staklis *J. Am. Chem. Soc.* **1965**, *87*, 1141; Acott; Beckwith; Hassanali *Aust. J. Chem.* **1968**, *21*, 185, 197; Baumgarten; Smith; Staklis *J. Org. Chem.* **1975**, *40*, 3554.

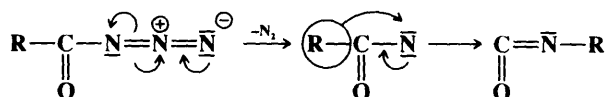
²¹⁵Loudon; Radhakrishna; Almond; Blodgett; Boutin *J. Org. Chem.* **1984**, *49*, 4272; Boutin; Loudon *J. Org. Chem.* **1984**, *49*, 4277; Pavlides; Chan; Pennington; McParland; Whitehead; Coutts *Synth. Commun.* **1988**, *18*, 1615.

²¹⁶Lazbin; Koser *J. Org. Chem.* **1986**, *51*, 2669; Vasudevan; Koser *J. Org. Chem.* **1988**, *53*, 5158.

²¹⁷Jew; Park; Park; Park; Cho *Tetrahedron Lett.* **1990**, *31*, 1559.

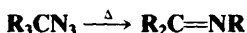
The *Curtius rearrangement* involves the pyrolysis of acyl azides to yield isocyanates.²¹⁸ The reaction gives good yields of isocyanates, since no water is present to hydrolyze them to the amine. Of course, they can be subsequently hydrolyzed, and indeed the reaction *can* be carried out in water or alcohol, in which case the products are amines, carbamates, or acylureas, as in **8-14**.²¹⁹ This is a very general reaction and can be applied to almost any carboxylic acid: aliphatic, aromatic, alicyclic, heterocyclic, unsaturated, and containing many functional groups. Acyl azides can be prepared as in **0-61** or by treatment of acylhydrazines (hydrazides) with nitrous acid (analogous to **2-50**). The Curtius rearrangement is catalyzed by Lewis or protic acids, but these are usually not necessary for good results.

The mechanism is similar to that in **8-14**:

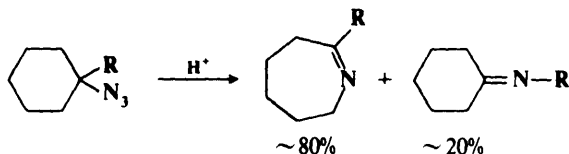


Also note the exact analogy between this reaction and **8-8**. However, in this case, there is no evidence for a free nitrene and it is probable that the steps are concerted.²²⁰

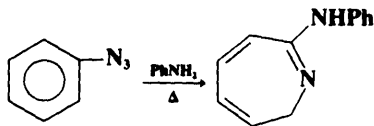
Alkyl azides can be similarly pyrolyzed to give imines, in an analogous reaction:²²¹



The R groups may be alkyl, aryl, or hydrogen, though if hydrogen migrates, the product is the unstable $\text{R}_2\text{C}=\text{NH}$. The mechanism is essentially the same as that of the Curtius rearrangement. However, in pyrolysis of tertiary alkyl azides, there is evidence that free alkyl nitrenes are intermediates.²²² The reaction can also be carried out with acid catalysis, in which case lower temperatures can be used, though the acid may hydrolyze the imine (**6-2**). Cycloalkyl azides give ring expansion.²²³



Aryl azides also give ring expansion on heating, e.g.,²²⁴



OS III, 846; IV, 819; V, 273; VI, 95, 910. Also see OS VI, 210.

²¹⁸For a review, see Banthorpe, in Patai *The Chemistry of the Azido Group*; Wiley: New York, 1971, pp. 397-405.

²¹⁹For a variation that conveniently produces the amine directly, see Pfister; Wyman *Synthesis* **1983**, 38. See also Capson; Poulter *Tetrahedron Lett.* **1984**, 25, 3515.

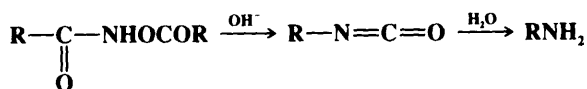
²²⁰See, for example, Lwowski *Angew. Chem. Int. Ed. Engl.* **1967**, 6, 897-906 [*Angew. Chem.* 79, 922-932]; Linke; Tissue; Lwowski *J. Am. Chem. Soc.* **1967**, 89, 6308; Smalley; Bingham *J. Chem. Soc. C* **1969**, 2481.

²²¹For a treatise on azides, which includes discussion of rearrangement reactions, see Scriven *Azides and Nitrenes*; Academic Press: New York, 1984. For a review of rearrangements of alkyl and aryl azides, see Stevens; Watts, Ref. 1, pp. 45-52. For reviews of the formation of nitrenes from alkyl and aryl azides, see, in Lwowski, Ref. 209, the chapters by Lewis; Saunders, pp. 47-97, pp. 47-78 and by Smith, pp. 99-162.

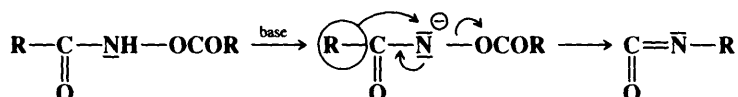
²²²Abramovitch; Kyba *J. Am. Chem. Soc.* **1974**, 96, 480; Montgomery; Saunders *J. Org. Chem.* **1976**, 41, 2368.

²²³Smith; Lakritz, cited in Smith, in Mayo, Ref. 114, vol. 1, p. 474.

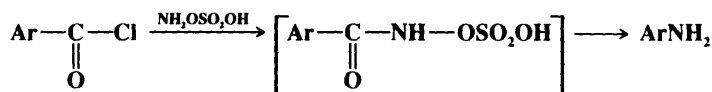
²²⁴Huisgen; Vossius; Appl *Chem. Ber.* **1958**, 91, 1, 12.

8-16 The Lossen Rearrangement**Hydro,acetoxo-(2/→1/*N*-alkyl)-migro-detachment**

The O-acyl derivatives of hydroxamic acids²²⁵ give isocyanates when treated with bases or sometimes even just on heating, in a reaction known as the *Lossen rearrangement*. The mechanism is similar to that of **8-14** and **8-15**:

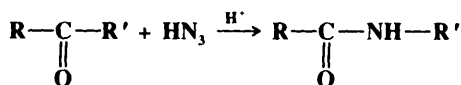


In a similar reaction, aromatic acyl halides are converted to amines in one laboratory step by treatment with hydroxylamine-O-sulfonic acid.²²⁶

**8-17** The Schmidt Reaction

There are actually three reactions called by the name *Schmidt reaction*, involving the addition of hydrazoic acid to carboxylic acids, aldehydes and ketones, and alcohols and olefins.²²⁷ The most common is the reaction with carboxylic acids, illustrated above.²²⁸ Sulfuric acid is the most common catalyst, but Lewis acids have also been used. Good results are obtained for aliphatic R, especially for long chains. When R is aryl, the yields are variable, being best for sterically hindered compounds like mesitoic acid. This method has the advantage over **8-14** and **8-15** that it is just one laboratory step from the acid to the amine, but conditions are more drastic.²²⁹ Under the acid conditions employed, the isocyanate is virtually never isolated.

The reaction between a ketone and hydrazoic acid is a method for “insertion” of NH between the carbonyl group and one R group, converting a ketone into an amide.²³⁰



Either or both of the R groups may be aryl. In general, dialkyl ketones and cyclic ketones react more rapidly than alkyl aryl ketones, and these more rapidly than diaryl ketones. The

²²⁵For a review of hydroxamic acids, see Bauer; Exner *Angew. Chem. Int. Ed. Engl.* **1974**, *13*, 376-384 [*Angew. Chem.* *86*, 419-428].

²²⁶Wallace; Barker; Wood *Synthesis* **1990**, 1143.

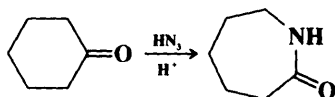
²²⁷For a review, see Banthorpe, Ref. 218, pp. 405-434.

²²⁸For a review, see Koldobskii; Ostrovskii; Gidasov *Russ. Chem. Rev.* **1978**, *47*, 1084-1094.

²²⁹For a comparison of reactions **8-14** to **8-17** as methods for converting an acid to an amine, see Smith, *Org. React.* **1946**, *3*, 337-449, pp. 363-366.

²³⁰For reviews, see Koldobskii; Tereschenko; Gerasimova; Bagal *Russ. Chem. Rev.* **1971**, *40*, 835-846; Beckwith, in Zabicky *The Chemistry of Amides*; Wiley: New York, 1970, pp. 137-145.

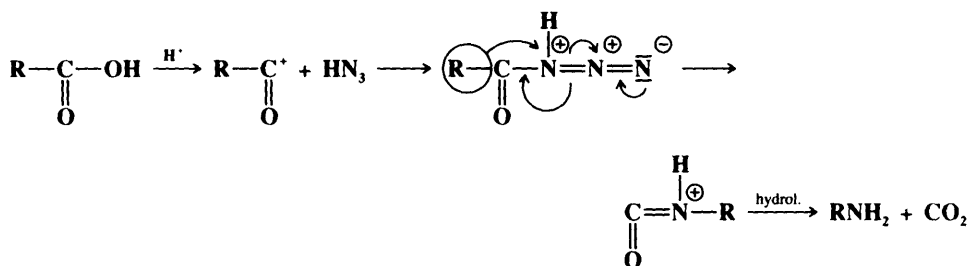
latter require sulfuric acid and do not react in concentrated HCl, which is strong enough for dialkyl ketones. Dialkyl and cyclic ketones react sufficiently faster than diaryl or aryl alkyl ketones—or carboxylic acids or alcohols—that these functions may be present in the same molecule without interference. Cyclic ketones give lactams.²³¹



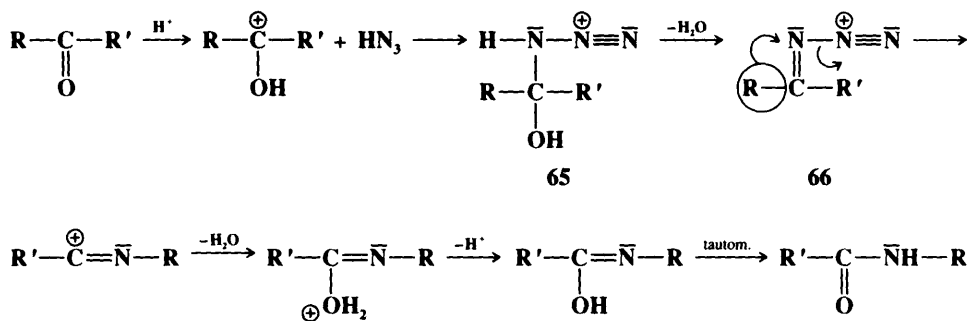
With alkyl aryl ketones, it is the aryl group that generally migrates to the nitrogen, except when the alkyl group is bulky.²³² The reaction has been applied to a few aldehydes, but rarely. With aldehydes the product is usually the nitrile (**6-22**). Even with ketones, conversion to the nitrile is often a side reaction, especially with the type of ketone that gives **7-38**.

Alcohols and olefins react with HN_3 to give alkyl azides, which in the course of reaction rearrange in the same way as discussed in reaction **8-15**.²²¹

There is evidence that the mechanism with carboxylic acids²²⁸ is similar to that of **8-15**, except that it is the protonated azide that undergoes the rearrangement:²³³



The first step is the same as that of the AAC1 mechanism (**0-10**), which explains why good results are obtained with hindered substrates. The mechanism with ketones is²³⁴



²³¹For a review with respect to bicyclic ketones, see Krow, *Tetrahedron* **1981**, 37, 1283-1307.

²³²Exceptions to this statement have been noted in the case of cyclic aromatic ketones bearing electron-donating groups in ortho and para positions: Bhalerao; Thyagarajan *Can. J. Chem.* **1968**, 46, 3367; Tomita; Minami; Uyeo *J. Chem. Soc. C* **1969**, 183.

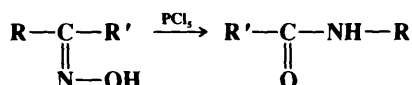
²³³There has been some controversy about this mechanism. For a discussion, see Vogler; Hayes *J. Org. Chem.* **1979**, 44, 3682.

²³⁴Smith *J. Am. Chem. Soc.* **1948**, 70, 320; Smith; Antoniadis *Tetrahedron* **1960**, 9, 210. A slightly different mechanism, involving direct rearrangement of **65**, has been shown in certain cases: Fikes; Shechter *J. Org. Chem.* **1979**, 44, 741. See also Bach; Wolber *J. Org. Chem.* **1972**, 47, 239.

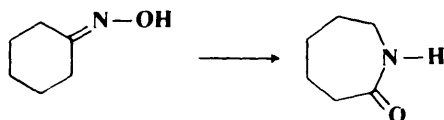
The intermediates **66** have been independently generated in aqueous solution.²³⁵ Note the similarity of this mechanism to those of "insertion" of CH₂ (**8-9**) and of O (**8-20**). The three reactions are essentially analogous, both in products and in mechanism.²³⁶ Also note the similarity of the latter part of this mechanism to that of the Beckmann rearrangement (**8-18**).

OS V, 408; VI, 368; VII, 254. See also OS V, 623.

8-18 The Beckmann Rearrangement Beckmann oxime–amide rearrangement



When oximes are treated with PCl₅ or a number of other reagents, they rearrange to substituted amides in a reaction called the *Beckmann rearrangement*.²³⁷ Among other reagents used have been concentrated H₂SO₄, formic acid, liquid SO₂, HMPA,²³⁸ SOCl₂,²³⁹ silica gel,²⁴⁰ P₂O₅–methanesulfonic acid,²⁴¹ HCl–HOAc–Ac₂O, and polyphosphoric acid.²⁴² The group that migrates is generally the one anti to the hydroxyl, and this is often used as a method of determining the configuration of the oxime. However, it is not unequivocal. It is known that with some oximes the syn group migrates and that with others, especially where R and R' are both alkyl, mixtures of the two possible amides are obtained. However, this behavior does not necessarily mean that the syn group actually undergoes migration. In most cases the oxime undergoes isomerization under the reaction conditions *before* migration takes place.²⁴³ The scope of the reaction is quite broad. R and R' may be alkyl, aryl, or hydrogen. However, hydrogen very seldom *migrates*, so the reaction is not generally a means of converting aldoximes to unsubstituted amides RCONH₂. This conversion can be accomplished, though, by treatment of the aldoxime with nickel acetate under neutral conditions²⁴⁴ or by heating the aldoxime for 60 hr at 100°C after it has been adsorbed onto silica gel.²⁴⁵ As in the case of the Schmidt rearrangement, when the oxime is derived from an alkyl aryl ketone, it is generally the aryl group that preferentially migrates. The oximes of cyclic ketones give ring enlargement,²⁴⁶ e.g.,



²³⁵Amyes; Richard *J. Am. Chem. Soc.* **1991**, 113, 1867.

²³⁶For evidence for this mechanism, see Koldobskii; Enin; Naumov; Ostrovskii; Tereshchenko; Bagal *J. Org. Chem. USSR* **1972**, 8, 242; Ostrovskii; Koshtaleva; Shirokova; Koldobskii; Gidasov *J. Org. Chem. USSR* **1974**, 10, 2365; Ref. 230.

²³⁷For reviews, see Gawley *Org. React.* **1968**, 35, 1-420; McCarty, in Patai *The Chemistry of the Carbon-Nitrogen Double Bond*; Wiley: New York, 1970, pp. 408-439.

²³⁸Monson; Broline *Can. J. Chem.* **1973**, 51, 942; Gupton; Idoux; Leonard; DeCrescenzo *Synth. Commun.* **1983**, 13, 1083.

²³⁹Butler; O'Donoghue *J. Chem. Res. (S)* **1983**, 18.

²⁴⁰Costa; Mestres; Riego *Synth. Commun.* **1982**, 12, 1003.

²⁴¹Eaton; Carlson; Lee *J. Org. Chem.* **1973**, 38, 4071.

²⁴²For a review of Beckmann rearrangements with polyphosphoric acid, see Beckwith, in Zabicky, Ref. 230, pp. 131-137.

²⁴³Lansbury; Mancuso *Tetrahedron Lett.* **1965**, 2445 have shown that some Beckmann rearrangements are *asymmetrically* nonstereospecific.

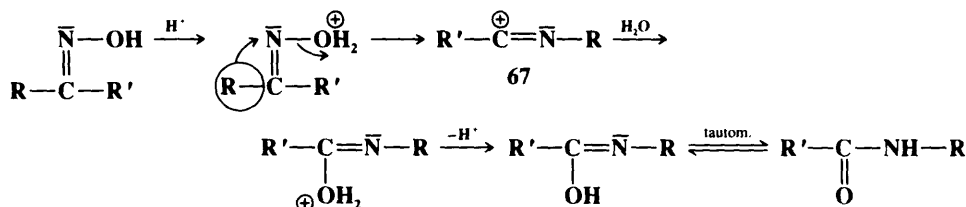
²⁴⁴Field; Hughmark; Shumaker; Marshall *J. Am. Chem. Soc.* **1961**, 83, 1983. See also Leusink; Meerbeek; Noltes *Recl. Trav. Chim. Pays-Bas* **1976**, 95, 123, **1977**, 96, 142.

²⁴⁵Chattopadhyaya; Rama Rao *Tetrahedron* **1974**, 30, 2899.

²⁴⁶For a review of such ring enlargements, see Vinnik; Zarakhani *Russ. Chem. Rev.* **1967**, 36, 51-64. For a review with respect to bicyclic oximes, see Ref. 231.

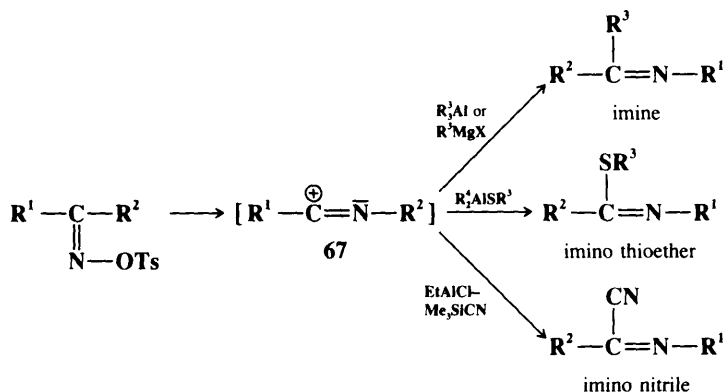
Not only do oximes undergo the Beckmann rearrangement, but so also do esters of oximes with many acids, organic and inorganic. A side reaction with many substrates is the formation of nitriles (the "abnormal" Beckmann rearrangement, 7-38). Cyclic ketones can be converted directly to lactams in one laboratory step by treatment with $\text{NH}_2\text{OSO}_2\text{OH}$ and formic acid (6-20 takes place first, then the Beckmann rearrangement).²⁴⁷

In the first step of the mechanism, the OH group is converted by the reagent to a better leaving group, e.g., proton acids convert it to OH_2^+ . After that, the mechanism follows a course analogous to that for the Schmidt reaction of ketones (8-17) from the formation of **66** on:²⁴⁸



The other reagents convert OH to an ester leaving group (e.g., OPCl_4 from PCl_5 and OSO_2OH from concentrated H_2SO_4 ²⁴⁹). Alternatively, the attack on **67** can be by the leaving group, if different from H_2O . Intermediates of the form **67** have been detected by nmr and uv spectroscopy.²⁵⁰ The rearrangement has also been found to take place by a different mechanism, involving formation of a nitrile by fragmentation, and then addition by a Ritter reaction (6-55).²⁵¹ Beckmann rearrangements have also been carried out photochemically.²⁵²

If the rearrangement of oxime sulfonates is induced by organoaluminum reagents,²⁵³ the intermediate **67** is captured by the nucleophile originally attached to the Al. By this means an oxime can be converted to an imine, an imino thioether, or an imino nitrile²⁵⁴ (in the



²⁴⁷Olah; Fung *Synthesis* **1979**, 537. See also Novoselov; Isaev; Yurchenko; Vodichka; Trshiska *J. Org. Chem. USSR* **1981**, 17, 2284.

²⁴⁸For summaries of the considerable evidence for this mechanism, see Donaruma; Heldt *Org. React.* **1960**, 11, 1-156, pp. 5-14; Smith, in Mayo, Ref. 114, vol. 1, 483-507, pp. 488-493.

²⁴⁹Gregory; Moodie; Schofield *J. Chem. Soc. B* **1970**, 338; Kim; Kawakami; Ando; Yukawa *Bull. Chem. Soc. Jpn.* **1979**, 52, 1115.

²⁵⁰Gregory; Moodie; Schofield, Ref. 249.

²⁵¹Hill; Conley; Chortyk *J. Am. Chem. Soc.* **1965**, 87, 5646; Palmere; Conley; Rabinowitz *J. Org. Chem.* **1972**, 37, 4095.

²⁵²See, for example, Izawa; Mayo; Tabata *Can. J. Chem.* **1969**, 47, 51; Cunningham; Ng Lim; Just *Can. J. Chem.* **1971**, 49, 2891; Sugimoto; Yagihashi *J. Chem. Soc., Perkin Trans. I* **1977**, 2488.

²⁵³For a review, see Maruoka; Yamamoto *Angew. Chem. Int. Ed. Engl.* **1985**, 24, 668-682 [*Angew. Chem.* 97, 670-683].

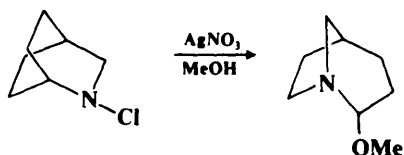
²⁵⁴Maruoka; Miyazaki; Ando; Matsumura; Sakane; Hattori; Yamamoto *J. Am. Chem. Soc.* **1983**, 105, 2831; Maruoka; Nakai; Yamamoto *Org. Synth.* **66**, 185.

last case, the nucleophile comes from added trimethylsilyl cyanide). The imine-producing reaction can also be accomplished with a Grignard reagent in benzene or toluene.²⁵⁵

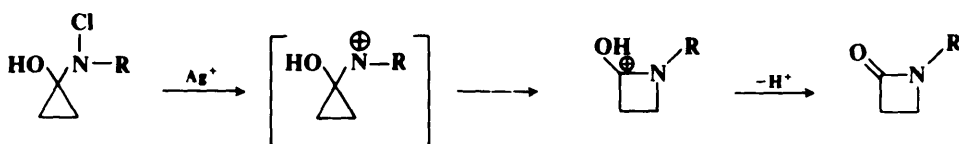
OS II, 76, 371; **66**, 185.

8-19 Stieglitz and Related Rearrangements

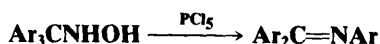
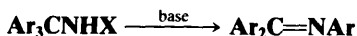
Methoxy-de-N-chloro-(2/→1/*N*-alkyl)-migr-o-substitution, etc.



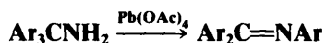
Besides the reactions discussed at **8-14** to **8-18**, a number of other rearrangements are known in which an alkyl group migrates from C to N. Certain bicyclic N-haloamines, for example N-chloro-2-azabicyclo[2.2.2]octane (above), undergo rearrangement when solvolyzed in the presence of silver nitrate.²⁵⁶ This reaction is similar to the Wagner–Meerwein rearrangement (**8-1**) and is initiated by the silver-catalyzed departure of the chloride ion.²⁵⁷ Similar reactions have been used for ring expansions and contractions, analogous to those discussed for reaction **8-3**.²⁵⁸ An example is the conversion of 1-(N-chloroamino)cyclopropanols to β -lactams.²⁵⁹



The name *Stieglitz rearrangement* is generally applied to the rearrangements of trityl N-haloamines and hydroxylamines. These reactions are similar to the rearrangements of alkyl



azides (**8-15**), and the name Stieglitz rearrangement is also given to the rearrangement of trityl azides. Another similar reaction is the rearrangement undergone by tritylamines when treated with lead tetraacetate:²⁶⁰



D. Carbon-to-Oxygen Migrations of R and Ar

²⁵⁵Hattori; Maruoka; Yamamoto *Tetrahedron Lett.* **1982**, 23, 3395.

²⁵⁶Gassman; Fox *J. Am. Chem. Soc.* **1967**, 89, 338. See also Schell; Ganguly *J. Org. Chem.* **1980**, 45, 4069; Davies; Malpass; Walker *J. Chem. Soc., Chem. Commun.* **1985**, 686; Hoffman; Kumar; Buntain *J. Am. Chem. Soc.* **1985**, 107, 4731.

²⁵⁷For C \rightarrow N rearrangements induced by AlCl_3 , see Kovacic; Lowery; Roskos *Tetrahedron* **1970**, 26, 529.

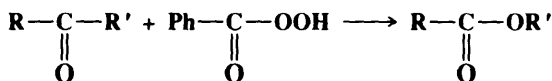
²⁵⁸Gassman; Carrasquillo *Tetrahedron Lett.* **1971**, 109; Hoffman; Buntain *J. Org. Chem.* **1988**, 53, 3316.

²⁵⁹Wasserman; Adickes; Espejo de Ochoa *J. Am. Chem. Soc.* **1971**, 93, 5586; Wasserman; Glazer; Hearn *Tetrahedron Lett.* **1973**, 4855.

²⁶⁰Sisti *Chem. Commun.* **1968**, 1272; Sisti; Milstein *J. Org. Chem.* **1974**, 39, 3932.

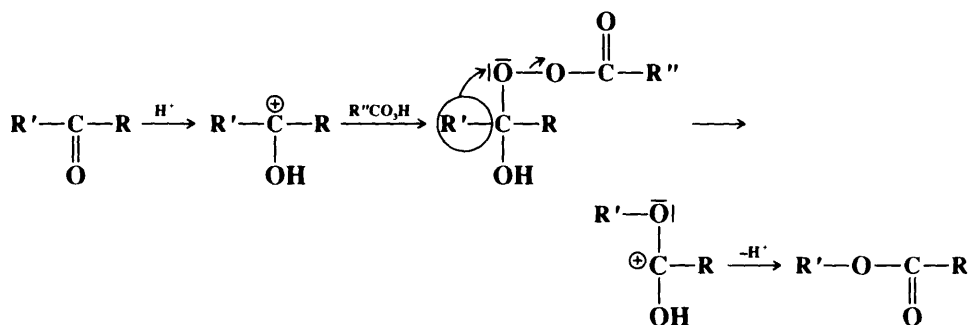
8-20 The Baeyer–Villiger Rearrangement

Oxy-insertion



The treatment of ketones with peracids such as perbenzoic or peracetic acid, or with other peroxy compounds in the presence of acid catalysts, gives carboxylic esters by “insertion” of oxygen.²⁶¹ The reaction is called the *Baeyer–Villiger rearrangement*.²⁶² A particularly good reagent is peroxytrifluoroacetic acid. Reactions with this reagent are rapid and clean, giving high yields of product, though it is often necessary to add a buffer such as Na₂HPO₄ to prevent transesterification of the product with trifluoroacetic acid. The reaction is often applied to cyclic ketones to give lactones.²⁶³ Enantioselective synthesis of chiral lactones from achiral ketones has been achieved by the use of enzymes as catalysts.²⁶⁴ For acyclic compounds, R' must usually be secondary, tertiary, or vinylic, although primary R' has been rearranged with peroxytrifluoroacetic acid,²⁶⁵ with BF₃–H₂O₂,²⁶⁶ and with K₂S₂O₈–H₂SO₄.²⁶⁷ For unsymmetrical ketones the approximate order of migration is tertiary alkyl > secondary alkyl, aryl > primary alkyl > methyl. Since the methyl group has a low migrating ability, the reaction provides a means of cleaving a methyl ketone R'COMe to produce an alcohol or phenol R'OH (by hydrolysis of the ester R'OCOME). The migrating ability of aryl groups is increased by electron-donating and decreased by electron-withdrawing substituents.²⁶⁸ Enolizable β-diketones do not react. α-Diketones can be converted to anhydrides.²⁶⁹ With aldehydes, migration of hydrogen gives the carboxylic acid, and this is a way of accomplishing 4-6. Migration of the other group would give formates, but this seldom happens, though aryl aldehydes have been converted to formates with H₂O₂ and a selenium compound²⁷⁰ (see also the Dakin reaction in 9-12).

The mechanism²⁷¹ is similar to those of the analogous reactions with hydrazoic acid (8-17 with ketones) and diazomethane (8-8):



²⁶¹For a list of reagents, with references, see Ref. 106, p. 843.

²⁶²For reviews, see Hudlický *Oxidations in Organic Chemistry*; American Chemical Society: Washington, 1990, pp. 186-195; Plesničar, in Trahanovsky *Oxidation in Organic Chemistry*, pt. C; Academic Press: New York, 1978, pp. 254-267; House *Modern Synthetic Reactions*, 2nd ed.; W.A. Benjamin: New York, 1972, pp. 321-329; Lewis, in *Augustine Oxidation*, vol. 1; Marcel Dekker: New York, 1969, pp. 237-244; Lee; *Uff Q. Rev. Chem. Soc.* **1967**, 21, 429-457, pp. 449-453. For a review of enzyme-catalyzed Baeyer–Villiger rearrangements, see Walsh; Chen *Angew. Chem. Int. Ed. Engl.* **1988**, 27, 333-343 [*Angew. Chem.* **100**, 342-352].

²⁶³For a review of the reaction as applied to bicyclic ketones, see Krow *Tetrahedron* **1981**, 37, 2697-2724.

²⁶⁴See Taschner; Black *J. Am. Chem. Soc.* **1988**, 110, 6892.

²⁶⁵Emmons; Lucas *J. Am. Chem. Soc.* **1955**, 77, 2287.

²⁶⁶McClure; Williams *J. Org. Chem.* **1962**, 27, 24.

²⁶⁷Deno; Billups; Kramer; Lastomirsky *J. Org. Chem.* **1970**, 35, 3080.

²⁶⁸For a report of substituent effects in the α, β, and γ positions of alkyl groups, see Noyori; Sato; Kobayashi *Bull. Chem. Soc. Jpn.* **1983**, 56, 2661.

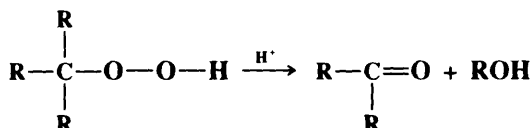
²⁶⁹For a study of the mechanism of this conversion, see Cullis; Arnold; Clarke; Howell; DeMira; Naylor; Nicholls *J. Chem. Soc., Chem. Commun.* **1987**, 1088.

²⁷⁰Syber *Synthesis* **1989**, 167. See also Godfrey; Sargent; Elix *J. Chem. Soc., Perkin Trans. 1* **1974**, 1353.

²⁷¹Proposed by Criegee *Liebigs Ann. Chem.* **1948**, 560, 127.

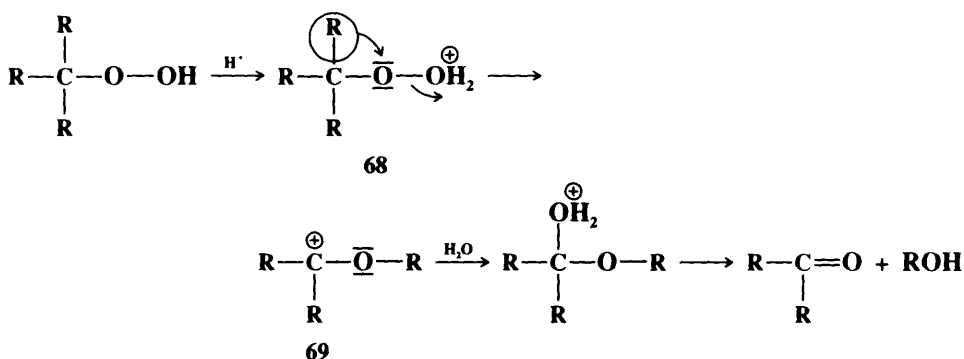
One important piece of evidence for this mechanism was that benzophenone- ^{18}O gave ester entirely labeled in the carbonyl oxygen, with none in the alkoxy oxygen.²⁷² Carbon-14 isotope-effect studies on acetophenones have shown that migration of aryl groups takes place in the rate-determining step,²⁷³ demonstrating that migration of Ar is concerted with departure of OCOR' .²⁷⁴ (It is hardly likely that migration would be the slow step if the leaving group departed first to give an ion with a positive charge on an oxygen atom, which would be a highly unstable species.)

8-21 Rearrangement of Hydroperoxides C-Alkyl-O-hydroxy-elimination



Hydroperoxides ($\text{R} = \text{alkyl, aryl, or hydrogen}$) can be cleaved by proton or Lewis acids in a reaction whose principal step is a rearrangement.²⁷⁵ The reaction has also been applied to peroxy esters $\text{R}_3\text{COOCOR}'$, but less often. When aryl and alkyl groups are both present, migration of aryl dominates. It is not necessary actually to prepare and isolate hydroperoxides. The reaction takes place when the alcohols are treated with H_2O_2 and acids. Migration of an alkyl group of a primary hydroperoxide provides a means for converting an alcohol to its next lower homolog ($\text{RCH}_2\text{OOH} \rightarrow \text{CH}_2=\text{O} + \text{ROH}$).

The mechanism is as follows:²⁷⁶



The last step is hydrolysis of the unstable hemiacetal. Alkoxy carbocation intermediates (**69**, $\text{R} = \text{alkyl}$) have been isolated in super-acid solution²⁷⁷ at low temperatures, and their structures proved by nmr.²⁷⁸ The protonated hydroperoxides (**68**) could not be observed in these solutions, evidently reacting immediately on formation.

OS V, 818.

²⁷²Doering; Dorfman *J. Am. Chem. Soc.* **1953**, *75*, 5595. For summaries of the other evidence, see Smith, Ref. 248, pp. 578-584.

²⁷³Palmer; Fry *J. Am. Chem. Soc.* **1970**, *92*, 2580. See also Mitsuhashi; Miyadera; Simamura; *Chem. Commun.* **1970**, 1301. For secondary isotope-effect studies, see Winnik; Stoute; Fitzgerald *J. Am. Chem. Soc.* **1974**, *96*, 1977.

²⁷⁴In some cases the rate-determining step has been shown to be the addition of peracid to the substrate [see, for example, Ogata; Sawaki *J. Org. Chem.* **1972**, *37*, 2953]. Even in these cases it is still highly probable that migration is concerted with departure of the nucleofuge.

²⁷⁵For reviews, see Yablokov *Russ. Chem. Rev.* **1980**, *49*, 833-842; Lee; Uff, Ref. 262, 445-449.

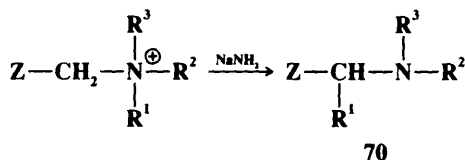
²⁷⁶For a discussion of the transition state involved in the migration step, see Wistuba; Rüchardt *Tetrahedron Lett.* **1981**, *22*, 3389.

²⁷⁷For a review of peroxy compounds in super acids, see Olah; Parker; Yoneda *Angew. Chem. Int. Ed. Engl.* **1978**, *17*, 909-931 [*Angew. Chem.* **90**, 962-984].

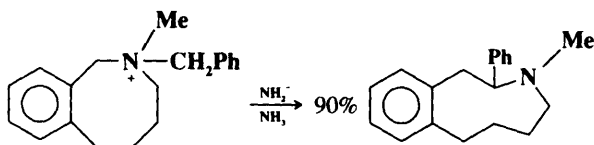
²⁷⁸Sheldon; van Doorn *Tetrahedron Lett.* **1973**, 1021.

E. Nitrogen-to-Carbon, Oxygen-to-Carbon, and Sulfur-to-Carbon Migration

8-22 The Stevens Rearrangement

Hydron-(2/*N*→1/alkyl)-migr-detachment

In the *Stevens rearrangement* a quaternary ammonium salt containing an electron-withdrawing group Z on one of the carbons attached to the nitrogen is treated with a strong base (such as NaOR or NaNH₂) to give a rearranged tertiary amine. Z is a group such as RCO, ROOC, phenyl, etc.²⁷⁹ The most common migrating groups are allylic, benzylic, benzhydryl, 3-phenylpropargyl, and phenacyl, though even methyl migrates to a sufficiently negative center.²⁸⁰ When an allylic group migrates, it may or may not involve an allylic rearrangement within the migrating group (see 8-37), depending on the substrate and reaction conditions. The reaction has been used for ring enlargement,²⁸¹ e.g.:



The mechanism has been the subject of much study.²⁸² That the rearrangement is intramolecular was shown by crossover experiments, by ¹⁴C labeling,²⁸³ and by the fact that retention of configuration is found at R¹.²⁸⁴ The first step is loss of the acidic proton to give the ylide **71**, which has been isolated.²⁸⁵ The finding²⁸⁶ that CIDNP spectra²⁸⁷ could be obtained in many instances shows that in these cases the product is formed directly from a free-radical precursor. The following radical pair mechanism was proposed:²⁸⁸

²⁷⁹For reviews of the Stevens rearrangement, see Lepley; Giumanini *Mech. Mol. Migr.* **1971**, 3, 297-440; Pine *Org. React.* **1970**, 18, 403-464. For reviews of the Stevens and the closely related Wittig rearrangement (8-23), see Stevens; Watts, Ref. 1, pp. 81-116; Wilt, in Kochi, Ref. 55, pp. 448-458; Iwai *Mech. Mol. Migr.* **1969**, 2, 73-116, pp. 105-113; Stevens *Prog. Org. Chem.* **1968**, 7, 48-74.

²⁸⁰Migration of aryl is rare, but has been reported: Heaney; Ward *Chem. Commun.* **1969**, 810; Truce; Heuring *Chem. Commun.* **1969**, 1499.

²⁸¹Elmasmodi; Cotelle; Barbry; Hasiak; Couturier *Synthesis* **1989**, 327.

²⁸²For example, see Pine *J. Chem. Educ.* **1971**, 48, 99-102.

²⁸³Stevens *J. Chem. Soc.* **1930**, 2107; Johnstone; Stevens *J. Chem. Soc.* **1955**, 4487.

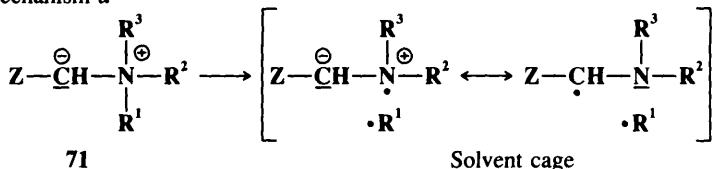
²⁸⁴Brewster; Kline *J. Am. Chem. Soc.* **1952**, 74, 5179; Schöllkopf; Ludwig; Ostermann; Patsch *Tetrahedron Lett.* **1969**, 3415.

²⁸⁵Jemison; Mageswaran; Ollis; Potter; Pretty; Sutherland; Thebtaranonth *Chem. Commun.* **1970**, 1201.

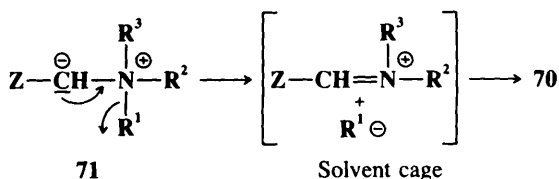
²⁸⁶Lepley *J. Am. Chem. Soc.* **1969**, 91, 1237. *Chem. Commun.* **1969**, 1460; Lepley; Becker; Giumanini *J. Org. Chem.* **1971**, 36, 1222; Baldwin; Brown; *J. Am. Chem. Soc.* **1969**, 91, 3646; Jemison; Morris *Chem. Commun.* **1969**, 1226; Ref. 285; Schöllkopf et al., Ref. 284.

²⁸⁷For a review of the application of CIDNP to rearrangement reactions, see Lepley, in Lepley; Closs *Chemically Induced Magnetic Polarization*; Wiley: New York, 1973, pp. 323-384.

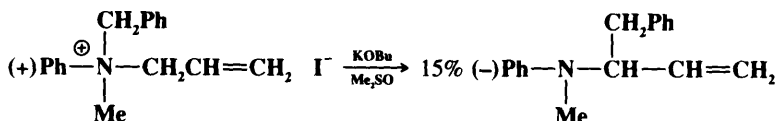
²⁸⁸Schöllkopf; Ludwig *Chem. Ber.* **1968**, 101, 2224; Ollis; Rey; Sutherland *J. Chem. Soc., Perkin Trans I.* **1983**, 1009, 1049.

Mechanism *a*

The radicals do not drift apart because they are held together by the solvent cage. According to this mechanism, the radicals must recombine rapidly in order to account for the fact that R¹ does not racemize. Other evidence in favor of mechanism *a* is that in some cases small amounts of coupling products (R¹R¹) have been isolated,²⁸⁹ which would be expected if some $\cdot\text{R}^1$ leaked from the solvent cage. However, not all the evidence is easily compatible with mechanism *a*.²⁹⁰ It is possible that another mechanism (*b*) similar to mechanism *a*, but involving ion pairs in a solvent cage instead of radical pairs, operates in some cases. A third

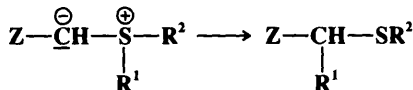
Mechanism *b*

possible mechanism would be a concerted 1,2-shift,²⁹¹ but the orbital symmetry principle requires that this take place with inversion at R¹.²⁹² (See p. 1126.) Since the actual migration takes place with retention, it cannot, according to this argument, proceed by a concerted mechanism. However, in the case where the migrating group is allylic, a concerted mechanism can also operate (8-37). An interesting finding compatible with all three mechanisms is that optically active allylbenzylmethylphenylammonium iodide (asymmetric nitrogen, see p. 98) gave an optically active product:²⁹³



The Sommelet-Hauser rearrangement competes when Z is an aryl group (see 3-26). Hofmann elimination competes when one of the R groups contains a β hydrogen atom (7-6 and 7-7).

Sulfur ylides containing a Z group give an analogous rearrangement, often also referred to as a Stevens rearrangement.²⁹⁴ In this case too, there is much evidence (including CIDNP)



²⁸⁹Schöllkopf et al., Ref. 284; Hennion; Shoemaker *J. Am. Chem. Soc.* **1970**, 92, 1769.

²⁹⁰See, for example, Pine; Catto; Yamagishi *J. Org. Chem.* **1970**, 35, 3663.

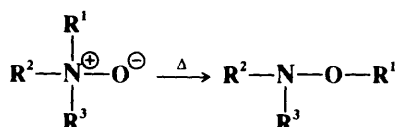
²⁹¹For evidence against this mechanism, see Jenny; Druey *Angew. Chem. Int. Ed. Engl.* **1962**, 1, 155 [*Angew. Chem.* 74, 152].

²⁹²Woodward; Hoffmann *The Conservation of Orbital Symmetry*; Academic Press: New York, 1970, p. 131.

²⁹³Hill; Chan *J. Am. Chem. Soc.* **1966**, 88, 866.

²⁹⁴For a review, see Olsen; Currie, in Patai *The Chemistry of The Thiol Group*, pt. 2; Wiley: New York, 1974, pp. 561-566.

that a radical-pair cage mechanism is operating,²⁹⁵ except that when the migrating group is allylic, the mechanism may be different (see 8-37). Another reaction with a similar mechanism²⁹⁶ is the *Meisenheimer rearrangement*,²⁹⁷ in which certain tertiary amine oxides rearrange on heating to give substituted hydroxylamines. The migrating group R¹ is almost

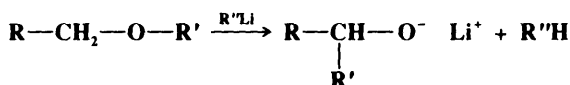


always allylic or benzylic.²⁹⁸ R² and R³ may be alkyl or aryl, but if one of the R groups contains a β hydrogen, Cope elimination (7-8) often competes.

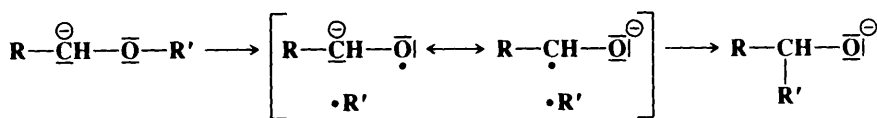
Certain tertiary benzylic amines, when treated with BuLi, undergo a rearrangement analogous to the Wittig rearrangement (8-23), e.g., PhCH₂NPh₂ → Ph₂CHNHPh.²⁹⁹ Only aryl groups migrate in this reaction.

Isocyanides, when heated in the gas phase or in nonpolar solvents, undergo a 1,2-intramolecular rearrangement to nitriles: RNC → RCN.³⁰⁰ In polar solvents the mechanism is different.³⁰¹

8-23 The Wittig Rearrangement Hydron-(2/O→1/alkyl)-migr-detachment



The rearrangement of ethers with alkylolithiums is called the *Wittig rearrangement* (not to be confused with the Wittig reaction, 6-47) and is similar to 8-22.²⁷⁹ However, a stronger base is required (e.g., phenyllithium or sodium amide). R and R' may be alkyl, aryl, or vinylic.³⁰² Also, one of the hydrogens may be replaced by an alkyl or aryl group, in which case the product is the salt of a tertiary alcohol. Migratory aptitudes here are allylic, benzylic > ethyl > methyl > phenyl.³⁰³ The following radical-pair mechanism³⁰⁴ (similar to



Solvent cage

²⁹⁵See, for example, Baldwin; Erickson; Hackler; Scott *Chem. Commun.* **1970**, 576; Schöllkopf; Schossig; Ostermann *Liebigs Ann. Chem.* **1970**, 737, 158; Iwamura; Iwamura; Nishida; Yoshida; Nakayama *Tetrahedron Lett.* **1971**, 63.

²⁹⁶For some of the evidence, see Schöllkopf; Ludwig *Chem. Ber.* **1968**, 101, 2224; Ostermann; Schöllkopf *Liebigs Ann. Chem.* **1970**, 737, 170; Lorand; Grant; Samuel; O'Connell; Zaro *Tetrahedron Lett.* **1969**, 4087.

²⁹⁷For a review, see Johnstone *Mech. Mol. Migr.* **1969**, 2, 249-266.

²⁹⁸Migration of aryl and of certain alkyl groups has also been reported. See Khuthier; Al-Mallah; Hanna; Abdulla *J. Org. Chem.* **1987**, 52, 1710, and references cited therein.

²⁹⁹Eisch; Dua; Kovacs *J. Org. Chem.* **1987**, 52, 4437; Eisch; Kovacs; Chobe *J. Org. Chem.* **1989**, 54, 1275.

³⁰⁰See Meier; Rüchardt *Chem. Ber.* **1987**, 120, 1; Meier; Müller; Rüchardt *J. Org. Chem.* **1987**, 52, 648; Pakusch; Rüchardt *Chem. Ber.* **1991**, 124, 971.

³⁰¹Meier; Rüchardt *Chimia* **1986**, 40, 238.

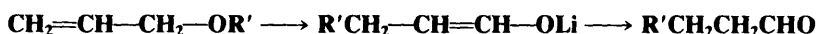
³⁰²For migration of vinyl, see Rautenstrauch; Büchi; Wüest *J. Am. Chem. Soc.* **1974**, 96, 2576.

³⁰³Wittig *Angew. Chem.* **1954**, 66, 10; Solov'yanov; Ahmed; Beletskaya; Reutov *J. Chem. Soc., Chem. Commun.* **1987**, 23, 1232.

³⁰⁴For a review of the mechanism, see Schöllkopf *Angew. Chem. Int. Ed. Engl.* **1970**, 9, 763-773 [*Angew. Chem.* **82**, 795-805].

mechanism *a* of **8-22**) is likely, after removal of the proton by the base. One of the radicals in the radical pair is a ketyl. Among the evidence for this mechanism is (1) the rearrangement is largely intramolecular; (2) migratory aptitudes are in the order of free-radical stabilities, not of carbanion stabilities³⁰⁵ (which rules out an ion-pair mechanism similar to mechanism *b* of **8-22**); (3) aldehydes are obtained as side products;³⁰⁶ (4) partial racemization of R' has been observed³⁰⁷ (the remainder of the product retained its configuration); (5) crossover products have been detected;³⁰⁸ and (6) when ketyl radicals and R• radicals from different precursors were brought together, similar products resulted.³⁰⁹ However, there is evidence that at least in some cases the radical-pair mechanism accounts for only a portion of the product, and some kind of concerted mechanism can also take place.³¹⁰ Most of the above investigations were carried out with systems where R' is alkyl, but a radical-pair mechanism has also been suggested for the case where R' is aryl.³¹¹ When R' is allylic a concerted mechanism can operate (**8-37**).

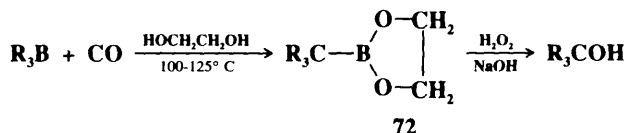
When R is vinylic it is possible, by using a combination of an alkyl lithium and *t*-BuOK, to get migration to the γ carbon (as well as to the α carbon), producing an enolate that, on hydrolysis, gives an aldehyde:³¹²



There are no OS references, but see OS **66**, 14, for a related reaction.

F. Boron-to-Carbon Migrations.³¹³ For another reaction involving boron-to-carbon migration, see **0-99**.

8-24 Conversion of Boranes to Tertiary Alcohols



Trialkylboranes (which can be prepared from olefins by **5-12**) react with carbon monoxide³¹⁴ at 100 to 125°C in the presence of ethylene glycol to give the 2-bora-1,3-dioxolanes **72**, which

³⁰⁵Lansbury; Pattison; Sidler; Bieber *J. Am. Chem. Soc.* **1966**, 88, 78; Schäfer; Schöllkopf; Walter *Tetrahedron Lett.* **1968**, 2809.

³⁰⁶For example, see Hauser; Kantor *J. Am. Chem. Soc.* **1951**, 73, 1437; Cast; Stevens; Holmes *J. Chem. Soc.* **1960**, 3521.

³⁰⁷Schöllkopf; Fabian *Liebigs Ann. Chem.* **1961**, 642, 1; Schöllkopf; Schäfer *Liebigs Ann. Chem.* **1963**, 663, 22; Felkin; Frajeran *Tetrahedron Lett.* **1977**, 3485; Hebert; Welvart *J. Chem. Soc., Chem. Commun.* **1980**, 1035; *Nouv. J. Chim.* **1981**, 5, 327.

³⁰⁸Lansbury; Pattison *J. Org. Chem.* **1962**, 27, 1933; *J. Am. Chem. Soc.* **1962**, 84, 4295.

³⁰⁹Garst; Smith *J. Am. Chem. Soc.* **1973**, 95, 6870.

³¹⁰Garst; Smith *J. Am. Chem. Soc.* **1976**, 98, 1526. For evidence against this, see Hebert; Welvart; Ghelfenstein; Szwarc *Tetrahedron Lett.* **1983**, 24, 1381.

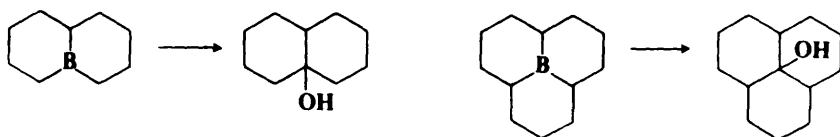
³¹¹Eisch; Kovacs; Rhee *J. Organomet. Chem.* **1974**, 65, 289.

³¹²Schlosser; Strunk *Tetrahedron* **1989**, 45, 2649.

³¹³For reviews, see Matteson, in Hartley *The Chemistry of the Metal-Carbon Bond*, vol. 4; Wiley: New York, 1984, pp. 307-409, pp. 346-387; Pelter; Smith; Brown *Borane Reagents*; Academic Press: New York, 1988, pp. 256-301; Negishi; Idacavage *Org. React.* **1985**, 33, 1-246; Suzuki *Top. Curr. Chem.* **1983**, 112, 67-115; Pelter, in Mayo, Ref. 1, vol. 2, pp. 95-147; *Chem. Soc. Rev.* **1982**, 11, 191-225; Cragg; Koch *Chem. Soc. Rev.* **1977**, 6, 393-412; Weill-Raynal *Synthesis* **1976**, 633-651; Cragg *Organoboranes in Organic Synthesis*; Marcel Dekker: New York, 1973, pp. 249-300; Pactzold; Grundke *Synthesis* **1973**, 635-660.

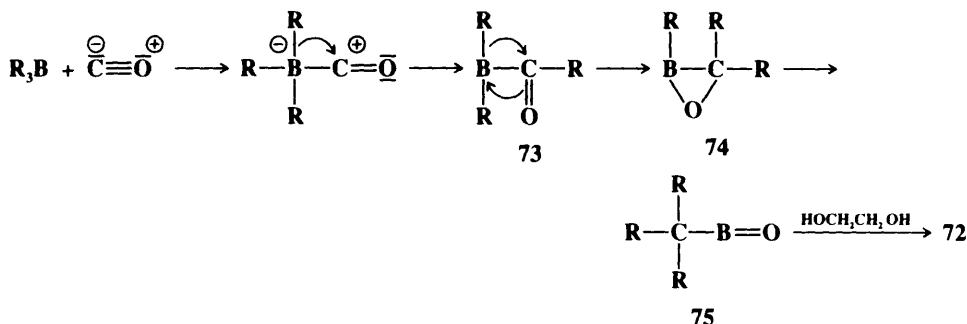
³¹⁴For discussions of the reactions of boranes with CO, see Negishi *Intra-Sci. Chem. Rep.* **1973**, 7(1), 81-94; Brown *Boranes in Organic Chemistry*; Cornell University Press: Ithaca, NY, 1972, pp. 343-371; *Acc. Chem. Res.* **1969**, 2, 65-72.

are easily oxidized (2-28) to tertiary alcohols.³¹⁵ The R groups may be primary, secondary, or tertiary, and may be the same or different.³¹⁶ Yields are high and the reaction is quite useful, especially for the preparation of sterically hindered alcohols such as tricyclohexylcarbinol and tri-2-norbornylcarbinol, which are difficult to prepare by 6-29. Heterocycles in which boron is a ring atom react similarly (except that high CO pressures are required), and cyclic alcohols can be obtained from these substrates.³¹⁷ The preparation of such het-



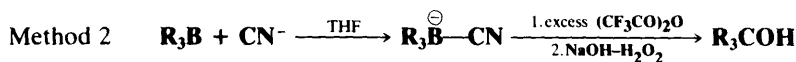
erocyclic boranes was discussed at 5-12. The overall conversion of a diene or triene to a cyclic alcohol has been described by H. C. Brown as "stitching" with boron and "riveting" with carbon.

Though the mechanism has not been investigated thoroughly, it has been shown to be intramolecular by the failure to find crossover products when mixtures of boranes are used.³¹⁸ The following scheme, involving three boron-to-carbon migrations, has been suggested.



The purpose of the ethylene glycol is to intercept the boronic anhydride 75, which otherwise forms polymers that are difficult to oxidize. As we shall see in 8-25 and 8-26, it is possible to stop the reaction after only one or two migrations have taken place.

There are two other methods for achieving the conversion $R_3B \rightarrow R_3COH$, which often give better results: (1) treatment with α,α -dichloromethyl methyl ether and the base lithium



76

³¹⁵Hillman *J. Am. Chem. Soc.* **1962**, *84*, 4715, **1963**, *85*, 982; Brown; Rathke *J. Am. Chem. Soc.* **1967**, *89*, 2737; Puzitskii; Pirozhkov; Ryabova; Pastukhova; Eidus *Bull. Acad. Sci. USSR, Div. Chem. Sci.* **1972**, *21*, 1939, **1973**, *22*, 1760; Brown; Cole; Srebnik; Kim *J. Org. Chem.* **1966**, *51*, 4925.

³¹⁶Brown; Negishi; Gupta *J. Am. Chem. Soc.* **1970**, *92*, 6648; Brown; Gupta *J. Am. Chem. Soc.* **1971**, *93*, 1818; Negishi; Brown *Synthesis* **1972**, 197.

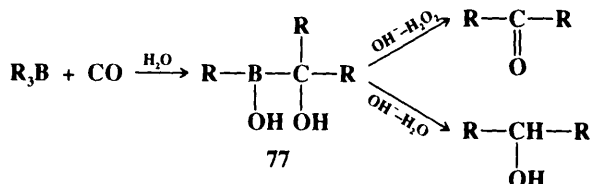
³¹⁷Brown; Negishi *J. Am. Chem. Soc.* **1967**, *89*, 5478; Knights; Brown *J. Am. Chem. Soc.* **1968**, *90*, 5283; Brown; Negishi; Dickason *J. Org. Chem.* **1985**, *50*, 520.

³¹⁸Brown; Rathke *J. Am. Chem. Soc.* **1967**, *89*, 4528.

triethylcarboxide;³¹⁹ (2) treatment with a suspension of sodium cyanide in THF followed by reaction of the resulting trialkylcyanoborate **76** with an excess (more than 2 moles) of trifluoroacetic anhydride.³²⁰ All the above migrations take place with retention of configuration at the migrating carbon.³²¹

Several other methods for the conversion of boranes to tertiary alcohols are also known.³²² OS VII, 427.

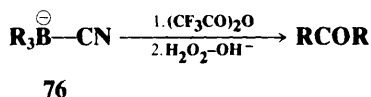
8-25 Conversion of Boranes to Secondary Alcohols or Ketones



If the reaction between trialkylboranes and carbon monoxide (**8-24**) is carried out in the presence of water followed by addition of NaOH, the product is a secondary alcohol. If H_2O_2 is added along with the NaOH, the corresponding ketone is obtained instead.³²³ Various functional groups (e.g., OAc, COOR, CN) may be present in R without being affected,³²⁴ though if they are in the α or β position relative to the boron atom, difficulties may be encountered. The reaction has been extended to the formation of unsymmetrical ketones by use of a borane of the form $\text{R}_2\text{R}'\text{B}$, where one of the groups migrates much less readily than the other (migratory aptitudes are in the order primary > secondary > tertiary).³¹⁸

The reaction follows the mechanism shown in **8-24** until formation of the borepoxide **74**. In the presence of water the third boron \rightarrow carbon migration does not take place, because the water hydrolyzes **74** to the diol **77**.

Trialkylboranes can also be converted to ketones by the cyanoborate procedure, mentioned in **8-24**. In this case the procedure is similar, but use of an equimolar amount of



trifluoroacetic anhydride leads to the ketone rather than the tertiary alcohol.³²⁵ By this procedure hexylboranes $\text{RR}'\text{R}''\text{B}$ ($\text{R}'' = \text{hexyl}$) can be converted to unsymmetrical ketones RCOR' .³²⁶ Like the carbon monoxide procedure, this method tolerates the presence of

³¹⁹Brown; Carlson *J. Org. Chem.* **1973**, 38, 2422; Brown; Katz; Carlson *J. Org. Chem.* **1973**, 38, 3968.

³²⁰Pelter; Hutchings; Smith *J. Chem. Soc., Chem. Commun.* **1973**, 186; Pelter; Hutchings; Smith; Williams *J. Chem. Soc., Perkin Trans. I* **1975**, 145; Pelter *Chem. Ind. (London)* **1973**, 206-209, *Intra-Sci. Chem. Rep.* **1973**, 7(1), 73-79.

³²¹See however Pelter; Maddocks; Smith *J. Chem. Soc., Chem. Commun.* **1978**, 805.

³²²See, for example, Lane; Brown *J. Am. Chem. Soc.* **1971**, 93, 1025; Brown; Yamamoto *Synthesis* **1972**, 699; Brown; Lane *Synthesis* **1972**, 303; Yamamoto; Brown *J. Chem. Soc., Chem. Commun.* **1973**, 801, *J. Org. Chem.* **1974**, 39, 861; Zweifel; Fisher *Synthesis* **1974**, 339; Midland; Brown; *J. Org. Chem.* **1975**, 40, 2845; Levy; Schwartz *Tetrahedron Lett.* **1976**, 2201; Hughes; Ncube; Pelter; Smith; Negishi; Yoshida *J. Chem. Soc., Perkin Trans. I* **1977**, 1172; Avasthi; Baba; Suzuki *Tetrahedron Lett.* **1980**, 21, 945; Baba; Avasthi; Suzuki *Bull. Chem. Soc. Jpn.* **1983**, 56, 1571; Pelter; Rao *J. Organomet. Chem.* **1985**, 285, 65; Junchai; Weike; Hongxun *J. Organomet. Chem.* **1989**, 367, C9; Junchai; Hongxun *J. Chem. Soc., Chem. Commun.* **1990**, 323.

³²³Brown; Rathke *J. Am. Chem. Soc.* **1967**, 89, 2738.

³²⁴Brown; Kabalka; Rathke *J. Am. Chem. Soc.* **1967**, 89, 4530.

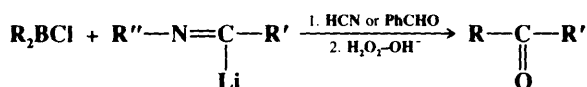
³²⁵Pelter; Smith; Hutchings; Rowe *J. Chem. Soc., Perkin Trans. I* **1975**, 129; Ref. 320. See also Pelter; Hutchings; Smith *J. Chem. Soc., Perkin Trans. I* **1975**, 142; Mallison; White; Pelter; Rowe; Smith *J. Chem. Res. (S)* **1978**, 234.

³²⁶This has been done enantioselectively: Brown; Bakshi; Singaram *J. Am. Chem. Soc.* **1988**, 110, 1529.

various functional groups in R. Another method involves the treatment of borinic acid esters (which can be prepared by treatment of dialkylchloroboranes with alcohols) with α,α -di-



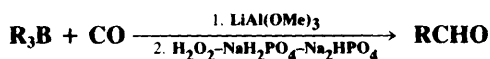
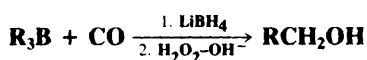
chloromethyl methyl ether and lithium triethylcarboxide.³²⁷ This method does not waste an R group, is carried out under mild conditions, and has been made enantioselective.³²⁸ A closely related method uses boronic esters RB(OR')_2 and LiCHCl_2 . By the use of chiral R' , this method has been used to prepare optically active alcohols.³²⁹ In still another procedure ketones are prepared by the reaction between dialkylchloroboranes and lithium aldimines³³⁰ (which can be prepared by 6-69).



For another conversion of trialkylboranes to ketones, see 8-28.³³¹ Other conversions of boranes to secondary alcohols are also known.³³²

OS VI, 137.

8-26 Conversion of Boranes to Primary Alcohols, Aldehydes, or Carboxylic Acids



When the reaction between a trialkylborane and carbon monoxide (8-24) is carried out in the presence of a reducing agent such as lithium borohydride or potassium triisopropoxyborohydride, the reduction agent intercepts the intermediate **73**, so that only one boron-to-carbon migration takes place, and the product is hydrolyzed to a primary alcohol or oxidized to an aldehyde.³³³ This procedure wastes two of the three R groups, but this problem can be avoided by the use of B-alkyl-9-BBN derivatives (p. 785). Since only the 9-alkyl group

³²⁷Carlson; Brown *J. Am. Chem. Soc.* **1973**, 95, 6876. *Synthesis* **1973**, 776.

³²⁸Brown; Srebnik; Bakshi; Cole *J. Am. Chem. Soc.* **1987**, 109, 5420; Brown; Gupta; Vara Prasad; Srebnik *J. Org. Chem.* **1988**, 53, 1391.

³²⁹For reviews, see Matteson *Mol. Struct. Energ.* **1988**, 5, 343-356, *Acc. Chem. Res.* **1988**, 21, 294-300, *Synthesis* **1986**, 973-985, pp. 980-983.

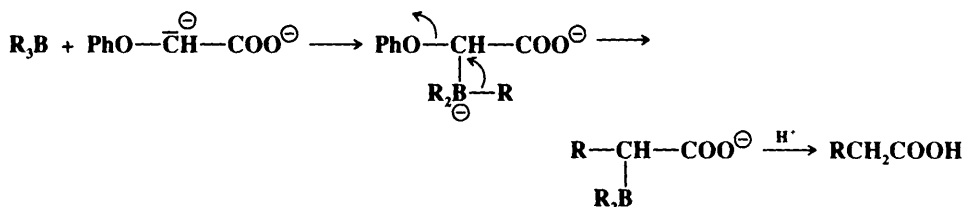
³³⁰Yamamoto; Kondo; Moritani *Tetrahedron Lett.* **1974**, 793; *Bull. Chem. Soc. Jpn.* **1975**, 48, 3682. See also Yamamoto; Kondo; Moritani *J. Org. Chem.* **1975**, 40, 3644.

³³¹For still other methods, see Brown; Levy; Midland *J. Am. Chem. Soc.* **1975**, 97, 5017; Ncube; Pelter; Smith *Tetrahedron Lett.* **1979**, 1893; Pelter; Rao, Ref. 322; Yogo; Koshino; Suzuki *Chem. Lett.* **1981**, 1059; Kulkarni; Lee; Brown *J. Org. Chem.* **1980**, 45, 4542, *Synthesis* **1982**, 193; Brown; Bhat; Basavaiah *Synthesis* **1983**, 885; Narayana; Periasamy *Tetrahedron Lett.* **1985**, 26, 6361.

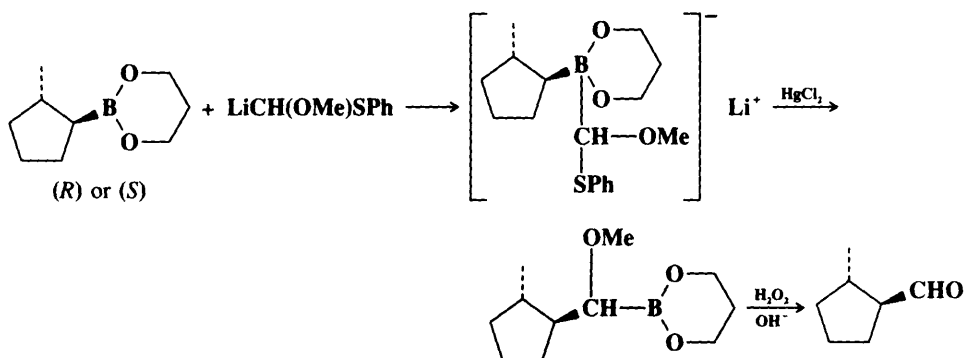
³³²See for example, Zweifel; Fisher, Ref. 322; Brown; Yamamoto *J. Am. Chem. Soc.* **1971**, 93, 2796, *Chem. Commun.* **1971**, 1535, *J. Chem. Soc., Chem. Commun.* **1972**, 71; Brown; DeLue *J. Am. Chem. Soc.* **1974**, 96, 311; Hubbard; Brown *Synthesis* **1978**, 676; Uguen *Bull. Soc. Chim. Fr.* **1981**, II-99.

³³³Brown; Rathke *J. Am. Chem. Soc.* **1967**, 89, 2740; Brown; Coleman; Rathke *J. Am. Chem. Soc.* **1968**, 90, 499; Brown; Hubbard; Smith *Synthesis* **1979**, 701. For discussions of the mechanism, see Brown; Hubbard *J. Org. Chem.* **1979**, 44, 467; Hubbard; Smith *J. Organomet. Chem.* **1984**, 276, C41.

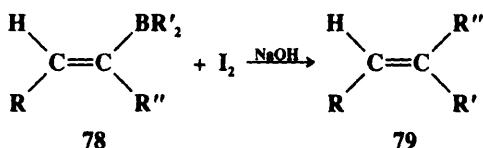
migrates, this method permits the conversion in high yield of an alkene to a primary alcohol or aldehyde containing one more carbon.³³⁴ When B-alkyl-9-BBN derivatives are treated with CO and lithium tri-*t*-butoxyaluminum hydride,³³⁵ other functional groups (e.g., CN and ester) can be present in the alkyl group without being reduced.³³⁶ Boranes can be directly converted to carboxylic acids by reaction with the dianion of phenoxycetic acid.³³⁷



Boronic esters $\text{RB}(\text{OR}')_2$ react with methoxy(phenylthio)methyl lithium $\text{LiCH}(\text{OMe})\text{SPh}$ to give salts, which, after treatment with HgCl_2 and then H_2O_2 , yield aldehydes.³³⁸ This synthesis has been made enantioselective, with high ee values ($> 99\%$), by the use of an optically pure boronic ester,³³⁹ e.g.:



8-27 Conversion of Vinylic Boranes to Alkenes



The reaction between trialkylboranes and iodine to give alkyl iodides was mentioned at 2-30. When the substrate contains a vinylic group, the reaction takes a different course,³⁴⁰

³³⁴Brown; Knights; Coleman *J. Am. Chem. Soc.* **1969**, *91*, 2144.

³³⁵Brown; Coleman *J. Am. Chem. Soc.* **1969**, *91*, 4606.

³³⁶For other methods of converting boranes to aldehydes, see Yamamoto; Shiono; Mukaiyama *Chem. Lett.* **1973**, 961; Negishi; Yoshida; Silveira; Chiou *J. Org. Chem.* **1975**, *40*, 814.

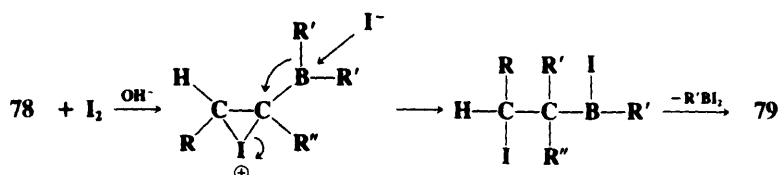
³³⁷Hara; Kishimura; Suzuki; Dhillon *J. Org. Chem.* **1990**, *55*, 6356. See also Brown; Imai *J. Org. Chem.* **1984**, *49*, 892.

³³⁸Brown; Imai *J. Am. Chem. Soc.* **1983**, *105*, 6285. For a related method that produces primary alcohols, see Brown; Imai; Perumal; Singaram *J. Org. Chem.* **1985**, *50*, 4032.

³³⁹Brown; Imai; Desai; Singaram *J. Am. Chem. Soc.* **1985**, *107*, 4980.

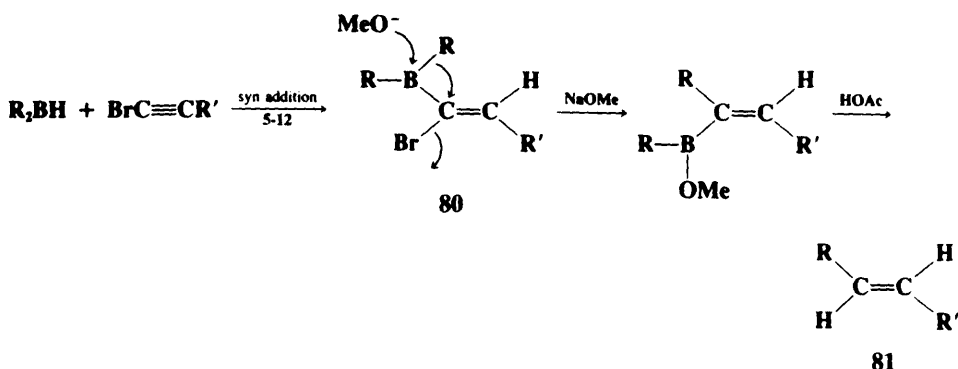
³⁴⁰Zweifel; Arzoumanian; Whitney *J. Am. Chem. Soc.* **1967**, *89*, 3652; Zweifel; Fisher *Synthesis* **1975**, 376; Brown; Basavaiah; Kulkarni; Bhat; Vara Prasad *J. Org. Chem.* **1988**, *53*, 239.

with one of the R' groups migrating to the carbon, to give alkenes **79**.³⁴¹ The reaction is stereospecific in two senses: (1) if the groups R and R'' are cis in the starting compound, they will be trans in the product; (2) there is retention of configuration within the migrating group R'.³⁴² Since vinylic boranes can be prepared from alkynes (5-12), this is a method for the addition of R' and H to a triple bond. If R'' = H, the product is a Z alkene. The mechanism is believed to be



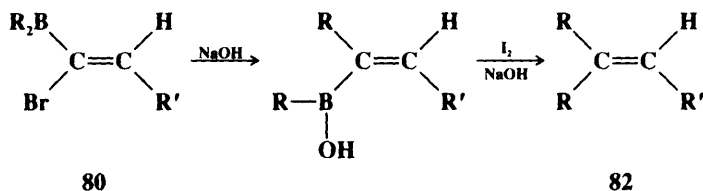
When R' is vinylic, the product is a conjugated diene.³⁴³

In another procedure, the addition of a dialkylborane to a 1-haloalkyne produces an α -halo vinylic borane (**80**).³⁴⁴ Treatment of this with NaOMe gives the rearrangement shown,



and protonolysis of the product produces the E-alkene **81**.³⁴² If R is a vinylic group the product is a 1,3-diene.³⁴⁵ If one of the groups is thexyl, the other migrates.³⁴⁶ This extends the scope of the synthesis, since dialkylboranes where one R group is thexyl are easily prepared.

A combination of both of the procedures described above results in the preparation of trisubstituted olefins.³⁴⁷ The entire conversion of haloalkyne to **82** can be carried out in one



³⁴¹For a list of methods of preparing alkenes using boron reagents, with references, see Ref. 106, pp. 218-222.

³⁴²Zweifel; Fisher; Snow; Whitney *J. Am. Chem. Soc.* **1971**, 93, 6309.

³⁴³Zweifel; Polston; Whitney *J. Am. Chem. Soc.* **1968**, 90, 6243; Brown; Ravindran *J. Org. Chem.* **1973**, 38, 1617; Hyuga; Takinami; Hara; Suzuki *Tetrahedron Lett.* **1986**, 27, 977.

³⁴⁴For improvements in this method, see Brown; Basavaiah; Kulkarni; Lee; Negishi; Katz *J. Org. Chem.* **1986**, 51, 5270.

³⁴⁵Negishi; Yoshida *J. Chem. Soc., Chem. Commun.* **1973**, 606. See also Negishi; Yoshida; Abramovitch; Lew; Williams *Tetrahedron* **1991**, 47, 343.

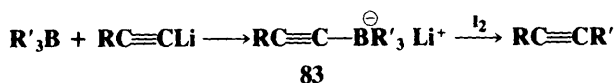
³⁴⁶Corey; Ravindranathan; *J. Am. Chem. Soc.* **1972**, 94, 4013; Negishi; Katz; Brown *Synthesis* **1972**, 555.

³⁴⁷Zweifel; Fisher *Synthesis* **1972**, 557.

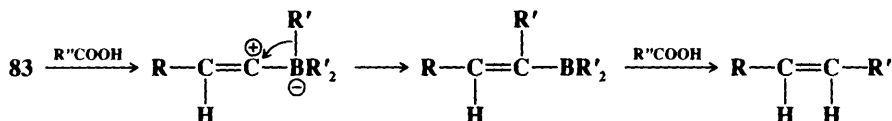
reaction vessel, without isolation of intermediates. An aluminum counterpart of the α -halo vinylic borane procedure has been reported.³⁴⁸

E-alkenes **81** can also be obtained³⁴⁹ by treatment of **78** ($R'' = H$) with cyanogen bromide or cyanogen iodide in CH_2Cl_2 ³⁵⁰ or with $Pd(OAc)_2-Et_3N$.³⁵¹

8-28 Formation of Alkynes, Alkenes, and Ketones from Boranes and Acetylides Alkyl-de-lithio-substitution

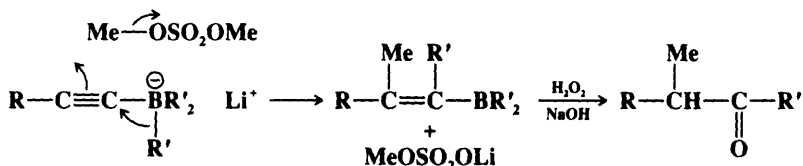


A hydrogen directly attached to a triple-bond carbon can be replaced in high yield by an alkyl or an aryl group, by treatment of the lithium acetylide with a trialkyl- or triarylborane, followed by reaction of the lithium alkynyltrialkylborate **83** with iodine.³⁵² R' may be primary or secondary alkyl as well as aryl, so the reaction has a broader scope than the older reaction **0-100**.³⁵³ R may be alkyl, aryl, or hydrogen, though in the last-mentioned case satisfactory yields are obtained only if lithium acetylide-ethylenediamine is used as the starting compound.³⁵⁴ Optically active alkynes can be prepared by using optically active thexylborinates $RR''BOR'$ ($R'' = \text{thexyl}$), where R is chiral, and $LiC\equiv CSiMe_3$.³⁵⁵ The reaction can be adapted to the preparation of alkenes³⁴¹ by treatment of **83** with an electrophile such as



propanoic acid³⁵⁶ or tributyltin chloride.³⁵⁷ The reaction with Bu_3SnCl produces the *Z* alkene stereoselectively.

Treatment of **83** with an electrophile such as methyl sulfate, allyl bromide, or triethyloxonium borofluoride, followed by oxidation of the resulting vinylic borane gives a ketone (illustrated for methyl sulfate):³⁵⁸



³⁴⁸Miller *J. Org. Chem.* **1969**, *54*, 998.

³⁴⁹For other methods of converting boranes to alkenes, see Pelter; Subrahmanyam; Laub; Gould; Harrison *Tetrahedron Lett.* **1975**, 1633; Utimoto; Uchida; Yamaya; Nozaki *Tetrahedron* **1977**, *33*, 1945; Ncube; Pelter; Smith *Tetrahedron Lett.* **1979**, 1895; Levy; Angelastro; Marinelli *Synthesis* **1980**, 945; Brown; Lee; Kulkarni *Synthesis* **1982**, 195; Pelter; Hughes; Rao *J. Chem. Soc., Perkin Trans. 1* **1982**, 719; Hoshi; Masuda; Arase *Bull. Chem. Soc. Jpn.* **1986**, *59*, 3985; Brown; Bhat *J. Org. Chem.* **1988**, *53*, 6009.

³⁵⁰Zweifel; Fisher; Snow; Whitney *J. Am. Chem. Soc.* **1972**, *94*, 6560.

³⁵¹Yatagai *Bull. Chem. Soc. Jpn.* **1980**, *53*, 1670.

³⁵²Suzuki; Miyaura; Abiko; Itoh; Brown; Sinclair; Midland *J. Am. Chem. Soc.* **1973**, *95*, 3080; *J. Org. Chem.* **1986**, *51*, 4507; Sikorski; Bhat; Cole; Wang; Brown *J. Org. Chem.* **1986**, *51*, 4521. For a review of reactions of organoborates, see Suzuki *Acc. Chem. Res.* **1982**, *15*, 178-184.

³⁵³For a study of the relative migratory aptitudes of R' , see Slayden *J. Org. Chem.* **1981**, *46*, 2311.

³⁵⁴Midland; Sinclair; Brown *J. Org. Chem.* **1974**, *39*, 731.

³⁵⁵Brown; Mahindroo; Bhat; Singaram *J. Org. Chem.* **1991**, *56*, 1500.

³⁵⁶Pelter; Harrison; Kirkpatrick *J. Chem. Soc., Chem. Commun.* **1973**, 544; Miyaura; Yoshinari; Itoh; Suzuki *Tetrahedron Lett.* **1974**, 2961; Pelter; Gould; Harrison *Tetrahedron Lett.* **1975**, 3327.

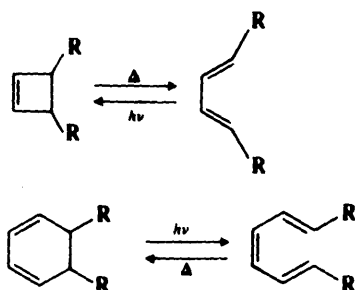
³⁵⁷Hooz; Mortimer *Tetrahedron Lett.* **1976**, 805; Wang; Chu *J. Org. Chem.* **1984**, *49*, 5175.

³⁵⁸Pelter; Bentley; Harrison; Subrahmanyam; Laub *J. Chem. Soc., Perkin Trans. 1* **1976**, 2419; Pelter; Gould; Harrison *J. Chem. Soc., Perkin Trans. 1* **1976**, 2428; Pelter; Drake *Tetrahedron Lett.* **1988**, *29*, 4181.

Non-1,2 Rearrangements

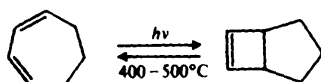
A. Electrocyclic Rearrangements

8-29 Electrocyclic Rearrangements of Cyclobutenes and 1,3-Cyclohexadienes
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 (6)*seco*-1/6/Detachment; (6)*cyclo*-1/6/Attachment

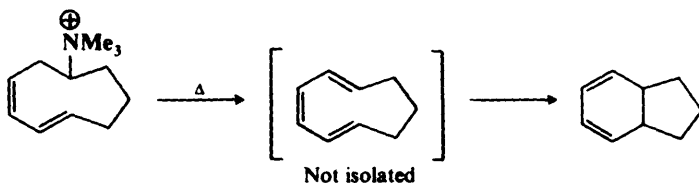
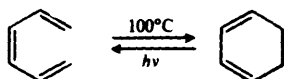


Cyclobutenes and 1,3-dienes can be interconverted by treatment with uv light or with heat. The thermal reaction is generally not reversible (though exceptions³⁵⁹ are known), and many cyclobutenes have been converted to 1,3-dienes by heating at temperatures between 100 and 200°C. The photochemical conversion can in principle be carried out in either direction, but most often 1,3-dienes are converted to cyclobutenes rather than the reverse, because the dienes are stronger absorbers of light at the wave lengths used.³⁶⁰ In a similar reaction, 1,3-cyclohexadienes interconvert with 1,3,5-trienes, but in this case the ring-closing process is generally favored thermally and the ring-opening process photochemically, though exceptions are known in both directions.³⁶¹

Some examples are



Ref. 362



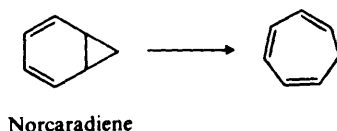
³⁵⁹For example; see Shumate; Neuman; Fonken *J. Am. Chem. Soc.* **1965**, 87, 3996; Gil-Av; Herling *Tetrahedron Lett.* **1967**, 1; Doorakian; Freedman *J. Am. Chem. Soc.* **1968**, 90, 3582; Brune; Schwab *Tetrahedron* **1969**, 25, 4375; Steiner; Michl *J. Am. Chem. Soc.* **1978**, 100, 6413.

³⁶⁰For examples of photochemical conversion of a cyclobutene to a 1,3-diene, see Scherer *J. Am. Chem. Soc.* **1968**, 90, 7352; Saltiel; Lim *J. Am. Chem. Soc.* **1969**, 91, 5404; Adam; Oppenländer; Zang *J. Am. Chem. Soc.* **1985**, 107, 3921; Dauben; Haubrich *J. Org. Chem.* **1988**, 53, 600.

³⁶¹For a review of photochemical rearrangements in trienes, see Dauben; McInnis; Michno, in Mayo, Ref. 1, vol. 3, pp. 91-129.

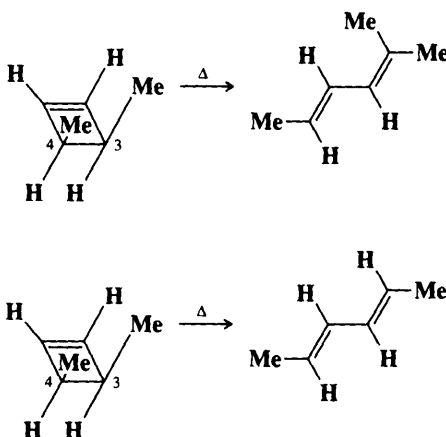
³⁶²Dauben; Cargill *Tetrahedron* **1961**, 12, 186; Chapman; Pasto; Borden; Griswold *J. Am. Chem. Soc.* **1962**, 84, 1220.

An interesting example of 1,3-cyclohexadiene—1,3,5-triene interconversion is the reaction of norcaradienes to give cycloheptatrienes.³⁶³ Norcaradienes give this reaction so readily



(because they are *cis*-1,2-divinylcyclopropanes, see p. 1131) that they cannot generally be isolated, though some exceptions are known³⁶⁴ (see also p. 869).

These reactions, called *electrocyclic rearrangements*,³⁶⁵ take place by pericyclic mechanisms. The evidence comes from stereochemical studies, which show a remarkable stereospecificity whose direction depends on whether the reaction is induced by heat or light. For example, it was found for the thermal reaction that *cis*-3,4-dimethylcyclobutene gave only *cis,trans*-2,4-hexadiene, while the *trans* isomer gave only the *trans-trans* diene.³⁶⁶



This is evidence for a four-membered cyclic transition state and arises from conrotatory motion about the C-3—C-4 bond. It is called conrotatory because both movements are

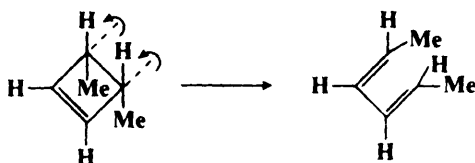
³⁶³For reviews of the norcaradiene–cycloheptatriene interconversion and the analogous benzene oxide–oxepin interconversion, see Maier *Angew. Chem. Int. Ed. Engl.* **1967**, *6*, 402-413 [*Angew. Chem.* **79**, 446-458]; Vogel; Günther *Angew. Chem. Int. Ed. Engl.* **1967**, *6*, 385-401 [*Angew. Chem.* **79**, 429-446]; Vogel *Pure Appl. Chem.* **1969**, *20*, 237-262.

³⁶⁴See Refs. 1043 and 1044 in Chapter 15.

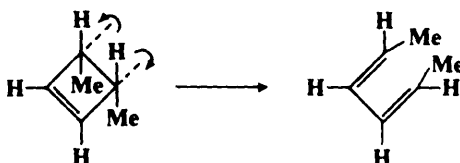
³⁶⁵For a monograph on thermal isomerizations, which includes electrocyclic and sigmatropic rearrangements, as well as other types, see Gajewski *Hydrocarbon Thermal Isomerizations*; Academic Press: New York, 1981. For a monograph on electrocyclic reactions, see Marvell *Thermal Electrocyclic Reactions*; Academic Press: New York, 1980. For reviews, see Dolbier; Koroniak *Mol. Struct. Energ.* **1988**, *8*, 65-81; Laarhoven *Org. Photochem.* **1987**, *9*, 129-224; George; Mitra; Sukumaran *Angew. Chem. Int. Ed. Engl.* **1980**, *19*, 973-983 [*Angew. Chem.* **92**, 1005-1014]; Jutz *Top. Curr. Chem.* **1978**, *73*, 125-230; Gilchrist; Storr *Organic Reactions and Orbital Symmetry*; Cambridge University Press: Cambridge, 1972, pp. 48-72; DeWolfe, in Bamford; Tipper *Comprehensive Chemical Kinetics*, vol. 9; Elsevier: New York, 1973; pp. 461-470; Crowley; Mazzocchi, in Zabicky *The Chemistry of Alkenes*, vol. 2; Wiley: New York, 1970, pp. 284-297; Criegee *Angew. Chem. Int. Ed. Engl.* **1968**, *7*, 559-565 [*Angew. Chem.* **80**, 585-591]; Vollmer; Servis *J. Chem. Educ.* **1968**, *45*, 214-220. For a review of isotope effects in these reactions, see Gajewski *Isot. Org. Chem.* **1987**, *7*, 115-176. For a related review, see Schultz; Motyka *Org. Photochem.* **1983**, *6*, 1-119.

³⁶⁶Winter *Tetrahedron Lett.* **1965**, 1207. Also see Vogel *Liebigs Ann. Chem.* **1958**, *615*, 14; Criegee; Noll *Liebigs Ann. Chem.* **1959**, *627*, 1.

clockwise (or both counterclockwise). Because both rotate in the same direction, the cis isomer gives the cis-trans diene:³⁶⁷



The other possibility (*disrotatory* motion) would have one moving clockwise while the other moves counterclockwise; the cis isomer would have given the cis-cis diene (shown) or the trans-trans diene:



If the motion had been disrotatory, this would still have been evidence for a cyclic mechanism. If the mechanism were a diradical or some other kind of noncyclic process, it is likely that no stereospecificity of either kind would have been observed. The reverse reaction is also conrotatory. In contrast, the photochemical cyclobutene—1,3-diene interconversion is *disrotatory* in either direction.³⁶⁸ On the other hand, the cyclohexadiene—1,3,5-triene interconversion shows precisely the opposite behavior. The thermal process is *disrotatory*, while the photochemical process is *conrotatory* (in either direction). These startling results are a consequence of the symmetry rules mentioned in Chapter 15 (p. 846).³⁶⁹ As in the case of cycloaddition reactions, we will use the frontier-orbital and Möbius–Hückel approaches.³⁷⁰

The Frontier-Orbital Method³⁷¹

As applied to these reactions, the frontier-orbital method may be expressed: *A σ bond will open in such a way that the resulting p orbitals will have the symmetry of the highest occupied π orbital of the product.* In the case of cyclobutenes, the HOMO of the product in the thermal reaction is the χ_2 orbital (Figure 18.1). Therefore, in a thermal process, the cyclo-

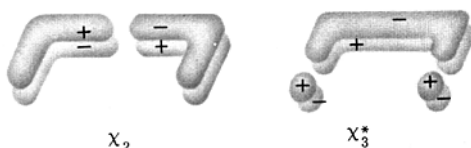


FIGURE 18.1 Symmetries of the χ_2 and χ_3^* orbitals of a conjugated diene.

³⁶⁷This picture is from Woodward; Hoffmann *J. Am. Chem. Soc.* **1965**, 87, 395, who coined the terms, *conrotatory* and *disrotatory*.

³⁶⁸Photochemical ring-opening of cyclobutenes can also be nonstereospecific. See Leigh; Zheng *J. Am. Chem. Soc.* **1991**, 113, 4019; Leigh; Zheng; Nguyen; Werstiuk; Ma *J. Am. Chem. Soc.* **1991**, 113, 4993, and references cited in these papers.

³⁶⁹Woodward; Hoffmann, Ref. 367. Also see Longuet-Higgins; Abrahamson *J. Am. Chem. Soc.* **1965**, 87, 2045; Fukui *Tetrahedron Lett.* **1965**, 2009.

³⁷⁰For the correlation diagram method, see Jones *Physical and Mechanistic Organic Chemistry*, 2nd ed.; Cambridge University Press: Cambridge, 1984, pp. 352-359; Yates *Hückel Molecular Orbital Theory*; Academic Press: New York, 1978, pp. 250-263; Ref. 897 in Chapter 15.

³⁷¹See Ref. 898 in Chapter 15.

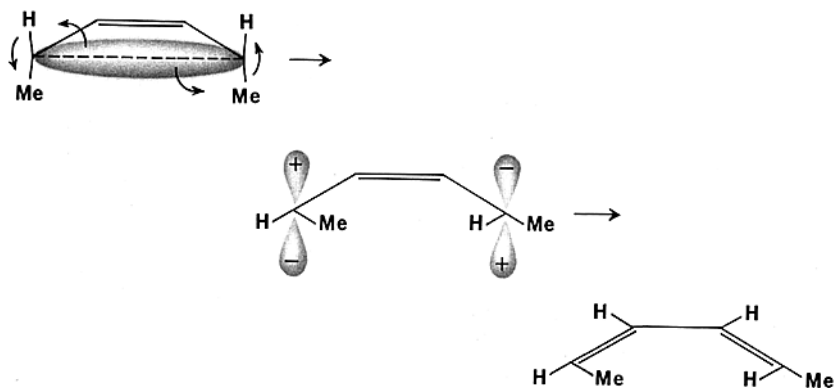


FIGURE 18.2 Thermal ring opening of 1,2-dimethylcyclobutene. The two hydrogens and two methyls are forced into conrotatory motion so that the resulting p orbitals have the symmetry of the HOMO of the diene.

butene must open so that on one side the positive lobe lies above the plane, and on the other side below it. Thus the substituents are forced into conrotatory motion (Figure 18.2). On the other hand, in the photochemical process, the HOMO of the product is now the χ_3 orbital (Figure 18.1), and in order for the p orbitals to achieve this symmetry (the two plus lobes on the same side of the plane), the substituents are forced into disrotatory motion.

We may also look at this reaction from the opposite direction (ring closing). For this direction the rule is that *those lobes of orbitals that overlap (in the HOMO) must be of the same sign*. For thermal cyclization of butadienes, this requires conrotatory motion (Figure 18.3). In the photochemical process the HOMO is the χ_3 orbital, so that disrotatory motion is required for lobes of the same sign to overlap.

*The Möbius–Hückel Method*³⁷²

As we saw on p. 848, in this method we choose a basis set of p orbitals and look for sign inversions in the transition state. Figure 18.4 shows a basis set for a 1,3-diene. It is seen that disrotatory ring closing (Figure 18.4a) results in overlap of plus lobes only, while in conrotatory closing (Figure 18.4b) there is one overlap of a plus with a minus lobe. In the first case we have zero sign inversions, while in the second there is one sign inversion. With zero (or an even number of) sign inversions, the disrotatory transition state is a Hückel

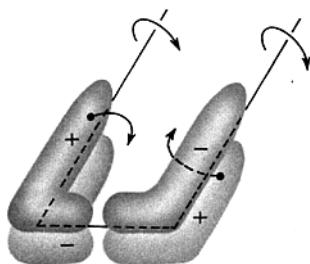


FIGURE 18.3 Thermal ring closing of a 1,3-diene. Conrotatory motion is required for two + lobes to overlap.

³⁷²See Ref. 899 in Chapter 15.

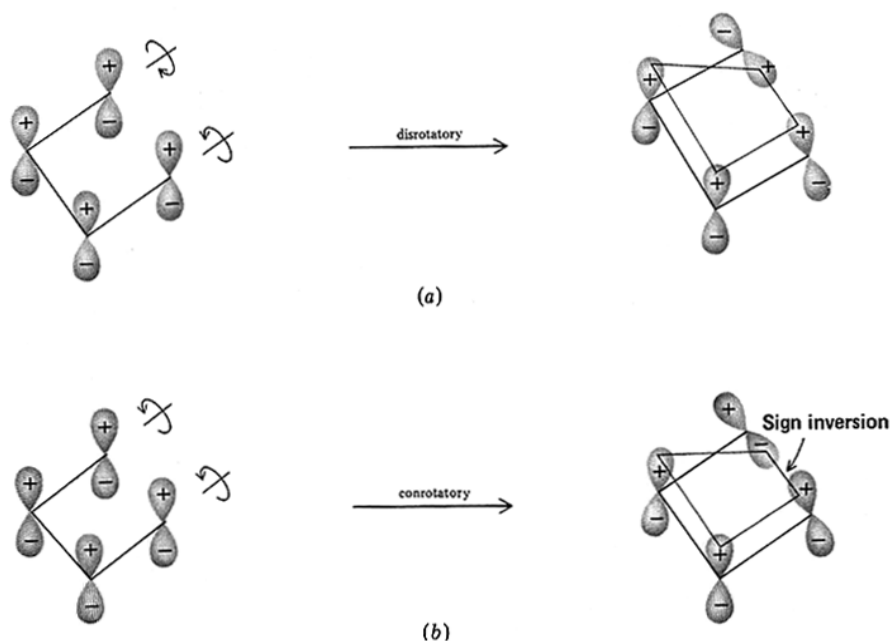
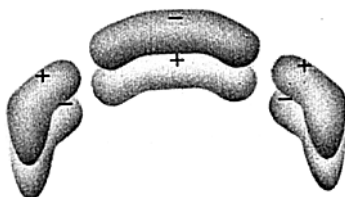


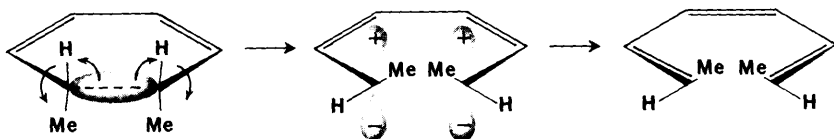
FIGURE 18.4 The 1,3-diene-cyclobutene interconversion. The orbitals shown are *not* molecular orbitals, but a basis set of *p* atomic orbitals. (a) Disrotatory ring closure gives zero sign inversions. (b) Conrotatory ring closure gives one sign inversion. We could have chosen to show any other basis set (for example, another basis set would have two plus lobes above the plane and two below, etc.). This would change the number of sign inversions, but the disrotatory mode would still have an even number of sign inversions, and the conrotatory mode an odd number, whichever basis set was chosen.

system, and so is allowed thermally only if the total number of electrons is $4n + 2$ (p. 848). Since the total here is 4, the disrotatory process is not allowed. On the other hand, the conrotatory process, with one sign inversion, is a Möbius system, which is thermally allowed if the total number is $4n$. The conrotatory process is therefore allowed thermally. For the photochemical reactions the rules are reversed: A reaction with $4n$ electrons requires a Hückel system, so only the disrotatory process is allowed.

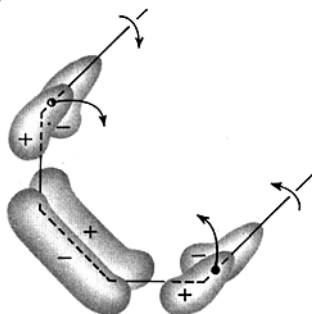
Both the frontier-orbital and the Möbius-Hückel methods can also be applied to the cyclohexadiene—1,3,5-triene reaction; in either case the predicted result is that for the thermal process, only the disrotatory pathway is allowed, and for the photochemical process, only the conrotatory. For example, for a 1,3,5-triene, the symmetry of the HOMO is



In the thermal cleavage of cyclohexadienes, then, the positive lobes must lie on the same side of the plane, requiring disrotatory motion:



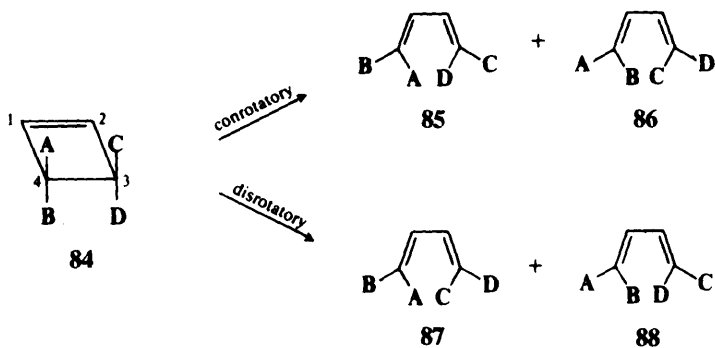
Disrotatory motion is also necessary for the reverse reaction, in order that the orbitals which overlap may be of the same sign:



All these directions are reversed for photochemical processes, because in each case a higher orbital, with inverted symmetry, is occupied.

In the Möbius-Hückel approach, diagrams similar to Figure 18.4 can be drawn for this case. Here too, the disrotatory pathway is a Hückel system and the conrotatory pathway a Möbius system, but since six electrons are now involved, the thermal reaction follows the Hückel pathway and the photochemical reaction the Möbius pathway.

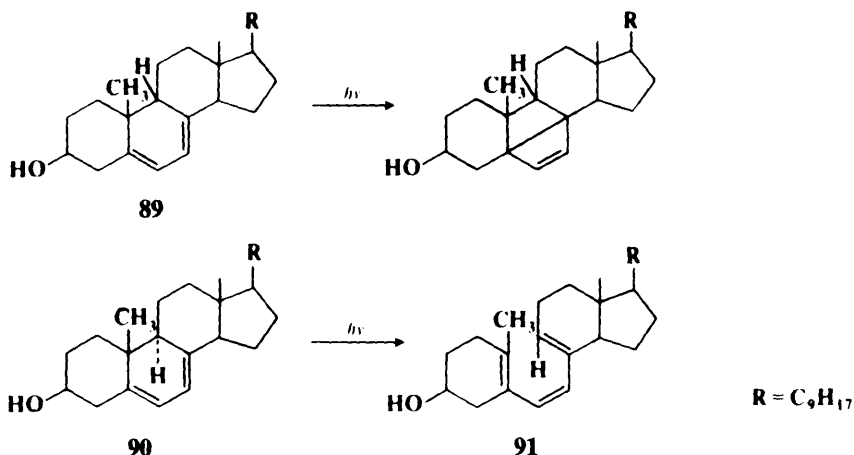
In the most general case, there are four possible products that can arise from a given cyclobutene or cyclohexadiene—two from the conrotatory and two from the disrotatory



pathway. For example, conrotatory ring opening of **84** gives either **85** or **86**, while disrotatory opening gives either **87** or **88**. The orbital-symmetry rules tell us when a given reaction will operate by the conrotatory and when by the disrotatory mode, but they do not say which

of the two possible conrotatory or disrotatory pathways will be followed. It is often possible, however, to make such predictions on steric grounds. For example, in the opening of **84** by the disrotatory pathway, **87** arises when groups A and C swing in toward each other (clockwise motion around C-4, counterclockwise around C-3), while **88** is formed when groups B and D swing in and A and C swing out (clockwise motion around C-3, counterclockwise around C-4). We therefore predict that when A and C are larger than B and D, the predominant or exclusive product will be **88**, rather than **87**. Predictions of this kind have largely been borne out.³⁷³ There is evidence, however, that steric effects are not the only factor, and that electronic effects also play a role, which may be even greater.³⁷⁴ An electron-donating group stabilizes the transition state when it rotates *outward*, because it mixes with the LUMO; if it rotates *inward*, it mixes with the HOMO, destabilizing the transition state.³⁷⁵ The compound 3-formylcyclobutene provided a test. Steric factors would cause the CHO (an electron-withdrawing group) to rotate outward; electronic effects would cause it to rotate inward. The experiment showed inward rotation.³⁷⁶

Cyclohexadienes are of course 1,3-dienes, and in certain cases it is possible to convert them to cyclobutenes instead of to 1,3,5-trienes.³⁷⁷ An interesting example is found in the pyrocalciferols. Photolysis of the syn isomer **89** (or of the other syn isomer, not shown)



leads to the corresponding cyclobutene,³⁷⁸ while photolysis of the anti isomers (one of them is **90**) gives the ring-opened 1,3,5-triene **91**. This difference in behavior is at first sight remarkable, but is easily explained by the orbital-symmetry rules. Photochemical ring opening to a 1,3,5-triene must be conrotatory. If **89** were to react by this pathway, the product would be the triene **91**, but this compound would have to contain a *trans*-cyclohexene ring (either the methyl group or the hydrogen would have to be directed inside the ring). On

³⁷³For example, see Baldwin; Krueger *J. Am. Chem. Soc.* **1969**, *91*, 6444; Spangler; Hennis *J. Chem. Soc., Chem. Commun.* **1972**, 24; Gesche; Klinger; Riesen; Tschamber; Zehnder; Streith *Helv. Chim. Acta* **1987**, *70*, 2087.

³⁷⁴Kirmse; Rondan; Houk *J. Am. Chem. Soc.* **1984**, *106*, 7989; Dolbier; Koroniak; Burton; Heinze; Bailey; Shaw; Hansen *J. Am. Chem. Soc.* **1987**, *109*, 219; Dolbier; Gray; Keaffaber; Celewicz; Koroniak *J. Am. Chem. Soc.* **1990**, *112*, 363; Hayes; Ingham; Saengchantara; Wallace *Tetrahedron Lett.* **1991**, *32*, 2953.

³⁷⁵For theoretical studies, see Rondan; Houk *J. Am. Chem. Soc.* **1985**, *107*, 2099; Buda; Wang; Houk *J. Org. Chem.* **1989**, *54*, 2264; Kallel; Wang; Spellmeyer; Houk *J. Am. Chem. Soc.* **1990**, *112*, 6759.

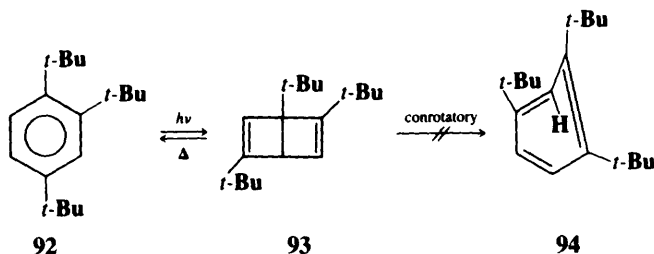
³⁷⁶Rudolf; Spellmeyer; Houk *J. Org. Chem.* **1987**, *52*, 3708; Piers; Lu *J. Org. Chem.* **1989**, *54*, 2267.

³⁷⁷For a discussion of the factors favoring either direction, see Dauben; Kellogg; Seeman; Vietmeyer; Wendschuh *Pure Appl. Chem.* **1973**, *33*, 197-215.

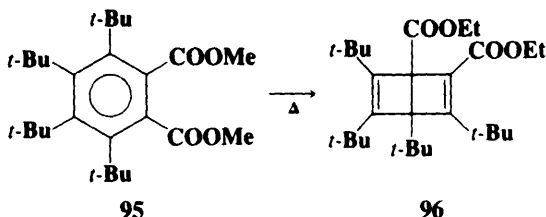
³⁷⁸Dauben; Fonken *J. Am. Chem. Soc.* **1959**, *81*, 4060. This was the first reported example of the conversion of a 1,3-diene to a cyclobutene.

the other hand, photochemical conversion to a cyclobutene must be disrotatory, but if **90** were to give this reaction, the product would have to have a trans-fused ring junction. Compounds with such ring junctions are known (p. 132) but are very strained. Stable *trans*-cyclohexenes are unknown (p. 158). Thus, **89** and **90** give the products they do owing to a combination of orbital-symmetry rules and steric influences.

The 1,3-diene—cyclobutene interconversion can even be applied to benzene rings. For example,³⁷⁹ photolysis of 1,2,4-tri-*t*-butylbenzene (**92**) gives 1,2,5-tri-*t*-butyl[2.2.0]hexadiene (**93**, a Dewar benzene).³⁸⁰ The reaction owes its success to the fact that once **93** is formed,



it cannot, under the conditions used, revert to **92** by either a thermal or a photochemical route. The orbital-symmetry rules prohibit thermal conversion of **93** to **92** by a pericyclic mechanism, because thermal conversion of a cyclobutene to a 1,3-diene must be conrotatory, and conrotatory reaction of **93** would result in a 1,3,5-cyclohexatriene containing one trans double bond (**94**), which is of course too strained to exist. **93** cannot revert to **92** by a photochemical pathway either, because light of the frequency used to excite **92** would not be absorbed by **93**. This is thus another example of a molecule that owes its stability to the orbital-symmetry rules (see p. 865). Pyrolysis of **93** does give **92**, probably by a diradical mechanism.³⁸¹ In the case of **95** and **96**, the Dewar benzene is actually more stable than the



benzene. **95** rearranges to **96** in 90% yield at 120°. ³⁸² In this case thermolysis of the benzene gives the Dewar benzene (rather than the reverse), because of the strain of four adjacent *t*-butyl groups on the ring.

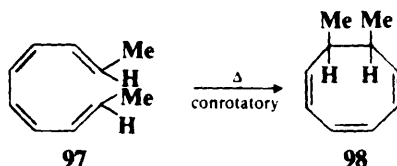
³⁷⁹Unsubstituted Dewar benzene has been obtained, along with other photoproducts, by photolysis of benzene: Ward; Wishnok *J. Am. Chem. Soc.* **1968**, *90*, 1085; Bryce-Smith; Gilbert; Robinson *Angew. Chem. Int. Ed. Engl.* **1971**, *10*, 745 [*Angew. Chem.* **83**, 803]. For other examples, see Arnett; Bollinger *Tetrahedron Lett.* **1964**, 3803; Camaggi; Gozzo; Cevidalli *Chem. Commun.* **1966**, 313; Haller *J. Am. Chem. Soc.* **1966**, *88*, 2070. *J. Chem. Phys.* **1967**, *47*, 1117; Barlow; Haszeldine; Hubbard *Chem. Commun.* **1969**, 202; Lemal; Staros; Austel *J. Am. Chem. Soc.* **1969**, *91*, 3373.

³⁸⁰van Tamelen; Pappas *J. Am. Chem. Soc.* **1962**, *84* 3789; Wilzbach; Kaplan *J. Am. Chem. Soc.* **1965**, *87*, 4004; van Tamelen; Pappas; Kirk *J. Am. Chem. Soc.* **1971**, *93*, 6092; van Tamelen *Acc. Chem. Res.* **1972**, *5*, 186-192. As mentioned on p. 865 (Ref. 1002), Dewar benzenes can be photolyzed further to give prismanes.

³⁸¹See, for example, Oth *Recl. Trav. Chim. Pays-Bas* **1968**, *87*, 1185; Adam; Chang *Int. J. Chem. Kinet.* **1969**, *1*, 487; Lechtken; Breslow; Schmidt; Turro *J. Am. Chem. Soc.* **1973**, *95*, 3025; Wingert; Irngartinger; Kallfass; Regitz *Chem. Ber.* **1987**, *120*, 825.

³⁸²Maier; Schneider *Angew. Chem. Int. Ed. Engl.* **1980**, *19*, 1022 [*Angew. Chem.* **95**, 1056]. See also Wingert; Maas; Regitz *Tetrahedron* **1986**, *42*, 5341.

A number of electrocyclic reactions have been carried out with systems of other sizes, e.g., conversion of the 1,3,5,7-octatetraene **97** to the cyclooctatriene **98**.³⁸³ The stereochem-

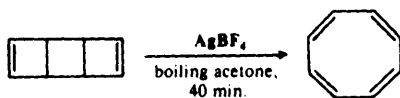


istry of these reactions can be predicted in a similar manner. The results of such predictions can be summarized according to whether the number of electrons involved in the cyclic process is of the form $4n$ or $4n + 2$ (where n is any integer including zero).

	Thermal reaction	Photochemical reaction
$4n$	conrotatory	disrotatory
$4n + 2$	disrotatory	conrotatory

Although the orbital-symmetry rules predict the stereochemical results in almost all cases, it is necessary to recall (p. 849) that they only say what is allowed and what is forbidden, but the fact that a reaction is allowed does not necessarily mean that that reaction takes place, and if an allowed reaction does take place, it does not *necessarily* follow that a concerted pathway is involved, since other pathways of lower energy may be available.³⁸⁴ Furthermore, a "forbidden" reaction might still be made to go, if a method of achieving its high activation energy can be found. This was, in fact, done for the cyclobutene—butadiene interconversion (*cis*-3,4-dichlorocyclobutene gave the forbidden *cis,cis*- and *trans,trans*-1,4-dichloro-1,3-cyclobutadienes, as well as the allowed *cis*, *trans* isomer) by the use of ir laser light.³⁸⁵ This is a thermal reaction. The laser light excites the molecule to a higher vibrational level (p. 232), but not to a higher electronic state.

As is the case for $2 + 2$ cycloaddition reactions (5-49), certain forbidden electrocyclic reactions can be made to take place by the use of metallic catalysts.³⁸⁶ An example is the silver ion-catalyzed conversion of tricyclo[4.2.0.0^{2,5}]octa-3,7-diene to cyclooctatetraene:³⁸⁷



This conversion is very slow thermally (i.e., without the catalyst) because the reaction must take place by a disrotatory pathway, which is disallowed thermally.³⁸⁸

³⁸³Marvell; Seubert *J. Am. Chem. Soc.* **1967**, 89, 3377; Huisgen; Dahmen; Huber *J. Am. Chem. Soc.* **1967**, 89, 7130, *Tetrahedron Lett.* **1969**, 1461; Dahmen; Huber *Tetrahedron Lett.* **1969**, 1465.

³⁸⁴For a discussion, see Baldwin; Andrist; Pinschmidt *Acc. Chem. Res.* **1972**, 5, 402-406.

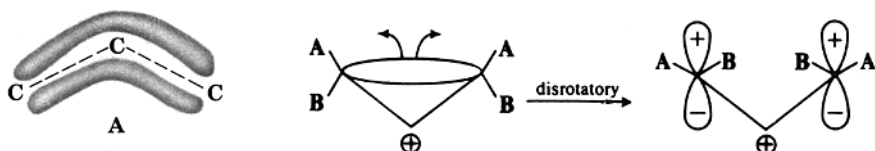
³⁸⁵Mao; Presser; John; Moriarty; Gordon *J. Am. Chem. Soc.* **1981**, 103, 2105.

³⁸⁶For a review, see Pettit; Sugahara; Wristers; Merk *Discuss. Faraday Soc.* **1969**, 47, 71-78. See also Ref. 993 in Chapter 15.

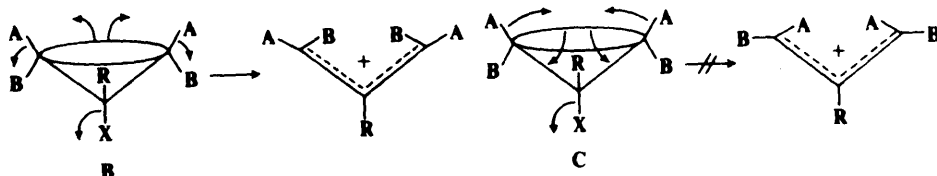
³⁸⁷Merk; Pettit *J. Am. Chem. Soc.* **1967**, 89, 4788.

³⁸⁸For discussions of how these reactions take place, see Slegier; Case; McKennis; Pettit *J. Am. Chem. Soc.* **1974**, 96, 287; Pinhas; Carpenter *J. Chem. Soc., Chem. Commun.* **1980**, 15.

The ring opening of cyclopropyl cations (pp. 345, 1076) is an electrocyclic reaction and is governed by the orbital symmetry rules.³⁸⁹ For this case we invoke the rule that the σ bond opens in such a way that the resulting p orbitals have the symmetry of the highest occupied orbital of the product, in this case, an allylic cation. We may recall that an allylic system has three molecular orbitals (p. 32). For the cation, with only two electrons, the highest occupied orbital is the one of the lowest energy (**A**). Thus, the cyclopropyl cation must



undergo a disrotatory ring opening in order to maintain the symmetry. (Note that, in contrast, ring opening of the cyclopropyl *anion* must be conrotatory,³⁹⁰ since in this case it is the next orbital of the allylic system which is the highest occupied, and this has the opposite symmetry.³⁹¹) However, it is very difficult to generate a free cyclopropyl cation (p. 345), and it is likely that in most cases, cleavage of the σ bond is concerted with departure of the leaving group in the original cyclopropyl substrate. This of course means that the σ bond provides anchimeric assistance to the removal of the leaving group (an S_N2 -type process), and we would expect that such assistance should come from the back side. This has an important effect on the direction of ring opening. The orbital-symmetry rules require that the ring opening be disrotatory, but as we have seen, there are two disrotatory pathways and the rules do not tell us which is preferred. But the fact that the σ orbital provides assistance from the back side means that the two substituents which are trans to the leaving group must move *outward*, not inward.³⁹² Thus, the disrotatory pathway that is followed is the one shown in **B**, not the one shown in **C**, because the former puts the electrons of the σ



bond on the side opposite that of the leaving group.³⁹³ Strong confirmation of this picture³⁹⁴ comes from acetolysis of *endo*-(**99**) and *exo*-bicyclo[3,1,0]hexyl-6-tosylate (**100**). The groups

³⁸⁹For discussions, see DePuy *Acc. Chem. Res.* **1968**, *1*, 33-41; Schöllkopf *Angew. Chem. Int. Ed. Engl.* **1968**, *7*, 588-598 [*Angew. Chem.* **80**, 603-613].

³⁹⁰For a review of ring opening of cyclopropyl anions and related reactions, see Boche *Top. Curr. Chem.* **1988**, *146*, 1-56.

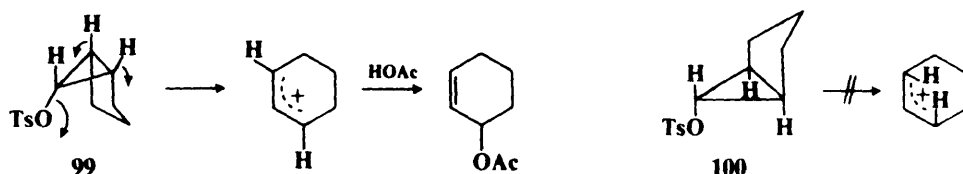
³⁹¹For evidence that this is so, see Newcomb; Ford *J. Am. Chem. Soc.* **1974**, *96*, 2968; Boche; Buckl; Martens; Schneider; Wagner *Chem. Ber.* **1979**, *112*, 2961; Coates; Last *J. Am. Chem. Soc.* **1983**, *105*, 7322. For a review of the analogous ring opening of epoxides, see Huisgen *Angew. Chem. Int. Ed. Engl.* **1977**, *16*, 572-585 [*Angew. Chem.* **89**, 589-602].

³⁹²This was first proposed by DePuy; Schnack; Hausser; Wiedemann *J. Am. Chem. Soc.* **1965**, *87*, 4006.

³⁹³It has been suggested that the pathway shown in **C** is possible in certain cases: Hausser; Grubber *J. Org. Chem.* **1972**, *37*, 2648; Hausser; Uchic *J. Org. Chem.* **1972**, *37*, 4087.

³⁹⁴There is much other evidence. For example, see Jefford; Medary *Tetrahedron Lett.* **1966**, 2069; Jefford; Wojnarski *Tetrahedron Lett.* **1968**, 199; Schleyer; Van Dine; Schöllkopf; Paust *J. Am. Chem. Soc.* **1966**, *88*, 2868; Sliwinski; Su; Schleyer *J. Am. Chem. Soc.* **1972**, *94*, 133; Sandler *J. Org. Chem.* **1967**, *32*, 3876; Ghosez; Slinckx; Glineur; Hoet; Laroche *Tetrahedron Lett.* **1967**, 2773; Parham; Yong *J. Org. Chem.* **1968**, *33*, 3947; Reese; Shaw *J. Am. Chem. Soc.* **1970**, *92*, 2566; Dolbier; Phanstiel *Tetrahedron Lett.* **1988**, 29, 53.

trans to the tosylate must move outward. For **99** this means that the two hydrogens can go outside the framework of the six-membered ring, but for **100** they are forced to go inside.

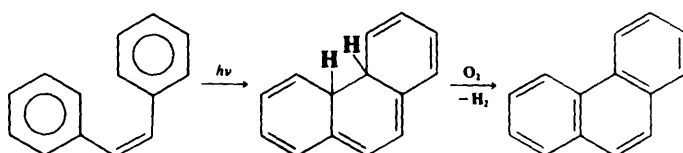


Consequently, it is not surprising that the rate ratio for solvolysis of **99:100** was found to be greater than 2.5×10^6 and that at 150°C **100** did not solvolyze at all.³⁹⁵ This evidence is kinetic. Unlike the cases of the cyclobutene—1,3-diene and cyclohexadiene—1,3,5-triene interconversions, the direct product here is a cation, which is not stable but reacts with a nucleophile and loses some of its steric integrity in the process, so that much of the evidence has been of the kinetic type rather than from studies of product stereochemistry. However, it has been shown by investigations in super acids, where it is possible to keep the cations intact and to study their structures by nmr, that in all cases studied the cation that is predicted by these rules is in fact formed.³⁹⁶

OS V, 235, 277, 467; VI, 39, 145, 196, 422, 427, 862.

8-30 Conversion of Stilbenes to Phenanthrenes

(6)cyclo-De-hydrogen-coupling (overall transformation)



Stilbenes can be converted to phenanthrenes by irradiation with uv light³⁹⁷ in the presence of an oxidizing agent such as dissolved molecular oxygen, FeCl_3 , Pd-C ,³⁹⁸ or iodine.^{398a} The reaction is a photochemically allowed conrotatory³⁹⁹ conversion of a 1,3,5-hexatriene to a cyclohexadiene, followed by removal of two hydrogen atoms by the oxidizing agent. The intermediate dihydrophenanthrene has been isolated.⁴⁰⁰ The use of substrates containing hetero atoms (e.g., PhN=NPh) allows the formation of heterocyclic ring systems. The actual reacting species must be the *cis*-stilbene, but *trans*-stilbenes can often be used, because they are isomerized to the *cis* isomers under the reaction conditions. The reaction can be extended to the preparation of many fused aromatic systems, e.g.,⁴⁰¹

³⁹⁵Schöllkopf; Fellenberger; Patsch; Schleyer; Su; Van Dine *Tetrahedron Lett.* **1967**, 3639.

³⁹⁶Schleyer; Su; Saunders; Rosenfeld *J. Am. Chem. Soc.* **1969**, 91, 5174.

³⁹⁷For reviews, see Mallory; Mallory *Org. React.* **1984**, 30, 1-456; Laarhoven *Recl. Trav. Chim. Pays-Bas* **1983**, 102, 185-204, 241-254; Blackburn; Timmons *Q. Rev., Chem. Soc.* **1969**, 23, 482-503; Stermitz; *Org. Photochem.* **1967**, 1, 247-282. For a review of electrocyclizations of conjugated aryl olefins in general, see Laarhoven *Org. Photochem.* **1989**, 10, 163-308.

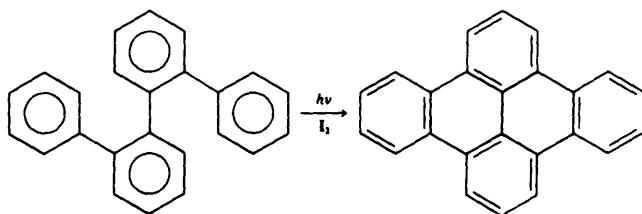
³⁹⁸Rawal; Jones; Cava *Tetrahedron Lett.* **1985**, 26, 2423.

^{398a}For the use of iodine plus propylene oxide in the absence of air, see Liu; Yang; Katz; Poindexter *J. Org. Chem.* **1991**, 56, 3769.

³⁹⁹Cuppen; Laarhoven *J. Am. Chem. Soc.* **1972**, 94, 5914.

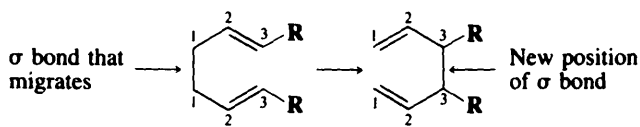
⁴⁰⁰Doyle; Benson; Filipescu *J. Am. Chem. Soc.* **1976**, 98, 3262.

⁴⁰¹Sato; Shimada; Hata *Bull. Chem. Soc. Jpn.* **1971**, 44, 2484.

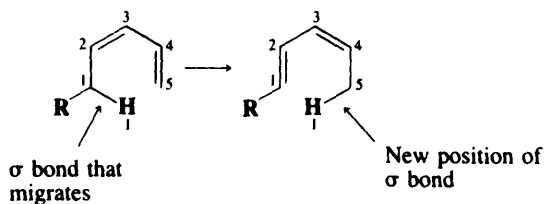


though not all such systems give reaction.⁴⁰²

B. Sigmatropic Rearrangements. A sigmatropic rearrangement is defined⁴⁰³ as migration, in an uncatalyzed intramolecular process, of a σ bond, adjacent to one or more π systems, to a new position in a molecule, with the π systems becoming reorganized in the process. Examples are



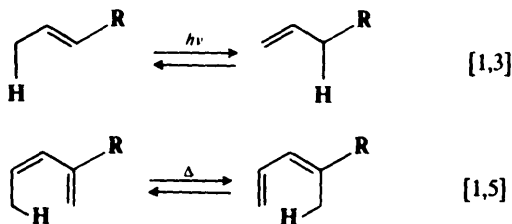
Reaction 8-34
A [3,3] sigmatropic rearrangement



Reaction 8-31
A [1,5] sigmatropic rearrangement

The order of a sigmatropic rearrangement is expressed by two numbers set in brackets: $[i,j]$. These numbers can be determined by counting the atoms over which each end of the σ bond has moved. Each of the original termini is given the number 1. Thus in the first example above, each terminus of the σ bond has migrated from C-1 to C-3, so the order is [3,3]. In the second example the carbon terminus has moved from C-1 to C-5, but the hydrogen terminus has not moved at all, so the order is [1,5].

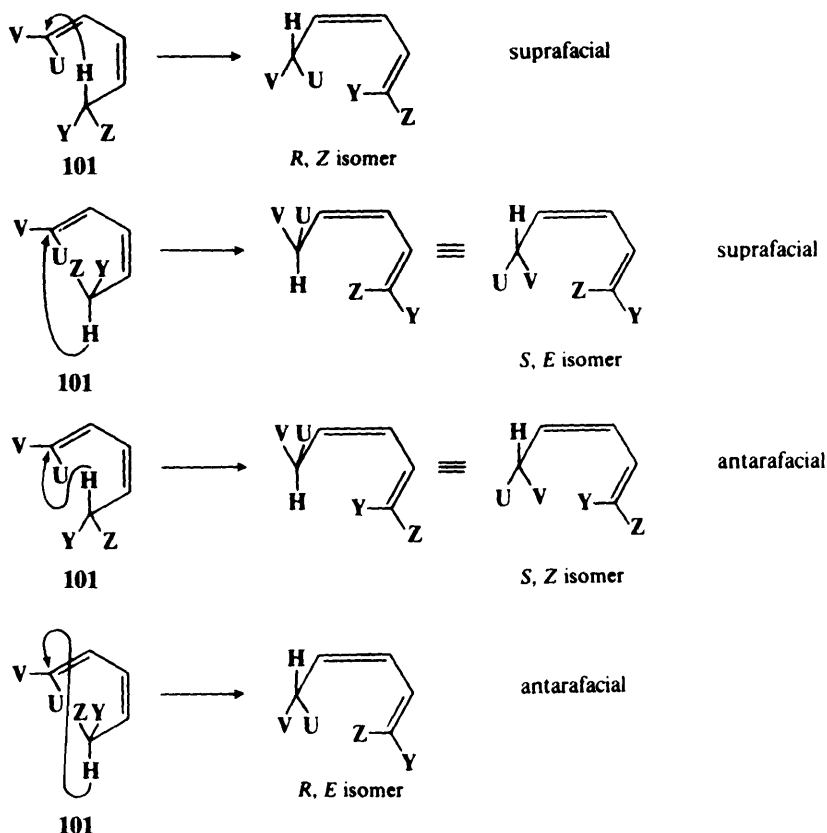
8-31 [1,*j*] Sigmatropic Migrations of Hydrogen
1/ \rightarrow 3/Hydrogen-migration; 1/ \rightarrow 5/Hydrogen-migration



⁴⁰²For a discussion and lists of photocyclizing and nonphotocyclizing compounds, see Laarhoven *Recl. Trav. Chim. Pays-Bas*, Ref. 397, pp. 185-204.

⁴⁰³Woodward; Hoffmann *The Conservation of Orbital Symmetry*; Academic Press: New York, 1970, p. 114.

Many examples of thermal or photochemical rearrangements in which a hydrogen atom migrates from one end of a system of π bonds to the other have been reported,⁴⁰⁴ though the reaction is subject to geometrical conditions. Pericyclic mechanisms are involved, and the hydrogen must, in the transition state, be in contact with both ends of the chain at the same time. This means that for [1,5] and longer rearrangements, the molecule must be able to adopt the cisoid conformation. Furthermore, there are two geometrical pathways by which any sigmatropic rearrangement can take place, which we illustrate for the case of a [1,5] sigmatropic rearrangement,⁴⁰⁵ starting with a substrate of the form **101**, where the migration origin is an asymmetric carbon atom and $U \neq V$. In one of the two pathways,



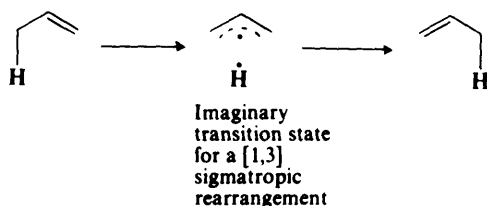
the hydrogen moves along the top or bottom face of the π system. This is called *suprafacial migration*. In the other pathway, the hydrogen moves *across* the π system, from top to bottom, or vice versa. This is *antarafacial* migration. Altogether, a single isomer like **101** can give four products. In a suprafacial migration, H can move across the top of the π system (as drawn above) to give the *R, Z* isomer, or it can rotate 180° and move across the

⁴⁰⁴For a monograph, see Gajewski, Ref. 365. For reviews, see Mironov; Fedorovich; Akhrem *Russ. Chem. Rev.* **1981**, *50*, 666-681; Spangler *Chem. Rev.* **1976**, *76*, 187-217; DeWolfe, in Bamford; Tipper, Ref. 365, pp. 474-480; Woodward; Hoffmann, Ref. 403, pp. 114-140; Hansen; Schmid *Chimia* **1970**, *24*, 89-99; Roth *Chimia* **1966**, *20*, 229-236.

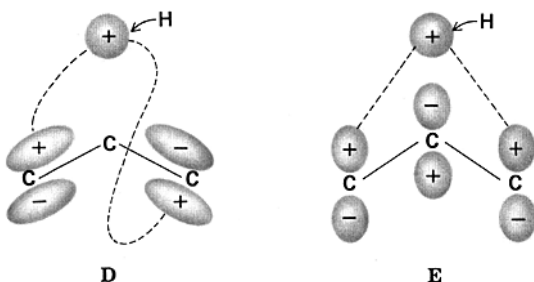
⁴⁰⁵Note that a [1,5] sigmatropic rearrangement of hydrogen is also an internal ene synthesis (**5-16**).

bottom of the π system to give the S,E isomer.⁴⁰⁶ The antarafacial migration can similarly lead to two diastereomers, in this case the S,Z and R,E isomers.

In any given sigmatropic rearrangement, only one of the two pathways is allowed by the orbital-symmetry rules; the other is forbidden. To analyze this situation we first use a modified frontier orbital approach.⁴⁰⁷ We will imagine that in the transition state the migrating H atom breaks away from the rest of the system, which we may treat as if it were a free radical.



Note that this is not what actually takes place; we merely imagine it in order to be able to analyze the process. In a [1,3] sigmatropic rearrangement the imaginary transition state consists of a hydrogen atom and an allyl radical. The latter species (p. 32) has three π orbitals, but the only one that concerns us here is the HOMO which, in a thermal rearrangement is **D**. The electron of the hydrogen atom is of course in a $1s$ orbital, which has only one lobe. The rule governing sigmatropic migration of hydrogen is *the H must move from a plus to a plus or from a minus to a minus lobe, of the highest occupied molecular*



*orbital; it cannot move to a lobe of opposite sign.*⁴⁰⁸ Obviously, the only way this can happen in a thermal [1,3] sigmatropic rearrangement is if the migration is antarafacial. Consequently, the rule predicts that antarafacial thermal [1,3] sigmatropic rearrangements are allowed, but the suprafacial pathway is forbidden. However, in a photochemical reaction, promotion of an electron means that **E** is now the HOMO; the suprafacial pathway is now allowed and the antarafacial pathway forbidden.

A similar analysis of [1,5] sigmatropic rearrangements shows that in this case the thermal reaction must be suprafacial and the photochemical process antarafacial. For the general case, with odd-numbered j , we can say that [1, j] suprafacial migrations are allowed thermally when j is of the form $4n + 1$, and photochemically when j has the form $4n - 1$; the opposite is true for antarafacial migrations.

⁴⁰⁶Since we are using the arbitrary designations U, V, Y, and Z, we have been arbitrary in which isomer to call R,Z and which to call S,E .

⁴⁰⁷See Woodward; Hoffmann, Ref. 403, pp. 114-140.

⁴⁰⁸This follows from the principle that bonds are formed only by overlap of orbitals of the same sign. Since this is a concerted reaction, the hydrogen orbital in the transition state must overlap simultaneously with one lobe from the migration origin and one from the terminus. It is obvious that both of these lobes must have the same sign.