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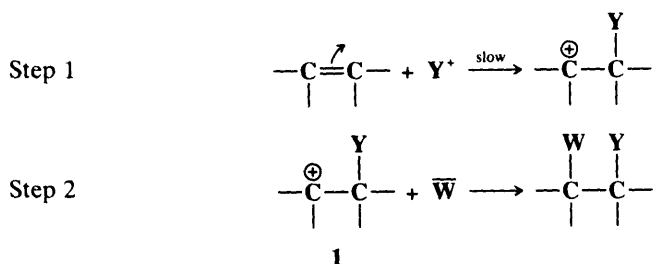
ADDITION TO CARBON-CARBON MULTIPLE BONDS

There are basically four ways in which addition to a double or triple bond can take place. Three of these are two-step processes, with initial attack by a nucleophile, an electrophile, or a free radical. The second step consists of combination of the resulting intermediate with, respectively, a positive species, a negative species, or a neutral entity. In the fourth type of mechanism, attack at the two carbon atoms of the double or triple bond is simultaneous. Which of the four mechanisms is operating in any given case is determined by the nature of the substrate, the reagent, and the reaction conditions. Some of the reactions in this chapter can take place by all four mechanistic types.

MECHANISMS

Electrophilic Addition¹

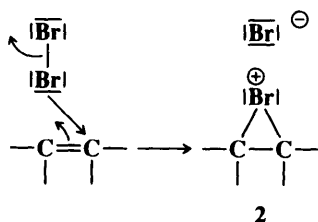
In this mechanism a positive species approaches the double or triple bond and in the first step forms a bond by converting the π pair of electrons into a σ pair:



The IUPAC designation for this mechanism is $A_E + A_N$ (or $A_H + A_N$ if $\text{Y}^+ = \text{H}^+$). As in electrophilic substitution (p. 502), Y need not actually be a positive ion but can be the

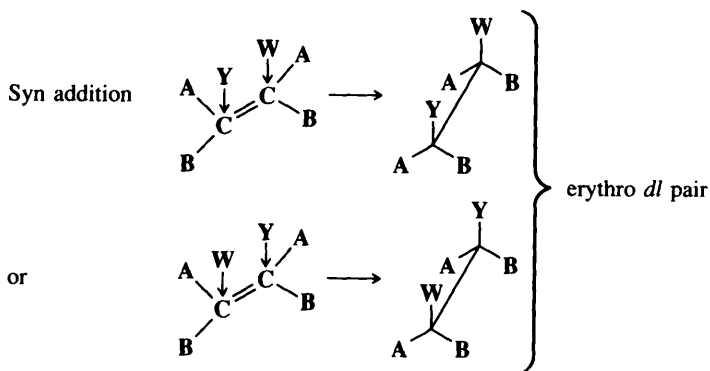
¹For a monograph, see de la Mare; Bolton *Electrophilic Additions to Unsaturated Systems*, 2nd ed.; Elsevier: New York, 1982. For reviews, see Schmid, in Patai *Supplement A: The Chemistry of Double-bonded Functional Groups*, vol. 2, pt. 1; Wiley: New York, 1989, pp. 679-731; Smit *Sov. Sci. Rev. Sect. B* **1985**, 7, 155-236; V'yunov; Ginak *Russ. Chem. Rev.* **1981**, 50, 151-163; Schmid; Garratt, in Patai *Supplement A: The Chemistry of Double-bonded Functional Groups*, vol. 1, pt. 2; Wiley: New York, 1977, pp. 725-912; Freeman *Chem. Rev.* **1975**, 75, 439-490; Bolton, in Bamford; Tipper *Comprehensive Chemical Kinetics*, vol. 9; Elsevier: New York, 1973, pp. 1-86; Dolbier *J. Chem. Educ.* **1969**, 46, 342-344.

positive end of a dipole or an induced dipole, with the negative part breaking off either during the first step or shortly after. The second step is a combination of **1** with a species carrying an electron pair and often bearing a negative charge. This step is the same as the second step of the S_N1 mechanism. Not all electrophilic additions follow the simple mechanism given above. In many brominations it is fairly certain that **1**, if formed at all, very rapidly cyclizes to a bromonium ion (**2**):



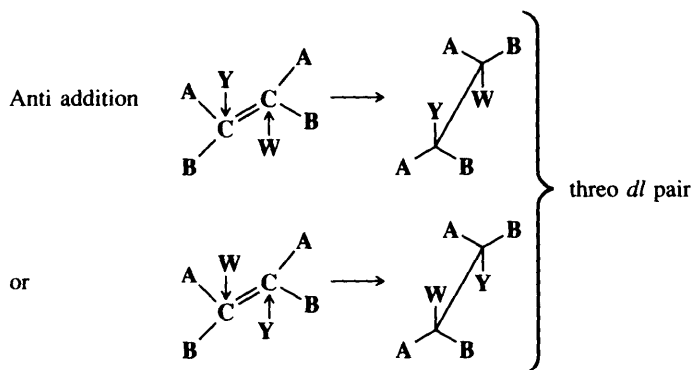
This intermediate is similar to those encountered in the neighboring-group mechanism of nucleophilic substitution (see p. 308). The attack of \bar{W} on an intermediate like **2** is an S_N2 step. Whether the intermediate is **1** or **2**, the mechanism is called $AdE2$ (electrophilic addition, bimolecular).

In investigating the mechanism of addition to a double bond, perhaps the most useful type of information is the stereochemistry of the reaction.² The two carbons of the double bond and the four atoms immediately attached to them are all in a plane (p. 8); there are thus three possibilities. Y and W may enter from the same side of the plane, in which case the addition is stereospecific and *syn*; they may enter from opposite sides for stereospecific *anti* addition; or the reaction may be nonstereospecific. In order to determine which of these possibilities is occurring in a given reaction, the following type of experiment is often done: YW is added to the *cis* and *trans* isomers of an olefin of the form $ABC=CBA$. We may use the *cis* olefin as an example. If the addition is *syn*, the product will be the erythro *dl* pair, because each carbon has a 50% chance of being attacked by Y :



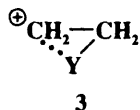
²For a review of the stereochemistry of electrophilic additions to double and triple bonds, see Fahey *Top. Stereochem.* **1968**, 3, 237-342. For a review of the synthetic uses of stereoselective additions, see Bartlett *Tetrahedron* **1980**, 36, 2-72, pp. 3-15.

On the other hand, if the addition is anti, the threo *dl* pair will be formed:

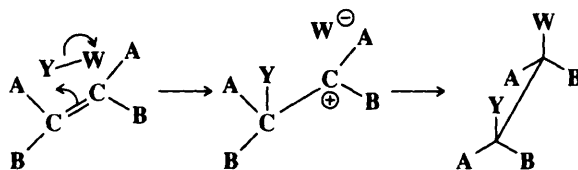


Of course, the *trans* isomer will give the opposite results: the threo pair if the addition is *syn* and the erythro pair if it is *anti*. The threo and erythro isomers have different physical properties. In the special case where $Y = W$ (as in the addition of Br_2), the "erythro pair" is a meso compound. In addition to triple-bond compounds of the type $\text{AC}\equiv\text{CA}$, *syn* addition results in a *cis* olefin and *anti* addition in a *trans* olefin. By the definition given on p. 137, addition to triple bonds cannot be stereospecific, though it can be, and often is, stereoselective.

It is easily seen that in reactions involving cyclic intermediates like **2** addition must be *anti*, since the second step is an $\text{S}_{\text{N}}2$ step and must occur from the back side. It is not so easy to predict the stereochemistry for reactions involving **1**. If **1** has a relatively long life, the addition should be nonstereospecific, since there will be free rotation about the single bond. On the other hand, there may be some factor that maintains the configuration, in which case W may come in from the same side or the opposite side, depending on the circumstances. For example, the positive charge might be stabilized by an attraction for Y that does not involve a full bond:



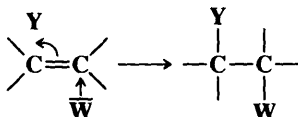
The second group would then come in *anti*. A circumstance that would favor *syn* addition would be the formation of an ion pair after the addition of Y :³



Since W is already on the same side of the plane as Y , collapse of the ion pair leads to *syn* addition.

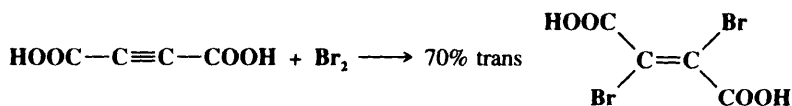
³Dewar *Angew. Chem. Int. Ed. Engl.* **1964**, *3*, 245-249 [*Angew. Chem.* *76*, 320-325]; Heasley; Bower; Dougharty; Easdon; Heasley; Arnold; Carter; Yaeger; Gipe; Shellhamer *J. Org. Chem.* **1980**, *45*, 5150.

Another possibility is that anti addition might, at least in some cases, be caused by the operation of a mechanism in which attack by W and Y are essentially simultaneous but from opposite sides:



This mechanism, called the ADE3 mechanism (*termolecular addition*, IUPAC A_NA_E),⁴ has the disadvantage that three molecules must come together in the transition state. However, it is the reverse of the E2 mechanism for elimination, for which the transition state is known to possess this geometry (p. 983).

There is much evidence that when the attack is by Br⁺ (or a carrier of it), the bromonium ion **2** is often an intermediate and the addition is anti. As long ago as 1911, McKenzie and Fischer independently showed that treatment of maleic acid with bromine gave the *dl* pair of 2,3-dibromosuccinic acid, while fumaric acid (the *trans* isomer) gave the meso compound.⁵ Many similar experiments have been performed since with similar results. For triple bonds, stereoselective anti addition was shown even earlier. Bromination of dicarboxyacetylene gave 70% of the *trans* isomer.⁶



There is other evidence for mechanisms involving **2**. We have already mentioned (p. 312) that bromonium ions have been isolated in stable solutions in nucleophilic substitution reactions involving bromine as a neighboring group. Such ions have also been isolated in reactions involving addition of a Br⁺ species to a double bond.⁷ The following is further evidence. If the two bromines approach the double bond from opposite sides, it is very unlikely that they could come from the same bromine molecule. This means that if the reaction is performed in the presence of nucleophiles, some of these will compete in the second step with the bromide liberated from the bromine. It has been found, indeed, that treatment of ethylene with bromine in the presence of chloride ions gives some 1-chloro-2-bromoethane along with the dibromoethane.⁸ Similar results are found when the reaction is carried out in the presence of water (**5-27**) or of other nucleophiles.⁹ Ab initio molecular

⁴For evidence for this mechanism, see, for example, Hammond; Nevitt *J. Am. Chem. Soc.* **1954**, *76*, 4121; Bell; Pring *J. Chem. Soc. B* **1966**, 1119; Pincock; Yates *J. Am. Chem. Soc.* **1968**, *90*, 5643; Fahey; Lee *J. Am. Chem. Soc.* **1967**, *89*, 2780, **1968**, *90*, 2124; Fahey; Monahan *J. Am. Chem. Soc.* **1970**, *92*, 2816; Fahey; Payne; Lee *J. Org. Chem.* **1974**, *39*, 1124; Roberts *J. Chem. Soc., Perkin Trans. 2* **1976**, 1374; Pasto; Gadberry *J. Am. Chem. Soc.* **1978**, *100*, 1469; Naab; Staab *Chem. Ber.* **1978**, *111*, 2982.

⁵This was done by Fischer *Liebigs Ann. Chem.* **1911**, 386, 374; McKenzie *Proc. Chem. Soc.* **1911**, 150, *J. Chem. Soc.* **1912**, 101, 1196.

⁶Michael *J. Prakt. Chem.* **1892**, *46*, 209.

⁷Strating; Wieringa; Wynberg *Chem. Commun.* **1969**, 907; Olah *Angew. Chem. Int. Ed. Engl.* **1973**, *12*, 173-212, p. 207 [*Angew. Chem.* **85**, 183-225]; Slebocka-Tilk; Ball; Brown *J. Am. Chem. Soc.* **1985**, *107*, 4504.

⁸Francis *J. Am. Chem. Soc.* **1925**, *47*, 2340.

⁹See, for example, Zefirov; Koz'min; Dan'kov; Zhdankin; Kirin *J. Org. Chem. USSR* **1984**, *20*, 205.

orbital studies show that **2** is more stable than its open isomer **1** ($Y = \text{Br}$).¹⁰ There is evidence that formation of **2** is reversible.¹¹

However, a number of examples have been found where addition of bromine is not stereospecifically anti. For example, the addition of Br_2 to *cis*- and *trans*-1-phenylpropenes in CCl_4 was nonstereospecific.¹² Furthermore, the stereospecificity of bromine addition to stilbene depends on the dielectric constant of the solvent. In solvents of low dielectric constant, the addition was 90 to 100% anti, but with an increase in dielectric constant, the reaction became less stereospecific, until, at a dielectric constant of about 35, the addition was completely nonstereospecific.¹³ Likewise in the case of triple bonds, stereoselective anti addition was found in bromination of 3-hexyne, but both *cis* and *trans* products were obtained in bromination of phenylacetylene.¹⁴ These results indicate that a bromonium ion is not formed where the open cation can be stabilized in other ways (e.g., addition of Br^+ to 1-phenylpropene gives the ion $\text{Ph}^{\oplus}\text{CHCHBrCH}_3$, which is a relatively stable benzylic cation) and that there is probably a spectrum of mechanisms between complete bromonium ion (**2**, no rotation) formation and completely open-cation (**1**, free rotation) formation, with partially bridged bromonium ions (**3**, restricted rotation) in between.¹⁵ We have previously seen cases (e.g., p. 315) where cations require more stabilization from outside sources as they become intrinsically less stable themselves.¹⁶ Further evidence for the open cation mechanism where aryl stabilization is present was reported in an isotope effect study of addition of Br_2 to $\text{ArCH}=\text{CHCHAr}'$ ($\text{Ar} = p$ -nitrophenyl, $\text{Ar}' = p$ -tolyl). The ^{14}C isotope effect for one of the double bond carbons (the one closer to the NO_2 group) was considerably larger than for the other one.¹⁷

Attack by Cl^+ ,¹⁸ I^+ ,¹⁹ and RS^{+20} is similar to that by Br^+ ; there is a spectrum of mechanisms between cyclic intermediates and open cations. As might be expected from our discussion in Chapter 10 (p. 312), iodonium ions compete with open carbocations more effectively than bromonium ions, while chloronium ions compete less effectively. There is

¹⁰Hamilton; Schaefer *J. Am. Chem. Soc.* **1990**, *112*, 8260.

¹¹Brown; Gedye; Slebocka-Tilk; Buschek; Kopecky *J. Am. Chem. Soc.* **1984**, *106*, 4515; Bellucci; Bianchini; Chiappe; Marioni; Spagna *J. Am. Chem. Soc.* **1988**, *110*, 546; Ruasse; Motallebi; Galland *J. Am. Chem. Soc.* **1991**, *113*, 3440; Bellucci; Bianchini; Chiappe; Brown; Slebocka-Tilk; *J. Am. Chem. Soc.* **1991**, *113*, 8012; Bennet; Brown; McClung; Klobukowski; Aarts; Santarsiero; Bellucci; Bianchini; *J. Am. Chem. Soc.* **1991**, *113*, 8532.

¹²Fahcy; Schneider *J. Am. Chem. Soc.* **1968**, *90*, 4429. See also Rolston; Yates *J. Am. Chem. Soc.* **1969**, *91*, 1469, 1477, 1483.

¹³Buckles; Bader; Thurmaier *J. Org. Chem.* **1962**, *27*, 4523; Heublein *J. Prakt. Chem.* **1966**, [4] *31*, 84. See also Buckles; Miller; Thurmaier *J. Org. Chem.* **1967**, *32*, 888; Heublein; Lauterbach *J. Prakt. Chem.* **1969**, *311*, 91; Ruasse; Dubois *J. Am. Chem. Soc.* **1975**, *97*, 1977. For the dependence of stereospecificity in this reaction on the solvent concentration, see Bellucci; Bianchini; Chiappe; Marioni *J. Org. Chem.* **1990**, *55*, 4094.

¹⁴Pincock; Yates *Can. J. Chem.* **1970**, *48*, 3332.

¹⁵For other evidence for this concept, see Pincock; Yates *Can. J. Chem.* **1970**, *48*, 2944; Heasley; Chamberlain *J. Org. Chem.* **1970**, *35*, 539; Dubois; Toulecc; Barbier *Tetrahedron Lett.* **1970**, 4485; Dalton; Davis *Tetrahedron Lett.* **1972**, 1057; Wilkins; Regulski *J. Am. Chem. Soc.* **1972**, *94*, 6016; Sisti; Meyers *J. Org. Chem.* **1973**, *38*, 4431; McManus; Peterson *Tetrahedron Lett.* **1975**, 2753; Abraham; Monasterios *J. Chem. Soc., Perkin Trans. 1* **1973**, 1446; Ruasse; Argile; Dubois *J. Am. Chem. Soc.* **1978**, *100*, 7645; *J. Org. Chem.* **1979**, *44*, 1173; Schmid; Modro; Yates *J. Org. Chem.* **1980**, *45*, 665; Ruasse; Argile *J. Org. Chem.* **1983**, *48*, 202; Cadogan; Cameron; Gosney; Highcock; Newlands *J. Chem. Soc., Chem. Commun.* **1985**, 1751. For a review, see Ruasse *Acc. Chem. Res.* **1990**, *23*, 87-93.

¹⁶In a few special cases, stereospecific syn addition of Br_2 has been found, probably caused by an ion pair mechanism as shown on p. 736; Naae *J. Org. Chem.* **1980**, *45*, 1394.

¹⁷Kokil; Fry *Tetrahedron Lett.* **1986**, *27*, 5051.

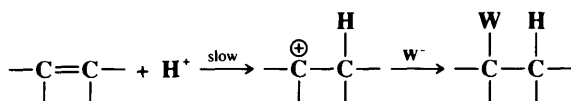
¹⁸Fahcy, Ref. 2, pp. 273-277.

¹⁹Hassner; Boerwinkle; Levy *J. Am. Chem. Soc.* **1970**, *92*, 4879.

²⁰For reviews of thiiranium and/or thiirenium ions, see Capozzi; Modena, in Bernardi; Csizmadia; Mangini *Organic Sulfur Chemistry*; Elsevier: New York, 1985, pp. 246-298; Smit, Ref. 1, pp. 180-202; Dittmer; Patwardhan, in Stirling *The Chemistry of the Sulphonium Group*, pt. 1; Wiley: New York, 1981, pp. 387-412; Capozzi; Lucchini; Modena; *Rev. Chem. Intermed.* **1979**, *2*, 347-375; Schmid *Top. Sulfur Chem.* **1977**, *3*, 102-117; Mueller *Angew. Chem. Int. Ed. Engl.* **1969**, *8*, 482-492 [*Angew. Chem.* *81*, 475-484]. The specific nature of the 3-membered sulfur-containing ring is in dispute; see Smit; Zefirov; Bodrikov; Krimer *Acc. Chem. Res.* **1979**, *12*, 282-288; Bodrikov; Borisov; Chumakov; Zefirov; Smit *Tetrahedron Lett.* **1980**, *21*, 115; Schmid; Garratt; Dean *Can. J. Chem.* **1987**, *65*, 1172; Schmid; Strukelj; Dalipi *Can. J. Chem.* **1987**, *65*, 1945.

kinetic and spectral evidence that at least in some cases, for example in the addition of Br₂ or ICl, the electrophile forms a π complex with the alkene before a covalent bond is formed.²¹

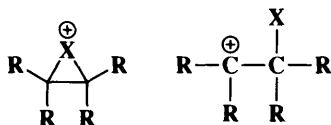
When the electrophile is a proton,²² a cyclic intermediate is not possible, and the mechanism is the simple A_H + A_N process shown before



This is an A-SE2 mechanism (p. 374). There is a great deal of evidence²³ for it, including:

1. The reaction is general-acid, not specific-acid-catalyzed, implying rate-determining proton transfer from the acid to the double bond.²⁴

2. The existence of open carbocation intermediates is supported by the contrast in the pattern of alkyl substituent effects²⁵ with that found in brominations, where cyclic intermediates are involved. In the latter case substitution of alkyl groups on H₂C=CH₂ causes a cumulative rate acceleration until all four hydrogens have been replaced by alkyl groups,



because each group helps to stabilize the positive charge.²⁶ In addition of HX the effect is not cumulative. Replacement of the two hydrogens on one carbon causes great rate increases (primary → secondary → tertiary carbocation), but additional substitution on the other carbon produces little or no acceleration.²⁷ This is evidence for open cations when a proton is the electrophile.²⁸

3. Open carbocations are prone to rearrange (Chapter 18). Many rearrangements have been found to accompany additions of HX and H₂O).²⁹

²¹See Norlander; Haky; Landino *J. Am. Chem. Soc.* **1980**, *102*, 7487; Fukuzumi; Kochi *Int. J. Chem. Kinet.* **1983**, *15*, 249; Schmid; Gordon *Can. J. Chem.* **1984**, *62*, 2526. **1986**, *64*, 2171; Bellucci; Bianchini; Ambrosetti *J. Am. Chem. Soc.* **1985**, *107*, 2464; Bellucci; Bianchini; Chiappe; Marioni; Ambrosetti; Brown; Slebocka-Tilk *J. Am. Chem. Soc.* **1989**, *111*, 2640.

²²For a review of the addition of HCl, see Sergeev; Smirnov; Rostovshchikova *Russ. Chem. Rev.* **1983**, *52*, 259-274.

²³For other evidence, see Baliga; Whalley *Can. J. Chem.* **1964**, *42*, 1019. **1965**, *43*, 2453; Gold; Kessick *J. Chem. Soc.* **1965**, 6718; Corriu; Guenzet *Tetrahedron* **1970**, *26*, 671; Simandoux; Torck; Hellin; Coussemant *Bull. Soc. Chim. Fr.* **1972**, 4402, 4410; Bernasconi; Boyle *J. Am. Chem. Soc.* **1974**, *96*, 6070; Hampel; Just; Pisanenko; Pritzkow *J. Prakt. Chem.* **1976**, *318*, 930; Allen; Tidwell *J. Am. Chem. Soc.* **1983**, *104*, 3145.

²⁴Kresge; Chiang; Fitzgerald; McDonald; Schmid *J. Am. Chem. Soc.* **1971**, *93*, 4907; Loudon; Noyce *J. Am. Chem. Soc.* **1969**, *91*, 1433; Schubert; Keeffe *J. Am. Chem. Soc.* **1972**, *94*, 559; Chiang; Kresge *J. Am. Chem. Soc.* **1985**, *107*, 6363.

²⁵Bartlett; Sargent *J. Am. Chem. Soc.* **1965**, *87*, 1297; Schmid; Garratt *Can. J. Chem.* **1973**, *51*, 2463.

²⁶See, for example, Anantkrishnan; Ingold *J. Chem. Soc.* **1935**, 1396; Swern, in Swern *Organic Peroxides*, vol. 2; Wiley: New York, 1971, pp. 451-454; Nowlan; Tidwell *Acc. Chem. Res.* **1977**, *10*, 252-258.

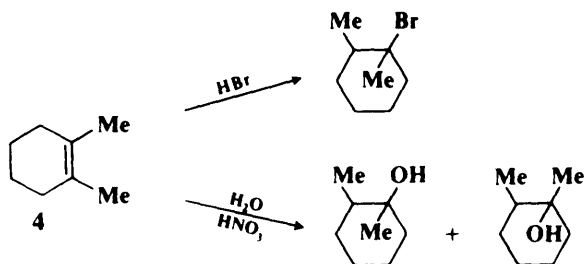
²⁷Bartlett; Sargent, Ref. 25; Riesz; Taft; Boyd *J. Am. Chem. Soc.* **1957**, *79*, 3724.

²⁸A similar result (open cations) was obtained with carbocations Ar₂CH⁺ as electrophiles: Mayr; Pock *Chem. Ber.* **1986**, *119*, 2473.

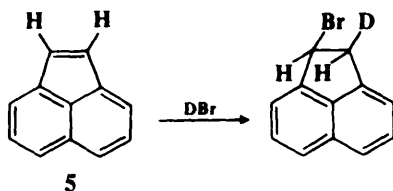
²⁹For example, see Whitmore; Johnston *J. Am. Chem. Soc.* **1933**, *55*, 5020; Fahey; McPherson *J. Am. Chem. Soc.* **1969**, *91*, 3865; Bundel¹; Ryabstev; Sorokin; Reutov *Bull. Acad. Sci. USSR, Div. Chem. Sci.* **1969**, 1311; Pocker; Stevens *J. Am. Chem. Soc.* **1969**, *91*, 4205; Staab; Wittig; Naab *Chem. Ber.* **1978**, *111*, 2965; Stammann; Griesbaum *Chem. Ber.* **1980**, *113*, 598.

It may also be recalled that vinylic ethers react with proton donors in a similar manner (see 0-6).

The stereochemistry of HX addition is varied. Examples are known of predominant syn, anti, and nonstereoselective addition. It was found that treatment of 1,2-dimethylcyclohexene (**4**) with HBr gave predominant anti addition,³⁰ while addition of water to **4** gave equal amounts of the cis and trans alcohols:³¹

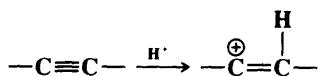


On the other hand, addition of DBr to acenaphthylene (**5**) and to indene and 1-phenylpropene gave predominant syn addition.³²



In fact it has been shown that the stereoselectivity of HCl addition can be controlled by changing the reaction conditions. Addition of HCl to **4** in CH_2Cl_2 at -98°C gave predominantly syn addition, while in ethyl ether at 0°C , the addition was mostly anti.³³

Addition of HX to triple bonds has the same mechanism, though the intermediate in this case is a vinylic cation:³⁴



In all these cases (except for the AdE3 mechanism) we have assumed that formation of the intermediate (**1**, **2**, or **3**) is the slow step and attack by the nucleophile on the intermediate

³⁰Hammond; Nevitt, Ref. 4; See also Fahey; Monahan, Ref. 4; Pasto; Meyer; Lepeska *J. Am. Chem. Soc.* **1974**, *96*, 1858.

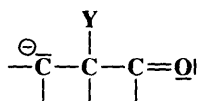
³¹Collins; Hammond *J. Org. Chem.* **1960**, *25*, 911.

³²Dewar; Fahey *J. Am. Chem. Soc.* **1963**, *85*, 2245, 2248. For a review of syn addition of HX, see Ref. 3.

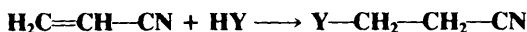
³³Becker; Grob *Synthesis* **1973**, 789. See also Marcuzzi; Melloni; Modena *Tetrahedron Lett.* **1974**, 413; Naab; Staab, Ref. 4.

³⁴For reviews of electrophilic addition to alkynes, including much evidence, see Rappoport *React. Intermed. (Plenum)* **1983**, *3*, 427-615, pp. 428-440; Stang; Rappoport; Hanack; Subramanian *Vinyl Cations*; Academic Press: New York, 1979, pp. 24-151; Stang *Prog. Phys. Org. Chem.* **1973**, *10*, 205-325; Modena; Tonellato *Adv. Phys. Org. Chem.* **1971**, *9*, 185-280, pp. 187-231; Richey; Richey, in Olah; Schleyer *Carbonium Ions*, vol. 2; Wiley: New York, 1970, pp. 906-922.

Protonation of the enolate ion is chiefly at the oxygen, which is more negative than the carbon, but this produces the enol, which tautomerizes. So although the net result of the reaction is addition to a carbon-carbon double bond, the *mechanism* is 1,4 nucleophilic addition to the $C=C-C=O$ (or similar) system and is thus very similar to the mechanism of addition to carbon-oxygen double and similar bonds (see Chapter 16). When Z is CN or a $C=O$ group, it is also possible for Y^- to attack at *this* carbon, and this reaction sometimes competes. When it happens, it is called 1,2 addition. 1,4 addition to these substrates is also known as *conjugate addition*. Y^- almost never attacks at the 3 position, since the resulting carbanion would have no resonance stabilization:⁴¹

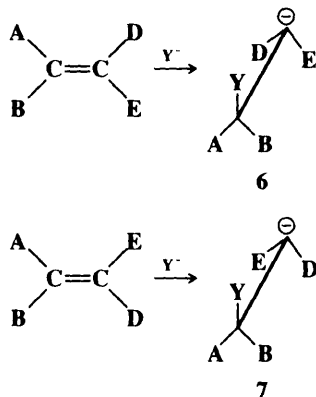


An important substrate of this type is acrylonitrile, and 1,4 addition to it is called *cynoethylation* because the Y is cyanoethylated:



With any substrate, when Y is an ion of the type $Z-\overset{\ominus}{\text{C}}\text{R}_2$ (Z is as defined above; R may be alkyl, aryl, hydrogen, or another Z), the reaction is called the *Michael reaction* (see 5-17). In this book we will call all other reactions that follow this mechanism *Michael-type additions*. Systems of the type $C=C-C=C-Z$ can give 1,2, 1,4, or 1,6 addition.⁴² Michael-type reactions are reversible, and compounds of the type $\text{YCH}_2\text{CH}_2\text{Z}$ can often be decomposed to YH and $\text{CH}_2=\text{CHZ}$ by heating, either with or without alkali.

If the mechanism for nucleophilic addition is the simple carbanion mechanism outlined on p. 741, the addition should be nonstereospecific, though it might well be stereoselective (see p. 137 for the distinction). For example, the *E* and *Z* forms of an olefin $\text{ABC}=\text{CDE}$ would give 6 and 7:



If the carbanion has even a short lifetime, 6 and 7 will assume the most favorable conformation before the attack of W. This is of course the same for both, and when W attacks, the same product will result from each. This will be one of two possible diastereomers, so the reaction will be stereoselective; but since the *cis* and *trans* isomers do not give rise to

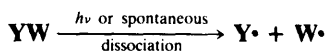
⁴¹For 1,8 addition to a trienone, see Barbot; Kadib-Elban; Miginiac *J. Organomet. Chem.* **1988**, 345, 239.

⁴²However, attack at the 3 position has been reported when the 4 position contains one or two carbanion-stabilizing groups such as SiMe_3 ; Klumpp; Mierop; Vriclink; Brugman; Schakel *J. Am. Chem. Soc.* **1985**, 107, 6740.

different isomers, it will not be stereospecific. Unfortunately, this prediction has not been tested on open-chain olefins. Except for Michael-type substrates, the stereochemistry of nucleophilic addition to double bonds has been studied only in cyclic systems, where only the *cis* isomer exists. In these cases the reaction has been shown to be stereoselective, with *syn* addition reported in some cases⁴³ and *anti* addition in others.⁴⁴ When the reaction is performed on a Michael-type substrate, $C=C-Z$, the hydrogen does not arrive at the carbon directly but only through a tautomeric equilibrium. The product naturally assumes the most thermodynamically stable configuration, without relation to the direction of original attack of *Y*. In one such case (the addition of EtOD and of Me_3CSD to *trans*- $MeCH=CHCOOEt$) predominant *anti* addition was found; there is evidence that the stereoselectivity here results from the final protonation of the enolate, and not from the initial attack.⁴⁵ For obvious reasons, additions to triple bonds cannot be stereospecific. As with electrophilic additions, nucleophilic additions to triple bonds are usually stereoselective and *anti*,⁴⁶ though *syn* addition⁴⁷ and nonstereoselective addition⁴⁸ have also been reported.

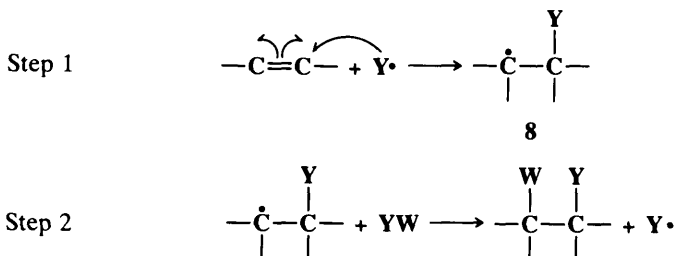
Free-Radical Addition

The mechanism of free-radical addition⁴⁹ follows the pattern discussed in Chapter 14 (pp. 677-678). A radical is generated by



or $R\cdot$ (from some other source) + $YW \longrightarrow RW + Y\cdot$

Propagation then occurs by



⁴³For example, Truce; Levy *J. Org. Chem.* **1963**, 28, 679.

⁴⁴For example, Truce; Levy *J. Am. Chem. Soc.* **1961**, 83, 4641; Zefirov; Yur'ev; Prikazchikova; Bykhovskaya *J. Gen. Chem. USSR* **1963**, 33, 2100.

⁴⁵Mohrig; Fu; King; Warnet; Gustafson *J. Am. Chem. Soc.* **1990**, 112, 3665.

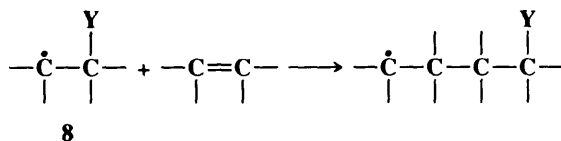
⁴⁶Truce; Simms *J. Am. Chem. Soc.* **1956**, 78, 2756; Shostakovskii; Chekulaeva; Kondrat'eva; Lopatin *Bull. Acad. Sci. USSR, Div. Chem. Sci.* **1962**, 2118; Théron; Vessière *Bull. Soc. Chim. Fr.* **1968**, 2994; Bowden; Price *J. Chem. Soc. B* **1970**, 1466, 1472; Raunio; Frey *J. Org. Chem.* **1971**, 36, 345; Truce; Tichenor *J. Org. Chem.* **1972**, 37, 2391.

⁴⁷Truce; Goldhamer; Kruse *J. Am. Chem. Soc.* **1959**, 81, 4931; Dolfini *J. Org. Chem.* **1965**, 30, 1298; Winterfeldt; Preuss *Chem. Ber.* **1966**, 99, 450; Hayakawa; Kamikawaji; Wakita; Kanematsu *J. Org. Chem.* **1984**, 49, 1985.

⁴⁸Gracheva; Laba; Kul'bovskaya; Shostakovskii *J. Gen. Chem. USSR* **1963**, 33, 2431; Truce; Brady *J. Org. Chem.* **1966**, 31, 3543; Prilezhaeva; Vasil'ev; Mikhaleshvili; Bogdanov *Bull. Acad. Sci., USSR, Div. Chem. Sci.* **1970**, 1820.

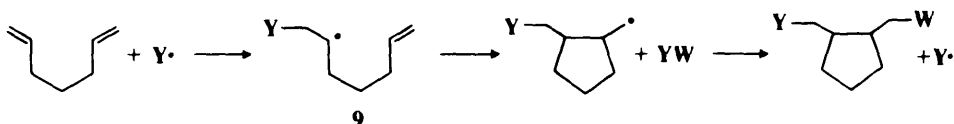
⁴⁹For a monograph on this subject, see Huyser *Free-Radical Chain Reactions*; Wiley: New York, 1970. Other books with much of interest in this field are Nonhebel; Walton *Free-Radical Chemistry*; Cambridge University Press: London, 1974; Pyor *Free Radicals*; McGraw-Hill: New York, 1965. For reviews, see Giese *Rev. Chem. Intermed.* **1986**, 7, 3-11, *Angew. Chem. Int. Ed. Engl.* **1983**, 22, 753-764 [*Angew. Chem.* 95, 771-782]; Amiel, in Patai; Rappoport *The Chemistry of Functional Groups, Supplement C*, pt. 1; Wiley: New York, 1983, pp. 341-382; Abell, in Bamford; Tipper *Comprehensive Chemical Kinetics*, vol. 18; Elsevier: New York, 1976, pp. 111-165; Abell, in Kochi *Free Radicals*, vol. 2; Wiley: New York, 1973, pp. 63-112; Minisci *Acc. Chem. Res.* **1975**, 8, 165-171; Julia, in Viehe *Acetylenes*; Marcel Dekker: New York, 1969, pp. 335-354; Elad *Org. Photochem.* **1969**, 2, 168-212; Schönberg *Preparative Organic Photochemistry*; Springer: New York, 1968, pp. 155-181; Cadogan; Perkins, in Patai, Ref. 36, pp. 585-632.

Step 2 is an abstraction, so W is nearly always univalent, either hydrogen or halogen (p. 683). Termination of the chain can occur in any of the ways discussed in Chapter 14. If **8** adds to another olefin molecule,



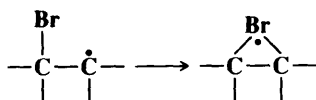
a dimer is formed. This can add to still another, and chains, long or short, may be built up. This is the mechanism of free-radical polymerization. Short polymeric molecules (called *telomers*), formed in this manner, are often troublesome side products in free-radical addition reactions.

When free radicals are added to 1,5- or 1,6-dienes, the initially formed radical can add intramolecularly to the other bond, leading to a cyclic product, e.g.,⁵⁰



Radicals of the type **9**, generated in other ways, also undergo these cyclizations. Both five- and six-membered rings can be formed in these reactions (see p. 752).

The free-radical addition mechanism just outlined predicts that the addition should be nonstereospecific, at least if **8** has any but an extremely short lifetime. However, the reactions may be stereoselective, for reasons similar to those discussed for nucleophilic addition on p. 742. Not all free-radical additions have been found to be stereoselective, but many are. For example, addition of HBr to 1-bromocyclohexene gave only *cis*-1,2-dibromocyclohexane and none of the *trans* isomer (anti addition),⁵¹ and propyne (at -78 to -60°C) gave only *cis*-1-bromopropene (anti addition).⁵² However, stereospecificity has been found only in a few cases. The most important of these is addition of HBr to 2-bromo-2-butene under free-radical conditions at -80°C . Under these conditions, the *cis* isomer gave 92% of the *meso* product, while the *trans* isomer gave mostly the *dl* pair.⁵³ This stereospecificity disappeared at room temperature, where both olefins gave the same mixture of products (about 78% of the *dl* pair and 22% of the *meso* compound), so the addition was still stereoselective but no longer stereospecific. The stereospecificity at low temperatures is probably caused by a stabilization of the intermediate radical through the formation of a bridged bromine radical, of the type mentioned on p. 682:



⁵⁰For reviews of these and other free-radical cyclization reactions, see RajanBabu *Acc. Chem. Res.* **1991**, *24*, 139-145; Beckwith *Rev. Chem. Intermed.* **1986**, *7*, 143-154; Giese *Radicals in Organic Synthesis: Formation of Carbon-Carbon Bonds*; Pergamon: Elmsford, NY, 1986, pp. 141-209; Surzur *React. Intermed. (Plenum)* **1982**, *2*, 121-295; Julia *Acc. Chem. Res.* **1972**, *4*, 386-392; *Pure Appl. Chem.* **1974**, *40*, 553-567, **1967**, *15*, 167-183; Nonhebel; Walton, *Ref.* **49**, pp. 533-544; Wilt, in Kochi, *Ref.* **49**, vol. 1, pp. 418-446. For a review of cyclizations in general, see Thebtaranonth; Thebtaranonth *Tetrahedron* **1990**, *46*, 1385-1489.

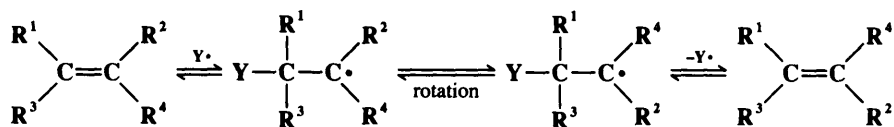
⁵¹Goering; Abell; Aycock *J. Am. Chem. Soc.* **1952**, *74*, 3588. See also LeBel; Czaja; DeBoer *J. Org. Chem.* **1969**, *34*, 3112.

⁵²Skell; Allen *J. Am. Chem. Soc.* **1958**, *80*, 5997.

⁵³Goering; Larsen *J. Am. Chem. Soc.* **1957**, *79*, 2653, **1959**, *81*, 5937. Also see Skell; Allen *J. Am. Chem. Soc.* **1959**, *81*, 5383; Skell; Freeman *J. Org. Chem.* **1964**, *29*, 2524.

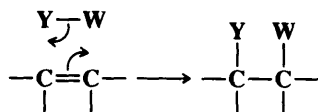
This species is similar to the bromonium ion that is responsible for stereospecific anti addition in the electrophilic mechanism. Further evidence for the existence of such bridged radicals was obtained by addition of $\text{Br}\cdot$ to olefins at 77 K. ESR spectra of the resulting species were consistent with bridged structures.⁵⁴

For many radicals step 1 ($\text{C}=\text{C} + \text{Y}\cdot \rightarrow \cdot\text{C}-\text{C}-\text{Y}$) is reversible. In such cases free radicals can cause cis \rightarrow trans isomerization of a double bond by the pathway⁵⁵



Cyclic Mechanisms

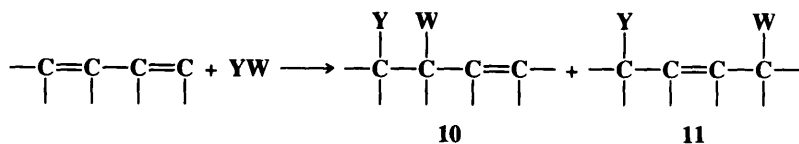
There are some addition reactions where the initial attack is not at one carbon of the double bond, but both carbons are attacked simultaneously. Some of these are four-center mechanisms, which follow this pattern:



In others there is a five- or a six-membered transition state. In these cases the addition to the double or triple bond must be syn. The most important reaction of this type is the Diels-Alder reaction (5-47).

Addition to Conjugated Systems

When electrophilic addition is carried out on a compound with two double bonds in conjugation, a 1,2-addition product (**10**) is often obtained, but in most cases there is also a 1,4-addition product (**11**), often in larger yield:^{55a}



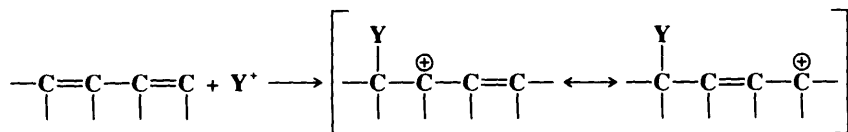
If the diene is unsymmetrical, there may be two 1,2-addition products. The competition between two types of addition product comes about because the carbocation resulting from

⁵⁴Abell; Piette *J. Am. Chem. Soc.* **1962**, *84*, 916. See also Leggett; Kennerly; Kohl *J. Chem. Phys.* **1974**, *60*, 3264.

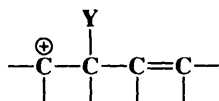
⁵⁵Benson; Egger; Golden *J. Am. Chem. Soc.* **1965**, *87*, 468; Golden; Furuyama; Benson *Int. J. Chem. Kinet.* **1969**, *1*, 57.

^{55a}For a review of electrophilic addition to conjugated dienes, see Khristov; Angelov; Petrov *Russ. Chem. Rev.* **1991**, *60*, 39-56.

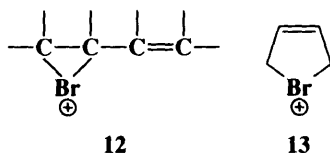
attack by Y^+ is a resonance hybrid, with partial positive charges at the 2 and 4 positions:



W^- may then attack either position. The original attack of Y^+ is always at the end of the conjugated system because an attack at a middle carbon would give a cation unstabilized by resonance:



In the case of electrophiles like Br^+ , which can form cyclic intermediates, both 1,2- and 1,4-addition products can be rationalized as stemming from an intermediate like **12**. Direct nucleophilic attack by W^- would give the 1,2-product, while the 1,4-product could be formed by attack at the 4 position, by an $SN2'$ -type mechanism (see p. 329). Intermediates like **13**



have been postulated but ruled out for Br and Cl by the observation that chlorination or bromination of butadiene gives trans 1,4-products.⁵⁶ If an ion like **13** were the intermediate, the 1,4-products would have to have the cis configuration.

In most cases more 1,4- than 1,2-addition product is obtained. This may be a consequence of thermodynamic control of products, as against kinetic. In most cases, under the reaction conditions, **10** is converted to a mixture of **10** and **11** which is richer in **11**. That is, either isomer gives the same mixture of both, which contains more **11**. It was found that at low temperatures, butadiene and HCl gave only 20 to 25% 1,4-adduct, while at high temperatures, where attainment of equilibrium is more likely, the mixture contained 75% 1,4-product.⁵⁷ 1,2-Addition predominated over 1,4- in the reaction between DCl and 1,3-pentadiene, where the intermediate was the symmetrical (except for the D label) $CH_3CH^{\oplus}\text{---}\overset{\ominus}{C}H\text{---}CHCH_2D$.⁵⁸ Ion pairs were invoked to explain this result, since a free ion would be expected to be attacked by Cl^- equally well at both positions, except for the very small isotope effect.

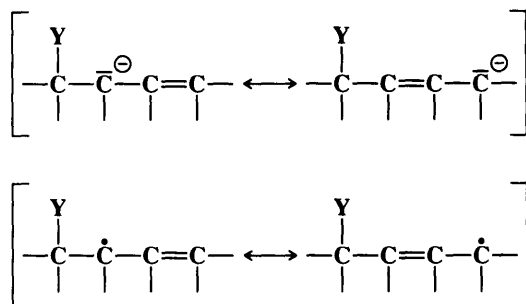
Addition to conjugated systems can also be accomplished by any of the other three mechanisms. In each case there is competition between 1,2 and 1,4 addition. In the case of

⁵⁶Mislow; Hellman *J. Am. Chem. Soc.* **1951**, 73, 244; Mislow *J. Am. Chem. Soc.* **1953**, 75, 2512.

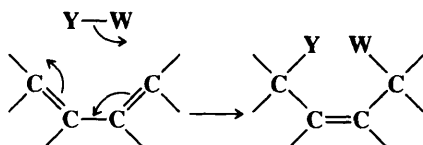
⁵⁷Kharasch; Kritchevsky; Mayo *J. Org. Chem.* **1938**, 2, 489.

⁵⁸Nordlander; Owuor; Haky *J. Am. Chem. Soc.* **1979**, 101, 1288.

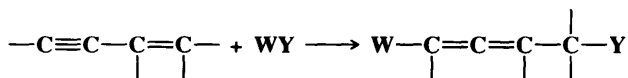
nucleophilic or free-radical attack,⁵⁹ the intermediates are resonance hybrids and behave



like the intermediate from electrophilic attack. Dienes can give 1,4 addition by a cyclic mechanism in this way:



Other conjugated systems, including trienes, enynes, diynes, etc., have been studied much less but behave similarly. 1,4 addition to enynes is an important way of making allenes:



ORIENTATION AND REACTIVITY

Reactivity

As with electrophilic aromatic substitution (Chapter 11), electron-donating groups increase the reactivity of a double bond toward electrophilic addition and electron-withdrawing groups decrease it. This is illustrated in Tables 15.1 and 15.2.⁶⁰ As a further illustration it may be mentioned that the reactivity toward electrophilic addition of a group of olefins increased in the order $\text{CCl}_3\text{CH}=\text{CH}_2 < \text{Cl}_2\text{CHCH}=\text{CH}_2 < \text{ClCH}_2\text{CH}=\text{CH}_2 < \text{CH}_3\text{CH}_2=\text{CH}_2$.⁶¹ For nucleophilic addition the situation is reversed. These reactions are best carried out on substrates containing three or four electron-withdrawing groups, two of the most common being $\text{F}_2\text{C}=\text{CF}_2$ ⁶² and $(\text{NC})_2\text{C}=\text{C}(\text{CN})_2$.⁶³ The effect of substituents is so great that it is

⁵⁹For a review of free-radical addition to conjugated dienes, see Afanas'ev; Samokhvalov *Russ. Chem. Rev.* **1969**, 38, 318-329.

⁶⁰Table 15.1 is from de la Mare *Q. Rev., Chem. Soc.* **1949**, 3, 126-145, p. 145. Table 15.2 is from Dubois; Mouvier *Tetrahedron Lett.* **1963**, 1325. See also Dubois; Mouvier *Bull. Soc. Chim. Fr.* **1968**, 1426; Grosjean; Mouvier; Dubois *J. Org. Chem.* **1976**, 41, 3869, 3872.

⁶¹Shelton; Lee *J. Org. Chem.* **1960**, 25, 428.

⁶²For a review of additions to $\text{F}_2\text{C}=\text{CF}_2$ and other fluoroolefins, see Chambers; Mobbs *Adv. Fluorine Chem.* **1965**, 4, 51-112.

⁶³For reviews of additions to tetracyanoethylene, see Fatiadi *Synthesis* **1987**, 249-284, 749-789; Dhar *Chem. Rev.* **1967**, 67, 611-622.

TABLE 15.1 Relative reactivity of some olefins toward bromine in acetic acid at 24°C⁶⁰

Olefin	Relative rate
PhCH=CH ₂	Very fast
PhCH=CHPh	18
CH ₂ =CHCH ₂ Cl	1.6
CH ₂ =CHCH ₂ Br	1.0
PhCH=CHBr	0.11
CH ₂ =CHBr	0.0011

TABLE 15.2 Relative reactivity of some olefins toward bromine in methanol⁶⁰

Olefin	Relative rate
CH ₂ =CH ₂	3.0 × 10 ¹
CH ₃ CH ₂ CH=CH ₂	2.9 × 10 ³
cis-CH ₃ CH ₂ CH=CHCH ₃	1.3 × 10 ⁵
(CH ₃) ₂ C=C(CH ₃) ₂	2.8 × 10 ⁷

possible to make the statement that *simple olefins do not react by the nucleophilic mechanism, and polyhalo or polycyano olefins do not generally react by the electrophilic mechanism*.⁶⁴ There are some reagents that attack only as nucleophiles, e.g., ammonia, and these add only to substrates susceptible to nucleophilic attack. Other reagents attack only as electrophiles, and, for example, F₂C=CF₂ does not react with these. In still other cases, the same reagent reacts with a simple olefin by the electrophilic mechanism and with a polyhalo olefin by a nucleophilic mechanism. For example, Cl₂ and HF are normally electrophilic reagents, but it has been shown that Cl₂ adds to (NC)₂C=CHCN with initial attack by Cl⁻⁶⁵ and that HF adds to F₂C=CClF with initial attack by F⁻.⁶⁶ Compounds that have a double bond conjugated with a Z group (as defined on p. 741) nearly always react by a nucleophilic mechanism.⁶⁷ These are actually 1,4 additions, as discussed on p. 742. A number of studies have been made of the relative activating abilities of various Z groups.⁶⁸ On the basis of these studies, the following order of decreasing activating ability has been suggested: Z = NO₂, COAr, CHO, COR, SO₂Ar, CN, COOR, SOAr, CONH₂, CONHR.⁶⁹

It seems obvious that electron-withdrawing groups enhance nucleophilic addition and inhibit electrophilic addition because they lower the electron density of the double bond. This is probably true, and yet similar reasoning does not always apply to a comparison between double and triple bonds.⁷⁰ There is a higher concentration of electrons between the carbons of a triple bond than in a double bond, and yet triple bonds are *less* subject to electrophilic attack and *more* subject to nucleophilic attack than double bonds.⁷¹ This statement is not universally true, but it does hold in most cases. In compounds containing both double and triple bonds (nonconjugated), bromine, an electrophilic reagent, always adds

⁶⁴Such reactions can take place under severe conditions. For example, electrophilic addition could be accomplished with F₂C=CHF in super-acid solutions [Olah; *Mo J. Org. Chem.* **1972**, *37*, 1028] although F₂C=CF₂ did not react under these conditions. For reviews of electrophilic additions to fluoroolefins, see Belen'kii; *German Sov. Sci. Rev. Sect. B* **1984**, *5*, 183-218; Dyatkin; Mochalina; Knunyants *Russ. Chem. Rev.* **1966**, *35*, 417-427. *Fluorine Chem. Rev.* **1969**, *3*, 45-71; Ref. 62, pp. 77-81.

⁶⁵Dickinson; Wiley; McKusick *J. Am. Chem. Soc.* **1960**, *82*, 6132. For another example, see Atkinson; de la Mare; Larsen *J. Chem. Soc., Perkin Trans. 2* **1983**, 271.

⁶⁶Miller; Fried; Goldwhite *J. Am. Chem. Soc.* **1960**, *82*, 3091.

⁶⁷For a review of electrophilic reactions of such compounds, see Müllen; Wolf, in Patai; Rappoport, Ref. 37, pp. 513-558.

⁶⁸See, for example, Friedman; Wall *J. Org. Chem.* **1966**, *31*, 2888; Ring; Tesoro; Moore *J. Org. Chem.* **1967**, *32*, 1091.

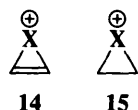
⁶⁹Shenhav; Rappoport; Patai *J. Chem. Soc. B* **1970**, 469.

⁷⁰For reviews of ionic additions to triple bonds, see, in Patai *The Chemistry of the Carbon-Carbon Triple Bond*; Wiley: New York, 1978, the articles by Schmid, pt. 1, pp. 275-341, and by Dickstein; Miller, pt. 2, pp. 813-955; Miller; Tanaka *Sel. Org. Transform.* **1970**, *1*, 143-238; Winterfeldt, in Viche, Ref. 49, pp. 267-334. For comparisons of double and triple bond reactivity, see Melloni; Modena; Tonellato *Acc. Chem. Res.* **1981**, *14*, 227-233; Allen; Chiang; Kresge; Tidwell *J. Org. Chem.* **1982**, *47*, 775.

⁷¹For discussions, see Daniels; Bauer *J. Chem. Educ.* **1958**, *35*, 444; DeYoung; Ehrlich; Berliner *J. Am. Chem. Soc.* **1977**, *99*, 290; Strozic; Caramella; Houk *J. Am. Chem. Soc.* **1979**, *101*, 1340.

to the double bond.⁷² In fact, all reagents that form bridged intermediates like **2** react faster with double than with triple bonds. On the other hand, addition of electrophilic H⁺ (acid-catalyzed hydration, **5-2**; addition of hydrogen halides, **5-1**) takes place at about the same rates for alkenes as for corresponding alkynes.⁷³ Furthermore, the presence of electron-withdrawing groups lowers the alkene/alkyne rate ratio. For example, while styrene PhCH=CH₂ was brominated 3000 times faster than PhC≡CH, the addition of a second phenyl group (PhCH=CHPh vs. PhC≡CPh) lowered the rate ratio to about 250.⁷⁴ In the case of *trans*-MeOOCCH=CHCOOMe vs. MeOOC≡CCOOMe, the triple bond compound was actually brominated faster.⁷⁵

Still, it is true that in general triple bonds are more susceptible to nucleophilic and less to electrophilic attack than double bonds, in spite of their higher electron density. One explanation is that the electrons in the triple bond are held more tightly because of the smaller carbon-carbon distance; it is thus harder for an attacking electrophile to pull out a pair. There is evidence from far-uv spectra to support this conclusion.⁷⁶ Another possible explanation has to do with the availability of the unfilled orbital in the alkyne. It has been shown that a π* orbital of bent alkynes (such as cyclooctyne) has a lower energy than the π* orbital of alkenes, and it has been suggested⁷⁷ that linear alkynes can achieve a bent structure in their transition states when reacting with an electrophile. Where electrophilic addition involves bridged-ion intermediates, those arising from triple bonds (**14**) are more strained than the corresponding **15** and furthermore are antiaromatic systems (see p. 56),



which **15** are not. This may be a reason why electrophilic addition by such electrophiles as Br, I, SR, etc., is slower for triple than for double bonds.⁷⁸ As might be expected, triple bonds connected to a Z group (C≡C—Z) undergo nucleophilic addition especially well.⁷⁹

Although alkyl groups in general increase the rates of electrophilic addition, we have already mentioned (p. 739) that there is a different pattern depending on whether the intermediate is a bridged ion or an open carbocation. For brominations and other electrophilic additions in which the first step of the mechanism is rate-determining, the rates for substituted alkenes correlate well with the ionization potentials of the alkenes, which means that steric effects are not important.⁸⁰ Where the second step is rate-determining [e.g., oxymercuration (**5-2**), hydroboration (**5-13**)], steric effects are important.⁸⁰

Free-radical additions can occur with any type of substrate. The determining factor is the presence of a free-radical attacking species. Some reagents, e.g., HBr, RSH, attack by ionic mechanisms if no initiator is present, but in the presence of a free-radical initiator, the mechanism changes and the addition is of the free-radical type. Nucleophilic radicals

⁷²Petrov *Russ. Chem. Rev.* **1960**, 29, 489-509.

⁷³Melloni; Modena; Tonellato, *Ref.* 70, p. 228.

⁷⁴Robertson; Dasent; Milburn; Oliver *J. Chem. Soc.* **1950**, 1628.

⁷⁵Wolf; Ganguly; Berliner *J. Am. Chem. Soc.* **1985**, 50, 1053.

⁷⁶Walsh *Q. Rev., Chem. Soc.* **1948**, 2, 73-91.

⁷⁷Ng; Jordan; Krebs; Rüger *J. Am. Chem. Soc.* **1982**, 104, 7414.

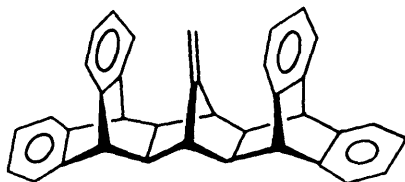
⁷⁸Nevertheless, bridged ions **14** have been implicated in some additions to triple bonds. See, for example, Pincock; Yates, *Ref.* 14; Mauger; Berliner *J. Am. Chem. Soc.* **1972**, 94, 194; Bassi; Tonellato *J. Chem. Soc., Perkin Trans. 1* **1973**, 669; Schmid; Modro; Lenz; Garratt; Yates *J. Org. Chem.* **1976**, 41, 2331.

⁷⁹For a review of additions to these substrates, see Winterfeldt *Angew. Chem. Int. Ed. Engl.* **1967**, 6, 423-434 [*Angew. Chem.* 79, 389-400], *Newer Methods Prep. Org. Chem.* **1971**, 6, 243-279.

⁸⁰Nelson; Cooper; Soundararajan *J. Am. Chem. Soc.* **1989**, 111, 1414; Nelson; Soundararajan *Tetrahedron Lett.* **1988**, 29, 6207.

(see p. 679) behave like nucleophiles in that the rate is increased by the presence of electron-withdrawing groups in the substrate. The reverse is true for electrophilic radicals.⁸¹ However, nucleophilic radicals react with alkynes more slowly than with the corresponding alkenes,⁸² which is contrary to what might have been expected.⁸³

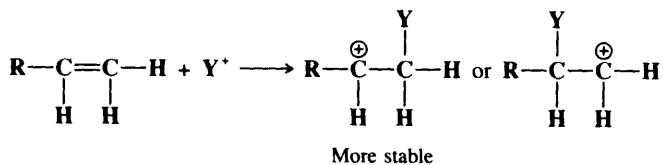
Steric influences are important in some cases. In catalytic hydrogenation, where the substrate must be adsorbed onto the catalyst surface, the reaction becomes more difficult with increasing substitution. The hydrocarbon **16**, in which the double bond is entombed

**16**

between the benzene rings, does not react with Br_2 , H_2SO_4 , O_3 , BH_3 , CBr_2 , or other reagents that react with most double bonds.⁸⁴ A similarly inactive compound is tetra-*t*-butylallene $(t\text{-Bu})_2\text{C}=\text{C}=\text{C}(t\text{-Bu})_2$, which is inert to Br_2 , Cl_2 , O_3 , and catalytic hydrogenation.⁸⁵

Orientation

When an unsymmetrical reagent is added to an unsymmetrical substrate, the question arises: Which side of the reagent goes to which side of the double or triple bond? For electrophilic attack, the answer is given by *Markovnikov's rule: the positive portion of the reagent goes to the side of the double or triple bond that has more hydrogens.*⁸⁶ A number of explanations have been suggested for this regioselectivity, but the most probable is that Y^+ adds to that side that will give the more stable carbocation. Thus, when an alkyl group is present, secondary carbocations are more stable than primary:



We may ask: How does Y^+ "know" which side will give the more stable carbocation? As in the similar case of electrophilic aromatic substitution (p. 508), we invoke the Hammond postulate and say that the lower energy carbocation is preceded by the lower energy transition state. Markovnikov's rule also applies for halogen substituents because the halogen stabilizes

⁸¹For reviews of reactivity in free-radical additions, see Tedder *Angew. Chem. Int. Ed. Engl.* **1982**, *21*, 401-410 [*Angew. Chem.* *94*, 433-442]; Tedder; Walton *Tetrahedron* **1980**, *36*, 701-707.

⁸²Giese; Lachhein *Angew. Chem. Int. Ed. Engl.* **1982**, *21*, 768 [*Angew. Chem.* *94*, 780].

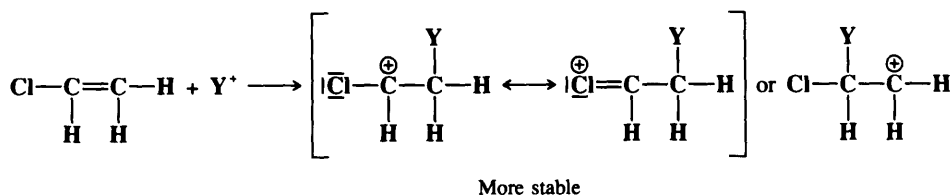
⁸³For a discussion of reactivity and orientation of polar radicals, see Volovik; Dyadyusha; Staninets *J. Org. Chem. USSR* **1986**, *22*, 1224.

⁸⁴Butler; Gupta; Ng; Nyburg *J. Chem. Soc., Chem. Commun.* **1980**, 596.

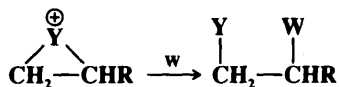
⁸⁵Bolze; Eierdanz; Schlüter; Massa; Grahn; Berndt *Angew. Chem. Int. Ed. Engl.* **1982**, *21*, 924 [*Angew. Chem.* *94*, 927].

⁸⁶For discussions of Markovnikov's rule, see Isenberg; Grdinic *J. Chem. Educ.* **1969**, *46*, 601; Grdinic; Isenberg, *Intra-Sci. Chem. Rep.* **1970**, *4*, 145-162.

the carbocation by resonance:



Markovnikov's rule is also usually followed where bromonium ions or other three-membered rings are intermediates.⁸⁷ This means that in these cases attack by W must resemble the S_N1 rather than the S_N2 mechanism (see p. 369), though the overall stereospecific anti



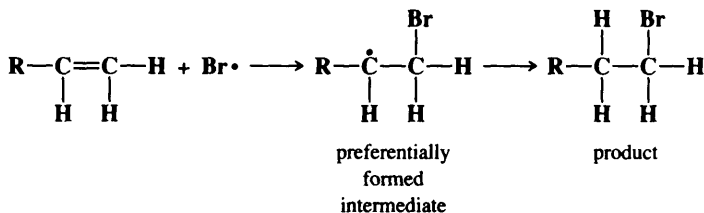
addition in these reactions means that the nucleophilic substitution step is taking place with inversion of configuration.

Olefins containing strong electron-withdrawing groups may violate Markovnikov's rule.

For example, attack at the Markovnikov position of $\text{Me}_3\text{N}^{\oplus}-\text{CH}=\text{CH}_2$ would give an ion with positive charges on adjacent atoms. The compound $\text{CF}_3\text{CH}=\text{CH}_2$ has been reported to give electrophilic addition with acids in an anti-Markovnikov direction, but it has been shown⁸⁸ that, when treated with acids, this compound does not give simple electrophilic addition at all; the apparently anti-Markovnikov products are formed by other pathways.

For nucleophilic addition the direction of attack has been studied very little, except for Michael-type addition, with compounds of the type $\text{C}=\text{C}-\text{Z}$. Here the negative part of the reagent almost always attacks regioselectively at the carbon that does not carry the Z (see p. 742).

In free-radical addition⁸⁹ the main effect seems to be steric.⁹⁰ All substrates $\text{CH}_2=\text{CHX}$ are preferentially attacked at the CH_2 , regardless of the identity of X or of the attacking radical. With a reagent such as HBr, this means that the addition is anti-Markovnikov:



Thus the observed orientation in both kinds of HBr addition (Markovnikov electrophilic and anti-Markovnikov free radical) is caused by formation of the secondary intermediate.

⁸⁷This has been graphically demonstrated by direct treatment of stabilized bromonium ions by nucleophiles: Dubois; Chrétien *J. Am. Chem. Soc.* **1978**, *100*, 3506.

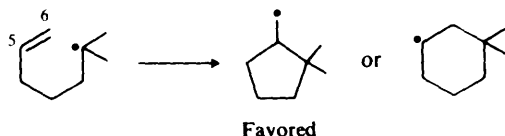
⁸⁸Myhre; Andrews *J. Am. Chem. Soc.* **1970**, *92*, 7595, 7596. See also Newton *J. Chem. Educ.* **1987**, *64*, 531.

⁸⁹For reviews of orientation in free-radical additions, see Tedder; Walton *Tetrahedron* **1980**, *36*, 701-707. *Adv. Phys. Org. Chem.* **1978**, *16*, 51-86. *Acc. Chem. Res.* **1976**, *9*, 183-191. See also Giese, Ref. 49; Tedder *J. Chem. Educ.* **1984**, *61*, 237.

⁹⁰See, however, Riemenschneider; Bartels; Dornow; Drechsel-Grau; Eichel; Luthé; Matter; Michaelis; Boldt *J. Org. Chem.* **1987**, *52*, 205; Gleicher; Mahiou; Aretakis *J. Org. Chem.* **1989**, *54*, 308.

In the electrophilic case it forms because it is more stable than the primary; in the free-radical case because it is sterically preferred. The stability order of the free-radical intermediates is also usually in the same direction: $3^\circ > 2^\circ > 1^\circ$ (p. 188), but this factor is apparently less important than the steric factor. Internal olefins with no groups present to stabilize the radical usually give an approximately 1:1 mixture.

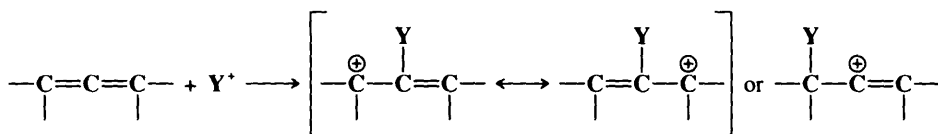
In *intramolecular* additions of radicals containing a 5,6 double bond,⁵⁰ both five- and six-membered rings can be formed, but in most cases⁹¹ the five-membered rings are greatly preferred kinetically, even (as in the case shown) where five-membered ring closure means



generating a primary radical and six-membered ring closure a secondary radical. This phenomenon may be caused by more favorable entropy factors leading to a five-membered ring, as well as by stereoelectronic factors, but other explanations have also been offered.⁹² Similar behavior is found when the double bond is in other positions (from the 3,4 to the 7,8 position). In each case the smaller ring (*Exo-Trig* addition) is preferred to the larger (*Endo-Trig* addition)⁹³ (see the Baldwin rules, p. 212). However, when a radical that is unsaturated in the 5,6 position contains an alkyl group in the 5 position, formation of the 6-membered ring is generally favored.⁹⁴

For conjugated dienes, attack by a positive ion, a negative ion, or a free radical is almost always at the *end* of the conjugated system, since in each case this gives an intermediate stabilized by resonance. In the case of an unsymmetrical diene, the more stable ion is formed. For example, isoprene $\text{CH}_2=\text{CMeCH}=\text{CH}_2$, treated with HCl gives only $\text{Me}_2\text{CClCH}=\text{CH}_2$ and $\text{Me}_2\text{C}=\text{CHCH}_2\text{Cl}$, with none of the product arising from attack at the other end. $\text{PhCH}=\text{CHCH}=\text{CH}_2$ gives only $\text{PhCH}=\text{CHCHClCH}_3$ since it is the only one of the eight possible products that has a double bond in conjugation with the ring and that results from attack by H^+ at an end of the conjugated system.

When allenes are attacked by electrophilic reagents,⁹⁵ Markovnikov's rule would predict that the attack should be at the end of the system, since there are no hydrogens in the middle. Attack at the center gives a carbocation stabilized by resonance, but not immediately.



⁹¹For an exception, see Wilt *Tetrahedron* **1985**, *41*, 3979.

⁹²For discussions, see Beckwith *Tetrahedron* **1981**, *37*, 3073-3100; Verhoeven *Revl. Trav. Chim. Pays-Bas* **1980**, *99*, 143. For molecular mechanics force-field approaches to this problem, see Beckwith; Schiesser *Tetrahedron* **1985**, *41*, 3925; Spellmeyer; Houk *J. Org. Chem.* **1987**, *52*, 959.

⁹³See Beckwith; Easton; Serelis *J. Chem. Soc., Chem. Commun.* **1980**, 482.

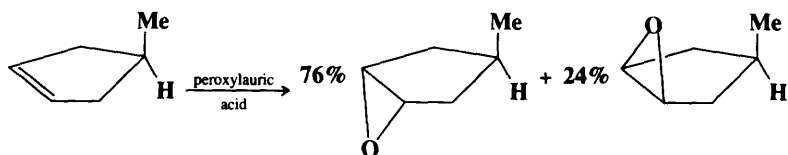
⁹⁴See Chuang; Gallucci; Hart; Hoffman *J. Org. Chem.* **1988**, *53*, 3218, and references cited therein.

⁹⁵For a monograph on addition to allenes, see Schuster; Coppola *Allenes in Organic Synthesis*; Wiley: New York, 1984. For reviews, see Pasto *Tetrahedron* **1984**, *40*, 2805-2827; Smadja *Chem. Rev.* **1983**, *83*, 263-320; in Landor *The Chemistry of Allenes*, vol. 2; Academic Press: New York, 1982, articles by Landor, Jacobs, and Hopf, pp. 351-577; Stang; Rappoport; Hanack; Subramanian, Ref. 34, pp. 152-167; Blake, in Patai *The Chemistry of Ketenes, Allenes and Related Compounds*, pt. 1; Wiley: New York, 1980; pp. 342-357; Modena; Tonellato, Ref. 34, pp. 215-231; Richey; Richey Ref. 34, pp. 917-922; Caserio *Sel. Org. Transform.* **1970**, *1*, 239-299; Taylor *Chem. Rev.* **1967**, *67*, 317-359, pp. 338-346; Mavrov; Kucherov *Russ. Chem. Rev.* **1967**, *36*, 233-249; Griesbaum *Angew. Chem. Int. Ed. Engl.* **1966**, *5*, 933-946 [*Angew. Chem.* **78**, 953-966].

In order for such stabilization to be in effect the three p orbitals must be parallel, and it requires a rotation about the C—C bond for this to happen.⁹⁶ Therefore, the stability of the allylic cation has no effect on the transition state, which still has a geometry similar to that of the original allene (p. 102). Probably because of this, attack on the unsubstituted $\text{CH}_2=\text{C}=\text{CH}_2$ is most often at the end carbon, to give a vinylic cation, though center attack has also been reported. However, as alkyl or aryl groups are substituted on the allene carbons, attack at the middle carbon becomes more favorable because the resulting cation is stabilized by the alkyl or aryl groups (it is now a secondary, tertiary, or benzylic cation). For example, allenes of the form $\text{RCH}=\text{C}=\text{CH}_2$ are still attacked most often at the end, but with $\text{RCH}=\text{C}=\text{CHR}'$ center attack is more prevalent. Tetramethylallene is also attacked predominantly at the center carbon.⁹⁷ Free radicals⁹⁸ attack allenes most often at the end,⁹⁹ though attack at the middle has also been reported.¹⁰⁰ As with electrophilic attack and for the same reason, the stability of the allylic radical has no effect on the transition state of the reaction between a free radical and an allene. Again, as with electrophilic attack, the presence of alkyl groups increases the extent of attack by a radical at the middle carbon.¹⁰¹

Stereochemical Orientation

It has already been pointed out that some additions are syn, with both groups, approaching from the same side, and that others are anti, with the groups approaching from opposite sides of the double or triple bond. For cyclic compounds there are further aspects of steric orientation. In syn addition to an unsymmetrical cyclic olefin, the two groups can come in from the more-hindered face or from the less-hindered face of the double bond. The rule is that syn addition is usually, though not always, from the less-hindered face. For example, epoxidation of 4-methylcyclopentene gave 76% addition from the less-hindered and 24% from the more-hindered face.¹⁰²



In anti addition to a cyclic substrate, the initial attack by the electrophile is also from the less-hindered face. However, many (though not all) electrophilic additions to norbornene and similar strained bicycloalkenes are syn additions.¹⁰³ In these cases attack is always from

⁹⁶For evidence that this is so, see Okuyama; Izawa; Fueno *J. Am. Chem. Soc.* **1973**, 95, 6749.

⁹⁷For example, see Bianchini; Guillemonat *Bull. Soc. Chim. Fr.* **1968**, 2120; Pittman *Chem. Commun.* **1969**, 122; Poutsma; Ibarbia *J. Am. Chem. Soc.* **1971**, 93, 440.

⁹⁸For a review, see Jacobs, in Landor, Ref. 95, vol. 2, pp. 399-415.

⁹⁹Griesbaum; Oswald; Quiram; Naegle *J. Org. Chem.* **1963**, 28, 1952.

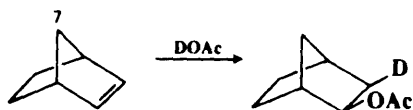
¹⁰⁰See, for example, Pasto; L'Hermine *J. Org. Chem.* **1990**, 55, 685.

¹⁰¹For example, see Byrd; Caserio *J. Org. Chem.* **1972**, 37, 3881; Pasto; Warren; Morrison *J. Org. Chem.* **1981**, 46, 2837. See however Bartels; Boldt *Liebigs Ann. Chem.* **1981**, 40.

¹⁰²Henbest; McCullough *Proc. Chem. Soc.* **1962**, 74.

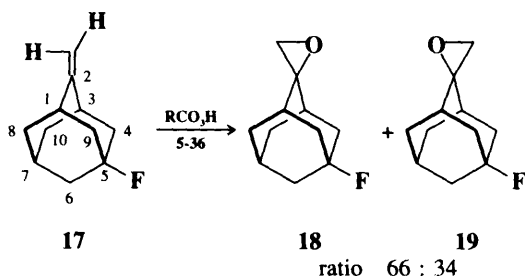
¹⁰³For a discussion, see Traylor *Acc. Chem. Res.* **1969**, 2, 152-160.

the exo side, e.g.,¹⁰⁴



unless the exo side is blocked by substituents in the 7 position, in which case endo attack may predominate; e.g., 7,7-dimethylnorbornene undergoes syn-endo epoxidation (5-36) and hydroboration¹⁰⁵ (5-12). However, addition of DCl and F₃CCOOD to, and oxymercuration (5-2) of, 7,7-dimethylnorbornene proceed syn-exo in spite of the methyl groups in the 7 position.¹⁰⁶ Similarly, free-radical additions to norbornene and similar molecules are often syn-exo, though anti additions and endo attacks are also known.¹⁰⁷

Electronic effects can also play a part in determining which face is attacked. In the adamantane derivative **17** steric effects are about the same for each face of the double bond. Yet epoxidation, dibromocarbene attack (5-50), and hydroboration (5-12) all predominantly



take place from the face that is syn to the electron-withdrawing fluorine.¹⁰⁸ In the case shown, about twice as much **18** was formed, compared to **19**. Similar results have been obtained on other substrates:¹⁰⁹ groups that are electron-withdrawing by the field effect ($-I$) direct attack from the syn face; $+I$ groups from the anti face, for both electrophilic and nucleophilic attack. These results are attributed¹¹⁰ to hyperconjugation: For the adamantane case, there is overlap between the σ^* orbital of the newly-forming bond (between the attacking species and C-2 in **17**) and the filled σ orbitals of the C _{α} —C _{β} bonds on the opposite side. The four possible bonds are C-3—C-4 and C-1—C-9 on the syn side and C-3—C-10 and C-1—C-8 on the anti side. The preferred pathway is the one where the incoming group has the more electron-rich bonds on the side *opposite* to it (these are the ones it overlaps with). Since the electron-withdrawing F has its greatest effect on the bonds closest to it, the C-1—C-8 and C-3—C-10 bonds are more electron rich, and the group comes in on the face syn to the F.

¹⁰⁴Cristol; Morrill; Sanchez *J. Org. Chem.* **1966**, *31*, 2719; Brown; Kawakami; Liu *J. Am. Chem. Soc.* **1970**, *92*, 5536; Alverne; Anker; Laurent; Haufe; Beguin *Tetrahedron* **1988**, *44*, 3551; Koga; Ozawa; Morokuma *J. Phys. Org. Chem.* **1990**, *3*, 519.

¹⁰⁵Brown; Kawakami *J. Am. Chem. Soc.* **1970**, *92*, 201, 1990; Brown; Kawakami; Liu *J. Am. Chem. Soc.* **1973**, *95*, 2209.

¹⁰⁶Brown; Liu *J. Am. Chem. Soc.* **1975**, *97*, 600, 2469; Brown; Kawakami *J. Am. Chem. Soc.* **1973**, *95*, 8665; Tidwell; Traylor *J. Org. Chem.* **1968**, *33*, 2614.

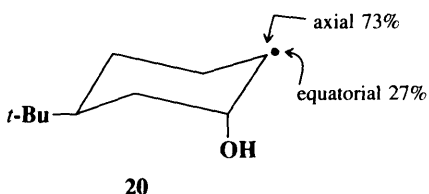
¹⁰⁷For a review of free-radical addition to these systems, see Azovskaya; Prilezhaeva *Russ. Chem. Rev.* **1972**, *41*, 516-528.

¹⁰⁸Srivastava; le Noble *J. Am. Chem. Soc.* **1987**, *109*, 5874. See also Bodepudi; le Noble *J. Am. Chem. Soc.* **1991**, *113*, 2001.

¹⁰⁹Johnson; Tait; Cieplak *J. Am. Chem. Soc.* **1987**, *109*, 5875; Cieplak; Tait; Johnson *J. Am. Chem. Soc.* **1989**, *111*, 8447.

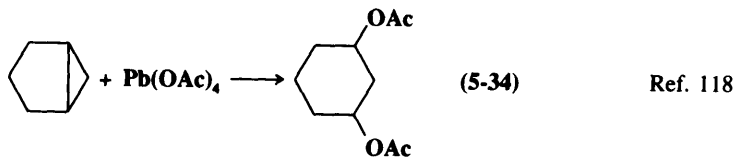
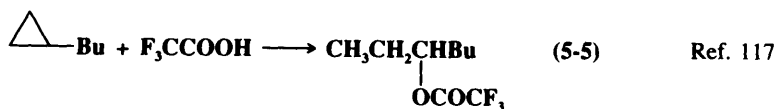
¹¹⁰Cieplak *J. Am. Chem. Soc.* **1981**, *103*, 4540. See also Jorgensen *Chemtracts: Org. Chem.* **1988**, *1*, 71.

It has been mentioned that additions of Br_2 and HOBr are often anti because of formation of bromonium ions and that free-radical addition of HBr is also anti. When the substrate in any of these additions is a cyclohexene, the addition is not only anti but the initially formed product is conformationally specific too, being mostly diaxial.¹¹¹ This is so because diaxial opening of the three-membered ring preserves a maximum coplanarity of the participating centers in the transition state; indeed, on opening, epoxides also give diaxial products.¹¹² However, the initial diaxial product may then pass over to the diequatorial conformer unless other groups on the ring render the latter less stable than the former. In free-radical additions to cyclohexenes in which cyclic intermediates are not involved, the initial attack by the radical is also usually from the axial direction,¹¹³ resulting in a diaxial initial product if the overall addition is anti. The direction from which unsymmetrical radicals attack has also been studied.¹¹⁴ For example, when the radical **20** adds to a double bond it preferentially does so anti to the OH group, leading to a diaxial trans product.¹¹⁴



Addition to Cyclopropane Rings¹¹⁵

We have previously seen (p. 152) that in some respects, cyclopropane rings resemble double bonds.¹¹⁶ It is not surprising, therefore, that cyclopropanes undergo addition reactions analogous to those undergone by double-bond compounds, resulting in the opening of the three-membered rings, e.g. (the reaction numbers of the analogous addition reactions are given in parentheses),



¹¹¹Barton, in *Theoretical Organic Chemistry, The Kekulé Symposium*; Butterworth: London, 1959, pp. 127-143; Goering; Abell; Aycok *J. Am. Chem. Soc.* **1952**, *74*, 3588; Goering; Sims *J. Am. Chem. Soc.* **1955**, *77*, 3465; Shoppee; Akhtar; Lack *J. Chem. Soc.* **1964**, 877; Readio; Skell *J. Org. Chem.* **1966**, *31*, 753, 759.

¹¹²For example, see Anselmi; Berti; Catelani; Lecce; Monti *Tetrahedron* **1977**, *33*, 2771.

¹¹³Huysen; Benson; Sinnige *J. Org. Chem.* **1967**, *32*, 622; LeBel; Czaja; DeBoer, Ref. 51.

¹¹⁴For a review, see Giese *Angew. Chem. Int. Ed. Engl.* **1989**, *28*, 969-980 [*Angew. Chem.* **101**, 993-1004].

¹¹⁵For a review, see Charton, in Zabicky *The Chemistry of Alkenes*, vol 2.; Wiley: New York, 1970, pp. 569-592. For reviews of the use of cyclopropanes in organic synthesis, see Reissig *Top. Curr. Chem.* **1988**, *144*, 73-135; Wong; Hon; Tse; Yip; Tanko; Hudlicky *Chem. Rev.* **1989**, *89*, 165-198.

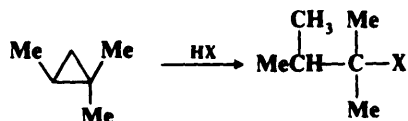
¹¹⁶The analogies are by no means complete: see Gordon *J. Chem. Educ.* **1967**, *44*, 461.

¹¹⁷Peterson; Thompson *J. Org. Chem.* **1968**, *33*, 968.

¹¹⁸Moon *J. Org. Chem.* **1964**, *39*, 3456.

Other examples are discussed at 5-2, 5-11, and 5-49.

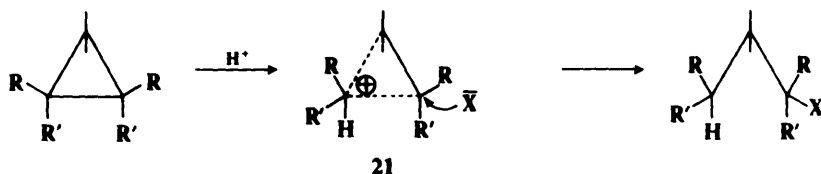
Additions to cyclopropanes can take place by any of the four mechanisms already discussed in this chapter, but the most important type involves electrophilic attack.¹¹⁹ For substituted cyclopropanes, these reactions usually follow Markovnikov's rule, though exceptions are known and the degree of regioselectivity is often small. The application of Markovnikov's rule to these substrates can be illustrated by the reaction of 1,1,2-trimethylcyclopropane with HX.¹²⁰ The rule predicts that the electrophile (in this case H⁺)



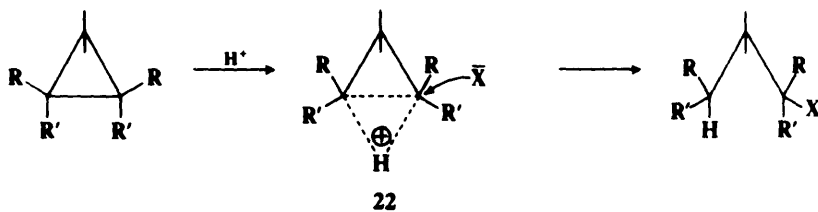
goes to the carbon with the most hydrogens and the nucleophile goes to the carbon that can best stabilize a positive charge (in this case the tertiary rather than the secondary carbon). The stereochemistry of the reaction can be investigated at two positions—the one that becomes connected to the electrophile and the one that becomes connected to the nucleophile. The results at the former position are mixed. Additions have been found to take place with 100% retention,¹²¹ 100% inversion,¹²² and with mixtures of retention and inversion.¹²³ At the carbon that becomes connected to the nucleophile the result is usually inversion, though retention has also been found,¹²⁴ and elimination, rearrangement, and racemization processes often compete, indicating that in many cases a positively charged carbon is generated at this position.

At least three mechanisms have been proposed for electrophilic addition (these mechanisms are shown for attack by HX, but analogous mechanisms can be written for other electrophiles).

Mechanism a



Mechanism b



¹¹⁹For a review, see DePuy *Top. Curr. Chem.* **1973**, *40*, 73-101. For a list of references to pertinent mechanistic studies, see Wiberg; Kass *J. Am. Chem. Soc.* **1985**, *107*, 988

¹²⁰Kramer *J. Am. Chem. Soc.* **1970**, *92*, 4344.

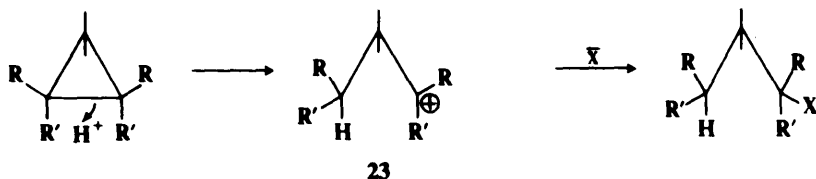
¹²¹For example, see DePuy; Breitbeil; DeBruin *J. Am. Chem. Soc.* **1966**, *88*, 3347; Hendrickson; Boeckman *J. Am. Chem. Soc.* **1969**, *91*, 3269.

¹²²For example, see LaLonde; Ding; Tobias *J. Am. Chem. Soc.* **1967**, *89*, 6651; Warnet; Wheeler *Chem. Commun.* **1971**, 547; Hogeveen; Roobeek; Volger *Tetrahedron Lett.* **1972**, 221; Battiste; Mackiernan *Tetrahedron Lett.* **1972**, 4095. See also Jensen; Patterson; Dinizo *Tetrahedron Lett.* **1974**, 1315; Coxon; Steel; Whittington *J. Org. Chem.* **1990**, *55*, 4136.

¹²³Nickon; Hammons *J. Am. Chem. Soc.* **1964**, *86*, 3322; Hammons; Probasco; Sanders; Whalen *J. Org. Chem.* **1968**, *33*, 4493; DePuy; Fünfschilling; Andrist; Olson *J. Am. Chem. Soc.* **1977**, *99*, 6297.

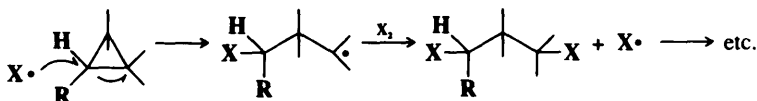
¹²⁴Cristol; Lim; Dahl *J. Am. Chem. Soc.* **1970**, *92*, 4013; Hendrickson; Boeckman *J. Am. Chem. Soc.* **1971**, *93*, 4491.

Mechanism c

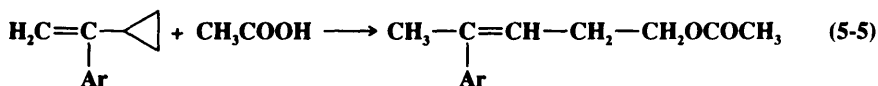


Mechanism *a* involves a corner-protonated cyclopropane¹²⁵ (**21**); we have already seen examples of such ions in the 2-norbornyl and 7-norbornenyl cations (pp. 321, 314). Mechanism *b* involves an edge-protonated cyclopropane (**22**). Mechanism *c* consists of a one-step SE_2 -type attack by H^+ to give the classical cation **23**, which then reacts with the nucleophile. Although the three mechanisms as we have drawn them show retention of configuration at the carbon that becomes attached to the proton, mechanisms *a* and *c* at least can also result in inversion at this carbon. Unfortunately, the evidence on hand at present does not allow us unequivocally to select any of these as the exclusive mechanism in all cases. Matters are complicated by the possibility that more than one edge-protonated cyclopropane is involved, at least in some cases. There is strong evidence for mechanism *b* with the electrophiles Br^+ and Cl^+ ;¹²⁶ and for mechanism *a* with D^+ and Hg^{2+} .¹²⁷ Ab initio studies show that the corner-protonated **21** is slightly more stable (about 1.4 kcal/mole, 6 kJ/mol) than the edge-protonated **22**.¹²⁸ There is some evidence against mechanism *c*.¹²⁹

Free-radical additions to cyclopropanes have been studied much less, but it is known that Br_2 and Cl_2 add to cyclopropanes by a free-radical mechanism in the presence of uv light. The addition follows Markovnikov's rule, with the initial radical attacking the least-substituted carbon and the second group going to the most-substituted position. Several investigations have shown that the reaction is stereospecific at one carbon, taking place with inversion there, but nonstereospecific at the other carbon.¹³⁰ A mechanism that accounts for this behavior is¹³¹



In some cases conjugate addition has been performed on systems where a double bond is "conjugated" with a cyclopropyl ring. An example is¹³²



¹²⁵For reviews of protonated cyclopropanes, see Collins *Chem. Rev.* **1969**, 69, 543-550; Lee *Prog. Phys. Org. Chem.* **1970**, 7, 129-187.

¹²⁶Coxon; Steel; Whittington; Battiste *J. Org. Chem.* **1989**, 54, 1383; Coxon; Steel; Whittington *J. Org. Chem.* **1989**, 54, 3702.

¹²⁷Lambert; Chelius; Schulz; Carpenter *J. Am. Chem. Soc.* **1990**, 112, 3156; Lambert; Chelius; Bible; Hadju *J. Am. Chem. Soc.* **1991**, 113, 1331.

¹²⁸Koch; Liu; Schleyer *J. Am. Chem. Soc.* **1989**, 111, 3479, and references cited therein.

¹²⁹Wiberg; Kass, Ref. 119

¹³⁰Maynes; Applequist *J. Am. Chem. Soc.* **1973**, 95, 856; Incremona; Upton *J. Am. Chem. Soc.* **1972**, 94, 301; Shea; Skell *J. Am. Chem. Soc.* **1973**, 95, 6728; Poutsma *J. Am. Chem. Soc.* **1965**, 87, 4293; Jarvis *J. Org. Chem.* **1970**, 35, 924; Upton; Incremona *J. Org. Chem.* **1976**, 41, 523.

¹³¹For free-radical addition to [1.1.1]propellane and bicyclo[1.1.0]butane, see Wiberg; Waddell; Laidig *Tetrahedron Lett.* **1986**, 27, 1553.

¹³²Sarel; Ben-Shoshan *Tetrahedron Lett.* **1965**, 1053. See also Danishefsky *Acc. Chem. Res.* **1979**, 12, 66-72.

REACTIONS

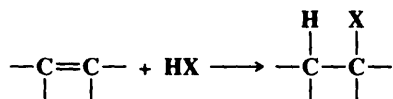
Reactions are classified by type of reagent. All reactions where hydrogen adds to one side of the double bond are treated first.

Reactions in Which Hydrogen Adds to One Side

A. Halogen on the Other Side

5-1 Addition of Hydrogen Halides

Hydro-halo-addition



Any of the four hydrogen halides can be added to double bonds.¹³³ HI, HBr, and HF¹³⁴ add at room temperature. The addition of HCl is more difficult and usually requires heat.²² The reaction has been carried out with a large variety of double-bond compounds, including conjugated systems, where both 1,2 and 1,4 addition are possible. A convenient method for the addition of HF involves the use of a polyhydrogen fluoride-pyridine solution.¹³⁵ When the substrate is mixed with this solution in a solvent such as THF at 0°C, alkyl fluorides are obtained in moderate-to-high yields.

The addition of hydrogen halides to simple olefins, in the absence of peroxides, takes place by an electrophilic mechanism, and the orientation is in accord with Markovnikov's rule.¹³⁶ When peroxides are added, the addition of HBr occurs by a free-radical mechanism and the orientation is anti-Markovnikov (p. 751).¹³⁷ It must be emphasized that this is true only for HBr. Free-radical addition of HF and HI has never been observed, even in the presence of peroxides, and of HCl only rarely. In the rare cases where free-radical addition of HCl was noted, the orientation was still Markovnikov, presumably because the more stable *product* was formed.¹³⁸ Free-radical addition of HF, HI, and HCl is energetically unfavorable (see the discussions on pp. 683, 693). It has often been found that anti-Markovnikov addition of HBr takes place even when peroxides have not been added. This happens because the substrate alkenes absorb oxygen from the air, forming small amounts of peroxides (4-9). Markovnikov addition can be ensured by rigorous purification of the substrate, but in practice this is not easy to achieve, and it is more common to add inhibitors, e.g., phenols or quinones, which suppress the free-radical pathway. The presence of free-radical precursors such as peroxides does not inhibit the ionic mechanism, but the radical reaction, being a chain process, is much more rapid than the electrophilic reaction. In most cases it is possible to control the mechanism (and hence the orientation) by adding peroxides

¹³³For a list of references, see Larock *Comprehensive Organic Transformations*; VCH: New York, 1989, pp. 322-323.

¹³⁴For reviews of addition of HF, see Sharts; Sheppard *Org. React.* **1974**, *21*, 125-406, pp. 192-198, 212-214; Hudlický *The Chemistry of Organic Fluorine Compounds*, 2nd ed.; Ellis Horwood: Chichester, 1976, pp. 36-41.

¹³⁵Olah; Welch; Vankar; Nojima; Kerekes; Olah *J. Org. Chem.* **1979**, *44*, 3872. For related methods, see Yoneda; Abe; Fukuhara; Suzuki *Chem. Lett.* **1983**, 1135; Olah; Li *Synlett* **1990**, 267.

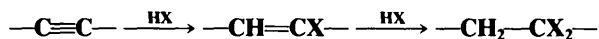
¹³⁶For reviews of electrophilic addition of HX, see Ref. 22, and Dewar, Ref. 3.

¹³⁷For reviews of free-radical addition of HX, see Thaler *Methods Free-Radical Chem.* **1969**, *2*, 121-227, pp. 182-195.

¹³⁸Mayo *J. Am. Chem. Soc.* **1962**, *84*, 3964.

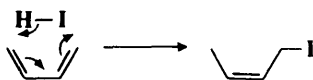
to achieve complete free-radical addition, or inhibitors to achieve complete electrophilic addition, though there are some cases where the ionic mechanism is fast enough to compete with the free-radical mechanism and complete control cannot be attained. Markovnikov addition of HBr, HCl, and HI has also been accomplished, in high yields, by the use of phase transfer catalysis.¹³⁹ For alternative methods of adding HBr (or HI) with anti-Markovnikov orientation, see 2-30.

It is also possible to add one¹⁴⁰ or two moles of any of the four hydrogen halides to triple bonds.

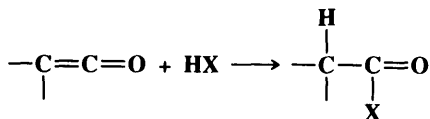


Markovnikov's rule ensures that *gem*-dihalides and not *vic*-dihalides are the products of the addition of two moles.

HX are electrophilic reagents, and many polyhalo and polycyano alkenes, e.g., $\text{Cl}_2\text{C}=\text{CHCl}$, do not react with them at all in the absence of free-radical conditions. When such reactions do occur, however, they take place by a nucleophilic addition mechanism, i.e., initial attack is by X^- . This type of mechanism also occurs with Michael-type substrates $\text{C}=\text{C}-\text{Z}$,¹⁴¹ where the orientation is always such that the halogen goes to the carbon that does not bear the Z, so the product is of the form $\text{X}-\text{C}-\text{CH}-\text{Z}$, even in the presence of free-radical initiators. HI adds 1,4 to conjugated dienes in the gas phase by a pericyclic mechanism:¹⁴²



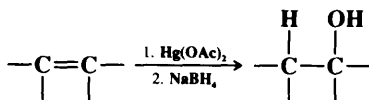
HX can be added to ketenes¹⁴³ to give acyl halides:



OS I, 166; II, 137, 336; III, 576; IV, 238, 543; VI, 273; VII, 59.

B. Oxygen on the Other Side

5-2 Hydration of Double Bonds Hydro-hydroxy-addition



¹³⁹Landini; Rolla *J. Org. Chem.* **1980**, 45, 3527.

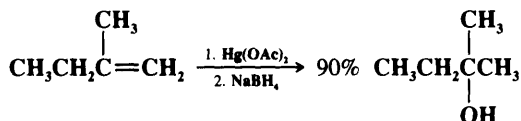
¹⁴⁰For a convenient method of adding one mole of HCl or HBr to a triple bond, see Cousseau; Gouin *J. Chem. Soc., Perkin Trans. I* **1977**, 1797; Cousseau *Synthesis* **1980**, 805. For the addition of one mole of HI, see Kamiya; Chikami; Ishii *Synlett* **1990**, 675.

¹⁴¹For an example, see Marx *Tetrahedron* **1983**, 39, 1529.

¹⁴²Gorton; Walsh *J. Chem. Soc., Chem. Commun.* **1972**, 782. For evidence that a pericyclic mechanism may be possible, even for an isolated double bond, see Sergeev; Stepanov; Leenson; Smirnov; Pupyshv; Tyurina; Mashyanov *Tetrahedron* **1982**, 38, 2585.

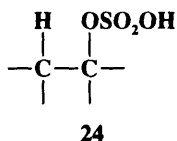
¹⁴³For reviews of additions to ketenes, and their mechanisms, see Tidwell *Acc. Chem. Res.* **1990**, 23, 273-279; Seikaly; Tidwell *Tetrahedron* **1986**, 42, 2587-2613; Satchell; Satchell *Chem. Soc. Rev.* **1975**, 4, 231-250.

Olefins can be hydrated quickly under mild conditions in high yields without rearrangement products by the use of *oxymercuration*¹⁴⁴ (addition of oxygen and mercury) followed by *in situ* treatment with sodium borohydride¹⁴⁵ (**2-24**). For example, 2-methyl-1-butene treated with mercuric acetate,¹⁴⁶ followed by NaBH₄, gave 2-methyl-2-butanol:

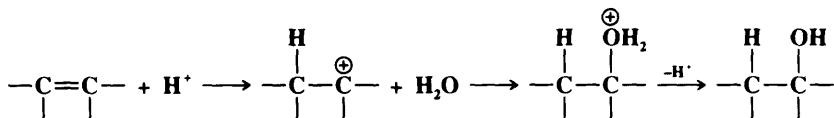


This method, which is applicable to mono-, di-, tri-, and tetraalkyl as well as phenyl-substituted olefins, gives almost complete Markovnikov addition. Hydroxy, methoxy, acetoxy, halo, and other groups may be present in the substrate without, in general, causing difficulties.¹⁴⁷ When two double bonds are present in the same molecule, the use of ultrasound allows oxymercuration of the less-substituted one without affecting the other.¹⁴⁸

Double bonds can also be hydrated by treatment with water and an acid catalyst. The most common catalyst is sulfuric acid, but other acids, such as nitric or perchloric can also be used. The mechanism is electrophilic and begins with attack by a proton (see p. 739). The negative attacking species may be HSO₄⁻ (or similar ion in the case of other acids) to give the initial product **24** which can be isolated, but under the conditions of the reaction,



is usually hydrolyzed to the alcohol (**0-4**). However, the conjugate base of the acid is not the only possible species that attacks the initial carbocation. The attack can also be by water:



When the reaction proceeds by this pathway, **24** and similar intermediates are not involved and the mechanism is exactly (by the principle of microscopic reversibility) the reverse of E1 elimination of alcohols (**7-1**).¹⁴⁹ It is likely that the mechanism involves both pathways.

¹⁴⁴For a monograph, see Larock *Solution/Demercuration Reactions in Organic Synthesis*; Springer: New York, 1986. For reviews of this and other oxymetallation reactions, see Kitching *Organomet. React.* **1972**, *3*, 319-398. *Organomet. Chem. Rev.* **1968**, *3*, 61-134; Oullette, in Trahanovsky *Oxidation in Organic Chemistry*, pt. B; Academic Press: New York, 1973, pp. 140-166; House *Modern Synthetic Reactions*, 2nd ed.; W. A. Benjamin: New York, 1972, pp. 387-396; Zefirov *Russ. Chem. Rev.* **1965**, *34*, 527-536.

¹⁴⁵Brown; Geoghegan *J. Am. Chem. Soc.* **1967**, *89*, 1522. *J. Org. Chem.* **1970**, *35*, 1844. **1972**, *37*, 1937; Brown; Geoghegan; Lynch; Kurek; *J. Org. Chem.* **1972**, *37*, 1941; Moon; Waxman *Chem. Commun.* **1967**, 1283; Moon; Takakis; Waxman *J. Org. Chem.* **1969**, *34*, 2951; Moon; Ganz; Waxman *Chem. Commun.* **1969**, 866; Johnson; Rickborn *Chem. Commun.* **1968**, 1073; Klein; Levene *Tetrahedron Lett.* **1969**, 4833; Chamberlain; Whitham *J. Chem. Soc. B* **1970**, 1382; Barrelle; Apparu *Bull. Soc. Chim. Fr.* **1972**, 2016.

¹⁴⁶For a review of this reagent, see Butler, in Pizey *Synthetic Reagents*, vol. 4; Wiley: New York, 1981, pp. 1-145.

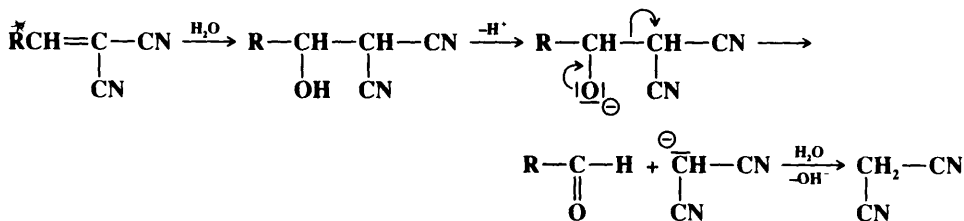
¹⁴⁷See the extensive tables in Larock, Ref. 144, pp. 4-71.

¹⁴⁸Einhorn; Einhorn; Luche *J. Org. Chem.* **1989**, *54*, 4479.

¹⁴⁹For discussions of the mechanism, see Vinnik; Obratsov *Russ. Chem. Rev.* **1990**, *59*, 63-77; Liler *Reaction Mechanisms in Sulphuric Acid*; Academic Press: New York, 1971, pp. 210-225.

The initial carbocation occasionally rearranges to a more stable one. For example, hydration of $\text{CH}_2=\text{CHCH}(\text{CH}_3)_2$ gives $\text{CH}_3\text{CH}_2\text{COH}(\text{CH}_3)_2$. With ordinary olefins the addition predominantly follows Markovnikov's rule. Another method for Markovnikov addition of water consists of simultaneously adding an oxidizing agent (O_2) and a reducing agent (either $\text{Et}_3\text{SiH}^{150}$ or a secondary alcohol such as 2-propanol¹⁵¹) to the olefin in the presence of a cobalt-complex catalyst. No rearrangement is observed with this method. The corresponding alkane and ketone are usually side products.

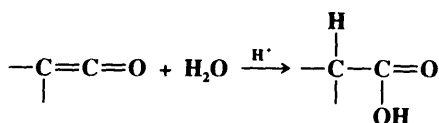
Water can be added indirectly, with anti-Markovnikov orientation, by treatment of the alkene with a 1:1 mixture of $\text{PhCH}_2\text{NEt}_3^+ \text{BH}_4^-$ and Me_3SiCl , followed by addition of an aqueous solution of K_2CO_3 .¹⁵² For another method of anti-Markovnikov hydration, see 5-12. With substrates of the type $\text{C}=\text{C}-\text{Z}$ (Z is as defined on p. 741) the product is almost always $\text{HO}-\text{C}-\text{CH}-\text{Z}$ and the mechanism is usually nucleophilic,¹⁵³ though electrophilic addition gives the same product¹⁵⁴ since a cation $\text{CH}-\overset{\oplus}{\text{C}}-\text{Z}$ would be destabilized by the positive charges (full or partial) on two adjacent atoms. However, the other product, $\text{HC}-\text{CH}(\text{OH})\text{Z}$, was obtained by treatment of the substrate with O_2 , PhSiH_3 , and a manganese-complex catalyst.¹⁵⁵ When the substrate is of the type $\text{RCH}=\text{CZZ}'$, addition of water may result in cleavage of the adduct, to give an aldehyde and $\text{CH}_2\text{ZZ}'$, e.g.,¹⁵⁶



The cleavage step is an example of 2-41.

Conjugated dienes are seldom hydrated.

The addition of water to enol ethers causes hydrolysis to aldehydes or ketones (0-6). Ketenes add water to give carboxylic acids in a reaction catalyzed by acids:¹⁵⁷



¹⁵⁰Isayama; Mukaiyama *Chem. Lett.* **1989**, 569.

¹⁵¹Inoki; Kato; Takai; Isayama; Yamada; Mukaiyama *Chem. Lett.* **1989**, 515.

¹⁵²Baskaran; Gupta; Chidambaram; Chandrasekaran *J. Chem. Soc., Chem. Commun.* **1989**, 903.

¹⁵³For example, see Fedor; De; Gurwara *J. Am. Chem. Soc.* **1973**, 95, 2905; Jensen; Hashtroudi *J. Org. Chem.* **1976**, 41, 3299; Bernasconi; Leonarduzzi *J. Am. Chem. Soc.* **1982**, 104, 5133, 5143.

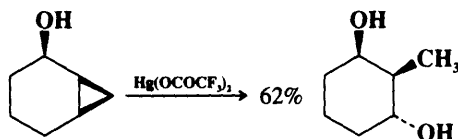
¹⁵⁴For example, see Noyce; DeBruin *J. Am. Chem. Soc.* **1968**, 90, 372.

¹⁵⁵Inoki; Kato; Isayama; Mukaiyama *Chem. Lett.* **1990**, 1869.

¹⁵⁶Bernasconi; Fox; Kanavarioti; Panda *J. Am. Chem. Soc.* **1986**, 108, 2372; Bernasconi; Paschalis *J. Am. Chem. Soc.* **1989**, 111, 5893, and other papers in this series.

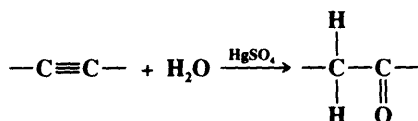
¹⁵⁷For discussions of the mechanism, see Poon; Satchell *J. Chem. Soc., Perkin Trans. 2* **1983**, 1381; **1986**, 1485; Allen; Tidwell *J. Am. Chem. Soc.* **1987**, 109, 2774; Allen; Stevenson; Tidwell *J. Org. Chem.* **1989**, 54, 2843; Ref. 143.

The oxymercuration procedure (with mercuric trifluoroacetate) has been used to open cyclopropane rings, e.g.,¹⁵⁸



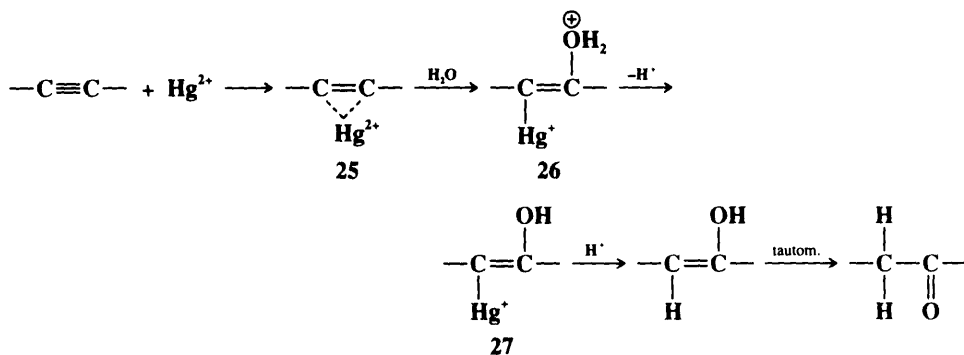
OS IV, 555, 560; VI, 766. Also see OS V, 818.

5-3 Hydration of Triple Bonds Dihydro-oxo-biaddition



The hydration of triple bonds is generally carried out with mercuric ion salts (often the sulfate or acetate) as catalysts.¹⁵⁹ Mercuric oxide in the presence of an acid is also a common reagent. Since the addition follows Markovnikov's rule, only acetylene gives an aldehyde. All other triple-bond compounds give ketones (for a method of reversing the orientation for terminal alkynes, see 5-12). With alkynes of the form $\text{RC}\equiv\text{CH}$ methyl ketones are formed almost exclusively, but with $\text{RC}\equiv\text{CR}'$ both possible products are usually obtained. The reaction can be conveniently carried out with a catalyst prepared by impregnating mercuric oxide onto Nafion-H (a superacidic perfluorinated resinsulfonic acid).¹⁶⁰

The first step of the mechanism is formation of a complex (25) (ions like Hg^{2+} form complexes with alkynes—p. 80). Water then attacks in an $\text{S}_{\text{N}}2$ -type process to give the intermediate 26, which loses a proton to give 27. Hydrolysis of 27 (an example of 2-24)



gives the enol, which tautomerizes to the product. A spectrum of the enol was detected by flash photolysis when phenylacetylene was hydrated photolytically.¹⁶¹

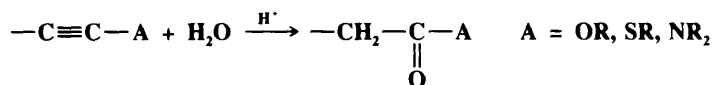
¹⁵⁸Collum; Mohamadi; Hallock *J. Am. Chem. Soc.* **1983**, *105*, 6882; Collum; Still; Mohamadi *J. Am. Chem. Soc.* **1986**, *108*, 2094.

¹⁵⁹For reviews, see Larock, Ref. 144, pp. 123-148; Khan; Martell *Homogeneous Catalysis by Metal Complexes*, vol. 2; Academic Press: New York, 1974, pp. 91-95. For a list of reagents, with references, see Ref. 133, pp. 596-597.

¹⁶⁰Olah; Meidar *Synthesis* **1978**, 671.

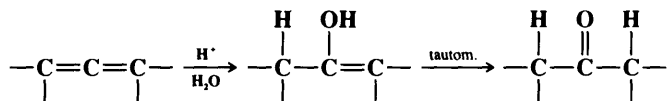
¹⁶¹Chiang; Kresge; Capponi; Wirz *Helv. Chim. Acta* **1986**, *69*, 1331.

Carboxylic esters, thiol esters, and amides can be made, respectively, by acid-catalyzed hydration of acetylenic ethers, thioethers,¹⁶² and ynamines, without a mercuric catalyst.¹⁶³



This is ordinary electrophilic addition, with rate-determining protonation as the first step.¹⁶⁴ Certain other alkynes have also been hydrated to ketones with strong acids in the absence of mercuric salts.¹⁶⁵ Simple alkynes can also be converted to ketones by heating with formic acid, without a catalyst.¹⁶⁶

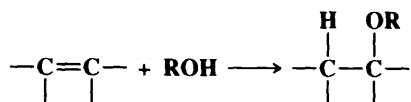
Allenes can also be hydrolyzed to ketones, with an acid catalyst.¹⁶⁷



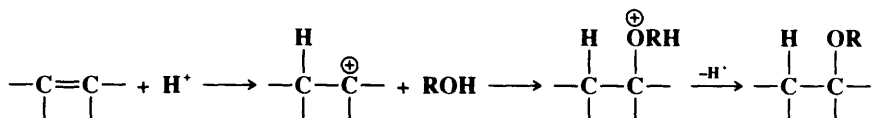
OS III, 22; IV, 13; V, 1024.

5-4 Addition of Alcohols and Phenols

Hydro-alkoxy-addition



The addition of alcohols and phenols to double bonds is catalyzed by acids or bases. When the reactions are acid-catalyzed, the mechanism is electrophilic, with H^+ as the attacking species. The resulting carbocation combines with a molecule of alcohol:



The addition, therefore, follows Markovnikov's rule. Primary alcohols give better results than secondary, and tertiary alcohols are very inactive. This is a convenient method for the preparation of tertiary ethers by the use of a suitable olefin such as $\text{Me}_2\text{C}=\text{CH}_2$.

For those substrates more susceptible to nucleophilic attack, e.g., polyhalo olefins and olefins of the type $\text{C}=\text{C}-\text{Z}$, it is better to carry out the reaction in basic solution, where the attacking species is RO^- .¹⁶⁸ The reactions with $\text{C}=\text{C}-\text{Z}$ are of the Michael type, and OR goes to the side away from the Z . Since triple bonds are more susceptible to nucleophilic

¹⁶²For a review of acetylenic ethers and thioethers, see Brandsma; Bos; Arens, in Viehe, Ref. 49, pp. 751-860.

¹⁶³Arens *Adv. Org. Chem.* **1960**, 2, 163; Ref. 162, pp. 774-775.

¹⁶⁴Hogevcen; Drenth *Recl. Trav. Chim. Pays-Bas* **1963**, 82, 375, 410; Verhelst; Drenth *J. Am. Chem. Soc.* **1974**, 96, 6692; Banait; Hojatti; Findlay; Kresge *Can. J. Chem.* **1987**, 65, 441.

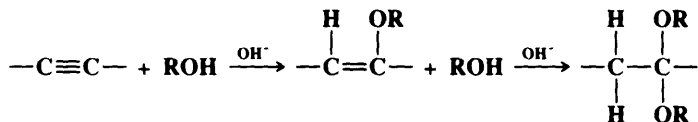
¹⁶⁵See, for example, Noyce; Schiavelli *J. Org. Chem.* **1968**, 33, 845; *J. Am. Chem. Soc.* **1968**, 90, 1020, 1023.

¹⁶⁶Menashe; Reshef; Shvo *J. Org. Chem.* **1991**, 56, 2912.

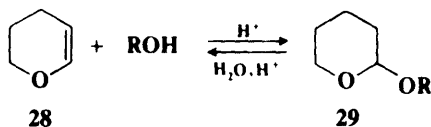
¹⁶⁷For example, see Fedorova; Petrov *J. Gen. Chem. USSR* **1962**, 32, 1740; Mühlstadt; Graef *Chem. Ber.* **1967**, 100, 223; Cramer; Tidwell *J. Org. Chem.* **1981**, 46, 2683.

¹⁶⁸For a review with respect to fluorolefins, see Ref. 62, pp. 53-61.

attack than double bonds, it might be expected that bases would catalyze addition to triple bonds particularly well. This is the case, and enol ethers and acetals can be produced by this reaction:¹⁶⁹



Because enol ethers are more susceptible than triple bonds to electrophilic attack, the addition of alcohols to enol ethers can also be catalyzed by acids.¹⁷⁰ One utilization of this reaction involves the compound dihydropyran (**28**), which is often used to protect the OH



groups of primary and secondary¹⁷¹ alcohols and phenols.¹⁷² The tetrahydropyranyl acetal formed by this reaction (**29**) is stable to bases, Grignard reagents, LiAlH_4 , and oxidizing agents, any of which can be used to react with functional groups located within the R group. When the reactions are completed, **29** is easily cleaved by treatment with dilute acids (**0-6**). The addition of alcohols to enol ethers is also catalyzed by CoCl_2 .¹⁷³

In base-catalyzed addition to triple bonds the rate falls in going from a primary to a tertiary alcohol, and phenols require more severe conditions. Other catalysts, namely, BF_3 and mercuric salts, have also been used in addition of ROH to triple bonds.

Alcohols can be added to certain double-bond compounds (cyclohexenes, cycloheptenes) photochemically¹⁷⁴ in the presence of a photosensitizer such as benzene. The mechanism is electrophilic and Markovnikov orientation is found. The olefins react in their first excited triplet states.¹⁷⁵

The oxymercuration-demercuration procedure mentioned in **5-2** can be adapted to the preparation of ethers (Markovnikov orientation) if the oxymercuration is carried out in an alcohol ROH as solvent,¹⁷⁶ e.g., 2-methyl-1-butene in ethanol gives EtMe_2COEt .¹⁷⁷ Primary alcohols give good yields when mercuric acetate is used, but for secondary and tertiary alcohols it is necessary to use mercuric trifluoroacetate.¹⁷⁸ However, even with this reagent the method fails where the product would be a ditertiary ether. Alkynes generally give acetals. If the oxymercuration is carried out in the presence of a hydroperoxide instead of an alcohol, the product (after demercuration with NaBH_4) is an alkyl peroxide (peroxymercuration).¹⁷⁹

¹⁶⁹For a review, see Shostakovskii; Trofimov; Atavin; Lavrov *Russ. Chem. Rev.* **1968**, *37*, 907-919.

¹⁷⁰For discussions of the mechanism, see Touleec; El-Alaoui; Bertrand *J. Chem. Soc., Perkin Trans. 2* **1987**, 1517; Kresge; Yin *J. Phys. Org. Chem.* **1989**, *2*, 43.

¹⁷¹Tertiary alcohols can also be protected in this way if triphenylphosphine hydrobromide is used as a catalyst: Bolitt; Mioskowski; Shin; Falck *Tetrahedron Lett.* **1988**, *29*, 4583.

¹⁷²For useful catalysts for this reaction, some of which are also applicable to tertiary alcohols, see Miyashita; Yoshikoshi; Grieco *J. Org. Chem.* **1977**, *42*, 3772; Olah; Husain; Singh *Synthesis* **1985**, 703; Johnston; Marston; Krieger; Goe *Synthesis* **1988**, 393.

¹⁷³Iqbal; Srivastava; Gupta; Khan *Synth. Commun.* **1989**, *19*, 901.

¹⁷⁴For a review of the photochemical protonation of double and triple bonds, see Wan; Yates *Rev. Chem. Intermed.* **1984**, *5*, 157-181.

¹⁷⁵Marshall *Acc. Chem. Res.* **1969**, *2*, 33-40.

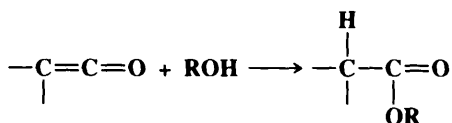
¹⁷⁶For a review, with tables of many examples, see Larock, Ref. 144, pp. 162-345.

¹⁷⁷Brown; Rei *J. Am. Chem. Soc.* **1969**, *91*, 5646.

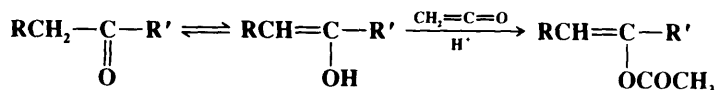
¹⁷⁸Brown; Kurek; Rei; Thompson *J. Org. Chem.* **1984**, *49*, 2551, **1985**, *50*, 1171.

¹⁷⁹Ballard; Bloodworth *J. Chem. Soc. C* **1971**, 945; Sokolov; Reutov *J. Org. Chem. USSR* **1969**, *5*, 168. For a review, see Larock, Ref. 144, pp. 346-366.

Both alcohols and phenols add to ketenes to give carboxylic esters:¹⁸⁰



This has been done intramolecularly (with the ketene end of the molecule generated and used in situ) to form medium- and large-ring lactones.¹⁸¹ In the presence of a strong acid, ketene reacts with aldehydes or ketones (in their enol forms) to give enol acetates:

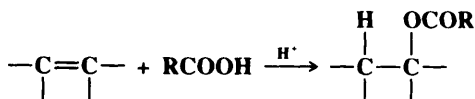


Alcohols can also add to olefins in a different way (see 5-22).

OS III, 371, 774, 813; IV, 184, 558; VI, 916; VII, 66, 160, 304, 334, 381; 67, 52; 69, 238.

5-5 Addition of Carboxylic Acids

Hydro-acyloxy-addition



Carboxylic esters are produced by the addition of carboxylic acids to olefins, a reaction that is usually acid-catalyzed (by proton or Lewis acids¹⁸²) and similar in mechanism to 5-4. Since Markovnikov's rule is followed, hard-to-get esters of tertiary alcohols can be prepared from olefins of the form $\text{R}_2\text{C}=\text{CHR}$.¹⁸³ When a carboxylic acid that contains a double bond in the chain is treated with a strong acid, the addition occurs internally and the product is a γ - and/or a δ -lactone, regardless of the original position of the double bond in the chain, since strong acids catalyze double bond shifts (2-2).¹⁸⁴ The double bond always migrates to a position favorable for the reaction, whether this has to be toward or away from the carboxyl group. Carboxylic esters have also been prepared by the acyloxymercuration–demercuration of olefins (similar to the procedures mentioned in 5-2 and 5-4).¹⁸⁵

Triple bonds can give enol esters or acylals when treated with carboxylic acids. Mercuric

¹⁸⁰Quadbeck *Newer Methods Prep. Org. Chem.* **1963**, 2, 133-161. See also Chihara; Teratini; Ogawa *J. Chem. Soc., Chem. Commun.* **1981**, 1120. For discussions of the mechanism see Tille; Pracejus *Chem. Ber.* **1967**, 100, 196-210; Brady; Vaughn; Hoff *J. Org. Chem.* **1969**, 34, 843; Ref. 143; Jähme; Rüchardt *Tetrahedron Lett.* **1982**, 23, 4011; Poon; Satchell *J. Chem. Soc., Perkin Trans. 2* **1984**, 1083; **1985**, 1551.

¹⁸¹Boeckman; Pruitt *J. Am. Chem. Soc.* **1989**, 111, 8286.

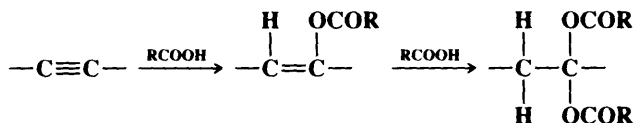
¹⁸²See, for example, Guenzet; Camps *Bull. Soc. Chim. Fr.* **1973**, 3167, *Tetrahedron* **1974**, 30, 849; Ballantine; Davies; Purnell; Rayanakorn; Thomas; Williams *J. Chem. Soc., Chem. Commun.* **1981**, 8.

¹⁸³See, for example, Peterson; Tao *J. Org. Chem.* **1964**, 29, 2322.

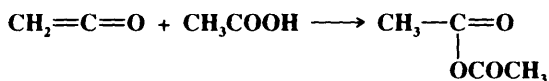
¹⁸⁴For a review of such lactonizations, see Ansell; Palmer *Q. Rev., Chem. Soc.* **1964**, 18, 211-225.

¹⁸⁵For a review, see Larock, Ref. 144, pp. 367-442.

salts are usually catalysts,¹⁸⁶ and vinylic mercury compounds $\begin{array}{c} | \\ \text{---C=C---OCOR} \\ | \\ \text{HgX} \end{array}$ are intermediates.¹⁸⁷ Terminal alkynes $\text{RC}\equiv\text{CH}$ react with CO_2 , a secondary amine $\text{R}'_2\text{NH}$, and a



ruthenium complex catalyst, to give enol carbamates $\text{RCH}=\text{CHOC}(=\text{O})\text{NR}'_2$.¹⁸⁸ This reaction has also been performed intramolecularly, to produce unsaturated lactones.¹⁸⁹ With ketenes, carboxylic acids give anhydrides¹⁹⁰ and acetic anhydride is prepared industrially in this manner:

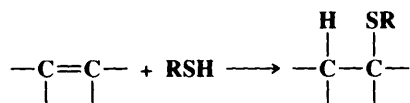


Carboxylic esters can also be obtained by the addition to olefins of diacyl peroxides.¹⁹¹ These reactions are catalyzed by copper and are free-radical processes.

OS III, 853; IV, 261, 417, 444; V, 852, 863; VII, 30, 411. Also see OS I, 317.

C. Sulfur on the Other Side

5-6 Addition of H_2S and Thiols Hydro-alkylthio-addition



H_2S and thiols add to olefins by electrophilic, nucleophilic, or free-radical mechanisms.¹⁹² In the absence of initiators the addition to simple olefins is by an electrophilic mechanism, similar to that in 5-4, and Markovnikov's rule is followed. However, this reaction is usually very slow and often cannot be done or requires very severe conditions unless a proton or Lewis acid catalyst is used. For example, the reaction can be performed in concentrated

¹⁸⁶For the use of rhodium complex catalysts, see Bianchini; Meli; Peruzzini; Zanobini; Bruneau; Dixneuf *Organometallics* **1990**, 9, 1155.

¹⁸⁷See for example, Bach; Woodard; Anderson; Glick *J. Org. Chem.* **1982**, 47, 3707; Alekseeva; Chalov; Temkin *J. Org. Chem. USSR* **1983**, 19, 431; Bassetti; Floris *J. Org. Chem.* **1986**, 51, 4140, *J. Chem. Soc., Perkin Trans. 2* **1988**, 227; Grishin; Bazhenov; Ustyniuk; Zefirov; Kartashov; Sokolova; Skorobogatova; Chernov *Tetrahedron Lett.* **1988**, 29, 4631; Camps; Monthéard; Benzaïd *Bull. Soc. Chim. Fr.* **1989**, 123. Ruthenium complexes have also been used as catalysts; Rotem; Shvo *Organometallics*, **1983**, 2, 1689; Rupp; Dixneuf *Tetrahedron Lett.* **1986**, 27, 6323; Mitsudo; Hori; Yamakawa; Watanabe *J. Org. Chem.* **1987**, 52, 2230.

¹⁸⁸Mitsudo; Hori; Yamakawa; Watanabe *Tetrahedron Lett.* **1987**, 28, 4417; Mahé; Sasaki; Bruneau; Dixneuf *J. Org. Chem.* **1989**, 54, 1518.

¹⁸⁹See, for example, see Sofia; Katzenellenbogen *J. Org. Chem.* **1985**, 50, 2331. For a list of other examples, see Ref. 133, p. 950.

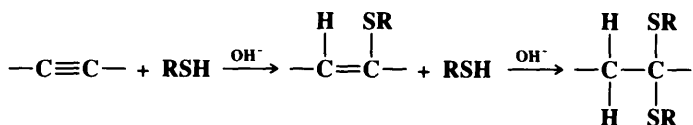
¹⁹⁰For discussions of the mechanism, see Briody; Lillford; Satchell *J. Chem. Soc. B* **1968**, 885; Corriu; Guenzet; Camps; Rey *Bull. Soc. Chim. Fr.* **1970**, 3679; Blake; Vayjooee *J. Chem. Soc., Perkin Trans. 2* **1976**, 1533.

¹⁹¹Kharasch; Fono *J. Org. Chem.* **1959**, 24, 606; Kochi *J. Am. Chem. Soc.* **1962**, 84, 1572.

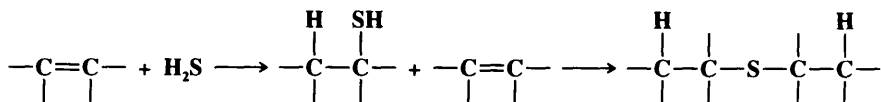
¹⁹²For a review, see Wardell, In Patai *The Chemistry of the Thiol Group*, pt. 1; Wiley: New York, 1974, pp. 169-178.

H_2SO_4 ¹⁹³ or together with AlCl_3 .¹⁹⁴ In the presence of free-radical initiators, H_2S and thiols add to double and triple bonds by a free-radical mechanism and the orientation is anti-Markovnikov.¹⁹⁵ In fact, the orientation can be used as a diagnostic tool to indicate which mechanism is operating. Free-radical addition can be done with H_2S , RSH (R may be primary, secondary, or tertiary), ArSH , or RCOSH .¹⁹⁶ R may contain various functional groups. The olefins may be terminal, internal, contain branching, be cyclic, and have various functional groups including OH, COOH, COOR, NO_2 , RSO_2 , etc. With alkynes it is possible to add 1 or 2 moles of RSH .

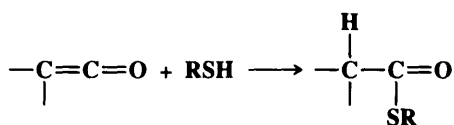
When thiols are added to substrates susceptible to nucleophilic attack, bases catalyze the reaction and the mechanism is nucleophilic. These substrates may be of the Michael type¹⁹⁷ or may be polyhalo olefins or alkynes.¹⁶⁹ As with the free-radical mechanism, alkynes can give either vinylic thioethers or dithioacetals:



By any mechanism, the initial product of addition of H_2S to a double bond is a thiol, which is capable of adding to a second molecule of olefin, so that sulfides are often produced:



Ketenes add thiols to give thiol esters:



OS III, 458; IV, 669; 65, 215. See also OS 69, 169.

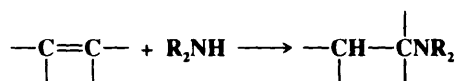
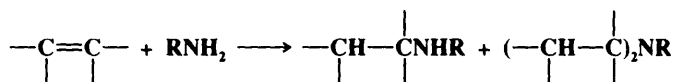
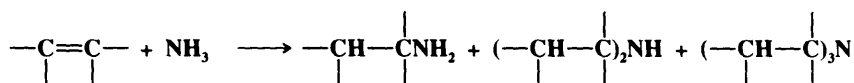
¹⁹³Shostakovskii; Kul'bovskaia; Gracheva; Laba; Yakushina *J. Gen. Chem. USSR* **1962**, 32, 707.

¹⁹⁴Belley; Zamboni *J. Org. Chem.* **1989**, 54, 1230.

¹⁹⁵For reviews of free-radical addition of H_2S and RSH , see Voronkov; Martynov; Mirskova *Sulfur Rep.* **1986**, 6, 77-95; Griesbaum *Angew. Chem. Int. Ed. Engl.* **1970**, 9, 273-287 [*Angew. Chem.* 82, 276-290]; Oswald; Griesbaum, in Kharasch; Meyers *Organic Sulfur Compounds*, vol. 2; Pergamon: Elmsford, NY, 1966, pp. 233-256; Stacey; Harris *Org. React.* **1963**, 13, 150-376, pp. 165-196, 247-324.

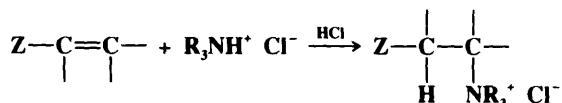
¹⁹⁶For a review of the addition of thio acids, see Janssen, in Patai *The Chemistry of Carboxylic Acids and Esters*; Wiley: New York, 1969, pp. 720-723.

¹⁹⁷Michael substrates usually give the expected orientation. For a method of reversing the orientation for RS groups (the RS group goes α to the $\text{C}=\text{O}$ bond of a $\text{C}=\text{C}-\text{C}=\text{O}$ system), see Gassman; Gilbert; Cole *J. Org. Chem.* **1977**, 42, 3233.

D. Nitrogen on the Other Side**5-7 Addition of Ammonia and Amines****Hydro-amino-addition**

Ammonia and primary and secondary amines add to olefins that are susceptible to nucleophilic attack.¹⁹⁸ Ammonia gives three possible products, since the initial product is a primary amine, which may add to a second molecule of olefin, etc. Similarly, primary amines give both secondary and tertiary products. In practice it is usually possible to control which product predominates. Since ammonia and amines are much weaker acids than water, alcohols, and thiols (see 5-2, 5-4, 5-6) and since acids could hardly catalyze the reaction (because they would turn NH_3 into NH_4^+), this reaction does not occur by an electrophilic mechanism and so gives very low yields, if any, with ordinary olefins, unless extreme conditions are used (e.g., 178-200°C, 800-1000 atm, and the presence of metallic Na, for the reaction between NH_3 and ethylene¹⁹⁹). The mechanism is nearly always nucleophilic, and the reaction is generally performed on polyhalo olefins,²⁰⁰ Michael-type substrates, and alkynes. As expected, on Michael-type substrates the nitrogen goes to the carbon that does not carry the Z. With substrates of the form $\text{RCH}=\text{CZZ}'$, the same type of cleavage of the adduct can take place as in 5-2.²⁰¹

Other nitrogen compounds, among them hydroxylamine, hydrazines, amides (RCONH_2 and RCONHR' including imides and lactams), and sulfonamides, also add to olefins. In the case of amides, basic catalysts are required, since amides are not good enough nucleophiles for the reaction and must be converted to RCONH^- . Even with amines, basic catalysts are sometimes used, so that RNH^- or R_2N^- is the actual nucleophile. Tertiary amines (except those that are too bulky) add to Michael-type substrates in a reaction that is catalyzed by acids like HCl or HNO_3 to give the corresponding quaternary ammonium salts.²⁰²



The tertiary amine can be aliphatic, cycloalkyl, or heterocyclic (including pyridine).

¹⁹⁸For reviews, see Gasc; Lattes; Périé *Tetrahedron* **1983**, *39*, 703-731; Pines; Stalick *Base-Catalyzed Reactions of Hydrocarbons and Related Compounds*; Academic Press: New York, 1977, pp. 423-454; Suminov; Kost *Russ. Chem. Rev.* **1969**, *38*, 884-899; Gibson, in Patai *The Chemistry of the Amino Group*; Wiley: New York, 1968, pp. 61-65.

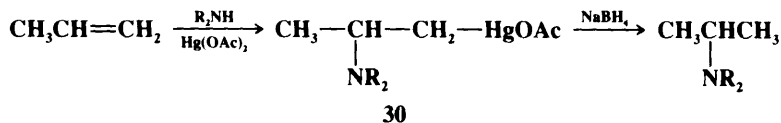
¹⁹⁹Howk; Little; Scott; Whitman *J. Am. Chem. Soc.* **1954**, *76*, 1899.

²⁰⁰For a review with respect to fluoroolefins, see Chambers; Mobbs *Adv. Fluorine Chem.* **1965**, *4*, 51-112, pp. 62-68.

²⁰¹See, for example, Bernasconi; Murray *J. Am. Chem. Soc.* **1986**, *108*, 5251, 5257; Bernasconi; Bunnell *J. Org. Chem.* **1988**, *53*, 2001.

²⁰²Le Berre; Delacroix *Bull. Soc. Chim. Fr.* **1973**, 640, 647. See also Vogel; Büchi *Org. Synth.* **66**, 29.

NH_3 can be added to double bonds (even ordinary double bonds) in an indirect manner by the use of hydroboration (5-12) followed by treatment with NH_2Cl or $\text{NH}_2\text{OSO}_2\text{OH}$ (2-31). This produces a primary amine with anti-Markovnikov orientation. An indirect way of adding a primary or secondary amine to a double bond consists of aminomercuration followed by reduction (see 5-2 for the analogous oxymercuration-demercuration procedure), e.g.,²¹¹

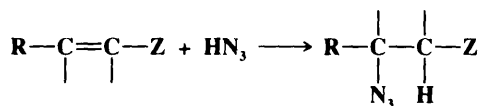


The addition of a secondary amine (shown above) produces a tertiary amine, while addition of a primary amine gives a secondary amine. The overall orientation follows Markovnikov's rule. Amido- and sulfamidomercuration-demercuration²¹² and nitromercuration²¹³ have also been accomplished (see also 6-55). For conversion of 30 to other products, see 5-40 and 5-41.

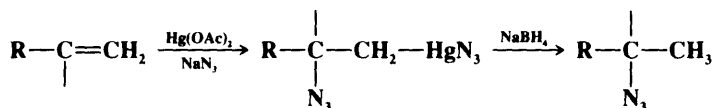
OS I, 196; III, 91, 93, 244, 258; IV, 146, 205; V, 39, 575, 929; VI, 75, 943; 66, 29; 67, 44, 48. See also OS VI, 932.

5-8 Addition of Hydrazoic Acid

Hydro-azido-addition



Hydrazoic acid can be added to certain Michael-type substrates (Z is as defined on p. 741) to give β -azido compounds.²¹⁴ The reaction apparently fails if R is phenyl. HN_3 also adds to enol ethers $\text{CH}_2=\text{CHOR}$ to give $\text{CH}_3-\text{CH}(\text{OR})\text{N}_3$, and to silyl enol ethers,²¹⁵ but it does not add to ordinary alkenes unless a Lewis acid catalyst, such as TiCl_4 , is used, in which case good yields of azide can be obtained.²¹⁵ HN_3 can also be added indirectly to ordinary olefins by azidomercuration, followed by demercuration,²¹⁶ analogous to the similar



procedures mentioned in 5-2, 5-4, 5-5, and 5-7. The method can be applied to terminal alkenes or strained cycloalkenes (e.g., norbornene) but fails for unstrained internal alkenes.

²¹¹For a review, see Larock, Ref. 144, pp. 443-504. See also Barluenga; Percz-Prieto; Asensio *Tetrahedron* **1990**, 46, 2453.

²¹²For a review, see Larock, Ref. 144, pp. 505-521.

²¹³Bachman; Whitehouse *J. Org. Chem.* **1967**, 32, 2303. For a review, see Larock, Ref. 144, pp. 528-531.

²¹⁴Boyer *J. Am. Chem. Soc.* **1951**, 73, 5248; Harvey; Ratts *J. Org. Chem.* **1966**, 31, 3907. For a review, see Biffin; Miller; Paul, in Patai *The Chemistry of the Azido Group*; Wiley: New York, 1971, pp. 120-136.

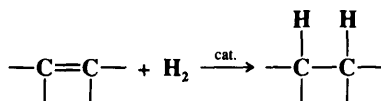
²¹⁵Hassner; Fibiger; Andisik *J. Org. Chem.* **1984**, 49, 4237.

²¹⁶Heathcock *Angew. Chem. Int. Ed. Engl.* **1969**, 8, 134 [*Angew. Chem.* 81, 148]. For a review, see Larock, Ref. 144, pp. 522-527.

E. Hydrogen on Both Sides

5-9 Hydrogenation of Double and Triple Bonds²¹⁷

Dihydro-addition



Most carbon-carbon double bonds, whether substituted by electron-donating or electron-withdrawing substituents, can be catalytically hydrogenated, usually in quantitative or near-quantitative yields.²¹⁸ Almost all known alkenes added hydrogen at temperatures between 0 and 275°C. Many functional groups may be present in the molecule, e.g., OH, COOH, NH₂, CHO, COR, COOR, or CN. Some of these groups are also susceptible to catalytic reduction, but it is usually possible to find conditions under which double bonds can be reduced selectively²¹⁹ (see Table 19.2). The catalysts used can be divided into two broad classes, both of which mainly consist of transition metals and their compounds: (1) catalysts insoluble in the reaction medium (*heterogeneous catalysts*). Among the most effective are Raney nickel,²²⁰ palladium-on-charcoal (perhaps the most common), NaBH₄-reduced nickel²²¹ (also called nickel boride), platinum metal or its oxide, rhodium, ruthenium, and zinc oxide.²²² (2) Catalysts soluble in the reaction medium (*homogeneous catalysts*).²²³ The most important is chlorotris(triphenylphosphine)rhodium RhCl(PH₃)₃,²²⁴ (*Wilkinson's catalyst*),²²⁵ which catalyzes the hydrogenation of many olefinic compounds without disturbing such groups as COOR, NO₂, CN, or COR present in the same molecule.²²⁶ Even unsaturated

²¹⁷For a review, see Mitsui; Kasahara, in Zabicky, Ref. 115, vol. 2, pp. 175-214.

²¹⁸For books on catalytic hydrogenation, see Rylander *Hydrogenation Methods*; Academic Press: New York, 1985. *Catalytic Hydrogenation in Organic Synthesis*; Academic Press: New York, 1979. *Catalytic Hydrogenation over Platinum Metals*; Academic Press: New York, 1967; Červený *Catalytic Hydrogenation*; Elsevier: New York, 1986 (this book deals mostly with industrial aspects); Freifelder *Catalytic Hydrogenation in Organic Synthesis*; Wiley: New York, 1978. *Practical Catalytic Hydrogenation*; Wiley: New York, 1971; Augustine *Catalytic Hydrogenation*; Marcel Dekker: New York, 1965. For reviews, see Parker, in Hartley *The Chemistry of the Metal-carbon Bond*, vol. 4; Wiley: New York, 1987, pp. 979-1047; Carruthers *Some Modern Methods of Organic Synthesis*, 3rd ed.; Cambridge University Press: Cambridge, 1986, pp. 411-431; Colquhoun; Holton; Thompson; Twigg *New Pathways for Organic Synthesis*; Plenum: New York, 1984, pp. 266-300, 325-334; Kalinkin; Kolomnikova; Parnes; Kursanov *Russ. Chem. Rev.* **1979**, *48*, 332-342; Candlin; Rennie, 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. 97-117; House, Ref. 144, pp. 1-34.

²¹⁹For a discussion, see Rylander *Catalytic Hydrogenation over Platinum Metals*, Ref. 218, pp. 59-120.

²²⁰For a review of Raney nickel, see Pizey, Ref. 146, vol. 2, 1974, pp. 175-311. Double bonds have been reduced with Raney nickel alone; with no added H₂. The hydrogen normally present in this reagent was sufficient; *Pojer Chem. Ind. (London)* **1986**, 177.

²²¹Paul; Buisson; Joseph *Ind. Eng. Chem.* **1952**, *44*, 1006; Brown *Chem. Commun.* **1969**, 952; *J. Org. Chem.* **1970**, *35*, 1900. For a review of reductions with nickel boride and related catalysts, see Ganem; Osby *Chem. Rev.* **1986**, *86*, 763-780.

²²²For reviews of hydrogenation with metal oxides, see Minachev; Khodakov; Nakhshunov *Russ. Chem. Rev.* **1976**, *45*, 142-154; Kokes; Dent *Adv. Catal.* **1972**, *22*, 1-50 (ZnO).

²²³For a monograph, see James *Homogeneous Hydrogenation*; Wiley: New York, 1973. For reviews, see Collman; Hegedus; Norton; Finke *Principles and Applications of Organotransition Metal Chemistry*; University Science Books: Mill Valley, CA, 1987, pp. 523-564; Birch; Williamson *Org. React.* **1976**, *24*, 1-186; James *Adv. Organomet. Chem.* **1979**, *17*, 319-405; Harmon; Gupta; Brown *Chem. Rev.* **1973**, *73*, 21-52; Strohmeier *Fortschr. Chem. Forsch.* **1972**, *25*, 71-104; Heck *Organotransition Metal Chemistry*; Academic Press: New York, 1974, pp. 55-65; Rylander *Organic Syntheses with Noble Metal Catalysts*; Academic Press: New York, 1973, pp. 60-76; Lyons; Rennick; Burmeister *Ind. Eng. Chem., Prod. Res. Dev.* **1970**, *9*, 2-20; Vol'pin; Kolomnikov *Russ. Chem. Rev.* **1969**, *38*, 273-289.

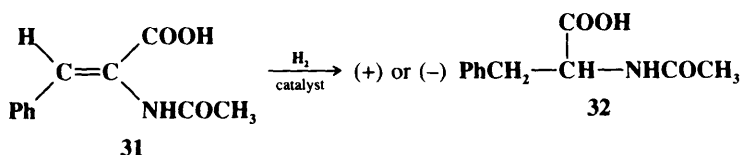
²²⁴Young; Osborn; Jardine; Wilkinson *Chem. Commun.* **1965**, 131; Osborn; Jardine; Young; Wilkinson *J. Chem. Soc. A* **1966**, 1711; Osborn; Wilkinson *Inorg. Synth.* **1967**, *10*, 67; Biellmann *Bull. Soc. Chim. Fr.* **1968**, 3055; van Bekkum; van Rantwijk; van de Putte *Tetrahedron Lett.* **1969**, 1.

²²⁵For a review of Wilkinson's catalyst, see Jardine, *Prog. Inorg. Chem.* **1981**, *28*, 63-202.

²²⁶Harmon; Parsons; Cooke; Gupta; Schoolenberg *J. Org. Chem.* **1969**, *34*, 3684. See also Mohrig; Dabora; Foster; Schultz *J. Org. Chem.* **1984**, *49*, 5179.

aldehydes can be reduced to saturated aldehydes,²²⁷ though in this case decarbonylation (**4-41**) may be a side reaction. Among other homogeneous catalysts are chlorotris(triphenylphosphine)hydridoruthenium(II) $(\text{Ph}_3\text{P})_3\text{RuClH}$,²²⁸ which is specific for terminal double bonds (other double bonds are hydrogenated slowly or not at all), and pentacyanocobaltate(II) $\text{Co}(\text{CN})_5^{3-}$, which is effective for double and triple bonds only when they are part of conjugated systems²²⁹ (the conjugation may be with $\text{C}=\text{C}$, $\text{C}=\text{O}$, or an aromatic ring). Homogeneous catalysts often have the advantages of better catalyst reproducibility and better selectivity. They are also less susceptible to catalyst poisoning²³⁰ (heterogeneous catalysts are usually poisoned by small amounts of sulfur, often found in rubber stoppers, or by sulfur-containing compounds such as thiols and sulfides).²³¹ On the other hand, heterogeneous catalysts are usually easier to separate from the reaction mixture.

Optically active homogeneous (as well as heterogeneous) catalysts have been used to achieve partially asymmetric (enantioselective) hydrogenations of certain prochiral substrates.²³² For example,²³³ hydrogenation of **31** with a suitable catalyst gives (+) or (-) **32**



(depending on which enantiomer of the catalyst is used) with an enantiomeric excess as high as 96%.²³⁴ Prochiral substrates that give such high optical yields generally contain functional groups similar to those in **31**.²³⁵ The catalyst in such cases²³⁶ is usually a ruthenium- or rhodium-phosphine in which the phosphine is optically active either because of an asymmetric phosphorus atom, e.g., **33**,²³⁷ or because of a chiral group connected to the phosphorus,

²²⁷Jardine; Wilkinson *J. Chem. Soc. C* **1967**, 270.

²²⁸Hallman; Evans; Osborn; Wilkinson *Chem. Commun.* **1967**, 305; Hallman; McGarvey; Wilkinson *J. Chem. Soc. A* **1968**, 3143; Jardine; McQuillin *Tetrahedron Lett.* **1968**, 5189.

²²⁹Kwiatek; Mador; Seyler *J. Am. Chem. Soc.* **1962**, *84*, 304; Jackman; Hamilton; Lawlor *J. Am. Chem. Soc.* **1968**, *90*, 1914; Funabiki; Matsumoto; Tarama *Bull. Chem. Soc. Jpn.* **1972**, *45*, 2723; Reger; Habib; Fauth *Tetrahedron Lett.* **1979**, 115.

²³⁰Birch; Walker *Tetrahedron Lett.* **1967**, 1935.

²³¹For a review of catalyst poisoning by sulfur, see Barbier; Lamy-Pitara; Marcot; Boitiaux; Cosyns; Verna *Adv. Catal.* **1990**, *37*, 279-318.

²³²For reviews, see, in Morrison *Asymmetric Synthesis*, vol. 5; Academic Press: New York, 1985, the reviews by Halpern, pp. 41-69; Koenig, pp. 71-101; Harada, pp. 345-383; Ojima; Clos; Bastos *Tetrahedron* **1989**, *45*, 6901-6939, pp. 6902-6916; Jardine, in Hartley, Ref. 218, pp. 751-775; Nógrádi *Stereoselective Synthesis*; VCH: New York, 1986, pp. 53-87; Knowles *Acc. Chem. Res.* **1983**, *16*, 106-112; Brunner *Angew. Chem. Int. Ed. Engl.* **1983**, *22*, 897-907 [*Angew. Chem.* *95*, 921-931]; Klabunovskii *Russ. Chem. Rev.* **1982**, *51*, 630-643; Čaplar; Comisso; Šunjić *Synthesis* **1981**, 85-116; Morrison; Masler; Neuberger *Adv. Catal.* **1976**, *25*, 81-124; Kagan *Pure Appl. Chem.* **1975**, *43*, 401-421; Bogdanović *Angew. Chem. Int. Ed. Engl.* **1973**, *12*, 954-964 [*Angew. Chem.* *85*, 1013-1023]. See also Ref. 94 in Chapter 4.

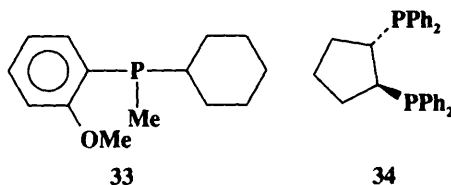
²³³For some other recent examples, see Hayashi; Kawamura; Ito *Tetrahedron Lett.* **1988**, *29*, 5969; Muramatsu; Kawano; Ishii; Saburi; Uchida *J. Chem. Soc., Chem. Commun.* **1989**, 769; Amrani; Lecomte; Sinou; Bakos; Toth; Heil *Organometallics* **1989**, *8*, 542; Yamamoto; Ikeda; Lin *J. Organomet. Chem.* **1989**, *370*, 319; Waymouth; Pino *J. Am. Chem. Soc.* **1990**, *112*, 4911; Ohta; Takaya; Noyori *Tetrahedron Lett.* **1990**, *31*, 7189; Ashby; Halpern *J. Am. Chem. Soc.* **1991**, *113*, 589; Heiser; Broger; Cramer *Tetrahedron: Asymmetry* **1991**, *2*, 51; Burk *J. Am. Chem. Soc.* **1991**, *113*, 8518.

²³⁴Koenig, in Morrison, Ref. 232, p. 74.

²³⁵For tables of substrates that have been enantioselectively hydrogenated, see Koenig, in Morrison, Ref. 232, pp. 83-101.

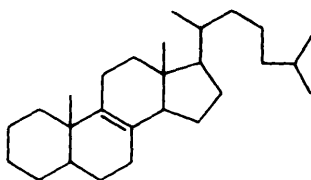
²³⁶For a list of these, with references, see Ref. 133, p. 7. For reviews of optically active nickel catalysts, see Izumi *Adv. Catal.* **1983**, *32*, 215-271. *Angew. Chem. Int. Ed. Engl.* **1971**, *10*, 871-881 [*Angew. Chem.* *83*, 956-966]. For a review of the synthesis of some of these phosphines, see Mortreux; Petit; Buono; Peiffer *Bull. Soc. Chim. Fr.* **1987**, 631-639.

²³⁷Knowles; Sabacky; Vineyard *J. Chem. Soc., Chem. Commun.* **1972**, 10. See also Vineyard; Knowles; Sabacky; Bachman; Weinkauff *J. Am. Chem. Soc.* **1977**, *99*, 5946.



e.g., **34**.²³⁸ Other types of catalysts, for example, titanocenes with chiral cyclopentadienyl ligands, have given enantioselective hydrogenation of olefins that lack functional groups such as COOH or NHCOCH₃, for example, 2-phenyl-1-butene.²³⁹ Enantioselective reduction of certain olefins has also been achieved by reducing with baker's yeast.²⁴⁰

Hydrogenations in most cases are carried out at room temperature and just above atmospheric pressure, but some double bonds are more resistant and require higher temperatures and pressures. The resistance is usually a function of increasing substitution and is presumably caused by steric factors. Trisubstituted double bonds require, say, 25°C and 100 atm, while tetrasubstituted double bonds may require 275°C and 1000 atm. Among the double bonds most difficult to hydrogenate or which cannot be hydrogenated at all are those common to two rings, as in the steroid shown. Hydrogenations, even at about atmospheric



pressure, are ordinarily performed in a special hydrogenator, but this is not always necessary. Both the catalyst and the hydrogen can be generated in situ, by treatment of H₂PtCl₆ or RhCl₃ with NaBH₄;²⁴¹ ordinary glassware can then be used. The great variety of catalysts available often allows an investigator to find one that is highly selective. For example, the catalyst Pd(salen) encapsulated in zeolites permitted the catalytic hydrogenation of 1-hexene in the presence of cyclohexene.²⁴²

Although catalytic hydrogenation is the method most often used, double bonds can be reduced by other reagents, as well. Among these are sodium in ethanol, sodium and *t*-butyl alcohol in HMPA,²⁴³ lithium and aliphatic amines²⁴⁴ (see also **5-10**), chromous ion,²⁴⁵ zinc and acids, sodium hypophosphate and Pd-C,²⁴⁶ (EtO)₃SiH-Pd(OAc)₂,²⁴⁷ trifluoroacetic acid

²³⁸Allen; Gibson; Green; Skinner; Bashkin; Grebenik *J. Chem. Soc., Chem. Commun.* **1983**, 895.

²³⁹Halterman; Vollhardt; Welker; Bläser; Boese *J. Am. Chem. Soc.* **1987**, 109, 8105.

²⁴⁰See, for example, Gramatica; Manitto; Monti; Speranza *Tetrahedron* **1988**, 44, 1299; Ohta; Kobayashi; Ozaki *J. Org. Chem.* **1989**, 54, 1802. For reviews of baker's yeast, see Csuk; Glänzer *Chem. Rev.* **1991**, 91, 49-97; Servi *Synthesis* **1990**, 1-25.

²⁴¹Brown; Sivasankaran *J. Am. Chem. Soc.* **1962**, 84, 2828; Brown; Brown *J. Am. Chem. Soc.* **1962**, 84, 1494, 1945, 2829; *J. Org. Chem.* **1966**, 31, 3989.

²⁴²Kowalak; Weiss; Balkus *J. Chem. Soc., Chem. Commun.* **1991**, 57.

²⁴³Angibeaud; Larchevêque; Normant; Tchoubar *Bull. Soc. Chim. Fr.* **1968**, 595; Whitesides; Ehmman *J. Org. Chem.* **1970**, 35, 3565.

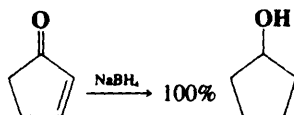
²⁴⁴Benkeser; Schroll; Sauve *J. Am. Chem. Soc.* **1955**, 77, 3378.

²⁴⁵For example, see Castro; Stephens *J. Am. Chem. Soc.* **1964**, 86, 4358; Castro; Stephens; Mojé *J. Am. Chem. Soc.* **1966**, 88, 4964.

²⁴⁶Sala; Doria; Passarotti *Tetrahedron Lett.* **1984**, 25, 4565.

²⁴⁷Tour; Pandalwar *Tetrahedron Lett.* **1990**, 31, 4719.

and triethylsilane Et_3SiH ,²⁴⁸ hydrazine (if a small amount of oxidizing agent, such as air, H_2O_2 , or cupric ion is present),²⁴⁹ hydroxylamine and ethyl acetate,²⁵⁰ and $\text{NH}_2\text{OSO}_3\text{H}$.²⁵¹ However, metallic hydrides, such as lithium aluminum hydride and sodium borohydride, do not in general reduce carbon-carbon double bonds, although this can be done in special cases where the double bond is polar, as in 1,1-diarylethenes²⁵² and in enamines.²⁵³ In certain cases²⁵⁴ these metallic hydride reagents may also reduce double bonds in conjugation with $\text{C}=\text{O}$ bonds, as well as reducing the $\text{C}=\text{O}$ bonds, e.g.,²⁵⁵



NaBH_4 has a greater tendency than LiAlH_4 to effect this double reduction, though even with NaBH_4 the product of single reduction (of the $\text{C}=\text{O}$ bond) is usually formed in larger amount than the doubly reduced product. LiAlH_4 gives significant double reduction only in cinnamyl systems, e.g., with $\text{PhCH}=\text{CHCOOH}$.²⁵⁶

Reduction of only the $\text{C}=\text{C}$ bond of conjugated $\text{C}=\text{C}-\text{C}=\text{O}$ and $\text{C}=\text{C}-\text{C}\equiv\text{N}$ systems²⁵⁷ has been achieved by many reducing agents,²⁵⁸ a few of which are H_2 and a Rh catalyst,²⁵⁹ $\text{Bu}_3\text{SnH}-\text{Pd}(\text{PPh}_3)_4$,²⁶⁰ $\text{Bu}_3\text{SnH}-\text{CuI}-\text{LiCl}$,²⁶¹ $\text{Zn}-\text{Cu}$ in boiling MeOH ,²⁶² $\text{Mg}-\text{MeOH}$,²⁶³ diisobutylaluminum hydride- $\text{MeCu}-\text{HMPA}$,²⁶⁴ $\text{PhSiH}_3-\text{Mo}(\text{CO})_6$,²⁶⁵ $[(\text{Ph}_3\text{P})\text{CuH}]_6$,²⁶⁶ $\text{Zn}-\text{NiCl}_2$ in the presence of ultrasound,²⁶⁷ $\text{Al}-\text{NiCl}_2$,²⁶⁸ potassium triphenylborohydride,²⁶⁹ $\text{CO}-\text{Se}-\text{H}_2\text{O}$,²⁷⁰ and catecholborane.²⁷¹ See 6-25 for methods of re-

²⁴⁸Kursanov; Parnes; Bassova; Loim; Zdanovich *Tetrahedron* **1967**, 23, 2235; Doyle; McOsker *J. Org. Chem.* **1978**, 43, 693. For a monograph, see Kursanov; Parnes; Kalinkin; Loim *Ionic Hydrogenation and Related Reactions*; Harwood Academic Publishers: Chur, Switzerland, 1985. For a review, see Kursanov; Parnes; Loim *Synthesis* **1974**, 633-651.

²⁴⁹Corey; Mock; Pasto *Tetrahedron Lett.* **1961**, 347; Hünig; Müller; Thier *Tetrahedron Lett.* **1961**, 353; Furst; Berlo; Hooton *Chem. Rev.* **1965**, 65, 51-68, pp. 64-65; Kondo; Murai; Sonoda *Tetrahedron Lett.* **1977**, 3727.

²⁵⁰Wade; Amin *Synth. Commun.* **1982**, 12, 287.

²⁵¹Appel; Büchner *Liebigs Ann. Chem.* **1962**, 654, 1; Dürckheimer *Liebigs Ann. Chem.* **1969**, 721, 240. For a review of the reagent hydroxylamine-O-sulfonic acid, see Wallace *Org. Prep. Proced. Int.* **1982**, 14, 265-307.

²⁵²See Granoth; Segall; Leader; Alkabetz *J. Org. Chem.* **1976**, 41, 3682.

²⁵³For a review of the reduction of enamines and indoles with NaBH_4 and a carboxylic acid, see Gribble; Nutaitis *Org. Prep. Proced. Int.* **1985**, 17, 317-384. Enamines can also be reduced by formic acid; see Nilsson; Carlson *Acta Chem. Scand. Sect. B* **1985**, 39, 187.

²⁵⁴For discussion, see Meyer *J. Chem. Educ.* **1981**, 58, 628.

²⁵⁵Brown; Hess *J. Org. Chem.* **1969**, 34, 2206. For other methods of reducing both double bonds, see Ref. 133, p. 540.

²⁵⁶Nystrom; Brown *J. Am. Chem. Soc.* **1947**, 69, 2548, **1948**, 70, 3738; Gammill; Gold; Mizsak *J. Am. Chem. Soc.* **1980**, 102, 3095.

²⁵⁷For a review of the reduction of α,β -unsaturated carbonyl compounds, see Keinan; Greenspoon, in Patai; Rappoport, Ref. 37, pt. 2, pp. 923-1022. For a review of the stereochemistry of catalytic hydrogenation of α,β -unsaturated ketones, see Augustine *Adv. Catal.* **1976**, 25, 56-80.

²⁵⁸For a long list of these, with references, see Ref. 133, pp. 8-17.

²⁵⁹Djerassi; Gutzwiller *J. Am. Chem. Soc.* **1966**, 88, 4537; Cabello; Campelo; Garcia; Luna; Marinas *J. Org. Chem.* **1986**, 51, 1786; Ref. 226.

²⁶⁰Keinan; Gleize *Tetrahedron Lett.* **1982**, 23, 477; Four; Guibe *Tetrahedron Lett.* **1982**, 23, 1825.

²⁶¹Lipshutz; Ung; Sengupta *Synlett* **1989**, 64.

²⁶²Sondengam; Fomum; Charles; Akam *J. Chem. Soc., Perkin. Trans. 1* **1983**, 1219.

²⁶³Youn; Yon; Pak *Tetrahedron Lett.* **1986**, 27, 2409; Hudlicky; Sinai-Zingde; Natchus *Tetrahedron Lett.* **1987**, 28, 5287.

²⁶⁴Tsuda; Hayashi; Satomi; Kawamoto; Saegusa *J. Org. Chem.* **1986**, 51, 537.

²⁶⁵Keinan; Perez *J. Org. Chem.* **1987**, 52, 2576.

²⁶⁶Mahoney; Brestensky; Stryker *J. Am. Chem. Soc.* **1988**, 110, 291.

²⁶⁷Petrier; Luche *Tetrahedron Lett.* **1987**, 28, 2347, 2351.

²⁶⁸Hazarika; Barua *Tetrahedron Lett.* **1989**, 30, 6567.

²⁶⁹Kim; Park; Yoon *Synth. Commun.* **1988**, 18, 89.

²⁷⁰Nishiyama; Makino; Hamanaka; Ogawa; Sonoda *Bull. Chem. Soc. Jpn.* **1989**, 62, 1682.

²⁷¹Evans; Fu *J. Org. Chem.* **1990**, 55, 5678.

ducing C=O bonds in the presence of conjugated C=C bonds. LiAlH_4 also reduces the double bonds of allylic alcohols²⁷² and NaBH_4 in MeOH-THF reduces α,β -unsaturated nitro compounds to nitroalkanes.²⁷³ Furthermore, both LiAlH_4 and NaBH_4 , as well as NaH, reduce ordinary alkenes and alkynes when complexed with transition metal salts, such as FeCl_2 or CoBr_2 .²⁷⁴

The inertness of ordinary double bonds toward metallic hydrides is quite useful, since it permits reduction of, say, a carbonyl or nitro group, without disturbing a double bond in the same molecule (see Chapter 19 for a discussion of selectivity in reduction reactions). Sodium in liquid ammonia also does not reduce ordinary double bonds,²⁷⁵ although it does reduce alkynes, allenes, conjugated dienes,²⁷⁶ and aromatic rings (5-10).

Another hydrogenation method is called *transfer hydrogenation*.²⁷⁷ In this method the hydrogen comes from another organic molecule, which is itself oxidized. A transition-metal catalyst, heterogeneous or homogeneous, is frequently employed. A common reducing agent is cyclohexene, which, when a palladium catalyst is used, is oxidized to benzene, losing 2 moles of hydrogen.

Triple bonds can be reduced, either by catalytic hydrogenation or by the other methods mentioned. The comparative reactivity of triple and double bonds depends on the catalyst. With most catalysts, e.g., Pd, triple bonds are hydrogenated more easily, and therefore it is possible to add just 1 mole of hydrogen and reduce a triple bond to a double bond (usually a stereoselective syn addition) or to reduce a triple bond without affecting a double bond present in the same molecule.²⁷⁸ A particularly good catalyst for this purpose is the Lindlar catalyst ($\text{Pd}-\text{CaCO}_3-\text{PbO}$).²⁷⁹ Triple bonds can also be selectively reduced to double bonds with diisobutylaluminum hydride (DIBALH),²⁸⁰ with tetramethyldihydrodisiloxane-HOAc and a Pd(0) catalyst,²⁸¹ with activated zinc (see 2-38),²⁸² with a zinc-copper couple,²⁸³ or (internal triple bonds only) with alkali metals (Na, Li) in liquid ammonia or a low-molecular-weight amine.²⁸⁴ Terminal alkynes are not reduced by the Na-NH₃ procedure because they are converted to acetylide ions under these conditions. However, terminal triple bonds can be reduced to double bonds by the addition to the Na-NH₃ solution of $(\text{NH}_4)_2\text{SO}_4$, which liberates the free ethynyl group.²⁸⁵

An indirect method²⁸⁶ of double-bond reduction involves hydrolysis of boranes (prepared

²⁷²For discussions of the mechanism of this reaction, see Snyder *J. Org. Chem.* **1967**, 32, 3531; Borden *J. Am. Chem. Soc.* **1968**, 90, 2197; Blunt; Hartshorn; Soong; Munro *Aust. J. Chem.* **1982**, 35, 2519; Vincens; Fadel; Vidal *Bull. Soc. Chim. Fr.* **1987**, 462.

²⁷³Varma; Kabalka *Synth. Commun.* **1985**, 15, 151.

²⁷⁴See for example Sato; Sato; Sato *J. Organomet. Chem.* **1976**, 122, C25, **1977**, 131, C26; Fujisawa; Sugimoto; Ohta *Chem. Lett.* **1976**, 581; Ashby; Lin *J. Org. Chem.* **1978**, 43, 2567; Chung *J. Org. Chem.* **1979**, 44, 1014. See also Osby; Heinzman; Ganem *J. Am. Chem. Soc.* **1986**, 108, 67.

²⁷⁵There are some exceptions. See, for example, Butler *Synth. Commun.* **1977**, 7, 441, and references cited therein.

²⁷⁶For a review of reductions of α,β -unsaturated carbonyl compounds with metals in liquid NH₃, see Caine, *Org. React.* **1976**, 23, 1-258.

²⁷⁷For reviews, see Johnstone; Wilby; Entwistle *Chem. Rev.* **1985**, 85, 129; Brieger; Nestrick *Chem. Rev.* **1974**, 74, 567-580.

²⁷⁸For reviews of the hydrogenation of alkynes, see Hutchins; Hutchins, in Patai; Rappoport, Ref. 49, pt. 1, pp. 571-601; Marvell; Li *Synthesis* **1973**, 457-468; Gutmann; Lindlar, in Viehe, Ref. 70, pp. 355-363.

²⁷⁹Lindlar; Dubuis *Org. Synth. V*, 880. See also Rajaram; Narula; Chawla; Dev *Tetrahedron* **1983**, 39, 2315; McEwen; Guttieri; Maier; Laine; Shvo *J. Org. Chem.* **1983**, 48, 4436.

²⁸⁰Wilke; Müller *Chem. Ber.* **1956**, 89, 444. *Liebigs Ann. Chem.* **1960**, 629, 224; Gensler; Bruno *J. Org. Chem.* **1963**, 28, 1254; Eisch; Kaska *J. Am. Chem. Soc.* **1966**, 88, 2213. For a catalyst with even better selectivity for triple bonds, see Ulan; Maier; Smith *J. Org. Chem.* **1987**, 52, 3132.

²⁸¹Trost; Braslau *Tetrahedron Lett.* **1989**, 30, 4657.

²⁸²Aeressens; van der Heiden; Heus; Brandsma *Synth. Commun.* **1990**, 20, 3421; Chou; Clark; White *Tetrahedron Lett.* **1991**, 32, 299.

²⁸³Sondengam; Charles; Akam *Tetrahedron Lett.* **1980**, 21, 1069.

²⁸⁴For a list of methods of reducing triple to double bonds, with syn or anti addition, see Ref. 133, pp. 212-214.

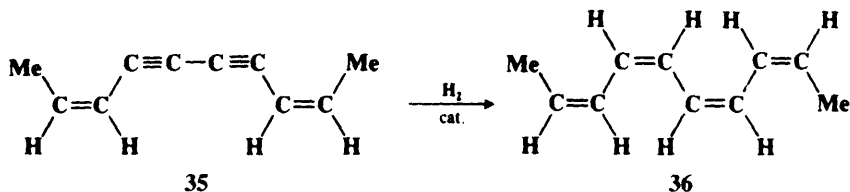
²⁸⁵Henne; Greenlee *J. Am. Chem. Soc.* **1943**, 65, 2020.

²⁸⁶For a review, see Zweifel *Intra-Sci. Chem. Rep.* **1973**, 7(2), 181-189.

by 5-12). Trialkylboranes can be hydrolyzed by refluxing with carboxylic acids,²⁸⁷ while monoalkylboranes RBH_2 can be hydrolyzed with base.²⁸⁸ Triple bonds can be similarly reduced, to cis olefins.²⁸⁹

Conjugated dienes can add hydrogen by 1,2 or 1,4 addition. Selective 1,4 addition can be achieved by hydrogenation in the presence of carbon monoxide, with bis(cyclopentadienyl)chromium as catalyst.²⁹⁰ With allenes²⁹¹ catalytic hydrogenation usually reduces both double bonds, but reduction of just one double bond, to give an olefin, has been accomplished by treatment with Na-NH_3 ²⁹² or with DIBALH,²⁹³ and by hydrogenation with $\text{RhCl}(\text{PPh}_3)_3$ as catalyst.²⁹⁴

Most catalytic reductions of double or triple bonds, whether heterogeneous or homogeneous, have been shown to be syn, with the hydrogens entering from the less-hindered side of the molecule.²⁹⁵ Stereospecificity can be investigated only for tetrasubstituted olefins (except when the reagent is D_2), which are the hardest to hydrogenate, but the results of these investigations show that the addition is usually 80 to 100% syn, though some of the anti addition product is normally also found and in some cases predominates. Catalytic hydrogenation of alkynes is nearly always stereoselective, giving the cis olefin (usually at least 80%), even when it is thermodynamically less stable. For example, **35** gave **36**, even though the steric hindrance is such that a planar molecule is impossible.²⁹⁶ This is thus a



useful method for preparing cis olefins.²⁹⁷ However, when steric hindrance is too great, the trans olefin may be formed. One factor that complicates the study of the stereochemistry of heterogeneous catalytic hydrogenation is that exchange of hydrogens takes place, as can be shown by hydrogenation with deuterium.²⁹⁸ Thus deuteration of ethylene produced all the possible deuterated ethylenes and ethanes (even C_2H_6), as well as HD.²⁹⁹ With 2-butene, it was found that double-bond migration, cis-trans isomerization, and even exchange of hydrogen with groups not on the double bond could occur; e.g., $\text{C}_4\text{H}_2\text{D}_8$ and C_4HD_9 were detected on treatment of *cis*-2-butene with deuterium and a catalyst.³⁰⁰ Indeed, *alkanes*

²⁸⁷Brown; Murray *Tetrahedron* **1986**, *42*, 5497; Kabalka; Newton; Jacobus *J. Org. Chem.* **1979**, *44*, 4185.

²⁸⁸Weinheimer; Marisco *J. Org. Chem.* **1962**, *27*, 1926.

²⁸⁹Brown; Zweifel *J. Am. Chem. Soc.* **1959**, *81*, 1512.

²⁹⁰Miyake; Kondo *Angew. Chem. Int. Ed. Engl.* **1968**, *7*, 631 [*Angew. Chem.* **80**, 663]. For other methods, with references, see Ref. 133, p. 211.

²⁹¹For a review, see Schuster; Coppola, Ref. 95, pp. 57-61.

²⁹²Gardner; Narayana *J. Org. Chem.* **1961**, *26*, 3518; Vaidyanathaswamy; Joshi; Devaprabhakara *Tetrahedron Lett.* **1971**, 2075.

²⁹³Montury; Goré *Tetrahedron Lett.* **1980**, *21*, 51.

²⁹⁴Bhagwat; Devaprabhakara *Tetrahedron Lett.* **1972**, 1391.

²⁹⁵For a review of homogeneous hydrogenation directed to only one face of a substrate molecule, see Brown *Angew. Chem. Int. Ed. Engl.* **1987**, *26*, 190-203 [*Angew. Chem.* **99**, 169-182].

²⁹⁶Holme; Jones; Whiting *Chem. Ind. (London)* **1956**, 928.

²⁹⁷For a catalyst that leads to trans olefins, see Burch; Muettterties; Teller; Williams *J. Am. Chem. Soc.* **1982**, *104*, 4257.

²⁹⁸For a review of the use of deuterium to study the mechanism of heterogeneous organic catalysis, see Gudkov *Russ. Chem. Rev.* **1986**, *55*, 259-270.

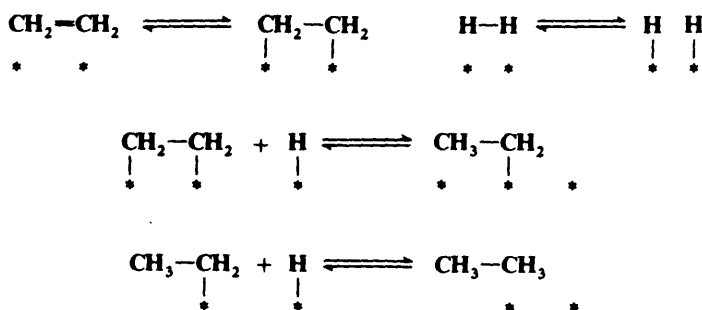
²⁹⁹Turkevich; Schissler; Irsa *J. Phys. Chem.* **1951**, *55*, 1078.

³⁰⁰Wilson; Otvos; Stevenson; Wagner *Ind. Eng. Chem.* **1953**, *45*, 1480.

have been found to exchange with deuterium over a catalyst,³⁰¹ and even without deuterium, e.g., $\text{CH}_4 + \text{CD}_4 \rightarrow \text{CHD}_3 + \text{CH}_3\text{D}$ in the gas phase, with a catalyst. All this makes it difficult to investigate the stereochemistry of heterogeneous catalytic hydrogenation.

Catalytic hydrogenation of triple bonds and the reaction with DIBALH usually give the cis olefin. Most of the other methods of triple-bond reduction lead to the more thermodynamically stable trans olefin. However, this is not the case with the method involving hydrolysis of boranes or with the reductions with activated zinc, hydrazine, or $\text{NH}_2\text{OSO}_3\text{H}$, which also give the cis products.

The mechanism of the heterogenous catalytic hydrogenation of double bonds is not thoroughly understood because it is a very difficult reaction to study.³⁰² Because the reaction is heterogeneous, kinetic data, though easy to obtain (measurement of decreasing hydrogen pressure), are difficult to interpret. Furthermore, there are the difficulties caused by the aforementioned hydrogen exchange. The currently accepted mechanism for the common two-phase reaction was originally proposed in 1934.³⁰³ According to this, the olefin is adsorbed onto the surface of the metal, though the nature of the actual bonding is unknown,³⁰⁴



despite many attempts to elucidate it.³⁰⁵ The metallic site is usually indicated by an asterisk. For steric reasons it is apparent that adsorption of the olefin takes place with its less-hindered side attached to the catalyst surface. The fact that addition of hydrogen is generally also from the less-hindered side indicates that the hydrogen too is probably adsorbed on the catalyst surface before it reacts with the olefin. It is likely that the H_2 molecule is cleaved to hydrogen atoms in the act of being adsorbed. It has been shown that platinum catalyzes homolytic cleavage of hydrogen molecules.³⁰⁶ In the second step one of the adsorbed hydrogen atoms becomes attached to a carbon atom, creating in effect, an alkyl radical (which is still bound to the catalyst though only by one bond) and two vacant catalyst sites. Finally, another hydrogen atom (not necessarily the one originally connected to the first hydrogen) combines with the radical to give the reaction product, freed from the catalyst surface, and two more vacant sites. All the various side reactions, including hydrogen exchange and isomerism, can be explained by this type of process. For example, Figure 15.1 shows the

³⁰¹For a review, see Gudkov; Balandin *Russ. Chem. Rev.* **1966**, *35*, 756-761. For an example of intramolecular exchange, see Lebrilla; Maier *Tetrahedron Lett.* **1983**, *24*, 1119. See also Poretti; Gümamm *Helv. Chim. Acta* **1985**, *68*, 1160.

³⁰²For reviews, see Webb, in Bamford; Tipper *Comprehensive Chemical Kinetics*, vol. 20; Elsevier: New York, 1978, pp. 1-121; Clarke; Rooney *Adv. Catal.* **1976**, *25*, 125-183; Siegel *Adv. Catal.* **1966**, *16*, 123-177; Burwell *Chem. Eng. News* **1966**, *44*(34), 56-67.

³⁰³Horiuti; Polanyi *Trans. Faraday Soc.* **1934**, *30*, 1164.

³⁰⁴See, for example, Burwell; Schrage *J. Am. Chem. Soc.* **1965**, *87*, 5234.

³⁰⁵See, for example, McKee *J. Am. Chem. Soc.* **1962**, *84*, 1109; Ledoux *Nouv. J. Chim.* **1978**, *2*, 9; Bautista; Campelo; García; Guardado; Luna; Marinas *J. Chem. Soc., Perkin Trans. 2* **1989**, 493.

³⁰⁶Krasna *J. Am. Chem. Soc.* **1961**, *83*, 289.

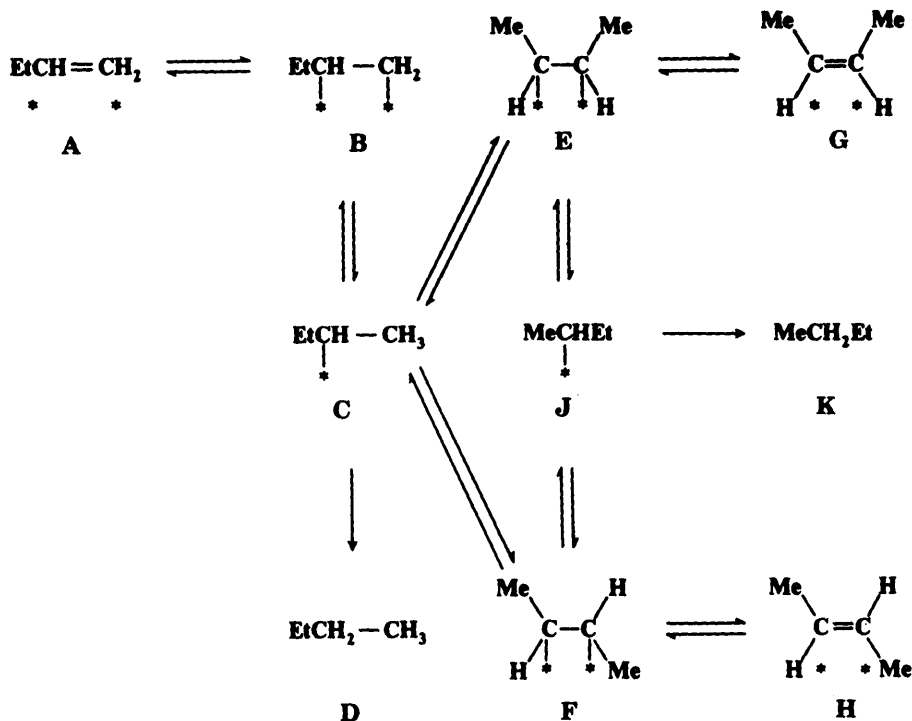
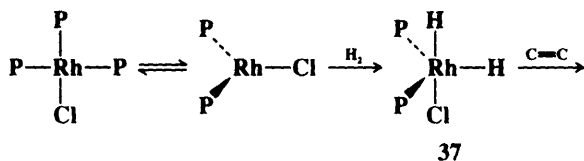


FIGURE 15.1 Steps in the hydrogenation of 1-butene.

steps that may be occurring in hydrogenation of 1-butene.³⁰⁷ In this scheme the normal reaction is represented by $A \rightarrow B \rightarrow C \rightarrow D$, double-bond migration by $A \rightarrow B \rightarrow C \rightarrow E \rightarrow G$, cis-trans isomerization by $H \rightarrow F \rightarrow C \rightarrow E \rightarrow G$, and hydrogen exchange by $A \rightarrow B \rightarrow C \rightarrow E \rightarrow J \rightarrow K$. Although this mechanism is satisfactory as far as it goes,³⁰⁸ there are still questions it does not answer, among them questions³⁰⁹ involving the nature of the asterisk, the nature of the bonding, and the differences caused by the differing nature of each catalyst.³¹⁰

The mechanism of homogeneous hydrogenation³¹¹ catalyzed by $\text{RhCl}(\text{PH}_3\text{P})_3$ ³¹² involves



³⁰⁷Smith; Burwell *J. Am. Chem. Soc.* **1962**, *84*, 925.

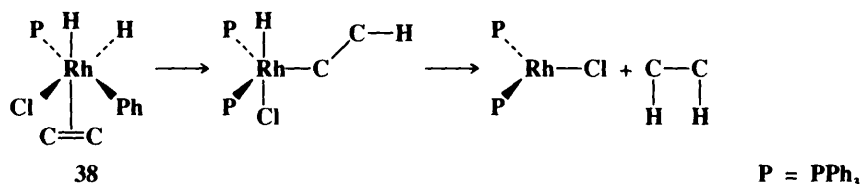
³⁰⁸A different mechanism has been proposed by Zaera; Somorjai *J. Am. Chem. Soc.* **1984**, *106*, 2288, but there is evidence against it: Beebe; Yates *J. Am. Chem. Soc.* **1986**, *108*, 663. See also Thomson; Webb *J. Chem. Soc., Chem. Commun.* **1976**, 526.

³⁰⁹For discussions, see Augustine; Yaghmaie; Van Peppen *J. Org. Chem.* **1984**, *49*, 1865; Maier *Angew. Chem. Int. Ed. Engl.* **1989**, *28*, 135-145 [*Angew. Chem.* **101**, 135-146].

³¹⁰For a study of the detailed structure of Lindlar catalysts (which were shown to consist of seven distinct chemical phases), see Schlögl; Noack; Zbinden; Reller *Helv. Chim. Acta* **1987**, *70*, 627.

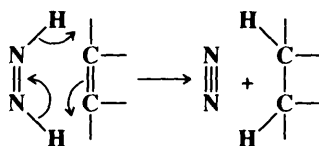
³¹¹For reviews, see Crabtree *Organometallic Chemistry of the Transition Metals*; Wiley: New York, 1988, pp. 190-200; Jardine, in Hartley, Ref. 218, vol. 4, pp. 1049-1071.

³¹²Osborn; Jardine; Young; Wilkinson, Ref. 224; Jardine; Osborn; Wilkinson *J. Chem. Soc. A* **1967**, 1574; Montelatici; van der Ent; Osborn; Wilkinson *J. Chem. Soc. A* **1968**, 1054; Wink; Ford *J. Am. Chem. Soc.* **1985**, *107*, 1794; Koga; Daniel; Han; Fu; Morokuma *J. Am. Chem. Soc.* **1987**, *109*, 3455.



reaction of the catalyst with hydrogen to form a metal hydride $(\text{PPh}_3)_2\text{RhH}_2\text{Cl}$ (**37**), which rapidly transfers two hydrogen atoms to the alkene. The intermediate **37** can be isolated. If a mixture of H_2 and D_2 is used, the product contains only dideuterated and nondeuterated compounds; no monodeuterated products are found, indicating that (unlike the case of heterogeneous catalysis) H_2 or D_2 has been added to one olefin molecule and that no exchange takes place.³¹² Although conversion of **38** to the products takes place in two steps,³¹³ the addition of H_2 to the double bond is syn.

In the above-mentioned reactions with hydrazine and hydroxylamine, the actual reducing species is diimide $\text{NH}=\text{NH}$, which is formed from N_2H_4 by the oxidizing agent and from NH_2OH by the ethyl acetate.³¹⁴ Although both the syn and anti forms of diimide are produced, only the syn form reduces the double bond,³¹⁵ at least in part by a cyclic mechanism:³¹⁶



The addition is therefore stereospecifically syn³¹⁷ and, like catalytic hydrogenation, generally takes place from the less-hindered side of a double bond, though not much discrimination in this respect is observed where the difference in bulk effects is small.³¹⁸ Diimide reductions are most successful with symmetrical multiple bonds ($\text{C}=\text{C}$, $\text{C}\equiv\text{C}$, $\text{N}=\text{N}$) and are not useful for those inherently polar ($\text{C}\equiv\text{N}$, $\text{C}=\text{N}$, $\text{C}=\text{O}$, etc.). Diimide is not stable enough for isolation at ordinary temperatures, though it has been prepared³¹⁹ as a yellow solid at -196°C .

When double bonds are reduced by lithium in ammonia or amines, the mechanism is similar to that of the Birch reduction (**5-10**).³²⁰ The reduction with trifluoroacetic acid and Et_3SiH has an ionic mechanism, with H^+ coming in from the acid and H^- from the silane.²⁴⁸ In accord with this mechanism, the reaction can be applied only to those olefins which when

³¹³Biellmann; Jung *J. Am. Chem. Soc.* **1968**, *90*, 1673; Hussey; Takeuchi *J. Am. Chem. Soc.* **1969**, *91*, 672; Heathcock; Poulter *Tetrahedron Lett.* **1969**, 2755; Smith; Shuford *Tetrahedron Lett.* **1970**, 525; Atkinson; Luke *Can. J. Chem.* **1970**, *48*, 3580.

³¹⁴For reviews of hydrogenations with diimide, see Pasto; Taylor *Org. React.* **1991**, *40*, 91-155; Miller *J. Chem. Educ.* **1965**, *42*, 254-259; House, Ref. 144, pp. 248-256. For reviews of diimides, see Back *Rev. Chem. Intermed.* **1984**, *5*, 293-323; Hünig; Müller; Thier *Angew. Chem. Int. Ed. Engl.* **1965**, *4*, 271-280 [*Angew. Chem.* **77**, 368-377].

³¹⁵Aylward; Sawistowska *J. Chem. Soc.* **1964**, 1435.

³¹⁶Ref. 249; van Tameelen; Dewey; Lease; Pirkle *J. Am. Chem. Soc.* **1961**, *83*, 4302; Willis; Back; Parsons; Purdon *J. Am. Chem. Soc.* **1977**, *99*, 4451.

³¹⁷Corey; Pasto; Mock *J. Am. Chem. Soc.* **1961**, *83*, 2957.

³¹⁸van Tameelen; Timmons *J. Am. Chem. Soc.* **1962**, *84*, 1067.

³¹⁹Wiberg; Fischer; Bachhuber *Chem. Ber.* **1974**, *107*, 1456. *Angew. Chem. Int. Ed. Engl.* **1977**, *16*, 780 [*Angew. Chem.* **89**, 828]. See also Trombetti *Can. J. Phys.* **1968**, *46*, 1005; Bondybey; Nibler *J. Chem. Phys.* **1973**, *58*, 2125; Craig; Kliever; Shih *J. Am. Chem. Soc.* **1979**, *101*, 2480.

³²⁰For a review of the steric course of this reaction, see Toromanoff *Bull. Soc. Chim. Fr.* **1987**, 893-901. For a review of this reaction as applied to α,β -unsaturated ketones, see Russell, in Patai; Rappoport, Ref. 37, pt. 2, pp. 471-512.

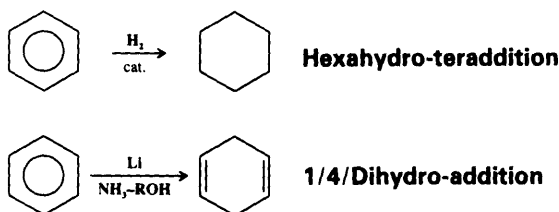
protonated can form a tertiary carbocation or one stabilized in some other way, e.g., by α OR substitution.³²¹ It has been shown, by the detection of CIDNP, that reduction of α -methylstyrene by hydridopentacarbonylmanganese(I) $\text{HMn}(\text{CO})_5$ involves free-radical addition.³²²

The occurrence of hydrogen exchange and double-bond migration in heterogeneous catalytic hydrogenation means that the hydrogenation does not necessarily take place by straightforward addition of two hydrogen atoms at the site of the original double bond. Consequently, this method is not synthetically useful for adding D_2 to a double or triple bond in a regioselective or stereospecific manner. However, this objective can be achieved (with syn addition) by a homogeneous catalytic hydrogenation, which usually adds D_2 without scrambling³²³ or by the use of one of the diimide methods.³¹⁷ Deuterium can also be regioselectively added by the hydroboration-reduction procedure previously mentioned.

Reductions of double and triple bonds are found at OS I, 101, 311; II, 191, 491; III, 385, 586, 742, 794; IV, 136, 298, 302, 304, 408, 887; V, 16, 96, 277, 281, 993; VI, 68, 459; VII, 226, 287, 524; 68, 64, 182.

Catalysts and apparatus for hydrogenation are found at OS I, 61, 463; II, 142; III, 176, 181, 685; V, 880.

5-10 Hydrogenation of Aromatic Rings



Aromatic rings can be reduced by catalytic hydrogenation,³²⁴ but higher temperatures (100 to 200°C) are required than for ordinary double bonds.³²⁵ Though the reaction is usually carried out with heterogeneous catalysts, homogeneous catalysts have also been used; conditions are much milder with these.³²⁶ Mild conditions are also successful in hydrogenations with phase transfer catalysts.³²⁷ Many functional groups, such as OH, O^- , COOH, COOR, NH_2 , etc., do not interfere with the reaction, but some groups may be preferentially reduced. Among these are CH_2OH groups, which undergo hydrogenolysis to CH_3 (0-78). Phenols may be reduced to cyclohexanones, presumably through the enol. Heterocyclic compounds are often reduced. Thus furan gives tetrahydrofuran. With benzene rings it is usually impossible to stop the reaction after only one or two bonds have been reduced, since olefins are more easily reduced than aromatic rings.³²⁸ Thus, 1 mole of benzene, treated with 1

³²¹Parnes; Bolestova; Kursanov *Bull. Acad. Sci. USSR, Div. Chem. Sci.* **1972**, 21, 1927.

³²²Sweany; Halpern *J. Am. Chem. Soc.* **1977**, 99, 8335. See also Thomas; Shackleton; Wright; Gillis; Colpa; Baird *J. Chem. Soc., Chem. Commun.* **1986**, 312; Garst; Bockman; Batlaw *J. Am. Chem. Soc.* **1986**, 108, 1689; Bullock; Samsel *J. Am. Chem. Soc.* **1987**, 109, 6542.

³²³Biellmann; Liesenfelt *Bull. Soc. Chim. Fr.* **1966**, 4029; Birch; Walker *Tetrahedron Lett.* **1966**, 4939; *J. Chem. Soc. C* **1966**, 1894; Morandi; Jensen *J. Org. Chem.* **1969**, 34, 1889. See, however, Atkinson; Luke, Ref. 313.

³²⁴For reviews, see Karakhanov; Dedov; Loktev *Russ. Chem. Rev.* **1985**, 54, 171-184; Weitkamp *Adv. Catal.* **1968**, 18, 1-110 (for naphthalenes).

³²⁵For a highly active heterogeneous Rh catalyst, see Timmer; Thewissen; Meinema; *Bulten Recl. Trav. Chim. Pays-Bas* **1990**, 109, 87.

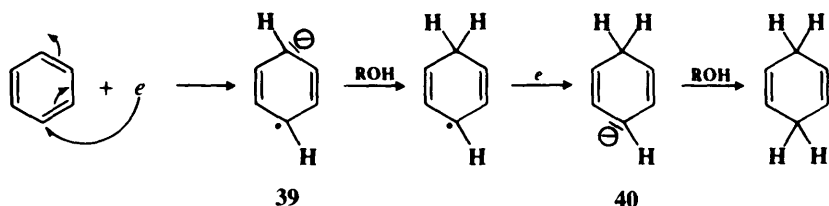
³²⁶For reviews, see Bennett *CHEMTECH* **1980**, 10, 444-446; Muetterties; Bleeke *Acc. Chem. Res.* **1979**, 12, 324-331.

³²⁷Januszkiewicz; Alper *Organometallics* **1983**, 2, 1055.

³²⁸For an indirect method of hydrogenating benzene to cyclohexene, see Harman; Taube *J. Am. Chem. Soc.* **1988**, 110, 7906.

mole of hydrogen, gives no cyclohexadiene or cyclohexene but $\frac{1}{3}$ mole of cyclohexane and $\frac{2}{3}$ mole of recovered benzene. This is not true for all aromatic systems. With phenanthrene, for example, it is easy to stop after only the 9,10-bond has been reduced (see p. 43).

When aromatic rings are reduced by lithium (or potassium or sodium) in liquid ammonia (such reductions are known as *dissolving metal reductions*), usually in the presence of an alcohol (often ethyl, isopropyl, or *t*-butyl alcohol), 1,4 addition of hydrogen takes place and nonconjugated cyclohexadienes are produced.³²⁹ This reaction is called the *Birch reduction*.³³⁰ Ammonia obtained commercially often has iron salts as impurities that lower the yield in the Birch reduction. Therefore it is often necessary to distill the ammonia. When substituted aromatic compounds are subjected to the Birch reduction, electron-donating groups such as alkyl or alkoxy decrease the rate of the reaction and are generally found on the nonreduced positions of the product. For example, anisole gives 1-methoxy-1,4-cyclohexadiene, not 3-methoxy-1,4-cyclohexadiene. On the other hand, electron-withdrawing groups such as COOH or CONH₂ increase the reaction rate and are found on the reduced positions of the product.³³¹ The mechanism involves solvated electrons,³³² which are transferred from the metal to the solvent and thence to the ring:³³³



The sodium becomes oxidized to Na⁺ and creates a radical ion (39).³³⁴ There is a great deal of evidence from esr spectra for these species.³³⁵ The radical ion accepts a proton from the alcohol to give a radical, which is reduced to a carbanion by another sodium atom. Finally, 40 accepts another proton. Thus the function of the alcohol is to supply protons, since with most substrates ammonia is not acidic enough for this purpose. In the absence of the alcohol, products arising from dimerization of 39 are frequently obtained. There is evidence³³⁶ at least with some substrates, e.g., biphenyl, that the radical ion corresponding to 39 is converted to the carbanion corresponding to 40 by a different pathway, in which the order of the steps is reversed: first a second electron is gained to give a dianion,³³⁴ which then acquires a proton, producing the intermediate corresponding to 40.

³²⁹For a procedure that converts benzene to pure 1,4-cyclohexadiene, see Brandsma; van Soolingen; Andringa *Synth. Commun.* **1990**, 20, 2165.

³³⁰For a monograph, see Akhrem; Reshotova; Titov *Birch Reduction of Aromatic Compounds*; Plenum: New York, 1972. For reviews, see Rabideau *Tetrahedron* **1989**, 45, 1579-1603; Birch; Subba Rao *Adv. Chem. Org. Chem.* **1972**, 8, 1-65; Kaiser *Synthesis* **1972**, 391-415; Harvey *Synthesis* **1970**, 161-172; House, Ref. 144, pp. 145-150, 173-209; Hüchel *Fortschr. Chem. Forsch* **1966**, 6, 197-250; Smith, in *Augustine Reduction Techniques and Applications in Organic Synthesis*; Marcel Dekker: New York, 1968, pp. 95-170.

³³¹These regioselectivities have generally been explained by molecular-orbital considerations regarding the intermediates involved. For example, see Birch; Hinde; Radom *J. Am. Chem. Soc.* **1980**, 102, 3370, 4074, 6430; **1981**, 103, 284; Zimmerman; Wang *J. Am. Chem. Soc.* **1990**, 112, 1280. For methods of reversing the regioselectivities, see Epling; Florio *Tetrahedron Lett.* **1986**, 27, 1469; Rabideau; Karrick *Tetrahedron Lett.* **1987**, 28, 2481.

³³²For reviews of solvated electrons and related topics, see Dye *Prog. Inorg. Chem.* **1984**, 32, 327-441; Alpatova; Kristalik; Pleskov *Top. Curr. Chem.* **1987**, 138, 149-219.

³³³Birch; Nasipuri *Tetrahedron* **1959**, 6, 148.

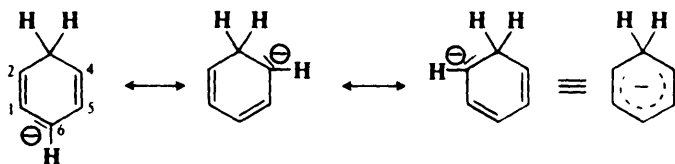
³³⁴For a review of radical ions and diions generated from aromatic compounds, see Holy *Chem. Rev.* **1974**, 74, 243-277.

³³⁵For example, see Jones, in Kaiser; Kevan *Radical Ions*; Wiley: New York, 1968, pp. 245-274; Bowers *Adv. Magn. Reson.* **1965**, 1, 317-396; Carrington *Q. Rev., Chem. Soc.* **1963**, 17, 67-99.

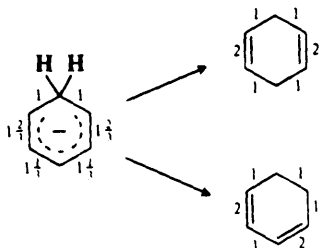
³³⁶Lindow; Cortez; Harvey *J. Am. Chem. Soc.* **1972**, 94, 5406; Rabideau; Peters; Huser *J. Org. Chem.* **1981**, 46, 1593.

Ordinary olefins are usually unaffected by Birch-reduction conditions, and double bonds may be present in the molecule if they are not conjugated with the ring. However, phenylated olefins, internal alkynes (p. 775), and conjugated olefins (with C=C or C=O) are reduced under these conditions.

It may be noted that **40** is a resonance hybrid; i.e., we can write two additional canonical forms:



The question therefore arises: Why does the carbanion pick up a proton at the 6 position to give the 1,4-diene? Why not at the 2 position to give the 1,3-diene?³³⁷ An answer to this question has been proposed by Hine, who has suggested that this case is an illustration of the operation of the *principle of least motion*.³³⁸ According to this principle, "those elementary reactions will be favored that involve the least change in atomic position and electronic configuration."³³⁸ The principle can be applied to the case at hand in the following manner (simplified): The valence-bond bond orders (p. 26) for the six carbon-carbon bonds (on the assumption that each of the three forms contributes equally) are (going around the ring) $1\frac{1}{3}$, 1, 1, $1\frac{1}{3}$, $1\frac{1}{3}$, and $1\frac{1}{3}$. When the carbanion is converted to the diene, these bond orders change as follows:



It can be seen that the two bonds whose bond order is 1 are unchanged in the two products, but for the other four bonds there is a change. If the 1,4-diene is formed, the change is $\frac{1}{3} + \frac{1}{3} + \frac{1}{3} + \frac{1}{3}$, while formation of the 1,3-diene requires a change of $\frac{1}{3} + \frac{2}{3} + \frac{2}{3} + \frac{1}{3}$. Since a greater change is required to form the 1,3-diene, the principle of least motion predicts formation of the 1,4-diene. This may not be the only factor, because the ¹³C nmr spectrum of **40** shows that the 6 position has a somewhat greater electron density than the 2 position, which presumably would make the former more attractive to a proton.³³⁹

Reduction of aromatic rings with lithium³⁴⁰ or calcium³⁴¹ in amines (instead of ammonia)

³³⁷For a discussion of this question, see Rabideau; Huser *J. Org. Chem.* **1983**, *48*, 4266.

³³⁸Hine *J. Org. Chem.* **1966**, *31*, 1236. For a review of this principle, see Hine *Adv. Phys. Org. Chem.* **1977**, *15*, 1-61. See also Tec *J. Am. Chem. Soc.* **1969**, *91*, 7144; Jochum; Gasciger; Ugi *Angew. Chem. Int. Ed. Engl.* **1980**, *19*, 495-505 [*Angew. Chem.* **92**, 503-513].

³³⁹Bates; Brenner; Cole; Davidson; Forsythe; McCombs; Roth *J. Am. Chem. Soc.* **1973**, *95*, 926.

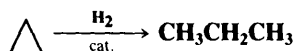
³⁴⁰Benkeser; Robinson; Sauve; Thomas *J. Am. Chem. Soc.* **1955**, *77*, 3230; Reggel; Friedel; Wender *J. Org. Chem.* **1957**, *22*, 891; Benkeser; Agnihotri; Burrous; Kaiser; Mallan; Ryan *J. Org. Chem.* **1964**, *29*, 1313; Kwart; Conley *J. Org. Chem.* **1973**, *38*, 2011.

³⁴¹Benkeser; Kang *J. Org. Chem.* **1979**, *44*, 3737; Benkeser; Belmonte; Kang *J. Org. Chem.* **1983**, *48*, 2796. See also Benkeser; Laugal; Rappa *Tetrahedron Lett.* **1984**, *25*, 2089.

proceeds further and cyclohexenes are obtained. It is thus possible to reduce a benzene ring, by proper choice of reagent, so that one, two, or all three double bonds are reduced.³⁴²

OS **I**, 99, 499; **II**, 566; **III**, 278, 742; **IV**, 313, 887, 903; **V**, 398, 400, 467, 591, 670, 743, 989; **VI**, 371, 395, 461, 731, 852, 856, 996; **VII**, 249.

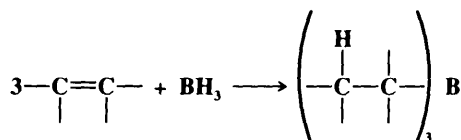
5-11 Reductive Cleavage of Cyclopropanes



Cyclopropanes can be cleaved by catalytic hydrogenolysis.³⁴³ Among the catalysts used have been Ni, Pd, and Pt. The reaction can often be run under mild conditions.³⁴⁴ Certain cyclopropane rings, especially cyclopropyl ketones and aryl-substituted cyclopropanes,³⁴⁵ can be reductively cleaved by an alkali metal (generally Na or Li) in liquid ammonia.³⁴⁶

F. A Metal on the Other Side

5-12 Hydroboration



When olefins are treated with borane³⁴⁷ in ether solvents, BH₃ adds across the double bond.³⁴⁸ Borane cannot be prepared as a stable pure compound³⁴⁹ (it dimerizes to diborane B₂H₆), but it is commercially available in the form of complexes with THF, Me₂S,³⁵⁰ phosphines, or tertiary amines. The olefins can be treated with a solution of one of these complexes (THF-BH₃ reacts at 0°C and is the most convenient to use; R₃N-BH₃ generally require temperatures of about 100°C; however, the latter can be prepared as air-stable liquids or solids, while the former can only be used as relatively dilute solutions in THF and are decomposed by moisture in air) or with a mixture of NaBH₄ and BF₃ etherate, which generates borane in situ.³⁵¹ Ordinarily, the process cannot be stopped with the addition of one molecule of BH₃ because the resulting RBH₂ adds to another molecule of olefin to give R₂BH, which in turn adds to a third olefin molecule, so that the isolated product is a trialkylborane R₃B. The reaction can be performed on alkenes with one to four substituents,

³⁴²One, two, or all three double bonds of certain aromatic nitrogen heterocycles can be reduced with metallic hydrides such as NaBH₄ or LiAlH₄. For a review, see Keay *Adv. Heterocycl. Chem.* **1986**, *39*, 1-77.

³⁴³For reviews, see Charton, *Ref.* 115, pp. 588-592; Newham *Chem. Rev.* **1963**, *63*, 123-137; Rylander *Catalytic Hydrogenation over Platinum Metals*, *Ref.* 218, pp. 469-474.

³⁴⁴See, for example, Woodworth; Buss; Schleyer *Chem. Commun.* **1968**, 569.

³⁴⁵See, for example, Walborsky; Pierce *J. Org. Chem.* **1968**, *33*, 4102; Walborsky; Aronoff; Schulman *J. Org. Chem.* **1970**, *36*, 1036.

³⁴⁶For a review, see Staley *Sel. Org. Transform.* **1972**, *2*, 309-348.

³⁴⁷For a review of this reagent, see Lane, in Pizey, *Ref.* 146, vol. 3, 1977, pp. 1-191.

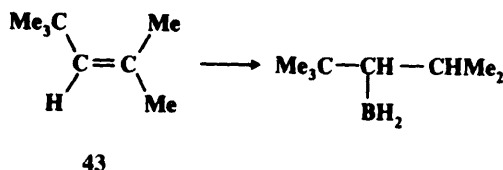
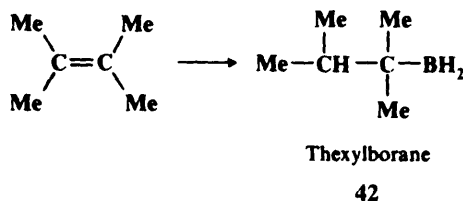
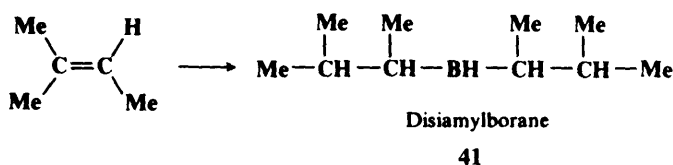
³⁴⁸For books on this reaction and its manifold applications, see Pelter; Smith; Brown *Borane Reagents*; Academic Press: New York, 1988; Brown *Boranes in Organic Chemistry*; Cornell University Press: Ithaca, NY, 1972; *Organic Syntheses Via Boranes*; Wiley: New York, 1975; Cragg *Organoboranes in Organic Synthesis*; Marcel Dekker: New York, 1973. For reviews, see Matteson, in Hartley, *Ref.* 218, vol. 4, pp. 307-409, pp. 315-337; Smith *Chem. Ind. (London)* **1987**, 603-611; Brown; Vara Prasad *Heterocycles* **1987**, *25*, 641-567; Suzuki; Dhillon *Top. Curr. Chem.* **1986**, *130*, 23-88.

³⁴⁹Mappes; Fehlner *J. Am. Chem. Soc.* **1970**, *92*, 1562; Fehlner *J. Am. Chem. Soc.* **1971**, *93*, 6366.

³⁵⁰For a review of BH₃·SMe₂, see Hutchins; Cistone *Org. Prep. Proced. Int.* **1981**, *13*, 225-240.

³⁵¹For a list of hydroborating reagents, with references, see *Ref.* 133, pp. 497-499.

including cyclic olefins, but when the olefin is moderately hindered, the product is the dialkylborane R_2BH or even the monoalkylborane RBH_2 .³⁵² For example, **41** (*disiamylborane*), **42** (*thexylborane*),³⁵³ and **44** have been prepared in this manner. Monoalkylboranes



RBH_2 (which can be prepared from hindered olefins, as above) and dialkylboranes R_2BH also add to olefins, to give the mixed trialkylboranes RR'_2B and $R_2R'B$, respectively. Surprisingly, when methylborane $MeBH_2$,³⁵⁴ which is not a bulky molecule, adds to olefins in the solvent THF, the reaction can be stopped with one addition to give the dialkylboranes $RMeBH$.³⁵⁵ Reaction of this with a second olefin produces the trialkylborane $RR'MeB$.³⁵⁶ Other monoalkylboranes, *i*-PrBH₂, *n*-BuBH₂, *s*-BuBH₂, and *t*-BuBH₂, behave similarly with internal olefins, but not with olefins of the type $RCH=CH_2$.³⁵⁷

In all cases the boron goes to the side of the double bond that has more hydrogens, whether the substituents are aryl or alkyl.³⁵⁸ Thus the reaction of **43** with BH_3 gives 98% **44** and only 2% of the other product. This actually follows Markovnikov's rule, since boron is more positive than hydrogen. However, the regioselectivity is caused mostly by steric factors, though electronic factors also play a part. Studies of the effect of ring substituents on rates and on the direction of attack in hydroboration of substituted styrenes showed that the attack by boron has electrophilic character.³⁵⁹ When both sides of the double bond are

³⁵²Unless coordinated with a strong Lewis base such as a tertiary amine, mono and dialkylboranes actually exist as dimers e.g., $R_2B \begin{array}{c} \diagup \quad \diagdown \\ \text{H} \quad \text{H} \\ \diagdown \quad \diagup \\ \text{BR}_2 \end{array}$; Brown; Klender *Inorg. Chem.* **1962**, *1*, 204.

³⁵³For a review of the chemistry of thexylborane, see Negishi; Brown *Synthesis* **1974**, 77-89.

³⁵⁴Prepared from lithium methylborohydride and HCl; Brown; Cole; Srebnik; Kim *J. Org. Chem.* **1986**, *51*, 4925.

³⁵⁵Srebnik; Cole; Brown *Tetrahedron Lett.* **1987**, *28*, 3771; *J. Org. Chem.* **1990**, *55*, 5051.

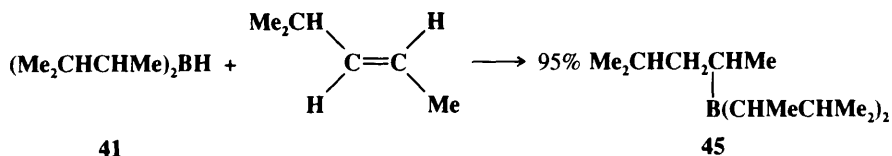
³⁵⁶For a method of synthesis of $RR'R''B$, see Kulkarni; Basavaiah; Zaidlewicz; Brown *Organometallics* **1982**, *1*, 212.

³⁵⁷Srebnik; Cole; Ramachandran; Brown *J. Org. Chem.* **1989**, *54*, 6085.

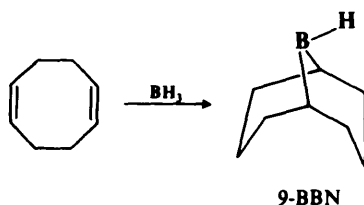
³⁵⁸For a thorough discussion of the regioselectivity with various types of substrate and hydroborating agents, see Cragg, Ref. 348, pp.63-84, 137-197. See also Brown; Vara Prasad; Zee *J. Org. Chem.* **1986**, *51*, 439.

³⁵⁹Brown; Sharp *J. Am. Chem. Soc.* **1966**, *88*, 5851; Klein; Dunkelblum; Wolff *J. Organomet. Chem.* **1967**, *7*, 377. See also Marshall; Prager *Aust. J. Chem.* **1979**, *32*, 1251.

monosubstituted or both disubstituted, about equal amounts of each isomer are obtained. However, it is possible in such cases to make the addition regioselective by the use of a large attacking molecule. For example, treatment of iso-PrCH=CHMe with borane gave 57% of product with boron on the methyl-bearing carbon and 43% of the other, while treatment with **41** gave 95% **45** and only 5% of the other isomer.³⁶⁰



Another reagent with high regioselectivity is 9-borabicyclo[3.3.1]nonane (9-BBN), which is prepared by hydroboration of 1,5-cyclooctadiene:³⁶¹



9-BBN has the advantage that it is stable in air. Borane is quite unselective and attacks all sorts of double bonds. Disiamylborane, 9-BBN, and similar molecules are far more selective and preferentially attack less-hindered bonds, so it is often possible to hydroborate one double bond in a molecule and leave others unaffected or to hydroborate one olefin in the presence of a less reactive olefin.³⁶² For example, 1-pentene can be removed from a mixture of 1- and 2-pentenes, and a cis olefin can be selectively hydroborated in a mixture of the cis and trans isomers.

A hydroboration reagent with greater regioselectivity than BH_3 (for terminal alkenes or those of the form $\text{R}_2\text{C}=\text{CHR}$) is monochloroborane³⁶³ BH_2Cl coordinated with dimethyl sulfide (the hydroboration product is a dialkylchloroborane R_2BCl).³⁶⁴ For example, 1-hexene gave 94% of the anti-Markovnikov product with $\text{BH}_3\text{-THF}$, but 99.2% with $\text{BH}_2\text{Cl-SMe}_2$. Treatment of alkenes with dichloroborane-dimethyl sulfide $\text{BHCl}_2\text{-SMe}_2$ in the presence of BF_3 ³⁶⁵ or with BCl_3 and Me_3SiH ³⁶⁶ gives alkylchloroboranes RBCl_2 .

An important use of the hydroboration reaction is that alkylboranes, when oxidized with hydrogen peroxide and NaOH , are converted to alcohols (**2-28**). This is therefore an indirect way of adding H_2O across a double bond in an anti-Markovnikov manner. However, boranes undergo many other reactions as well. Among other things, they react with α -halo carbonyl compounds to give alkylated products (**0-99**), with α,β -unsaturated carbonyl compounds to give Michael-type addition of R and H (**5-19**), with CO to give alcohols and ketones (**8-24**

³⁶⁰Brown; Zweifel *J. Am. Chem. Soc.* **1961**, 83, 1241.

³⁶¹See Knights; Brown *J. Am. Chem. Soc.* **1968**, 90, 5280, 5281; Brown; Chen *J. Org. Chem.* **1981**, 46, 3978; Soderquist; Brown *J. Org. Chem.* **1981**, 46, 4599.

³⁶²Brown; Mocrifkofer *J. Am. Chem. Soc.* **1963**, 85, 2063; Zweifel; Brown *J. Am. Chem. Soc.* **1963**, 85, 2066; Zweifel; Ayyangar; Brown *J. Am. Chem. Soc.* **1963**, 85, 2072; Ref. 359.

³⁶³For a review of haloboranes, see Brown; Kulkarni *J. Organomet. Chem.* **1982**, 239, 23-41.

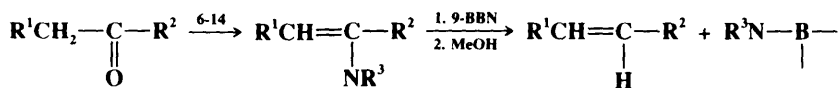
³⁶⁴Brown; Ravindran; Kulkarni *J. Org. Chem.* **1979**, 44, 2417.

³⁶⁵Brown; Ravindran; Kulkarni *J. Org. Chem.* **1980**, 45, 384; Brown; Racherla *J. Org. Chem.* **1986**, 51, 895.

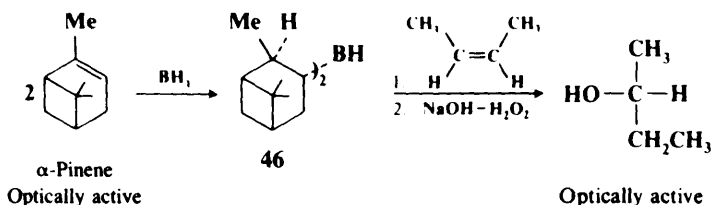
³⁶⁶Undararajan; Matteson *J. Org. Chem.* **1990**, 55, 2274.

to **8-26**); they can be reduced with carboxylic acids, providing an indirect method for reduction of double bonds (**5-9**), or they can be oxidized with chromic acid or pyridinium chlorochromate to give ketones³⁶⁷ or aldehydes (from terminal olefins),³⁶⁸ dimerized with silver nitrate and NaOH (**4-34**), isomerized (**8-11**), or converted to amines (**2-31**) or halides (**2-30**). They are thus useful intermediates for the preparation of a wide variety of compounds.

Such functional groups as OR, OH, NH₂, SMe, halogen, and COOR may be present in the molecule,³⁶⁹ but not groups that are reducible by borane. Hydroboration of enamines with 9-BBN provides an indirect method for reducing an aldehyde or ketone to an alkene, e.g.,³⁷⁰



Use of the reagent diisopinocampheylborane **46** (prepared by treating optically active α -pinene with BH₃) results in enantioselective hydroboration-oxidation.³⁷¹ Alcohols with op-



tical purities as high as 98% have been obtained in this way.³⁷² However, **46** does not give good results with even moderately hindered alkenes; a better reagent for these compounds is isopinocampheylborane³⁷³ though optical yields are lower. Limonylborane,³⁷⁴ 2- and 4-dicaranylboranes,³⁷⁵ a myrtanylborane,³⁷⁶ and dilongifolylborane³⁷⁷ have also been used. The method has been improved³⁷⁸ by synthesizing the chiral isopinocampheylborane in the presence of tetramethylethylenediamine (TMED), whereupon a TMED-isopinocampheylborane adduct is formed. This adduct,³⁷⁹ in Et₂O, reacts with a prochiral alkene to give a dialkylborane RBHR' (R' = isocampheyl). The RBHR' crystallizes from THF in 99–100% optical

³⁶⁷Brown; Garg *J. Am. Chem. Soc.* **1961**, *83*, 2951; *Tetrahedron* **1986**, *42*, 5511; Rao; Devaprabhakara; Chandrasekaran *J. Organomet. Chem.* **1978**, *162*, C9; Parish; Parish; Honda *Synth. Commun.* **1990**, *20*, 3265.

³⁶⁸Brown; Kulkarni; Rao; Patil *Tetrahedron* **1986**, *42*, 5515.

³⁶⁹See, for example, Brown; Unni *J. Am. Chem. Soc.* **1968**, *90*, 2902; Brown; Gallivan *J. Am. Chem. Soc.* **1968**, *90*, 2906; Brown; Sharp *J. Am. Chem. Soc.* **1968**, *90*, 2915.

³⁷⁰Singaram; Rangaishenvi; Brown; Goralski; Hasha *J. Org. Chem.* **1991**, *56*, 1543.

³⁷¹Brown; Ayyangar; Zweifel *J. Am. Chem. Soc.* **1964**, *86*, 397; Brown; Singaram *J. Org. Chem.* **1984**, *49*, 945; Brown; Vara Prasad *J. Am. Chem. Soc.* **1986**, *108*, 2049.

³⁷²For reviews of enantioselective syntheses with organoboranes, see Brown *Chemtracts: Org. Chem.* **1988**, *1*, 77-88; Brown; Singaram *Acc. Chem. Res.* **1988**, *21*, 287-293; *Pure Appl. Chem.* **1987**, *59*, 879-894; Srebniak; Ramachandran *Aldrichimica Acta* **1987**, *20*, 9-24; Matteson. Ref. 348, pp. 381-395; Brown; Jadhav; Singaram *Mod. Synth. Methods* **1986**, *4*, 307-356; Matteson *Synthesis* **1986**, 973-985; Brown; Jadhav, in Morrison. Ref. 232, vol. 2, 1983, pp. 1-43; Brown; Jadhav; Mandal *Tetrahedron* **1981**, *37*, 3547-3587.

³⁷³Brown; Jadhav; Mandal *J. Org. Chem.* **1982**, *47*, 5074. See also Brown; Weissman; Perumal; Dhokte *J. Org. Chem.* **1990**, *55*, 1217.

³⁷⁴Jadhav; Kulkarni *Heterocycles* **1982**, *18*, 169.

³⁷⁵Brown; Vara Prasad; Zaidlewicz *J. Org. Chem.* **1988**, *53*, 2911.

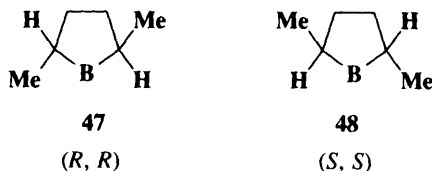
³⁷⁶Kiesgen de Richter; Bonato; Follet; Kamenka *J. Org. Chem.* **1990**, *55*, 2855.

³⁷⁷Jadhav; Brown *J. Org. Chem.* **1981**, *46*, 2988.

³⁷⁸Brown; Singaram *J. Am. Chem. Soc.* **1984**, *106*, 1797; Brown; Gupta; Vara Prasad *Bull. Chem. Soc. Jpn.* **1988**, *61*, 93.

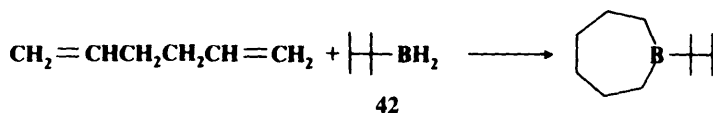
³⁷⁹For the crystal structure of this adduct, see Soderquist; Hwang-Lee; Barnes *Tetrahedron Lett.* **1988**, *29*, 3385.

purity (the other diastereomer remains in solution). The optically pure RBHR' is treated with acetaldehyde to produce α -pinene and optically pure R_2BH , which can be converted to optically pure alcohols or to other products.³⁸⁰ Since both (+) and (-) α -pinene are readily available, both enantiomers can be prepared. The chiral cyclic boranes *trans*-2,5-dimethylborolanes (**47** and **48**) also add enantioselectively to olefins (except olefins of the

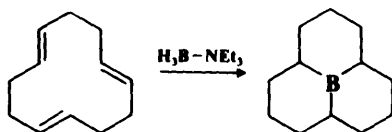


form $RR'C=CH_2$) to give boranes of high optical purity.³⁸¹ When chiral boranes are added to trisubstituted olefins of the form $RR'C=CHR''$, two new chiral centers are created, and, with **47** or **48**, only one of the four possible diastereomers is predominantly produced, in yields greater than 90%.³⁸¹ This has been called *double-asymmetric synthesis*.³⁸²

The double bonds in a conjugated diene are hydroborated separately, i.e., there is no 1,4 addition. However, it is not easy to hydroborate just one of a conjugated system, since conjugated double bonds are less reactive than isolated ones. The xylborane³⁵³ (**42**) is particularly useful for achieving the cyclic hydroboration of dienes, conjugated or nonconjugated,³⁸³ e.g.,



Rings of five, six, or seven members can be formed in this way. Similar cyclization can also be accomplished with other monoalkylboranes and, in some instances, with BH_3 itself.³⁸⁴ One example is the formation of 9-BBN, shown above. Another is conversion of 1,5,9-cyclododecatriene to *perhydro-9b*-boraphenylene:³⁸⁵



Triple bonds³⁸⁶ can be monohydroborated to give vinylic boranes, which can be reduced with carboxylic acids to *cis* alkenes or oxidized and hydrolyzed to aldehydes or ketones. Terminal alkynes give aldehydes by this method, in contrast to the mercuric or acid-catalyzed addition of water discussed at 5-3. However, terminal alkynes give vinylic boranes³⁸⁷ (and

³⁸⁰For another method of preparing optically pure mono- and dialkylboranes, see Brown; Singaram; Cole *J. Am. Chem. Soc.* **1985**, *107*, 460.

³⁸¹Masamune; Kim; Petersen; Sato; Veenstra; Imai *J. Am. Chem. Soc.* **1985**, *107*, 4549.

³⁸²For another enantioselective hydroboration method, see p. 788.

³⁸³Brown; Pfaffenberger *J. Am. Chem. Soc.* **1967**, *89*, 5475; Brown; Negishi *J. Am. Chem. Soc.* **1972**, *94*, 3567.

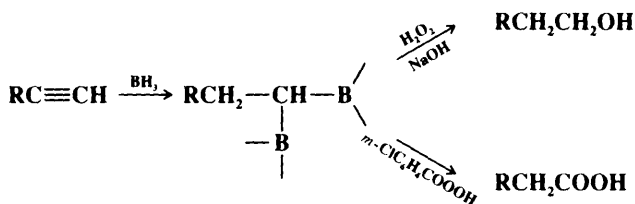
³⁸⁴For a review of cyclic hydroboration, see Brown; Negishi *Tetrahedron* **1977**, *33*, 2331-2357. See also Brown; Pai; Naik *J. Org. Chem.* **1984**, *49*, 1072.

³⁸⁵Rotermund; Köster *Liebigs Ann. Chem.* **1965**, *686*, 153; Brown; Negishi; Dickason *J. Org. Chem.* **1985**, *50*, 520.

³⁸⁶For a review of hydroboration of triple bonds, see Hudrlík; Hudrlík, in Patai, Ref. 70, pt. 1, pp. 203-219.

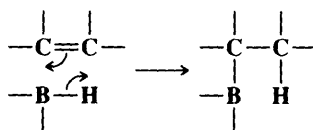
³⁸⁷For a review of the preparation and reactions of vinylic boranes, see Brown; Campbell *Aldrichimica Acta* **1981**, *14*, 1-11.

hence aldehydes) only when treated with a hindered borane such as **41**, **42**, or catecholborane (p. 615),³⁸⁸ or with $\text{BHBr}_2\text{-SMe}_2$.³⁸⁹ The reaction between terminal alkynes and BH_3 produces 1,1-dibora compounds, which can be oxidized either to primary alcohols (with



$\text{NaOH-H}_2\text{O}_2$) or to carboxylic acids (with *m*-chloroperbenzoic acid).³⁹⁰ Double bonds can be hydroborated in the presence of triple bonds if the reagent is 9-BBN.³⁹¹ On the other hand, dimesitylborane selectively hydroborates triple bonds in the presence of double bonds.³⁹² Furthermore, it is often possible to hydroborate selectively one particular double bond of a nonconjugated diene.³⁹³ When the reagent is catecholborane, hydroboration is catalyzed by rhodium complexes, such as Wilkinson's catalyst.³⁹⁴ Enantioselective hydroboration-oxidation has been achieved by the use of optically active rhodium complexes.³⁹⁵

For most substrates, the addition in hydroboration is stereospecific and syn, with attack taking place from the less-hindered side.³⁹⁶ The mechanism³⁹⁷ may be a cyclic four-center one:³⁹⁸



When the substrate is an allylic alcohol or amine, the addition is generally anti,³⁹⁹ though the stereoselectivity can be changed to syn by the use of catecholborane and the rhodium complexes mentioned above.⁴⁰⁰ Because the mechanism is different, use of this pro-

³⁸⁸Brown; Gupta *J. Am. Chem. Soc.* **1972**, *94*, 4370, **1975**, *97*, 5249. For a review of catecholborane, see Lane; Kabalka *Tetrahedron* **1976**, *32*, 981-990.

³⁸⁹Brown; Campbell *J. Org. Chem.* **1980**, *45*, 389.

³⁹⁰Zweifel; Arzoumanian *J. Am. Chem. Soc.* **1967**, *89*, 291.

³⁹¹Brown; Coleman *J. Org. Chem.* **1979**, *44*, 2328.

³⁹²Pelter; Singaram; Brown *Tetrahedron Lett.* **1983**, *24*, 1433.

³⁹³For a list of references, see Gautam; Singh; Dhillon *J. Org. Chem.* **1988**, *53*, 187. See also Suzuki; Dhillon, Ref. 348.

³⁹⁴Männig; Nöth *Angew. Chem. Int. Ed. Engl.* **1985**, *24*, 878 [*Angew. Chem.* *97*, 854]. For a review, see Burgess; Ohlmeyer *Chem. Rev.* **1991**, *91*, 1179-1191.

³⁹⁵Burgess; Ohlmeyer *J. Org. Chem.* **1988**, *53*, 5178; Hayashi; Matsumoto; Ito *J. Am. Chem. Soc.* **1989**, *111*, 3426; Sato; Miyaoura; Suzuki *Tetrahedron Lett.* **1990**, *31*, 231; Brown; Lloyd-Jones *Tetrahedron: Asymmetry* **1990**, *1*, 869.

³⁹⁶Kabalka; Bowman *J. Org. Chem.* **1973**, *38*, 1607; Brown; Zweifel *J. Am. Chem. Soc.* **1961**, *83*, 2544; Bergbreiter; Rainville *J. Org. Chem.* **1976**, *41*, 3031; Kabalka; Newton; Jacobus *J. Org. Chem.* **1978**, *43*, 1567.

³⁹⁷For kinetic studies, see Wang; Brown *J. Org. Chem.* **1980**, *45*, 5303, *J. Am. Chem. Soc.* **1982**, *104*, 7148; Vishwakarma; Fry *J. Org. Chem.* **1980**, *45*, 5306; Brown; Chandrasekharan; Wang *J. Org. Chem.* **1983**, *48*, 2901. *Pure Appl. Chem.* **1983**, *55*, 1387-1414; Chandrasekharan; Brown *J. Org. Chem.* **1985**, *50*, 518; Nelson; Cooper *Tetrahedron Lett.* **1986**, *27*, 4693; Brown; Chandrasekharan *J. Org. Chem.* **1988**, *53*, 4811.

³⁹⁸Brown; Zweifel *J. Am. Chem. Soc.* **1959**, *81*, 247; Pasto; Lepeska; Balasubramanian *J. Am. Chem. Soc.* **1972**, *94*, 6090; Pasto; Lepeska; Cheng *J. Am. Chem. Soc.* **1972**, *94*, 6083; Narayana; Periasamy *J. Chem. Soc., Chem. Commun.* **1987**, 1857. See, however, Jones *J. Org. Chem.* **1972**, *37*, 1886.

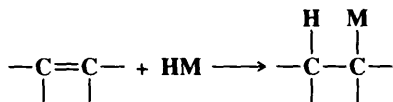
³⁹⁹See Still; Barrish *J. Am. Chem. Soc.* **1983**, *105*, 2487.

⁴⁰⁰See Evans; Fu; Hovcyda *J. Am. Chem. Soc.* **1988**, *110*, 6917; Burgess; Cassidy; Ohlmeyer *J. Org. Chem.* **1991**, *56*, 1020; Burgess; Ohlmeyer *J. Org. Chem.* **1991**, *56*, 1027.

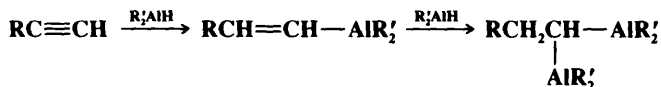
cedure can result in a change in regioselectivity as well, e.g., styrene $\text{PhCH}=\text{CH}_2$ gave $\text{PhCH}(\text{OH})\text{CH}_3$.⁴⁰¹

OS VI, 719, 852, 919, 943; VII, 164, 339, 402, 427; 68, 130.

5-13 Other Hydrometalation Hydro-metallo-addition



Metal hydrides of groups 13 and 14 of the periodic table (e.g., AlH_3 , GaH_3) as well as many of their alkyl and aryl derivatives (e.g., R_2AlH , Ar_3SnH) add to double bonds to give organometallic compounds.⁴⁰² The hydroboration reaction (5-12) is the most important example, but other important metals in this reaction are aluminum,⁴⁰³ silicon, tin,⁴⁰⁴ and zirconium⁴⁰⁵ (a group 4 metal). Some of these reactions are uncatalyzed, but in other cases various types of catalyst have been used.⁴⁰⁶ Hydrozirconation is most commonly carried out with Cp_2ZrHCl (Cp = cyclopentadienyl),⁴⁰⁷ known as *Schwartz's reagent*. The mechanism with group 13 hydrides seems to be electrophilic (or four-centered pericyclic with some electrophilic characteristics) while with group 14 hydrides a mechanism involving free radicals seems more likely. Dialkylmagnesiums have been obtained by adding MgH_2 to double bonds.⁴⁰⁸ RMgX can be added to an alkene $\text{R}'\text{CH}=\text{CH}_2$ to give $\text{R}'\text{CH}_2\text{CH}_2\text{MgX}$, with TiCl_4 as a catalyst (see also 8-12).⁴⁰⁹ With some reagents triple bonds⁴¹⁰ can add 1 or 2 moles, e.g.,⁴¹¹



⁴⁰¹Hayashi; Matsumoto; Ito. Ref. 395; Zhang; Lou; Guo; Dai *J. Org. Chem.* **1991**, 56, 1670.

⁴⁰²Negishi *Adv. Met.-Org. Chem.* **1989**, 1, 177-207; Eisch *The Chemistry of Organometallic Compounds*; Macmillan: New York, 1967, pp. 107-111. See also Eisch; Fichter *J. Organomet. Chem.* **1983**, 250, 63.

⁴⁰³For reviews of organoaluminums in organic synthesis, see Dzhemilev; Vostrikova; Tolstikov *Russ. Chem. Rev.* **1990**, 59, 1157-1173; Maruoka; Yamamoto *Tetrahedron* **1988**, 44, 5001-5032.

⁴⁰⁴For a review with respect to Al, Si, and Sn, see Negishi *Organometallics in Organic Synthesis*, vol. 1; Wiley: New York, 1980, pp. 45-48, 357-363, 406-412. For reviews of hydrosilylation, see Ojima, in Patai; Rappoport *The Chemistry of Organic Silicon Compounds*, pt. 2; Wiley: New York, 1989, pp. 1479-1526; Alberti; Pedulli *Rev. Chem. Intermed.* **1987**, 8, 207-246; Speier *Adv. Organomet. Chem.* **1979**, 17, 407-447; Andrianov; Souček; Khananashvili *Russ. Chem. Rev.* **1979**, 48, 657-668.

⁴⁰⁵For reviews of hydrozirconation, and the uses of organozirconium compounds, see Negishi; Takahashi *Synthesis* **1988**, 1-19; Dzhemilev; Vostrikova; Tolstikov *J. Organomet. Chem.* **1986**, 304, 17-39; Schwartz; Labinger *Angew. Chem. Int. Ed. Engl.* **1976**, 15, 333-340 [*Angew. Chem.* **88**, 402-409].

⁴⁰⁶See, for example, Oertle; Wettter *Tetrahedron Lett.* **1985**, 26, 5511; Randolph; Wrighton *J. Am. Chem. Soc.* **1986**, 108, 3366; Maruoka; Sano; Shinoda; Nakai; Yamamoto *J. Am. Chem. Soc.* **1986**, 108, 6036; Miyake; Yamamura *Chem. Lett.* **1989**, 981; Doyle; High; Nesloney; Clayton; Lin *Organometallics* **1991**, 10, 1225.

⁴⁰⁷For a method of preparing this reagent (which is also available commercially), see Buchwald; LaMaire; Nielsen; Watson; King *Tetrahedron Lett.* **1987**, 28, 3895. It can also be generated in situ: Lipshutz; Keil; Ellsworth *Tetrahedron Lett.* **1990**, 31, 7257.

⁴⁰⁸For a review, see Bogdanović *Angew. Chem. Int. Ed. Engl.* **1985**, 24, 262-273 [*Angew. Chem.* **97**, 253-264].

⁴⁰⁹For a review, see Sato *J. Organomet. Chem.* **1985**, 285, 53-64. For another catalyst, see Hoveyda; Xu *J. Am. Chem. Soc.* **1991**, 113, 5079.

⁴¹⁰For a review of the hydrometalation of triple bonds, see Ref. 386, pp. 219-232.

⁴¹¹Wilke; Müller *Liebigs Ann. Chem.* **1960**, 629, 222; Eisch; Kaska *J. Am. Chem. Soc.* **1966**, 88, 2213; Eisch; Rhee *Liebigs Ann. Chem.* **1975**, 565.

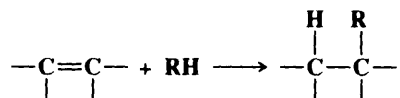
When 2 moles are added, electrophilic addition generally gives 1,1-dimetallic products (as with hydroboration), while free-radical addition usually gives the 1,2-dimetallic products.

OS VII, 456; 66, 60; 67, 86; 69, 106. See also OS 66, 43, 75.

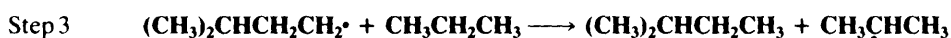
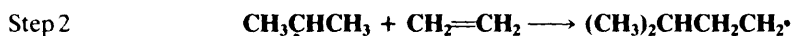
G. Carbon on the Other Side

5-14 Addition of Alkanes

Hydro-alkyl-addition

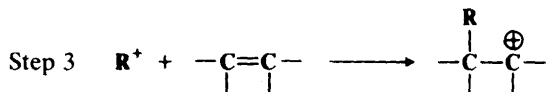
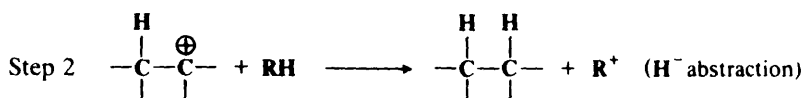
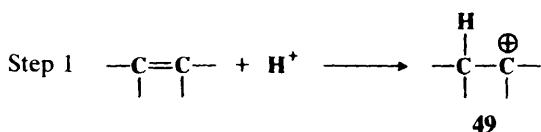


There are two important ways of adding alkanes to olefins—the thermal method and the acid-catalysis method.⁴¹² Both give chiefly mixtures, and neither is useful for the preparation of relatively pure compounds in reasonable yields. However, both are useful industrially. In the thermal method the reactants are heated to high temperatures (about 500°C) at high pressures (150 to 300 atm) without a catalyst. As an example, propane and ethylene gave 55.5% isopentane, 7.3% hexanes, 10.1% heptanes, and 7.4% alkenes.⁴¹³ The mechanism is undoubtedly of a free-radical type and can be illustrated by one possible sequence in the reaction between propane and ethylene:



There is kinetic evidence that the initiation takes place primarily by steps like 1, which are called *symproportionation* steps⁴¹⁴ (the opposite of disproportionation, p. 194).

In the acid-catalysis method, a proton or Lewis acid is used as the catalyst and the reaction is carried out at temperatures between -30 and 100°C. This is a Friedel-Crafts process with a carbocation mechanism⁴¹⁵ (illustrated for a proton acid catalyst):

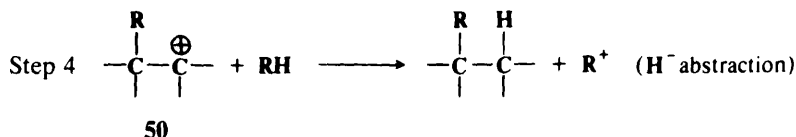


⁴¹²For reviews, see Shuikin; Lebedev *Russ. Chem. Rev.* **1966**, 35, 448-455; Schmerling, in Olah *Friedel-Crafts and Related Reactions*, vol. 2; Wiley: New York, 1964, pp. 1075-1111, 1121-1122.

⁴¹³Frey; Hepp *Ind. Eng. Chem.* **1936**, 28, 1439.

⁴¹⁴Metzger *Angew. Chem. Int. Ed. Engl.* **1983**, 22, 889 [*Angew. Chem.* 95, 914]; Hartmanns; Klenke; Metzger *Chem. Ber.* **1986**, 119, 488.

⁴¹⁵For a review, see Mayr *Angew. Chem. Int. Ed. Engl.* **1990**, 29, 1371-1384 [*Angew. Chem.* 102, 1415-1428].



50 often rearranges before it abstracts a hydride ion, explaining, for example, why the principal product from the reaction between isobutane and ethylene is 2,3-dimethylbutane. It is also possible for **49** (or **50**) instead of abstracting a hydride ion, to add to another mole of olefin, so that not only rearrangement products but also dimeric and polymeric products are frequent. If the tri- or tetrasubstituted olefins are treated with Me_4Si , HCl , and AlCl_3 , they become protonated to give a tertiary carbocation, which reacts with the Me_4Si to give a product that is the result of addition of H and Me to the original alkene.⁴¹⁶ (For a free-radical hydro-methyl-addition, see **5-20**.)

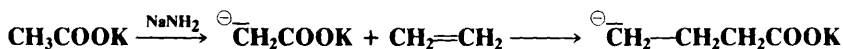
The addition of secondary or tertiary cations (generated from the corresponding alcohols, esters, or alkenes) to 1,1-dichloroethene gives carboxylic acids by hydrolysis of the intermediate ions (see **0-3**):⁴¹⁷



The reaction can also be base-catalyzed, in which case there is nucleophilic addition and a carbanion mechanism.⁴¹⁸ Carbanions most often used are those stabilized by one or more α -aryl groups. For example, toluene adds to styrene in the presence of sodium to give 1,3-diphenylpropane:⁴¹⁹



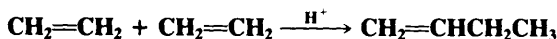
Conjugated dienes give 1,4 addition.⁴²⁰ This reaction has also been performed with salts of carboxylic acids in what amounts to a method of alkylation of carboxylic acids⁴²¹ (see also **0-96**).



OS I, 229; IV, 665; VII, 479.

5-15 Addition of Alkenes and/or Alkynes to Alkenes and/or Alkynes

Hydro-alkenyl-addition



⁴¹⁶Bolestova; Parnes; Kursanov *J. Org. Chem. USSR* **1983**, *19*, 2175.

⁴¹⁷For reviews, see Bott *Angew. Chem. Int. Ed. Engl.* **1980**, *19*, 171-178 [*Angew. Chem.* *92*, 169-176]; Bott; Hellmann *Angew. Chem. Int. Ed. Engl.* **1966**, *5*, 870-874 [*Angew. Chem.* *78*, 932-936]. *Newer Methods Prep. Org. Chem.* **1971**, *6*, 67-80.

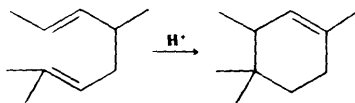
⁴¹⁸For reviews, see Pines; Stalick, Ref. 198, pp. 240-422; Pines *Acc. Chem. Res.* **1974**, *7*, 155-162; Pines; Schaap *Adv. Catal.* **1960**, *12*, 117-148, pp. 126-146.

⁴¹⁹Pines; Wunderlich *J. Am. Chem. Soc.* **1958**, *80*, 6001.

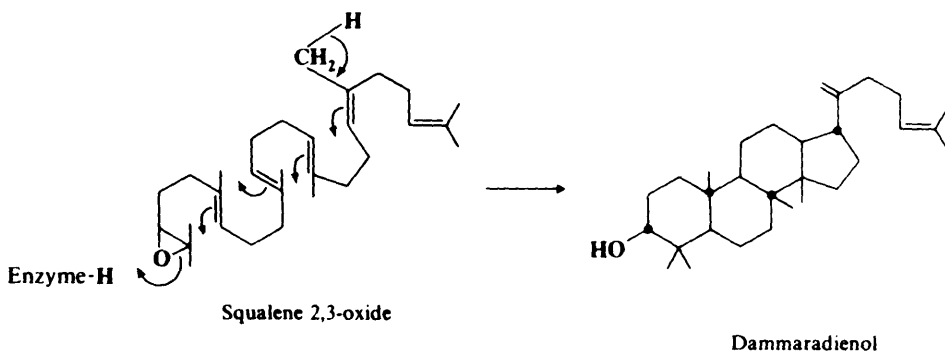
⁴²⁰Eberhardt; Peterson *J. Org. Chem.* **1965**, *30*, 82; Pines; Stalick *Tetrahedron Lett.* **1968**, 3723.

⁴²¹Schmerling; Toekelt *J. Am. Chem. Soc.* **1962**, *84*, 3694.

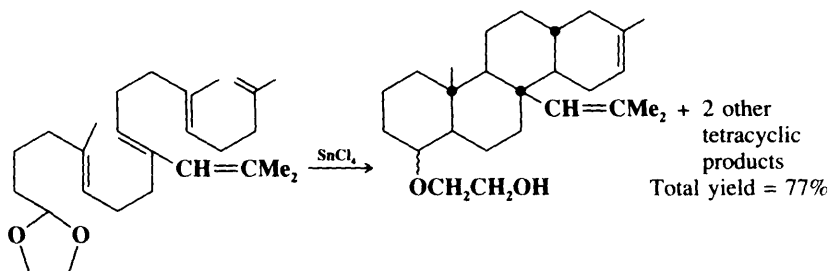
With certain substrates, alkenes can be dimerized by acid catalysts, so that the product is a dimer that contains one double bond.⁴²² This reaction is more often carried out internally, e.g.,



Processes of this kind are important in the biosynthesis of steroids and tetra- and pentacyclic terpenes. For example, squalene 2,3-oxide is converted by enzymic catalysis to dammaradienol.



The squalene \rightarrow lanosterol biosynthesis (which is a key step in the biosynthesis of cholesterol) is similar. The idea that the biosynthesis of such compounds involves this type of multiple ring closing was proposed in 1955 and is known as the *Stork-Eschenmoser hypothesis*.⁴²³ Such reactions can also be carried out in the laboratory, without enzymes.⁴²⁴ By putting cation-stabilizing groups at positions at which positive charges develop, Johnson and co-workers have been able to close as many as four rings stereoselectively and in high yield, in one operation.⁴²⁵ An example is



which uses the $\text{CH}=\text{CMe}_2$ group as the cation-stabilizing auxiliary.

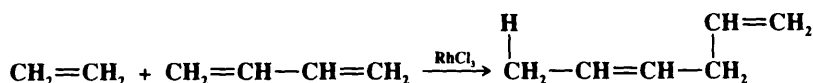
⁴²²For a review, see Onsager; Johansen, in Hartley; Patai *The Chemistry of the Metal-Carbon Bond*, vol. 3; Wiley: New York, 1985, pp. 205-257.

⁴²³Stork; Burgstahler *J. Am. Chem. Soc.* **1955**, *77*, 5068; Eschenmoser; Ruzicka; Jeger; Arigoni *Helv. Chim. Acta* **1955**, *38*, 1890.

⁴²⁴For reviews, see Gnonlonfoun *Bull. Soc. Chim. Fr.* **1988**, 862-869; Sutherland *Chem. Soc. Rev.* **1980**, *9*, 265-280; Johnson *Angew. Chem. Int. Ed. Engl.* **1976**, *15*, 9-17 [*Angew. Chem.* **88**, 33-40], *Bioorg. Chem.* **1976**, *5*, 51-98. *Acc. Chem. Res.* **1968**, *1*, 1-8; van Tamelen *Acc. Chem. Res.* **1975**, *8*, 152-158. For a review of the stereochemical aspects, see Bartlett, in Morrison, Ref. 232, vol. 3, pp. 341-409.

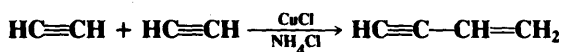
⁴²⁵Johnson; Telfer; Cheng; Schubert *J. Am. Chem. Soc.* **1987**, *109*, 2517; Johnson; Lindell; Steele *J. Am. Chem. Soc.* **1987**, *109*, 5852; Guay; Johnson; Schubert *J. Org. Chem.* **1989**, *54*, 4731.

The addition of olefins to olefins⁴²⁶ can also be accomplished by bases⁴²⁷ as well as by the use of catalyst systems⁴²⁸ consisting of nickel complexes and alkylaluminum compounds (known as *Ziegler catalysts*),⁴²⁹ catalysts derived from rhodium chloride,⁴³⁰ and other transition metal catalysts. These and similar catalysts also catalyze the 1,4-addition of olefins to conjugated dienes,⁴³¹ e.g.,



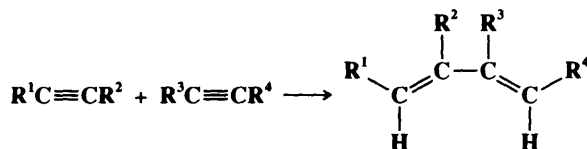
and the dimerization of 1,3-butadienes to octatrienes.⁴³²

In the presence of cuprous chloride and ammonium chloride, acetylene adds to another molecule of itself to give vinylacetylene.



This type of alkyne dimerization is also catalyzed by certain nickel complexes, as well as other catalysts⁴³³ and has been carried out internally to convert diynes to large-ring cycloalkynes with an exocyclic double bond.⁴³⁴

In another type of alkyne dimerization, two molecules of alkyne, the same or different, can be coupled to give a 1,3-diene⁴³⁵



In this method, one alkyne is treated with Schwartz's reagent (see 5-13) to produce a vinylic zirconium intermediate. Addition of MeLi or MeMgBr, followed by the second alkyne, gives another intermediate, which, when treated with aqueous acid, gives the diene in moderate-to-good yields. The stereoisomer shown is the one formed in usually close to 100% purity. If the second intermediate is treated with I₂ instead of aqueous acid, the 1,4-diiodo-1,3-diene is obtained instead, in comparable yield and isomeric purity. This reaction can

⁴²⁶For a review of olefin dimerization and oligomerization with all catalysts, see Fel'dblyum; Obeshchalova *Russ. Chem. Rev.* **1968**, *37*, 789-797.

⁴²⁷For a review, see Pines *Synthesis* **1974**, 309-327.

⁴²⁸For reviews, see Pillai; Ravindranathan; Sivaram *Chem. Rev.* **1986**, *86*, 353-399; Jira; Friciesleben *Organomet. React.* **1972**, *3*, 1-190, pp. 117-130; Heck, Ref. 223, pp. 84-94, 150-157; Khan; Martell, Ref. 159, vol. 2, pp. 135-15; Rylander Ref. 223, pp. 175-196; Tsuji *Adv. Org. Chem.* **1969**, *6*, 109-255, pp. 213-220.

⁴²⁹See for example, Onsager; Wang; Blindheim *Helv. Chim. Acta* **1969**, *52*, 187, 230; Fischer; Jonas; Misbach; Stabba; Wilke *Angew. Chem. Int. Ed. Engl.* **1973**, *12*, 943 [*Angew. Chem.* **85**, 1002].

⁴³⁰Cramer *J. Am. Chem. Soc.* **1965**, *87*, 4717; *Acc. Chem. Res.* **1968**, *1*, 186-191; Kobayashi; Taira *Tetrahedron* **1968**, *24*, 5763; Takahashi; Okura; Keii *J. Am. Chem. Soc.* **1975**, *97*, 7489.

⁴³¹Alderson; Jenner; Lindsey *J. Am. Chem. Soc.* **1965**, *87*, 5638. For a review see Su *Adv. Organomet. Chem.* **1979**, *17*, 269-318.

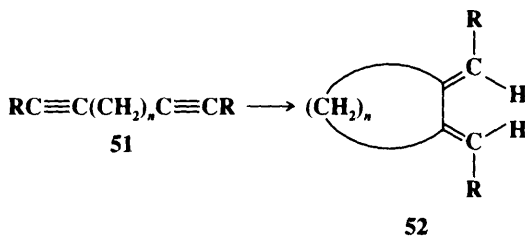
⁴³²See, for example, Denis; Jean; Croizy; Mortreux; Petit *J. Am. Chem. Soc.* **1990**, *112*, 1292.

⁴³³See for example, Carlton; Read *J. Chem. Soc., Perkin Trans. 1* **1978**, 1631; Schmitt; Singer *J. Organomet. Chem.* **1978**, *153*, 165; Selimov; Rutman; Dzhemilev *J. Org. Chem. USSR* **1983**, *19*, 1621.

⁴³⁴Trost; Matsubara; Carinji *J. Am. Chem. Soc.* **1989**, *111*, 8745.

⁴³⁵Buchwald; Nielsen *J. Am. Chem. Soc.* **1989**, *111*, 2870.

also be done intramolecularly: Dienes **51** can be cyclized to *E,E* exocyclic dienes **52** by treatment with a zirconium complex.⁴³⁶



Rings of 4, 5, and 6 members were obtained in high yield; 7-membered rings in lower yield. When the reaction is applied to enynes, compounds similar to **52** but with only one double bond are obtained.⁴³⁷

In a conversion that is formally similar, substituted alkenes ($\text{CH}_2=\text{CH}-\text{Y}$; $\text{Y} = \text{R}, \text{COOMe}, \text{OAc}, \text{CN}, \text{etc.}$) can be dimerized to substituted alkanes $\text{CH}_3\text{CHYCHYCH}_3$ by photolysis in an H_2 atmosphere, using Hg as a photosensitizer.⁴³⁸ Still another procedure involves palladium-catalyzed addition of vinylic halides to triple bonds to give 1,3-dienes.⁴³⁹

Olefins and alkynes can also add to each other to give cyclic products in other ways (see **5-49** and **5-51**).

OS **65**, **42**; **66**, **52**, **75**; **67**, **48**.

5-16 The Ene Synthesis

Hydro-allyl-addition



Olefins can add to double bonds in a reaction different from those discussed in **5-15**, which, however, is still formally the addition of RH to a double bond. This reaction is called the *ene synthesis*⁴⁴⁰ and bears a certain similarity to the Diels-Alder reaction (**5-47**). For the reaction to proceed without a catalyst, one of the components must be a reactive dienophile (see **5-47** for a definition of this word) such as maleic anhydride, but the other (which supplies the hydrogen) may be a simple alkene such as propene. There has been much discussion of the mechanism of this reaction, and both concerted pericyclic (as shown above) and stepwise mechanisms have been suggested. The reaction between maleic anhydride and optically active $\text{PhCHMeCH}=\text{CH}_2$ gave an optically active product,⁴⁴¹ which is strong evi-

⁴³⁶Nugent; Thorn; Harlow *J. Am. Chem. Soc.* **1987**, *109*, 2788. See also Trost; Lee *J. Am. Chem. Soc.* **1988**, *110*, 7255; Tamao; Kobayashi; Ito *J. Am. Chem. Soc.* **1989**, *111*, 6478.

⁴³⁷RajanBabu; Nugent; Taber; Fagan *J. Am. Chem. Soc.* **1988**, *110*, 7128.

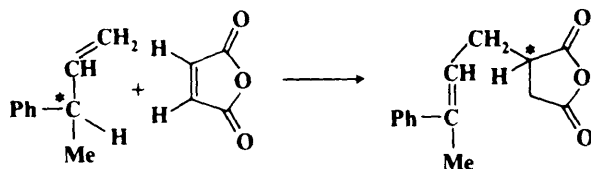
⁴³⁸Muedas; Ferguson; Crabtree *Tetrahedron Lett.* **1989**, *30*, 3389.

⁴³⁹Arcadi; Bernocchi; Burini; Cacchi; Marinelli; Pietroni *Tetrahedron Lett.* **1989**, *30*, 3465.

⁴⁴⁰Alder; Brachel *Liebigs Ann. Chem.* **1962**, *651*, 141. For a monograph, see Carruthers *Cycloaddition Reactions in Organic Synthesis*; Pergamon: Elmsford, NY, 1990. For reviews, see Boyd, in Patai *Supplement A: The Chemistry of Double-bonded Functional Groups*, vol. 2, pt. 1; Wiley: New York, 1989, pp. 477-525; Keung; Alper *J. Chem. Educ.* **1972**, *49*, 97-100; Hoffmann *Angew. Chem. Int. Ed. Engl.* **1969**, *8*, 556-577 [*Angew. Chem.* *81*, 597-618]. For reviews of intramolecular ene reactions see Taber *Intramolecular Diels-Alder and Alder Ene Reactions*; Springer: New York, 1984; pp. 61-94; Oppolzer; Snieckus *Angew. Chem. Int. Ed. Engl.* **1978**, *17*, 476-486 [*Angew. Chem.* *90*, 506-507]; Conia; Le Perchech *Synthesis* **1975**, 1-19. For a review of ene reactions in which one of the reactants bears a Si atom, see Dubac; Laporterie *Chem. Rev.* **1987**, *87*, 319-334.

Rabinovitz *J. Am. Chem. Soc.* **1964**, *86*, 965. See also Garsky; Koster; Arnold *J. Am. Chem. Soc.* **1974**, *96*, 1000; phenson; Mattern *J. Org. Chem.* **1976**, *41*, 3614; Nahm; Cheng *J. Org. Chem.* **1986**, *51*, 5093.

dence for a concerted rather than a stepwise mechanism.⁴⁴² The reaction can be extended

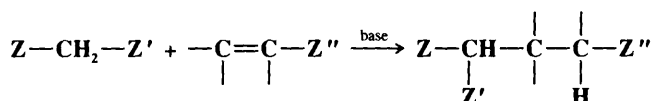


to less-reactive enophiles by the use of Lewis-acid catalysts, especially alkylaluminum halides.⁴⁴³ The Lewis-acid catalyzed reaction probably has a stepwise mechanism.⁴⁴⁴

OS IV, 766; V, 459. See also OS 65, 159.

5-17 The Michael Reaction

Hydro-bis(ethoxycarbonyl)methyl-addition, etc.



Compounds containing electron-withdrawing groups (Z is defined on p. 741) add, in the presence of bases, to olefins of the form C=C-Z (including quinones). This is called the *Michael reaction* and involves conjugate addition.⁴⁴⁵ The base removes the acidic proton and then the mechanism is as outlined on p. 741. The reaction has been carried out with malonates, cyanoacetates, acetoacetates, other β -keto esters, and compounds of the form ZCH₃, ZCH₂R, ZCHR₂, and ZCHRZ', including carboxylic esters, ketones, aldehydes, nitriles, nitro compounds,⁴⁴⁶ and sulfones, as well as other compounds with relatively acidic hydrogens, such as indenes and fluorenes. These reagents do not add to ordinary double bonds, except in the presence of free-radical initiators (5-22). 1,2 addition (to the C=O or C \equiv N group) often competes and sometimes predominates (6-41).⁴⁴⁷ In particular, α,β -unsaturated aldehydes seldom give 1,4 addition.⁴⁴⁸ The Michael reaction has traditionally been performed in protic solvents, with catalytic amounts of base, but more recently better yields with fewer side reactions have been obtained in some cases by using an equimolar amount of base to convert the nucleophile to its enolate form (*preformed enolate*). In particular, preformed enolates are often used where stereoselective reactions are desired.⁴⁴⁹

⁴⁴²For other evidence for a concerted mechanism see Benn; Dwyer; Chappell *J. Chem. Soc., Perkin Trans. 2* **1977**, 533; Jenner; Salem; El'yanov; Gonikberg *J. Chem. Soc., Perkin Trans. 2* **1989**, 1671.

⁴⁴³For reviews, see Chaloner, in Hartley, Ref. 218, vol. 4, pp. 456-460; Snider *Acc. Chem. Res.* **1980**, *13*, 426-432.

⁴⁴⁴See Snider; Ron *J. Am. Chem. Soc.* **1985**, *107*, 8160.

⁴⁴⁵For reviews, see Yanovskaya; Kryshal; Kulganek *Russ. Chem. Rev.* **1984**, *53*, 744-756; Bergmann; Ginsburg; Pappo *Org. React.* **1959**, *10*, 179-560; House, Ref. 144, pp. 595-623. The subject is also discussed at many places in Stowell *Carbanions in Organic Synthesis*; Wiley: New York, 1979.

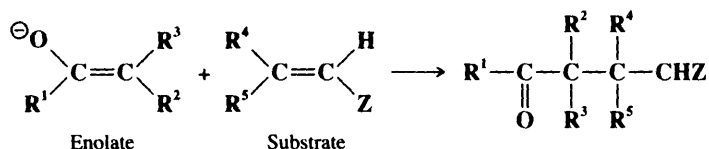
⁴⁴⁶For reviews of Michael reactions where Z or Z' is nitro see Yoshikoshi; Miyashita *Acc. Chem. Res.* **1985**, *18*, 284-290; Baer; Urbas, in Feuer *The Chemistry of the Nitro and Nitroso Groups*, pt. 2; Wiley: New York, 1970, pp. 130-148.

⁴⁴⁷For a discussion of 1,2 vs. 1,4 addition, see Oare; Heathcock, *Top. Stereochem.* **1989**, Ref. 449, pp. 232-236.

⁴⁴⁸For reports of successful 1,4 additions to α,β -unsaturated aldehydes, see Kryshal; Kulganek; Kucherov; Yanovskaya *Synthesis* **1979**, 107; Yamaguchi; Yokota; Minami *J. Chem. Soc., Chem. Commun.* **1991**, 1088.

⁴⁴⁹For reviews of stereoselective Michael additions, see Oare; Heathcock *Top. Stereochem.* **1991**, *20*, 87-170. **1989**, *19*, 227-407.

In a Michael reaction with suitably different R groups, two new chiral centers are created:

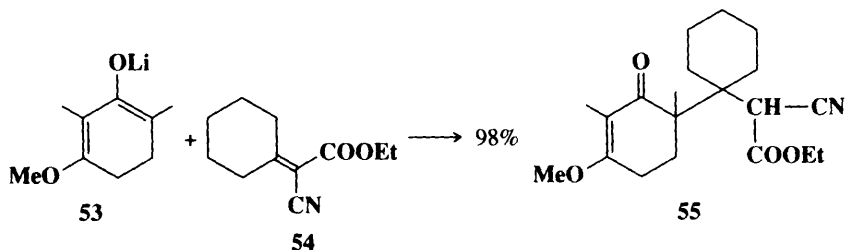


Thus the product in such cases can exist as two pairs of enantiomers.⁴⁵⁰ In a diastereoselective process one of the two pairs is formed exclusively or predominantly, as a racemic mixture. Many such examples have been reported.⁴⁴⁹ In many of these cases, both the enolate and substrate can exist as *Z* or *E* isomers. With enolates derived from ketones or carboxylic esters, *E* enolates gave the syn pair of enantiomers (p. 115), while *Z* enolates gave the anti pair.⁴⁵¹

When either or both of the reaction components has a chiral substituent, the reaction can be enantioselective (only one of the four diastereomers formed predominantly), and this has been accomplished a number of times.⁴⁵² Enantioselective addition has also been achieved by the use of a chiral catalyst⁴⁵³ and by using optically active enamines instead of enolates.⁴⁵⁴

Mannich bases (see 6-16) and β -halo carbonyl compounds can also be used as substrates; these are converted to the $\text{C}=\text{C}-\text{Z}$ compounds in situ by the base (6-16, 7-13).⁴⁵⁵ Substrates of this kind are especially useful in cases where the $\text{C}=\text{C}-\text{Z}$ compound is unstable. The reaction of $\text{C}=\text{C}-\text{Z}$ compounds with enamines (2-19) can also be considered a Michael reaction. Michael reactions are reversible (7-20).

When the substrate contains *gem-Z* groups, e.g., 54, bulky groups can be added, if the



reaction is carried out under aprotic conditions. For example, addition of enolate 53 to 54 gave 55 in which two adjacent quaternary centers have been formed.⁴⁵⁶

In certain cases, Michael reactions can take place under acidic conditions.⁴⁵⁷

⁴⁵⁰For a more extended analysis, see Oare; Heathcock *Top. Stereochem.* **1989**, Ref. 449, pp. 237-242.

⁴⁵¹For example, see Oare; Heathcock *J. Org. Chem.* **1990**, 55, 157.

⁴⁵²See, for example, Corey; Peterson *Tetrahedron Lett.* **1985**, 26, 5025; Calderari; Seebach *Helv. Chim. Acta* **1985**, 68, 1592; Tomioka; Ando; Yasuda; Koga *Tetrahedron Lett.* **1986**, 27, 715; Posner; Switzer *J. Am. Chem. Soc.* **1986**, 108, 1239; Enders; Demir; Rendenbach *Chem. Ber.* **1987**, 120, 1731.

⁴⁵³Yura; Iwasaka; Mukaiyama *Chem. Lett.* **1988**, 1021; Yura; Iwasaka; Narasaka; Mukaiyama *Chem. Lett.* **1988**, 1025; Desimoni; Quadrelli; Righetti *Tetrahedron* **1990**, 46, 2927.

⁴⁵⁴See d'Angelo; Reviel; Volpe; Pfau *Tetrahedron Lett.* **1988**, 29, 4427.

⁴⁵⁵Mannich bases react with ketones *without* basic catalysts to give 1,5-diketones, but this process, known as the *thermal-Michael reaction*, has a different mechanism; Brown; Buchanan; Curran; McLay *Tetrahedron* **1968**, 24, 4565; Gill; James; Lions; Potts *J. Am. Chem. Soc.* **1952**, 74, 4923.

⁴⁵⁶Holton; Williams; Kennedy *J. Org. Chem.* **1986**, 51, 5480.

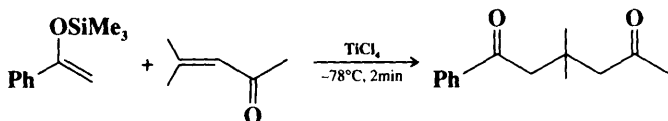
⁴⁵⁷See Hajos; Parrish *J. Org. Chem.* **1974**, 39, 1612. *Org. Synth. VII*, 363.

Michael reactions are sometimes applied to substrates of the type $C\equiv C-Z$, e.g.,

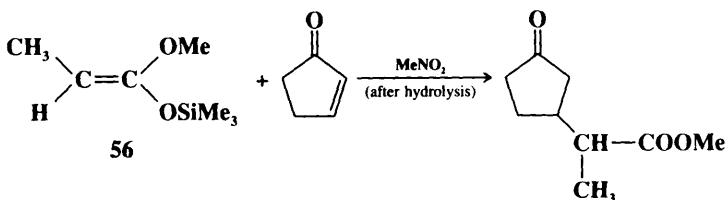


Indeed, because of the greater susceptibility of triple bonds to nucleophilic attack, it is even possible for nonactivated alkynes, e.g., acetylene, to be substrates in this reaction.⁴⁵⁸

In a closely related reaction, silyl enol ethers add to α,β -unsaturated ketones and esters when catalyzed⁴⁵⁹ by $TiCl_4$, e.g.,⁴⁶⁰

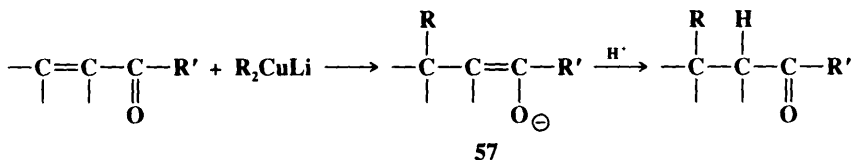


This reaction, also, has been performed diastereoselectively.⁴⁶¹ Allylic silanes $R_2C=CHCH_2SiMe_3$ can be used instead of silyl enol ethers (the *Sakurai reaction*).⁴⁶² Similarly, silyl ketene acetals, e.g., **56**, give δ -keto esters, in $MeNO_2$ as solvent, for example,⁴⁶³



OS I, 272; II, 200; III, 286; IV, 630, 652, 662, 776; V, 486, 1135; VI, 31, 648, 666, 940; VII, 50, 363, 368, 414, 443; **65**, 12, 98; **66**, 37; **69**, 173, 226. See also OS **65**, 236.

5-18 1,4 Addition of Organometallic Compounds to Activated Double Bonds Hydro-alkyl-addition



⁴⁵⁸See, for example, Makosza *Tetrahedron Lett.* **1966**, 5489.

⁴⁵⁹Other catalysts have also been used. For a list of catalysts, with references, see Ref. 133, pp. 793-795. See also Mukaiyama; Kobayashi; Tamura; Sagawa *Chem. Lett.* **1987**, 491; Mukaiyama; Kobayashi *J. Organomet. Chem.* **1990**, 382, 39.

⁴⁶⁰Narasaka; Soai; Aikawa; Mukaiyama *Bull. Chem. Soc. Jpn.* **1976**, 49, 779; Saigo; Osaki; Mukaiyama *Chem. Lett.* **1976**, 163; Matsuda *J. Organomet. Chem.* **1987**, 321, 307; Narasaka *Org. Synth.* 65, 12. See also Yoshikoshi; Miyashita. Ref. 446.

⁴⁶¹See Heathcock; Uehling *J. Org. Chem.* **1986**, 51, 279; Mukaiyama; Tamura; Kobayashi *Chem. Lett.* **1986**, 1017, 1817, 1821, **1987**, 743.

⁴⁶²Hosomi; Sakurai *J. Am. Chem. Soc.* **1977**, 99, 1673; Jellal; Santelli *Tetrahedron Lett.* **1980**, 21, 4487; Sakurai; Hosomi; Hayashi *Org. Synth. VII*, 443. For a review, see Fleming; Dunoguès; Smithers *Org. React.* **1989**, 37, 57-575, pp. 127-132, 335-370. For a review of intramolecular additions, see Schinzer *Synthesis* **1988**, 263-273.

⁴⁶³RajanBabu *J. Org. Chem.* **1984**, 49, 2083.

Lithium dialkylcopper reagents (see 0-87) add to α,β -unsaturated aldehydes⁴⁶⁴ and ketones ($R' = H, R, Ar$) to give conjugate addition products⁴⁶⁵ in a reaction closely related to the Michael reaction. α,β -Unsaturated esters are less reactive,⁴⁶⁶ and the corresponding acids do not react at all. R can be primary alkyl, vinylic, or aryl. If Me_3SiCl is present, the reaction takes place much faster and with higher yields; in this case the product is the silyl enol ether of 57 (see 2-23).⁴⁶⁷ The use of Me_3SiCl also permits good yields with allylic R groups.⁴⁶⁸

Various functional groups such as OH and unconjugated C=O groups may be present in the substrate.⁴⁶⁹ A characteristic of the reaction is that only one of the R groups of R_2CuLi adds to the substrate; the other is wasted. This can be a limitation where the precursor (RLi or RCu, see 2-35) is expensive or available in limited amounts. The difficulty can be overcome by using one of the mixed reagents $R(R'C\equiv C)CuLi$,⁴⁷⁰ $R(O-t-Bu)CuLi$,⁴⁷¹ or $R(PhS)CuLi$,⁴⁷² each of which transfers only the R group. These reagents are easily prepared by the reaction of RLi with $R'C\equiv CCu$ ($R' = n-Pr$ or $t-Bu$), $t-BuOCu$, or $PhSCu$, respectively. A further advantage of the mixed reagents is that good yields of addition product are achieved when R is tertiary, so that use of one of them permits the introduction of a tertiary alkyl group. The mixed reagents $R(CN)CuLi$ ⁴⁷³ (prepared from RLi and CuCN) and $R_2Cu(CN)Li_2$ ⁴⁷⁴ also selectively transfer the R group.⁴⁷⁵ The reaction has also been carried out with α,β -acetylenic ketones, esters, and nitriles.⁴⁷⁶ Conjugate addition to α,β -unsaturated and acetylenic acids and esters, as well as ketones, can be achieved by the use of the coordinated reagents $RCu\cdot BF_3$ ($R =$ primary).⁴⁷⁷ Alkylcopper compounds RCu ($R =$ primary or secondary alkyl) have also been used with tetramethylethylenediamine and Me_3SiCl to give silyl enol ethers from α,β -unsaturated ketones in high yield.⁴⁷⁸

There is generally little or no competition from 1,2 addition (to the C=O). However, when R is allylic, 1,4 addition is observed with some substrates and 1,2 addition with others.⁴⁷⁹ R_2CuLi also add to α,β -unsaturated sulfones⁴⁸⁰ but not to simple α,β -unsaturated nitriles.⁴⁸¹

⁴⁶⁴Chuit; Foulon; Normant *Tetrahedron* **1980**, *36*, 2305, **1981**, *37*, 1385. For a review, see Alexakis; Chuit; Comerçon-Bourgain; Foulon; Jabri; Mangeney; Normant *Pure Appl. Chem.* **1984**, *56*, 91-98. A better reagent for the addition of a methyl group to an α,β -unsaturated aldehyde is $Me_2Cu_3Li_2$; Clive; Farina; Beaulieu, *J. Org. Chem.* **1982**, *47*, 2572.

⁴⁶⁵House; Respass; Whitesides *J. Org. Chem.* **1966**, *31*, 3128. For reviews, see Posner *Org. React.* **1972**, *19*, 1-113; House *Acc. Chem. Res.* **1976**, *9*, 59-67. For examples of the use of this reaction in the synthesis of natural products, see Posner *An Introduction to Synthesis Using Organocopper Reagents*; Wiley: New York 1980, pp. 10-67. For a list of organocopper reagents that give this reaction, with references, see Ref. 133, pp. 805-809, 916-920.

⁴⁶⁶ R_2CuLi also add to N-tosylated α,β -unsaturated amides: Nagashima; Ozaki; Washiyama; Itoh *Tetrahedron Lett.* **1985**, *26*, 657.

⁴⁶⁷Corey; Boaz *Tetrahedron Lett.* **1985**, *26*, 6019; Alexakis; Berlan; Besace *Tetrahedron Lett.* **1986**, *27*, 1047; Matsuzaki; Horiguchi; Nakamura; Kuwajima *Tetrahedron* **1989**, *45*, 349; Horiguchi; Komatsu; Kuwajima *Tetrahedron Lett.* **1989**, *30*, 7087; Linderman; McKenzie *J. Organomet. Chem.* **1989**, *361*, 31; Bertz; Smith *Tetrahedron* **1990**, *46*, 4091. For a list of references, see Ref. 133, p. 748.

⁴⁶⁸Lipshutz; Ellsworth; Dimock; Smith *J. Am. Chem. Soc.* **1990**, *112*, 4404.

⁴⁶⁹For the use of enol tosylates of 1,2-diketones as substrates, see Charonnat; Mitchell; Keogh *Tetrahedron Lett.* **1990**, *31*, 315.

⁴⁷⁰Corey; Beames *J. Am. Chem. Soc.* **1972**, *94*, 7210; House; Umen *J. Org. Chem.* **1973**, *38*, 3893; Corey; Floyd; Lipshutz *J. Org. Chem.* **1978**, *43*, 3419.

⁴⁷¹Posner; Whitten *Tetrahedron Lett.* **1973**, 1815.

⁴⁷²Posner; Whitten; Sterling *J. Am. Chem. Soc.* **1973**, *95*, 7788.

⁴⁷³Gorlier; Hamon; Levisalles; Wagnon *J. Chem. Soc., Chem. Commun.* **1973**, 88. For another useful mixed reagent see Ledlie; Miller *J. Org. Chem.* **1979**, *44*, 1006.

⁴⁷⁴Lipshutz; Wilhelm; Kozlowski *Tetrahedron Lett.* **1982**, *23*, 3755; Lipshutz *Tetrahedron Lett.* **1983**, *24*, 127.

⁴⁷⁵When the two R groups of $R_2Cu(CN)Li_2$ are different, one can be selectively transferred: Lipshutz; Wilhelm; Kozlowski *J. Org. Chem.* **1984**, *49*, 3938.

⁴⁷⁶For a list of references, see Ref. 133, pp. 237-238.

⁴⁷⁷For a review, see Yamamoto *Angew. Chem. Int. Ed. Engl.* **1986**, *25*, 947-959 [*Angew. Chem.* **98**, 945-957]. For a discussion of the role of the BF_3 , see Lipshutz; Ellsworth; Siahaan *J. Am. Chem. Soc.* **1988**, *110*, 4834, **1989**, *111*, 1351.

⁴⁷⁸Johnson; Marren *Tetrahedron Lett.* **1987**, *28*, 27.

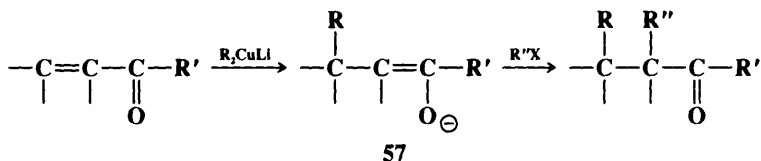
⁴⁷⁹House; Fischer *J. Org. Chem.* **1969**, *34*, 3615. See also Daviaud; Miginiac *Tetrahedron Lett.* **1973**, 3345.

⁴⁸⁰Posner; Brunelle *Tetrahedron Lett.* **1973**, 935.

⁴⁸¹House; Umen Ref. 470.

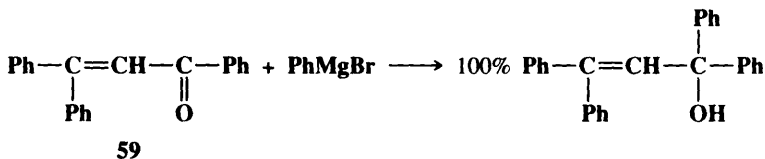
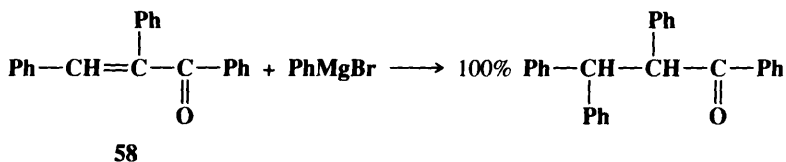
Organocopper reagents RCu (as well as certain R_2CuLi) add to α,β -unsaturated and acetylenic sulfoxides.⁴⁸²

Usually, after an enolate ion is generated from an α,β -unsaturated ketone, it is converted to the β -alkylated product as shown above. But it is often possible to have the enolate react with some other electrophile (*tandem vicinal difunctionalization*), in some cases at the O and in other cases at the C.⁴⁸³ For example, if an alkyl halide $\text{R}''\text{X}$ is present ($\text{R}'' =$ primary alkyl or allylic), and the solvent is 1,2-dimethoxyethane, the enolate **57** can be alkylated



directly.⁴⁸⁴ Thus, by this method, both the α and β positions of a ketone are alkylated in one synthetic operation (see also 5-53).

Grignard reagents also add to these substrates, but with these reagents, 1,2 addition may seriously compete:⁴⁸⁵ The product is often controlled by steric factors. Thus **58** with phenylmagnesium bromide gives 100% 1,4 addition, while **59** gives 100% 1,2 addition. In general,



substitution at the carbonyl group increases 1,4 addition, while substitution at the double bond increases 1,2 addition. In most cases both products are obtained, but α,β -unsaturated *aldehydes* nearly always give exclusive 1,2 addition when treated with Grignard reagents. However, the extent of 1,4 addition of Grignard reagents can be increased by the use of a copper ion catalyst, e.g., CuCl , $\text{Cu}(\text{OAc})_2$.⁴⁸⁶ It is likely that alkylcopper reagents, formed from RMgX and Cu^+ (cupric acetate is reduced to cuprous ion by excess RMgX), are the actual attacking species in these cases.⁴⁶⁵ Alkylolithiums,⁴⁸⁷ treated with compounds of the form $\text{C}=\text{C}-\text{COCH}_3$ and $\text{C}=\text{C}-\text{COOC}_2\text{H}_5$, gave only 1,2 addition,⁴⁸⁸ but 1,4 addition was achieved with esters of the form $\text{C}=\text{C}-\text{COOAr}$, where Ar was a bulky group such as 2,6-

⁴⁸²Truce; Lusch *J. Org. Chem.* **1974**, 39,3174, **1978**, 43, 2252.

⁴⁸³For reviews of such reactions, see Chapdelaine; Hulce *Org. React.* **1990**, 38, 225-653; Taylor *Synthesis* **1985**, 364-392. For a list of references, see Ref. 133, pp. 810-811, 922.

⁴⁸⁴Coates; Sandefur *J. Org. Chem.* **1974**, 39, 275; Posner; Lentz *Tetrahedron Lett.* **1977**, 3215.

⁴⁸⁵For a discussion of the factors affecting 1,2 vs. 1,4 addition, see Negishi, Ref. 404, pp. 127-133.

⁴⁸⁶Posner, Ref. 465.

⁴⁸⁷For a review of addition of organolithium compounds to double bonds, see Hunt *Org. Prep. Proced. Int.* **1989**, 21, 705-749.

⁴⁸⁸Rozhkov; Makin *J. Gen. Chem. USSR* **1964**, 34, 57. For a discussion of 1,2 vs. 1,4 addition with organolithiums, see Cohen; Abraham; Myers *J. Am. Chem. Soc.* **1987**, 109, 7923.

di-*t*-butyl-4-methoxyphenyl.⁴⁸⁹ Also, alkyllithiums can be made to give 1,4 addition with α,β -unsaturated ketones⁴⁹⁰ and aldehydes⁴⁹¹ if the reactions are conducted in the presence of HMPA. Among alkyllithiums that have been found to add 1,4 in this manner are 2-lithio-1,3-dithianes (see 0-97).⁴⁹² 1,4 Addition of alkyllithiums to α,β -unsaturated aldehydes can also be achieved by converting the aldehyde to a benzothiazole derivative (masking the aldehyde function),⁴⁹³ from which the aldehyde group can be regenerated.

However, neither Grignard reagents nor lithium dialkylcopper reagents generally add to ordinary C=C double bonds.⁴⁹⁴ Grignard reagents in general add only to double bonds susceptible to nucleophilic attack, e.g., fluoroolefins and tetracyanoethylene.⁴⁹⁵ However, active Grignard reagents (benzylic, allylic) also add to the double bonds of allylic amines,⁴⁹⁶ and of allylic and homoallylic alcohols,⁴⁹⁷ as well as to the triple bonds of propargyl alcohols and certain other alkynols.⁴⁹⁸ It is likely that cyclic intermediates are involved in these cases, in which the magnesium coordinates with the hetero atom. Organolithium reagents (primary, secondary, and tertiary alkyl and in some cases aryl) also add to the double and triple bonds of allylic and propargylic alcohols⁴⁹⁹ (in this case tetramethylethylenediamine is a catalyst) and to certain other olefins containing hetero groups such as OR, NR₂, or SR. Allylic, benzylic, and tertiary alkyl Grignard reagents also add to 1-alkenes and strained internal alkenes, e.g., norbornene, if the reaction is carried out not in ether but in a hydrocarbon solvent such as pentane or in the alkene itself as solvent, heated, under pressure if necessary, to 60 to 130°C.⁵⁰⁰ Yields are variable. *Intramolecular* addition of RMgX to completely unactivated double and triple bonds has been demonstrated,⁵⁰¹ e.g., refluxing of 6-chloro-1-heptene with Mg for 5 hr gave, after hydrolysis, an 88% yield of 1,2-dimethylcyclopentane.⁵⁰²

An alkynyl group can be added to the double bond of an α,β -unsaturated ketone by use of the diethylalkynylalane reagents Et₂AlC≡CR.⁵⁰³ In a similar manner, the alkenyl reagents R₂AlCH=CR₂ transfer an alkenyl group.⁵⁰⁴ Trialkylalanes R₃Al also add 1,4 to such ketones

⁴⁸⁹Cooke *J. Org. Chem.* **1986**, *51*, 1637.

⁴⁹⁰Sauvêtre; Scyden-Penne *Tetrahedron Lett.* **1976**, 3949; Roux; Wartski; Scyden-Penne *Tetrahedron* **1981**, *37*, 1927. *Synth. Commun.* **1981**, *11*, 85.

⁴⁹¹El-Bouz; Wartski *Tetrahedron Lett.* **1980**, *21*, 2897.

⁴⁹²Lucchetti; Dumont; Krief *Tetrahedron Lett.* **1979**, 2695; Brown; Yamaichi *J. Chem. Soc., Chem. Commun.* **1979**, 100; Ref. 491. See also Bürstinghaus; Seebach *Chem. Ber.* **1977**, *110*, 841.

⁴⁹³Corey; Boger *Tetrahedron Lett.* **1978**, *9*. For another indirect method, see Sato; Okazaki; Otera; Nozaki *Tetrahedron Lett.* **1988**, *29*, 2979.

⁴⁹⁴For reviews of the addition of RM to isolated double bonds see Wardell; Paterson, in Hartley; Patai, Ref. 422, vol. 2, 1985, pp. 219-338, pp. 268-296; Vara Prasad; Pillai *J. Organomet. Chem.* **1983**, *259*, 1-30.

⁴⁹⁵Gardner; Kochi *J. Am. Chem. Soc.* **1976**, *98*, 558.

⁴⁹⁶Richey; Moses; Domalski; Erickson; Heyn *J. Org. Chem.* **1981**, *46*, 3773.

⁴⁹⁷Eisch; Husk *J. Am. Chem. Soc.* **1965**, *87*, 4194; Felkin; Kaeseberg *Tetrahedron Lett.* **1970**, 4587; Richey; Szucs *Tetrahedron Lett.* **1971**, 3785; Eisch; Merkley *J. Am. Chem. Soc.* **1979**, *101*, 1148; Kang *Organometallics* **1984**, *3*, 525.

⁴⁹⁸Eisch; Merkley Ref. 497; Von Rein; Richey *Tetrahedron Lett.* **1971**, 3777; Miller; Reichenbach *Synth. Commun.* **1976**, *6*, 319. See also Duboudin; Jousseau *J. Organomet. Chem.* **1979**, *168*, 1. *Synth. Commun.* **1979**, *9*, 53.

⁴⁹⁹For a review of the addition of organolithium compounds to double or triple bonds, see Wardell, in Zuckerman *Inorganic Reactions and Methods*, vol. 11; VCH: New York, 1988, pp. 129-142.

⁵⁰⁰Lehmkuhl; Reinehr *J. Organomet. Chem.* **1970**, *25*, C47; **1973**, *57*, 29; Lehmkuhl; Janssen *Liebigs Ann. Chem.* **1978**, 1854. This is actually a type of ene reaction. For a review of the intramolecular version of this reaction, see Oppolzer *Angew. Chem. Int. Ed. Engl.* **1989**, *28*, 38-52 [*Angew. Chem.* *101*, 39-53].

⁵⁰¹See, for example, Richey; Rees *Tetrahedron Lett.* **1966**, 4297; Drozd; Ustynuk; Tsel'eva; Dmitriev *J. Gen. Chem. USSR* **1969**, *39*, 1951; Felkin; Umpleby; Hagaman; Wenkert *Tetrahedron Lett.* **1972**, 2285; Hill; Myers *J. Organomet. Chem.* **1979**, *173*, 1.

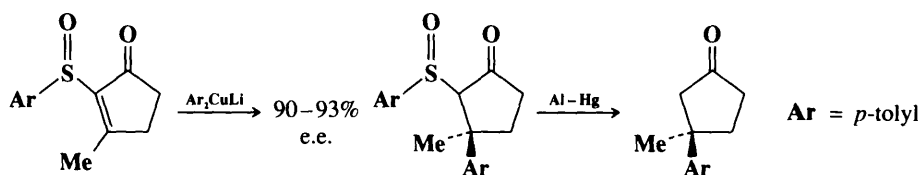
⁵⁰²For intramolecular addition of RLi and R₂CuLi, see Wender; White *J. Am. Chem. Soc.* **1988**, *110*, 2218; Bailey; Nurmi; Patricia; Wang *J. Am. Chem. Soc.* **1987**, *109*, 2442.

⁵⁰³Hooz; Layton *J. Am. Chem. Soc.* **1971**, *93*, 7320; Schwartz; Carr; Hansen; Dayrit *J. Org. Chem.* **1980**, *45*, 3053.

⁵⁰⁴Hooz; Layton *Can. J. Chem.* **1973**, *51*, 2098. For a similar reaction with an alkenylzirconium reagent, see Schwartz; Loots; Kosugi *J. Am. Chem. Soc.* **1980**, *102*, 1333; Dayrit; Schwartz *J. Am. Chem. Soc.* **1981**, *103*, 4466.

in the presence of nickel acetylacetonate.⁵⁰⁵ Also used for 1,4 addition to these ketones are trialkylzinc lithium reagents R_3ZnLi (reagents of the type RMe_2ZnLi transfer only R),⁵⁰⁶ alkyl- and arylmanganese chlorides, catalyzed by $CuCl$ (this reagent is successful for α,β -unsaturated aldehydes and esters also),⁵⁰⁷ arylpalladium compounds,⁵⁰⁸ and arylmercury compounds with phase transfer catalysts.⁵⁰⁹ Diarylzinc compounds (prepared with the aid of ultrasound) in the presence of nickel acetylacetonate, undergo 1,4 addition not only to α,β -unsaturated ketones, but also to α,β -unsaturated aldehydes.⁵¹⁰ An allyl group can be added, to α,β -unsaturated carboxylic esters, amides and nitriles, with $CH_2=CHCH_2SiMe_3$ and F^- ion.⁵¹¹ This reagent gave better results than lithium diallylcuprate. Functionalized allylic groups can be added to terminal alkynes with allylic halides, zinc, and ultrasound, to give 1,4-dienes.⁵¹² An alkyl group can be added to nitroolefins with $RCu(CN)ZnI$ ⁵¹³ or with a trialkylalane; when one of the R groups of the latter is alkenyl, it is the one transferred.⁵¹⁴ Trialkylalanes and dialkylzinc compounds add to triple bonds in the presence of a zirconium complex.⁵¹⁵ An aryl group can be added to a triple bond with an aryl iodide and a $Pd-HCOOH-R_3N$ catalyst.⁵¹⁶

As with the Michael reaction (5-17) the 1,4 addition of organometallic compounds has been performed diastereoselectively⁵¹⁷ and enantioselectively.⁵¹⁸ In one example of the latter,⁵¹⁹ α,β -unsaturated sulfoxides that are optically active because of chirality at sulfur (p. 100) have given high enantiomeric excesses, e.g.,⁵²⁰



⁵⁰⁵Jeffery; Meisters; Mole *J. Organomet. Chem.* **1974**, *74*, 365; Bagnell; Meisters; Mole *Aust. J. Chem.* **1975**, *28*, 817; Ashby; Heinsohn *J. Org. Chem.* **1974**, *39*, 3297. See also Sato; Oikawa; Sato *Chem. Lett.* **1979**, 167; Kunz; Pecs *J. Chem. Soc., Perkin Trans. 1* **1989**, 1168.

⁵⁰⁶Isobe; Kondo; Nagasawa; Goto *Chem. Lett.* **1977**, 679; Watson; Kjonaas *Tetrahedron Lett.* **1986**, *27*, 1437; Tückmantel; Oshima; Nozaki *Chem. Ber.* **1986**, *119*, 1581; Kjonaas; Vawter *J. Org. Chem.* **1986**, *51*, 3993.

⁵⁰⁷Cahiez; Alami *Tetrahedron Lett.* **1989**, *30*, 3541, 7365, **1990**, *31*, 7423.

⁵⁰⁸Cacchi; Arcadi *J. Org. Chem.* **1983**, *48*, 4236.

⁵⁰⁹Cacchi; Misiti; Palmieri *Tetrahedron* **1981**, *37*, 2941.

⁵¹⁰de Souza Barboza; Pétrier; Luche *Tetrahedron Lett.* **1985**, *26*, 829; Pétrier; de Souza Barboza; Dupuy; Luche *J. Org. Chem.* **1985**, *50*, 5761.

⁵¹¹Majetich; Casares; Chapman; Behnke *J. Org. Chem.* **1986**, *51*, 1745.

⁵¹²Knochel; Normant *J. Organomet. Chem.* **1986**, *309*, 1.

⁵¹³Retherford; Yeh; Schipor; Chen; Knochel *J. Org. Chem.* **1989**, *54*, 5200.

⁵¹⁴Pecunioso; Menicagli *Tetrahedron* **1987**, *43*, 5411, *J. Org. Chem.* **1988**, *53*, 45.

⁵¹⁵Negishi; Van Horn; Yoshida; Rand *Organometallics* **1983**, *2*, 563.

⁵¹⁶Cacchi; Felici; Pietroni *Tetrahedron Lett.* **1984**, *25*, 3137.

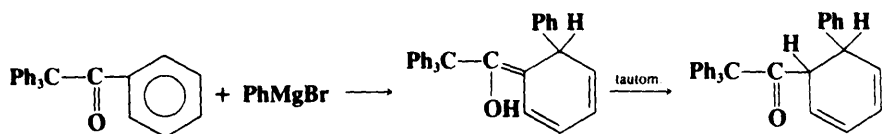
⁵¹⁷For some examples, see Isobe; Funabashi; Ichikawa; Mio; Goto *Tetrahedron Lett.* **1984**, *25*, 2021; Kawasaki; Tomioka; Koga *Tetrahedron Lett.* **1985**, *26*, 3031; Yamamoto; Nishii; Ibuka *J. Chem. Soc., Chem. Commun.* **1987**, 464, 1572; Smith; Dunlap; Sulikowski *Tetrahedron Lett.* **1988**, *29*, 439; Smith; Trumper *Tetrahedron Lett.* **1988**, *29*, 443; Alexakis; Sedrani; Mangeney; Normant *Tetrahedron Lett.* **1988**, *29*, 4411; Larchevêque; Tamagnan; Petit *J. Chem. Soc., Chem. Commun.* **1989**, 31; Page; Prodger; Hursthouse; Mazid *J. Chem. Soc., Perkin Trans. 1* **1990**, 167; Corey; Hannon *Tetrahedron Lett.* **1990**, *31*, 1393.

⁵¹⁸For reviews, see Posner *Acc. Chem. Res.* **1987**, *20*, 72-78; in Morrison, Ref. 232, vol. 2, 1983, the articles by Tomioka; Koga pp. 201-224; Posner, pp. 225-241.

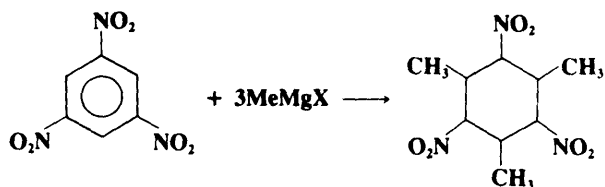
⁵¹⁹For other examples, see Oppolzer; Moretti; Godel; Meunier; Löhner *Tetrahedron Lett.* **1983**, *24*, 4971; Helmchen; Wegner *Tetrahedron Lett.* **1985**, *26*, 6051; Corey; Naef; Hannon *J. Am. Chem. Soc.* **1986**, *108*, 7114; Dieter; Tokles *J. Am. Chem. Soc.* **1987**, *109*, 2040; Ahn; Klassen; Lippard *Organometallics* **1990**, *9*, 3178; Alexakis; Sedrani; Mangeney *Tetrahedron Lett.* **1990**, *31*, 345; Rossiter; Eguchi *Tetrahedron Lett.* **1990**, *31*, 965; Bolm; Ewald *Tetrahedron Lett.* **1990**, *31*, 5011; Jansen; Feringa *J. Org. Chem.* **1990**, *55*, 4168; Soai; Okudo; Okamoto *Tetrahedron Lett.* **1991**, *32*, 95.

⁵²⁰Posner; Kogan; Hulce *Tetrahedron Lett.* **1984**, *25*, 383.

In certain cases, Grignard reagents add 1,4 to aromatic systems, e.g.,⁵²¹

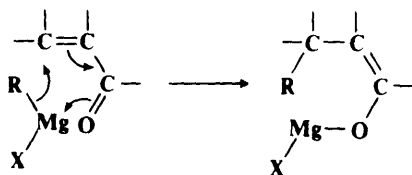


Such cyclohexadienes are easily oxidizable to benzenes (often by atmospheric oxygen), so this reaction becomes a method of alkylating and arylating suitably substituted (usually hindered) aryl ketones. A similar reaction has been reported for aromatic nitro compounds:⁵²²



Both Grignard and R_2CuLi reagents⁵²³ have also been added to triple-bond systems of the form $C\equiv C-C=O$.⁵²⁴

The mechanisms of most of these reactions are not well known. The 1,4 uncatalyzed Grignard reaction has been postulated to proceed by a cyclic mechanism



but there is evidence against it.⁵²⁵ The R_2CuLi and copper-catalyzed Grignard additions may involve a number of mechanisms, since the actual attacking species and substrates are so diverse.⁵²⁶ A free-radical mechanism of some type (perhaps SET) has been suggested⁵²⁷

⁵²¹This example is from Schmidlin; Wohl *Ber.* **1910**, *43*, 1145; Mosher; Huber *J. Am. Chem. Soc.* **1953**, *75*, 4604. For a review of such reactions see Fuson *Adv. Organomet. Chem.* **1964**, *1*, 221-238.

⁵²²Severin; Schmitz *Chem. Ber.* **1963**, *96*, 3081. See also Bartoli; Bosco; Baccolini *J. Org. Chem.* **1980**, *45*, 522; Bartoli *Acc. Chem. Res.* **1984**, *17*, 109-115; Bartoli; Dalpozzo; Grossi *J. Chem. Soc., Perkin Trans. 2* **1989**, 573. For a study of the mechanism, see Bartoli; Bosco; Cantagalli; Dalpozzo; Ciminale *J. Chem. Soc., Perkin Trans. 2* **1985**, 773.

⁵²³For example see Corey; Kim; Chen; Takeda *J. Am. Chem. Soc.* **1972**, *94*, 4395; Anderson; Corbin; Cotterrell; Cox; Henrick; Schaub; Siddall *J. Am. Chem. Soc.* **1975**, *97*, 1197.

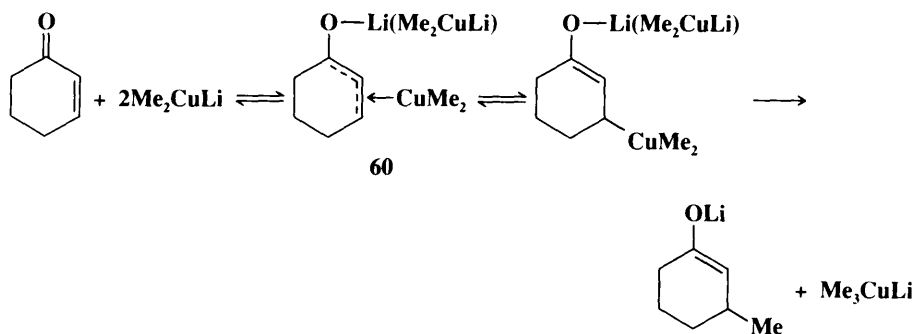
⁵²⁴For a review of the addition of organometallic reagents to conjugated enynes see Miginiac *J. Organomet. Chem.* **1982**, *238*, 235-266.

⁵²⁵House; Thompson *J. Org. Chem.* **1963**, *28*, 360; Klein *Tetrahedron* **1964**, *20*, 465. See however Marets; Rivière *Bull. Soc. Chim. Fr.* **1970**, 4320.

⁵²⁶For some mechanistic investigations see Berlan; Battioni; Koosha *J. Organomet. Chem.* **1978**, *152*, 359. *Bull. Soc. Chim. Fr.* **1979**, II-183; Four; Riviere; Tang *Tetrahedron Lett.* **1977**, 3879; Casey; Cesa *J. Am. Chem. Soc.* **1979**, *101*, 4236; Smith; Hannah *Tetrahedron* **1979**, *35*, 1183; Krauss; Smith *J. Am. Chem. Soc.* **1981**, *103*, 141; Bartoli; Bosco; Dal Pozzo; Ciminale *J. Org. Chem.* **1982**, *47*, 5227; Corey; Boaz *Tetrahedron Lett.* **1985**, *26*, 6015; Yamamoto; Yamada; Ueyehara *J. Am. Chem. Soc.* **1987**, *109*, 5820; Ullenius; Christenson *Pure Appl. Chem.* **1988**, *60*, 57; Christenson; Olsson; Ullenius *Tetrahedron* **1989**, *45*, 523; Krause *Tetrahedron Lett.* **1989**, *30*, 5219.

⁵²⁷See, for example, House; Umen *J. Am. Chem. Soc.* **1972**, *94*, 5495; Ruden; Litterer *Tetrahedron Lett.* **1975**, 2043; House; Snoble *J. Org. Chem.* **1976**, *41*, 3076; Wigal; Grunwell; Hershberger; *J. Org. Chem.* **1991**, *56*, 3759.

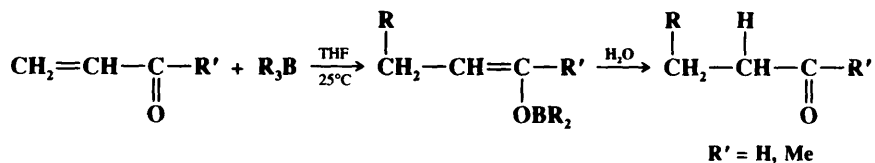
though the fact that retention of configuration at R has been demonstrated in several cases rules out a completely free R• radical.⁵²⁸ For simple α,β -unsaturated ketones, such as 2-cyclohexenone, and Me_2CuLi , there is evidence⁵²⁹ for this mechanism:



60 is a d, π^* complex, with bonding between copper, as a base supplying a pair of d electrons, and the enone as a Lewis acid using the π^* orbital of the allylic system.⁵²⁹ The ^{13}C nmr spectrum of an intermediate similar to **60** has been reported.⁵³⁰ The addition of R_3Al takes place by a free-radical mechanism.⁵⁰⁵

For the addition of organocopper reagents to alkynes and conjugated dienes, see **5-53**.
OS IV, 93; V, 762; VI, 442, 666, 762, 786; **65**, 203; **66**, 43, 52, 95.

5-19 The Addition of Boranes to Activated Double Bonds Hydro-alkyl-addition (overall transformation)



Trialkylboranes rapidly add to the double bonds of acrolein, methyl vinyl ketone, and certain of their derivatives in THF at 25°C to give enol borinates, which can be hydrolyzed to aldehydes or ketones.⁵³¹ The water may be present from the beginning, so the reaction can be run in one laboratory step. Since the boranes can be prepared from olefins (**5-12**), this reaction provides a means of lengthening a carbon chain by three or four carbons, respectively. Compounds containing a terminal alkyl group, such as crotonaldehyde $\text{CH}_3\text{CH}=\text{CHCHO}$ and 3-penten-2-one, fail to react under these conditions, as does acrylonitrile, but these compounds can be induced to react by the slow and controlled addition of O_2 or by initiation with peroxides or uv light.⁵³² A disadvantage is that only one of the

⁵²⁸Näf; Degen *Helv. Chim. Acta* **1971**, *54*, 1939; Whitesides; Kendall *J. Org. Chem.* **1972**, *37*, 3718. See also Ref. 465.

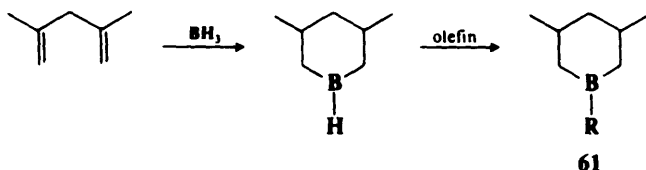
⁵²⁹Corey; Hannon; Boaz *Tetrahedron* **1989**, *45*, 545.

⁵³⁰Bertz; Smith *J. Am. Chem. Soc.* **1989**, *111*, 8276.

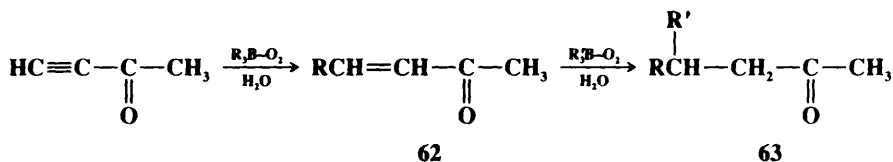
⁵³¹Suzuki; Arase; Matsumoto; Itoh; Brown; Rogić; Rathke *J. Am. Chem. Soc.* **1967**, *89*, 5708; Köster; Zimmermann; Fenzl *Liebigs Ann. Chem.* **1976**, 1116. For reviews see Pelter; Smith; Brown; Ref. 348, pp. 301-305, 318-323; Brown; Midland *Angew. Chem. Int. Ed. Engl.* **1972**, *11*, 692-700, pp. 694-698 [*Angew. Chem.* **84**, 702-710]; Kabalka *Intra-Sci. Chem. Rep.* **1973**, *7*(1), 57-64; Brown *Boranes in Organic Chemistry*, Ref. 348, pp. 413-433.

⁵³²Brown; Kabalka *J. Am. Chem. Soc.* **1970**, *92*, 712, 714. See also Utimoto; Tanaka; Furubayashi; Nozaki *Tetrahedron Lett.* **1973**, 787; Miyaura; Kashiwagi; Itoh; Suzuki *Chem. Lett.* **1974**, 395.

three R groups of R_3B adds to the substrate, so that the other two are wasted. This difficulty is overcome by the use of a B-alkyl borinate such as **61**,⁵³³ which can be prepared as shown.



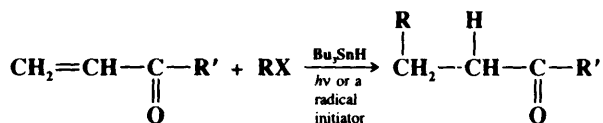
61 (R = *t*-butyl) can be made by treatment of **61** (R = OMe) with *t*-BuLi. The use of this reagent permits *t*-butyl groups to be added. B-1-Alkenyl-9-BBN compounds B-RCH=CR'-9-BBN (prepared by treatment of alkynes with 9-BBN or of RCH=CR'Li with B-methoxy-9-BBN⁵³⁴) add to methyl vinyl ketones to give, after hydrolysis, γ,δ -unsaturated ketones,⁵³⁵ though B-R-9-BBN, where R = a saturated group, are not useful here, because the R group of these reagents does not preferentially add to the substrate.⁵³³ The corresponding B-1-alkynyl-9-BBN compounds also give the reaction.⁵³⁶ Like the three substrates mentioned above, 3-butyne-2-one fails to react in the absence of air but undergoes the reaction when exposed to a slow stream of air.⁵³⁷



Since the product, **62**, is an α,β -unsaturated ketone, it can be made to react with another BR_3 , the same or different, to produce a wide variety of ketones **63**.

The fact that these reactions are catalyzed by free-radical initiators and inhibited by galvinoxyl⁵³⁸ (a free-radical inhibitor) indicates that free-radical mechanisms are involved.

5-70 The Addition of Tin and Mercury Hydrides to Activated Double Bonds Hydro-alkyl-addition



In a reaction similar to **5-19**, alkyl groups can be added to olefins activated by such groups as COR', COOR', CN, and even Ph.⁵³⁹ In the method illustrated above, the R group comes

⁵³³Brown; Negishi *J. Am. Chem. Soc.* **1971**, *93*, 3777.

⁵³⁴Brown; Bhat; Rajagopalan *Organometallics* **1986**, *5*, 816.

⁵³⁵Jacob; Brown *J. Am. Chem. Soc.* **1976**, *98*, 7832; Satoh; Serizawa; Hara; Suzuki *J. Am. Chem. Soc.* **1985**, *107*, 5225. See also Molander; Singaram; Brown *J. Org. Chem.* **1984**, *49*, 5024. Alkenyldialkoxyboranes, together with BF_3 -etherate, also transfer vinylic groups; Hara; Hyuga; Aoyama; Sato; Suzuki *Tetrahedron Lett.* **1990**, *31*, 247.

⁵³⁶Sinclair; Molander; Brown *J. Am. Chem. Soc.* **1977**, *99*, 954. See also Molander; Brown *J. Org. Chem.* **1977**, *42*, 3106.

⁵³⁷Suzuki; Nozawa; Itoh; Brown; Kabalka; Holland *J. Am. Chem. Soc.* **1970**, *92*, 3503.

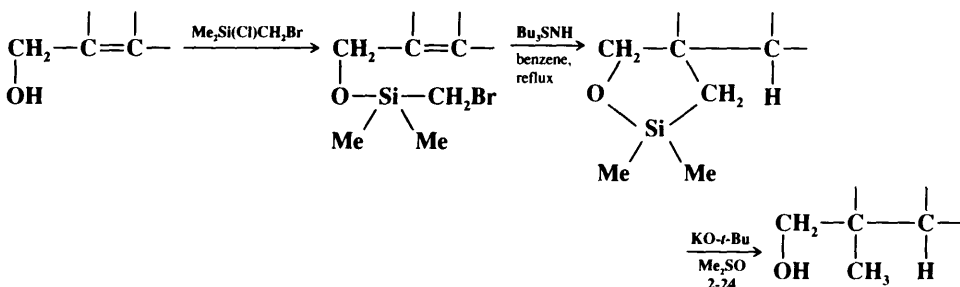
⁵³⁸Kabalka; Brown; Suzuki; Honma; Arase; Itoh *J. Am. Chem. Soc.* **1970**, *92*, 710. See also Arase; Masuda; Suzuki *Bull. Chem. Soc. Jpn.* **1976**, *49*, 2275.

⁵³⁹For reviews, see Giese, Ref. 50, pp. 36-68; Giese *Angew. Chem. Int. Ed. Engl.* **1985**, *24*, 553-565 [*Angew. Chem.* *97*, 555-567]; Larock *Organomercury Compounds in Organic Synthesis*; Springer: New York, 1985, pp. 263-273. The last review includes a table with many examples of the mercury method. For a list of reagents, with references, see Ref. 133, pp. 915-916.

from an alkyl halide (R = primary, secondary, or tertiary alkyl; X = Br or I) and the hydrogen from the tin hydride. Organomercury hydrides RHgH , generated in situ from RHgX and NaBH_4 , can also be used.⁵⁴⁰ When the tin method is used, Bu_3SnH can also be generated in a similar way, from R_3SnX and NaBH_4 . The tin method has a broader scope (e.g., it can be used on $\text{CH}_2=\text{CCl}_2$), but the mercury method uses milder reaction conditions. Like **5-19**, these additions have free-radical mechanisms. The reaction has been used for free-radical cyclizations of the type discussed on p. 752.⁵⁴¹ Such cyclizations normally give predominant formation of 5-membered rings, but large rings (11 to 20 members) have also been synthesized by this reaction.⁵⁴²

Free-radical addition of an aryl group and a hydrogen has been achieved by treatment of activated olefins with a diazonium salt and TiCl_3 .⁵⁴³

In a related reaction, a methyl group and a hydrogen can be added indirectly to the double bond of an otherwise unactivated allylic alcohol in this manner:⁵⁴⁴

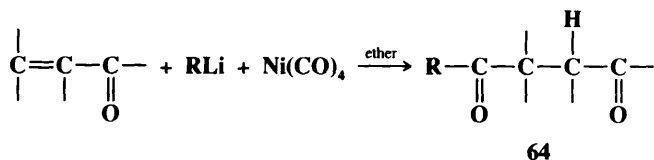


This procedure has been used to introduce angular methyl groups (methyl groups at the bridgeheads of fused rings).⁵⁴⁵

OS VII, 105.

5-21 Acylation of Activated Double Bonds and of Triple Bonds

Hydro-acyl-addition



An acyl group can be introduced into the 4 position of an α,β -unsaturated ketone by treatment with an organolithium compound and nickel carbonyl.⁵⁴⁶ The product is a 1,4-

⁵⁴⁰For the use of tris(trimethylsilyl)silane instead, see Giese; Koppang; Chatgililoglu *Tetrahedron Lett.* **1989**, 30, 681.

⁵⁴¹For reviews, see Jasperse; Curran; Fevig *Chem. Rev.* **1991**, 91, 1237-1286; Curran *Adv. Free Radical Chem. (Greenwich, Conn.)* **1990**, 1, 121-157; Giese, Ref. 50, pp. 151-169. For a list of references, see Ref. 133, pp. 215-216.

⁵⁴²See Porter; Chang *J. Am. Chem. Soc.* **1987**, 109, 4976.

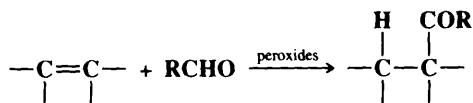
⁵⁴³Citterio; Vismara *Synthesis* **1980**, 291. For other methods of adding an alkyl or aryl group and a hydrogen to activated double bonds by free-radical processes, see Cacchi; Palmieri *Synthesis* **1984**, 575; Lebedev; Lopatina; Berestova; Petrov; Beletskaya *J. Org. Chem. USSR* **1986**, 22, 1238; Barton; Crich *J. Chem. Soc., Perkin Trans. I* **1986**, 1603; Luche; Allavena *Tetrahedron Lett.* **1988**, 29, 5369; Varea; González-Núñez; Rodrigo-Chiner; Asensio *Tetrahedron Lett.* **1989**, 30, 4709; Barton; Sarma *Tetrahedron Lett.* **1990**, 31, 1965.

⁵⁴⁴Stork; Sofia *J. Am. Chem. Soc.* **1986**, 108, 6826. See also Stork *Bull. Chem. Soc. Jpn.* **1988**, 61, 149.

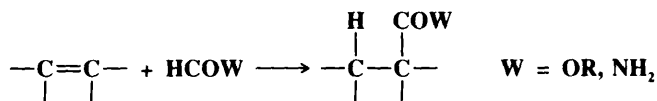
⁵⁴⁵Stork; Mah *Tetrahedron Lett.* **1989**, 30, 3609.

⁵⁴⁶Corey; Hegedus *J. Am. Chem. Soc.* **1969**, 91, 4926.

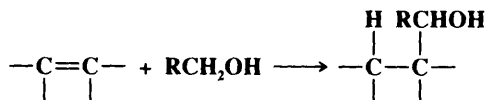
5-22 Addition of Alcohols, Amines, Carboxylic Esters, Aldehydes, etc.
Hydro-acyl-addition, etc.



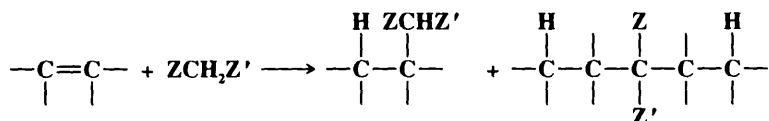
Aldehydes, formates, primary, and secondary alcohols, amines, ethers, alkyl halides, compounds of the type $\text{Z---CH}_2\text{---Z}'$, and a few other compounds add to double bonds in the presence of free-radical initiators.⁵⁵⁸ This is formally the addition of RH to a double bond, but the "R" is not just any carbon but one connected to an oxygen or a nitrogen, a halogen, or to two Z groups (defined as on p. 464). The addition of aldehydes is illustrated above. Formates and formamides⁵⁵⁹ add similarly:



Alcohols, ethers, amines, and alkyl halides add as follows (shown for alcohols):



$\text{ZCH}_2\text{Z}'$ compounds react at the carbon bearing the active hydrogen:⁵⁶⁰



Similar additions have been successfully carried out with carboxylic acids, anhydrides,⁵⁶¹ acyl halides, carboxylic esters, nitriles, and other types of compounds.⁵⁶²

These reactions are not successful when the olefin contains electron-withdrawing groups such as halo or carbonyl groups. A free-radical initiator is required, usually peroxides or

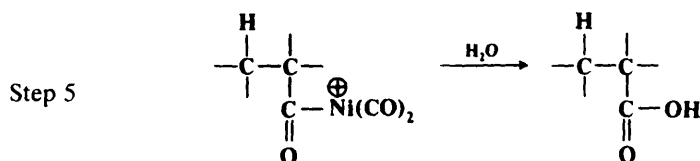
⁵⁵⁸For reviews see Giese, Ref. 50, pp. 69-77; Vogel *Synthesis* **1970**, 99-140; Huyser, Ref. 49, pp.152-159; Elad *Fortschr. Chem. Forsch.* **1967**, 7, 528-558.

⁵⁵⁹Elad, Ref. 558, pp. 530-543.

⁵⁶⁰For example, see Cadogan; Hey; Sharp *J. Chem. Soc. C* **1966**, 1743; *J. Chem. Soc. B* **1967**, 803; Hájek; Málek *Coll. Czech. Chem. Commun.* **1979**, 44, 3695.

⁵⁶¹de Klein *Recl. Trav. Chim. Pays-Bas* **1975**, 94, 48.

⁵⁶²Allen; Cadogan; Hey *J. Chem. Soc.* **1965**, 1918; Cadogan *Pure Appl. Chem.* **1967**, 15, 153-165, pp. 153-158. See also Giese; Zwick *Chem. Ber.* **1982**, 115, 2526; Giese; Erfort *Chem. Ber.* **1983**, 116, 1240.

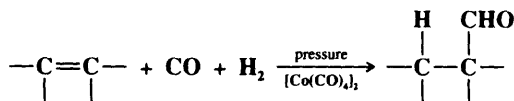


Step 3 is an electrophilic substitution. The principal step of the mechanism, step 4, is a rearrangement.

In either the acid catalysis or the nickel carbonyl (or other metallic catalyst) method, if alcohols, thiols, amines, etc. are used instead of water, the product is the corresponding ester, thiol ester, or amide, instead of the carboxylic acid.

5-24 Hydroformylation

Hydro-formyl-addition



Olefins can be hydroformylated⁵⁷⁴ by treatment with carbon monoxide and hydrogen over a catalyst. The most common catalysts are cobalt carbonyls and rhodium complexes⁵⁷⁵ [e.g., hydridocarbonyltris(triphenylphosphine)rhodium], but other transition metal compounds have also been used. Cobalt catalysts are less active than the rhodium type, and catalysts of other metals are less active still.⁵⁷⁶ Commercially, this is called the *oxo process*, but it can be carried out in the laboratory in an ordinary hydrogenation apparatus. The order of reactivity is straight-chain terminal olefins > straight-chain internal olefins > branched-chain olefins. Conjugated dienes give dialdehydes when rhodium catalysts are used⁵⁷⁷ but saturated monoaldehydes (the second double bond is reduced) with cobalt carbonyls. 1,4- and 1,5-dienes may give cyclic ketones.⁵⁷⁸ Many functional groups, e.g., OH, CHO, COOR, CN, can be present in the molecule, though halogens usually interfere. Hydroformylation of triple bonds proceeds very slowly, and few examples have been reported.⁵⁷⁹ Among the side

⁵⁷⁴For reviews, see Kalck; Peres; Jenck *Adv. Organomet. Chem.* **1991**, 32, 121-146; Davies, in Hartley; Patai, Ref. 422, vol. 3, pp. 361-389; Pino; Piacenti; Bianchi, in Wender; Pino, Ref. 565, pp. 43-231; Cornils, in Falbe *New Syntheses with Carbon Monoxide*, Ref. 565, pp. 1-225; Collman et al., Ref. 223, pp. 621-632; Pino *J. Organomet. Chem.* **1980**, 200, 223-242; Pruett *Adv. Organomet. Chem.* **1979**, 17, 1-60; Stille; James, in Patai, Ref. 1, pt. 2, pp. 1099-1166; Heck, Ref. 223, pp. 215-224; Khan; Martell, Ref. 159, vol. 2, pp. 39-60; Falbe *Carbon Monoxide in Organic Synthesis*, Ref. 565, pp. 3-77; Chalk; Harrod *Adv. Organomet. Chem.* **1968**, 6, 119-170. For a review with respect to fluoroolefins, see Ohshiro; Hirao, Ref. 571.

⁵⁷⁵For example, see Osborn; Wilkinson; Young *Chem. Commun.* **1965**, 17; Brown; Wilkinson *Tetrahedron Lett.* **1969**, 1725, *J. Chem. Soc. A* **1970**, 2753; Stefani; Consiglio; Botteghi; Pino *J. Am. Chem. Soc.* **1973**, 95, 6504; Bott *Chem. Ber.* **1975**, 108, 997; van Leeuwen; Roobeck *J. Organomet. Chem.* **1983**, 258, 343; Salvadori; Vitulli; Raffaelli; Lazzaroni *J. Organomet. Chem.* **1983**, 258, 351; Collman; Belmont; Brauman *J. Am. Chem. Soc.* **1983**, 105, 7288; Brown; Kent *J. Chem. Soc., Perkin Trans. 1* **1987**, 1597; Hanson; Davis *J. Chem. Educ.* **1987**, 64, 928; Jackson; Perlmutter; Suh *J. Chem. Soc., Chem. Commun.* **1987**, 724; Hendriksen; Oswald; Ansell; Leta; Kastrup *Organometallics* **1989**, 8, 1153; Lazzaroni; Uccello-Barretta; Benetti *Organometallics* **1989**, 8, 2323; Amer; Alper *J. Am. Chem. Soc.* **1990**, 112, 3674. For a review of the rhodium-catalyzed process, see Jardine, in Hartley, Ref. 218, vol. 4, pp. 733-818, pp. 778-784.

⁵⁷⁶Collman et al., Ref. 223, p. 630.

⁵⁷⁷Fell; Rupilius *Tetrahedron Lett.* **1969**, 2721.

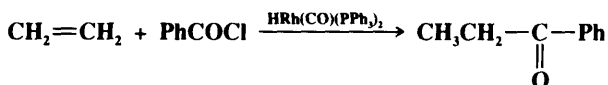
⁵⁷⁸For a review of ring closure reactions with CO, see Mullen, in Falbe *New Syntheses with Carbon Monoxide*, Ref. 565, pp. 414-439. See also Eilbracht; Hüttmann; Deussen *Chem. Ber.* **1990**, 123, 1063, and other papers in this series.

⁵⁷⁹For examples with rhodium catalysts, see Fell; Beutler *Tetrahedron Lett.* **1972**, 3455; Botteghi; Salomon *Tetrahedron Lett.* **1974**, 4285. For an indirect method, see Campi; Fitzmaurice; Jackson; Perlmutter; Smallridge *Synthesis* **1987**, 1032.

reactions are the aldol reaction (6-39), acetal formation, the Tishchenko reaction (9-70), and polymerization. Stereoselective syn addition has been reported.⁵⁸⁰ Asymmetric hydroformylation has been accomplished with a chiral catalyst.⁵⁸¹

When dicobalt octacarbonyl $[\text{Co}(\text{CO})_4]_2$ is the catalyst, the species that actually adds to the double bond is tricarbonylhydrocobalt $\text{HCo}(\text{CO})_3$.⁵⁸² Carbonylation $\text{RCo}(\text{CO})_3 + \text{CO} \rightarrow \text{RCo}(\text{CO})_4$ takes place, followed by a rearrangement and a reduction of the C—Co bond, similar to steps 4 and 5 of the nickel carbonyl mechanism shown in 5-23. The reducing agent in the reduction step is tetracarbonylhydrocobalt $\text{HCo}(\text{CO})_4$,⁵⁸³ or, under some conditions, H_2 .⁵⁸⁴ When $\text{HCo}(\text{CO})_4$ was the agent used to hydroformylate styrene, the observation of CIDNP indicated that the mechanism is different, and involves free radicals.⁵⁸⁵ Alcohols can be obtained by allowing the reduction to continue after all the carbon monoxide is used up. It has been shown⁵⁸⁶ that the formation of alcohols is a second step, occurring after the formation of aldehydes, and that $\text{HCo}(\text{CO})_3$ is the reducing agent.

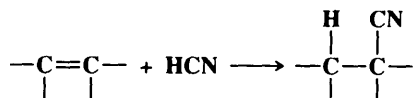
An indirect method for the hydroformylation of olefins involves formation of the trialkylborane (5-12) and treatment of this with carbon monoxide and a reducing agent (see 8-26). *Hydroacylation* of alkenes has been accomplished, in variable yields, by treatment with an acyl halide and a rhodium complex catalyst, e.g.,⁵⁸⁷



OS VI, 338.

5-25 Addition of HCN

Hydro-cyano-addition



Ordinary olefins do not react with HCN, but polyhalo olefins and olefins of the form $\text{C}=\text{C}-\text{Z}$ add HCN to give nitriles.⁵⁸⁸ The reaction is therefore a nucleophilic addition and is base-

⁵⁸⁰See, for example, Haelg; Consiglio; Pino *Helv. Chim. Acta* **1981**, *64*, 1865.

⁵⁸¹For reviews, see Ojima; Hirai, in Morrison, Ref. 232, vol. 5, 1985, pp. 103-145, pp. 125-139; Consiglio; Pino *Top. Curr. Chem.* **1982**, *105*, 77-123. See also Kollár; Bakos; Tóth; Heil *J. Organomet. Chem.* **1988**, *350*, 277, **1989**, *370*, 257; Pottier; Mortreux; Petit *J. Organomet. Chem.* **1989**, *370*, 333; Stille; Su; Brechot; Parrinello; Hegedus *Organometallics* **1991**, *10*, 1183; Consiglio; Nefkens; Borer *Organometallics* **1991**, *10*, 2046.

⁵⁸²Heck; Breslow, *Chem. Ind. (London)* **1960**, 467, *J. Am. Chem. Soc.* **1961**, *83*, 4023; Karapinka; Orchin *J. Org. Chem.* **1961**, *26*, 4187; Whyman *J. Organomet. Chem.* **1974**, *81*, 97; Mirbach *J. Organomet. Chem.* **1984**, 265, 205. For discussions of the mechanism see Orchin *Acc. Chem. Res.* **1981**, *14*, 259-266; Versluis; Ziegler; Baerends; Ravenek *J. Am. Chem. Soc.* **1989**, *111*, 2018.

⁵⁸³Alemdaroglu; Penninger; Oltay *Monatsh. Chem.* **1976**, *107*, 1153; Ungváry; Markó *Organometallics* **1982**, *1*, 1120.

⁵⁸⁴See Kovács; Ungváry; Markó *Organometallics* **1986**, *5*, 209.

⁵⁸⁵Bockman; Garst; King; Markó; Ungváry *J. Organomet. Chem.* **1985**, 279, 165.

⁵⁸⁶Aldridge; Jonassen *J. Am. Chem. Soc.* **1963**, *85*, 886.

⁵⁸⁷Schwartz; Cannon *J. Am. Chem. Soc.* **1974**, *96*, 4721. For some other hydroacylation methods see Cooke; Parlman *J. Am. Chem. Soc.* **1977**, *99*, 5222; Larock; Bernhardt *J. Org. Chem.* **1978**, *43*, 710; Suggs *J. Am. Chem. Soc.* **1979**, *101*, 489; Isnard; Denise; Sneed; Cognion; Durual *J. Organomet. Chem.* **1982**, *240*, 285; Zudin; Il' nich; Likholobov; Yermakov *J. Chem. Soc., Chem. Commun.* **1984**, 545; Kondo; Akazome; Tsuji; Watanabe *J. Org. Chem.* **1990**, *55*, 1286.

⁵⁸⁸For reviews see Friedrich, in Patai; Rappoport, Ref. 49, pt. 2, pp. 1345-1390; Nagata; Yoshioka *Org. React.* **1977**, *25*, 255-476; Brown, in Wender; Pino, Ref. 565, pp. 655-672; Friedrich; Wallenfels, in Rappoport *The Chemistry of the Cyano Group*; Wiley: New York, 1970, pp. 68-72.

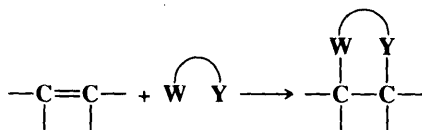
catalyzed. When Z is COR or, more especially, CHO, 1,2 addition (6-51) is an important competing reaction and may be the only reaction. Triple bonds react very well when catalyzed by an aqueous solution of CuCl, NH₄Cl, and HCl or by Ni or Pd compounds.⁵⁸⁹ The HCN can be generated in situ from acetone cyanohydrin (see 6-49), avoiding the use of the poisonous HCN.⁵⁹⁰ One or two moles of HCN can be added to a triple bond, since the initial product is a Michael-type substrate. Acrylonitrile is commercially prepared this way, by the addition of HCN to acetylene. Alkylaluminum cyanides, e.g., Et₂AlCN, or mixtures of HCN and trialkylalanes R₃Al are especially good reagents for conjugate addition of HCN⁵⁹¹ to α,β-unsaturated ketones and α,β-unsaturated acyl halides. HCN can be added to ordinary olefins in the presence of dicobalt octacarbonyl⁵⁹² or certain other transition-metal compounds.⁵⁹³ An indirect method for the addition of HCN to ordinary olefins uses an isocyanide RNC and Schwartz's reagent (see 5-13); this method gives anti-Markovnikov addition.⁵⁹⁴ *t*-Butyl isocyanide and TiCl₄ have been used to add HCN to C=C-Z olefins.⁵⁹⁵

OS I, 451; II, 498; III, 615; IV, 392, 393, 804; V, 239, 572; VI, 14.

For addition of ArH, see 1-12 (Friedel-Crafts alkylation).

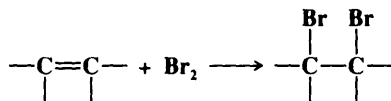
Reactions in Which Hydrogen Adds to Neither Side

Some of these reactions are *cycloadditions* (reactions 5-36, 5-37, 5-42, and 5-45 to 5-52). In such cases addition to the multiple bond closes a ring:



A. Halogen on One or Both Sides

5-26 Halogenation of Double and Triple Bonds (Addition of Halogen, Halogen) Dihalo-addition



⁵⁸⁹Jackson; Lovel *Aust. J. Chem.* **1983**, 36, 1975.

⁵⁹⁰Jackson; Perlmutter *Chem. Br.* **1986**, 338.

⁵⁹¹For a review, see Nagata; Yoshioka Ref. 588.

⁵⁹²Arthur; England; Pratt; Whitman *J. Am. Chem. Soc.* **1954**, 76, 5364.

⁵⁹³For a review, see Brown, Ref. 588, pp. 658-667. For a review of the nickel-catalyzed process, see Tolman; McKinney; Seidel; Druliner; Stevens *Adv. Catal.* **1985**, 33, 1-46. For studies of the mechanism see Tolman; Seidel; Druliner; Domaille *Organometallics* **1984**, 3, 33; Druliner *Organometallics* **1984**, 3, 205; Bäckvall; Andell *Organometallics* **1986**, 5, 2350; McKinney; Roe *J. Am. Chem. Soc.* **1986**, 108, 5167; Funabiki; Tatsami; Yoshida *J. Organomet. Chem.* **1990**, 384, 199. See also Jackson; Lovel; Perlmutter; Smallridge *Aust. J. Chem.* **1988**, 41, 1099.

⁵⁹⁴Buchwald; LeMaire *Tetrahedron Lett.* **1987**, 28, 295.

⁵⁹⁵Ito; Kato; Imai; Saegusa *J. Am. Chem. Soc.* **1982**, 104, 6449.

Most double bonds are easily halogenated⁵⁹⁶ with bromine, chlorine, or interhalogen compounds.⁵⁹⁷ Iodination has also been accomplished, but the reaction is slower.⁵⁹⁸ Under free-radical conditions, iodination proceeds more easily.⁵⁹⁹ However, vic-diiodides are generally unstable and tend to revert to iodine and the olefin. The order of activity for some of the reagents is $\text{BrCl} > \text{ICl}^{600} > \text{Br}_2 > \text{IBr} > \text{I}_2$.⁶⁰¹ Mixed halogenations have also been achieved by other methods. Mixtures of Br_2 and Cl_2 have been used to give bromochlorination,⁶⁰² as has tetrabutylammonium dichlorobromate $\text{Bu}_4\text{NBrCl}_2$;⁶⁰³ iodochlorination has been achieved with CuCl_2 and either I_2 , HI , CdI_2 , or other iodine donors;⁶⁰⁴ iodo-fluorination⁶⁰⁵ with mixtures of AgF and I_2 ;⁶⁰⁶ and mixtures of N-bromo amides in anhydrous HF give bromofluorination.⁶⁰⁷ Bromo-, iodo-, and chlorofluorination have also been achieved by treatment of the substrate with a solution of Br_2 , I_2 , or an N-halo amide in polyhydrogen fluoride-pyridine;⁶⁰⁸ while addition of I along with Br, Cl, or F has been accomplished with the reagent bis(pyridine)iodyl tetrafluoroborate $\text{I}(\text{Py})_2\text{BF}_4$ and Br^- , Cl^- , or F^- , respectively.⁶⁰⁹ This reaction (which is also successful for triple bonds⁶¹⁰) can be extended to addition of I and other nucleophiles, e.g., NCO , OH , OAc , and NO_2 .⁶⁰⁹

Under ordinary conditions fluorine itself is too reactive to give simple addition; it attacks other bonds and mixtures are obtained.⁶¹¹ However, F_2 has been successfully added to certain double bonds in an inert solvent at low temperatures (-78°C), usually by diluting the F_2 gas with Ar or N_2 .⁶¹² Addition of fluorine has also been accomplished with other reagents, e.g., CoF_3 ,⁶¹³ XeF_2 ,⁶¹⁴ and a mixture of PbO_2 and SF_4 .⁶¹⁵

⁵⁹⁶For a list of reagents that have been used for di-halo-addition, with references, see Ref. 133, pp. 319-321.

⁵⁹⁷For a monograph, see de la Mare *Electrophilic Halogenation*; Cambridge University Press: Cambridge, 1976. For a review, see House, Ref. 144, pp. 422-431.

⁵⁹⁸Sumrell; Wyman; Howell; Harvey *Can. J. Chem.* **1964**, *42*, 2710; Zanger; Rabinowitz *J. Org. Chem.* **1975**, *40*, 248.

⁵⁹⁹Skell; Pavlis *J. Am. Chem. Soc.* **1964**, *86*, 2956; Ayres; Michejda; Rack *J. Am. Chem. Soc.* **1971**, *93*, 1389.

⁶⁰⁰For a review of ICl , see McClelland, in Pizey, Ref. 146, vol. 5, 1983, pp. 85-164.

⁶⁰¹White; Robertson *J. Chem. Soc.* **1939**, 1509.

⁶⁰²Buckles; Forrester; Burham; McGee *J. Org. Chem.* **1960**, *25*, 24.

⁶⁰³Negoro; Ikeda *Bull. Chem. Soc. Jpn.* **1986**, *59*, 3519.

⁶⁰⁴Baird; Surridge; Buza *J. Org. Chem.* **1971**, *36*, 2088, 3324.

⁶⁰⁵For a review of mixed halogenations where one side is fluorine, see Sharts; Sheppard *Org. React.* **1974**, *21*, 125-406, pp. 137-157. See also German; Zemskov, Ref. 612. For a review of halogen fluorides in organic synthesis, see Boguslavskaya *Russ. Chem. Rev.* **1984**, *53*, 1178-1194.

⁶⁰⁶Hall; Jones *Can. J. Chem.* **1973**, *51*, 2902. See also Zupan; Pollak *J. Org. Chem.* **1976**, *41*, 2179. *J. Chem. Soc., Perkin Trans. 1* **1976**, 1745; Rozen; Brand *Tetrahedron Lett.* **1980**, *21*, 4543; Evans; Schauble *Synthesis* **1987**, 551; Kuroboshi; Hiyama *Synlett* **1991**, 185.

⁶⁰⁷Robinson; Finckenor; Oliveto; Gould *J. Am. Chem. Soc.* **1959**, *81*, 2191; Bowers *J. Am. Chem. Soc.* **1959**, *81*, 4107; Pattison; Peters; Dean *Can. J. Chem.* **1965**, *43*, 1689. For other methods, see Boguslavskaya; Chuvatkin; Kartashov; Ternovskoi *J. Org. Chem. USSR* **1987**, *23*, 230; Shimizu; Nakahara; Yoshioka *J. Chem. Soc., Chem. Commun.* **1989**, 1881.

⁶⁰⁸Olah; Nojima; Kerekes *Synthesis* **1973**, 780; Ref. 135. For other halofluorination methods, see Rozen; Brand *J. Org. Chem.* **1985**, *50*, 3342, **1986**, *51*, 222; Alvernhe; Laurent; Haufe *Synthesis* **1987**, 562; Camps; Chamorro; Gasol; Guerrero *J. Org. Chem.* **1989**, *54*, 4294; Ichihara; Funabiki; Hanafusa *Tetrahedron Lett.* **1990**, *31*, 3167.

⁶⁰⁹Barluenga; González; Campos; Asensio *Angew. Chem. Int. Ed. Engl.* **1985**, *24*, 319 [*Angew. Chem.* **97**, 341].

⁶¹⁰Barluenga; Rodríguez; González; Campos; Asensio *Tetrahedron Lett.* **1986**, *27*, 3303.

⁶¹¹See, for example, Fuller; Stacey; Tatlow; Thomas *Tetrahedron* **1962**, *18*, 123.

⁶¹²Merritt; Stevens *J. Am. Chem. Soc.* **1966**, *88*, 1822; Merritt *J. Am. Chem. Soc.* **1967**, *89*, 609; Barton; Lister-James; Hesse; Pechet; Rozen *J. Chem. Soc., Perkin Trans. 1* **1982**, 1105; Rozen; Brand *J. Org. Chem.* **1986**, *51*, 3607. For reviews of the use of F_2 in organic synthesis, see Haas; Lieb *Chimia* **1985**, *39*, 134-140; Purrington; Kagen; Patrick *Chem. Rev.* **1986**, *86*, 997-1018. See also German; Zemskov *New Fluorinating Agents in Organic Synthesis*; Springer: New York, 1989.

⁶¹³Rausch; Davis; Osborne *J. Org. Chem.* **1963**, *28*, 494.

⁶¹⁴Zupan; Pollak *J. Org. Chem.* **1974**, *39*, 2646, **1976**, *41*, 4002, **1977**, *42*, 1559, *Tetrahedron Lett.* **1974**, 1015; Gregorič; Zupan *J. Org. Chem.* **1979**, *44*, 1255; Shackelford *J. Org. Chem.* **1979**, *44*, 3485; Filler *Isr. J. Chem.* **1978**, *17*, 71-79. For a review of fluorination with xenon fluorides see Zupan, in Patai; Rappoport *The Chemistry of Functional Groups, Supplement D*, pt. 1; Wiley: New York, 1983, pp. 657-679.

⁶¹⁵Bissell; Fields *J. Org. Chem.* **1964**, *29*, 1591.

The reaction with bromine is very rapid and is easily carried out at room temperature. Bromine is often used as a test, qualitative or quantitative, for unsaturation.⁶¹⁶ The vast majority of double bonds can be successfully brominated. Even when aldehyde, ketone, amine, etc. functions are present in the molecule, they do not interfere, since the reaction with double bonds is faster.

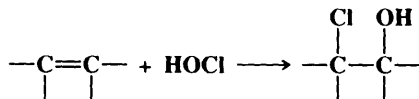
Several other reagents add Cl₂ to double bonds, among them SO₂Cl₂,⁶¹⁷ PCl₅,⁶¹⁸ Me₃SiCl-MnO₂,⁶¹⁹ MoCl₅,⁶²⁰ KMnO₄-oxalyl chloride,^{620a} and iodobenzene dichloride PhICl₂.⁶²¹ A convenient reagent for the addition of Br₂ to a double bond on a small scale is the commercially available pyridinium bromide perbromide C₅H₅NH⁺ Br₃⁻.⁶²² Br₂ or Cl₂ can also be added with CuBr₂ or CuCl₂ in the presence of a compound such as acetonitrile, methanol, or triphenylphosphine.⁶²³

The mechanism is usually electrophilic (see p. 737), but when free-radical initiators (or uv light) are present, addition can occur by a free-radical mechanism.⁶²⁴ Once Br• or Cl• radicals are formed, however, substitution may compete (4-1 and 4-2). This is especially important when the olefin has allylic hydrogens. Under free-radical conditions (uv light) bromine or chlorine adds to the benzene ring to give, respectively, hexabromo- and hexachlorocyclohexane. These are mixtures of stereoisomers (see p. 131).⁶²⁵

Conjugated systems give both 1,2 and 1,4 addition.⁶²⁵ Triple bonds add bromine, though generally more slowly than double bonds (see p. 748). Molecules that contain both double and triple bonds are preferentially attacked at the double bond. Two moles of bromine can be added to triple bonds to give tetrabromo products. There is evidence that the addition of the first mole of bromine to a triple bond may take place by a nucleophilic mechanism.⁶²⁶ I₂ on Al₂O₃ adds to triple bonds to give good yields of 1,2-diiodoalkenes.⁶²⁷ With allenes it is easy to stop the reaction after only 1 mole has added, to give X-C-CX=C.⁶²⁸ Addition of halogen to ketenes gives α-halo acyl halides, but the yields are not good.

OS I, 205, 521; II, 171, 177, 270, 408; III, 105, 123, 127, 209, 350, 526, 531, 731, 785; IV, 130, 195, 748, 851, 969; V, 136, 370, 403, 467; VI, 210, 422, 675, 862, 954.

5-27 Addition of Hypohalous Acids and Hypohalites (Addition of Halogen, Oxygen) Hydroxy-chloro-addition, etc.⁶²⁹



⁶¹⁶For a review of this, see Kuchar, in Patai, Ref. 36, pp. 273-280.

⁶¹⁷Kharasch; Brown *J. Am. Chem. Soc.* **1939**, *61*, 3432.

⁶¹⁸Spiegler; Tinker *J. Am. Chem. Soc.* **1939**, *61*, 940.

⁶¹⁹Bellesia; Ghelfi; Pagnoni; Pinetti *J. Chem. Res. (S)* **1989**, *108*, 360.

⁶²⁰Uemura; Onoe; Okano *Bull. Chem. Soc. Jpn.* **1974**, *47*, 3121; San Filippo; Sowinski; Romano *J. Am. Chem. Soc.* **1975**, *97*, 1599. See also Nugent *Tetrahedron Lett.* **1978**, 3427.

^{620a}Markó; Richardson *Tetrahedron Lett.* **1991**, *32*, 1831.

⁶²¹See, for example, Tanner; Gidley *J. Org. Chem.* **1968**, *33*, 38; Masson; Thuillier *Bull. Soc. Chim. Fr.* **1969**, 4368; Lasne; Thuillier *Bull. Soc. Chim. Fr.* **1974**, 249.

⁶²²Fieser; Fieser *Reagents for Organic Synthesis*, vol. 1; Wiley: New York, 1967, pp. 967-970. For a discussion of the mechanism with Br₃⁻, see Bellucci; Bianchini; Vecchiani *J. Org. Chem.* **1986**, *51*, 4224.

⁶²³Koyano *Bull. Chem. Soc. Jpn.* **1970**, *43*, 1439, 3501; Uemura; Tabata; Kimura; Ichikawa *Bull. Chem. Soc. Jpn.* **1971**, *44*, 1973; Or; Levy; Asscher; Vofsi *J. Chem. Soc., Perkin Trans. 2* **1974**, 857; Uemura; Okazaki; Onoe; Okano *J. Chem. Soc., Perkin Trans. 1* **1977**, 676; Ref. 604.

⁶²⁴For example, see Poutsma *J. Am. Chem. Soc.* **1965**, *87*, 2161, 2172, *J. Org. Chem.* **1966**, *31*, 4167; Dessau, *J. Am. Chem. Soc.* **1979**, *101*, 1344.

⁶²⁵For a review, see Cais, in Patai, Ref. 36, pp. 993-999.

⁶²⁶Sinn; Hopperditzel; Sauermann *Monatsh. Chem.* **1965**, *96*, 1036.

⁶²⁷Hondrogiannis; Lee; Kabalka; Pagni *Tetrahedron Lett.* **1989**, *30*, 2069.

⁶²⁸For a review of additions of halogens to allenes, see Jacobs, in Landor, Ref. 95, vol. 2, pp. 466-483.

⁶²⁹Addends are listed in order of priority in the Cahn-Ingold-Prelog system (p. 109).

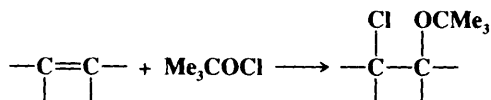
HOCl, HOBr, and HOI can be added to olefins⁶³⁰ to produce halohydrins.⁶³¹ HOBr and HOCl are often generated in situ by the reaction between water and Br₂ or Cl₂ respectively. HOI, generated from I₂ and H₂O, also adds to double bonds, if the reaction is carried out in tetramethylene sulfone-CHCl₃⁶³² or if an oxidizing agent such as HIO₃ is present.⁶³³ HOF has also been added, but this reagent is difficult to prepare in a pure state and detonations occur.⁶³⁴ HOBr can also be conveniently added by the use of a reagent consisting of an N-bromo amide [e.g., N-bromosuccinimide (NBS) or N-bromoacetamide] and a small amount of water in a solvent such as Me₂SO or dioxane.⁶³⁵ An especially powerful reagent for HOCl addition is *t*-butyl hydroperoxide (or di-*t*-butyl peroxide) along with TiCl₄. This reaction is generally complete within 15 min at -78°C.⁶³⁶ Chlorohydrins can be conveniently prepared by treatment of the alkene with Chloramine T (TsNCl⁻ Na⁺)⁶³⁷ in acetone-water.⁶³⁸ HOI can be added by treatment of alkenes with periodic acid and NaHSO₃.⁶³⁹

The mechanism of HOX addition is electrophilic, with initial attack by the positive halogen end of the HOX dipole. Following Markovnikov's rule, the positive halogen goes to the side of the double bond that has more hydrogens. The resulting carbocation (or bromonium or iodonium ion) reacts with OH⁻ or H₂O to give the product. If the substrate is treated with Br₂ or Cl₂ (or another source of positive halogen such as NBS) in an

alcohol or a carboxylic acid solvent, it is possible to obtain, directly $\text{X}-\overset{\text{R}}{\underset{\text{R}}{\text{C}}}-\overset{\text{R}}{\underset{\text{R}}{\text{C}}}-\text{OR}$ or $\text{X}-\overset{\text{R}}{\underset{\text{R}}{\text{C}}}-\overset{\text{R}}{\underset{\text{R}}{\text{C}}}-\text{OCOR}$, respectively (see also 5-35).⁶⁴⁰ Even the weak nucleophile CF₃SO₂O⁻

can participate in the second step: The addition of Cl₂ or Br₂ to olefins in the presence of this ion resulted in the formation of some β-haloalkyl triflates.⁶⁴¹ There is evidence that the mechanism with Cl₂ and H₂O is different from that with HOCl.⁶⁴² HOCl and HOBr can be added to triple bonds to give dihalo carbonyl compounds —CX₂—CO—.

t-Butyl hypochlorite, hypobromite, and hypoiodite⁶⁴³ add to double bonds to give halogenated *t*-butyl ethers, e.g.,



This is a convenient method for the preparation of tertiary ethers. When Me₃COCl or Me₃COBr is added to olefins in the presence of excess ROH, the ether produced is

⁶³⁰For a list of reagents used to accomplish these additions, with references, see Ref. 133, pp. 325-327.

⁶³¹For a review, see Boguslavskaya *Russ. Chem. Rev.* **1972**, *41*, 740-749.

⁶³²Cambie; Noall; Potter; Rutledge; Woodgate *J. Chem. Soc., Perkin Trans. 1* **1977**, 266.

⁶³³See, for example, Cornforth; Green *J. Chem. Soc. C* **1970**, 846; Furrow *Int. J. Chem. Kinet.* **1982**, *14*, 927; Antonioletti; D'Auria; De Mico; Piancatelli; Scettri *Tetrahedron* **1983**, *39*, 1765.

⁶³⁴Migliorese; Appelman; Tsangaris *J. Org. Chem.* **1979**, *44*, 1711.

⁶³⁵For examples, see Dalton; Hendrickson; Jones *Chem. Commun.* **1966**, 591; Dalton; Dutta *J. Chem. Soc. B* **1971**, 85; Sisti *J. Org. Chem.* **1970**, *35*, 2670.

⁶³⁶Klunder; Caron; Uchiyama; Sharpless *J. Org. Chem.* **1985**, *50*, 912.

⁶³⁷For reviews of this reagent, see Bremner, in Pizey, Ref. 146, vol. 6, 1985, pp. 9-59; Campbell; Johnson *Chem. Rev.* **1978**, *78*, 65-79.

⁶³⁸Damin; Garapon; Sillion *Synthesis* **1981**, 362.

⁶³⁹Ohta; Sakata; Takeuchi; Ishii *Chem. Lett.* **1990**, 733.

⁶⁴⁰For a list of reagents that accomplish alkoxy-halo-addition, with references, see Ref. 133, pp. 327-328.

⁶⁴¹Zefirov; Koz'min; Sorokin; Zhdankin *J. Org. Chem. USSR* **1982**, *18*, 1546. For reviews of this and related reactions, see Zefirov; Koz'min *Acc. Chem. Res.* **1985**, *18*, 154, *Sov. Sci. Rev., Sect. B* **1985**, *7*, 297-339.

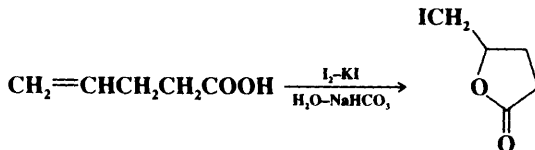
⁶⁴²Buss; Rockstuhl; Schnurpfel *J. Prakt. Chem.* **1982**, 324, 197.

⁶⁴³Glover; Goosen *Tetrahedron Lett.* **1980**, 21, 2005.

$X-C=C-OR$.⁶⁴⁴ Vinylic ethers give β -halo acetals.⁶⁴⁵ A mixture of Cl_2 and SO_3 at $-78^\circ C$

converts alkenes to 2-chloro chlorosulfates $ClCHRCHROSO_2Cl$, which are stable compounds.⁶⁴⁶ Chlorine acetate [solutions of which are prepared by treating Cl_2 with $Hg(OAc)_2$ in an appropriate solvent] adds to olefins to give acetoxy chlorides.⁶⁴⁷ The latter are also produced⁶⁴⁸ by treatment of olefins with a mixture of $PdCl_2$ and $CuCl_2$ in acetic acid⁶⁴⁹ or with chromyl chloride CrO_2Cl_2 in acetyl chloride.⁶⁵⁰ Acetoxy fluorides have been obtained by treatment of olefins with CH_3COOF .⁶⁵¹

An internal example of the addition of X and OCOR is called *halolactonization*;⁶⁵² e.g.,



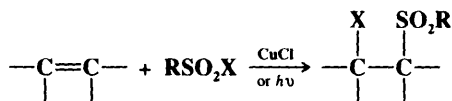
This reaction has been used mostly to prepare iodo lactones, but bromo lactones and, to a lesser extent, chloro lactones, have also been prepared. In the case of γ,δ -unsaturated acids, 5-membered rings (γ -lactones) are predominantly formed (as shown above; note that Markovnikov's rule is followed), but 6-membered and even 4-membered lactones have also been made by this procedure. Thallium reagents, along with the halogen, have also been used.⁶⁵³

For a method of iodoacetyl addition, see 5-35.

OS I, 158; IV, 130, 157; VI, 184, 361, 560; VII, 164; 67, 105; 69, 38.

5-28 Addition of Sulfur Compounds (Addition of Halogen, Sulfur)

Alkylsulfonyl-chloro-addition, etc.⁶⁵⁴



Sulfonyl halides add to double bonds, to give β -halo sulfones, in the presence of free-radical initiators or uv light. A particularly good catalyst is cuprous chloride.⁶⁵⁵ Triple bonds behave

⁶⁴⁴Bresson; Dauphin; Geneste; Kergomard; Lacourt *Bull. Soc. Chim. Fr.* **1970**, 2432, **1971**, 1080.

⁶⁴⁵Weissermel; Lederer *Chem. Ber.* **1963**, 96, 77.

⁶⁴⁶Zefirov; Koz'min; Sorokin *J. Org. Chem.* **1984**, 49, 4086.

⁶⁴⁷de la Mare; Wilson; Rosser *J. Chem. Soc., Perkin Trans. 2* **1973**, 1480; de la Mare; O'Connor; Wilson *J. Chem. Soc., Perkin Trans. 2* **1975**, 1150. For the addition of bromine acetate see Wilson; Woodgate *J. Chem. Soc., Perkin Trans. 2* **1976**, 141.

⁶⁴⁸For a list of reagents that accomplish acyloxy-halo-addition, with references, see Ref. 133, pp. 328-329.

⁶⁴⁹Henry *J. Org. Chem.* **1967**, 32, 2575, **1973**, 38, 1681. For a 1,4 example of this addition, see Bäckvall; Nyström; Nordberg *J. Am. Chem. Soc.* **1985**, 107, 3676; Nyström; Rein; Bäckvall *Org. Synth.* 67, 105.

⁶⁵⁰Bäckvall Young; Sharpless *Tetrahedron Lett.* **1977**, 3523.

⁶⁵¹Rozen; Lerman; Kol; Hebel *J. Org. Chem.* **1985**, 50, 4753.

⁶⁵²For reviews, see Cardillo; Orena *Tetrahedron* **1990**, 46, 3321-3408; Dowle; Davies *Chem. Soc. Rev.* **1979**, 8, 171-197. For a list of reagents that accomplish this, with references, see Ref. 133, pp. 945-946. For a review with respect to the stereochemistry of the reaction, see Bartlett, in Morrison, Ref. 232, vol. 3, 1984, pp. 411-454, pp. 416-425.

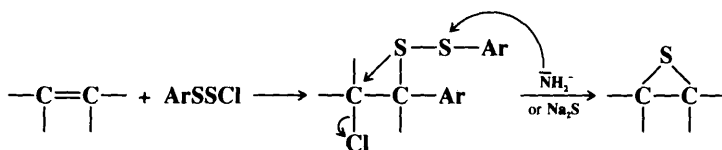
⁶⁵³See Cambie; Rutledge; Somerville; Woodgate *Synthesis* **1988**, 1009, and references cited therein.

⁶⁵⁴When a general group (such as halo) is used, its priority is that of the lowest member of its group (see footnote 629). Thus the general name for this transformation is halo-alkylsulfonyl-addition because "halo" has the same priority as "fluoro," its lowest member.

⁶⁵⁵Asscher; Vofsi *J. Chem. Soc.* **1964**, 4962; Truce; Goralski; Christensen; Bavry *J. Org. Chem.* **1970**, 35, 4217; Sinnreich; Asscher *J. Chem. Soc., Perkin Trans. 1* **1972**, 1543.

similarly, to give β -halo- α,β -unsaturated sulfones.⁶⁵⁶ In a similar reaction, sulfonyl chlorides, RSCl , give β -halo thioethers.⁶⁵⁷ The latter may be free-radical or electrophilic additions, depending on conditions. The addition of MeS and Cl has also been accomplished by treating the olefin with Me_3SiCl and Me_2SO .⁶⁵⁸ The use of Me_3SiBr and Me_2SO does not give this result; dibromides (**5-26**) are formed instead. MeS and F have been added by treatment of the olefin with dimethyl(methylthio)sulfonium fluoroborate $\text{Me}_2\text{SSMe}^+\text{BF}_4^-$ and triethylamine tris-hydrofluoride $\text{Et}_3\text{N}\cdot 3\text{HF}$.⁶⁵⁹ β -Iodo thiocyanates can be prepared from alkenes by treatment with I_2 and isothiocyanatotributylstannane Bu_3SnNCS .⁶⁶⁰ Bromothiocyantation can be accomplished with Br_2 and thallium(I) thiocyanate.⁶⁶¹

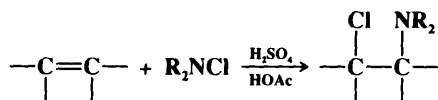
β -Halo disulfides, formed by addition of arenethiosulfonyl chlorides to double-bond compounds, are easily converted to thiiranes by treatment with sodium amide or sodium sulfide.⁶⁶²



The overall episulfidation is a stereospecific syn addition.

OS 65, 90. See also OS VII, 251.

5-29 Addition of Halogen and an Amino Group (Addition of Halogen, Nitrogen) Dialkylamino-chloro-addition



The groups R_2N and Cl can be added directly to olefins, allenes, conjugated dienes, and alkynes, by treatment with dialkyl- N -chloroamines and acids.⁶⁶³ These are free-radical additions, with initial attack by the $\text{R}_2\text{NH}\cdot^+$ radical ion.⁶⁶⁴ N -Halo amides RCONHX add RCONH and X to double bonds under the influence of uv light or chromous chloride.⁶⁶⁵ For an indirect way of adding NH_2 and I to a double bond, see 5-32.

⁶⁵⁶Truce; Wolf *J. Org. Chem.* **1971**, 36, 1727; Amiel *J. Org. Chem.* **1971**, 36, 3691, 3697, **1974**, 39, 3867; Zakharkin; Zhigareva *J. Org. Chem. USSR* **1973**, 9, 918; Okuyama; Izawa; Fucno *J. Org. Chem.* **1974**, 39, 351.

⁶⁵⁷For reviews, see Rasteikiene; Greiciute; Lin'kova; Knunyants *Russ. Chem. Rev.* **1977**, 46, 548-564; Kühle *Synthesis* **1971**, 563-586.

⁶⁵⁸Bellesia; Ghelfi; Pagnoni; Pinetti *J. Chem. Res. (S)* **1987**, 238. See also Liu; Nyangulu *Tetrahedron Lett.* **1988**, 29, 5467.

⁶⁵⁹Haufe; Alvernh; Anker; Laurent; Saluzzo *Tetrahedron Lett.* **1988**, 29, 2311.

⁶⁶⁰Woodgate; Janssen; Rutledge; Woodgate; Cambie *Synthesis* **1984**, 1017, and references cited therein. See also Watanabe; Uemura; Okano *Bull. Chem. Soc. Jpn.* **1983**, 56, 2458.

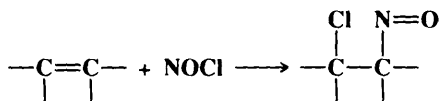
⁶⁶¹Cambie; Larsen; Rutledge; Woodgate *J. Chem. Soc., Perkin Trans. I* **1981**, 58.

⁶⁶²Fujisawa; Kobori *Chem. Lett.* **1972**, 935. For another method of olefin-thiirane conversion, see Capozzi; Capozzi; Menichetti *Tetrahedron Lett.* **1988**, 29, 4177.

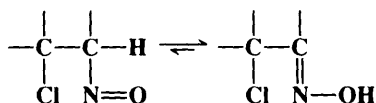
⁶⁶³Neale; Hinman *J. Am. Chem. Soc.* **1963**, 85, 2666; Neale; Marcus *J. Org. Chem.* **1967**, 32, 3273; Minisci; Galli; Cecere *Tetrahedron Lett.* **1966**, 3163. For reviews see Mirskova; Drozdova; Levkovskaya; Voronkov *Russ. Chem. Rev.* **1989**, 58, 250-271; Neale *Synthesis* **1971**, 1-15; Sosnovsky; Rawlinson *Adv. Free-Radical Chem.* **1972**, 4, 203-284, pp. 238-249.

⁶⁶⁴For a review of these species, see Chow; Danen; Nelson; Rosenblatt *Chem. Rev.* **1978**, 78, 243-274.

⁶⁶⁵Tuailon; Couture; Lessard *Can. J. Chem.* **1987**, 65, 2194, and other papers in this series. For a review, see Labeish; Petrov *Russ. Chem. Rev.* **1989**, 58, 1048-1061.

5-30 Addition of NOX and NO₂X (Addition of Halogen, Nitrogen)**Nitroso-chloro-addition**

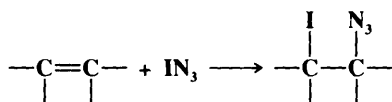
There are three possible products when NOCl is added to olefins.⁶⁶⁶ The initial product is always the β-halo nitroso compound, but these are stable only if the carbon bearing the nitrogen has no hydrogen. If it has, the nitroso compound tautomerizes to the oxime:



With some olefins, the initial β-halo nitroso compound is oxidized by the NOCl to a β-halo nitro compound.⁶⁶⁷ Many functional groups can be present without interference, e.g., COOH, COOR, CN, OR. The mechanism in most cases is probably simple electrophilic addition, and the addition is usually anti, though syn addition has been reported in some cases.⁶⁶⁸ Markovnikov's rule is followed, the positive NO going to the carbon that has more hydrogens.

Nitryl chloride NO₂Cl also adds to olefins, to give β-halo nitro compounds, but this is a free-radical process. The NO₂ goes to the less-substituted carbon.⁶⁶⁹ Nitryl chloride also adds to triple bonds to give the expected 1-nitro-2-chloro olefins.⁶⁷⁰ FNO₂ can be added to olefins⁶⁷¹ by treatment with HF in HNO₃⁶⁷² or by addition of the olefin to a solution of nitronium tetrafluoroborate NO₂⁺ BF₄⁻ (see 1-2) in 70% polyhydrogen fluoride-pyridine solution⁶⁷³ (see also 5-26).

OS IV, 711; V, 266, 863.

5-31 Addition of XN₃ (Addition of Halogen, Nitrogen)**Azido-iodo-addition**

The addition of iodine azide to double bonds gives β-iodo azides.⁶⁷⁴ The addition is stereospecific and anti, suggesting that the mechanism involves a cyclic iodonium ion interme-

⁶⁶⁶For a review, see Kadzyauskas; Zefirov *Russ. Chem. Rev.* **1968**, *37*, 543-550.

⁶⁶⁷For a review of the preparation of halo nitro compounds see Shvekhgeimer; Smirnyagin; Sadykov; Novikov *Russ. Chem. Rev.* **1968**, *37*, 351-363.

⁶⁶⁸For example, see Meinwald; Meinwald; Baker *J. Am. Chem. Soc.* **1964**, *86*, 4074.

⁶⁶⁹Shechter *Rec. Chem. Prog.* **1964**, *25*, 55-76.

⁶⁷⁰Schlubach; Braun *Liebigs Ann. Chem.* **1959**, 627, 28.

⁶⁷¹For a review, see Sharts; Sheppard *Org. React.* **1974**, *21*, 125-406, pp. 236-243.

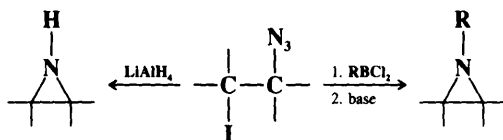
⁶⁷²Knunyants; German; Rozhkov *Bull. Acad. Sci. USSR, Div. Chem. Sci.* **1963**, 1794.

⁶⁷³Olah; Nojima *Synthesis* **1973**, 785.

⁶⁷⁴For reviews, see Dehnicke *Angew. Chem. Int. Ed. Engl.* **1979**, *18*, 507-514 [*Angew. Chem.* **91**, 527-534]; Hassner *Acc. Chem. Res.* **1971**, *4*, 9-16; Biffin; Miller; Paul, *Ref.* 214, pp. 136-147.

diate.⁶⁷⁵ The reaction has been performed on many double-bond compounds, including allenes⁶⁷⁶ and α,β -unsaturated ketones. Similar reactions can be performed with BrN_3 ⁶⁷⁷ and ClN_3 . 1,4 addition has been found with acyclic conjugated dienes.⁶⁷⁸ In the case of BrN_3 both electrophilic and free-radical mechanisms are important,⁶⁷⁹ while with ClN_3 the additions are chiefly free-radical.⁶⁸⁰ IN_3 also adds to triple bonds to give β -iodo- α,β -unsaturated azides.⁶⁸¹

β -Iodo azides can be reduced to aziridines with LiAlH_4 ⁶⁸² or converted to N-alkyl- or N-arylaziridines by treatment with an alkyl- or arylchloroborane followed by a base.⁶⁸³ In



both cases the azide is first reduced to the corresponding amine (primary or secondary, respectively) and ring closure (**0-43**) follows.

OS VI, 893.

5-32 Addition of INCO (Addition of Halogen, Nitrogen)

Isocyanato-iodo-addition



In a reaction similar to **5-31**, iodine isocyanate adds to double bonds to give β -iodo isocyanates.⁶⁸⁴ The addition is stereospecific and anti; the mechanism similar to that shown in **5-31**. The reaction has been applied to mono-, di-, and some trisubstituted olefins. The orientation generally follows Markovnikov's rule, the positive iodine adding to the less highly substituted side. α,β -Unsaturated carbonyl compounds do not react. Triple bonds give β -iodo- α,β -unsaturated isocyanates in low yields.⁶⁸⁵ Allenes add 1 mole of INCO to give β -iodo- β,γ -unsaturated isocyanates.⁶⁸⁶ Since an isocyanate group can be hydrolyzed to an amino group ($\text{RNCO} \rightarrow \text{RNH}_2$, **6-3**), the method is an indirect way of adding H_2N and I to double bonds.

OS VI, 795.

⁶⁷⁵See, however, Cambie; Hayward; Rutledge; Smith-Palmer; Swedlund; Woodgate *J. Chem. Soc., Perkin Trans. 1* **1979**, 180.

⁶⁷⁶Hassner; Keogh *J. Org. Chem.* **1986**, *51*, 2767.

⁶⁷⁷Azido-bromo-addition has also been done with another reagent: Olah; Wang; Li; Prakash *Synlett* **1990**, 487.

⁶⁷⁸Hassner; Keogh *Tetrahedron Lett.* **1975**, 1575.

⁶⁷⁹Hassner; Boerwinkle *J. Am. Chem. Soc.* **1968**, *90*, 217; Hassner; Teeter *J. Org. Chem.* **1971**, *36*, 2176.

⁶⁸⁰Even IN_3 can be induced to add by a free-radical mechanism [see, for example, Cambie; Jurilina; Rutledge; Swedlund; Woodgate *J. Chem. Soc., Perkin Trans. 1* **1982**, 327]. For a review of free-radical additions of XN_3 , see Hassner *Intra-Sci. Chem. Rep.* **1970**, *4*, 109-114.

⁶⁸¹Hassner; Isbister; Friederang *Tetrahedron Lett.* **1969**, 2939.

⁶⁸²Hassner; Matthews; Fowler *J. Am. Chem. Soc.* **1969**, *91*, 5046.

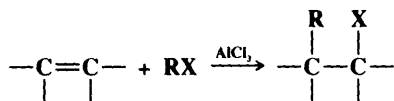
⁶⁸³Levy; Brown *J. Am. Chem. Soc.* **1973**, *95*, 4067.

⁶⁸⁴Heathcock; Hassner *Angew. Chem. Int. Ed. Engl.* **1963**, *2*, 213 [*Angew. Chem.* **75**, 344]; Birckenbach; Linhard *Ber.* **1931**, *64B*, 961, 1076; Drehfahl; Ponsold *Chem. Ber.* **1960**, *93*, 519; Hassner; Hoblitt; Heathcock; Kropp; Lorber *J. Am. Chem. Soc.* **1970**, *92*, 1326; Gebelein; Rosen; Swern *J. Org. Chem.* **1969**, *34*, 1677; Cambie; Hume; Rutledge; Woodgate *Aust. J. Chem.* **1983**, *36*, 2569.

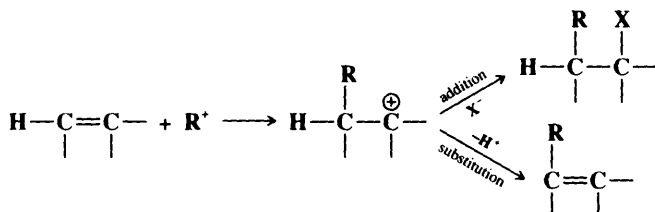
⁶⁸⁵Grimwood; Swern *J. Org. Chem.* **1967**, *32*, 3665.

⁶⁸⁶Greibrokk *Acta Chem. Scand.* **1973**, *27*, 3368.

5-33 Addition of Alkyl Halides (Addition of Halogen, Carbon) Alkyl-halo-addition⁶⁵⁴

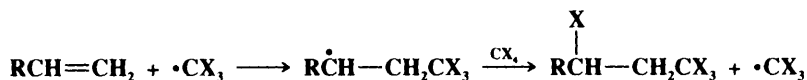


Alkyl halides can be added to olefins in the presence of a Friedel-Crafts catalyst, most often AlCl_3 .⁶⁵⁷ The yields are best for tertiary R. Secondary R can also be used, but primary R give rearrangement products (as with 1-12). Methyl and ethyl halides, which cannot rearrange, give no reaction at all. The attacking species is the carbocation formed from the alkyl halide and the catalyst (see 1-12).⁶⁵⁸ The addition therefore follows Markovnikov's rule, with the cation going to the carbon with more hydrogens. Substitution is a side reaction, arising from loss of hydrogen from the carbocation formed when the original carbocation attacks the double bond:



Conjugated dienes can add 1,4.⁶⁵⁹ Triple bonds also undergo the reaction, to give vinylic halides.⁶⁹⁰

CCl_4 , BrCCl_3 , ICF_3 , and similar simple polyhalo alkanes add to olefins in good yield.⁶⁹¹ These are free-radical additions and require initiation, e.g.,⁶⁹² by peroxides, metal halides (e.g., FeCl_2 , CuCl),⁶⁹³ or uv light. The initial attack is by the carbon, and it goes to the carbon with more hydrogens, as in most free-radical attack:



This type of polyhalo alkane adds to halogenated olefins in the presence of AlCl_3 by an electrophilic mechanism. This is called the *Prins reaction* (not to be confused with the other Prins reaction, 6-53).⁶⁹⁴

ArX can be added across double bonds, in a free-radical process, by treatment of olefins

⁶⁵⁷For a review, see Schmerling, in Olah, Ref. 412, vol. 2, pp. 1133-1174. See also Mayr; Striepe *J. Org. Chem.* **1983**, *48*, 1159; Mayr; Schade; Rubow; Schneider *Angew. Chem. Int. Ed. Engl.* **1987**, *26*, 1029 [*Angew. Chem.* **99**, 1059]. For a list of references, see Ref. 133, p. 342.

⁶⁵⁸For a discussion of the mechanism, see Pock; Mayr; Rubow; Wilhelm *J. Am. Chem. Soc.* **1986**, *108*, 7767.

⁶⁵⁹Kolyaskina; Petrov *J. Gen. Chem. USSR* **1962**, *32*, 1067.

⁶⁶⁰See, for example, Maroni; Melloni; Modena *J. Chem. Soc., Perkin Trans. I* **1973**, 2491, **1974**, 353.

⁶⁶¹For reviews, see Freidlina; Velichko *Synthesis* **1977**, 145-154; Freidlina; Chukovskaya *Synthesis* **1974**, 477-488.

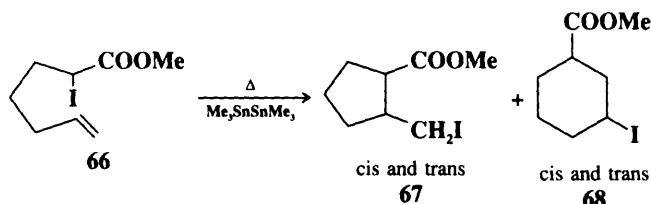
⁶⁶²For other initiators, see Matsumoto; Nakano; Takasu; Nagai *J. Org. Chem.* **1978**, *43*, 1734; Tsuji; Sato; Nagashima *Tetrahedron* **1985**, *41*, 393; Bland; Davis; Durrant *J. Organomet. Chem.* **1985**, *280*, 397; Phelps; Bergbreiter; Lee; Villani; Weinreb *Tetrahedron Lett.* **1989**, *30*, 3915.

⁶⁶³For example, see Asscher; Vofsi *J. Chem. Soc.* **1963**, 1887, 3921, *J. Chem. Soc. B* **1968**, 947; Murai; Tsutsumi *J. Org. Chem.* **1966**, *31*, 3000; Martin; Steiner; Streith; Winkler; Bellus *Tetrahedron* **1985**, *41*, 4057. For the addition of CH_2Cl_2 and PhBr , see Mitani; Nakayama; Koyama *Tetrahedron Lett.* **1980**, *21*, 4457.

⁶⁶⁴For a review with respect to fluoroolefins, see Paleta *Fluorine Chem. Rev.* **1977**, *8*, 39-71.

with diazonium salts, although Meerwein arylation (substitution) (**4-19**) competes.⁶⁹⁵ This addition can be either 1,2 or 1,4 with conjugated dienes.⁶⁹⁶ Addition of ArX can also be accomplished by treatment with an arylmercury halide ArHgX in the presence of CuX₂, LiX, and a palladium compound catalyst, usually Li₂PdCl₄.⁶⁹⁷ In this case also, substitution (**4-20**) is a side reaction. Yields of addition product are increased by increasing the concentration of CuX₂. Palladium compounds also catalyze the addition of allylic halides to alkynes.⁶⁹⁸

A variant of the free-radical addition method has been used for ring closure. For example, treatment of **66** with the free-radical initiator hexamethylditin gave a mixture of *cis*- and



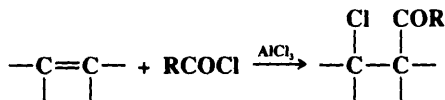
trans-**67**, with a small amount of *cis*- and *trans*-**68** (total yield 83%).⁶⁹⁹ The reaction has been performed with α -iodo esters, ketones, and malonates.

For another method of adding R and I to a triple bond, see 5-53.

OS II, 312; IV, 727; V, 1076; VI, 21; VII, 290.

5-34 Addition of Acyl Halides (Addition of Halogen, Carbon)

Acyl-halo-addition



Acyl halides have been added to many olefins, in the presence of Friedel–Crafts catalysts. The reaction has been applied to straight-chain, branched, and cyclic olefins, but to very few containing functional groups, other than halogen.⁷⁰⁰ The mechanism is similar to that of 5-33, and, as in that case, substitution competes (**2-15**). Increasing temperature favors substitution,⁷⁰¹ and good yields of addition products can be achieved if the temperature is kept under 0°C. The reaction usually fails with conjugated dienes, since polymerization predominates.⁷⁰² The reaction can be performed on triple-bond compounds, producing com-

⁶⁹⁵For example, see Iurkevich; Dombrovskii; Terent'ev *J. Gen. Chem. USSR* **1958**, 28, 226; Fedorov; Pribytkova; Kanishchev; Dombrovskii *J. Org. Chem. USSR* **1973**, 9, 1517; Cleland *J. Org. Chem.* **1961**, 26, 3362, **1969**, 34, 744; Doyle; Siegfried; Elliott; Dellaria *J. Org. Chem.* **1977**, 42, 2431; Ganushchak; Obushak; Polishchuk *J. Org. Chem. USSR* **1986**, 22, 2291.

⁶⁹⁶For example, see Dombrovskii; Ganushchak *J. Gen. Chem. USSR* **1961**, 31, 1191, **1962**, 32, 1867; Ganushchak; Golik; Migaichuk *J. Org. Chem. USSR* **1972**, 8, 2403.

⁶⁹⁷Heck *J. Am. Chem. Soc.* **1968**, 90, 5538. See also Bäckvall; Nordberg *J. Am. Chem. Soc.* **1980**, 102, 393.

⁶⁹⁸Kaneda; Uchiyama; Fujiwara; Imanaka; Teranishi *J. Org. Chem.* **1979**, 44, 55.

⁶⁹⁹Curran; Chang *J. Org. Chem.* **1989**, 54, 3140; Curran; Chen; Spletzer; Seong; Chang *J. Am. Chem. Soc.* **1989**, 111, 8872. See also Ichinose; Matsunaga; Fugami; Oshima; Utimoto *Tetrahedron Lett.* **1989**, 30, 3155.

⁷⁰⁰For reviews, see Groves *Chem. Soc. Rev.* **1972**, 1, 73-97; House, Ref. 144, pp. 786-797; Nenitzescu; Balaban, in Olah, Ref. 412, vol. 3, 1964, pp. 1033-1152.

⁷⁰¹Jones; Taylor; Rudd *J. Chem. Soc.* **1961**, 1342.

⁷⁰²For examples of 1,4 addition at low temperatures, see Melikyan; Babayan; Atanesyan; Badanyan *J. Org. Chem. USSR* **1984**, 20, 1884.

pounds of the form $\text{RCO}-\text{C}=\text{C}-\text{Cl}$.⁷⁰³ A *formyl* group and a halogen can be added to

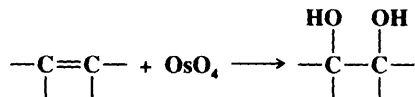
triple bonds by treatment with N,N-disubstituted formamides and POCl_3 (Vilsmeier conditions, see 1-15).⁷⁰⁴

OS IV, 186; VI, 883; 69, 238.

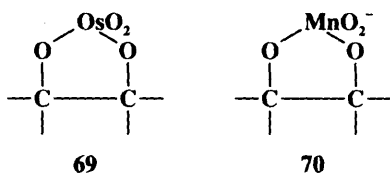
B. Oxygen, Nitrogen, or Sulfur on One or Both Sides

5-35 Hydroxylation (Addition of Oxygen, Oxygen)

Dihydroxy-addition



There are many reagents that add two OH groups to a double bond.⁷⁰⁵ OsO_4 ⁷⁰⁶ and alkaline KMnO_4 ⁷⁰⁷ give syn addition, from the less-hindered side of the double bond. Osmium tetroxide adds rather slowly but almost quantitatively. The cyclic ester **69** is an intermediate and can be isolated,⁷⁰⁸ but is usually decomposed in solution, with sodium sulfite in ethanol



or other reagents. Bases catalyze the reaction by coordinating with the ester. The chief drawback to this reaction is that OsO_4 is expensive and highly toxic, so that its use has been limited to small-scale preparations of scarce materials. However, the same result (syn addition) can be accomplished more economically by the use of H_2O_2 , with OsO_4 present in catalytic amounts.⁷⁰⁹ *t*-Butyl hydroperoxide in alkaline solution,⁷¹⁰ N-methylmorpholine-N-oxide,⁷¹¹ and $\text{K}_3\text{Fe}(\text{CN})_6$ ⁷¹² have been substituted for H_2O_2 in this procedure. Another method uses polymer-bound OsO_4 .⁷¹³

⁷⁰³For example see Nifant'ev; Grachev; Bakinovskii; Kara-Murza; Kochetkov *J. Appl. Chem. USSR* **1963**, 36, 646; Savenkov; Khokhlov; Nazarova; Mochalkin *J. Org. Chem. USSR* **1973**, 9, 914; Martens; Janssens; Hoornaert *Tetrahedron* **1975**, 31, 177; Brownstein; Morrison; Tan *J. Org. Chem.* **1985**, 50, 2796.

⁷⁰⁴*Yen Ann. Chim. (Paris)* **1962**, [13] 7, 785.

⁷⁰⁵For reviews, see Hudlický *Oxidations in Organic Chemistry*; American Chemical Society: Washington, 1990, pp. 67-73; Haines *Methods for the Oxidation of Organic Compounds*; Academic Press: New York, 1985, pp. 73-98, 278-294; Sheldon; Kochi *Metal-Catalyzed Oxidations of Organic Compounds*; Academic Press: New York, 1981, pp. 162-171, 294-296. For a list of reagents, with references, see Ref. 133, pp. 494-496.

⁷⁰⁶For a review, see Schröder *Chem. Rev.* **1980**, 80, 187-213. OsO_4 was first used for this purpose by Criegee *Liebigs Ann. Chem.* **1936**, 522, 75.

⁷⁰⁷For a review, see Fatiadi *Synthesis* **1987**, 85-127, pp. 86-96.

⁷⁰⁸For a molecular orbital study of the formation of **69**, see Jørgensen; Hoffmann *J. Am. Chem. Soc.* **1986**, 108, 1867.

⁷⁰⁹Milas; Sussman *J. Am. Chem. Soc.* **1936**, 58, 1302, **1937**, 59, 2345. For a review, see Rylander, Ref. 223, pp. 121-133. For another procedure that uses H_2O_2 , see Venturello; Gambaro *Synthesis* **1989**, 295.

⁷¹⁰Akashi; Palermo; Sharpless *J. Org. Chem.* **1978**, 43, 2063.

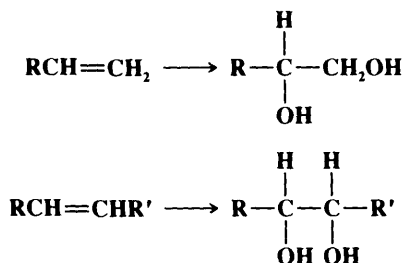
⁷¹¹VanRheenen; Kelly; Cha *Tetrahedron Lett.* **1976**, 1973; Iwasawa; Kato; Narasaka *Chem. Lett.* **1988**, 1721. See also Ray; Matteson *Tetrahedron Lett.* **1980**, 449.

⁷¹²Minato; Yamamoto; Tsuji *J. Org. Chem.* **1990**, 55, 766.

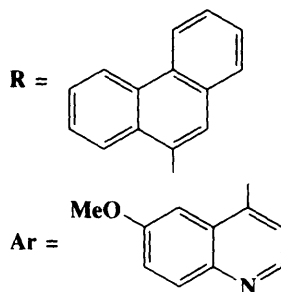
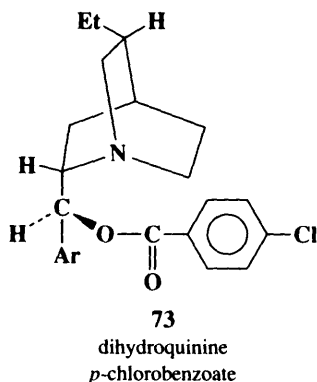
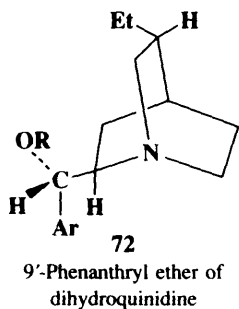
⁷¹³Cainelli; Contento; Manescalchi; Plessi *Synthesis* **1989**, 45.

halo ester; the addition is anti and a nucleophilic replacement of the iodine occurs. However, in the presence of water, neighboring-group participation is prevented or greatly decreased by solvation of the ester function, and the mechanism is the normal S_N2 process,⁷²⁰ so the monoacetate is syn and hydrolysis gives the glycol that is the product of overall syn addition. Although the Woodward method results in overall syn addition, the product may be different from that with OsO_4 or $KMnO_4$, since the overall syn process is from the more-hindered side of the olefin.⁷²¹ Both the Prevost and the Woodward methods⁷²² have also been carried out in high yields with thallium(I) acetate and thallium(I) benzoate instead of the silver carboxylates.⁷²³

With suitable substrates, addition of two OH groups creates either one or two new chiral centers:



Addition to olefins of the form $RCH=CH_2$ has been made enantioselective, and addition to $RCH=CHR'$ both diastereoselective⁷²⁴ and enantioselective, by using optically active amines, such as **72**, **73** (derivatives of the naturally occurring quinine and quinidine),



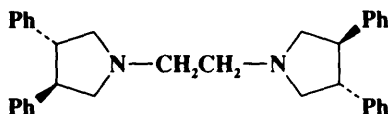
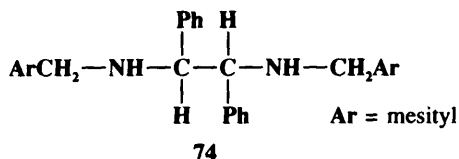
⁷²⁰For another possible mechanism that accounts for the stereochemical result of the Woodward method, see Woodward; Brucher *J. Am. Chem. Soc.* **1958**, *80*, 209.

⁷²¹For another method of syn hydroxylation, which can be applied to either face, see Corey; Das *Tetrahedron Lett.* **1982**, *23*, 4217.

⁷²²For some related methods, see Jasserand; Girard; Rossi; Granger *Tetrahedron Lett.* **1976**, 1581; Ogata; Aoki *J. Org. Chem.* **1966**, *31*, 1625; Mangoni; Adinolfi; Barone; Parrilli *Tetrahedron Lett.* **1973**, 4485; *Gazz. Chim. Ital.* **1975**, *105*, 377; Horiuchi; Satoh *Chem. Lett.* **1988**, 1209; Campi; Deacon; Edwards; Fitzroy; Giunta; Jackson; Trainor *J. Chem. Soc., Chem. Commun.* **1989**, 407.

⁷²³Cambie; Hayward; Roberts; Rutledge *J. Chem. Soc., Chem. Commun.* **1973**, 359; *J. Chem. Soc., Perkin Trans. I* **1974**, 1858, 1864; Cambie; Rutledge *Org. Synth.* *VI*, 348.

⁷²⁴For diastereoselective, but not enantioselective, addition of OsO_4 , see Cha; Christ; Kishi *Tetrahedron Lett.* **1983**, *24*, 3943, 3947; *Tetrahedron* **1984**, *40*, 2247; Stork; Kahn *Tetrahedron Lett.* **1983**, *24*, 3951; Vedejs; McClure *J. Am. Chem. Soc.* **1986**, *108*, 1094; Evans; Kaldor *J. Org. Chem.* **1990**, *55*, 1698.



75

74,⁷²⁵ or **75**,⁷²⁶ along with OsO₄.⁷²⁷ These amines bind to the OsO₄ in situ as chiral ligands, causing it to add asymmetrically.⁷²⁸ This has been done both with the stoichiometric and with the catalytic method.⁷²⁹ The catalytic method has been extended to conjugated dienes, which give tetrahydroxy products diastereoselectively.⁷³⁰

Ligands **72** and **73** not only cause enantioselective addition, but also accelerate the reaction, so that they may be useful even where enantioselective addition is not required.⁷³¹ Although **72** and **73** are not enantiomers, they give enantioselective addition to a given olefin in the opposite sense; e.g., styrene predominantly gave the (*R*) diol with **72**, and the (*S*) diol with **73**.⁷³² Enantioselective and diastereoselective addition have also been achieved by using preformed derivatives of OsO₄, already containing chiral ligands,⁷³³ and by the use of OsO₄ on olefins that have a chiral group elsewhere in the molecule.⁷³⁴

Olefins can also be oxidized with metallic acetates such as lead tetraacetate⁷³⁵ or thallium(III) acetate⁷³⁶ to give bisacetates of glycols.⁷³⁷ Oxidizing agents such as benzoquinone, MnO₂, or O₂, along with palladium acetate, have been used to convert conjugated dienes to 1,4-diacetoxy-2-alkenes (1,4 addition).⁷³⁸

OS II, 307; III, 217; IV, 317; V, 647; VI, 196, 342, 348.

⁷²⁵Corey; Jardine; Virgil; Yuen; Connell *J. Am. Chem. Soc.* **1989**, *111*, 9243; Corey; Lotto *Tetrahedron Lett.* **1990**, *31*, 2665.

⁷²⁶Tomioka; Nakajima; Koga *J. Am. Chem. Soc.* **1987**, *109*, 6213, *Tetrahedron Lett.* **1990**, *31*, 1741; Tomioka; Nakajima; Iitaka; Koga *Tetrahedron Lett.* **1988**, *29*, 573.

⁷²⁷Wai; Marko; Svendsen; Finn; Jacobsen; Sharpless *J. Am. Chem. Soc.* **1989**, *111*, 1123; Lohray; Kalantar; Kim; Park; Shibata; Wai; Sharpless *Tetrahedron Lett.* **1989**, *30*, 2041; Kwong; Sorato; Ogina; Chen; Sharpless *Tetrahedron Lett.* **1990**, *31*, 2999; Shibata; Gilheany; Blackburn; Sharpless *Tetrahedron Lett.* **1990**, *31*, 3817; Sharpless et al., *J. Org. Chem.* **1991**, *56*, 4585.

⁷²⁸For discussions of the mechanism of the enantioselectivity, see Jørgensen *Tetrahedron Lett.* **1990**, *31*, 6417; Ogino; Chen; Kwong; Sharpless *Tetrahedron Lett.* **1991**, *32*, 3965.

⁷²⁹For other examples of asymmetric dihydroxylation, see Yamada; Narasaka *Chem. Lett.* **1986**, 131; Tokles; Snyder *Tetrahedron Lett.* **1986**, *27*, 3951; Annunziata; Cinquini; Cozzi; Raimondi; Stefanelli *Tetrahedron Lett.* **1987**, *28*, 3139; Hirama; Oishi; Itō *J. Chem. Soc., Chem. Commun.* **1989**, 665.

⁷³⁰Park; Kim; Sharpless *Tetrahedron Lett.* **1991**, *32*, 1003.

⁷³¹Sharpless et al., Ref. 727. See also Jacobsen; Marko; France; Svendsen; Sharpless *J. Am. Chem. Soc.* **1989**, *111*, 737.

⁷³²Jacobsen; Marko; Mungall; Schröder; Sharpless *J. Am. Chem. Soc.* **1988**, *110*, 1968.

⁷³³Kokubo; Sugimoto; Uchida; Tanimoto; Okano *J. Chem. Soc., Chem. Commun.* **1983**, 769.

⁷³⁴Hauser; Ellenberger; Clardy; Bass *J. Am. Chem. Soc.* **1984**, *106*, 2458; Johnson; Barbachyn *J. Am. Chem. Soc.* **1984**, *106*, 2459.

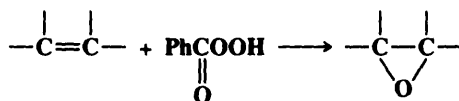
⁷³⁵For a review, see Moriarty *Sel. Org. Transform.* **1972**, *2*, 183-237.

⁷³⁶See, for example, Uemura; Miyoshi; Tabata; Okano *Tetrahedron* **1981**, *37*, 291. For a review of the reactions of thallium(III) compounds with olefins, see Uemura, in Hartley, Ref. 218, vol. 4, pp. 473-538, pp. 497-513. For a review of thallium(III) acetate and trifluoroacetate, see Uemura, in Pizey, Ref. 146, vol. 5, 1983, pp. 165-187.

⁷³⁷For another method see Fristad; Peterson *Tetrahedron* **1984**, *40*, 1469.

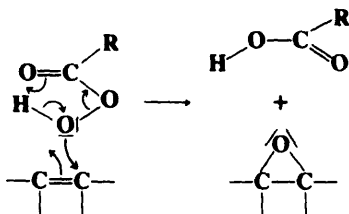
⁷³⁸See Bäckvall; Nordberg *J. Am. Chem. Soc.* **1981**, *103*, 4959; Bäckvall; Byström; Nordberg *J. Org. Chem.* **1984**, *49*, 4619; Bäckvall; Awasthi; Renko *J. Am. Chem. Soc.* **1987**, *109*, 4750. For articles on this and related reactions, see Bäckvall *Bull. Soc. Chim. Fr.* **1987**, 665-670, *New J. Chem.* **1990**, *14*, 447-452. For another method, see Uemura; Fukuzawa; Patil; Okano *J. Chem. Soc., Perkin Trans. 1* **1985**, 499.

5-36 Epoxidation (Addition of Oxygen, Oxygen) epi-Oxy-addition



Olefins can be epoxidized with any of a number of peracids,⁷³⁹ of which *m*-chloroperbenzoic has been the most often used. The reaction, called the *Prilezhaev reaction*, has wide utility.⁷⁴⁰ Alkyl, aryl, hydroxyl, ester, and other groups may be present, though not amino groups, since these are affected by the reagent. Electron-donating groups increase the rate, and the reaction is particularly rapid with tetraalkyl olefins. Conditions are mild and yields are high. Other peracids, especially peracetic and perbenzoic, are also used; trifluoroperacetic acid⁷⁴¹ and 3,5-dinitroperoxybenzoic acid⁷⁴² are particularly reactive ones.

The following one-step mechanism⁷⁴³ was proposed by Bartlett:⁷⁴⁴



Evidence for this mechanism is as follows:⁷⁴⁵ (1) The reaction is second order. If ionization were the rate-determining step, it would be first order in peracid. (2) The reaction readily takes place in nonpolar solvents, where formation of ions is inhibited. (3) Measurements of the effect on the reaction rate of changes in the substrate structure show that there is no carbocation character in the transition state.⁷⁴⁶ (4) The addition is stereospecific (i.e., a trans olefin gives a trans epoxide and a cis olefin a cis epoxide) even in cases where electron-donating substituents would stabilize a hypothetical carbocation intermediate. However, where there is an OH group in the allylic or homoallylic position, the stereospecificity diminishes or disappears, with both cis and trans isomers giving predominantly or exclusively the product where the incoming oxygen is syn to the OH group. This probably indicates a transition state in which there is hydrogen bonding between the OH group and the peroxy acid.⁷⁴⁷

⁷³⁹For a list of reagents, including peracids and others, used for epoxidation, with references, see Ref. 133, pp. 456-461.

⁷⁴⁰For reviews, see Hudlický, Ref. 705, pp. 60-64; Haines, Ref. 705, pp. 98-117, 295-303; Dryuk *Russ. Chem. Rev.* **1985**, *54*, 986-1005; Plesničar, in Trahanovsky *Oxidation in Organic Chemistry*, pt. C; Academic Press: New York, 1978, pp. 211-252; Swern, in Swern *Organic Peroxides*, vol. 2; Wiley: New York, 1971, pp. 355-533; Metelitsa *Russ. Chem. Rev.* **1972**, *41*, 807-821; Hiatt, in Augustine; Trecker *Oxidation*, vol. 2; Marcel Dekker: New York, 1971, pp. 113-140; House, Ref. 144, pp. 292-321. For a review pertaining to the stereochemistry of the reaction, see Berti *Top. Stereochem.* **1973**, *7*, 93-251, pp. 95-187.

⁷⁴¹Emmons; Pagano *J. Am. Chem. Soc.* **1955**, *77*, 89.

⁷⁴²Rastetter; Richard; Lewis *J. Org. Chem.* **1978**, *43*, 3163.

⁷⁴³For discussions of the mechanism, see Dryuk *Tetrahedron* **1976**, *32*, 2855-2866; Finn; Sharpless, in Morrison, Ref. 232, vol. 5, pp. 247-308. For a review of polar mechanisms involving peroxides, see Plesničar in Patai *The Chemistry of Peroxides*; Wiley: New York, 1983, pp. 521-584.

⁷⁴⁴Bartlett *Rec. Chem. Prog.* **1957**, *18*, 111. For other proposed mechanisms see Kwart; Hoffman *J. Org. Chem.* **1966**, *31*, 419; Hanzlik; Shearer *J. Am. Chem. Soc.* **1975**, *97*, 5231.

⁷⁴⁵Ogata; Tabushi *J. Am. Chem. Soc.* **1961**, *83*, 3440. See also Woods; Beak *J. Am. Chem. Soc.* **1991**, *113*, 6281.

⁷⁴⁶Khalil; Pritzkow *J. Prakt. Chem.* **1973**, *315*, 58; Schneider; Becker; Philipp *Chem. Ber.* **1961**, *114*, 1562; Batog; Savenko; Batrak; Kucher *J. Org. Chem. USSR* **1961**, *17*, 1860.

⁷⁴⁷See Berti, Ref. 740, pp. 130-162.

catalyzed by a complex of a transition metal such as V, Mo, Ti, or Co.⁷⁵⁹ The reaction with oxygen, which can also be carried out without a catalyst, is probably a free-radical process.⁷⁶⁰

In the *Sharpless asymmetric epoxidation*,⁷⁶¹ allylic alcohols are converted to optically active epoxides in better than 90% enantiomeric excess, by treatment with *t*-BuOOH, titanium tetrakispropoxide and optically active diethyl tartrate.⁷⁶² The Ti(OCHMe₂)₄ and diethyl tartrate can be present in catalytic amounts (5-10 mole %) if molecular sieves are present.⁷⁶³ Since both (+) and (-) diethyl tartrate are readily available, and the reaction is stereospecific, either enantiomer of the product can be prepared. The method has been successful for a wide range of primary allylic alcohols, where the double bond is mono-, di-, tri-, and tetrasubstituted.⁷⁶⁴ This procedure, in which an optically active catalyst is used to induce asymmetry, has proved to be one of the most important methods of asymmetric synthesis, and has been used to prepare a large number of optically active natural products and other compounds. Among these are the 8 L-aldohexoses (the unnatural isomers), which were totally synthesized with the aid of this method, starting from a common precursor, 4-benzhydryloxy-(*E*)-but-2-en-ol.⁷⁶⁵ The mechanism of the Sharpless epoxidation is believed to involve attack on the substrate by a compound⁷⁶⁶ formed from the titanium alkoxide and the diethyl tartrate to produce a complex that also contains the substrate and the *t*-BuOOH.⁷⁶⁷ Ordinary alkenes (without an allylic OH group) have been enantioselectively epoxidized with sodium hypochlorite (commercial bleach) and an optically active manganese-complex catalyst.⁷⁶⁸

Among other reagents for converting olefins to epoxides⁷⁶⁹ are H₂O₂, catalyzed by tungstic acid or its derivatives,⁷⁷⁰ F₂-H₂O-MeCN,⁷⁷¹ and magnesium monoperoxyphthalate.⁷⁷² The last reagent, which is commercially available, has been shown to be a good substitute for *m*-chloroperbenzoic acid in a number of reactions.⁷⁷³

⁷⁵⁹For a review, see Jørgensen *Chem. Rev.* **1989**, *89*, 431-458.

⁷⁶⁰For reviews, see Van Santen; Kuipers *Adv. Catal.* **1987**, *35*, 265-321; Filippova; Blyumberg *Russ. Chem. Rev.* **1982**, *51*, 582-591.

⁷⁶¹For reviews, see Pfenninger *Synthesis* **1986**, 89-116; Rossiter, in Morrison, Ref. 232, vol. 5, pp. 193-246. For histories of its discovery, see Sharpless *Chem. Br.* **1986**, 38-44, *CHEMTECH* **1985**, 692-700.

⁷⁶²Katsuki; Sharpless *J. Am. Chem. Soc.* **1980**, *102*, 5974; Rossiter; Katsuki; Sharpless *J. Am. Chem. Soc.* **1981**, *103*, 464; Sharpless; Woodard; Finn *Pure Appl. Chem.* **1983**, *55*, 1823-1836.

⁷⁶³Gao; Hanson; Klunder; Ko; Masamune; Sharpless *J. Am. Chem. Soc.* **1987**, *109*, 5765. For another improvement, see Wang; Zhou *Tetrahedron* **1987**, *43*, 2935.

⁷⁶⁴See the table in Finn; Sharpless, Ref. 743, pp. 249-250. See also Schweiter; Sharpless *Tetrahedron Lett.* **1985**, *26*, 2543.

⁷⁶⁵Ko; Lee; Masamune; Reed; Sharpless; Walker *Tetrahedron* **1990**, *46*, 245. For other stereospecific syntheses of monosaccharides, see Mukaiyama; Suzuki; Yamada; Tabusa *Tetrahedron* **1990**, *46*, 265, and references cited therein.

⁷⁶⁶Very similar compounds have been prepared and isolated as solids whose structures have been determined by x-ray crystallography: Williams; Pedersen; Sharpless; Lippard *J. Am. Chem. Soc.* **1984**, *106*, 6430.

⁷⁶⁷For a review of the mechanism, see Finn; Sharpless, Ref. 743. For other mechanistic studies, see Jørgensen; Wheeler; Hoffmann *J. Am. Chem. Soc.* **1987**, *109*, 3240; Hawkins; Sharpless *Tetrahedron Lett.* **1987**, *28*, 2825; Carlier; Sharpless *J. Org. Chem.* **1989**, *54*, 4016; Corey *J. Org. Chem.* **1990**, *55*, 1693; Woodard; Finn; Sharpless *J. Am. Chem. Soc.* **1991**, *113*, 106; Finn; Sharpless *J. Am. Chem. Soc.* **1991**, *113*, 113; Takano; Iwebuchi; Ogasawara *J. Am. Chem. Soc.* **1991**, *113*, 2786.

⁷⁶⁸Jacobsen; Zhang; Muci; Ecker; Deng *J. Am. Chem. Soc.* **1991**, *113*, 7063. See also Irie; Noda; Ito; Katsuki *Tetrahedron Lett.* **1991**, *32*, 1055; Irie; Ito; Katsuki *Synlett* **1991**, 265; Halterman; Jan *J. Org. Chem.* **1991**, *56*, 5253.

⁷⁶⁹For other methods of converting olefins to epoxides, see Balavoine; Eskenazi; Meunier; Rivière *Tetrahedron Lett.* **1984**, *25*, 3187; Tezuka; Iwaki *J. Chem. Soc., Perkin Trans. 1* **1984**, 2507; Samsel; Srinivasan; Kochi *J. Am. Chem. Soc.* **1985**, *107*, 7606; Xie; Xu; Hu; Ma; Hou; Tao *Tetrahedron Lett.* **1988**, *29*, 2967; Bruice *Aldrichimica Acta* **1988**, *21*, 87-94; Adam; Curci; Edwards *Acc. Chem. Res.* **1989**, *22*, 205-211; Troisi; Cassidei; Lopez; Mello; Curci *Tetrahedron Lett.* **1989**, *30*, 257; Rodriguez; Dulcère *J. Org. Chem.* **1991**, *56*, 469.

⁷⁷⁰See, for example, Bortolini; Di Furia; Modena; Seraglia *J. Org. Chem.* **1985**, *50*, 2688; Prat; Lett *Tetrahedron Lett.* **1986**, *27*, 707; Prandi; Kagan; Mimoun *Tetrahedron Lett.* **1986**, *27*, 2617; Venturello; D'Aloisio *J. Org. Chem.* **1988**, *53*, 1553.

⁷⁷¹Rozen; Kol *J. Org. Chem.* **1990**, *55*, 5155.

⁷⁷²Brougham; Cooper; Cummerson; Heaney; Thompson *Synthesis* **1987**, 1015; Querci; Ricci *J. Chem. Soc., Chem. Commun.* **1989**, 889.

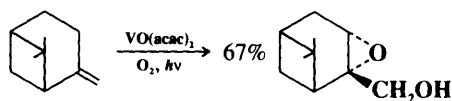
⁷⁷³Brougham et al., Ref. 772.

It would be useful if triple bonds could be similarly epoxidized to give oxirenes. However, oxirenes are not stable compounds.⁷⁷⁴ Two of them have been trapped in solid argon matrices



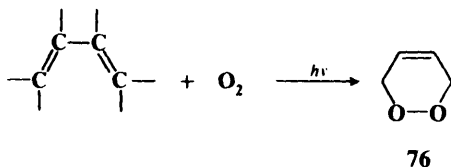
at very low temperatures, but they decayed on warming to 35 K.⁷⁷⁵ Oxirenes probably form in the reaction,⁷⁷⁶ but react further before they can be isolated. Note that oxirenes bear the same relationship to cyclobutadiene that furan does to benzene and may therefore be expected to be antiaromatic (see p. 55).

In a different type of reaction, olefins are photooxygenated (with singlet O₂, see 4-9) in the presence of a Ti, V, or Mo complex to give epoxy alcohols formally derived from allylic hydroxylation followed by epoxidation, e.g.,⁷⁷⁷

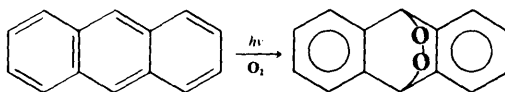


OS I, 494; IV, 552, 860; V, 191, 414, 467, 1007; VI, 39, 320, 679, 862; VII, 121, 126, 461; 66, 203.

5-37 Photooxidation of Dienes (Addition of Oxygen, Oxygen) (2 + 4)OC,OC-cyclo-Peroxy-1/4/addition



Conjugated dienes react with oxygen under the influence of light to give cyclic peroxides 76.⁷⁷⁸ The reaction has mostly⁷⁷⁹ been applied to cyclic dienes.⁷⁸⁰ The scope extends to certain aromatic compounds,⁷⁸¹ e.g.,



⁷⁷⁴For a review of oxirenes, see Lewars *Chem. Rev.* **1983**, 83, 519-534.

⁷⁷⁵Torres; Bourdelande; Clement; Strausz *J. Am. Chem. Soc.* **1983**, 105, 1698. See also Laganis; Janik; Curphey; Lemal *J. Am. Chem. Soc.* **1983**, 105, 7457.

⁷⁷⁶McDonald; Schwab *J. Am. Chem. Soc.* **1964**, 86, 4866; Ibne-Rasa; Pater; Ciabattoni; Edwards *J. Am. Chem. Soc.* **1973**, 95, 7894; Ogata; Sawaki; Inoue *J. Org. Chem.* **1973**, 38, 1044.

⁷⁷⁷Adam; Braun; Griesbeck; Lucchini; Staab; Will *J. Am. Chem. Soc.* **1989**, 111, 203.

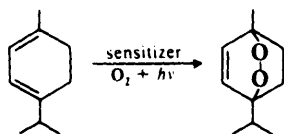
⁷⁷⁸For reviews, see Ciennan *Tetrahedron* **1991**, 47, 1343-1382. *Adv. Oxygenated Processes* **1988**, 1, 85-122; Wasserman; Ives *Tetrahedron* **1981**, 37, 1825-1852; Denny; Nickon *Org. React.* **1973**, 20, 133-336; Adams in Augustine; Trecker, Ref. 740, vol. 2, pp. 65-112; Gollnick *Adv. Photochem.* **1968**, 6, 1-122; Schönberg, Ref. 49, pp. 382-397; Gollnick; Schenck in Hamer *1,4-Cycloaddition Reactions*; Academic Press: New York, 1967, pp. 255-344; Arbuzov *Russ. Chem. Rev.* **1965**, 34, 558-574.

⁷⁷⁹For many examples with acyclic dienes, see Matsumoto; Dobashi; Kuroda; Kondo *Tetrahedron* **1985**, 41, 2147.

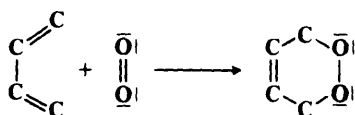
⁷⁸⁰For reviews of cyclic peroxides, see Saito; Nittala, in Patai, Ref. 743, pp. 311-374; Balci *Chem. Rev.* **1981**, 81, 91-108; Adam; Bloodworth *Top. Curr. Chem.* **1981**, 97, 121-158.

⁷⁸¹For reviews, see in Wasserman; Murray *Singlet Oxygen*; Academic Press: New York, 1979, the articles by Wasserman; Lipshutz, pp. 429-509; Saito; Matsuura, pp. 511-574; Rigaudy *Pure Appl. Chem.* **1968**, 16, 169-186.

Besides those dienes and aromatic rings that can be photooxidized directly, there is a larger group that give the reaction in the presence of a photosensitizer such as eosin (see p. 241). Among these is α -terpinene, which is converted to ascaridole:

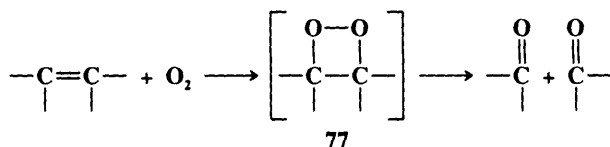


As in **4-9**, it is not the ground-state oxygen (the triplet), that reacts, but the excited singlet state,⁷⁸² so the reaction is actually a Diels-Alder reaction (see **5-47**) with singlet oxygen as dienophile:⁷⁸³



Like **5-47**, this reaction is reversible.

We have previously discussed the reaction of singlet oxygen with double-bond compounds to give hydroperoxides (**4-9**), but singlet oxygen can also react with double bonds in another way to give a dioxetane intermediate⁷⁸⁴ (**77**), which usually cleaves to aldehydes or ketones⁷⁸⁵



but has been isolated.⁷⁸⁶ Both the 6-membered cyclic peroxides **76**⁷⁸⁷ and the 4-membered **77**⁷⁸⁸ have been formed from oxygenation reactions that do not involve singlet oxygen. If **77** are desired, better reagents⁷⁸⁹ are triphenyl phosphite ozonide $(\text{PhO})_3\text{PO}_3$ and triethylsilyl hydrotrioxide Et_3SiOOOH , though yields are not high.⁷⁹⁰

⁷⁸²For books and reviews on singlet oxygen, see Ref. 216 in Chapter 14.

⁷⁸³Footo; Wexler *J. Am. Chem. Soc.* **1964**, *86*, 3880; Corey; Taylor *J. Am. Chem. Soc.* **1964**, *86*, 3881; Footo; Wexler; Ando *Tetrahedron Lett.* **1965**, 4111; Monroe *J. Am. Chem. Soc.* **1981**, *103*, 7253. See also Hathaway; Paquette *Tetrahedron Lett.* **1985**, *41*, 2037; O'Shea; Footo *J. Am. Chem. Soc.* **1988**, *110*, 7167.

⁷⁸⁴For reviews, see Adam; Cilento *Angew. Chem. Int. Ed. Engl.* **1983**, *22*, 529-542 [*Angew. Chem.* *95*, 525-538]; Schaap; Zaklika in Wasserman; Murray, Ref. 781, pp. 173-242; Bartlett *Chem. Soc. Rev.* **1976**, *5*, 149-163. For discussions of the mechanisms see Frimer *Chem. Rev.* **1979**, *79*, 359-387; Clennan; Nagraba *J. Am. Chem. Soc.* **1988**, *110*, 4312.

⁷⁸⁵For discussions see Kearns *Chem. Rev.* **1971**, *71*, 395-427, pp. 422-424; Footo *Pure Appl. Chem.* **1971**, *27*, 635-645.

⁷⁸⁶For reviews of 1,2-dioxetanes see Adam, in Patai, Ref. 743, pp. 829-920; Bartlett; Landis, in Wasserman; Murray Ref. 781, pp. 243-286; Adam *Adv. Heterocycl. Chem.* **1977**, *21*, 437-481. See also Inoue; Hakushi; Turro *Kokagaku Toronkai Koen Yoshishu* **1979**, 150 [*C.A.* *92*, 214798q]; Adam; Encarnación *Chem. Ber.* **1982**, *115*, 2592; Adam; Baader *Angew. Chem. Int. Ed. Engl.* **1984**, *23*, 166 [*Angew. Chem.* *96*, 156].

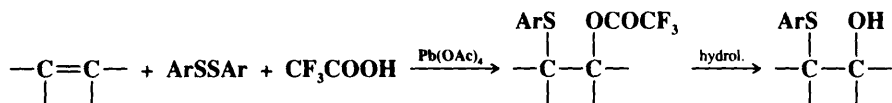
⁷⁸⁷See Nelson; Teasley; Kapp *J. Am. Chem. Soc.* **1986**, *108*, 5503.

⁷⁸⁸For a review, see Nelson *Acc. Chem. Res.* **1987**, *20*, 269-276.

⁷⁸⁹For another reagent, see Curci; Lopez; Troisi; Rashid; Schaap *Tetrahedron Lett.* **1987**, *28*, 5319.

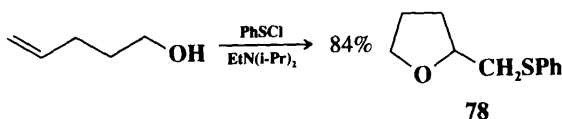
⁷⁹⁰Posner; Weitzberg; Nelson; Murr; Seliger *J. Am. Chem. Soc.* **1987**, *109*, 278.

5-38 Hydroxysulfenylation (Addition of Oxygen, Sulfur)
Hydroxy-arythio-addition (overall transformation)



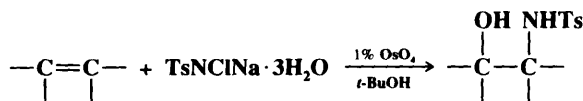
A hydroxy and an arylthio group can be added to a double bond by treatment with an aryl disulfide and lead tetraacetate in the presence of trifluoroacetic acid.⁷⁹¹ Manganese and copper acetates have been used instead of Pb(OAc)₄.⁷⁹² Addition of the groups OH and RSO has been achieved by treatment of olefins with O₂ and a thiol RSH.⁷⁹³ Two RS groups were added, to give *vic*-dithiols, by treatment of the alkene with a disulfide RSSR and BF₃-etherate.⁷⁹⁴

In a number of cases, addition of an ether group and a thioether group has been carried

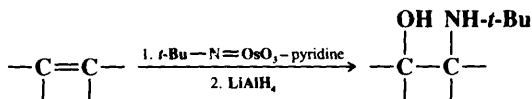


out internally. For example, 4-penten-1-ol, treated with benzenesulfonyl chloride and ethyl-diisopropylamine, gave the tetrahydrofuran **78**.⁷⁹⁵

5-39 Oxyamination (Addition of Oxygen, Nitrogen)
Tosylamino-hydroxy-addition



N-Tosylated β-hydroxy alkylamines (which can be easily hydrolyzed to β-hydroxyamines⁷⁹⁶) can be prepared⁷⁹⁷ by treatment of alkenes with the trihydrate of Chloramine-T⁶³⁷ and a catalytic amount of OsO₄. In some cases yields can be improved by the use of phase-transfer catalysis.⁷⁹⁸ The reaction has been carried out enantioselectively.⁷⁹⁹ In another procedure, certain β-hydroxy secondary alkylamines can be prepared by treatment of alkenes with the osmium compounds *t*-Bu—N=OsO₃, followed by reductive cleavage with LiAlH₄ of the



⁷⁹¹Trost; Ochiai; McDougal *J. Am. Chem. Soc.* **1978**, *100*, 7103. For a related reaction, see Zefirov; Zyk; Kutateladze; Kolbasenko; Lapin *J. Org. Chem. USSR* **1986**, *22*, 190.

⁷⁹²Bewick; Mellor; Owton *J. Chem. Soc., Perkin Trans. I* **1985**, 1039; Bewick; Mellor; Milano; Owton *J. Chem. Soc., Perkin Trans. I* **1985**, 1045; Samii; Ashmawy; Mellor *Tetrahedron Lett.* **1986**, *27*, 5289.

⁷⁹³Chung; D'Souza; Szmant *J. Org. Chem.* **1987**, *52*, 1741, and other papers in this series.

⁷⁹⁴Caserio; Fisher; Kim *J. Org. Chem.* **1985**, *50*, 4390.

⁷⁹⁵Tuladhar; Fallis *Tetrahedron Lett.* **1987**, *28*, 523. For a list of other examples, with references, see Ref. 133, pp. 451-452.

⁷⁹⁶For some reactions of the oxyamination products, see Bäckvall; Oshima; Palermo; Sharpless *J. Org. Chem.* **1979**, *44*, 1953.

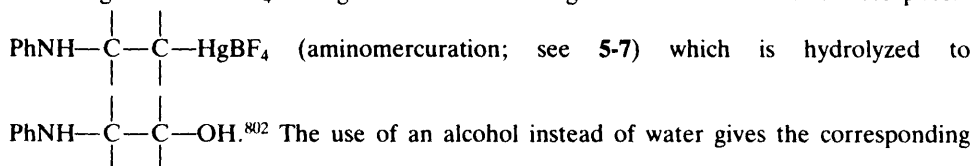
⁷⁹⁷Sharpless; Chong; Oshima *J. Org. Chem.* **1976**, *41*, 177.

⁷⁹⁸Herranz; Sharpless *J. Org. Chem.* **1978**, *43*, 2544.

⁷⁹⁹Hassinc; Gorsanc; Pecher; Martin *Bull. Soc. Chim. Belg.* **1985**, *94*, 759.

initially formed osmic esters.⁸⁰⁰ It is presumed that $\text{Ts}-\text{N}=\text{OsO}_3$ is an intermediate in the Chloramine-T reaction. Another oxyamination reaction involves treatment of a palladium complex of the olefin with a secondary or primary amine, followed by lead tetraacetate or another oxidant.⁸⁰¹

β -Amino alcohols can be prepared by treatment of an olefin with a reagent prepared from HgO and HBF_4 along with aniline to give an aminomercurial compound

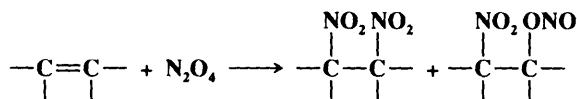


amino ether.

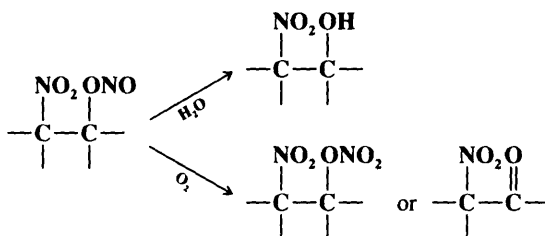
OS VII, 223, 375.

5-40 Addition of N_2O_4 and Related Reactions (Addition of Nitrogen, Nitrogen or Nitrogen, Oxygen)

Dinitro-addition; Nitro-nitrosooxy-addition



When olefins are treated with N_2O_4 in an ether, ester, or alkane as solvent, *vic*-dinitro compounds and β -nitro alkyl nitrites are produced.⁸⁰³ The reaction can be successfully performed with all kinds of olefins and acetylenes. Generally, both products are produced. The dinitro compound is usually stable, but the ester is quite reactive. Upon addition of water or alcohol it is hydrolyzed to a β -nitro alcohol. If oxygen is added, it is oxidized to a β -nitro alkyl nitrate or an α -nitro aldehyde or ketone.



The nitrate is stable. Even without deliberate addition of oxygen, it is not uncommon to find some nitrate or ketone. It is therefore possible to prepare four types of compound in this reaction, not counting the nitrite.

⁸⁰⁰Sharpless; Patrick; Truesdale; Biller *J. Am. Chem. Soc.* **1975**, 97, 2305; Hentges; Sharpless *J. Org. Chem.* **1980**, 45, 2257. For another method, in which the NH in the product is connected to an easily removable protecting group, see Herranz; Biller; Sharpless *J. Am. Chem. Soc.* **1978**, 100, 3596; Herranz; Sharpless *J. Org. Chem.* **1980**, 45, 2710.

⁸⁰¹Bäckvall; Björkman *J. Org. Chem.* **1980**, 45, 2893, *Acta Chem. Scand., Ser. B* **1984**, 38, 91; Bäckvall; Bystrom *J. Org. Chem.* **1982**, 47, 1126.

⁸⁰²Barluenga; Alonso-Cires; Asensio *Synthesis* **1981**, 376.

⁸⁰³For reviews, see Ogata, in Trahanovsky, Ref. 740, pt. C pp. 309-313; Larson, in Feuer, Ref. 446, pt. 1, 1969, pp. 316-323.

The mechanism is probably of the free-radical type,⁸⁰⁴ with initial attack by NO₂ to give $\begin{array}{c} | \\ -\dot{C}-C-NO_2 \\ | \end{array}$ as the intermediate for both products. In accord with this, the nitro group

(in the nitrite derivatives) is found on the side with more hydrogens. An NO₂ and an acetamido (AcNH) group can be added to arylalkenes (with the NHAc going to the side closer to the aryl group) with nitronium tetrafluoroborate in MeCN.⁸⁰⁵ Unsubstituted alkenes give poor yields.

OS VI, 837.

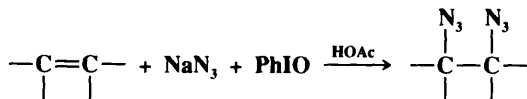
5-41 Diamination (Addition of Nitrogen, Nitrogen)

Di(alkylarylamino)-addition



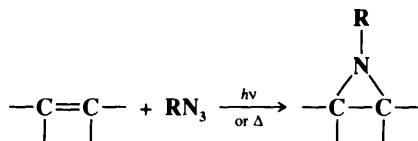
Primary (R = H) and secondary aromatic amines react with alkenes in the presence of thallium(III) acetate to give *vic*-diamines in good yields.⁸⁰⁶ The reaction is not successful for primary aliphatic amines. In another procedure, olefins can be diaminated by treatment with the osmium compounds R₂NOsO₂ and R₃NOsO (R = *t*-Bu),⁸⁰⁷ analogous to the osmium compound mentioned at 5-39. The palladium-promoted method of 5-39 has also been extended to diamination.⁸⁰⁸ Alkenes can also be diaminated⁸⁰⁹ indirectly by treatment of the aminomercurial compound mentioned in 5-39 with a primary or secondary aromatic amine.⁸¹⁰

Two azido groups can be added to double bonds by treatment with sodium azide and iodobenzene in acetic acid.⁸¹¹



5-42 Formation of Aziridines (Addition of Nitrogen, Nitrogen)

epi-Arylimino-addition, etc.



⁸⁰⁴Shechter; Gardikes; Pagano *J. Am. Chem. Soc.* **1959**, *81*, 5420; Shechter; Gardikes; Cantrell; Tiers *J. Am. Chem. Soc.* **1967**, *89*, 3005.

⁸⁰⁵Bloom; Fleischmann; Mellor *J. Chem. Soc., Perkin Trans. 1* **1984**, 2357.

⁸⁰⁶Gómez Aranda; Barluenga; Aznar *Synthesis* **1974**, 504.

⁸⁰⁷Chong; Oshima; Sharpless *J. Am. Chem. Soc.* **1977**, *99*, 3420. See also Sharpless; Singer *J. Org. Chem.* **1976**, *41*, 2504.

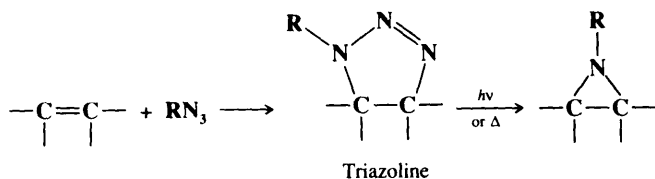
⁸⁰⁸Bäckvall *Tetrahedron Lett.* **1978**, 163.

⁸⁰⁹For other diamination methods, see Michejda; Campbell *J. Am. Chem. Soc.* **1979**, *101*, 7687; Becker; White; Bergman *J. Am. Chem. Soc.* **1980**, *102*, 5676; Becker; Bergman *Organometallics* **1983**, *2*, 787; Jung; Kohn *Tetrahedron Lett.* **1984**, *25*, 399; *J. Am. Chem. Soc.* **1985**, *107*, 2931; Osowska-Pacewicz; Zwierzak *Synthesis* **1990**, 505.

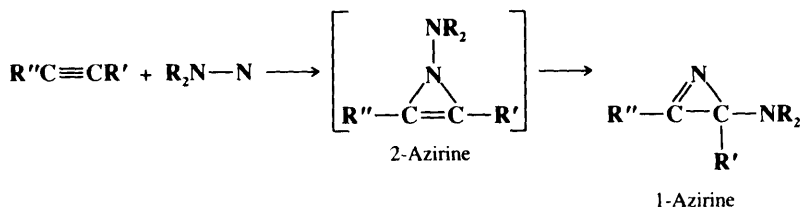
⁸¹⁰Barluenga; Alonso-Cires; Asensio *Synthesis* **1979**, 962.

⁸¹¹Moriarty; Khosrowshahi *Tetrahedron Lett.* **1986**, *27*, 2809. For other methods, see Minisci; Galli *Tetrahedron Lett.* **1962**, 533; Fristad; Brandvold; Peterson; Thompson *J. Org. Chem.* **1985**, *50*, 3647.

Aziridines can be prepared directly from double-bond compounds by photolysis or thermolysis of a mixture of the substrate and an azide.⁸¹² The reaction has been carried out with R = aryl, cyano, EtOOC, and RSO₂, as well as other groups. The reaction can take place by at least two pathways. In one, the azide is converted to a nitrene, which adds to the double bond in a manner analogous to that of carbene addition (5-50). In the other pathway a 1,3 dipolar addition (5-46) takes place to give a triazoline (which can be isolated), followed by extrusion of nitrogen (7-46). Evidence for the nitrene pathway is most compelling for



R = acyl groups. As discussed on p. 202, singlet nitrenes add stereospecifically while triplet nitrenes do not. Diphenyl sulfimide Ph₂SNH converts Michael-type substrates to the corresponding aziridines.⁸¹³ Aminonitrenes R₂NN have been shown to add to triple bonds to

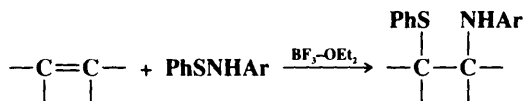


give 1-azirines, which arise from rearrangement of the initially formed 2-azirines.⁸¹⁴ Like oxirenes (see 5-36), 2-azirines are unstable, probably because of antiaromaticity.

Nitrenes can also add to aromatic rings to give ring-expansion products analogous to those mentioned in 5-50.⁸¹⁵

OS VI, 56.

5-43 Aminosulfenylation (Addition of Nitrogen, Sulfur) Arylamino-arylthio-addition



An amino group and an arylthio group can be added to a double bond by treatment with a sulfenamide PhSNHAr in the presence of BF₃-etherate.⁸¹⁶ The addition is anti, and the

⁸¹²For reviews, see Dermer; Ham *Ethylenimine and Other Aziridines*; Academic Press: New York, 1969, pp. 68-79; Muller; Hamer *1,2-Cycloaddition Reactions*; Wiley: New York, 1967.

⁸¹³Furukawa; Yoshimura; Ohtsu; Akasaka; Oae *Tetrahedron* **1980**, 36, 73. For other methods see Groves; Takahashi *J. Am. Chem. Soc.* **1983**, 105, 2073; Mahy; Bedi; Battioni; Mansuy *J. Chem. Soc., Perkin Trans. 2* **1988**, 1517; Atkinson; Kelly *J. Chem. Soc., Perkin Trans. 1* **1989**, 1515.

⁸¹⁴Anderson; Gilchrist; Rees *Chem. Commun.* **1969**, 147.

⁸¹⁵For example, see Hafner; König *Angew. Chem. Int. Ed. Engl.* **1963**, 2, 96 [*Angew. Chem.* 75, 89]; Lwowski; Johnson *Tetrahedron Lett.* **1967**, 891.

⁸¹⁶Benati; Montavocchi; Spagnolo *Tetrahedron Lett.* **1984**, 25, 2039. See also Brownbridge *Tetrahedron Lett.* **1984**, 25, 3759.

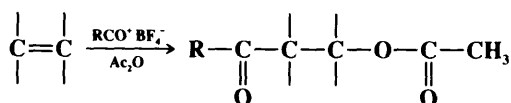
mechanism probably involves a thiiranium ion.⁸¹⁷ In another aminosulfenylation procedure, the substrate is treated with dimethyl(methylthio)sulfonium fluoroborate $\text{MeSSMe}_2^+ \text{BF}_4^-$ and ammonia or an amine,⁸¹⁸ the latter acting as a nucleophile. This reaction was extended

to other nucleophiles:⁸¹⁹ N_3^- , NO_2^- , CN^- , OH^- , and OAc^- to give $\text{MeS}-\text{C}(\text{Me})_2-\text{C}(\text{Me})_2-\text{A}$, where

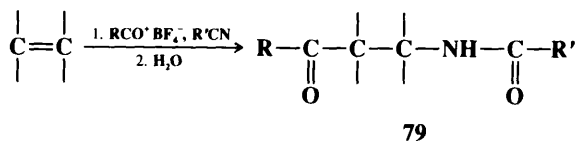
$\text{A} = \text{N}_3, \text{NO}_2, \text{CN}, \text{OH},$ and OAc , respectively. An RS ($\text{R} =$ alkyl or aryl) and an NHCOMe group have been added in an electrochemical procedure.⁸²⁰

5-44 Acylacyloxylation and Acylamidation (Addition of Oxygen, Carbon, or Nitrogen, Carbon)

Acyl-acyloxy-addition

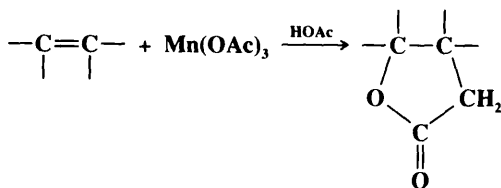


An acyl and an acyloxy group can be added to a double bond by treatment with an acyl fluoroborate and acetic anhydride.⁸²¹ As expected, the addition follows Markovnikov's rule, with the electrophile Ac^+ going to the carbon with more hydrogens. In an analogous reaction, an acyl and an amido group can be added, if a nitrile is used in place of the anhydride:



This reaction has also been carried out on triple bonds, to give the unsaturated analogs of **79** (syn addition).⁸²³

5-45 The Conversion of Olefins to γ -Lactones (Addition of Oxygen, Carbon)



⁸¹⁷See Ref. 20.

⁸¹⁸Trost; Shibata *J. Am. Chem. Soc.* **1982**, *104*, 3225; Caserio; Kim. *J. Am. Chem. Soc.* **1982**, *104*, 3231.

⁸¹⁹Trost; Shibata; Martin *J. Am. Chem. Soc.* **1982**, *104*, 3228; Trost; Shibata, Ref. 818. For an extension that allows A to be $\text{C}\equiv\text{CR}$, see Trost; Martin *J. Am. Chem. Soc.* **1984**, *106*, 4263.

⁸²⁰Bewick; Coe; Mellor; Owton *J. Chem. Soc., Perkin Trans. 1* **1985**, 1033.

⁸²¹Shastin; Balenkova *J. Org. Chem. USSR* **1984**, *20*, 870.

⁸²²Shastin; Balenkova *J. Org. Chem. USSR* **1984**, *20*, 1235; Gridnev; Shastin; Balenkova *J. Org. Chem. USSR* **1987**, *23*, 1389; Gridnev; Buevich; Sergeev; Balenkova *Tetrahedron Lett.* **1989**, *30*, 1987.

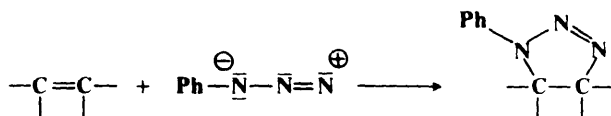
⁸²³Gridnev; Balenkova *J. Org. Chem. USSR* **1988**, *24*, 1447.

Olefins react with manganese(III) acetate to give γ -lactones.⁸²⁴ The mechanism is probably free-radical, involving addition of $\cdot\text{CH}_2\text{COOH}$ to the double bond. Lactone formation has also been accomplished by treatment of olefins with lead tetraacetate,⁸²⁵ with α -bromo carboxylic acids in the presence of benzoyl peroxide as catalyst,⁸²⁶ and with dialkyl malonates and iron(III) perchlorate $\text{Fe}(\text{ClO}_4)_3 \cdot 9\text{H}_2\text{O}$.⁸²⁷ Olefins can also be converted to γ -lactones by indirect routes.⁸²⁸

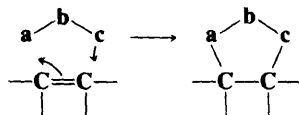
OS VII, 400.

For addition of aldehydes and ketones, see the Prins reaction (6-53), and reactions 6-63 and 6-64.

5-46 1,3-Dipolar Addition (Addition of Oxygen, Nitrogen, Carbon)



Azides add to double bonds to give triazolines. This is one example of a large group of reactions (2 + 3 cycloadditions) in which five-membered heterocyclic compounds are prepared by addition of 1,3-dipolar compounds to double bonds (see Table 15.3).⁸²⁹ These are compounds that have a sequence of three atoms a—b—c, of which a has a sextet of electrons in the outer shell and c an octet with at least one unshared pair. The reaction can then be formulated as



⁸²⁴Bush; Finkbeiner *J. Am. Chem. Soc.* **1968**, *90*, 5903; Heiba; Dessau; Kochl *J. Am. Chem. Soc.* **1968**, *90*, 5905; Heiba; Dessau; Rodewald *J. Am. Chem. Soc.* **1974**, *96*, 7977; Midgley; Thomas *J. Chem. Soc., Perkin Trans. 2* **1984**, 1537; Ernst; Fristad *Tetrahedron Lett.* **1985**, *26*, 3761; Shundo; Nishiguchi; Matsubara; Hirashima *Tetrahedron* **1991**, *47*, 831. See also Corey; Gross *Tetrahedron Lett.* **1985**, *26*, 4291.

⁸²⁵Heiba; Dessau; Kochl *J. Am. Chem. Soc.* **1968**, *90*, 2706.

⁸²⁶Nakano; Kayama; Nagai *Bull. Chem. Soc. Jpn.* **1987**, *60*, 1049. See also Kraus; Landgrebe *Tetrahedron Lett.* **1984**, *25*, 3939.

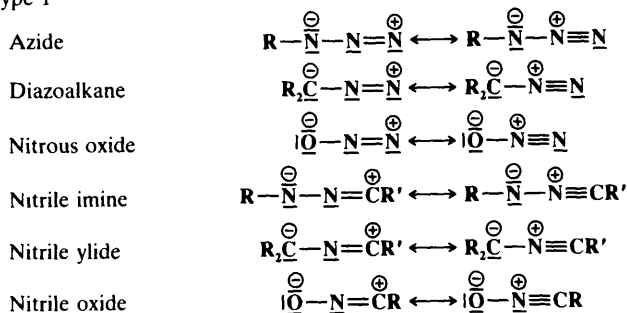
⁸²⁷Citterio; Sebastiano; Nicolini; Santi *Synlett* **1990**, 42.

⁸²⁸See, for example, Boldt; Thielecke; Etz Müller *Chem. Ber.* **1969**, *102*, 4157; Das Gupta; Felix; Kempe; Eschenmoser *Helv. Chim. Acta* **1972**, *55*, 2198; Bäuml; Tscheschlok; Pock; Mayr *Tetrahedron Lett.* **1988**, *29*, 6925.

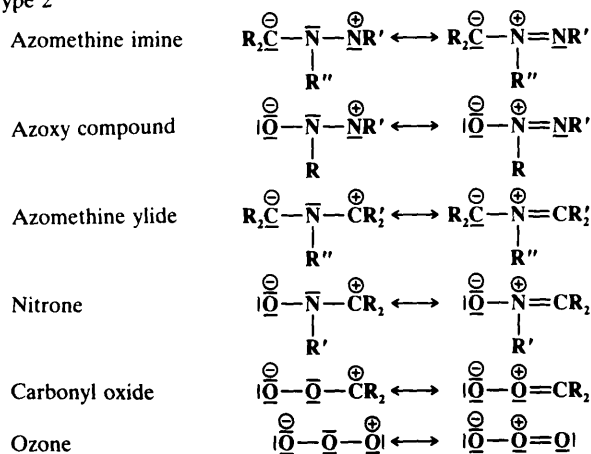
⁸²⁹For a treatise, see Padwa *1,3-Dipolar Cycloaddition Chemistry*, 2 vols.; Wiley: New York, 1984. For general reviews, see Carruthers, Ref. 440; Drygina; Garnovskii *Russ. Chem. Rev.* **1986**, *55*, 851-866; Samuilov; Konovalov *Russ. Chem. Rev.* **1984**, *53*, 332-342; Beltrame, in Bamford; Tipper, Ref. 1, vol. 9, pp. 117-131; Huisgen; Grashey; Sauer, in Patai, Ref. 36, vol. 1, pp. 806-878; Huisgen *Helv. Chim. Acta* **1967**, *50*, 2421-2439, *Bull. Soc. Chim. Fr.* **1965**, 3431-3440, *Angew. Chem. Int. Ed. Engl.* **1963**, *2*, 565-598, 633-645 [*Angew. Chem.* *75*, 604-637, 742-754]. For specific monographs and reviews, see Torrsell *Nitrile Oxides, Nitrones, and Nitronates in Organic Synthesis*; VCH: New York, 1988; Scriven *Azides and Nitrenes*; Academic Press: New York, 1984; Stanovnik *Tetrahedron* **1991**, *47*, 2925-2945 (dialkylalkanes); Kanemasa; Tsuge *Heterocycles* **1990**, *30*, 719-736 (nitrile oxides); Paton *Chem. Soc. Rev.* **1989**, *18*, 33-52 (nitrile sulfides); Terao; Aono; Achiwa *Heterocycles* **1988**, *27*, 981-1008 (azomethine ylides); Vedejs *Adv. Cycloaddit.* **1988**, *1*, 33-51 (azomethine ylides); DeShong; Lander; Leguin; Dicken *Adv. Cycloaddit.* **1988**, *1*, 87-128 (nitrones); Balasubramanian *Org. Prep. Proced. Int.* **1985**, *17*, 23-47 (nitrones); Confalone; Huie *Org. React.* **1988**, *36*, 1-173 (nitrones); Padwa, in *Horspool Synthetic Organic Photochemistry*; Plenum: New York, 1984, pp. 313-374 (nitrile ylides); Bianchi; Gandolfi; Grünanger in Patai; Rappoport, Ref. 49, pp. 752-784 (nitrile oxides); Black; Crozier; Davis *Synthesis* **1975**, 205-221 (nitrones); Stuckwisch *Synthesis* **1973**, 469-483 (azomethine ylides, azomethine imines). For reviews of intramolecular 1,3-dipolar additions see Padwa, in Padwa, treatise cited above, vol. 2, pp. 277-406; Padwa; Schoffstall *Adv. Cycloaddit.* **1990**, *2*, 1-89; Tsuge; Hatta; Hisano, in Patai *Supplement A: The Chemistry of Double-bonded Functional Groups*, vol. 2, pt. 1; Wiley: New York, 1989, pp. 345-475; Padwa *Angew. Chem. Int. Ed. Engl.* **1976**, *15*, 123-136 [*Angew. Chem.* *88*, 131-144]. For a review of azomethine ylides, see Tsuge; Kanemasa *Adv. Heterocycl. Chem.* **1989**, *45*, 231-349. For reviews of 1,3-dipolar cycloreversions, see Bianchi; Gandolfi, in Padwa, treatise cited above, vol. 2, pp. 451-542; Bianchi; De Micheli; Gandolfi *Angew. Chem. Int. Ed. Engl.* **1979**, *18*, 721-738 [*Angew. Chem.* *91*, 781-798]. For a related review, see Petrov; Petrov *Russ. Chem. Rev.* **1987**, *56*, 152-162. For the use of this reaction to synthesize natural products, see papers in *Tetrahedron* **1985**, *41*, 3447-3568.

TABLE 15.3 Some common 1,3-dipolar compounds

Type 1

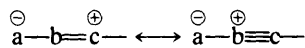


Type 2



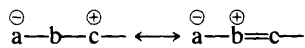
Since compounds with six electrons in the outer shell of an atom are usually not stable, the a—b—c system is actually one canonical form of a resonance hybrid, for which at least one other form can be drawn (see Table 15.3). 1,3-Dipolar compounds can be divided into two main types:

1. Those in which the dipolar canonical form has a double bond on the sextet atom and the other canonical form has a triple bond on that atom:



If we limit ourselves to the first row of the periodic table, b can only be nitrogen, c can be carbon or nitrogen, and a can be carbon, oxygen, or nitrogen; hence there are six types. Among these are azides (a = b = c = N), illustrated above, and diazoalkanes.

2. Those in which the dipolar canonical form has a single bond on the sextet atom and the other form has a double bond:

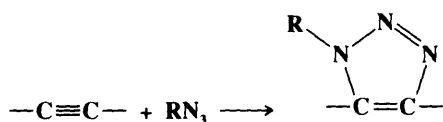


Here b can be nitrogen or oxygen, and a and c can be nitrogen, oxygen, or carbon, but there are only 12 types, since, for example, N—N—C is only another form of C—N—N. Examples are shown in Table 15.3.

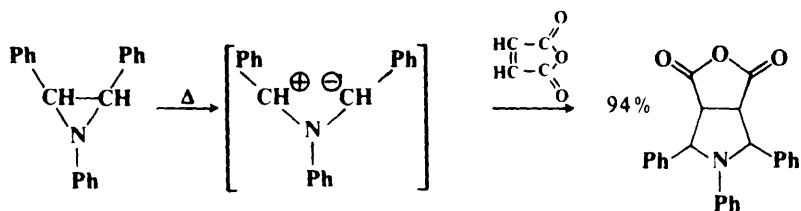
Of the 18 systems, some of which are unstable and must be generated in situ,⁸³⁰ the reaction has been accomplished for at least 15, though not in all cases with a carbon-carbon double bond (the reaction also can be carried out with other double bonds⁸³¹). Not all olefins undergo 1,3-dipolar addition equally well. The reaction is most successful for those that are good dienophiles in the Diels-Alder reaction (5-47). The addition is stereospecific and syn, and the mechanism is probably a one-step concerted process, as illustrated above.⁸³² As expected for this type of mechanism, the rates do not vary much with changes in solvent.⁸³³ There are no simple rules covering orientation in 1,3-dipolar additions. Regioselectivities are complicated but have been explained by molecular-orbital treatments.⁸³⁴ When the 1,3-dipolar compound is a thiocarbonyl ylide ($R_2C=S^{\oplus}-CH_2^{\ominus}$) the addition has been shown to be nonstereospecific with certain substrates (though stereospecific with others), indicating a nonsynchronous mechanism in these cases, and in fact, a diionic intermediate (see mechanism c on p. 857) has been trapped in one such case.⁸³⁵

Conjugated dienes generally give exclusive 1,2 addition, though 1,4 addition (a 3 + 4 cycloaddition) has been reported.⁸³⁶

Carbon-carbon triple bonds can also undergo 1,3-dipolar addition.⁸³⁷ For example, azides give triazoles:



The 1,3-dipolar reagent can in some cases be generated by the in situ opening of a suitable three-membered ring system. For example, aziridines can add to activated double bonds to give pyrrolidines, e.g.,⁸³⁸



⁸³⁰For a review of some aspects of this, see Grigg *Chem. Soc. Rev.* **1987**, *16*, 89-121.

⁸³¹For a review of 1,3-dipolar addition to other double bonds, see Bianchi; De Micheli; Gandolfi, in Patai, Ref. 1, pt. 1, pp. 369-532. For a review of such addition to the C=S bond, see Dunn; Rudolf *Carbon Disulfide in Organic Chemistry*; Wiley: New York, 1989, pp. 97-119.

⁸³²For a review, see Huisgen *Adv. Cycloaddit.* **1988**, *1*, 1-31. For discussions, see Huisgen *J. Org. Chem.* **1976**, *41*, 403; Firestone *Tetrahedron* **1977**, *33*, 3009-3039; Harcourt *Tetrahedron* **1978**, *34*, 3125; Haque *J. Chem. Educ.* **1984**, *61*, 490; Al-Sader; Kadri *Tetrahedron Lett.* **1985**, *26*, 4661; Houk; Firestone; Munchausen; Mueller; Arison; Garcia *J. Am. Chem. Soc.* **1985**, *107*, 7227; Majchrzak; Warkentin *J. Phys. Org. Chem.* **1990**, *3*, 339.

⁸³³For a review of the role of solvents in this reaction, see Kadaba *Synthesis* **1973**, 71-84.

⁸³⁴For a review, see Houk; Yamaguchi, in Padwa *1,3-Dipolar Cycloaddition Chemistry*, Ref. 829, vol. 2, pp. 407-450. See also Burdisso; Gandolfi; Quartieri; Rastelli *Tetrahedron* **1987**, 159.

⁸³⁵Huisgen; Mloston; Langhals *J. Am. Chem. Soc.* **1986**, *108*, 6401; *J. Org. Chem.* **1986**, *51*, 4085; Mloston; Langhals; Huisgen *Tetrahedron Lett.* **1989**, *30*, 5373; Huisgen; Mloston *Tetrahedron Lett.* **1989**, *30*, 7041.

⁸³⁶Baran; Mayr *J. Am. Chem. Soc.* **1987**, *109*, 6519.

⁸³⁷For reviews, see Bastide; Hamelin; Texier; Quang *Bull. Soc. Chim. Fr.* **1973**, 2555-2579; 2871-2887; Fuks; Viehe in Viehe Ref. 49, p. 460-477.

⁸³⁸For a review, see Lown, in Padwa, Ref. 834, vol. 1, pp. 653-732.

Aziridines also add to $C\equiv C$ triple bonds as well as to other unsaturated linkages, including $C=O$, $C=N$, and $C\equiv N$.⁸³⁹ In some of these reactions it is a $C-N$ bond of the aziridine that opens rather than the $C-C$ bond.

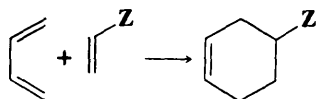
For other 2 + 3 cycloadditions, see 5-48.

OS V, 957, 1124; VI, 592, 670; 67, 133. Also see OS IV, 380.

C. Carbon on Both Sides. Reactions 5-47 to 5-52 are cycloaddition reactions.⁸⁴⁰

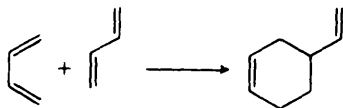
5-47 The Diels–Alder Reaction

(2 + 4)cyclo-Ethylene-1/4/addition or (4 + 2)cyclo-[But-2-ene-1,4-diy]-1/2/addition, etc.



In the *Diels–Alder reaction* a double bond adds 1,4 to a conjugated diene (a 2 + 4 cycloaddition),⁸⁴¹ so the product is always a six-membered ring. The double-bond compound is called a *dienophile*. The reaction is easy and rapid and of very broad scope.⁸⁴² Ethylene and simple olefins make poor dienophiles, although the reaction has been carried out with these compounds. Most dienophiles are of the form $-C=C-Z$ or $Z-C=C-Z'$, where Z and

Z' are CHO, COR,⁸⁴³ COOH, COOR, COCl, COAr, CN,⁸⁴⁴ NO₂,⁸⁴⁵ Ar, CH₂OH, CH₂Cl, CH₂NH₂, CH₂CN, CH₂COOH, halogen, or C=C. In the last case, the dienophile is itself a diene:



When two dienes react, mixtures are quite possible. Thus, butadiene and isoprene ($CH_2=CH-CMe=CH_2$) gave all nine possible Diels–Alder adducts, as well as eight-mem-

⁸³⁹For reviews, see Lown *Rec. Chem. Prog.* **1971**, 32, 51-83; Gladysheva; Sineokov; Etlis *Russ. Chem. Rev.* **1970**, 39, 118-129.

⁸⁴⁰For a system of classification of cycloaddition reactions, see Huisgen *Angew. Chem. Int. Ed. Engl.* **1968**, 7, 321-328 [*Angew. Chem.* 80, 329-337]. For a review of certain types of cycloadditions leading to 3- to 6-membered rings involving 2, 3, or 4 components, see Posner *Chem. Rev.* **1986**, 86, 831-844. See also the series *Advances in Cycloaddition*.

⁸⁴¹For a monograph, see Wasserman *Diels–Alder Reactions*; Elsevier: New York, 1965. For reviews, see Roush *Adv. Cycloaddit.* **1990**, 2, 91-146; Carruthers, Ref. 440; Brieger; Bennett *Chem. Rev.* **1980**, 80, 63-97; Oppolzer *Angew. Chem. Int. Ed. Engl.* **1977**, 16, 10-23 [*Angew. Chem.* 89, 10-24]; Beltrame, in Bamford; Tipper, Ref. 1, vol. 9, pp. 94-117; Huisgen; Grashey; Sauer, in Patai, Ref. 36, vol. 1, pp. 878-929; Carruthers, Ref. 218, pp. 183-244; Sauer *Angew. Chem. Int. Ed. Engl.* **1966**, 5, 211-230, **1967**, 6, 16-33 [*Angew. Chem.* 78, 233-252, 79, 76-94]. For a monograph on intramolecular Diels–Alder reactions see Taber, Ref. 440. For reviews, see Deslongchamps *Aldrichimica Acta* **1991**, 24, 43-56; Craig *Chem. Soc. Rev.* **1987**, 16, 187-238; Salakhov; Ismailov *Russ. Chem. Rev.* **1986**, 55, 1145-1163; Fallis *Can. J. Chem.* **1984**, 62, 183-234. For a long list of references to various aspects of the Diels–Alder reaction, see Ref. 133, pp. 263-272.

⁸⁴²For a review of reactivity in the Diels–Alder reaction, see Konovalov *Russ. Chem. Rev.* **1983**, 52, 1064-1080.

⁸⁴³For a review of Diels–Alder reactions with cyclic enones, see Fringuelli; Taticchi; Wenkert *Org. Prep. Proced. Int.* **1990**, 22, 131-165.

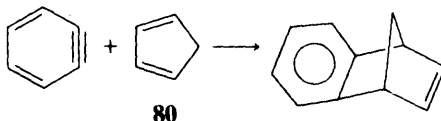
⁸⁴⁴For a review of the Diels–Alder reaction with acrylonitrile, see Butskus *Russ. Chem. Rev.* **1962**, 31, 283-294. For a review of tetracyanoethylene as a dienophile, see Ciganek; Linn; Webster, in Rappoport, Ref. 588, pp. 449-453.

⁸⁴⁵For a review of the Diels–Alder reaction with nitro compounds, see Novikov; Shuekhgeimer; Dudinskaya *Russ. Chem. Rev.* **1960**, 29, 79-94.

bered rings and trimers.⁸⁴⁶ Particularly common dienophiles are maleic anhydride⁸⁴⁷ and quinones.⁸⁴⁸ Triple bond compounds ($-\text{C}\equiv\text{C}-\text{Z}$ or $\text{Z}-\text{C}\equiv\text{C}-\text{Z}'$) may be dienophiles⁸⁴⁹



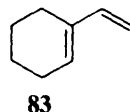
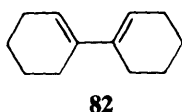
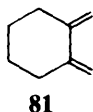
as may allenes, though allenes without activating groups are very poor dienophiles.⁸⁵⁰ Ketenes, however, do not undergo Diels-Alder reactions.⁸⁵¹ Benzyne, although not isolable, act as dienophiles and can be trapped with dienes,⁸⁵² e.g.,



The low reactivity of ethylene can be overcome by using phenyl vinyl sulfone $\text{PhSO}_2\text{CH}=\text{CH}_2$ instead.⁸⁵³ The PhSO_2 group can be easily removed with Na-Hg after the ring-closure reaction. Similarly, phenyl vinyl sulfoxide $\text{PhSOCH}=\text{CH}_2$ can be used as a synthon for acetylene.⁸⁵⁴ In this case PhSOH is lost from the sulfoxide product (**7-12**).

Besides carbon-carbon multiple bonds, other double- and triple-bond compounds can be dienophiles, giving rise to heterocyclic compounds. Among these are $\text{N}\equiv\text{C}-$, $-\text{N}=\text{C}-$, $-\text{N}=\text{N}-$, $\text{O}=\text{N}-$, and $-\text{C}=\text{O}$ compounds⁸⁵⁵ and, as we have seen (**5-37**), even molecular oxygen.

Dienes can be open-chain, inner-ring (e.g., **80**), outer-ring⁸⁵⁶ (e.g., **81**), across rings (e.g., **82**), or inner-outer (e.g., **83**), except that they may not be frozen into a transoid conformation



⁸⁴⁶Johnstone; Quan *J. Chem. Soc.* **1963**, 935.

⁸⁴⁷For a review of Diels-Alder reactions with maleic anhydride see Kloetzel *Org. React.* **1948**, *4*, 1-59.

⁸⁴⁸For reviews of Diels-Alder reactions with quinones, see Finley, in Patai *Ref.* **38**, vol. 1, pt. 2, pp. 986-1018, vol. 2, pt. 1 (edited by Patai; Rappoport), 1988, pp. 537-717, pp. 614-645. For a review of the synthesis of quinones using Diels-Alder reactions, see Naruta; Maruyama, in the same treatise, vol. 2, pt. 1, pp. 241-402, pp. 277-303.

⁸⁴⁹For reviews of triple bonds in cycloaddition reactions, see Bastide; Henri-Rousseau, in Patai, *Ref.* **70**, pt. 1, pp. 447-522; Fuks; Viehe, in Viehe, *Ref.* **49**, pp. 477-508.

⁸⁵⁰For a review of allenes as dienes or dienophiles, see Hopf, in Landor, *Ref.* **95**, vol. 2, pp. 563-577.

⁸⁵¹Ketenes react with conjugated dienes to give 1,2 addition (see **5-49**).

⁸⁵²For a review of benzyne as dienophiles, see Hoffmann *Dehydrobenzene and Cycloalkynes*; Academic Press: New York, 1967, pp. 200-239. For a review of the reactions of benzyne with heterocyclic compounds see Bryce; Vernon *Adv. Heterocycl. Chem.* **1981**, *28*, 183-229.

⁸⁵³Carr; Williams; Paquette *J. Org. Chem.* **1983**, *48*, 4976; Kinney; Crouse; Paquette *J. Org. Chem.* **1983**, *48*, 4986.

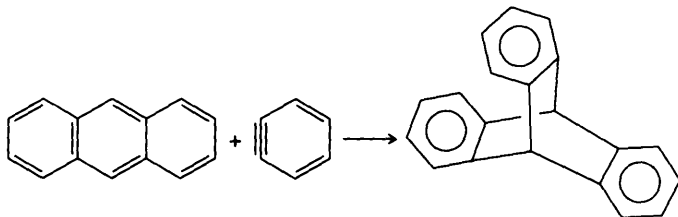
⁸⁵⁴Paquette; Moerck; Harichian; Magnus *J. Am. Chem. Soc.* **1978**, *100*, 1597. For other acetylene synthons see De Lucchi; Lucchini; Pasquato; Modena *J. Org. Chem.* **1984**, *49*, 596; Hermeling; Schäfer *Angew. Chem. Int. Ed. Engl.* **1984**, *23*, 233 [*Angew. Chem.* **96**, 238]. For a review, see De Lucchi; Modena *Tetrahedron* **1984**, *40*, 2585-2632. For a review of 2 + 2 and 2 + 4 cycloadditions of vinylic sulfides, sulfoxides, and sulfones, see De Lucchi; Pasquato *Tetrahedron* **1988**, *44*, 6755-6794.

⁸⁵⁵For monographs on dienes and dienophiles with hetero atoms, see Boger; Weinreb *Hetero Diels-Alder Methodology in Organic Synthesis*; Academic Press: New York, 1987; Hamer, *Ref.* **778**. For reviews, see Weinreb; Scola *Chem. Rev.* **1989**, *89*, 1525-1534; Boger, in Lindberg *Strategies and Tactics in Organic Synthesis*, vol. 2; Academic Press: New York, 1989, pp. 1-56; Kametani; Hibino *Adv. Heterocycl. Chem.* **1987**, *42*, 245-333; Boger *Tetrahedron* **1983**, *39*, 2869-2939; Weinreb; Staib *Tetrahedron* **1982**, *38*, 3087-3128; Weinreb; Levin *Heterocycles* **1979**, *12*, 949-975; Desimoni; Tacconi *Chem. Rev.* **1975**, *75*, 651-692; Kresze; Firl *Fortschr. Chem. Forsch.* **1969**, *11*, 245-284. See also *Ref.* **862**.

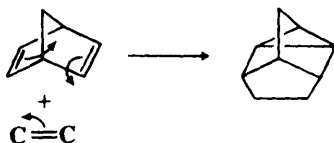
⁸⁵⁶For reviews of Diels-Alder reactions of some of these compounds, see Charlton; Alauddin *Tetrahedron* **1987**, *43*, 2873-2889; Oppolzer *Synthesis* **1978**, 793-802.

(see p. 842). They need no special activating groups, and nearly all conjugated dienes undergo the reaction with suitable dienophiles.⁸⁵⁷

Aromatic compounds can also behave as dienes.⁸⁵⁸ Benzene is very unreactive toward dienophiles; very few dienophiles (one of them is benzyne) have been reported to give Diels–Alder adducts with it.⁸⁵⁹ Naphthalene and phenanthrene are also quite resistant, though naphthalene has given Diels–Alder addition at high pressures.⁸⁶⁰ However, anthracene and other compounds with at least three linear benzene rings give Diels–Alder reactions readily. The interesting compound triptycene can be prepared by a Diels–Alder reaction between benzyne and anthracene:⁸⁶¹



Certain heterocyclic aromatic rings (among them furans)⁸⁶² can also behave as dienes in the Diels–Alder reaction. Some hetero dienes that give the reaction are —C=C—C=O , O=C—C=O , and N=C—C=N .⁸⁵⁴ For both all-carbon and hetero systems, the “diene” can be a conjugated enyne. If the geometry of the molecule is suitable, the diene can even be nonconjugated, e.g.,⁸⁶³



This last reaction is known as the *homo-Diels–Alder reaction*.

⁸⁵⁷For a monograph on dienes, with tables showing more than 800 types, see Fringuelli; Taticchi *Dienes in the Diels–Alder Reaction*; Wiley: New York, 1990. For a review of Diels–Alder reactions with 2-pyrones, see Shusherina *Russ. Chem. Rev.* **1974**, *43*, 851-861. For reviews of dienes with hetero substituents, see Danishefsky *Chemtracts: Org. Chem.* **1989**, *2*, 273-297; Petrzilka; Grayson *Synthesis* **1981**, 753-786. For a review of dienes containing a 1-CONR₂ group, see Smith *Org. Prep. Proced. Int.* **1990**, *22*, 315-397.

⁸⁵⁸For a review, see Wagner–Jauregg *Synthesis* **1980**, 165-214, 769-798. See also Balaban; Biermann; Schmidt *Nouv. J. Chim.* **1985**, *9*, 443.

⁸⁵⁹Miller; Stiles *J. Am. Chem. Soc.* **1963**, *85*, 1798; Meyerson; Fields *Chem. Ind. (London)* **1966**, 1230; Ciganek *Tetrahedron Lett.* **1967**, 3321; Friedman *J. Am. Chem. Soc.* **1967**, *89*, 3071; Liu; Krespan *J. Org. Chem.* **1969**, *34*, 1271.

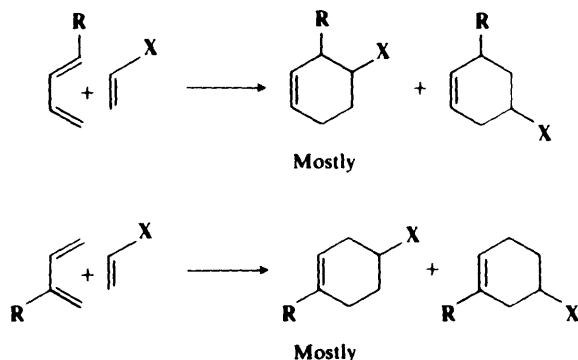
⁸⁶⁰Jones; Mangold; Plieninger *Tetrahedron* **1962**, *18*, 267; Plieninger; Wild; Westphal *Tetrahedron* **1969**, *25*, 5561.

⁸⁶¹Wittig; Niethammer *Chem. Ber.* **1960**, *93*, 944; Wittig; Härle; Knauss; Niethammer *Chem. Ber.* **1960**, *93*, 951. For a review of triptycene, see Skvarchenko; Shalaev; Klabunovskii *Russ. Chem. Rev.* **1974**, *43*, 951-966.

⁸⁶²For reviews, see Katritzky; Dennis *Chem. Rev.* **1989**, *89*, 827-861; Schmidt *Acc. Chem. Res.* **1986**, *19*, 250-259; Boger *Chem. Rev.* **1986**, *86*, 781-793.

⁸⁶³See, for example, Fickes; Metz *J. Org. Chem.* **1978**, *43*, 4057; Paquette; Kesselmayr; Künzer *J. Org. Chem.* **1988**, *53*, 5183.

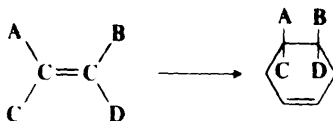
When an unsymmetrical diene adds to an unsymmetrical dienophile, there are two possible products (not counting stereoisomers):



Although mixtures are often obtained, usually one predominates, the one indicated above. This regioselectivity, in which the “ortho” or “para” product is favored over the “meta,” has been explained by molecular-orbital considerations.⁸⁶⁴ When X = NO₂, regioselectivity to give the “ortho” or “para” product was very high at room temperature, and this method, combined with subsequent removal of the NO₂ (see 0-82) has been used to perform regioselective Diels–Alder reactions.⁸⁶⁵

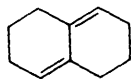
The stereochemistry of the Diels–Alder reaction can be considered from several aspects:

1. With respect to the dienophile, the addition is stereospecifically syn, with very few exceptions.⁸⁶⁶ This means that groups that are cis in the olefin will be cis in the cyclohexene ring:



2. With respect to 1,4-disubstituted dienes, fewer cases have been investigated, but here too the reaction is stereospecific and syn. Thus, *trans,trans*-1,4-diphenylbutadiene gives *cis*-1,4-diphenylcyclohexene derivatives.

3. The diene must be in the cisoid conformation. If it is frozen into the transoid conformation, as in **84**, the reaction does not take place. The diene either must be frozen into the cisoid conformation or must be able to achieve it during the reaction.



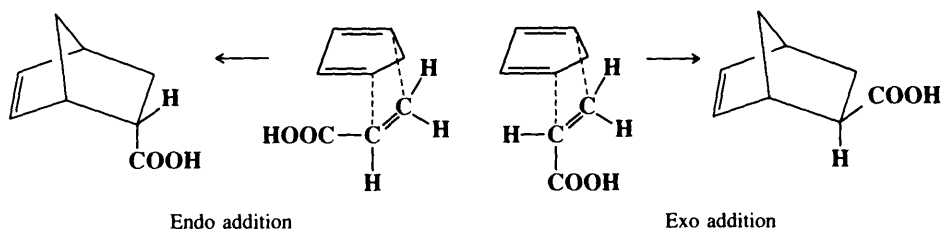
84

⁸⁶⁴Feuer; Herndon; Hall *Tetrahedron* **1968**, *24*, 2575; Inukai; Sato; Kojima *Bull. Chem. Soc. Jpn.* **1972**, *45*, 891; Epiotis *J. Am. Chem. Soc.* **1973**, *95*, 5624; Sustmann *Pure Appl. Chem.* **1974**, *40*, 569-593; Trost; Vladuchick; Bridges *J. Am. Chem. Soc.* **1980**, *102*, 3554; Alston; Gordon; Ottenbrite; Cohen *J. Org. Chem.* **1983**, *48*, 5051; Kahn; Pau; Overman; Hehre *J. Am. Chem. Soc.* **1986**, *108*, 7381.

⁸⁶⁵Danishefsky; Hershenson *J. Org. Chem.* **1979**, *44*, 1180; Ono; Miyake; Kamimura; Kaji *J. Chem. Soc., Perkin Trans. 1* **1987**, 1929. For another method of controlling regioselectivity, see Kraus; Liras *Tetrahedron Lett.* **1989**, *30*, 1907.

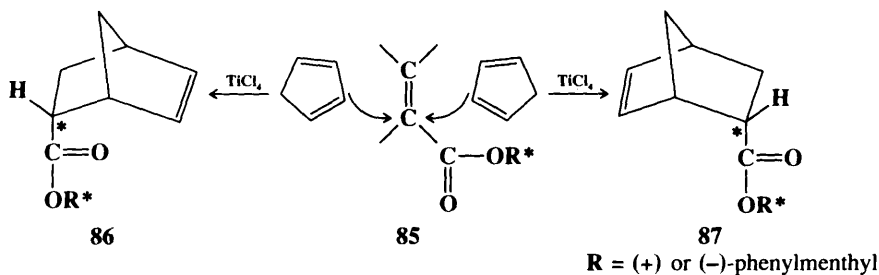
⁸⁶⁶For an exception, see Meier; Eckes; Niedermann; Kolshorn *Angew. Chem. Int. Ed. Engl.* **1987**, *26*, 1046 [*Angew. Chem.* *99*, 1040].

4. When the diene is cyclic, there are two possible ways in which addition can occur if the dienophile is not symmetrical. The larger side of the dienophile may be under the ring (*endo* addition), or it may be the smaller side (*exo* addition):



Most of the time, the addition is predominantly *endo*; i.e., the more bulky side of the olefin is under the ring, and this is probably true for open-chain dienes also.⁸⁶⁷ However, exceptions are known, and in many cases mixtures of *exo* and *endo* addition products are found.⁸⁶⁸

5. In some cases, the Diels–Alder reaction can be made enantioselective.⁸⁶⁹ Most such work has used a chiral dienophile (e.g., **85**) and an achiral diene,⁸⁷⁰ along with a Lewis acid catalyst (see below). In such cases addition of the diene to the two faces of **85** takes place at different rates, and **86** and **87** are formed in different amounts.⁸⁷¹ In the case illustrated,



hydrolysis of the product removes the chiral R group, making it a chiral auxiliary in this reaction. Asymmetric Diels–Alder reactions have also been carried out with achiral dienes and dienophiles, but with an optically active catalyst.⁸⁷²

Electron-donating substituents in the diene accelerate the reaction; electron-withdrawing groups retard it. For the dienophile it is just the reverse: donating groups decrease the rate,

⁸⁶⁷See, for example, Baldwin; Reddy *J. Org. Chem.* **1989**, *54*, 5264.

⁸⁶⁸See, for example, Alder; Günzl *Chem. Ber.* **1960**, *93*, 809; Stockmann *J. Org. Chem.* **1961**, *26*, 2025; Jones; Wife *J. Chem. Soc., Chem. Commun.* **1973**, 421; Lindsay Smith; Norman; Stillings *Tetrahedron* **1978**, *34*, 1381; Müller; Bernardinelli; Rodriguez; Pfyffer; Schaller *Chimia* **1987**, *41*, 244.

⁸⁶⁹For reviews, see Taschner *Org. Synth: Theory Appl.* **1989**, *1*, 1-101; Helmchen; Karge; Weetman *Mod. Synth. Methods* **1986**, *4*, 261-306; Paquette, in Morrison, Ref. 232, vol. 3, pp. 455-501; Oppolzer *Angew. Chem. Int. Ed. Engl.* **1984**, *23*, 876-889 [*Angew. Chem.* **96**, 840-854]. See also the list of references in Macaulay; Fallis *J. Am. Chem. Soc.* **1990**, *112*, 1136.

⁸⁷⁰For the use of chiral dienes, see Fisher; Hehre; Kahn; Overman *J. Am. Chem. Soc.* **1988**, *110*, 4625; Menezes; Zezza; Sheu; Smith *Tetrahedron Lett.* **1989**, *30*, 3295; Charlton; Plourde; Penner *Can. J. Chem.* **1989**, *67*, 1010; Tripathy; Carroll; Thornton *J. Am. Chem. Soc.* **1990**, *112*, 6743, **1991**, *113*, 7630; Rieger; Breitmaier *Synthesis* **1990**, 697.

⁸⁷¹Oppolzer; Kurth; Reichlin; Moffatt *Tetrahedron Lett.* **1981**, *22*, 2545. See also Walborsky; Barash; Davis *Tetrahedron* **1963**, *19*, 2333; Furuta; Iwanaga; Yamamoto *Tetrahedron Lett.* **1986**, *27*, 4507; Evans; Chapman; Bisaha *J. Am. Chem. Soc.* **1988**, *110*, 1238; Mattay; Mertes; Maas *Chem. Ber.* **1989**, *122*, 327; Alonso; Carretero; Garcia Ruano *Tetrahedron Lett.* **1989**, *30*, 3853; Tomioka; Hamada; Suenaga; Koga *J. Chem. Soc., Perkin Trans. 1* **1990**, 426; Cativiela; López; Mayor *Tetrahedron: Asymmetry* **1990**, *1*, 61.

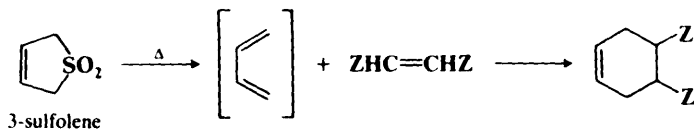
⁸⁷²For a review, see Narasaka *Synthesis* **1991**, 1-11. For some recent examples, see Bir; Kaufmann *J. Organomet. Chem.* **1990**, *390*, 1; Rebiere; Riant; Kagan *Tetrahedron: Asymmetry* **1990**, *1*, 199; Terada; Mikami; Nakai *Tetrahedron Lett.* **1991**, *32*, 935; Corey; Imai; Zhang *J. Am. Chem. Soc.* **1991**, *113*, 728; Narasaka; Tanaka; Kanai *Bull. Chem. Soc. Jpn.* **1991**, *64*, 387; Hawkins; Loren *J. Am. Chem. Soc.* **1991**, *113*, 7794.

and withdrawing groups increase it. Cyclic dienes, in which the cisoid conformation is built in, usually react faster than the corresponding open-chain compounds, which have to achieve the cisoid conformation by rotation.⁸⁷³

As should be apparent from the foregoing, many interesting compounds can be prepared by the Diels–Alder reaction, some of which would be hard to make in any other way. It has thus been exceedingly useful. Competing reactions are polymerization of the diene or dienophile, or both, and 1,2 cycloaddition (5-49). However, yields are usually quite high. No catalyst is needed, though it has been found that Lewis acids catalyze some Diels–Alder reactions,⁸⁷⁴ usually those in which Z in the dienophile is a C=O or C=N group. A Lewis acid catalyst usually increases both the regioselectivity of the reaction (in the sense given above) and the extent of endo addition,⁸⁷⁵ and, in the case of enantioselective reactions, the extent of enantioselectivity. Some Diels–Alder reactions can also be catalyzed by the addition of a stable cation radical, e.g., tris(4-bromophenyl)aminium hexachloroantimonate $\text{Ar}_3\text{N}^+ \text{SbCl}_6^-$.⁸⁷⁶

A number of other methods have been reported for the acceleration of Diels–Alder reactions, including the use of a microwave oven,⁸⁷⁷ water as a solvent (a hydrophobic effect),⁸⁷⁸ 5 M LiClO_4 in Et_2O as solvent,⁸⁷⁹ absorption of the reactants on chromatographic absorbents,⁸⁸⁰ and the use of an ultracentrifuge⁸⁸¹ (one of several ways to achieve reaction at high pressures).⁸⁸²

The Diels–Alder reaction is usually reversible and has been used to protect double bonds.⁸⁸³ A convenient substitute for butadiene in the Diels–Alder reaction is the compound



3-sulfolene since the latter is a solid which is easy to handle while the former is gas.⁸⁸⁴ Butadiene is generated in situ by a reverse Diels–Alder reaction (see 7-25).

There are, broadly speaking, three possible mechanisms that have been considered for

⁸⁷³Sauer; Lang; Mielert *Angew. Chem. Int. Ed. Engl.* **1962**, *1*, 268 [*Angew. Chem.* **74**, 352]; Sauer; Wiest *Angew. Chem. Int. Ed. Engl.* **1962**, *1*, 269 [*Angew. Chem.* **74**, 353]. See, however, Scharf; Plum; Fleischhauer; Schleker *Chem. Ber.* **1979**, *112*, 862.

⁸⁷⁴Yates; Eaton *J. Am. Chem. Soc.* **1960**, *82*, 4436; Fray; Robinson *J. Am. Chem. Soc.* **1961**, *83*, 249; Inukai; Kojima *J. Org. Chem.* **1967**, *32*, 869, 872; Laszlo; Lucchetti *Tetrahedron Lett.* **1984**, *25*, 4387; Bonnesen; Puckett; Honeychuck; Hersh *J. Am. Chem. Soc.* **1989**, *111*, 6070. For review of the role of the catalyst in increasing reactivity, see Kiselev; Kononov *Russ. Chem. Rev.* **1989**, *58*, 230-249.

⁸⁷⁵For discussions see Houk; Strozier *J. Am. Chem. Soc.* **1973**, *95*, 4094; Alston; Ottenbrite *J. Org. Chem.* **1975**, *40*, 1111.

⁸⁷⁶For a review, see Bauld; *Tetrahedron* **1989**, *45*, 5307-5363.

⁸⁷⁷Giguere; Bray; Duncan; Majetich *Tetrahedron Lett.* **1986**, *27*, 4945; Berlan; Giboreau; Lefeuvre; Marchand *Tetrahedron Lett.* **1991**, *32*, 2363.

⁸⁷⁸Rideout; Breslow *J. Am. Chem. Soc.* **1980**, *102*, 7816. For a review, see Breslow *Acc. Chem. Res.* **1991**, *24*, 159-164. See also Grieco; Garner; He *Tetrahedron Lett.* **1983**, 1897; Blokzijl; Blandamer; Engberts *J. Am. Chem. Soc.* **1991**, *113*, 4241; Breslow; Rizzo *J. Am. Chem. Soc.* **1991**, *113*, 4340.

⁸⁷⁹Grieco; Nunes; Gaul *J. Am. Chem. Soc.* **1990**, *112*, 4595. See also Braun; Sauer *Chem. Ber.* **1986**, *119*, 1269; Forman; Dailey *J. Am. Chem. Soc.* **1991**, *113*, 2761.

⁸⁸⁰Veselovsky; Gybin; Lozanova; Moiseenkov; Smit; Caple *Tetrahedron Lett.* **1988**, *29*, 175.

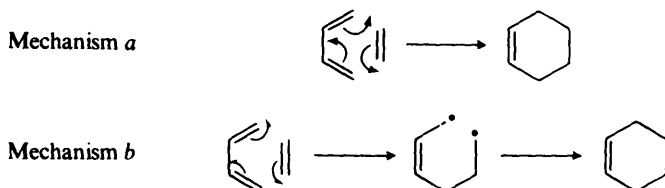
⁸⁸¹Dolata; Bergman *Tetrahedron Lett.* **1987**, *28*, 707.

⁸⁸²For reviews, see Isaacs; George *Chem. Br.* **1987**, 47-54; Asano; le Noble *Chem. Rev.* **1978**, *78*, 407-489. See also Firestone; Smith *Chem. Ber.* **1989**, *122*, 1089.

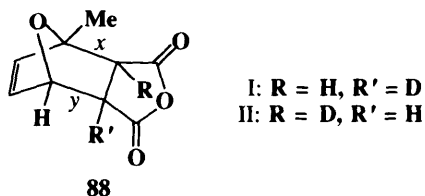
⁸⁸³For reviews of the reverse Diels–Alder reaction, see Ichihara *Synthesis* **1987**, 207-222; Lasne; Ripoll *Synthesis* **1985**, 121-143; Ripoll; Rouessac; Rouessac *Tetrahedron* **1978**, *34*, 19-40; Brown *Pyrolytic Methods in Organic Chemistry*; Academic Press: New York, 1980, pp. 259-281; Kwart; King *Chem. Rev.* **1968**, *68*, 415-447.

⁸⁸⁴Sample; Hatch *Org. Synth. VI*, 454. For a review, see Chou; Tso *Org. Prep. Proced. Int.* **1989**, *21*, 257-296.

the uncatalyzed Diels–Alder reaction.⁸⁸⁵ In mechanism *a* there is a cyclic six-centered transition state and no intermediate. The reaction is concerted and occurs in one step. In



mechanism *b* one end of the diene fastens to one end of the dienophile first to give a diradical, and then, in a second step, the other ends become fastened. A diradical formed in this manner must be a singlet; i.e., the two unpaired electrons must have opposite spins, by an argument similar to that outlined on p. 196. The third mechanism (*c*, not shown) is similar to mechanism *b*, but the initial bond and the subsequent bond are formed by movements of electron pairs and the intermediate is a diion. There have been many mechanistic investigations of the Diels–Alder reaction. The bulk of the evidence suggests that most Diels–Alder reactions take place by the one-step cyclic mechanism *a*,⁸⁸⁶ although it is possible that a diradical⁸⁸⁷ or even a diion⁸⁸⁸ mechanism may be taking place in some cases. The main evidence in support of mechanism *a* is as follows: (1) The reaction is stereospecific in both the diene and dienophile. A completely free diradical or diion probably would not be able to retain its configuration. (2) In general, the rates of Diels–Alder reactions depend very little on the nature of the solvent. This would rule out a diion intermediate because polar solvents increase the rates of reactions that develop charges in the transition state. (3) It was shown that, in the decomposition of **88**, the isotope effect k_I/k_{II} was equal to 1.00 within experimental error.⁸⁸⁹ If bond *x* broke before bond *y*, there should surely be a



secondary isotope effect. This result strongly indicates that the bond breaking of *x* and *y* is simultaneous. This is the reverse of a Diels–Alder reaction, and by the principle of microscopic reversibility, the mechanism of the forward reaction should involve simultaneous formation of bonds *x* and *y*. Subsequently, a similar experiment was carried out on the forward reaction⁸⁹⁰ and the result was the same. There is also other evidence for mechanism

⁸⁸⁵For reviews, see Sauer; Sustmann *Angew. Chem. Int. Ed. Engl.* **1980**, *19*, 779-807 [*Angew. Chem.* *92*, 773-801]; Houk *Top. Curr. Chem.* **1979**, *79*, 1-40; Seltzer *Adv. Alicyclic Chem.* **1968**, *2*, 1-57; Ref. 841. For a review of the application of quantum-chemical methods to the study of this reaction, see Babichev; Kovtunencko; Voitenko; Tytilin *Russ. Chem. Rev.* **1988**, *57*, 397-405.

⁸⁸⁶For a contrary view, see Dewar; Pierini *J. Am. Chem. Soc.* **1984**, *106*, 203; Dewar; Olivella; Stewart *J. Am. Chem. Soc.* **1986**, *108*, 5771. For arguments against this view, see Houk; Lin; Brown *J. Am. Chem. Soc.* **1986**, *108*, 554; Hancock; Wood *J. Chem. Soc., Chem. Commun.* **1988**, 351; Gajewski; Peterson; Kagel; Huang *J. Am. Chem. Soc.* **1989**, *111*, 9078.

⁸⁸⁷See, for example, Bartlett; Mallet *J. Am. Chem. Soc.* **1976**, *98*, 143; Jenner; Rimmelin *Tetrahedron Lett.* **1980**, *21*, 3039; Van Mele; Huybrechts *Int. J. Chem. Kinet.* **1987**, *19*, 363. **1989**, *21*, 967.

⁸⁸⁸For a reported example, see Gassman; Gorman *J. Am. Chem. Soc.* **1990**, *112*, 8624.

⁸⁸⁹Seltzer *J. Am. Chem. Soc.* **1963**, *85*, 1360, **1965**, *87*, 1534. For a review of isotope effect studies of Diels–Alder and other pericyclic reactions, see Gajewski *Isot. Org. Chem.* **1987**, *7*, 115-176.

⁸⁹⁰Van Sickle; Rodin *J. Am. Chem. Soc.* **1964**, *86*, 3091.

a.⁸⁹¹ However, the fact that the mechanism is concerted does not necessarily mean that it is synchronous. In the transition state of a synchronous reaction both new σ bonds would be formed to the same extent, but a Diels–Alder reaction with non-symmetrical components might very well be non-synchronous; i.e., it could have a transition state in which one bond has been formed to a greater degree than the other.⁶⁷¹

In another aspect of the mechanism, the effects of electron-donating and electron-withdrawing substituents (p. 843) indicate that the diene is behaving as a nucleophile and the dienophile as an electrophile. However, this can be reversed. Perchlorocyclopentadiene reacts better with cyclopentene than with maleic anhydride and not at all with tetracyanoethylene, though the latter is normally the most reactive dienophile known. It is apparent, then, that this diene is the electrophile in its Diels–Alder reactions.⁸⁹³ Reactions of this type are said to proceed with *inverse electron demand*.⁸⁹⁴

We have emphasized that the Diels–Alder reaction generally takes place rapidly and conveniently. In sharp contrast, the apparently similar dimerization of olefins to cyclobutanes (5-49) gives very poor results in most cases, except when photochemically induced. Fukui, Woodward, and Hoffmann have shown that these contrasting results can be explained by the *principle of conservation of orbital symmetry*,⁸⁹⁵ which predicts that certain reactions are allowed and others forbidden. The orbital-symmetry rules (also called the Woodward–Hoffmann rules) apply *only to concerted reactions*, e.g., mechanism a, and are based on the principle that reactions take place in such a way as to maintain maximum bonding throughout the course of the reaction. There are several ways of applying the orbital-symmetry principle to cycloaddition reactions, three of which are used more frequently than others.⁸⁹⁶ Of these three we will discuss two: the frontier-orbital method and the Möbius–Hückel method. The third, called the correlation diagram method,⁸⁹⁷ is less convenient to apply than the other two.

⁸⁹¹See, for example, Dewar; Pyron *J. Am. Chem. Soc.* **1970**, *92*, 3098; Brun; Jenner *Tetrahedron* **1972**, *28*, 3113; Doering; Franck-Neumann; Hasselmann; Kaye *J. Am. Chem. Soc.* **1972**, *94*, 3833; McCabe; Eckert *Acc. Chem. Res.* **1974**, *7*, 251-257; Berson; Dervan; Malherbe; Jenkins *J. Am. Chem. Soc.* **1976**, *98*, 5937; Rucker; Lang; Sauer; Friege; Sustmann *Chem. Ber.* **1980**, *113*, 1663; Tolbert; Ali *J. Am. Chem. Soc.* **1981**, *103*, 2104.

⁸⁹²Woodward; Katz *Tetrahedron* **1959**, *5*, 70; Liu; Schmidt *Tetrahedron* **1971**, *27*, 5289; Dewar; Pyron, Ref. 891; Papadopoulos; Jenner *Tetrahedron Lett.* **1982**, *23*, 1889; Houk; Loncharich; Blake; Jorgensen *J. Am. Chem. Soc.* **1989**, *111*, 9172; Lehd; Jensen *J. Org. Chem.* **1990**, *55*, 1034.

⁸⁹³Sauer; Wiest *Angew. Chem. Int. Ed. Engl.* **1962**, *1*, 269 [*Angew. Chem.* **74**, 353].

⁸⁹⁴For a review, see Boger; Patel *Prog. Heterocycl. Chem.* **1989**, *1*, 30-64.

⁸⁹⁵For monographs, see Gilchrist; Storr *Organic Reactions and Orbital Symmetry*, 2nd ed.; Cambridge University Press: Cambridge, 1979; Fleming *Frontier Orbitals and Organic Chemical Reactions*; Wiley: New York, 1976; Woodward; Hoffmann *The Conservation of Orbital Symmetry*; Academic Press: New York, 1970 [the text of this book also appears in *Angew. Chem. Int. Ed. Engl.* **1969**, *8*, 781-853; *Angew. Chem.* **81**, 797-869]; Lehr; Marchand *Orbital Symmetry*; Academic Press, New York, 1972. For reviews, see Pearson *J. Chem. Educ.* **1981**, *58*, 753-757; in Klopman *Chemical Reactivity and Reaction Paths*; Wiley: New York, 1974, the articles by Fujimoto; Fukui, pp. 23-54; Klopman, pp. 55-165; Herndon; Feuer; Giles; Otteson; Silber, pp. 275-299; Michl, pp. 301-338; Simonetta *Top. Curr. Chem.* **1973**, *42*, 1-47; Houk *Surv. Prog. Chem.* **1973**, *6*, 113-208; Vollmer; Servis *J. Chem. Educ.* **1970**, *47*, 491-500; Gill *Essays Chem.* **1970**, *1*, 43-76. *Q. Rev., Chem. Soc.* **1968**, *22*, 338-389; Seebach *Fortschr. Chem. Forsch.* **1969**, *11*, 177-215; Miller *Adv. Phys. Org. Chem.* **1968**, *6*, 185-332; Millie *Bull. Soc. Chim. Fr.* **1966**, 4031-4038. For a review of applications to inorganic chemistry, see Pearson *Top. Curr. Chem.* **1973**, *41*, 75-112.

⁸⁹⁶For other approaches see Epiotis *Theory of Organic Reactions*; Springer: New York, 1978; Epiotis; Shaik *J. Am. Chem. Soc.* **1978**, *100*, 1, 9; Halevi *Angew. Chem. Int. Ed. Engl.* **1976**, *15*, 593-607 [*Angew. Chem.* **88**, 664-679]; Shen *J. Chem. Educ.* **1973**, *50*, 238-242; Salem *J. Am. Chem. Soc.* **1968**, *90*, 543, 553; Trindle *J. Am. Chem. Soc.* **1970**, *92*, 3251, 3255; Mulder; Oosterhoff *Chem. Commun.* **1970**, 305, 307; Goddard *J. Am. Chem. Soc.* **1970**, *92*, 7520, **1972**, *94*, 793; Herndon *Chem. Rev.* **1972**, *72*, 157-179; Perrin *Chem. Br.* **1972**, *8*, 163-173; Langlet; Malrieu *J. Am. Chem. Soc.* **1972**, *94*, 7254; Pearson *J. Am. Chem. Soc.* **1972**, *94*, 8287; Mathieu, *Bull. Soc. Chim. Fr.* **1973**, 807; Silver; Karplus *J. Am. Chem. Soc.* **1975**, *97*, 2645; Day *J. Am. Chem. Soc.* **1975**, *97*, 2431; Mok; Nye *J. Chem. Soc., Perkin Trans. 2* **1975**, 1810; Ponc *Collect. Czech. Chem. Commun.* **1984**, *49*, 455, **1985**, *50*, 1121; Hua-ming; De-xiang *Tetrahedron* **1986**, *42*, 515; Bernardi; Olivucci; Robb *Res. Chem. Intermed.* **1989**, *12*, 217, *Acc. Chem. Res.* **1990**, *23*, 405.

⁸⁹⁷For excellent discussions of this method see Woodward; Hoffmann, Ref. 895; Jones *Physical and Mechanistic Organic Chemistry*, 2nd ed.; Cambridge University Press: Cambridge, 1984, pp. 352-366; Klumpp *Reactivity in Organic Chemistry*; Wiley: New York, 1982, pp. 378-389; Yates *Hückel Molecular Orbital Theory*; Academic Press: New York, 1978, pp. 263-276.

The Frontier-Orbital Method⁸⁹⁸

As applied to cycloaddition reactions the rule is that reactions are allowed only when all overlaps between the highest-occupied molecular orbital (HOMO) of one reactant and the lowest-unoccupied molecular orbital (LUMO) of the other are such that a positive lobe overlaps only with another positive lobe and a negative lobe only with another negative lobe. We may recall that monoolefins have two π molecular orbitals (p. 9) and that conjugated dienes have four (p. 31), as shown in Figure 15.2. A concerted cyclization of two monoolefins (a 2 + 2 reaction) is not allowed because it would require that a positive lobe overlap with a negative lobe (Figure 15.3). On the other hand, the Diels-Alder reaction (a 2 + 4 reaction) is allowed, whether considered from either direction (Figure 15.4).

These considerations are reversed when the ring closures are photochemically induced since in such cases an electron is promoted to a vacant orbital before the reaction occurs. Obviously, the 2 + 2 reaction is now allowed (Figure 15.5) and the 2 + 4 reaction disallowed. The reverse reactions follow the same rules, by the principle of microscopic reversibility. In fact, Diels-Alder adducts are usually cleaved quite readily, while cyclobutanes, despite the additional strain, require more strenuous conditions.

The Möbius-Hückel Method⁸⁹⁹

In this method, the orbital symmetry rules are related to the Hückel aromaticity rule discussed in Chapter 2. Hückel's rule, which states that a cyclic system of electrons is aromatic (hence, stable) when it consists of $4n + 2$ electrons, applies of course to molecules in their ground states. In applying the orbital symmetry principle we are not concerned with ground states, but with transition states. In the present method we do not examine the molecular

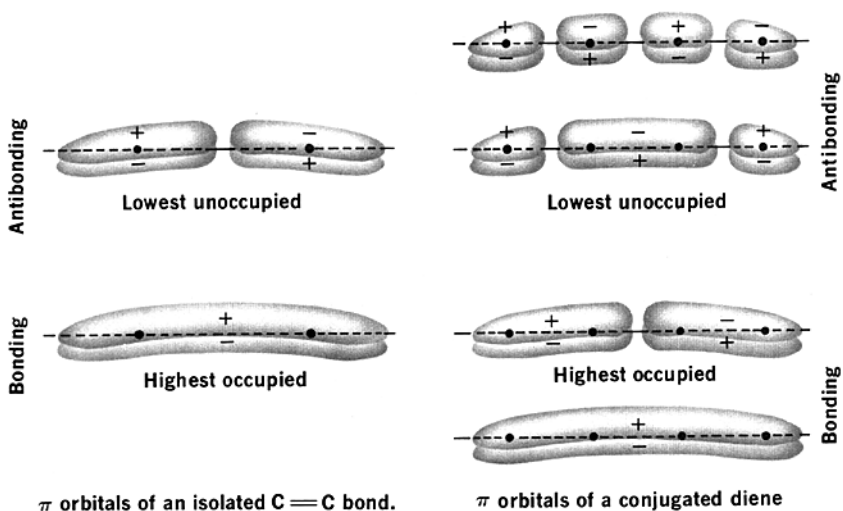


FIGURE 15.2 Schematic drawings of the π orbitals of an isolated C=C bond and a conjugated diene.

⁸⁹⁸Fukui; Fujimoto *Bull. Chem. Soc. Jpn.* **1967**, *40*, 2018, **1969**, *42*, 3399; Fukui *Fortschr. Chem. Forsch.* **1970**, *15*, 1-85, *Acc. Chem. Res.* **1971**, *4*, 57-64; Houk *Acc. Chem. Res.* **1975**, *8*, 361-369. See also Chu *Tetrahedron* **1978**, *34*, 645. For a monograph on frontier orbitals see Fleming, Ref. 895. For reviews, see Fukui *Angew. Chem. Int. Ed. Engl.* **1982**, *21*, 801-809 [*Angew. Chem.* **94**, 852-861]; Houk, in Marchand; Lehr, *Pericyclic Reactions*, vol. 2; Academic Press: New York, 1977, pp. 181-271.

⁸⁹⁹Zimmerman, in Marchand; Lehr, Ref. 898, pp. 53-107, *Acc. Chem. Res.* **1971**, *4*, 272-280, *J. Am. Chem. Soc.* **1966**, *88*, 1564, 1566; Dewar *Angew. Chem. Int. Ed. Engl.* **1971**, *10*, 761-775 [*Angew. Chem.* **83**, 859-875]; Jefford; Burger *Chimia* **1971**, *25*, 297-307; Herndon *J. Chem. Educ.* **1981**, *58*, 371-376.

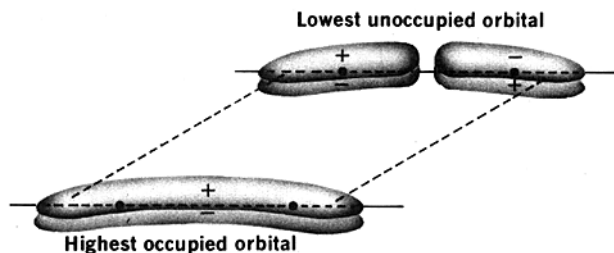


FIGURE 15.3 Overlap of orbitals in a thermal $2 + 2$ cycloaddition.

orbitals themselves, but rather the p orbitals before they overlap to form the molecular orbitals. Such a set of p orbitals is called a *basis set* (Figure 15.6). In investigating the possibility of a concerted reaction, we put the basis sets into the position they would occupy in the transition state. Figure 15.7 shows this for both the $2 + 2$ and the $2 + 4$ ring closures. What we look for are *sign inversions*. In Figure 15.7 we can see that there are no sign inversions in either case. That is, the dashed line connects only lobes with a minus sign. Systems with *zero or an even number of sign inversions* are called *Hückel systems*. Because they have no sign inversions, both of these systems are Hückel systems. Systems with an *odd number of sign inversions* are called *Möbius systems* (because of the similarity to the Möbius strip, which is a mathematical surface, shown in Figure 15.8). Möbius systems do not enter into either of these reactions, but an example of such a system is shown on p. 1114.

The rule may then be stated: *A thermal pericyclic reaction involving a Hückel system is allowed only if the total number of electrons is $4n + 2$. A thermal pericyclic reaction involving a Möbius system is allowed only if the total number of electrons is $4n$.* For photochemical reactions these rules are reversed. Since both the $2 + 4$ and $2 + 2$ cycloadditions are Hückel systems, the Möbius-Hückel method predicts that the $2 + 4$ reaction, with 6 electrons, is thermally allowed, but the $2 + 2$ reaction is not. One the other hand, the $2 + 2$ reaction is allowed photochemically, while the $2 + 4$ reaction is forbidden.

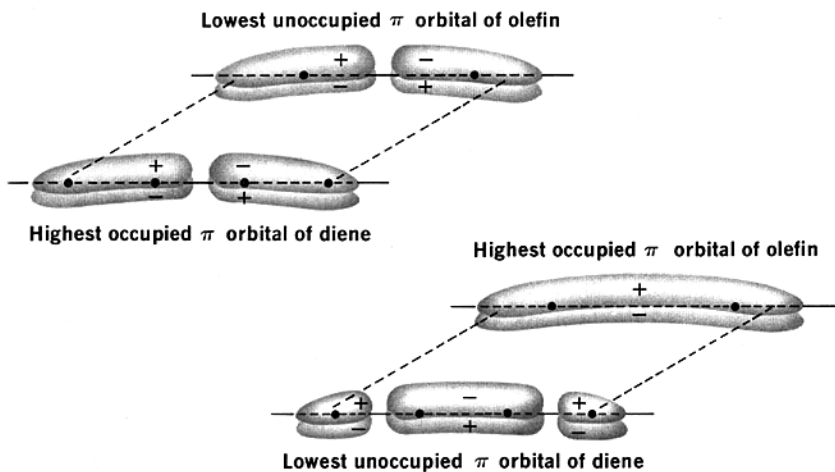


FIGURE 15.4 Two ways for orbitals to overlap in a thermal $2 + 4$ cycloaddition.

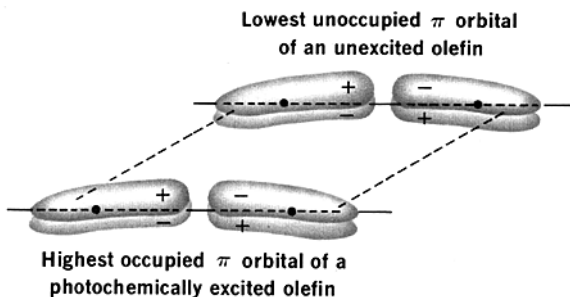


FIGURE 15.5 Overlap of orbitals in a photochemical $2 + 2$ cycloaddition.

Note that both the $2 + 2$ and $2 + 4$ transition states are Hückel systems no matter what basis sets we chose. For example, Figure 15.9 shows other basis sets we might have chosen. In every case there will be zero or an even number of sign inversions.

Thus, the frontier-orbital and Hückel–Möbius methods (and the correlation-diagram method as well) lead to the same conclusions: thermal $2 + 4$ cycloadditions and photochemical $2 + 2$ cycloadditions (and the reverse ring openings) are allowed, while photochemical $2 + 4$ and thermal $2 + 2$ ring closings (and openings) are forbidden. Application of the same procedures to other ring closures shows that $4 + 4$ and $2 + 6$ ring closures and openings require photochemical induction while the $4 + 6$ and $2 + 8$ reactions can take place only thermally (see 5-52). In general, cycloaddition reactions allowed thermally are those with $4n + 2$ electrons, while those allowed photochemically have $4n$ electrons.

It must be emphasized once again that the rules apply only to cycloaddition reactions that take place by cyclic mechanisms, i.e., where two σ bonds are formed (or broken) at about the same time.⁹⁰⁰ The rule does not apply to cases where one bond is clearly formed (or broken) before the other. It must further be emphasized that the fact that the thermal Diels–Alder reaction (mechanism *a*) is allowed by the principle of conservation of orbital symmetry does not constitute proof that any given Diels–Alder reaction proceeds by this mechanism. The principle merely says the mechanism is allowed, not that it must go by this pathway. However, the principle does say that thermal $2 + 2$ cycloadditions in which the molecules assume a face-to-face geometry cannot⁹⁰¹ take place by a cyclic mechanism because

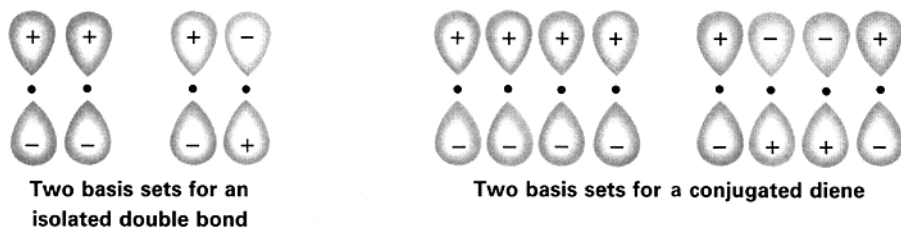


FIGURE 15.6 Some basis sets.

⁹⁰⁰For a discussion of concertedness in these reactions see Lehr; Marchand, in Marchand; Lehr, Ref. 898, vol. 1, pp. 1-51.

⁹⁰¹The possibility has been raised that some disallowed reactions may nevertheless proceed by concerted mechanisms: see Schmidt *Helv. Chim. Acta* **1971**, *54*, 862, *Tetrahedron Lett.* **1972**, 581; Muszkat; Schmidt *Helv. Chim. Acta* **1971**, *54*, 1195; Baldwin; Andrist; Pinschmidt *Acc. Chem. Res.* **1972**, *5*, 402-406; Berson *Acc. Chem. Res.* **1972**, *5*, 406-414; Baldwin, in Marchand; Lehr, Ref. 898, vol. 2, pp. 273-302.

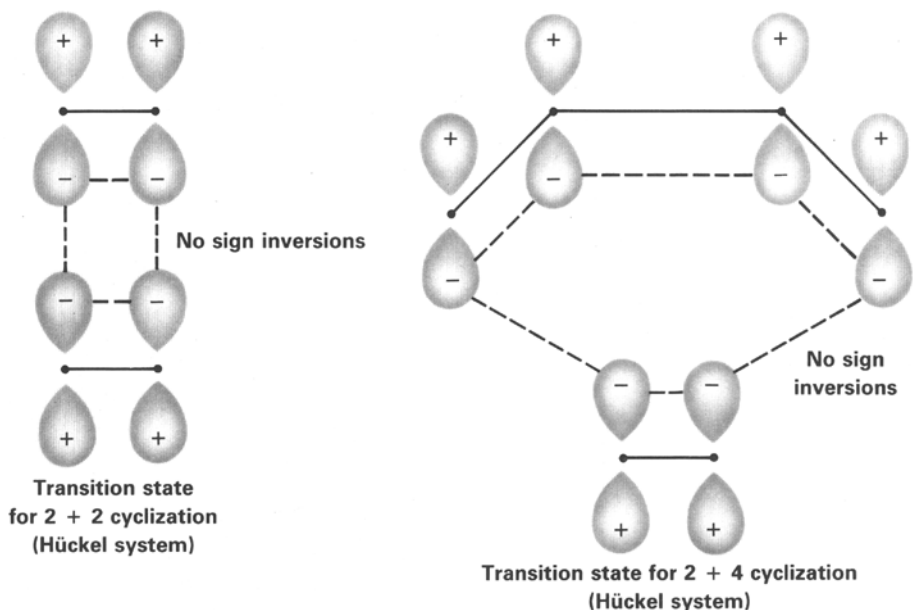


FIGURE 15.7 Transition states illustrating Hückel–Möbius rules for cycloaddition reactions.

their activation energies would be too high (however, see below). As we shall see (5-49), such reactions largely occur by two-step mechanisms. Similarly, 2 + 4 photochemical cycloadditions are also known, but the fact that they are not stereospecific indicates that they also take place by the two-step diradical mechanism (mechanism *b*).⁹⁰²

In all of the above discussion we have assumed that a given molecule forms both the new σ bonds from the same face of the π system. This manner of bond formation, called *suprafacial*, is certainly most reasonable and almost always takes place. The subscript *s* is used to designate this geometry, and a normal Diels–Alder reaction would be called a [π_2 _{*s*} + π_4 _{*s*}] cycloaddition (the subscript π indicates that π electrons are involved in the

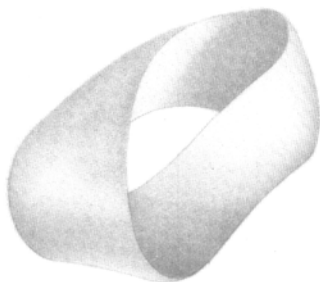


FIGURE 15.8 A Möbius strip. Such a strip is easily constructed by twisting a thin strip of paper 180° and fastening the ends together.

⁹⁰²For example, see Sieber; Heimgartner; Hansen; Schmid *Helv. Chim. Acta* **1972**, *55*, 3005. For discussions see Bartlett; Helgeson; Wersel *Pure Appl. Chem.* **1968**, *16*, 187-200; Seeley *J. Am. Chem. Soc.* **1972**, *94*, 4378; Kaupp *Angew. Chem. Int. Ed. Engl.* **1972**, *11*, 313, 718 [*Angew. Chem.* **84**, 259, 718].

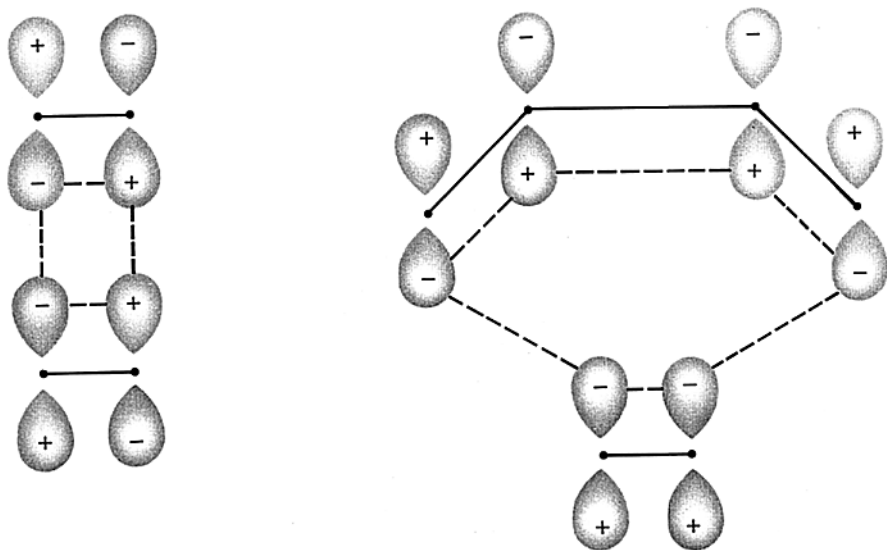
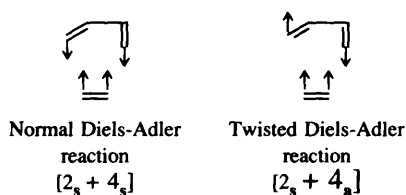


FIGURE 15.9 Transition states for 2 + 2 and 2 + 4 cyclizations involving other basis sets.

cycloaddition). However, we can conceive of another approach in which the newly forming bonds of the diene lie on *opposite* faces of the π system, i.e., they point in opposite directions.



This type of orientation of the newly formed bonds is called *antarafacial*, and the reaction would be a $[\pi 2_s + \pi 4_a]$ cycloaddition (a stands for antarafacial). We can easily show by the frontier-orbital method that this reaction (and consequently the reverse ring-opening reactions) are thermally forbidden and photochemically allowed. Thus in order for a $[\pi 2_s + \pi 4_a]$ reaction to proceed, overlap between the highest occupied π orbital of the olefin and the lowest unoccupied π orbital of the diene would have to occur as shown in Figure 15.10, with a + lobe overlapping a - lobe. Since like signs are no longer overlapping, the thermal reaction is now forbidden. Similarly, thermal $[\pi 2_a + \pi 4_s]$ and $[\pi 2_a + \pi 2_a]$ cyclizations are forbidden, while thermal $[\pi 2_a + \pi 4_a]$ and $[\pi 2_s + \pi 2_a]$ cyclizations are allowed, and these considerations are reversed for the corresponding photochemical processes. Of course, an antarafacial approach is highly unlikely in a 2 + 4 cyclization,⁹⁰³ but larger ring closures could take place by such a pathway, and 2 + 2 thermal cyclizations, where the $[\pi 2_s + \pi 2_s]$ pathway is forbidden, can also do so in certain cases (see 5-49). We therefore see that whether a given cycloaddition is allowed or forbidden depends on the geometry of approach of the two molecules involved.

Symmetry considerations have also been advanced to explain predominant endo addi-

⁹⁰³A possible photochemical $[\pi 2_a + \pi 4_s]$ cycloaddition has been reported: Hart; Miyashi; Buchanan; Sasson *J. Am. Chem. Soc.* **1974**, *96*, 4857.

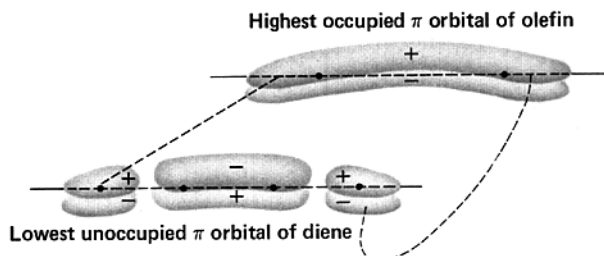
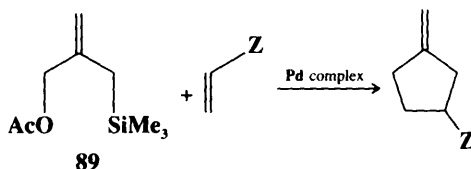


FIGURE 15.10 Overlap of orbitals in an antarafacial thermal 2 + 4 cycloaddition.

tion.⁹⁰⁴ In the case of 2 + 4 addition of butadiene to itself, the approach can be exo or endo. It can be seen (Figure 15.11) that whether the highest-occupied molecular orbital of the diene overlaps with the lowest-unoccupied molecular orbital of the olefin or vice versa, the endo orientation is stabilized by additional secondary overlap of orbitals⁹⁰⁵ of like sign (dashed lines between heavy dots). Addition from the exo direction has no such stabilization. Evidence for secondary orbital overlap as the cause of predominant endo orientation, at least in some cases, is that 4 + 6 cycloaddition is predicted by similar considerations to proceed with predominant exo orientation, and that is what is found.⁹⁰⁶ However, this explanation does not account for endo orientation in cases where the dienophile does not possess additional π orbitals, and a number of alternative explanations have been offered.⁹⁰⁷

OS II, 102; III, 310, 807; IV, 238, 311, 738, 890, 964; V, 60, 96, 414, 424, 604, 985, 1037; VI, 82, 196, 422, 427, 445, 454; VII, 4, 312, 485; 65, 98; 66, 142; 67, 163; 68, 198, 206; 69, 31. For a reverse Diels–Alder reaction, see OS VII, 339. See also OS VII, 326.

5-48 All-Carbon 2 + 3 Cycloadditions



Several methods have been reported for the formation of cyclopentanes by 2 + 3 cycloadditions.⁹⁰⁸ One type involves reagents that produce intermediates **90** or **91**.⁹⁰⁹ A synthetically useful example⁹¹⁰ uses 2-[(trimethylsilyl)methyl]-2-propen-1-yl acetate (**89**) (which is com-

⁹⁰⁴Hoffmann; Woodward *J. Am. Chem. Soc.* **1965**, *87*, 4388.

⁹⁰⁵For reviews of secondary orbital interactions, see Ginsburg *Tetrahedron* **1983**, *39*, 2095-2135; Gleiter; Paquette *Acc. Chem. Res.* **1983**, *16*, 328-334.

⁹⁰⁶See, for example, Cookson; Drake; Hudec; Morrison *Chem. Commun.* **1966**, *15*; Itô; Fujise; Okuda; Inoue *Bull. Chem. Soc. Jpn.* **1966**, *39*, 1351; Paquette; Barrett *J. Am. Chem. Soc.* **1966**, *88*, 2590; Paquette; Barrett; Kuhla *J. Am. Chem. Soc.* **1969**, *91*, 3616; Houk; Woodward *J. Am. Chem. Soc.* **1970**, *92*, 4143, 4145; Jones; Kncen *J. Chem. Soc., Chem. Commun.* **1973**, 420.

⁹⁰⁷See, for example, Houk; Luskus *J. Am. Chem. Soc.* **1971**, *93*, 4606; Kobuke; Sugimoto; Furukawa; Fucno *J. Am. Chem. Soc.* **1972**, *94*, 3633; Jacobson *J. Am. Chem. Soc.* **1973**, *95*, 2579; Mellor; Webb *J. Chem. Soc., Perkin Trans. 2* **1974**, *17*, 26; Fox; Cardona; Kiwiët *J. Org. Chem.* **1987**, *52*, 1469.

⁹⁰⁸For a list of methods, with references, see Trost; Seoane; Mignani; Acemoglu *J. Am. Chem. Soc.* **1989**, *111*, 7487.

⁹⁰⁹For reviews, see Trost *Pure Appl. Chem.* **1988**, *60*, 1615-1626. *Angew. Chem. Int. Ed. Engl.* **1986**, *25*, 1-20 [*Angew. Chem.* **98**, 1-20].

⁹¹⁰See, for example, Trost; Lynch; Renaud; Steinman *J. Am. Chem. Soc.* **1986**, *108*, 284.

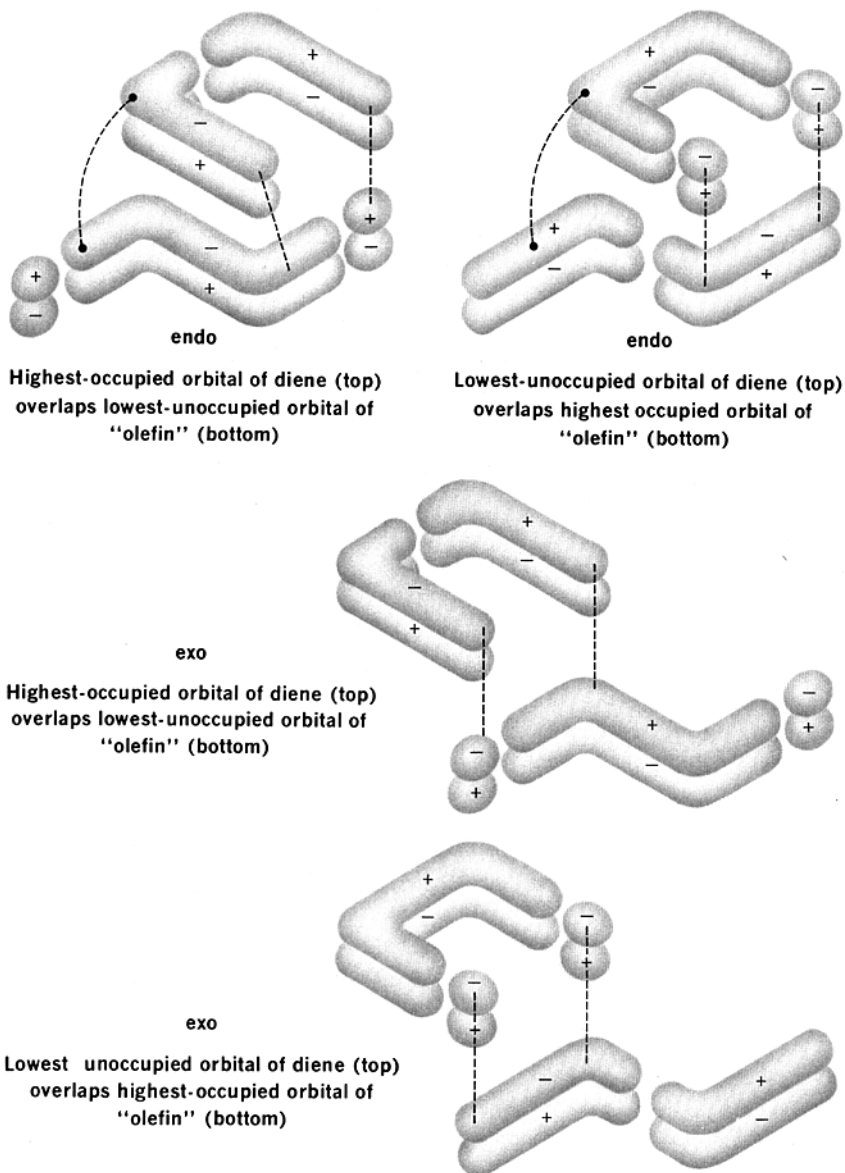
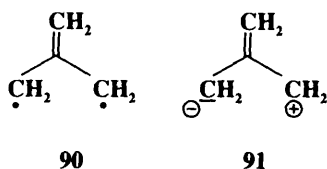
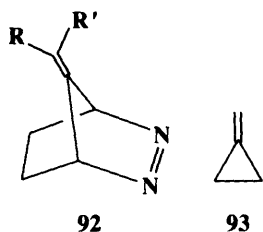


FIGURE 15.11 Overlap of orbitals in 2 + 4 cycloaddition of dienes.

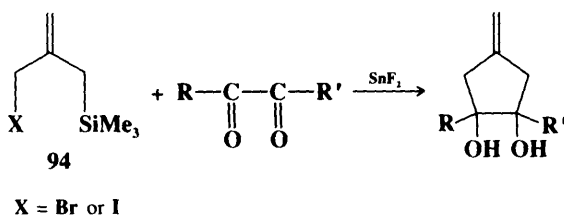


mercally available) and a palladium or other transition metal catalyst to generate **90** or **91**, which adds to double bonds, to give, in good yields, cyclopentanes with an exocyclic double

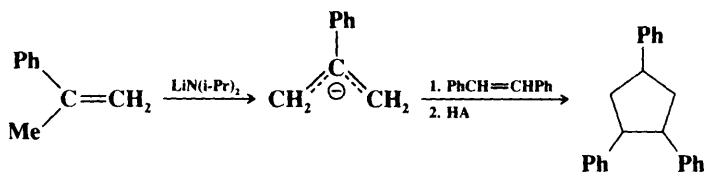
bond. Similar or identical intermediates generated from bicyclo azo compounds **92** (see



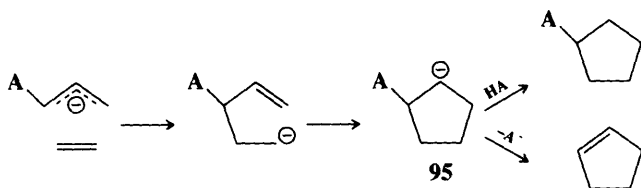
7-46)⁹¹¹ or methylenecyclopropane **93**⁹¹² also add to activated double bonds. With suitable substrates the addition can be enantioselective.⁹¹³ The reagent **94**, similar to **89**, forms cis 5-membered cyclic unsaturated diols when treated with α -diketones in the presence of SnF_2 .



In a different type of procedure, 2 + 3 cycloadditions are performed with allylic anions. Such reactions are called 1,3-anionic cycloadditions.⁹¹⁵ For example, α -methylstyrene adds to stilbene on treatment with the strong base lithium diisopropylamide.⁹¹⁶



The mechanism can be outlined as



⁹¹¹For a review, see Little *Chem. Rev.* **1986**, *86*, 875-884.

⁹¹²See Yamago; Nakamura *J. Am. Chem. Soc.* **1989**, *111*, 7285.

⁹¹³See Binger; Schäfer *Tetrahedron Lett.* **1988**, *29*, 529; Chaigne; Gotteland; Malacria *Tetrahedron Lett.* **1989**, *30*, 1803.

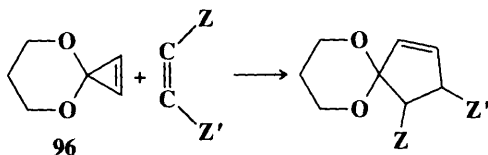
⁹¹⁴Molander; Shubert *J. Am. Chem. Soc.* **1986**, *108*, 4683.

⁹¹⁵For reviews, see Kauffmann *Top. Curr. Chem.* **1980**, *92*, 109-147, pp. 111-116; *Angew. Chem. Int. Ed. Engl.* **1974**, *13*, 627-639 [*Angew. Chem.* *86*, 715-727].

⁹¹⁶Eidenschink; Kauffmann *Angew. Chem. Int. Ed. Engl.* **1972**, *11*, 292 [*Angew. Chem.* *84*, 292].

In the case above, **95** is protonated in the last step by the acid HA, but if the acid is omitted and a suitable nucleofuge is present, it may leave, resulting in a cyclopentene.⁹¹⁷ In these cases the reagent is an allylic anion, but similar 2 + 3 cycloadditions involving allylic cations have also been reported.⁹¹⁸

In a third type of procedure,⁹¹⁹ cyclopropene ketal **96** reacts with olefins bearing two

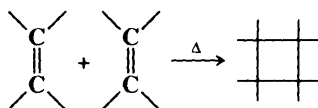


electron-withdrawing groups Z to give cyclopentenes.⁹²⁰

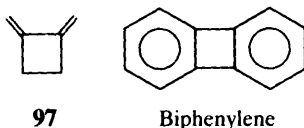
OS **65**, 32; **66**, 8.

5-49 Dimerization of Olefins

(2 + 2)cyclo-Ethylene-1/2/addition



The thermal reaction between two molecules of olefin to give cyclobutane derivatives (a 2 + 2 cycloaddition) can be carried out where the olefins are the same or different, but the reaction is not a general one for olefins.⁹²¹ Dimerization of like olefins occurs with the following compounds: F₂C=CX₂ (X = F or Cl) and certain other fluorinated alkenes (though not F₂C=CH₂), allenes (to give derivatives of **97**),⁹²² benzynes (to give biphenylene deriv-



atives), activated olefins (e.g., styrene, acrylonitrile, butadiene), and certain methylene-cyclopropanes.⁹²³ Substituted ketenes dimerize to give cyclobutene derivatives (**98**) as the

⁹¹⁷See, for example, Padwa; Yeske *J. Am. Chem. Soc.* **1988**, *110*, 1617; Beak; Burg *J. Org. Chem.* **1989**, *54*, 1647.

⁹¹⁸For example, see Hoffmann; Vathke-Ernst *Chem. Ber.* **1981**, *114*, 2208, 2898; Klein; Mayr *Angew. Chem. Int. Ed. Engl.* **1981**, *20*, 1027 [*Angew. Chem.* **93**, 1069]; Noyori; Hayakawa *Tetrahedron* **1985**, *41*, 5879.

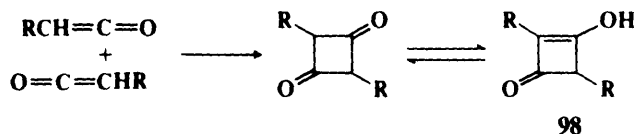
⁹¹⁹For some other methods of making cyclopentanes or cyclopentenones by 2 + 3 cycloadditions, see Danheiser; Carini; Fink; Basak *Tetrahedron* **1983**, *39*, 935; Shimizu; Ohashi; Tsuji *Tetrahedron Lett.* **1985**, *26*, 3825; Marino; Laborde *J. Org. Chem.* **1987**, *52*, 1; Curran; Chen *J. Am. Chem. Soc.* **1987**, *109*, 6558; Feldman; Romanelli; Ruckle; Miller *J. Am. Chem. Soc.* **1988**, *110*, 3300; Herndon; Turner; Schnatter *J. Am. Chem. Soc.* **1988**, *110*, 3334; Ghera; Yechezkel; Hassner *Tetrahedron Lett.* **1990**, *31*, 3653; Crimmins; Nantermet *J. Org. Chem.* **1990**, *55*, 4235. For a review of a 2 + 2 + 1 method (the Pauson-Khand reaction), see Schore *Org. React.* **1991**, *40*, 1-90.

⁹²⁰Boger; Brotherton *J. Am. Chem. Soc.* **1986**, *108*, 6695, 6713; Boger; Wysocki *J. Org. Chem.* **1988**, *53*, 3408.

⁹²¹For reviews, see Carruthers, Ref. 440; Reinhoudt *Adv. Heterocycl. Chem.* **1977**, *21*, 253-321; Roberts; Sharts *Org. React.* **1962**, *12*, 1-56; Gilchrist; Storr, Ref. 895, pp. 173-212; Beltrame, in Bamford; Tipper, Ref. 1, vol. 9, pp. 131-152; Huisgen; Grashey; Sauer, in Patai, Ref. 36, pp. 779-802. For a review of the use of 2 + 2 cycloadditions in polymerization reactions see Dilling, *Chem. Rev.* **1983**, *83*, 1-47. For a list of references, see Ref. 133, pp. 82-83, 659-660.

⁹²²For a review, see Fischer, in Patai, Ref. 36, pp. 1064-1067.

⁹²³Dolbier; Lomas; Garza; Harmon; Tarrant *Tetrahedron* **1972**, *28*, 3185.



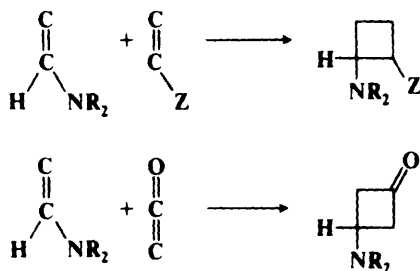
major primary products, though ketene itself dimerizes in a different manner, to give an unsaturated β -lactone (6-63).⁹²⁴

Different olefins combine as follows:

1. $\text{F}_2\text{C}=\text{CX}_2$ ($\text{X} = \text{F}$ or Cl), especially $\text{F}_2\text{C}=\text{CF}_2$, form cyclobutanes with many olefins. Compounds of this type even react with conjugated dienes to give four-membered rings rather than undergoing normal Diels-Alder reactions.⁹²⁵

2. Allenes⁹²⁶ and ketenes⁹²⁷ react with activated olefins and alkynes. Ketenes give 1,2 addition, even with conjugated dienes.⁹²⁸ Ketenes also add to unactivated olefins if sufficiently long reaction times are used.⁹²⁹ Allenes and ketenes also add to each other.⁹³⁰

3. Enamines⁹³¹ form four-membered rings with Michael-type olefins⁹³² and ketenes.⁹³³ In both cases, only enamines from aldehydes give stable four-membered rings:



The reaction of enamines with ketenes can be conveniently carried out by generating the ketene in situ from an acyl halide and a tertiary amine.

4. Olefins with electron-withdrawing groups may form cyclobutanes with olefins containing electron-donating groups. The enamine reactions, mentioned above, are examples

⁹²⁴Farnum; Johnson; Hess; Marshall; Webster *J. Am. Chem. Soc.* **1965**, *87*, 5191; Dehmlow; Pickardt; Slopianka; Fastabend; Drechsler; Soufi *Liebigs Ann. Chem.* **1987**, 377.

⁹²⁵Bartlett; Montgomery; Seidel *J. Am. Chem. Soc.* **1964**, *86*, 616; De Cock; Piettre; Lahousse; Janousek; Merényi; Viehe *Tetrahedron* **1985**, *41*, 4183.

⁹²⁶For reviews of 2 + 2 cycloadditions of allenenes, see Schuster; Coppola, Ref. 95, pp. 286-317; Hopf, in Landor, Ref. 95, vol. 2, pp. 525-562; Ghosez; O'Donnell, in Marchand; Lehr, Ref. 898, vol. 2, pp. 79-140; Baldwin; Fleming *Fortschr. Chem. Forsch.* **1970**, *15*, 281-310.

⁹²⁷For reviews of cycloadditions of ketenes, see Ghosez; O'Donnell, Ref. 926; Brady *Synthesis* **1971**, 415-422; Luknitskii; Vovsi *Russ. Chem. Rev.* **1969**, *38*, 487-494; Ulrich *Cycloaddition Reactions of Heterocumulenes*; Academic Press: New York, 1967, pp. 38-121; Holder *J. Chem. Educ.* **1976**, *53*, 81-85. For a review of intramolecular cycloadditions of ketenes to alkenes, see Snider *Chem. Rev.* **1988**, *88*, 793-811.

⁹²⁸See, for example, Martin; Gott; Goodlett; Hasek *J. Org. Chem.* **1965**, *30*, 4175; Brady; O'Neal *J. Org. Chem.* **1967**, *32*, 2704; Huisgen; Feiler; Otto *Tetrahedron Lett.* **1968**, 4491, *Chem. Ber.* **1969**, *102*, 3475. For indirect methods of the 1,4 addition of the elements of ketene to a diene see Freeman; Balls; Brown *J. Org. Chem.* **1968**, *33*, 2211; Corey; Ravindranathan; Terashima *J. Am. Chem. Soc.* **1971**, *93*, 4326. For a review of ketene equivalents see Ranganathan; Ranganathan; Mehrotra *Synthesis* **1977**, 289-296.

⁹²⁹Huisgen; Feiler *Chem. Ber.* **1969**, *102*, 3391; Brady; Patel *J. Org. Chem.* **1973**, *38*, 4106; Bak; Brady *J. Org. Chem.* **1979**, *44*, 107.

⁹³⁰Bampfield; Brook; McDonald *J. Chem. Soc., Chem. Commun.* **1975**, 132; Gras; Bertrand *Nouv. J. Chim.* **1981**, *5*, 521.

⁹³¹For a review of cycloaddition reactions of enamines, see Cook, in *Cook Enamines*, 2nd ed.; Marcel Dekker: New York, 1988, pp. 347-440.

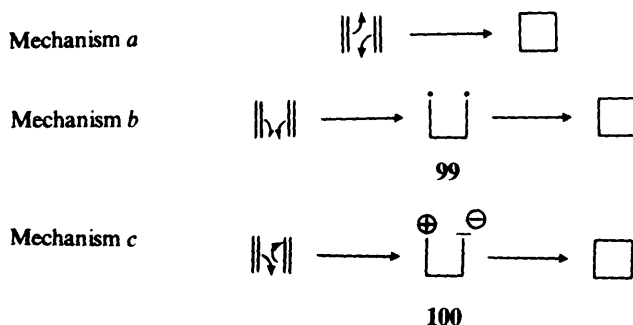
⁹³²Brannock; Bell; Goodlett; Thweatt *J. Org. Chem.* **1964**, *29*, 813.

⁹³³Berchtold; Harvey; Wilson *J. Org. Chem.* **1961**, *26*, 4776; Opitz; Kleeman *Liebigs Ann. Chem.* **1963**, *665*, 114; Hasek; Gott; Martin *J. Org. Chem.* **1966**, *31*, 1931.

of this, but it has also been accomplished with tetracyanoethylene and similar molecules, which give substituted cyclobutanes when treated with olefins of the form $C=C-A$, where A may be OR,⁹³⁴ SR (enol and thioenol ethers),⁹³⁵ cyclopropyl,⁹³⁶ or certain aryl groups.⁹³⁷

Solvents are not necessary for 2 + 2 cycloadditions. They are usually carried out at 100 to 225°C under pressure, although the reactions in group 4 occur under milder conditions.

The reaction is similar to the Diels–Alder (in action, not in scope), and if dienes are involved, the latter reaction may compete, though most olefins react with a diene either entirely by 1,2 or entirely by 1,4 addition. Three mechanisms can be proposed⁹³⁸ analogous to those proposed for the Diels–Alder reaction. Mechanism *a* is a concerted pericyclic process, and mechanisms *b* and *c* are two-step reactions involving, respectively, a diradical (**99**) and a diion (**100**) intermediate. As in 5-47, a diradical intermediate must be a singlet.



In searching for ways to tell which mechanism is operating in a given case, we would expect mechanism *c* to be sensitive to changes in solvent polarity, while mechanisms *a* and *b* should be insensitive. We would also expect mechanism *a* to be stereospecific, while mechanisms *b* and *c* probably would not be stereospecific, though if the second step of these processes takes place very rapidly, before **99** or **100** has a chance to rotate about the newly formed single bond, stereospecificity might be observed. Because of entropy considerations such rapid ring closure might be more likely here than in a 2 + 4 cycloaddition.

There is evidence that the reactions can take place by all three mechanisms, depending on the structure of the reactants. A thermal $[\pi 2_s + \pi 2_s]$ mechanism is ruled out for most of these substrates by the orbital symmetry rules, but a $[\pi 2_s + \pi 2_a]$ mechanism is allowed (p. 851), and there is much evidence that ketenes and certain other linear molecules⁹³⁹ in which the steric hindrance to such an approach is minimal can and often do react by this mechanism. In a $[\pi 2_s + \pi 2_a]$ cycloaddition the molecules must approach each other in such a way (Figure 15.12a) that the + lobe of the HOMO of one molecule (I) overlaps with both + lobes of the LUMO of the other (II), even though these lobes are on opposite sides of the nodal plane of II. The geometry of this approach requires that the groups S and U of molecule II project *into* the plane of molecule I. This has not been found to happen for ordinary

⁹³⁴For a review with ketene acetals $R_2C=C(OR')_2$, see Scheeren *Recl. Trav. Chim. Pays-Bas* **1986**, *105*, 71-84.

⁹³⁵Williams; Wiley; McKusick *J. Am. Chem. Soc.* **1962**, *84*, 2210.

⁹³⁶Nishida; Moritani; Teraji *J. Org. Chem.* **1973**, *38*, 1878.

⁹³⁷Nagata; Shiota; Nogami; Mikawa *Chem. Lett.* **1973**, 1087; Shiota; Yoshida; Nogami; Mikawa *Chem. Lett.* **1973**, 1271.

⁹³⁸For a review, see Bartlett *Q. Rev., Chem. Soc.* **1970**, *24*, 473-497.

⁹³⁹There is evidence that a cyclopentyne (generated in situ) also adds to a double bond by an antarafacial process: Gilbert; Baze *J. Am. Chem. Soc.* **1984**, *106*, 1885.

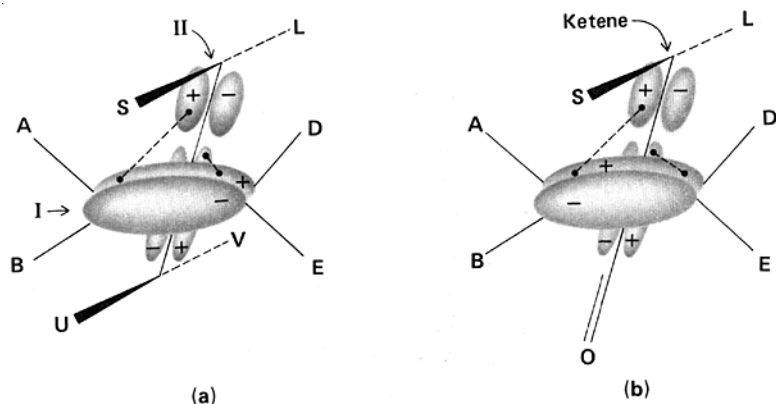
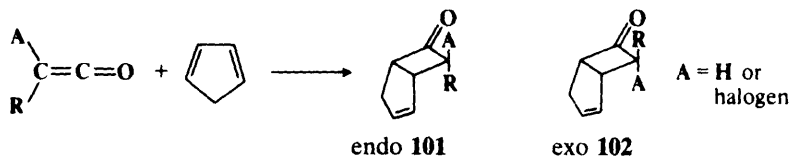


FIGURE 15.12 Orbital overlap in $\pi_2 + \pi_2$ cycloaddition between (a) two olefin molecules and (b) a ketene and an olefin. S and L stand for small and large.

alkenes,⁹⁴⁰ but if molecule II is a ketene (Figure 15.12b), the group marked U is not present and the $[\pi_2 + \pi_2]$ reaction can take place. Among the evidence⁹⁴¹ for this mechanism⁹⁴² is the following: (1) The reactions are stereospecific.⁹⁴³ (2) The isomer that forms is the *more-hindered one*. Thus methylketene plus cyclopentadiene gave only the endo product (**101**, A = H, R = CH₃).⁹⁴⁴ Even more remarkably, when haloalkyl ketenes RXC=C=O were treated with cyclopentadiene, the endo-exo ratio of the product (**101**, **102**, A = halogen)



actually *increased* substantially when R was changed from Me to iso-Pr to *t*-Bu!⁹⁴⁵ One would expect preferential formation of the exo products (**102**) from $[\pi_2 + \pi_2]$ cycloadditions where the molecules approach each other face-to-face, but a $[\pi_2 + \pi_2]$ process leads to endo products because the ketene molecule (which for steric reasons would approach with its smaller group directed toward the olefin) must twist as shown in Figure 15.13 (L = larger;

⁹⁴⁰See, for example, Padwa; Koehn; Masaracchia; Osborn; Trecker *J. Am. Chem. Soc.* **1971**, *93*, 3633; Bartlett; Cohen; Elliott; Hummel; Minns; Sharts; Fukunaga *J. Am. Chem. Soc.* **1972**, *94*, 2899.

⁹⁴¹For other evidence, see Baldwin; Kapecki *J. Am. Chem. Soc.* **1970**, *92*, 4874; Brook; Griffiths *Chem. Commun.* **1970**, 1344; Frey; Isaacs *J. Chem. Soc. B* **1970**, 830; Egger *Int. J. Chem. Kinet.* **1973**, *5*, 285; Moon; Kolesar *J. Org. Chem.* **1974**, *39*, 995; Isaacs; Hatcher *J. Chem. Soc., Chem. Commun.* **1974**, 593; Hassner; Cory; Sartoris *J. Am. Chem. Soc.* **1976**, *98*, 7698; Gheorghiu; Părvulescu; Drăghici; Elian *Tetrahedron* **1981**, *37 Suppl.*, 143. See, however, Holder; Graf; Duesler; Moss *J. Am. Chem. Soc.* **1983**, *105*, 2929.

⁹⁴²On the other hand, molecular orbital calculations predict that the cycloaddition of ketenes to olefins does not take place by a $[\pi_2 + \pi_2]$ mechanism: Wang; Houk *J. Am. Chem. Soc.* **1990**, *112*, 1754; Bernardi; Bottoni; Robb; Venturini *J. Am. Chem. Soc.* **1990**, *112*, 2106; Valentí; Pericàs; Moyano *J. Org. Chem.* **1990**, *55*, 3582.

⁹⁴³Huisgen; Feiler; Binsch *Angew. Chem. Int. Ed. Engl.* **1964**, *3*, 753 [*Angew. Chem.* **76**, 892], *Chem. Ber.* **1969**, *102*, 3460; Martin; Goodlett; Burpitt *J. Org. Chem.* **1965**, *30*, 4309; Montaigne; Ghosez *Angew. Chem. Int. Ed. Engl.* **1968**, *7*, 221 [*Angew. Chem.* **80**, 194]; Bertrand; Gras; Gore *Tetrahedron* **1975**, *31*, 857; Marchand-Brynaert; Ghosez *J. Am. Chem. Soc.* **1972**, *94*, 2870; Huisgen; Mayr *Tetrahedron Lett.* **1975**, 2965, 2969.

⁹⁴⁴Brady; Hoff; Roe; Parry *J. Am. Chem. Soc.* **1969**, *91*, 5679; Rey; Roberts; Dieffenbacher; Dreiding *Helv. Chim. Acta* **1970**, *53*, 417. See also Brady; Parry; Stockton *J. Org. Chem.* **1971**, *36*, 1486; DoMinh; Strausz *J. Am. Chem. Soc.* **1970**, *92*, 1766; Isaacs; Stanbury *Chem. Commun.* **1970**, 1061; Brook; Harrison; Duke *Chem. Commun.* **1970**, 589; Dehmlow, *Tetrahedron Lett.* **1973**, 2573; Rey; Roberts; Dreiding; Roussel; Vanlierde; Toppet; Ghosez *Helv. Chim. Acta* **1982**, *65*, 703.

⁹⁴⁵Brady; Roe *J. Am. Chem. Soc.* **1970**, *92*, 4618.

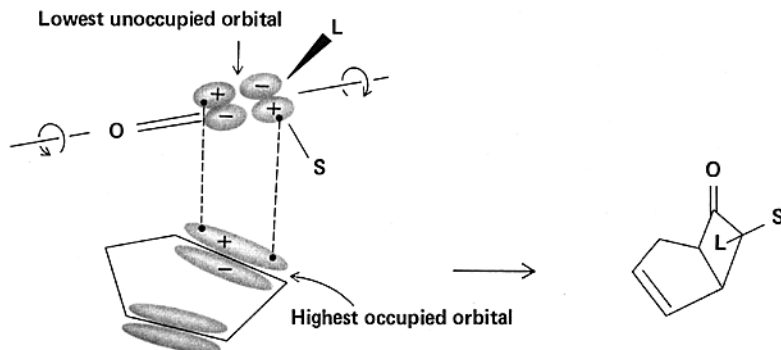
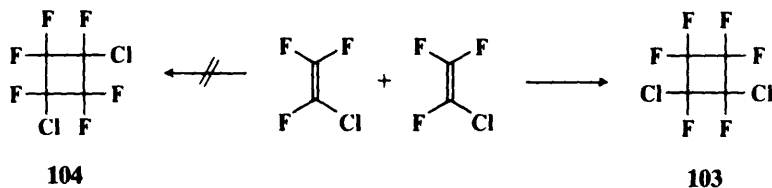


FIGURE 15.13 Orbital overlap in the reaction of a ketene with cyclopentadiene. S and L stand for small and large.

S = smaller group) in order for the + lobes to interact and this swings the larger group into the endo position.⁹⁴⁶ The experimental results in which the amount of endo isomer increases with the increasing size of the R group would seem to be contrary to what would be expected from considerations of steric hindrance (we may call them *masochistic steric effects*), but they are just what is predicted for a $[\pi_2s + \pi_2a]$ reaction. (3) There is only moderate polar solvent acceleration.⁹⁴⁷ (4) The rate of the reaction is not very sensitive to the presence of electron-withdrawing or electron-donating substituents.⁹⁴⁸ Because cycloadditions involving allenes are often stereospecific, it has been suggested that these also take place by the $[\pi_2s + \pi_2a]$ mechanism,⁹⁴⁹ but the evidence in these cases is more consistent with the diradical mechanism *b*.⁹⁵⁰

The diradical mechanism *b* is most prominent in the reactions involving fluorinated alkenes.⁹⁵¹ These reactions are generally not stereospecific⁹⁵² and are insensitive to solvent effects. Further evidence that a diion is not involved is that head-to-head coupling is found when an unsymmetrical molecule is dimerized. Thus dimerization of $F_2C=CFCl$ gives **103**,



⁹⁴⁶Brook; Harrison; Duke, Ref. 944.

⁹⁴⁷Brady; O'Neal *J. Org. Chem.* **1967**, *32*, 612; Huisgen; Feiler; Otto *Tetrahedron Lett.* **1968**, 4485. *Chem. Ber.* **1969**, *102*, 3444; Sterk *Z. Naturforsch., Teil B* **1972**, *27*, 143.

⁹⁴⁸Baldwin; Kapecki *J. Am. Chem. Soc.* **1970**, *92*, 4868; Isaacs; Stanbury *J. Chem. Soc., Perkin Trans. 2* **1973**, 166.

⁹⁴⁹For example, see Kiefer; Okamura *J. Am. Chem. Soc.* **1968**, *90*, 4187; Baldwin; Roy *Chem. Commun.* **1969**, 1225; Moore; Bach; Ozretich *J. Am. Chem. Soc.* **1969**, *91*, 5918.

⁹⁵⁰Muscio; Jacobs *Tetrahedron Lett.* **1969**, 2867; Taylor; Warburton; Wright *J. Chem. Soc. C* **1971**, 385; Dai; Dolbier *J. Am. Chem. Soc.* **1972**, *94*, 3946; Duncan; Weyler; Moore *Tetrahedron Lett.* **1973**, 4391; Grimme; Rother *Angew. Chem. Int. Ed. Engl.* **1973**, *12*, 505 [*Angew. Chem.* **85**, 512]; Levek; Kiefer *J. Am. Chem. Soc.* **1976**, *98*, 1875; Pasto; Heid; Warren *J. Am. Chem. Soc.* **1982**, *104*, 3676; Pasto; Yang *J. Org. Chem.* **1986**, *51*, 1676; Dolbier; Seabury *Tetrahedron Lett.* **1987**, *28*, 1491, *J. Am. Chem. Soc.* **1987**, *109*, 4393; Dolbier; Weaver *J. Org. Chem.* **1990**, *55*, 711.

⁹⁵¹It has been argued that the mechanism here is not the diradical mechanism, but the $[\pi_2s + \pi_2a]$ mechanism: Roberts *Tetrahedron* **1985**, *41*, 5529.

⁹⁵²Montgomery; Schueller; Bartlett *J. Am. Chem. Soc.* **1964**, *86*, 621; Bartlett; Hummel; Elliott; Minns *J. Am. Chem. Soc.* **1972**, *94*, 2898.

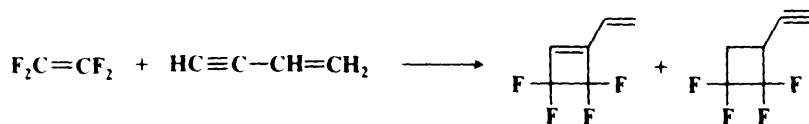
not **104**. If one pair of electrons moved before the other, the positive end of one molecule would be expected to attack the negative end of the other.⁹⁵³

The diion mechanism⁹⁵⁴ *c* has been reported for at least some of the reactions⁹⁵⁵ in categories 3 and 4,⁹⁵⁶ as well as some ketene dimerizations.⁹⁵⁷ For example, the rate of the reaction between 1,2-bis(trifluoromethyl)-1,2-dicyanoethene and ethyl vinyl ether was strongly influenced by changes in solvent polarity.⁹⁵⁸ Some of these reactions are nonstereospecific, but others are stereospecific.⁹⁵⁹ As previously indicated, it is likely that in the latter cases the diionic intermediate closes before rotation can take place. Such rapid ring closure is more likely for a diion than for a diradical because of the attraction between the opposite charges. Other evidence for the diion mechanism in these cases is that reaction rates are greatly dependent on the presence of electron-donating and electron-withdrawing groups and that it is possible to trap the diionic intermediates.

Whether a given olefin reacts by the diradical or diion mechanism depends, among other things, on the groups attached to it. For example, phenyl and vinyl groups at the α positions of **99** or **100** help to stabilize a diradical, while donors such as oxygen and nitrogen favor a diion (they stabilize the positively charged end).⁹⁶⁰ A table on p. 451 of reference 960 shows which mechanism is more likely for 2 + 2 cycloadditions of various pairs of olefins.

Thermal cleavage of cyclobutanes⁹⁶¹ to give two olefin molecules (*cycloreversion*),⁹⁶² the reverse of 2 + 2 cycloaddition) operates by the diradical mechanism, and the [_o2_s + _o2_a] pathway has not been found⁹⁶³ (the subscripts σ indicate that σ bonds are involved in this reaction).

In some cases, double bonds add to triple bonds to give cyclobutenes, apparently at about the same rate that they add to double bonds, e.g.,



About equal amounts

The addition of triple bonds to triple bonds would give cyclobutadienes, and this has not been observed, except where these rearrange before they can be isolated (see **5-51**)⁹⁶⁴ or in the presence of a suitable coordination compound, so that the cyclobutadiene is produced in the form of a complex (p. 55).⁹⁶⁵

⁹⁵³For additional evidence based on radical stabilities, see Silversmith; Kitahara; Caserio; Roberts *J. Am. Chem. Soc.* **1958**, *80*, 5840; Ref. 925; Doering; Guyton *J. Am. Chem. Soc.* **1978**, *100*, 3229.

⁹⁵⁴For reviews of this mechanism, see Huisgen *Acc. Chem. Res.* **1977**, *10*, 117-124, 199-206; Huisgen; Schug; Steiner *Bull. Soc. Chim. Fr.* **1976**, 1813-1820.

⁹⁵⁵For a review of cycloadditions with polar intermediates, see Gompper *Angew. Chem. Int. Ed. Engl.* **1969**, *8*, 312-327 [*Angew. Chem.* *81*, 348-363].

⁹⁵⁶The reactions of ketenes with enamines are apparently not concerted but take place by the diionic mechanism: Otto; Feiler; Huisgen *Angew. Chem. Int. Ed. Engl.* **1968**, *7*, 737 [*Angew. Chem.* *80*, 759].

⁹⁵⁷See Moore; Wilbur *J. Am. Chem. Soc.* **1978**, *100*, 6523.

⁹⁵⁸Proskow; Simmons; Cairns *J. Am. Chem. Soc.* **1966**, *88*, 5254. See also Huisgen *Pure Appl. Chem.* **1980**, *52*, 2283-2302.

⁹⁵⁹Proskow; Simmons; Cairns, Ref. 958; Huisgen; Steiner *J. Am. Chem. Soc.* **1973**, *95*, 5054, 5055.

⁹⁶⁰Hall *Angew. Chem. Int. Ed. Engl.* **1983**, *22*, 440-455 [*Angew. Chem.* *95*, 448-464].

⁹⁶¹See Frey *Adv. Phys. Org. Chem.* **1966**, *4*, 147-193, pp. 170-175, 180-183.

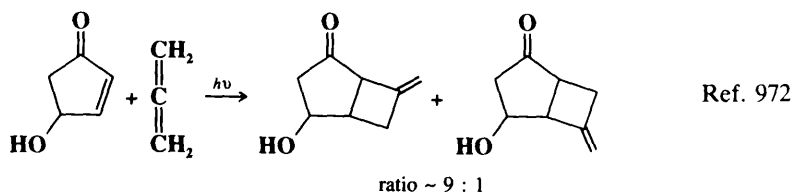
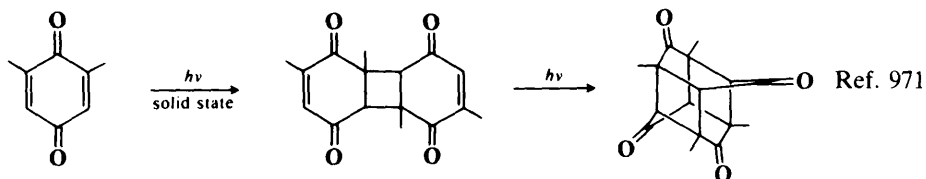
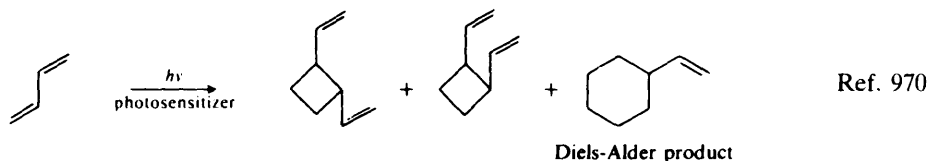
⁹⁶²For reviews of 2 + 2 cycloreversions, see Schaumann; Ketcham *Angew. Chem. Int. Ed. Engl.* **1982**, *21*, 225-247 [*Angew. Chem.* *94*, 231-253]; Brown, Ref. 883, pp. 247-259.

⁹⁶³See, for example, Cocks; Frey; Stevens *Chem. Commun.* **1969**, 458; Srinivasan; Hsu *J. Chem. Soc., Chem. Commun.* **1972**, 1213; Paquette; Kukla *Tetrahedron Lett.* **1973**, 1241; Paquette; Carmody *J. Am. Chem. Soc.* **1976**, *98*, 8175. See however Cant; Coxon; Hartshorn *Aust. J. Chem.* **1975**, *28*, 391; Doering; Roth; Breuckmann; Figge; Lennartz; Fessner; Prinzbach *Chem. Ber.* **1988**, *121*, 1.

⁹⁶⁴For a review of these cases, and of cycloadditions of triple bonds to double bonds, see Fuks; Viehe, in Viehe, Ref. 49, pp. 435-442.

⁹⁶⁵D'Angelo; Ficini; Martinon; Riche; Sevin *J. Organomet. Chem.* **1979**, *177*, 265. For a review, see Hogeveen; Kok in Patai; Rappoport, Ref. 49, pt. 2, pp. 981-1013.

Although thermal 2 + 2 cycloaddition reactions are essentially limited to the cases described above, many (though by no means all) double-bond compounds undergo such reactions *when photochemically excited* (either directly or by a photosensitizer—see p. 241), even if they are not in the above categories.⁹⁶⁶ Simple alkenes absorb in the far uv (p. 235), which is difficult to reach experimentally, though this problem can sometimes be overcome by the use of suitable photosensitizers. The reaction has been applied to simple alkenes⁹⁶⁷ (especially to strained compounds such as cyclopropenes and cyclobutenes), but more often the double-bond compounds involved are conjugated dienes,⁹⁶⁸ α,β -unsaturated ketones,⁹⁶⁹ acids, or acid derivatives, or quinones, since these compounds, because they are conjugated, absorb at longer wavelengths (p. 234). Both dimerizations and mixed additions are common, some examples being (see also the example on p. 246):



⁹⁶⁶For reviews, see Demuth; Mikhail *Synthesis* **1989**, 145-162; Ninomiya; Naito *Photochemical Synthesis*; Academic Press: New York, 1989, pp. 58-109; Ramamurthy; Venkatesan *Chem. Rev.* **1987**, *87*, 433-481; Lewis *Adv. Photochem.* **1986**, *13*, 165-235; Wender, in Coyle *Photochemistry in Organic Synthesis*; Royal Society of Chemistry: London, 1986, pp. 163-188; Schreiber *Science* **1985**, *227*, 857-863; Neckers; Tinnemans, in Horspool *Synthetic Organic Photochemistry*; Plenum: New York, 1984, pp. 285-311; Baldwin *Org. Photochem.* **1981**, *5*, 123-225; Turro *Modern Molecular Photochemistry*; W.A. Benjamin: New York, 1978, pp. 417-425, 458-465; Kricka; Ledwith *Synthesis* **1974**, 539-549; Herndon *Top. Curr. Chem.* **1974**, *46*, 141-179; Sammes *Q. Rev., Chem. Soc.* **1970**, *24*, 37-68, pp. 46-55; Crowley; Mazzocchi, in Zabicky, Ref. 115, pp. 297-316; Turro; Dalton; Weiss *Org. Photochem.* **1969**, *2*, 1-62; Trecker *Org. Photochem.* **1969**, *2*, 63-116; Scharf *Fortschr. Chem. Forsch.* **1969**, *11*, 216-244; Steinmetz *Fortschr. Chem. Forsch.* **1967**, *7*, 445-527; Fonken *Org. Photochem.* **1967**, *1*, 197-246; Chapman; Lenz *Org. Photochem.* **1967**, *1*, 283-321; Schönberg, Ref. 49, pp. 70-96, 109-117; Warriner; Bremner *Rev. Pure Appl. Chem.* **1966**, *16*, 117-173, pp. 122-128.

⁹⁶⁷For examples of nonphotosensitized dimerization of simple alkenes, see Arnold; Abraytys *Chem. Commun.* **1967**, 1053; Yamazaki; Cvetanović *J. Am. Chem. Soc.* **1969**, *91*, 520.

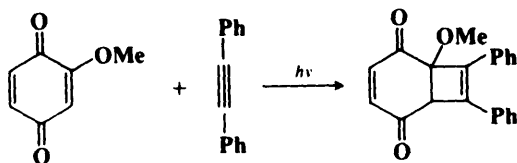
⁹⁶⁸For a review, see Dilling *Chem. Rev.* **1969**, *69*, 845-877.

⁹⁶⁹For reviews of various aspects of this subject, see Cossy; Carrupt; Vogel, in Patai *Supplement A: The Chemistry of Double-bonded Functional Groups*, vol. 2, pt. 2; Wiley: New York, 1989, pp. 1369-1565; Kemernitskii; Ignatov; Levina *Russ. Chem. Rev.* **1988**, *57*, 270-282; Weedon, in Horspool, Ref. 966, pp. 61-143; Lenz *Rev. Chem. Intermed.* **1981**, *4*, 369-404; Margaretha *Chimia* **1975**, *29*, 203-209; Bauslaugh *Synthesis* **1970**, 287-300; Eaton *Acc. Chem. Res.* **1968**, *1*, 50-57.

⁹⁷⁰Hammond; Turro; Fischer *J. Am. Chem. Soc.* **1961**, *83*, 4674; Liu; Turro; Hammond *J. Am. Chem. Soc.* **1965**, *87*, 3406; Cundall; Griffiths *Trans. Faraday Soc.* **1965**, *61*, 1968; DeBoer; Turro; Hammond *Org. Synth. V*, 528.

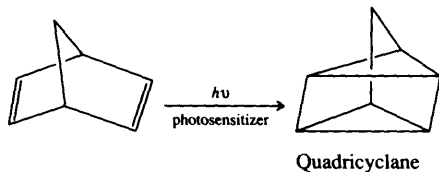
⁹⁷¹Cookson; Cox; Hudec *J. Chem. Soc.* **1961**, 4499.

⁹⁷²Stensen; Svendsen; Hofer; Sydnæs *Acta Chem. Scand., Ser. B* **1988**, *42*, 259.

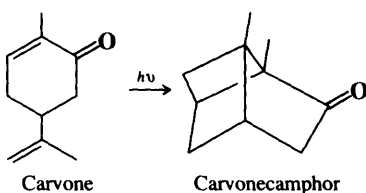


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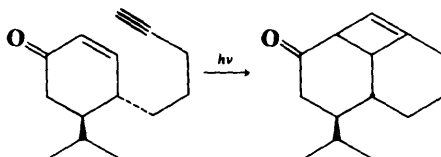
Photochemical 2 + 2 cycloadditions can also take place intramolecularly if a molecule has two double bonds that are properly oriented.⁹⁷⁴ The cyclization of the quinone dimer shown above is one example. Other examples are



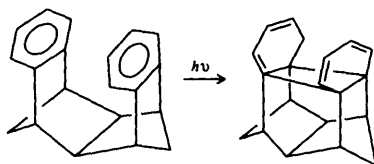
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⁹⁷³Pappas; Pappas *Tetrahedron Lett.* **1967**, 1597.

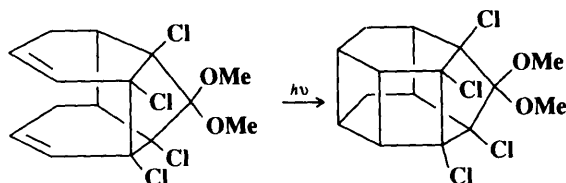
⁹⁷⁴For reviews, see Becker; Haddad *Org. Photochem.* **1989**, *10*, 1-162; Crimmins *Chem. Rev.* **1988**, *88*, 1453-1473; Oppolzer *Acc. Chem. Res.* **1982**, *15*, 135-141; Prinzbach *Pure Appl. Chem.* **1968**, *16*, 17-46; Dilling *Chem. Rev.* **1966**, *66*, 373-393.

⁹⁷⁵Hammond; Turro; Fischer, Ref. 970; Dauben; Cargill *Tetrahedron* **1961**, *15*, 197. See also Cristol; Snell *J. Am. Chem. Soc.* **1958**, *80*, 1950.

⁹⁷⁶Ciamician; Silber *Ber.* **1908**, *41*, 1928; Büchi; Goldman *J. Am. Chem. Soc.* **1957**, *79*, 4741.

⁹⁷⁷Koft; Smith *J. Am. Chem. Soc.* **1984**, *106*, 2115.

⁹⁷⁸Fessner; Prinzbach; Rihs *Tetrahedron Lett.* **1983**, *24*, 5857.



Ref. 979

It is obvious that many molecules can be constructed in this way that would be difficult to make by other procedures. However, attempted cyclizations of this kind are not always successful. In many cases polymeric or other side products are obtained instead of the desired product.

It is possible that some of these photochemical cycloadditions take place by a $[\pi 2_s + \pi 2_s]$ mechanism (which is of course allowed by orbital symmetry); when and if they do, one of the molecules must be in the excited singlet state (S_1) and the other in the ground state.⁹⁸⁰ The nonphotosensitized dimerizations of *cis*- and *trans*-2-butene are stereospecific,⁹⁸¹ making it likely that the $[\pi 2_s + \pi 2_s]$ mechanism is operating in these reactions. However, in most cases it is a triplet excited state that reacts with the ground-state molecule; in these cases the diradical (or in certain cases, the diionic) mechanism is taking place. In one intramolecular case, the intermediate diradical has been trapped.⁹⁸² Photosensitized $2\pi + 2\pi$ cycloadditions almost always involve the triplet state and hence a diradical (or diionic) mechanism.

The photochemical diradical mechanism is not quite the same as the thermal diradical mechanism. In the thermal mechanism the initially formed diradical must be a singlet, but in the photochemical process a triplet excited state is adding to a ground state (which is of course a singlet). Thus, in order to conserve spin,⁹⁸³ the initially formed diradical must be a triplet; i.e., the two electrons must have the same spin. Consequently the second, or ring-closing, step of the mechanism cannot take place at once, because a new bond cannot form from a combination of two electrons with the same spin, and the diradical has a reasonably long lifetime before collisions with molecules in the environment allow a spin inversion to take place and the diradical to cyclize. We would therefore predict nonstereospecificity, and that is what is found.⁹⁸⁴ It has been believed that at least some $2 + 2$ photocycloadditions take place by way of exciplex intermediates⁹⁸⁵ [an *exciplex*⁹⁸⁶ is an excited EDA complex (p. 79) which is dissociated in the ground state; in this case one double bond is the donor and the other the acceptor], but there is evidence against this.⁹⁸⁷

It has been found that certain $2 + 2$ cycloadditions which do not occur thermally can be made to take place without photochemical initiation by the use of certain catalysts, usually

⁹⁷⁹Mehta; Padma; Ōsawa; Barbiric; Mochizuki *Tetrahedron Lett.* **1987**, 28, 1295.

⁹⁸⁰We have previously seen (p. 242) that reactions between two excited molecules are extremely rare.

⁹⁸¹Yamazaki; Cvetanović, Ref. 967; Yamazaki; Cvetanović; Irwin *J. Am. Chem. Soc.* **1976**, 98, 2198. For other likely examples, see Lewis; Hoyle; Johnson *J. Am. Chem. Soc.* **1975**, 97, 3267; Lewis; Kojima *J. Am. Chem. Soc.* **1988**, 110, 8660.

⁹⁸²Becker; Haddad; Sahali *Tetrahedron Lett.* **1989**, 30, 2661.

⁹⁸³This is an example of the Wigner spin conservation rule (p. 241). Note that spin conservation is something entirely different from symmetry conservation.

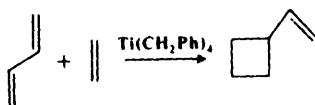
⁹⁸⁴See, for example, Liu; Hammond *J. Am. Chem. Soc.* **1967**, 89, 4936; Kramer; Bartlett *J. Am. Chem. Soc.* **1972**, 94, 3934.

⁹⁸⁵See, for example, Farid; Doty; Williams *J. Chem. Soc., Chem. Commun.* **1972**, 711; Mizuno; Pac; Sakurai *J. Am. Chem. Soc.* **1974**, 96, 2993; Caldwell; Creed *Acc. Chem. Res.* **1980**, 13, 45-50; Mattes; Farid *Acc. Chem. Res.* **1982**, 15, 80-86; Swapna; Lakshmi; Rao; Kunwar *Tetrahedron* **1989**, 45, 1777.

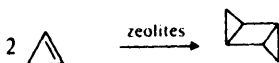
⁹⁸⁶For a review of exciplexes, see Davidson *Adv. Phys. Org. Chem.* **1983**, 19, 1-130.

⁹⁸⁷Schuster; Heibel; Brown; Turro; Kumar *J. Am. Chem. Soc.* **1988**, 110, 8261.

transition-metal compounds.⁹⁸⁸ Examples are:



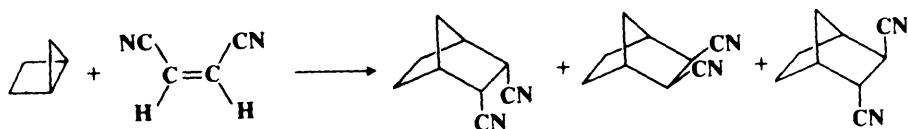
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Among the catalysts used are Lewis acids⁹⁹¹ and phosphine-nickel complexes.⁹⁹² Certain of the reverse cyclobutane ring openings can also be catalytically induced (8-40). The role of the catalyst is not certain and may be different in each case. One possibility is that the presence of the catalyst causes a forbidden reaction to become allowed, through coordination of the catalyst to the π or σ bonds of the substrate.⁹⁹³ In such a case the reaction would of course be a concerted 2_s + 2_s process. However, the available evidence is more consistent with nonconcerted mechanisms involving metal-carbon σ -bonded intermediates, at least in most cases.⁹⁹⁴ For example, such an intermediate was isolated in the dimerization of norbornadiene, catalyzed by iridium complexes.⁹⁹⁵

Thermal cycloadditions leading to four-membered rings can also take place between a cyclopropane ring and an alkene or alkyne⁹⁹⁶ bearing electron-withdrawing groups.⁹⁹⁷ These reactions are 2 + 2 cycloadditions. Ordinary cyclopropanes do not undergo the reaction, but it has been accomplished with strained systems such as bicyclo[1.1.0]butanes⁹⁹⁸ and bicyclo[2.1.0]pentanes. For example, bicyclo[2.1.0]pentane reacts with maleonitrile (or fu-



maronitrile) to give all three isomers of 2,3-dicyanonorbornane, as well as four other products.⁹⁹⁹ The lack of stereospecificity and the negligible effect of solvent on the rate indicate

⁹⁸⁸For reviews, see Dzhemilev; Khusnutdinov; Tolstikov *Russ. Chem. Rev.* **1987**, *56*, 36-51; Kricka; Ledwith, Ref. 966.

⁹⁸⁹Cannell *J. Am. Chem. Soc.* **1972**, *94*, 6867.

⁹⁹⁰Schipperijn; Lukas *Tetrahedron Lett.* **1972**, 231.

⁹⁹¹West; Kwitowski *J. Am. Chem. Soc.* **1968**, *90*, 4697; Lukas; Baardman; Kouwenhoven *Angew. Chem. Int. Ed. Engl.* **1976**, *15*, 369 [*Angew. Chem.* **88**, 412].

⁹⁹²See, for example, Hoover; Lindsey *J. Org. Chem.* **1969**, *34*, 3051; Noyori; Ishigami; Hayashi; Takaya *J. Am. Chem. Soc.* **1973**, *95*, 1674; Yoshikawa; Aoki; Kiji; Furukawa *Tetrahedron* **1974**, *30*, 405.

⁹⁹³For discussions, see Labunskaya; Shebalova; Khidekel' *Russ. Chem. Rev.* **1974**, *43*, 1-16; Mango *Top. Curr. Chem.* **1974**, *45*, 39-91, *Tetrahedron Lett.* **1973**, 1509, *Intra-Sci. Chem. Rep.* **1972**, *6* (3), 171-187, *CHEMTECH* **1971**, *1*, 758-765, *Adv. Catal.* **1969**, *20*, 291-325; Mango; Schachtschneider *J. Am. Chem. Soc.* **1971**, *93*, 1123, **1969**, *91*, 2484; van der Lugt *Tetrahedron Lett.* **1970**, 2281; Wristers; Brener; Pettit *J. Am. Chem. Soc.* **1970**, *92*, 7499.

⁹⁹⁴See, for example, Cassar; Halpern *Chem. Commun.* **1970**, 1082; Doyle; McMeeking; Binger *J. Chem. Soc., Chem. Commun.* **1976**, 376; Grubbs; Miyashita; Liu; Burk *J. Am. Chem. Soc.* **1977**, *99*, 3863.

⁹⁹⁵Fraser; Bird; Bezman; Shapley; White; Osborn *J. Am. Chem. Soc.* **1973**, *95*, 597.

⁹⁹⁶Gassman; Mansfield *J. Am. Chem. Soc.* **1968**, *90*, 1517, 1524.

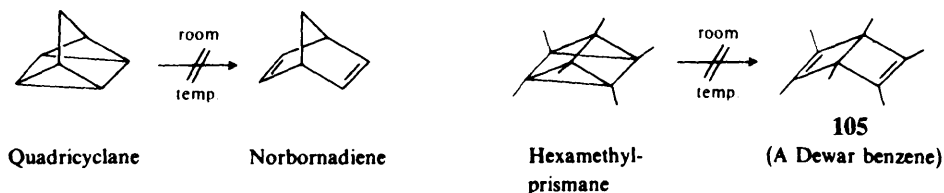
⁹⁹⁷For a review, see Gassman *Acc. Chem. Res.* **1971**, *4*, 128-136.

⁹⁹⁸Cairncross; Blanchard *J. Am. Chem. Soc.* **1966**, *88*, 496.

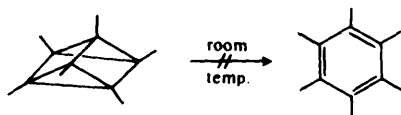
⁹⁹⁹Gassman; Mansfield; Murphy *J. Am. Chem. Soc.* **1969**, *91*, 1684.

a diradical mechanism. Photochemical¹⁰⁰⁰ and metal-catalyzed¹⁰⁰¹ „2 + „2 cycloadditions have also been reported.

In 5-47 we used the principle of conservation of orbital symmetry to explain why certain reactions take place readily and others do not. The orbital-symmetry principle can also explain why certain molecules are stable though highly strained. For example, quadricyclane and hexamethylprismane¹⁰⁰² are thermodynamically much less stable (because much more strained) than their corresponding isomeric dienes, norbornadiene and hexamethylbicyclo[2.2.0]hexadiene (**105**).¹⁰⁰³ Yet the former two compounds can be kept indefinitely at



room temperature, although in the absence of orbital-symmetry considerations it is not easy to understand why the electrons simply do not move over to give the more stable diene isomers. The reason is that both these reactions involve the conversion of a cyclobutane ring to a pair of double bonds (a „2 + „2 process) and, as we have seen, a thermal process of this sort is forbidden by the Woodward–Hoffmann rules. The process is allowed photochemically, and we are not surprised to find that both quadricyclane and hexamethylprismane are photochemically converted to the respective dienes at room temperature or below.¹⁰⁰⁴ It is also possible to conceive of simple bond rearrangements whereby hexamethylprismane is converted to hexamethylbenzene, which of course is far more stable than either hexa-



methylprismane or **105**. It has been calculated that hexamethylbenzene is at least 90 kcal/mol (380 kJ/mol) more stable than hexamethylprismane. The fact that hexamethylprismane does not spontaneously undergo this reaction has prompted the observation¹⁰⁰⁵ that the prismane has “the aspect of an angry tiger unable to break out of a paper cage.” However, a correlation diagram for this reaction¹⁰⁰⁵ discloses that it too is a symmetry-forbidden process. All three of these “forbidden” reactions do take place when the compounds are heated, but the diradical mechanism is likely under these conditions.¹⁰⁰⁶

¹⁰⁰⁰Freeman; Balls *J. Org. Chem.* **1967**, *32*, 2354; Wiskott; Schleyer *Angew. Chem. Int. Ed. Engl.* **1967**, *6*, 694 [*Angew. Chem.* **79**, 680]; Prinzbach; Eberbach *Chem. Ber.* **1968**, *101*, 4083; Prinzbach; Sedelmeier; Martin *Angew. Chem. Int. Ed. Engl.* **1977**, *16*, 103 [*Angew. Chem.* **89**, 111].

¹⁰⁰¹See, for example, Volger; Hogeveen; Gaasbeek *J. Am. Chem. Soc.* **1969**, *91*, 218; Katz; Cereface *J. Am. Chem. Soc.* **1969**, *91*, 2405, 6519.

¹⁰⁰²This compound can be prepared by photolysis of **105**, another example of an intramolecular photochemical 2 + 2 cycloaddition: Lemal; Lokensgard *J. Am. Chem. Soc.* **1966**, *88*, 5934; Schäfer; Criegee; Askani; Grüner *Angew. Chem. Int. Ed. Engl.* **1967**, *6*, 78 [*Angew. Chem.* **79**, 54].

¹⁰⁰³For a review of this compound, see Schäfer; Hellmann *Angew. Chem. Int. Ed. Engl.* **1967**, *6*, 518-525 [*Angew. Chem.* **79**, 566-573].

¹⁰⁰⁴These conversions can also be carried out by the use of transition metal catalysts: Hogeveen; Volger *Chem. Commun.* **1967**, 1133; *J. Am. Chem. Soc.* **1967**, *89*, 2486; Kaiser; Childs; Maitlis *J. Am. Chem. Soc.* **1971**, *93*, 1270; Landis; Gremaud; Patrick *Tetrahedron Lett.* **1982**, *23*, 375; Maruyama; Tamiaki *Chem. Lett.* **1987**, 683.

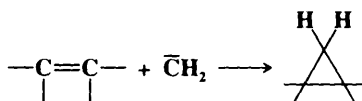
¹⁰⁰⁵Woodward; Hoffmann Ref. 895, pp. 107-112.

¹⁰⁰⁶See, for example, Oth *Recl. Trav. Chim. Pays-Bas* **1968**, *87*, 1185.

Bicyclo[2.2.0]hexadienes and prismanes are *valence isomers* of benzenes.¹⁰⁰⁷ These compounds actually have the structures that were proposed for benzenes in the nineteenth century. Prismanes have the Ladenburg formula, and bicyclo[2.2.0]hexadienes have the Dewar formula. Because of this bicyclo[2.2.0]hexadiene is often called Dewar benzene. On p. 26 it was mentioned that Dewar formulas are canonical forms (though not very important) of benzenes. Yet they also exist as separate compounds in which the positions of the nuclei are different from those of benzenes.

OS V, 54, 235, 277, 297, 370, 393, 424, 459, 528; VI, 378, 571, 962, 1002, 1024, 1037; VII, 177, 256, 315; 68, 32, 41; 69, 199, 205. For the reverse reaction, see OS V, 734.

5-50 The Addition of Carbenes and Carbenoids to Double and Triple Bonds *epi-Methylene-addition*



Carbenes and substituted carbenes add to double bonds to give cyclopropane derivatives (1 + 2 cycloaddition).¹⁰⁰⁸ Many derivatives of carbene, e.g., PhCH, ROCH,¹⁰⁰⁹ Me₂C=C, C(CN)₂, have been added to double bonds, but the reaction is most often performed with CH₂ itself, with halo and dihalocarbenes,¹⁰¹⁰ and with carbalkoxycarbenes¹⁰¹¹ (generated from diazoacetic esters). Alkylcarbenes HCR have been added to olefins,¹⁰¹² but more often these rearrange to give olefins (p. 201). The carbene can be generated in any of the ways normally used (p. 198). However, most reactions in which a cyclopropane is formed by treatment of an olefin with a carbene "precursor" do not actually involve free carbene intermediates. In some cases it is certain that free carbenes are not involved, and in other cases there is doubt. Because of this, the term *carbene transfer* is often used to cover all reactions in which a double bond is converted to a cyclopropane, whether a carbene or a carbenoid (p. 199) is actually involved.

Carbene itself is extremely reactive and gives many side reactions, especially insertion reactions (2-20), which greatly reduce yields. When it is desired to add CH₂ for preparative purposes, free carbene is not used, but the Simmons-Smith procedure (p. 870) or some other method that does not involve free carbenes is employed instead. Halocarbenes are less active than carbenes, and this reaction proceeds quite well, since insertion reactions do not interfere.¹⁰¹³ A few of the many ways¹⁰¹⁴ in which halocarbenes or carbenoids are

¹⁰⁰⁷For reviews of valence isomers of benzene, see Kobayashi; Kumadaki *Adv. Heterocycl. Chem.* **1982**, *31*, 169-206. *Acc. Chem. Res.* **1981**, *14*, 76-82; van Tamelen *Acc. Chem. Res.* **1972**, *5*, 186-192. *Angew. Chem. Int. Ed. Engl.* **1965**, *4*, 738-745 [*Angew. Chem.* **77**, 759-767]; Bolesov *Russ. Chem. Rev.* **1968**, *37*, 666-670; Viehe *Angew. Chem. Int. Ed. Engl.* **1965**, *4*, 746-751 [*Angew. Chem.* **77**, 768-773]; Ref. 1003.

¹⁰⁰⁸For reviews, see, in Rappoport *The Chemistry of the Cyclopropyl Group*; Wiley: New York, 1987, the reviews by Tsuji; Nishida, pt. 1, pp. 307-373; Verhé; De Kimpe, pt. 1, pp. 445-564; Marchand, in Patai, Ref. 1, pt. 1, pp. 534-607, 625-635; Bethell, in McManus *Organic Reactive Intermediates*; Academic Press: New York, 1973, pp. 101-113; in Patai, Ref. 36, the articles by Cadogan; Perkins, pp. 633-671; Huisgen; Grashey; Sauer, pp. 755-776; Kirmse *Carbene Chemistry*, 2nd ed.; Academic Press: New York, 1971, pp. 85-122, 267-406. For a review of certain intramolecular additions, see Burke; Grieco *Org. React.* **1979**, *26*, 361-475. For a list of reagents, with references, see Ref. 133, pp. 71-79.

¹⁰⁰⁹For a review, see Schöllkopf *Angew. Chem. Int. Ed. Engl.* **1968**, *7*, 588-598 [*Angew. Chem.* **80**, 603-613].

¹⁰¹⁰For a review of the addition of halocarbenes, see Parham; Schweizer *Org. React.* **1963**, *13*, 55-90.

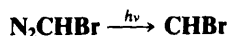
¹⁰¹¹For a review, see Dave; Warnhoff *Org. React.* **1970**, *18*, 217-401.

¹⁰¹²For example see Frey *J. Chem. Soc.* **1962**, 2293.

¹⁰¹³For reviews of carbene selectivity in this reaction, see Moss *Acc. Chem. Res.* **1989**, *22*, 15-21, **1980**, *13*, 58-64. For a review with respect to halocarbenes, see Kostikov; Molchanov; Khlebnikov *Russ. Chem. Rev.* **1989**, *58*, 654-666.

¹⁰¹⁴Much of the work in this field has been carried out by Seyferth and co-workers; see, for example, Seyferth; Burlitch; Minasz; Mui; Simmons; Treiber; Dowd *J. Am. Chem. Soc.* **1965**, *87*, 4259; Seyferth; Haas *J. Organomet. Chem.* **1972**, *46*, C33. *J. Org. Chem.* **1975**, *40*, 1620; Seyferth; Hopper *J. Org. Chem.* **1972**, *37*, 4070, *J. Organomet. Chem.* **1973**, *51*, 77; Seyferth; Haas; Dagani *J. Organomet. Chem.* **1976**, *104*, 9.

generated for this reaction are the following,¹⁰¹⁵ most of which involve formal elimination (the first two steps of the S_N1cB mechanism, p. 356):

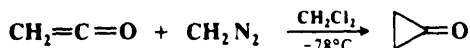


The reaction between CHCl₃ and OH⁻ is often carried out under phase transfer conditions.¹⁰¹⁹ It has been shown that the reaction between PhCHCl₂ and *t*-BuOK produces a carbenoid, but when the reaction is run in the presence of a crown ether, the free PhCCl is formed instead.¹⁰²⁰ Dihalocyclopropanes are very useful compounds¹⁰²¹ that can be reduced to cyclopropanes, treated with magnesium or sodium to give allenes (8-3), or converted to a number of other products.

Olefins of all types can be converted to cyclopropane derivatives by this reaction (though difficulty may be encountered with sterically hindered ones).¹⁰²² Even tetracyanoethylene, which responds very poorly to electrophilic attack, gives cyclopropane derivatives with carbenes.¹⁰²³ Conjugated dienes give 1,2 addition:¹⁰²⁴



Addition of a second mole gives bicyclopropyl derivatives.¹⁰²⁵ 1,4 addition is rare but has been reported in certain cases.¹⁰²⁶ Carbene adds to ketene to give cyclopropanone.¹⁰²⁷



¹⁰¹⁵A much longer list, with references, is given in Kirmse, *Carbene Chemistry*, Ref. 1008, pp. 313-319. See also Ref. 133, pp. 73-75.

¹⁰¹⁶For a review of the use of phenyl(trihalomethyl)mercury compounds as dihalocarbene or dihalocarbenoid precursors, see Seyferth *Acc. Chem. Res.* **1972**, *5*, 65-74. For a review of the synthesis of cyclopropanes with the use of organomercury reagents, see Larock, Ref. 539, pp. 341-380.

¹⁰¹⁷For reviews of fluorinated carbenes, see Seyferth in Moss; Jones *Carbenes*, vol. 2; Wiley: New York, 1975, pp. 101-158; Sheppard; Sharts *Organic Fluorine Chemistry*; W. A. Benjamin: New York, 1969, pp. 237-270.

¹⁰¹⁸Dolbier; Burkholder *Tetrahedron Lett.* **1988**, *29*, 6749.

¹⁰¹⁹For reviews of the use of phase-transfer catalysis in the addition of dihalocarbenes to C=C bonds, see Starks; Liotta *Phase Transfer Catalysis*; Academic Press: New York, 1978, pp. 224-268; Weber; Gokel *Phase Transfer Catalysis in Organic Synthesis*; Springer: New York, 1977, pp. 18-43, 58-62. For a discussion of the mechanism, see Gol'dberg; Shimanskaya *J. Org. Chem. USSR* **1984**, *20*, 1212.

¹⁰²⁰Moss; Pilkiewicz *J. Am. Chem. Soc.* **1974**, *96*, 5632; Moss; Lawrynowicz *J. Org. Chem.* **1984**, *49*, 3828.

¹⁰²¹For reviews of dihalocyclopropanes, see Banwell; Reum *Adv. Strain Org. Chem.* **1991**, *1*, 19-64; Kostikov; Molchanov; Hopf *Top. Curr. Chem.* **1990**, *155*, 41-80; Weyerstahl, in Patai; Rappoport, Ref. 614, pt. 2, pp. 1451-1497; Barlet; Vo-Quang *Bull. Soc. Chim. Fr.* **1969**, 3729-3760.

¹⁰²²Dehmow; Eulenberger *Liebigs Ann. Chem.* **1979**, 1112.

¹⁰²³Cairns; McKusick *Angew. Chem.* **1961**, *73*, 520.

¹⁰²⁴Woodworth; Skell *J. Am. Chem. Soc.* **1957**, *79*, 2542.

¹⁰²⁵Orchin; Herrick *J. Org. Chem.* **1959**, *24*, 139; Nakhapetyan; Safonova; Kazanskii *Bull. Acad. Sci. USSR Div. Chem. Sci.* **1962**, 840; Skattebøl *J. Org. Chem.* **1964**, *29*, 2951.

¹⁰²⁶Anastassiou; Cellura; Ciganek *Tetrahedron Lett.* **1970**, 5267; Jefford; Mareda; Gehret; Kabengele; Graham; Burger *J. Am. Chem. Soc.* **1976**, *98*, 2585; Mayr; Heigl *Angew. Chem. Int. Ed. Engl.* **1985**, *24*, 579 [*Angew. Chem.* **97**, 567]; Jenneskens; de Wolf; Bickelhaupt *Angew. Chem. Int. Ed. Engl.* **1985**, *24*, 585 [*Angew. Chem.* **97**, 568]; Le; Jones; Bickelhaupt; de Wolf *J. Am. Chem. Soc.* **1989**, *111*, 8491; Kraakman; de Wolf; Bickelhaupt *J. Am. Chem. Soc.* **1989**, *111*, 8534; Hudlicky; Seoane; Price; Gadamasetti *Synlett* **1990**, 433; Lambert; Ziemnicka-Merchant *J. Org. Chem.* **1990**, *55*, 3460.

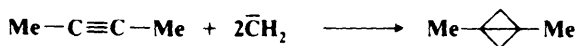
¹⁰²⁷Turro; Hammond *Tetrahedron* **1968**, *24*, 6017; Rothgery; Holt; McGee *J. Am. Chem. Soc.* **1975**, *97*, 4971. For a review of cyclopropanones, see Wasserman; Berdahl; Lu, in Rappoport, Ref. 1008, pt. 2, pp. 1455-1532.

Allenes react with carbenes to give cyclopropanes with exocyclic unsaturation:¹⁰²⁸

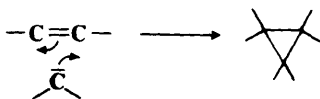


A second mole gives spiropentanes. In fact, any size ring with an exocyclic double bond can be converted by a carbene to a spiro compound.¹⁰²⁹

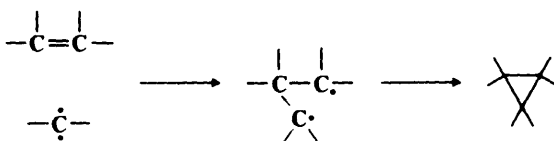
Triple-bond compounds¹⁰³⁰ react with carbenes to give cyclopropanes, except that in the case of acetylene itself, the cyclopropanes first formed cannot be isolated because they rearrange to allenes.¹⁰³¹ Cyclopropanones (p. 53) are obtained by hydrolysis of dihalocyclopropanes.¹⁰³² It has proved possible to add 2 moles of a carbene to an alkyne to give a bicyclobutane:¹⁰³³



Most carbenes are electrophilic, and, in accord with this, electron-donating substituents on the olefin increase the rate of the reaction, and electron-withdrawing groups decrease it,¹⁰³⁴ though the range of relative rates is not very great.¹⁰³⁵ As discussed on p. 196, carbenes in the singlet state (which is the most common state) react stereospecifically and syn,¹⁰³⁶ probably by a one-step mechanism,¹⁰³⁷ similar to mechanism *a* of 5-47 and 5-49:



Infrared spectra of a carbene and the cyclopropane product have been observed in an argon matrix at 12 to 45 K.¹⁰³⁸ Carbenes in the triplet state react nonstereospecifically,¹⁰³⁹ probably by a diradical mechanism, similar to mechanism *b* of 5-47 and 5-49:



¹⁰²⁸For reviews of the addition of carbenes and carbenoids to allenes, see Landor, in Landor, Ref. 95, vol. 2, pp. 351-360; Bertrand *Bull. Soc. Chim. Fr.* **1968**, 3044-3054. For a review of the synthetic uses of methylenecyclopropanes and cyclopropanes, see Binger; Büch *Top. Curr. Chem.* **1967**, *135*, 77-151.

¹⁰²⁹For a review of the preparation of spiro compounds by this reaction, see Krapcho *Synthesis* **1978**, 77-126.

¹⁰³⁰For reviews, see Fuks; Viehe, in Viehe, Ref. 49, pp. 427-434; Closs *Adv. Alicyclic Chem.* **1966**, *1*, 53-127, pp. 58-65.

¹⁰³¹Frey *Chem. Ind. (London)* **1960**, 1266.

¹⁰³²Vol'pin; Koreshkov; Kursanov *Bull. Acad. Sci. USSR Div. Chem. Sci.* **1959**, 535.

¹⁰³³Doering; Coburn *Tetrahedron Lett.* **1965**, 991. Also see Mahler *J. Am. Chem. Soc.* **1962**, *84*, 4600.

¹⁰³⁴Skell; Garner *J. Am. Chem. Soc.* **1956**, *78*, 5430; Doering; Henderson *J. Am. Chem. Soc.* **1958**, *80*, 5274; Mitsch; Rodgers *Int. J. Chem. Kinet.* **1969**, *1*, 439.

¹⁰³⁵For a review of reactivity in this reaction, with many comprehensive tables of data, see Moss in Jones; Moss *Carbenes*, vol. 1; Wiley: New York, 1973, pp. 153-304. See also Cox; Gould; Hacker; Moss; Turro *Tetrahedron Lett.* **1983**, *24*, 5313.

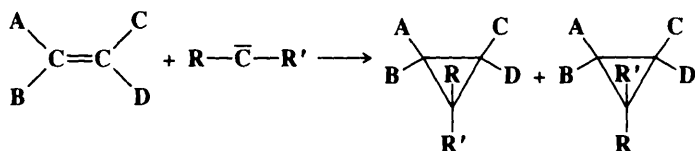
¹⁰³⁶Woodworth; Skell *J. Am. Chem. Soc.* **1959**, *81*, 3383; Jones; Ando; Hendrick; Kulczycki; Howley; Hummel; Malament *J. Am. Chem. Soc.* **1972**, *94*, 7469.

¹⁰³⁷For evidence that at least some singlet carbenes add by a two-step mechanism, see Giese; Lee; Neumann *Angew. Chem. Int. Ed. Engl.* **1982**, *21*, 310 [*Angew. Chem.* **94**, 320].

¹⁰³⁸Nefedov; Zuev; Maltsev; Tomilov *Tetrahedron Lett.* **1989**, *30*, 763.

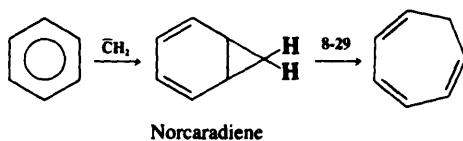
¹⁰³⁹Skell; Klebe *J. Am. Chem. Soc.* **1960**, *82*, 247. See also Jones; Tortorelli; Gaspar; Lambert *Tetrahedron Lett.* **1978**, 4257.

For carbenes or carbenoids of the type $R-C-R'$ there is another aspect of stereochemistry.¹⁰⁴⁰ When these species are added to all but symmetrical olefins, two isomers are possible, even if the four groups originally on the double-bond carbons maintain their configurations:



Which isomer is predominantly formed depends on R , R' , and on the method by which the carbene or carbenoid is generated. Most studies have been carried out on monosubstituted species ($R' = H$), and in these studies it is found that aryl groups generally prefer the more substituted side (syn addition) while carbethoxy groups usually show anti stereoselectivity. When $R =$ halogen, free halocarbenes show little or no stereochemical preference, while halocarbenoids exhibit a preference for syn addition. Beyond this, it is difficult to make simple generalizations.

Carbenes are so reactive that they add to the "double bonds" of aromatic rings. The products are usually not stable and rearrange to give ring expansion. Carbene reacts with benzene to give cycloheptatriene.¹⁰⁴¹



but not all carbenes are reactive enough to add to benzene. The norcaradiene intermediate cannot be isolated in this case¹⁰⁴² (it undergoes an electrocyclic rearrangement, **8-29**), though certain substituted norcaradienes, e.g., the product of addition of $C(CN)_2$ to benzene,¹⁰⁴³ have been isolated.¹⁰⁴⁴ With CH_2 , insertion is a major side reaction, and, for example, benzene gives toluene as well as cycloheptatriene. A method of adding CH_2 to benzene rings without the use of free carbene is the catalytic decomposition of CH_2N_2 in the aromatic compound as solvent with $CuCl$ or $CuBr$.¹⁰⁴⁵ By this method better yields of cycloheptatrienes are obtained without insertion side products. $CHCl$ is active enough to add to benzene, but dihalocarbenes do not add to benzene or toluene, only to rings with greater electron density.

¹⁰⁴⁰For reviews of the stereochemistry of carbene and carbenoid addition to double bonds, see Moss *Sel. Org. Transform.* **1970**, *1*, 35-88; Closs *Top Stereochem.* **1968**, *3*, 193-235. For a discussion of enantioselectivity in this reaction, see Nakamura *Pure App. Chem.* **1978**, *50*, 37.

¹⁰⁴¹Doering; Knox *J. Am. Chem. Soc.* **1951**, *75*, 297.

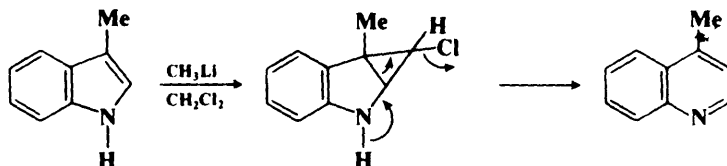
¹⁰⁴²It has been detected by uv spectroscopy: Rubin *J. Am. Chem. Soc.* **1981**, *103*, 7791.

¹⁰⁴³Ciganek *J. Am. Chem. Soc.* **1967**, *89*, 1454.

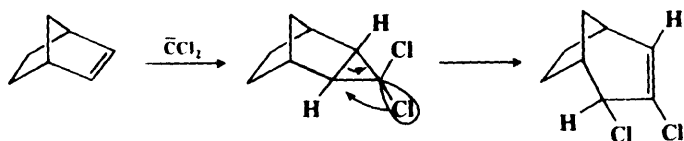
¹⁰⁴⁴See, for example, Mukai; Kubota; Toda *Tetrahedron Lett.* **1967**, 3581; Maier; Heep *Chem. Ber.* **1968**, *101*, 1371; Ciganek *J. Am. Chem. Soc.* **1971**, *93*, 2207; Dürr; Kober *Tetrahedron Lett.* **1972**, 1255, 1259; Vogel; Wiedemann; Roth; Eimer; Günther *Liebigs Ann. Chem.* **1972**, *759*, 1; Bannerman; Cadogan; Gosney; Wilson *J. Chem. Soc., Chem. Commun.* **1975**, 618; Takeuchi; Kitagawa; Senzaki; Okamoto *Chem. Lett.* **1983**, 73; Kawase; Iyoda; Oda *Angew. Chem. Int. Ed. Engl.* **1987**, *26*, 559 [*Angew. Chem.* **99**, 572].

¹⁰⁴⁵Wittig; Schwarzenbach *Liebigs Ann. Chem.* **1961**, *650*, 1; Müller; Fricke *Liebigs Ann. Chem.* **1963**, *661*, 38; Müller; Kessler; Fricke; Kiedaisch *Liebigs Ann. Chem.* **1961**, *675*, 63.

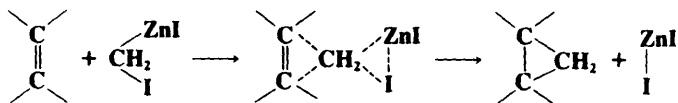
Pyrroles and indoles can be expanded, respectively, to pyridines and quinolines by treatment with halocarbenes,¹⁰⁴⁶ e.g.,



In such cases a side reaction that sometimes occurs is expansion of the *six-membered* ring. Ring expansion can occur even with nonaromatic compounds, when the driving force is supplied by relief of strain,¹⁰⁴⁷ e.g.,



As previously mentioned, free carbene is not very useful for additions to double bonds since it gives too many side products. The *Simmons-Smith procedure* accomplishes the same result without a free carbene intermediate and without insertion side products.¹⁰⁴⁸ This procedure involves treatment of the double-bond compound with CH_2I_2 and a Zn-Cu couple and leads to cyclopropane derivatives in good yields.¹⁰⁴⁹ The Zn-Cu couple can be prepared in several ways,¹⁰⁵⁰ of which heating Zn dust with CuCl in ether under nitrogen¹⁰⁵¹ is particularly convenient. The reaction has also been done with unactivated zinc and ultrasound.¹⁰⁵² When TiCl_4 is used along with Zn and CuCl, CH_2I_2 can be replaced by the cheaper CH_2Br_2 .¹⁰⁵³ The actual attacking species is an organozinc intermediate, probably $(\text{ICH}_2)_2\text{Zn}\cdot\text{ZnI}_2$. This intermediate is stable enough for solutions of it to be isolable.¹⁰⁵⁴ An x-ray crystallographic investigation of the intermediate, complexed with a diether, has been reported.¹⁰⁵⁵ The addition is stereospecifically syn, and a concerted mechanism is likely, perhaps¹⁰⁵⁶



¹⁰⁴⁶For a review of the reactions of heterocyclic compounds with carbenes, see Rees; Smithen *Adv. Heterocycl. Chem.* **1964**, *3*, 57-78.

¹⁰⁴⁷Jefford; Gunsher; Hill; Brun; Le Gras; Waegell *Org. Synth.* **VI**, 142. For a review of the addition of halocarbenes to bridged bicyclic olefins see Jefford *Chimia* **1970**, *24*, 357-363.

¹⁰⁴⁸For reviews, see Simmons; Cairns; Vladuchick; Hoiness *Org. React.* **1973**, *20*, 1-131; Furukawa; Kawabata *Adv. Organomet. Chem.* **1974**, *12*, 83-134, pp. 84-103.

¹⁰⁴⁹Simmons; Smith *J. Am. Chem. Soc.* **1959**, *81*, 4256.

¹⁰⁵⁰Shank; Shechter *J. Org. Chem.* **1959**, *24*, 1525; LeGoff *J. Org. Chem.* **1964**, *29*, 2048. For the use of a Zn-Ag couple, see Denis; Girard; Conia *Synthesis* **1972**, 549.

¹⁰⁵¹Rawson; Harrison *J. Org. Chem.* **1970**, *35*, 2057.

¹⁰⁵²Repič; Vogt *Tetrahedron Lett.* **1982**, *23*, 2729; Repič; Lee; Giger *Org. Prep. Proced. Int.* **1984**, *16*, 25.

¹⁰⁵³Friedrich; Lunetta; Lewis *J. Org. Chem.* **1969**, *54*, 2388.

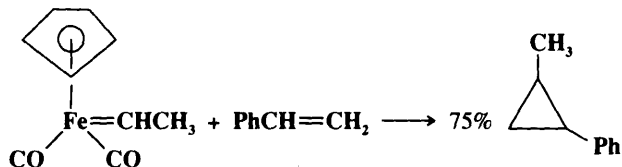
¹⁰⁵⁴Blanchard; Simmons *J. Am. Chem. Soc.* **1964**, *86*, 1337.

¹⁰⁵⁵Denmark; Edwards; Wilson *J. Am. Chem. Soc.* **1991**, *113*, 723.

¹⁰⁵⁶Simmons; Blanchard; Smith *J. Am. Chem. Soc.* **1964**, *86*, 1347.

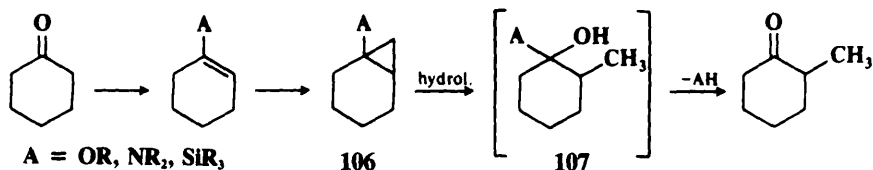
With the Simmons–Smith procedure, as with free carbenes, conjugated dienes give 1,2 addition,¹⁰⁵⁷ and allenes give methylenecyclopropanes or spiropentanes. An alternative way of carrying out the Simmons–Smith reaction is by treatment of the substrate with CH_2I_2 or another dihalomethane and Et_2Zn in ether. This method can be adapted to the introduction of RCH and ArCH by the use of RCHI_2 or ArCHI_2 instead of the dihalomethane.¹⁰⁵⁸ In another method, CH_2I_2 or MeCHI_2 is used along with an alane R_3Al to transfer CH_2 or MeCH .¹⁰⁵⁹ For the conversion of enolates to cyclopropanols, CH_2I_2 has been used along with SmI_2 .¹⁰⁶⁰

Free carbenes can also be avoided by using transition metal–carbene complexes $\text{L}_n\text{M}=\text{CRR}'$ (L = a ligand, M = a metal), which add the group CRR' to double bonds.¹⁰⁶¹ An example is¹⁰⁶²



These complexes can be isolated in some cases; in others they are generated in situ from appropriate precursors, of which diazo compounds are among the most important. These compounds, including CH_2N_2 and others, react with metals or metal salts (copper, palladium, and rhodium are most commonly used) to give the carbene complexes that add CRR' to double bonds.¹⁰⁶³ Optically active complexes have been used for enantioselective cyclopropane synthesis.¹⁰⁶⁴

The Simmons–Smith reaction has been used as the basis of a method for the indirect α methylation of a ketone.¹⁰⁶⁵ The ketone (illustrated for cyclohexanone) is first converted to an enol ether, e.g., by **6-6**, or to an enamine (**6-14**) or silyl enol ether (**2-23**). Application of the Simmons–Smith reaction gives the norcarane derivative **106**, which is then cleaved



¹⁰⁵⁷Overberger; Halek *J. Org. Chem.* **1963**, *28*, 867.

¹⁰⁵⁸Furukawa; Kawabata; Nishimura *Tetrahedron Lett.* **1968**, 3495; Nishimura; Kawabata; Furukawa *Tetrahedron* **1969**, *25*, 2647; Miyano; Hashimoto *Bull. Chem. Soc. Jpn.* **1973**, *46*, 892; Friedrich; Biresaw *J. Org. Chem.* **1982**, *47*, 1615.

¹⁰⁵⁹Maruoka; Fukutani; Yamamoto *J. Org. Chem.* **1985**, *50*, 4412, *Org. Synth.* *67*, 176.

¹⁰⁶⁰Imamoto; Takiyama *Tetrahedron Lett.* **1987**, *28*, 1307. See also Molander; Harring *J. Org. Chem.* **1989**, *54*, 3525.

¹⁰⁶¹For reviews, see Helquist *Adv. Met.-Org. Chem.* **1991**, *2*, 143-194; Brookhart; Studabaker *Chem. Rev.* **1987**, *87*, 411-432; Syatkovskii; Babitskii *Russ. Chem. Rev.* **1984**, *53*, 672-682.

¹⁰⁶²Brookhart; Tucker; Husk *J. Am. Chem. Soc.* **1983**, *105*, 258.

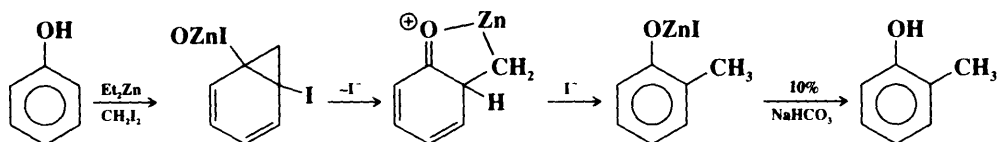
¹⁰⁶³For reviews, see Adams; Spero *Tetrahedron* **1991**, *47*, 1765-1808; Collman et al., Ref. 223, pp. 800-806; Maas *Top. Curr. Chem.* **1987**, *137*, 75-253; Doyle *Chem. Rev.* **1986**, *86*, 919-939, *Acc. Chem. Res.* **1986**, *19*, 348-356; Heck, Ref. 568, pp. 401-407; Wulfman; Poling *React. Intermed. (Plenum)* **1980**, *1*, 321-512; Müller; Kessler; Zeeh *Fortschr. Chem. Forsch.* **1966**, *7*, 128-171.

¹⁰⁶⁴Brookhart; Liu *Organometallics* **1989**, *8*, 1572, *J. Am. Chem. Soc.* **1991**, *113*, 939; Brookhart; Liu; Goldman; Timmers; Williams *J. Am. Chem. Soc.* **1991**, *113*, 927; Lowenthal; Abiko; Masamune *Tetrahedron Lett.* **1990**, *31*, 6005; Evans; Woerpel; Hinman; Faul *J. Am. Chem. Soc.* **1991**, *113*, 726. For asymmetric Simmons–Smith reactions, see Mori; Arai; Yamamoto *Tetrahedron* **1986**, *42*, 6447; Mash; Nelson; Heidt *Tetrahedron Lett.* **1987**, *28*, 1865; Sugimura; Futagawa; Yoshikawa; Tai *Tetrahedron Lett.* **1989**, *30*, 3807. See also Ojima; Clos; Bastos, Ref. 232, pp. 6919-6921.

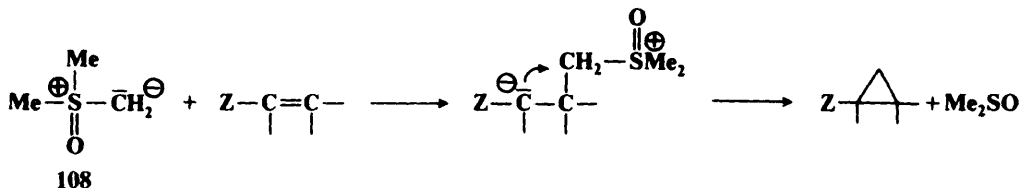
¹⁰⁶⁵See Wenkert; Mueller; Reardon; Sathé; Scharf; Tosi *J. Am. Chem. Soc.* **1970**, *92*, 7428 for the enol ether procedure; Kuehne; King *J. Org. Chem.* **1973**, *38*, 304 for the enamine procedure; Conia *Pure Appl. Chem.* **1975**, *43*, 317-326 for the silyl ether procedure.

(addition of water to a cyclopropane ring) to an intermediate **107**, which loses ROH, RNH₂, or R₃SiH, producing the methylated ketone. Cleavage of **106** is carried out by acid hydrolysis if A is OR, by basic hydrolysis if A is SiR₃,¹⁰⁶⁶ and by neutral hydrolysis in aqueous methanol if A is NR₂.

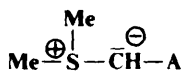
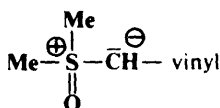
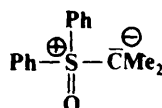
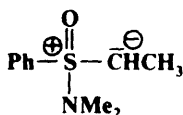
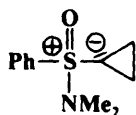
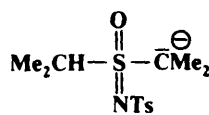
In another variation, phenols can be ortho-methylated in one laboratory step, by treatment with Et₂Zn and CH₂I₂.¹⁰⁶⁷ The following mechanism was proposed:



Double-bond compounds that undergo the Michael reaction (5-17) can be converted to cyclopropane derivatives with sulfur ylides.¹⁰⁶⁸ Among the most common of these is dimethylsulfonium methylide (**108**),¹⁰⁶⁹ which is widely used to transfer CH₂ to activated



double bonds, but other sulfur ylides, e.g., **109** (A = acyl,¹⁰⁷⁰ carboethoxy¹⁰⁷¹), **110**,¹⁰⁷² and **111**,¹⁰⁷³ which transfer CHA, CH-vinyl, and CMe₂, respectively, have also been used. CHR

**109****110****111****112****113****114**

and CR₂ can be added in a similar manner with certain nitrogen-containing compounds. For example, the ylides¹⁰⁷⁴ **112** and **113** and the carbanion **114** can be used, respectively, to add

¹⁰⁶⁶In the case of silyl enol ethers the inner bond can be cleaved with FeCl₃, giving a ring-enlarged β-chloro ketone: Ito; Fujii; Saegusa *J. Org. Chem.* **1976**, *41*, 2073; *Org. Synth.* *VI*, 327.

¹⁰⁶⁷Lehnert; Sawyer; Macdonald *Tetrahedron Lett.* **1989**, *30*, 5215.

¹⁰⁶⁸For a monograph and reviews on sulfur ylides, see Chapter 2, Ref. 53.

¹⁰⁶⁹Truce; Badiger *J. Org. Chem.* **1964**, *29*, 3277; Corey; Chaykovsky *J. Am. Chem. Soc.* **1965**, *87*, 1353; Agami; Prevost *Bull. Soc. Chim. Fr.* **1967**, 2299. For a review of this reagent, see Gololobov; Nesmeyanov; Lysenko; Boldeskul *Tetrahedron* **1987**, *43*, 2609-2651.

¹⁰⁷⁰Trost *J. Am. Chem. Soc.* **1967**, *89*, 138. See also Nozaki; Takaku; Kondô *Tetrahedron* **1966**, *22*, 2145.

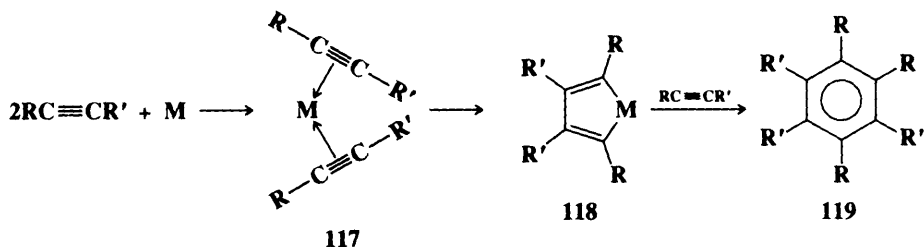
¹⁰⁷¹Payne *J. Org. Chem.* **1967**, *32*, 3351.

¹⁰⁷²LaRochelle; Trost; Krepeski *J. Org. Chem.* **1971**, *36*, 1126; Marino; Kaneko *Tetrahedron Lett.* **1973**, 3971, 3975.

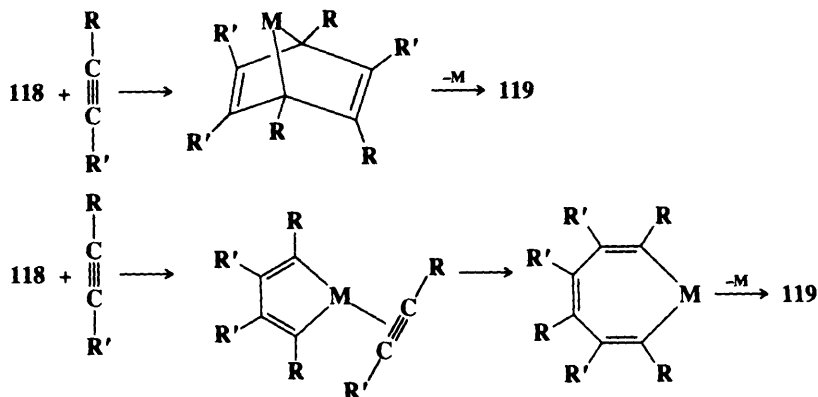
¹⁰⁷³Corey; Jautelat *J. Am. Chem. Soc.* **1967**, *89*, 3912.

¹⁰⁷⁴For a review of sulfoximides R₂S(O)NR₂ and ylides derived from them, see Kennewell; Taylor *Chem. Soc. Rev.* **1980**, *9*, 477-498.

In contrast to the spontaneous reaction, the catalyzed process seldom gives the 1,2,3-trisubstituted benzene isomer from an acetylene $\text{RC}\equiv\text{CH}$. The chief product is usually the 1,2,4-isomer, with lesser amounts of the 1,3,5-isomer also generally obtained, but little if any of the 1,2,3-isomer. The mechanism of the catalyzed reaction to form benzenes¹⁰⁸³ is believed to go through a species **117** in which two molecules of alkyne coordinate with the



metal, and another species **118**, a five-membered heterocyclic intermediate.¹⁰⁸⁴ Such intermediates (where $\text{M} = \text{Rh}, \text{Ir},$ or Ni) have been isolated and shown to give benzenes when treated with alkynes.¹⁰⁸⁵ Note that this pathway accounts for the predominant formation of the 1,2,4-isomer. Two possibilities for the last step are a Diels–Alder reaction, and a ring expansion, each followed by extrusion of the metal.^{1085a}



In at least one case the mechanism is different, going through a cyclobutadiene–nickel complex (p. 55), which has been isolated.¹⁰⁸⁶

When benzene, in the gas phase, was adsorbed onto a surface of 10% rhodium-on-alumina, the reverse reaction took place, and acetylene was formed.¹⁰⁸⁷

¹⁰⁸³For studies of the mechanism of the reaction that produces cyclooctatetraenes, see Diercks; Stamp; Kopf; tom Dieck *Angew. Chem. Int. Ed. Engl.* **1984**, 23, 893 [*Angew. Chem.* **96**, 891]; Colborn; Vollhardt *J. Am. Chem. Soc.* **1986**, 108, 5470; Lawrie; Gable; Carpenter *Organometallics* **1989**, 8, 2274.

¹⁰⁸⁴See, for example, Colborn; Vollhardt *J. Am. Chem. Soc.* **1981**, 103, 6259; Kochi *Organometallic Mechanisms and Catalysis*; Academic Press: New York, 1978, pp. 428–432; Collman et al., Ref. 223, pp. 870–877; Eisch; Sexsmith *Res. Chem. Intermed.* **1990**, 13, 149–192.

¹⁰⁸⁵See, for example, Collman; Kang *J. Am. Chem. Soc.* **1967**, 89, 844; Collman *Acc. Chem. Res.* **1968**, 1, 136–143; Yamazaki; Hagihara *J. Organomet. Chem.* **1967**, 7, P22; Wakatsuki; Kuramitsu; Yamazaki *Tetrahedron Lett.* **1974**, 4549; Moseley; Maitlis *J. Chem. Soc., Dalton Trans.* **1974**, 169; Müller *Synthesis* **1974**, 761–774; Eisch; Galle *J. Organomet. Chem.* **1975**, 96, C23; McAlister; Bercaw; Bergman *J. Am. Chem. Soc.* **1977**, 99, 1666.

^{1085a}There is evidence that the mechanism of the last step more likely resembles the Diels–Alder pathway than the ring expansion pathway: Bianchini et al. *J. Am. Chem. Soc.* **1991**, 113, 5127.

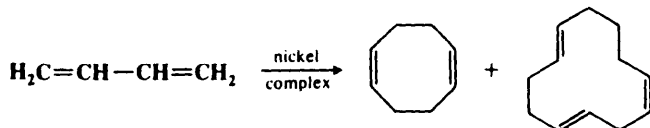
¹⁰⁸⁶Mauret; Alphonse *J. Organomet. Chem.* **1984**, 276, 249. See also Pepermans; Willem; Gielen; Hoogzand *Bull. Soc. Chim. Belg.* **1988**, 97, 115.

¹⁰⁸⁷Parker; Hexter; Siedle *J. Am. Chem. Soc.* **1985**, 107, 4584.

For addition of triple bonds to triple bonds, but not with ring formation, see 5-15. OS VII, 256.

5-52 Other Cycloaddition Reactions

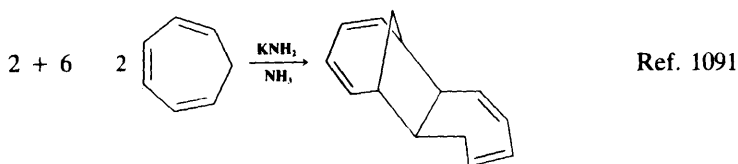
cyclo-[But-2-en-1,4-diyl]-1/4/addition, etc.



Conjugated dienes can be dimerized or trimerized at their 1,4 positions (formally, 4 + 4 and 4 + 4 + 4 cycloadditions) by treatment with certain complexes or other transition-metal compounds.¹⁰⁸⁸ Thus butadiene gives 1,5-cyclooctadiene and 1,5,9-cyclododecatriene.¹⁰⁸⁹ The relative amount of each product can be controlled by use of the proper catalyst. For example, Ni:P(OC₆H₄-o-Ph)₃ gives predominant dimerization, while Ni(cyclooctadiene)₂ gives mostly trimerization. The products arise, not by direct 1,4 to 1,4 attack, but by stepwise mechanisms involving metal-olefin complexes.¹⁰⁹⁰

As we saw in 5-47, the Woodward-Hoffmann rules allow suprafacial concerted cycloadditions to take place thermally if the total number of electrons is 4*n* + 2 and photochemically if the number is 4*n*. Furthermore, forbidden reactions become allowed if one molecule reacts antarafacially. It would thus seem that syntheses of many large rings could easily be achieved. However, when the newly formed ring is eight-membered or greater, concerted mechanisms, though allowed by orbital symmetry for the cases stated, become difficult to achieve because of the entropy factor (the two ends of one system must simultaneously encounter the two ends of the other), unless one or both components are cyclic, in which case the molecule has many fewer possible conformations. There have been a number of reports of cycloaddition reactions leading to eight-membered and larger rings, some thermally and some photochemically induced, but (apart from the dimerization and trimerization of butadienes mentioned above, which are known not to involve direct 4 + 4 or 4 + 4 + 4 cycloaddition) in most cases evidence is lacking to indicate whether they are concerted or stepwise processes.

Some examples are

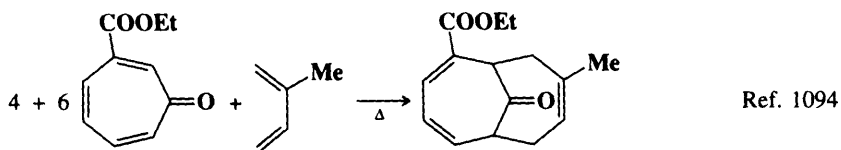
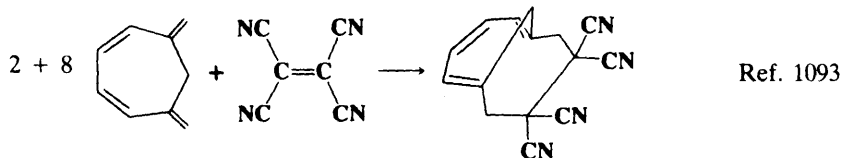
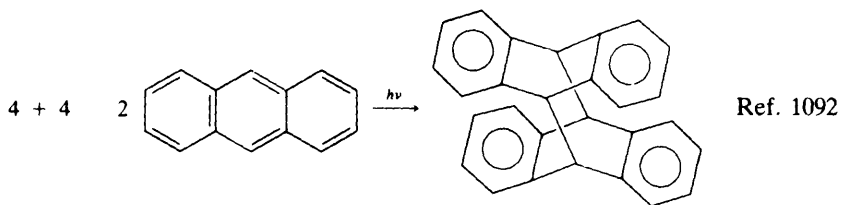


¹⁰⁸⁸For reviews, see Wilke *Angew. Chem. Int. Ed. Engl.* **1988**, 27, 186-206 [*Angew. Chem.* 100, 189-211], *J. Organomet. Chem.* **1980**, 200, 349-364; Tolstikov; Dzhemilev *Sov. Sci. Rev., Sect. B* **1985**, 7, 237-295, pp. 278-290; Heimbach; Schenkluhn *Top. Curr. Chem.* **1980**, 92, 45-108; Heimbach *Angew. Chem. Int. Ed. Engl.* **1973**, 12, 975-989 [*Angew. Chem.* 85, 1035-1049]; Baker *Chem. Rev.* **1973**, 73, 487-530, pp. 489-512; Semmelhack *Org. React.* **1972**, 19, 115-198, pp. 128-143; Heimbach; Jolly; Wilke *Adv. Organomet. Chem.* **1970**, 8, 29-86, pp. 48-83; Khan; Martell, Ref. 159, pp. 159-163; Heck, Ref. 223, pp. 157-164.

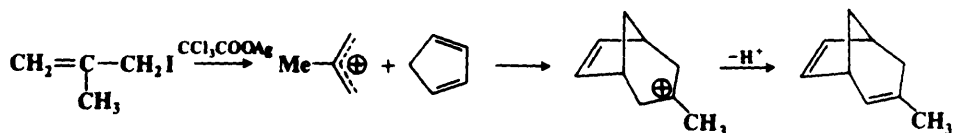
¹⁰⁸⁹For a review of the 1,5,9-cyclododecatrienes (there are four stereoisomers, of which the *ttt* is shown above), see Rona *Intra-Sci. Chem. Rep.* **1971**, 5, 105-148.

¹⁰⁹⁰For example, see Heimbach; Wilke *Liebigs Ann. Chem.* **1969**, 727, 183; Barnett; Büssemeier; Heimbach; Jolly; Krüger; Tkatchenko; Wilke *Tetrahedron Lett.* **1972**, 1457; Barker; Green; Howard; Spencer; Stone *J. Am. Chem. Soc.* **1976**, 98, 3373; Graham; Stephenson *J. Am. Chem. Soc.* **1977**, 99, 7098.

¹⁰⁹¹Staley; Orvedal *J. Am. Chem. Soc.* **1974**, 96, 1618. In this case the reagent converted one molecule of cycloheptatriene to the cycloheptatrienyl anion (p. 46), which then added stepwise to the other molecule.

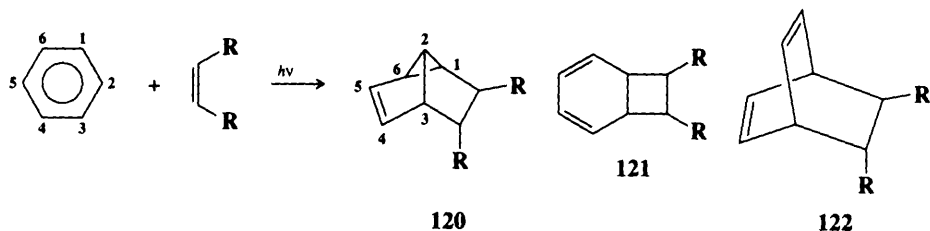


The suprafacial thermal addition of an allylic cation to a diene (a 3 + 4 cycloaddition) is allowed by the Woodward–Hoffmann rules (this reaction would be expected to follow the same rules as the Diels–Alder reaction¹⁰⁹⁵). Such cycloadditions can be carried out¹⁰⁹⁶ by treatment of a diene with an allylic halide in the presence of a suitable silver salt, e.g.,¹⁰⁹⁷



This reaction has even been carried out with benzene assuming the role of the diene.¹⁰⁹⁸

Benzene rings can undergo photochemical cycloaddition with olefins.¹⁰⁹⁹ The major product is usually the 1,3 addition product **120** (in which a 3-membered ring has also been formed), though some of the 1,2 product **121** (**5-49**) is sometimes formed as well. (**121** is



¹⁰⁹²Shönberg, Ref. 49, pp. 97-99.

¹⁰⁹³Farrant; Feldmann *Tetrahedron Lett.* **1970**, 4979.

¹⁰⁹⁴Garst; Roberts; Houk; Rondan *J. Am. Chem. Soc.* **1984**, *106*, 3882.

¹⁰⁹⁵Because the HOMO of an allylic cation, p. 33, has the same symmetry as the HOMO of an alkene.

¹⁰⁹⁶For reviews of 3 + 4 cycloadditions see Mann *Tetrahedron* **1986**, *42*, 4611-4659; Hoffmann *Angew. Chem. Int. Ed. Engl.* **1984**, *23*, 1-19, **1973**, *12*, 819-835 [*Angew. Chem.* **96**, 29-48, **85**, 877-894]; Noyori *Acc. Chem. Res.* **1979**, *12*, 61-66.

¹⁰⁹⁷Hoffmann; Joy; Suter *J. Chem. Soc. B* **1968**, 57.

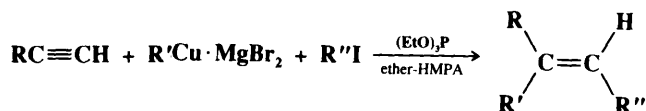
¹⁰⁹⁸Hoffmann; Hill *Angew. Chem. Int. Ed. Engl.* **1974**, *13*, 136 [*Angew. Chem.* **86**, 127].

¹⁰⁹⁹For reviews, see Wender; Ternansky; deLong; Singh; Olivero; Rice *Pure Appl. Chem.* **1990**, *62*, 1597-1602; Wender; Siggel; Nuss *Org. Photochem.* **1989**, *10*, 357-473; Gilbert, in Horspool, Ref. 966, pp. 1-60. For a review of this and related reactions, see McCullough *Chem. Rev.* **1987**, *87*, 811-860.

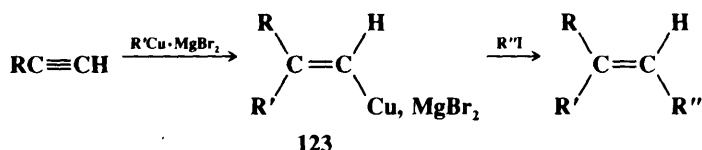
usually the main product where the olefin bears electron-withdrawing groups and the aromatic compound electron-donating groups, or vice versa.) The 1,4 product **122** is rarely formed. The reaction has also been run with benzenes substituted with alkyl, halo, OR, CN, and other groups, and with acyclic and cyclic olefins bearing various groups.¹¹⁰⁰

OS VI, 512; VII, 485.

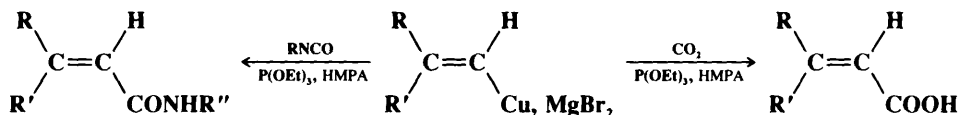
5-53 The Addition of Two Alkyl Groups to an Alkyne Dialkyl-addition



Two different alkyl groups can be added to a terminal alkyne¹¹⁰¹ in one laboratory step by treatment with an alkylcopper–magnesium bromide reagent (called *Normant reagents*)¹¹⁰² and an alkyl iodide in ether–HMPA containing triethyl phosphite.¹¹⁰³ The groups add stereoselectively syn. The reaction, which has been applied to primary¹¹⁰⁴ R' and to primary, allylic, benzylic, vinylic, and α-alkoxyalkyl R'', involves initial addition of the alkylcopper reagent,¹¹⁰⁵ followed by a coupling reaction (0-87):



Acetylene itself (R = H) undergoes the reaction with R₂CuLi instead of the Normant reagent.¹¹⁰⁶ The use of R' containing functional groups has been reported.¹¹⁰⁷ If the alkyl iodide is omitted, the vinylic copper intermediate **123** can be converted to a carboxylic acid by the addition of CO₂ (see 6-34) or to an amide by the addition of an isocyanate



(see 6-36), in either case in the presence of HMPA and a catalytic amount of triethyl phosphite.¹¹⁰⁸ The use of I₂ results in a vinylic iodide.¹¹⁰⁹

¹¹⁰⁰See the table in Wender; Siggel; Nuss, Ref. 1099, pp. 384-415.

¹¹⁰¹For reviews of this and related reactions, see Raston; Salem, in Hartley, Ref. 218, vol. 4, pp. 159-306, pp. 233-248; Normant; Alexakis *Synthesis* **1981**, 841-870; Hudrlik, in Patai, Ref. 70, pt. 1 pp. 233-238. For a list of reagents and references for this and related reactions, see Ref. 133, pp. 233-238.

¹¹⁰²For the composition of these reagents see Ashby; Smith; Goel *J. Org. Chem.* **1981**, 46, 5133; Ashby; Goel *J. Org. Chem.* **1983**, 48, 2125.

¹¹⁰³Normant; Cahiez; Chuit; Alexakis; Villieras *J. Organomet. Chem.* **1972**, 40, C49; Alexakis; Cahiez; Normant; Villieras *Bull. Soc. Chim. Fr.* **1977**, 693; Gardette; Alexakis; Normant *Tetrahedron* **1985**, 41, 5887. For an extensive list of references see Marfat; McGuirk; Helquist *J. Org. Chem.* **1979**, 44, 3888.

¹¹⁰⁴For a method of using secondary and tertiary R, see Rao; Periasamy *Tetrahedron Lett.* **1988**, 29, 4313.

¹¹⁰⁵The initial product, **123**, can be hydrolyzed with acid to give RR'C=CH₂. See Westmijze; Kleijn; Meijer; Vermeer *Recl. Trav. Chim. Pays-Bas* **1981**, 100, 98, and references cited therein.

¹¹⁰⁶Alexakis; Normant; Villieras *Tetrahedron Lett.* **1976**, 3461; Alexakis; Cahiez; Normant *Synthesis* **1979**, 826, *Tetrahedron* **1980**, 36, 1961; Furber; Taylor; Burford *J. Chem. Soc., Perkin Trans. 1* **1986**, 1809.

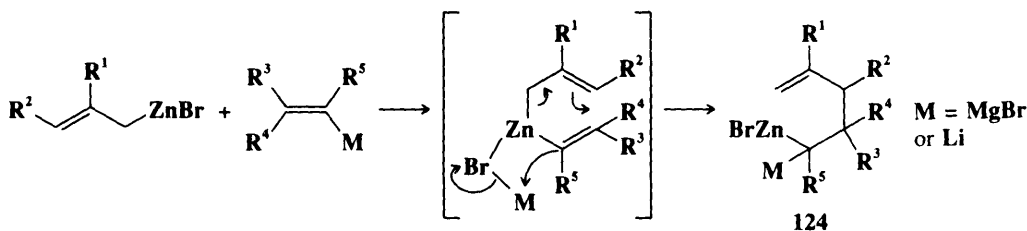
¹¹⁰⁷Rao; Knochel *J. Am. Chem. Soc.* **1991**, 113, 5735.

¹¹⁰⁸Normant; Cahiez; Chuit; Villieras *J. Organomet. Chem.* **1973**, 54, C53.

¹¹⁰⁹Alexakis; Cahiez; Normant *Org. Synth. VII*, 290.

Similar reactions, in which two alkyl groups are added to a triple bond, have been carried out with trialkylalanes R_3Al , with zirconium complexes as catalysts.¹¹¹⁰

Allylic zinc bromides add to vinylic Grignard and lithium reagents to give the *gem*-

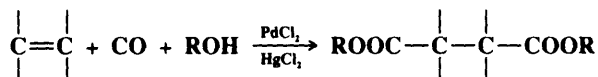


dimetallo compounds **124**. The two metallo groups can be separately reacted with various nucleophiles.¹¹¹¹

OS VII, 236, 245, 290.

5-54 Dicarboxylation of Olefins and Acetylenes

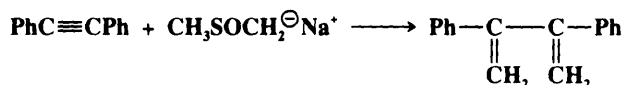
Dicarboxy-addition



Alkenes can be converted to succinic esters by reaction with carbon monoxide, an alcohol, and palladium chloride in the presence of mercuric chloride.¹¹¹² The addition is mostly syn. In similar reaction, both terminal and internal alkynes can be converted to esters of maleic acid.

5-55 The Conversion of Diphenylacetylene to a Butadiene

Dimethylene-biaddition



Diphenylacetylene reacts with methylsulfinyl carbanion to give 2,3-diphenylbutadiene.¹¹¹³ Neither the scope nor the mechanism of the reaction seems to have been investigated.

OS VI, 531.

¹¹¹⁰Yoshida; Negishi *J. Am. Chem. Soc.* **1981**, *103*, 4985; Rand; Van Horn; Moore; Negishi *J. Org. Chem.* **1981**, *46*, 4093; Negishi; Van Horn; Yoshida *J. Am. Chem. Soc.* **1985**, *107*, 6639. For reviews, see Negishi *Acc. Chem. Res.* **1987**, *20*, 65-72; *Pure Appl. Chem.* **1981**, *53*, 2333-2356; Negishi; Takahashi *Aldrichimica Acta* **1985**, *18*, 31-47.

¹¹¹¹Knochel; Normant *Tetrahedron Lett.* **1986**, *27*, 1039, 1043, 4427, 4431, 5727.

¹¹¹²Heck *J. Am. Chem. Soc.* **1972**, *94*, 2712. See also Fenton; Steinwand *J. Org. Chem.* **1972**, *37*, 2034; Stille; Divakaruni *J. Org. Chem.* **1979**, *44*, 3474; Catellani; Chiusoli; Peloso *Tetrahedron Lett.* **1983**, *24*, 813; Deprés; Coelho; Greene *J. Org. Chem.* **1985**, *50*, 1972.

¹¹¹³Iwai; Ide *Org. Synth.* *VI*, 531.