CHAPTER 13

Aromatic Substitution, Nucleophilic and Organometallic

On p. 481, it was pointed out that nucleophilic substitutions proceed so slowly at an aromatic carbon that the reactions of Chapter 10 are not feasible for aromatic substrates. There are, however, exceptions to this statement, and it is these exceptions that form the subject of this chapter.[1] Reactions that *are* successful at an aromatic substrate are largely of four kinds: (*1*) reactions activated by electron-withdrawing groups ortho and para to the leaving group; (*2*) reactions catalyzed by very strong bases and proceeding through aryne intermediates; (*3*) reactions initiated by electron donors; and (*4*) reactions in which the nitrogen of a diazonium salt is replaced by a nucleophile. It is noted that solvent effects can be important.[2] Also, not all the reactions discussed in this chapter fit into these categories, and certain transition-metal catalyzed coupling reaction are included because they involve replacement of a leaving group on an aromatic ring.

MECHANISMS

There are four principal mechanisms for aromatic nucleophilic substitution.[3] Each of the four is similar to one of the aliphatic nucleophilic substitution mechanisms discussed in Chapter 10.

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[1] For a review of aromatic nucleophilic substitution, see Zoltewicz, J.A. *Top. Curr. Chem.* ***1975***, *59*, 33.

[2] Acevedo, O.; Jorgensen, W.L. *Org. Lett.* ***2004***, *6*, 2881.

[3] For a monograph on aromatic nucleophilic substitution mechanisms, see Miller, J. *Aromatic Nucleophilic Substitution*, Elsevier, NY, ***1968***. For reviews, see Bernasconi, C.F. *Chimia* ***1980***, *34*, 1; *Acc. Chem. Res.* ***1978***, *11*, 147; Bunnett, J.F. *J. Chem. Educ.* ***1974***, *51*, 312; Ross, S.D., in Bamford, C.H.; Tipper, C.F.H. *Comprehensive Chemical Kinetics*, Vol. 13; Elsevier, NY, ***1972***, pp. 407–431; Buck, P. *Angew. Chem, Int. Ed.* ***1969***, *8*, 120; Buncel, E.; Norris, A.R.; Russell, K.E. *Q. Rev. Chem. Soc.* ***1968***, *22*, 123; Bunnett, J.F. *Tetrahedron* ***1993***, *49*, 4477; Zoltewicz, J.A. *Top. Curr. Chem.* ***1975***, *59*, 33.

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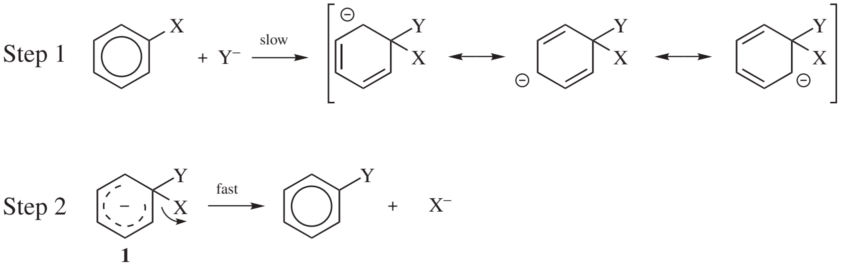
Michael B. Smith and Jerry March

The S_NAr Mechanism[4]

By far the most important mechanism for nucleophilic aromatic substitution consists of two steps, attack of the nucleophilic species at the ipso carbon of the aromatic ring (the carbon bearing the leaving group in this case), followed by elimination of the leaving group and regeneration of the aromatic ring.



The first step is usually, but not always, rate determining. It can be seen that this mechanism greatly resembles the tetrahedral mechanism discussed in Chapter 16 and, in another way, the arenium ion mechanism of electrophilic aromatic substitution discussed in Chapter 11. In all three cases, the attacking species forms a bond with the substrate, giving an intermediate, such as **1**, and then the leaving group departs. We refer to this mechanism as the S_NAr mechanism.[5] The IUPAC designation is $A_N + D_N$ (the same as for the tetrahedral mechanism; compare the designation $A_E + D_E$ for the arenium ion mechanism). This mechanism is generally found where activating groups are present on the ring (see p. 864).

There is a great deal of evidence for the mechanism; we shall discuss only some of it.[3] Probably the most convincing evidence was the isolation, as long ago as 1902, of the intermediate **2** in the reaction between 2,4,6-trinitrophenetole and methoxide ion.[6] Intermediates of this type are stable salts, called *Meisenheimer* or *Meisenheimer–Jackson salts*,[7] and many more have been isolated.[8] The structures

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[4] High pressure S_NAr reactions are known. see Barrett, I.C.; Kerr, M.A. *Tetrahedron Lett.* ***1999***, *40*, 2439.

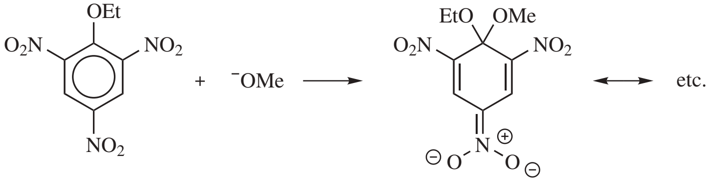
[5] The mechanism has also been called by other names, including the S_N2Ar, the addition–elimination, and the intermediate complex mechanism. See Wu, Z.; Glaser, R. *J. Am. Chem. Soc.* ***2004***, *126*, 10632. See also, Terrier, F.; Mokhtari, M.; Goumont, T.; Hallé, J.-C.; Buncel, E. *Org. Biomol. Chem.* ***2003***, *1*, 1757.

[6] Meisenheimer, J. *Liebigs Ann. Chem.* ***1902***, *323*, 205. Similar salts were isolated even earlier by Jackson, C.L.; see Jackson, C.L.; Gazzolo, F.H. *Am. Chem. J.* ***1900***, *23*, 376; Jackson, C.L.; Earle, R.B. *Am. Chem. J.*, ***1903***, *29*, 89.

[7] Nucleophilic aromatic substitution for heteroatom nucleophiles through electrochemical oxidation of intermediate σ-complexes (Meisenheimer complexes) in simple nitroaromatic compounds has been reported, see Gallardo, I.; Guirado, G.; Marquet, J. *J. Org. Chem.* ***2002***, *67*, 2548.

[8] For a monograph on Meisenheimer salts and on this mechanism, see Buncel, E.; Crampton, M.R.; Strauss, M.J.; Terrier, F. *Electron Deficient Aromatic- and Heteroaromatic-Base Interactions*, Elsevier, NY, ***1984***. For reviews of structural and other studies, see Illuminati, G.; Stegel, F. *Adv. Heterocycl. Chem.* ***1983***, *34*, 305; Artamkina, G. A.; Egorov, M.P.; Beletskaya, I.P. *Chem. Rev.* ***1982***, *82*, 427; Terrier, F. *Chem. Rev.* ***1982***, *82*, 77; Strauss, M.J. *Chem. Rev.* ***1970***, *70*, 667; *Acc. Chem. Res.* ***1974***, *7*, 181; Hall, T.N.; Poranski, Jr., C.F., in Feuer, H. *The Chemistry of the Nitro and Nitroso Groups*, pt. 2; Wiley, NY, ***1970***, pp. 329–384; Crampton, M.R. *Adv. Phys. Org. Chem.* ***1969***, *7*, 211; Foster R.; Fyfe, C.A. *Rev. Pure Appl. Chem.* ***1966***, *16*, 61.

of several of these intermediates



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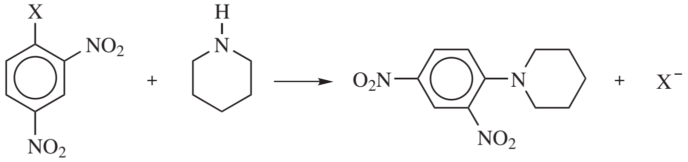
have been proved by NMR[9] and by X-ray crystallography.[10] Further evidence comes from studies of the effect of the leaving group on the reaction. If the mechanism were similar to either the S_N1 or S_N2 mechanisms described in Chapter 10, the Ar–X bond would be broken in the rate-determining step. In the S_NAr mechanism, this bond is not broken until after the rate-determining step (i.e. if step 1 is rate determining). There is some evidence that electron transfer may be operative during this process.[11] We would predict from this that if the S_NAr mechanism is operating, a change in leaving group should not have much effect on the reaction rate. In the reaction of dinitro compound **3** with piperidine,



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when X was Cl, Br, I, SOPh, SO_2Ph, or *p*-nitrophenoxy, the rates differed only by a factor of ~5.[12] This behavior would not be expected in a reaction in which the Ar–X bond is broken in the rate-determining step. We do not expect the rates to be *identical*, because the nature of X affects the rate at which Y attacks. An increase in the electronegativity of X causes a decrease in the electron density at the site of attack, resulting in a faster attack by a nucleophile. Thus, in the reaction just mentioned, when X = F, the relative rate was 3300 (compared with I = 1). The very fact that fluoro is the best leaving group among the halogens in most aromatic nucleophilic substitutions is good evidence that the mechanism is different from the S_N1

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[9] First done by Crampton, M.R.; Gold, V. *J. Chem. Soc. B* ***1966***, 893. A good review of spectral studies is found, in Buncel, E.; Crampton, M.R.; Strauss, M.J.; Terrier, F. *Electron Deficient Aromatic- and Heteroaromatic-Base Interactions*, Elsevier, NY, ***1984***, pp. 15–133.

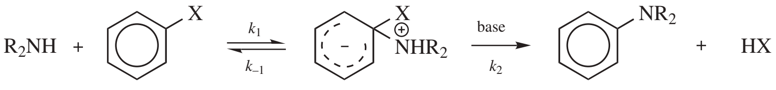
[10] Destro, R.; Gramaccioli, C.M.; Simonetta, M. *Acta Crystallogr.* ***1968***, *24*, 1369; Ueda, H.; Sakabe, M.; Tanaka, J.; Furusaki, A. *Bull. Chem. Soc. Jpn.* ***1968***, *41*, 2866; Messmer, G.G.; Palenik, G.J. *Chem. Commun.* ***1969***, 470.

[11] Grossi, L. *Tetrahedron Lett.* ***1992***, *33*, 5645.

[12] Bunnett, J.F.; Garbisch Jr., E.W.; Pruitt, K.M. *J. Am. Chem. Soc.* ***1957***, *79*, 385. See Gandler, J.R.; Setiarahardjo, I.U.; Tufon, C.; Chen, C. *J. Org. Chem.* ***1992***, *57*, 4169 for a more recent example.

and the S_N2 mechanisms, where fluoro is by far the poorest leaving group of the halogens. This is an example of the element effect (p. 475).

The pattern of base catalysis of reactions with amine nucleophiles provides additional evidence. These reactions are catalyzed by bases only when a relatively poor leaving group (e.g., OR) is present (not Cl or Br) and only when relatively bulky amines are nucleophiles.[13] Bases could not catalyze step 1, but if amines are nucleophiles, bases can catalyze step 2. Base catalysis is found precisely in those cases where the amine moiety cleaves easily but X does not, so that k_{-1} is large and step 2 is rate determining. This is evidence for the S_NAr mechanism because it implies two steps. Furthermore, in cases where bases *are* catalysts, they catalyze only at



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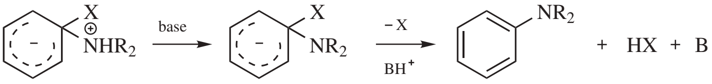
low base concentrations: a plot of the rate against the base concentration shows that small increments of base rapidly increase the rate until a certain concentration of base is reached, after which further base addition no longer greatly affects the rate. This behavior, based on a partitioning effect (see p. 660), is also evidence for the S_NAr mechanism. At low base concentration, each increment of base, by increasing the rate of step 2, increases the fraction of intermediate that goes to product rather than reverting to reactants. At high base concentration the process is virtually complete: there is very little reversion to reactants and the rate becomes dependent on step 1. Just how bases catalyze step 2 has been investigated. For protic solvents two proposals have been presented. One is that step 2 consists of two steps: rate-determining deprotonation of **4** followed by rapid loss of X,



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and that bases catalyze the reaction by increasing the rate of the deprotonation step.[14] According to the other proposal, loss of X assisted by BH^+ is rate determining.[15] Two mechanisms, both based on kinetic evidence, have been proposed for aprotic solvents, such as benzene. In both proposals the ordinary S_NAr mechanism

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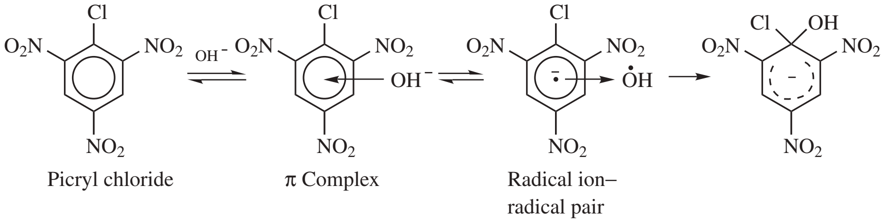
[13] Kirby, A.J.; Jencks, W.P. *J. Am. Chem. Soc.* ***1965***, *87*, 3217; Bunnett, J.F.; Bernasconi, C.F. *J. Org. Chem.* ***1970***, *35*, 70; Bernasconi, C.F.; Schmid, P. *J. Org. Chem.* ***1967***, *32*, 2953; Bernasconi, C.F.; Zollinger, H. *Helv. Chim. Acta* ***1966***, *49*, 103; ***1967***, *50*, 1; Pietra, F.; Vitali, D. *J. Chem. Soc. B* ***1968***, 1200; Chiacchiera, S.M.; Singh, J.O.; Anunziata, J.D.; Silber, J.J. *J. Chem. Soc. Perkin Trans. 2* ***1987***, 987.

[14] Bernasconi, C.F.; de Rossi, R.H.; Schmid, P. *J. Am. Chem. Soc.* ***1977***, *99*, 4090, and references cited therein.

[15] Bunnett, J.F.; Sekiguchi, S.; Smith, L.A. *J. Am. Chem. Soc.* ***1981***, *103*, 4865, and references cited therein.

operates, but in one the attacking species involves two molecules of the amine (the *dimer mechanism*),[16] while in the other there is a cyclic transition state.[17] Further evidence for the S_NAr mechanism has been obtained from $^{18}O/^{16}O$ and $^{15}N/^{14}N$ isotope effects.[18]

Step 1 of the S_NAr mechanism has been studied for the reaction between picryl chloride (as well as other substrates) and ^{-}OH ions (**13-1**), and spectral evidence has been reported[19] for two intermediates, one a π complex (p. 662), and the other a radical ion–radical pair:



As with the tetrahedral mechanism at an acyl carbon, nucleophilic catalysis (p. 1259) has been demonstrated with an aryl substrate, in certain cases.[20] There is also evidence of an interaction of anions with the π-cloud of aromatic compounds.[21]

The S_N1 Mechanism

For aryl halides and sulfonates, even active ones, a unimolecular S_N1 mechanism (IUPAC: $D_N + A_N$) is very rare; it has only been observed for aryl triflates in which both ortho positions contain bulky groups (*tert*-butyl or SiR_3).[22] It is in reactions with diazonium salts[23] that this mechanism is important:[24]

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[16] For a review of this mechanism, see Nudelman, N.S. *J. Phys. Org. Chem.* ***1989***, *2*, 1. See also Nudelman, N.S.; Montserrat, J.M. *J. Chem. Soc. Perkin Trans. 2* ***1990***, 1073.

[17] Banjoko, O.; Bayeroju, I.A. *J. Chem. Soc. Perkin Trans. 2* ***1988***, 1853; Jain, A.K.; Gupta, V.K.; Kumar, A. *J. Chem. Soc. Perkin Trans. 2* ***1990***, 11.

[18] Hart, C.R.; Bourns, A.N. *Tetrahedron Lett.* ***1966***, 2995; Ayrey, G.; Wylie, W.A. *J. Chem. Soc. B* ***1970***, 738.

[19] Bacaloglu, R.; Blaskó, A.; Bunton, C.A.; Dorwin, E.; Ortega, F.; Zucco, C. *J. Am. Chem. Soc.* ***1991***, *113*, 238, and references cited therein. For earlier reports, based on kinetic data, of complexes with amine nucleophiles, see Forlani, L. *J. Chem. Res. (S)* ***1984***, 260; Hayami, J.; Otani, S.; Yamaguchi, F.; Nishikawa, Y. *Chem. Lett.* ***1987***, 739; Crampton, M.R.; Davis, A.B.; Greenhalgh, C.; Stevens, J.A. *J. Chem. Soc. Perkin Trans. 2* ***1989***, 675.

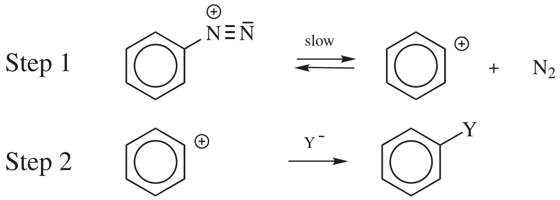
[20] See Muscio, Jr., O.J.; Rutherford, D.R. *J. Org. Chem.* ***1987***, *52*, 5194.

[21] Quiñonero, D.; Garau, C.; Rotger, C.; Frontera, A.; Ballester, P.; Costa, A.; Deyà. P.M. *Angew. Chem. Int. Ed.* ***2002***, *41*, 3389, and references cited therein.

[22] Himeshima, Y.; Kobayashi, H.; Sonoda, T. *J. Am. Chem. Soc.* ***1985***, *107*, 5286.

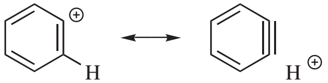
[23] See Glaser, R.; Horan, C.J.; Nelson, E.D.; Hall, M.K. *J. Org. Chem.* ***1992***, *57*, 215 for the influence of neighboring group interactions on the electronic structure of diazonium ions.

[24] Aryl iodonium salts Ar_2I^+ also undergo substitutions by this mechanism (and by a free-radical mechanism).



Among the evidence for the S_N1 mechanism[25] with aryl cations as intermediates,[26,27] is the following:[28]

1. The reaction rate is first order in diazonium salt and independent of the concentration of Y.
2. When high concentrations of halide salts are added, the product is an aryl halide but the rate is independent of the concentration of the added salts.
3. The effects of ring substituents on the rate are consistent with a unimolecular rate-determining cleavage.[29]
4. When reactions were run with substrate deuterated in the ortho position, isotope effects of ~1.22 were obtained.[30] It is difficult to account for such high secondary isotope effects in any other way except that an incipient phenyl cation is stabilized by hyperconjugation,[31] which is reduced when hydrogen is replaced by deuterium.



5. That the first step is reversible cleavage[32] was demonstrated by the observation that when $\mathrm{Ar}^{15}\overset{\mathrm{H}}{\mathrm{N}}{\equiv}\mathrm{N}$ was the reaction species, recorvered starting

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[25] For additional evidence, see Lorand, J.P. *Tetrahedron Lett.* ***1989***, *30*, 7337.

[26] For a review of aryl cations, see Ambroz, H.B.; Kemp, T.J. *Chem. Soc. Rev.* ***1979***, *8*, 353.

[27] For a monograph, see Stang, P.J.; Rappoport, Z.; Hanack, M.; Subramanian, L.R. *Vinyl Cations*, Academic Press, NY, 1979. For reviews of aryl and/or vinyl cations, see Hanack, M. *Pure Appl. Chem.* ***1984***, *56*, 1819, *Angew. Chem. Int. Ed.* ***1978***, *17*, 333; *Acc. Chem. Res.* ***1976***, *9*, 364; Rappoport, Z. *Reactiv. Intermed.* (*Plenum*) ***1983***, *3*, 427; Ambroz, H.B.; Kemp, T.J. *Chem. Soc. Rev.* ***1979***, *8*, 353; Modena, G.; Tonellato, U. *Adv. Phys. Org. Chem.* ***1971***, *9*, 185; Stang, P.J. *Prog. Org. Chem.* ***1973***, *10*, 205. See also, Charton, M. *Mol. Struct. Energ.* ***1987***, *4*, 271. For a computational study, see Glaser, R.; Horan, C.J.; Lewis, M.; Zollinger, H. *J. Org. Chem.* ***1999***, *64*, 902.

[28] For a review, see Zollinger, H. *Angew. Chem, Int. Ed.* ***1978***, *17*, 141. For discussions, see Swain, C.G.; Sheats, J.E.; Harbison, K.G. *J. Am. Chem. Soc.* ***1975***, *97*, 783, 796; Burri, P.; Wahl, Jr., G.H.; Zollinger, H. *Helv. Chim. Acta* ***1974***, *57*, 2099; Richey Jr., H.G.; Richey, J.M., in Olah, G.A.; Schleyer, P.v.R. *Carbonium Ions*, Vol. 2, Wiley, NY, ***1970***, pp. 922–931; Zollinger, H. *Azo and Diazo Chemistry*, Wiley, NY, ***1961***, pp. 138–142; Miller, J. *Aromatic Nucleophilic Substitution*, Elsevier, NY, ***1968***, pp. 29–40.

[29] Lewis, E.S.; Miller, E.B. *J. Am. Chem. Soc.* ***1953***, *75*, 429.

[30] Swain, C.G.; Sheats, J.E.; Gorenstein, D.G.; Harbison, K.G. *J. Am. Chem. Soc.* ***1975***, *97*, 791.

[31] See Apeloig, Y.; Arad, D. *J. Am. Chem. Soc.* ***1985***, *107*, 5285.

[32] For discussions, see Williams, D.L.H.; Buncel, E. *Isot. Org. Chem.* Vol. 5, Elsevier, Amsterdam, The Netherlands, ***1980***, 147, 212; Zollinger, H. *Pure Appl. Chem.* ***1983***, *55*, 401.

material contained not only $\mathrm{Ar}^{15}\overset{\mathrm{H}}{\mathrm{N}}{\equiv}\mathrm{N}$, but also $\mathrm{Ar}\overset{\mathrm{H}}{\mathrm{N}}{\equiv}{}^{15}\mathrm{N}$.[33,34] This could arise only If the nitrogen breaks away from the ring and then returns. Additional evidence was obtained by treating $\mathrm{Ph}\overset{\mathrm{H}}{\mathrm{N}}{\equiv}{}^{15}\mathrm{N}$ with unlabeled N_2 at various pressures. At 300 atm, the recovered product had lost ~3% of the labeled nitrogen, indicating that PhN_2^+ was exchanging with atmospheric N_2.[34]

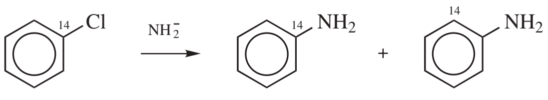
There is kinetic and other evidence[35] that step 1 is more complicated and involves two steps, both reversible:

$$\mathrm{ArN}_2^+ \rightleftharpoons \underset{\mathbf{5}}{[\mathrm{Ar}^+\ \mathrm{N}_2]} \rightleftharpoons \mathrm{Ar}^+ + \mathrm{N}_2$$

Intermediate **5**, which is probably some kind of a tight ion–molecule pair, has been trapped with carbon monoxide.[36]

The Benzyne Mechanism[37]

Some aromatic nucleophilic substitutions are clearly different in character from those that occur by the S_NAr mechanism (or the S_N1 mechanism). These substitutions occur on aryl halides that have no activating groups; bases are required that are stronger than those normally used; and most interesting of all, the incoming group does not always take the position vacated by the leaving group. That the latter statement is true was elegantly demonstrated by the reaction of 1-^{14}C-chlorobenzene with potassium amide:



The product consisted of almost equal amounts of aniline labeled in the 1 position and in the 2 position.[38]

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[33] Lewis, E.S.; Kotcher, P.G. *Tetrahedron* ***1969***, *25*, 4873; Lewis, E.S.; Holliday, R.E. *J. Am. Chem. Soc.* ***1969***, *91*, 426; Tröndlin, F.; Medina, R.; Rüchardt, C. *Chem. Ber.* ***1979***, *112*, 1835.

[34] Bergstrom, R.G.; Landell, R.G.M.; Wahl Jr., G.H.; Zollinger, H. *J. Am. Chem. Soc.* ***1976***, *98*, 3301.

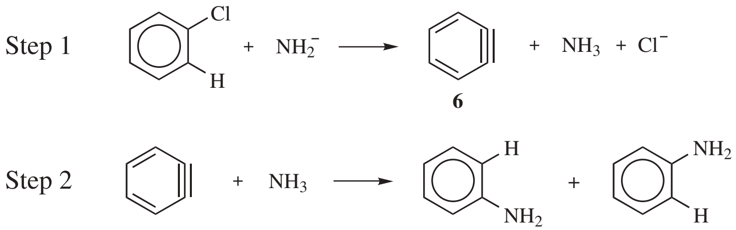
[35] Szele, I.; Zollinger, H. *Helv. Chim. Acta* ***1981***, *64*, 2728.

[36] Ravenscroft, M.D.; Skrabal, P.; Weiss, B.; Zollinger, H. *Helv. Chim. Acta* ***1988***, *71*, 515.

[37] For a monograph, see Hoffmann, R.W. *Dehydrobenzene and Cycloalkynes*, Academic Press, NY, ***1967***. For reviews, see Gilchrist, T.L., in Patai, S.; Rappoport, Z. *The Chemistry of Functional Groups, Supplement C* pt. 1, Wiley, NY, ***1983***, pp. 383–419; Bryce, M.R.; Vernon, J.M. *Adv. Heterocycl. Chem.* ***1981***, *28*, 183; Levin R.H. *React. Intermed.* (*Wiley*) ***1985***, *3*, 1; ***1981***, *2*, 1; ***1978***, *1*, 1; Nefedov, O.M.; D'yachenko, A.I.; Prokof'ev, A.K. *Russ. Chem. Rev.* ***1977***, *46*, 941; Fields, E.K., in McManus, S.P. *Organic Reactive Intermediates*, Academic Press, NY, ***1973***, pp. 449–508; Heaney, H. *Fortschr. Chem. Forsch.* ***1970***, *16*, 35; *Essays Chem.* ***1970***, *1*, 95; Hoffmann, R.W., in Viehe, H.G. *Acetylenes*, Marcel Dekker, NY, ***1969***, pp. 1063–1148; Fields, E.K.; Meyerson, S. *Adv. Phys. Org. Chem.* ***1968***, *6*, 1; Witting, G. *Angew. Chem. Int. Ed.* ***1965***, *4*, 731.

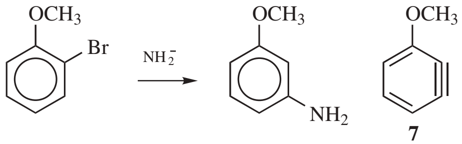
[38] Roberts, J.D.; Semenow, D.A.; Simmons, H.E.; Carlsmith, L.A. *J. Am. Chem. Soc.* ***1965***, *78*, 601.

A mechanism that can explain all these facts involves elimination followed by addition. In step 1, a suitable base removes the ortho hydrogen, with subsequent (or concomitant) loss of the chlorine (leaving group) to



generate symmetrical intermediate **6**[39] is called benzyne (see below).[40] In step 2, benzyne is attacked by the NH_3 at either of two positions, which explains why about half of the aniline produced from the radioactive chlorobenzene was labeled at the 2 position. The fact that the 1 and 2 positions were not labeled equally is the result of a small isotope effect. Other evidence for this mechanism is the following:

1. If the aryl halide contains two ortho substituents, the reaction should not be able to occur. This is indeed the case.[36]
2. It had been known many years earlier that aromatic nucleophilic substitution occasionally results in substitution at a different position. This is called *cine substitution*[41] and can be illustrated by the conversion of *o*-bromoanisole to *m*-aminoanisole.[42] In this particular case, only the meta isomer is



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formed. The reason a 1:1 mixture is not formed is that the intermediate **7** is not symmetrical and the methoxy group directs the incoming group meta, but not ortho (see p. 867). However, not all cine substitutions proceed by this kind of mechanism (see **13-30**).

3. The fact that the order of halide reactivity is Br > I > Cl > F (when the reaction is performed with KNH_2 in liquid NH_3) shows that the S_NAr mechanism is not operating here.[38]

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[39] For a discussion of the structure of *m*- and *p*-benzynes, see Hess, Jr., B.A. *Eur. J. Org. Chem.* ***2001***, 2185.

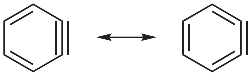
[40] For other methods to generate benzyne, see Kitamura, T.; Meng, Z.; Fujiwara, Y. *Tetrahedron Lett.* ***2000***, *41*, 6611, and references cited therein; Kawabata, H.; Nishino, T.; Nishiyama, Y.; Sonoda, N. *Tetrahedron Lett.* ***2002***, *43*, 4911, and references cited therein.

[41] For a review, see Suwiński, J.; wierczek, K. *Tetrahedron* ***2001***, *57*, 1639.

[42] This example is from Gilman, H.; Avakian, S. *J. Am. Chem. Soc.* ***1945***, *67*, 349. For a table of many such examples, see Bunnett, J.F.; Zahler, R.E. *Chem. Rev.* ***1951***, *49*, 273, p. 385.

In the conversion of the substrate to **7**, either proton removal or subsequent loss of halide ion can be rate determining. In fact, the unusual leaving-group order just mentioned (Br > I > Cl) stems from a change in the rate-determining step. When the leaving group is Br or I, proton removal is rate-determining and the rate order for this step is F > Cl > Br > I. When Cl or F is the leaving group, cleavage of the C–X bond is rate determining and the order for this step is I > Br > Cl > F. Confirmation of the latter order was found in a direct competitive study. *meta*-Dihalobenzenes in which the two halogens are different were treated with $^{-}NH_2$.[43] In such compounds, the most acidic hydrogen is the one between the two halogens; when it leaves, the remaining anion can lose either halogen. Therefore, a study of which halogen is preferentially lost provides a direct measure of leaving-group ability. The order was found to be I > Br > Cl.[43,44]

Species, such as **6** and **7**, are called *benzynes* (sometimes *dehydrobenzenes*), or more generally, *arynes*,[45] and the mechanism is known as the *benzyne mechanism*. Benzynes are very reactive. Neither benzyne nor any other aryne has yet been isolated under ordinary conditions,[46] but benzyne has been isolated in an argon matrix at 8 K,[47] where its IR spectrum could be observed. In addition, benzynes can be trapped; for example, they undergo the Diels–Alder reaction (see **15-60**). Note that the extra pair of electrons does not affect the aromaticity. However, evaluation by a series of aromaticity indicators, including magnetic susceptibility anisotropies and exaltations, nucleus-independent chemical shifts (NICS), and aromatic stabilization energies, and valence-bond Pauling resonance energies point to the *o*-benzyne > *m*-benzyne > *p*-benzyne aromaticity order.[48] The relative order with respect to benzene depends on the aromaticity criterion.[48] The aromtic sextet from the aromatic precursor functions as a closed ring, and the two additional electrons are merely located in a π orbital that covers only two carbons. Benzynes do not have a formal triple bond, since two canonical forms (**A** and **B**) contribute to the hybrid. The IR spectrum, mentioned above, indicates that **A** contributes more than **B**. Not only benzene rings, but other aromatic



A **B**

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[43] Bunnett, J.F.; Kearley, Jr., F.J. *J. Org. Chem.* ***1971***, *36*, 184.

[44] For a discussion of the diminished reactivity of ortho-substituted bromides, see Kalendra, D.M.; Sickles, B.R. *J. Org. Chem.* ***2003***, *68*, 1594.

[45] For the use of arynes in organic synthesis see Pellissier, H.; Santelli, M. *Tetrahedron* ***2003***, *59*, 701.

[46] For the measurement of aryne lifetimes in solution, see Gaviña, F.; Luis, S.V.; Costero, A.M.; Gil, P. *Tetrahedron* ***1986***, *42*, 155.

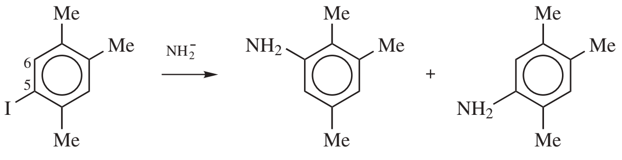
[47] Chapman, O.L.; Mattes, K.; McIntosh, C.L.; Pacansky, J.; Calder, G.V.; Orr, G. *J. Am. Chem. Soc.* ***1973***, *95*, 6134. For the ir spectrum of pyridyne trapped in a matrix, see Nam, H.; Leroi, G.E. *J. Am. Chem. Soc.* ***1988***, *110*, 4096. For spectra of transient arynes, see Berry, R.S.; Spokes, G.N.; Stiles, M. *J. Am. Chem. Soc.* ***1962***, *84*, 3570; Brown, R.D.; Godfrey, P.D.; Rodler, M. *J. Am. Chem. Soc.* ***1986***, *108*, 1296.

[48] DeProft, F.; Schleyer, P.v.R.; van Lenthe, J.H.; Stahl, F.; Geerlings, P. *Chem. Eur. J.* ***2002***, *8*, 3402.

rings[49] and even nonaromatic rings (p. 475) can react through this kind of intermediate. Of course, the non-aromatic rings do have a formal triple bond. When a benzyne unit is fused to a small ring, strain induced regioselectivity observed in its reactions.[50]

The $S_{RN}1$ Mechanism

When 5-iodo-1,2,4-trimethylbenzene **7** was treated with KNH_2 in NH_3, **8** and **10** were formed in the ratio 0.63:1. From what we have already seen, the presence of an unactivated substrate, a strong base, and the occurrence of cine substitution along with normal substitution would be strong indications of a benzyne mechanism. Yet if that were so, the 6-iodo isomer of **8** should have given **9** and **10** in the same ratio (because the same aryne intermediate would be formed in both cases), but in this case the ratio of **9–10** was 5.9:1 (the chloro and bromo analogs did give the same ratio, 1.46:1, showing that the benzyne mechanism may be taking place there).



8 **9** **10**

To explain the iodo result, it has been proposed[51] that besides the benzyne mechanism, this free-radical mechanism is also operating here:

$$ArI \xrightarrow[\text{donor}]{\text{electron}} ArI^{\bullet -} \longrightarrow Ar^{\bullet} + I^-$$

$$Ar^{\bullet} + NH_2^- \longrightarrow ArNH_2^{\bullet -} + ArI \longrightarrow ArNH_2 + ArI^{\bullet -}$$

followed by terminations steps

This is called the $S_{RN}1$ mechanism,[52] and many other examples are known (see **13-3**, **13-4**, **13-6**, **13-14**). The IUPAC designation is $T + D_N + A_N$.[53] Note that the

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[49] For reviews of *hetarynes* (benzyne intermediates in heterocyclic rings), see van der Plas, H.C.; Roeterdink, F., in Patai, S.; Rappoport, Z. *The Chemistry of Functional Groups, Supplement C*, pt. 1, Wiley, NY, ***1983***, pp. 421–511; Reinecke, M.G. *React. Intermed. (Plenum)* ***1982***, *2*, 367; *Tetrahedron* ***1982***, *38*, 427; den Hertog, H.J.; van der Plas, H.C., in Viehe, H.G. *Acetylenes*, Marcel Dekker, NY, ***1969***, pp. 1149–1197, *Adv. Heterocycl. Chem.* ***1971***, *40*, 121; Kauffmann, T.; Wirthwein, R. *Angew. Chem, Int. Ed.* ***1971***, *10*, 20; Kauffmann, T. *Angew. Chem, Int. Ed.* ***1965***, *4*, 543; Hoffmann, R.W. *Dehydrobenzene and Cycloalkynes*, Academic Press, NY, ***1967***, pp. 275–309.

[50] Hamura, T.; Ibusuki, Y.; Sato, K.; Matsumoto, T.; Osamura, Y.; Suzuki, K. *Org. Lett.* ***2003***, *5*, 3551.

[51] Kim, J.K.; Bunnett, J.F. *J. Am. Chem. Soc.* ***1970***, *92*, 7463, 7464.

[52] For a monograph, see Rossi, R.A.; de Rossi, R.H. *Aromatic Substitution by the $S_{RN}1$ Mechanism*, American Chemical Society, Washington, 1983. For reviews, see Savéant, J. *Adv. Phys. Org. Chem.* ***1990***, *26*, 1; Russell, G.A. *Adv. Phys. Org. Chem.* ***1987***, *23*, 271; Norris, R.K. in Patai, S. Rappoport, Z. *The Chemistry of Functional Groups, Supplement D*, pt. 1, Wiley, NY, ***1983***, pp. 681–701; Chanon, M.; Tobe, M.L. *Angew. Chem, Int. Ed.* ***1982***, *21*, 1; Rossi, R.A. *Acc. Chem. Res.* ***1982***, *15*, 164; Beletskaya, I.P.; Drozd, V.N. *Russ. Chem. Rev.* ***1979***, *48*, 431; Bunnett, J.F. *Acc. Chem. Res.* ***1978***, *11*, 413; Wolfe, J.F.; Carver, D.R. *Org. Prep. Proced. Int.* ***1978***, *10*, 225. For a review of this mechanism with aliphatic substrates, see Rossi, R.A.; Pierini, A.B.; Palacios, S.M. *Adv. Free Radical Chem.* (*Greenwich, Conn.*) ***1990***, *1*, 193. For 'thermal' $S_{RN}1$ reactions, see Costentin, C.; Hapiot, P.; Médebielle, M.; Savéant, J.-M. *J. Am. Chem. Soc.* ***1999***, *121*, 4451.

[53] The symbol T is used for electron transfer.

last step of the mechanism produces $ArI^{\bullet -}$ radical ions, so the process is a chain mechanism (see p. 936).[54] An electron donor is required to initiate the reaction. In the case above it was solvated electrons from KNH_2 in NH_3. Evidence was that the addition of potassium metal (a good producer of solvated electrons in ammonia) completely suppressed the cine substitution. Further evidence for the $S_{RN}1$ mechanism was that addition of radical scavengers (which would suppress a free-radical mechanism) led to **9:10** ratios much closer to 1.46:1. Numerous other observations of $S_{RN}1$ mechanisms that were stimulated by solvated electrons and inhibited by radical scavengers have also been recorded.[55] Further evidence for the $S_{RN}1$ mechanism in the case above was that some 1,2,4-trimethylbenzene was found among the products. This could easily be formed by abstraction by $Ar^\bullet$ of H from the solvent NH_3. Besides initiation by solvated electrons,[56] $S_{RN}1$ reactions have been initiated photochemically,[57] electrochemically,[58] and even thermally.[59]

The $S_{RN}1$ reactions have a fairly wide scope. The efficiency of the reaction has been traced to the energy level of the radical anion of the substitution product.[60] There is no requirement for activating groups or strong bases, but in DMSO haloarenes are less reactive as the stability of the anion increases.[61] The reaction has also been done in liquid ammonia, promoted by ultrasound (p. 349),[62] and ferrous ion has been used as a catalyst.[63] Alkyl, alkoxy, aryl, and COO^- groups do not interfere, although Me_2N, O^-, and NO_2 groups do interfere. Cine substitution is not found.

Other Mechanisms

There is no clear-cut proof that a one-step S_N2 mechanism, so important at a saturated carbon, ever actually occurs with an aromatic substrate. The hypothetical aromatic S_N2 process is sometimes called the *one-stage* mechanism to distinguish it from the *two-stage* S_NAr mechanism. A "clean" example of a $S_{RN}2$ reaction has been reported, the conversion of **11** to **12** in methanol.[64] Both the $S_{RN}1$ and $S_{RN}{}^2$ reactions have been reviewed.[65]

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[54] For a discussion, see Amatore, C.; Pinson, J.; Savéant, J.; Thiébault, A. *J. Am. Chem. Soc.* ***1981***, *103*, 6930.

[55] Bunnett, J.F. *Acc. Chem. Res.* ***1978***, *11*, 413.

[56] Savéant, J.-M. *Tetrahedron* ***1994***, *50*, 10117.

[57] For reviews of photochemical aromatic nucleophilic substitutions, see Cornelisse, J.; de Gunst, G.P.; Havinga, E. *Adv. Phys. Org. Chem.* ***1975***, *11*, 225; Cornelisse, J. *Pure Appl. Chem.* ***1975***, *41*, 433; Pietra, F. *Q. Rev. Chem. Soc.* ***1969***, *23*, 504, p. 519.

[58] For a review, see Savéant, J. *Acc. Chem. Res.* ***1980***, *13*, 323. See also, Alam, N.; Amatore, C.; Combellas, C.; Thiébault, A.; Verpeaux, J.N. *J. Org. Chem.* ***1990***, *55*, 6347.

[59] Swartz, J.E.; Bunnett, J.F. *J. Org. Chem.* ***1979***, *44*, 340, and references cited therein.

[60] Galli, C.; Gentili, P.; Guarnieri, A. *Gazz. Chim. Ital.*, ***1995***, *125*, 409.

[61] Borosky, G.L.; Pierini, A.B.; Rossi, R.A. *J. Org. Chem.* ***1992***, *57*, 247.

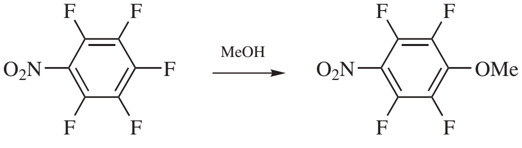
[62] Manzo, P.G.; Palacios, S.M.; Alonso, R.A. *Tetrahedron Lett.* ***1994***, *35*, 677.

[63] Galli, C.; Gentili, P.; *J. Chem. Soc. Perkin Trans. 2* ***1993***, 1135.

[64] Marquet, J.; Jiang, Z.; Gallardo, I.; Batlle, A.; Cayón, E. *Tetrahedron Lett.* ***1993***, *34*, 2801. Also see, Keegstra, M.A. *Tetrahedron* ***1992***, *48*, 2681.

[65] Rossi, R.A.; Palacios, S.M. *Tetrahedron* ***1993***, *49*, 4485.

Some of the reactions in this chapter operate by still other mechanisms, among them an addition–elimination mechanism (see **13-17**). A new mechanism has been reported in aromatic chemistry, a reductively activated 'polar' nucleophilic aromatic substitution.[66] The reaction of phenoxide with *p*-dinitrobenzene in DMF shows radical features that cannot be attributed to a radical anion, and it is not $S_{RN}2$. The new designation was proposed to account for these results.



11 **12**

REACTIVITY

The Effect of Substrate Structure

In the discussion of electrophilic aromatic substitution (Chapter 11) equal attention was paid to the effect of substrate structure on reactivity (activation or deactivation) and on orientation. The question of orientation was important because in a typical substitution there are four or five hydrogens that could serve as leaving groups. This type of question is much less important for aromatic nucleophilic substitution, since in most cases there is only one potential leaving group in a molecule. Therefore attention is largely focused on the reactivity of one molecule compared with another and not on the comparison of the reactivity of different positions within the same molecule.

S_NAr Mechanism. These substitutions are accelerated by electron-withdrawing groups, especially in positions ortho and para to the leaving group[67] and hindered by electron-attracting groups. This is, of course, opposite to the effects of these groups on electrophilic substitutions, and the reasons are similar to those discussed in Chapter 11 (p. 660). Table 13.1 contains a list of groups arranged approximately in order of activating or deactivating ability.[68] Nitrogen atoms are also strongly activating (especially to the α and γ positions) and are even more so when quaternized.[69] Both 2- and 4-chloropyridine, for example, are often used as substrates. Heteroaromatic amine *N*-oxides are readily attacked by nucleophiles in the 2 and 4 positions, but the oxygen is generally lost in these reactions.[70]

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[66] Marquet, J.; Casado, F.; Cervera, M.; Espín, M.; Gallardo, I.; Mir, M.; Niat, M. *Pure Appl. Chem.* ***1995***, *67*, 703.

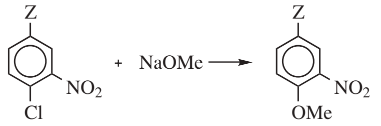
[67] The effect of meta substituents has been studied much less, but it has been reported that here too, electron-withdrawing groups increase the rate: See Nurgatin, V.V.; Sharnin, G.P.; Ginzburg, B.M. *J. Org. Chem, USSR* ***1983***, *19*, 343.

[68] For additional tables of this kind, see Miller, J. *Aromatic Nucleophilic Substitution*, Elsevier, NY, ***1968***, pp. 61–136.

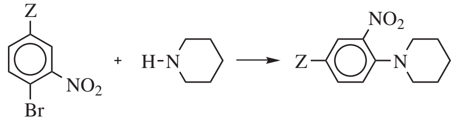
[69] Miller, J.; Parker, A.J. *Aust. J. Chem.* ***1958***, *11*, 302.

[70] Berliner, E.; Monack, L.C. *J. Am. Chem. Soc.* ***1952***, *74*, 1574.

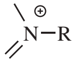
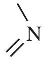
TABLE 13.1. Groups Listed in Approximate Descending Order of Activating Ability in the S_NAr Mechanism[68]



at 0°C[71] (*a*)[a]



at 25°C[72] (*a*)[a]

Comments[b]	Group Z	Relative Rate of Reaction (*a*) H = 1[69]	 (*b*) NH_2 = 1[70]
Activates halide exchange at room temperature	N_2^+		
Activates reaction with strong nucleophiles at room temperature	 (heterocyclic)		
Activate reactions with strong nucleophiles at 80–100°C	NO	5.22 × 10^6	
	NO_2	6.73 × 10^5	Very fast
	 (heterocyclic)		
With nitro also present, activate reactions with strong nucleophiles at room temperature	SO_2Me		
	NMe_3^+		
	CF_3		
	CN	3.81 × 10^4	
	CHO	2.02 × 10^4	
With nitro also present, activate reactions with strong nucleophiles at 40–60°C	COR		
	COOH		
	SO_3^-		
	Br		6.31 × 10^4
	Cl		4.50 × 10^4
	I		4.36 × 10^4
	COO^-		2.02 × 10^4
	H		8.06 × 10^3
	F		2.10 × 10^3
	CMe_3		1.37 × 10^3
	Me		1.17 × 10^3

(*continued*)

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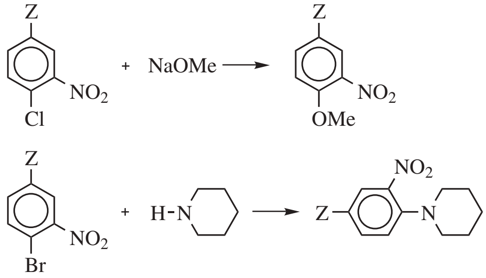
[71] For reviews of reactivity of nitrogen-containing heterocycles, see Illuminati, G. *Adv. Heterocycl. Chem.* ***1964***, *3*, 285; Shepherd, R.G.; Fedrick, J.L. *Adv. Heterocycl. Chem.* ***1965***, *4*, 145.

[72] For reviews, see Albini, A.; Pietra, S. *Heterocyclic N-Oxides*; CRC Press: Boca Raton, FL, ***1991***, pp. 142–180; Katritzky, A.R.; Lagowski, J.M. *Chemistry of the Heterocyclic N-Oxides*, Academic Press, NY, ***1971***, pp. 258–319, 550–553.

TABLE 13.1. (*Continued*)



at 0°C[71] *(a)*

at 25°C[72] *(a)*

Comments[b]	Group Z	Relative Rate of Reaction (*a*) H = 1[69]	 (*b*) NH_2 = 1[70]
	OMe		145
	NMe_2		9.77
	OH		4.70
	NH_2		1

[a] For reaction (*a*) the rates are relative to **H**; *for (b)* they are relative to NH_2.
[b] The comments on the left column are from Ref. 73.

The most highly activating group, N_2^+, is seldom deliberately used to activate a reaction, but it sometimes happens that in the diazotization of a compound, such as *p*-nitroaniline or *p*-chloroaniline, the group para to the diazonium group is replaced by OH from the solvent or by X from $ArN_2^+ X^-$, to the surprise and chagrin of the investigator, who was trying only to replace the diazonium group and to leave the para group untouched. By far, the most common activating group is the nitro group and the most common substrates are 2,4-dinitrophenyl halides and 2,4,6-trinitrophenyl halides (also called picryl halides).[74] Polyfluorobenzenes[75] (e.g., C_6F_6), also undergo aromatic nucleophilic substitution quite well.[76] Benzene rings that lack activating substituents are generally not useful substrates for the S_NAr mechanism, because the two extra electrons in **1** are in an antibonding orbital (p. 34). Activating groups, by withdrawing electron density, are able to stabilize the intermediates and the

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[73] Bunnett, J.F.; Zahler, R.E. *Chem. Rev.* ***1951***, *49*, 273, p. 308.

[74] For a review of the activating effect of nitro groups, see de Boer, T.J.; Dirkx, I.P., in Feuer, H. *The Chemistry of the Nitro and Nitroso Groups*, pt. 1, Wiley, NY, ***1970***, pp. 487–612.

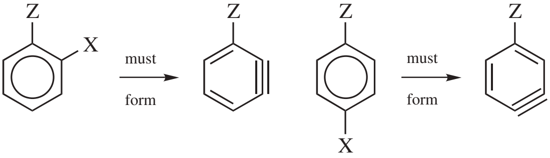
[75] Fluorine significantly activates ortho and meta positions, and slightly deactivates (see Table 13.1) para positions: Chambers, R.D.; Seabury, N.J.; Williams, D.L.H.; Hughes, N. *J. Chem. Soc. Perkin Trans. 1* ***1988***, 255.

[76] For reviews, see Yakobson, G.G.; Vlasov, V.M. *Synthesis* ***1976***, 652; Kobrina, L.S. *Fluorine Chem. Rev.* ***1974***, *7*, 1.

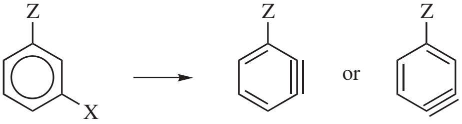
transition states leading to them. Reactions taking place by the S_NAr mechanism are also accelerated when the aromatic ring is coordinated with a transition metal.[77]

Just as electrophilic aromatic substitutions were found more or less to follow the Hammett relationship (with σ^+ instead of σ; see p. 402), so do nucleophilic substitutions, with σ^- instead of σ for electron-withdrawing groups.[78]

Benzyne Mechanism. Two factors affect the position of the incoming group, the first being the direction in which the aryne forms.[79] When there are groups ortho or para to the leaving group, there is no choice:



but when a meta group is present, the aryne can form in two different ways:



In such cases, the more acidic hydrogen is removed. Since acidity is related to the field effect of Z, it can be stated that an electron-attracting Z favors removal of the ortho hydrogen while an electron-donating Z favors removal of the para hydrogen. The second factor is that the aryne, once formed, can be attacked at two positions. The favored position for nucleophilic attack is the one that leads to the more stable carbanion intermediate, and this in turn also depends on the field effect of Z. For *-I* groups, the more stable carbanion is the one in which the negative charge is closer to the substituent. These principles are illustrated by the reaction of the three dichlorobenzenes (**13-15**) with alkali-metal

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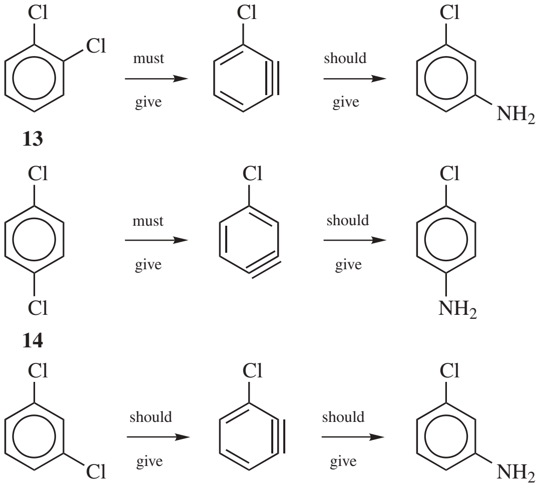
[77] For a review, see Balas, L.; Jhurry, D.; Latxague, L.; Grelier, S.; Morel, Y.; Hamdani, M.; Ardoin, N.; Astruc, D. *Bull. Soc. Chim. Fr.* ***1990***, 401. For a discussion of iron assisted nucleophilic aromatic substitution on the solid phase, see Ruhland, T.; Bang, K.S.; Andersen, K. *J. Org. Chem.* ***2002***, *67*, 5257.

[78] For a discussion of linear free-energy relationships in this reaction, see Bartoli, G.; Todesco, P.E. *Acc. Chem. Res.* ***1977***, *10*, 125. For a list of σ^- values, see Table 9.4 on p. 404.

[79] This analysis is from Roberts, J.D.; Vaughan, C.W.; Carlsmith, L.A.; Semenow, D.A. *J. Am. Chem. Soc.* ***1956***, *78*, 611. For a discussion, see Hoffmann, R.W. *Dehydrobenzene and Cycloalkynes*, Academic Press, NY, ***1973***, pp. 134–150.

amides to give the predicted products shown.



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14

15

In each case, the predicted product was the one chiefly formed.[80] The observation that *m*-aminoanisole is obtained, mentioned on p. 860, is also in accord with these predictions.

The Effect of the Leaving Group[81]

The common leaving groups in aliphatic nucleophilic substitution (halide, sulfate, sulfonate, NR_3^+, etc.) are also common leaving groups in aromatic nucleophilic substitutions, but the groups NO_2, OR, OAr, SO_2R,[82] and SR, which are not generally lost in aliphatic systems, *are* leaving groups when attached to aromatic rings. Surprisingly, NO_2 is a particularly good leaving group.[83] An approximate order of leaving-group ability is[84] $F > NO_2 > OTs > SOPh > Cl,\ Br,\ I > N_3 > NR_3^+ >$ OAr, OR, SR, NH_2. However, this depends greatly on the nature of the nucleophile, as illustrated by the fact that $C_6Cl_5OCH_3$ treated with NH_2^- gives mostly $C_6Cl_5NH_2$; that is, one methoxy group is replaced in preference to five chlorines.[85] As usual, OH can be a leaving group if it is converted to an inorganic ester. Among

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[80] Wotiz, J.H.; Huba, F. *J. Org. Chem.* ***1959***, *24*, 595. Eighteen other reactions also gave products predicted by these principles. See also, Caubere, P.; Lalloz, L. *Bull. Soc. Chim. Fr.* ***1974***, 1983, 1989, 1996; Biehl, E.R.; Razzuk, A.; Jovanovic, M.V.; Khanapure, S.P. *J. Org. Chem.* ***1986***, *51*, 5157.

[81] For a review, see Miller, J. *Aromatic Nucleophilic Substitution*, Elsevier, NY, ***1968***, pp. 137–179.

[82] See, for example, Furukawa, N.; Ogawa, S.; Kawai, T.; Oae, S. *J. Chem. Soc. Perkin Trans. 1* ***1984***, 1839.

[83] For a review, see Beck, J.R. *Tetrahedron* ***1978***, *34*, 2057. See also, Effenberger, F.; Koch, M.; Streicher, W. *Chem. Ber.* ***1991***, *24*, 163.

[84] Loudon, J.D.; Shulman, N. *J. Chem. Soc.* ***1941***, 772; Suhr, H. *Chem. Ber.* ***1963***, *97*, 3268.

[85] Kobrina, L.S.; Yakobson, G.G. *J. Gen. Chem. USSR* ***1963***, *33*, 3238.

the halogens, fluoro is generally a much better leaving group than the other halogens, which have reactivities fairly close together. The order is usually Cl > Br > I, but not always.[86] The leaving-group order is quite different from that for the S_N1 or S_N2 mechanisms. The most likely explanation is that the first step of the S_NAr mechanism is usually rate determining, and this step is promoted by groups with strong *–I* effects. This would explain why fluoro and nitro are such good leaving groups when this mechanism is operating. Fluoro is the poorest leaving group of the halogens when the second step of the S_NAr mechanism is rate determining or when the benzyne mechanism is operating. The four halogens, as well as SPh, NMe_3^+, and $OPO(OEt)_2$, have been shown to be leaving groups in the $S_{RN}1$ mechanism.[55] The only important leaving group in the S_N1 mechanism is N_2^+.

The Effect of the Attacking Nucleophile[87]

It is not possible to construct an invariant nucleophilicity order because different substrates and different conditions lead to different orders of nucleophilicity, but an overall approximate order is $^-NH_2 > Ph_3C^- > PhNH^-$ (aryne mechanism) $> ArS^- > RO^{\neq} > R_2NH > ArO^- > {}^-OH > ArNH_2 > NH_3 > I^- > Br^- > Cl^- > H_2O > ROH$.[88] As with aliphatic nucleophilic substitution, nucleophilicity is generally dependent on base strength and nucleophilicity increases as the attacking atom moves down a column of the periodic table, but there are some surprising exceptions, for example, ^-OH, a stronger base than ArO^-, is a poorer nucleophile.[89] In a series of similar nucleophiles, such as substituted anilines, nucleophilicity *is* correlated with base strength. Oddly, the cyanide ion is not a nucleophile for aromatic systems, except for sulfonic acid salts and in the von Richter (**13-30**) and Rosenmund-von Braun (**13-8**) reactions, which are special cases.

REACTIONS

In the first part of this section, reactions are classified according to attacking species, with all leaving groups considered together, except for hydrogen and N_2^+, which are treated subsequently. Finally, a few rearrangement reactions are discussed.

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[86] Reinheimer, J.D.; Taylor, R.C.; Rohrbaugh, P.E. *J. Am. Chem. Soc.* ***1961***, *83*, 835; Ross, S.D. *J. Am. Chem. Soc.* ***1959***, *81*, 2113; Bunnett, J.F.; Garbisch Jr., E.W.; Pruitt, K.M. *J. Am. Chem. Soc.* ***1957***, *79*, 385; Parker, R.E.; Read, T.O. *J. Chem. Soc.* ***1962***, 9, 3149; Litvinenko, L.M.; Shpan'ko, L.V.; Korostylev, A.P. *Doklad. Chem.* ***1982***, *266*, 309.

[87] For a review, see Miller, J. *Aromatic Nucleophilic Substitution*, Elsevier, NY, ***1968***, pp. 180–233.

[88] This list is compiled from data, in Bunnett, J.F. ; Zahler, R.E. *Chem. Rev.* ***1951***, *49*, 273, p. 340; Bunnett, J.F. *Q. Rev. Chem. Soc.* ***1958***, *12*, 1, p. 13; Sauer, J.; Huisgen, R. *Angew. Chem.* ***1960***, *72*, 294, p. 311; Bunnett, J.F. *Annu. Rev. Phys. Chem.* ***1963***, *14*, 271.

[89] For studies of nucleophilicity in the $S_{RN}1$ mechanism, see Amatore, C.; Combellas, C.; Robveille, S.; Savéant, J.; Thiébault, A. *J. Am. Chem. Soc.* ***1986***, *108*, 4754, and references cited therein.

ALL LEAVING GROUPS EXCEPT HYDROGEN AND N_2^+

A. Oxygen Nucleophiles

13-1 Hydroxylation of Aromatic Compounds

Hydroxy-de-halogenation

$$\mathrm{ArBr} + \mathrm{OH}^- \longrightarrow \mathrm{ArOH}$$

Aryl halides are converted to phenols if activating groups are present or if exceedingly strenuous conditions are employed.[90] When the reaction is carried out at high temperatures, cine substitution is observed, indicating a benzyne mechanism.[91] The reaction has been done using NaOH on Montmorillonite K10 and $AgNO_3$ with microwave irradiation.[92]

A slightly related reaction involves the amino group of naphthylamines can be replaced by a hydroxyl group by treatment with aqueous bisulfite.[93] The scope is greatly limited; the amino group (which may be NH_2 or NHR) must be on a naphthalene ring, with very few exceptions. The reaction is reversible (see **13-6**), and both the forward and reverse reactions are called the *Bucherer reaction*.

$$\mathrm{ArMgX} \xrightarrow{\mathrm{B(OMe)_3}} \mathrm{ArB(OMe)_2} \xrightarrow[\mathrm{H_2O_2}]{\mathrm{H^+}} \mathrm{ArOH}$$

An indirect method for conversion of an aryl halide to a phenol involves initial conversion to an organometallic, followed by oxidation to the phenol. For the conversion of aryl Grignard reagents to phenols, a good procedure is the use of trimethyl borate followed by oxidation with H_2O_2 in acetic acid[94] (see **12-31**). Phenols have been obtained from unactivated aryl halides by treatment with borane and a metal such as lithium, followed by oxidation with alkaline H_2O_2.[95] Arylboronic acids, $ArB(OH)_2$, are oxidized by aqueous hydrogen peroxide to give the corresponding phenol.[96] The reaction of an aromatic compound with a borane in the

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[90] For a review of $^-$OH and $^-$OR as nucleophiles in aromatic substitution, see Fyfe, C.A., in Patai, S. *The Chemistry of the Hydroxyl Group*, pt. 1, Wiley, NY, ***1971***, pp. 83–124.

[91] The benzyne mechanism for this reaction is also supported by ^{14}C labeling experiments: Bottini, A.T.; Roberts, J.D. *J. Am. Chem. Soc.* ***1957***, *79*, 1458; Dalman, G.W.; Neumann, F.W. *J. Am. Chem. Soc.* ***1968***, *90*, 1601.

[92] Hashemi, M.M.; Akhbari, M. *Synth. Commun.* ***2004***, *34*, 2783.

[93] For reviews, see Seeboth, H. *Angew. Chem, Int. Ed.* ***1967***, *6*, 307; Gilbert, E.E. *Sulfonation and Related Reactions*; Wiley, NY, ***1965***, pp. 166–169.

[94] Hawthorne, M.F. *J. Org. Chem.* ***1957***, *22*, 1001. For other procedures, see Lewis, N.J.; Gabhe, S.Y. *Aust. J. Chem.* ***1978***, *31*, 2091; Hoffmann, R.W.; Ditrich, K. *Synthesis* ***1983***, 107.

[95] Pickles, G.M.; Thorpe, F.G. *J. Organomet. Chem.* ***1974***, *76*, C23.

[96] Simon, J.; Salzbrunn, S.; Prakash, G.K.S.; Petasis, N.A.; Olah, G.A. *J. Org. Chem.* ***2001***, *66*, 633.

presence of an iridium catalyst, followed by oxidation with aqueous Oxone® gave the corresponding phenol.[97] Aryllithium reagents have been converted to phenols by treatment with oxygen.[98]In a related indirect method, arylthallium bis(trifluoroacetates) (prepared by **12-23**) can be converted to phenols by treatment with lead tetraacetate followed by triphenylphosphine and then dilute NaOH.[99] Diarylthallium trifluoroacetates undergo the same reaction.[100]

OS **I**, 455; **II**, 451; **V**, 632. Also see, OS **V**, 918.

13-2 Alkali Fusion of Sulfonate Salts

Oxido-de-sulfonato-substitution

$$ArSO_3^- \xrightarrow[300\text{–}320°C]{\text{NaOH fusion}} ArO^-$$

Aryl sulfonic acids can be converted, through their salts, to phenols, by alkali fusion. In spite of the extreme conditions, the reaction gives fairly good yields, except when the substrate contains other groups that are attacked by alkali at the fusion temperatures. Milder conditions can be used when the substrate contains activating groups, but the presence of deactivating groups hinders the reaction. The mechanism is obscure, but a benzyne intermediate has been ruled out by the finding that cine substitution does not occur.[101]

OS **I**, 175; **III**, 288.

13-3 Replacement by OR or OAr

Alkoxy-de-halogenation

$$ArBr + OR^- \longrightarrow ArOR$$

This reaction is similar to **13-1** and, like that one, generally requires activated substrates.[90,102] With unactivated substrates, side reactions predominate, though aryl methyl ethers have been prepared from unactivated chlorides by treatment with MeO^- in HMPA.[103] This reaction gives better yields than **13-1** and is

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[97] Maleczka Jr., R.E.; Shi, F.; Holmes, D.; Smith III, M.R. *J. Am. Chem. Soc.* ***2003***, *125*, 7792.

[98] Parker, K.A.; Koziski, K.A. *J. Org. Chem.* ***1987***, *52*, 674. For other reagents, see Taddei, M.; Ricci, A. *Synthesis* ***1986***, 633; Einhorn, J.; Luche, J.; Demerseman, P. *J. Chem. Soc. Chem. Commun.* ***1988***, 1350.

[99] Taylor, E.C.; Altland, H.W.; Danforth, R.H.; McGillivray, G.; McKillop, A. *J. Am. Chem. Soc.* ***1970***, *92*, 3520.

[100] Taylor, E.C.; Altland, H.W.; McKillop, A. *J. Org. Chem.* ***1975***, *40*, 2351.

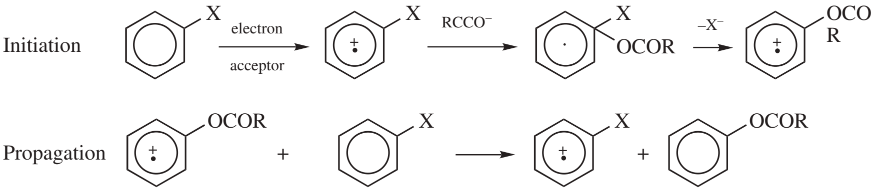
[101] Buzbee, L.R. *J. Org. Chem.* ***1966***, *31*, 3289; Oae, S.; Furukawa, N.; Kise, M.; Kawanishi, M. *Bull. Chem. Soc. Jpn.* ***1966***, *39*, 1212.

[102] See Gujadhur, R.; Venkataraman, D. *Synth. Commun.* ***2001***, *31*, 2865.

[103] Shaw, J.E.; Kunerth, D.C.; Swanson, S.B. *J. Org. Chem.* ***1976***, *41*, 732; Testaferri, L.; Tiecco, M.; Tingoli, M.; Chianelli, D.; Montanucci, M. *Tetrahedron* ***1983***, *39*, 193.

used more often. A good solvent is liquid ammonia. Aryl chlorides react with phenol and KOH with microwave irradiation to give the diaryl ether.[104] Potassium phenoxide reacts with iodobenzene in an ionic solvent at 100°C with CuCl.[105] The NaOMe reacted with *o*- and *p*-fluoronitrobenzenes $\sim 10^9$ times faster in NH_3 at −70°C than in MeOH.[106] Phase-transfer catalysis has also been used.[107] Phenols reacted with aryl fluorides with K_2CO_3/DMSO[108] or aryl chlorides with KOH,[109] with microwave irradiation, to give the diaryl ether. Aryl carbonates react with aryl oxides.[110] Phenolic compounds react with aryl fluorides in the presence of LiOH in DMF to give the diaryl ether.[111] Aryl iodides react with phenols in the presence of K_2CO_3, CuI and Raney nickel alloy.[112]

In addition to halides, leaving groups can be other OR, and so on, even OH.[113] Acid salts, $RCOO^-$, are sometimes used as nucleophiles. Good yields of aryl benzoates can be obtained by the treatment of aryl halides with cuprous benzoate in diglyme or xylene at 140–160°C.[114] Unactivated substrates have been converted to carboxylic esters in low-to-moderate yields under oxidizing conditions.[115] The following chain mechanism, called the $S_{ON}2$ mechanism,[116] has been suggested:[115]



For aroxide nucleophiles, the reaction is promoted by copper salts,[117] and when these are used, activating groups need not be present. Indeed, unactivated aryl

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[104] Rebeiro, G.L.; Khadilkar, B.M. *Synth. Commun.* ***2003***, *33*, 1405.

[105] In bmim BF_4, 1-butyl-3-methylimidazolium tetrafluoroborate: Chauhan, S.M.S.; Jain, N.; Kumar, A.; Srinivas, K.A. *Synth. Commun.* ***2003***, *33*, 3607.

[106] Kizner, T.A.; Shteingarts, V.D. *J. Org. Chem, USSR* ***1984***, *20*, 991.

[107] Artamanova, N.N.; Seregina, V.F.; Shner, V.F.; Salov, B.V.; Kokhlova, V.M.; Zhdamarova, V.N. *J. Org. Chem, USSR* ***1989***, *25*, 554.

[108] Li, F.; Wang, Q.; Ding, Z.; Tao, F. *Org. Lett.* ***2003***, *5*, 2169.

[109] Chaouchi, M.; Loupy, A.; Marque, S.; Petit, A. *Eur. J. Org. Chem.* ***2002***, 1278.

[110] Castro, E.A.; Pavez, P.; Santos, J.G. *J. Org. Chem.* ***2001***, *66*, 3129.

[111] Ankala, S.V.; Fenteany, G. *Synlett* ***2003***, 825.

[112] Xu, L.-W.; Xia, C.-G.; Li, J.-W.; Hu, X.-X. *Synlett* ***2003***, 2071.

[113] Oae, S.; Kiritani, R. *Bull. Chem. Soc. Jpn.* ***1964***, *37*, 770; ***1966***, *39*, 611.

[114] Cohen, T.; Wood, J.; Dietz Jr., A.G. *Tetrahedron Lett.* ***1974***, 3555.

[115] Jönsson, L.; Wistrand, L. *J. Org. Chem.* ***1984***, *49*, 3340.

[116] First proposed by Alder, R.W. *J. Chem. Soc. Chem. Commun.* ***1980***, 1184.

[117] For a review of copper-assisted aromatic nucleophilic substitution, see Lindley, J. *Tetrahedron* ***1984***, *40*, 1433. For other examples, see Marcoux, J.-F.; Doye, S.; Buchwald, S.L. *J. Am. Chem. Soc.* ***1997***, *119*, 10539; Ma, D.; Cai, Q. *Org. Lett.* ***2003***, *5*, 3799.

halides, such as 4-iodoanisole, were coupled to allylic alcohols using a CuI catalyst in the presence of 2% 1,10-phenanthroline and cesium carbonate.[118] This method of preparation of diaryl ethers is called the *Ullmann ether synthesis*[119] and should not be confused with the Ullmann biaryl synthesis (**13-11**). The reactivity order is typical of nucleophilic substitutions, despite the presence of the copper salts.[120] Because aryloxycopper(I) reagents ArOCu react with aryl halides to give ethers, it has been suggested that they are intermediates in the Ullmann ether synthesis.[121] Indeed, high yields of ethers can be obtained by reaction of ROCu or ArOCu with aryl halides.[122] Alcohols, via the alkoxide, displace the halogen group in aryl halides to give aryl ethers in the presence of a palladium catalyst.[123] A palladium catalyzed, intramolecular displacement of an aryl halide with a pendant alkoxide unit leads to dihydrobenzofurans.[124] Nickel catalysts have also been used.[125] The reaction has been done by heating aryl iodides and phenols in an ionic liquid.[126]

Unactivated substrates also react with phenoxide ion with electrochemical catalysis in liquid NH_3–Me_2SO, to give diaryl ethers, presumably by the $S_{RN}1$ mechanism.[127] Diaryl ethers can be prepared from activated aryl halides by treatment with a triaryl phosphate, $(ArO)_3PO$.[128]

OS **I**, 219; **II**, 445; **III**, 293, 566; **V**, 926; **VI**, 150; **X**, 418.

B. Sulfur Nucleophiles

13-4 Replacement by SH or SR

Mercapto-de-halogenation $\mathrm{ArBr} + \mathrm{SH}^- \longrightarrow \mathrm{ArSH}$

Alkylthio-de-halogenation $\mathrm{ArBr} + \mathrm{SR}^- \longrightarrow \mathrm{ArSR}$

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[118] Wolter, M.; Nordmann, G.; Job, G.E.; Buchwald, S.L. *Org. Lett.* ***2002***, *4*, 973.

[119] For reviews of the Ullmann ether synthesis see Moroz, A.A.; Shvartsberg, M.S. *Russ. Chem. Rev.* ***1974***, *43*, 679; Kunz, K.; Scholz, U.; Ganzer, D. *Synlett* ***2003***, 2428.

[120] Weingarten, H. *J. Org. Chem.* ***1964***, *29*, 977, 3624.

[121] Kawaki, T.; Hashimoto, H. *Bull. Chem. Soc. Jpn.* ***1972***, *45*, 1499.

[122] Whitesides, G.M.; Sadowski, J.S.; Lilburn, J. *J. Am. Chem. Soc.* ***1974***, *96*, 2829.

[123] Parrish, C.A.; Buchwald, S.L. *J. Org. Chem.* ***2001***, *66*, 2498; Torraca, K.E.; Huang, X.; Parrish, C.A.; Buchwald, S.L. *J. Am. Chem. Soc.* ***2001***, *123*, 10770.

[124] Kuwabe, S.-i.; Torraca, K.E.; Buchwald, S.L. *J. Am. Chem. Soc.* ***2001***, *123*, 12202.

[125] Mann, G.; Hartwig, J.F. *J. Org. Chem.* ***1997***, *62*, 5413.

[126] In bmiI, 1-butyl-3-methylimidazolium iodide: Luo, Y.; Wu, J.X.; Ren, R.X. *Synlett* ***2003***, 1734.

[127] Alam, N.; Amatore, C.; Combellas, C.; Pinson, J.; Savéant, J.; Thiébault, A.; Verpeaux, J. *J. Org. Chem.* ***1988***, *53*, 1496.

[128] Ohta, A.; Iwasaki, Y.; Akita, Y. *Synthesis* ***1982***, 828. For other procedures, see Bates, R.B.; Janda, K.D. *J. Org. Chem.* ***1982***, *47*, 4374; Sammes, P.G.; Thetford, D.; Voyle, M. *J. Chem. Soc. Perkin Trans. 1* ***1988***, 3229.

Aryl thiols and thioethers can be prepared by reactions that are similar to **13-1** and **13-3**.[129] Activated aryl halides generally give good results, but side reactions are occasionally important. Some reagents give the thiol directly. 4-bromonitrobenzene reacts with Na_3SPO_3, in refluxing methanol, to give 4-nitrothiophenol.[130] Diaryl sulfides can be prepared by the use of ^{-}SAr.[131] Even unactivated aryl halides react with ^{-}SAr if polar aprotic solvents, for example, DMF,[132] DMSO[133] 1-methyl-2-pyrrolidinone,[134] or HMPA,[135] are used, though the mechanisms are still mostly or entirely nucleophilic substitution. 2-Iodothiophene reacts directly with thiophenol to give 2-phenylthiothiophene.[136] Unactivated aryl halides also give good yields of sulfides on treatment with ArS^{-} or RS^{-} (generated *in situ* from the corresponding thiol) in the presence of a palladium catalyst.[137] Copper catalysts have also been used.[138] Thiophenols were coupled to indoles in the presence of a vanadium catalyst.[139] Aryl iodides react with dialkyl disulfides and a nickel catalyst to give aryl alkyl sulfides.[140] Diaryl sulfides can also be prepared (in high yields) by treatment of unactivated aryl iodides with ArS^{-} in liquid ammonia under irradiation.[141] The mechanism in this case is probably $S_{RN}1$. The reaction (with unactivated halides) has also been carried out electrolytically, with a nickel complex catalyst.[142]

Arylboronic acids, $(ArB(OH)_2$, react with thiols and copper(II) acetate to give the corresponding alkyl aryl sulfide.[143] Arylboronic acids also react with *N*-methylthiosuccinimide, with a copper catalyst, to give the aryl methyl sulfide.[144] In the presence of a palladium catalyst, thiophenols react with diaryliodonium salts, Ar_2I^{+-} BF_4, to give the unsymmetrical diaryl sulfide.[145]

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[129] For a review of sulfur nucleophiles in aromatic substitution, see Peach, M.E., in Patai, S. *The Chemistry of the Thiol Group*, pt. 2, Wiley, NY, ***1974***, pp. 735–744.

[130] Bieniarz, C.; Cornwell, M.J. *Tetrahedron Lett.* ***1993***, *34*, 939.

[131] For generation of ArS^{-} with a phosphazine base and the copper-catalyzed displacement of Ar'I, see Palomo, C.; Oiarbide, M.; López, R.; Gómez-Bengoa, E. *Tetrahedron Lett.* ***2000***, *41*, 1283.

[132] Campbell, J.R. *J. Org. Chem.* ***1964***, *29*, 1830; Testaferri, L.; Tiecco, M.; Tingoli, M.; Chianelli, D.; Montanucci, M. *Synthesis* ***1983***, 751. For the extension of this to selenides, see Tiecco, M.; Testaferri, L.; Tingoli, M.; Chianelli, D.; Montanucci, M. *J. Org. Chem.* ***1983***, *48*, 4289.

[133] Bradshaw, J.S.; South, J.A.; Hales, R.H. *J. Org. Chem.* ***1972***, *37*, 2381.

[134] Caruso, A.J.; Colley, A.M.; Bryant, G.L. *J. Org. Chem.* ***1991***, *56*, 862; Shaw, J.E. *J. Org. Chem.* ***1991***, *56*, 3728.

[135] Cogolli, P.; Maiolo, F.; Testaferri, L.; Tingoli, M.; Tiecco, M. *J. Org. Chem.* ***1979***, *44*, 2642. See also Testaferri, L.; Tingoli, M.; Tiecco, M. *Tetrahedron Lett.* ***1980***, *21*, 3099; Suzuki, H.; Abe, H.; Osuka, A. *Chem. Lett.* ***1980***, 1363.

[136] Lee, S.B.; Hong, J.-I. *Tetrahedron Lett.* ***1995***, *36*, 8439.

[137] Itoh, T.; Mase, T. *Org. Lett.* ***2004***, *6*, 4587.

[138] Kwong, F.Y.; Buchwald, S.L. *Org. Lett.* ***2002***, *4*, 3517; Wu, Y.-J.; He, H. *Synlett* ***2003***, 1789; Deng, W.; Zou, Y.; Wang, Y.-F.;Liu, L.; Guo, Q.-X. *Synlett* ***2004***, 1254.

[139] Maeda, Y.; Koyabu, M.; Nishimura, T.; Uemura, S. *J. Org. Chem.* ***2004***, *69*, 7688.

[140] Tankguchi, N. *J. Org. Chem.* ***204***, *69*, 6904.

[141] Bunnett, J.F.; Creary, X. *J. Org. Chem.* ***1974***, *39*, 3173, 3611.

[142] Meyer, G.; Troupel, M. *J. Organomet. Chem.* ***1988***, *354*, 249.

[143] Herradua, P.S.; Pendola, K.A.; Guy, R.K. *Org. Lett.* ***2000,*** *2*, 2019.

[144] Savarin, C.; Srogl, J.; Liebeskind, L.S. *Org. Lett.* ***2002***, *4*, 4309.

[145] Wang, L.; Chen, Z.-C. *Synth. Commun.* ***2001***, *31*, 1227.

Other sulfur nucleophiles also react with activated aryl halides:

$$2\,ArX + S_2^{2-} \longrightarrow Ar{-}S{-}S{-}Ar \qquad ArX + SCN^- \longrightarrow ArSCN$$

$$ArX + SO_3^{2-} \longrightarrow Ar{-}SO_3^- \qquad ArX + RSO_2^- \longrightarrow Ar{-}SO_2{-}R$$

Aryl sulfones have been prepared from sulfinic acid salts, aryl iodides and CuI.[146] Formation of thiocyanates from unactivated aryl halides has been accomplished with charcoal supported copper(I) thiocyanate.[147] The copper catalyzed reaction of NaO_2SMe and aryl iodides give the aryl methyl sulfone.[148] A similar synthesis of diaryl sulfones has been reported using a palladium catalyst.[149]

An indirect method for the synthesis of aryl alkyl sulfides involves treatment of an aryl halide with butyllithium and then elemental sulfur. The resulting thiophenoxide anion reacts with an alkyl halide to give the targeted sulfide.[150]

Aryl selenides (ArSeAr and ArSeAr') can be prepared by similar methodology. Symmetrical diaryl selenides were prepared by the reaction of iodobenzene with diphenyl diselenide (PhSeSePh), in the presence of Mg and a copper catalyst.[151] Aryl halides react with tin selenides ($ArSeSnR_3$), with a copper catalyst, to give the diaryl selenide.[152]

OS **I**, 220; **III**, 86, 239, 667; **V**, 107, 474; **VI**, 558, 824. Also see, OS **V**, 977.

C. Nitrogen Nucleophiles

13-5 Replacement by NH_2, NHR, or NR_2

Amino-de-halogenation

Amido-de-halogenation

$$R_3N \quad + \quad Ar{-}X \xrightarrow[\text{R = H, alkyl (1 and 2°)}]{} R_2N{-}Ar$$

Activated aryl halides react quite well with ammonia and with primary and secondary amines to give the corresponding arylamines. Primary and secondary amines usually give better results than ammonia, with piperidine especially reactive. Picryl chloride (2,4,6-trinitrochlorobenzene) is often used to form amine derivatives. 2,4-Dinitrofluorobenzene is used to tag the amino end of a peptide or protein chain. Other leaving groups in this reaction may be NO_2,[153] N_3, OSO_2R, OR, SR, N=NAr (where Ar contains electron-withdrawing groups)[154] and even NR_2.[155]

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[146] Suzuki, H.; Abe, H. *Tetrahedron Lett.* ***1995***, *36*, 6239.

[147] Clark, J.H.; Jones, C.W.; Duke, C.V.A.; Miller, J.M. *J. Chem. Soc. Chem. Commun.* ***1989***, 81. See also, Yadav, J.S.; Reddy, B.V.S.; Shubashree, S.; Sadashiv, K. *Tetrahedron Lett.* ***2004***, *45*, 2951.

[148] Baskin, J.M.; Wang, Z. *Org. Lett.* ***2002***, *4*, 4423.

[149] Cacchi, S.; Fabrizi, G.; Goggiamani, A.; Parisi, L.M. *Org. Lett.* ***2002***, *4*, 4719; Cacchi, S.; Fabrizi, G.; Goggiamani, A.; Parisi, L.M.; Bernini, R. *J. Org. Chem.* ***2004***, *69*, 5608.

[150] Ham, J.; Yang, I.; Kang, H. *J. Org. Chem.* ***2004***, *69*, 3236.

[151] Taniguchi, N.; Onami, T. *J. Org. Chem.* **2004**, 69, 915; Taniguchi, N.; Onami, T. *Synlett* ***2003***, 829.

[152] Beletskaya, I.P.; Sigeev, A.S.; Peregudov, A.S.; Petrovlskii, P.V. *Tetrahedron Lett.* ***2003***, *44*, 7039.

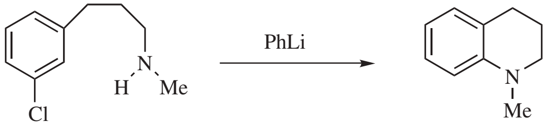
[153] For a reaction with an aryllithium reagent, see Yang, T.; Cho, B.P. *Tetrahedron Lett.* ***2003***, *44*, 7549.

[154] Kazankov, M.V.; Ginodman, L.G. *J. Org. Chem, USSR* ***1975***, *11*, 451.

[155] Sekiguchi, S.; Horie, T.; Suzuki, T. *J. Chem. Soc. Chem. Commun.* ***1988***, 698.

Aryl triflates were shown to react directly with secondary amines in *N*-methylpyrrolidine solvent using microwave irradiation.[156] Activated halides can be converted to diethylamino compounds ArX → $ArNMe_2$ by treatment with HMPA.[157] Aniline derivatives react with activated aromatic rings, in the presence of tetrabutylammonium fluoride and under photolysis conditions, to give a *N,N*-diarylamine.[158] Arylation of amines with aryl halides has also been done in ionic liquids.[159]

Unactivated aryl halides can be converted to amines by the use of $NaNH_2$, NaNHR, or $NaNR_2$.[160] Lithium dialkylamides also react with aryl halides to give the *N*-arylamine.[161] With these reagents, the benzyne mechanism generally operates, so cine substitution is often found. The reaction of an amine, an aryl halide, and potassium *tert*-butoxide generates the *N*-aryl amine.[162] *N*-Arylation was accomplished with butyllithium and a secondary amine using Ni/C-diphenylphosphinoferrocene (dppf).[163] Ring closure has been effected by this type of reaction,[164] as in the conversion of **16** to the tetrahydroquinoline.



16

Larger rings can be prepared using this approach: 8 and even 12 membered. Triarylamines have been prepared in a similar manner from ArI and Ar_2' NLi, even with unactivated ArI.[165] In the *Goldberg reaction*, an aryl bromide reacts with an acetanilide in the presence of K_2CO_3 and CuI to give an *N*-acetyldiarylamine, which can be hydrolyzed to a diarylamine: ArBr + Ar′NHAc → ArAr′NAc.[166] Aryl fluorides react in the presence of KF-alumina and 18-crown-6 in DMSO.[167] Lithium amides have been shown to react directly with aryl halides.[168] Aryl fluorides react

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with amines in the presence of potassium carbonate/DMSO and ultrasound,[169] and aryl chlorides react on basic alumina with microwave irradiation.[170] 2-Chloronitrobenzene also reacts with aniline derivatives directly with microwave irradiation.[171] 2-Fluoropyridine reacts with R_2NBH_3Li to give the 2-aminoalkylpyridine.[172]

The reaction of amines with unactivated aryl halides requires a catalyst in most cases to initiate the reaction. There are several approaches that result in *N*-aryl amines, but recent work with aryl halides, amines, and palladium catalysts has proven quite useful.[173] Aryl halides react with amines (including aniline derivatives) in the presence of palladium catalysts to give the *N*-aryl amine.[174] Palladium catalysts have been used with aniline and or triflates[175] to give the secondary amine. Palladium catalysts have been used in conjunction with aryl halides and aliphatic amines–amide bases.[176] A considerable amount of work[177] has been done to vary the nature of the ligand and the palladium catalyst, as well as the base.[178] Aryl halides also react with aliphatic amines,[179] including cyclopropylamines,[180] and an intramolecular version of this reaction generates bicyclic amines (hydroindole derivatives).[181] Primary aliphatic amines can be converted to tertiary *N,N*-diarylalkylamines in a two-step procedure using palladium catalysts.[182] Aryl halides are

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converted to *N,N*-diaryl tertiary amines by reaction with *N*-alkylaniline derivatives and a palladium catalyst.[183] Beginning with a primary aromatic amine and two different aryl halides (ArBr and Ar'Cl), a triarylamine with three different aryl groups can be prepared using a palladium catalyst.[184] Polymer-bound phosphine ligands have been used in conjunction with a palladium catalyst,[185] and polymer-bound amines have been *N*-arylated with a palladium catalyst followed by treatment with trifluoroacetic acid to release the aniline derivative.[186] Palladium-catalyzed aminoalkylation of aryl halides has been reported using microwave irradiation.[187] Aryl halides (Ar–X) have also been converted to the aniline derivative ($Ar–NH_2$) by reaction of the halide with an imine and a palladium catalyst, followed by hydrolysis.[188] Similarly, aniline derivatives have been prepared by the reaction of aryl chlorides with silylamines (Ph_3SiNH_2) using lithium hexamethyldisilazide and a palladium catalyst.[189] Amines react with $Ph_2I^+BF_4^-$, in the presence of palladium catalysts,[190] or a CuI catalyst[191] to give the *N*-phenyl amine. These reactions have been done in ionic liquids using a palladium catalyst.[192] Arylation of the amine unit of primary enamino ketones was accomplished using a palladium catalyst.[193] Mono-arylation of a 1,2-diamine is possible.[194] Aminoalkylation of heteroaromatic rings is possible, as in the reaction of 3-bromothiophene with a primary amine and a palladium catalyst.[195] 2-Halopyridines react to give the 2-aminoalkyl pyridine.[196] Carbazole derivatives were prepared from 2-iodoaniline and 2-trimethylsilylphenol *O*-triflates, using cesium fluoride and then a palladium catalyst.[197]

Nickel catalysts have been used in the reaction of aryl halides with *N*-alkyl aniline derivatives.[198] Nickel catalyst also allow the conversion of aryl halides to *N*-arylamines via reaction with aliphatic amines.[199] An intramolecular reaction of a

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pendant aminoalkyl unit with an aryl chloride moiety, catalyzed by nickel(0) gave a dihydroindole.[200] Copper catalysts allow the reaction of diarylamines and aryl halides to give the corresponding triarylamine,[201] or with aliphatic amines to give the *N*-arylamine.[202] Aniline reacts with aryl iodides an a copper catalyst and potassium *tert*-butoxide to give triphenylamine.[203] A polymer-bound copper catalyst was used in conjunction with aliphatic amines and arylboronic acids.[204] Amino alcohols react with aryl iodides and a copper catalyst to give the *N*-arylamino alcohol.[205] Treatment of alkylamines with arylboronic acids $ArB(OH)_2$ and $Cu(OAc)_2$ gave the *N*-aryl amine in 63% yield.[206] Similar reaction with arylamines, such as aniline, gave the diarylamine.[207] Arylboronic acids convert aziridines to *N*-arylaziridines,[208] and amino esters to *N*-arylated amino esters,[209] both reactions using a copper catalyst. An arylbismuth reagent reacts with aliphatic amines, in the presence of copper(II) acetate, to give an *N*-arylamine.[210] *N*-Arylation of pyrroles was accomplished by the reaction of an arylboronic acid and a copper catalyst.[211] *N*-Arylindoles[212] and *N*-arylimidazoles[213] were prepared from aryl halide using a copper catalyst. Diarylzinc reagents react with *N*-(OBz) amine derivatives, with a copper catalyst, to give the *N*-aryl amine.[214]

In a related reaction, trifluoroarylboronates react with copper(II) acetate and then an aliphatic amine to give the *N*-phenylamine.[215]

The metal catalyzed reaction with ammonia or amines likely proceeds by the S_NAr mechanism.[216] This reaction, with phase-transfer catalysis, has been used to synthesize triarylamines.[217] Copper ion catalysts (especially cuprous oxide or iodide) also permit the Gabriel synthesis (**10-41**) to be applied to aromatic substrates. Aryl bromides or iodides are refluxed with potassium phthalimide and

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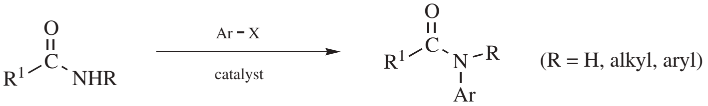
Cu_2O or CuI in dimethylacetamide to give *N*-aryl phthalimides, which can be hydrolyzed to primary aryl amines.[218]

In certain cases, the $S_{RN}1$ mechanism has been found (p. 550). When the substrate is a heterocyclic aromatic nitrogen compound, still a different mechanism [the S_N(ANRORC) mechanism], involving opening and reclosing of the aromatic ring, has been shown to take place.[219]

There are a number of indirect approaches for the preparation of aryl amines. Activated aromatic compounds can be directly converted to the *N*-aryl amine with hydroxylamine in the presence of strong bases.[220] Conditions are mild and yields are high. Aryl halides can be converted to the corresponding Grignard reagent (**12-38**). Subsequent reaction of arylmagnesium halides with allyl azide ($CH_2{=}CHCH_2N_3$) followed by hydrolysis leads to the corresponding aniline derivative.[221] Aryl halides can be converted to the aryllithium via halogen–lithium exchange or hydrogen–lithium exchange (**12-38**, **12-39**). Molecular nitrogen (N_2) reacts with aryllithium compounds in the presence of compounds of such transition metals as titanium (e.g., $TiCl_4$), chromium, molybdenum, or vanadium to give (after hydrolysis) primary aromatic amines ($ArLi + N_2 +$ transition metal salts $\rightarrow ArNH_2$, after hydrolysis).[222] Primary aromatic amines $ArNH_2$ were converted to diaryl amines ArNHPh by treatment with $Ph_3Bi(OAc)_2$[223] and a copper powder catalyst.[224] Aryl Grignard reagents react with nitroaryl compounds to give, after reduction with $FeCl_3/NaBH_4$, a diaryl amine.[225]



The use of transition-metal catalysts allows aryl halides to react with the nitrogen of amides or carbamates, as well as amines, to give the corresponding *N*-aryl amide or *N*-aryl carbamate. Amides react with aryl halides in the presence of a palladium catalyst[226] or a copper catalyst.[227] *N*-Aryl lactams are prepared by the reaction of a lactam with an aryl halide in the presence of a palladium catalyst.[228]

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β-Lactams also react.[229] The reaction of 2-oxazolidinones with aryl halides in the presence of a palladium catalyst gave the *N*-aryl-2-oxazolidinone.[230] Amides react with $PhSi(OMe)_3/Cu(OAc)_2/Bu_4NF$ to give the *N*-aryl amide.[231] *N*-Boc hydrazine derivatives ($BocNHNH_2$) gave the *N*-phenyl derivative $BocN(Ph)NH_2$ when reacted with iodobenzene and a catalytic amount of CuI and 10% of 1,10-phenanthroline.[232] 3-Bromothiophene was converted to the 3-amido derivative with an amide and CuI-dimethylethylenediamine,[233] and *N*-(2-thiophene)-2-pyrrolidinone was similarly prepared from 2-iodothiophene, the lactam and a copper catalyst.[234] *N*-Arylation of urea is also possible using a copper catalyst.[235] The reaction of a vinyl triflate with benzamide and a palladium catalyst gave the corresponding enamide (C=C–NHC=O).[236]

The transition-metal catalyzed couplings of primary or secondary phosphines with aryl halides or sulfonate esters to give arylphosphines is known.[237] Palladium catalyzed conversion of aryl halides to aryl phosphines using (trimethylsilyl)diphenylphosphine is known, and tolerates many functional groups (not those that are easily reducible, such as aldehydes because zinc metal[238] is often used as a coreagent), but it is mainly limited to aryl iodides.[239] Diphenylphosphine reacts with aryl iodides and a copper catalyst to give the triarylphosphine.[240] Aryl iodides also react with secondary phosphine and 5% Pd/C to give the *P*-arylphosphine.[241] Tertiary phosphines can also be used via aryl–aryl exchange, as in the reaction of an aryl triflate and triphenylphosphine and a palladium catalyst, for example, gave the arylphosphine ($ArPPh_2$).[242]

Arylsulfonic acid chlorides ($ArSO_2Cl$) have been shown to react with arylboronic acids, $Ar'B(OH)_2$, in the presence of a palladium catalyst, to give the corresponding biaryl (Ar–Ar').[243]

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[237] Cai, D.; Payack, J.F.; Bender, D.R.; Hughes, D.L.; Verhoeven, T.R.; Reider, P.J. *J. Org. Chem.* ***1994***, *59*, 7180; Herd, O.; Heβler, A.; Machnitzki, P.; Tepper, M.; Stelzer, O. *Catalysis Today* ***1998***, *42*, 413; Gelpke, A.E.S.; Kooijman, H.; Spek, A.L.; Hiemstra, H. *Chem. Eur. J.* ***1999***, *5*, 2472; Ding, K.; Wang, Y.; Yun, H.; Liu, J.; Wu, Y.; Terada, M.; Okubo, Y.; Mikami, K. *Chem. Eur. J.* ***1999***, *5*, 1734; Vyskocil, S.; Smrcina, M.; Hanus, V.; Polasek, M.; Kocovsky, P. *J. Org. Chem.* ***1998***, *63*, 7738; Martorell, G.; Garcias, X.; Janura, M.; Saá, J.M. *J. Org. Chem.* ***1998***, *63*, 3463; Bringmann, G.; Wuzik, A.; Vedder, C.; Pfeiffer, M.; Stalke, D. *Chem. Commun.* ***1998***, 1211; Lipshutz, B.H.; Buzard, D.H.; Yun, C.S. *Tetrahedron Lett.* ***1999***, *40*, 201.

[238] Ager, D.J.; Laneman, S. *Chem. Commun.* ***1997***, 2359.

[239] Tunney, B.H.; Stille, J.K. *J. Org. Chem.* ***1987***, *52*, 748.

[240] Van Allen, D.; Venkataraman, D. *J. Org. Chem.* ***2003***, *68*, 4590.

[241] Stadler, A.; Kappe, C.O. *Org. Lett.* ***2002***, *4*, 3541.

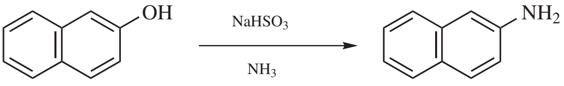
[242] Kwong, F.Y.; Lai, C.W.; Tian, Y.; Chan, K.S. *Tetrahedron Lett.* ***2000***, *41*, 10285; Kwong, F.Y.; Lai, C.W.; Chan, K.S. *Tetrahedron Lett.* ***2002***, *43*, 3537.

[243] Dubbaka, S.R.; Vogel, P. *Org. Lett.* ***2004***, *6*, 95.

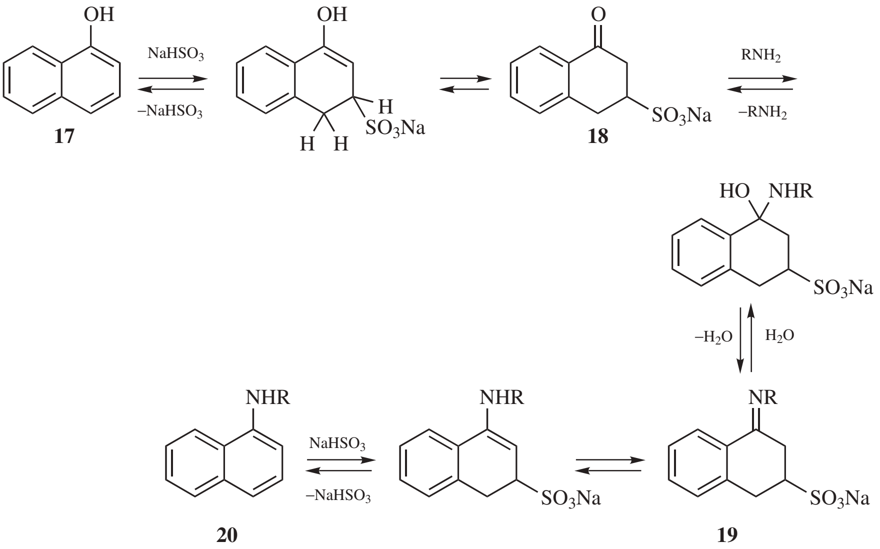
OS **I**, 544; **II**, 15, 221, 228; **III**, 53, 307, 573; **IV**, 336, 364; **V**, 816, 1067; **VII**, 15. OS **III**, 664.

OS X, 423.

13-6 Replacement of a Hydroxy Group by an Amino Group **Amino-de-hydroxylation**



The reaction of naphthols with ammonia and sodium bisulfite[81] is called the *Bucherer reaction*. Primary amines can be used instead of ammonia, in which case *N*-substituted naphthylamines are obtained. In addition, primary naphthylamines can be converted to secondary ($\text{ArNH}_2 + \text{RNH}_2 + \text{NaSO}_3 \rightarrow \text{ArNHR}$), by a transamination reaction. The mechanism of the Bucherer reaction amounts to a kind of overall addition–elimination, via **18** and **19**.[244]



The first step in either direction consists of addition of NaHSO_3 to one of the double bonds of the ring, which gives an enol from **17** (or enamine from **20**) that tautomerizes to the keto form **18** (or imine form, **19**). The conversion of **18** to **19** (or vice versa) is an example of **16-13** (or **16-2**). Evidence for this mechanism was the isolation of **18**[245] and the demonstration that for β-naphthol treated with ammonia and HSO_3^-, the rate of the reaction depends only on the substrate and on

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[244] Rieche, A.; Seeboth, H. *Liebigs Ann. Chem.* ***1960***, *638*, 66.

[245] Rieche, A.; Seeboth, H. *Liebigs Ann. Chem.* ***1960***, *638*, 43, 57.

HSO_3^-, indicating that ammonia is not involved in the rate-determining step.[246] If the starting compound is a β-naphthol, the intermediate is a 2-keto-4-sulfonic acid compound, so the sulfur of the bisulfite in either case attacks meta to the OH or NH_2.[247]

Hydroxy groups on benzene rings can be replaced by NH_2 groups if they are first converted to aryl diethyl phosphates. Treatment of these with KNH_2 and potassium metal in liquid ammonia gives the corresponding primary aromatic amines.[248] The mechanism of the second step is $S_{RN}1$.[249]

OS **III**, 78.

D. Halogen Nucleophiles

13-7 The Introduction of Halogens

Halo-de-halogenation, and so on.

$$Ar{-}X + X'^- \rightleftarrows Ar{-}X' + X^-$$

It is possible to replace a halogen on a ring by another halogen[250] if the ring is activated. In such cases there is an equilibrium, but it is usually possible to shift this in the desired direction by the use of an excess of added halide ion.[251] A phenolic hydroxy group can be replaced by chloro with PCl_5 or $POCl_3$, but only if activated. Unactivated phenols give phosphates when treated with $POCl_3$: $3\ ArOH + POCl_3 \rightarrow (ArO)_3PO$. Phenols, even unactivated ones, can be converted to aryl bromides by treatment with Ph_3PBr_2[252] (see **10-47**) and to aryl chlorides by treatment with $PhPCl_4$.[253]

Halide exchange is particularly useful for putting fluorine into a ring, since there are fewer alternate ways of doing this than for the other halogens. Activated aryl chlorides give fluorides when treated with KF in DMF, DMSO, or dimethyl sulfone.[254] Reaction of aryl halides with Bu_4PF/HF is also effective for exchanging a halogen with fluorine.[255] Halide exchange can also be accomplished with copper halides. Since the leaving-group order in this case is $I > Br > Cl \gg F$ (which means that iodides cannot normally be made by this method), the S_NAr mechanism is

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[246] Kozlov, V.V.; Veselovskaia, I.K. *J. Gen. Chem. USSR* ***1958***, *28*, 3359.

[247] Rieche, A.; Seeboth, H. *Liebigs Ann. Chem.* ***1960***, *638*, 76.

[248] Rossi, R.A.; Bunnett, J.F. *J. Org. Chem.* ***1972***, *37*, 3570.

[249] For another method of converting phenols to amines, see Scherrer, R.A.; Beatty, H.R. *J. Org. Chem.* ***1972***, *37*, 1681.

[250] For a list of reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 671–672.

[251] Sauer, J.; Huisgen, R. *Angew. Chem.* ***1960***, *72*, 294, p. 297.

[252] Wiley, G.A.; Hershkowitz, R.L.; Rein, B.M.; Chung, B.C. *J. Am. Chem. Soc.* ***1964***, *86*, 964; Wiley, G.A.; Rein, B.M.; Hershkowitz, R.L. *Tetrahedron Lett.* ***1964***, 2509; Schaefer, J.P.; Higgins, J. *J. Org. Chem.* ***1967***, *32*, 1607.

[253] Bay, E.; Bak, D.A.; Timony, P.E.; Leone-Bay, A. *J. Org. Chem.* ***1990***, *55*, 3415.

[254] Kimura, Y.; Suzuki, H. *Tetrahedron Lett.* ***1989***, *30*, 1271. For the use of phase-transfer catalysis in this reaction, see Yoshida, Y.; Kimura, Y. *Chem. Lett.* ***1988***, 1355. For a review of the preparation of aryl fluorides by halogen exchange, see Dolby-Glover, L. *Chem. Ind.* (*London*) ***1986***, 518.

[255] Uchibori, Y.; Umeno, M.; Seto, H.; Qian, Z.; Yoshioka, H. *Synlett* ***1992***, 345.

probably not operating.[256] However, aryl iodides have been prepared from bromides, by the use of Cu supported on charcoal or Al_2O_3,[257] with an excess of NaI and a copper catalyst,[258] and by treatment with excess KI and a nickel catalyst.[259] Interestingly, aryl chlorides have been prepared from aryl iodides using 2 equivalents of $NiCl_2$ in DMF, with microwave irradiation.[260]

An indirect halogen exchange treated aryl bromides with *n*-butyllithium and the 5-(iodomethyl)-γ-butyrolactone, giving the aryl iodide and the lithium salt of 4-pentenoic acid.[261] Aryl iodides[262] and fluorides can be prepared from arylthallium bis(trifluoroacetates) (see **12-23**), indirectly achieving the conversions ArH → ArI and ArH → ArF. The bis(trifluoroacetates) react with KI to give ArI in high yields.[263] Aryllead triacetates $ArPb(OAc)_3$ can be converted to aryl fluorides by treatment with BF_3–etherate.[264] Treatment of $PhB(OH)_2$ with *N*-iodosuccinimide gives iodobenzene.[265] Arylboronic acids (**12-28**) can be converted to the corresponding aryl bromides by reaction with 1,3-dibromo-5,5-dimethylhydantoin and 5 mol % NaOMe.[266] Other aryl halides can be prepared using 1,3-dihalo-5,5-dimethylhydantoins.

OS **III**, 194, 272, 475; **V**, 142, 478; **VIII**, 57; **81**, 98.

The reduction of phenols and phenolic esters and ethers is discussed in Chapter 19 (see **19-38** and **19-35**). The reaction ArX → ArH is treated in Chapter 11 (reaction **11-39**), although, depending on reagent and conditions, it can be nucleophilic or free-radical substitution, as well as electrophilic.

E. Carbon Nucleophiles[267]

Some formations of new aryl–carbon bonds formed from aryl substrates have been considered in Chapter 10 (see **10-57**, **10-68**, **10-76**, **10-77**).

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[256] Bacon, R.G.R.; Hill, H.A.O. *J. Chem. Soc.* ***1964***, 1097, 1108. See also Nefedov, V.A.; Tarygina, L.K.; Kryuchkova, L.V.; Ryabokobylko, Yu.S. *J. Org. Chem, USSR* ***1981***, *17*, 487; Suzuki, H.; Kondo, A.; Ogawa, T. *Chem. Lett.* ***1985***, 411; Liedholm, B.; Nilsson, M. *Acta Chem. Scand. Ser. B* ***1988***, *42*, 289; Clark, J.H.; Jones, C.W.; Duke, C.V.A.; Miller, J.M. *J. Chem. Res. (S)* ***1989***, 238.

[257] Clark, J.H.; Jones, C.W. *J. Chem. Soc. Chem. Commun.* ***1987***, 1409.

[258] Klapars, A.; Buchwald, S.L. *J. Am. Chem. Soc.* ***2002***, *124*, 14844.

[259] Yang, S.H.; Li, C.S.; Cheng, C.H. *J. Org. Chem.* ***1987***, *52*, 691.

[260] Arvela, R.K.; Leadbeater, N.E. *Synlett* ***2003***, 1145.

[261] Harrowven, D.C.; Nunn, M.I.T.; Fenwick, D.R. *Tetrahedron Lett.* ***2001***, *42*, 7501.

[262] For reviews of the synthesis of aryl iodides, see Merkushev, E.B. *Synthesis* ***1988***, 923; *Russ. Chem. Rev.* ***1984***, *53*, 343.

[263] Taylor, E.C.; Kienzle, F.; McKillop, A. *Org. Synth.* ***VI***, 826; Taylor, E.C.; Katz, A.H.; Alvarado, S.I.; McKillop, A. *J. Organomet. Chem.* ***1985***, *285*, C9. For reviews, see Usyatinskii, A.Ya.; Bregadze, V.I. *Russ. Chem. Rev.* ***1988***, *57*, 1054; Uemura, S., in Hartley, F. R.; Patai, S. *The Chemistry of the Metal–Carbon Bond*, Vol. 4, Wiley, NY, pp. 473–538. See also, Ishikawa, N.; Sekiya, A. *Bull. Chem. Soc. Jpn.* ***1974***, *47*, 1680; Taylor, E.C.; Altland, H.W.; McKillop, A. *J. Org. Chem.* ***1975***, *40*, 2351.

[264] De Meio, G.V.; Pinhey, J.T. *J. Chem. Soc. Chem. Commun.* ***1990***, 1065.

[265] Thiebes, C.; Prakash, G.K.S.; Petasis N.A.; Olah, G.A. *Synlett* ***1998***, 141.

[266] Szumigala, Jr., R.H.; Devine, P.N.; Gauthier Jr., D.R.; Volante, R.P. *J. Org. Chem.* ***2004***, *69*, 566.

[267] For a review of many of these reactions, see Artamkina, G.A.; Kovalenko, S.V.; Beletskaya, I.P.; Reutov, O.A. *Russ. Chem. Rev.* ***1990***, *59*, 750.

13-8 Cyanation of Aromatic Rings

Cyano-de-halogenation
Cyano-de-metalation

$$\text{Ar-X} \longrightarrow \text{Ar-CN}$$

The reaction between aryl halides and cuprous cyanide is called the *Rosenmund-von Braun reaction*.[268] Reactivity is in the order I > Br > Cl > F, indicating that the S_NAr mechanism does not apply.[269] Other cyanides (e.g., KCN and NaCN) do not react with aryl halides, even activated ones. This reaction has been done in ionic liquids using CuCN.[270] The reaction has also been done in water using CuCN, a phase transfer catalyst, and microwave irradiation.[271]

Aryl halides reaction with metal cyanides, often with another transition metal catalyst, to give aryl nitriles (aryl cyanides). Aryl halides react with $Zn(CN)_2$ and a palladium catalyst, for example, to give the aryl nitrile.[272] Similarly, aryl iodides react with CuCN and a palladium catalyst to give the aryl nitrile.[273] Potassium cyanide (KCN) reacts in a similar manner with a palladium catalyst.[274] Sodium cyanide has been used with a copper catalyst and 20% KI.[275] The reaction of aryl iodides and sodium cyanoborohydride/catechol, with a palladium catalyst, generates the aryl nitrile.[276] Aryl bromides react with $Ni(CN)_2$ with microwave irradiation to give ArCN.[277] In general, alkali cyanides do convert aryl halides to nitriles[278] in dipolar aprotic solvents in the presence of Pd(II) salts[279] or copper[280] or nickel[281]

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[268] For a review of cyano-de-halogenation, see Ellis, G.P.; Romney-Alexander, T.M. *Chem. Rev.* ***1987***, *87*, 779.

[269] For discussions of the mechanism, see Couture, C.; Paine, A.J. *Can. J. Chem.* ***1985***, *63*, 111; Connor, J.A.; Leeming, S.W.; Price, R. *J. Chem. Soc. Perkin Trans. 1* ***1990***, 1127.

[270] In bmiI, 1-*n*-butyl-3-methylimidazolium iodide: Wu, J.X.; Beck, B.; Ren, R.X. *Tetrahedron Lett.* ***2002***, *43*, 387.

[271] Arvela, R.K.; Leadbeater, N.W.; Torenius, H.M.; Tye, H. *Org. Biomol. Chem.* ***2003***, *1*, 1119.

[272] Jin, F.; Confalone, P.N. *Tetrahedron Lett.* ***2000***, *41*, 3271; Zhang, A.; Neumeyer, J.L. *Org. Lett.* ***2003***, *5*, 201; Marcantonio, K.M.; Frey, L.F.; Liu, Y.; Chen, Y.; Strine, J.; Phenix, B.; Wallace, D.J.; Chen, C.-y. *Org. Lett.* ***2004***, *6*, 3723; Ramnauth, J.; Bhardwaj, N.; Renton, P.; Rakhit, S.; Maddaford, S.P. *Synlett* ***2003***, 2237. See Erker, T.; Nemec, S. *Synthesis* ***2004***, 23.

[273] Sakamoto, T.; Ohsawa, K. *J. Chem. Soc. Perkin Trans. 1* ***1999***, 2323.

[274] Sundermeier, M.; Zapf, A.; Beller, M.; Sans, J. *Tetrahedron Lett.* ***2001***, *42*, 6707; Yang, C.; Williams, J.M. *Org. Lett.* ***2004***, *6*, 2837 (this reaction used a catalytic amount of tributyltin chloride as well).

[275] Zanon, J.; Klapers, A.; Buchwald, S.L. *J. Am. Chem. Soc.* ***2003***, *125*, 2890.

[276] Jiang, B.; Kan, Y.; Zhang, A. *Tetrahedron* ***2001***, *57*, 1581.

[277] Arvela, R.K.; Leadbeater, N.E. *J. Org. Chem.* ***2003***, *68*, 9122.

[278] For a list of reagents that convert aryl halides to cyanides, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 1705–1709.

[279] Takagi, K.; Okamoto, T.; Sakakibara, Y.; Ohno, A.; Oka, S.; Hayama, N. *Bull. Chem. Soc. Jpn,*. ***1975***, *48*, 3298; ***1976***, *49*, 3177. See also Sekiya, A.; Ishikawa, N. *Chem. Lett.* ***1975***, 277; Takagi, K.; Sasaki, K.; Sakakibara, Y. *Bull. Chem. Soc. Jpn.* ***1991***, *64*, 1118.

[280] Connor, J.A.; Gibson, D.; Price, R. *J. Chem. Soc. Perkin Trans. 1* ***1987***, 619.

[281] Cassar, L.; Foà, M.; Montanari, F.; Marinelli, G.P. *J. Organomet. Chem.* ***1979***, *173*, 335; Sakakibara, Y.; Okuda, F.; Shimobayashi, A.; Kirino, K.; Sakai, M.; Uchino, N.; Takagi, K. *Bull. Chem. Soc. Jpn.* ***1988***, *61*, 1985.

complexes. A nickel complex also catalyzes the reaction between aryl triflates and KCN to give aryl nitriles.[282]

Arylthallium bis(trifluoroacetates) (see **12-23**) can be converted to aryl nitriles by treatment with copper(I) cyanide in acetonitrile.[283] Another procedure uses excess aqueous KCN followed by photolysis of the resulting complex ion $ArTl(CN)_3^-$ in the presence of excess KCN.[284] Alternatively, arylthallium acetates react with $Cu(CN)_2$ or CuCN to give aryl nitriles.[285] Yields from this procedure are variable, ranging from almost nothing to 90 or 100%. Aromatic ethers ArOR[286] have been photochemically converted to ArCN.

An indirect method involves the reaction of an aromatic ring with *tert*-butyllithium, particularly when there is a directing group (see **13-17**), followed by reaction with PhOCN (phenyl cyanate) to give the aryl nitrile.[287] another indirect method involve the palladium catalyzed reaction of aryl bromides with the cyanohydrin of acetone $[Me_2C(OH)CN]$ to give ArCN.[288]

OS **III**, 212, 631.

13-9 Coupling of Aryl and Alkyl Organometallic Compounds with Aryl Halides, Ethers, and Carboxylic Esters

Aryl-de-halogenation, and so on

$$\text{Ar–X} \quad + \quad \text{Ar}'\text{–M} \quad \longrightarrow \quad \text{Ar–Ar}'$$

$$\text{Ar–X} \quad + \quad \text{R–M} \quad \longrightarrow \quad \text{Ar–R}$$

A number of methods involving transition metals have been used to prepare unsymmetrical biaryls (see also, **13-11**). The uncatalyzed coupling of aryl halides and metalated aryls (particularly aryllithium reagents) is also known, including cyclization of organolithium reagents to aromatic rings.[289] Noncatalyzed coupling reactions of aryllithium reagents and haloarenes can proceed via the well-known aryne route but in some cases, a novel addition–elimination pathway is possible when substituents facilitate a chelation-driven nucleophilic substitution pathway.[290] Such noncatalyzed coupling reactions often proceed with high regioselectivity and high yield.[290] Several noncatalyzed alternative routes are available. 2-Bromopyridine reacts with pyrrolidine, at 130°C with microwave irradiation, to give 2-(2-pyrrolidino)pyridine.[291] Aryl iodides undergo homo-coupling to give the biaryl by

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[282] Chambers, M.R.I.; Widdowson, D.A. *J. Chem. Soc. Perkin Trans. 1* ***1989***, 1365; Takagi, K.; Sakakibara, Y. *Chem. Lett.* ***1989***, 1957.

[283] Taylor, E.C.; Katz, A.H.; McKillop, A. *Tetrahedron Lett.* ***1984***, *25*, 5473.

[284] Taylor, E.C.; Altland, H.W.; McKillop, A. *J. Org. Chem.* ***1975***, *40*, 2351.

[285] Uemura, S.; Ikeda, Y.; Ichikawa, K. *Tetrahedron* ***1972***, *28*, 3025.

[286] Letsinger. R.L.; Colb, A.L. *J. Am. Chem. Soc.* ***1972***, *94*, 3665.

[287] Sato, N. *Tetrahedron Lett.* ***2002***, *43*, 6403.

[288] Sundermeier, M.; Zapf, A.; Beller, M. *Angew. Chem. Int. Ed.* ***2003***, *42*, 1661.

[289] For a review of cyclization of organolithium reagents, see Clayden, J.; Kenworthy, M.N. *Synthesis* ***2004***, 1721.

[290] See Becht, J.-M.; Gissot, A.; Wagner, A.; Mioskowski, C. *Chem. Eur. J.* ***2003***, *9*, 3209.

[291] Narayan, S.; Seelhammer, T.; Gawley, R.E. *Tetrahedron Lett.* ***2004***, *45*, 757.

heating with triethylamine in an ionic liquid.[292] Arylsiloxanes react with aryl halides, for example, to give the biaryl derivative.[293] The reaction of $NaBPh_4$ (sodium tetraphenylborate) and a silyl dichloride (Ph_2SiCl_2) gives biphenyl.[294]

There are many catalytic methods. A homo-coupling type reaction was reported in which $PhSnBu_3$ was treated with 10% $CuCl_2$, 0.5 equivalents of iodine and heated in DMF to give biphenyl.[295] Arylsulfonyl chlorides also react with $ArSnBu_3$ with palladium and copper catalysts to give the biaryl.[296] Aryl halides undergo homo-coupling to give the biaryl with a palladium catalyst[297] or a nickel catalyst.[298] In general, aryl tin compounds couple with aryl halides.[299] An aryltin–aryl halide coupling has been done in ionic liquids.[300] Aryl iodides have been coupled to form symmetric biphenyls using $Pd(OAc)_2$[301] and self-coupling occurs with aryl triflates under electrolysis conditions with a palladium catalyst.[302] A "double-coupling" reaction involving 2-trimethysilylphenol *O*-triflate, allyltributyltin and allyl chloride, with CsF and a palladium catalyst, gave 1,2-diallylbenzene.[303] Another homo-coupling reaction of pyridyl bromides was reported using $NiBr_2$ under electrolytic conditions.[304] Thiophene derivatives,[305] pyrrole,[306] azoles,[307] quinoline,[308] and indolizine[309] have been coupled to aryl halides using a palladium catalyst.

Grignard reagents couple with aryl halides without a palladium catalyst, by the benzyne mechanism,[310] but an iron catalyzed coupling reaction was reported,[311] as

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[292] In bmim PF_6, 1-butyl-3-methylimidazolium hexafluorophosphate: Park, S.B.; Alper, H. *Tetrahedron Lett.* ***2004***, *45*, 5515.

[293] Mori, A.; Suguro, M. *Synlett* ***2001***, 845; Murata, M.; Shimazaki, R.; Watanabe, S.; Masuda, Y. *Synthesis* ***2001***, 2231.

[294] Sakurai, H.; Morimoto, C.; Hirao, T. *Chem. Lett.* ***2001***, 1084. See also, Powell, D.A.; Fu, G.C. *J. Am. Chem. Soc.* ***2004***, *126*, 7788.

[295] Kang, S.-K.; Baik, T.-G.; Jiao, X.H.; Lee, Y.-T. *Tetrahedron Lett.* ***1999***, ***40***, 2383.

[296] Dubbaka, S.R.; Vogel, P. *J. Am. Chem. Soc.* ***2003***, *125*, 15292.

[297] Silveira, P.B.; Lando, V.R.; Dupont, J.; Monteiro, A.L. *Tetrahedron Lett.* ***2002***, *43*, 2327; Kuroboshi, M.; Waki, Y.; Tanaka, H. *Synlett* ***2002***, 637. See also, Venkatraman, S.; Li, C.-J. *Org. Lett.* ***1999***, *1*, 1133.

[298] Leadbeater, N.E.; Resouly, S.M. *Tetrahedron Lett.* ***1999***, *40*, 4243.

[299] Wang, J.; Scott, A.I. *Tetrahedron Lett.* ***1996***, *37*, 3247; Saá, J.M.; Martorell, G.; García-Raso, A. *J. Org. Chem.* ***1992***, *57*, 678; Littke, A.F.; Schwarz, L.; Fu, G.C. *J. Am. Chem. Soc.* ***2002***, *124*, 6343; Kim, Y.M.; Yu, S. *J. Am. Chem. Soc.* ***2003***, *125*, 1696.

[300] Grasa, G.A.; Nolan, S.P. *Org. Lett.* ***2001***, *3*, 119.

[301] Penalva, V.; Hassan, J.; Lavenot, L.; Gozzi, C.; Lemaire, M. *Tetrahedron Lett.* ***1998***, *39*, 2559.

[302] Jutand, A.; Négri, S.; Mosleh, A. *J. Chem. Soc, Chem. Commun.* ***1992***, 1729.

[303] Yoshikawa, E.; Radhakrishnan, K.V.; Yamamoto, Y. *Tetrahedron Lett.* ***2000***, *41*, 729.

[304] de Franç a, K.W.R.; Navarro, M.; Léonel, É; Durandetti, M.; Nédélec, J.-Y. *J. Org. Chem.* ***2002***, *67*, 1838.

[305] Glover, B.; Harvey, K.A.; Liu, B.; Sharp, M.J.; Tymoschenko, M.F. *Org. Lett.* ***2003***, *5*, 301.

[306] With $ZnCl_2$ as an additive, see Rieth, R.D.; Mankand, N.P.; Calimano, E.; Sadighi, J.P. *Org. Lett.* ***2004***, *6*, 3981.

[307] Sezen, B.; Sames, D. *Org. Lett.* ***2003***, *5*, 3607.

[308] Quintin, J.; Franck, X.; Hocquemiller, R.; Figadère, B. *Tetrahedron Lett.* ***2002***, *43*, 3547.

[309] Park, C.-H.; Ryabova, V.; Seregin, I. V.; Sromek, A. W.; Gevorgyan, V. *Org. Lett.* ***2004***, *6*, 1159.

[310] Du, C.F.; Hart, H.; Ng, K.D. *J. Org. Chem.* ***1986***, *51*, 3162.

[311] Fürstner, A.; Leitner, A.; Méndez, M.; Krause, H. *J. Am. Chem. Soc.* ***2002***, *124*, 13856.

well as a nickel-[312] and a cobalt-catalyzed reaction.[313] The coupling reaction of an excess of a Grignard reagent (RMgX) with methoxy aromatic compounds, when the aromatic ring contains multiple alkoxy groups, proceeds with replacement of the OMe group by R.[314] Aryl Grignard reagents coupled with phenyl allyl sulfone, in the presence of an iron catalyst, to give $ArCH_2CH{=}CH_2$.[315] In a similar manner, aryl sulfone coupled with aryl Grignard reagents in the presence of a nickel catalyst.[316] Arylmagnesium compounds couple to give the symmetrical biaryl in the presence of $TiCl_4$.[317] Arylmagnesium halides couple with aryl tosylates in the presence of a palladium catalyst to give unsymmetrical biaryls,[318] and to halopyridines to give the arylated pyridine.[319] Aryl Grignard reagents can be coupled to aryliodonium salts, with $ZnCl_2$ and a palladium catalyst, to give the biaryl.[320] Specialized aryl bismuth compounds have been used with a palladium catalyst to convert aryl chlorides to biaryls,[321] and specialized alkyl indium complexes have been used with a palladium catalyst to give arenes.[322] α-Lithio lactams are coupled to aryl bromides using a palladium catalyst, giving α-aryl lactams.[323]

The homo-coupling of arylzinc iodides with a palladium catalyst has been reported.[324] Vinyl halides, in the presence of an arylmagnesium halides, $ZnCl_2$ and a palladium catalyst, give the styrene compound.[325] Aryl triflates (halides) couple with ArZn(halide) reagents in the presence of a nickel catalyst.[326] Aryl triflates were coupled to triphenylbismuth using a palladium catalyst.[327] Homo-coupling of triphenylbismuth is known,[328] as well as the coupling of arylbismuth reagents to aryliodonium salts[329] and to aryltin compounds[330] with palladium chloride. Similar coupling was accomplished with aryltellurium compounds.[331] Aryl iodides undergo

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a homo-coupling in the presence of hydroquinone and a palladium catalyst.[332] Arylgermanium compounds are coupled with aryl iodides using tetrabutylammonium fluoride and a palladium catalyst.[333] Both alkylmanganese compounds (RMnCl)[334] and Ph_3In[335] react with aryl halides or aryl triflates to give the arene, as do arylbismuth regents with aryl triflates.[336] Aryl halides couple to vinyl acetates, with a cobalt catalyst, to give the styrene derivative.[337] Aryl halides react with cyclopentadiene and Cp_2ZrCl_2 and a palladium catalyst to give pentaphenylcyclopentadiene.[338] Aryl halides also react with phenols to form biaryls using a rhodium catalyst.[339] Diaryliodonium salts react with $PhPb(OAc)_3$ and a palladium catalyst to give the biaryl.[340] Arylsilanes can be coupled to aryl iodides using a palladium catalyst.[341] Aryl halides reacts with acrolein diethyl acetal under electrolysis conditions and a nickel catalyst to give the allyl arene ($Ar{-}CH_2CH{=}CHOEt$).[342]

Unsymmetrical binaphthyls were synthesized by photochemically stimulated reaction of naphthyl iodides with naphthoxide ions in an $S_{RN}1$ reaction.[343] Methyl chloroacetate coupled with aryl iodides under electrolysis conditions, using a nickel catalyst.[344] Unsymmetrical biaryls were prepared from two aryl iodides using a CuI catalyst and microwave irradiation.[345]

Alkylboronic acids are coupled to aryl halides using a palladium catalyst,[346] analogous to the Suzuki reaction in **13-12**. Conversely, arylboronic acids can be coupled to aliphatic halides.[347] Arylboronic acids can be coupled to allylic alcohols as well.[348] Arylboronic acids (**12-28**) were shown to react directly with benzene in the presence of $Mn(OAc)_3$.[349] Arylboronic acids also couple with alkyl halides in

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the presence of palladium(II) acetate[350] or a nickel catalyst.[351] Vinylboronic acids coupled to aryl halides to give the vinyl coupling product.[352] Vinylboronic acids have been coupled to aryldiazonium salts (**13-25**) without added base, using a palladium catalyst with an imidazolium ligand.[353]

Alkyltrifluoroborates (RBF_3K, see **12-28**) react with aryl triflates[354] or aryl halides,[355] or aryliodonium salts[356] with a palladium catalyst, to give the arene. The reaction is compatible with sensitive functionality, such as an epoxide unit.

It is possible to couple metalated alkyl compounds to aryl compounds. The lithium enolate anion of an ester was coupled to an aryl halide, for example, using a palladium catalyst.[357]

Chiral vinyl sulfoxides have been coupled to aryl iodides to give a chiral allylic aryl compounds ($C{=}C\text{-}CH_2{-}Ar$), in a three-step procedure with good enantioselectivity.[358]

The reaction of a cyclic zirconium–diene complex and an aryl diiodide, with CuCl, leads to highly substituted naphthalene derivatives.[359]

OS **VI**, 916; **VIII**, 430, 586; **X**, 9, 448.

13-10 Arylation and Alkylation of Alkenes

Alkylation or **Alkyl-de-hydrogenation**, and so on

$$R_2C{=}CH_2 \quad + \quad Ar\text{-}X \xrightarrow{\text{Pd(0)}} R_2C{=}CH{-}Ar$$

Arylation of alkenes can also be achieved[360] by treatment with an "arylpalladium" reagent, typical generated *in situ* from an aryl halide or other suitably functionalized aromatic compound and a palladium(0) catalyst.[361] Other methods

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are available for this arylation reaction.[362] Treatment of an arylmercury compound (either Ar_2Hg or ArHgX) with $LiPdCl_3$ (ArHgX → "ArPdX") can generate the appropriate intermediate,[363] and in some cases other noble metal salts have been used. The palladium catalyzed aryl–alkene coupling reaction is known as *the Heck reaction*. The reaction works best with aryl iodides, although conditions have been developed for aryl bromides and aryl chlorides.[364] Aryldiazonium salts (**13-25**), rather than aryl halides, have also been used in the Heck reaction.[365] When 2,3,4,5,6-pentafluorobromobezene was used as a substrate, coupling occurred via the bromine, giving the pentafluorophenyl alkene.[366] Aryl halides bearing ortho-substituents also under the coupling reaction.[367] Heteroaryl halides can be used in the couple reaction.[368] Note that acetanilide derivatives reacted with conjugated esters to give the Heck product in acetic acid using a palladium catalyst.[369] Other activated aromatic compounds couple in a similar manner using palladium catalysts[370] unactivated aromatic compounds using special reaction conditions.[371]

Unlike **13-26**, the Heck reaction is not limited to activated substrates. The substrate can be a simple alkene, or it can contain a variety of functional groups, such as ester, ether,[372,373] carboxyl, phenolic, or cyano groups.[374] Coupling with vinyl ethers has been reported, C=C—OR → C=C(Ar)OR.[375] The Heck reaction can be done with heterocyclic compounds,[376] and the C—C unit of compounds, such as indene, react with aryl iodides and palladium catalyst without the need for

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preparing the halide.[377] The Heck reaction has also been performed intramolecularly.[378] Asymmetric Heck reactions are known[379] and the effects of high pressure have been studied.[380]

Ethylene is the most reactive alkene. Increasing substitution lowers the reactivity. Substitution therefore takes place at the less highly substituted side of the double bond.[381] The aryl halide or aryl triflate can be coupled to dienes,[382] allenes,[383] allylic silanes,[384] allylic amines,[385] vinyl phosphonate esters,[386] and with terminal alkynes.[387] Alkylation can also be accomplished, but only if the alkyl group lacks a β-hydrogen, for example, the reaction is successful for the introduction of methyl, benzyl, and neopentyl groups.[388] However, vinylic groups, even those possessing β-hydrogens, have been successfully introduced (to give 1,3-dienes) by the reaction of the alkene with a vinylic halide in the presence of a trialkylamine and a palladium(0) catalyst.[389] Aryl iodides can be coupled to 1-methyl-1-vinyl- and 1-methyl-1-(prop-2-enyl)silacyclobutane with desilyation, using a palladium catalyst and Bu_4NF, to give the corresponding styrene derivative.[390] Indene reacts with iodobenzene with a palladium catalyst to give the phenylindene (80:20 C3/C2).[391]

Control of regiochemistry is a serious problem in the addition to unsymmetrical alkenes. Some regioselectivity can be obtained by the use of alkenes attached to an

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auxiliary coordinating group,[392] the use of special ligands and acrylate or styrene as substrates.[393] Steric effects are thought to control regioselectivity,[394] but electronic influences have also been proposed.[395] It has been shown that the presence of steric effects generally improve 1,2-selectivity, and that electronic effects can be used to favor 1,2- or 2,1-selectivity.[396]

Phosphine free catalysts[397] and halogen-free reactions[398] are known for the Heck reaction. Improvements on the palladium catalyst system are constantly being reported,[399] including polymer-supported catalysts.[400] The influence of the ligand has been examined.[401] Efforts have been made to produce a homogeneous catalyst for the Heck reaction.[402] The Heck reaction can be done in aq. media,[403] in perfluorinated solvents,[404] in polyethylene glycol,[405] in neat tricaprylmethylammonium

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chloride,[406] and in supercritical CO_2 (see p. 414).[407] A noncatalytic reaction was reported using supercritical water.[408] The reaction has been done on solid support,[409] including Montmorillonite clay,[410] glass beads,[411] on a reverse-phase silica support,[412] and using microwave irradiation.[413] A microwave irradiated Heck coupling was done in water using a palladium catalyst.[414] The Heck reaction has also been in ionic liquids,[415] and it is known that the nature of the halide is important in such reactions.[416]

The evidence is in accord with an addition–elimination mechanism (addition of ArPdX followed by elimination of HPdX) in most cases.[417] In the conventionally accepted reaction mechanism,[418] a four-coordinate aryl–Pd(II) intermediate is formed by oxidative addition of the aryl halide to a Pd(0) complex prior to olefin addition. This suggests that cleavage of the dimeric precursor complex, reduction of Pd^{2+}, and ligand dissociation combine to give a viable catalytic species.[419] If these processes occur on a time scale comparable to that of the catalytic reaction, nonsteady-state catalysis could occur while the active catalyst is forming, and an

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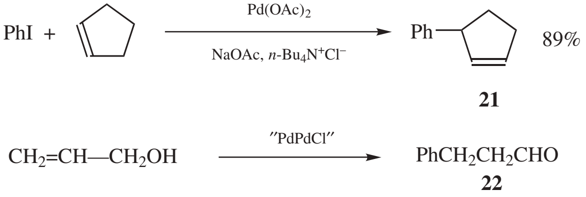
analysis of reaction kinetics under dry conditions was reported.[419] In this study, the mechanism requires a first-order dependence on olefin concentration, and anomalous kinetics may be observed when the rate-limiting step is not directly on the catalytic cycle.[419]



21

22

The reactions are stereospecific, yielding products expected from syn addition followed by syn elimination.[420] Because the product is formed by an elimination step, with suitable substrates double bond migration can occur, resulting in allylic rearrangement (as in the reaction of cyclopentene and iodobenzene to give **21**).[421] Primary and secondary allylic alcohols (and even non-allylic unsaturated alcohols[422]) give aldehydes, such as **22** or ketones that are products of double-bond migration.[423] Similarly, dihydrofurans react with aryl triflates and a palladium catalyst that includes a chiral ligand, to give the 5-phenyl-3,4-dihydrofuran with good enantioselectivity.[424] A similar reaction was reported for an *N*-carbamoyl dihydropyrrole.[425] It has been reported that double bond isomerization can be suppressed in intramolecular Heck reactions done in supercritical CO_2 (see p. 414).[426] The mechanistic implications of asymmetric Heck reactions has been examined.[427]

There are a number of variations of this reaction, including the use of transition metal catalyst other than palladium. A silane-tethered, intramolecular Heck reaction has been reported.[428] Arylphosphonic acids, $ArP(=O)(OH)_2$, couple to aryl alkenes in the presence of a palladium catalyst.[429] Aryl halides couple with vinyl

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[429] Inoue, A.; Shinokubo, H.; Oshima, K. *J. Am. Chem. Soc.* ***2003***, *125*, 1484.

tin reagents to form styrene derivatives in the presence of a nickel catalyst.[430] Aryl chlorides were coupled to conjugated esters using a $RuCl_3 \cdot 3\ H_2O$, in an atmosphere of O_2 and CO.[431] Alkenyl organometallic compounds have been coupled to aryl halides, including allenyltin compounds ($C{=}C{=}C\text{-}SnR_3$).[432] Divinylindium chloride, $(CH_2{=}CH)_2InCl$, reacted with an aryl iodide in aq. THF with a palladium catalyst to give the styrene derivative.[433] Trialkenylindium reagents reacted similarly with aryl halides and a palladium catalyst.[434] Arylzinc chlorides (ArZncl) were coupled to vinyl chlorides using a palladium catalyst,[435] and vinyl zinc compounds were coupled to aryl iodides.[436] Aryliodonium salts can be coupled to conjugated alkenes in a Heck-like manner using a palladium catalyst.[437] In the presence of trimethylsilylmagnesium chloride, primary alkyl halides coupled to aryl alkenes to give the substituted alkene ($R'{-}CH{=}CHAr$), using a cobalt catalyst.[438]

Arylboronic acids (**12-28**) have been coupled to conjugated alkenes to give the aryl–alkene coupling product using a palladium catalyst,[439] a ruthenium catalyst with copper(II) acetate,[440] or a rhodium catalyst.[441] Arylboronic acids have also been coupled to vinyl halides[442] or vinyl tosylates[443] using a palladium catalyst. Note that the reaction of an arylboronic acid and 1,2-dibromoethane, with KOH and a palladium catalyst leads to the styrene derivative.[444] vinylboronic acids have been coupled to aryl halides using a palladium catalyst.[445] Styrene derivatives have been prepared by the reaction of aryl halides and 2,4,6-trivinylcyclotriboroxane, with a palladium catalyst.[446] Conjugated esters can be coupled to benzene using a palladium acetate/benzoquinone catalyst, *tert*-butyl hydroperoxide in acetic acid–acetic anhydride, at 90°C in a sealed tube.[447] Vinyl silanes were converted to styrene derivatives upon treatment with Bu_4NF, and aryl iodide and a palladium

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catalyst.[448] Arylsilanes were coupled to alkenes to give the styrene derivative using palladium acetate and an oxygen atmosphere,[449] for Bu_4NF and an iridium catalyst.[450]

In a related reaction, vinyltrifluoroborates $C{=}C\text{-}BF_3^+\ X^-$ (**12-28**), are coupled to aryl halides with a palladium catalyst to give the styrene derivative.[451]

In an unusual variation, an aryl compound bearing a tertiary alcohol substituent ($ArCMe_2OH$) reacted with aryl halides and a palladium catalyst to give the biaryl.[452] Benzoyl chloride was coupled to styrene to form PhCH=CHPh using a rhodium catalyst.[453] Benzoic acid was coupled to styrene to give the same type of product using a palladium catalyst and a diacyl peroxide.[454]

OS **VI**, 815; **VII**, 361; **81**, 42, 54, 63, 263

13-11 Homo-Coupling of Aryl Halides: The Ullmann Reaction

De-halogen-coupling

$$2\ \text{ArI} \xrightarrow[\Delta]{\text{Cu}} \text{Ar—Ar}$$

The coupling of aryl halides with copper is called the *Ullmann reaction*.[455] The reaction is clearly related to **13-9**, but involves aryl copper intermediates. The reaction is of broad scope and has been used to prepare many symmetrical and unsymmetrical biaryls.[456] When a mixture of two different aryl halides is used, there are three possible products, but often only one is obtained. For example, picryl chloride and iodobenzene gave only 2,4,6-trinitrobiphenyl.[457] The best leaving group is iodo, and the reaction is most often done on aryl iodides, but bromides, chlorides, and even thiocyanates have been used.

The effects of other groups on the ring are unusual. The nitro group is strongly activating, but only in the ortho (not meta or para) position.[458] Both R and OR groups activate in all positions. Not only do OH, NH_2, NHR, and NHCOR inhibit

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[448] Denmark, S.E.; Yans, S.-M. *Org. Lett.* ***2001***, *3*, 1749; Itami, K.; Nokami, T.; Yoshida, J.-I. *J. Am. Chem. Soc.* ***2001***, *123*, 5600; Hanamoto, T.; Kobayashi, T.; Kondo, M. *Synlett* ***2001***, 281; Hanamoto, T.; Kobayashi, T. *J. Org. Chem.* ***2003***, *68*, 6354. See also Taguchi, H.; Ghoroku, K.; Tadaki, M.; Tsubouchi, A.; Takeda, T. *J. Org. Chem.* ***2002***, *67*, 8450.

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[457] Rule, H.G.; Smith, F.R. *J. Chem. Soc.* ***1937***, 1096.

[458] Forrest, J. *J. Chem. Soc.* ***1960***, 592.

the reaction, as would be expected for aromatic nucleophilic substitution, but so do COOH (but not COOR), SO_2NH_2, and similar groups for which the reaction fails completely. These groups inhibit the coupling reaction by causing side reactions.

The mechanism is not known with certainty. It seems likely that it is basically a two-step process, similar to that of the Wurtz reaction (**10-56**), which can be represented schematically by

$$\text{Step 1} \quad \text{ArI} + \text{Cu} \longrightarrow \text{ArCu}$$

$$\text{Step 2} \quad \text{ArCu} + \text{ArI} \longrightarrow \text{Ar—Ar}$$

Organocopper compounds have been trapped by coordination with organic bases.[459] In addition, aryl copper compounds (ArCu) have been independently prepared and shown to give biaryls (Ar—Ar') when treated with aryl iodides Ar'I.[460] A similar reaction has been used for ring closure:[461]

An important alternative to the Ullmann method is the use of certain nickel complexes.[462] This method has also been used intramolecularly.[463] Aryl halides ArX can also be converted to Ar—Ar[464] by treatment with activated Ni metal,[465] with Zn and nickel complexes,[466] with aqueous alkaline sodium formate, Pd—C, and a phase-transfer catalyst,[467] and in an electrochemical process catalyzed by a nickel complex.[468]

An asymmetric Ullmann reaction has also been reported.[469]

OS **III**, 339; **V**, 1120.

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[459] Lewin, A.H.; Cohen, T. *Tetrahedron Lett.* ***1965***, 4531.

[460] For examples, see Nilsson, M. *Tetrahedron Lett.* ***1966***, 675; Cairncross, A.; Sheppard, W.A. *J. Am. Chem. Soc.* ***1968***, *90*, 2186; Ullenius, C. *Acta Chem. Scand.* ***1972***, *26*, 3383; Mack, A.G.; Suschitzky, H.; Wakefield, B.J. *J. Chem. Soc. Perkin Trans. 1* ***1980***, 1682.

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[462] See, for example Semmelhack, M.F.; Helquist, P.M.; Jones, L.D. *J. Am. Chem. Soc.* ***1971***, *93*, 5908; Clark, F.R.S.; Norman, R.O.C.; Thomas, C.B. *J. Chem. Soc. Perkin Trans. 1* ***1975***, 121; Tsou, T.T.; Kochi, J.K. *J. Am. Chem. Soc.* ***1979***, *101*, 7547; Colon, I.; Kelsey, D.R. *J. Org. Chem.* ***1986***, *51*, 2627; Lourak, M.; Vanderesse, R.; Fort, Y.; Caubere, P. *J. Org. Chem.* ***1989***, *54*, 4840, 4844; Iyoda, M.; Otsuka, H.; Sato, K.; Nisato, N.; Oda, M. *Bull. Chem. Soc. Jpn.* ***1990***, *63*, 80. For a review of the mechanism, see Amatore, C.; Jutand, A. *Acta Chem. Scand.* ***1990***, *44*, 755.

[463] See, for example, Karimipour, M.; Semones, A.M.; Asleson, G.L.; Heldrich, F.J. *Synlett*, ***1990***, 525.

[464] For a list of reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 82–84.

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The palladium-catalyzed coupling of aryl halides and other aryl substrates with aromatic rings containing a suitable leaving group is now well established. Other nucleophiles can be coupled to aryl halides.[470] The reaction has become so significant in organic chemistry that the transformations have been categorized as named reactions, and are discussed in Sections **13-14** and **13-15**.

13-12 Coupling of Aryl Compounds With Arylboronic acid Derivatives

Aryl-de-halogenation, and so on **Aryl-de-boronylation**, and so on

$$\text{Ar—Br} + \text{Ar}'\text{B(OH)}_2 \xrightarrow{\text{PdL}_4} \text{Ar—Ar}'$$

Aryl triflates react with arylboronic acids, ArB(OH)_2 (**12-28**),[471] or with organoboranes,[472] in the presence of a palladium catalyst,[473] to give the arene in what is called *Suzuki coupling* (or *Suzuki–Miyaura coupling*).[474] Aryl halides are commonly used, and aryl sulfonates have been used.[475] Even hindered boronic acids give good yields of the coupled product.[476] Homo-coupling of arylboronic acids has been reported.[477] Coupling of the alkynes to form a diyne (see **14-16**) can be a problem is some cases, although the aryl–alkyne coupling usually predominates.[478] Some aromatic compounds are so reactive that a catalyst may not be required. Using tetrabutylammonium bromide, phenylboronic acid was coupled to 2-bromofuran without a catalyst.[479]

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[470] For a review, see Prim, D.; Campagne, J.-M.; Joseph, D.; Andrioletti, B. *Tetrahedron* ***2002***, *58*, 2041.

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[478] See, for example, Chow, H.-F.; Wan, C.-W.; Low, K.-H.; Yeung, Y.-Y. *J. Org. Chem.* ***2001***, *66*, 1910.

[479] Bussolari, J.C.; Rehborn, D.C. *Org. Lett.* ***1999***, *1*, 965.

Different conditions (including additives and solvent) for the reaction have been reported,[480] often focusing on the palladium catalyst itself,[481] or the ligand.[482] Catalysts have been developed for deactivated aryl chlorides,[483] and nickel catalysts have been used.[484] Modifications to the basic procedure include tethering the aryl triflate[485] or the boronic acid[486] to a polymer, allowing a polymer-supported Suzuki reaction. Polymer-bound palladium complexes have also been used.[487,488] The reaction has been done neat on alumina,[489] and on alumina with microwave irradiation.[490] Suzuki coupling has also been done in ionic liquids,[491] in supercritical

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[488] Wang, Y; Sauer, D.R. *Org. Lett.* ***2004***, *6*, 2793.

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CO_2[492] (see p. 414), and in water with microwave irradiation[493] or in water with a palladium catalyst, air, and tetrabutylammonium fluoride.[494] A solvent free (neat) Suzuki reactions have been reported.[495] A variety of functional groups are compatible with Suzuki coupling, including $Ar_2P{=}O$,[496] CHO,[497] C=O of a ketone,[498] CO_2R,[499] cyclopropyl,[500] NO_2,[501] CN,[488] and halogen substituents.[502]

There are many structural variations of the reaction that give it enormous synthetic potential. Halogenated heteroaromatic compounds react. 2-Halopyridines react with arylboronic acids and a palladium catalyst to give 2-arylpyridines.[503] Other heterocycles have been similarly arylated.[504] 4-Pyridylboronic acids have been used.[505] The reaction of phenylboronic acid and a diallyl amide which contained a vinyl bromide, led to ring closure as well as incorporation of the phenyl group, give an *N*-tosylpyrrolidine with an exocyclic methylene unit.[506] Vinyl halides react with arylboronic acids to give alkenyl derivatives (vinyl arenes, C=C—Ar).[507] Alkylation can accompany arylation if alkyl halides are added, as in the conversion of iodobenzene to 2,6-dibutylbiphenyl.[508]

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[495] Nielsen, S.F.; Peters, D.; Axelsson, O. *Synth. Commun.* ***2000***, *30*, 3501; Kabalka, G.W.; Wang, L.; Pagni, R.M.; Hair, C.M.; Namboodiri, V. *Synthesis* ***2003***, 217.

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[497] Hesse, S.; Kirsch, G. *Synthesis* ***2001***, 755; Phan, N.T.S.; Brown, D.H.; Styring, P. *Tetrahedron Lett.* ***2004***, *45*, 7915.

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[500] Ma, H.-r.; Wang, X.-L.; Deng, M.-z. *Synth. Commun.* ***1999***, *29*, 2477.

[501] Tao, B.; Boykin, D.W. *J. Org. Chem.* ***2004***, *69*, 4330; Li, J.-H.; Liu, W.-J. *Org. Lett.* ***2004***, *6*, 2809; Widdowson, D.A.; Wilhelm, R. *Chem. Commun.* ***2003***, 578.

[502] Colacot, T.J.; Shea, H.A. *Org. Lett.* ***2004***, *6*, 3731; DeVasher, R.B.; Moore, L.R.; Shaughnessy, K.H. *J. Org. Chem.* ***2004***, *69*, 7919.

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[507] Shen, W. *Synlett* ***2000***, 737.

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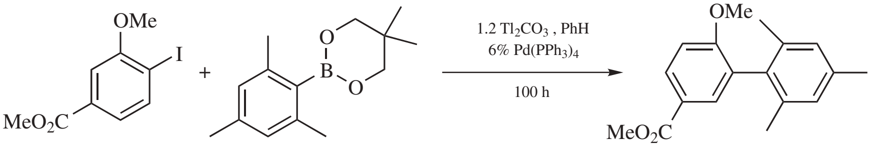
Since many biaryls are chiral due to atropisomerism (see p. 147), the use of a chiral catalyst, and/or a chiral ligand can lead to enantioselectivity in the Suzuki coupling.[509]

Arylsulfonates can be coupled to aryl triflates using a palladium catalyst,[510] and arylboronic acids couple with aryl sulfonate esters.[511] Aryl boronic acids are coupled with aryl ammonium salts to give the biaryl, with a nickel catalyst.[512] Allylic acetates have been coupled to arylboronic acids using nickel bis(acetylacetonate) and diisobutylaluminum hydride.[513] Aryl halides couple with ArB(IR'$_2$) species with a palladium catalyst.[514] Arylboronic acids couple with the phenyl group of Ph_2TeCl_2 with a palladium catalyst.[515] 3-Iodopyridine reacted with NaBPh and palladium acetate, with microwave irradiation, to give 3-phenylpyridine.[516] Tributyltinaryl compounds were coupled to the aryl group of $Ar_2I^+BF_4^-$ with a nickel catalyst.[517] Organoboranes are coupled to aryl halides with a palladium catalyst.[518] Aryl silanes can be coupled to aryl iodides using Ag_2O and a palladium catalyst,[519] and arylsiloxanes ArSi(OR)$_3$, are coupled to aryl halides with Bu_4NF and a palladium catalyst.[520]

Arylborates (**12-28**), ArB(OR)$_2$, can be used in place of the boronic acid. The coupling reaction of aryl iodide **23** with boronate **24**, for example, gave the biaryl.[521] Aryl and heteroarylboroxines (**25**) can be coupled to aryl halides using a palladium catalyst.[522]



23 **24**

For a mechanistic viewpoint,[523] the Suzuki coupling proceeds via oxidative addition of areneboronic acids to give a Pd(0) species, followed by 1,2 arene migration to an electron-deficient palladium atom, eventually leading to very fast reductive

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[509] Nishimura, T.; Araki, H.; Maeda, Y.; Uemura, S. *Org. Lett.* ***2003***, *5*, 2997; Navarro, O.; Kelly III, R.A.; Nolan, S.P. *J. Am. Chem. Soc.* ***2003***, *125*, 16194.

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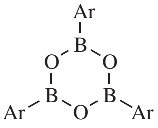
[521] Chaumeil, H.; Signorella, S.; Le Drian, C. *Tetrahedron* ***2000***, *56*, 9655.

[522] Cioffi, C.L.; Spencer, W.T.; Richards, J.J.; Herr, R.J. *J. Org.Chem.* ***2004***, *69*, 2210.

[523] For a review, see Esponet, P.; Echavarren, A.M. *Angew. Chem. Int. Ed.* ***2004***, *43*, 4704.

elimination to afford biaryls.[524] Several intermediates of the oxidative coupling process have been identified by electrospray ionization mass spectrometry.[525]



25

A Suzuki-type coupling reaction has been reported involving acyl halides. When arylboronic acids were reacted with benzoyl chloride and $PdCl_2$, the product was the diaryl ketone.[526] This coupling reaction was also accomplished using a palladium(0) catalyst.[527] Cyclopropylboronic acids couple with benzoyl chloride, in the presence of Ag_2O and a palladium catalyst, to give the cyclopropyl ketone.[528] A nickel catalyst has been used,[529] and $Ph_3P/Ni/C$—BuLi has also been used.[530] Arylboronic acids have also been coupled to anhydrides,[531] and the methoxy group of anisole derivatives has been replaced with phenyl using phenylboronic acid and a ruthenium catalyst.[532]

In a related reaction, aryltrifluoroborates $PhBF_3^+ X^-$ (**12-28**), are coupled to aryl halides with a palladium catalyst to give the biaryl.[533]

OS **75**, 53, 61

The coupling reactions of alkylboronic acids are covered in **13-17**.

OS X, 102, 467; **81**, 89.

13-13 Aryl–Alkyne Coupling Reactions

Alkynyl-de-halogenation, and so on

$$ArI + RC{\equiv}CCu \longrightarrow ArC{\equiv}CR$$

When aryl halides react with copper acetylides to give 1-aryl alkynes, the reaction is known as *Stephens–Castro coupling*.[534] Both aliphatic and aromatic

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[524] Moreno-Mañas, M.; Pérez, M.; Pleixats, R. *J. Org. Chem.* ***1996***, *61*, 2346.

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[529] Leadbeater, N.E.; Resouly, S.M. *Tetrahedron* ***1999***, *55*, 11889.

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substituents can be attached to the alkyne unit, and a variety of aryl iodides has been used. Benzonitrile was shown to react with alkynyl zinc bromides, with a nickel catalyst and after electrolysis to give the diarylalkyne, where the cyano unit was replaced with an alkyne unit.[535]

$$\text{Ar-X} + \text{RC}{\equiv}\text{CH} \xrightarrow{\text{Pd(0)}} \text{Ar-C}{\equiv}\text{CR}$$

A palladium–catalyzed variation is also known in which an aryl halide reacts with a terminal alkyne to give 1-aryl alkynes is called the *Sonogashira coupling*.[536] Terminal aryl alkynes react with aryl iodides and palladium(0)[537] to give the corresponding diaryl alkyne.[538] As with all of the metal-catalyzed reactions in this chapter, work has been done to vary reaction conditions, including the catalyst,[539] the ligand, the solvent,[540] and additives.[541] copper-free palladium/DABCO catalysts have been used.[542] Aryl iodides are more reactive than aryl fluorides.[543] Alkynes can be coupled to heteroaromatic compounds via the heteroaryl halide.[544] The coupling reaction has been done neat, with microwave irradiation on KF-alumina,[545] and in aqueous polyethylene glycol.[546] The aryl–alkyne coupling has also been done in solution with microwave irradiation.[547] Sonogashira coupling

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[535] Penney, J.M.; Miller, J.A. *Tetrahedron Lett.* ***2004***, *45*, 4989.

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[540] The reaction has been done in aqueous media, see Bhattacharya, S.; Sengupta, S. *Tetrahedron Lett.* ***2004***, *45*, 8733.

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was reported on microbeads,[548] with nanoparticulate nickel powder,[549] and the aryl iodide was tethered to a polymer for a solid-state reaction that included the use of microwave irradiation, and cleavage from the polymer using trifluoroacetic acid.[550] Polymer supported catalysts are known.[551] Conversion of 1-lithioalkynes to the corresponding alkynyl zinc reagent allows coupling with aryl iodides when a palladium catalyst is used.[552] Coupling with alkynyl tin compounds is also known.[553] The 1-lithioalkyne was directly coupled to aryl bromides in the presence of $B(O\textit{i}Pr)_3$ and a palladium catalyst,[554] where an alkynylboronic acid was generated *in situ*.

A variation was reported with environmental importance, where the triphenylphosphine by-product was scavenged by addition of Merrifield resin.[555] A copper-free Sonogashira coupling has been reported, in triethylamine[556] and in an ionic liquid.[557] A copper and amine-free reaction was reported in normal solvents, such as THF.[558] An interesting example of the versatility of the coupling reaction is the coupling of propargyl bromide and an aryl iodide, in the presence of an amine, giving the aryl aminomethylalkyne.[559] The coupling of 4-chloroacetophenone with 1-phenylethyne shows that the carbonyl group is compatible with this reaction.[560]

Diaryliodonium salts react with terminal alkynes to give the phenyl alkyne.[561] A variation couples the phenyl group of $Ph_2I^+OTf^-$ with an en-yne using a palladium catalyst.[562] Aryl sulfonate esters can be coupled to terminal alkynes using a palladium catalyst in polymethylhydrosiloxane.[563] Aryl halides are coupled to alkynyltrifluoroborates ($R{-}C{\equiv}C{-}BF_3K$, **12-28**) using a palladium catalyst.[564] The boron trifluoride induced palladium-catalyzed cross-coupling reaction of 1-aryltriazenes with areneboronic acids has been reported.[565]

A variation of this aryl–alkyne coupling reaction reacted methylthioalkynes ($R{-}C{\equiv}C{-}SMe$) with arylboronic acids and a palladium catalyst to give the aryl alkyne ($R{-}C{\equiv}C{-}Ar$).[566] 1-Trialkylsilylalkynes ($R_3Si{-}C{\equiv}C{-}R'$) were coupled

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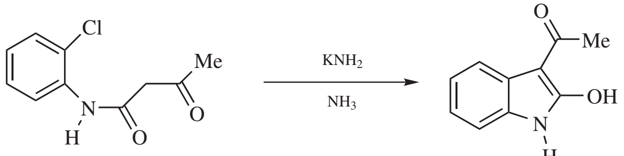
to aryl iodides using a palladium catalyst.[567] A triphenylstibine, $Ph_3Sb(OAc)_2$, was used to transfer a phenyl group to the alkyne carbon of $PhC{\equiv}CSiMe_3$, using palladium and CuI catalysts.[568] Aryl iodides were also coupled to lithium alkynyl borate complexes, $Li[R{-}C{\equiv}C{-}B(OR')_3$, to give the aryl alkyne.[569] Note that diphenylethyne was prepared from bromobenzene and 2-chloro-1-bromoethane using KOH, 18-crown-6 and a palladium catalyst.[570]

13-14 Arylation at a Carbon Containing an Active Hydrogen

Bis(ethoxycarbonyl)methyl-de-halogenation, and so on

The arylation of compounds of the form ZCH_2Z' is analogous to **10-67**, where Z is as defined as an electron withdrawing group (ester, cyano, sulfonyl, etc.). Activated aryl halides generally give good results.[571] Even unactivated aryl halides can be employed if the reaction is carried out in the presence of a strong base, such as $NaNH_2$[572] or LDA. Compounds of the form ZCH_2Z', even simple ketones[573] and carboxylic esters have been arylated in this manner. The reaction with unactivated halides proceeds by the benzyne mechanism and represents a method for extending the malonic ester (and similar) syntheses to aromatic compounds. The base performs two functions: it removes a proton from ZCH_2Z' and catalyzes the benzyne mechanism. The reaction has been used for ring closure, as in the formation of **26**.[574]



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[571] There is evidence for both the S_NAr mechanism (see Leffek, K.T.; Matinopoulos-Scordou, A.E. *Can. J. Chem.* ***1977***, *55*, 2656, 2664) and the $S_{RN}1$ mechanism (see Zhang, X.; Yang, D.; Liu, Y.; Chen, W.; Cheng, J. *Res. Chem. Intermed.* ***1989***, *11*, 281).

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The coupling of active methylene compounds and unactivated aryl halides can also be done with copper halide catalysts[93] (the *Hurtley reaction*).[575] A palladium catalyst can be used for the coupling of malonate esters with unactivated aryl halides.[576] Bis(sulfones), $CH_2(SO_2Ar)_2$, react with aryl halides in the presence of a palladium catalyst.[577] Similar coupling was accomplished with $CH_2(CN)_2$ and a nickel catalyst.[578] Malonic and β-keto esters can be arylated at the α-carbon in high yields by treatment with aryllead tricarboxylates [$ArPb(OAc)_3$],[579] and with triphenylbismuth carbonate (Ph_3BiCO_3)[580] and other bismuth reagents.[581] In a related process, manganese(III) acetate was used to convert a mixture of ArH and ZCH_2Z' to ArCHZZ′.[582]

The reaction of the enolate anions ketones and aldehydes, generated *in situ* by addition of a suitable base, with aryl halides can be accomplished by treatment with a palladium catalyst.[583] Formation of an enolate anion of a conjugated ketone (cyclohexenone) via reaction with LDA (see p. 389), in the presence of Ph_3BiCl_2, leads to the α-phenyl conjugated ketone (6-phenylcyclohex-2-enone).[584] An ester reacted with $TiCl_4$ and *N,N*-dimethylanline to give the para-substitution product. (Me_2N—Ar—$CHRCO_2Et$).[585] The enolate anion of lactams will react with aryl halides in the presence of a palladium catalyst go via the 3-aryl lactam.[586] When the enolate anion of a ketone is generated in the presence of a palladium catalyst and a chiral phosphine ligand, the α-aryl ketone is formed with good enantioselectivity.[587]

Compounds of the form CH_3Z can be arylated by treatment with an aryl halide in liquid ammonia containing Na or K, as in the formation of **27** and **28**.[588]

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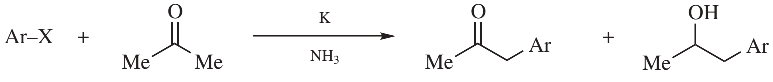
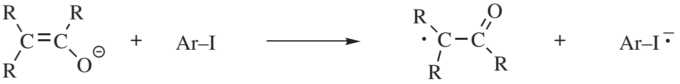


27 **28**

When the solution is irradiated with near-UV light, but Na or K is omitted, the same products are obtained (though in different proportions).[589] In either case, other leaving groups can be used instead of halogens (e.g., NR_3^+, SAr) and the mechanism is the $S_{RN}1$ mechanism. Iron(II) salts have also been used to initiate this reaction.[590] The reaction can also take place without an added initiator. The reaction of 2-fluoroanisole and KHMDS, and 4 equivalents of 2-cyanopropane, leads to substitution of the fluorine atom by CMe_2CN.[591] A similar reaction as reported using a palladium catalyst.[592] Nitroethane was converted to 2-phenylnitroethane using bromobenzene and a palladium catalyst.[593]

Enolate ions of ketones react with PhI in the dark.[594] In this case, it has been suggested[595] that initiation takes place by formation of a radical, such as **29**.



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This is an SET mechanism (see p. 444). The photostimulated reaction has also been used for ring closure.[596] In certain instances of the intermolecular reaction there is evidence that the leaving group exerts an influence on the product ratios, even when it has already departed at the time that product selection takes place.[597]

OS **V**, 12, 263; **VI**, 36, 873, 928; **VII**, 229.

13-15 Conversion of Aryl Substrates to Carboxylic Acids, Their Derivatives, Aldehydes, and Ketones[598]

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Alkoxycarbonyl-de-halogenation, and so on

$$\text{ArX} + \text{CO} + \text{ROH} \xrightarrow[\text{Pd complex}]{\text{base}} \text{ArCOOR}$$

Carbonylation of aryl bromides and iodides with carbon monoxide, an alcohol, a base, and a palladium catalyst, give carboxylic esters. Even very sterically hindered alkoxides can be used to produce the corresponding ester.[599] The use of H_2O, RNH_2, or an alkali metal or calcium carboxylate[600] instead of ROH, gives the carboxylic acid,[601] amide,[602] or mixed anhydride, respectively.[603] Heating an aryl iodide, CO in ethanol and DBU, with a palladium catalyst, gave the ethyl ester of the aryl carboxylic acid.[604] A similar result was obtained when an aryl iodide was heated in ethanol with triethylamine, CO and Pd/C.[605] Ester formation via carbonylation was done is supercritical CO_2 (see p. 414).[606] With certain palladium catalysts, aryl chlorides[607] and aryl triflates[608] can also be substrates. Aryl carboxylic acids were also prepared from aryl iodides by heating in DMF with lithium formate, LiCl, acetic anhydride and a palladium catalyst.[609] A silica-supported palladium reagent has been used to convert iodobenzene to butyl benzoate, in the presence of CO and butanol.[610] 2-Chloropyridine was converted the butyl pyridine 2-carboxylate with this procedure.[611] Halogenated biaryls can be converted to the tricyclic ketone, 9-fluorenone, by an intramolecular carbonylation reaction with CO and a palladium catalyst.[612] A surrogate reagent used instead of CO is dicobalt octacarbonyl $CO_2(CO)_8$.[613] Aryl chlorides have been converted to carboxylic acids by an electrochemical synthesis,[614] and aryl iodides to aldehydes by treatment with

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CO, Bu_3SnH, and $NCCMe_2N{=}NCMe_2CN$ (AIBN).[615] Aryl ketones can be prepared from aryltrimethylsilanes $ArSiMe_3$ and acyl chlorides in the presence of $AlCl_3$.[616] Aryllithium and Grignard reagents react with iron pentacarbonyl to give aldehydes ArCHO.[617] The reaction of CO with aryllithium may occur by electron transfer.[618]

Aryl iodides are converted to unsymmetrical diaryl ketones on treatment with arylmercury halides and nickel carbonyl: $ArI + Ar'HgX + Ni(CO)_4 \rightarrow ArCOAr'$.[619] Aryl iodides are carbonylated to give the aryl alkyl ketone with CO and R_3In.[620] Arylthallium bis(trifluoroacetates), $ArTl(O_2CCF_3)_2$ (see **12-23**), can be carbonylated with CO, an alcohol, and a $PdCl_2$ catalyst to give esters.[621] Organomercury compounds undergo a similar reaction.[622] The aryllead reagent $PhPb(OAc)_3$, was converted to benzophenone using NaOMe, CO and a palladium catalyst.[623] Aryl iodides containing an ortho substituent with a β-cyano group that served as the source of a carbonyl group, was converted to a bicyclic ketone with a palladium catalyst at 130°C in aqueous DMF.[624]

Diaryl ketones can also be prepared by coupling aryl iodides with phenylboronic acid (**12-28**), in the presence of CO and a palladium catalyst.[625] This reaction has been extended to heteroaromatic systems, with the preparation of phenyl 4-pyridyl ketone from phenylboronic acid and 4-iodopyridine.[626] 2-Bromopyridine as coupled with phenylboronic acid, CO and a palladium catalyst to give phenyl 2-pyridyl ketone.[627] An interesting reaction treated a titanocycle (**30**) with CO to give the cyclobutanone.[628] Carbonylation of an alkyne and an aryl halide, with CO

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[619] Rhee, I.; Ryang, M.; Watanabe, T.; Omura, H.; Murai, S.; Sonoda, N. *Synthesis* ***1977***, 776; Ryu, I.; Ryang, M.; Rhee, I.; Omura, H.; Murai, S.; Sonoda, N. *Synth. Commun.* ***1984***, *14*, 1175 and cited references. For other acylation reactions, see Tanaka, M. *Synthesis* ***1981***, 47; *Bull. Chem. Soc. Jpn.* ***1981***, *54*, 637; Bumagin, N.A.; Ponomarov, A.B.; Beletskaya, I.P. *Tetrahedron Lett.* ***1985***, *26*, 4819; Koga, T.; Makinouchi, S.; Okukado, N. *Chem. Lett.* ***1988***, 1141; Echavarren, A.M.; Stille, J.K. *J. Am. Chem. Soc.* ***1988***, *110*, 1557; Hatanaka, Y.; Hiyama, T. *Chem. Lett.* ***1989***, 2049.

[620] Lee, P.H.; Lee, S.W.; Lee, K. *Org. Lett.* ***2003***, *5*, 1103. With a palladium catalyst, see Pena, M.A.; Sestelo, J.P.; Sarandeses, L.A. *Synthesis* ***2003***, 780. For a reaction that used R_4InLi, see Lee, S.W.; Kee, K.; Seomoon, D.; Kim, S.; Kim, H.; Kim, H.; Shim, E.; Lee, M.; Lee, S.; Kim, S.; Lee, P.H. *J. Org. Chem.* ***2004***, *69*, 4852.

[621] Larock, R.C.; Fellows, C.A. *J. Am. Chem. Soc.* ***1982***, *104*, 1900.

[622] Baird Jr., W.C.; Hartgerink, R.L.; Surridge, J.H. *J. Org. Chem.* ***1985***, *50*, 4601.

[623] Kang, S.-K.; Ryu, H.-C.; Choi, S.-C. *Synth. Commun.* ***2001***, *31*, 1035.

[624] Pletnev, A.A.; Larock, R.C. *J. Org. Chem.* ***2002***, *67*, 9428.

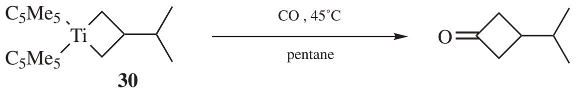
[625] Ishiyama, T.; Kizaki, H.; Miyaura, N.; Suzuki, A. *Tetrahedron Lett.* ***1993***, *34*, 7595.

[626] Couve-Bonnaire, S.; Caprentier, J.-F.; Mortreux, A.; Castanet, Y. *Tetrahedron Lett.* ***2001***, *42*, 3689.

[627] Maerten, E.; Hassouna, F.; Couve-Bonnaire, S.; Mortreux, A.; Carpentiere, J.-F.; Castanet, Y. *Synlett* ***2003***, 1874.

[628] Carter, C.A.G.; Greidanus, G.; Chen, J.-X.; Stryker, J.M. *J. Am. Chem. Soc.* ***2001***, *123*, 8872.

and palladium and copper catalysts, gave the alkynyl ketone RC≡C(C=O)Ar.[629]



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Note that seleno esters (ArCOSeAr) were prepared from aryl iodides, CO, $PhSeSnBu_3$, and a palladium catalyst.[630]

13-16 Arylation of Silanes

Silyl and Silyloxy-de-halogenation, and so on

$$\text{Ar–X} \quad + \quad \text{Ar}'\text{SiR}_2 \quad \longrightarrow \quad \text{Ar–SiR}_3$$

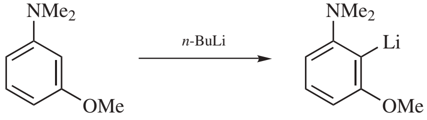
In the presence of transition-metal catalysts, such as palladium, trialkoxysilanes [$HSi(OR)_3$] react with aryl halides to give the corresponding arylsilane.[631] This transformation is an alternative to the Suzuki coupling (**13-10**).[632] A similar reaction was reported using a rhodium catalyst.[633] Arylsilanes can be coupled to aryl iodides in aqueous media.[634] Arylsilanes react with alkyl halides to give the corresponding arene, in the presence of a palladium catalyst.[635] Suzuki-type coupling using $Me_3SiSiMe_3$ leads to aryl silanes.[636]

An alternative approach reacts aryllithium reagents with siloxanes [$Si(OR)_4$], to give the aryl derivative $ArSi(OR)_3$.[637]

HYDROGEN AS LEAVING GROUP[638]

13-17 Alkylation and Arylation

Alkylation or Alkyl-de-hydrogenation, and so on



31 **32**

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[630] Nishiyama, Y.; Tokunaga, K.; Kawamatsu, H.; Sonoda, N. *Tetrahedron Lett.* ***2002***, *43*, 1507.

[631] Manoso, A.S.; DeShong, P. *J. Org. Chem.* ***2001***, *66*, 7449.

[632] DeShong, P.; Handy, C.J.; Mowery, M.W. *Pure Appl. Chem.* ***2000***, *72*, 1655; Seganish, W.M.; DeShong, P. *Org. Lett.* ***2004***, *6*, 4379.

[633] Murata, M.; Ishikura, M.; Nagata, M.; Watanabe, S.; Masuda, Y. *Org. Lett.* ***2002***, *4*, 1843.

[634] Denmark, S.E.; Ober, M.H. *Org. Lett.* ***2003***, *5*, 1357.

[635] Mowery, M.E.; DeShong, P. *J. Org. Chem.* ***1999***, *64*, 3266; Lee, J.-y.; Fu, G.C. *J. Am. Chem. Soc.* ***2003***, *125*, 5616.

[636] Gooßen, L.J.; Ferwanah, A.-R.S. *Synlett* ***2000***, 1801.

[637] Manoso, A.S.; Ahn, C.; Soheili, A.; Handy, C.J.; Correia, R.; Seganish, W.M.; DeShong, P. *J. Org. Chem.* ***2004***, *69*, 8305.

[638] For reviews, see Chupakhin, O.N.; Postovskii, I.Ya. *Russ. Chem. Rev.* ***1976***, *45*, 454. For a review of reactivity and mechanism in these cases, see Chupakhin, O.N.; Charushin, V.N.; van der Plas, H.C. *Tetrahedron* ***1988***, *44*, 1.

The alkylation of aromatic rings was introduced, in part, in section **10-57**. The reaction of an aromatic ring with an organolithium reagent can give H—Li exchange to form an aryllithium. This reaction tends to be slow in the absence of diamine additives or if there are activating substituents on the aryl halide.[639] When heteroatom substituents are present as in **31**, however, the reaction is facile and the lithium goes into the 2 position (as in **32**).[640] This regioselectivity can be quite valuable synthetically, and is now known as *directed ortho metalation*[641] (see **10-57**). Lithiation reactions do not necessarily rely on a complex-induced proximity effect.[642] With TMEDA/*n*-butyllithium-mediate arene lithiation reactions, the viability of directive effects (complex-induced proximate effects) has been questioned,[643] although it is not clear if this extends to other systems (particularly when there is a strong coordinating group, such as carbamate).[644] The 2 position is much more acidic than the 3 position (see Table 8.1), but a negative charge at C-3 is in a more favorable position to be stabilized by the Li^+. Formation of the ortho arylmagnesium compound has been accomplished with bases of the form $(R_2N)_2Mg$.[645] Note that H—Li exchange can be faster than Cl—Li exchange. Treatment of 2-chloro-5-phenylpyridine with *tert*-butyllithium leads to lithiation on the phenyl ring rather than Li—Cl exchange, and subsequent treatment with dimethyl sulfate gave 2-chloro-5-(2-methylphenyl)pyridine.[646] Heteroaromatic rings do react, however. The reaction of 2-chloropyridine with 3 equivalents of butyllithium-$Me_2NCH_2CH_2OLi$ and then iodomethane gave 2-chloro-6-methylpyridine.[647] The reaction of *N*-triisopropylsilyl indole with *tert*-butyllithium and then iodomethane gave the 3-methyl derivative.[648] Furfural (furan 2-carboxaldehyde) reacts with aryl iodides in the presence of a palladium catalyst to give the 5-arylfuran 2-carboxaldehyde.[649]

Benzene, naphthalene, and phenanthrene have been alkylated with alkyllithium reagents, though the usual reaction with these reagents is **12-22**,[650] and Grignard reagents have been used to alkylate naphthalene.[651] The addition–elimination

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[639] See, for example, Becht, J.-M.; Gissot, A.; Wagner, A.; Misokowski, C. *Tetrahedron Lett.* ***2004***, *45*, 9331.

[640] Slocum, D.W.; Jennings, C.A. *J. Org. Chem.* ***1976***, *41*, 3653. However, the regioselectivity can depend on reaction conditions: See Meyers, A.I.; Avila, W.B. *Tetrahedron Lett.* ***1980***, 3335.

[641] For a reviews of directed ortho metallation, see Snieckus, V. *Chem. Rev.* ***1990***, *90*, 879; Gschwend, H.W.; Rodriguez, H.R. *Org. React.* ***1979***, *26*, 1. See Green, L.; Chauder, B.; Snieckus, V. *J. Heterocylic Chem.* ***1999***, *36*, 1453. Also see Green, L.; Chauder, B.; Snieckus, V. *J. Heterocyclic Chem.* ***1999***, *36*, 1453. See Slocum, D.W.; Dietzel, P. *Tetrahedron Lett.* ***1999***, *40*, 1823.

[642] Chadwick, S.T.; Rennels, R.A.; Rutherford, J.L.; Collum, D.B. *J. Am. Chem. Soc.* ***2000***, *122*, 8640; Collum, D.B. *Acc. Chem. Res.* ***1992***, *25*, 448.

[643] Chadwick, S.T.; Rennels, R.A.; Rutherford, J.L.; Collum, D.B. *J. Am. Chem. Soc.* ***2000***, *122*, 8640.

[644] Hay, D. R.; Song, Z.; Smith, S.G.; Beak, P. *J. Am. Chem. Soc.* ***1988***, *110*, 8145.

[645] Eaton, P.E.; Lee, C.; Xiong, Y. *J. Am. Chem. Soc.* ***1989***, *111*, 8016.

[646] Fort, Y. Rodriguez, A.L. *J. Org. Chem.* ***2003***, *68*, 4918.

[647] Choppin, S. Gros, P.; Fort, Y. *Org. Lett.* ***2000***, *2*, 803.

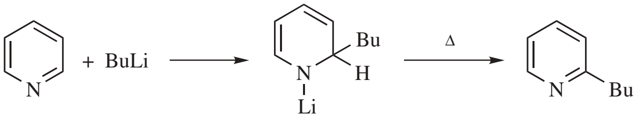
[648] Matsuzono, M.; Fukuda, T.; Iwao, M. *Tetrahedron Lett.* ***2001***, *42*, 7621.

[649] McClure, M.S.; Glover, B.; McSorley, E.; Millar, A.; Osterhout, M.H.; Roschangar, F. *Org. Lett.* ***2001***, *3*, 1677.

[650] Eppley, R.L.; Dixon, J.A. *J. Am. Chem. Soc.* ***1968***, *90*, 1606.

[651] Bryce-Smith, D.; Wakefield, B.J. *Tetrahedron Lett.* ***1964***, 3295.

mechanism apparently applies in these cases too. A protected form of benzaldehyde (protected as the benzyl imine) has been similarly alkylated at the *ortho*-position with butyllithium.[652]



The alkylation of heterocyclic nitrogen compounds[653] with alkyllithium reagents is called *Ziegler alkylation*. Aryllithium reagents give arylation. The reaction occurs by an addition–elimination mechanism and the adduct can be isolated.[654] Upon heating of the adduct, elimination of LiH occurs and an alkylated product is obtained. With respect to the 2-carbon the first step is the same as that of the S_NAr mechanism. The difference is that the unshared pair of electrons on the nitrogen combines with the lithium, so the extra pair of ring electrons has a place to go: it becomes the new unshared pair on the nitrogen. Heteroaromatic compounds can be alkylated. Pyrrole, for example, reacts with an allylic halide and zinc to give primarily the 3-substituted pyrrole.[655]

Mercuration of aromatic compounds[656] can be accomplished with mercuric salts, most often $Hg(OAc)_2$[657] to give ArHgOAc. This is ordinary electrophilic aromatic substitution and takes place by the arenium ion mechanism (p. 657).[658] Aromatic compounds can also be converted to arylthallium bis(trifluoroacetates) $ArTl(OOCCF_3)_2$ by treatment with thallium(III) trifluoroacetate[659] in trifluoroacetic acid.[660] These arylthallium compounds can be converted to phenols, aryl iodides or fluorides (**12-31**), aryl cyanides (**12-34**), aryl nitro compounds,[661] or aryl esters

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[652] Flippin, L.A.; Carter, D.S.; Dubree, N.J.P. *Tetrahedron Lett.* ***1993***, *34*, 3255.

[653] For a review of substitution by carbon groups on a nitrogen heterocycle, see Vorbrüggen, H.; Maas, M. *Heterocycles*, ***1988***, *27*, 2659. For a related review, see Comins, D.L.; O'Connor, S. *Adv. Heterocycl. Chem.* ***1988***, *44*, 199.

[654] See, for example, Armstrong, D.R.; Mulvey, R.E.; Barr, D.; Snaith, R.; Reed, D. *J. Organomet. Chem.* ***1988***, *350*, 191.

[655] Yadav, J.S.; Reddy, B.V.S.; Reddy, P.M.; Srinivas, Ch. *Tetrahedron Lett.* ***2002***, *43*, 5185.

[656] For reviews, see Larock, R.C. *Organomercury Compounds in Organic Synthesis*, Springer, NY, ***1985***, pp. 60–97; Wardell, J.L., in Zuckerman, J.J. *Inorganic Reactions and Methods*, Vol. 11, VCH, NY, ***1988***, pp. 308–318.

[657] For a review of mercuric acetate, see Butler, R.N., in Pizey, J.S. *Synthetic Reagents*, Vol. 4, Wiley, NY, ***1981***, pp. 1–145.

[658] For a review, see Taylor, R., in Bamford, C.H.; Tipper, C.F.H. *Comprehensive Chemical Kinetics*, vol. 13, Elsevier, NY, ***1972***, pp. 186–194. An alternative mechanism, involving radial cations, has been reported: Courtneidge, J.L.; Davies, A.G.; McGuchan, D.C.; Yazdi, S.N. *J. Organomet. Chem.* ***1988***, *341*, 63.

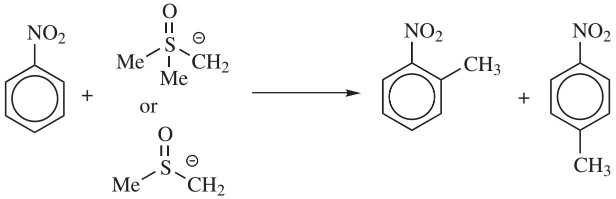
[659] For a review of this reagent, see Uemura, S., in Pizey, J.S. *Synthetic Reagents*, Vol. 5, Wiley, NY, ***1983***, pp. 165–241.

[660] Taylor, E.C.; Kienzle, F.; McKillop, A. *Org. Synth.* ***VI***, 826; Taylor, E.C.; Katz, A.H.; Alvarado, S.I.; McKillop, A. *J. Organomet. Chem.* ***1985***, *285*, C9. For reviews, see Usyatinskii, A.Ya.; Bregadze, V.I. *Russ. Chem. Rev.* ***1988***, *57*, 1054; Uemura, S., in Hartley, F.R.; Patai, S. *The Chemistry of the Metal-Carbon Bond*, Vol. 4, Wiley, NY, pp. 473–538.

[661] Uemura, S.; Toshimitsu, A.; Okano, M. *Bull. Chem. Soc. Jpn.* ***1976***, *49*, 2582.

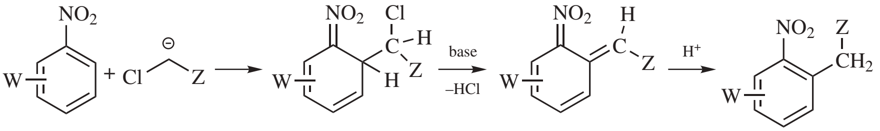
(**12-33**). The mechanism of thallation appears to be complex, with electrophilic and electron-transfer mechanisms both taking place.[662] Transient metalated aryl complexes can be formed that react with another aromatic compound. Aryl iodides reacted with benzene to form a biaryl in the presence of an iridium catalyst.[663] Aniline derivatives reacted with $TiCl_4$ to give the para-homo coupling product (R_2N—Ar—Ar—NR_2).[664]

Aromatic nitro compounds can be methylated with dimethyloxosulfonium methylid[665] or the methylsulfinyl carbanion (obtained by treatment of DMSO with a strong base):[666]



The latter reagent also methylates certain heterocyclic compounds (e.g., quinoline) and certain fused aromatic compounds (e.g., anthracene, phenanthrene).[666,667] The reactions with the sulfur carbanions are especially useful, since none of these substrates can be methylated by the Friedel–Crafts procedure (**11-10**). It has been reported[668] that aromatic nitro compounds can also be alkylated, not only with methyl but with other alkyl and substituted alkyl groups as well, in ortho and para positions, by treatment with an alkyllithium compound (or, with lower yields, a Grignard reagent), followed by an oxidizing agent, such as Br_2 or DDQ (p. 1710).

A different kind of alkylation of nitro compounds uses carbanion nucleophiles that have a chlorine at the carbanionic carbon. The following process takes place:[669]



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[662] Lau, W.; Kochi, J.K. *J. Am. Chem. Soc.* ***1984***, *106*, 7100; ***1986***, *108*, 6720.

[663] Fujita, K.-i.; Nonogawa, M.; Yamaguchi, R. *Chem. Commun.* ***2004***, 1926.

[664] Periasamy, M.; Jayakumar, K.N.; Bharathi, P. *J. Org. Chem.* ***2000***, *65*, 3548.

[665] Traynelis, V.J.; McSweeney, J.V. *J. Org. Chem.* ***1966***, *31*, 243.

[666] Russell, G.A.; Weiner, S.A. *J. Org. Chem.* ***1966***, *31*, 248.

[667] Argabright, P.A.; Hofmann, J.E.; Schriesheim, A. *J. Org. Chem.* ***1965***, *30*, 3233; Trost, B.M. *Tetrahedron Lett.* ***1966***, 5761; Yamamoto, Y.; Nisimura, T.; Nozaki, H. *Bull. Chem. Soc. Jpn.* ***1971***, *44*, 541.

[668] Kienzle, F. *Helv. Chim. Acta* ***1978***, *61*, 449.

[669] In some cases, the intermediate bearing the CHCl(Z) unit has been isolated: Stahly, G.P.; Stahly, B.C.; Maloney, J.R. *J. Org. Chem.* ***1988***, *53*, 690.

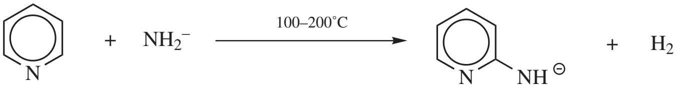
This type of process is called *vicarious nucleophilic substitution of hydrogen*.[670] The Z group is electron -withdrawing (e.g., SO_2R, SO_2OR, SO_2NR_2, COOR, or CN); it stabilizes the negative charge. The carbanion attacks the activated ring ortho or para to the nitro group.[671] Hydride ion H^- is not normally a leaving group, but in this case the presence of the adjacent Cl allows the hydrogen to be replaced. Hence, Cl is a "vicarious" leaving group. Other leaving groups have been used (e.g., OMe, SPh), but Cl is generally the best. Many groups W in ortho, meta, or para positions do not interfere. The reaction is also successful for di- and trinitro compounds, for nitronaphthalenes,[672] and for many nitro heterocycles. $Z{-}^{\ominus}CR{-}Cl$ may also be used.[673] When Br_3C^- or Cl_3C^- is the nucleophile the product is $ArCHX_2$, which can easily be hydrolyzed to ArCHO.[674] This is therefore an indirect way of formylating an aromatic ring containing one or more NO_2 groups, which cannot be done by any of the formylations mentioned in Chapter 11 (**11-1–11-18**).

Replacement of an amino group is possible. When aniline derivatives were treated with allyl bromide and *tert*-butyl nitrite (*t*-BuONO), the aryl–allyl coupling product was formed ($Ar{-}NH_2 \rightarrow Ar{-}CH_2CH{=}CH_2$).[675]

For the introduction of CH_2SR groups into phenols, see **11-23**. See also **14-19**.
OS **II**, 517.

13-18 Amination of Nitrogen Heterocycles

Amination or **Amino-de-hydrogenation**



Pyridine and other heterocyclic nitrogen compounds can be aminated with alkali-metal amides in a process called the *Chichibabin reaction*.[676] The attack is always in the 2 position unless both such positions are filled, in which case the 4 position is attacked. Substituted alkali-metal amides (e.g., RNH^- and R_2N^-) have also been used. The mechanism is probably similar to that of **13-17** The existence of intermediate ions, such as **33**

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[670] Goliński, J.; Mąkosza, M. *Tetrahedron Lett.* ***1978***, 3495. For reviews, see Mąkosza, M. *Synthesis* ***1991***, 103; *Russ. Chem. Rev.* ***1989***, *58*, 747; Mąkosza, M.; Winiarski, J. *Acc. Chem. Res.* ***1987***, *20*, 282.

[671] For a discussion of the mechanism, of vicarious nucleophilic aromatic substitution, see Mąkosza, M.; Lemek, T.; Kwast, A.; Terrier, F. *J. Org. Chem.* ***2002***, *67*, 394.

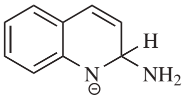
[672] Mąkosza, M.; Danikiewicz, W.; Wojciechowski, K. *Liebigs Ann. Chem.* ***1987***, 711.

[673] See Mudryk, B.; Mąkosza, M. *Tetrahedron* ***1988***, *44*, 209.

[674] Mąkosza, M.; Owczarczyk, Z. *J. Org. Chem.* ***1989***, *54*, 5094. See also, Mąkosza, M.; Winiarski, J. *Chem. Lett.* ***1984***, 1623.

[675] Ek, F.; Axelsson, O.; Wistrand, L.-G.; Frejd, T. *J. Org. Chem.* ***2002***, *67*, 6376.

[676] For reviews, see Vorbrüggen, H. *Adv. Heterocycl. Chem.* ***1990***, *49*, 117; McGill, C.K.; Rappa, A. *Adv. Heterocycl. Chem.* ***1988***, *44*, 1; Pozharskii, A.F.; Simonov, A.M.; Doron'kin, V.N. *Russ. Chem. Rev.* ***1978***, *47*, 1042.



33

(from quinoline) has been demonstrated by NMR spectra.[677] A pyridyne type of intermediate was ruled out by several observations including the facts that 3-ethylpyridine gave 2-amino-3-ethylpyridine[678] and that certain heterocycles that cannot form an aryne could nevertheless be successfully aminated. Nitro compounds do not give this reaction,[679] but they have been aminated ($ArH \rightarrow ArNH_2$ or ArNHR) via the vicarious substitution principle (see **13-17**), using 4-amino- or 4-alkylamino-1,2,4-triazoles as nucleophiles.[680] The vicarious leaving group in this case is the triazole ring. Note, however, that 3-nitropyridine was converted to 6-amino-3-nitropyridine by reaction with KOH, hydroxylamine and $ZnCl_2$.[681]

Analogous reactions have been carried out with hydrazide ions, R_2NNH^-.[682] A mixture of NO_2 and O_3, with excess $NaHSO_3$, converted pyridine to 3-aminopyridine.[683] For other methods of aminating aromatic rings, see **11-6**.

There are no *Organic Syntheses* references, but see OS **V**, 977, for a related reaction.

NITROGEN AS LEAVING GROUP

The diazonium group can be replaced by a number of groups.[684] Some of these are nucleophilic substitutions, with S_N1 mechanisms (p. 432), but others are free-radical reactions and are treated in Chapter 14. The solvent in all these reactions is usually water. With other solvents it has been shown that the S_N1 mechanism is favored by solvents of low nucleophilicity, while those of high nucleophilicity favor free-radical mechanisms.[685] The N_2^+ group[686] can be replaced by Cl^-, Br^-, and CN^-, by a nucleophilic mechanism (see OS **IV**, 182), but the Sandmeyer reaction is much more useful (**14-20**). Transition metal catalyzed reactions are known involving aryldiazonium salts, and diazonium variants of the Heck reaction (**13-10**) and Suzuki coupling (**13-12**) were discussed previously. As mentioned on p. 866 it must be

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[677] Zoltewicz, J.A.; Helmick, L.S.; Oestreich, T.M.; King, R.W.; Kandetzki, P.E. *J. Org. Chem.* ***1973***, *38*, 1947; Woźniak, M.; Baránski, A.; Nowak, K.; van der Plas, H.C. *J. Org. Chem.* ***1987***, *52*, 5643.

[678] Ban, Y.; Wakamatsu, T. *Chem. Ind.* (*London*) ***1964***, 710.

[679] See, for example, Levitt, L.S.; Levitt, B.W. *Chem. Ind.* (*London*) ***1975***, 520.

[680] Katritzky, A.R.; Laurenzo, K.S. *J. Org. Chem.* ***1986***, *51*, 5039; ***1988***, *53*, 3978.

[681] Bakke, J.M.; Svensen, H.; Trevisan, R. *J. Chem. Soc. Perkin Trans. 1* ***2001***, 376.

[682] Kauffmann, T.; Hansen, J.; Kosel, C.; Schoeneck, W. *Liebigs Ann. Chem.* ***1962***, *656*, 103.

[683] Suzuki, H.; Iwaya, M.; Mori, T. *Tetrahedron Lett.* ***1997***, *38*, 5647.

[684] For a review of such reactions, see Wulfman, D.S., in Patai, S. *The Chemistry of Diazonium and Diazo Groups*, pt. 1, Wiley, NY, ***1978***, pp. 286–297.

[685] Szele, I.; Zollinger, H. *Helv. Chim. Acta* ***1978***, *61*, 1721.

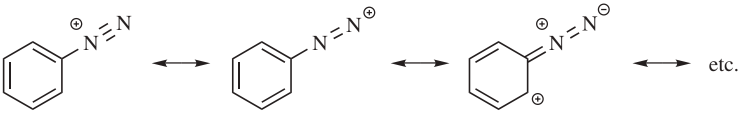
[686] For a discussion of the global and local electrophilicity patterns of diazonium ions, see Pérez, P. *J. Org. Chem.* ***2003***, *68*, 5886.

kept in mind that the N_2^+ group can activate the removal of another group on the ring. In a few cases, nitrogen groups, such as nitro or ammonium can be replaced.

13-19 Diazotization

$$\mathrm{Ar{-}NH_2} \quad + \quad \mathrm{HONO} \longrightarrow \mathrm{Ar{-}\overset{\oplus}{N}{\equiv}N}$$

When primary aromatic amines are treated with nitrous acid, diazonium salts are formed.[687] The reaction also occurs with aliphatic primary amines, but aliphatic diazonium ions are extremely unstable, even in solution (see p. 500). Aromatic diazonium ions are more stable, because of the resonance interaction between the nitrogens and the ring:



34 **35**

Incidentally, **34** contributes more to the hybrid than **35**, as shown by bond-distance measurements.[688] In benzenediazonium chloride, the C—N distance is ~1.42 Å, and the N—N distance ~1.08 Å,[689] which values fit more closely to a single and a triple bond than to two double bonds (see Table 1.5). Even aromatic diazonium salts are stable only at low temperatures, usually only < 5°C, although more stable ones, such as the diazonium salt obtained from sulfanilic acid, are stable up to 10 or 15°C. Diazonium salts are usually prepared in aqueous solution and used without isolation,[690] although it is possible to prepare solid diazonium salts if desired (see **13-23**). The stability of aryl diazonium salts can be increased by crown ether complexion.[691]

For aromatic amines, the reaction is very general. Halogen, nitro, alkyl, aldehyde, sulfonic acid, and so on, groups do not interfere. Since aliphatic amines do not react with

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[687] For reviews, see, in Patai, S. *The Chemistry of Diazonium and Diazo Groups*, Wiley, NY, ***1978***, the articles by Hegarty, A.F. pt. 2, pp. 511–591, and Schank, K. pt. 2, pp. 645–657; Godovikova, T.I.; Rakitin, O.A.; Khmel'nitskii, L.I. *Russ. Chem. Rev.* ***1983***, *52*, 440; Challis, B.C.; Butler, A.R., in Patai, S. *The Chemistry of the Amino Group*; Wiley, NY, ***1968***, pp. 305–320. For a review with respect to heterocyclic amines, see Butler, A.R. *Chem. Rev.* ***1975***, *75*, 241.

[688] For a review of diazonium salt structures, see Sorriso, S., in Patai, S. *The Chemistry of Diazonium and Diazo Groups*, pt. 1, Wiley, NY, ***1978***, pp. 95–105.

[689] Rømming, C. *Acta Chem. Scand.* ***1959***, *13*, 1260; ***1963***, *17*, 1444; Sorriso, S., in Patai, S. *The Chemistry of Diazonium and Diazo Groups*, pt. 1, Wiley, NY, ***1978***, p. 98; Ball, R.G.; Elofson, R.M. *Can. J. Chem.* ***1985***, *63*, 332.

[690] For a review of reactions of diazonium salts, see Wulfman, D.S., in Patai, S. *The Chemistry of Diazonium and Diazo Groups*, pt. 1, Wiley, NY, ***1978***, pp. 247–339.

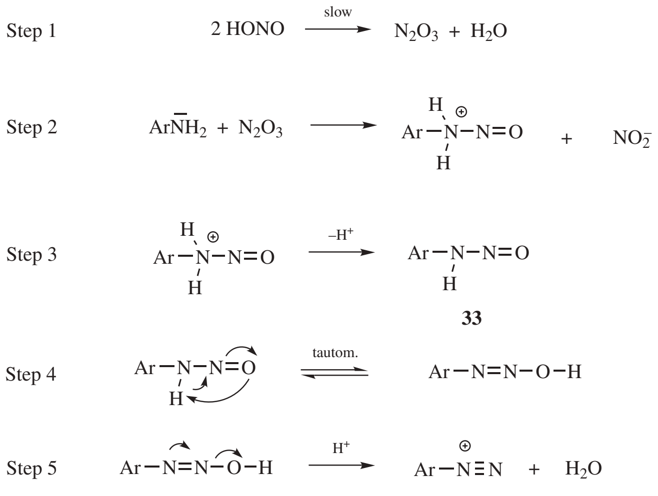
[691] Korzeniowski, S.H.; Leopold, A.; Beadle, J.R.; Ahern, M.F.; Sheppard, W.A.; Khanna, R.K.; Gokel, G.W. *J. Org. Chem.* ***1981***, *46*, 2153, and references cited therein. For reviews, see Bartsch, R.A., in Patai, S.; Rappoport, Z. *The Chemistry of Functional Groups, Supplement C* pt. 1, Wiley, NY, ***1983***, pp. 889–915; Bartsch, R.A. *Prog. Macrocyclic Chem.* ***1981***, *2*, 1.

nitrous acid below a pH ∼ 3, it is even possible, by working at a pH ∼ 1, to diazotize an aromatic amine without disturbing an aliphatic amino group in the same molecule.[692]

$$\text{EtOOC—CH}_2\text{—NH}_2 + \text{HONO} \longrightarrow \text{EtOOC—CH=}\overset{\oplus}{\text{N}}\text{=N}$$

If an aliphatic amino group is a to a COOR, CN, CHO, COR, and so on, and has an a hydrogen, treatment with nitrous acid gives not a diazonium salt, but a *diazo compound*.[693] Such diazo compounds can also be prepared, often more conveniently, by treatment of the substrate with isoamyl nitrite and a small amount of acid.[694] Certain heterocyclic amines also give diazo compounds rather than diazonium salts.[695]

Despite the fact that diazotization takes place in acid solution, the actual species attacked is not the salt of the amine, but the small amount of free amine present.[696] It is because aliphatic amines are stronger bases than aromatic ones that at pH values < 3 there is not enough free amine present for the former to be diazotized, while the latter still undergo the reaction. In dilute acid the actual attacking species is N_2O_3, which acts as a carrier of NO^+. Evidence is that the reaction is second order in nitrous acid and, at sufficiently low acidities, the amine does not appear in the rate expression.[697] Under these conditions the mechanism is



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[692] Kornblum, N.; Iffland, D.C. *J. Am. Chem. Soc.* ***1949***, *71*, 2137.

[693] For a monograph on diazo compounds, see Regitz, M.; Maas, G. *Diazo Compounds*, Academic Press, NY, ***1986***. For reviews, see, in Patai, S. *The Chemistry of Diazonium and Diazo Groups*, pt. 1, Wiley, NY, ***1978***, the articles by Regitz, M. pt. 2, pp. 659–708, 751–820, and Wulfman, D.S.; Linstrumelle, G.; Cooper, C.F. pt. 2, pp. 821–976.

[694] Takamura, N.; Mizoguchi, T.; Koga, K.; Yamada, S. *Tetrahedron* ***1975***, *31*, 227.

[695] Butler, R.N., in Patai, S. *The Chemistry of the Amino Group*, Wiley, NY, ***1968***, p. 305.

[696] Challis, B.C.; Ridd, J.H. *J. Chem. Soc.* ***1962***, 5197, 5208; Challis, B.C.; Larkworthy, L.F.; Ridd, J.H. *J. Chem. Soc.* ***1962***, 5203.

[697] Hughes, E.D.; Ingold, C.K.; Ridd, J.H. *J. Chem. Soc.* ***1958***, 58, 65, 77, 88; Hughes, E.D.; Ridd, J.H. *J. Chem. Soc.* ***1958***, 70, 82.

There exists other evidence for this mechanism.[698] Other attacking species can be NOCl, $H_2NO_2^+$, and at high acidities even NO^+. Nucleophiles (e.g., Cl^-, SCN^-, thiourea) catalyze the reaction by converting the HONO to a better electrophile (e.g., $HNO_2 + Cl^- + H^+ \rightarrow NOCl + H_2O$).[699]

N-Aryl ureas are converted to the aryldiazonium nitrate upon treatment with $NaNO_2$ and H_2SO_4 in dioxane[700] or with DMF—NO_2 in DMF.[701]

There are many preparations of diazonium salts listed in *Organic Syntheses*, but they are always prepared for use in other reactions. We do not list them here, but under reactions in which they are used. The preparation of aliphatic diazo compounds can be found in OS **III**, 392; **IV**, 424. See also, OS **VI**, 840.

13-20 Hydroxylation of Aryldiazonium Salts

Hydroxy-de-diazoniation

$$ArN_2^+ \quad + \quad H_2O \longrightarrow ArOH$$

This reaction is formally analogous to **13-1**, but with a N_2^+ leaving group rather than a halide. Water is usually present whenever diazonium salts are made, but at these temperatures (0–5°C) the reaction proceeds very slowly. When it is *desired* to have OH replace the diazonium group, the excess nitrous acid is destroyed and the solution is usually boiled. Some diazonium salts require even more vigorous treatment, for example, boiling with aqueous sulfuric acid or with trifluoroacetic acid containing potassium trifluoroacetate.[702] The reaction can be performed on solutions of any diazonium salts, but hydrogen sulfates are preferred to chlorides or nitrates, since in these cases there is competition from the nucleophiles Cl^- or NO_3^-. A better method, which is faster, avoids side reactions, takes place at room temperature, and gives higher yields consists of adding Cu_2O to a dilute solution of the diazonium salt dissolved in a solution containing a large excess of $Cu(NO_3)_2$.[703] Aryl radicals are intermediates when this method is used. It has been shown that aryl radicals are at least partly involved when ordinary hydroxy-de-diazoniation is carried out in weakly alkaline aqueous solution.[704] Decomposition of arenediazonium tetrafluoroborates in F_3CSO_2OH gives aryl triflates directly, in high yields.[705]

OS **I**, 404; **III**, 130, 453, 564; **V**, 1130.

[698] For discussions, see Williams, D.L.H. *Nitrosation*, Cambridge University Press, Cambridge, ***1988***, pp. 95–109; Ridd, J.H. *Q. Rev. Chem. Soc.* ***1961***, *15*, 418, p. 422.

[699] Williams, D.L.H. *Nitrosation*; Cambridge University Press, Cambridge, ***1988***, pp. 84–93.

[700] Zhang, Z.; Zhang, Q.; Zhang, S.; Liu,, X.; Zhao, G. *Synth. Commun.* ***2001***, *31*, 329.

[701] Zhang, O.Z.; Zhang, S.; Zhang, J. *Synth. Commun.* ***2001***, *31*, 1243.

[702] Horning, D.E.; Ross, D.A.; Muchowski, J.M. *Can. J. Chem.* ***1973***, *51*, 2347.

[703] Cohen, T.; Dietz, Jr., A.G.; Miser, J.R. *J. Org. Chem.* ***1977***, *42*, 2053.

[704] Dreher, E.; Niederer, P.; Rieker, A.; Schwarz, W.; Zollinger, H. *Helv. Chim. Acta* ***1981***, *64*, 488.

[705] Yoneda, N.; Fukuhara, T.; Mizokami, T.; Suzuki, A. *Chem. Lett.* ***1991***, 459.

13-21 Replacement by Sulfur-Containing Groups

Mercapto-de-diazoniation, and so on

$$\begin{array}{llll}
\mathrm{ArN_2^+} + \mathrm{HS^-} & \longrightarrow & \mathrm{ArSH} & \\
\mathrm{ArN_2^+} + \mathrm{S^{2-}} & \longrightarrow & \mathrm{ArSAr} & \\
\mathrm{ArN_2^+} + \mathrm{RS^-} & \longrightarrow & \mathrm{ArSR} & \\
\mathrm{ArN_2^+} + \mathrm{SCN^-} & \longrightarrow & \mathrm{ArSCN} & + \ \mathrm{ArNCS}
\end{array}$$

These reactions are convenient methods for incorporating a sulfur-containing group onto an aromatic ring. With Ar'S^-, diazosulfides Ar—N=N—S—Ar' are intermediates,[706]which can in some cases be isolated.[707] Thiophenols can be made as shown above, but more often the diazonium ion is treated with EtO–CSS^- or S_2^{2-}, which give the expected products, and these are easily convertible to thiophenols. Aryldiazonium salts are prepared by the reaction of an aniline derivative with an alkyl nitrite (RONO), and when formed in the presence of dimethyl disulfide (MeS–SMe), the product is the thioether, Ar–S–Me.[708] Aryl triflates have been converted to the aryl thiol using NaST(P5) and a palladium catalyst, followed by treatment with tetrabutylammonium fluoride[709] (see also, **14-22**).

OS **II**, 580; **III**, 809 (but see OS **V**, 1050). Also see, OS **II**, 238.

13-22 Replacement by Iodine

Iodo-de-diazoniation

$$\mathrm{ArN_2^+} + \mathrm{I^-} \longrightarrow \mathrm{ArI}$$

One of the best methods for the introduction of iodine into aromatic rings (see **13-7**) is the reaction of diazonium salts with iodide ions. Analogous reactions with chloride, bromide, and fluoride ions give poorer results, and **14-20** and **13-23** are preferred for the preparation of aryl chlorides, bromides, and fluorides. However, when other diazonium reactions are carried out in the presence of these ions, halides are usually side products. Aniline has also been converted to fluorobenzene by treatment with *t*-BuONO and SiF_4 followed by heating.[710] A related reaction between PhN=N–NC_4H_8 and iodine gave iodobenzene.[711]

The actual attacking species is probably not only I^- if it is I^- at all. The iodide ion is oxidized (by the diazonium ion, nitrous acid, or some other oxidizing agent)

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[706] Abeywickrema, A.N.; Beckwith, A.L.J. *J. Am. Chem. Soc.* ***1986***, *108*, 8227, and references cited therein.

[707] See, for example, Price, C.C.; Tsunawaki, S. *J. Org. Chem.* ***1963***, *28*, 1867.

[708] Allaire, F.S.; Lyga, J.W. *Synth. Commun.* ***2001***, *31*, 1857.

[709] Arnould, J.C.; Didelot, M.; Cadilhac, C.; Pasquet, M.J. *Tetrahedron Lett.* ***1996***, *37*, 4523.

[710] Tamura, M.; Shibakami, M.; Sekiya, A. *Eur. J. Org. Chem.* ***1998***, 725.

[711] Wu, Z.; Moore, J.S. *Tetrahedron Lett.* ***1994***, *35*, 5539.

to iodine, which in a solution containing iodide ions is converted to I_3^-; this is the actual attacking species, at least partly. This was shown by isolation of $ArN_2^+ I_3^-$ salts, which, on standing, gave ArI.[712] From this, it can be inferred that the reason the other halide ions give poor results is not that they are poor nucleophiles but that they are poor reducing agents (compared with iodide). There is also evidence for a free-radical mechanism.[713]

The hydroxyl group of a phenol can be replaced with iodine. The reaction of phenol with a boronic ester and a palladium catalyst, followed by reaction with NaI and chloramine-T converts phenol to iodobenzene.[714]

OS **II**, 351, 355, 604; **V**, 1120.

13-23 The Schiemann Reaction

Fluoro-de-diazoniation (overall transformation)

$$ArN_2^+ BF_4^- \xrightarrow{\Delta} ArF + N_2 \quad BF_3$$

Heating of diazonium fluoroborates (the *Schiemann* or *Balz–Schiemann reaction*) is by far the best way of introducing fluorine into an aromatic ring.[715] In the most common procedure, the fluoroborate salts are prepared by diazotizing as usual with nitrous acid and HCl and then adding a cold aqueous solution of $NaBF_4$, HBF_4, or NH_4BF_4. A precipitate forms, which is dried, and the salt is heated in the dry state. These salts are unusually stable for diazonium salts, and the reaction is usually successful. In general, any aromatic amine that can be diazotized will form a BF_4^- salt, usually with high yields. The diazonium fluoroborates can be formed directly from primary aromatic amines with *tert*-butyl nitrite and BF_3–etherate.[716] The reaction has also been carried out on $ArN_2^+ PF_6^-$, $ArN_2^+ SbF_6^-$, and $ArN_2^+ AsF_6^-$ salts, in many cases with better yields.[717] Aryl chlorides and bromides are more commonly prepared by the Sandmeyer reaction (**14-20**). In an alternative procedure, aryl fluorides have been prepared by treatment of aryltriazenes $Ar{-}N{=}N{-}NR_2$ with 70% HF in pyridine.[718]

The mechanism is of the S_N1 type. That aryl cations are intermediates was shown by the following experiments:[719] Aryl diazonium chlorides are known to

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[712] Carey, J.G.; Millar, I.T. *Chem. Ind.* (*London*) ***1960***, 97.

[713] Singh, P.R.; Kumar, R. *Aust. J. Chem.* ***1972***, *25*, 2133; Kumar, R.; Singh, P.R. *Tetrahedron Lett.* ***1972***, 613; Meyer, G.; Rössler, K.; Stöcklin, G. *J. Am. Chem. Soc.* ***1979***, *101*, 3121; Packer, J.E.; Taylor, R.E.R. *Aust. J. Chem.* ***1985***, *38*, 991; Abeywickrema, A.N.; Beckwith, A.L.J. *J. Org. Chem.* ***1987***, *52*, 2568.

[714] Thompson, A.L.S.; Kabalka, G.W.; Akula, M.R.; Huffman, J.W. *Synthesis* ***2005***, 547.

[715] For a review, see Suschitzky, H. *Adv. Fluorine Chem.* ***1965***, *4*, 1.

[716] Doyle, M.P.; Bryker, W.J. *J. Org. Chem.* ***1979***, *44*, 1572.

[717] Rutherford, K.G.; Redmond, W.; Rigamonti, J. *J. Org. Chem.* ***1961***, *26*, 5149; Sellers, C.; Suschitzky, H. *J. Chem. Soc. C* ***1968***, 2317.

[718] Rosenfeld, M.N.; Widdowson, D.A. *J. Chem. Soc. Chem. Commun.* ***1979***, 914. For another alternative procedure, see Yoneda, N.; Fukuhara, T.; Kikuchi, T.; Suzuki, A. *Synth. Commun.* ***1989***, *19*, 865.

[719] See also, Swain, C.G.; Sheats, J.E.; Harbison, K.G. *J. Am. Chem. Soc.* ***1975***, *97*, 783, 796; Becker, H.G.O.; Israel, G. *J. Prakt. Chem.* ***1979***, *321*, 579.

arylate other aromatic rings by a free-radical mechanism (see **13-27**). In radical arylation it does not matter whether the other ring contains electron-withdrawing or electron-donating groups; in either case a mixture of isomers is obtained, since the attack is not by a charged species. If an aryl radical were an intermediate in the Schiemann reaction and the reaction were run in the presence of other rings, it should not matter what kinds of groups were on these other rings: Mixtures of biaryls should be obtained in all cases. But if an aryl cation is an intermediate in the Schiemann reaction, compounds containing meta-directing groups, that is, meta directing for *electrophilic* substitutions, should be meta-arylated and those containing ortho–para-directing groups should be ortho– and para arylated, since an aryl cation should behave in this respect like any electrophile (see Chapter 11). Experiments have shown[720] that such orientation is observed, demonstrating that the Schiemann reaction has a positively charged intermediate. The attacking species, in at least some instances, is not F^- but BF_4^-.[721]

OS **II**, 188, 295, 299; **V**, 133.

13-24 Conversion of Amines to Azo Compounds

***N*-Arylimino-de-dihydro-bisubstitution**

$$\mathrm{ArNH_2} \quad + \quad \mathrm{Ar'NO} \xrightarrow{\mathrm{HOAc}} \mathrm{Ar{-}N{=}N{-}Ar'}$$

Aromatic nitroso compounds combine with primary arylamines in glacial acetic acid to give symmetrical or unsymmetrical azo compounds (the *Mills reaction*).[722] A wide variety of substituents may be present in both aryl groups. Unsymmetrical azo compounds have also been prepared by the reaction between aromatic nitro compounds $ArNO_2$ and *N*-acyl aromatic amines Ar'NHAc.[723] The use of phase-transfer catalysis increased the yields.

13-25 Methylation, Vinylation, and Arylation of Diazonium Salts

Methyl-de-diazoniation, and so on

$$\mathrm{ArN_2^+} \quad + \quad \mathrm{Me_4Sn} \xrightarrow[\mathrm{MeCN}]{\mathrm{Pd(OAc)_2}} \mathrm{ArMe}$$

A methyl group can be introduced into an aromatic ring by treatment of diazonium salts with tetramethyltin and a palladium acetate catalyst.[724] The reaction has been performed with Me, Cl, Br, and NO_2 groups on the ring. A vinylic group can

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[720] Makarova, L.G.; Matveeva, M.K. *Bull. Acad. Sci. USSR Div. Chem. Sci.* ***1958***, 548; Makarova, L.G.; Matveeva, M.K.; Gribchenko, E.A. *Bull. Acad. Sci. USSR Div. Chem. Sci.* ***1958***, 1399.

[721] Swain, C.G.; Rogers, R.J. *J. Am. Chem. Soc.* ***1975***, *97*, 799.

[722] For a review, see Boyer, J.H., in Feuer, H. *The Chemistry of the Nitro and Nitroso Groups*, pt. 1, Wiley, NY, ***1969***, pp. 278–283.

[723] Ayyangar, N.R.; Naik, S.N.; Srinivasan, K.V. *Tetrahedron Lett.* ***1989***, *30*, 7253.

[724] Kikukawa, K.; Kono, K.; Wada, F.; Matsuda, T. *J. Org. Chem.* ***1983***, *48*, 1333.

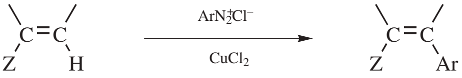
be introduced with $CH_2{=}CHSnBu_3$. When an aryl amine is treated with *tert*-butyl hyponitrite (*t*-BuONO) and allyl bromide, the nitrogen is displaced to the give allyl–aryl compound.[725]

Aryl diazonium salts can be used coupled with alkenes in a Heck-like reaction (**12-15**).[726] Other reactive aryl species also couple with aryldiazonium salts in the presence of a palladium catalyst.[727] A Suzuki type coupling (**13-9**) has also been reported using arylboronic acids, aryldiazonium salts and a palladium catalyst.[728]

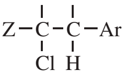
Aryltrifluoroborates (**12-28**) react with aryldiazonium salts in the presence of a palladium catalyst to give the corresponding biaryl.[729] Arylborate esters also reacat using a palladium catlsyt, and the aryl dizaonium unit reacts faster than an aryl halide.[730]

13-26 Arylation of Activated Alkenes by Diazonium Salts: Meerwein Arylation

Arylation or **Aryl-de-hydrogenation**



Alkenes activated by an electron-withdrawing group (Z may be C=C, halogen, C=O, Ar, CN, etc.) can be arylated by treatment with a diazonium salt and a cupric chloride[731] catalyst. This is called the *Meerwein arylation reaction*.[732] Addition of ArCl to the double bond (to give) is a side reaction (**15-46**). In an improved procedure, an arylamine is treated with an alkyl nitrite (generating ArN_2^+ *in situ*) and a copper(II) halide in the presence of the alkene.[733]



$$\mathrm{Z}-\underset{\mathrm{Cl}}{\overset{|}{\underset{|}{\mathrm{C}}}}-\underset{\mathrm{H}}{\overset{|}{\underset{|}{\mathrm{C}}}}-\mathrm{Ar}$$

The mechanism is probably of the free-radical type, with $\mathrm{AR}^{\bullet}$ (**36**) forming as in **14-20**, and then halogen transfer to give **37** or elimination to give **38**.[734]

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[725] Ek, F.; Wistrand, L.-G.; Frejd, T. *J. Org. Chem.* ***2003***, *68*, 1911.

[726] Sengupta, S.; Bhattacharya, S. *J. Chem. Soc. Perkin Trans. 1* ***1993***, 1943.

[727] Darses, S.; Genêt, J.-P.; Brayer, J.-L.; Demoute, J.-P. *Tetrahedron Lett.* ***1997***, *38*, 4393.

[728] Darses, S.; Jeffery, T.; Genêt, J.-P.; Brayer, J.-L.; Demoute, J.-P. *Tetrahedron Lett.* ***1996***, *37*, 3857.

[729] Darses, S.; Michaud, G.; Genêt, J.-P. *Eur. J. Org. Chem.* ***1999***, 1875.

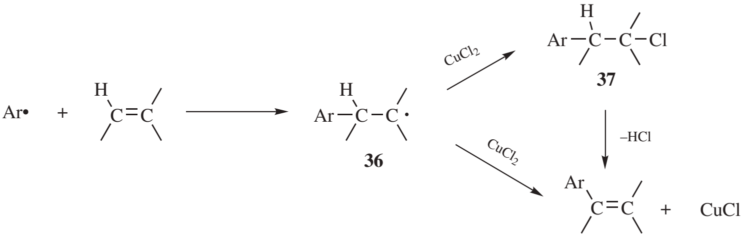
[730] Willis, D.M.; Strongin, R.M. *Tetahedron Lett.* ***2000***, *41*, 6271.

[731] $FeCl_2$ is also effective: Ganushchak, N.I.; Obushak, N.D.; Luka, G.Ya. *J. Org. Chem. USSR* ***1981***, *17*, 765.

[732] For reviews, see Dombrovskii, A.V. *Russ. Chem. Rev.*, ***1984***, *53*, 943; Rondestvedt, Jr., C.S. *Org. React.*, ***1976***, *24*, 225.

[733] Doyle, M.P.; Siegfried, B.; Elliott, R.C.; Dellaria Jr., J.F. *J. Org. Chem.* ***1977***, *42*, 2431.

[734] Dickerman, S.C.; Vermont, G.B. *J. Am. Chem. Soc.* ***1962***, *84*, 4150; Morrison, R.T.; Cazes, J.; Samkoff, N.; Howe, C.A. *J. Am. Chem. Soc.* ***1962***, *84*, 4152.



36 37 38

The radical **36** can react with cupric chloride by two pathways, one of which leads to addition and the other to substitution. Even when the addition pathway is taken, however, the substitution product may still be formed by subsequent elimination of HCl. Note that radical reactions are presented in Chapter 14, but the coupling of an alkene with an aromatic compound containing a leaving group prompted its placement here. Note also the similarity to the Heck reaction in **13-10**.

A variation of this reaction uses a palladium–copper catalyst on Montmorillonite clay. When aniline reacted with methyl acrylate in acetic acid and the Pd–Cu–Montmorillonite K10, $PhCH{=}CHCO_2Me$ was obtained.[735]

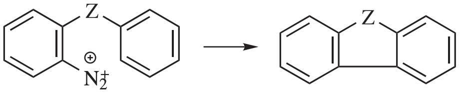
OS **IV**, 15.

13-27 Arylation of Aromatic Compounds by Diazonium Salts

Arylation or **Aryl-de-hydrogenation**

$$ArH \quad + \quad Ar'N_2^+ \; X^- \xrightarrow{OH^-} Ar{-}Ar'$$

When the normally acidic solution of a diazonium salt is made alkaline, the aryl portion of the diazonium salt can couple with another aromatic ring. Known as the *Gomberg* or *Gomberg–Bachmann reaction*,[736] it has been performed on several types of aromatic rings and on quinones. Yields are not high (usually <40%) because of the many side reactions undergone by diazonium salts, though higher yields have been obtained under phase-transfer conditions.[737] The conditions of the Meerwein reaction (**13-26**), treatment of the solution with a copper-ion catalyst, have also been used, as has the addition of sodium nitrite in Me_2SO (to benzene diazonium fluoroborate in DMSO).[738]



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[735] Waterlot, C.; Couturier, D.; Rigo, B. *Tetrahedron Lett.* ***2000*** *41*, 317.

[736] For reviews, see Bolton, R.; Williams, G.H. *Chem. Soc. Rev.*, ***1986***, *15*, 261; Hey, D.H. *Adv. Free-Radical Chem.* ***1966***, *2*, 47. For a review applied to heterocyclic substrates, see Vernin, G.; Dou, H.J.; Metzger, J. *Bull. Soc. Chim. Fr.* ***1972***, 1173.

[737] Beadle, J.R.; Korzeniowski, S.H.; Rosenberg, D.E.; Garcia-Slanga, B.J.; Gokel, G.W. *J. Org. Chem.* ***1984***, *49*, 1594.

[738] Kamigata, N.; Kurihara, T.; Minato, H.; Kobayashi, M. *Bull. Chem. Soc. Jpn.* ***1971***, *44*, 3152.

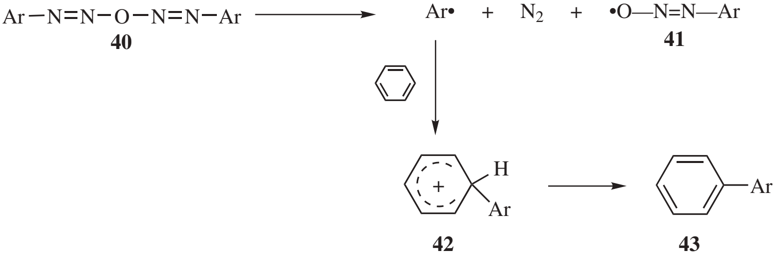
When the Gomberg–Bachmann reaction is performed intramolecularly as in the formation of **39**, either by the alkaline solution or by the copper-ion procedure, it is called the *Pschorr ring closure*[739] and yields are usually somewhat higher. Still higher yields have been obtained by carrying out the Pschorr reaction electrochemically.[740] The Pschorr reaction has been carried out for Z = CH=CH, CH_2CH_2, NH, C=O, CH_2, and quite a few others. A rapid and convenient way to carry out the Pschorr synthesis is to diazotize the amine substrate with isopropyl nitrite in the presence of sodium iodide, in which case the ring-closed product is formed in one step.[741]

Other compounds with nitrogen–nitrogen bonds have been used instead of diazonium salts. Among these are *N*-nitroso amides [ArN(NO)COR], triazenes,[742] and azo compounds. Still another method involves treatment of an aromatic primary amine directly with an alkyl nitrite in an aromatic substrate as solvent.[743]

In each case, the mechanism involves generation of an aryl radical from a covalent azo compound. In acid solution, diazonium salts are ionic and their reactions are polar. When they cleave, the product is an aryl cation (see p. 856). However, in neutral or basic solution, diazonium ions are converted to covalent compounds, and these cleave to give free radicals (Ar• and Z•). Note that radical reactions are presented in Chapter 14, but the coupling of an aromatic ring with an aromatic compound containing a leaving group prompted its placement here. Note the similarity to the Suzuki reaction in **13-12**.

$$\mathrm{Ar{-}N{=}N{-}Z} \longrightarrow \mathrm{Ar\bullet} + \mathrm{N{\equiv}N} + \mathrm{Z\bullet}$$

Under Gomberg–Bachmann conditions, the species that cleaves is the anhydride, **40**.[744]



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[739] For a review, see Abramovitch, R.A. *Adv. Free-Radical Chem.* ***1966***, *2*, 87.

[740] Elofson, R.M.; Gadallah, F.F. *J. Org. Chem.* ***1971***, *36*, 1769.

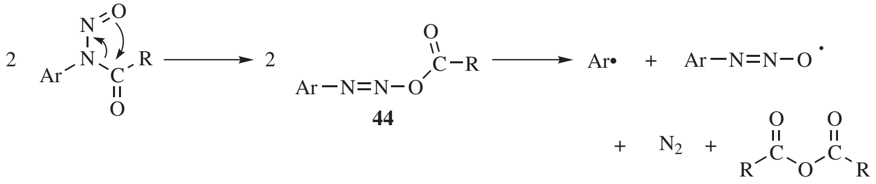
[741] Chauncy, B.; Gellert, E. *Aust. J. Chem.* ***1969***, *22*, 993. See also, Duclos, Jr., R.I.; Tung, J.S.; Rappoport, H. *J. Org. Chem.* ***1984***, *49*, 5243.

[742] See, for example, Patrick, T.B.; Willaredt, R.P.; DeGonia, D.J. *J. Org. Chem.* ***1985***, *50*, 2232; Butler, R.N.; O'Shea, P.D.; Shelly, D.P. *J. Chem. Soc. Perkin Trans. 1*, ***1987***, 1039.

[743] Cadogan, J.I.G. *J. Chem. Soc.* ***1962***, 4257; Fillipi, G.; Vernin, G.; Dou, H.J.; Metzger, J.; Perkins, M.J. *Bull. Soc. Chim. Fr.* ***1974***, 1075.

[744] Rüchardt, C.; Merz, E. *Tetrahedron Lett.* ***1964***, 2431; Eliel, E.L.; Saha, J.G.; Meyerson, S. *J. Org. Chem.* ***1965***, *30*, 2451.

The aryl radical thus formed attacks the substrate to give the intermediate **42** (see p. 940), from which the radical **41** abstracts hydrogen to give the product, **43**. *N*-Nitroso amides probably rearrange to *N*-acyloxy compounds (**44**), which cleave to give aryl radicals.[745] There is evidence that the reaction with alkyl nitrites also involves attack by aryl radicals.[746]



44

The Pschorr reaction can take place by two different mechanisms, depending on conditions: (*1*) attack by an aryl radical (as in the Gomberg–Bachmann reaction) or (*2*) attack by an aryl cation (similar to the S_N1 mechanism discussed on p. 857).[747] Under certain conditions the ordinary Gomberg–Bachmann reaction can also involve attack by aryl cations.[748]

OS **I**, 113; **IV**, 718.

13-28 Aryl Dimerization With Diazonium Salts

De-diazonio-coupling; Arylazo-de-diazonio-substitution

$$2\,ArN_2^+ \xrightarrow[\text{or}\quad Cu\,+\,H^+]{Cu^+} Ar{-}Ar \;+\; 2\,N_2 \quad \text{or} \quad Ar{-}N{=}N{-}Ar \;+\; N_2$$

When diazonium salts are treated with cuprous ion (or with copper and acid, in which case it is called the *Gatterman method*), two products are possible. If the ring contains electron-withdrawing groups, the main product is the biaryl, but the presence of electron-donating groups leads mainly to the azo compound. This reaction is different from **13-27** (and from **19-14**) in that *both* aryl groups in the product originate from ArN_2^+, that is, hydrogen is not a leaving group in this reaction. The mechanism probably involves free radicals.[749]

OS **I**, 222; **IV**, 872. Also see, OS **IV**, 273.

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[745] Cadogan, J.I.G.; Murray, C.D.; Sharp, J.T. *J. Chem. Soc. Perkin Trans. 2*, ***1976***, 583, and references cited therein.

[746] Gragerov, I.P.; Levit, A.F. *J. Org. Chem. USSR* ***1968***, *4*, 7.

[747] For an alternative to the second mechanism, see Gadallah, F.F.; Cantu, A.A.; Elofson, R.M. *J. Org. Chem.* ***1973***, *38*, 2386.

[748] For examples; see Kobori, N.; Kobayashi, M.; Minato, H. *Bull. Chem. Soc. Jpn.* ***1970***, *43*, 223; Cooper, R.M.; Perkins, M.J. *Tetrahedron Lett.* ***1969***, 2477; Burri, P.; Zollinger, H. *Helv. Chim. Acta* ***1973***, *56*, 2204; Eustathopoulos, H.; Rinaudo, J.; Bonnier, J.M. *Bull. Soc. Chim. Fr.* ***1974***, 2911. For a discussion, see Zollinger, H. *Acc. Chem. Res.* ***1973***, *6*, 335, 338.

[749] See Cohen, T.; Lewarchik, R.J.; Tarino, J.Z. *J. Am. Chem. Soc.* ***1974***, *96*, 7753.

13-29 Replacement of Nitro

Alkyl-de-nitration, Hydroxy and alkoxy-de-nitration, Halo-de-nitration

$$\text{Ar-NO}_2 \longrightarrow \text{Ar-R}$$

In some cases, the nitrogen group of an aromatic nitro compound can be replaced with an alkyl group. The reaction of 1,4-dinitrobenzene with potassium *tert*-butoxide in the presence of BEt_3, for example, gave 4-ethylnitrobenzene.[750]

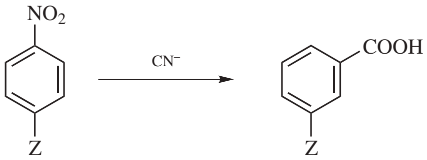
Other nucleophiles can replace a nitrogen-containing group. The reaction of hydroxide with Ar–Y, where Y = nitro,[751] azide, NR_3^+, and so on gives the corresponding phenol. This latter reaction works with alkoxide nucleophiles to give the corresponding aryl ether. The nitro can be replaced with chloro by use of NH_4Cl, PCl_5, $SOCl_2$, HCl, Cl_2, or CCl_4. Some of these reagents operate only at high temperatures and the mechanism is not always nucleophilic substitution. Activated aromatic nitro compounds can be converted to fluorides with fluoride ion.[752]

The reaction of vinyl nitro compounds ($C{=}C{-}NO_2$) and aryl iodide to give the styrene compound ($C{=}C{-}Ar$) was reported using BEt_3 and exposure to air.[753]

REARRANGEMENTS

13-30 The von Richter Rearrangement

Hydro-de-nitro-*cine*-substitution



When aromatic nitro compounds are treated with cyanide ion, the nitro group is displaced and a carboxyl group enters with cine substitution (p. 860), always ortho to the displaced group, never meta or para. The scope of this reaction, called the *von Richter rearrangement*, is variable.[754] As with other nucleophilic aromatic substitutions, the reaction gives best results when electron-withdrawing groups are in ortho and para positions, but yields are low, usually <20% and never >50%.

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[750] Palani, N.; Jayaprakash, K.; Hoz, S. *J. Org. Chem.* ***2003***, *68*, 4388.

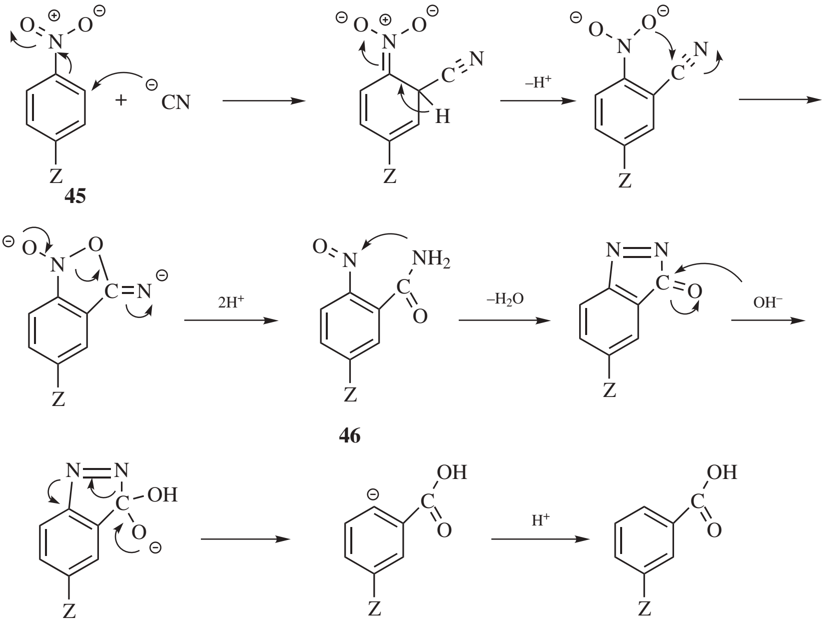
[751] For a convenient way of achieving this conversion, see Knudsen, R.D.; Snyder, H.R. *J. Org. Chem.* ***1974***, *39*, 3343.

[752] Attiná, M.; Cacace, F.; Wolf, A.P. *J. Chem. Soc. Chem. Commun.* ***1983***, 108; Clark, J.H.; Smith, D.K. *Tetrahedron Lett.* ***1985***, *26*, 2233; Suzuki, H.; Yazawa, N.; Yoshida, Y.; Furusawa,O.; Kimura, O. *Bull. Chem. Soc. Jpn.* ***1990***, *63*, 2010; Effenberger, F.; Streicher, W. *Chem. Ber.* ***1991***, *124*, 157.

[753] Liu, J.-T.; Jang, Y.-J.; Shih, Y.-K.; Hu, S.-R.; Chu, C.-M.; Yao, C.-F. *J. Org. Chem.* ***2001***, *66*, 6021.

[754] For a review, see Shine, H.J. *Aromatic Rearrangements*, Elsevier, NY, ***1967***, pp. 326–335.

At one time it was believed that a nitrile, ArCN, was an intermediate, since cyanide is the reagent and nitriles are hydrolyzable to carboxylic acids under the reaction conditions (**16-4**). However, a remarkable series of results proved this belief to be in error. Bunnett and Rauhut demonstrated[755] that α-naphthyl cyanide is *not* hydrolyzable to α-naphthoic acid under conditions at which β-nitronaphthalene undergoes the von Richter rearrangement to give α-naphthoic acid. This proved that the nitrile cannot be an intermediate. It was subsequently demonstrated that N_2 is a major product of the reaction.[756] It had previously been assumed that all the nitrogen in the reaction was converted to ammonia, which would be compatible with a nitrile intermediate, since ammonia is a hydrolysis product of nitriles. At the same time it was shown that NO_2^- is not a major product. The discovery of nitrogen indicated that a nitrogen–nitrogen bond must be formed during the course of the reaction. A mechanism in accord with all the facts was proposed by Rosenblum:[756]



Note that **46** is a stable compound; hence it should be possible to prepare it independently and to subject it to the conditions of the von Richter rearrangement. This was done and the correct products are obtained.[757] Further evidence is that when **45** (Z = Cl or Br) was treated with cyanide in $H_2{}^{18}O$, half the oxygen in the product was labeled, showing that one of the oxygens of the carboxyl group came from the nitro group and one from the solvent, as required by this mechanism.[758]

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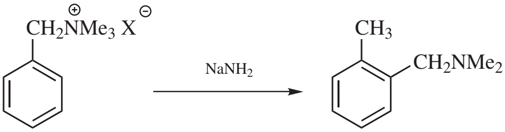
[755] Bunnett, J.F.; Rauhut, M.M. *J. Org. Chem.* ***1956***, *21*, 934, 944.

[756] Rosenblum, M. *J. Am. Chem. Soc.* ***1960***, *82*, 3796.

[757] Ibne-Rasa, K.M.; Koubek, E. *J. Org. Chem.* ***1963***, *28*, 3240.

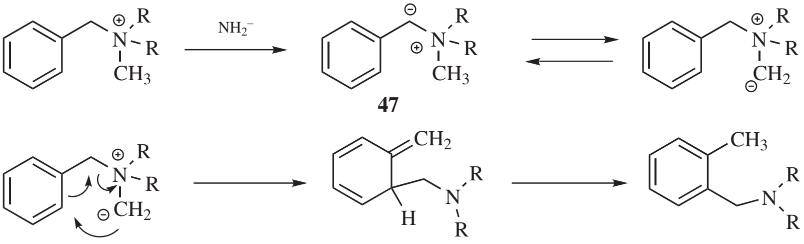
[758] Samuel, D. *J. Chem. Soc.* ***1960***, 1318. For other evidence, see Cullen, E.; L'Ecuyer, P. *Can. J. Chem.* ***1961***, *39*, 144, 155, 382; Ullman, E.F.; Bartkus, E.A. *Chem. Ind.* (*London*) ***1962***, 93.

13-31 The Sommelet–Hauser Rearrangement



Benzylic quaternary ammonium salts, when treated with alkali-metal amides, undergo a rearrangement called the *Sommelet–Hauser rearrangement.*[759] Since the product is a benzylic tertiary amine, it can be further alkylated and the product again subjected to the rearrangement. This process can be continued around the ring until an ortho position is blocked.[760]

The rearrangement occurs with high yields and can be performed with various groups present in the ring.[761] The reaction is most often carried out with three methyl groups on the nitrogen, but other groups can also be used, though if a β-hydrogen is present, Hofmann elimination (**17-7**) often competes. The *Stevens rearrangement* (**18-21**) is also a competing process.[762] When both rearrangements are possible, the Stevens is favored at high temperatures and the Sommelet–Hauser at low temperatures.[763] The mechanism is



48

The benzylic hydrogen is most acidic and is the one that first loses a proton to give the ylid **47**. However, **48**, which is present in smaller amount, is the species

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[759] For reviews, see Pine, S.H. *Org. React.*, ***1970***, *18*, 403; Lepley, A.R.; Giumanini, A.G. *Mech. Mol. Migr.* ***1971***, *3*, 297; Wittig, G. *Bull. Soc. Chim. Fr.* ***1971***, 1921; Stevens, T.S.; Watts, W.E. *Selected Molecular Rearrangements*, Van Nostrand-Reinhold, Princeton, ***1973***, pp. 81–88; Shine, H.J.*Aromatic Rearrangements*, Elsevier, NY, ***1967***, pp. 316–326. Also see, Klunder, J.M. *J. Heterocyclic Chem.* ***1995***, *32*, 1687.

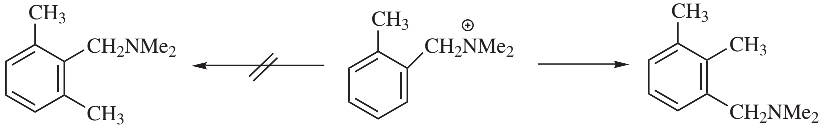
[760] Beard, W.Q.; Hauser, C.R. *J. Org. Chem.* ***1960***, *25*, 334.

[761] Jones, G.C.; Beard, W.Q.; Hauser, C.R. *J. Org. Chem.* ***1963***, *28*, 199.

[762] For a method that uses nonbasic conditions, and gives high yields of the Sommelet–Hauser product, with little or no Stevens rearrangement, see Nakano, M.; Sato, Y. *J. Org. Chem.* ***1987***, *52*, 1844; Shirai, N.; Sato, Y. *J. Org. Chem.* ***1988***, *53*, 194.

[763] Wittig, G.; Streib, H. *Liebigs Ann. Chem.* ***1953***, *584*, 1.

that undergoes the rearrangement, shifting the equilibrium in its favor. This mechanism is an example of a [2,3] sigmatropic rearrangement (see **18-35**). Another mechanism that might be proposed is one in which a methyl group actually breaks away (in some form) from the nitrogen and then attaches itself to the ring. That this is not so was shown by a product study.[764] If the second mechanism were true, **49** should give **50**, but the first mechanism predicts the formation of **51**, which is what was actually obtained.[765]



50 **49** **51**

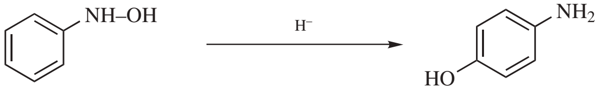
The mechanism as we have pictured it can lead only to an ortho product. However, a small amount of para product has been obtained in some cases.[766] A mechanism[767] in which there is a dissociation of the ArC—N bond (similar to the ion-pair mechanism of the Stevens rearrangement, p. 1622) has been invoked to explain the para products that are observed.

Sulfur ylids containing a benzylic group (analogous to **48**) undergo an analogous rearrangement.[768]

OS **IV**, 585.

13-32 Rearrangement of Aryl Hydroxylamines

1/*C*-Hydro-5/*N*-hydroxy-interchange



Aryl hydroxylamines treated with acids rearrange to aminophenols.[769] Although this reaction (known as the *Bamberger rearrangement*) is similar in appearance to

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[764] For other evidence for the mechanism given, see Hauser, C.R.; Van Eenam, D.N. *J. Am. Chem. Soc.* ***1957***, *79*, 5512; Jones, F.N.; Hauser, C.R. *J. Org. Chem.* ***1961***, *26*, 2979; Puterbaugh, W.H.; Hauser, C.R. *J. Am. Chem. Soc.* ***1964***, *86*, 1105; Pine, S.H.; Sanchez, B.L. *Tetrahedron Lett.* ***1969***, 1319; Shirai, N.; Watanabe, Y.; Sato, Y. *J. Org. Chem.* ***1990***, *55*, 2767.

[765] Kantor, S.W.; Hauser, C.R. *J. Am. Chem. Soc.* ***1951***, *73*, 4122.

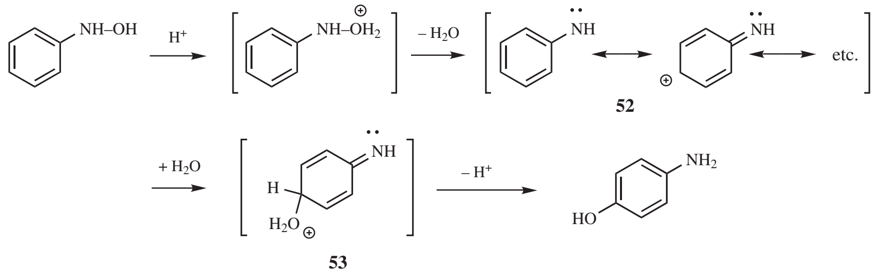
[766] Pine, S.H. *Tetrahedron Lett.* ***1967***, 3393; Pine, S.H. *Org. React.* ***1970***, *18*, 403, p. 418.

[767] Bumgardner, C.L. *J. Am. Chem. Soc.* ***1963***, *85*, 73.

[768] See Block, E. *Reactions of Organosulfur Compounds*, Academic Press, NY, ***1978***, pp. 118–124.

[769] For a review, see Shine, H.J. *Aromatic Rearrangements*, Elsevier, NY, ***1967***, pp. 182–190.

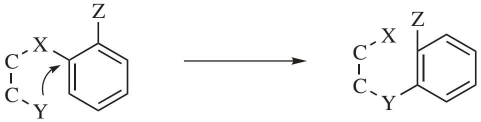
11-28–11-32, the attack on the ring is not electrophilic but nucleophilic. The rearrangement is intermolecular, with the following mechanism:



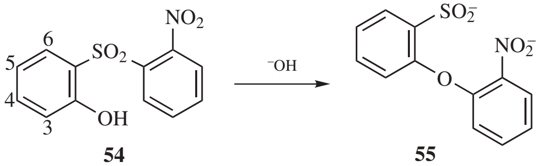
Among the evidence[770] for this mechanism are the facts that other products are obtained when the reaction is run in the presence of competing nucleophiles, for example, *p*-ethoxyaniline when ethanol is present, and that when the para position is blocked, compounds similar to **53** are isolated. In the case of 2,6-dimethylphenylhydroxylamine, the intermediate nitrenium ion **52** was trapped, and its lifetime in solution was measured.[771] The reaction of **52** with water was found to be diffusion controlled.[288]

OS **IV**, 148.

13-33 The Smiles Rearrangement



The *Smiles rearrangement* actually comprises a group of rearrangements that follow the pattern given above.[772] A specific example is the reaction of **54** with hydroxide to give **55**.



54 **55**

Smiles rearrangements are simply intramolecular nucleophilic substitutions. In the example given, SO_2Ar is the leaving group and ArO^- the nucleophile, and the nitro group serves to activate its ortho position. Halogens also serve as activating

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[770] For additional evidence, see Sone, T.; Hamamoto, K.; Seiji, Y.; Shinkai, S.; Manabe, O. *J. Chem. Soc. Perkin Trans. 2* ***1981***, 1596; Kohnstam, G.; Petch, W.A.; Williams, D.L.H. *J. Chem. Soc. Perkin Trans. 2* ***1984***, 423; Sternson, L.A.; Chandrasakar, R. *J. Org. Chem. 1984, 49*, 4295, and references cited therein.

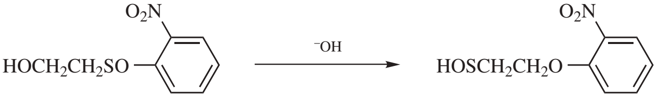
[771] Fishbein, J.C.; McClelland, R.A. *J. Am. Chem. Soc.* ***1987***, *109*, 2824.

[772] For reviews, see Truce, W.E.; Kreider, E.M.; Brand, W.W. *Org. React.*, ***1971***, *18*, 99; Shine, H.J. *Aromatic Rearrangements*, Elsevier, NY, ***1967***, pp. 307–316; Stevens, T.S.; Watts, W.E. *Selected Molecular Rearrangements*, Van Nostrand-Reinhold, Princeton, NJ, ***1973***, pp. 120–126.

groups.[773] The ring at which the substitution takes place is nearly always activated, usually by ortho or para nitro groups. Here X is usually S, SO, SO_2,[774] O, or COO, and Y is usually the conjugate base of OH, NH_2, NHR, or SH. The reaction has even been carried out with $Y = CH_2^-$ (phenyllithium was the base here).[775]

The reaction rate is greatly enhanced by substitution in the 6 position of the attacking ring, for steric reasons. For example, a methyl, chloro, or bromo group in the 6 position of **54** caused the rate to be $\sim 10^5$ times faster than when the same groups were in the 4 position,[776] though electrical effects should be similar at these positions. The enhanced rate comes about because the most favorable conformation the molecule can adopt to suit the bulk of the 6-substituent is also the conformation required for the rearrangement. Thus, less entropy of activation is required.

Although the Smiles rearrangement is usually carried out on compounds containing two rings, this need not be the case, as in the formation of **56**.[777]



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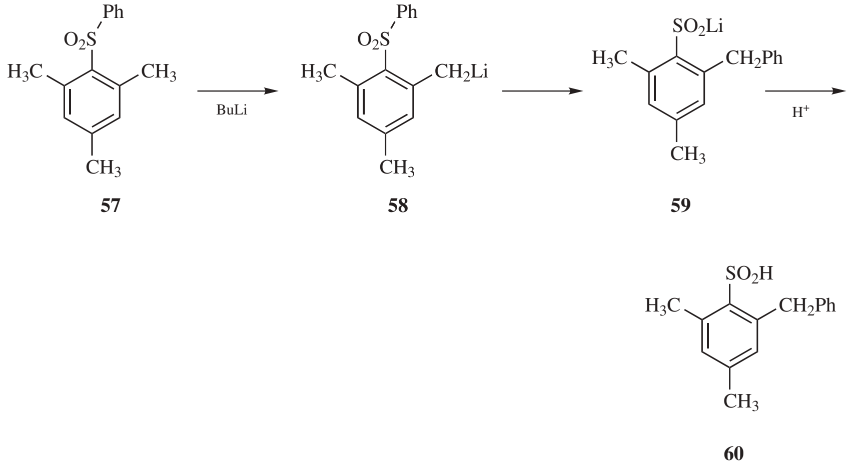
In this case, the sulfenic acid (**56**) is unstable[778] and the actual products isolated were the corresponding sulfinic acid (RSO_2H) and disulfide (R_2S_2).



57 **58** **59**

60

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[773] Bonvicino, G.E.; Yogodzinski, L.H.; Hardy Jr., R.A. *J. Org. Chem.* ***1962***, *27*, 4272; Nodiff, E.H.; Hausman, M. *J. Org. Chem.* ***1964***, *29*, 2453; Grundon, M.F.; Matier, W.L. *J. Chem. Soc., B*, ***1966***, 266; Schmidt, D.M.; Bonvicino, G.E. *J. Org. Chem.* ***1984***, *49*, 1664.

[774] For a review for the case of $X = SO_2$, see Cerfontain, H. *Mechanistic Aspects in Aromatic Sulfonation and Desulfonation*; Wiley, NY, ***1968***, pp. 262–274.

[775] Truce, W.E.; Robbins, C.R.; Kreider, E.M. *J. Am. Chem. Soc.* ***1966***, *88*, 4027; Drozd, V.N.; Nikonova, L.A. *J. Org. Chem, USSR* ***1969***, *5*, 313.

[776] Bunnett, J.F.; Okamoto, T. *J. Am. Chem. Soc.* ***1956***, *78*, 5363.

[777] Kent, B.A.; Smiles, S. *J. Chem. Soc.* ***1934***, 422.

[778] For a stable sulfenic acid, see Nakamura, N. *J. Am. Chem. Soc.* ***1983***, *105*, 7172.

In the Smiles rearrangement, the nucleophile Y is most often the conjugate base of SH, SO_2NHR, SO_2NH_2, NH_2, NHR, OH, OR. There are few examples where Y is a carbanion, and the most common example is probably the *Truce–Smiles rearrangement*, where L—YH is an *o*-tolyl group.[779] The prototypical Truce–Smiles rearrangement requires use of a strong base to form the benzylic carbanion that undergoes the rearrangement. When sulfone **57** was treated with butyllithium, for example, deprotonation led to the benzylic lithium compound **58**. Truce–Smiles rearrangement led to **59**, and hydrolysis gave the sulfinic acid, **60**.[779] Truce–Smiles rearrangements with stabilized benzylic carbanions are known,[780] and rearrangements of carbanions in general fall under this category.[781] Relatively few examples have been reported, however.[782] Truce–Smiles rearrangements of sulfones that proceed through a six-membered transition state have been reported.[783] In another example, displacement of an activated aryl fluoride with *o*-hydroxyacetophenone gave a product that was *C*-arylated adjacent to the ketone.[784]

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[779] Truce, W.E.; Ray Jr., W.J.; Norman, O.L.; Eickemeyer, D.B. *J. Am. Chem. Soc.* ***1958***, *80*, 3625.

[780] Erickson, W.R.; McKennon, M.J. *Tetrahedron Lett.* ***2000***, *41*, 4541.

[781] Fukazawa, Y.; Kato, N.; Itô, S. *Tetrahedron Lett.* ***1982***, *23*, 437.

[782] Hirota, T.; Tomita, K.; Sasaki, K.; Okuda, K.; Yoshida, M.; Kashino, S. *Heterocycles* ***2001***, *55*, 741; Bayne, D.W.; Nicol, A.J.; Tennant, G.*J. Chem. Soc. Chem. Commun.* ***1975***, 782; Hoffman, R.V.; Jankowski, B.C.; Carr, C.S.; Duesler, E.N. *J. Org. Chem.* ***1986***, *51*, 130.

[783] Truce, W.E.; Hampton, D.C. *J. Org. Chem.* ***1963***, *28*, 2276.

[784] Mitchell, L.H.; Barvian, N.C. *Tetrahedron Lett.* ***2004***, *45*, 5669.

CHAPTER 14

Substitution Reactions: Free Radicals

MECHANISMS

Free-Radical Mechanisms in General[1]

A free-radical process consists of at least two steps. The first step involves the *formation* of free radicals, usually by homolytic cleavage of bond, that is, a cleavage in which each fragment retains one electron:

$$\mathrm{A{-}B} \longrightarrow \mathrm{A}\bullet \ + \ \mathrm{B}\bullet$$

This is called an *initiation* step. It may happen spontaneously or may be induced by heat[2] or light (see the discussion on p. 279), depending on the type of bond.[3] Peroxides, including hydrogen peroxide, dialkyl, diacyl, and alkyl acyl peroxides, and peroxyacids are the most common source of free radicals induced spontaneously or by heat, but other organic compounds with low-energy bonds, such as azo compounds, are also used. Molecules that are cleaved by light are most often chlorine, bromine, and various ketones (see Chapter 7). Radicals can also be formed

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[1] For books on free-radical mechanisms, see Nonhebel, D.C.; Tedder, J.M.; Walton, J.C. *Radicals*, Cambridge University Press, Cambridge, ***1979***; Nonhebel, D.C.; Walton. J.C. *Free-Radical Chemistry*, Cambridge University Press, London, ***1974***; Huyser, E.S. *Free-Radical Chain Reactions*, Wiley, NY, ***1970***; Pryor, W.A. *Free Radicals*, McGraw-Hill, NY, ***1966***; For reviews, see Huyser, E.S., in McManus, S.P. *Organic Reactive Intermediates*, Academic Press, NY, ***1973***, pp. 1–59. For monographs on the use of free-radical reactions in synthesis see Giese, B. *Radicals in Organic Synthesis, Formation of Carbon-Carbon Bonds*, Pergamon, Elmsford, NY, ***1986***; Davies, D.I.; Parrott, M.J. *Free Radicals in Organic Synthesis*, Springer, NY, ***1978***. For reviews, see Curran, D.P. *Synthesis* **1988**, 417, 489; Ramaiah, M. *Tetrahedron* **1987**, *43*, 3541.

[2] For a study of the thermolysis of free-radical initiators, see Engel, P.S.; Pan, L.; Ying, Y.; Alemany, L.B. *J. Am. Chem. Soc.* ***2001***, *123*, 3706.

[3] See Fokin, A.A.; Schreiner, P.R. *Chem. Rev.* ***2002***, *102*, 1551.

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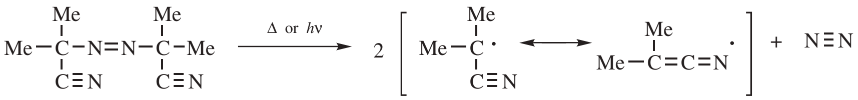
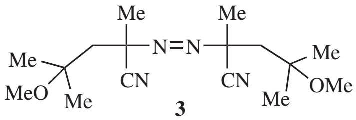
Michael B. Smith and Jerry March

in another way, by a one-electron transfer (loss or gain), for example, $A^+ + e^- \rightarrow A\bullet$. One-electron transfers usually involve inorganic ions or electrochemical processes.

Dialkyl peroxides (ROOR) or alkyl hydroperoxides (ROOH) decompose to hydroxy radicals (HO•) or alkoxy radicals (RO•) when heated.[4] Cumene hydroperoxide ($PhCMe_2OOH$), bi-*tert*-butylperoxide ($Me_3COOCMe_3$),[5] and benzoyl peroxide [$(PhCO)O_2$] undergo homolytic cleavage at temperatures compatible with many organic reactions, allowing some control of the reaction, and they are reasonably soluble in organic solvents. In general, when a peroxide decomposes, the oxygen radical remains in a "cage" for $\sim 10^{-11}$ s before diffusing away. The radical can recombine (dimerize), or react with other molecules. Azo compounds, characterized by a —N=N— bond, are free-radical precursors that liberate nitrogen gas (N≡N) upon decomposition. azobis(isobutyronitrile) (AIBN, **1**) is a well-known example, which decomposes to give nitrogen and the cyano stabilized radical, **2**.[6] Homolytic dissociation of symmetrical diazo compounds may be stepwise.[7] A derivative has been developed that decomposes to initiate radical reactions at room temperature, 2,2′-azobis(2,4-dimethyl-4-methoxyvaleronitrile), **3**.[8] Water soluble azo compounds are known, and can be used as radical initiators.[9] Other sources of useful radicals are available. Alkyl hypochlorites (R—O—Cl) generate chlorine radicals (Cl•) and alkoxy radicals (RO•) when heated.[10] Heating *N*-alkoxydithiocarbamates is another useful source of alkoxy radicals, RO•.[11]



1 **2**



3

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[4] For a table of approximate decomposition temperatures for several common peroxides, see Lazár, M.; Rychlý, J.; Klimo, V.; Pelikán, P.; Valko, L. *Free Radicals in Chemistry and Biology*, CRC Press, Washington, DC, ***1989***, p. 12.

[5] Lazár, M.; Rychlý, J.; Klimo, V.; Pelikán, P.; Valko, L. *Free Radicals in Chemistry and Biology*, CRC Press, Washington, DC, ***1989***, p. 13.

[6] Yoshino, K.; Ohkatsu, J.; Tsuruta, T. *Polym. J.* ***1977***, *9*, 275; von J. Hinz, A.; Oberlinner, A.; Rüchardt, C. *Tetrahedron Lett.* ***1973***, 1975.

[7] Dannenberg, J.J.; Rocklin, D. *J. Org. Chem.* ***1982***, *47*, 4529. See also, Newman, Jr, R.C.; Lockyer Jr, G.D. *J. Am. Chem Soc.* ***1983***, *105*, 3982.

[8] Kita, Y.; Sano, A.; Yamaguchi, T.; Oka, M.; Gotanda, K.; Matsugi, M. *Tetrahedron Lett.* ***1997***, *38*, 3549.

[9] Yorimitsu, H.; Wakabayashi, K.; Shinokubo, H; Oshima, K. *Tetrahedron Lett.* ***1999***, *40* , 519.

[10] Davies, D.I.; Parrott, M.J. *Free Radicals in Organic Synthesis*, Springer–Verlag, Berlin, ***1978***, p. 9; Chattaway, F.D.; Baekeberg, O.G. *J. Chem. Soc.* ***1923***, *123*, 2999.

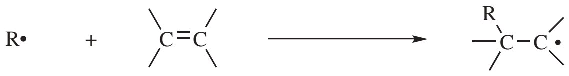
[11] Kim, S.; Lim, C.J.; Song, S.-E.; Kang, H.-Y. *Synlett* ***2001***, 688.

Note that aldehydes can also be a source of acyl radicals (•C=O) via reaction with transition metal salts such as Mn(III) acetate or Fe(II) compounds.[12] Another useful variation employs imidoyl radicals as synthons for unstable aryl radicals.[13]

The second step involves the *destruction* of free radicals. This usually happens by a process opposite to the first, namely, a combination of two like or unlike radicals to form a new bond:[14]

$$A\bullet \;+\; B\bullet \longrightarrow A{-}B$$

This type of step is called *termination*, and it ends the reaction as far as these particular radicals are concerned.[15] However, it is not often that termination follows *directly* upon initiation. The reason is that most radicals are very reactive and will react with the first available species with which they come in contact. In the usual situation, in which the concentration of radicals is low, this is much more likely to be a molecule than another radical. When a radical (which has an odd number of electrons) reacts with a molecule (which has an even number), the total number of electrons in the products must be odd. The product in a particular step of this kind may be one particle, as in the addition of a radical to a π-bond, which in this case is



4

another free radical, **4**; or abstraction of an atom such as hydrogen to give two particles, R—H and the new radical R′•.

$$R\bullet \;+\; R'H \longrightarrow RH \;+\; R'\bullet$$

In this latter case, one particle must be a neutral molecule and one a free radical. In both of these examples, a *new radical is generated.* This type of step is called *propagation*, since the newly formed radical can now react with another molecule and produce another radical, and so on, until two radicals do meet each other and terminate the sequence. The process just described is called a *chain reaction*,[16] and there may be hundreds or thousands of propagation steps between an initiation and a termination. Two other types of propagation reactions do not involve a

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[12] Davies, D.I.; Parrott, M.J. *Free Radicals in Organic Synthesis* Springer–Verlag, Berlin, ***1978***, p. 69; Sosnovsky, G. *Free Radical Reactions in Preparative Organic Chemistry*, MacMillan, New York, ***1964***; Vinogradov, M.G.; Nikishin, G.I. *Usp. Khim*, ***1971***, *40*, 1960; Nikishin, G.I.; Vinogradov, M.G.; Il'ina, G.P. *Synthesis* ***1972***, 376; Nikishin, G.I.; Vinogradov, M.G.; Verenchikov, S.P.; Kostyukov, I.N.; Kereselidze, R.V. *J. Org. Chem, USSR* ***1972***, *8*, 539 (Engl, p. 544).

[13] Fujiwara, S.-i.; Matsuya, T.; Maeda, H.; Shin-ike, T.; Kambe, N.; Sonoda, N. *J. Org. Chem.* ***2001***, *66*, 2183.

[14] For a review of the stereochemistry of this type of combination reaction, see Porter, N.A.; Krebs, P.J. *Top. Stereochem.* ***1988***, *18*, 97.

[15] Another type of termination is disproportionation (see p. 280).

[16] For a discussion of radical chain reactions from a synthetic point of view, see Walling, C. *Tetrahedron* ***1985***, *41*, 3887.

molecule at all. These are (*1*) cleavage of a radical into, necessarily, a radical and a molecule and (*2*) rearrangement of one radical to another (see Chapter 18). When radicals are highly reactive, for example, alkyl radicals, chains are long, since reactions occur with many molecules; but with radicals of low reactivity, for example, aryl radicals, the radical may be unable to react with anything until it meets another radical, so that chains are short, or the reaction may be a nonchain process. In any particular chain process, there is usually a wide variety of propagation and termination steps. Because of this, these reactions lead to many products and are often difficult to treat kinetically.[17]

$$\mathrm{R{-}CH_2\bullet} + n\text{-}\mathrm{Bu_3Sn{-}H} \longrightarrow \mathrm{R{-}CH_2{-}H} + n\text{-}\mathrm{Bu_3Sn\bullet}$$

$$n\text{-}\mathrm{Bu_3Sn\bullet} + n\text{-}\mathrm{Bu_3Sn\bullet} \longrightarrow n\text{-}\mathrm{Bu_3Sn{-}Sn}n\text{-}\mathrm{Bu_3}$$

A useful variation of propagation and termination combines the two processes. When a carbon radical (R•) is generated in the presence of tributyltin hydride (n-Bu_3SnH), a hydrogen atom is transferred to the radical to give R—H and a new radical, n-$Bu_3Sn\bullet$. The tin radical reacts with a second tin radical to give n-Bu_3 Sn—Sn—n-Bu_3. The net result is that the carbon radical is reduced to give the desired product and the tin dimer can be removed from the reaction. Tin hydride transfers a hydrogen atom in a chain propagation sequence that produces a new radical, but terminates the carbon radical sequence. Dimerization of the tin radical then terminates that radical process. Silanes, such as triethylsilane (Et_3SiH), has also been used as an effective radical reducing agent.[18] The rate constants for the reaction of both tributytin hydride and $(Me_3Si)_3Si$—H with acyl radical has been measured and the silane quenches the radical faster than the tin hydride.[19] bis(Tri-n-butylstannyl)benzopinacolate has also been used as a thermal source of n-$Bu_3Sn\bullet$, used to mediate radical reactions.[20]

The following are some general characteristics of free-radical reactions:[21]

1. Reactions are fairly similar whether they are occurring in the vapor or liquid phase, though solvation of free radicals in solution does cause some differences.[22]
2. They are largely unaffected by the presence of acids or bases or by changes in the polarity of solvents, except that nonpolar solvents may suppress competing ionic reactions.

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[17] For a discussion of the kinetic aspects of radical chain reactions, see Huyser, E.S. *Free-Radical Chain Reactions*, Wiley, NY, ***1970***, pp. 39–65.

[18] Chatgilialoglu, C.; Ferreri, C.; Lucarini, M. *J. Org. Chem.* ***1993***, *58*, 249.

[19] Chatgilialoglu, C.; Lucarini, M. *Tetrahedron Lett.* ***1995***, *36*, 1299.

[20] Hart, D.J.; Krishnamurthy, R.; Pook, L.M.; Seely, F.L. *Tetrahedron Lett.* ***1993***, *34*, 7819.

[21] See Beckwith, A.L.J. *Chem. Soc. Rev.* ***1993***, *22*, 143 for a discussion of selectivity in radical reactions.

[22] For a discussion, see Mayo, F.R. *J. Am. Chem. Soc.* ***1967***, *89*, 2654.

3. They are initiated or accelerated by typical free-radical sources, such as the peroxides, referred to, or by light. In the latter case, the concept of quantum yield applies (p. 349). Quantum yields can be quite high, for example, 1000, if each quantum generates a long chain, or low, in the case of nonchain processes.
4. Their rates are decreased or the reactions are suppressed entirely by substances that scavenge free radicals, for example, nitric oxide, molecular oxygen, or benzoquinone. These substances are called *inhibitors*.[23]

This chapter discusses free-radical substitution reactions. Free-radical additions to unsaturated compounds and rearrangements are discussed in Chapters 15 and 18, respectively. Fragmentation reactions are covered, in part, in Chapter 17. In addition, many of the oxidation–reduction reactions considered in Chapter 19 involve free-radical mechanisms. Several important types of free-radical reactions do not usually lead to reasonable yields of pure products and are not generally treated in this book. Among these are polymerizations and high-temperature pyrolyses.

Free-Radical Substitution Mechanisms[24]

In a free-radical substitution reaction

$$\mathrm{R{-}X} \longrightarrow \mathrm{R{-}Y}$$

there must first be a cleavage of the substrate RX so that R• radicals are produced. This can happen by a spontaneous cleavage

$$\mathrm{R{-}X} \longrightarrow \mathrm{R\bullet} + \mathrm{X\bullet}$$

or it can be caused by light or heat, or, more often, there is no actual cleavage, but R• is produced by an *abstraction* of another atom, X but the radical W•.

$$\mathrm{R{-}X} + \mathrm{W\bullet} \longrightarrow \mathrm{R\bullet} + \mathrm{W{-}X}$$

The radical W• is produced by adding a compound, such as a peroxide, that spontaneously forms free radicals. Such a compound is called an *initiator* (see above). Once R• is formed, it can go to product in two ways, by another atom abstraction, such as the reaction with A—B to form R—A and a new radical B•.

$$\mathrm{R\bullet} + \mathrm{A{-}B} \longrightarrow \mathrm{R{-}A} + \mathrm{B\bullet}$$

Another reaction is coupling with another radical to form the neutral product R—Y.

$$\mathrm{R\bullet} + \mathrm{Y\bullet} \longrightarrow \mathrm{R{-}Y}$$

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[23] For a review of the action of inhibitors, see Denisov, E.T.; Khudyakov, I.V. *Chem. Rev.* ***1987***, *87*, 1313.

[24] For a review, see Poutsma, M.L., in Kochi, J.K. *Free Radicals*, Vol. 2, Wiley, NY, ***1973***, pp. 113–158.

In a reaction with a moderately long chain, much more of the product will be produced by abstraction (4) than by coupling (5). Cleavage steps like (2) have been called S_H1 (H for homolytic), and abstraction steps like (3) and (4) have been called S_H2; reactions can be classified as S_H1 or SH_2 on the basis of whether RX is converted to R by (2) or (3).[25] Most chain substitution mechanisms follow the pattern (3), (4), (3), (4)••• Chains are long and reactions go well where both (3) and (4) are energetically favored (no worse that slightly endothermic (see pp. 944, 959). The IUPAC designation of a chain reaction that follows the pattern (3),(4)••• is $A_rD_R + A_RD_r$ (R stands for radical).

With certain radicals the transition state in an abstraction reaction has some polar character. For example, consider the abstraction of hydrogen from the methyl group of toluene by a bromine atom. Since bromine is more electronegative than carbon, it is reasonable to assume that in the transition state there is a separation of charge, with a partial negative charge on the halogen and a partial positive charge on the carbon:

$$\overset{\delta+}{\mathrm{PhCH_2}}\cdots\cdots\cdots\mathrm{H}\cdots\cdots\cdots\overset{\delta-}{\mathrm{Br}}$$

Evidence for the polar character of the transition state is that electron-withdrawing groups in the para position of toluene (which would destabilize a positive charge) decrease the rate of hydrogen abstraction by bromine while electron-donating groups increase it.[26] However, substituents have a smaller effect here ($\rho \sim -1.4$) than they do in reactions where a completely ionic intermediate is involved, for example, the S_N1 mechanism (see p. 487). Other evidence for polar transition states in radical abstraction reactions is mentioned on p. 948. For abstraction by radicals such as methyl or phenyl, polar effects are very small or completely absent. For example, rates of hydrogen abstraction from ring-substituted toluenes by the methyl radical were relatively unaffected by the presence of electron-donating or electron-withdrawing substituents.[27] Those radicals (e.g., Br•) that have a tendency to abstract electron-rich hydrogen atoms are called *electrophilic radicals*.

When the reaction step R—X → R• takes place at a chiral carbon, racemization is almost always observed because free radicals do not retain configuration. Exceptions to this rule are found at cyclopropyl substrates, where both inversion[28] and retention[29] of configuration have been reported, and in the reactions mentioned on p. 942. Enantioselective radical processes have been reviewed.[30]

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[25] Eliel, E.L., in Newman, M.S. *Steric Effects in Organic Chemistry*, Wiley, NY, ***1956***, pp. 142–143.

[26] For example, see Pearson, R.; Martin, J.C. *J. Am. Chem. Soc.* ***1963***, *85*, 354, 3142; Kim, S.S.; Choi, S.Y.; Kang, C.H. *J. Am. Chem. Soc.* ***1985***, *107*, 4234.

[27] For example, see Kalatzis, E.; Williams, G.H. *J. Chem. Soc. B* ***1966***, 1112; Pryor, W.A.; Tonellato, U.; Fuller, D.L.; Jumonville, S. *J. Org. Chem.* ***1969***, *34*, 2018.

[28] Altman, L.J.; Nelson, B.W. *J. Am. Chem. Soc.* ***1969***, *91*, 5163.

[29] Jacobus, J.; Pensak, D. *Chem. Commun.* ***1969***, 400.

[30] Sibi, M.P.; Manyem, S.; Zimmerman, J. *Chem. Rev.* ***2003***, *103*, 3263.

Mechanisms at an Aromatic Substrate[31]

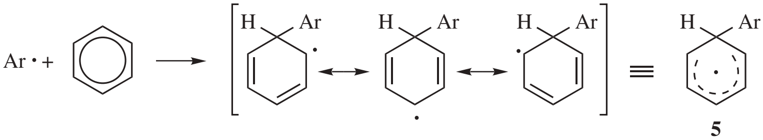
When R in reaction (1) is aromatic, the simple abstraction mechanism just discussed may be operating, especially in gas-phase reactions. However, mechanisms of this type cannot account for all reactions of aromatic substrates. In processes, such as the following (see **13-27**, **14-17**, and **14-18**):

$$\mathrm{Ar}\bullet \quad + \quad \mathrm{ArH} \longrightarrow \mathrm{Ar{-}Ar}$$

which occur in solution, the coupling of two rings cannot be explained on the basis of a simple abstraction

$$\mathrm{Ar}\bullet \quad + \quad \mathrm{ArH} \longrightarrow \mathrm{Ar{-}Ar} \quad + \quad \mathrm{H}\bullet$$

since, as discussed on p. 944, abstraction of an entire group, such as phenyl, by a free radical is very unlikely. The products can be explained by a mechanism similar to that of electrophilic and nucleophilic aromatic substitution. In the first step, the radical attacks the ring in much the same way as would an electrophile or a nucleophile:



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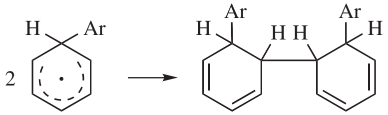
The intermediate radical **5** is relatively stable because of the resonance. The reaction can terminate in three ways: by simple coupling to give **6**, by disproportionation to give **7**,



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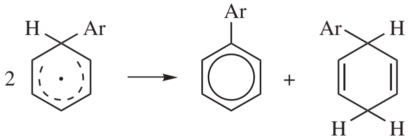

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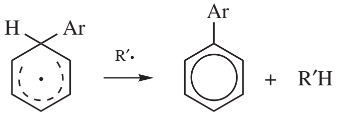
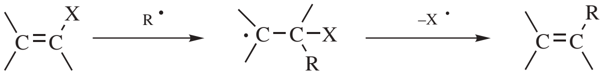
[31] For reviews, see Kobrina, L.S. *Russ. Chem. Rev.* ***1977***, *46*, 348; Perkins, M.J., in Kochi, J.K. *Free Radicals*, Vol. 2, Wiley, NY, ***1973***, pp. 231–271; Bolton, R.; Williams, G.H. *Adv. Free-Radical Chem.* ***1975***, *5*, 1; Nonhebel, D.C.; Walton, J.C. *Free-Radical Chemistry*, Cambridge University Press, London, ***1974***, pp. 417–469; Minisci, F.; Porta, O. *Adv. Heterocycl. Chem.* ***1974***, *16*, 123; Bass, K.C.; Nababsing, P. *Adv. Free-Radical Chem.* ***1972***, *4*, 1; Hey, D.H. *Bull. Soc. Chim. Fr.* ***1968***, 1591.

or, if a species (R′•) is present that abstracts hydrogen, by abstraction to give **8**.[32]



8

Coupling product **6** is a partially hydrogenated quaterphenyl. Of course, the coupling need not be ortho–ortho, and other isomers can also be formed. Among the evidence for steps (9) and (10) was isolation of compounds of types **6** and **7**,[33] though normally under the reaction conditions dihydrobiphenyls like **7** are oxidized to the corresponding biphenyls. Other evidence for this mechanism is the detection of the intermediate **5** by CIDNP[34] and the absence of isotope effects, which would be expected if the rate-determining step were (7), which involves cleavage of the Ar—H bond. In the mechanism just given, the rate-determining step (8) does not involve loss of hydrogen. The reaction between aromatic rings and the HO• radical takes place by the same mechanism. Intramolecular hydrogen-transfer reactions of aryl radicals are known.[35] A similar mechanism has been shown for substitution at some vinylic[36] and acetylenic substrates, giving the substituted alkene **9**.[37] The kinetics of radical heterolysis reactions that form alkene radical cations has been studied.[38]



9

This is reminiscent of the nucleophilic tetrahedral mechanism at a vinylic carbon (p. 477).

There are a number of transition-metal mediated coupling reaction of aromatic substrates that probably proceed by radical coupling. It is also likely that many of these reactions do not proceed by free radicals, but rather by metal-mediated radicals or by ligand transfer on the metal. Reactions in these categories were presented

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[32] Compound **5** can also be oxidized to the arene ArPh by atmospheric O_2. For a discussion of the mechanism of this oxidation, see Narita, N.; Tezuka, T. *J. Am. Chem. Soc.* ***1982***, *104*, 7316.

[33] De Tar, D.F.; Long, R.A.J. *J. Am. Chem. Soc.* ***1958***, *80*, 4742. See also, DeTar, D.F.; Long, R.A.J.; Rendleman, J.; Bradley, J.; Duncan, P. *J. Am. Chem. Soc.* ***1967***, *89*, 4051; DeTar, D.F. *J. Am. Chem. Soc.* ***1967***, *89*, 4058. See also, Jandu, K.S.; Nicolopoulou, M.; Perkins, M.J. *J. Chem. Res. (S)* ***1985***, 88.

[34] Fahrenholtz, S.R.; Trozzolo, A.M. *J. Am. Chem. Soc.* ***1972***, *94*, 282.

[35] Curran, D.P.; Fairweather, N. *J. Org. Chem.* ***2003***, *68*, 2972.

[36] The reaction of vinyl chloride with Cl^- favors the σ-route (nucleophilic attack at the σ-bond) over the π-route (nucleophilic attack at the π-bond), but vinyl chloride is not an experimentally viable substrate and cannot be considered as representative for the vinyl S_N2 reaction. The π-route is anticipated in substituted vinylic halide reactions, where electron-withdrawing groups are attached to the vinylic carbon. See Bach, R. D.; Baboul, A. G.; Schlegel, H. B. *J. Am. Chem. Soc*, ***2001***, *123*, 5787.

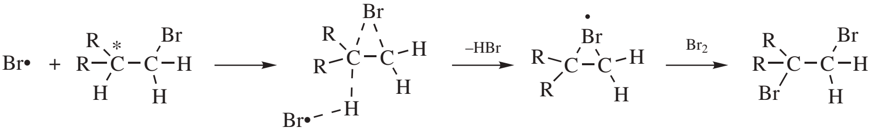
[37] Russell, G.A.; Ngoviwatchai, P. *Tetrahedron Lett.* ***1986***, *27*, 3479, and references cited therein.

[38] Horner, J.H.; Bagnol, L.; Newcomb, M. *J. Am. Chem. Soc.* ***2004***, *126*, 14979.

in Chapter 13 for convenient correlation with other displacement reactions of aryl halides, aryl diazonium salts, and so on.

Neighboring-Group Assistance in Free-Radical Reactions

In a few cases, it has been shown that cleavage steps (2) and abstraction steps (3) have been accelerated by the presence of neighboring groups. Photolytic halogenation (**14-1**) is a process that normally leads to mixtures of many products. However, bromination of carbon chains containing a bromine atom occurs with high regioselectivity. Bromination of alkyl bromides gave 84–94% substitution at the carbon adjacent to the bromine already in the molecule.[39] This result is especially surprising because, as we will see (p. 947), positions close to a polar group, such as bromine, should actually be *deactivated* by the electron-withdrawing field effect of the bromine. The unusual regioselectivity is explained by a mechanism in which abstraction (3) is assisted by a neighboring bromine atom, as in **10**.[40]



10 **11**

In the normal mechanism, Br• abstracts a hydrogen from RH, leaving R•. When a bromine is present in the proper position, it assists this process, giving a cyclic intermediate (a *bridged free radical*, **11**).[41] In the final step (very similar to $R\bullet + Br_2 \rightarrow RBr + Br\bullet$), the ring is broken. If this mechanism is correct, the configuration at the substituted carbon (marked *) should be retained. This has been shown to be the case: optically active 1-bromo-2-methylbutane gave 1,2-dibromo-2-methylbutane with retention of configuration.[40] Furthermore, when this reaction was carried out in the presence of DBr, the "recovered" 1-bromo-2-methylbutane was found to be deuterated in the 2 position, and its configuration was retained.[42] This is just what would be predicted if some of the **11** present abstracted D from DBr. There is evidence that Cl can form bridged radicals,[43]

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[39] Thaler, W.A. *J. Am. Chem. Soc.* ***1963***, *85*, 2607. See also, Traynham, J.G.; Hines, W.G. *J. Am. Chem. Soc.* ***1968***, *90*, 5208; Ucciani, E.; Pierri, F.; Naudet, M. *Bull. Soc. Chim. Fr.* ***1970***, 791; Hargis, J.H. *J. Org. Chem.* ***1973***, *38*, 346.

[40] Skell, P.S.; Tuleen, D.L.; Readio, P.D. *J. Am. Chem. Soc.* ***1963***, *85*, 2849. For other stereochemical evidence, see Huyser, E.S.; Feng, R.H.C. *J. Org. Chem.* ***1971***, *36*, 731. For another explanation, see Lloyd, R.V.; Wood, D.E. *J. Am. Chem. Soc.* ***1975***, *97*, 5986. Also see Cope, A.C.; Fenton, S.W. *J. Am. Chem. Soc.* ***1951***, *73*, 1668.

[41] For a monograph, see Kaplan, L. *Bridged Free Radicals*, Marcel Dekker, NY, ***1972***. For reviews, see Skell, P.S.; Traynham, J.G. *Acc. Chem. Res.* ***1984***, *17*, 160; Skell, P.S.; Shea, K.J. in Kochi, J.K. *Free Radicals*, Vol. 2, Wiley, NY, ***1973***, pp. 809–852.

[42] Shea, K.J.; Skell, P.S. *J. Am. Chem. Soc.* ***1973***, *95*, 283.

[43] Everly, C.R.; Schweinsberg, F.; Traynham, J.G. *J. Am. Chem. Soc.* ***1978***, *100*, 1200; Wells, P.R.; Franke, F.P. *Tetrahedron Lett.* ***1979***, 4681.

though ESR spectra show that the bridging is not necessarily symmetrical.[44] Still more evidence for bridging by Br has been found in isotope effect and other studies.[45] However, evidence from CIDNP shows that the methylene protons of the β-bromoethyl radical are not equivalent, at least while the radical is present in the radical pair [PhCOO••CH_2CH_2Br] within a solvent cage.[46] This evidence indicates that under these conditions $BrCH_2CH_2$• is not a symmetrically bridged radical, but it could be unsymmetrically bridged. A bridged intermediate has also been invoked, when a bromo group is in the proper position, in the Hunsdiecker reaction[47] (**14-30**), and in abstraction of iodine atoms by the phenyl radical.[48] Participation by other neighboring groups (e.g. SR, SiR_3, SnR_3) has also been reported.[49]

REACTIVITY

Reactivity for Aliphatic Substrates[50]

In a chain reaction, the step that determines what the product will be is most often an abstraction step. What is abstracted by a free radical is almost never a tetra-[51] or tervalent atom[52] (except in strained systems, see p. 1027)[53] and seldom a divalent one.[54] Nearly always it is univalent, and so, for organic compounds, it is hydrogen or halogen. For example, a reaction between a chlorine atom and ethane gives an

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[44] Bowles, A.J.; Hudson, A.; Jackson, R.A. *Chem. Phys. Lett.* ***1970***, *5*, 552; Cooper, J.; Hudson, A.; Jackson, R.A. *Tetrahedron Lett.* ***1973***, 831; Chen, K.S.; Elson, I.H.; Kochi, J.K. *J. Am. Chem. Soc.* ***1973***, *95*, 5341.

[45] Skell, P.S.; Pavlis, R.R.; Lewis, D.C.; Shea, K.J. *J. Am. Chem. Soc.* ***1973***, *95*, 6735; Juneja, P.S.; Hodnett, E.M. *J. Am. Chem. Soc.* ***1967***, *89*, 5685; Lewis, E.S.; Kozuka, S. *J. Am. Chem. Soc.* ***1973***, *95*, 282; Cain, E.N.; Solly, R.K. *J. Chem. Soc., Chem. Commun.* ***1974***, 148; Chenier, J.H.B.; Tremblay, J.P.; Howard, J.A. *J. Am. Chem. Soc.* ***1975***, *97*, 1618; Howard, J.A.; Chenier, J.H.B.; Holden, D.A. *Can. J. Chem.* ***1977***, *55*, 1463. See, however, Tanner, D.D.; Blackburn, E.V.; Kosugi, Y.; Ruo, T.C.S. *J. Am. Chem. Soc.* ***1977***, *99*, 2714.

[46] Hargis, J.H.; Shevlin, P.B. *J. Chem. Soc., Chem. Commun.* ***1973***, 179.

[47] Applequist, D.E.; Werner, N.D. *J. Org. Chem.* ***1963***, *28*, 48.

[48] Danen, W.C.; Winter, R.L. *J. Am. Chem. Soc.* ***1971***, *93*, 716.

[49] Tuleen, D.L.; Bentrude, W.G.; Martin, J.C. *J. Am. Chem. Soc.* ***1963***, *85*, 1938; Fisher, T.H.; Martin, J.C. *J. Am. Chem. Soc.* ***1966***, *88*, 3382; Jackson, R.A.; Ingold, K.U.; Griller, D.; Nazran, A.S. *J. Am. Chem. Soc.* ***1985***, *107*, 208. For a review of neighboring-group participation in cleavage reactions, especially those involving SiR_3 as a neighboring group, see Reetz, M.T. *Angew. Chem. Int. Ed.* ***1979***, *18*, 173.

[50] For a review of the factors involved in reactivity and regioselectivity in free-radical substitutions and additions, see Tedder, J.M. *Angew. Chem. Int. Ed.* ***1982***, *21*, 401.

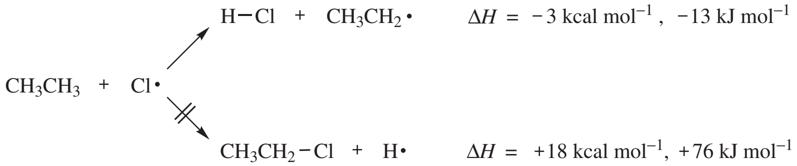
[51] Abstraction of a tetravalent carbon has been seen in the gas phase in abstraction by F• of R from RCl: Firouzbakht, M.L.; Ferrieri, R.A.; Wolf, A.P.; Rack, E.P. *J. Am. Chem. Soc.* ***1987***, *109*, 2213.

[52] See, for example, Back, R.A. *Can. J. Chem.* ***1983***, *61*, 916.

[53] For an example of an abstraction occurring to a small extent at an unstrained carbon atom, see Jackson, R.A.; Townson, M. *J. Chem. Soc. Perkin Trans. 2* ***1980***, 1452. See also, Johnson, M.D. *Acc. Chem. Res.* ***1983***, *16*, 343.

[54] For a monograph on abstractions of divalent and higher valent atoms, see Ingold, K.U.; Roberts, B.P. *Free-Radical Substitution Reactions*, Wiley, NY, ***1971***.

ethyl radical, not a hydrogen atom:



The principal reason for this is steric. A univalent atom is much more exposed to attack by the incoming radical than an atom with a higher valence. Another reason is that in many cases abstraction of a univalent atom is energetically more favored. For example, in the reaction given above, a C_2H_5—H bond is broken ($D = 100$ kcal mol^{-1}, 419 kJ mol^{-1}, from Table 5.3) whichever pathway is taken, but in the former case an H—Cl bond is formed ($D = 103$ kcal mol^{-1}, 432 kJ mol^{-1}) while in the latter case it is a C_2H_5—Cl bond ($D = 82$ kcal mol^{-1}, 343 kJ mol^{-1}). Thus the first reaction is favored because it is exothermic by 3 kcal mol^{-1} (100–103) [13 kJ mol^{-1} (419–432)], while the latter is endothermic by 18 kcal mol^{-1} (100–82) [76 kJ mol^{-1} (419–343)].[55] However, the steric reason is clearly more important, because even in cases where ΔH is not very different for the two possibilities, the univalent atom is chosen.[56] *Ab initio* studies have probed the transition structures for radical hydrogen abstractions.[57]

Most studies of aliphatic reactivity have been made with hydrogen as the leaving atom and chlorine atoms as the abstracting species.[58] In these reactions, every hydrogen in the substrate is potentially replaceable and mixtures are usually obtained. However, the abstracting radical is not totally unselective, and some positions on a molecule lose hydrogen more easily than others. *Ab initio* studies have studied the factors controlling hydrogen abstraction by radicals.[59] For hydrogen abstraction by the *tert*-butoxy radical (*t*-Bu—O•) the factors that influence rate in their order of importance are structure of the radical > substituent effects[60] > solvent effects.[61] We discuss the position of attack under several headings:[62]

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[55] The parameter ΔH for a free-radical abstraction reaction can be regarded simply as the difference in D values for the bond being broken and the one formed.

[56] Giese, B.; Hartung, J. *Chem. Ber.* ***1992***, *125*, 1777.

[57] Eksterowicz, J.E.; Houk, K.N. *Tetrahedron Lett.* ***1993***, *34*, 427; Damm, W.; Dickhaut, J.; Wetterich, F.; Giese, B. *Tetrahedron Lett.* ***1993***, *34*, 431.

[58] For a review that lists many rate constants for abstraction of hydrogen at various positions of many molecules, see Hendry, D.G.; Mill, T.; Piszkiewicz, L.; Howard, J.A.; Eigenmann, H.K. *J. Phys. Chem. Ref. Data* ***1974***, *3*, 937; Roberts, B.P.; Steel, A.J. *Tetrahedron Lett.* ***1993***, *34*, 5167. See Tanko, J.M.; Blackert, J.F. *J. Chem. Soc. Perkin Trans. 2* ***1996***, 1775 for the absolute rate constants for abstraction of chlorine by alkyl radicals.

[59] Zavitsas, A.A. *J. Chem. Soc. Perkin Trans. 2* ***1998***, 499; Roberts, B.P. *J. Chem. Soc. Perkin Trans. 2* ***1996***, 2719.

[60] See Wen, Z.; Li, Z.; Shang, Z.; Cheng, J.-P. *J. Org. Chem.* ***2001***, *66*, 1466.

[61] Kim, S.S.; Kim, S.Y.; Ryou, S.S.; Lee, C.S.; Yoo, K.H. *J. Org. Chem.* ***1993***, *58*, 192.

[62] For reviews, see Tedder, J.M. *Tetrahedron* ***1982***, *38*, 313; Kerr, J.A., in Bamford, C.H.; Tipper, C.F.H. *Comprehensive Chemical Kinetics*, Vol. 18, Elsevier, NY, ***1976***, pp. 39–109; Russell, G.A., in Kochi, J.K. *Free Radicals*, Vol. 2, Wiley, NY, ***1973***, pp. 275–331; Rüchardt, C. *Angew. Chem. Int. Ed.* ***1970***, *9*, 830; Poutsma, M.L. *Methods Free-Radical Chem.* ***1969***, *1*, 79; Davidson, R.S. *Q. Rev. Chem. Soc.* ***1967***, *21*, 249; Pryor, W.A.; Fuller, D.L.; Stanley, J.P. *J. Am. Chem. Soc.* ***1972***, *94*, 1632.

TABLE 14.1. Relative Susceptibility to Attack by Cl• of Primary, Secondary, and Tertiary Positions at 100 and 600°C in the Gas Phase[63]

Temperature, °C	Primary	Secondary	Tertiary
100	1	4.3	7.0
600	1	2.1	2.6

1. *Alkanes*. The tertiary hydrogens of an alkane are the ones preferentially abstracted by almost any radical, with secondary hydrogens being next preferred. This is in the same order as *D* values for these types of C—H bonds (Table 5.3). The extent of the preference depends on the selectivity of the abstracting radical and on the temperature. Table 14.1 shows[63] that at high temperatures selectivity decreases, as might be expected.[64] An example of the effect of radical selectivity may be noted in a comparison of fluorine atoms with bromine atoms. For the former, the ratio of primary to tertiary abstraction (of hydrogen) is 1:1.4, while for the less reactive bromine atom this ratio is 1:1600. With certain large radicals there is a steric factor that may change the selectivity pattern. For example, in the photochemical chlorination of isopentane in H_2SO_4 with *N*-chloro-di-*tert*-butylamine and *N*-chloro-*tert*-butyl-*tert*-pentylamine, the primary hydrogens are abstracted 1.7 times *faster* than the tertiary hydrogen.[65] In this case, the attacking radicals (the radical ions $R_2NH\bullet^+$, see p. 958) are bulky enough for steric hindrance to become a major factor.

12

Cyclopropylcarbinyl radicals (**12**) are alkyl radicals, but they undergo rapid ring opening to give butenyl radicals.[66] The rate constant for this process has been measured by picosecond radical kinetic techniques to be in the range of $10^7\,M^{-1}\,s^{-1}$ for the parent[67] to $10^{10}\,M^{-1}\,s^{-1}$ for substituted derivatives.[68] Cyclobutylcarbinyl radicals undergo the cyclobutylcarbinyl to

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[63] Hass, H.B.; McBee, E.T.; Weber, P. *Ind. Eng. Chem.* ***1936***, *28*, 333.

[64] For a similar result with phenyl radicals, see Kopinke, F.; Zimmermann, G.; Anders, K. *J. Org. Chem.* ***1989***, *54*, 3571.

[65] Deno, N.C.; Fishbein, R.; Wyckoff, J.C. *J. Am. Chem. Soc.* ***1971***, *93*, 2065. Similar steric effects, though not a reversal of primary-tertiary reactivity, were found by Dneprovskii, A.N.; Mil'tsov, S.A. *J. Org. Chem. USSR* ***1988***, *24*, 1836.

[66] Nonhebel, D.C. *Chem. Soc. Rev.* ***1993***, *22*, 347.

[67] Engel, P.S.; He, S.-L.; Banks, J.T.; Ingold, K.U.; Lusztyk, J. *J. Org. Chem.* ***1997***, *62*, 1210.

[68] Choi, S.-Y.; Newcomb, M. *Tetrahedron* ***1995***, *51*, 657; Choi, S.-Y.; Toy, P.H.; Newcomb, M. *J. Org. Chem.* ***1998***, *63*, 8609. See Martinez, F.N.; Schlegel, H.B.; Newcomb, M. *J. Org. Chem.* ***1996***, *61*, 8547; ***1998***, *63*, 3618 for *ab initio* studies to determine rate constants.

4-pentenyl radical process,[69] but examples are generally limited to the parent system and phenyl-substituted derivatives.[70] Cyclization of the 4-pentenyl radical is usually limited to systems where a stabilized radical can be formed.[71] The effect of substituents has been studied.[72] This process has been observed in bicyclo[4.1.0]heptan-4-ones.[73]

The rate of the ring-opening reaction of **5**,[74] and other substrates have been determined using an indirect method for the calibration[75] of fast radical reactions, applicable for radicals with lifetimes as short as 1 ps.[76] This 'radical clock'[77] method is based on the use of Barton's use of pyridine-2-thione-*N*-oxycarbonyl esters as radical precursors and radical trapping by the highly reactive thiophenol and benzeneselenol.[78] A number of radical clock substrates are known.[79] Other radical clock processes include: racemization of radicals with chiral conformations,[80] one-carbon ring expansion in cyclopentanones,[81] norcarane and spiro[2,5]octane,[82] α- and β-thujone radical rearrangements,[83] and cyclopropylcarbinyl radicals or alkoxycarbonyl radicals containing stabilizing substituents.[84]

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[69] For a triplet radical in electron transfer cycloreversion of a cyclobutane, see Miranda, M.A.; Izquierdo, M.A.; Galindo, F. *J. Org. Chem.* ***2002***, *67*, 4138.

[70] Beckwith, A.L.J.; Moad, G. *J. Chem. Soc, Perkin Trans. 2* ***1980***, 1083; Ingold, K.U.; Maillard, B.; Walton, J.C. *J. Chem. Soc, Perkin Trans. 2* ***1981***, 970; Walton, J.C. *J. Chem. Soc, Perkin Trans. 2* ***1989***, 173; Choi, S.-Y.; Horner, J.H.; Newcomb, M. *J. Org. Chem.* ***2000***, *65*, 4447; Newcomb, M.; Horner, J.H.; Emanuel, C.J. *J. Am. Chem. Soc.* ***1997***, *119*, 7147.

[71] Clark, A.J.; Peacock, J.L. *Tetrahedron Lett.* ***1998***, *39*, 1265; Cerreti, A.; D'Annibale, A.; Trogolo, C.; Umani, F. *Tetrahedron Lett.* ***2000***, *41*, 3261; Ishibashi, H.; Higuchi, M.; Ohba, M.; Ikeda, M. *Tetrahedron Lett.* ***1998***, *39*, 75; Ishibashi, H.; Nakamura, N.; Sato, S.; Takeuchi, M.; Ikeda, M. *Tetrahedron Lett.* ***1991***, *32*, 1725; Ogura, K.; Sumitani, N.; Kayano, A.; Iguchi, H.; Fujita, M. *Chem. Lett.* ***1992***, 1487.

[72] Baker, J.M.; Dolbier Jr, W.R. *J. Org. Chem.* ***2001***, *66*, 2662.

[73] Kirschberg, T.; Mattay, J. *Tetrahedron Lett.* ***1994***, *35*, 7217.

[74] Mathew, L.; Warkentin, J. *J. Am. Chem. Soc.* ***1986***, *108*, 7981; For an article clocking tertiary cyclopropylcarbinyl radical rearrangements, see Engel, P.S.; He, S.-L.; Banks, J.T.; Ingold, K.U.; Lusztyk, J. *J. Org. Chem.* ***1997***, *62*, 1212, 5656.

[75] See Hollis, R.; Hughes, L.; Bowry, V.W.; Ingold, K.U. *J. Org. Chem.* ***1992***, *57*, 4284.

[76] Newcomb, M.; Toy, P.H. *Acc. Chem. Res.* ***2000***, *33*, 449. See Horn, A.H.C.; Clark, T. *J. Am. Chem. Soc.* ***2003***, *125*, 2809.

[77] For a review, see Griller, D.; Ingold, K.U. *Acc. Chem. Res.* ***1980***, *13*, 317.

[78] Newcomb, M.; Park, S.-U. *J. Am. Chem. Soc.* ***1986***, *108*, 4132; Newcomb, M.; Glenn, A.G. *J. Am. Chem. Soc.* ***1989***, *111*, 275; Newcomb, M.; Johnson, C.C.; Manek, M.B.; Varick, T.R. *J. Am. Chem. Soc.* ***1992***, *114*, 10915; Newcomb, M.; Varick, T.R.; Ha, C.; Manek, M.B.; Yue, X. *J. Am. Chem. Soc.* ***1992***, *114*, 8158.

[79] See Kumar, D.; de Visser, S.P.; Sharma, P.K.; Cohen, S.; Shaik, S. *J. Am. Chem. Soc.* ***2004***, *126*, 1907.

[80] Buckmelter, A.J.; Kim, A.I.; Rychnovsky, S.D. *J. Am. Chem. Soc.* ***2000***, *122*, 9386; Rychnovsky, S.D.; Hata, T.; Kim, A.I.; Buckmelter, A.J. *Org. Lett.* ***2001***, *3*, 807.

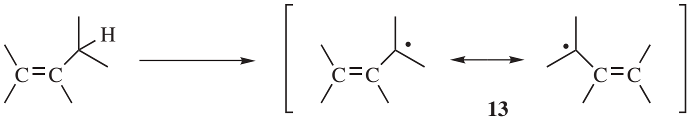
[81] Chatgilialoglu, C.; Timokhin, V. I.; Ballestri, M. *J. Org. Chem.* ***1998***, *63*, 1327.

[82] For an application and leading references, see Auclair, K.; Hu, Z.; Little, D. M.; Ortiz de Montellano, P. R.; Groves, J. T. *J. Am. Chem. Soc.* ***2002***, *124*, 6020.

[83] He, X.; Ortiz de Montellano, P. R. *J. Org. Chem.* ***2004***, *69*, 5684.

[84] Beckwith, A.L.J.; Bowry, V.W. *J. Am. Chem. Soc.* ***1994***, *116*, 2710. See Cooksy, A.L.; King, H.F.; Richardson, W.H. *J. Org. Chem.* ***2003***, *68*, 9441.

2. *Alkenes*. When the substrate molecule contains a double bond, treatment with chlorine or bromine usually leads to addition rather than substitution. However, for other radicals (and even for chlorine or bromine atoms when they do abstract a hydrogen) the position of attack is perfectly clear. Vinylic hydrogens are practically never abstracted, and allylic hydrogens are greatly preferred to other positions of the molecule. Allylic hydrogen abstraction from a cyclic alkenes is usually faster than abstraction from an acyclic alkene.[85] This is generally attributed[86] to resonance stabilization of the allylic radical, **13**. As might be expected, allylic rearrangements (see p. 469) are common in these cases.[87]



13

3. *Alkyl Side Chains of Aromatic Rings*. The preferential position of attack on a side chain is usually the one to the ring. Both for active radicals, such as chlorine and phenyl, and for more selective ones, such as bromine, such attack is faster than that at a primary carbon, but for the active radicals benzylic attack is slower than for tertiary positions, while for the selective ones it is faster. Two or three aryl groups on a carbon activate its hydrogens even more, as would be expected from the resonance involved. These statements can be illustrated by the following abstraction ratios:[88]

	Me–H	$MeCH_2$–H	Me_2CH–H	Me_3C–H	$PhCH_2$–H	Ph_2CH–H	Ph_3C–H
Br	0.0007	1	220	19,400	64,000	1.1×10^6	6.4×10^6
Cl	0.004	1	4.3	6.0	1.3	2.6	9.5

However, many anomalous results have been reported for these substrates. The benzylic position is not always the most favored. One thing certain is that *aromatic* hydrogens are seldom abstracted if there are aliphatic ones to compete (note from Table 5.3, that *D* for Ph–H is higher than that for any alkyl H bond). Several $\sigma\bullet$ scales (similar to the σ, σ^+, and σ^- scales discussed in Chapter 9) have been developed for benzylic radicals.[89]

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[85] Rothenberg, G.; Sasson, Y. *Tetrahedron* ***1998***, *54*, 5417.

[86] See however Kwart, H.; Brechbiel, M.; Miles, W.; Kwart, L.D. *J. Org. Chem.* ***1982***, *47*, 4524.

[87] For reviews, see Wilt, J.W., in Kochi, J.K. *Free Radicals*, Vol. 1, Wiley, NY, ***1973***, pp. 458–466.

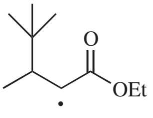
[88] Russell, G.A., in Kochi, J.K. *Free Radicals*, Vol. 2, Wiley, NY, ***1973***, p. 289.

[89] See, for example, Dinçtürk, S.; Jackson, R.A. *J. Chem. Soc. Perkin Trans. 2* ***1981***, 1127; Dust, J.M.; Arnold, D.R. *J. Am. Chem. Soc.* ***1983***, *105*, 1221, 6531; Creary, X.; Mehrsheikh-Mohammadi, M.E.; McDonald, S. *J. Org. Chem.* ***1987***, *52*, 3254; ***1989***, *54*, 2904; Fisher, T.H.; Dershem, S.M.; Prewitt, M.L. *J. Org. Chem.* ***1990***, *55*, 1040.

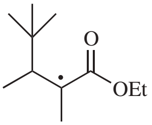
4. *Compounds Containing Electron-Withdrawing Substituents.* In halogenations, electron-withdrawing groups greatly deactivate adjacent positions. Compounds of the type Z–CH_2–CH_3 are attacked predominantly or exclusively at the β position when Z is COOH, COCl, COOR, SO_2Cl, or CX_3. Such compounds as acetic acid and acetyl chloride are not attacked at all. This is in sharp contrast to electrophilic halogenations (**12-4–12-6**), where *only* the α position is substituted. This deactivation of a positions is also at variance with the expected stability of the resulting radicals, since they would be expected to be stabilized by resonance similar to that for allylic and benzylic radicals. This behavior is a result of the polar transition states discussed on p. 939. Halogen atoms are electrophilic radicals and look for positions of high electron density. Hydrogens on carbon atoms next to electron-withdrawing groups have low electron densities (because of the field effect of Z) and are therefore shunned. Radicals that are not electrophilic do not display this behavior. For example, the methyl radical is essentially nonpolar and does not avoid positions next to electron-withdrawing groups; relative rates of abstraction at the α and β carbons of propionic acid are:[90]

	CH_3–CH_2–COOH	
Me•	1	7.8
Cl•	1	0.02

It is possible to generate radicals adjacent to electron-withdrawing groups. Radical **14** can be generated and it undergoes coupling reactions with little selectivity. When **15** is generated, however, it rapidly disproportionates rather than couples, giving the corresponding alkene and alkane.[91] Such radicals have also been shown to have a conformational preference for orientation of the orbital containing the single electron. In such cases, hydrogen abstraction proceeds with good stereoselectivity.[92]



14



15

Some radicals, for example, *tert*-butyl,[93] benzyl,[94] and cyclopropyl,[95] are *nucleophilic* (they tend to abstract electron-poor hydrogen atoms). The

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[90] Russell, G.A., in Kochi, J.K. *Free Radicals*, Vol. 2, Wiley, NY, ***1973***, p. 311.

[91] Porter, N.A.; Rosenstein, I.J. *Tetrahedron Lett.* ***1993***, *34*, 7865.

[92] Giese, B.; Damm, W.; Wetterich, F.; Zeitz, H.-G. *Tetrahedron Lett.* ***1992***, *33*, 1863.

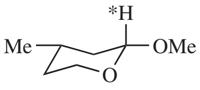
[93] Pryor, W.A.; Tang, F.Y.; Tang, R.H.; Church, D.F. *J. Am. Chem. Soc.* ***1982***, *104*, 2885; Dütsch, H.R.; Fischer, H. *Int. J. Chem. Kinet.* ***1982***, *14*, 195.

[94] Clerici, A.; Minisci, F.; Porta, O. *Tetrahedron* ***1973***, *29*, 2775.

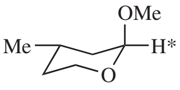
[95] Stefani, A.; Chuang, L.; Todd, H.E. *J. Am. Chem. Soc.* ***1970***, *92*, 4168.

phenyl radical appears to have a very small degree of nucleophilic character.[96] For longer chains, the field effect continues, and the β position is also deactivated to attack by halogen, though much less so than the α position. We have already mentioned (p. 939) that abstraction of an α hydrogen atom from ring-substituted toluenes can be correlated by the Hammett equation.

5. *Stereoelectronic Effects.* On p. 1258, we will see an example of a stereoelectronic effect. It has been shown that such effects are important where a hydrogen is abstracted from a carbon adjacent to a C—O or C—N bond. In such cases, hydrogen is abstracted from C—H bonds that have a relatively small dihedral angle ($\sim$30°) with the unshared orbitals of the O or N much more easily than from those with a large angle ($\sim$90°). For example, the starred hydrogen of **16** was abstracted $\sim$8 times faster than the starred hydrogen of **17**.[97]



16



17

The presence of an OR or SiR$_3$ substituent β- to the carbon bearing the radical accelerates the rate of halogen abstraction.[98]

Abstraction of a halogen has been studied much less,[99] but the order of reactivity is $RI > RBr > RCl \gg RF$.

There are now many cases where free-radical reactions are promoted by transition metals.[100]

Reactivity at a Bridgehead[101]

Many free-radical reactions have been observed at bridgehead carbons, as in formation of bromide **18** (see **14-30**),[102] demonstrating that the free radical need not be planar. However, treatment of norbornane with sulfuryl chloride and benzoyl

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[96] Suehiro, T.; Suzuki, A.; Tsuchida, Y.; Yamazaki, J. *Bull. Chem. Soc. Jpn.* ***1977***, *50*, 3324.

[97] Hayday, K.; McKelvey, R.D. *J. Org. Chem.* ***1976***, *41*, 2222. For additional examples, see Malatesta, V.; Ingold, K.U. *J. Am. Chem. Soc.* ***1981***, *103*, 609; Beckwith, A.L.J.; Easton, C.J. *J. Am. Chem. Soc.* ***1981***, *103*, 615; Beckwith, A.L.J.; Westwood, S.W. *Aust. J. Chem.* ***1983***, *36*, 2123; Griller, D.; Howard, J.A.; Marriott, P.R.; Scaiano, J.C. *J. Am. Chem. Soc.* ***1981***, *103*, 619. For a stereoselective abstraction step, see Dneprovskii, A.S.; Pertsikov, B.Z.; Temnikova, T.I. *J. Org. Chem. USSR* ***1982***, *18*, 1951. See also, Bunce, N.J.; Cheung, H.K.Y.; Langshaw, J. *J. Org. Chem.* ***1986***, *51*, 5421.

[98] Roberts, B.P.; Steel, A.J. *J. Chem. Soc. Perkin Trans. 2* ***1994***, 2411.

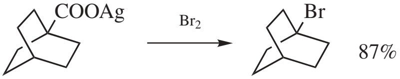
[99] For a review, see Danen, W.C. *Methods Free-Radical Chem.* ***1974***, *5*, 1.

[100] Iqbal, J.; Bhatia, B.; Nayyar, N.K. *Chem. Rev.* ***1994***, *94*, 519. See Hasegawa, E.; Curran, D.P. *Tetrahedron Lett.* ***1993***, *34*, 1717 for the rate of reaction for a primary akyl radical in the presence of SmI$_2$.

[101] For reviews, see Bingham, R.C.; Schleyer, P.v.R. *Fortschr. Chem. Forsch.* ***1971***, *18*, 1, see pp. 79–81; Fort, Jr, R.C.; Schleyer, P.v.R. *Adv. Alicyclic Chem.* ***1966***, *1*, 283, see p. 337.

[102] Grob, C.A.; Ohta, M.; Renk, E.; Weiss, A. *Helv. Chim. Acta* ***1958***, *41*, 1191.

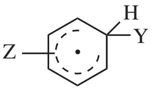
peroxide gave mostly 2-chloronorbornane, though the bridgehead position is tertiary.[103] So, while bridgehead free-radical substitution is possible, it is not preferred, presumably because of the strain involved.[104]



18

Reactivity in Aromatic Substrates

Free-radical substitution at an aromatic carbon seldom takes place by a mechanism in which a hydrogen is abstracted to give an aryl radical. Reactivity considerations here are similar to those in Chapters 11 and 13; that is, we need to know which position on the ring will be attacked to give the intermediate, **19**.



19

The obvious way to obtain this information is to carry out reactions with various Z groups and to analyze the products for percent ortho, meta, and para isomers, as has so often been done for electrophilic substitution. However, this procedure is much less accurate in the case of free-radical substitutions because of the many side reactions. It may be, for example, that in a given case the ortho position is more reactive than the para, but the intermediate from the para attack may go on to product while that from ortho attack gives a side reaction. In such a case, analysis of the three products does not give a true picture of which position is most susceptible to attack. The following generalizations can nevertheless be drawn, though there has been much controversy over just how meaningful such conclusions are[105]

1. All substituents increase reactivity at ortho and para positions over that of benzene. There is no great difference between electron-donating and electron-withdrawing groups.
2. Reactivity at meta positions is usually similar to that of benzene, perhaps slightly higher or lower. This fact, coupled with the preceding one, means that all substituents are activating and ortho–para directing; none are deactivating or (chiefly) meta directing.

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[103] Roberts, J.D.; Urbanek, L.; Armstrong, R. *J. Am. Chem. Soc.* ***1949***, *71*, 3049. See also, Kooyman, E.C.; Vegter, G.C. *Tetrahedron* ***1958***, *4*, 382; Walling, C.; Mayahi, M.F. *J. Am. Chem. Soc.* ***1959***, *81*, 1485.

[104] See, for example, Koch, V.R.; Gleicher, G.J. *J. Am. Chem. Soc.* ***1971***, *93*, 1657.

[105] De Tar, D.F. *J. Am. Chem. Soc.* ***1961***, *83*, 1014 (book review); Dickerman, S.C.; Vermont, G.B. *J. Am. Chem. Soc.* ***1962***, *84*, 4150; Morrison, R.T.; Cazes, J.; Samkoff, N.; Howe, C.A. *J. Am. Chem. Soc.* ***1962***, *84*, 4152; Ohta, H.; Tokumaru, K. *Bull. Chem. Soc. Jpn.* ***1971***, *44*, 3218; Vidal, S.; Court, J.; Bonnier, J. *J. Chem. Soc. Perkin Trans. 2* ***1973***, 2071; Tezuka, T.; Ichikawa, K.; Marusawa, H.; Narita, N. *Chem. Lett.* ***1983***, 1013.

TABLE 14.2. Partial Rate Factors for Attack of Substituted Benzenes by Phenyl Radicals Generated from Bz_2O_2[108]

	Partial Rate Factor		
Z	*o*	*m*	*p*
H	1	1	1
NO_2	5.50	0.86	4.90
CH_3	4.70	1.24	3.55
CMe_3	0.70	1.64	1.81
Cl	3.90	1.65	2.12
Br	3.05	1.70	1.92
MeO	5.6	1.23	2.31

3. Reactivity at ortho positions is usually somewhat greater than at para positions, except where a large group decreases ortho reactivity for steric reasons.

4. In direct competition, electron-withdrawing groups exert a somewhat greater influence than electron-donating groups. Arylation of para-disubstituted compounds XC_6H_4Y showed that substitution ortho to the group X became increasingly preferred as the electron-withdrawing character of X increases (with Y held constant).[106] The increase could be correlated with the Hammett σ_p values for X.

5. Substituents have a much smaller effect than in electrophilic or nucleophilic substitution; hence the partial rate factors (see p. 677) are not great.[107] Partial rate factors for a few groups are given in Table 14.2.[108]

6. Although hydrogen is the leaving group in most free-radical aromatic substitutions, ipso attack (p. 671) and ipso substitution (e.g., with Br, NO_2, or CH_3CO as the leaving group) have been found in certain cases.[109]

Reactivity in the Attacking Radical[110]

We have already seen that some radicals are much more selective than others (p. 944). The bromine atom is so selective that when only primary hydrogens are available, as in neopentane or *tert*-butylbenzene, the reaction is slow or nonexistent; and isobutane can be selectively brominated to give *tert*-butyl bromide in high yields.

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[106] Davies, D.I.; Hey, D.H.; Summers, B. *J. Chem. Soc. C* ***1970***, 2653.

[107] For a quantitative treatment, see Charton, M.; Charton, B. *Bull. Soc. Chim. Fr.* ***1988***, 199.

[108] Davies, D.I.; Hey, D.H.; Summers, B. *J. Chem. Soc. C* ***1971***, 2681.

[109] For reviews, see Traynham, J.G. *J. Chem. Educ.* ***1983***, *60*, 937; *Chem. Rev.* ***1979***, *79*, 323; Tiecco, M. *Acc. Chem. Res.* ***1980***, *13*, 51; *Pure Appl. Chem.* ***1981***, *53*, 239.

[110] For reviews with respect to $CH_3\bullet$ and $CF_3\bullet$, see Trotman-Dickenson, A.F. *Adv. Free-Radical Chem.* ***1965***, *1*, 1; Spirin, Yu.L. *Russ. Chem. Rev.* ***1969***, *38*, 529; Gray, P.; Herod, A.A.; Jones, A. *Chem. Rev.* ***1971***, *71*, 247.

TABLE 14.3. Some Common Free Radicals in Decreasing Order of Activity[a]

	E			E	
Radical	kcal $mol^{-1}e$	kJ $mol^{-1}e$	Radical	kcal mol^{-1}	kJ mol^{-1}
F•	0.3	1.3	H•	9.0	38
Cl•	1.0	4.2	Me•	11.8	49.4
MeO•	7.1	30	Br•	13.2	55.2
CF_3•	7.5	31			

[a]The *E* values represent activation energies for the reaction

$X\bullet + C_2H_6 \longrightarrow X{-}H + C_2H_5\bullet$ (Ref. 112)

i-Pr• is less active than Me• and *t*-Bu• still less so.[113]

However, toluene reacts with bromine atoms instantly. Bromination of other alkylbenzenes, for example, ethylbenzene and cumene, takes place exclusively at the a position,[111] emphasizing the selectivity of Br•. The dissociation energy *D* of the C—H bond is more important for radicals of low reactivity than for highly reactive radicals, since bond breaking in the transition state is greater. Thus, bromine shows a greater tendency than chlorine to attack α to an electron-withdrawing group because the energy of the C—H bond there is lower than in other places in the molecule.

Some radicals, for example, triphenylmethyl, are so unreactive that they abstract hydrogens very poorly if at all. Table 14.3 lists some common free radicals in approximate order of reactivity.[112]

It has been mentioned that some free radicals (e.g., chloro) are electrophilic and some (e.g., *tert*-butyl) are nucleophilic. It must be borne in mind that these tendencies are relatively slight compared with the electrophilicity of a positive ion or the nucleophilicity of a negative ion. The predominant character of a free radical is neutral, whether it has slight electrophilic or nucleophilic tendencies.

The Effect of Solvent on Reactivity[114]

As noted earlier, the solvent usually has little effect on free-radical substitutions in contrast to ionic ones: indeed, reactions in solution are often quite similar in character to those in the gas phase, where there is no solvent at all. However, in certain cases the solvent *can* make an appreciable difference. Chlorination of 2,3-dimethylbutane in aliphatic solvents gave about 60% $(CH_3)_2CHCH(CH_3)CH_2Cl$

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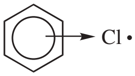
[111] Huyser, E.S. *Free-Radical Chain Reactions*, Wiley, NY, ***1970***, p. 97.

[112] Trotman-Dickenson, A.F. *Adv. Free-Radical Chem.* ***1965***, *1*, 1.

[113] Kharasch, M.S.; Hambling, J.K.; Rudy, T.P. *J. Org. Chem.* ***1959***, *24*, 303.

[114] For reviews, see Reichardt, C. *Solvent Effects in Organic Chemistry*; Verlag Chemie: Deerfield Beach, FL, ***1979***, pp. 110–123; Martin, J.C., in Kochi, J.K. *Free Radicals*, Vol. 2, Wiley, NY, ***1973***, pp. 493–524; Huyser, E.S. *Adv. Free-Radical Chem.* ***1965***, *1*, 77.

and 40% $(CH_3)_2CHCCl(CH_3)_2$, while in aromatic solvents the ratio became ~10:90.[115] This result is attributed to complex formation between the aromatic solvent and the chlorine atom that makes the chlorine more selective.[116] This type of effect is not found in cases where the differences in ability to abstract the atom are caused by field effects of electron-withdrawing groups (p. 948). In such cases, aromatic solvents make little difference.[117] The complex **20** has been detected[118] as a very short-lived species by observation of its visible spectrum in the pulse radiolysis of a solution of benzene in CCl_4.[119] Differences caused by solvents have also been reported in reactions of other radicals.[120] Some of the anomalous results obtained in the chlorination of aromatic side chains (p. 947) can also be explained by this type of complexing, in this case not with the solvent but with the reacting species.[121] Much smaller, though real, differences in selectivity have been found when the solvent in the chlorination of 2,3-dimethylbutane is changed from an alkane to CCl_4.[122] However, these differences are not caused by formation of a complex between Cl• and the solvent. There are cases,



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[115] Russell, G.A. *J. Am. Chem. Soc.* ***1958***, *80*, 4987, 4997, 5002; *J. Org. Chem.* ***1959***, *24*, 300.

[116] See also, Soumillion, J.P.; Bruylants, A. *Bull. Soc. Chim. Belg.* ***1969***, *78*, 425; Potter, A.; Tedder, J.M. *J. Chem. Soc. Perkin Trans. 2* ***1982***, 1689; Aver'yanov, V.A.; Ruban, S.G.; Shvets,V.F. *J. Org. Chem. USSR* ***1987***, *23*, 782; Aver'yanov, V.A.; Ruban, S.G. *J. Org. Chem. USSR* ***1987***, *23*, 1119; Raner, K.D.; Lusztyk, J.; Ingold, K.U. *J. Am. Chem. Soc.* ***1989***, *111*, 3652; Ingold, K.U.; Lusztyk, J.; Raner, K.D. *Acc. Chem. Res.* ***1990***, *23*, 219.

[117] Russell, G.A. *Tetrahedron* ***1960***, *8*, 101; Nagai, T.; Horikawa, Y.; Ryang, H.S.; Tokura, N. *Bull. Chem. Soc. Jpn.* ***1971***, *44*, 2771.

[118] It has been contended that another species, a chlorocyclohexadienyl radical (the structure of which is the same as **5**, except that Cl replaces Ar), can also be attacking when the solvent is benzene: Skell, P.S.; Baxter III, H.N.; Taylor, C.K. *J. Am. Chem. Soc.* ***1983***, *105*, 120; Skell, P.S.; Baxter III, H.N.; Tanko, J.M.; Chebolu, V. *J. Am. Chem. Soc.* ***1986***, *108*, 6300. For arguments against this proposal, see Bunce, N.J.; Ingold, K.U.; Landers, J.P.; Lusztyk, J.; Scaiano, J.C. *J. Am. Chem. Soc.* ***1985***, *107*, 5464; Walling, C. *J. Org. Chem.* ***1988***, *53*, 305; Aver'yanov, V.A.; Shvets, V.F.; Semenov, A.O. *J. Org. Chem. USSR* ***1990***, *26*, 1261.

[119] Bühler, R.E. *Helv. Chim. Acta* ***1968***, *51*, 1558. For other spectral observations, see Raner, K.D.; Lusztyk, J.; Ingold, K.U. *J. Phys. Chem.* ***1989***, *93*, 564.

[120] Walling, C.; Azar, J.C. *J. Org. Chem.* ***1968***, *33*, 3885; Ito, O.; Matsuda, M. *J. Am. Chem. Soc.* ***1982***, *104*, 568; Minisci, F.; Vismara, E.; Fontana, F.; Morini, G.; Serravalle, M.; Giordano, C. *J. Org. Chem.* ***1987***, *52*, 730.

[121] Russell, G.A.; Ito, O.; Hendry, D.G. *J. Am. Chem. Soc.* ***1963***, *85*, 2976; Corbiau, J.L.; Bruylants, A. *Bull. Soc. Chim. Belg.* ***1970***, *79*, 203, 211; Newkirk, D.D.; Gleicher, G.J. *J. Am. Chem. Soc.* ***1974***, *96*, 3543.

[122] See Raner, K.D.; Lusztyk, J.; Ingold, K.U. *J. Org. Chem.* ***1988***, *53*, 5220.

however, where the rate of reaction for trapping a radical depends on the polarity of the solvent, particularly in water.[123]

REACTIONS

The reactions in this chapter are classified according to leaving group. The most common leaving groups are hydrogen and nitrogen (from the diazonium ion); these are considered first.

HYDROGEN AS LEAVING GROUP

A. Substitution by Halogen

14-1 Halogenation at an Alkyl Carbon[124]

Halogenation or **Halo-de-hydrogenation**

$$\text{R—H} + \text{Cl}_2 \xrightarrow{h\nu} \text{R—Cl}$$

Alkanes can be chlorinated or brominated by treatment with chlorine or bromine in the presence of visible or UV light.[125] These reactions require a radical chain initiator, light, or higher temperatures.[126] The reaction can also be applied to alkyl chains containing many functional groups. The chlorination reaction is usually not useful for preparative purposes precisely because it is so general: Not only does substitution take place at virtually every alkyl carbon in the molecule, but di- and polychloro substitution almost invariably occur even if there is a large molar ratio of substrate to halogen.

When functional groups are present, the principles are those outlined on p. 945; favored positions are those α to aromatic rings, while positions α to electron-withdrawing groups are least likely to be substituted. Tertiary carbons are most likely to be attacked and primary least. Positions α to an OR group are very readily attacked. Nevertheless, mixtures are nearly always obtained. This can be contrasted to the regioselectivity of electrophilic halogenation (**12-4–12-6**), which always takes place α to a carbonyl group (except when the reaction is catalyzed by AgSbF_6; see following). Of course, if a *mixture* of chlorides is wanted, the reaction is usually

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[123] Tronche, C.; Martinez, F.N.; Horner, J.H.; Newcomb, M.; Senn, M.; Giese, B. *Tetrahedron Lett.* ***1996***, *37*, 5845.

[124] For lists of reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed, Wiley-VCH, NY, ***1999***, pp. 611–617.

[125] For reviews, see Poutsma, M.L., in Kochi, J.K. *Free Radicals*, Vol. 2, Wiley, NY, ***1973***, pp. 159–229; Huyser, E.S., in Patai, S. *The Chemistry of the Carbon-Halogen Bond*, pt. 1, Wiley, NY, ***1973***, pp. 549–607; Poutsma, M.L. *Methods Free-Radical Chem.* ***1969***, *1*, 79 (chlorination); Thaler, W.A. *Methods Free-Radical Chem.* ***1969***, *2*, 121 (bromination).

[126] Hill, C.L. *Activation and Functionalization of Alkanes*, Wiley, NY, ***1989***.

quite satisfactory. For obtaining pure compounds, the chlorination reaction is essentially limited to substrates with only one type of replaceable hydrogen (e.g., ethane, cyclohexane, neopentane). The most common are methylbenzenes and other substrates with methyl groups on aromatic rings, since few cases are known where halogen atoms substitute at an aromatic position.[127] Of course, ring substitution *does* take place in the presence of a positive-ion-forming catalyst (**11-10**). In addition to mixtures of various alkyl halides, traces of other products are obtained. These include H_2, alkenes, higher alkanes, lower alkanes, and halogen derivatives of these compounds. Solvent plays an important role in this process.[128]

The bromine atom is much more selective than the chlorine atom. As indicated on p. 952, it is often possible to brominate tertiary and benzylic positions selectively. High regioselectivity can also be obtained where the neighboring-group mechanism (p. 942) can operate.

As already mentioned, halogenation can be performed with chlorine or bromine. Fluorine has also been used,[129] but seldom, because it is too reactive and hard to control.[130] It often breaks carbon chains down into smaller units, a side reaction that sometimes becomes troublesome in chlorinations too. Fluorination[131] has been achieved by the use of chlorine trifluoride ClF_3 at −75°C.[132] For example, cyclohexane gave 41% fluorocyclohexane and methylcyclohexane gave 47% 1-fluoro-1-methylcyclohexane. Fluoroxytrifluoromethane CF_3OF fluorinates tertiary positions of certain molecules in good yields with high regioselectivity.[133] For example, adamantane gave 75% 1-fluoroadamantane. Fluorine at −70°C, diluted with N_2,[134] and bromine trifluoride at 25–35°C[135] are also highly regioselective for

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[127] Dermer, O.C.; Edmison, M.T. *Chem. Rev.* ***1957***, *57*, 77, pp. 110–112. An example of free-radical ring halogenation can be found in Engelsma, J.W.; Kooyman, E.C. *Revl. Trav. Chim. Pays-Bas*, ***1961***, *80*, 526, 537. For a review of aromatic halogenation in the gas phase, see Kooyman, E.C. *Adv. Free-Radical Chem.* ***1965***, *1*, 137.

[128] Dneprovskii, A.S.; Kuznetsov, D.V.; Eliseenkov, E.V.; Fletcher, B.; Tanko, J.M. *J. Org. Chem.* ***1998***, *63*, 8860.

[129] Rozen, S. *Acc. Chem. Res.* ***1988***, *21*, 307; Purrington, S.T.; Kagen, B.S.; Patrick, T.B. *Chem. Rev.* ***1986***, *86*, 997, pp. 1003–1005; Gerstenberger, M.R.C.; Haas, A. *Angew. Chem. Int. Ed.* ***1981***, *20*, 647; Hudlicky, M. *The Chemistry of Organic Fluorine Compounds*, 2nd ed., Ellis Horwood, Chichester, ***1976***; pp. 67–91. For descriptions of the apparatus necessary for handling F_2, see Vypel, H. *Chimia*, ***1985***, *39*, 305.

[130] However, there are several methods by which all the C—H bonds in a molecule can be converted to C—F bonds. For reviews, see Rozhkov, I.N., in Baizer, M.M.; Lund, H. *Organic Electrochemistry*, Marcel Dekker, NY, ***1983***, pp. 805–825; Lagow, R.J.; Margrave, J.L. *Prog. Inorg. Chem.* ***1979***, *26*, 161. See also, Adcock, J.L.; Horita, K.; Renk, E. *J. Am. Chem. Soc.* ***1981***, *103*, 6937; Adcock, J.L.; Evans, W.D. *J. Org. Chem.* ***1984***, *49*, 2719; Huang, H.; Lagow, R.J. *Bull. Soc. Chim. Fr.* ***1986***, 993.

[131] For a monograph on fluorinating agents, see German, L.; Zemskov, S. *New Fluorinating Agents in Organic Synthesis*, Springer, NY, ***1989***.

[132] Brower, K.R. *J. Org. Chem.* ***1987***, *52*, 798.

[133] Alker, D.; Barton, D.H.R.; Hesse, R.H.; Lister-James, J.; Markwell, R.E.; Pechet, M.M.; Rozen, S.; Takeshita, T.; Toh, H.T. *Nouv. J. Chem.* ***1980***, *4*, 239.

[134] Rozen, S.; Ben-Shushan, G. *J. Org. Chem.* ***1986***, *51*, 3522; Rozen, S.; Gal, C. *J. Org. Chem.* ***1987***, *52*, 4928; ***1988***, *53*, 2803; Alker, D.; Barton, D.H.R.; Hesse, R.H.; Lister-James, J.; Markwell, R.E.; Pechet, M.M.; Rozen, S.; Takeshita, T.; Toh, H.T. *Nouv. J. Chem.* ***1980***, *4*, 239.

[135] Boguslavskaya, L.S.; Kartashov, A.V.; Chuvatkin, N.N. *J. Org. Chem. USSR* ***1989***, *25*, 1835.

tertiary positions. These reactions probably have electrophilic,[136] not free-radical mechanisms. In fact, the success of the F_2 reactions depends on the suppression of free radical pathways, by dilution with an inert gas, by working at low temperatures, and/or by the use of radical scavengers.

Iodine can be used if the activating light has a wavelength of 184.9 nm,[137] but iodinations using I_2 alone are seldom attempted, largely because the HI formed reduces the alkyl iodide. The direct free-radical halogenation of aliphatic hydrocarbons with iodine is significantly endothermic relative to the other halogens, and the requisite chain reaction does not occur.[138] On the other hand, when iodine, CCl_4•2 AlI_3 react with an alkane in dibromomethane at −20°C, good yields of the iodoalkane are obtained.[139] The reaction of an alkane with *tert*-butylhypoiodite (*t*-BuOI) at 40°C gave the iodoalkane in good yield.[140] The reaction of alkanes with iodine and $PhI(OAc)_2$ generates the iodoalkane.[141] A radical protocol was developed using CI_4 with base. Cyclohexane could be iodinated, for example, with CI_4 in the presence of powdered NaOH.[142] The reaction led to the use of iodoform on solid NaOH as the iodination reagent of choice. α-Iodo ethers and α-iodolactones have been prepared from the parent ether or lactone via treatment with Et_4N•4 HF under electrolytic conditions.[143]

Many other halogenation agents have been employed, the most common of which is sulfuryl chloride SO_2Cl_2.[144] A mixture of Br_2 and HgO is a more active brominating agent than bromine alone.[145] The actual brominating agent in this case is believed to be bromine monoxide Br_2O. Among other agents used have been *N*-bromosuccinimide (NBS, see **14-3**), CCl_4,[146] $BrCCl_3$,[147] PCl_5,[148] and *N*-haloamines and sulfuric acid.[149] In all these cases, a chain-initiating catalyst is required, usually peroxides or UV light.

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[136] See, for example, Rozen, S.; Gal, C. *J. Org. Chem.* ***1987***, *52*, 2769.

[137] Gover, T.A.; Willard, J.E. *J. Am. Chem. Soc.* ***1960***, *82*, 3816.

[138] Liguori, L.; Bjørsvik, H.-R.; Bravo, A.; Fontana, R.; Minisci, F. *Chem. Commun.* ***1997***, 1501; Tanner, D.D.; Gidley, G.C. *J. Am. Chem. Soc.* ***1968***, *90*, 808; Tanner, D.D.; Rowe, J.R.; Potter, A. *J. Org. Chem.* ***1986***, *51*, 457.

[139] Akhrem, I.; Orlinkov, A.; Vitt, S.; Chistyakov, A. *Tetrahedron Lett.* ***2002***, *43*, 1333.

[140] Montoro, R.; Wirth, T. *Org. Lett.* ***2003***, *5*, 4729.

[141] Barluenga, J.; González-Bobes, F.; González, J.M. *Angew. Chem. Int. Ed.* ***2002***, *41*, 2556.

[142] Schreiner, P.R.; Lauenstein, O.; Butova, E.D.; Fokin, A.A. *Angew. Chem. Int. Ed.* ***1999***, *38*, 2786.

[143] Hasegawa, M.; Ishii, H.; Fuchigami, T. *Tetrahedron Lett.* ***2002***, *43*, 1503.

[144] For a review of this reagent, see Tabushi, I.; Kitaguchi, H., in Pizey, J.S. *Synthetic Reagents*, Vol. 4, Wiley, NY, ***1981***, pp. 336–396.

[145] Bunce, N.J. *Can. J. Chem.* ***1972***, *50*, 3109.

[146] For a discussion of the mechanism with this reagent, see Hawari, J.A.; Davis, S.; Engel, P.S.; Gilbert, B.C.; Griller, D. *J. Am. Chem. Soc.* ***1985***, *107*, 4721.

[147] Huyser, E.S. *J. Am. Chem. Soc.* ***1960***, *82*, 391; Baldwin, S.W.; O'Neill, T.H. *Synth. Commun.* ***1976***, *6*, 109.

[148] Wyman, D.P.; Wang, J.Y.C.; Freeman, W.R. *J. Org. Chem.* ***1963***, *28*, 3173.

[149] For reviews, see Minisci, F. *Synthesis* ***1973***, 1; Deno, N.C. *Methods Free-Radical Chem.* ***1972***, *3*, 135; Sosnovsky, G.; Rawlinson, D.J. *Adv. Free-Radical Chem.* ***1972***, *4*, 203.

A base-induced bromination has been reported. 2-Methyl butane reacts with 50% aq. NaOH and CBr_4, in a phase-transfer catalyst, to give a modest yields of 2-bromo-2-methylbutane.[150]

When chlorination is carried out with *N*-haloamines and sulfuric acid (catalyzed by either uv light or metal ions), selectivity is much greater than with other reagents.[149] In particular, alkyl chains are chlorinated with high regioselectivity at the position next to the end of the chain (the ω - 1 position).[151] Some typical selectivity values are[152]

$CH_3{-}CH_2{-}CH_2{-}CH_2{-}CH_2{-}CH_2{-}CH_3$ Ref. 153
1 56 29 14

$CH_3{-}CH_2{-}CH_2{-}CH_2{-}CH_2{-}CH_2{-}CH_2{-}CH_2{-}OH$ Ref. 154
1 92 3 1 1 2 0 0

$CH_3{-}CH_2{-}CH_2{-}CH_2{-}CH_2{-}CH_2{-}COOMe$ Ref. 155
3 72 20 4 1 0

Furthermore, di- and polychlorination are much less prevalent. Dicarboxylic acids are predominantly chlorinated in the middle of the chain,[156] and adamantane and bicyclo[2.2.2]octane at the bridgeheads[157] by this procedure. The reasons for the high ω - 1 specificity are not clearly understood.[158] Alkyl bromides can be regioselectively chlorinated one carbon away from the bromine (to give *vic*-bromochlorides) by treatment with PCl_5.[159] Alkyl chlorides can be converted to *vic*-dichlorides by treatment with $MoCl_5$.[160] Enhanced selectivity at a terminal position of *n*-alkanes has been achieved by absorbing the substrate onto a pentasil zeolite.[161] In another regioselective chlorination, alkanesulfonamides

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[150] Schreiner, P.R.; Lauentstein, O.; Kolomitsyn, I.V.; Nadi, S.; Kokin, A.A. *Angew. Chem. Int. Ed.* ***1998***, *37*, 1895.

[151] The ω - 1 regioselectivity diminishes when the chains are >10 carbons; see Deno, N.C.; Jedziniak, E.J. *Tetrahedron Lett.* ***1976***, 1259; Konen, D.A.; Maxwell, R.J.; Silbert, L.S. *J. Org. Chem.* ***1979***, *44*, 3594.

[152] The ω − 1 selectivity values shown here may actually be lower than the true values because of selective solvolysis of the ω − 1 chlorides in concentrated H_2SO_4: see Deno, N.C.; Pohl, D.G. *J. Org. Chem.* ***1975***, *40*, 380.

[153] Bernardi, R.; Galli, R.; Minisci, F. *J. Chem. Soc. B* ***1968***, 324. See also, Deno, N.C.; Gladfelter, E.J.; Pohl, D.G. *J. Org. Chem.* ***1979***, *44*, 3728; Fuller, S.E.; Lindsay Smith, J.R.; Norman, R.O.C.; Higgins, R. *J. Chem. Soc. Perkin Trans. 2* ***1981***, 545.

[154] Deno, N.C.; Billups, W.E.; Fishbein, R.; Pierson, C.; Whalen, R.; Wyckoff, J.C. *J. Am. Chem. Soc.* ***1971***, *93*, 438.

[155] Minisci, F.; Gardini, G.P.; Bertini, F. *Can. J. Chem.* ***1970***, *48*, 544.

[156] Kämper, F.; Schäfer, H.J.; Luftmann, H. *Angew. Chem. Int. Ed.* ***1976***, *15*, 306.

[157] Smith, C.V.; Billups, W.E. *J. Am. Chem. Soc.* ***1974***, *96*, 4307.

[158] It has been reported that the selectivity in one case is in accord with a pure electrostatic (field effect) explanation: Dneprovskii, A.S.; Mil'tsov, S.A.; Arbuzov, P.V. *J. Org. Chem. USSR* ***1988***, *24*, 1826. See also, Tanner, D.D.; Arhart, R.; Meintzer, C.P. *Tetrahedron* ***1985***, *41*, 4261; Deno, N.C.; Pohl, D.G. *J. Org. Chem.* ***1975***, *40*, 380.

[159] Luche, J.L.; Bertin, J.; Kagan, H.B. *Tetrahedron Lett.* ***1974***, 759.

[160] San Filippo Jr, J.; Sowinski, A.F.; Romano, L.J. *J. Org. Chem.* ***1975***, *40*, 3463.

[161] Turro, N.J.; Fehlner, J.R.; Hessler, D.P.; Welsh, K.M.; Ruderman, W.; Firnberg, D.; Braun, A.M. *J. Org. Chem.* ***1988***, *53*, 3731.

RCH_2-$CH_2CH_2SO_2NHR'$ are converted primarily to $RCHClCH_2CH_2SO_2NHR'$ by sodium peroxydisulfate $Na_2S_2O_8$ and $CuCl_2$.[162] For regioselective chlorination at certain positions of the steroid nucleus, see **19-2**.

In almost all cases, the mechanism involves a free-radical chain:

$$\begin{array}{lll}
\text{Initiation} & X_2 \xrightarrow{hv} 2\,X\bullet & \\
 & RH + X\bullet \longrightarrow R\bullet + XH & \\
\text{Propagation} & R\bullet + X_2 \longrightarrow RX + X\bullet & \\
\text{Termination} & R\bullet + X\bullet \longrightarrow RX &
\end{array}$$

When the reagent is halogen, initiation occurs as shown above.[163] When it is another reagent, a similar cleavage occurs (catalyzed by light or, more commonly, peroxides), followed by propagation steps that do not necessarily involve abstraction by halogen. For example, the propagation steps for chlorination by *tert*-butyl hypochlorite (*t*-BuOCl) have been formulated as[164]

$$\begin{array}{l}
RH + t\text{-}BuO\bullet \longrightarrow R\bullet + t\text{-}BuOH \\
R\bullet + t\text{-}BuOCl \longrightarrow RCl + t\text{-}BuO\bullet
\end{array}$$

and the abstracting radicals in the case of *N*-haloamines are the aminium radical cations $R_2NH\bullet^+$ (p. 693), with the following mechanism (in the case of initiation by Fe^{2+}):[149]

$$\begin{array}{ll}
\text{Initiation} & R_2NCl \xrightarrow{H^+} \overset{\oplus}{R_2NHCl} \xrightarrow{Fe^{2+}} R_2NH\bullet^{+} + \overset{\oplus}{FeCl} \\
 & R_2NH\bullet^{+} + RH \longrightarrow R_2NH_2 + R\bullet \\
\text{Propagation} & R\bullet + R_2NHCl \longrightarrow RCl + R_2NH\bullet^{+}
\end{array}$$

This mechanism is similar to that of the Hofmann–Löffler reaction (**18-40**).

The two propagation steps shown above for X_2 are those that lead directly to the principal products (RX and HX), but many other propagation steps are possible and many occur. Similarly, the only termination step shown is the one that leads to RX, but any two radicals may combine ($\bullet H$, $\bullet CH_3$, $\bullet Cl$, $\bullet CH_2CH_3$ in all combinations).

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[162] Nikishin, G.I.; Troyansky, E.I.; Lazareva, M.I. *Tetrahedron Lett.* ***1985***, *26*, 3743.

[163] There is evidence (unusually high amounts of multiply chlorinated products) that under certain conditions in the reaction of RH with Cl_2, the products of the second propagation step ($RX + X\bullet$) are enclosed within a solvent cage. See Skell, P.S.; Baxter III, H.N. *J. Am. Chem. Soc.* ***1985***, *107*, 2823; Raner, K.D.; Lusztyk, J.; Ingold, K.U. *J. Am. Chem. Soc.* ***1988***, *110*, 3519; Tanko, J.M.; Anderson III, F.E. *J. Am. Chem. Soc.* ***1988***, *110*, 3525.

[164] Carlsson, D.J.; Ingold, K.U. *J. Am. Chem. Soc.* ***1967***, *89*, 4885, 4891; Walling, C.; McGuiness, J.A. *J. Am. Chem. Soc.* ***1969***, *91*, 2053. See also, Zhulin, V.M.; Rubinshtein, B.I. *Bull. Acad. Sci. USSR Div. Chem. Sci*, ***1977***, *26*, 2082.

Thus, products like H_2, higher alkanes, and higher alkyl halides can be accounted for. When methane is the substrate, the rate-determining step is

$$CH_4 + Cl\bullet \longrightarrow \bullet CH_3 + HCl$$

since an isotope effect of 12.1 was observed at 0°C.[165] For chlorinations, chains are very long, typically 10^4–10^6 propagations before a termination step takes place.

The order of reactivity of the halogens can be explained by energy considerations. For the substrate methane, ΔH values for the two principal propagation steps are

	kcal mol^{-1}				kJ mol^{-1}			
Reaction	F_2	Cl_2	Br_2	I_2	F_2	Cl_2	Br_2	I_2
$CH_4 + X\bullet \rightarrow CH_3\bullet + HX$	−31	+2	+17	+34	−132	+6	+72	+140
$CH_4 + X_2 \rightarrow CH_3X + X\bullet$	−70	−26	−24	−21	−293	−113	−100	−87

In each case, D for CH_3—H is 105 kcal mol^{-1} (438 kJ mol^{-1}), while D values for the other bonds involved are given in Table 14.4.[166] Fluorine is so reactive[167] that neither uv light nor any other initiation is needed (total $\Delta H = -101$ kcal mol^{-1}; −425 kJ mol^{-1});[168] while Br_2 and I_2 essentially do not react with methane. The second step is exothermic in all four cases, but it cannot take place before the first, and it is this step that is very unfavorable for Br_2 and I_2. It is apparent that the most important single factor causing the order of halogen reactivity to be $F_2 > Cl_2 > Br_2 > I_2$ is the decreasing strength of the HX bond in the order HF > HCl > HBr > HI. The increased reactivity of secondary and tertiary positions is in accord with the decrease in D values for R—H in the order primary > secondary > tertiary (Table 5.3). (Note that for chlorination step 1 is exothermic for practically all substrates other than CH_4, since most other aliphatic C—H bonds are weaker than those in CH_4.)

Bromination and chlorination of alkanes and cycloalkanes can also take place by an electrophilic mechanism if the reaction is catalyzed by $AgSbF_6$.[169] Direct

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[165] Wiberg, K.B.; Motell, E.L. *Tetrahedron* ***1963***, *19*, 2009.

[166] Kerr, J.A., in Weast, R.C. *Handbook of Chemistry and Physics*, 69th ed., CRC Press, Boca Raton, FL, ***1988***, pp. F174–F189.

[167] It has been reported that the reaction of F atoms with CH_4 at 25 K takes place with practically zero activation energy: Johnson, G.L.; Andrews, L. *J. Am. Chem. Soc.* ***1980***, *102*, 5736.

[168] For F_2, the following initiation step is possible: $F_2 + RH \rightarrow R\bullet + F\bullet + HF$ [first demonstrated by Miller, Jr, W.T.; Koch, Jr, S.D.; McLafferty, F.W. *J. Am. Chem. Soc.* ***1956***, *78*, 4992]. ΔH for this reaction is equal to the small positive value of 5 kcal mol^{-1} (21 kJ mol^{-1}). The possibility of this reaction (which does not require an initiator) explains why fluorination can take place without UV light [which would otherwise be needed to furnish the 38 kcal mol^{-1} (159 kJ mol^{-1}) necessary to break the F—F bond]. Once the reaction has been initiated, the large amount of energy given off by the propagation steps is ample to cleave additional F_2 molecules. Indeed, it is the magnitude of this energy that is responsible for the cleavage of carbon chains by F_2.

[169] Olah, G.A.; Renner, R.; Schilling, P.; Mo, Y.K. *J. Am. Chem. Soc.* ***1973***, *95*, 7686. See also, Olah, G.A.; Wu, A.; Farooq, O. *J. Org. Chem.* ***1989***, *54*, 1463.

TABLE 14.4. Some *D* Values[166]

Bond	*D* kcal mol^{-1}	*D* kJ mol^{-1}
H—F	136	570
H—Cl	103	432
H—Br	88	366
H—I	71	298
F—F	38	159
Cl—Cl	59	243
Br—Br	46	193
I—I	36	151
CH_3—F	108	452
CH_3—Cl	85	356
CH_3—Br	70	293
CH_3—I	57	238

chlorination at a vinylic position by an electrophilic mechanism has been achieved with benzeneseleninyl chloride PhSe(O)Cl and $AlCl_3$ or $AlBr_3$.[170] However, while some substituted alkenes give high yields of chloro substitution products, others (e.g., styrene) undergo addition of Cl_2 to the double bond (**15-39**).[131] Electrophilic fluorination has already been mentioned (p. 956).

OS **II**, 89, 133, 443, 549; **III**, 737, 788; **IV**, 807, 921, 984; **V**, 145, 221, 328, 504, 635, 825; **VI**, 271, 404, 715; **VII**, 491; **VIII**, 161.

14-2 Halogenation at Silicon

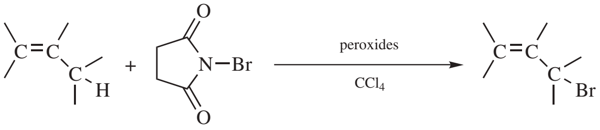
Halogenation or **Halo-de-hydrogenation**

$$R_3Si\text{–}H \longrightarrow R_3Si\text{–}X$$

Just as free-radical halogenation occurs at the carbon of an alkane, via hydrogen abstraction to form the radical, a similar reaction occurs at silicon. When triisopropylsilane (*i*Pr_3Si—H) reacts with *tert*-butyl hypochlorite at −10°C, the product is triisopropylchlorosilane (*i*Pr_3Si—Cl).[171]

14-3 Allylic and Benzylic Halogenation

Halogenation or **Halo-de-hydrogenation**



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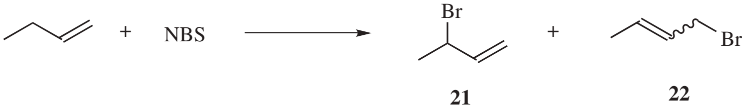
[170] Kamigata, N.; Satoh, T.; Yoshida, M. *Bull. Chem. Soc. Jpn.* ***1988***, *44*, 449.

[171] Chawla, R.; Larson, G.L. *Synth. Commun.* ***1999***, *29*, 3499.

This reaction is a special case of **14-1**, but is important enough to be treated separately.[172] Alkenes can be halogenated in the allylic position and also a benzylic position by a number of reagents, of which NBS[173] is by far the most common. When this reagent is used, the reaction is known as *Wohl–Ziegler bromination*. A nonpolar solvent is used, most often CCl_4, but the reaction has been done in an ionic liquid.[174] A variation in the reaction used NBS with 5% $Yb(OTf)_3$ and 5% $ClSiMe_3$.[175] Other *N*-bromo amides have also been used. Allylic chlorination has been carried out, with *N*-chlorosuccinimide, *tert*-butyl hypochlorite,[176] or with $NaClO/CeCl_3{\bullet}7\ H_2O$.[177] With any reagent an initiator is needed; this is usually AIBN (**1**), a peroxide, such as di-*tert*-butyl peroxide or benzoyl peroxide or, less often, UV light.

The reaction is usually quite specific at an allylic or benzylic position and good yields are obtained. However, when the allylic radical intermediate is unsymmetrical, allylic rearrangements can take place, so that mixtures of both possible products are obtained, **21** and **22**.



21 **22**

When a double bond has two different allylic positions (e.g., $CH_3CH{=}CHCH_2CH_3$), a secondary position is substituted more readily than a primary. The relative reactivity of tertiary hydrogen is not clear, though many substitutions at allylic tertiary positions have been performed.[178] It is possible to brominate both sides of the double bond.[179] Because of the electron-withdrawing nature of bromine, the second bromine substitutes on the other side of the double bond rather than α to the first bromine. Molecules with a benzylic hydrogen, such as toluene, react rapidly to give α-bromomethyl benzene (e.g., $PhCH_3 \rightarrow PhCH_2Br$).

N-Bromosuccinimide is also a highly regioselective brominating agent at other positions, including positions α to a carbonyl group, to a $C{\equiv}C$ triple bond, and to an aromatic ring (benzylic position). When both a double and a triple bond are in the same molecule, the preferred position is α to the triple bond.[180]

Dauben and McCoy demonstrated that the mechanism of allylic bromination is of the free-radical type,[181] showing that the reaction is very sensitive to free-radical

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[172] For a review, see Nechvatal, A. *Adv. Free-Radical Chem.* ***1972***, *4*, 175.

[173] For a review of this reagent, see Pizey, J.S. *Synthetic Reagents*, Vol. 2, Wiley, NY, ***1974***, pp. 1–63.

[174] In bmim PF_6, 1-butyl-3-methylimidazolium hexafluoorophosphate: Togo, H.; Hirai, T. *Synlett* ***2003***, 702.

[175] Yamanaka, M.; Arisawa, M.; Nishida, A.; Nakagawa, M. *Tetahedron Lett.* ***2002***, *43*, 2403.

[176] Walling, C.; Thaler, W.A. *J. Am. Chem. Soc.* ***1961***, *83*, 3877.

[177] Moreno-Dorado, F.J.; Guerra, F.M.; Manzano, F.L.; Aladro, F.J.; Jorge, Z.S.; Massanet, G.M. *Tetrahedron Lett.* ***2003***, *44*, 6691.

[178] Dauben, Jr, H.J.; McCoy, L.L. *J. Org. Chem.* ***1959***, *24*, 1577.

[179] Ucciani, E.; Naudet, M. *Bull. Soc. Chim. Fr.* ***1962***, 871.

[180] Peiffer, G. *Bull. Soc. Chim. Fr.* ***1963***, 537.

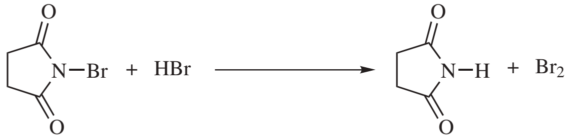
[181] Dauben, Jr, H.J.; McCoy, L.L. *J. Am. Chem. Soc.* ***1959***, *81*, 4863.

initiators and inhibitors and indeed does not proceed at all unless at least a trace of initiator is present. Subsequent work indicated that the species that actually abstracts hydrogen from the substrate is the bromine atom. The reaction is initiated by small amounts of Br•. Once it is formed, the main propagation steps are

Step 1 $\mathrm{Br}\bullet + \mathrm{RH} \longrightarrow \mathrm{R}\bullet + \mathrm{HBr}$

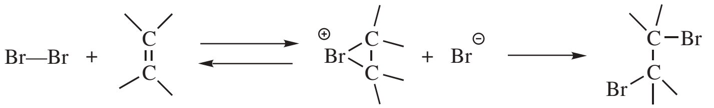
Step 2 $\mathrm{R}\bullet + \mathrm{Br_2} \longrightarrow \mathrm{RBr} + \mathrm{Br}\bullet$

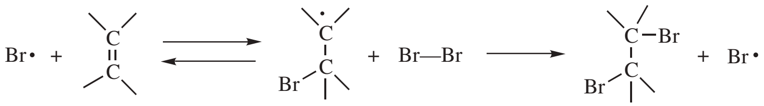
The source of the Br_2 is a fast ionic reaction between NBS and the HBr liberated in step 1:



The function of the NBS is therefore to provide a source of Br_2 in a low, steady-state concentration and to use up the HBr liberated in step 1.[182] The main evidence for this mechanism is that NBS and Br_2 show similar selectivity[183] and that the various *N*-bromo amides also show similar selectivity,[184] which is consistent with the hypothesis that the same species is abstracting in each case.[185]

It may be asked why, if Br_2 is the reacting species, it does not add to the double bond, either by an ionic or by a free-radical mechanism (see **15-39**). Apparently the concentration is too low. In bromination of a double bond, only one atom of an attacking bromine molecule becomes attached to the substrate, whether the addition is electrophilic or free radical:





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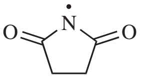
[182] This mechanism was originally suggested by Adam, J.; Gosselain, P.A.; Goldfinger, P. *Nature (London)*, ***1953***, *171*, 704; *Bull. Soc. Chim. Belg.* ***1956***, *65*, 533.

[183] Walling, C.; Rieger, A.L.; Tanner, D.D. *J. Am. Chem. Soc.* ***1963***, *85*, 3129; Russell, G.A.; Desmond, K.M. *J. Am. Chem. Soc.* ***1963***, *85*, 3139; Russell, G.A.; DeBoer, C.D.; Desmond, K.M. *J. Am. Chem. Soc.* ***1963***, *85*, 365; Pearson, R.; Martin, J.C. *J. Am. Chem. Soc.* ***1963***, *85*, 3142; Skell, P.S.; Tuleen, D.L.; Readio, P.D. *J. Am. Chem. Soc.* ***1963***, *85*, 2850.

[184] Walling, C.; Rieger, A.L. *J. Am. Chem. Soc.* ***1963***, *85*, 3134; Pearson, R.; Martin, J.C. *J. Am. Chem. Soc.* ***1963***, *85*, 3142; Incremona, J.H.; Martin, J.C. *J. Am. Chem. Soc.* ***1970***, *92*, 627.

[185] For other evidence, see Day, J.C.; Lindstrom, M.J.; Skell, P.S. *J. Am. Chem. Soc.* ***1974***, *96*, 5616.

The other bromine atom comes from another bromine-containing molecule or ion. This is clearly not a problem in reactions with benzylic species since the benzene ring is not prone to such addition reactions. If the concentration is sufficiently low, there is a low probability that the proper species will be in the vicinity once the intermediate forms. The intermediate in either case reverts to the initial species and the allylic substitution competes successfully. If this is true, it should be possible to brominate an alkene in the allylic position without competition from addition, even in the absence of NBS or a similar compound, if a very low concentration of bromine is used and if the HBr is removed as it is formed so that it is not available to complete the addition step. This has indeed been demonstrated.[186]



23

When NBS is used to brominate non-alkenyl substrates, such as alkanes, another mechanism, involving abstraction of the hydrogen of the substrate by the succinimidyl radical[187] **23** can operate.[188] This mechanism is facilitated by solvents (e.g., CH_2Cl_2, $CHCl_3$, or MeCN) in which NBS is more soluble, and by the presence of small amounts of an alkene that lacks an allylic hydrogen (e.g., ethene). The alkene serves to scavenge any Br• that forms from the reagent. Among the evidence for the mechanism involving **23** are abstraction selectivities similar to those of Cl• atoms and the isolation of β-bromopropionyl isocyanate ($BrCH_2CH_2CONCO$) which is formed by ring opening of **23**.

Allylic chlorination has also been carried out[189] with *N*-chlorosuccinimide (NCS) and either arylselenyl chlorides (ArSeCl), aryl diselenides (ArSeSeAr), or TsNSO as catalysts. Use of the selenium catalysts produces almost entirely the allylically rearranged chlorides in high yields. With TsNSO the products are the unrearranged chlorides in lower yields. Dichlorine monoxide Cl_2O, with no catalyst, also gives allylically rearranged chlorides in high yields.[190] A free-radical mechanism is unlikely in these reactions.

Allyl silanes react with transition metals bearing chlorine ligands to give allyl chlorides, where a chlorine replaces a Me_3Si unit.[191]

OS **IV**, 108; **V**, 825; **VI**, 462; **IX**, 191.

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[186] McGrath, B.P.; Tedder, J.M. *Proc. Chem. Soc.* ***1961***, 80.

[187] For a review of this radical, see Chow, Y.L.; Naguib, Y.M.A. *Rev. Chem. Intermed.* ***1984***, *5*, 325.

[188] Skell, P.S.; Day, J.C. *Acc. Chem. Res.* ***1978***, *11*, 381; Tanner, D.D.; Reed, D.W.; Tan, S.L.; Meintzer, C.P.; Walling, C.; Sopchik, A. *J. Am. Chem. Soc.* ***1985***, *107*, 6576; Lüning, U.; Seshadri, S.; Skell, P.S. *J. Org. Chem.* ***1986***, *51*, 2071; Zhang, Y.; Dong, M.; Jiang, X.; Chow, Y.L. *Can. J. Chem.* ***1990***, *68*, 1668.

[189] Hori, T.; Sharpless, K.B. *J. Org. Chem.* ***1979***, *44*, 4204.

[190] Torii, S.; Tanaka, H.; Tada, N.; Nagao, S.; Sasaoka, M. *Chem. Lett.* ***1984***, 877.

[191] Fujii, T.; Hirao, Y.; Ohshiro, Y. *Tetrahedron Lett.* ***1993***, *34*, 5601.

14-4 Halogenation of Aldehydes

Halogenation or **Halo-de-hydrogenation**

$$\text{RCHO} + \text{Cl}_2 \longrightarrow \text{RCOCl}$$

The α-halogenation reaction of carbonyl compounds was mentioned in Section **14-2**. A different halogenation reaction is possible in which aldehydes can be directly converted to acyl chlorides by treatment with chlorine, but the reaction operates only when the aldehyde does not contain an α hydrogen and even then it is not very useful. When there is an α hydrogen, α halogenation (**14-2, 12-4**) occurs instead. Other sources of chlorine have also been used, among them SO_2Cl_2[192] and *t*-BOCl.[193] The mechanisms are probably of the free-radical type. *N*-Bromosuccinimide, with AIBN (p. 935) as a catalyst, has been used to convert aldehydes to acyl bromides.[194]

OS **I**, 155.

B. Substitution by Oxygen

14-5 Hydroxylation at an Aromatic Carbon[195]

Hydroxylation or **Hydroxy-de-hydrogenation**

$$\text{ArH} + \text{H}_2\text{O}_2 + \text{FeSO}_4 \longrightarrow \text{ArOH}$$

A mixture of hydrogen peroxide and ferrous sulfate,[196] called *Fenton's reagent*,[197] can be used to hydroxylate aromatic rings, though yields are usually not high.[198] Biaryls are usually side products.[199] Among other reagents used have been H_2O_2 and titanous ion; O_2 and Cu(I)[200] or Fe(III),[201] a mixture of ferrous

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[192] Arai, M. *Bull. Chem. Soc. Jpn.* ***1964***, *37*, 1280; ***1965***, *38*, 252.

[193] Walling, C.; Mintz, M.J. *J. Am. Chem. Soc.* ***1967***, *89*, 1515.

[194] Markó, I.E.; Mekhalfia, A. *Tetrahedron Lett.* ***1990***, *31*, 7237. For a related procedure, see Cheung, Y. *Tetrahedron Lett.* ***1979***, 3809.

[195] For reviews, see Vysotskaya, N.A. *Russ. Chem. Rev.* ***1973***, *42*, 851; Sangster, D.F., in Patai, S. *The Chemistry of the Hydroxyl Group*, pt. 1, Wiley, NY, ***1971***, pp. 133–191; Metelitsa, D.I. *Russ. Chem. Rev.* ***1971***, *40*, 563; Enisov, E.T.; Metelitsa, D.I. *Russ. Chem. Rev.* ***1968***, *37*, 656; Loudon, J.D. *Prog. Org. Chem.* ***1961***, *5*, 47.

[196] For a review of reactions of H_2O_2 and metal ions with all kinds of organic compounds, including aromatic rings, see Sosnovsky, G.; Rawlinson, D.J., in Swern, D. *Organic Peroxides*, Vol. 2, Wiley, NY, ***1970***, pp. 269–336. See also, Sheldon, R.A.; Kochi, J.K. *Metal-Catalyzed Oxidations of Organic Compounds*, Academic Press, NY, ***1981***.

[197] For a discussion of Fenton's reagent, see Walling, C. *Acc. Chem. Res.* ***1975***, *8*, 125.

[198] Yields can be improved with phase transfer catalysis: Karakhanov, E.A.; Narin, S.Yu.; Filippova, T.Yu.; Dedov, A.G. *Doklad. Chem.* ***1987***, *292*, 81.

[199] See the discussion of the aromatic free-radical substitution mechanism on pp. $$$–$$$.

[200] See Karlin, K.D.; Hayes, J.C.; Gultneh, Y.; Cruse, R.W.; McKown, J.W.; Hutchinson, J.P.; Zubieta, J. *J. Am. Chem. Soc.* ***1984***, *106*, 2121; Cruse, R.W.; Kaderli, S.; Meyer, C.J.; Zuberbühler, A.D.; Karlin, K.D. *J. Am. Chem. Soc.* ***1988***, *110*, 5020; Ito, S.; Kunai, A.; Okada, H.; Sasaki, K. *J. Org. Chem.* ***1988***, *53*, 296.

[201] Funabiki, T.; Tsujimoto, M.; Ozawa, S.; Yoshida, S. *Chem. Lett.* ***1989***, 1267.

ion, oxygen, ascorbic acid, and ethylenetetraaminetetraacetic acid (*Udenfriend's reagent*);[202] O_2 and KOH in liquid NH_3;[203] and peroxyacids such as peroxynitrous and trifluoroperoxyacetic acids.

Much work has been done on the mechanism of the reaction with Fenton's reagent, and it is known that free aryl radicals (formed by a process, e.g., $HO\bullet + ArH \rightarrow AR\bullet + H_2O$) are not intermediates. The mechanism is essentially that outlined on p. $$$, with HO• as the attacking species,[204] formed by

$$Fe^{2+} + H_2O_2 \longrightarrow Fe^{3+} + OH^- + HO\bullet$$

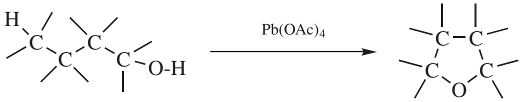
The rate-determining step is formation of HO• and not its reaction with the aromatic substrate.

An alternative oxidation of arene to phenol was reported using $Cu(NO_3)\bullet 3\ H_2O$, 30% hydrogen peroxide and a phosphate buffer.[205]

See also, **11-26**.

14-6 Formation of Cyclic Ethers

(5)*OC-cyclo*-Alkoxy-de-hydro-substitution



Alcohols with a hydrogen in the δ position can be cyclized with lead tetraacetate.[206] The reaction is usually carried out at ~80°C (most often in refluxing benzene), but can also be done at room temperature if the reaction mixture is irradiated with uv light. Tetrahydrofurans are formed in high yields. Little or no four- and six-membered cyclic ethers (oxetanes and tetrahydropyrans, respectively) are obtained even when γ and ε hydrogens are present. The reaction has also been carried out with a mixture of halogen (Br_2 or I_2) and a salt or oxide of silver or mercury (especially HgO or AgOAc),[207] with iodosobenzene diacetate and I_2,[208] and with ceric

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[202] Udenfriend, S.; Clark, C.T.; Axelrod, J.; Brodie, B.B. *J. Biol. Chem.* ***1954***, *208*, 731; Brodie, B.B.; Shore, P.A.; Udenfriend, S. *J. Biol. Chem.* ***1954***, *208*, 741. See also, Tamagaki, S.; Suzuki, K.; Tagaki, W. *Bull. Chem. Soc. Jpn.* ***1989***, *62*, 148, 153, 159.

[203] Malykhin, E.V.; Kolesnichenko, G.A.; Shteingarts, V.D. *J. Org. Chem. USSR* ***1986***, *22*, 720.

[204] Jefcoate, C.R.E.; Lindsay Smith, J.R.; Norman, R.O.C. *J. Chem. Soc. B* ***1969***, 1013; Brook, M.A.; Castle, L.; Lindsay Smith, J.R.; Higgins, R.; Morris, K.P. *J. Chem. Soc. Perkin Trans. 2* ***1982***, 687; Lai, C.; Piette, L.H. *Tetrahedron Lett.* ***1979***, 775; Kunai, A.; Hata, S.; Ito, S.; Sasaki, K. *J. Am. Chem. Soc.* ***1986***, *108*, 6012.

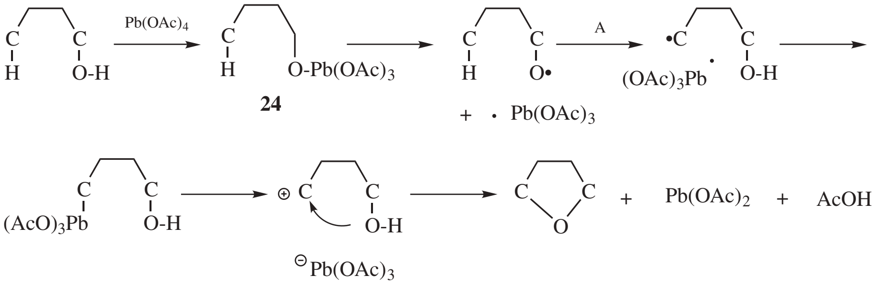
[205] Nasreen, A.; Adapa, S.R. *Org. Prep. Proceed. Int.* ***2000***, *32*, 373.

[206] For reviews, see Mihailović, M.Lj.; Partch, R. *Sel. Org. Transform.* ***1972***, *2*, 97; Milhailović, M.Lj.; Čeković, Z. *Synthesis* ***1970***, 209. For a review of the chemistry of lead tetraacetate, see Butler, R.N., in Pizey, J.S. *Synthetic Reagents*, Vol. 3, Wiley, NY, ***1977***, pp. 277–419.

[207] Akhtar, M.; Barton, D.H.R. *J. Am. Chem. Soc.* ***1964***, *86*, 1528; Sneen, R.A.; Matheny, N.P. *J. Am. Chem. Soc.* ***1964***, *86*, 3905, 5503; Roscher, N.M.; Shaffer, D.K. *Tetrahedron* ***1984***, *40*, 2643. For a review, see Kalvoda, J.; Heusler, K. *Synthesis* ***1971***, 501. For a list of references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed, Wiley-VCH, NY, ***1999***, pp. 889–890.

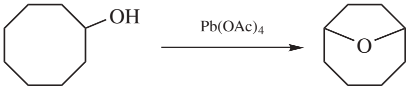
[208] Concepción, J.I.; Francisco, C.G.; Hernández, R.; Salazar, J.A.; Suárez, E. *Tetrahedron Lett.* ***1984***, *25*, 1953; Furuta, K.; Nagata, T.; Yamamoto, H. *Tetrahedron Lett.* ***1988***, *29*, 2215.

ammonium nitrate (CAN).[209] The following mechanism is likely for the lead tetraacetate reaction:[210]



though **24** has never been isolated. The step marked **A** is a 1,5 internal hydrogen abstraction. Such abstractions are well known (see **18-40**) and are greatly favored over 1,4 or 1,6 abstractions (the small amounts of tetrahydropyran formed result from 1,6 abstractions).[211]

Reactions that sometimes compete are oxidation to the aldehyde or acid (**19-3** and **19-22**) and fragmentation of the substrate. When the OH group is on a ring of at least seven members, a transannular product can be formed, as in the cyclization reaction of 1-octanol to **25**.[212]



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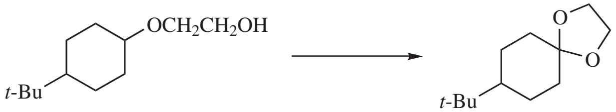
β-Hydroxy ethers can give cyclic acetals, such as **26**.[213]



26

There are no references in *Organic Syntheses*, but see OS **V**, 692; **VI**, 958, for related reactions.

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[209] See, for example, Trahanovsky, W.S.; Young, M.G.; Nave, P.M. *Tetrahedron Lett.* ***1969***, 2501; Doyle, M.P.; Zuidema, L.J.; Bade, T.R. *J. Org. Chem.* ***1975***, *40*, 1454.

[210] Mihailović, M.Lj.; Čeković, Z.; Maksimović, Z.; Jeremić, D.; Lorenc, Lj.; Mamuzi, R.I. *Tetrahedron* ***1965***, *21*, 2799.

[211] Mihailović, M.Lj.; Čeković, Z.; Jeremić, D. *Tetrahedron* ***1965***, *21*, 2813.

[212] Cope, A.C.; Gordon, M.; Moon, S.; Park, C.H. *J. Am. Chem. Soc.* ***1965***, *87*, 3119; Moriarty, R.M.; Walsh, H.G. *Tetrahedron Lett.* ***1965***, 465; Mihailović, M.Lj.; Čeković, Z.; Andrejević, V.; Matić, R.; Jeremić, D. *Tetrahedron* ***1968***, *24*, 4947.

[213] Furuta, K.; Nagata, T.; Yamamoto, H. *Tetrahedron Lett.* ***1988***, *29*, 2215.

14-7 Formation of Hydroperoxides

Hydroperoxy-de-hydrogenation

$$\text{RH} + \text{O}_2 \longrightarrow \text{R—O—O—H}$$

The slow atmospheric oxidation (*slow* meaning without combustion) of C—H to C—O—O—H is called *autoxidation*.[214] The reaction occurs when compounds are allowed to stand in air and is catalyzed by light, so unwanted autoxidations can be greatly slowed by keeping the compounds in dark places. Most autoxidations proceed by free-radical chain processes that involve peroxyl radicals.[215] To suppress autoxidation, an antioxidant can be added that will prevent or retard the reaction with atmospheric oxygen.[216] Although some lactone compounds are sold as antioxidants, many radicals derived from lactones show poor or no reactivity toward oxygen.[216] The hydroperoxides produced often react further to give alcohols, ketones, and more complicated products, so the reaction is not often used for preparative purposes, although in some cases hydroperoxides have been prepared in good yield.[217] It is because of autoxidation that foods, rubber, paint, lubricating oils, and so on deteriorate on exposure to the atmosphere over periods of time. On the other hand, a useful application of autoxidation is the atmospheric drying of paints and varnishes. As with other free-radical reactions of C—H bonds, some bonds are attacked more readily than others,[218] and these are the ones we have seen before (pp. 943–949), though the selectivity is very low at high temperatures and in the gas phase. The reaction can be carried out successfully at tertiary (to a lesser extent, secondary), benzylic,[219] and allylic (though allylic rearrangements are common) R.[220] 2-Phenylpropane reacted with oxygen to give $\text{PhMe}_2\text{C—OOH}$, for example. Another susceptible position is aldehydic C—H,

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[214] The term autoxidation actually applies to any slow oxidation with atmospheric oxygen. See Goosen, A.; Morgan, D.H. *J. Chem. Soc. Perkin Trans. 2* ***1994***, 557. For reviews, see Sheldon, R.A.; Kochi, J.K. *Adv. Catal.*, ***1976***, *25*, 272; Howard, W.G., in Kochi, J.K. *Free Radicals*, Vol. 2, Wiley, NY, ***1973***, pp. 3–62; Lloyd, W.G. *Methods Free-Radical Chem.* ***1973***, *4*, 1; Betts, J. *Q. Rev. Chem. Soc.* ***1971***, *25*, 265; Huyser, E.S. *Free-Radical Chain Reactions*, Wiley, NY, ***1970***, pp. 306–312; Chinn, L.J. *Selection of Oxidants in Synthesis* Marcel Dekker, NY, ***1971***, pp. 29–39; Ingold, K.U. *Acc. Chem. Res.* ***1969***, *2*, 1; Mayo, F.R. *Acc. Chem. Res.* ***1968***, *1*, 193. For monographs on these and similar reactions, see Bamford, C.H.; Tipper, C.F.H. *Comprehensive Chemical Kinetics*, Vol. 16, Elsevier, NY, ***1980***; Sheldon, R.A.; Kochi, J.K. *Metal-Catalyzed Oxidations of Organic Compounds*, Academic Press, NY, ***1981***.

[215] Ingold, K.U. *Acc. Chem. Res.* ***1969***, *2*, 1.

[216] Bejan, E.V.; Font-Sanchis, E.; Scaiano, J.C. *Org. Lett*, ***2001***, *3*, 4059; Scaiano, J.C.; Martin, A.; Yap, G.P.A.; Ingold, K.U. *Org. Lett.* ***2000***, *2*, 899.

[217] For a review of the synthesis of alkyl peroxides and hydroperoxides, see Sheldon, R.A., in Patai, S. *The Chemistry of Peroxides*, Wiley, NY, ***1983***, pp. 161–200.

[218] For a discussion, see Korcek, S.; Chenier, J.H.B.; Howard, J.A.; Ingold, K.U. *Can. J. Chem.* ***1972***, *50*, 2285, and other papers in this series.

[219] For a method that gives good yields at benzylic positions, see Santamaria, J.; Jroundi, R.; Rigaudy, J. *Tetrahedron Lett.* ***1989***, *30*, 4677.

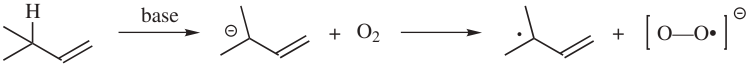
[220] For a review of autoxidation at allylic and benzylic positions, see Voronenkov, V.V.; Vinogradov, A.N.; Belyaev, V.A. *Russ. Chem. Rev.* ***1970***, *39*, 944.

but the peroxyacids so produced are not easily isolated[221] since they are converted to the corresponding carboxylic acids (**19-23**). The α positions of ethers are also easily attacked by oxygen [RO—C—H → RO—C—OOH], but the resulting hydroperoxides are seldom isolated. However, this reaction constitutes a hazard in the storage of ethers since solutions of these hydroperoxides and their rearrangement products in ethers are potential spontaneous explosives.[222]

Oxygen itself (a diradical) is not reactive enough to be the species that actually abstracts the hydrogen. But if a trace of free radical (say R′•) is produced by some initiating process, *it* reacts with oxygen[223] to give R′—O—O•; since this type of radical *does* abstract hydrogen, the chain is

$$\begin{aligned} R'OO\bullet + RH &\longrightarrow R\bullet + R'OOH \\ R\bullet + O_2 &\longrightarrow R{-}O{-}O\bullet \\ &\text{etc.} \end{aligned}$$

In at least some cases (in alkaline media)[224] the radical R• can be produced by formation of a carbanion and its oxidation (by O_2) to a radical, such as allylic radical **27**.[225]



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Autoxidations in alkaline media can also proceed by a different mechanism: $R{-}H + \text{base} \rightarrow R^- + O_2 \rightarrow ROO^-$.[226]

When alkenes are treated with oxygen that has been photosensitized (p. 341), they are substituted by OOH in the allylic position in a synthetically useful reaction.[227] Although superficially similar to autoxidation, this reaction is clearly different because 100% allylic rearrangement always takes place. The reagent here is not

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[221] Swern D. *Organic Peroxides*, Vol. 1, Wiley, NY, ***1970***, p. 313.

[222] For methods of detection and removal of peroxides from ether solvents, see Gordon, A.J.; Ford, R.A. *The Chemist's Companion*, Wiley, NY, ***1972***, p. 437; Burfield, D.R. *J. Org. Chem.* ***1982***, *47*, 3821.

[223] See, for example, Schwetlick, K. *J. Chem. Soc. Perkin Trans. 2* ***1988***, 2007.

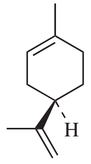
[224] For a review of base-catalyzed autoxidations in general, see Sosnovsky, G.; Zaret, E.H., in Swern, D. *Organic Peroxides*, Vol. 1, Wiley, NY, ***1970***, pp. 517–560.

[225] Barton, D.H.R.; Jones, D.W. *J. Chem. Soc.* ***1965***, 3563; Russell, G.A.; Bemis, A.G. *J. Am. Chem. Soc.* ***1966***, *88*, 5491.

[226] Gersmann, H.R.; Bickel, A.F. *J. Chem. Soc. B* ***1971***, 2230.

[227] For reviews, see Frimer, A.A.; Stephenson, L.M. in Frimer, A.A. *Singlet* O_2, Vol. 2, CRC Press, Boca Raton, FL, ***1985***, pp. 67–91; Wasserman, H.H.; Ives, J.L. *Tetrahedron* ***1981***, *37*, 1825; Gollnick, K.; Kuhn, H.J., in Wasserman, H.H.; Murray, R.W. *Singlet Oxygen*, Academic Press, NY, ***1979***, pp. 287–427; Denny, R.W.; Nickon, A. *Org. React.* ***1973***, *20*, 133; Adams, W.R., in Augustine, R.L. *Oxidation*, Vol. 2, Marcel Dekker, NY, ***1969***, pp. 65–112.

the ground-state oxygen (a triplet), but an excited singlet state[228] (in which all electrons are paired), and the function of the photosensitization is to promote the oxygen to this singlet state. Singlet oxygen can also be produced by nonphotochemical means,[229] for example, by the reaction between H_2O_2 and NaOCl[230] or sodium molybdate,[231] or between ozone and triphenyl phosphite.[232] Calcium peroxide diperoxohydrate ($CaO_2,2\,H_2O_2$) has been reported as a storable compound used for the chemical generation of singlet oxygen.[233] The oxygen generated by either photochemical or nonphotochemical methods reacts with alkenes in the same way;[234] this is evidence that singlet oxygen is the reacting species in the photochemical reaction and not some hypothetical complex between triplet oxygen and the photosensitizer, as had previously been suggested. The fact that 100% allylic rearrangement always takes place is incompatible with a free-radical mechanism, and further evidence that free radicals are not involved comes from the treatment of optically active limonene (**28**) with singlet oxygen. Among other products is the optically active hydroperoxide **29**, though if **30** were an intermediate, it could not give an optically active product since it possesses a plane of symmetry.[235] In contrast, autoxidation of **28** gave optically inactive **29** (a mixture of four diastereomers in which the two pairs of enantiomers are present as racemic mixtures). As this example shows, singlet oxygen reacts faster with more-highly substituted than with less-highly substituted alkenes. The order of alkene reactivity is



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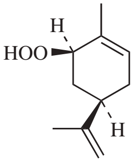

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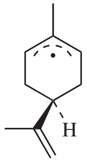

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[228] For books on singlet oxygen, see Frimer, A.A. *Singlet O_2*, 4 vols., CRC Press, Boca Raton, FL, ***1985***; Wasserman, H.H.; Murray, R.W. *Singlet Oxygen*, Academic Press, NY, ***1979***. For reviews, see Frimer, A.A., in Patai, S. *The Chemistry of Peroxides*, Wiley, NY, ***1983***, pp. 201–234; Gorman, A.A.; Rodgers, M.A.J. *Chem. Soc. Rev.* ***1981***, *10*, 205; Shinkarenko, N.V.; Aleskovskii, V.B. *Russ. Chem. Rev.* ***1981***, *50*, 220; Shlyapintokh, V.Ya.; Ivanov, V.B. *Russ. Chem. Rev.* ***1976***, *45*, 99; Ohloff, G. *Pure Appl. Chem.* ***1975***, *43*, 481; Kearns, D.R. *Chem. Rev.* ***1971***, *71*, 395; Wayne, R.P. *Adv. Photochem.* ***1969***, *7*, 311.

[229] For reviews, see Turro, N.J.; Ramamurthy, V., in de Mayo, P. *Rearrangements in Ground and Excited States*, Vol. 3, Academic Press, NY, ***1980***, pp. 1–23; Murray, R.W., in Wasserman, H.H.; Murray, R.W. *Singlet Oxygen*, Academic Press, NY, ***1979***, pp. 59–114. For a general monograph, see Adam, W.; Cilento, G. *Chemical and Biological Generation of Excited States*; Academic Press, NY, ***1982***.

[230] Foote, C.S.; Wexler, S. *J. Am. Chem. Soc.* ***1964***, *86*, 3879.

[231] Aubry, J.M.; Cazin, B.; Duprat, F. *J. Org. Chem.* ***1989***, *54*, 726.

[232] Murray, R.W.; Kaplan, M.L. *J. Am. Chem. Soc.* ***1969***, *91*, 5358; Bartlett, P.D.; Mendenhall, G.D.; Durham, D.L. *J. Org. Chem.* ***1980***, *45*, 4269.

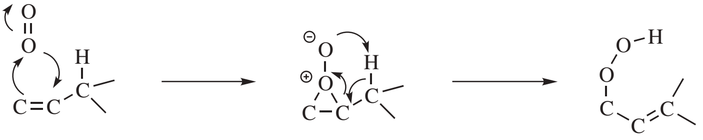
[233] Pierlot, C.; Nardello, V.; Schrive, J.; Mabille, C.; Barbillat, J.; Sombret, B.; Aubry, J.-M. *J. Org. Chem*, ***2002***, *67*, 2418.

[234] Foote, C.S.; Wexler, S.; Ando, W.; Higgins, R. *J. Am. Chem. Soc.* ***1968***, *90*, 975. See also, McKeown, E.; Waters, W.A. *J. Chem. Soc. B* **1966**, 1040.

[235] Schenck, G.O.; Gollnick, K.; Buchwald, G.; Schroeter, S.; Ohloff, G. *Liebigs Ann. Chem.* ***1964***, *674*, 93; Schenck, G.O.; Neumüller, O.; Ohloff, G.; Schroeter, S. *Liebigs Ann. Chem.* ***1965***, *687*, 26.

tetrasubstituted > trisubstituted > disubstituted. Electron-withdrawing substituents deactivate the alkene.[236] In simple trisubstituted alkenes, there is a general preference for the hydrogen to be removed from the more highly congested side of the double bond.[237] With *cis*-alkenes of the form RCH=CHR′, the hydrogen is removed from the larger R group.[238] Many functional groups in an allylic position cause the hydrogen to be removed from that side rather than the other (geminal selectivity).[239] Also, in alkyl-substituted alkenes, the hydrogen that is preferentially removed is the one geminal to the larger substituent on the double bond.[240]

Several mechanisms have been proposed for the reaction with singlet oxygen.[241] One of these is a pericyclic mechanism, similar to that of the ene synthesis (**15-23**) and to the first step of the reaction between alkenes and SeO_2 (**19-14**). However, there is strong evidence against this mechanism,[242] and a more likely mechanism involves addition of singlet oxygen to the double bond to give a perepoxide (**31**),[243] followed by internal proton transfer.[244]



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Still other proposed mechanisms involve diradicals or dipolar intermediates.[245]

OS **IV**, 895.

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[236] For example, see Foote, C.S.; Denny, R.W. *J. Am. Chem. Soc.* ***1971***, *93*, 5162.

[237] Orfanopoulos, M.; Bellamine, M.; Grdina, M.J.; Stephenson, L.M. *J. Am. Chem. Soc.* ***1979***, *101*, 275; Rautenstrauch, V.; Thommen, W.; Schulte-Elte, K.H. *Helv. Chim. Acta* ***1986***, *69*, 1638 and references cited therein.

[238] Orfanopoulos, M.; Stratakis, M.; Elemes, Y. *Tetrahedron Lett.* ***1989***, *30*, 4875.

[239] Clennan, E.L.; Chen, X.; Koola, J.J. *J. Am. Chem. Soc.* ***1990***, *112*, 5193, and references cited therein.

[240] Orfanopoulos, M.; Stratakis, M.; Elemes, Y. *J. Am. Chem. Soc.* ***1990***, *112*, 6417.

[241] For reviews of the mechanism, see Frimer, A.A.; Stephenson, L.M., in Frimer, A.A. *Singlet O_2*, Vol. 2, CRC Press, Boca Raton, FL, ***1985***, pp. 80–87; Stephenson, L.M.; Grdina, M.J.; Orfanopoulos, M. *Acc. Chem. Res.* ***1980***, *13*, 419; Gollnick, K.; Kuhn, H.J. Wasserman, H.H.; Murray, R.W. *Singlet Oxygen*, Academic Press, NY, ***1979***, pp. 288–341; Frimer, A.A. *Chem. Rev.* ***1979***, *79*, 359; Foote, C.S. *Acc. Chem. Res.* ***1968***, *1*, 104; *Pure Appl. Chem.* ***1971***, *27*, 635; Gollnick, K. *Adv. Photochem.* ***1968***, *6*, 1; Kearns, D.R. *Chem. Rev.* ***1971***, *71*, 395.

[242] Asveld, E.W.H.; Kellogg, R.M. *J. Org. Chem.* ***1982***, *47*, 1250.

[243] For a review of perepoxides as intermediates in organic reactions, see Mitchell, J.C. *Chem. Soc. Rev.* ***1985***, *14*, 399, p. 401.

[244] For evidence in favor of this mechanism, at least with some kinds of substrates, see Jefford, C.W.; Rimbault, C.G. *J. Am. Chem. Soc.* ***1978***, *100*, 6437; Okada, K.; Mukai, T. *J. Am. Chem. Soc.* ***1979***, *100*, 6509; Paquette, L.A.; Hertel, L.W.; Gleiter, R.; Böhm, M. *J. Am. Chem. Soc.* ***1978***, *100*, 6510; Wilson, S.L.; Schuster, G.B. *J. Org. Chem.* ***1986***, *51*, 2056; Davies, A.G.; Schiesser, C.H. *Tetrahedron Lett.* ***1989***, *30*, 7099; Orfanopoulos, M.; Smonou, I.; Foote, C.S. *J. Am. Chem. Soc.* ***1990***, *112*, 3607.

[245] See, for example, Jefford, C.W. *Helv. Chim. Acta* ***1981***, *64*, 2534.

14-8 Formation of Peroxides

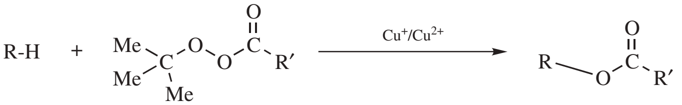
Alkyldioxy-de-hydrogenation

$$\text{RH} + \text{R'OOH} \xrightarrow{\text{CuCl}} \text{ROOR'}$$

Peroxy groups (ROO) can be introduced into susceptible organic molecules by treatment with a hydroperoxide in the presence of cuprous chloride or other catalysts, for example, cobalt and manganese salts.[246] Very high yields can be obtained. The type of hydrogen replaced is similar to that with NBS (**14-3**), that is, mainly benzylic, allylic, and tertiary. The mechanism is therefore of the free-radical type, involving ROO• formed from ROOH and the metal ion. The reaction can be used to demethylate tertiary amines of the form R_2NCH_3, since the product R_2NHCH_2OOR' can easily be hydrolyzed by acid (**10-6**) to give R_2NH.[247]

14-9 Acyloxylation

Acyloxylation or **Acyloxy-de-hydrogenation**



Susceptible positions of organic compounds can be directly acyloxylated[248] by *tert*-butyl peroxyesters, the most frequently used being acetic and benzoic (R′ = Me or Ph).[249] The reaction requires a catalyst (cuprous ion is the actual catalyst, but a trace is all that is necessary, and such traces are usually present in cupric compounds, so that these are often used) and without it is not selective. Susceptible positions are similar to those in **14-6**: benzylic, allylic, and the a position of ethers and sulfides. Terminal alkenes are substituted almost entirely in the 3 position, that is, with only a small amount of allylic rearrangement, but internal alkenes generally give mixtures containing a large amount of allylic-shift product. If the reaction with alkenes is carried out in an excess of

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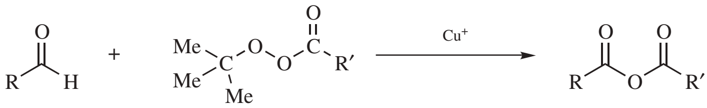
[246] For a review, see Sosnovsky, G.; Rawlinson, D.J., in Swern, D. *Organic Peroxides*, Vol. 2, Wiley, NY, ***1970***, pp. 153–268. See also, Murahashi, S.; Naota, T.; Kuwabara, T.; Saito, T.; Kumobayashi, H.; Akutagawa, S. *J. Am. Chem. Soc.* ***1990***, *112*, 7820; Sheldon, R.A., in Patai, S. *The Chemistry of Peroxides*, Wiley, NY, ***1983***, p. 161.

[247] See Murahashi, S.; Naota, T.; Yonemura, K. *J. Am. Chem. Soc.* ***1988***, *110*, 8256.

[248] For a list of reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed, Wiley-VCH, NY, ***1999***, pp. 1625–1630 *ff*, 1661–1663.

[249] For reviews, see Rawlinson, D.J.; Sosnovsky, G. *Synthesis* ***1972***, 1; Sosnovsky, G.; Rawlinson, D.J., in Swern, D. *Organic Peroxides*, Vol. 1, Wiley, NY, ***1970***, pp. 585–608; Doumaux, Jr, A.R. in Augustine, R.L. *Oxidation*, Vol. 2, Marcel Dekker, NY, ***1971***, pp. 141–185.

another acid R″COOH, the ester produced is of *that* acid ROCOR″. Aldehydes give anhydrides:



Acyloxylation has also been achieved with metallic acetates, such as lead tetraacetate,[250] mercuric acetate,[251] and palladium(II) acetate.[252] In the case of the lead and mercuric acetates, not only does the reaction take place at allylic and benzylic positions and at those α to an OR or SR group, but also at positions α to the carbonyl groups of aldehydes, ketones, or esters and at those a to two carbonyl groups (ZCH_2Z'). It is likely that in the latter cases it is the enol forms that react. Ketones can be α-acyloxylated indirectly by treatment of various enol derivatives with metallic acetates, for example, silyl enol ethers with silver carboxylates-iodine,[253] enol thioethers with lead tetraacetate,[254] and enamines[255] with lead tetraacetate[256] or thallium triacetate.[257] α,β-Unsaturated ketones can be acyloxylated in good yields in the α′ position with manganese triacetate.[258] Palladium acetate converts alkenes to vinylic and/or allylic acetates.[259] Lead tetraacetate even acyloxylates alkanes, in a slow reaction (10 days to 2 weeks), with tertiary and secondary positions greatly favored over primary ones.[260] Yields are as high as 50%. Acyloxylation of certain alkanes has also been reported with palladium(II) acetate.[261]

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[250] For a review of lead tetraacetate, see Butler, R.N., in Pizey, J.S. *Synthetic Reagents*, Vol. 3, Wiley, NY, p. 277.

[251] For reviews, see Larock, R.C. *Organomercury Compounds in Organic Synthesis*, Springer, NY, ***1985***, pp. 190–208; Rawlinson, D.J.; Sosnovsky, G. *Synthesis* ***1973***, 567.

[252] Hansson, S.; Heumann, A.; Rein, T.; Åkermark, B. *J. Org. Chem.* ***1990***, *55*, 975; Byström, S.E.; Larsson, E.M.; Åkermark, B. *J. Org. Chem.* ***1990***, *55*, 5674.

[253] Rubottom, G.M.; Mott, R.C.; Juve Jr, H.D. *J. Org. Chem.* ***1981***, *46*, 2717.

[254] Trost, B.M.; Tanigawa, Y. *J. Am. Chem. Soc.* ***1979***, *101*, 4413.

[255] For a review, see Cook, A.G., in Cook, A.G. *Enamines*, 2nd ed., Marcel Dekker, NY, ***1988***, pp. 251–258.

[256] See Butler, R.N. *Chem. Ind. (London)* ***1976***, 499.

[257] Kuehne, M.E.; Giacobbe, T.J. *J. Org. Chem.* ***1968***, *33*, 3359.

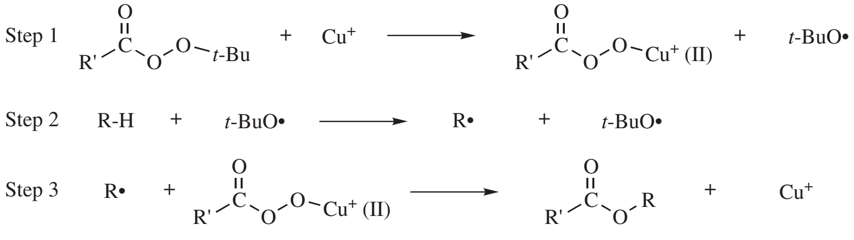
[258] Demir, A.S.; Sayrac, T.; Watt, D.S. *Synthesis* ***1990***, 1119.

[259] For reviews, see Rylander, P.N. *Organic Synthesis with Noble Metal Catalysts*, Academic Press, NY, ***1973***, pp. 80–87; Jira, R.; Freiesleben, W. *Organomet. React.* ***1972***, *3*, 1, pp. 44–84; Heck, R.F. *Fortschr. Chem. Forsch.* ***1971***, *16*, 221, pp. 231–237; Tsuji, J. *Adv. Org. Chem.* ***1969***, *6*, 109, pp. 132–143.

[260] Bestre, R.D.; Cole, E.R.; Crank, G. *Tetrahedron Lett.* ***1983***, *24*, 3891; Mosher, M.W.; Cox, J.L. *Tetrahedron Lett.* ***1985***, *26*, 3753.

[261] This was done in trifluoroacetic acid, and the products were trifluoroacetates: Sen, A.; Gretz, E.; Oliver, T.F.; Jiang, Z. *New J. Chem.* ***1989***, *13*, 755.

Studies of the mechanism of the cuprous-catalyzed reaction show that the most common mechanism is the following:[262]



32

This mechanism, involving a free radical R•, is compatible with the allylic rearrangements found.[263] The finding that *tert*-butyl peroxyesters labeled with ^{18}O in the carbonyl oxygen gave ester with 50% of the label in each oxygen[264] is in accord with a combination of R• with the intermediate **32**, in which the copper is ionically bound, so that the oxygens are essentially equivalent. Other evidence is that *tert*-butoxy radicals have been trapped with dienes.[265] Much less is known about the mechanisms of the reactions with metal acetates.[266]

Free-radical acyloxylation of aromatic substrates[267] has been accomplished with a number of reagents including copper(II) acetate,[268] benzoyl peroxide-iodine,[269] silver(II) complexes,[270] and cobalt(III) trifluoroacetate.[271]

OS **III**, 3; **V**, 70, 151; **VIII**, 137.

C. Substitution by Sulfur

14-10 Chlorosulfonation or Chlorosulfo-de-hydrogenation

$$RH + SO_2 + Cl_2 \xrightarrow{h\nu} RSO_2Cl$$

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[262] Kharasch, M.S.; Sosnovsky, G.; Yang, N.C. *J. Am. Chem. Soc.* ***1959***, *81*, 5819; Kochi, J.K.; Mains, H.E. *J. Org. Chem.* ***1965***, *30*, 1862. See also, Beckwith, A.L.J.; Zavitsas, A.A. *J. Am. Chem. Soc.* ***1986***, *108*, 8230.

[263] Goering, H.L.; Mayer, U. *J. Am. Chem. Soc.* ***1964***, *86*, 3753; Denney, D.B.; Appelbaum, A.; Denney, D.Z. *J. Am. Chem. Soc.* ***1962***, *84*, 4969.

[264] Denney, D.B.; Denney, D.Z.; Feig, G. *Tetrahedron Lett.* ***1959***, no. 15, p. 19.

[265] Kochi, J.K. *J. Am. Chem. Soc.* ***1962***, *84*, 2785, 3271; Story, P.R. *Tetrahedron Lett.* ***1962***, 401.

[266] See, for example, Jones, S.R.; Mellor, J.H. *J. Chem. Soc. Perkin Trans. 2* ***1977***, 511.

[267] For a review, see Haines, A.H. *Methods for the Oxidation of Organic Compounds*, Academic Press, NY, ***1985***, pp. 177–180, 351–355.

[268] Takizawa, Y.; Tateishi, A.; Sugiyama, J.; Yoshida, H.; Yoshihara, N. *J. Chem. Soc., Chem. Commun.* ***1991***, 104. See also Kaeding, W.W.; Kerlinger, H.O.; Collins, G.R. *J. Org. Chem.* ***1965***, *30*, 3754.

[269] For example, see Kovacic, P.; Reid, C.G.; Brittain, T.J. *J. Org. Chem.* ***1970***, *35*, 2152.

[270] Nyberg, K.; Wistrand, L.G. *J. Org. Chem.* ***1978***, *43*, 2613.

[271] Kochi, J.K.; Tank, R.T.; Bernath, T. *J. Am. Chem. Soc.* ***1973***, *95*, 7114; DiCosimo, R.; Szabo, H. *J. Org. Chem.* ***1986***, *51*, 1365.

The chlorosulfonation of organic molecules with chlorine and sulfur dioxide is called the *Reed reaction*.[272] In scope and range of products obtained, the reaction is similar to **14-1**. The mechanism is also similar, except that there are two additional main propagation steps:

$$\begin{aligned} R\bullet + SO_2 &\longrightarrow R{-}SO_2\bullet \\ R{-}SO_2\bullet + Cl_2 &\longrightarrow R{-}SO_2Cl + Cl\bullet \end{aligned}$$

Chlorosulfenation[273] can be accomplished by treatment with SCl_2 and UV light: $RH + SCl_2 \xrightarrow{h\nu} RSCl$.

D. Substitution by Nitrogen

14-11 The Direct Conversion of Aldehydes to Amides

Amination or **Amino-de-hydrogenation**

$$ArCHO \xrightarrow[NBS-AIBN]{NH_3} ArCONH_2$$

Aliphatic and aromatic aldehydes have been converted to the corresponding amides with ammonia or a primary or secondary amine, NBS, and a catalytic amount of AIBN (p. 935).[274] In a reaction of more limited scope, amides are obtained from aromatic and α,β-unsaturated aldehydes by treatment with dry ammonia gas and nickel peroxide.[275] Best yields (80–90%) are obtained at −25 to −20°C. In the nickel peroxide reaction the corresponding alcohols ($ArCH_2OH$) have also been used as substrates.

The reaction has also been performed with MnO_2 and NaCN along with ammonia or an amine at 0°C in isopropyl alcohol.[276] Aldehydes were also shown to react with hydroxylamine hydrochloride at 140°C in the presence of aluminum oxide and methanesulfonic acid.[277] Treatment of a aldehyde with iodine in aqueous ammonia, followed by oxidation with aqueous hydrogen peroxide generates a primary amide.[278] Secondary amines react with aldehydes to the an amide in using a palladium catalyst[279] or a rhodium catalyst.[280] For an indirect way of converting aldehydes to amides, see **12-32**. Thioamides $RCSNR'_2$ have been prepared in good yield

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[272] For a review, see Gilbert, E.E. *Sulfonation and Related Reactions*, Wiley, NY, ***1965***, pp. 126–131.

[273] Müller, E.; Schmidt, E.W. *Chem. Ber.* ***1963***, *96*, 3050; ***1964***, *97*, 2614. For a review of the formation and reactions of sulfenyl halides, see Kühle, E. *Synthesis* ***1970***, 561; ***1971***, 563, 617.

[274] Markó, I.E.; Mekhalfia, A. *Tetrahedron Lett.* ***1990***, *31*, 7237.

[275] Nakagawa, K.; Onoue, H.; Minami, K. *Chem. Commun.* ***1966***, 17.

[276] Gilman, N.W. *Chem. Commun.* ***1971***, 733.

[277] Sharghi, H.; Sarvari, M.H. *J. Chem. Res. (S)* ***2001***, 446.

[278] Shie, J.-J.; Fang, J.-M. *J. Org. Chem.* ***2003***, *68*, 1158.

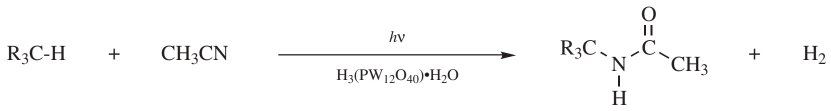
[279] Tamaru, Y.; Yamada, Y.; Yoshida, Z. *Synthesis* ***1983***, 474.

[280] Tillack, A.; Rudloff, I.; Beller, M. *Eur. J. Org. Chem.* ***2001***, 523.

from thioaldehydes (produced *in situ* from phosphoranes and sulfur) and secondary amines.[281]

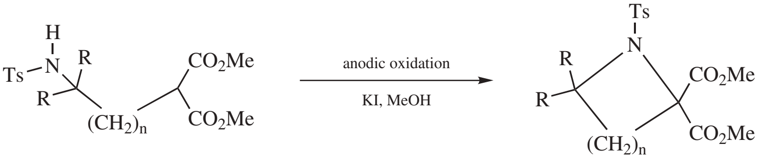
14-12 Amidation and Amination at an Alkyl Carbon

Acylamino-de-hydrogenation



When alkanes bearing a tertiary hydrogen are exposed to UV light in acetonitrile containing a heteropolytungstic acid, they are amidated.[282] The oxygen in the product comes from the tungstic acid. When the substrate bears two adjacent tertiary hydrogens, alkenes are formed (by loss of two hydrogens), rather than amides (**19-2**). Amidyl radicals can be generated by other means.[283]

An electrochemical method for amination has been reported by Shono and coworkers.[284] Derivatives of malonic esters containing an *N*-tosyl group were cyclized in high yields by anodic oxidation:



Three-, four-, and five-membered rings were synthesized by this procedure.

14-13 Substitution by Nitro

Nitro-de-carboxylation

In a reaction termed a “nitro-Hunsdiecker” (see **14-30**), vinyl carboxylic acids (conjugated acids) are treated with nitric acid and a catalytic amount of AIBN (p. 935). The product is the vinyl nitro compound, generated via decarboxylation of a radical intermediate.[285]

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[281] Okuma, K.; Komiya, Y.; Ohta, H. *Chem. Lett.* ***1988***, 1145.

[282] Renneke, R.F.; Hill, C.L. *J. Am. Chem. Soc.* ***1986***, *108*, 3528.

[283] Moutrille, C.; Zard, S.Z. *Chem. Commun.* ***2004***, 1848.

[284] Shono, T.; Matsumura, Y.; Katoh, S.; Ohshita, J. *Chem. Lett.* ***1988***, 1065.

[285] Das, J.P.; Sinha, P.; Roy, S. *Org. Lett.* ***2002***, *4*, 3055.

E. Substitution by Carbon

In these reactions, a new carbon–carbon bond is formed and they may be given the collective title *coupling reactions*. In each case, an alkyl or aryl radical is generated and then combines with another radical (a termination process) or attacks an aromatic ring or alkene to give the coupling product.[286]

14-14 Simple Coupling at a Susceptible Position

De-hydrogen-coupling

$$2\ \mathrm{RH} \longrightarrow \mathrm{R{-}R}$$

Alkane and alkyl substrates RH are treated with peroxides, which decompose to give a radical that abstracts a hydrogen from RH to give R•, which dimerizes. Dialkyl and diacyl peroxides have been used, as well as Fenton's reagent (p. 964). This reaction is far from general, though in certain cases respectable yields have been obtained. Among susceptible positions are those at a tertiary carbon,[287] as well as those α to a phenyl group (especially if there is also an α-alkyl or α-chloro group),[288] an ether group,[289] a carbonyl group,[290] a cyano group,[291] a dialkylamino group,[292] or a carboxylic ester group, either the acid or alcohol side.[293] Cross-coupling is possible in some cases. When toluene was heated with allyl bromide, in the presence of di-*tert*-butyl peroxide, 4-phenyl-1-butene was formed quantitatively.[294]

Conjugated amide were coupled via the γ-carbon to give good yields of the dimeric diamide, with an excess of samarium (II) iodide, and with modest enantioselectivity using a chiral additive.[295]

$$2\ \mathrm{RH} \xrightarrow[\mathrm{Hg}]{h\nu} \mathrm{R{-}R} + \mathrm{H_2}$$

[286] For a monograph on the formation of C–C bonds by radical reactions, see Giese, B. *Radicals in Organic Synthesis: Formation of Carbon–Carbon Bonds*, Pergamon, Elmsford, NY, ***1986***. For a review of arylation at carbon, see Abramovitch, R.A.; Barton, D.H.R.; Finet, J. *Tetrahedron* ***1988***, *44*, 3039. For a review of aryl–aryl coupling, see Sainsbury, M. *Tetrahedron* ***1980***, *36*, 3327.

[287] Meshcheryakov, A.P.; Érzyutova, E.I. *Bull. Acad. Sci. USSR Div. Chem. Sci*, ***1966***, 94.

[288] McBay, H.C.; Tucker, O.; Groves, P.T. *J. Org. Chem.* ***1959***, *24*, 536; Johnston, K.M.; Williams, G.H. *J. Chem. Soc.* ***1960***, 1168.

[289] Pfordte, K.; Leuschner, G. *Liebigs Ann. Chem.* ***1961***, *643*, 1.

[290] Kharasch, M.S.; McBay, H.C.; Urry, W.H. *J. Am. Chem. Soc.* ***1948***, *70*, 1269; Leffingwell, J.C. *Chem. Commun.* ***1970***, 357; Hawkins, E.G.E.; Large, R. *J. Chem. Soc. Perkin Trans. 1* ***1974***, 280.

[291] Kharasch, M.S.; Sosnovsky, G. *Tetrahedron* ***1958***, *3*, 97.

[292] Schwetlick, K.; Jentzsch, J.; Karl, R.; Wolter, D. *J. Prakt. Chem.* ***1964***, *[4] 25*, 95.

[293] Boguslavskaya, L.S.; Razuvaev, G.A. *J. Gen. Chem. USSR* ***1963***, *33*, 1967.

[294] Tanko, J.M.; Sadeghipour, M. *Angew. Chem. Int. Ed.* ***1999***, *38*, 159.

[295] Kikukawa, T.; Hanamoto, T.; Inanaga, J. *Tetrahedron Lett.* ***1999***, *40*, 7497.

Alkanes can be dimerized by vapor-phase mercury photosensitization[296] in a synthetically useful process. Best results are obtained for coupling at tertiary positions, but compounds lacking tertiary hydrogens (e.g., cyclohexane) also give good yields. Dimerization of *n*-alkanes gives secondary-secondary coupling in a nearly statistical distribution, with primary positions essentially unaffected. Alcohols and ethers dimerize at the position α to the oxygen [e.g., 2 EtOH → MeCH(OH)CH(OH)Me].

When a mixture of compounds is treated, cross-dimerization (to give **33**) and homodimerization take place statistically.

33

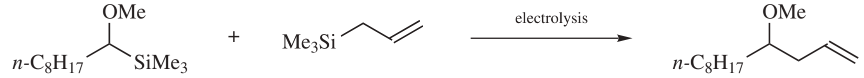
Even with the limitation on yield implied by the statistical process, cross-dimerization is still useful when one of the reactants is an alkane, because the products are easy to separate, and because of the few other ways to functionalize an alkane. The cross-coupling of an alkane with trioxane is especially valuable, because hydrolysis of the product (**10-6**) gives an aldehyde, thus achieving the conversion RH → RCHO. The mechanism probably involves abstraction of H by the excited Hg atom, and coupling of the resulting radicals.

The reaction has been extended to ketones, carboxylic acids and esters (all of which couple a to the C=O group), and amides (which couple α to the nitrogen) by running it in the presence of H_2.[297] Under these conditions it is likely that the excited Hg abstracts H• from H_2, and that the remaining H• abstracts H from the substrate. Radicals have also been generated at benzylic positions and shown to couple with epoxides, forming an alcohol.[298]

OS **IV**, 367; **V**, 1026; **VII**, 482.

14-15 Coupling at a Susceptible Position Via Silanes

De-silyl-coupling



34

Under electrochemical conditions it is possible to couple two silanes. The reaction of **34** and allyltrimethylsilane, for example, gave the corresponding homoallylic ether.[299]

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[296] Brown, S.H.; Crabtree, R.H. *J. Am. Chem. Soc.* ***1989***, *111*, 2935, 2946; *J. Chem. Educ.* ***1988***, *65*, 290.

[297] Boojamra, C.G.; Crabtree, R.H.; Ferguson, R.R.; Muedas, C.A. *Tetrahedron Lett.* ***1989***, *30*, 5583.

[298] Rawal, V.H.; Krishnamurthy, V.; Fabre, A. *Tetrahedron Lett.* ***1993***, *34*, 2899.

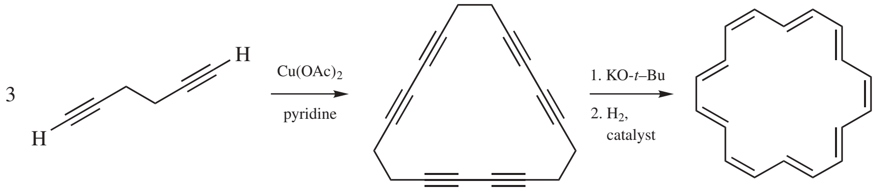
[299] Suga, S.; Suzuki, S.; Yamamoto, A.; Yoshida, J.-i. *J. Am. Chem. Soc.* ***2000***, *122*, 10244.

14-16 Coupling of Alkynes[300]

De-hydrogen-coupling

$$2\ R{-}C{\equiv}C{-}H \xrightarrow[\text{pyridine}]{CuX_2} R{-}C{\equiv}C{-}C{\equiv}C{-}R$$

Terminal alkynes can be coupled by heating with stoichiometric amounts of cupric salts in pyridine or a similar base. This reaction, which produces symmetrical diynes in high yields, is called the *Eglinton reaction*.[301] The large-ring annulenes of Sondheimer et al. (see p. 71) were prepared by rearrangement and hydrogenation of cyclic polyynes,[302] prepared by the Eglinton reaction with terminal diynes to give **35**, a cyclic trimer of 1,5-hexadiyne.[303] The corresponding tetramers (C_{24}), pentamers (C_{30}), and hexamers (C_{36}) were also formed. The Eglinton reaction is of wide scope. Many functional groups can be present on the alkyne. The oxidation is usually quite specific for triple-bond hydrogen.



35

Another common procedure is the use of catalytic amounts of cuprous salts in the presence of ammonia or ammonium chloride (this method is called the *Glaser reaction*). Atmospheric oxygen or some other oxidizing agent, such as permanganate or hydrogen peroxide is required in the latter procedure. This method is not satisfactory for cyclic coupling. Hydrogen peroxide, potassium permanganate, potassium ferricyanide, iodine or Cu(II) can be used instead of oxygen as oxidants.[304] Isolation of copper acetylide during the reaction can be avoided by doing the reaction in pyridine or cyclohexylamine, in the presence of catalytic amount of

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[300] For a review, see Siemsen, P.; Livingston, R.C.; Diederich, F. *Angew. Chem. Int. Ed.* ***2000***, *39*, 2632.

[301] For reviews, see Simándi, L.I., in Patai, S.; Rappoport, Z. *The Chemistry of Functional Groups, Supplement C* pt. 1, Wiley, NY, ***1983***, pp. 529–534; Nigh, W.G., in Trahanovsky, W.S. *Oxidation in Organic Chemistry*, pt. B, Academic Press, NY, ***1973***, pp. 11–31; Cadiot, P.; Chodkiewicz, W., in Viehe, H.G. *Acetylenes*; Marcel Dekker, NY; ***1969***, pp. 597–647.

[302] For a review of cyclic alkynes, see Nakagawa, M., in Patai, S. *The Chemistry of the Carbon-Carbon Triple Bond*, pt. 2, Wiley, NY, ***1978***, pp. 635–712.

[303] Sondheimer, F.; Wolovsky, R. *J. Am. Chem. Soc.* ***1962***, *84*, 260; Sondheimer, F.; Wolovsky, R.; Amiel, Y. *J. Am. Chem. Soc.* ***1962***, *84*, 274.

[304] Gunter, H.V. *Chemistry of Acetylenes*, Marcel Dekker, NY, ***1969***, pp. 597–647 and references cited therein.

$CuCl_3$.[305] If the Glaser reaction is done with a *N*,*N*,*N′*,*N′*-tetramethylethylenediamine–CuCl complex, the reaction proceeds in good yield in virtually any organic solvent.[306] When molecular oxygen is the oxidant, this modification of Glaser condensation is known as the *Hay reaction*. A variation couples terminal alkynes using $CuCl_2$ in supercritical CO_2 (see p. 414),[307] and in ionic liquids.[308] Coupling was also achieved using $CuCl_2$ on $KF—Al_2O_3$ with microwave irradiation.[309] Homocoupling of alkynyl amines $R_2N—C{\equiv}CH$ to give the diyne $R_2N—C{\equiv}C—C{\equiv}C\text{-}NR_2$ was reported in aerated acetone with 10% CuI and 20% TMEDA.[310]

Unsymmetrical diynes can be prepared by *Cadiot–Chodkiewicz* coupling:[311]

$$R-C{\equiv}C-H \quad + \quad R'-C{\equiv}C-Br \xrightarrow{Cu^+} R-C{\equiv}C-C{\equiv}C-R' \quad + \quad HBr$$

This may be regarded as a variation of **10-74**, but it must have a different mechanism since acetylenic halides give the reaction but ordinary alkyl halides do not, which is hardly compatible with a nucleophilic mechanism. However, the mechanism is not fully understood. One version of this reaction binds the alkynyl bromide unit to a polymer, and the di-yne is released from the polymer after the solid state transformation.[312] Alkynes have also been coupled using CuI and a palladium catalyst.[313] Propargyl halides also give the reaction,[314] as do 1-bromo propargylic alcohols ($Br—C{\equiv}C—CH_2OH$).[315] A variation of the Cadiot–Chodkiewicz method consists of treating a haloalkyne ($R'C{\equiv}CX$) with a copper acetylide ($RC{\equiv}CCu$).[316] The Cadiot–Chodkiewicz procedure can be adapted to the preparation of diynes in which $R' = H$ by the use of $BrC{\equiv}CSiEt_3$ and subsequent cleavage of the $SiEt_3$ group.[317] This protecting group can also be used in the Eglinton or Glaser methods.[318]

The mechanism of the Eglinton and Glaser reactions probably begins with loss of a proton

$$R-C{\equiv}C-H \xrightarrow{\text{base}} R-C{\equiv}C^-$$

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[305] Stansbury, H A.; Proops, W.R. *J. Org. Chem.* ***1962***, *27*, 320.

[306] Hay, A.S. *J. Org. Chem.* ***1960***, *25*, 1275; Hay, A S. *J. Org. Chem.* ***1962***, *27*, 3320.

[307] Li, J.; Jiang, H. *Chem. Commun.* ***1999***, 2369.

[308] In bmim PF_6, 1-butyl-3-methylimidazolium hexafluorophosphate: Yadav, J.S.; Reddy, B.V.S.; Reddy, K.B.; Gayathri, K.U.; Prasad, A.R. *Tetrahedron Lett.* ***2003***, *44*, 6493.

[309] Kabalka, G.W.; Wang, L.; Pagni, R.M. *Synlett* ***2001***, 108.

[310] Rodríguez, D.; Castedo, L.; Saá, C. *Synlett* ***2004***, 377.

[311] Chodkiewicz, W. *Ann. Chim. (Paris)* ***1957***, *[13] 2*, 819.

[312] Montierth, J.M.; DeMario, D.R.; Kurth, M.J.; Schore, N.E. *Tetrahedron* ***1998***, *54*, 11741.

[313] Liu, Q.; Burton, D.J. *Tetrahedron Lett.* ***1997***, *38*, 4371.

[314] Sevin, A.; Chodkiewicz, W.; Cadiot, P. *Bull. Soc. Chim. Fr.* ***1974***, 913.

[315] Marino, J.P.; Nguyen, H.N. *J. Org. Chem.* ***2002***, *67*, 6841.

[316] Curtis, R.F.; Taylor, J.A. *J. Chem. Soc. C* ***1971***, 186.

[317] Eastmond, R.; Walton, D.R.M. *Tetrahedron* ***1972***, *28*, 4591; Ghose, B.N.; Walton, D.R.M. *Synthesis* ***1974***, 890.

[318] Johnson, T.R.; Walton, D.R.M. *Tetrahedron* ***1972***, *28*, 5221.

since there is a base present and acetylenic protons are acidic. It is known, of course, that cuprous ion can form complexes with triple bonds. The last step is probably the coupling of two radicals:

$$R{-}C{\equiv}C\cdot \longrightarrow R{-}C{\equiv}C{-}C{\equiv}C{-}R$$

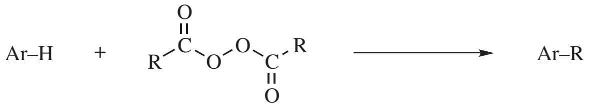
but just how the carbanion becomes oxidized to the radical and what part the cuprous ion plays (other than forming the acetylide salt) are matters of considerable speculation,[319] and depend on the oxidizing agent. One proposed mechanism postulated Cu(II) as the oxidant.[320] It has been shown that molecular oxygen forms adducts with Cu(I) supported by tertiary amines, which might be the intermediates in the Glaser reaction where molecular oxygen is the oxidant.[321] For the Hay reaction, the mechanism involves a $Cu^I/Cu^{III}/Cu^{II}/Cu^I$ catalytic cycle, and the key step for this reaction is the dioxygen activation during complexation of two molecules of acetylide with molecular oxygen, giving a Cu(III) complex.[322] This mechanism is supported by isolation and characterization of Cu(III) complexes formed under the conditions of the Glaser coupling.

Terminal alkynes are not the only reaction partners. 1-Trimethylsilyl alkynes ($R{-}C{\equiv}C{-}SiMe_3$) give the diyne $R{-}C{\equiv}C{-}C{\equiv}C{-}R$) upon reaction with CuCl[323] or $Cu(OAc)_2/Bu_4NF$.[324]

OS **V**, 517; **VI**, 68, 925; **VIII**, 63.

14-17 Alkylation and Arylation of Aromatic Compounds by Peroxides

Alkylation or **Alkyl-de-hydrogenation**



This reaction is most often carried out with R = aryl, so the net result is the same as in **13-27**, though the reagent is different.[325] It is used less often than **13-27**, but

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[319] See the discussions, in Nigh, W.G., in Trahanovsky, W.S. *Oxidation in Organic Chemistry*, pt. B, Academic Press, NY, ***1973***, pp. 27–31; Fedenok, L.G.; Berdnikov, V.M.; Shvartsberg, M.S. *J. Org. Chem. USSR* ***1973***, *9*, 1806; Clifford, A.A.; Waters, W.A. *J. Chem. Soc.* ***1963***, 3056.

[320] Bohlmann, F.; Schönowsky, H.; Inhoffen, E.; Grau, G. *Chem. Ber.* ***1964***, *97*, 794.

[321] Wieghardt, K.; Chaudhuri, P. *Prog. Inorg. Chem.* ***1987***, *37*, 329.

[322] Fomina, L.; Vazquez, B.; Tkatchouk, E.; Fomine, S. *Tetrahedron* ***2002***, *58*, 6741.

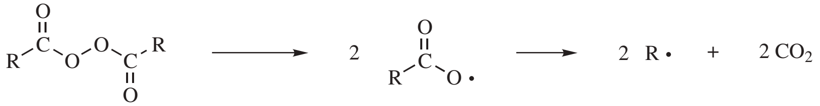
[323] Nishihara, Y.; Ikegashira, K.; Hirabayashi, K.; Ando, J.-i.; Mori, A.; Hiyama, T. *J. Org. Chem.* ***2000,*** *65*, 1780.

[324] Heuft, M.A.; Collins, S.K.; Yap, G.P.A.; Fallis, A.E. *Org. Lett.* ***2001***, *3*, 2883.

[325] For reviews, see Bolton, R.; Williams, G.H. *Chem. Soc. Rev.* ***1986***, *15*, 261; Hey, D.H. *Adv. Free-Radical Chem.* ***1966***, *2*, 47.

the scope is similar. When R = alkyl, the scope is more limited.[326] Only certain aromatic compounds, particularly benzene rings with two or more nitro groups, and fused ring systems, can be alkylated by this procedure. 1,4-Quinones can be alkylated with diacyl peroxides or with lead tetraacetate (methylation occurs with this reagent).

The mechanism is as shown on p. 940 (CIDNP has been observed[327]); the radicals are produced by



Since no relatively stable free radical is present (such as •O—N=N—Ar in **13-27**), most of the product arises from dimerization and disproportionation.[328] The addition of a small amount of nitrobenzene increases the yield of arylation product because the nitrobenzene is converted to diphenyl nitroxide, which abstracts the hydrogen from **5** and reduces the extent of side reactions.[329]

$$\text{ArH} + \text{Ar}'\text{Pb(OAc)}_3 \longrightarrow \text{ArAr}'$$

Aromatic compounds can also be arylated by aryllead tricarboxylates.[330] Best yields (~70–85%) are obtained when the substrate contains alkyl groups; an electrophilic mechanism is likely. Phenols are phenylated ortho to the OH group (and enols are a phenylated) by triphenylbismuth dichloride or by certain other Bi(V) reagents.[331] *O*-Phenylation is a possible side reaction. As with the aryllead tricarboxylate reactions, a free-radical mechanism is unlikely.[332]

OS **V**, 51. See also, OS **V**, 952; **VI**, 890.

14-18 Photochemical Arylation of Aromatic Compounds

Arylation or **Aryl-de-hydrogenation**

$$\text{ArH} + \text{Ar}'\text{I} \xrightarrow{h\nu} \text{ArAr}'$$

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[326] For reviews of the free-radical alkylation of aromatic compounds, see Tiecco, M.; Testaferri, L. *React. Intermed. (Plenum)* ***1983***, *3*, 61; Dou, H.J.; Vernin, G.; Metzger, J. *Bull. Soc. Chim. Fr.* ***1971***, 4593.

[327] Kaptein, R.; Freeman, R.; Hill, H.D.W.; Bargon, J. *J. Chem. Soc., Chem. Commun.* ***1973***, 953.

[328] We have given the main steps that lead to biphenyls. The mechanism is actually more complicated than this and includes >100 elementary steps resulting in many side products, including those mentioned on p. $$$: DeTar, D.F.; Long, R.A.J.; Rendleman, J.; Bradley, J.; Duncan, P. *J. Am. Chem. Soc.* ***1967***, *89*, 4051; DeTar, D.F. *J. Am. Chem. Soc.* ***1967***, *89*, 4058. See also, Jandu, K.S.; Nicolopoulou, M.; Perkins, M.J. *J. Chem. Res. (S)* ***1985***, 88.

[329] Chalfont, G.R.; Hey, D.H.; Liang, K.S.Y.; Perkins, M.J. *J. Chem. Soc. B* ***1971***, 233.

[330] Bell, H.C.; Kalman, J.R.; May, G.L.; Pinhey, J.T.; Sternhell, S. *Aust. J. Chem.* ***1979***, *32*, 1531.

[331] For a review, see Abramovitch, R.A.; Barton, D.H.R.; Finet, J. *Tetrahedron* ***1988***, *44*, 3039, pp. 3040–3047.

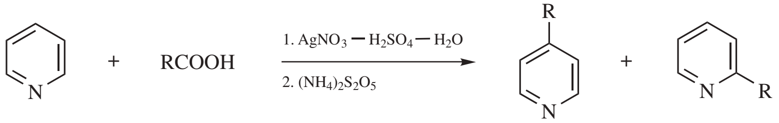
[332] Barton, D.H.R.; Finet, J.; Giannotti, C.; Halley, F. *J. Chem. Soc. Perkin Trans. 1* ***1987***, 241.

Another free-radical arylation method consists of the photolysis of aryl iodides in an aromatic solvent.[333] Yields are generally higher than in **13-27** or **14-17**. The aryl iodide may contain OH or COOH groups. The coupling reaction of iodobenzene and azulene to give a phenylazulene was reported (41% conversion and 85% yield).[334] The mechanism is similar to that of **13-27**. The aryl radicals are generated by the photolytic cleavage ArI → AR• + I•. The reaction has been applied to intramolecular arylation (analogous to the Pschorr reaction).[335] A similar reaction is photolysis of an arylthallium bis(trifluoroacetate) (**12-23**) in an aromatic solvent. Here too, an unsymmetrical biaryl is produced in good yields.[336] In this case, it is the C—Tl bond that is cleaved to give aryl radicals.

$$\mathrm{Ar'Tl(OCOCF_3)_2} \xrightarrow[\mathrm{ArH}]{h\nu} \mathrm{ArAr'}$$

14-19 Alkylation, Acylation, and Carbalkoxylation of Nitrogen Heterocycles[337]

Alkylation or **Alkyl-de-hydrogenation**, and so on



Alkylation of protonated nitrogen heterocycles (e.g., pyridines, quinolines) can be accomplished by treatment with a carboxylic acid, silver nitrate, sulfuric acid, and ammonium peroxydisulfate.[338] The R group can be primary, secondary, or tertiary. The attacking species is R•, formed by[339]

$$\begin{array}{lcl}
2\,\mathrm{Ag}^{+} + \mathrm{S_2O_8}^{2-} & \longrightarrow & 2\,\mathrm{Ag}^{2+} + 2\,\mathrm{SO_4}^{2-} \\
\mathrm{RCOOH} + \mathrm{Ag}^{2+} & \longrightarrow & \mathrm{RCOO}\bullet + \mathrm{H}^{+} + \mathrm{Ag}^{+} \\
\mathrm{RCOO}\bullet & \longrightarrow & \mathrm{R}\bullet + \mathrm{CO_2}
\end{array}$$

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[333] Wolf, W.; Kharasch, N. *J. Org. Chem.* ***1965***, *30*, 2493. For a review, see Sharma, R.K.; Kharasch, N. *Angew. Chem. Int. Ed.* ***1968***, *7*, 36.

[334] Ho, T.-I.; Ku, C.-K.; Liu, R.S.H. *Tetrahedron Lett.* ***2001***, *42*, 715.

[335] See, for example, Kupchan, S.M.; Wormser, H.C. *J. Org. Chem.* ***1965***, *30*, 3792; Jeffs, P.W.; Hansen, J.F. *J. Am. Chem. Soc.* ***1967***, *89*, 2798; Thyagarajan, B.S.; Kharasch, N.; Lewis, H.B.; Wolf, W. *Chem. Commun.* ***1967***, 614.

[336] Taylor, E.C.; Kienzle, F.; McKillop, A. *J. Am. Chem. Soc.* ***1970***, *92*, 6088.

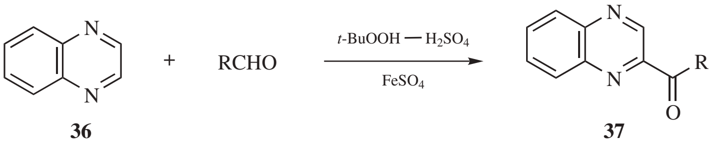
[337] For reviews; see Heinisch, G. *Heterocycles* ***1987***, *26*, 481; Minisci, F.; Vismara, E.; Fontana, F. *Heterocycles* ***1989***, *28*, 489; Minisci, F. *Top. Curr. Chem.* ***1976***, *62*, 1, pp. 17; *Synthesis* ***1973***, 1, pp. 12–19. For a review of substitution of carbon groups on nitrogen heterocycles see Vorbrüggen, H.; Maas, M. *Heterocycles* ***1988***, *27*, 2659.

[338] Fontana, F.; Minisci, F.; Barbosa, M.C.N.; Vismara, E. *Tetrahedron* ***1990***, *46*, 2525.

[339] Anderson, J.M.; Kochi, J.K. *J. Am. Chem. Soc.* ***1970***, *92*, 1651.

A hydroxymethyl group can be introduced (ArH → $ArCH_2OH$) by several variations of this method.[340] Alkylation of these substrates can also be accomplished by generating the alkyl radicals in other ways: from hydroperoxides and $FeSO_4$,[341] from alkyl iodides and H_2O_2—Fe(II),[342] from carboxylic acids and lead tetraacetate, or from the photochemically induced decarboxylation of carboxylic acids by iodosobenzene diacetate.[343]

Protonated nitrogen heterocycles, such as quinoxaline (**36**), can be acylated by treatment with an aldehyde, *tert*-butyl hydroperoxide, sulfuric acid, and ferrous sulfate, in this case giving **37**.[344]



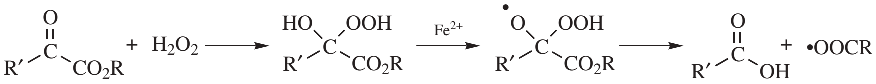
36 **37**

Photochemical alkylation of protonated quinoline occurred with $Ph_2Se(O_2Cc\text{-}C_6H_{11})_2$.[345]

Other positively charged heterocycles react as well. When *N*-fluoropyridinium triflate was treated with the enolate anion of acetone, 2-(2-oxopropyl)pyridine was formed in modest yield.[346]

These alkylation and acylation reactions are important because Friedel–Crafts alkylation and acylation (**11-11**, **11-17**) cannot be applied to most nitrogen heterocycles (see also **13-17**).

Protonated nitrogen heterocycles can be carbalkoxylated[347] by treatment with esters of α-keto acids and Fenton's reagent. Pyridine is carbalkoxylated at C-2 and C-4, for example. The attack is by •COOR radicals generated from the esters via a hydroperoxide (**38**).



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[340] See Citterio, A.; Gentile, A.; Minisci, F.; Serravalle, M.; Ventura, S. *Tetrahedron* ***1985***, *41*, 617; Katz, R.B.; Mistry, J.; Mitchell, M.B. *Synth. Commun.* ***1989***, *19*, 317.

[341] Minisci, F.; Selva, A.; Porta, O.; Barilli, P.; Gardini, G.P. *Tetrahedron* ***1972***, *28*, 2415.

[342] Fontana, F.; Minisci, F.; Barbosa, M.C.N.; Vismara, E. *Acta Chem. Scand*, ***1989***, *43*, 995.

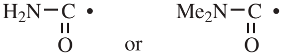
[343] Minisci, F.; Vismara, E.; Fontana, F.; Barbosa, M.C.N. *Tetrahedron Lett.* ***1989***, *30*, 4569.

[344] Caronna, T.; Gardini, G.P.; Minisci, F. *Chem. Commun.* ***1969***, 201; Arnoldi, A.; Bellatti, M.; Caronna, T.; Citterio, A.; Minisci, F.; Porta, O.; Sesana, G. *Gazz. Chim. Ital.* ***1977***, *107*, 491.

[345] Togo, H.; Miyagawa, N.; Yokoyama, M. *Chem. Lett*, ***1992***, 1677.

[346] Kiselyov, A.S.; Strekowski, L. *J. Org. Chem.* ***1993***, *58*, 4476.

[347] Bernardi, R.; Caronna, T.; Galli, R.; Minisci, F.; Perchinunno, M. *Tetrahedron Lett.* ***1973***, 645; Heinisch, G.; Lötsch, G. *Angew. Chem. Int. Ed.* ***1985***, *24*, 692.

Similarly, a carbamoyl group can be introduced[348] by the use of the radicals  $H_2N{-}C(=O)\bullet$ or $Me_2N{-}C(=O)\bullet$ generated from formamide or DMF and H_2SO_4, H_2O_2, and $FeSO_4$ or other oxidants.

N_2 AS LEAVING GROUP[349]

In these reactions diazonium salts are cleaved to aryl radicals,[350] in most cases with the assistance of copper salts. Reactions **13-27** and **13-26** may also be regarded as belonging to this category with respect to the attacking compound. For nucleophilic substitutions of diazonium salts (see **13-20–13-23**). Removal of nitrogen and replacement with a hydrogen atom is a reduction, found in Chapter 19.

14-20 Replacement of the Diazonium Group by Chlorine or Bromine

Chloro-de-diazoniation, and so on

$$ArN_2^+ + CuCl \longrightarrow ArCl$$

Treatment of diazonium salts with cuprous chloride or bromide leads to aryl chlorides or bromides, respectively. In either case, the reaction is called the *Sandmeyer reaction*.[351] The reaction can also be carried out with copper and HBr or HCl, in which case it is called the *Gatterman reaction* (not to be confused with **11-18**). The Sandmeyer reaction is not useful for the preparation of fluorides or iodides, but for bromides and chlorides it is of wide scope and is probably the best way of introducing bromine or chlorine into an aromatic ring. The yields are usually high.

The mechanism is not known with certainty, but is believed to take the following course:[352]

$$\begin{aligned} ArN_2^+X^- + CuX &\longrightarrow Ar\bullet + N_2 + CuX_2 \\ Ar\bullet + CuX_2 &\longrightarrow ArX + CuX \end{aligned}$$

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[348] Minisci, F.; Citterio, A.; Vismara, E.; Giordano, C. *Tetrahedron* ***1985***, *41*, 4157.

[349] For a review, see Wulfman, D.S., in Patai, S. *The Chemistry of Diazonium and Diazo Groups*, pt. 1, Wiley, NY, ***1978***, pp. 286–297.

[350] For reviews, see Galli, C. *Chem. Rev.* ***1988***, *88*, 765; Zollinger, H. *Acc. Chem. Res.* ***1973***, *6*, 355, pp. 339–341.

[351] Rate constants for this reaction have been determined. See Hanson, P.; Hammond, R.C.; Goodacre, P.R.; Purcell, J.; Timms, A.W. *J. Chem. Soc. Perkin Trans. 2* ***1994***, 691.

[352] Dickerman, S.C.; Weiss, K.; Ingberman, A.K. *J. Am. Chem. Soc.* ***1958***, *80*, 1904; Kochi, J.K. *J. Am. Chem. Soc.* ***1957***, *79*, 2942; Dickerman, S.C.; DeSouza, D.J.; Jacobson, N. *J. Org. Chem.* ***1969***, *34*, 710; Galli, C. *J. Chem. Soc. Perkin Trans. 2* ***1981***, 1459; ***1982***, 1139; ***1984***, 897. See also, Hanson, P.; Jones, J.R.; Gilbert, B.C.; Timms, A.W. *J. Chem. Soc. Perkin Trans. 2* ***1991***, 1009.

The first step involves a reduction of the diazonium ion by the cuprous ion, which results in the formation of an aryl radical. In the second step, the aryl radical abstracts halogen from cupric chloride, reducing it. The CuX is regenerated and is thus a true catalyst.

Aryl bromides and chlorides can be prepared from primary aromatic amines in one step by several procedures,[353] including treatment of the amine (*1*) with *tert*-butyl nitrite and anhydrous $CuCl_2$ or $CuBr_2$ at 65°C,[354] and (*2*) with *tert*-butyl thionitrite or *tert*-butyl thionitrate and $CuCl_2$ or $CuBr_2$ at room temperature.[355] These procedures are, in effect, a combination of **13-19** and the Sandmeyer reaction. A further advantage is that cooling to 0°C is not needed. A mixture of Me_3SiCl and $NaNO_2$ was used to convert aniline to chlorobenzene in a related reaction.[356]

For the preparation of fluorides and iodides from diazonium salts (see **13-32** and **13-31**).

$$ArN_2^+ + CuCN \longrightarrow ArCN$$

It is noted that the reaction of aryl diazonium salts with CuCN to give benzonitrile derivatives is also called the *Sandmeyer reaction*. It is usually conducted in neutral solution to avoid liberation of HCN.

OS **I**, 135, 136, 162, 170; **II**, 130; **III**, 185; **IV**, 160. Also see, OS **III**, 136; **IV**, 182. For the reaction with CuCN, see OS **I**, 514.

14-21 Replacement of the Diazonium Group by Nitro

Nitro-de-diazoniation

$$ArN_2^+ + NaNO_2 \xrightarrow{Cu^+} ArNO_2$$

Nitro compounds can be formed in good yields by treatment of diazonium salts with sodium nitrite in the presence of cuprous ion. The reaction occurs only in neutral or alkaline solution. This is not usually called the Sandmeyer reaction, although, like **14-20**, it was discovered by Sandmeyer. Tetrafluoroborate (BF_4–) is often used as the negative ion since the diminished nucleophilicity avoids competition from the chloride ion. The mechanism is probably like that of **14-20**.[357] If electron-withdrawing groups are present, the catalyst is not needed; $NaNO_2$ alone gives nitro compounds in high yields.[358]

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[353] For other procedures, see Brackman,W.; Smit, P.J. *Recl. Trav. Chim. Pays-Bas*, ***1966***, *85*, 857; Cadogan, J.I.G.; Roy, D.A.; Smith, D.M. *J. Chem. Soc. C* ***1966***, 1249.

[354] Doyle, M.P.; Siegfried, B.; Dellaria, Jr, J.F. *J. Org. Chem.* ***1977***, *42*, 2426.

[355] Oae, S.; Shinhama, K.; Kim, Y.H. *Bull. Chem. Soc. Jpn.* ***1980***, *53*, 1065.

[356] Lee, J.G.; Cha, H.T. *Tetrahedron Lett.* ***1992***, *33*, 3167.

[357] For discussions, see Opgenorth, H.; Rüchardt, C. *Liebigs Ann. Chem.* ***1974***, 1333; Singh, P.R.; Kumar, R.; Khanna, R.K. *Tetrahedron Lett.* ***1982***, *23*, 5191.

[358] Bagal, L.I.; Pevzner, M.S.; Frolov, A.N. *J. Org. Chem. USSR* ***1969***, *5*, 1767.

An alternative procedure used electrolysis, in 60% HNO_3 to convert 1-aminonaphthalene to naphthalene.[359]

OS **II**, 225; **III**, 341.

14-22 Replacement of the Diazonium Group by Sulfur-Containing Groups

Chlorosulfo-de-diazoniation

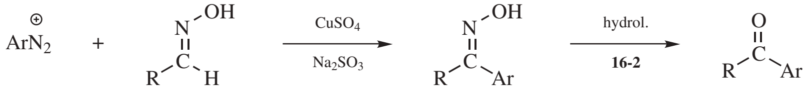
$$ArN_2{}^+ \quad + \quad SO_2 \quad \xrightarrow[HCl]{CuCl_2} \quad ArSO_2Cl$$

Diazonium salts can be converted to sulfonyl chlorides by treatment with sulfur dioxide in the presence of cupric chloride.[360] The use of $FeSO_4$ and copper metal instead of $CuCl_2$ gives sulfinic acids ($ArSO_2H$)[361] (see also, **13-21**).

OS **V**, 60; **VII**, 508.

14-23 Conversion of Diazonium Salts to Aldehydes, Ketones, or Carboxylic Acids

Acyl-de-diazoniation, and so on



Diazonium salts react with oximes to give aryl oximes, which are easily hydrolyzed to aldehydes (R = H) or ketones.[362] A copper sulfate-sodium sulfite catalyst is essential. In most cases higher yields (40–60%) are obtained when the reaction is used for aldehydes than for ketones. In another method[363] for achieving the conversion $ArN_2^+ \rightarrow ArCOR$, diazonium salts are treated with R_4Sn and CO with palladium acetate as catalyst.[364] In a different kind of reaction, silyl enol ethers of aryl ketones $Ar'C(OSiMe_3){=}CHR$ react with solid diazonium fluoroborates (ArN_2^+ BF_4^-) to give ketones ($ArCHRCOAr'$).[365] This is, in effect, an arylation of the aryl ketone.

Carboxylic acids can be prepared in moderate-to-high yields by treatment of diazonium fluoroborates with carbon monoxide and palladium acetate[366] or

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[359] Torii, S.; Okumoto, H.; Satoh, H.; Minoshima, T.; Kurozumi, S. *SynLett*, ***1995***, 439.

[360] Gilbert, E.E. *Synthesis* ***1969***, 1, p. 6.

[361] Wittig, G.; Hoffmann, R.W. *Org. Synth. V*, 60.

[362] Beech, W.F. *J. Chem. Soc.* ***1954***, 1297.

[363] For still another method, see Citterio, A.; Serravalle, M.; Vimara, E. *Tetrahedron Lett.* ***1982***, *23*, 1831.

[364] Kikukawa, K.; Idemoto, T.; Katayama, A.; Kono, K.; Wada, F.; Matsuda, T. *J. Chem. Soc. Perkin Trans. 1* ***1987***, 1511.

[365] Sakakura, T.; Hara, M.; Tanaka, M. *J. Chem. Soc., Chem. Commun.* ***1985***, 1545.

[366] Nagira, K.; Kikukawa, K.; Wada, F.; Matsuda, T. *J. Org. Chem.* ***1980***, *45*, 2365.

copper(II) chloride.[367] The mixed anhydride ArCOOCOMe is an intermediate that can be isolated. Other mixed anhydrides can be prepared by the use of other salts instead of sodium acetate.[368] An arylpalladium compound is probably an intermediate.[368]

OS **V**, 139.

METALS AS LEAVING GROUPS

14-24 Coupling of Grignard Reagents

De-metallo-coupling

$$2\,RMgX \xrightarrow{TlBr} RR$$

This organometallic coupling reaction is clearly related to the Wurtz coupling, discussed in **10-56**, and the coupling of other organometallic compounds is discussed in **14-25**. Grignard reagents can be coupled to give symmetrical dimers[369] by treatment with either thallium(I) bromide[370] or with a transition-metal halide, such as $CrCl_2$, $CrCl_3$, $CoCl_2$, $CoBr_2$, or $CuCl_2$.[371] The metallic halide is an oxidizing agent and becomes reduced. Both aryl and alkyl Grignard reagents can be dimerized by either procedure, though the TlBr method cannot be applied to R = primary alkyl or to aryl groups with ortho substituents. Aryl Grignard reagents can also be dimerized by treatment with 1,4-dichloro-2-butene, 1,4-dichloro-2-butyne, or 2,3-dichloropropene.[372] Vinylic and alkynyl Grignard reagents can be coupled (to give 1,3-dienes and 1,3-diynes, respectively) by treatment with thionyl chloride.[373] Primary alkyl, vinylic, aryl, and benzylic Grignard reagents give symmetrical dimers in high yield (~90%) when treated with a silver(I) salt (e.g., $AgNO_3$, AgBr, $AgClO_4$) in the presence of a nitrogen-containing oxidizing agent, such as lithium nitrate, methyl nitrate, or NO_2.[374] This method has been used to close rings of four, five, and six members.[375]

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[367] Olah, G.A.; Wu, A.; Bagno, A.; Prakash, G.K.S. *Synlett*, ***1990***, 596.

[368] Kikukawa, K.; Kono, K.; Nagira, K.; Wada, F.; Matsuda, T. *J. Org. Chem.* ***1981***, *46*, 4413.

[369] For a list of reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed, Wiley-VCH, NY, ***1999***, pp. 85–88.

[370] McKillop, A.; Elsom, L.F.; Taylor, E.C. *Tetrahedron* ***1970***, *26*, 4041.

[371] For reviews, see Kauffmann, T. *Angew. Chem. Int. Ed.* ***1974***, *13*, 291; Elsom, L.F.; Hunt, J.D.; McKillop, A. *Organomet. Chem. Rev. Sect. A* ***1972***, *8*, 135; Nigh, W.G., in Trahanovsky, W.S. *Oxidation in Organic Chemistry*, pt. B, Academic Press, NY, ***1973***, pp. 85–91.

[372] Taylor, S.K.; Bennett, S.G.; Heinz, K.J.; Lashley, L.K. *J. Org. Chem.* ***1981***, *46*, 2194; Cheng, J.; Luo, F. *Tetrahedron Lett.* ***1988***, *29*, 1293.

[373] Uchida, A.; Nakazawa, T.; Kondo, I.; Iwata, N.; Matsuda, S. *J. Org. Chem.* ***1972***, *37*, 3749.

[374] Tamura, M.; Kochi, J.K. *Bull. Chem. Soc. Jpn.* ***1972***, *45*, 1120.

[375] Whitesides, G.M.; Gutowski, F.D. *J. Org. Chem.* ***1976***, *41*, 2882.

The mechanisms of the reactions with metal halides, at least in some cases, probably begin with conversion of RMgX to the corresponding RM (**12-36**), followed by its decomposition to free radicals.[376]

OS **VI**, 488.

14-25 Coupling of Other Organometallic Reagents[332]

De-metallo-coupling

$$R_2CuLi \xrightarrow[-78^\circ C,\ THF]{O_2} RR$$

Lithium dialkylcopper reagents can be oxidized to symmetrical dimers by O_2 at −78°C in THF.[377] The reaction is successful for R = primary and secondary alkyl, vinylic, or aryl. Other oxidizing agents, for example, nitrobenzene, can be used instead of O_2. Vinylic copper reagents dimerize on treatment with oxygen, or simply on standing at 0°C for several days or at 25°C for several hours, to yield 1,3-dienes.[378] The finding of retention of configuration for this reaction demonstrates that free-radical intermediates are not involved.

The coupling reaction of Grignard reagents was discussed in **14-24**. Lithium organoaluminates ($LiAlR_4$) are dimerized to RR by treatment with $Cu(OAc)_2$.[379] Terminal vinylic alanes (prepared by **15-17**) can be dimerized to 1,3-dienes with CuCl in THF.[380] Symmetrical 1,3-dienes can also be prepared in high yields by treatment of vinylic mercury chlorides[381] with LiCl and a rhodium catalyst[382] and by treatment of vinylic tin compounds with a palladium catalyst.[383] Arylmercuric salts are converted to biaryls by treatment with copper and a catalytic amount of $PdCl_2$.[384] Vinylic, alkynyl, and aryl tin compounds were dimerized with

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[376] For a review of the mechanism, see Kashin, A.N.; Beletskaya, I.P. *Russ. Chem. Rev.* ***1982***, *51*, 503.

[377] Whitesides, G.M.; San Filippo, Jr, J.; Casey, C.P.; Panek, E.J. *J. Am. Chem. Soc.* ***1967***, *89*, 5302. See also, Kauffmann, T.; Kuhlmann, D.; Sahm, W.; Schrecken, H. *Angew. Chem. Int. Ed.* ***1968***, *7*, 541; Bertz, S.H.; Gibson, C.P. *J. Am. Chem. Soc.* ***1986***, *108*, 8286.

[378] Whitesides, G.M.; Casey, C.P.; Krieger, J.K. *J. Am. Chem. Soc.* ***1971***, *93*, 1379; Walborsky, H.M.; Banks, R.B.; Banks, M.L.A.; Duraisamy, M. *Organometallics* ***1982***, *1*, 667; Rao, S.A.; Periasamy, M. *J. Chem. Soc., Chem. Commun.* ***1987***, 495. See also, Lambert, G.J.; Duffley, R.P.; Dalzell, H.C.; Razdan, R.K. *J. Org. Chem.* ***1982***, *47*, 3350.

[379] Sato, F.; Mori, Y.; Sato, M. *Chem. Lett.* ***1978***, 1337.

[380] Zweifel, G.; Miller, R.L. *J. Am. Chem. Soc.* ***1970***, *92*, 6678.

[381] For reviews of coupling with organomercury compounds, see Russell, G.A. *Acc. Chem. Res.* ***1989***, *22*, 1; Larock, R.C. *Organomercury Compounds in Organic Synthesis*, Springer, NY, ***1985***, pp. 240–248.

[382] Larock, R.C.; Bernhardt, J.C. *J. Org. Chem.* ***1977***, *42*, 1680. For extension to unsymmetrical 1,3-dienes, see Larock, R.C.; Riefling, B. *J. Org. Chem.* ***1978***, *43*, 1468.

[383] Tolstikov, G.A.; Miftakhov, M.S.; Danilova, N.A.; Vel'der, Ya.L.; Spirikhin, L.V. *Synthesis* ***1989***, 633.

[384] Kretchmer, R.A.; Glowinski, R. *J. Org. Chem.* ***1976***, *41*, 2661. See also, Bumagin, N.A.; Kalinovskii, I.O.; Beletskaya, I.P. *J. Org. Chem. USSR* ***1982***, *18*, 1151; Larock, R.C.; Bernhardt, J.C. *J. Org. Chem.* ***1977***, *42*, 1680.

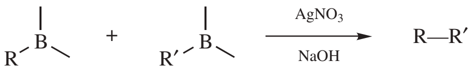
$Cu(NO_3)_2$.[385] Alkyl- and aryllithium compounds can be dimerized by transition-metal halides in a reaction similar to **14-24**.[386] Triarylbismuth compounds Ar_3Bi react with palladium(0) complexes to give biaryls ArAr.[387] Diethylzinc reacted with $Ph_2I^+ BF_4^-$ in the presence of palladium acetate, to give biphenyl.[388]

Unsymmetrical coupling of vinylic, alkynyl, and arylmercury compounds was achieved in moderate-to-good yields by treatment with alkyl and vinylic dialkylcopper reagents, for example, $PhCH{=}CHHgCl + Me_2CuLi \rightarrow PhCH{=}CHMe$.[389] Unsymmetrical biaryls were prepared by treating a cyanocuprate (ArCu(CN)Li, prepared from ArLi and CuCN) with an aryllithium (Ar′Li).[390]

A radical coupling reaction has been reported, in which an aryl halide reacted with Bu_3SnH, AIBN, and benzene, followed by treatment with methyllithium to give the biaryl.[391]

14-26 Coupling of Boranes

Alkyl-de-dialkylboration



Alkylboranes can be coupled by treatment with silver nitrate and base.[392] Since alkylboranes are easily prepared from alkenes (**15-16**), this is essentially a way of coupling and reducing alkenes; in fact, alkenes can be hydroborated and coupled in the same flask. For symmetrical coupling (R = R′) yields range from 60 to 80% for terminal alkenes and from 35 to 50% for internal ones. Unsymmetrical coupling has also been carried out,[393] but with lower yields. Arylboranes react similarly, yielding biaryls.[394] The mechanism is probably of the free-radical type.

Dimerization of two vinylborane units to give a conjugated diene can be achieved by treatment of divinylchloroboranes (prepared by addition of BH_2Cl to alkynes; see **15-16**) with methylcopper. (*E*,*E*)-1,3-Dienes are prepared in high

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[385] Ghosal, S.; Luke, G.P.; Kyler, K.S. *J. Org. Chem.* ***1987***, *52*, 4296.

[386] Morizur, J. *Bull. Soc. Chim. Fr.* ***1964***, 1331.

[387] Barton, D.H.R.; Ozbalik, N.; Ramesh, M. *Tetrahedron* ***1988***, *44*, 5661.

[388] Kang, S.-K.; Hong, R.-K.; Kim, T.-H.; Pyun, S.-J. *Synth. Commun.* ***1997***, *27*, 2351.

[389] Larock, R.C.; Leach, D.R. *Tetrahedron Lett.* ***1981***, *22*, 3435; *Organometallics* ***1982***, *1*, 74. For another method, see Larock, R.C.; Hershberger, S.S. *Tetrahedron Lett.* ***1981***, *22*, 2443.

[390] Lipshutz, B.H.; Siegmann, K.; Garcia, E. *J. Am. Chem. Soc.* ***1991***, *113*, 8161.

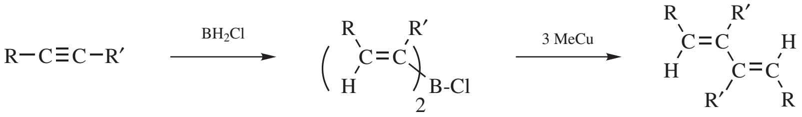
[391] Studer, A. ; Bossart, M.; Vasella, T. *Org. Lett.* ***2000***, *2*, 985.

[392] Pelter, A.; Smith, K.; Brown, H.C. *Borane Reagents*, Academic Press, NY, ***1988***, pp. 306–308.

[393] Brown, H.C.; Verbrugge, C.; Snyder, C.H. *J. Am. Chem. Soc.* ***1961***, *83*, 1001.

[394] Breuer, S.W.; Broster, F.A. *Tetrahedron Lett.* ***1972***, 2193.

yields.[395]



In a similar reaction, symmetrical conjugated diynes RC≡C—C≡CR can be prepared by reaction of lithium dialkyldialkynylborates, $Li^+ [R'_2B(C{\equiv}CR)_2]^-$, with iodine.[396]

HALOGEN AS LEAVING GROUP

The conversion of RX to RH can occur by a free-radical mechanism but is treated at **19-53**.

SULFUR AS LEAVING GROUP

14-27 Desulfurization

Hydro-de-thio-substitution, and so on

$$\text{RSH} \xrightarrow[\text{Ni}]{\text{H}_2} \text{RH}$$

$$\text{RSR}' \xrightarrow[\text{Ni}]{\text{H}_2} \text{RH} + \text{R}'\text{H}$$

Thiols and thioethers,[397] both alkyl and aryl, can be desulfurized by hydrogenolysis with Raney nickel.[398] The hydrogen is usually not applied externally, since Raney nickel already contains enough hydrogen for the reaction. Other sulfur compounds can be similarly desulfurized, among them disulfides (RSSR),

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[395] Yamamoto, Y.; Yatagai, H.; Maruyama, K.; Sonoda, A.; Murahashi, S. *J. Am. Chem. Soc.* ***1977***, *99*, 5652; *Bull. Chem. Soc. Jpn.* ***1977***, *50*, 3427. For other methods of dimerizing vinylic boron compounds, see Rao, V.V.R.; Kumar, C.V.; Devaprabhakara, D. *J. Organomet. Chem.* ***1979***, *179*, C7; Campbell, Jr, J.B.; Brown, H.C. *J. Org. Chem.* ***1980***, *45*, 549.

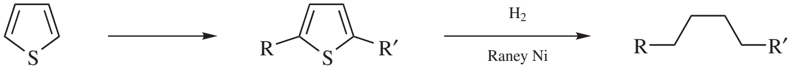
[396] Pelter, A.; Smith, K.; Tabata, M. *J. Chem. Soc., Chem. Commun.* ***1975***, 857. For extensions to unsymmetrical conjugated diynes, see Pelter, A.; Hughes, R.; Smith, K.; Tabata, M. *Tetrahedron Lett.* ***1976***, 4385; Sinclair, J.A.; Brown, H.C. *J. Org. Chem.* ***1976***, *41*, 1078.

[397] For a review of the reduction of thioethers, see Block, E., in Patai, S. *The Chemistry of Functional Groups, Supplement E*, pt. 1, Wiley, NY, ***1980***, pp. 585–600.

[398] For reviews, see Belen'kii, L.I., in Belen'kii, L.I. *Chemistry of Organosulfur Compounds*, Ellis Horwood, Chichester, ***1990***, pp. 193–228; Pettit, G.R.; van Tamelen, E.E. *Org. React.* ***1962***, *12*, 356; Hauptmann, H.; Walter, W.F. *Chem. Rev.* ***1962***, *62*, 347.

thiono esters (RCSOR′),[399] thioamides (RCDNHR′), sulfoxides, and dithioacetals. The last reaction, which is an indirect way of accomplishing reduction of a carbonyl to a methylene group (see **19-61**), can also give the alkene if an a hydrogen is present.[400] In most of the examples given, R can also be aryl. Other reagents[401] have also been used,[402] including samarium in acetic acid for desulfurization of vinyl sulfones.[403]

An important special case of RSR reduction is desulfurization of thiophene derivatives. This proceeds with concomitant reduction of the double bonds. Many compounds have been made by alkylation of thiophene (see **39**), followed by reduction to the corresponding alkane.



39

Thiophenes can also be desulfurized to alkenes ($RCH_2CH{=}CHCH_2R'$ from **39**) with a nickel boride catalyst prepared from nickel(II) chloride and $NaBH_4$ in methanol.[404] It is possible to reduce just one SR group of a dithioacetal by treatment with borane–pyridine in trifluoroacetic acid or in CH_2Cl_2 in the presence of $AlCl_3$.[405] Phenyl selenides RSePh can be reduced to RH with Ph_3SnH[406] and with nickel boride.[407]

The exact mechanisms of the Raney nickel reactions are still in doubt, though they are probably of the free-radical type.[408] It has been shown that reduction of thiophene proceeds through butadiene and butene, not through 1-butanethiol or other sulfur compounds, that is, the sulfur is removed before the double bonds

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[399] See Baxter, S.L.; Bradshaw, J.S. *J. Org. Chem.* ***1981***, *46*, 831.

[400] Fishman, J.; Torigoe, M.; Guzik, H. *J. Org. Chem.* ***1963***, *28*, 1443.

[401] For lists of reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed, Wiley-VCH, NY, ***1999***, pp. 53–60. For a review with respect to transition-metal reagents, see Luh, T.; Ni, Z. *Synthesis* ***1990***, 89. For some very efficient nickel-containing reagents, see Becker, S.; Fort, Y.; Vanderesse, R.; Caubère, P. *J. Org. Chem.* ***1989***, *54*, 4848.

[402] For example, diphosphorus tetraiodide by Suzuki, H.; Tani, H.; Takeuchi, S. *Bull. Chem. Soc. Jpn.* ***1985***, *58*, 2421; Shigemasa, Y.; Ogawa, M.; Sashiwa, H.; Saimoto, H. *Tetrahedron Lett.* ***1989***, *30*, 1277; $NiBr_2$–Ph_3P–$LiAlH_4$ by Ho, K.M.; Lam, C.H.; Luh, T. *J. Org. Chem.* ***1989***, *54*, 4474.

[403] Liu, Y.; Zhang, Y. *Org. Prep. Proceed. Int.* ***2001***, *33*, 376.

[404] Schut, J.; Engberts, J.B.F.N.; Wynberg, H. *Synth. Commun.* ***1972***, *2*, 415.

[405] Kikugawa, Y. *J. Chem. Soc. Perkin Trans. 1* ***1984***, 609.

[406] Clive, D.L.J.; Chittattu, G.; Wong, C.K. *J. Chem. Soc., Chem. Commun.* ***1978***, 41.

[407] Back, T.G. *J. Chem. Soc., Chem. Commun.* ***1984***, 1417.

[408] For a review, see Bonner, W.A.; Grimm, R.A., in Kharasch, N.; Meyers, C.Y. *The Chemistry of Organic Sulfur Compounds*, Vol. 2, Pergamon, NY, ***1966***, pp. 35–71, 410–413. For a review of the mechanism of desulfurization on molybdenum surfaces, see Friend, C.M.; Roberts, J.T. *Acc. Chem. Res.* ***1988***, *21*, 394.

are reduced. This was demonstrated by isolation of the olefins and the failure to isolate any potential sulfur-containing intermediates.[409]

OS **IV**, 638; **V**, 419; **VI**, 109, 581, 601. See also OS **VII**, 124, 476.

14-28 Conversion of Sulfides to Organolithium Compounds

Lithio-de-phenylthio-substitution

$$\mathrm{RSPh} \xrightarrow[\text{THF}]{\text{Li naphthalenide}} \mathrm{RLi}$$

Sulfides can be cleaved, with a phenylthio group replaced by a lithium,[410] by treatment with lithium or lithium naphthalenide in THF.[411] Good yields have been obtained with R = primary, secondary, or tertiary alkyl, or allylic,[412] and containing groups, such as double bonds or halogens. Dilithio compounds can be made from compounds containing two separated SPh groups, but it is also possible to replace just one SPh from a compound with two such groups on a single carbon, to give an α-lithio sulfide.[413] The reaction has also been used to prepare α-lithio ethers and α-lithio organosilanes.[410] For some of these compounds lithium 1-(dimethylamino)naphthalenide is a better reagent than either Li or lithium naphthalenide.[414] The mechanism is presumably of the free-radical type.

CARBON AS LEAVING GROUP

14-29 Decarboxylative Dimerization: The Kolbe Reaction

De-carboxylic-coupling

$$2\,\mathrm{RCOO^-} \xrightarrow{\text{electrolysis}} \mathrm{R{-}R}$$

Electrolysis of carboxylate ions, results in decarboxylation and combination of the resulting radicals to give the coupling product R—R. This coupling

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[409] Owens, P.J.; Ahmberg, C.H. *Can. J. Chem.* ***1962***, *40*, 941.

[410] For a review, see Cohen, T.; Bhupathy, M. *Acc. Chem. Res.* ***1989***, *22*, 152.

[411] Screttas, C.G.; Micha-Screttas, M. *J. Org. Chem.* ***1978***, *43*, 1064; ***1979***, *44*, 713.

[412] See Cohen, T.; Guo, B. *Tetrahedron* ***1986***, *42*, 2803.

[413] See, for example, Cohen, T.; Sherbine, J.P.; Matz, J.R.; Hutchins, R.R.; McHenry, B.M.; Willey, P.R. *J. Am. Chem. Soc.* ***1984***, *106*, 3245; Ager, D.J. *J. Chem. Soc. Perkin Trans. 1* ***1986***, 183; Screttas, C.G.; Micha-Screttas, M. *J. Org. Chem.* ***1978***, *43*, 1064; ***1979***, *44*, 713.

[414] See Cohen, T.; Matz, J.R. *Synth. Commun.* ***1980***, *10*, 311.

reaction is called the *Kolbe reaction* or the *Kolbe electrosynthesis*.[415] It is used to prepare symmetrical R—R, where R is straight chained, since little or no yield is obtained when there is a branching. The reaction is not successful for R = aryl. Many functional groups may be present, though many others inhibit the reaction.[415] Unsymmetrical RR′ have been made by coupling mixtures of acid salts.

A free-radical mechanism is involved:

$$\mathrm{RCOO^-} \xrightarrow[\text{oxidation}]{\text{electrolytic}} \mathrm{RCOO}\bullet \xrightarrow{-\mathrm{CO_2}} \mathrm{R}\bullet \longrightarrow \mathrm{R{-}R}$$

There is much evidence[416] for this mechanism, including side products (RH, alkenes) characteristic of free-radical intermediates and the fact that electrolysis of acetate ion in the presence of styrene caused some of the styrene to polymerize to polystyrene (such polymerizations can be initiated by free radicals, see p. 1015). Other side products (ROH, RCOOR) are sometimes found, stemming from further oxidation of the radical R• to a carbocation R^+.[417]

When the reaction is conducted in the presence of 1,3-dienes, additive dimerization can occur:[418]

$$2\,\mathrm{RCOO^-} + \mathrm{CH_2{=}CH{-}CH{=}CH_2} \longrightarrow \mathrm{RCH_2CH{=}CHCH_2CH_2CH{=}CHCH_2R}$$

The radical R• adds to the conjugated system to give $RCH_2CH{=}CHCH_2\bullet$, which dimerizes. Another possible product is $RCH_2CH{=}CHCH_2R$, from coupling of the two kinds of radicals.[419]

In a nonelectrolytic reaction, which is limited to R = primary alkyl, the thiohydroxamic esters **40** give dimers when irradiated at −64°C in an argon

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[415] For reviews, see Nuding, G.; Vögtle, F.; Danielmeier, K.; Steckhan, E. *Synthesis* ***1996***, 71; Schäfer, H.J. *Top. Curr. Chem.* ***1990***, *152*, 91; *Angew. Chem. Int. Ed.* ***1981***, *20*, 911; Fry, A.J. *Synthetic Organic Electrochemistry*, 2nd ed, Wiley, NY, ***1989***, pp. 238–253; Eberson, L.; Utley, J.H.P., in Baizer, M.M.; Lund, H. *Organic Electrochemistry*, Marcel Dekker, NY, ***1983***, pp. 435–462; Gilde, H. *Methods Free-Radical Chem.* ***1972***, *3*, 1; Eberson, L., in Patai, S. *The Chemistry of Carboxylic Acids and Esters*, Wiley, NY, ***1969***, pp. 53–101; Vijh, A.K.; Conway, B.E. *Chem. Rev.* ***1967***, *67*, 623.

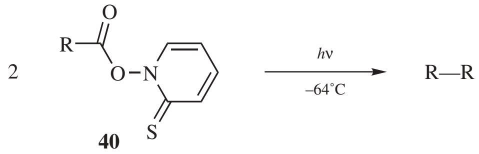
[416] For other evidence, see Kraeutler, B.; Jaeger, C.D.; Bard, A.J. *J. Am. Chem. Soc.* ***1978***, *100*, 4903.

[417] See Corey, E.J.; Bauld, N.L.; La Londe, R.T.; Casanova, Jr, J.; Kaiser, E.T. *J. Am. Chem. Soc.* ***1960***, *82*, 2645.

[418] Lindsey, Jr, R.V.; Peterson, M.L. *J. Am. Chem. Soc.* ***1959***, *81*, 2073; Khrizolitova, M.A.; Mirkind, L.A.; Fioshin, M.Ya. *J. Org. Chem. USSR* ***1968***, *4*, 1640; Bruno, F.; Dubois, J.E. *Bull. Soc. Chim. Fr.* ***1973***, 2270.

[419] Smith, W.B.; Gilde, H. *J. Am. Chem. Soc.* ***1959***, *81*, 5325; ***1961***, *83*, 1355; Schäfer, H.; Pistorius, R. *Angew. Chem. Int. Ed.* ***1972***, *11*, 841.

atmosphere:[420]



40

In another nonelectrolytic process, aryl acetic acids are converted to *vic*-diaryl compounds $2ArCR_2COOH \rightarrow ArCR_2CR_2Ar$ by treatment with sodium persulfate $Na_2S_2O_8$ and a catalytic amount of $AgNO_3$.[421] Photolysis of carboxylic acids in the presence of Hg_2F_2 leads to the dimeric alkane via decarboxylation.[422] Both of these reactions involve dimerization of free radicals. In still another process, electron-deficient aromatic acyl chlorides are dimerized to biaryls (2 ArCOCl → Ar—Ar) by treatment with a disilane R_3SiSiR_3 and a palladium catalyst.[423]

OS **III**, 401; **V**, 445, 463; **VII**, 181.

14-30 The Hunsdiecker Reaction

Bromo-de-carboxylation

$$RCOOAg + Br_2 \longrightarrow RBr + CO_2 + AgBr$$

Reaction of a silver salt of a carboxylic acid with bromine is called the *Hunsdiecker reaction*[424] and is a way of decreasing the length of a carbon chain by one unit.[425] The reaction is of wide scope, giving good results for *n*-alkyl R from 2 to 18 carbons and for many branched R too, producing primary, secondary, and tertiary bromides. Many functional groups may be present as long as they are not a substituted. The group R may also be aryl. However, if R contains unsaturation, the reaction seldom gives good results. Although bromine is the most often used halogen, chlorine and iodine have also been used. Catalytic Hunsdiecker reactions are known.[426]

When iodine is the reagent, the ratio between the reactants is very important and determines the products. A 1:1 ratio of salt/iodine gives the alkyl halide, as above.

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[420] Barton, D.H.R.; Bridon, D.; Fernandez-Picot, I.; Zard, S.Z. *Tetrahedron* ***1987***, *43*, 2733.

[421] Fristad, W.E.; Klang, J.A. *Tetrahedron Lett.* ***1983***, *24*, 2219.

[422] Habibi, M.H.; Farhadi, S. *Tetrahedron Lett.* ***1999***, *40*, 2821.

[423] Krafft, T.E.; Rich, J.D.; McDermott, P.J. *J. Org. Chem.* ***1990***, *55*, 5430.

[424] This reaction was first reported by the Russian composer–chemist Alexander Borodin: *Liebigs Ann. Chem.* ***1861***, *119*, 121.

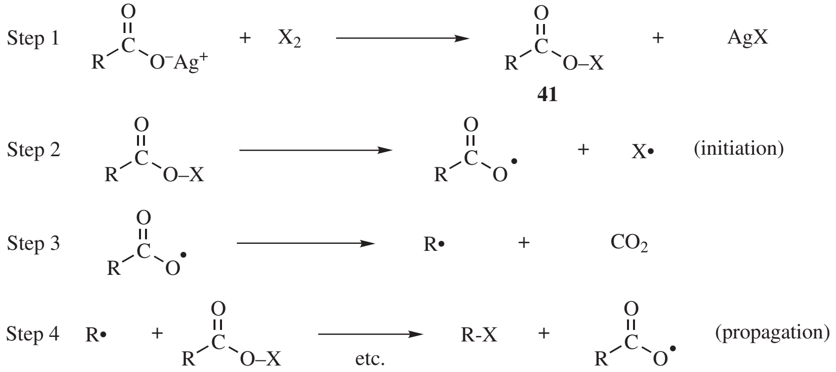
[425] For reviews, see Wilson, C.V. *Org. React.* ***1957***, *9*, 332; Johnson, R.G.; Ingham, R.K. *Chem. Rev.* ***1956***, *56*, 219. Also see, Naskar, D.; Chowdhury, S.; Roy, S. *Tetrahedron Lett.* ***1998***, *39*, 699.

[426] Das, J.P.; Roy, S. *J. Org. Chem.* ***2002***, *67*, 7861.

A 2:1 ratio, however, gives the ester RCOOR. This is called the *Simonini reaction* and is sometimes used to prepare carboxylic esters. The Simonini reaction can also be carried out with lead salts of acids.[427] A more convenient way to perform the Hunsdiecker reaction is by use of a mixture of the acid and mercuric oxide instead of the salt, since the silver salt must be very pure and dry and such pure silver salts are often not easy to prepare.[428]

Other methods for accomplishing the conversion RCOOH → RX are[429] (*1*) treatment of thallium(I) carboxylates[430] with bromine;[431] (*2*) treatment of carboxylic acids with lead tetraacetate and halide *ions* (Cl^-, Br^-, or I^-);[432] (*3*) reaction of the acids with lead tetraacetate and NCS, which gives tertiary and secondary chlorides in good yields, but is not good for R = primary alkyl or phenyl;[433] (*4*) treatment of thiohydroxamic esters with CCl_4, $BrCCl_3$ (which gives bromination), CHI_3, or CH_2I_2 in the presence of a radical initiator;[434] (*5*) photolysis of benzophenone oxime esters of carboxylic acids in CCl_4 ($RCON{=}CPh_2 \rightarrow RCl$).[435] Alkyl fluorides can be prepared in moderate to good yields by treating carboxylic acids RCOOH with XeF_2.[436] This method works best for R = primary and tertiary alkyl, and benzylic. Aromatic and vinylic acids do not react.

The mechanism of the Hunsdiecker reaction is believed to be as follows:



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[427] Bachman, G.B.; Kite, G.F.; Tuccarbasu, S.; Tullman, G.M. *J. Org. Chem.* ***1970***, *35*, 3167.

[428] Cristol, S.J.; Firth, W.C. *J. Org. Chem.* ***1961***, *26*, 280. See also, Meyers, A.I.; Fleming, M.P. *J. Org. Chem.* ***1979***, *44*, 3405, and references cited therein.

[429] For a list of reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed, Wiley-VCH, NY, ***1999***, pp. 741–744.

[430] These salts are easy to prepare and purify; see Ref. 501.

[431] McKillop, A.; Bromley, D.; Taylor, E.C. *J. Org. Chem.* ***1969***, *34*, 1172; Cambie, R.C.; Hayward, R.C.; Jurlina, J.L.; Rutledge, P.S.; Woodgate, P.D. *J. Chem. Soc. Perkin Trans. 1* ***1981***, 2608.

[432] Kochi, J.K. *J. Am. Chem. Soc.* ***1965***, *87*, 2500; *J. Org. Chem.* ***1965***, *30*, 3265. For a review, see Sheldon, R.A.; Kochi, J.K. *Org. React.* ***1972***, *19*, 279, pp. 326–334, 390–399.

[433] Becker, K.B.; Geisel, M.; Grob, C.A.; Kuhnen, F. *Synthesis* ***1973***, 493.

[434] Barton, D.H.R.; Lacher, B.; Zard, S.Z. *Tetrahedron* ***1987***, *43*, 4321; Stofer, E.; Lion, C. *Bull. Soc. Chim. Belg.* ***1987***, *96*, 623; Della, E.W.; Tsanaktsidis, J. *Aust. J. Chem.* ***1989***, *42*, 61.

[435] Hasebe, M.; Tsuchiya, T. *Tetrahedron Lett.* ***1988***, *29*, 6287.

[436] Patrick, T.B.; Johri, K.K.; White, D.H.; Bertrand, W.S.; Mokhtar, R.; Kilbourn, M.R.; Welch, M.J. *Can. J. Chem.* ***1986***, *64*, 138. For another method, see Grakauskas, V. *J. Org. Chem.* ***1969***, *34*, 2446.

The first step is not a free-radical process, and its actual mechanism is not known.[437] Compound **41** is an acyl hypohalite and is presumed to be an intermediate, though it has never been isolated from the reaction mixture. Among the evidence for the mechanism is that optical activity at R is lost (except when a neighboring bromine atom is present, see p. 942); if R is neopentyl, there is no rearrangement, which would certainly happen with a carbocation; and the side products, notably RR, are consistent with a free-radical mechanism. There is evidence that the Simonini reaction involves the same mechanism as the Hunsdiecker reaction, but that the alkyl halide formed then reacts with excess RCOOAg (**10-17**) to give the ester[438] (see also **19-12**).

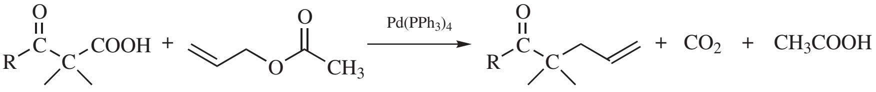
Vinyl carboxylic acids (conjugated acids) were shown to react with NBS and lithium acetate in aqueous acetonitrile, to give the corresponding vinyl bromide (C=C–COOH → C=C–Br), using microwave irradiation.[439] A similar reaction was reported using Na_2MoO_4, KBr and aqueous hydrogen peroxide.[440]

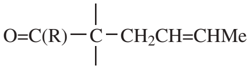
A related reaction reacts the sodium salt of an alkylsulfonic acid with thionyl chloride at 100°C, to give the alkyl chloride.[441]

OS **III**, 578; **V**, 126; **VI**, 179; **75**, 124; **X**, 237. See also OS **VI**, 403.

14-31 Decarboxylative Allylation

Allyl-de-carboxylation



The COOH group of a β-keto acid is replaced by an allylic group when the acid is treated with an allylic acetate and a palladium catalyst at room temperature.[442] The reaction is successful for various substituted allylic groups. The less highly substituted end of the allylic group forms the new bond. Thus, both $CH_2{=}CHCHMeOAc$ and $MeCH{=}CHCH_2OAc$ gave  $O{=}C(R){-}\overset{|}{\underset{|}{C}}{-}CH_2CH{=}CHMe$ as the product.

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[437] When Br_2 reacts with aryl R, at low temperature in inert solvents, it is possible to isolate a complex containing both Br_2 and the silver carboxylate: see Bryce-Smith, D.; Isaacs, N.S.; Tumi, S.O. *Chem. Lett.* ***1984***, 1471.

[438] Oae, S.; Kashiwagi, T.; Kozuka, S. *Bull. Chem. Soc. Jpn.* ***1966***, *39*, 2441; Bunce, N.J.; Murray, N.G. *Tetrahedron* ***1971***, *27*, 5323.

[439] Kuang, C.; Senboku, H.; Tokuda, M. *Synlett* ***2000***, 1439.

[440] Sinha, J.; Layek, S.; Bhattacharjee, M.; Mandal, G.C. *Chem. Commun.* ***2001***, 1916.

[441] Carlsen, P.H.J.; Rist, Ø.; Lund, T.; Helland, I. *Acta Chem. Scand. B* ***1995***, *49*, 701.

[442] Tsuda, T.; Okada, M.; Nishi, S.; Saegusa, T. *J. Org. Chem.* ***1986***, *51*, 421.

14-32 Decarbonylation of Aldehydes and Acyl Halides

Carbonyl-Extrusion

$$\text{RCHO} \xrightarrow{\text{RhCl(Ph}_3\text{P)}_3} \text{RH}$$

Aldehydes, both aliphatic and aromatic, can be decarbonylated[443] by heating with a rhodium catalyst[444] or other catalysts, such as palladium.[445] $RhCl(Ph_3P)_3$ is often called *Wilkinson's catalyst*.[446] In an older reaction, aliphatic (but not aromatic) aldehydes are decarbonylated by heating with di-*tert*-butyl peroxide or other peroxides,[447] usually in a solution containing a hydrogen donor, such as a thiol. The reaction has also been initiated with light, and thermally (without an initiator) by heating at ~500°C.

Wilkinson's catalyst has also been reported to decarbonylate aromatic acyl halides at 180°C (ArCOX → ArX).[448] This reaction has been carried out with acyl iodides,[449] bromides, and chlorides. Aliphatic acyl halides that lack an a hydrogen also give this reaction,[450] but if an α hydrogen is present, elimination takes place instead (**17-17**). Aromatic acyl cyanides give aryl cyanides (ArCOCN → ArCN).[451] Aromatic acyl chlorides and cyanides can also be decarbonylated with palladium catalysts.[452]

It is possible to decarbonylate acyl halides in another way, to give alkanes (RCOCl → RH). This is done by heating the substrate with tripropylsilane Pr_3SiH

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[443] For reviews, see Collman, J.P.; Hegedus, L.S.; Norton, J.R.; Finke, R.G. *Principles and Applications of Organotransition Metal Chemistry*, University Science Books, Mill Valley, CA ***1987***, pp. 768–775; Baird, M.C., in Patai, S. *The Chemistry of Functional Groups, Supplement B* pt. 2, Wiley, NY, ***1979***, pp. 825–857; Tsuji, J., in Wender, I.; Pino, P. *Organic Syntheses Via Metal Carbonyls*, Vol. 2, Wiley, NY, ***1977***, pp. 595–654; Tsuji, J.; Ohno, K. *Synthesis* ***1969***, 157; Bird, C.W. *Transition Metal Intermediates in Organic Synthesis*, Academic Press, NY, ***1967***, pp. 239–247.

[444] Ohno, K.; Tsuji, J. *J. Am. Chem. Soc.* ***1968***, *90*, 99; Baird, C.W.; Nyman, C.J.; Wilkinson, G. *J. Chem. Soc. A* ***1968***, 348.

[445] For a review, see Rylander, P.N. *Organic Synthesis with Noble Metal Catalysts*, Academic Press, NY, ***1973***, pp. 260–267.

[446] For a review of this catalyst, see Jardine, F.H. *Prog. Inorg. Chem.* ***1981***, *28*, 63.

[447] For reviews of free-radical aldehyde decarbonylations, see Vinogradov, M.G.; Nikishin, G.I. *Russ. Chem. Rev.* ***1971***, *40*, 916; Schubert, W.M.; Kintner, R.R., in Patai, S. *The Chemistry of the Carbonyl Group*, Vol. 1, Wiley, NY, ***1966***, pp. 711–735.

[448] Kampmeier, J.A.; Rodehorst, R.; Philip, Jr, J.B. *J. Am. Chem. Soc.* ***1981***, *103*, 1847; Blum, J.; Oppenheimer, E.; Bergmann, E.D. *J. Am. Chem. Soc.* ***1967***, *89*, 2338.

[449] Blum, J.; Rosenman, H.; Bergmann, E.D. *J. Org. Chem.* ***1968***, *33*, 1928.

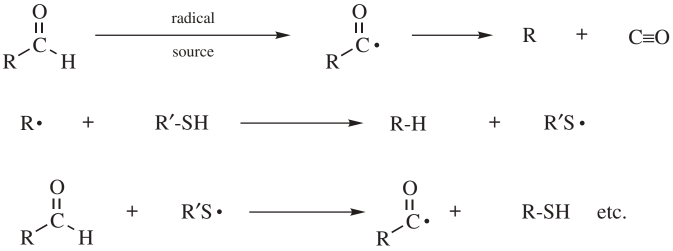
[450] Tsuji, J.; Ohno, K. *Tetrahedron Lett.* ***1966***, 4713; *J. Am. Chem. Soc.* ***1966***, *88*, 3452.

[451] Blum, J.; Oppenheimer, E.; Bergmann, E.D. *J. Am. Chem. Soc.* ***1967***, *89*, 2338.

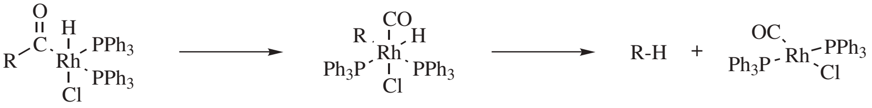
[452] Verbicky, Jr, J.W.; Dellacoletta, B.A.; Williams, L. *Tetrahedron Lett.* ***1982***, *23*, 371; Murahashi, S.; Naota, T.; Nakajima, N. *J. Org. Chem.* ***1986***, *51*, 898.

in the presence of *tert*-butyl peroxide.[453] Yields are good for R = primary or secondary alkyl and poor for R = tertiary alkyl or benzylic. There is no reaction when R = aryl. (See also the decarbonylation ArCOCl → ArAr mentioned in **14-29**.)

The mechanism of the peroxide- or light-induced reaction seems to be as follows (in the presence of thiols):[454]



The reaction of aldehydes with Wilkinson's catalyst goes through complexes of the form **42** and **43**, which have been trapped.[455] The reaction has been shown to give retention of configuration at a chiral R;[456] and deuterium labeling demonstrates that the reaction is intramolecular: RCOD give RD.[457] Free radicals are not involved.[458] The mechanism with acyl halides appears to be more complicated.[459]



42 **43**

For aldehyde decarbonylation by an electrophilic mechanism (see **11-34**).

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[453] Billingham, N.C.; Jackson, R.A.; Malek, F. *J. Chem. Soc. Perkin Trans. 1* ***1979***, 1137.

[454] Slaugh, L.H. *J. Am. Chem. Soc.* ***1959***, *81*, 2262; Berman, J.D.; Stanley, J.H.; Sherman, V.W.; Cohen, S.G. *J. Am. Chem. Soc.* ***1963***, *85*, 4010.

[455] Suggs, J.W. *J. Am. Chem. Soc.* ***1978***, *100*, 640; Kampmeier, J.A.; Harris, S.H.; Mergelsberg, I. *J. Org. Chem.* ***1984***, *49*, 621.

[456] Walborsky, H.M.; Allen, L.E. *J. Am. Chem. Soc.* ***1971***, *93*, 5465. See also, Tsuji, J.; Ohno, K. *Tetrahedron Lett.* ***1967***, 2173.

[457] Prince, R.H.; Raspin, K.A. *J. Chem. Soc. A* ***1969***, 612; Walborsky, H.M.; Allen, L.E. *J. Am Chem. Soc.* ***1971***, *93*, 5465. See, however, Baldwin, J.E.; Bardenm, T.C.; Pugh, R.L.; Widdison, W.C. *J. Org. Chem.* ***1987***, *52*, 3303.

[458] Kampmeier, J.A.; Harris, S.H.; Wedegaertner, D.K. *J. Org. Chem.* ***1980***, *45*, 315.

[459] Kampmeier, J.A.; Liu, T. *Organometallics* ***1989***, *8*, 2742.

CHAPTER 15

Addition to Carbon–Carbon Multiple Bonds

There are four fundamental 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, or attack upon 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 (concerted). 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 Addition[1]

In this mechanism, a positive species approaches the double or triple bond and in the first step forms a bond by donation of the π pair of electrons[2] to the electrophilic

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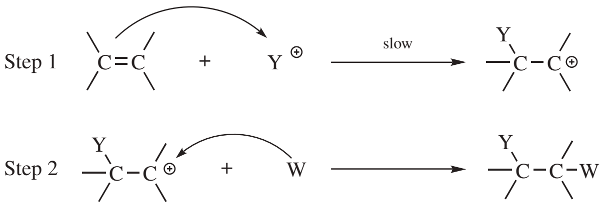
[1] For a monograph, see de la Mare, P.B.D.; Bolton, R. *Electrophilic Additions to Unsaturated Systems*, 2nd ed.; Elsevier, NY, ***1982***. For reviews, see Schmid, G.H., in Patai, S. *Supplement A: The Chemistry of Double-bonded Functional Groups*, Vol. 2, pt. 1, Wiley, NY, ***1989***, pp. 679–731; Smit, W.A. *Sov. Sci. Rev. Sect. B* ***1985***, *7*, 155; V'yunov, K.A.; Ginak, A.I. *Russ. Chem. Rev.* ***1981***, *50*, 151; Schmid, G.H.; Garratt, D.G., in Patai, S. *Supplement A: The Chemistry of Double-bonded Functional Groups*, Vol. 1, pt. 2, Wiley, NY, ***1977***, pp. 725–912; Freeman, F. *Chem. Rev.* ***1975***, *75*, 439; Bolton, R., in Bamford, C.H.; Tipper, C.F.H. *Comprehensive Chemical Kinetics*, Vol. 9, Elsevier, NY, ***1973***, pp. 1–86; Dolbier, Jr., W.R. *J. Chem. Educ.* ***1969***, *46*, 342.

[2] For a review of the π-nucleophilicity in carbon–carbon bond-forming reactions, see Mayr, H.; Kempf, B.; Ofial, A.R. *Acc. Chem. Res.* ***2003***, *36*, 66.

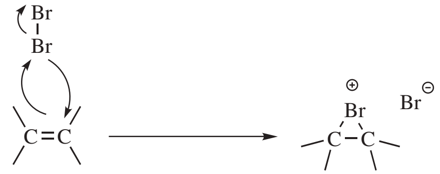
March's Advanced Organic Chemistry: Reactions, Mechanisms, and Structure, Sixth Edition, by
Michael B. Smith and Jerry March

species to form a σ pair:



1

The IUPAC designation for this mechanism is $A_E + A_N$ (or $A_H + A_N$ if $Y^+ = H^+$). As in electrophilic substitution (p. 658), Y need not actually be a positive ion but can be the 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**):



2

This intermediate is similar to those encountered in the neighboring-group mechanism of nucleophilic substitution (see p. 446). The attack of $\overline{w}$ on an intermediate like **2** is an S_N2 step. Whether the intermediate is **1** or **2**, the mechanism is called Ad_E2 (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.[3] The two carbons of the double bond and the four atoms immediately attached to them are all in a plane (p. 9); there are thus three possibilities. Both 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 alkene of the form ABC=CBA. We may use the cis alkene as an example. If the addition is syn, the product

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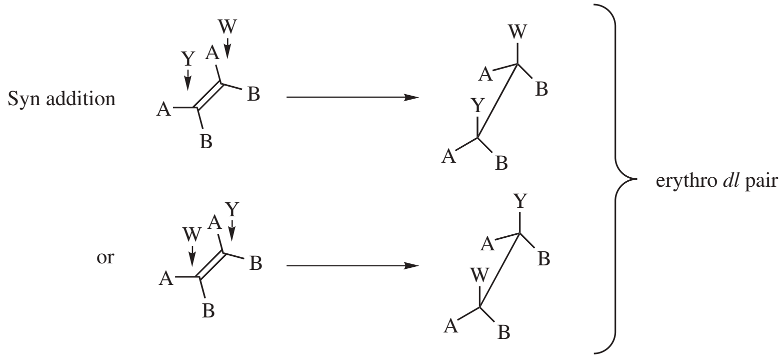
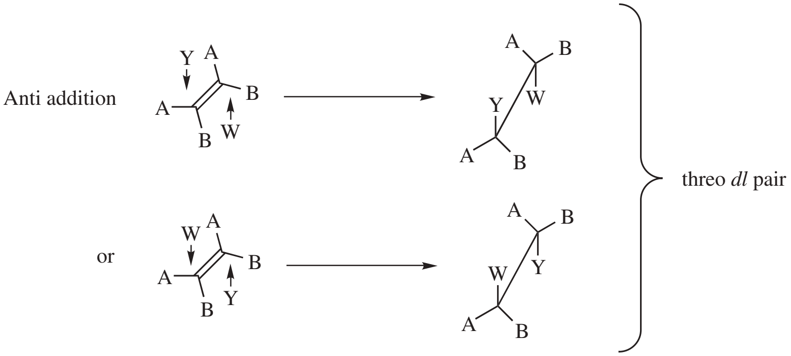
[3] For a review of the stereochemistry of electrophilic additions to double and triple bonds, see Fahey, R.C. *Top. Stereochem.* ***1968***, *3*, 237. For a review of the synthetic uses of stereoselective additions, see Bartlett, P.A. *Tetrahedron* ***1980***, *36*, 2, pp. 3–15.

will be the erythro *dl* pair, because each carbon has a 50% chance of being attacked by Y:

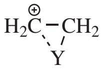


On the other hand, if the addition is anti, the threo *dl* pair will be formed:



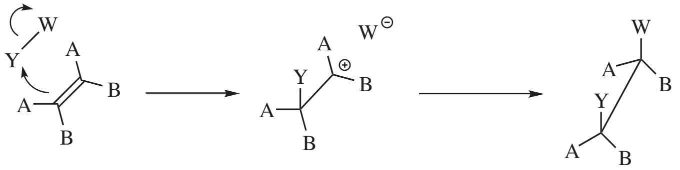
Of course, the trans isomer will give the opposite results: the threo pair if the addition is syn and the erythro pair if it is anti. The threo and erythro isomers have different physical properties. In the special case, where $Y = W$ (as in the addition of Br_2), the "erythro pair" is a meso compound. In addition to triple-bond compounds of the type $AC{\equiv}CA$, syn addition results in a cis alkene and anti addition in a trans alkene. By the definition given on p. 194 addition to triple bonds cannot be stereospecific, although 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 S_N2 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 (see **3**).



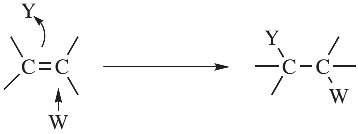
3

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:[4]



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

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 Ad_E3 mechanism (*termolecular addition*, IUPAC A_NA_E),[5] 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. 1478).

There is much evidence that when the attack is on 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.[6] 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%

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[4] Dewar, M.J.S. *Angew. Chem. Int. Ed.* ***1964***, *3*, 245; Heasley, G.E.; Bower, T.R.; Dougharty, K.W.; Easdon, J.C.; Heasley, V.L.; Arnold, S.; Carter, T.L.; Yaeger, D.B.; Gipe, B.T.; Shellhamer, D.F. *J. Org. Chem.* ***1980***, *45*, 5150.

[5] For evidence for this mechanism, see, for example, Hammond, G.S.; Nevitt, T.D. *J. Am. Chem. Soc.* ***1954***, *76*, 4121; Bell, R.P.; Pring, M. *J. Chem. Soc. B* ***1966***, 1119; Pincock, J.A.; Yates, K. *J. Am. Chem. Soc.* ***1968***, *90*, 5643; Fahey, R.C.; Payne, M.T.; Lee, D. *J. Org. Chem.* ***1974***, *39*, 1124; Roberts, R.M.G. *J. Chem. Soc. Perkin Trans. 2*, ***1976***, 1374; Pasto, D.J.; Gadberry, J.F. *J. Am. Chem. Soc.* ***1978***, *100*, 1469; Naab, P.; Staab, H.A. *Chem. Ber.* ***1978***, *111*, 2982.

[6] This was done by Fischer, E. *Liebigs Ann. Chem.* ***1911***, *386*, 374; McKenzie, A. *Proc. Chem. Soc.* ***1911***, 150; *J. Chem. Soc.* ***1912***, *101*, 1196.

of the trans isomer.[7]

70% trans

There is other evidence for mechanisms involving **2**. We have already mentioned (p. 449) 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.[8] 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.[9] Similar results are found when the reaction is carried out in the presence of water (**15-40**) or of other nucleophiles.[10] *Ab initio* molecular orbital studies show that **2** is more stable than its open isomer **1** ($Y = Br$).[11] There is evidence that formation of **2** is reversible.[12]

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.[13] 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 90–100% anti, but with an increase in dielectric constant, the reaction became less stereospecific, until, at a dielectric constant of $\sim$35, the addition was completely nonstereospecific.[14] Likewise in the case of triple bonds, stereoselective anti addition was found in bromi-

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[7] Michael, A. *J. Prakt. Chem.* ***1892***, *46*, 209.

[8] Strating, J.; Wieringa, J.H.; Wynberg, H. *Chem. Commun.* ***1969***, 907; Olah, G.A. *Angew. Chem. Int. Ed.* ***1973***, *12*, 173, p. 207; Slebocka-Tilk, H.; Ball, R.G.; Brown, R.S. *J. Am. Chem. Soc.* ***1985***, *107*, 4504.

[9] Francis, A.W. *J. Am. Chem. Soc.* ***1925***, *47*, 2340.

[10] See, for example, Zefirov, N.S.; Koz'min, A.S.; Dan'kov, Yu.V.; Zhdankin, V.V.; Kirin, V.N. *J. Org. Chem. USSR* ***1984***, *20*, 205.

[11] Hamilton, T.P.; Schaefer III, H.F. *J. Am. Chem. Soc.* ***1990***, *112*, 8260.

[12] Brown, R.S.; Gedye, R.; Slebocka-Tilk, H.; Buschek, J.M.; Kopecky, K.R. *J. Am. Chem. Soc.* ***1984***, *106*, 4515; Ruasse, M.; Motallebi, S.; Galland, B. *J. Am. Chem. Soc.* ***1991***, *113*, 3440; Bellucci, G.; Bianchini, R.; Chiappe, C.; Brown, R.S.; Slebocka-Tilk, H. *J. Am. Chem. Soc.* ***1991***, *113*, 8012; Bennet, A.J.; Brown, R.S.; McClung, R.E.D.; Klobukowski, M.; Aarts, G.H.M.; Santarsiero, B.D.; Bellucci, G.; Bianchini, R. *J. Am. Chem. Soc.* ***1991***, *113*, 8532.

[13] Fahey, R.C.; Schneider, H. *J. Am. Chem. Soc.* ***1968***, *90*, 4429. See also, Rolston, J.H.; Yates, K. *J. Am. Chem. Soc.* ***1969***, *91*, 1469, 1477, 1483.

[14] Heublein, G. *J. Prakt. Chem.* ***1966***, *[4] 31*, 84. See also, Buckles, R.E.; Miller, J.L.; Thurmaier, R.J. *J. Org. Chem.* ***1967***, *32*, 888; Heublein, G.; Lauterbach, H. *J. Prakt. Chem.* ***1969***, *311*, 91; Ruasse, M.; Dubois, J.E. *J. Am. Chem. Soc.* ***1975***, *97*, 1977. For the dependence of stereospecificity in this reaction on the solvent concentration, see Bellucci, G.; Bianchini, R.; Chiappe, C.; Marioni, F. *J. Org. Chem.* ***1990***, *55*, 4094.

nation of 3-hexyne, but both cis and trans products were obtained in bromination of phenylacetylene.[15] 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 $PhC^{\oplus}HCHBrCH_3$, 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.[16] We have previously seen cases (e.g., p. 461) where cations require more stabilization from outside sources as they become intrinsically less stable themselves.[17] 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 ArCH=CHCHAr' (Ar = *p*-nitrophenyl, 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.[18]

When the π-bond of an alkene attacks Cl^+,[19] I^+,[20] and RS^+,[21] the result is similar to that when the electrophile is Br^+; there is a spectrum of mechanisms between cyclic intermediates and open cations. As might be expected from our discussion in Chapter 10 (p. 446), iodonium ions compete with open carbocations more effectively than bromonium ions, while chloronium ions compete less effectively. There is kinetic and spectral evidence that at least in some cases, for example, in the addition of Br_2 or ICl, the electrophile forms a π complex with the alkene before a covalent bond is formed.[22]

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[15] Pincock, J.A.; Yates, K. *Can. J. Chem.* ***1970***, *48*, 3332.

[16] For other evidence for this concept, see Pincock, J.A.; Yates, K. *Can. J. Chem.* ***1970***, *48*, 2944; Heasley, V.L.; Chamberlain, P.H. *J. Org. Chem.* ***1970***, *35*, 539; Dubois, J.E.; Toullec, J.; Barbier, G. *Tetrahedron Lett.* ***1970***, 4485; Dalton, D.R.; Davis, R.M. *Tetrahedron Lett.* ***1972***, 1057; Wilkins, C.L.; Regulski, T.W. *J. Am. Chem. Soc.* ***1972***, *94*, 6016; Sisti, A.J.; Meyers, M. *J. Org. Chem.* ***1973***, *38*, 4431; McManus, S.P.; Peterson, P.E. *Tetrahedron Lett.* ***1975***, 2753; Abraham, R.J.; Monasterios, J.R. *J. Chem. Soc. Perkin Trans. 1*, ***1973***, 1446; Schmid, G.H.; Modro, A.; Yates, K. *J. Org. Chem.* ***1980***, *45*, 665; Ruasse, M.; Argile, A. *J. Org. Chem.* ***1983***, *48*, 202; Cadogan, J.I.G.; Cameron D.K.; Gosney, I.; Highcock, R.M.; Newlands, S.F. *J. Chem. Soc., Chem. Commun.* ***1985***, 1751. For a review, see Ruasse, M. *Acc. Chem. Res.* ***1990***, *23*, 87.

[17] In a few special cases, stereospecific syn addition of Br_2 has been found, probably caused by an ion pair mechanism as shown on p. 1002: Naae, D.G. *J. Org. Chem.* ***1980***, *45*, 1394.

[18] Kokil, P.B.; Fry, A. *Tetrahedron Lett.* ***1986***, *27*, 5051.

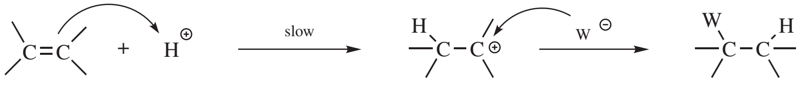
[19] Fahey, R.C. *Top. Stereochem.* ***1968***, *3*, 237, pp. 273–277.

[20] Hassner, A.; Boerwinkle, F.; Levy, A.B. *J. Am. Chem. Soc.* ***1970***, *92*, 4879.

[21] For reviews of thiiranium and/or thiirenium ions, see Capozzi, G.; Modena, G., in Bernardi, F.; Csizmadia, I.G.; Mangini, A. *Organic Sulfur Chemistry*, Elsevier, NY, ***1985***, pp. 246–298; Smit, W.A. *Sov. Sci. Rev. Sect. B* ***1985***, *7*, 155, see pp. 180–202; Dittmer, D.C.; Patwardhan, B.H., in Stirling, C.J.M. *The Chemistry of the Sulphonium Group*, pt. 1, Wiley, NY, ***1981***, pp. 387–412; Capozzi, G.; Lucchini, V.; Modena, G.; *Rev. Chem. Intermed.* ***1979***, *2*, 347; Schmid, G.H. *Top. Sulfur Chem.* ***1977***, *3*, 102; Mueller, W.H. *Angew. Chem. Int. Ed.* ***1969***, *8*, 482. The specific nature of the three-membered sulfur-containing ring is in dispute; see Smit, W.A.; Zefirov, N.S.; Bodrikov, I.V.; Krimer, M.Z. *Acc. Chem. Res.* ***1979***, *12*, 282; Bodrikov, I.V.; Borisov, A.V.; Chumakov, L.V.; Zefirov, N.S.; Smit, W.A. *Tetrahedron Lett.* ***1980***, *21*, 115; Schmid, G.H.; Garratt, D.G.; Dean, C.L. *Can. J. Chem.* ***1987***, *65*, 1172; Schmid, G.H.; Strukelj, M.; Dalipi, S. *Can. J. Chem.* ***1987***, *65*, 1945.

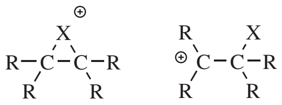
[22] See Nordlander, J.E.; Haky, J.E.; Landino, J.P. *J. Am. Chem. Soc.* ***1980***, *102*, 7487; Fukuzumi, S.; Kochi, J.K. *Int. J. Chem. Kinet.* ***1983***, *15*, 249; Schmid, G.H.; Gordon, J.W. *Can. J. Chem.* ***1984***, *62*, 2526; ***1986***, *64*, 2171; Bellucci, G.; Bianchini, R.; Chiappe, C.; Marioni, F.; Ambrosetti, R.; Brown, R.S.; Slebocka-Tilk, H. *J. Am. Chem. Soc.* ***1989***, *111*, 2640.

When the electrophile is a proton,[23] a cyclic intermediate is not possible, and the mechanism is the simple $A_H + A_N$ process shown before



This is an A-S_E2 mechanism (p. 525). There is a great deal of evidence[24] 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.[25]
2. The existence of open carbocation intermediates is supported by the contrast in the pattern of alkyl substituent effects[26] with that found in brominations, where cyclic intermediates are involved. In the latter case, substitution of alkyl groups on $H_2C{=}CH_2$ causes a cumulative rate acceleration



   until all four hydrogens have been replaced by alkyl groups, because each group helps to stabilize the positive charge.[27] 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.[28] This is evidence for open cations when a proton is the electrophile.[29]

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[23] For a review of the addition of HCl, see Sergeev, G.B.; Smirnov, V.V.; Rostovshchikova, T.N. *Russ. Chem. Rev.* ***1983***, *52*, 259.

[24] For other evidence, see Baliga, B.T.; Whalley, E. *Can. J. Chem.* ***1964***, *42*, 1019; ***1965***, *43*, 2453; Gold, V.; Kessick, M.A. *J. Chem. Soc.* ***1965***, 6718; Corriu, R.; Guenzet, J. *Tetrahedron* ***1970***, *26*, 671; Simandoux, J.; Torck, B.; Hellin, M.; Coussemant, F. *Bull. Soc. Chim. Fr.* ***1972***, 4402, 4410; Bernasconi, C.F.; Boyle, Jr., W.J. *J. Am. Chem. Soc.* ***1974***, *96*, 6070; Hampel, M.; Just, G.; Pisanenko, D.A.; Pritzkow, W. *J. Prakt. Chem.* ***1976***, *318*, 930; Allen, A.D.; Tidwell, T.T. *J. Am. Chem. Soc.* ***1983***, *104*, 3145.

[25] Loudon, G.M.; Noyce, D.S. *J. Am. Chem. Soc.* ***1969***, *91*, 1433; Schubert, W.M.; Keeffe, J.R. *J. Am. Chem. Soc.* ***1972***, *94*, 559; Chiang, Y.; Kresge, A.J. *J. Am. Chem. Soc.* ***1985***, *107*, 6363.

[26] Bartlett, P.D.; Sargent, G.D. *J. Am. Chem. Soc.* ***1965***, *87*, 1297; Schmid, G.H.; Garratt, D.G. *Can. J. Chem.* ***1973***, *51*, 2463.

[27] See, for example, Anantakrishnan, S.V.; Ingold, C.K. *J. Chem. Soc.* ***1935***, 1396; Swern, D. in Swern *Organic Peroxides*, Vol. 2, Wiley, NY, ***1971***, pp. 451–454; Nowlan, V.J.; Tidwell, T.T. *Acc. Chem. Res.* ***1977***, *10*, 252.

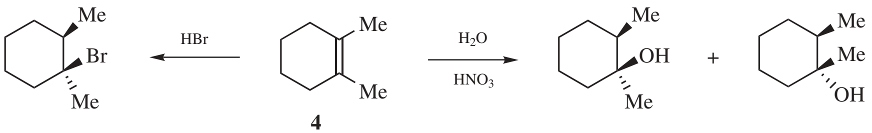
[28] Bartlett, P.D.; Sargent, G.D. *J. Am. Chem. Soc.* ***1965***, *87*, 1297; Riesz, P.; Taft, R.W.; Boyd, R.H. *J. Am. Chem. Soc.* ***1957***, *79*, 3724.

[29] A similar result (open cations) was obtained with carbocations Ar_2CH^+ as electrophiles: Mayr, H.; Pock, R. *Chem. Ber.* ***1986***, *119*, 2473.

3. Open carbocations are prone to rearrange (Chapter 18). Many rearrangements have been found to accompany additions of HX and H_2O.[30]

It may also be recalled that vinylic ethers react with proton donors in a similar manner (see **10-6**).

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,[31] while addition of water to **4** gave equal amounts of the cis and trans alcohols:[32]



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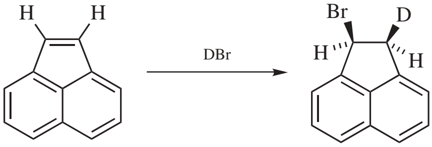
On the other hand, addition of DBr to acenaphthylene (**5**) and to indene and 1-phenylpropene gave predominant syn addition.[33]



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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.[34]

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[30] For example, see Whitmore, F.C.; Johnston, F. *J. Am. Chem. Soc.* ***1933***, *55*, 5020; Fahey, R.C.; McPherson, C.A. *J. Am. Chem. Soc.* ***1969***, *91*, 3865; Bundel, Yu.G.; Ryabstev, M.N.; Sorokin, V.I.; Reutov, O.A. *Bull. Acad. Sci. USSR Div. Chem. Sci.* ***1969***, 1311; Pocker, Y.; Stevens, K.D. *J. Am. Chem. Soc.* ***1969***, *91*, 4205; Staab, H.A.; Wittig, C.M.; Naab, P. *Chem. Ber.* ***1978***, *111*, 2965; Stammann, G.; Griesbaum, K. *Chem. Ber.* ***1980***, *113*, 598.

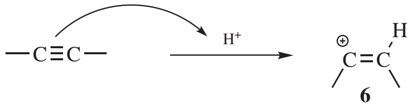
[31] Hammond, G.S.; Nevitt, T.D. *J. Am. Chem. Soc.* ***1954***, *76*, 4121; See also, Fahey, R.C.; Monahan, M.W. *J. Am. Chem. Soc.* ***1970***, *92*, 2816; Pasto, D.J.; Meyer, G.R.; Lepeska, B. *J. Am. Chem. Soc.* ***1974***, *96*, 1858.

[32] Collins, C.H.; Hammond, G.S. *J. Org. Chem.* ***1960***, *25*, 911.

[33] Dewar, M.J.S.; Fahey, R.C. *J. Am. Chem. Soc.* ***1963***, *85*, 2245, 2248. For a review of syn addition of HX, see Dewar, M.J.S. *Angew. Chem. Int. Ed.* ***1964***, *3*, 245; Heasley, G.E.; Bower, T.R.; Dougharty, K.W.; Easdon, J.C.; Heasley, V.L.; Arnold, S.; Carter, T.L.; Yaeger, D.B.; Gipe, B.T.; Shellhamer, D.F. *J. Org. Chem.* ***1980***, *45*, 5150.

[34] Becker, K.B.; Grob, C.A. *Synthesis* ***1973***, 789. See also, Marcuzzi, F.; Melloni, G.; Modena, G. *Tetrahedron Lett.* ***1974***, 413; Naab, P.; Staab, H.A. *Chem. Ber.* ***1978***, *111*, 2982.

Addition of HX to triple bonds has the same mechanism, although the intermediate in this case is a vinylic cation, **6**.[35]



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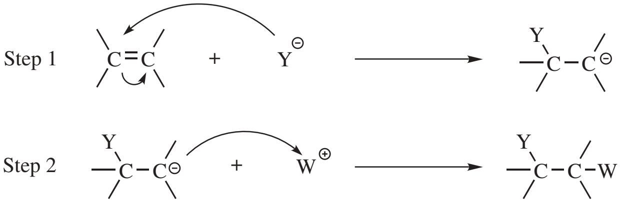
In all these cases (except for the Ad_E3 mechanism), we assumed that formation of the intermediate (**1**, **2**, or **3**) is the slow step and attack by the nucleophile on the intermediate is rapid, and this is probably true in most cases. However, some additions have been found in which the second step is rate determining.[36]

Nucleophilic Addition[37]

In the first step of nucleophilic addition, a nucleophile brings its pair of electrons to one carbon atom of the double or triple bond, creating a carbanion. The second step is combination of this carbanion with a positive species:



This mechanism is the same as the simple electrophilic one shown on p. 999 except that the charges are reversed (IUPAC $A_N + A_E$ or $A_N + A_H$). When the alkene contains a good leaving group (as defined for nucleophilic substitution), substitution is a side reaction (this is nucleophilic substitution at a vinylic substrate, see p. $$$).

In the special case of addition of HY to a substrate of the form —C=C—Z, where Z = CHO, COR[38] (including quinones[39]), COOR, $CONH_2$, CN, NO_2, SOR,

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[35] For reviews of electrophilic addition to alkynes, including much evidence, see Rappoport, Z. *React. Intermed. (Plenum)* ***1983***, *3*, 427, pp. 428–440; Stang, P.J.; Rappoport, Z.; Hanack, M.; Subramanian, L.R. *Vinyl Cations*; Academic Press, NY, ***1979***, pp. 24–151; Stang, P.J. *Prog. Phys. Org. Chem.* ***1973***, *10*, 205; Modena, G.; Tonellato, U. *Adv. Phys. Org. Chem.* ***1971***, *9*, 185, pp. 187–231; Richey, Jr., H.G.; Richey, J.M., in Olah, G.A.; Schleyer, P.V.R. *Carbonium Ions*, Vol. 2, Wiley, NY, ***1970***, pp. 906–922.

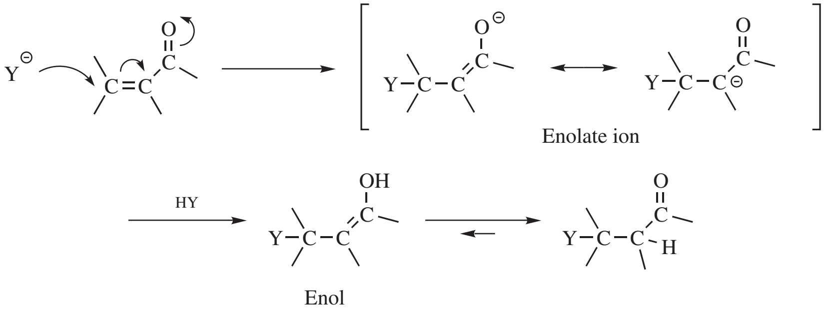
[36] See, for example, Rau, M.; Alcais, P.; Dubois, J.E. *Bull. Soc. Chim. Fr.* ***1972***, 3336; Bellucci, G.; Berti, G.; Ingrosso, G.; Mastrorilli, E. *Tetrahedron Lett.* ***1973***, 3911.

[37] For a review, see Patai, S.; Rappoport, Z., in Patai, S. *The Chemistry of Alkenes*, Vol. 1, Wiley, NY, ***1964***, pp. 469–584.

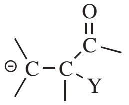
[38] For reviews of reactions of C=C–C=O compounds, see, in Patai, S.; Rappoport, Z. *The Chemistry of Enones*, pt. 1, Wiley, NY, ***1989***, the articles by Boyd, G.V. pp. 281–315; Duval, D.; Géribaldi, S. pp. 355–469.

[39] For reviews of addition reactions of quinones, see Kutyrev, A.A.; Moskva, V.V. *Russ. Chem. Rev.* ***1991***, *60*, 72; Finley, K.T., in Patai, S.; Rappoport, Z. *The Chemistry of the Quinonoid Compounds*, Vol. 2, pt. 1, Wiley, NY, ***1988***, pp. 537–717, see pp. 539–589; Finley, K.T., in Patai, S. *The Chemistry of the Quinonoid Compounds*, pt. 2, Wiley, NY, ***1974***, pp. 877–1144.

SO_2R,[40] and so on, addition nearly always follows a nucleophilic mechanism,[41] with Y^- bonding with the carbon *away* from the Z group, for example,



Protonation of the enolate ion is chiefly at the oxygen, which is more negative than the carbon, but this produces the enol, which tautomerizes (see p. 102). 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*. The Y^- ion almost never attacks at the 3 position, since the resulting carbanion would have no resonance stabilization:[42]



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

$$H_3C{=}CH{-}CN \quad + \quad H{-}Y \longrightarrow Y{-}CH_2{-}CH_2{-}CV$$

With any substrate, when Y is an ion of the type $Z{-}C^{\ominus}R_2$ (Z is as defined above; R may be alkyl, aryl, hydrogen, or another Z), the reaction is called the *Michael reaction* (see **15-24**). 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

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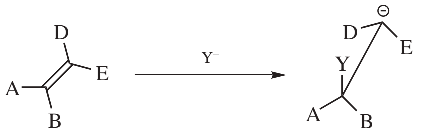
[40] For a review of vinylic sulfones, see Simpkins, N.S. *Tetrahedron* ***1990***, *46*, 6951. For a review of conjugate addition to cycloalkenyl sulfones, see Fuchs, P.L.; Braish, T.F. *Chem. Rev.* ***1986***, *86*, 903.

[41] For a review of the mechanism with these substrates, see Bernasconi, C.F. *Tetrahedron* ***1989***, *45*, 4017.

[42] For 1,8-addition to a trienone, see Barbot, F.; Kadib-Elban, A.; Miginiac, P. *J. Organomet. Chem.* ***1988***, *345*, 239.

1,2-1,4- or 1,6-addition.[43] Michael-type reactions are reversible, and compounds of the type YCH_2CH_2Z can often be decomposed to YH and $CH_2{=}CHZ$ by heating, either with or without alkali.

If the mechanism for nucleophilic addition is the simple carbanion mechanism outlined on p. 1007, the addition should be nonstereospecific, although it might well be stereoselective (see p. 194 for the distinction). For example, the (*E*) and (*Z*) forms of an alkene ABC=CDE would give **7** and **8**.



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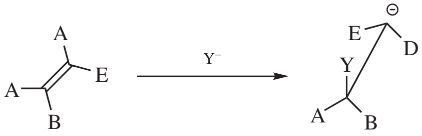

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If the carbanion has even a short lifetime, **7** and **8** will assume the most favorable conformation before the attack of W. This is of course the same for both, and when W attacks, the same product will result from each. This will be one of two possible diastereomers, so the reaction will be stereoselective; but since the cis and trans isomers do not give rise to different isomers, it will not be stereospecific. Unfortunately, this prediction has not been tested on open-chain alkenes. 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 cases[44] and anti addition in others.[45] 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.[46] For obvious reasons, additions to triple bonds cannot be stereospecific. As with electrophilic additions, nucleophilic additions to triple bonds are usually stereoselective and

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[43] However, attack at the 3 position has been reported when the 4 position contains one or two carbanion-stabilizing groups such as $SiMe_3$: Klumpp, G.W.; Mierop, A.J.C.; Vrielink, J.J.; Brugman, A.; Schakel, M. *J. Am. Chem. Soc.* ***1985***, *107*, 6740.

[44] For example, Truce, W.E.; Levy, A.J. *J. Org. Chem.* ***1963***, *28*, 679.

[45] For example, Truce, W.E.; Levy, A.J. *J. Am. Chem. Soc.* ***1961***, *83*, 4641; Zefirov, N.S.; Yur'ev, Yu.K.; Prikazchikova, L.P.; Bykhovskaya, M.Sh. *J. Gen. Chem. USSR* ***1963***, *33*, 2100.

[46] Mohrig, J.R.; Fu, S.S.; King, R.W.; Warnet, R.; Gustafson, G. *J. Am. Chem. Soc.* ***1990***, *112*, 3665.

anti,[47] although syn addition[48] and nonstereoselective addition[49] have also been reported.

Free-Radical Addition

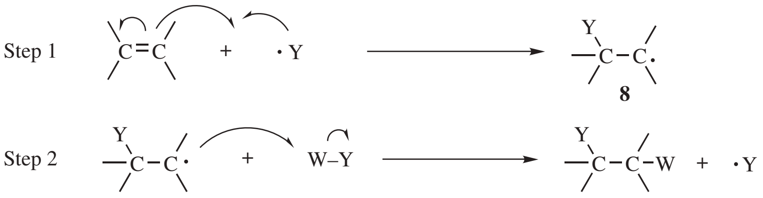
The mechanism of free-radical addition[50] follows the pattern discussed in Chapter 14 (pp. 934–939). The method of principal component analysis has been used to analyze polar and enthalpic effect in radical addition reactions.[51] A radical is generated by

$$\mathrm{YW} \xrightarrow[\text{dissociation}]{h\nu \text{ or spontaneous}} \mathrm{Y}\bullet + \mathrm{W}\bullet$$

or

$$\mathrm{R}\bullet \ \text{(from some other source)} + \mathrm{YW} \longrightarrow \mathrm{RW} + \mathrm{Y}\bullet$$

Propagation then occurs by



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[47] Truce, W.E.; Simms, J.A. *J. Am. Chem. Soc.* ***1956***, *78*, 2756; Shostakovskii, M.F.; Chekulaeva, I.A.; Kondrat'eva, L.V.; Lopatin, B.V. *Bull. Acad. Sci. USSR Div. Chem. Sci.* ***1962***, 2118; Théron F.; Vessière, R. *Bull. Soc. Chim. Fr.* ***1968***, 2994; Bowden, K.; Price, M.J. *J. Chem. Soc. B* ***1970***, 1466, 1472; Raunio, E.K.; Frey, T.G. *J. Org. Chem.* ***1971***, *36*, 345; Truce, W.E.; Tichenor, G.J.W. *J. Org. Chem.* ***1972***, *37*, 2391.

[48] Truce, W.E.; Goldhamer, D.M.; Kruse, R.B. *J. Am. Chem. Soc.* ***1959***, *81*, 4931; Dolfini, J.E. *J. Org. Chem.* ***1965***, *30*, 1298; Winterfeldt, E.; Preuss, H. *Chem. Ber.* ***1966***, *99*, 450; Hayakawa, K.; Kamikawaji, Y.; Wakita, A.; Kanematsu, K. *J. Org. Chem.* ***1984***, *49*, 1985.

[49] Gracheva, E.P.; Laba, V.I.; Kul'bovskaya, N.K.; Shostakovskii, M.F. *J. Gen. Chem. USSR* ***1963***, *33*, 2431; Truce, W.E.; Brady, D.G. *J. Org. Chem.* ***1966***, *31*, 3543; Prilezhaeva, E.N.; Vasil'ev, G.S.; Mikhaleshvili, I.L.; Bogdanov, V.S. *Bull. Acad. Sci. USSR Div. Chem. Sci.* ***1970***, 1820.

[50] For a monograph on this subject, see Huyser, E.S. *Free-Radical Chain Reactions*, Wiley, NY, ***1970***. Other books with much of interest in this field are Nonhebel, D.C.; Walton, J.C. *Free-Radical Chemistry*; Cambridge University Press: London, ***1974***; Pyor, W.A. *Free Radicals*; McGraw-Hill, NY, ***1965***. For reviews, see Giese, B. *Rev. Chem. Intermed.* ***1986***, *7*, 3; *Angew. Chem. Int. Ed.* ***1983***, *22*, 753; Amiel, Y., in Patai, S.; Rappoport, Z. *The Chemistry of Functional Groups, Supplement C* pt. 1, Wiley, NY, ***1983***, pp. 341–382; Abell, P.I., in Bamford, C.H.; Tipper, C.F.H. *Comprehensive Chemical Kinetics*, Vol. 18; Elsevier, NY, ***1976***, pp. 111–165; Abell, P.I. in Kochi, J.K. *Free Radicals*, Vol. 2, Wiley, NY, ***1973***, pp. 63–112; Minisci, F. *Acc. Chem. Res.* ***1975***, *8*, 165; Julia, M., in Viehe, H.G. *Acetylenes*; Marcel Dekker, NY, ***1969***, pp. 335–354; Elad, D. *Org. Photochem.* ***1969***, *2*, 168; Schönberg, A. *Preparative Organic Photochemistry*, Springer, NY, ***1968***, pp. 155–181; Cadogan, J.I.G.; Perkins, M.J., in Patai, S. *The Chemistry of Alkenes*, Vol. 1, Wiley, NY, ***1964***, pp. 585–632.

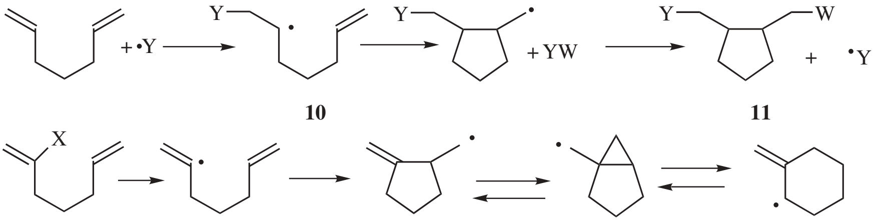
[51] Héberger, K.; Lopata, A. *J. Chem. Soc. Perkin Trans. 2*, ***1995***, 91.

Step 2 is an abstraction (an atom transfer), so W is nearly always univalent, either hydrogen or halogen (p. 943). Termination of the chain can occur in any of the ways discussed in Chapter 14. If **9** adds to another alkene molecule,

9

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 (**10**) can add intramolecularly to the other bond, leading to a cyclic product (**11**).[52] When the radical is generated from an precursor that gives vinyl radical **12**, however, cyclization leads to **13**, which is in equilibrium with cyclopropylcarbinyl radical (**14**) via a 5-exo-trig reaction.[53] A 6-endo-trig reaction leads to **15**, but unless there are perturbing substituent effects, however, cyclopropanation should be the major process.



10 **11**

12 **13** **14** **15**

Radicals of the type **10**, generated in other ways, also undergo these cyclizations. Both five- and six-membered rings can be formed in these reactions (see p. 1021).

The free-radical addition mechanism just outlined predicts that the addition should be non-stereospecific, at least if **9** has any, but an extremely short lifetime. However, the reactions may be stereoselective, for reasons similar to those discussed for nucleophilic addition on p. 1007. Not all free-radical additions have been found to be selective, but many are. For example, addition of HBr to 1-bromocyclohexene is regioselective in that it gave only *cis*-1,2-dibromocyclohexane

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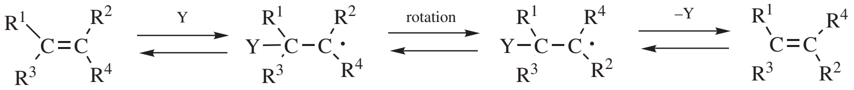
[52] For reviews of these and other free-radical cyclization reactions, see RajanBabu, T.V. *Acc. Chem. Res.* ***1991***, *24*, 139; Beckwith, A.L.J. *Rev. Chem. Intermed.* ***1986***, *7*, 143; Giese, B. *Radicals in Organic Synthesis: Formation of Carbon-Carbon Bonds*, Pergamon, Elmsford, NY, ***1986***, pp. 141–209; Surzur, J. *React. Intermed. (Plenum)* ***1982***, *2*, 121–295; Julia, M. *Acc. Chem. Res.* ***1972***, *4*, 386; *Pure Appl. Chem.* ***1974***, *40*, 553; ***1967***, *15*, 167–183; Nonhebel, D.C.; Walton, J.C. *Free-Radical Chemistry*, Cambridge University Press, London, ***1974***, pp. 533–544; Wilt, J.W., in Kochi, J.K. *Free Radicals*, Vol. 1, Wiley, NY, ***1973***, pp. 418–446. For a review of cyclizations in general, see Thebtaranonth, C.; Thebtaranonth, Y. *Tetrahedron* ***1990***, *46*, 1385.

[53] Denis, R.C.; Rancourt, J.; Ghiro, E.; Boutonnet, F.; Gravel, D. *Tetrahedron Lett.* ***1993***, *34*, 2091.

and none of the trans isomer (anti addition),[54] and propyne (at −78 to −60°C) gave only *cis*-1-bromopropene (anti addition), making it stereoselective.[55] However, stereospecificity has been found only in a few cases. Selectivity was observed in radical cyclization reactions of functionalized alkenes, which proceeded via a trans-ring closure.[56] The most important case is probably 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.[57] This stereospecificity disappeared at room temperature, where both alkenes gave the same mixture of products (~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. 942:

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 Br• to alkenes at 77 K. The ESR spectra of the resulting species were consistent with bridged structures.[58]

For many radicals, step 1 (C=C + Y• → •C–C–Y) is reversible. In such cases, free radicals can cause cis → trans isomerization of a double bond by the pathway[59]



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

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[54] Goering, H.L.; Abell, P.I.; Aycock, B.F. *J. Am. Chem. Soc.* ***1952***, *74*, 3588. See also, LeBel, N.A.; Czaja, R.F.; DeBoer, A. *J. Org. Chem.* ***1969***, *34*, 3112.

[55] Skell, P.S.; Allen, R.G. *J. Am. Chem. Soc.* ***1958***, *80*, 5997.

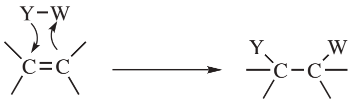
[56] Ogura, K.; Kayano, A.; Fujino, T.; Sumitani, N.; Fujita, M. *Tetrahedron Lett.* ***1993***, *34*, 8313.

[57] Goering, H.L.; Larsen, D.W. *J. Am. Chem. Soc.* ***1957***, *79*, 2653; ***1959***, *81*, 5937. Also see, Skell, P.S.; Freeman, P.K. *J. Org. Chem.* ***1964***, *29*, 2524.

[58] Abell, P.I.; Piette, L.H. *J. Am. Chem. Soc.* ***1962***, *84*, 916. See also, Leggett, T.L.; Kennerly, R.E.; Kohl, D.A. *J. Chem. Phys.* ***1974***, *60*, 3264.

[59] Benson, S.W.; Egger, K.W.; Golden, D.M. *J. Am. Chem. Soc.* ***1965***, *87*, 468; Golden, D.M.; Furuyama, S.; Benson, S.W. *Int. J. Chem. Kinet.* ***1969***, *1*, 57.

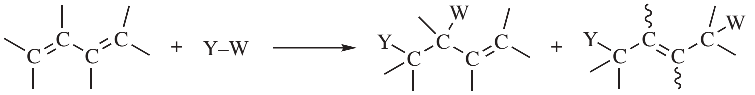
four-center mechanisms, which follow this pattern:



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 (**15-60**).

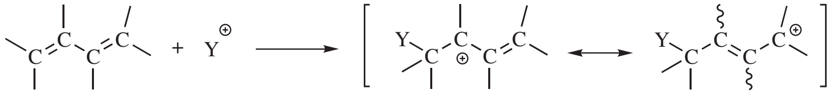
Addition to Conjugated Systems

When electrophilic addition is carried out on a compound with two double bonds in conjugation, a 1,2-addition product (**16**) is often obtained, but in most cases there is also a 1,4-addition product (**17**), often in larger yield:[60]

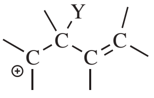


16 **17**

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 attack on 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 **18**. 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 S_N2'-type mechanism (see p. 470). Intermediates like **19** have been postulated, but ruled out for Br and Cl

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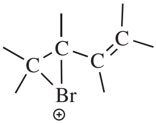
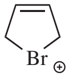
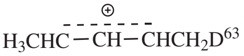
[60] For a review of electrophilic addition to conjugated dienes, see Khristov, V.Kh.; Angelov, Kh.M.; Petrov, A.A. *Russ. Chem. Rev.* ***1991***, *60*, 39.

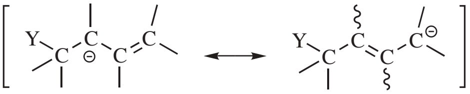
by the observation that chlorination

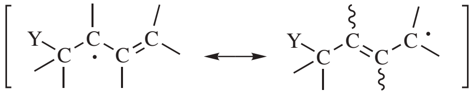

18


19

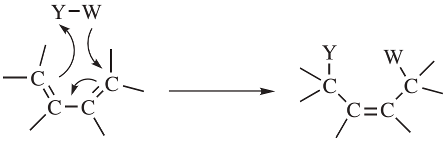
or bromination of butadiene gives trans 1,4-products.[61] If an ion like **19** were the intermediate, the 1,4-products would have to have the cis configuration.

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, **16** is converted to a mixture of **16** and **17** which is richer in **17**. That is, either isomer gives the same mixture of both, which contains more **17**. It was found that at low temperatures, butadiene and HCl gave only 20–25% 1,4-adduct, while at high temperatures, where attainment of equilibrium is more likely, the mixture contained 75% 1,4-product.[62] 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)  $\mathrm{H_3CHC\overset{-\,-}{-}\overset{\oplus}{C}H\overset{-\,-}{-}CHCH_2D}^{63}$ [63] Ion pairs were invoked to explain this result, since a free ion would be expected to be attacked by $\mathrm{Cl^-}$ 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 nucleophilic or free-radical attack,[64] 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:



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[61] Mislow, K. *J. Am. Chem. Soc.* ***1953***, *75*, 2512.

[62] Kharasch, M.S.; Kritchevsky, J.; Mayo, F.R. *J. Org. Chem.* ***1938***, *2*, 489.

[63] Nordlander, J.E.; Owuor, P.O.; Haky, J.E. *J. Am. Chem. Soc.* ***1979***, *101*, 1288.

[64] For a review of free-radical addition to conjugated dienes, see Afanas'ev, I.B.; Samokhvalov, G.I. *Russ. Chem. Rev.* ***1969***, *38*, 318.

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

Radical addition to conjugated systems is an important part of chain propagation reactions. The rate constants for addition of cyclohexyl radical to conjugated amides have been measured, and shown to be faster than addition to styrene.[65] In additions to $RCH{=}C(CN)_2$ systems, where the R group has a chiral center, the Felkin–Ahn rule (p. 169) is followed and the reaction proceeds with high selectivity.[66] Addition of some radicals, such as $(Me_3Si)_3Si\bullet$, is reversible and this can lead to poor selectivity or isomerization.[67]

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.[68] As a further illustration it may be mentioned that the reactivity toward electrophilic addition of a group of alkenes increased in the order $CCl_3CH{=}CH_2 < Cl_2CHCH{=}CH_2 < ClCH_2CH{=}CH_2 < CH_3CH_2{=}CH_2$.[69] 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 $F_2C{=}CF_2$[70] and $(NC)_2C{=}C(CN)_2$.[71] The effect of substituents is so great that it is possible to make the statement that *simple alkenes do not react by the nucleophilic mechanism, and polyhalo or polycyano alkenes do not generally react by the electrophilic mechanism.*[72]

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[65] Curran, D.P.; Qi, H.; Porter, N.A.; Su, Q.; Wu, W.-X. *Tetrahedron Lett.* ***1993***, *34*, 4489.

[66] Giese, B.; Damm, W.; Roth, M.; Zehnder, M. *Synlett* ***1992***, 441.

[67] Ferreri, C.; Ballestri, M.; Chatgilialoglu, C. *Tetrahedron Lett.* ***1993***, *34*, 5147.

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

[69] Shelton, J.R.; Lee, L. *J. Org. Chem.* ***1960***, *25*, 428.

[70] For a review of additions to $F_2C{=}CF_2$ and other fluoroalkenes, see Chambers, R.D.; Mobbs, R.H. *Adv. Fluorine Chem.* ***1965***, *4*, 51.

[71] For reviews of additions to tetracyanoethylene, see Fatiadi, A.J. *Synthesis* ***1987***, 249, 749; Dhar, D.N. *Chem. Rev.* ***1967***, *67*, 611.

[72] Such reactions can take place under severe conditions. For example, electrophilic addition could be accomplished with $F_2C{=}CHF$ in super acid solutions [Olah, G.A.; Mo, Y.K. *J. Org. Chem.* ***1972***, *37*, 1028] although $F_2C{=}CF_2$ did not react under these conditions. For reviews of electrophilic additions to fluoroalkenes, see Belen'kii, G.G.; German, L.S. *Sov. Sci. Rev. Sect. B* ***1984***, *5*, 183; Dyatkin, B.L.; Mochalina, E.P.; Knunyants, I.L. *Russ. Chem. Rev.* ***1966***, *35*, 417; *Fluorine Chem. Rev.* ***1969***, *3*, 45; Chambers, R.D.; Mobbs, R.H. *Adv. Fluorine Chem.* ***1965***, *4*, 51, pp. 77–81.

TABLE 15.1. Relative Reactivity of Some Alkenes Toward Bromine in Acetic Acid at 24°C[68]

Alkene	Relative Rate
$PhCH{=}CH_2$	Very fast
$PhCH{=}CHPh$	18
$CH_2{=}CHCH_2Cl$	1.6
$CH_2{=}CHCH_2Br$	1.0
$PhCH{=}CHBr$	0.11
$CH_2{=}CHBr$	0.0011

TABLE 15.2. Relative Reactivity of Some Alkenes Toward Bromine in Methanol[68]

Alkene	Relative Rate
$CH_2{=}CH_2$	3.0×10^1
$CH_3CH_2CH{=}CH_2$	$2/9 \times 10^3$
cis-$CH_3CH_2CH{=}CHCH_3$	1.3×10^5
$(CH_3)_2C{=}C(CH_3)_2$	2.8×10^7

There are some reagents that attack only as nucleophiles, for example, ammonia, and these add only to substrates susceptible to nucleophilic attack. Other reagents attack only as electrophiles, and, for example, $F_2C{=}CF_2$ does not react with these. In still other cases, the same reagent reacts with a simple alkene by the electrophilic mechanism and with a polyhalo alkene by a nucleophilic mechanism. For example, Cl_2 and HF are normally electrophilic reagents, but it has been shown that Cl_2 adds to $(N{\equiv}C)_2C{=}CHC{\equiv}N$ with initial attack by Cl^-[73] and that HF adds to $F_2C{=}CClF$ with initial attack by F^-.[74] Compounds that have a double bond conjugated with a Z group (as defined on p. 1007) nearly always react by a nucleophilic mechanism.[75] These are actually 1,4-additions, as discussed on p. 1008. A number of studies have been made of the relative activating abilities of various Z groups.[76] On the basis of these studies, the following order of decreasing activating ability has been suggested: Z = NO_2, COAr, CHO, COR, SO_2Ar, CN, COOR, SOAr, $CONH_2$, CONHR.[77]

It seems obvious that electron-withdrawing groups enhance nucleophilic addition and inhibit electrophilic addition because they lower the electron density of

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[73] Dickinson, C.L., Wiley, D.W.; McKusick, B.C. *J. Am. Chem. Soc.* ***1960***, *82*, 6132. For another example, see Atkinson, R.C.; de la Mare, P.B.D.; Larsen, D.S. *J. Chem. Soc. Perkin Trans. 2*, ***1983***, 271.

[74] Miller, Jr., W.T.; Fried, J.H.; Goldwhite, H. *J. Am. Chem. Soc.* ***1960***, *82*, 3091.

[75] For a review of electrophilic reactions of such compounds, see Müllen, K.; Wolf, P., in Patai, S.; Rappoport, Z. *The Chemistry of Enones*, pt. 1, Wiley, NY, ***1989***, pp. 513–558.

[76] See, for example, Friedman, M.; Wall, J.S. *J. Org. Chem.* ***1966***, *31*, 2888; Ring, R.N.; Tesoro, G.C.; Moore, D.R. *J. Org. Chem.* ***1967***, *32*, 1091.

[77] Shenhav, H.; Rappoport, Z.; Patai, S. *J. Chem. Soc. B* ***1970***, 469.

the double bond. Addition of electrophilic radicals to electron rich alkenes has been reported,[78] so the reaction is possible in some cases. This is probably true, and yet similar reasoning does not always apply to a comparison between double and triple bonds.[79] 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 attack at an electrophilic site and *more* subject to nucleophilic attack than double bonds.[80] 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 to the double bond.[81] 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, **15-3**; addition of hydrogen halides, **15-2**) takes place at about the same rates for alkenes as for corresponding alkynes.[82] Furthermore, the presence of electron-withdrawing groups lowers the alkene/alkyne rate ratio. For example, while styrene $PhCH{=}CH_2$ was brominated 3000 times faster than $PhC{\equiv}CH$, the addition of a second phenyl group ($PhCH{=}CHPh$ versus $PhC{\equiv}CPh$) lowered the rate ratio to about 250.[83] In the case of *trans*-$MeOOCCH{=}CHCOOMe$ versus $MeOOCC{\equiv}CCOOMe$, the triple bond compound was actually brominated faster.[84]

As mentioned, it is true that in general triple bonds are more susceptible to nucleophilic and less to attack on an electrophilic site 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.[85] 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 (e.g., cyclooctyne) has a lower energy than the π^* orbital of alkenes, and it has been suggested[86] 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 (**20**) are more strained than the corresponding **21** and furthermore are antiaromatic systems

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[78] Curran, D.P.; Ko, S.-B. *Tetrahedron Lett.* ***1998***, *39*, 6629.

[79] For reviews of ionic additions to triple bonds, see, in Patai, S. *The Chemistry of the Carbon–Carbon Triple Bond*, Wiley, NY, ***1978***, the articles by Schmid, G.H. pt. 1, pp. 275–341, and by Dickstein, J.I.; Miller, S.I. pt. 2, pp. 813–955; Miller, S.I.; Tanaka, R. *Sel. Org. Transform.* ***1970***, *1*, 143; Winterfeldt, E., in Viehe, H.G. *Acetylenes*, Marcel Dekker, NY, ***1969***, pp. 267–334. For comparisons of double and triple bond reactivity, see Melloni, G.; Modena, G.; Tonellato, U. *Acc. Chem. Res.* ***1981***, *14*, 227; Allen, A.D.; Chiang, Y.; Kresge, A.J.; Tidwell, T.T. *J. Org. Chem.* ***1982***, *47*, 775.

[80] For discussions, see Daniels, R.; Bauer, L. *J. Chem. Educ.* ***1958***, *35*, 444; DeYoung, S.; Ehrlich, S.; Berliner, E. *J. Am. Chem. Soc.* ***1977***, *99*, 290; Strozier, R.W.; Caramella, P.; Houk, K.N. *J. Am. Chem. Soc.* ***1979***, *101*, 1340.

[81] Petrov, A.A. *Russ. Chem. Rev.* ***1960***, *29*, 489.

[82] Melloni, G.; Modena, G.; Tonellato, U. *Acc. Chem. Res.* ***1981***, *14*, 227, p. 228.

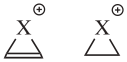
[83] Robertson, P.W.; Dasent, W.E.; Milburn, R.M.; Oliver, W.H. *J. Chem. Soc.* ***1950***, 1628.

[84] Wolf, S.A.; Ganguly, S.; Berliner, E. *J. Am. Chem. Soc.* ***1985***, *50*, 1053.

[85] Walsh, A.D. *Q. Rev. Chem. Soc.* ***1948***, *2*, 73.

[86] Ng, L.; Jordan, K.D.; Krebs, A.; Rüger, W. *J. Am. Chem. Soc.* ***1982***, *104*, 7414.

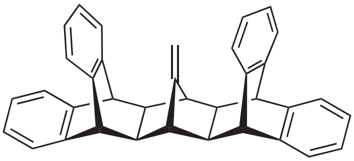
(see p. 73), which **21** are not. This may be a reason why electrophilic addition by such electrophiles as Br, I, SR, and so on, is slower for triple than for double bonds.[87] As might be expected, triple bonds connected to a Z group (C≡C–Z) undergo nucleophilic addition especially well.[88]



20 **21**

Although alkyl groups in general increase the rates of electrophilic addition, we have already mentioned (p. 1005) 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.[89] Where the second step is rate determining [e.g., oxymercuration (**15-3**), hydroboration (**15-17**)], steric effects are important.[88]

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 (see p. 938) 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.[90] However, nucleophilic radicals react with alkynes more slowly than with the corresponding alkenes,[91] which is contrary to what might have been expected.[92]



22

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[87] Nevertheless, bridged ions **15** have been implicated in some additions to triple bonds. See, for example, Pincock, J.A.; Yates, K. *Can. J. Chem.* ***1970***, *48*, 3332; Mauger, E.; Berliner, E. *J. Am. Chem. Soc.* ***1972***, *94*, 194; Bassi, P.; Tonellato, U. *J. Chem. Soc. Perkin Trans. 1*, ***1973***, 669; Schmid, G.H.; Modro, A.; Lenz, F.; Garratt, D.G.; Yates, K. *J. Org. Chem.* ***1976***, *41*, 2331.

[88] For a review of additions to these substrates, see Winterfeldt, E. *Angew. Chem. Int. Ed.* ***1967***, *6*, 423; *Newer Methods Prep. Org. Chem.* ***1971***, *6*, 243.

[89] Nelson, D.J.; Cooper, P.J.; Soundararajan, R. *J. Am. Chem. Soc.* ***1989***, *111*, 1414; Nelson, D.J.; Soundararajan, R. *Tetrahedron Lett.* ***1988***, *29*, 6207.

[90] For reviews of reactivity in free-radical additions, see Tedder, J.M. *Angew. Chem. Int. Ed.* ***1982***, *21*, 401; Tedder, J.M.; Walton, J.C. *Tetrahedron* ***1980***, *36*, 701.

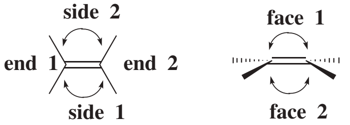
[91] Giese, B.; Lachhein, S. *Angew. Chem. Int. Ed.* ***1982***, *21*, 768.

[92] For a discussion of reactivity and orientation of polar radicals, see Volovik, S.V.; Dyadyusha, G.G.; Staninets, V.I. *J. Org. Chem. USSR* ***1986***, *22*, 1224.

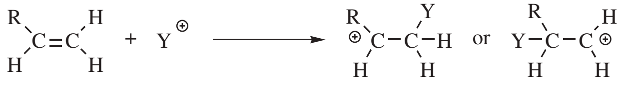
Steric influences are important in some cases. In catalytic hydrogenation, where the substrate must be adsorbed onto the catalyst surface, the reaction becomes more difficult with increasing substitution. The hydrocarbon **22**, in which the double bond is entombed between the benzene rings, does not react with Br_2, H_2SO_4, O_3, BH_3, **:**CBr_2, or other reagents that react with most double bonds.[93] A similarly inactive compound is tetra-*tert*-butylallene ($(t\text{-Bu})_2C{=}C{=}C(t\text{-Bu})_2$), which is inert to Br_2, Cl_2, O_3, and catalytic hydrogenation.[94]

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? The terms side and face are arbitrary, and a simple guide is shown to help understand the arguments used here. For electrophilic attack, the answer is given by

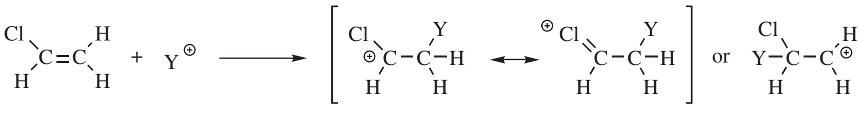


Markovnikov's rule: The positive portion of the reagent goes to the side of the double or triple bond that has more hydrogens.[95] A number of explanations have been suggested for this regioselectivity, but the most probable is that Y^+ adds to that side that will give the more stable carbocation. This premise has been examined by core electron spectroscopy and by theoretical analysis.[96] Thus, when an alkyl group is present, secondary carbocations are more stable than primary:



More stable

We may ask: Why does Y^+ add to give the more stable carbocation? As in the similar case of electrophilic aromatic substitution (p. 658), 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 the carbocation by resonance:



More stable

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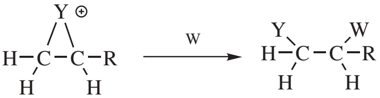
[93] Butler, D.N.; Gupt, I.; Ng, W.W.; Nyburg, S.C. *J. Chem. Soc., Chem. Commun.* ***1980***, 596.

[94] Bolze, R.; Eierdanz, H.; Schlüter, K.; Massa, W.; Grahn, W.; Berndt, A. *Angew. Chem. Int. Ed.* ***1982***, *21*, 924.

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

[96] Sæthre, L.J.; Thomas, T.D.; Svensson, S. *J. Chem. Soc. Perkin Trans. 2*, ***1997***, 749.

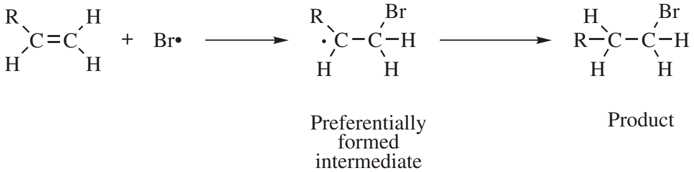
Markovnikov's rule is also usually followed where bromonium ions or other three-membered rings are intermediates.[97] This means that in these cases attack by W must resemble the S_N1 rather than the S_N2 mechanism (see p. 517), although the overall stereospecific anti addition in these reactions means that the nucleophilic substitution step is taking place with inversion of configuration.



Alkenes containing strong electron-withdrawing groups may violate Markovnikov's rule. For example, attack at the Markovnikov position of Me_3N^+—CH=CH_2 would give an ion with positive charges on adjacent atoms. The compound $CF_3CH{=}CH_2$ has been reported to give electrophilic addition with acids in an anti-Markovnikov direction, but it has been shown[98] 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. Molecular electrostatic potentials for the π-region of substituted alkenes were studied, with electron donating and withdrawing substituents (based on the increase or decrease in the negative character of V_{min}-most negative-valued point), and plots of V_{min} shows a good linear correlation with the Hammett σρ constants, suggesting similar substituent electronic effects for substituted ethylenes and substituted benzenes.[99]

For nucleophilic addition the direction of attack has been studied very little, except for Michael-type addition, with compounds of the type C=C–Z. Here the negative part of the reagent almost always attacks regioselectively at the carbon that does not carry the Z (see p. 1008).

In free-radical addition[100] the main effect seems to be steric.[101] All substrates $CH_2{=}CHX$ preferentially react at the CH_2, regardless of the identity of X or of the radical. With a reagent such as HBr, this means that the addition is anti-Markovnikov:



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

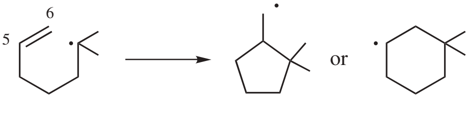
[98] Myhre, P.C.; Andrews, G.D. *J. Am. Chem. Soc.* ***1970***, *92*, 7595, 7596. See also, Newton, T.A. *J. Chem. Educ.* ***1987***, *64*, 531.

[99] Suresh, C.H.; Koga, N.; Gadre, S.R. *J. Org. Chem.* ***2001***, *66*, 6883.

[100] For reviews of orientation in free-radical additions, see Tedder, J.M.; Walton, J.C. *Tetrahedron* ***1980***, *36*, 701; *Adv. Phys. Org. Chem.* ***1978***, *16*, 51; *Acc. Chem. Res.* ***1976***, *9*, 183. See also, Giese, B. *Rev. Chem. Intermed.* ***1986***, *7*, 3; Tedder, J.M. *J. Chem. Educ.* ***1984***, *61*, 237.

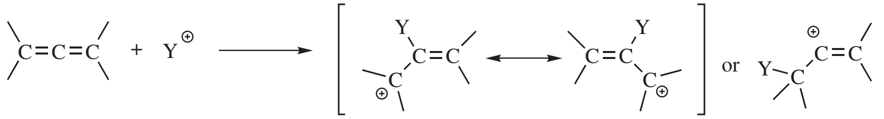
[101] See, however, Riemenschneider, K.; Bartels, H.M.; Dornow, R.; Drechsel-Grau, E.; Eichel, W.; Luthe, H.; Matter, Y.M.; Michaelis, W.; Boldt, P. *J. Org. Chem.* ***1987***, *52*, 205; Gleicher, G.J.; Mahiou, B.; Aretakis, A.J. *J. Org. Chem.* ***1989***, *54*, 308.

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. 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. 272), but this factor is apparently less important than the steric factor. Internal alkenes with no groups present to stabilize the radical usually give an ~1:1 mixture via 5-exo–trig and 6-endo–trig (see Badwin's rules p. $$$) reactions.



In *intramolecular* additions of radicals containing a 5,6 double bond,[52] both five- and six-membered rings can be formed, but in most cases[102] 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.[103] 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)[104] (see the Baldwin rules, p. 305). However, when a radical that is unsaturated in the 5,6 position contains an alkyl group in the 5 position, formation of the six-membered ring is generally favored.[105]

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 ($CH_2{=}CMeCH{=}CH_2$), treated with HCl gives only $Me_2CClCH{=}CH_2$ and $Me_2C{=}CHCH_2Cl$, with none of the product arising from attack at the other end. $PhCH{=}CHCH{=}CH_2$ gives only $PhCH{=}CHCHClCH_3$ 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.



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[102] For an exception, see Wilt, J.W. *Tetrahedron* ***1985***, *41*, 3979.

[103] For discussions, see Beckwith, A.L.J. *Tetrahedron* ***1981***, *37*, 3073; Verhoeven, J.W. *Revl. Trav. Chim. Pays-Bas* ***1980***, *99*, 143. For molecular mechanics force-field approaches to this problem, see Beckwith, A.L.J.; Schiesser, C.H. *Tetrahedron* ***1985***, *41*, 3925; Spellmeyer, D.C.; Houk, K.N. *J. Org. Chem.* ***1987***, *52*, 959.

[104] See Beckwith, A.L.J.; Easton, C.J.; Serelis, A.K. *J. Chem. Soc., Chem. Commun.* ***1980***, 482.

[105] See Chuang, C.; Gallucci, J.C.; Hart, D.J.; Hoffman, C. *J. Org. Chem.* ***1988***, *53*, 3218, and references cited therein.

When allenes attack electrophilic reagents,[106] Markovnikov's rule would predict that the formation of the new bond should be at the end of the system, since there are no hydrogens in the middle. Reaction at the center gives a carbocation stabilized by resonance, but not immediately. 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.[107] 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. 148). Probably because of this, attack on the unsubstituted $CH_2{=}C{=}CH_2$ is most often at the end carbon, to give a vinylic cation, although 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 $RCH{=}C{=}CH_2$ are still attacked most often at the end, but with RCH=C=CHR' center attack is more prevalent. Tetramethylallene is also attacked predominantly at the center carbon.[108] Free radicals[109] attack allenes most often at the end,[110] although attack at the middle has also been reported.[111] 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.[112]

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 steric orientation must be considered. In syn addition to an unsymmetrical cyclic alkene,

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[106] For a monograph on addition to allenes, see Schuster, H.F.; Coppola, G.M. *Allenes in Organic Synthesis* Wiley, NY, ***1984***. For reviews, see Pasto, D.J. *Tetrahedron* **1984**, *40*, 2805; Smadja, W. *Chem. Rev.* ***1983***, *83*, 263; in Landor, S.R. *The Chemistry of Allenes*, Vol. 2; Academic Press, NY, ***1982***, articles by Landor, S.R., Jacobs, T.L.; Hopf, H. pp. 351–577; Stang, P.J.; Rappoport, Z.; Hanack, M.; Subramanian, L.R. *Vinyl Cations*, Academic Press, NY, ***1979***, pp. 152–167; Blake, P., in Patai, S. *The Chemistry of Ketenes, Allenes and Related Compounds*, pt. 1, Wiley, NY, ***1980***; pp. 342–357; Modena, G.; Tonellato, U. *Adv. Phys. Org. Chem.* ***1971***, *9*, 185, pp. 215–231; Richey, Jr., H.G.; Richey, J.M., in Olah, G.A.; Schleyer, P.V.R. *Carbonium Ions*, Vol. 2, Wiley, NY, ***1970***, pp. 917–922; Caserio, M.C. *Sel. Org. Transform.*, ***1970***, *1*, 239; Taylor, D.R. *Chem. Rev.* ***1967***, *67*, 317, 338–346; Mavrov, M.V.; Kucherov, V.F. *Russ. Chem. Rev.* ***1967***, *36*, 233; Griesbaum, K. *Angew. Chem. Int. Ed.* ***1966***, *5*, 933.

[107] For evidence that this is so, see Okuyama, T.; Izawa, K.; Fueno, T. *J. Am. Chem. Soc.* ***1973***, *95*, 6749.

[108] For example, see Bianchini, J.; Guillemonat, A. *Bull. Soc. Chim. Fr.* ***1968***, 2120; Pittman Jr., C.U. *Chem. Commun.* ***1969***, 122; Poutsma, M.L.; Ibarbia, P.A. *J. Am. Chem. Soc.* ***1971***, *93*, 440.

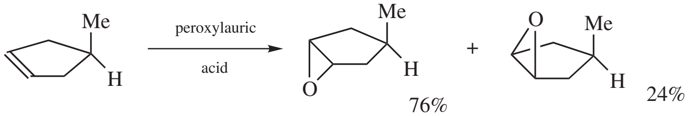
[109] For a review, see Jacobs, T.L., in Landor, S.R. *The Chemistry of Allenes*, Vol. 2, Academic Press, NY, ***1982***, pp. 399–415.

[110] Griesbaum, K.; Oswald, A.A.; Quiram, E.R.; Naegele, W. *J. Org. Chem.* ***1963***, *28*, 1952.

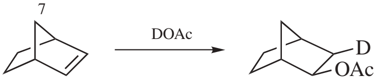
[111] See, for example, Pasto, D.J.; L'Hermine, G. *J. Org. Chem.* ***1990***, *55*, 685.

[112] For example, see Byrd, L.R.; Caserio, M.C. *J. Org. Chem.* ***1972***, *37*, 3881; Pasto, D.J.; Warren, S.E.; Morrison, M.A. *J. Org. Chem.* ***1981***, *46*, 2837. See, however, Bartels, H.M.; Boldt, P. *Liebigs Ann. Chem.* ***1981***, 40.

the two groups can come in from the more- or from the less-hindered face of the double bond. The rule is that syn addition is usually, although 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.[113]

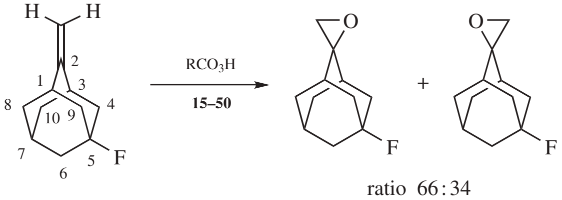


In anti addition to a cyclic substrate, the initial attack on the electrophile is also from the less-hindered face. However, many (although not all) electrophilic additions to norbornene and similar strained bicycloalkenes are syn additions.[114] In these cases reaction is always from the exo side, as in formation of **23**,[115]



23

unless the exo side is blocked by substituents in the 7 position, in which case endo attack may predominate; for example, 7,7-dimethylnorbornene undergoes syn–endo epoxidation (**15-50**) and hydroboration[116] (**15-16**). However, addition of DCl and F_3CCOOD to, and oxymercuration (**15-2**) of, 7,7-dimethylnorbornene proceeds syn–exo in spite of the methyl groups in the 7 position.[117] Similarly, free-radical additions to norbornene and similar molecules are often syn–exo, although anti additions and endo attacks are also known.[118]



24 **25** **26**

Electronic effects can also play a part in determining which face reacts preferentially with the electrophilic species. In the adamantane derivative **24**, steric

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[113] Henbest, H.B.; McCullough, J.J. *Proc. Chem. Soc.* ***1962***, 74.

[114] For a discussion, see Traylor, T.G. *Acc. Chem. Res.* ***1969***, *2*, 152.

[115] Cristol, S.J.; Morrill, T.C.; Sanchez, R.A. *J. Org. Chem.* ***1966***, *31*, 2719; Brown, H.C.; Kawakami, J.H.; Liu, K. *J. Am. Chem. Soc.* ***1970***, *92*, 5536; Alvernhe, G.; Anker, D.; Laurent, A.; Haufe, G.; Beguin, C. *Tetrahedron* ***1988***, *44*, 3551; Koga, N.; Ozawa, T.; Morokuma, K. *J. Phys. Org. Chem.* ***1990***, *3*, 519.

[116] Brown, H.C.; Kawakami, J.H.; Liu, K. *J. Am. Chem. Soc.* ***1973***, *95*, 2209.

[117] Brown, H.C.; Liu, K. *J. Am. Chem. Soc.* ***1975***, *97*, 600, 2469; Tidwell, T.T.; Traylor, T.G. *J. Org. Chem.* ***1968***, *33*, 2614.

[118] For a review of free-radical addition to these systems, see Azovskaya, V.A.; Prilezhaeva, E.N. *Russ. Chem. Rev.* ***1972***, *41*, 516.

effects are about the same for each face of the double bond. Yet epoxidation, dibromocarbene reactions (**15-64**), and hydroboration (**15-16**) all predominantly take place from the face that is syn to the electron-withdrawing fluorine.[119] In the case shown, about twice as much **25** was formed, compared to **26**. Similar results have been obtained on other substrates:[120] 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 attributed[121] 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 **24**) and the filled σ orbitals of the C_α—C_β bonds on the opposite side. This is called the *Cieplak effect*. The $LiAlH_4$ reduction of 2-axial methyl or methoxy cyclohexanones supports Cieplak's proposal.[122] In addition reactions of methanol to norbornanones, however, little evidence was found to support the Cieplak effect.[123] 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.

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.[124] 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.[125] 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 reaction with the radical is also usually from the axial direction,[126] resulting in a diaxial initial product if the overall addition is anti. The direction from which unsymmetrical radicals react has also been studied.[127] For example, when the radical **27** adds

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[119] Srivastava, S.; le Noble, W.J. *J. Am. Chem. Soc.* ***1987***, *109*, 5874. See also, Bodepudi, V.R.; le Noble, W.J. *J. Org. Chem.* ***1991***, *56*, 2001.

[120] Cieplak, A.S.; Tait, B.D.; Johnson, C.R. *J. Am. Chem. Soc.* ***1989***, *111*, 8447.

[121] Cieplak, A.S. *J. Am. Chem. Soc.* ***1981***, *103*, 4540. See also, Jorgensen, W.L. *Chemtracts: Org. Chem.* ***1988***, *1*, 71.

[122] Senda, Y.; Nakano, S.; Kunii, H.; Itoh, H. *J. Chem. Soc. Perkin Trans. 2*, ***1993***, 1009.

[123] Coxon, J.M.; McDonald, D.Q. *Tetrahedron* ***1992***, *48*, 3353.

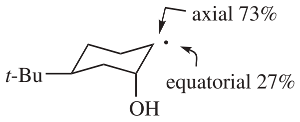
[124] Barton, D.H.R., in *Theoretical Organic Chemistry The Kekulé Symposium*, Butterworth: London, ***1959***, pp. 127–143; Goering, H.L.; Sims, L.L. *J. Am. Chem. Soc.* ***1955***, *77*, 3465; Shoppee, C.W.; Akhtar, M.I.; Lack, R.E. *J. Chem. Soc.* ***1964***, 877; Readio, P.D.; Skell, P.S. *J. Org. Chem.* ***1966***, *31*, 753, 759.

[125] For example, see Anselmi, C.; Berti, G.; Catelani, G.; Lecce, L.; Monti, L. *Tetrahedron* ***1977***, *33*, 2771.

[126] Huyser, E.S.; Benson, H.; Sinnige, H.J. *J. Org. Chem.* ***1967***, *32*, 622; LeBel, N.A.; Czaja, R.F.; DeBoer, A. *J. Org. Chem.* ***1969***, *34*, 3112

[127] For a review, see Giese, B. *Angew. Chem. Int. Ed.* ***1989***, *28*, 969.

to a double bond it preferentially does so anti to the OH group, leading to a diaxial trans product.[125]

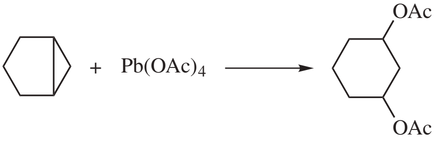


27

Addition to Cyclopropane Rings[128]

We have previously seen (p. 218) that in some respects, cyclopropane rings resemble double bonds.[129] 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, as in the two examples shown where reaction numbers relating the reaction to alkene chemistry are in parentheses.

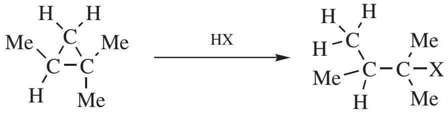
(**15-2**)



(**15-47**) Ref. [130]

Other examples are discussed at **15-3**, **15-15**, and **15-63**.

Additions to cyclopropanes can take place by any of the four mechanisms already discussed in this chapter, but the most important type involves attack on an electrophile.[131] For substituted cyclopropanes, these reactions usually follow Markovnikov's rule, although 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.[132] The rule predicts that the electrophile (in this case H^+) goes to the carbon



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[128] For a review, see Charton, M., in Zabicky, J. *The Chemistry of Alkenes*, Vol 2., Wiley, NY, ***1970***, pp. 569–592. For reviews of the use of cyclopropanes in organic synthesis see Reissig, H. *Top. Curr. Chem.* ***1988***, *144*, 73; Wong, H.N.C.; Hon, M.; Tse, C.; Yip, Y.; Tanko, J.; Hudlicky, T. *Chem. Rev.* ***1989***, *89*, 165.

[129] The analogies are by no means complete: see Gordon, A.J. *J. Chem. Educ.* ***1967***, *44*, 461.

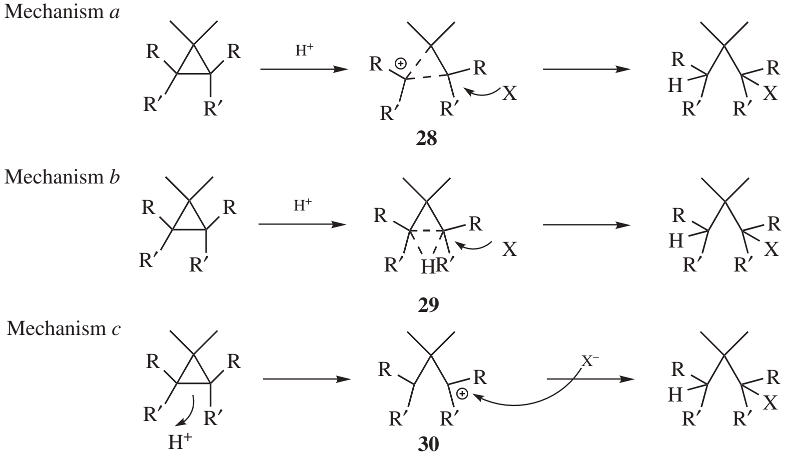
[130] Moon, S. *J. Org. Chem.* ***1964***, *39*, 3456.

[131] For a review, see DePuy, C.H. *Top. Curr. Chem.* ***1973***, *40*, 73–101. For a list of references to pertinent mechanistic studies, see Wiberg, K.B.; Kass, S.R. *J. Am. Chem. Soc.* ***1985***, *107*, 988.

[132] Kramer, G.M. *J. Am. Chem. Soc.* ***1970***, *92*, 4344.

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,[133] 100% inversion,[134] and with mixtures of retention and inversion.[135] At the carbon that becomes connected to the nucleophile the result is usually inversion, although retention has also been found,[136] 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* involves a corner-protonated cyclopropane[137] (**28**); we have already seen examples of such ions in the 2-norbornyl and 7-norbornenyl cations (pp. 453, 460). Mechanism *b* involves an edge-protonated cyclopropane (**29**). Mechanism *c*

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[133] For example, see DePuy, C.H.; Breitbeil, F.W.; DeBruin, K.R. *J. Am. Chem. Soc.* ***1966***, *88*, 3347; Hendrickson, J.B.; Boeckman, Jr., R.K. *J. Am. Chem. Soc.* ***1969***, *91*, 3269.

[134] For example, see LaLonde, R.T.; Ding, J.; Tobias, M.A. *J. Am. Chem. Soc.* ***1967***, *89*, 6651; Warnet, R.J.; Wheeler, D.M.S. *Chem. Commun.* ***1971***, 547; Hogeveen, H.; Roobeek, C.F.; Volger, H.C. *Tetrahedron Lett.* ***1972***, 221; Battiste, M.A.; Mackiernan, J. *Tetrahedron Lett.* ***1972***, 4095. See also, Jensen, F.R.; Patterson, D.B.; Dinizo, S.E. *Tetrahedron Lett.* ***1974***, 1315; Coxon, J.M.; Steel, P.J.; Whittington, B.I. *J. Org. Chem.* ***1990***, *55*, 4136.

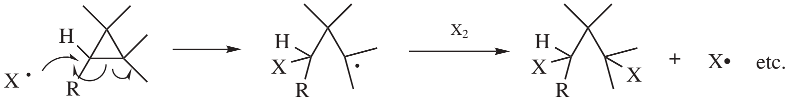
[135] Nickon, A.; Hammons, J.H. *J. Am. Chem. Soc.* ***1964***, *86*, 3322; Hammons, J.H.; Probasco, E.K.; Sanders, L.A.; Whalen, E.J. *J. Org. Chem.* ***1968***, *33*, 4493; DePuy, C.H.; Fünfschilling, P.C.; Andrist, A.H.; Olson, J.M. *J. Am. Chem. Soc.* ***1977***, *99*, 6297.

[136] Cristol, S.J.; Lim, W.Y.; Dahl, A.R. *J. Am. Chem. Soc.* ***1970***, *92*, 4013; Hendrickson, J.B.; Boeckman, Jr., R.K. *J. Am. Chem. Soc.* ***1971***, *93*, 4491.

[137] For reviews of protonated cyclopropanes, see Collins, C.J. *Chem. Rev.* ***1969***, *69*, 543; Lee, C.C. *Prog. Phys. Org. Chem.* ***1970***, *7*, 129.

consists of a one-step S_E2-type attack on H^+ to give the classical cation **30**, 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^+;[138] and for mechanism *a* with D^+ and Hg^{2+}.[139] *Ab initio* studies show that the corner-protonated **28** is slightly more stable (~1.4 kcal mol^{-1}, 6 kJ mol^{-1}) than the edge-protonated **29**.[140] There is some evidence against mechanism *c*.[141]

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 reacting at 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.[142] A mechanism that accounts for this behavior is[143]



In some cases, conjugate addition has been performed on systems where a double bond is "conjugated" with a cyclopropyl ring. An example is the formation of **31**.[144]

31

(15-6)

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[138] Coxon, J.M.; Steel, P.J.; Whittington, B.I.; Battiste, M.A. *J. Org. Chem.* ***1989***, *54*, 1383; Coxon, J.M.; Steel, P.J.; Whittington, B.I. *J. Org. Chem.* ***1989***, *54*, 3702.

[139] Lambert, J.B.; Chelius, E.C.; Bible, Jr., R.H.; Hadju, E. *J. Am. Chem. Soc.* ***1991***, *113*, 1331.

[140] Koch, W.; Liu, B.; Schleyer, P.v.R. *J. Am. Chem. Soc.* ***1989***, *111*, 3479, and references cited therein.

[141] Wiberg, K.B.; Kass, S.R. *J. Am. Chem. Soc.* ***1985***, *107*, 988.

[142] Maynes, G.G.; Applequist, D.E. *J. Am. Chem. Soc.* ***1973***, *95*, 856; Incremona, J.H.; Upton, C.J. *J. Am. Chem. Soc.* ***1972***, *94*, 301; Shea, K.J.; Skell, P.S. *J. Am. Chem. Soc.* ***1973***, *95*, 6728; Poutsma, M.L. *J. Am. Chem. Soc.* ***1965***, *87*, 4293; Jarvis, B.B. *J. Org. Chem.* ***1970***, *35*, 924; Upton, C.J.; Incremona, J.H. *J. Org. Chem.* ***1976***, *41*, 523.

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

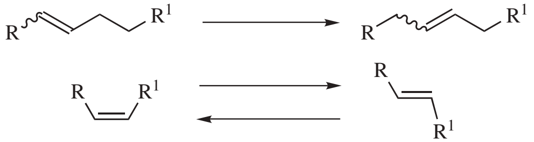
[144] Sarel, S.; Ben-Shoshan, B. *Tetrahedron Lett.* ***1965***, 1053. See also, Danishefsky, S. *Acc. Chem. Res.* ***1979***, *12*, 66.

REACTIONS

Reactions are classified by type of reagent. Isomerization of double and triple bonds is followed by examination of all reactions, where hydrogen adds to one side of the double or triple bond.

ISOMERIZATION OF DOUBLE AND TRIPLE BONDS

15-1 Isomerization



There are several reagents that lead to isomerization of a double bond to form a new alkene. In general, there is an energetic preference of an α,β- versus. β,γ-double bond.[145] Transition metals have been used to induce isomerization of alkenes. Allylic arenes ($Ar\text{-}CH_2CH{=}CH_2$) have been converted to the corresponding (*Z*-)1-propenyl arene ($Ar\text{-}CH{=}CHMe$ using a ruthenium catalyst[146] or a polymer-supported iridium catalyst.[147] Allyl decyl ether ($CH_2{=}CHCH_2OC_{10}H_{21}$) was isomerized to 1-decyloxy-1-propene ($CH_3CH{=}CHOC_{10}H_{21}$) by treatment with $NaHFe(CO)_4$.[148] Double-bond migration has been observed in sulfide photoirradiation, induced by singlet oxygen.[149] *N*-Acyl allylamine can be isomerized to the *N*-acyl enamine by heating with a ruthenium catalyst.[150] Many of these reactions were discussed in **12-2**.

For conjugated carbonyl compounds that have a hydrogen atom at the γ-position (C-4), it is possible to move a double bond *out* of conjugation. Photolysis of conjugated esters, at −40°C in the presence of *N,N*- dimethylaminoethanol, gave the nonconjugated ester.[151] Heating an *N*-allylic amide (*N*-C—C=C) with $Fe(CO)_5$, neat, gave the enamide (*N*-C=C—C).[152]

Isomerization of (*E/Z*) isomers is another important transformation.[153] Isomerization of (*E*)- and (*Z*)-conjugated amides is effected photochemically[154]

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[145] Lee, P.S.; Du, W.; Boger, D.L.; Jorgensen, W.L. *J. Org. Chem.* ***2004***, *69*, 5448.

[146] Sato, T.; Komine, N.; Hirano, M.; Komiya, S. *Chem. Lett.* ***1999***, 441.

[147] Baxendale, I.R.; Lee, A.-L.; Ley, S.V. *Synlett* ***2002***, 516.

[148] Crivello, J.V.; Kong, S. *J. Org. Chem.* ***1998***, *63*, 6745.

[149] Clennan, E.L.; Aebisher, D. *J. Org. Chem.* ***2002***, *67*, 1036.

[150] Krompiec, S.; Pigulla, M.; Krompiec, M.; Baj, S.; Mrowiec-Bialon, J.; Kasperczyk, J. *Tetrahedron Lett.* ***2004***, *45*, 5257.

[151] Bargiggia, F.; Piva, O. *Tetrahedron Asymmetry* ***2001***, *12*, 1389.

[152] Sergeyev, S.; Hesse, M. *Synlett* ***2002***, 1313.

[153] For a review, see Dugave, C.; Demange, L. *Chem. Rev.* ***2003***, *103*, 2475.

[154] Kinbara, K.; Saigo, K. *Bull. Chem. Soc. Jpn.* ***1996***, *69*, 779; Wada, T.; Shikimi, M.; Inoue, Y.; Lem, G.; Turro, N.J. *Chem. Commun.* ***2001***, 1864.

(photoisomerization[155]). There is a rather high energy barrier for the excited state required for (*E/Z*) isomerization.[156] Isomerization of the C=C units in dienes is also induced photochemically.[157] Isomerization of cyclic alkenes is more difficult but cyclooctene is isomerized photochemically.[158] The photosensitized cis–trans isomerization of 1,2-dichloroethylenes have been reported,[159] and also the photoisomerization of cis/trans cyclooctene.[160] Radical-induced (*E/Z*) isomerization is known.[161]

Conjugated aldehydes have been isomerized using thiourea in DMF.[162] A 1:1 mixture of cis/trans styrene derivatives was isomerized to a 90% yield of the trans styrene derivatives was reported using a palladium catalyst.[163] Thermal cis–trans isomerization of 1,3-diphenyltriazenes has been reported, in aqueous solution.[164]

REACTIONS IN WHICH HYDROGEN ADDS TO ONE SIDE

A. Halogen on the Other Side

15-2 Addition of Hydrogen Halides

Hydro-halo-addition

Any of the four hydrogen halides can be added to double bonds.[165] HI, HBr, and HF[166] add at room temperature. The addition of HCl is more difficult and usually requires heat,[23] although HCl adds easily in the presence of silica gel.[167] The reaction has been carried out with a large variety of double-bond compounds, including

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[155] Inoue, Y.; Yamasaki, N.; Yokoyama, T.; Tai, A. *J. Org. Chem.* ***1992***, *57*, 1332.

[156] Arai, T.; Takahashi, O. *J. Chem. Soc., Chem. Commun.* ***1995***, 1837.

[157] Wakamatsu, K.; Takahashi, Y.; Kikuchi, K.; Miyashi, T. *J. Chem. Soc. Perkin Trans. 2*, ***1996***, 2105.

[158] Tsuneishi, H.; Hakushi, T.; Inoue, Y. *J. Chem. Soc. Perkin Trans. 2*, ***1996***, 1601; Inoue, Y.; Tsuneishi, H.; Hakushi, T.; Yagi, K.; Awazu, K.; Onuki, H. *Chem. Commun.* ***1996***, 2627; Tsuneishi, H.; Hakushi, T.; Tai, A.; Inoue, Y. *J. Chem. Soc. Perkin Trans. 2*, ***1995***, 2057.

[159] Kokubo, K.; Kakimoto, H.; Oshima, T. *J. Am. Chem. Soc.* ***2002***, *124*, 6548.

[160] Wada, T.; Sugahara, N.; Kawano, M.; Inoue, Y. *Chem. Lett.* ***2000***, 1174.

[161] Baag, Md.M.; Kar, A.; Argade, N.P. *Tetrahedron* ***2003***, *59*, 6489.

[162] Phillips, O.A.; Eby, P.; Maiti, S.N. *Synth. Commun.* ***1995***, *25*, 87.

[163] Yu, J.; Gaunt, M.J.; Spencer, J.B. *J. Org. Chem.* ***2002***, *67*, 4627.

[164] Chen, N.; Barra, M.; Lee, I.; Chahal, N. *J. Org. Chem.* ***2002***, *67*, 2271.

[165] For a list of references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 633–636.

[166] For reviews of addition of HF, see Sharts, C.M.; Sheppard, W.A. *Org. React.* ***1974***, *21*, 125, 192–198, 212–214; Hudlický, M. *The Chemistry of Organic Fluorine Compounds*, 2nd ed., Ellis Horwood, Chichester, ***1976***, pp. 36–41.

[167] Kropp, P.J.; Daus, K.A.; Tubergen, M.W.; Kepler, K.D.; Wilson, V.P.; Craig, S.L.; Baillargeon, M.M.; Breton, G.W. *J. Am. Chem. Soc.* ***1993***, *115*, 3071.

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.[168] 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 alkenes, in the absence of peroxides, takes place by an electrophilic mechanism, and the orientation is in accord with Markovnikov's rule.[169] The addition follows second order kinetics.[170] When peroxides are added, the addition of HBr occurs by a free-radical mechanism and the orientation is anti-Markovnikov (p. 1021).[171] 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.[172] Free-radical addition of HF, HI, and HCl is energetically unfavorable (see the discussions on pp. 943, 959). 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 (**14-7**). 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, for example, 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 to achieve complete free-radical addition, or inhibitors to achieve complete electrophilic addition, although 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.[173] For alternative methods of adding HBr (or HI) with anti-Markovnikov orientation, see **12-31**.

It is also possible to add 1[174] or 2 equivalents of any of the four hydrogen halides to triple bonds. Markovnikov's rule ensures that *gem*-dihalides and not *vic*-dihalides

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[168] Olah, G.A.; Welch, J.T.; Vankar, Y.D.; Nojima, M.; Kerekes, I.; Olah, J.A. *J. Org. Chem.* ***1979***, *44*, 3872. For related methods, see Yoneda, N.; Abe, T.; Fukuhara, T.; Suzuki, A. *Chem. Lett.* ***1983***, 1135; Olah, G.A.; Li, X. *Synlett* ***1990***, 267.

[169] For reviews of electrophilic addition of HX, see Sergeev, G.B.; Smirnov, V.V.; Rostovshchikova, T.N.; *Russ. Chem. Rev.* ***1983***, *52*, 259, and Dewar, M.J.S. *Angew. Chem. Int. Ed.* ***1964***, *3*, 245.

[170] Boregeaud, R.; Newman, H.; Schelpe, A.; Vasco, V.; Hughes, D.E.P. *J. Chem. Soc., Perkin Trans. 2*, ***2002***, 810.

[171] For reviews of free-radical addition of HX, see Thaler, W.A. *Methods Free-Radical Chem.* ***1969***, *2*, 121, see pp. 182–195.

[172] Mayo, F.R. *J. Am. Chem. Soc.* ***1962***, *84*, 3964.

[173] Landini, D.; Rolla, F. *J. Org. Chem.* ***1980***, *45*, 3527.

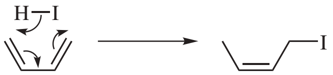
[174] For a convenient method of adding one mole of HCl or HBr to a triple bond, see Cousseau, J.; Gouin, L. *J. Chem. Soc. Perkin Trans. 1*, ***1977***, 1797; Cousseau, J. *Synthesis* ***1980***, 805. For the addition of one mole of HI, see Kamiya, N.; Chikami, Y.; Ishii, Y. *Synlett* ***1990***, 675.

are the products of the addition of two equivalents.

$$—C\ C— \xrightarrow{HX} —CH{=}CX— \xrightarrow{HX} —CH_2—CX_2—$$

Chlorotrimethylsilane can be added to alkenes to give alkyl chlorides. 1-Hexene reacts with Me_3SiCl in water to give 2-chlorohexane.[175] Treatment of an alkene with KHF_2 and SiF_4 leads to the alkyl fluoride,[176] and bromotrimethylsilane adds to alkynes to give the vinyl bromide.[177] Trichloroisocyanuric acid reacts with terminal alkenes in water to give the 1-chloro alkane.[178]

HX are electrophilic reagents, and many polyhalo and polycyano alkenes, for example, $Cl_2C{=}CHCl$, do not react with them at all in the absence of free-radical conditions. Vinylcyclopropanes, however, react with opening of the cyclopropane ring to give a homoallylic chloride.[179] When such reactions do occur, however, they take place by a nucleophilic addition mechanism, that is, initial attack is by X^-. This type of mechanism also occurs with Michael-type substrates C=C—Z,[180] There 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 X—C—CH—Z, even in the presence of free-radical initiators. Hydrogen iodine adds 1,4 to conjugated dienes in the gas phase by a pericyclic mechanism:[181]



HX can be added to ketenes[182] to give acyl halides:

$$>C{=}C{=}O + H\text{-}X \longrightarrow —\overset{H}{C}—C(=O)X$$

OS **I**, 166; **II**, 137, 336; **III**, 576; **IV**, 238, 543; **VI**, 273; **VII**, 59; **80**, 129.

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[175] Boudjouk, P.; Kim, B.-K.; Han, B.-H. *Synth. Commun.* ***1996***, *26*, 3479.

[176] Tamura, M.; Shibakami, M.; Kurosawa, S.; Arimura, T.; Sekiya, A. *J. Chem. Soc., Chem. Commun.* ***1995***, 1891.

[177] Su, M.; Yu, W.; Jin, Z. *Tetrahedron Lett.* ***2001***, *42*, 3771.

[178] Mendonça, G.F.; Sanseverino, A.M.; de Mattos, M.C.S. *Synthesis* ***2003***, 45.

[179] Siriwardana, A.I.; Nakamura, I.; Yamamoto, Y. *Tetrahedron Lett.* ***2003***, *44*, 985.

[180] For an example, see Marx, J.N. *Tetrahedron* ***1983***, *39*, 1529.

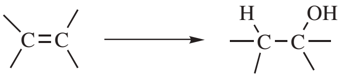
[181] Gorton, P.J.; Walsh, R. *J. Chem. Soc., Chem. Commun.* ***1972***, 782. For evidence that a pericyclic mechanism may be possible, even for an isolated double bond, see Sergeev, G.B.; Stepanov, N.F.; Leenson, I.A.; Smirnov, V.V.; Pupyshev, V.I.; Tyurina, L.A.; Mashyanov, M.N. *Tetrahedron* ***1982***, *38*, 2585.

[182] For reviews of additions to ketenes, and their mechanisms, see Tidwell, T.T. *Acc. Chem. Res.* ***1990***, *23*, 273; Seikaly, H.R.; Tidwell, T.T. *Tetrahedron* ***1986***, *42*, 2587; Satchell, D.P.N.; Satchell, R.S. *Chem. Soc. Rev.* ***1975***, *4*, 231.

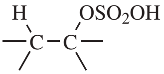
B. Oxygen on the Other Side

15-3 Hydration of Double bonds

Hydro-hydroxy-addition

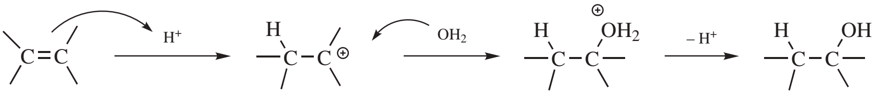


Double bonds can be hydrated by treatment with water and an acid catalyst. The most common catalyst is sulfuric acid, but other acids that have relatively non-nucleophilic counterions, such as nitric or perchloric can also be used. The mechanism is electrophilic and begins with attack of the π-bond on an acidic proton (see p. 1005). The resulting carbocation is then attacked by negative species, such as HSO_4^- (or similar counterion in the case of other acids), to give the initial product **32**, which can be isolated in some cases, but under the conditions of the



32

reaction, is usually hydrolyzed to the alcohol (**10-4**). 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 to form **33**.



33

When the reaction proceeds by this pathway, **32** and similar intermediates are not involved and the mechanism is exactly (by the principle of microscopic reversibility) the reverse of El elimination of alcohols (**17-1**).[183] It is likely that the mechanism involves both pathways. *The initial carbocation occasionally rearranges to a more stable one.* For example, hydration of $CH_2{=}CHCH(CH_3)_2$ gives $CH_3CH_2COH(CH_3)_2$. With ordinary alkenes 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 Et_3SiH[184] or a secondary alcohol, e.g., 2-propanol[185]) to the alkene in the presence of a cobalt-complex catalyst. No rearrangement is observed with this

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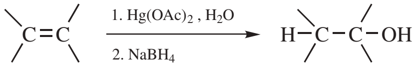
[183] For discussions of the mechanism, see Vinnik, M.I.; Obraztsov, P.A. *Russ. Chem. Rev.* ***1990***, *59*, 63; Liler, M. *Reaction Mechanisms in Sulphuric Acid*, Academic Press, NY, ***1971***, pp. 210–225.

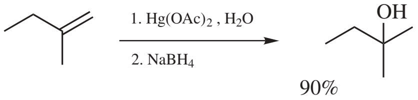
[184] Isayama, S.; Mukaiyama, T. *Chem. Lett.* ***1989***, 569.

[185] Inoki, S.; Kato, K.; Takai, T.; Isayama, S.; Yamada, T.; Mukaiyama, T. *Chem. Lett.* ***1989***, 515.

method. The corresponding alkane and ketone are usually side products.



Alkenes can be hydrated quickly under mild conditions in high yields without rearrangement products by the use of *oxymercuration*[186] (addition of oxygen and mercury) followed by *in situ* treatment with sodium borohydride[187] (**12-24**). For example, 2-methyl-1-butene treated with mercuric acetate,[188] followed by $NaBH_4$, gave 2-methyl-2-butanol.



This method, which is applicable to mono-, di-, tri-, and tetraalkyl as well as phenyl-substituted alkenes, gives almost complete Markovnikov addition. Hydroxy, methoxy, acetoxy, halo, and other groups may be present in the substrate without, in general, causing difficulties.[189] 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.[190] A related reaction treats an alkene with zinc borohydride on silica gel to give a 35:65 mixture of secondary:primary alcohols.[191]

Water can be added indirectly, with anti-Markovnikov orientation, by treatment of the alkene with a 1:1 mixture of $PhCH_2NEt_3^+\ BH_4^-$ and Me_3SiCl, followed by addition of an aqueous solution of K_2CO_3.[192] Reaction of alkenes with $Ti(BH_4)_3$, and then aqueous K_2CO_3 also leads to the anti-Markovnikov alcohol.[193] Reaction of

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[186] For a monograph, see Larock, R.C. *Solvation/Demercuration Reactions in Organic Synthesis*, Springer, NY, ***1986***. For reviews of this and other oxymetallation reactions, see Kitching, W. *Organomet. React.* ***1972***, *3*, 319; *Organomet. Chem. Rev.* ***1968***, *3*, 61; Oullette, R.J., in Trahanovsky, W.S. *Oxidation in Organic Chemistry*, pt. B; Academic Press, NY, ***1973***, pp. 140–166; House, H.O. *Modern Synthetic Reactions*, 2nd ed., W.A. Benjamin, NY, ***1972***, pp. 387–396; Zefirov, N.S. *Russ. Chem. Rev.* ***1965***, *34*, 527.

[187] Brown, H.C.; Geoghegan, Jr., P.J. *J. Org. Chem.* ***1972***, *37*, 1937; Brown, H.C.; Geoghegan, Jr., P.J.; Lynch, G.J.; Kurek, J.T. *J. Org. Chem.* ***1972***, *37*, 1941; Moon, S.; Takakis, I.M.; Waxman, B.H. *J. Org. Chem.* ***1969***, *34*, 2951; Moon, S.; Ganz, C.; Waxman, B.H. *Chem. Commun.* ***1969***, 866; Johnson, M.R.; Rickborn, B. *Chem. Commun.* ***1968***, 1073; Klein, J.; Levene, R. *Tetrahedron Lett.* ***1969***, 4833; Chamberlain, P.; Whitham, G.H. *J. Chem. Soc. B* ***1970***, 1382; Barrelle, M.; Apparu, M. *Bull. Soc. Chim. Fr.* ***1972***, 2016.

[188] For a review of this reagent, see Butler, R.N., in Pizey, J.S. *Synthetic Reagents*, Vol. 4, Wiley, NY, ***1981***, pp. 1–145.

[189] See the extensive tables, in Larock, R.C. *Solvation/Demercuration Reactions in Organic Synthesis*, Springer, NY, ***1986***, pp. 4–71.

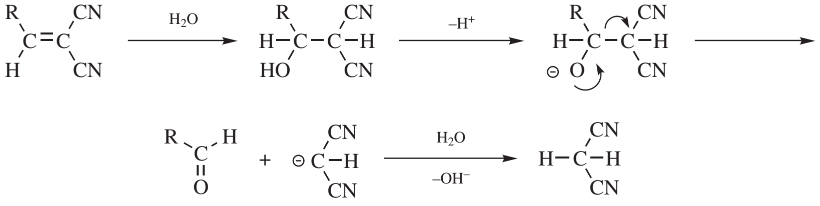
[190] Einhorn, J.; Einhorn, C.; Luche, J.L. *J. Org. Chem.* ***1989***, *54*, 4479.

[191] Ranu, B.C.; Sarkar, A.; Saha, M.; Chakraborty, R. *Tetrahedron* ***1994***, *50*, 6579; Campelo, J.M.; Chakraborty, R.; Marinas, J.M. *Synth. Commun.* ***1996***, *26*, 1639; Ranu, B.C.; Chakraborty, R.; Saha, M. *Tetrahedron Lett.* ***1993***, *34*, 4659.

[192] Baskaran, S.; Gupta, V.; Chidambaram, N.; Chandrasekaran, S. *J. Chem. Soc., Chem. Commun.* ***1989***, 903.

[193] Kumar, K.S.R.; Baskaran, S.; Chandrasekaran, S. *Tetrahedron Lett.* ***1993***, *34*, 171.

terminal alkynes with water and ruthenium catalyst, followed by sequential treatment with long chain sulfates and then ammonium salts gave the aldehyde via anti-Markovnikov addition of water.[194] With substrates of the type C═C─Z (Z is as defined on p. 1007) the product is almost always HO─C─CH─Z and the mechanism is usually nucleophilic,[195] although electrophilic addition gives the same product[196] since a cation CH─C─Z would be destabilized by the positive charges (full or partial) on two adjacent atoms. However, the α-hydroxy compound HC─CH(OH)Z, was obtained by treatment of the substrate with O_2, $PhSiH_3$, and a manganese- complex catalyst.[197] When the substrate is of the type RCH═CZZ′, CZZ′, addition of water may result in cleavage of the adduct, to give an aldehyde and CH_2ZZ', **34**.[198] The cleavage step is an example of **12-41**



34

For another method of anti-Markovnikov hydration, see hydroboration (**15-16**).

Alkenes react with PhO_2BH and a niobium catalyst, followed by oxidation with $NaOO^-$, to give the alcohol,[199] and Cp_2TiCl_4 can also be used.[200] Reaction with $HSiCl_3$ and a chiral palladium catalyst, followed by reaction with KF and hydrogen peroxide, leads to the alcohol with high asymmetric induction.[201] Conjugated alkenes also react with $PhSiH_2$ and oxygen, with a manganese catalyst, to give an α-hydroxy ketone.[202] Alkenes react with molecular oxygen in the presence of a cobalt porphyrin catalyst, and reduction with $P(OMe)_3$ leads to the secondary alcohol.[203] This procedure has also been used to hydrate conjugated dienes,[204] although conjugated dienes are seldom hydrated.

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[194] Alvarez, P.; Basetti, M.; Gimeno, J.; Mancini, G. *Tetrahedron Lett.* ***2001***, *42*, 8467.

[195] For example, see Fedor, L.R.; De, N.C.; Gurwara, S.K. *J. Am. Chem. Soc.* ***1973***, *95*, 2905; Jensen, J.L.; Hashtroudi, H. *J. Org. Chem.* ***1976***, *41*, 3299; Bernasconi, C.F.; Leonarduzzi, G.D. *J. Am. Chem. Soc.* ***1982***, *104*, 5133, 5143.

[196] For example, see Noyce, D.S.; DeBruin, K.E. *J. Am. Chem. Soc.* ***1968***, *90*, 372.

[197] Inoki, S.; Kato, K.; Isayama, S.; Mukaiyama, T. *Chem. Lett.* ***1990***, 1869; Magnus, P.; Scott, D.A.; Fielding, M.R. *Tetrahedron Lett.* ***2001***, *42*, 4127.

[198] Bernasconi, C.F.; Fox, J.P.; Kanavarioti, A.; Panda, M. *J. Am. Chem. Soc.* ***1986***, *108*, 2372; Bernasconi, C.F.; Paschalis, P. *J. Am. Chem. Soc.* ***1989***, *111*, 5893, and other papers in this series.

[199] Burgess, K.; Jaspars, M. *Tetrahedron Lett.* ***1993***, *34*, 6813.

[200] Burgess, K.; van der Donk, W.A. *Tetrahedron Lett.* ***1993***, *34*, 6817.

[201] Uozumi, Y.; Hayashi, T. *Tetrahedron Lett.* ***1993***, *34*, 2335.

[202] Magnus, P.; Payne, A.H.; Waring, M.J.; Scott, D.A.; Lynch, V. *Tetrahedron Lett.* ***2000***, *41*, 9725.

[203] Matsushita, Y.; Sugamoto, K.; Matsui, T. *Chem. Lett.* ***1993***, 925.

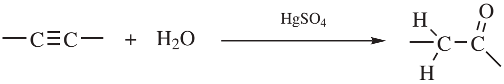
[204] Matshshita, Y.; Sugamoto, K.; Nakama, T.; Sakamoto, T.; Matsui, T.; Nakayama, M. *Tetrahedron Lett.* ***1995***, *36*, 1879.

The addition of water to enol ethers causes hydrolysis to aldehydes or ketones (**10-6**). Ketenes add water to give carboxylic acids ($R_2C{=}C{=}O \rightarrow R_2COOH$) in a reaction catalyzed by acids:[205]

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

15-4 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.[206] 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 **15-16**). With alkynes of the form RC≡CH methyl ketones are formed almost exclusively, but with RC≡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, see p. 236).[207] Terminal alkynes react with water at 200°C with microwave irradiation to give the corresponding methyl ketone.[208] A gold catalyst was used in aqueous methanol with 50% sulfuric acid to convert terminal alkynes to the ketone.[209] Conversion of phenyl acetylene to acetophenone was accomplished in water at 100°C with a catalytic amount of Tf_2NH (trifluoromethanesulfonimide).[210] In a modified reaction, internal alkynes were treated with 2-aminophenol in refluxing dioxane using a palladium catalyst to produce the corresponding ketone.[211]

Hydration of terminal alkynes can proceed with anti-Markovnikov addition. When 1-octyne was heated with water, isopropanol and a ruthenium catalyst, for example, the product was octanal.[212] A similar reaction was reported in aqueous acetone using a ruthenium catalyst.[213] The presence of certain functionality can

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[205] For discussions of the mechanism, see Poon, N.L.; Satchell, D.P.N. *J. Chem. Soc. Perkin Trans. 2*, ***1983***, 1381; ***1986***, 1485; Tidwell, T.T. *Acc. Chem. Res.* ***1990***, *23*, 273; Seikaly, H.R.; Tidwell, T.T. *Tetrahedron* ***1986***, *42*, 2587; Satchell, D.P.N.; Satchell, R.S. *Chem. Soc. Rev.* ***1975***, *4*, 231.

[206] For reviews, see Larock, R.C. *Solvation/Demercuration Reactions in Organic Synthesis*, Springer, NY, ***1986***, pp. 123–148; Khan, M.M.T.; Martell, A.E. *Homogeneous Catalysis by Metal Complexes*, Vol. 2, Academic Press, NY, ***1974***, pp. 91–95. For a list of reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 1217–1219.

[207] Olah, G.A.; Meidar, D. *Synthesis* ***1978***, 671.

[208] Vasudevan, A.; Verzas, M.K. *Synlett* ***2004***, 631.

[209] Mizushima, E.; Sato, K.; Hayashi, T.; Tanaka, M. *Angew. Chem. Int. Ed.* ***2002***, *41*, 4563.

[210] Tsuchimoto, T.; Joya, T.; Shirakawa, E.; Kawakami, Y. *Synlett* ***2000***, 1777.

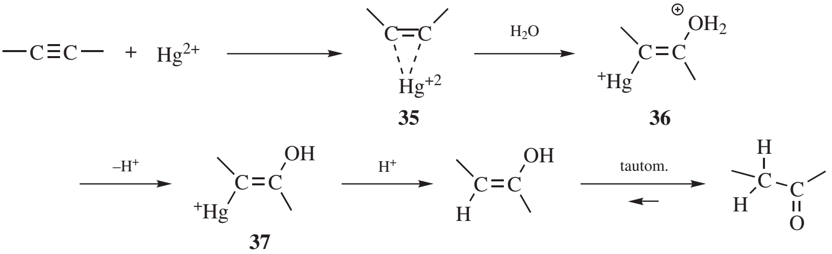
[211] Shimada, T.; Yamamoto, Y. *J. Am. Chem. Soc.* ***2002***, *124*, 12670.

[212] Suzuki, T.; Tokunaga, M.; Wakatsuki, Y. *Org. Lett.* ***2001***, *3*, 735.

[213] Grotjahn, D.B.; Lev, D.A. *J. Am. Chem. Soc.* ***2004***, *126*, 12232.

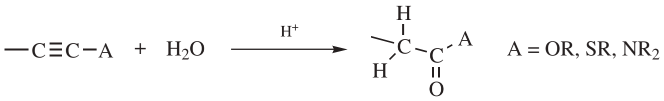
influence the regioselectivity of hydration. 1-Seleno alkynes, such as PhSe-C≡C-Ph, react with tosic acid in dichloromethane to give a seleno ester PhSeC(=O)SH_2Ph after treatment with water.[214]

The first step of the mechanism is formation of a complex (**35**) (ions like Hg^{2+} form complexes with alkynes, p. 115). Water then attacks in an S_N2-type process to give the intermediate **36**,



which loses a proton to give **37**. Hydrolysis of **37** (an example of **12-34**) gives the enol, which tautomerizes to the product. A spectrum of the enol was detected by flash photolysis when phenylacetylene was hydrated photolytically.[215]

Carboxylic esters, thiol esters, and amides can be made, respectively, by acid-catalyzed hydration of acetylenic ethers, thioethers,[216] and ynamines, without a mercuric catalyst:[217]



This is ordinary electrophilic addition, with rate-determining protonation as the first step.[218] Certain other alkynes have also been hydrated to ketones with strong acids in the absence of mercuric salts.[219] Simple alkynes can also be converted to ketones by heating with formic acid, without a catalyst.[220] Lactones have been prepared from trimethylsilyl alkenes containing an hydroxyl unit elsewhere in the molecule, when reacted with molecular oxygen, $CuCl_2$, and a palladium catalyst.[221]

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[214] Sheng, S.; Liu, X. *Org. Prep. Proceed. Int.* ***2002***, *34*, 499.

[215] Chiang, Y.; Kresge, A.J.; Capponi, M.; Wirz, J. *Helv. Chim. Acta* ***1986***, *69*, 1331.

[216] Braga, A.L.; Martins, T.L.C.; Silveira, C.C.; Rodrigues, O.E.D. *Tetrahedron* ***2001***, *57*, 3297. For a review of acetylenic ethers and thioethers, see Brandsma, L.; Bos, H.J.T.; Arens, J.F., in Viehe, H.G. *Acetylenes*, Marcel Dekker, NY, ***1969***, pp. 751–860.

[217] Arens, J.F. *Adv. Org. Chem.* ***1960***, *2*, 163; Brandsma, L.; Bos, H.J.T.; Arens, J.F., in Viehe, H.G. *Acetylenes*, Marcel Dekker, NY, ***1969***, pp. 774–775.

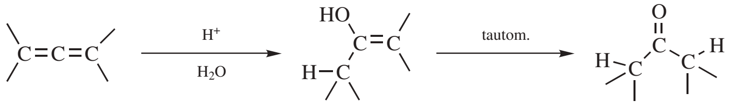
[218] Hogeveen, H.; Drenth, W. *Recl. Trav. Chim. Pays-Bas* ***1963***, *82*, 375, 410; Verhelst, W.F.; Drenth, W. *J. Am. Chem. Soc.* ***1974***, *96*, 6692; Banait, N.; Hojatti, M.; Findlay, P.; Kresge, A.J. *Can. J. Chem.* ***1987***, *65*, 441.

[219] See, for example, Noyce, D.S.; Schiavelli, M.D. *J. Org. Chem.* ***1968***, *33*, 845; *J. Am. Chem. Soc.* ***1968***, *90*, 1020, 1023.

[220] Menashe, N.; Reshef, D.; Shvo, Y. *J. Org. Chem.* ***1991***, *56*, 2912.

[221] Compain, P.; Goré, J.; Vatèle, J.-M. *Tetrahedron* ***1996***, *52*, 10405.

Allenes can also be hydrolyzed to ketones, with an acid catalyst.[222]

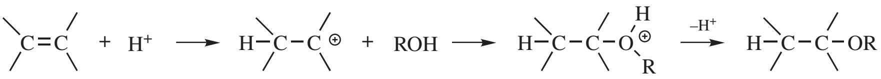


OS **III**, 22; **IV**, 13; **V**, 1024.

15-5 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 species attacked by the π-bond. The resulting carbocation combines with a molecule of alcohol to give an oxonium ion, **38**.



38

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 alkene, such as $Me_2C{=}CH_2$. Addition of alcohols to allylic systems can proceed with rearrangement, and the use of chiral additive can lead to asymmetric induction.[223]

Alcohols add intramolecularly to alkenes to generate cyclic ethers, often bearing a hydroxyl unit,.[224] but not always.[225] Furan derivatives are available for alkene-ketones using $CuCl_2$ and a palladium catalyst,[226] but chromium catalysts have been used for a similar purpose.[227] A gold catalyst was used with conjugated ketones bearing an alkyne substituent to give fused-ring furans.[228] Pyrone derivatives are available by the coupling of conjugated ketones bearing an alcohol unit, via an addition

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[222] For example, see Fedorova, A.V.; Petrov, A.A. *J. Gen. Chem. USSR* ***1962***, *32*, 1740; Mühlstadt, M.; Graefe, J. *Chem. Ber.* ***1967***, *100*, 223; Cramer, P.; Tidwell, T.T. *J. Org. Chem.* ***1981***, *46*, 2683.

[223] See Nakamura, H.; Ishihara, K.; Yamamoto, H. *J. Org. Chem.* ***2002***, *67*, 5124.

[224] Bhaumik, A.; Tatsumi, T. *Chem. Commun.* ***1998***, 463; Gruttadauria, M.; Aprile, C.; Riela, S.; Noto, R. *Tetrahedron Lett.* ***2001***, *42*, 2213.

[225] Miura, K.; Hondo, T.; Okajima, S.; Nakagawa, T.; Takahashi, T.; Hosomi, A. *J. Org. Chem.* ***2002***, *67*, 6082; Marotta, E.; Foresti, E.; Marcelli, T.; Peri, F.; Righi, P.; Scardovi, N.; Rosini, G. *Org. Lett.* ***2002***, *4*, 4451.

[226] Han, X.; Widenhoefer, R.A. *J. Org. Chem.* ***2004***, *69*, 1738.

[227] Miki, K.; Nishino, F.; Ohe, K.; Uemura, S. *J. Am. Chem. Soc.* ***2002***, *124*, 5260.

[228] Yao, T.; Zhang, X.; Larock, R.C. *J. Am. Chem. Soc.* ***2004***, *126*, 11164.

elimination process mediated by a palladium catalyst.[229] Intramolecular addition of alcohols to alkenes can be promoted by a palladium catalyst, with migration of the double bond in the final product.[230] Rhenium compounds,[231] titanium compounds,[232] or platinum compounds[233] facilitate this cyclization reaction to form functionalized tetrahydrofurans or tetrahydrofurans. Allylic alcohols have been converted to 2-bromo oxetanes using $Br(collidine)_2^+$ PF_6.[234] It is noted that the reaction of an alkene–alcohol and *N*-iodosuccinimide with a chiral titanium catalyst leads to a tetrahydrofuran with a pendant iodoalkyl group, with modest enantioselectivity.[235]

Allenes react with alcohols and allenic alcohols have been converted to tetrahydrofuran derivatives bearing a vinyl group at the α-position, using diphenyliodonium salts.[236] In the presence of allylic bromide and a palladium catalyst, allenic alcohols lead to allylically substituted dihydrofurans.[237] Intramolecular addition of alcohols to allenes leads to cyclic vinyl ethers.[238] Alcohols add intramolecularly to a vinylidene dithiane under electrolytic conditions to form a tetrahydrofuran derivative with a pendant dithiane group.[239]

In the presence of other reagents, functionalized ethers can be formed. In methanol with an R—Se—Br reagent, alkenes are converted to selenoalkyl ethers (MeO—C—C—SeR).[240]

An interesting "double" addition was reported in which 2-(hydroxymethyl)phenol reacted with 2,3-dimethyl-2-butene in the presence of lithium perchlorate and Montmorillonite clay/water to give benzopyrans, but the reaction proceeded via an *O*-quinomethane generated *in situ*.[241]

Alcohols add to alkynes under certain conditions to give vinyl ethers. In an excess of alcohol, and in the presence of a platinum catalyst, internal alkynes are converted to ketals.[242] The alcohol to alkyne addition reaction is quite useful for the preparation of heterocycles. Dihydrofurans,[243] furans,[244] benzofurans,[245] and pyran

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[229] Reiter, M.; Ropp, S.; Gouverneur, V. *Org. Lett.* ***2004***, *6*, 91

[230] Rönn, M.; Bäckvall, J.-E.; Andersson, P.G. *Tetrahedron Lett.* ***1995***, *36*, 7749; Semmelhack, M.F.; Epa, W.R. *Tetrahedron Lett.* ***1993***, *34*, 7205. See Tiecco, M.; Testaferri, L.; Santi, C. *Eur. J. Org. Chem.* ***1999***, 797.

[231] Kennedy, R.M.; Tang, S. *Tetrahedron Lett.* ***1992***, *33*, 3729; McDonald, F.E.; Towne, T.B. *J. Org. Chem.* ***1995***, *60*, 5750.

[232] Lattanzi, A.; Della Sala, G.G.D.; Russo, M.; Screttri, A. *Synlett* ***2001***, 1479.

[233] Qian, H.; Han, X.; Widenhoefer, R.A. *J. Am. Chem. Soc.* ***2004***, *126*, 9536.

[234] Albert, S.; Robin, S.; Rousseau, G. *Tetrahedron Lett.* ***2001***, *42*, 2477.

[235] Kang, S.H.; Park, C.M.; Lee, S.B.; Kim, M. *Synlett* ***2004***, 1279.

[236] In this case, the phenyl group also added to the allene. Kang, S.-K.; Baik, T.-G.; Kulak, A.N. *Synlett* ***1999***, 324.

[237] Ma, S.; Gao, W. *J. Org. Chem.* ***2002***, *67*, 6104.

[238] Mukai, C.; Ohta, M.; Yamashita, H.; Kitagaki, S. *J. Org. Chem.* ***2004***, *69*, 6867.

[239] Sun, Y.; Liu, B.; Kao, J.; Andred′Avignon, D.; Moeller, K.D. *Org. Lett.* ***2001***, *3*, 1729. See also, Mukai, C.; Yamashita, H.; Hanaoka, M. *Org. Lett.* ***2001***, *3*, 3385.

[240] Back, T.G.; Moussa, Z.; Parvez, M. *J. Org. Chem.* ***2002***, *67*, 499.

[241] Chiba, K.; Hirano, T.; Kitano, Y.; Tada, M. *Chem. Commun.* ***1999***, 691.

[242] Hartman, J.W.; Sperry, L. *Tetrahedron Lett.* ***2004***, *45*, 3787.

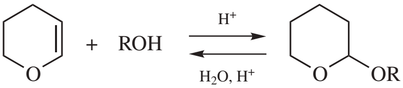
[243] Gabriele, B.; Salerno, G.; Lauria, E. *J. Org. Chem.* ***1999***, *64*, 7687.

[244] Qing, F.L.; Gao, W.-Z.; Ying, J. *J. Org. Chem.* ***2000***, *65*, 2003. See Kel'in, A.V.; Gevorgyan, V. *J. Org. Chem.* ***2002***, *67*, 95.

[245] Nan, Y.; Miao, H.; Yang, Z. *Org. Lett.* ***2000***, *2*, 297. See also, Arcadi, A.; Cacchi, S.; DiGiuseppe, S.; Fabrizi, G.; Marinelli, F. *Synlett* ***2002***, 453.

derivatives[246] have been prepared using this approach. Tetrahydrofurans bearing an exocyclic double bond (vinylidene tetrahydrofurans) were prepared from alkynyl alcohols and a silver carbonate catalyst.[247]

For those substrates, more susceptible to nucleophilic attack, for example, polyhalo alkenes and alkenes of the type C=C—Z, it is better to carry out the reaction in basic solution, where the attacking species is RO^-.[248] The reactions with C=C—Z are of the Michael type, and OR goes to the side away from the Z.[249] Since triple bonds are more susceptible to nucleophilic 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.[250] 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.[251] One utilization of this reaction involves the compound dihydropyran



39 **40**

(**39**), which is often used to protect the OH groups of primary and secondary[252] alcohols and phenols.[253] The tetrahydropyranyl acetal formed by this reaction (**40**) 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, **40** is easily cleaved by treatment with dilute acids (**10-6**). The addition of alcohols to enol ethers is also catalyzed by $CoCl_2$.[254]

Conjugate addition of alcohols to conjugated esters, using ceric ammonium nitrate and LiBr, gave the corresponding α-bromo-β-alkoxy ester.[255]

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.

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[246] Davidson, M.H.; McDonald, F.E. *Org. Lett.* ***2004***, *6*, 1601.

[247] Pale, P.; Chuche, J. *Eur. J. Org. Chem.* ***2000***, 1019.

[248] For a review with respect to fluoroalkenes, see Chambers, R.D.; Mobbs, R.H. *Adv. Fluorine Chem.* ***1965***, *4*, 51, pp. 53–61.

[249] For an example using a rhodium catalyst, See Farnsworth, M.V.; Cross, M.J.; Louie, J. *Tetrahedron Lett.* ***2004***, *45*, 7441.

[250] For a review, see Shostakovskii, M.F.; Trofimov, B.A.; Atavin, A.S.; Lavrov, V.I. *Russ. Chem. Rev.* ***1968***, *37*, 907.

[251] For discussions of the mechanism, see Toullec, J.; El-Alaoui, M.; Bertrand, R. *J. Chem. Soc. Perkin Trans. 2*, ***1987***, 1517; Kresge, A.J.; Yin, Y. *J. Phys. Org. Chem.* ***1989***, *2*, 43.

[252] Tertiary alcohols can also be protected in this way if triphenylphosphine hydrobromide is used as a catalyst: Bolitt, V.; Mioskowski, C.; Shin, D.; Falck, J.R. *Tetrahedron Lett.* ***1988***, *29*, 4583.

[253] For useful catalysts for this reaction, some of which are also applicable to tertiary alcohols, see Miyashita, M.; Yoshikoshi, A.; Grieco, P.A. *J. Org. Chem.* ***1977***, *42*, 3772; Olah, G.A.; Husain, A.; Singh, B.P. *Synthesis* ***1985***, 703; Johnston, R.D.; Marston, C.R.; Krieger, P.E.; Goem G.L. *Synthesis* ***1988***, 393.

[254] Iqbal, J.; Srivastava, R.R.; Gupta, K.B.; Khan, M.A. *Synth. Commun.* ***1989***, *19*, 901.

[255] Roy, S.C.; Guin, C.; Rana, K.K.; Maiti, G. *Synlett* ***2001***, 226.

Alcohols can be added to certain double-bond compounds (cyclohexenes, cycloheptenes) photochemically[256] in the presence of a photosensitizer such as benzene. The mechanism is electrophilic and Markovnikov orientation is found. The alkenes react in their first excited triplet states.[257]

The oxymercuration–demercuration procedure mentioned in **15-3** can be adapted to the preparation of ethers (Markovnikov orientation) if the oxymercuration is carried out in an alcohol ROH as solvent,[258] for example 2-methyl-1-butene in ethanol gives $EtMe_2COEt$.[259] Primary alcohols give good yields when mercuric acetate is used, but for secondary and tertiary alcohols it is necessary to use mercuric trifluoroacetate.[260] However, even this reagent fails where the product would be a ditertiary ether. It is possible to combine the alcohol reactant with another reagent. The reaction of an alkene with iodine and allyl alcohol, in the presence of HgO, gave the *vic*-iodo ether.[261] Alkene-alcohols react with mercuric trifluoroacetate and the aq. KBr (with $LiBH_4/BEt_3$) to give a derivative bearing an iodoalkyl substituent, —O—C—CH(I)R.[262] 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 (peroxy-mercuration).[263] This can be done intramolecularly.[264]

Both alcohols and phenols add to ketenes to give carboxylic esters [$R_2C{=}C{=}O + ROH \rightarrow R_2CHCO_2R$].[265] This has been done intramolecularly (with the ketene end of the molecule generated and used *in situ*) to form medium- and large-ring lactones.[266] In the presence of a strong acid, ketene reacts with aldehydes or ketones (in their enol forms) to give enol acetates. 1,4-Asymmetric induction is possible when chiral alcohols add to ketenes.[267]

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[256] For a review of the photochemical protonation of double and triple bonds, see Wan, P.; Yates, K. *Rev. Chem. Intermed.* ***1984***, *5*, 157.

[257] Marshall, J.A. *Acc. Chem. Res.* ***1969***, *2*, 33.

[258] For a review, with tables of many examples, see Larock, R.C. *Solvation/Demercuration Reactions in Organic Synthesis*, Springer, NY, ***1986***, pp. 162–345.

[259] Brown, H.C.; Rei, M. *J. Am. Chem. Soc.* ***1969***, *91*, 5646.

[260] Brown, H.C.; Kurek, J.T.; Rei, M.; Thompson, K.L. *J. Org. Chem.* ***1984***, *49*, 2551; ***1985***, *50*, 1171.

[261] Talybov, G.M.; Mekhtieva, V.Z.; Karaev, S.F. *Russ. J. Org. Chem.* ***2001***, *37*, 600.

[262] Kang, S.H.; Kim, M. *J. Am. Chem. Soc.* ***2003***, *125*, 4684. For an enantioselective example, see Kang, S.H.; Lee, S.B.; Park, C.M. *J. Am. Chem. Soc.* ***2003***, *125*, 15748.

[263] Ballard, D.H.; Bloodworth, A.J. *J. Chem. Soc. C* ***1971***, 945; Sokolov, V.I.; Reutov, O.A. *J. Org. Chem. USSR* ***1969***, *5*, 168. For a review, see Larock, R.C. *Solvation/Demercuration Reactions in Organic Synthesis*, Springer, NY, ***1986***, pp. 346–366.

[264] Garavelas, A.; Mavropoulos, I.; Perlmutter, P.; Westman, F. *Tetrahedron Lett.* ***1995***, *36*, 463.

[265] Quadbeck, G. *Newer Methods Prep. Org. Chem.* ***1963***, *2*, 133–161. See also, Chihara, T.; Teratini, S.; Ogawa, H. *J. Chem. Soc., Chem. Commun.* ***1981***, 1120. For discussions of the mechanism, see Tille, A.; Pracejus, H. *Chem. Ber.* ***1967***, *100*, 196–210; Brady, W.T.; Vaughn, W.L.; Hoff, E.F. *J. Org. Chem.* ***1969***, *34*, 843; Tidwell, T.T. *Acc. Chem. Res.* ***1990***, *23*, 273; Seikaly, H.R.; Tidwell, T.T. *Tetrahedron* ***1986***, *42*, 2587; Satchell, D.P.N.; Satchell, R.S. *Chem. Soc. Rev.* ***1975***, *4*, 231.; Jähme, J.; Rüchardt, C. *Tetrahedron Lett.* ***1982***, *23*, 4011; Poon, N.L.; Satchell, D.P.N. *J. Chem. Soc. Perkin Trans. 2*, ***1984***, 1083; ***1985***, 1551.

[266] Boeckman, Jr., R.K.; Pruitt, J.R. *J. Am. Chem. Soc.* ***1989***, *111*, 8286.

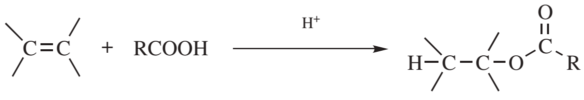
[267] Cannizzaro, C.E.; Strassner, T.; Houk, K.N. *J. Am. Chem. Soc.* ***2001***, *123*, 2668.

Alcohols can also add to alkenes via the α-carbon (see **15-33**).

OS **III**, 371, 774, 813; **IV**, 184, 558; **VI**, 916; **VII**, 66, 160, 304, 334, 381; **VIII**, 204, 254; **IX**, 472.

15-6 Addition of Carboxylic Acids to Form Esters

Hydro-acyloxy-addition



Carboxylic esters are produced by the addition of carboxylic acids to alkenes, a reaction that is usually acid-catalyzed (by proton or Lewis acids[268]) and similar in mechanism to **15-5**. Since Markovnikov's rule is followed, hard-to-get esters of tertiary alcohols can be prepared from alkenes of the form $R_2C{=}CHR$.[269] A combination of V_2O_5 and trifluoroacetic acid converts alkenes to trifluoroacetate esters.[270] 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 (**12-2**).[271] The double bond always migrates (also see, **15-1**) to a position favorable for the reaction, whether this has to be toward or away from the carboxyl group. The use of a chiral *Cinchonidine* alkaloid additive leads to lactone formation with modest enantioselectivity.[272] In the presence of diphenyl diselenide and DDQ, alkene carboxylic acids react of form the lactone with a phenylselenomethyl group ($PhSeCH_2$—) at C-5.[273] Carboxylic esters have also been prepared by the acyloxymercuration-demercuration of alkenes (similar to the procedures mentioned in **15-3** and **15-4**).[274] Conjugated esters has been converted to β-lactones with photolysis and added tributyltin hydride, radical cyclization conditions (**15-30**).[275] Addition of carboxylic acids to alkenes to form esters or lactones is catalyzed by palladium compounds.[276] Thallium acetate also promotes this cyclization reaction.[277]

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[268] See, for example, Guenzet, J.; Camps, M. *Tetrahedron* ***1974***, *30*, 849; Ballantine, J.A.; Davies, M.; Purnell, H.; Rayanakorn, M.; Thomas, J.M.; Williams, K.J. *J. Chem. Soc., Chem. Commun.* ***1981***, 8.

[269] See, for example, Peterson, P.E.; Tao, E.V.P. *J. Org. Chem.* ***1964***, *29*, 2322.

[270] Choudary, B.M.; Reddy, P.N. *J. Chem. Soc., Chem. Commun.* ***1993***, 405.

[271] For a review of such lactonizations, see Ansell, M.F.; Palmer, M.H. *Q. Rev. Chem. Soc.* ***1964***, *18*, 211.

[272] Wang, M.; Gao, L.X.; Mai, W.P.; Xia, A.X.; Wang, F.; Zhang, S.B. *J. Org. Chem.* ***2004***, *69*, 2874.

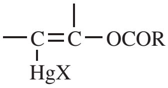
[273] Tiecco, M.; Testaferri, L.; Temperini, A.; Bagnoli, L.; Marini, F.; Santi, C. *Synlett* ***2001***, 1767.

[274] For a review, see Larock, R.C. *Solvation/Demercuration Reactions in Organic Synthesis*, Springer, NY, ***1986***, pp. 367–442.

[275] Castle, K.; Hau, C.-S.; Sweeney, J.B.; Tindall, C. *Org. Lett.* ***2003***, *5*, 757.

[276] Larock, R.C.; Hightower, T.R. *J. Org. Chem.* ***1993***, *58*, 5298; Annby, U.; Stenkula, M.; Andersson, C.-M. *Tetrahedron Lett.* ***1993***, *34*, 8545.

[277] Ferraz, H.M.C.; Ribeiro, C.M.R. *Synth. Commun.* ***1992***, *22*, 399.

Triple bonds can give enol esters[278] or acylals when treated with carboxylic acids. Mercuric salts are usually catalysts,[279] and vinylic mercury compounds  $-\underset{\mathrm{HgX}}{\mathrm{C}}=\overset{|}{\mathrm{C}}-\mathrm{OCOR}$ are intermediates.[280] Terminal alkynes RC≡CH react with CO_2, a secondary amine R'_2 NH, and a ruthenium complex catalyst, to give enol carbamates RCH=CHOC(=O)NR. [281] This reaction has also been performed intramolecularly, to produce unsaturated lactones.[282] Cyclic unsaturated lactones (internal vinyl esters) have been generated from alkyne-carboxylic acids using a palladium catalyst[283] or a ruthenium catalyst.[284] Carboxylic esters can also be obtained by the addition to alkenes of diacyl peroxides.[285] These reactions are catalyzed by copper and are free-radical processes.

Allene carboxylic acids have been cyclized to butenolides with copper(II) chloride.[286] Allene esters were converted to butenolides by treatment with acetic acid and LiBr.[287] Cyclic carbonates can be prepared from allene alcohols using carbon dioxide and a palladium catalyst, and the reaction was accompanied by arylation when iodobenzene was added.[288] Diene carboxylic acids have been cyclized using acetic acid and a palladium catalyst to form lactones that have an allylic acetate elsewhere in the molecule.[289] With ketenes, carboxylic acids give anhydrides[290] and acetic anhydride is prepared industrially in this manner $[CH_2{=}C{=}O + MeCO_2H \rightarrow (MeC{=}O)_2O]$.

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[278] Goossen, L.J.; Paetzold, J.; Koley, D. *Chem. Commun.* ***2003***, 706. For a rhenium catalyzed example, see Hua, R.; Tian, X. *J. Org. Chem.* ***2004***, *69*, 5782.

[279] For the use of rhodium complex catalysts, see Bianchini, C.; Meli, A.; Peruzzini, M.; Zanobini, F.; Bruneau, C.; Dixneuf, P.H. *Organometallics* ***1990***, *9*, 1155.

[280] See for example, Bach, R.D.; Woodard, R.A.; Anderson, T.J.; Glick, M.D. *J. Org. Chem.* ***1982***, *47*, 3707; Bassetti, M.; Floris, B. *J. Chem. Soc. Perkin Trans. 2*, ***1988***, 227; Grishin, Yu.K.; Bazhenov, D.V.; Ustynyuk, Yu.A.; Zefirov, N.S.; Kartashov, V.R.; Sokolova, T.N.; Skorobogatova, E.V.; Chernov, A.N. *Tetrahedron Lett.* ***1988***, *29*, 4631. Ruthenium complexes have also been used as catalysts. See Rotem, M.; Shvo, Y. *Organometallics* ***1983***, *2*, 1689; Mitsudo, T.; Hori, Y.; Yamakawa, Y.; Watanabe, Y. *J. Org. Chem.* ***1987***, *52*, 2230.

[281] Mitsudo, T.; Hori, Y.; Yamakawa, Y.; Watanabe, Y. *Tetrahedron Lett.* ***1987***, *28*, 4417; Mahé, R.; Sasaki, Y.; Bruneau, C.; Dixneuf, P.H. *J. Org. Chem.* ***1989***, *54*, 1518.

[282] See, for example, Sofia, M.J.; Katzenellenbogen, J.A. *J. Org. Chem.* ***1985***, *50*, 2331. For a list of other examples, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, p. 1895.

[283] Liao, H.-Y.; Cheng, C.-H. *J. Org. Chem.* ***1995***, *60*, 3711

[284] Jiménez-Tenorio, M.; Puerta, M.C.; Valerga, P.; Moreno-Dorado, F.J.; Guerra, F.M.; Massanet, G.M. *Chem. Commun.* ***2001***, 2324.

[285] Kharasch, M.S.; Fono, A. *J. Org. Chem.* ***1959***, *24*, 606; Kochi, J.K. *J. Am. Chem. Soc.* ***1962***, *84*, 1572.

[286] Ma, S.; Wu, S. *J. Org. Chem.* ***1999***, *64*, 9314.

[287] Ma, S.; Li, L.; Wei, Q.; Xie, H.; Wang, G.; Shi, Z.; Zhang, J. *Pure. Appl. Chem.* ***2000***, *72*, 1739.

[288] Uemura, K.; Shiraishi, D.; Noziri, M.; Inoue, Y. *Bull. Chem. Soc. Jpn.* ***1999***, *72*, 1063.

[289] Verboom, R.C.; Persson, B.A.; Bäckvall, J.-E. *J. Org. Chem.* ***2004***, *69*, 3102.

[290] For discussions of the mechanism, see Briody, J.M.; Lillford, P.J.; Satchell, D.P.N. *J. Chem. Soc. B* ***1968***, 885; Corriu, R.; Guenzet, J.; Camps, M.; Reye, C. *Bull. Soc. Chim. Fr.* ***1970***, 3679; Blake, P.G.; Vayjooee, M.H.B. *J. Chem. Soc. Perkin Trans. 2*, ***1976***, 1533.

Sulfonic acids add to alkenes and alkynes. The reaction of an alkyne with *para*-toluenesulfonic acid and treatment with silica gives the vinyl sulfonate (C=C—OSO_2Tol).[291] Cyclic sulfonates can be generated by the reaction of an allylic sulfonate salt (C=C—C—OSO_3^-) with silver nitrate in acetonitrile containing an excess of bromine and a catalytic amount of water.[292] Sultones are formed when alkenes react with PhIO and two equivalents of Me_2SiSO_3Cl.[293]

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

C. Sulfur on the Other Side

15-7 Addition of H_2S and Thiols

Hydro-alkylthio-addition

Hydrogen sulfide (H_2S) and thiols add to alkenes to give alkyl thiols or sulfides by electrophilic, nucleophilic, or free-radical mechanisms.[294] In the absence of initiators, the addition to simple alkenes is by an electrophilic mechanism, similar to that in **15-5**, 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 H_2SO_4[295] or together with $AlCl_3$.[296] 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.[297] The addition of thiophenol to an alkene with a zeolite also leads to the anti-Markovnikov sulfide.[298] Additives can influence the regioselectivity. Styrene reacts with thiophenol to give primarily the anti-Markovnikov product, whereas addition of thiophenol in the presence of Montmorillonite K10 clay gives primarily the Markovnikov addition product.[299] 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,

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[291] Braga, A.L.; Emmerich, D.J.; Silveira, C.C.; Martins, T.L.C.; Rodrigues, O.E.D. *Synlett* ***2001***, 371.

[292] Steinmann, J.E.; Phillips, J.H.; Sanders, W.J.; Kiessling, L.L. *Org. Lett.* ***2001***, *3*, 3557.

[293] Bassindale, A.R.; Katampe, I.; Maesano, M.G.; Patel, P.; Taylor, P.G. *Tetrahedron Lett.* ***199***, *40*, 7417.

[294] For a review, see Wardell, J.L., in Patai, S. *The Chemistry of the Thiol Group*, pt. 1, Wiley, NY, ***1974***, pp. 69–178.

[295] Shostakovskii, M.F.; Kul'bovskaya, N.K.; Gracheva, E.P.; Laba, V.I.; Yakushina, L.M. *J. Gen. Chem. USSR* ***1962***, *32*, 707.

[296] Belley, M.; Zamboni, R. *J. Org. Chem.* ***1989***, *54*, 1230.

[297] For reviews of free-radical addition of H_2S and RSH, see Voronkov, M.G.; Martynov, A.V.; Mirskova, A.N. *Sulfur Rep.*, ***1986***, *6*, 77; Griesbaum, K. *Angew. Chem. Int. Ed.* ***1970***, *9*, 273; Oswald, A.A.; Griesbaum, K., in Kharasch, N.; Meyers, C.Y. *Organic Sulfur Compounds*, Vol. 2, Pergamon, Elmsford, NY, ***1966***, pp. 233–256; Stacey, F.W.; Harris Jr., J.F. *Org. React.* ***1963***, *13*, 150, pp. 165–196, 247–324.

[298] Kumar, P.; Pandey, R.K.; Hegde, V.R. *Synlett* ***1999***, 1921.

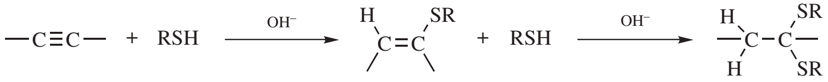
[299] Kanagasabapathy, S.; Sudalai, A.; Benicewicz, B.C. *Tetrahedron Lett.* ***2001***, *42*, 3791.

secondary, or tertiary), ArSH, or RCOSH.[300] The R group may contain various functional groups. The alkenes may be terminal, internal, contain branching, be cyclic, and have various functional groups including OH, COOH, COOR, NO_2, RSO_2, and so on. Addition of Ph_3SiSH to terminal alkenes under radical conditions also leads to the primary thiol.[301]

Alkynes react with thiols to give vinyl sulfides. With alkynes it is possible to add 1 or 2 equivalents of RSH, giving a vinyl sulfide[302] or a dithioketal, respectively. Alternative preparations are available, as in the reaction of a terminal alkyne with $Cp_2Zr(H)Cl$ followed by PhSCl to give the vinyl sulfide with the SPh unit at the less substituted position (PhCH=CHSPh).[303] The intramolecular addition of a thiol to an ene-yne, with a palladium catalyst, leads to substituted thiophene derivatives.[304]

The fundamental addition reaction can be modified by the use of transition metals and different reagents. Alkenes react with diphenyl disulfide in the presence of $GaCl_3$ to give the product with two phenylthio units, PhS—C—C—SPh).[305] The reaction of an alkyne with diphenyl disulfide and a palladium catalyst leads to the bis-vinyl sulfide, PhS—C=C—SPh.[306]

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 type[307] or may be polyhalo alkenes or alkynes.[250] As with the free-radical mechanism, alkynes can give either vinylic thioethers or dithioacetals:



$$-\text{C}\equiv\text{C}- \;+\; \text{RSH} \xrightarrow{\text{OH}^-} \text{C(H)}=\text{C(SR)} \;+\; \text{RSH} \xrightarrow{\text{OH}^-} -\text{CH}_2-\text{C(SR)}_2-$$

Thiols add to alkenes under photochemical conditions to form thioethers, and the reaction can be done intramolecularly to give cyclic thioethers.[308] Thiols also add to alkynes and with a palladium catalyst, vinyl sulfides can be formed.[309] Thiocarbonates function as thiol surrogates, converting alkenes to alkyl thiol in the presence of $TiCl_4$; and CuO.[310]

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 alkene, so that sulfides

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[300] For a review of the addition of thio acids, see Janssen, M.J., in Patai, S. *The Chemistry of Carboxylic Acids and Esters*, Wiley, NY, ***1969***, pp. 720–723.

[301] Haché, B.; Gareau, Y. *Tetrahedron Lett.* ***1994***, *35*, 1837.

[302] See Arjona, O.; Medel, R.; Rojas, J.; Costa, A.M.; Vilarrasa, J. *Tetrahedron Lett.* ***2003***, *44*, 6369.

[303] Huang, X.; Zhong, P.; Guo, W.-r. *Org. Prep. Proceed. Int.* ***1999***, *31*, 201.

[304] Gabriele, B.; Salerno, G.; Fazio, A. *Org. Lett.* ***2000***, *2*, 351.

[305] Usugi, S.; Yorimitsu, H.; Shinokubo, H.; Oshima, K. *Org. Lett.* ***2004***, *6*, 601.

[306] Ananikov, V.P.; Beletskaya, I.P. *Org. Biomol. Chem.* ***2004***, *2*, 284.

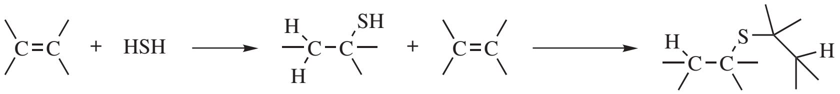
[307] Michael substrates usually give the expected orientation. For a method of reversing the orientation for RS groups (the RS group goes a to the C=O bond of a C=C—C=O system), see Gassman, P.G.; Gilbert, D.P.; Cole, S.M. *J. Org. Chem.* ***1977***, *42*, 3233.

[308] Kirpichenko, S.V.; Tolstikova, L.L.; Suslova, E.N.; Voronkov, M.G. *Tetrahedron Lett.* ***1993***, *34*, 3889.

[309] Kuniyasu, H.; Ogawa, A.; Sato, K.-I.; Ryu, I.; Kambe, N.; Sonoda, N. *J. Am. Chem. Soc.* ***1992***, *114*, 5902.

[310] Mukaiyama, T.; Saitoh, T.; Jona, H. *Chem. Lett.* ***2001***, 638.

are often produced:



As with alcohols, ketenes add thiols to give thiol esters [$R_2C{=}C{=}O + RSH \rightarrow R_2CHCOSR$].[311]

Selenium compounds (RSeH) add in a similar manner to thiols.[312] Vinyl selenides can be prepared from alkynes using diphenyl diselenide and sodium borohydride.[313]

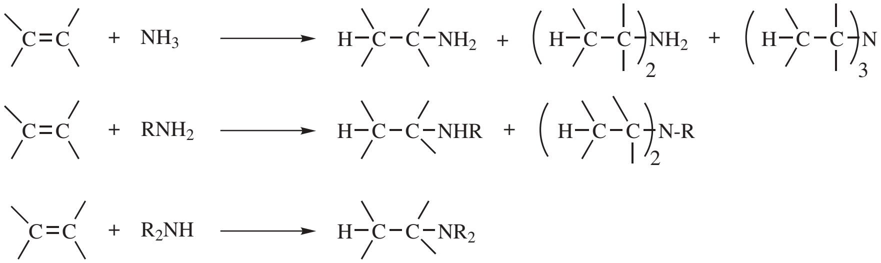
The conjugate addition of thiols to α,β-unsaturated carbonyl derivatives is discussed in **15-31**.

OS **III**, 458; **IV**, 669; **VIII**, 302. See also, OS **VIII**, 458.

D. Nitrogen or Phosphorus on the Other Side

15-8 Addition of Ammonia and Amines, Phosphines, and Related Compounds

Hydro-amino-addition
Hydro-phosphino-addition



Ammonia and primary and secondary amines add to alkenes *that are susceptible* to nucleophilic attack.[314] Ammonia and amines are much weaker acids than water, alcohols, and thiols (see **15-3**, **15-5**, **15-7**) and since acids turn NH_3 into the weak

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[311] For an example, see Blake, A.J.; Friend, C.L.; Outram, R.J.; Simpkins, N.S.; Whitehead, A.J. *Tetrahedron Lett.* ***2001***, *42*, 2877.

[312] Kuniyasu, H.; Ogawa, A.; Sato, K.-I.; Ryu, I.; Sonoda, N. *Tetrahedron Lett.* ***1992***, *33*, 5525.

[313] Dabdoub, M.J.; Baroni, A.C.M.; Lenardão, E.J.; Gianeti, T.R.; Hurtado, G.R. *Tetrahedron* ***2001***, *57*, 4271.

[314] For reviews, see Gasc, M.B.; Lattes, A.; Périé, J.J. *Tetrahedron* ***1983***, *39*, 703; Pines, H.; Stalick, W.M. *Base-Catalyzed Reactions of Hydrocarbons and Related Compounds*, Academic Press, NY, ***1977***, pp. 423–454; Suminov, S.I.; Kost, A.N. *Russ. Chem. Rev.* ***1969***, *38*, 884; Gibson, M.S., in Patai, S. *The Chemistry of the Amino Group*, Wiley, NY, ***1968***, pp. 61–65; Beller, M.; Breindl, C.; Eichberger, M.; Hartung, C.G.; Seayad, J.; Thiel, O.R.; Tillack, A.; Trauthwein, H. *Synlett* ***2002***, 1579. For a discussion of Markovnikov versus anti-Markovnikov selectivity, see Tillack, A.; Khedkar, V.; Beller, M. *Tetrahedron Lett.* ***2004***, *45*, 8875.

acid, the ammonium ion NH_4^+, this reaction does not occur by an electrophilic mechanism. The reaction tends to give very low yields, if any, with ordinary alkenes, 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 ethylene[315]). Amine alkenes give cyclic amines as the major product, in good yield, when treated with *n*-butyllithium.[316] Ammonia gives three possible products, since the initial product is a primary amine, which may add to a second molecule of alkene, and so on. Similarly, primary amines give both secondary and tertiary products. In practice it is usually possible to control which product predominates. The mechanism is nearly always nucleophilic, and the reaction is generally performed on polyhalo alkenes[317] and alkynes.[318] Ammonia adds to alkenes photochemically.[319] Reaction of a secondary amine with butyllithium generates an amide base, which reacts with alkenes to give alkyl amines,[320] and can add intramolecularly to an alkene to form a pyrrolidine.[321] Pyrroles can be generated in this manner.[322] *N*-Chloroamines add to alkenes intramolecularly to give β-chloropyrrolidines.[323]

Conjugated carbonyl compounds react via conjugate addition with amines to give β-amino derivatives (see **15-31**)[324] As expected, on Michael-type substrates the nitrogen goes to the carbon that does not carry the Z. With substrates of the form RCH=CZZ′, the same type of cleavage of the adduct can take place as in **15-3**.[325]

There are many examples of transition catalyzed addition of nitrogen compounds to alkenes, alkynes,[326] and so on. Secondary amines can be added to certain nonactivated alkenes if palladium(II) complexes are used as catalysts.[327]

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[315] Howk, B.W.; Little, E.L.; Scott, S.L.; Whitman, G.M. *J. Am. Chem. Soc.* ***1954***, *76*, 1899.

[316] Ates, A.; Quinet, C. *Eur. J. Org. Chem.* ***2003***, 1623.

[317] For a review with respect to fluoroalkenes, see Chambers, R.D.; Mobbs, R.H. *Adv. Fluorine Chem.* ***1965***, *4*, 51–112, pp. 62–68.

[318] For an intramolecular example see Cossy, J.; Belotti, D.; Bellosta, V.; Boggio, C. *Tetrahedron Lett.* ***1997***, *38*, 2677. For intramolecular addition to a 1-ethoxy alkyne, see MaGee, D.I.; Ramaseshan, M. *Synlett* ***1994***, 743.

[319] Yasuda, M.; Kojima, R.; Ohira, R.; Shiragami, T.; Shima, K. *Bull. Chem. Soc. Jpn.* ***1998***, *71*, 1655.

[320] Hartung, C.G.; Breindl, C.; Tillack, A.; Beller, M. *Tetrahedron* ***2000***, *56*, 5157.

[321] Fujita, H.; Tokuda, M.; Nitta, M.; Suginome, H. *Tetrahedron Lett.* ***1992***, *33*, 6359.

[322] Dieter, R.K.; Yu, H. *Org. Lett.* ***2000***, *2*, 2283.

[323] Göttlich, R. *Synthesis* ***2000***, 1561; Göttlich, R.; Noack, M. *Tetrahedron Lett* ***2001***, *42*, 7771 For a reaction with an *N*-bromoamine, see Outurquin, F.; Pannecoucke, X.; Berthe, B.; Paulmier, C. *Eur. J. Org. Chem.* ***2002***, 1007. For a $TiCl_3$—$AlMe_3$ mediated reaction, see Sjöholm, Å.; Hemmerling, M.; Pradeille, N.; Somfai, P. *J. Chem. Soc., Perkin Trans. 1* ***2001***, 891. For a variation with a sulfonamide and iodine, see Jones, A.D.; Knight, D.W.; Hibbs, D.E. *J. Chem. Soc., Perkin Trans. 1* ***2001***, 1182

[324] See Cossu, S.; DeLucchi, O.; Durr, R. *Synth. Commun.* ***1996***, *26*, 4597 for an example involing methyl 2-propynoate.

[325] See, for example, Bernasconi, C.F.; Murray, C.J. *J. Am. Chem. Soc.* ***1986***, *108*, 5251, 5257; Bernasconi, C.F.; Bunnell, R.D. *J. Org. Chem.* ***1988***, *53*, 2001.

[326] For a review, see Doye, S. *Synlett* ***2004***, 1653.

[327] For a review, see Gasc, M.B.; Lattes, A.; Périé, J.J. *Tetrahedron* ***1983***, *39*, 703. For a review of metal-catalyzed nucleophilic addition, see Bäckvall, J. *Adv. Met.-Org. Chem.* ***1989***, *1*, 135. See Löber, O.; Kawatsura, M.; Hartwig, J.F. *J. Am. Chem. Soc.* ***2001***, *123*, 4366.

The complexation lowers the electron density of the double bond, facilitating nucleophilic attack.[328] Markovnikov orientation is observed and the addition is anti.[329] Molybdenum,[330] titanium,[331] Yttrium,[332] and rhodium compounds[333] have been used in the addition of amines to alkenes. An intramolecular addition of an amine unit to an alkene to form a pyrrolidine was reported using a palladium catalyst,[334] a lanthanide reagent,[335] or an yttrium reagent.[336] Aniline reacts with dienes and a palladium catalyst to give allylic amines.[337] Diene amines react with samarium catalysts to give 2-alkenyl pyrrolidines.[338] Addition of secondary amines to dihydropyrans using a palladium catalyst gave the corresponding aminal (an α-amino ether).[339] Reduction of nitro compounds in the presence of rhodium catalysts, in the presence of alkenes, CO and H_2, leads to an amine unit adding to the alkene moiety.[340] Secondary amines react with alkenes to give the alkyl amine using a rhodium catalyst in a CO/H_2 atmosphere,[341] but modification of the chromium catalyst and conditions led to an enamine.[342] Note that the reaction of an alkene and a secondary amine with a rhodium catalyst can also give an enamine.[343]

Other nitrogen compounds, among them hydroxylamine and hydroxylamines,[344] hydrazines, and amides (**15-9**), also add to alkenes. Azodicarboxylates (Boc-N=N-Boc) react with alkenes, in the presence of $PhSiH_3$ and a cobalt catalyst, to give

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[328] For a discussion of the mechanism, see Hegedus, L.S.; Åkermark, B.; Zetterberg, K.; Olsson, L.F. *J. Am. Chem. Soc.* ***1984***, *106*, 7122.

[329] Åkermark, B.; Zetterberg, K. *J. Am. Chem. Soc.* ***1984***, *106*, 5560; Utsunomiya, M.; Hartwig, J.F. *J. Am. Chem. Soc.* ***2003***, *125*, 14286.

[330] Srivastava, R.S.; Nicholas, K.M. *Chem. Commun.* ***1996***, 2335.

[331] Ackermann, L.; Kaspr, L.T.; Gschrei, C.J. *Org. Lett.* ***2004***, *6*, 2515. See Castro, I.G.; Tillack, A.; Hartung, C.G.; Beller, M. *Tetrahedron Lett.* ***2003***, *44*, 3217.

[332] O'Shaughnessy, P.N.; Scott, P. *Tetrahedron Asymmetry* ***2003***, *14*, 1979.

[333] The anti-Markovkinov amine is produced: Utsunomiya, M.; Kuwano, R.; Kawatsura, M.; Hartwig, J.F. *J. Am. Chem. Soc.* ***2003***, *125*, 5608; Utsonomiya, M.; Hartwig, J.F. *J. Am. Chem. Soc.* ***2004***, *126*, 2702; Ahmed, M.; Seayad, A.M.; Jackstell, R.; Beller, M. *J. Am. Chem. Soc.* ***2003***, *125*, 10311.

[334] Fix, S.R.; Brice, J.L.; Stahl, S.S. *Angew. Chem. Int. Ed.* ***2002***, *41*, 164.

[335] Molander, G.A.; Dowdy, E.D. *J. Org. Chem.* ***1998***, *63*, 8983; Ryu, J.-S.; Marks, T.J.; McDonald, F.E. *Org. Lett.* ***2001***, *3*, 3091. The use of a chiral lanthanum catalyst led to pyrrolidines with modest asymmetric induction: Hong, S.; Tian, S.; Metz, M.V.; Marks, T.J. *J. Am. Chem. Soc.* ***2003***, *125*, 14768.

[336] Kim, Y.K.; Livinghouse, T.; Bercaw, J.E. *Tetrahedron Lett.* ***2001***, *42*, 2933.

[337] Minami, T.; Okamoto, H.; Ikeda, S.; Tanaka, R.; Ozawa, F.; Yoshifuji, M. *Angew. Chem. Int. Ed.* ***2001***, *40*, 4501.

[338] Hong, S.; Marks, T.J. *J. Am. Chem. Soc.* ***2002***, *124*, 7886.

[339] Cheng, X.; Hii, K.K. *Tetrahedron* ***2001***, *57*, 5445.

[340] Rische, T.; Eilbracht, P. *Tetrahedron* ***1998***, *54*, 8441; Akazome, M.; Kondo, T.; Watanabe, Y. *J. Org. Chem.* ***1994***, *59*, 3375.

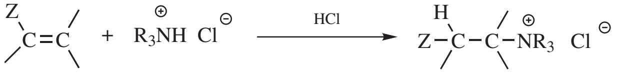
[341] Rische, J.; Bärfacker, L.; Eilbracht, P. *Eur. J. Org. Chem.* ***1999***, 653; Lin, Y.-S.; El Ali, B.; Alper, H. *Tetrahedron Lett.* ***2001***, *42*, 2423.

[342] Ahmed, M.; Seayad, A.M.; Jackstell, R.; Beller, M. *Angew. Chem. Int. Ed.* ***2003***, *42*, 5615.

[343] Tillack, A.; Trauthwein, H.; Hartung, C.G.; Eichberger, M.; Pitter, S.; Jansen, A.; Beller, M. *Monat. Chem.* ***2000***, *131*, 1327.

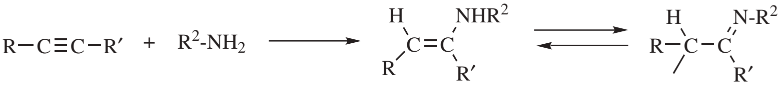
[344] Lin, X.; Stien, D.; Weinreb, S.M. *Tetrahedron Lett.* ***2000***, *41*, 2333; Singh, S.; Nicholas, K.M. *Synth. Commun.* ***2001***, *31*, 3087.

alkylhydrazides [RN(Boc)–NHBoc].[345] 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.[346]



The tertiary amine can be aliphatic, cycloalkyl, or heterocyclic (including pyridine). The reaction of NaOH with an amine containing two distal alkene units, followed by addition of a neodymium catalyst leads to a bicyclic amine.[347]

Primary amines add to triple bonds[348] to give enamines that have a hydrogen on the nitrogen and (analogously to enols) tautomerize to the more stable imines, **41**.[349]



41

The reaction has been done with a palladium catalyst,[350] a titanium catalyst,[351] a tantalum catalyst,[352] and with a gold catalyst.[353] An intramolecular addition of amines to an alkyne unit in the presence of a palladium catalyst generated heterocyclic or cyclic amine compounds.[354] The titanium catalyzed addition of primary

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[345] Waser, J.; Carreira, E.M. *J. Am. Chem. Soc.* ***2004***, *126*, 5676.

[346] Le Berre, A.; Delacroix, A. *Bull. Soc. Chim. Fr.* ***1973***, 640, 647. See also, Vogel, D.E.; Büchi, G. *Org. Synth., 66*, 29.

[347] Molander, G.A.; Pack, S.K. *J. Org. Chem.* ***2003***, *68*, 9214.

[348] For a review of addition of ammonia and amines to triple bonds, see Chekulaeva, I.A.; Kondrat'eva, L.V. *Russ. Chem. Rev.* ***1965***, *34*, 669. For reactions with aniline, see Haak, E.; Bytschkov, I.; Doye, S. *Angew. Chem. Int. Ed.* ***1999***, *38*, 3389; Hartung, C.G.; Tillack, A.; Trauthwein, H.; Beller, M. *J. Org. Chem.* ***2001***, *66*, 6339.

[349] For example, see Kruse, C.W.; Kleinschmidt, R.F. *J. Am. Chem. Soc.* ***1961***, *83*, 213, 216.

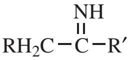
[350] Kadota, I.; Shibuya, A.; Lutete, L.M.; Yamamoto, Y. *J. Org. Chem.* ***1999***, *64*, 4570.

[351] Khedkar, V.; Tillack, A.; Beller, M. *Org. Lett.* ***2003***, *5*, 4767; Tillack, A.; Castro, I.G.; Hartung, C.G.; Beller, M. *Angew. Chem. Int. Ed.* ***2002***, *41*, 2541.

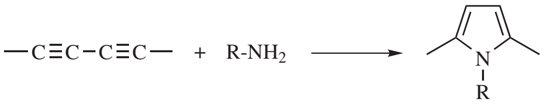
[352] Anderson, L.L.; Arnold, J.; Bergman R.G. *Org. Lett.* ***2004***, *6*, 2519; Shi, Y.; Hall, C.; Ciszewski, J.T.; Cao, C.; Odom, A.L. *Chem. Commun.* ***2003***, 586; Cao, C.; Li, Y.; Shi, Y.; Odom, A.L. *Chem. Commun.*, ***2004***, 2002.

[353] Mizushima, E.; Hayashi, T.; Tanaka, M. *Org. Lett.* ***2003***, *5*, 3349.

[354] Müller, T.E. *Tetrahedron Lett.* ***1998***, *39*, 5961; Hiroya, K.; Matsumoto, S.; Sakamoto, T. *Org. Lett.* ***2004***, *6*, 2953; Lutete, L.M.; Kadota, I.; Yamamoto, Y. *J. Am. Chem. Soc.* ***2004***, *126*, 1622; Hiroya, K.; Itoh, S.; Ozawa, M.; Kanamori, Y.; Sakamoto, T. *Tetrahedron Lett.* ***2002***, *43*, 1277. See also, Karur, S.; Kotti, S.R.S.S.; Xu, X.; Cannon, J.F.; Headley, A.; Li, G. *J. Am. Chem. Soc.* ***2003***, *125*, 13340.

amines to alkynes give the enamine, which can be hydrogenated (**15-11**) to give the corresponding amine.[355] A variation treats an alkynyl imine with CuI to form pyrroles.[356] *N,N*-Diphenylhydrazine reacts with diphenyl acetylene and a titanium catalyst to give indole derivatives.[357] Treatment of an imine of 2-alkynyl benzaldehyde with iodide gave a functionalized isoquinoline.[358] When ammonia is used instead of a primary amine, the corresponding  $RH_2C-\overset{\overset{\displaystyle NH}{\|}}{C}-R'$ is not stable enough for isolation, but polymerizes. Ammonia and primary amines (aliphatic and aromatic) add to conjugated diynes to give pyrroles, **42**.[359] A similar preparation of pyrroles was reported by heating non-conjugated diynes with aniline and a titanium catalyst.[360] This is not 1,4-addition, but 1,2-addition twice. Conjugated ene-ynes containing an amino group also give pyrroles with a palladium catalyst.[361]

Allenes are reaction partners,[362] and amines add to allenes in the presence of a catalytic amount of CuBr[363] or palladium compounds.[364] Intramolecular reaction of allene amines lead to dihydropyrroles, using a gold catalyst.[365]



42

Treatment of an allene amine with a ruthenium catalyst, 10% of $TiCl_4$ and methyl vinyl ketone to give a product of amine addition followed by Michael addition, a pyrrolidine derivative with a pendant alkenyl ketone unit.[366] Cyclic imines can be prepared from allene amines using a titanium catalyst.[367]

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[355] Haak, E.; Siebeneicher, H.; Doye, S. *Org. Lett.* ***2000***, *2*, 1935; Bytschkov, I.; Doye, S. *Eur. J. Org. Chem.* ***2001***, 4411. For a variation using sodium cyanoborohydride and zinc chloride as the reducing agent, see Heutling, A.; Doye, S. *J. Org. Chem.* ***2002***, *67*, 1961.

[356] Kel'in, A.; Sromek, A.W.; Gevorgyan, V. *J. Am. Chem. Soc.* ***2001***, *123*, 2074. Another variation used a chromium carbene species to generate pyrroles from imino ene-ynes: Zhang, Y.; Herndon, J.W. *Org. Lett.* ***2003***, *5*, 2043.

[357] Ackermann, L.; Born, R. *Tetrahedron Lett.* ***2004***, *45*, 9541. For a different approach using hypervalent iodine, see Barluenga, J.; Trincado, M.; Rubio, E.; González, J.M. *Angew. Chem. Int. Ed.* ***2003***, *42*, 2406.

[358] Huang, Q.; Hunter, J.A.; Larock, R.C *J. Org. Chem.* ***2002***, *67*, 3437.

[359] Schult, K.E.; Reisch, J.; Walker, H. *Chem. Ber.* ***1965***, *98*, 98.

[360] Ramanathan, B.; Keith, A.J.; Armstrong, D.; Odom, A.L. *Org. Lett.* ***2004***, *6*, 2957.

[361] Gabriele, B.; Salerno, G.; Fazio, A.; Bossio, M.R. *Tetrahedron Lett.* ***2001***, *42*, 1339; Gabriele, B.; Salerno, G.; Fazio, A. *J. Org. Chem.* ***2003***, *68*, 7853.

[362] Meguro, M.; Yamamoto, Y. *Tetrahedron Lett.* ***1998***, *39*, 5421.

[363] Geri, R.; Polizzi, C.; Lardicci, L.; Caporusso, A.M. *Gazz. Chim. Ital.*, ***1994***, *124*, 241.

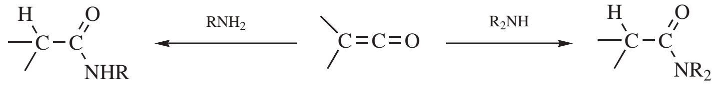
[364] Davies, I.W.; Scopes, D.I.C.; Gallagher, T. *Synlett* ***1993***, 85.

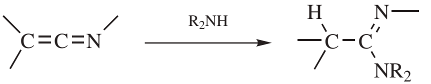
[365] Morita, N.; Krause, N. *Org. Lett.* ***2004***, *6*, 4121.

[366] Trost, B.M.; Pinkerton, A.B.; Kremzow, D. *J. Am. Chem. Soc.* ***2000***, *122*, 12007.

[367] Ackermann, L.; Bergman, R.G. *Org. Lett.* ***2002***, *4*, 1475; Ackerman, L.; Bergman, R.G.; Loy, R.N. *J. Am. Chem. Soc.* ***2003***, *125*, 11956.

Primary and secondary amines add to ketenes to give, respectively, *N*-substituted and *N,N*-disubstituted amides:[368] and to ketenimines to give amidines, **43**.[369]

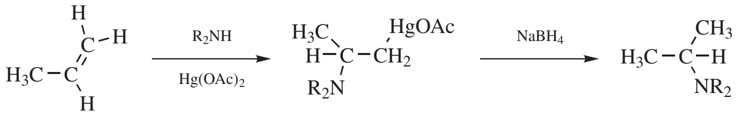




43

R = H or alkyl

NH_3 can be added to double bonds (even ordinary double bonds) in an indirect manner by the use of hydroboration (**15-16**) followed by treatment with NH_2Cl or NH_2OSO_2OH (**12-32**). 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 **15-3** for the analogous oxymercuration–demercuration procedure), to give amine **45**.[370]



44 **45**

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. For conversion of **44** to other products, see **15-53**.

Phosphines add to alkenes to give alkyl phosphines and to alkynes to give vinyl phosphines. In the presence of an ytterbium (Yb) catalyst, diphenylphosphine added to diphenyl acetylene to give the corresponding vinyl phosphine.[371] A palladium catalyst was used for the addition *o*-diphenylphosphine to terminal alkynes, giving the anti-Markovnikov vinyl phosphine but a nickel catalyst led to the Markovnikov vinyl phosphine.[372] Alkenes also react with diarylphosphines

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[368] For discussions of the mechanism of this reaction, see Briody, J.M.; Satchell, D.P.N. *Tetrahedron* ***1966***, *22*, 2649; Tidwell, T.T. *Acc. Chem. Res.* ***1990***, *23*, 273; Satchell, D.P.N.; Satchell, R.S. *Chem. Soc. Rev.* ***1975***, *4*, 231. For an enantioselective reaction, see Hodous, B.L.; Fu, G.C. *J. Am. Chem. Soc.* ***2002***, *124*, 10006.

[369] Stevens, C.L.; Freeman, R.C.; Noll, K. *J. Org. Chem.* ***1965***, *30*, 3718.

[370] For a review, see Larock, R.C. *Solvation/Demercuration Reactions in Organic Synthesis*, Springer, NY, ***1986***, pp. 443–504. See also, Barluenga, J.; Perez-Prieto, J.; Asensio, G. *Tetrahedron* ***1990***, *46*, 2453.

[371] Takaki, K.; Koshoji, G.; Komeyama, K.; Takeda, M.; Shishido, T.; Kitani, A.; Takehira, K. *J. Org. Chem.* ***2003***, *68*, 6554.

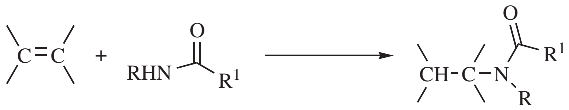
[372] Kazankova, M.A.; Efimova, I.V.; Kochetkov, A.N.; Atanas'ev, V.V.; Beletskaya, I.P.; Dixneuf, P.H. *Synlett* ***2001***, 497.

and a nickel catalyst. to give the alkyl phosphine[373] Silylphosphines ($R_3Si—PAr_2$) react with alkenes and Bu_4NF to give the anti-Markovnikov ally phosphine.[374] Phosphine oxides can be prepared by the reaction of an aryl substituted alkene and diphenylphosphine oxide, $Ph_2P(=O)H$.[375] Diphenylphosphine oxide also reacted with terminal alkynes to give the anti-Markovnikov vinyl phosphine oxide using a rhodium catalyst.[376] Phosphonate esters were similar prepared from alkenes and diethyl phosphite, $(EtO_2)P(=O)H$, and a manganese catalyst in a reaction exposed to oxygen.[377] Similar addition was observed in the reaction of an alkene with NaH_2PO_2 to give the phosphinate, $RCH=CH_2 \rightarrow RCH_2CH_2PH(=O)ONa$.[378] Palladium catalysts were used for the preparation of similar compounds from alkenes[379] and the reaction of terminal alkynes with dimethyl phosphite and a nickel catalyst gave the Markovnikov vinyl phosphonate ester.[380] Other phosphites were added to dienes to give an allylic phosphonate ester using a palladium catalyst.[381] Diarylphosphines react with vinyl ethers and a nickel catalyst to give α-alkoxy phosphonate esters.[382]

OS **I**, 196; **III**, 91, 93, 244, 258; **IV**, 146, 205; **V**, 39, 575, 929; **VI**, 75, 943; **VIII**,188, 190, 536; **80**, 75. See also, OS **VI**, 932.

15-9 Addition of Amides

Hydro-amido-addition



Under certain conditions, amides can add directly to alkenes to form *N*-alkylated amides. Sulfonamides react in a similar manner. 3-Pentenamide was cyclized to 5-methyl-2-pyrrolidinone by treatment with trifluorosulfonic acid.[383] Acyl hydrazine derivatives also cyclized in the presence of hypervalent iodine reagents to give lactams.[384] When a carbamate was treated with Bu_3SnH, and AIBN, addition to an alkene led to a bicyclic lactam.[385]

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[373] Shulyupin, M.O.; Kazankova, M.A.; Beletskaya, I.P. *Org. Lett.*, ***2002***, *4*, 761.

[374] Hayashi, M.; Matsuura, Y.; Watanabe, Y. *Tetrahedron Lett.* ***2004***, *45*, 9167.

[375] Bunlaksananusorn, T.; Knochel, P. *J. Org. Chem.* ***2004***, *69*, 4595; Rey, P.; Taillades, J.; Rossi, J.C.; Gros, G. *Tetrahedron Lett.* ***2003***, *44*, 6169.

[376] Han, L.-B.; Zhao, C.-Q.; Tanaka, M. *J. Org. Chem.* ***2001***, *66*, 5929.

[377] Tayama, O.; Nakano, A.; Iwahama, T.; Sakaguchi, S.; Ishii, Y. *J. Org. Chem.* ***2004***, *69*, 5494.

[378] Deprèle, S.; Montchamp, J.-L. *J. Org. Chem.* ***2001***, *66*, 6745.

[379] Deprèle, S.; Montchamp, J.-L. *J. Am. Chem. Soc.* ***2002***, *124*, 9386.

[380] Han, L.-B.; Zhang, C.; Yazawa, H.; Shimada, S. *J. Am. Chem. Soc.* ***2004***, *126*, 5080.

[381] Mirzaei, F.; Han, L.-B.; Tanaka, M. *Tetrahedron Lett.* ***2001***, *42*, 297.

[382] Kazankova, M.A.; Shulyupin, M.O.; Beletskaya, I.P. *Synlett* ***2003***, 2155.

[383] Marson, C.M.; Fallah, A. *Tetrahedron Lett.* ***1994***, *35*, 293.

[384] Scartozzi, M.; Grondin, R.; Leblanc, Y. *Tetrahedron Lett.* ***1992***, *33*, 5717.

[385] Callier, A.-C.; Quiclet-Sire, B.; Zard, S.Z. *Tetrahedron Lett.* ***1994***, *35*, 6109.

The reaction can be done intramolecularly. *N*-Benzyl pent-4-ynamide reacted with tetrabutylammonium fluoride to an alkylidene lactam.[386] Similar addition of a tosylamide-alkene, with a palladium catalyst, led to a vinyl *N*-tosyl pyrrolidine.[387] Similar cyclization reactions occur with tosylamide-alkynes.[388]

Treatment of triflamide alkenes with triflic acid gives the corresponding *N*-triflyl cyclic amine.[389] Using an alkene halide and an *N*-chlorosulfonamide, an amide is generated *in situ*, and addition to the alkene gives a pyrrolidine derivative.[390] *N*-Bromocarbamates also add to alkenes, in the presence of $BF_3•OEt_2$ to give a *vic*-bromo *N*-Boc amine.[391] The titanium catalyzed reaction of alkenyl *N*-tosylamines give *N*-tosyl cyclic amines.[392]

Alkynes and allenes also react with amides. Phenylthiomethyl alkynes were converted to *N*-Boc-*N*-phenylthio allenes with Boc azide and an iron catalyst.[393] The palladium-catalyzed reaction of an allene amide, with iodobenzene, leads to *N*-sulfonyl aziridines having an allylic group at C1.[394] Other allene *N*-tosylamines similarly give *N*-tosyl tetrahydropyridines.[395]

Imides can also add to alkenes or alkynes. Ethyl 2-propynoate reacted with phthalimide, in the presence of a palladium catalyst, to give ethyl 2-phthalimido-2-propenoate.[396]

15-10 Addition of Hydrazoic Acid

Hydro-azido-addition

Hydrazoic acid (HN_3) can be added to certain Michael-type substrates (Z is as defined on p. 1007) to give β-azido compounds.[397] The reaction apparently fails if R

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[386] Jacobi, P.A.; Brielmann, H.L.; Hauck, S.I. *J. Org. Chem.* ***1996***, *61*, 5013.

[387] Larock, R.C.; Hightower, T.R.; Hasvold, L.A.; Peterson, K.P. *J. Org. Chem.* ***1996***, *61*, 3584; Harris, Jr., G.D.; Herr, R.J.; Weinreb, S.M. *J. Org. Chem.* ***1993***, *58*, 5452. See also, Pinho, P.; Minnaard, A.J.; Feringa, B.L. *Org. Lett.* ***2003***, *5*, 259.

[388] Luo, F.-T.; Wang, R.-T. *Tetrahedron Lett.* ***1992***, *33*, 6835.

[389] Schlummer, B.; Hartwig, J.F. *Org. Lett.* ***2002***, *4*, 1471; Haskins, C.M.; Knight, D.W. *Chem. Commun.* ***2002***, 2724.

[390] Minakata, S.; Kano, D.; Oderaotoshi, Y.; Komatsu, M. *Org. Lett.* ***2002***, *4*, 2097.

[391] Ś liwnń ska, A.; Zwierzak, A. *Tetrahedron* ***2003***, *59*, 5927.

[392] Miura, K.; Hondo, T.; Nakagawa, T.; Takahashi, T.; Hosomi, A. *Org. Lett.* ***2000***, *2*, 385.

[393] Bacci, J.P.; Greenman, K.L.; van Vranken, D.L. *J. Org. Chem.* ***2003***, *68*, 4955.

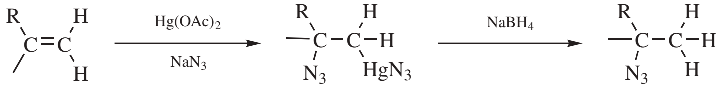
[394] Ohno, H.; Toda, A.; Miwa, Y.; Taga, T.; Osawa, E.; Yamaoka, Y.; Fujii, N.; Ibuka, T. *J. Org. Chem.* ***1999***, *64*, 2992.

[395] Rutjes, F.P.J.T.; Tjen, K.C.M.F.; Wolf, L.B.; Karstens, W.F.J.; Schoemaker, H.E.; Hiemstra, H. *Org. Lett.* ***1999***, *1*, 717; Na, S.; Yu, F.; Gao, W. *J. Org. Chem.* ***2003***, *68*, 5943; Ma. S.; Gao, W. *Org. Lett.* ***2002***, *4*, 2989.

[396] Trost, B.M.; Dake, G.R. *J. Am. Chem. Soc.* ***1997***, *119*, 7595.

[397] Boyer, J.H. *J. Am. Chem. Soc.* ***1951***, *73*, 5248; Harvey, G.R.; Ratts, K.W. *J. Org. Chem.* ***1966***, *31*, 3907. For a review, see Biffin, M.E.C.; Miller, J.; Paul, D.B., in Patai, S. *The Chemistry of the Azido Group*, Wiley, NY, ***1971***, pp. 120–136.

is phenyl. The HN_3 also adds to enol ethers $CH_2{=}CHOR$ to give $CH_3{-}CH(OR)N_3$, and to silyl enol ethers,[398] 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.[398] Hydrazoic acid can also be added indirectly to ordinary alkenes by azidomercuration, followed by demercuration,[399] analogous to the similar procedures

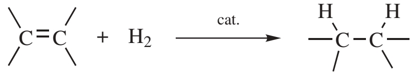


mentioned in **15-3**, **15-5**, **15-6**, and **15-8**. The method can be applied to terminal alkenes or strained cycloalkenes (e.g., norbornene) but fails for unstrained internal alkenes.

E. Hydrogen on Both Sides

15-11 Hydrogenation of Double and Triple Bonds[400]

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.[401] Almost all known alkenes added hydrogen at temperatures between 0 and 275°C. The catalysts used can be divided into

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[398] Hassner, A.; Fibiger, R.; Andisik, D. *J. Org. Chem.* ***1984***, *49*, 4237.

[399] Heathcock, C.H. *Angew. Chem. Int. Ed.* ***1969***, *8*, 134. For a review, see Larock, R.C. *Solvation/Demercuration Reactions in Organic Synthesis*, Springer, NY, ***1986***, pp. 522–527.

[400] For a review, see Mitsui, S.; Kasahara, A., in Zabicky, J. *The Chemistry of Alkenes*, Vol. 2, Wiley, NY, ***1970***, pp. 175–214. Also see, Smith, M.B. *Organic Synthesis*, 2nd ed., McGraw-Hill, NY, ***2001***, pp. 369–382.

[401] For books on catalytic hydrogenation, see Rylander, P.N. *Hydrogenation Methods*, Academic Press, NY, ***1985***; *Catalytic Hydrogenation in Organic Synthesis*, Academic Press, NY, ***1979***; *Catalytic Hydrogenation over Platinum Metals*, Academic Press, NY, ***1967***; Červený, L. *Catalytic Hydrogenation*, Elsevier, NY, ***1986*** (this book deals mostly with industrial aspects); Freifelder, M. *Catalytic Hydrogenation in Organic Synthesis*, Wiley, NY, ***1978***; *Practical Catalytic Hydrogenation*, Wiley, NY, ***1971***; Augustine, R.L. *Catalytic Hydrogenation*, Marcel Dekker, NY, ***1965***. For reviews, see Parker, D., in Hartley, F.R. *The Chemistry of the Metal–Carbon Bond*, Vol. 4, Wiley, NY, ***1987***, pp. 979–1047; Carruthers, W. *Some Modern Methods of Organic Synthesis* 3rd ed., Cambridge University Press, Cambridge, ***1986***, pp. 411–431; Colquhoun, H.M.; Holton, J.; Thompson, D.J.; Twigg, M.V. *New Pathways for Organic Synthesis*, Plenum, NY, ***1984***, pp. 266–300, 325–334; Kalinkin, M.I.; Kolomnikova, G.D.; Parnes, Z.N.; Kursanov, D.N. *Russ. Chem. Rev.* ***1979***, *48*, 332; Candlin, J.P.; Rennie, R.A.C. in Bentley, K.W.; Kirby, G.W. *Elucidation of Organic Structures by Physical and Chemical Methods*, 2nd ed. (Vol. 4 of Weissberger, A. *Techniques of Chemistry*), pt. 2, Wiley, NY, ***1973***, pp. 97–117; House, H.O. *Modern Synthetic Reactions*, 2nd ed., W.A. Benjamin, NY, ***1972***, pp, 1–34.

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,[402] palladium-on-charcoal (perhaps the most common),[403] $NaBH_4$-reduced nickel[404] (also called nickel boride), platinum metal or its oxide, rhodium, ruthenium, and zinc oxide.[405] (*2*) Catalysts soluble in the reaction medium (*homogeneous catalysts*).[406] An important example is chlorotris(triphenylphosphine)rhodium, $RhCl(Ph_3P)_3$,[407] (**100**, *Wilkinson's catalyst*),[408] which catalyzes the hydrogenation of many alkenyl compounds without disturbing such groups as COOR, NO_2, CN, or COR present in the same molecule.[409] Even unsaturated aldehydes can be reduced to saturated aldehydes,[410] although in this case decarbonylation (**14-32**) may be a side reaction. In general, for catalytic hydrogenation, many functional groups may be present in the molecule, for example, OH, COOH, NR_2 including NH_2, N(R)COR′ including carbamates,[411] CHO, COR, COOR, or CN. Vinyl esters can be hydrogenated using homogeneous rhodium catalyst.[412] Enamides are hydrogenated, with excellent enantioselectivity, using chiral rhodium catalysts.[413] Some of these groups are also susceptible to catalytic reduction, but it is usually possible to find conditions

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[402] For a review of Raney nickel, see Pizey, J.S. *Synthetic Reagents*, Vol. 2, Wiley, NY, ***1974***, pp. 175–311. Double bonds have been reduced with Raney nickel alone; with no added H_2. The hydrogen normally present in this reagent was sufficient: Pojer, P.M. *Chem. Ind. (London)* ***1986***, 177.

[403] A recyclable $Pd/CaCO_3$ catalyst in polyethylene glycol (PEG) as been reported. See Chandrasekhar, S.; Narsihmulu, Ch.; Chandrashekar, G.; Shyamsunder, T. *Tetrahedron Lett.* ***2004***, *45*, 2421.

[404] Paul, R.; Buisson, P.; Joseph, N. *Ind. Eng. Chem.* ***1952***, *44*, 1006; Brown, C.A. *Chem. Commun.* ***1969***, 952; *J. Org. Chem.* ***1970***, *35*, 1900. For a review of reductions with nickel boride and related catalysts, see Ganem, B.; Osby, J.O. *Chem. Rev.* ***1986***, *86*, 763.

[405] For reviews of hydrogenation with metal oxides, see Minachev, Kh.M.; Khodakov, Yu.S.; Nakhshunov, V.S. *Russ. Chem. Rev.* ***1976***, *45*, 142; Kokes, R.J.; Dent, A.L. *Adv. Catal.* ***1972***, *22*, 1 (ZnO).

[406] For a monograph, see James, B.R. *Homogeneous Hydrogenation*, Wiley, NY, ***1973***. For reviews, see Collman, J.P.; Hegedus, L.S.; Norton, J.R.; Finke, R.G. *Principles and Applications of Organotransition Metal Chemistry*, University Science Books, Mill Valley, CA ***1987***, pp. 523–564; Birch, A.J.; Williamson, D.H. *Org. React.* ***1976***, *24*, 1; James, B.R. *Adv. Organomet. Chem.* ***1979***, *17*, 319; Harmon, R.E.; Gupta, S.K.; Brown, D.J. *Chem. Rev.* ***1973***, *73*, 21; Strohmeier, W. *Fortschr. Chem. Forsch.* ***1972***, *25*, 71; Heck, R.F. *Organotransition Metal Chemistry*, Academic Press, NY, ***1974***, pp. 55–65; Rylander, P.N. *Organic Syntheses with Noble Metal Catalysts*, Academic Press, NY, ***1973***, pp. 60–76; Lyons, J.E.; Rennick, L.E.; Burmeister, J.L. *Ind. Eng. Chem. Prod. Res. Dev.* ***1970***, *9*, 2; Vol'pin, M.E.; Kolomnikov, I.S. *Russ. Chem. Rev.* ***1969***, *38*, 273.

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[408] For a review of Wilkinson's catalyst, see Jardine, F.H. *Prog. Inorg. Chem.* ***1981***, *28*, 63–202.

[409] Harmon, R.E.; Parsons, J.L.; Cooke, D.W.; Gupta, S.K.; Schoolenberg, J. *J. Org. Chem.* ***1969***, *34*, 3684. See also, Mohrig, J.R.; Dabora, S.L.; Foster, T.F.; Schultz, S.C. *J. Org. Chem.* ***1984***, *49*, 5179.

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[411] Hattori, K.; Sajiki, H.; Hirota, K. *Tetrahedron* ***2000***, *56*, 8433.

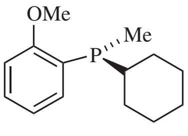
[412] Tang, W.; Liu, D.; Zhang, X *Org. Lett.* ***2003***, *5*, 205.

[413] Jia, X.; Guo, R.; Li, X.; Yao, X.; Chan, A.S.C. *Tetrahedron Lett.* ***2002***, *43*, 5541; Reetz, M.T.; Mehler, G.; Meiswinkel, A.; Sell, T. *Tetrahedron Lett.* ***2002***, *43*, 7941; Reetz, M.T.; Mehler, G. *Tetrahedron Lett.* ***2003***, *44*, 4593.

under which double bonds can be reduced selectively[414] (see Table 19.2). Controlling the solvent allows catalytic hydrogenation of an alkene in the presence of an aromatic nitro group.[415]

Among other homogeneous catalysts are chlorotris(triphenylphosphine)hydridoruthenium(II), $(Ph_3P)_3RuClH$,[416] which is specific for terminal double bonds (other double bonds are hydrogenated slowly or not at all), and pentacyanocobaltate(II), $Co(CN)_5{}^{3-}$, which is effective for double and triple bonds only when they are part of conjugated systems[417] (the conjugation may be with C=C, C=O, or an aromatic ring). Colloidal palladium has also been used as a catalyst,[418] and a polymer bound ruthenium catalyst has also been used.[419] A polymer incarcerated palladium catalyst gave the hydrogenated product in quantitative yields.[420] Rhodium on mesoporous silica can be used to hydrogenate alkenes.[421] A nanoparticulate palladium catalyst in an ionic liquid has been used for the hydrogenation of alkenes.[422]

Homogeneous catalysts often have the advantages of better catalyst reproducibility and better selectivity. They are also less susceptible to catalyst poisoning[423] (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).[424] On the other hand, heterogeneous catalysts are usually easier to separate from the reaction mixture.



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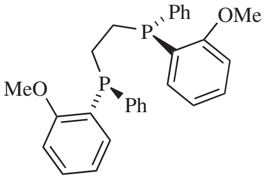

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[414] For a discussion, see Rylander, P.N. *Catalytic Hydrogenation over Platinum Metals*, Academic Press, NY, ***1967***, pp. 59–120. Also see, Hudlický, M. *Reductions in Organic Chemistry*, Ellis Horwood Ltd., Chichester, ***1984***.

[415] Jourdant, A.; González-Zamora, E.; Zhu, J. *J. Org. Chem.* ***2002***, *67*, 3163.

[416] Hallman, P.S.; McGarvey, B.R.; Wilkinson, G. *J. Chem. Soc. A* ***1968***, 3143; Jardine, F.H.; McQuillin, F.J. *Tetrahedron Lett.* ***1968***, 5189.

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[420] Okamoto, K.; Akiyama, R.; Kobayashi, S. *J. Org. Chem.* ***2004***, *69*, 2871. See also, Bremeyer, N.; Ley, S.V.; Ramarao, C.; Shirley, I.M.; Smith, S.C. *Synlett* ***2002***, 1843.

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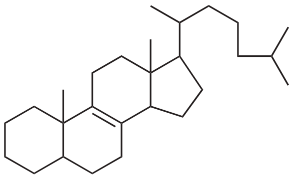
[422] In bmim PF_6, 1-butyl-3-methylimidazolium hexafluorophosphate: Huang, J.; Jiang, T.; Han, B.; Gao, H.; Chang, Y.; Zhao, G.; Wu, W. *Chem. Commun.* ***2003***, 1654.

[423] Birch, A.J.; Walker, K.A.M. *Tetrahedron Lett.* ***1967***, 1935.

[424] For a review of catalyst poisoning by sulfur, see Barbier, J.; Lamy-Pitara, E.; Marecot, P.; Boitiaux, J.P.; Cosyns, J.; Verna, F. *Adv. Catal.* ***1990***, *37*, 279–318.

Unfunctionalized alkenes are hydrogenated with good diastereoselectivity and enantioselectivity using various metal catalysts and chiral ligands.[425] Soluble, chiral homogeneous catalysts are usually the best choice, especially for alkenes. The transition-metal catalyst (rhodium and ruthenium are probably the most common) is usually prepared with suitable chiral ligands prior to addition to the reaction, or an achiral catalyst, such as Wilkinson's catalyst, **100**: $RhCl(Ph_3P)_3$, is added along with a chiral ligand. The chiral ligand is typically a phosphine. In one case, the phosphorous may be chiral, as in **101** (called R-camp),[426] but pyramidal inversion at elevated temperatures (see p. 142) limits the utility of such ligands. The alliterative is to prepare a phosphine containing a chiral carbon, and bis(phosphines), such as **102** (called dipamp)[427] are the most common. There are many variations of chiral bis(phosphine) ligands. Mono-phosphine ligands have also been used.[428] Titanocenes[429] with chiral cyclopentadienyl ligands have given enantioselective hydrogenation of unfunctionalized alkenes, such as 2-phenyl-1-butene.[430] Chiral poisoning has been used as a strategy for asymmetric catalysis.[431]

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 steroid **103**. Hydrogenations, even at about atmospheric pressure, are ordinarily performed in a special hydrogenator, but this is



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[425] **Zr**: Troutman, M.V.; Appella, D.H.; Buchwald, S.L. *J. Am. Chem. Soc.* ***1999***, *121*, 4916. **Ir**: Xu, G.; Gilbertson, S.R. *Tetrahedron Lett.* ***2003***, *44*, 953; Tang, W.; Wang, W.; Zhang, X. *Angew. Chem. Int. Ed.* ***2003***, *42*, 943; Cozzi, P.G.; Menges, F.; Kaiser, S. *Synlett* ***2003***, 833. Special ligands: Perry, M.C.; Cui, X.; Powell, M.T.; Hou, D.-R.; Reibenspies, J.H.; Burgess, K. *J. Am. Chem. Soc.* ***2003***, *125*, 113.

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[427] Brown, J.M.; Chaloner, P.A. *J. Chem. Soc., Chem. Commun.* ***1980***, 344; ***1978***, 321; *Tetrahedron Lett.* ***1978***, 1877; *J. Am. Chem. Soc.* ***1980***, *102*, 3040.

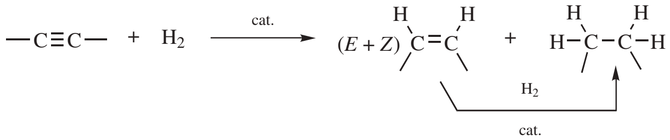
[428] Huang, H.; Zheng, Z.; Luo, H.; Bai, C.; Hu, X.; Chen, H. *J. Org. Chem.* ***2004***, *69*, 2355; Hua, Z.; Vassar, V.C.; Ojima, I. *Org. Lett.* ***2003***, *5*, 3831. For a review, see Jerphagnon, T.; Renaud, J.-L.; Bruneau, C. *Tetrahedron Asymmetry* ***2004***, *15*, 2101.

[429] Burk, M.J.; Gross, M.F. *Tetrahedron Lett.* ***1994***, *35*, 9363.

[430] Halterman, R.L.; Vollhardt, K.P.C.; Welker, M.E.; Bläser, D.; Boese, R. *J. Am. Chem. Soc.* ***1987***, *109*, 8105; Lee, N.E.; Buchwald, S.L. *J. Am. Chem. Soc.* ***1994***, *116*, 5985.

[431] Faller, J.W.; Parr, J. *J. Am. Chem. Soc.* ***1993***, *115*, 804.

not always necessary. Both the catalyst and the hydrogen can be generated *in situ*, by treatment of H_2PtCl_6 or $RhCl_3$ with $NaBH_4$;[432] 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.[433] It has been shown that the pressure of the reaction can influence enantioselectivity in asymmetric catalytic hydrogenations.[434]



Triple bonds can be reduced, either by catalytic hydrogenation or by the other methods mentioned in the following two sections. 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 equivalent 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.[435] A particularly good catalyst for this purpose is the Lindlar catalyst ($Pd\text{-}CaCO_3\text{—}PbO$).[436] An alternative catalyst used for selective hydrogenation to cis-alkenes is palladium on barium sulfate ($BaSO_4$) catalyst, poisoned with quinoline[437] (sometimes called the *Rosenmund catalyst*). Palladium on calcium carbonate in polyethylene glycol (PEG) has also bee used as a recyclable catalyst system.[438] Hydrogenation using a palladium catalyst on pumice was shown to give the cis-alkene with excellent selectivity.[439] Hydrogenation of a C≡C unit occurs in the presence of other functional groups, including NR_2 including NH_2,[440] and sulfonyl.[441]

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[432] Brown, C.A.; Sivasankaran, K. *J. Am. Chem. Soc.* ***1962***, *84*, 2828; Brown, C.A.; Brown, H.C. *J. Am. Chem. Soc.* ***1962***, *84*, 1494, 1945, 2829; *J. Org. Chem.* ***1966***, *31*, 3989.

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[434] Sun, Y.; Landau, R.N.; Wang, J.; LeBlond, C.; Blackmond, D.G. *J. Am. Chem. Soc.* ***1996***, *118*, 1348.

[435] For reviews of the hydrogenation of alkynes, see Hutchins, R.O.; Hutchins, M.G.K., in Patai, S.; Rappoport, Z. *The Chemistry of Functional Groups, Supplement C* pt. 1, Wley, NY, ***1983***, pp. 571–601; Marvell, E.N.; Li, T. *Synthesis* ***1973***, 457; Gutmann, H.; Lindlar, H., in Viehe, H.G. *Acetylenes*, Marcel Dekker, NY, ***1969***, pp. 355–363.

[436] Lindlar, H.; Dubuis, R. *Org. Synth.* ***V***, 880. See also, Rajaram, J.; Narula, A.P.S.; Chawla, H.P.S.; Dev, S. *Tetrahedron* ***1983***, *39*, 2315; McEwen, A.B.; Guttieri, M.J.; Maier, W.F.; Laine, R.M.; Shvo, Y. *J. Org. Chem.* ***1983***, *48*, 4436.

[437] Cram, D.J.; Allinger, N.L. *J. Am. Chem. Soc.* ***1956***, *78*, 2518; Rosenmund, K.W. *Ber.* ***1918***, *51*, 585; Mosettig, E.; Mozingo, R. *Org. React.* ***1948***, *4*, 362.

[438] Chandrasekhar, S.; Narsihmulu, Ch.; Chandrashekar, G.; Shyamsunder, T. *Tetrahedron Lett.* ***2004***, *45*, 2421.

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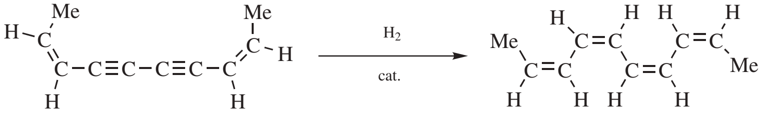
[440] Campos, K.R.; Cai, D.; Journet, M.; Kowal, J.J.; Larsen, R.D.; Reider, P.J. *J. Org. Chem.* ***2001***, *66*, 3634.

[441] Zhong, P.; Huang, X.; Ping-Guo, M. *Tetrahedron* ***2000***, *56*, 8921.

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.[442] With allenes[443] catalytic hydrogenation usually reduces both double bonds.

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.[444] Stereospecificity can be investigated only for tetrasubstituted alkenes (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 80–100% syn, although 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 alkene (usually at least 80%), even when it is thermodynamically less stable. For example, **104** gave **105**, even although the steric hindrance is such that a planar molecule is impossible.[445] This is thus a useful method for preparing cis alkenes.[446] However, when steric hindrance is too great, the trans alkene 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.[447] Thus deuterogenation of ethylene produced all the possible deuterated ethylenes and ethanes (even C_2H_6), as well as HD.[448] 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; for example, $C_4H_2D_8$ and C_4HD_9 were detected on treatment of *cis*-2-butene with deuterium and a catalyst.[449] Indeed, *alkanes* have been found to exchange with deuterium over a catalyst,[450] and even without deuterium, for example, $CH_4 + CD_4 \rightarrow CHD_3 + CH_3D$



104 **105**

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[442] Miyake, A.; Kondo, H. *Angew. Chem. Int. Ed.* ***1968***, *7*, 631. For other methods, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 403–404.

[443] For a review, see Schuster, H.F.; Coppola, G.M. *Allenes in Organoic Synthesis* Wiley, NY, ***1984***, pp. 57–61.

[444] For a review of homogeneous hydrogenation directed to only one face of a substrate molecule, see Brown, J.M. *Angew. Chem. Int. Ed.* ***1987***, *26*, 190.

[445] Holme, D.; Jones, E.R.H.; Whiting, M.C. *Chem. Ind. (London)* ***1956***, 928.

[446] For a catalyst that leads to trans alkenes, see Burch, R.R.; Muetterties, E.L.; Teller, R.G.; Williams, J.M. *J. Am. Chem. Soc.* ***1982***, *104*, 4257.

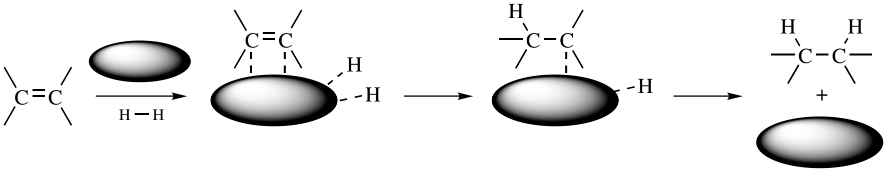
[447] For a review of the use of deuterium to study the mechanism of heterogeneous organic catalysis see Gudkov, B.S. *Russ. Chem. Rev.* ***1986***, *55*, 259.

[448] Turkevich, J.; Schissler, D.O.; Irsa, P. *J. Phys. Chem.* ***1951***, *55*, 1078.

[449] Wilson, J.N.; Otvos, J.W.; Stevenson, D.P.; Wagner, C.D. *Ind. Eng. Chem.* ***1953***, *45*, 1480.

[450] For a review, see Gudkov, B.S.; Balandin, A.A. *Russ. Chem. Rev.* ***1966***, *35*, 756. For an example of intramolecular exchange, see Lebrilla, C.B.; Maier, W.F. *Tetrahedron Lett.* ***1983***, *24*, 1119. See also, Poretti, M.; Gäumann, T. *Helv. Chim. Acta* ***1985***, *68*, 1160.

D in the gas phase, with a catalyst. All this makes it difficult to investigate the stereochemistry of heterogeneous catalytic hydrogenation.



The mechanism of the heterogeneous catalytic hydrogenation of double bonds is not thoroughly understood because it is a very difficult reaction to study.[451] Because the reaction is heterogeneous, kinetic data, although 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.[452] According to this, the alkene is adsorbed onto the surface of the metal, although the nature of the actual bonding is unknown,[453] despite many attempts to elucidate it.[454] In the 1934 work, the metallic site was indicated by an asterisk, but here we use ⬭. For steric reasons it is apparent that adsorption of the alkene takes place with its less-hindered side attached to the catalyst surface, probably as an η^2 complex (see p. 116). 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 alkene. It is likely that as the H_2 molecule is adsorbed on (coordinated to) the metal catalyst, cleavage occurs to give η^1- coordinated hydrogen atoms (see p. $$$). Note that this model suggest a single metal particle for coordination of the alkene and the hydrogen atoms, but the hydrogen atoms and the alkene could be coordinated to different metal particles. It has been shown that platinum catalyzes homolytic cleavage of hydrogen molecules.[455] In the second step, one of the adsorbed (η^1-coordinated) hydrogen atoms becomes attached to a carbon atom, creating in effect, an alkyl radical (which is still bound to the catalyst although only by one bond, probably η^1-coordination). Transfer of a hydrogen atom to carbon opens a site on the metal catalyst for coordination to additional hydrogen atoms. Finally, another hydrogen atom (not necessarily the one originally connected to the first hydrogen) combines with the radical

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[451] For reviews, see Webb, G., in Bamford, CH.; Tipper, C.F.H. *Comprehensive Chemical Kinetics*, Vol. 20, Elsevier, NY, ***1978***, pp. 1–121; Clarke, J.K.A.; Rooney, J.J. *Adv. Catal.* ***1976***, *25*, 125–183; Siegel, S. *Adv. Catal.* ***1966***, *16*, 123–177; Burwell, Jr., R.L. *Chem. Eng. News* ***1966***, *44(34)*, 56–67.

[452] Horiuti, I.; Polanyi, M. *Trans. Faraday Soc.* ***1934***, *30*, 1164.

[453] See, for example, Burwell, Jr., R.L.; Schrage, K. *J. Am. Chem. Soc.* ***1965***, *87*, 5234.

[454] See, for example, McKee, D.W. *J. Am. Chem. Soc.* ***1962***, *84*, 1109; Ledoux, M.J. *Nouv. J. Chim.* ***1978***, *2*, 9; Bautista, F.M.; Campelo, J.M.; Garcia, A.; Guardeño, R.; Luna, D.; Marinas, J.M. *J. Chem. Soc. Perkin Trans. 2*, ***1989***, 493.

[455] Krasna, A.I. *J. Am. Chem. Soc.* ***1961***, *83*, 289.

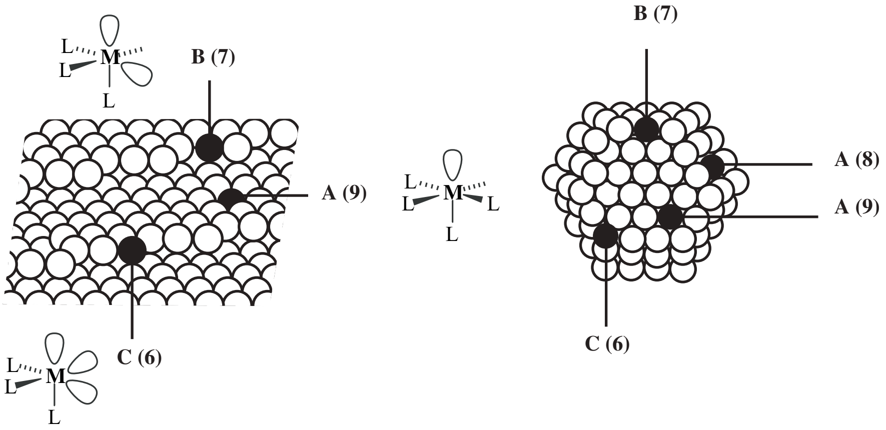

Fig. 15.1. The principal surface and particle sites for heterogeneous catalysts.

to give the reaction product, freed from the catalyst surface, and the metal catalyst that is now available for coordination of additional hydrogen atoms and/or alkenes. All the various side reactions, including hydrogen exchange and isomerism, can be explained by this type of process.[456] Although this mechanism is satisfactory as far as it goes,[457] there are still questions it does not answer, among them questions[458] involving the nature of the asterisk, the nature of the bonding, and the differences caused by the differing nature of each catalyst.[459]

Heterogeneous catalysis occurs at the surface of the metal catalyst, and there are different types of metal particles on the surface. Maier suggested the presence of **terrace-**, **step-**, and **kink**-type atoms (in Fig. 6.1)[460] on the surface of a heterogeneous catalyst. These terms refer to different atom types, characterized by the number of nearest neighbors,[460] which correspond to different transition-metal fragments, as well as to different coordination states of that metal.[461] A terrace-type atom (A in Fig. 15.1) typically has eight or nine neighbors and corresponds to a geometry shown for the ML_5 particle. The step type of atom (B) usually has seven neighbors and can be correlated with the geometry shown for the ML_4

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[456] Smith, G.V.; Burwell Jr., R.L. *J. Am. Chem. Soc.* ***1962***, *84*, 925.

[457] A different mechanism has been proposed by Zaera, F.; Somorjai, G.A. *J. Am. Chem. Soc.* ***1984***, *106*, 2288, but there is evidence against it: Beebe, Jr., T.P.; Yates Jr., J.T. *J. Am. Chem. Soc.* ***1986***, *108*, 663. See also, Thomson, S.J.; Webb, G. *J. Chem. Soc., Chem. Commun.* ***1976***, 526.

[458] For discussions, see Augustine, R.L.; Yaghmaie, F.; Van Peppen, J.F. *J. Org. Chem.* ***1984***, *49*, 1865; Maier, W.F. *Angew. Chem. Int. Ed.* ***1989***, *28*, 135.

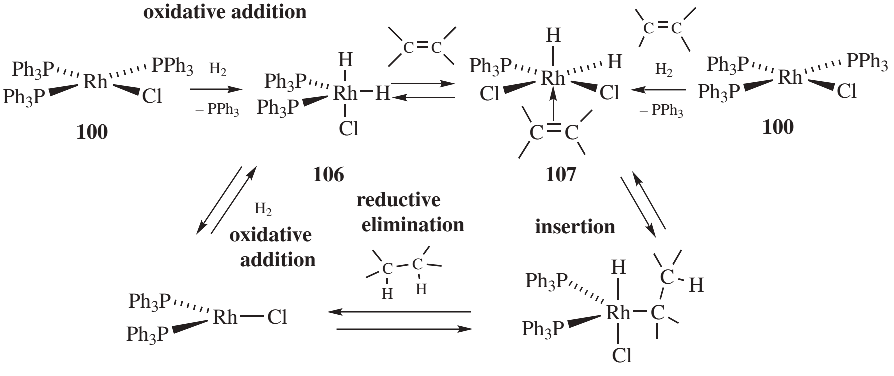
[459] For a study of the detailed structure of Lindlar catalysts (which were shown to consist of seven distinct chemical phases), see Schlögl, R.; Noack, K.; Zbinden, H.; Reller, A. *Helv. Chim. Acta* ***1987***, *70*, 627.

[460] Maier, W.F. *Angew. Chem. Int. Ed.* ***1989***, *28*, 135.

[461] Maier, W.F., in Rylander, P.N.; Greenfield, H.; Augustine, R.L. *Catalysis of Organic Reactions*, Marcel Dekker, NY, ***1988***, pp. 211–231, Cf. p. 220.

particle. Finally, the kink-type atom (C) has six neighbors and corresponds to geometry shown for the ML_3 particle. In general, as the particle size increases, the relative concentration of terrace atoms will increase, whereas small particle size favors the kink type of surface atoms.

The mechanism of homogeneous hydrogenation[462] catalyzed by $RhCl(Ph_3P)_3$ (**100**, Wilkinson's catalyst)[463] involves reaction of the catalyst with hydrogen to form a metal hydride $(PPh_3)_2RhH_2Cl$ (**106**).[464] Replacement of a triphenylphosphine ligand with two toms of hydrogen constitutes an oxidative addition.



After coordination of the alkene to form **107**, transfer of hydrogen to carbon is an insertion process, presumably generating **109**, and a second insertion liberates the hydrogenated compound, and rhodium species **108**, which adds hydrogen by oxidative addition to give **106**. Alternatively, replacement of triphenylphosphine can lead to **107**, with two hydrogen atoms and a η^2-alkene complex. If a mixture of H_2 and D_2 is used, the product contains only dideuterated and non-deuterated compounds; no mono-deuterated products are found, indicating that (unlike the case of heterogeneous catalysis) H_2 or D_2 has been added to one alkene molecule and that no exchange takes place.[330] Although conversion of **107** to the products takes place in two steps,[465] the addition of H_2 to the double bond is syn, although bond rotation in **109** can lead to stereochemical mixtures.

The occurrence of hydrogen exchange and double-bond migration in heterogeneous catalytic hydrogenation means that the hydrogenation does not necessarily

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[462] For reviews, see Crabtree, R.H. *Organometallic Chemistry of the Transition Metals*, Wiley, NY, ***1988***, pp. 190–200; Jardine, F.H. in Hartley, F.R. *The Chemistry of the Metal-Carbon Bond*, Vol. 4, Wiley, NY, ***1987***, pp. 1049–1071.

[463] Montelatici, S.; van der Ent, A.; Osborn, J.A.; Wilkinson, G. *J. Chem. Soc. A* ***1968***, 1054; Wink, D.; Ford, P.C. *J. Am. Chem. Soc.* ***1985***, *107*, 1794; Koga, N.; Daniel, C.; Han, J.; Fu, X.Y.; Morokuma, K. *J. Am. Chem. Soc.* ***1987***, *109*, 3455.

[464] Tolman, C.A.; Meakin, P.Z.; Lindner, D.L.; Jesson, J.P. *J. Am. Chem. Soc.* ***1976***, *96*, 2762.

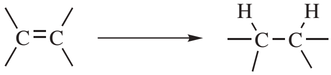
[465] Biellmann, J.F.; Jung, M.J. *J. Am. Chem. Soc.* ***1968***, *90*, 1673; Hussey, A.S.; Takeuchi, Y. *J. Am. Chem. Soc.* ***1969***, *91*, 672; Heathcock, C.H.; Poulter, S.R. *Tetrahedron Lett.* ***1969***, 2755; Smith, G.V.; Shuford, R.J. *Tetrahedron Lett.* ***1970***, 525; Atkinson, J.G.; Luke, M.O. *Can. J. Chem.* ***1970***, *48*, 3580.

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 scrambling[466] or by the use of one of the diimide methods (**15-12**). 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, 794; **IV**, 298, 304, 408; **V**, 16, 96, 277; **VI**, 68, 459; **VII**, 226, 287; **VIII**, 420. 609; **IX**, 169, 533.

Catalysts and apparatus for hydrogenation are found at OS **I**, 61, 463; **II**, 142; **III**, 176, 181, 685; **V**, 880; **VI**, 1007.

15-12 Other Reductions of Double and Triple Bonds



Although catalytic hydrogenation is the method most often used, double or triple bonds can be reduced by other reagents, as well. Among these are sodium in ethanol, sodium and *tert*-butyl alcohol in HMPA,[467] lithium and aliphatic amines[468] (see also, **15-13**), zinc and acids, sodium hypophosphate and Pd—C,[469] $(EtO)_3$-$SiHPd(OAc)_2$,[470] triethylsilane Et_3SiH and trifluoroacetic acid[471] or palladium chloride,[472] and hydroxylamine and ethyl acetate.[473] Trialkylsilanes (R_3SiH) in conjunction with an acid will reduce double bonds.[474] Siloxanes (RO_3SiH) and a ruthenium catalyst, followed by treatment with AgF convert alkynes to *trans*-alkenes.[475] Poly(methylhydrosiloxane) was used for reduction of conjugated alkenes using a copper carbene complex.[476] Reduction of alkynes with silanes and a ruthenium catalyst, followed by treatment with CuI and Bu_4NF gave the

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[466] Biellmann, J.F.; Liesenfelt, H. *Bull. Soc. Chim. Fr.* ***1966***, 4029; Birch, A.J.; Walker, K.A.M. *Tetrahedron Lett.* ***1966***, 4939, *J. Chem. Soc. C* ***1966***, 1894; Morandi, J.R.; Jensen, H.B. *J. Org. Chem.* ***1969***, *34*, 1889. See, however, Atkinson, J.G.; Luke, M.O. *Can. J. Chem.* ***1970***, *48*, 3580.

[467] Angibeaud, P.; Larchevêque, M.; Normant, H.; Tchoubar, B. *Bull. Soc. Chim. Fr.* ***1968***, 595; Whitesides, G.M.; Ehmann, W.J. *J. Org. Chem.* ***1970***, *35*, 3565.

[468] Benkeser, R.A.; Schroll, G.; Sauve, D.M. *J. Am. Chem. Soc.* ***1955***, *77*, 3378.

[469] Sala, R.; Doria, G.; Passarotti, C. *Tetrahedron Lett.* ***1984***, *25*, 4565.

[470] Tour, J.M.; Pendalwar, S.L. *Tetrahedron Lett.* ***1990***, *31*, 4719.

[471] For a review, see Kursanov, D.N.; Parnes, Z.N.; Loim, N.M. *Synthesis* ***1974***, 633. Also see, Doyle, M.P.; McOsker, C.C. *J. Org. Chem.* ***1978***, *43*, 693. For a monograph, see Kursanov, D.N.; Parnes, Z.N.; Kalinkin, M.I.; Loim, N.M. *Ionic Hydrogenation and Related Reactions*, Harwood Academic Publishers, Chur, Switzerland, ***1985***.

[472] Mirza-Aghayan, M.; Boukherroub, R.; Bolourtchian, M.; Hosseini, M. *Tetrahedron Lett.* ***2003***, *44*, 4579.

[473] Wade, P.A.; Amin, N.V. *Synth. Commun.* ***1982***, *12*, 287.

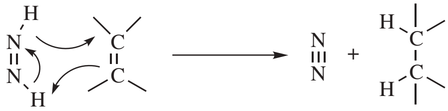
[474] Masuno, M.N.; Molinski, T.F. *Tetrahedron Lett.* ***2001***, *42*, 8263.

[475] Fürstner, A.; Radkowski, K. *Chem. Commun.* ***2002***, 2182.

[476] Jurkauskas, V.; Sakighi, J.P.; Buchwald, S.L. *Org. Lett.* ***2003***, *5*, 2417.

trans- alkene.[477] Samarium iodide in water and a triamine additive led to reduction of alkenes.[478] Similar reduction was reported using $Co_2(CO)_8$ and an excess of water in dimethoxyethane.[479] Reduction of an alkyne to an alkene can be done via an organometallic, by heating the alkyne with indium metal in aqueous ethanol.[480] Alkynes are reduced with palladium acetate and sodium ethoxide. In methanol the product is the alkane, whereas in THF the product is the cis-alkene.[481]

In the above-mentioned reactions with hydrazine and hydroxylamine, the actual reducing species is diimide NH=NH, which is formed from N_2H_4 by the oxidizing agent and from NH_2OH by the ethyl acetate.[482] The rate of this reaction has been studied.[483] Although both the syn and anti forms of diimide are produced, only the syn form reduces the double bond,[484] at least in part by a cyclic mechanism:[485]



The addition is therefore stereospecifically syn[486] and, like catalytic hydrogenation, generally takes place from the less-hindered side of a double bond, although not much discrimination in this respect is observed where the difference in bulk effects is small.[487] Diimide reductions are most successful with symmetrical multiple bonds (C=C, C≡C, N=N) and are not useful for those inherently polar (C≡N, C=N, C=O, etc.). Diimide is not stable enough for isolation at ordinary temperatures, although it has been prepared[488] as a yellow solid at −196°C. *N*-Arylsulfonylhydrazines bearing a phosphonate ester unit converted 1,1-diiodoalkenes ($C{=}CI_2$) to *gem*-diiodides, ($CH{-}CHI_2$).[489]

An indirect method[490] of double-bond reduction involves hydrolysis of boranes (prepared by **15-16**). Trialkylboranes can be hydrolyzed by refluxing with carboxylic

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[477] Trost, B.M.; Ball, Z.T.; Jöge, T. *J. Am. Chem. Soc.* ***2002***, *124*, 7922.

[478] Dahlén, A.; Hilmersson, G. *Tetrahedron Lett.* ***2003***, *44*, 2661.

[479] Lee, H.-Y.; An, M. *Tetrahedron Lett.* ***2003***, *44*, 2775.

[480] Ranu, B.C.; Dutta, J.; Guchhait, S.K. *J. Org. Chem.* ***2001***, *66*, 5624.

[481] Wei, L.-L.; Wei, L.-M.; Pan, W.-B.; Leou, S.-P.; Wu, M.-J. *Tetrahedron Lett.* ***2003***, *44*, 1979.

[482] For reviews of hydrogenations with diimide, see Pasto, D.J.; Taylor, R.T. *Org. React.* ***1991***, *40*, 91; Miller, C.E. *J. Chem. Educ.* ***1965***, *42*, 254; House, H.O. *Modern Synthetic Reaction*, 2nd ed., W.A. Benjamin, NY, ***1972***, pp. 248–256. For reviews of diimides, see Back, R.A. *Rev. Chem. Intermed.* ***1984***, *5*, 293; Hünig, S.; Müller, H.R.; Thier, W. *Angew. Chem. Int. Ed.* ***1965***, *4*, 271.

[483] Nelson, D.J.; Henley, R.L.; Yao, Z.; Smith, T.D. *Tetrahedron Lett.* ***1993***, *34*, 5835.

[484] Aylward, F.; Sawistowska, M.H. *J. Chem. Soc.* ***1964***, 1435.

[485] van Tamelen, E.E.; Dewey, R.S.; Lease, M.F.; Pirkle, W.H. *J. Am. Chem. Soc.* ***1961***, *83*, 4302; Willis, C.; Back, R.A.; Parsons, J.A.; Purdon, J.G. *J. Am. Chem. Soc.* ***1977***, *99*, 4451.

[486] Corey, E.J.; Pasto, D.J.; Mock, W.L. *J. Am. Chem. Soc.* ***1961***, *83*, 2957.

[487] van Tamelen, E.E.; Timmons, R.J. *J. Am. Chem. Soc.* ***1962***, *84*, 1067.

[488] Wiberg, N.; Fischer, G.; Bachhuber, H. *Chem. Ber.* ***1974***, *107*, 1456; *Angew. Chem. Int. Ed.* ***1977***, *16*, 780. See also, Trombetti, A. *Can. J. Phys.* ***1968***, *46*, 1005; Bondybey, V.E.; Nibler, J.W. *J. Chem. Phys.* ***1973***, *58*, 2125; Craig, N.C.; Kliewer, M.A.; Shih, N.C. *J. Am. Chem. Soc.* ***1979***, *101*, 2480.

[489] Cloarec, J.-M.; Charette, A.B. *Org. Lett.* ***2004***, *6*, 4731.

[490] For a review, see Zweifel, G. *Intra-Sci. Chem. Rep.* ***1973***, *7(2)*, 181–189.

acids,[491] while monoalkylboranes, RBH_2, can be hydrolyzed with base.[492] Triple bonds can be similarly reduced, to cis alkenes.[493] Further reduction is also possible. When an alkyne was treated with decaborane and Pd/C in methanol, two equivalents of hydrogen are transferred to give the alkane.[494] Hydrogenation with Ni_2B on borohydride exchange resin (BER) has also been used.[495] Reduction occurs *in situ* when an alkene is treated with $NaBH_4$, $NiCl_2$•6 H_2O with moist alumina.[496] Reduction of alkenes occurs with *tert*-butylamine•borane complex in methanol with 10% Pd/C.[497]

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-diarylethenes[498] and in enamines.[499] Lithium aluminum hydride reduces cyclopropenes with a pendant alcohol in the allylic position to the corresponding cyclopropane.[500]

Triple bonds can also be selectively reduced to double bonds with diisobutylaluminum hydride (Dibal-H),[501] with activated zinc (see **12-38**),[502] with hydrogen and Bi_2B–borohydride exchange resin,[503] or (internal triple bonds only) with alkali metals (Na, Li) in liquid ammonia or a low-molecular-weight amine.[504] Terminal alkynes are not reduced by the Na—NH_3 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—NH_3 solution of $(NH_4)_2SO_4$, which liberates the free ethynyl group.[505] The reaction of a terminal alkyne with

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[491] Brown, H.C.; Murray, K.J. *Tetrahedron* ***1986***, *42*, 5497; Kabalka, G.W.; Newton, Jr., R.J.; Jacobus, J. *J. Org. Chem.* ***1979***, *44*, 4185.

[492] Weinheimer, A.J.; Marisco, W.E. *J. Org. Chem.* ***1962***, *27*, 1926.

[493] Brown, H.C.; Zweifel, G. *J. Am. Chem. Soc.* ***1959***, *81*, 1512.

[494] Lee, S.H.; Park, Y.J.; Yoon, C.M. *Tetrahedron Lett.* ***2000***, *41*, 887.

[495] Choi, J.; Yoon, N.M. *Synthesis* ***1996***, 597.

[496] Yakabe, S.; Hirano, M.; Morimoto, T. *Tetrahedron Lett.* ***2000***, *41*, 6795.

[497] Couturier, M.; Andresen, B.M.; Tucker, J.L.; Dubé, P.; Brenek, S.J.; Negri, J.J. *Tetrahedron Lett.* ***2001***, *42*, 2763.

[498] See Granoth, I.; Segall, Y.; Leader, H.; Alkabets, R. *J. Org. Chem.* ***1976***, *41*, 3682.

[499] For a review of the reduction of enamines and indoles with $NaBH_4$ and a carboxylic acid, see Gribble, G.W.; Nutaitis, C.F. *Org. Prep. Proced. Int.* ***1985***, *17*, 317. Enamines can also be reduced by formic acid; see Nilsson, A.; Carlson, R. *Acta Chem. Scand. Sect. B* ***1985***, *39*, 187.

[500] Zohar, E.; Marek, I. *Org. Lett.* ***2004***, *6*, 341.

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

[502] Aerssens, M.H.P.J.; van der Heiden, R.; Heus, M.; Brandsma, L. *Synth. Commun.* ***1990***, *20*, 3421; Chou, W.; Clark, D.L.; White, J.B. *Tetrahedron Lett.* ***1991***, *32*, 299. See Sakai, M.; Takai, Y.; Mochizuki, H.; Sasaki, K.; Sakakibara, Y. *Bull. Chem. Soc. Jpn.* ***1994***, *67*, 1984 for reduction with a $NiBr_2$–Zn reagent.

[503] Choi, J.; Yoon, N.M. *Tetrahedron Lett.* ***1996***, *37*, 1057.

[504] For a list of methods of reducing triple to double bonds, with syn or anti addition, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 405–410.

[505] Henne, A.L.; Greenlee, K.W. *J. Am. Chem. Soc.* ***1943***, *65*, 2020.

lithium naphthalenide and $NiCl_2$ effectively reduced the alkyne unit (i.e., $PhC{\equiv}CH \rightarrow PhCH_2CH_3$).[506] This reagent is also effect for the reduction of simple alkenes.[507] A mixture of $NaBH_4$ and $BiCl_3$ also reduced certain alkenes[508] and An alkyne unit was reduced to an alkene, in the presence of a phenylthio group elsewhere in the molecule, using $Cp_2Zr(H)Cl$.[509]

Reduction of just one double bond of an allene, to give an alkene, has been accomplished by treatment with Na—NH_3[510] or with Dibal-H,[511] and by hydrogenation with $RhCl(PPh_3)_3$ as catalyst.[512]

When double bonds are reduced by lithium in ammonia or amines, the mechanism is similar to that of the Birch reduction (**15-13**).[513] The reduction with trifluoroacetic acid and Et_3SiH has an ionic mechanism, with H^+ coming in from the acid and H^- from the silane.[290] In accord with this mechanism, the reaction can be applied only to those alkenes, which when protonated can form a tertiary carbocation or one stabilized in some other way, for example, by a OR substitution.[514] It has been shown, by the detection of CIDNP, that reduction of α-methylstyrene by hydridopentacarbonylmanganese(I), $HMn(CO)_5$, involves free-radical addition.[515]

Catalytic hydrogenation of triple bonds and the reaction with Dibal-H usually give the cis-alkene (**15-11**). Most of the other methods of triple-bond reduction lead to the more thermodynamically stable trans alkene. However, this is not the case with the method involving hydrolysis of boranes or with the reductions with activated zinc, hydrazine, or NH_2OSO_3H, which also give the cis products.

The fact that ordinary double bonds are inert 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,[516] although it does reduce alkynes, allenes, conjugated dienes,[517] and aromatic rings (**15-13**).

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[506] Alonso, F.; Yus, M. *Tetrahedron Lett.* ***1997***, *38*, 149.

[507] Alonso, F.; Yus, M. *Tetrahedron Lett.* ***1996***, *37*, 6925.

[508] Ren, P.-D.; Pan, S.-F.; Dong, T.-W.; Wu, S.-H. *Synth. Commun.* ***1996***, *26*, 763.

[509] Lipshutz, B.H.; Lindsley, C.; Bhandari, A. *Tetrahedron Lett.* ***1994***, *35*, 4669.

[510] Gardner, P.D.; Narayana, M. *J. Org. Chem.* ***1961***, *26*, 3518; Vaidyanathaswamy, R.; Joshi, G.C.; Devaprabhakara, D. *Tetrahedron Lett.* ***1971***, 2075.

[511] Montury, M.; Goré, J. *Tetrahedron Lett.* ***1980***, *21*, 51.

[512] Bhagwat, M.M.; Devaprabhakara, D. *Tetrahedron Lett.* ***1972***, 1391.

[513] For a review of the steric course of this reaction, see Toromanoff, E. *Bull. Soc. Chim. Fr.* ***1987***, 893–901. For a review of this reaction as applied to α,β-unsaturated ketones, see Russell, G.A., in Patai, S.; Rappoport, Z. *The Chemistry of Enones*, pt. 2, Wiley, NY, ***1989***, pp. 471–512.

[514] Parnes, Z.N.; Bolestova, G.I.; Kursanov, D.N. *Bull. Acad. Sci. USSR Div. Chem. Sci.* ***1972***, *21*, 1927.

[515] Sweany, R.L.; Halpern, J. *J. Am. Chem. Soc.* ***1977***, *99*, 8335. See also, Thomas, M.J.; Shackleton, T.A.; Wright, S.C.; Gillis, D.J.; Colpa, J.P.; Baird, M.C. *J. Chem. Soc., Chem. Commun.* ***1986***, 312; Garst, J.F.; Bockman, T.M.; Batlaw, R. *J. Am. Chem. Soc.* ***1986***, *108*, 1689; Bullock, R.M.; Samsel, E.G. *J. Am. Chem. Soc.* ***1987***, *109*, 6542.

[516] There are some exceptions. See, for example, Butler, D.N. *Synth. Commun.* ***1977***, *7*, 441, and references cited therein.

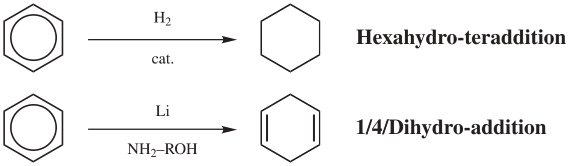
[517] For a review of reductions of α,β-unsaturated carbonyl compounds with metals in liquid NH_3, see Caine, D. *Org. React.* ***1976***, *23*, 1–258.

Another hydrogenation method is called *transfer hydrogenation*.[518] In this method the hydrogen comes from another organic molecule, which is itself oxidized. A transition-metal catalyst, heterogeneous or homogeneous, is frequently employed. Dendritic catalysts have been used for asymmetric transfer hydrogenation.[519] A common reducing agent is cyclohexene, which, when a palladium catalyst is used, is oxidized to benzene, losing 2 mol of hydrogen.

Enantioselective reduction of certain alkenes has also been achieved by reducing with baker's yeast.[520]

Reductions of double and triple bonds are found at OS **III**, 586, 742; **IV**, 136, 302, 887; **V**, 281, 993; **VII**, 524; **80**, 120.

15-13 Hydrogenation of Aromatic Rings



Aromatic rings can be reduced by catalytic hydrogenation,[521] but higher temperatures (100–200°C) are required than for ordinary double bonds.[522] although the reaction is usually carried out with heterogeneous catalysts, homogeneous catalysts have also been used; conditions are much milder with these.[523] Mild conditions are also successful in hydrogenations with phase transfer catalysts.[524] Hydrogenation in ionic liquids is known,[525] and also hydrogenation in supercritical ethane containing water.[526] Many functional groups, such as OH, O^-, COOH, COOR, NH_2, 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 (**19-54**). Phenols may be reduced to cyclohexanones, presumably through the enol. Heterocyclic compounds are often reduced. Thus furan gives THF. The

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[518] For reviews, see Johnstone, R.A.W.; Wilby, A.H.; Entwistle, I.D. *Chem. Rev.* ***1985***, *85*, 129; Brieger, G.; Nestrick, T.J. *Chem. Rev.* ***1974***, *74*, 567.

[519] Chen, Y.-C.; Wu, T.-F.; Deng, J.-G.; Liu, H.; Cui, X.; Zhu, J.; Kiang, Y.-Z.; Choi, M.C.K.; Chan, A.S.C. *J. Org. Chem.* ***2002***, *67*, 5301.

[520] See, for example, Ferraboschi, P.; Reza-Elahi, S.; Verza, E.; Santaniello, E. *Tetrahedron Asymmetry* ***1999***, *10*, 2639. For reviews of baker's yeast, see Csuk, R.; Glänzer, B.I. *Chem. Rev.* ***1991***, *91*, 49; Servi, S. *Synthesis* ***1990***, 1.

[521] For reviews, see Karakhanov, E.A.; Dedov, A.G.; Loktev, A.S. *Russ. Chem. Rev.* ***1985***, *54*, 171.

[522] For a highly active heterogeneous Rh catalyst, see Timmer, K.; Thewissen, D.H.M.W.; Meinema, H.A.; Bulten, E.J. *Recl. Trav. Chim. Pays-Bas* ***1990***, *109*, 87.

[523] For reviews, see Bennett, M. *CHEMTECH* ***1980***, *10*, 444–446; Muetterties, E.L.; Bleeke, J.R. *Acc. Chem. Res.* ***1979***, *12*, 324. See also, Tsukinoki, T.; Kanda, T.; Liu, G.-B.; Tsuzuki, H.; Tashiro, M. *Tetrahedron Lett.* ***2000***, *41*, 5865.

[524] Januszkiewicz, K.R.; Alper, H. *Organometallics* ***1983***, *2*, 1055.

[525] In bmim BF_4, 1-butyl-3-methylimidazolium tetrafluoroborate: Dyson, P.J.; Ellis, D.J.; Parker, D.G.; Welton, T. *Chem. Commun.* ***1999***, 25.

[526] Bonilla, R.J.; James, B.R.; Jessop, P.G. *Chem. Commun.* ***2000***, 941.

nitrogen-containing ring of quinolines is reduced by hydrogenation using iodine and an iridium catalyst.[527] Catalytic hydrogenation of the five-membered ring in indole derivatives using a chiral rhodium catalyst gave hydroindoles with excellent enantioselectivity.[528]

With benzene rings it is usually impossible to stop the reaction after only one or two bonds have been reduced, since alkenes are more easily reduced than aromatic rings.[529] Thus, 1 equivalent of benzene, treated with 1 equivalent of hydrogen, gives no cyclohexadiene or cyclohexene, but $\frac{1}{3}$ equivalent of cyclohexane and $\frac{2}{3}$ equivalent of recovered benzene. This is not true for all aromatic systems. With anthracene, for example, it is easy to stop after only the 9,10-bond has been reduced (see p. 59). Hydrogenation of phenol derivatives can lead to conjugated cyclohexenones.[530] Hydrogenation of toluene in an ionic liquid using a ruthenium catalyst gave methylcyclohexane.[531]

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 *tert*-butyl alcohol), 1,4-addition of hydrogen takes place and nonconjugated cyclohexadienes are produced.[532] This reaction is called the *Birch reduction*.[533] Heterocycles, such as pyrroles,[534] furans,[535] pyridines,[536] and indolones,[537] can be reduced using Birch reduction. 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 alkoxyl 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 $CONH_2$,

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[527] Wang, W.-B.; Lu, S.-M.; Yang, P.-Y.; Han, X.-W.; Zhou, Y.-G. *J. Am. Chem. Soc.* ***2003***, *125*, 10536.

[528] Kuwano, R.; Kaneda, K.; Ito, T.; Sato, K.; Kurokawa, T.; Ito, Y. *Org. Lett.* ***2004***, *6*, 2213.

[529] For an indirect method of hydrogenating benzene to cyclohexene, see Harman, W.D.; Taube, H. *J. Am. Chem. Soc.* ***1988***, *110*, 7906.

[530] Higashijima, M.; Nishimura, S. *Bull. Chem. Soc. Jpn.* ***1992***, *65*, 824.

[531] In bmim BF_4, 1-butyl-3-methylimidazolium tetrafluoroborate: Boxwell, C.J.; Dyson, P.J.; Ellis, D.J.; Welton, T. *J. Am. Chem. Soc.* ***2002***, *124*, 9334.

[532] For a procedure that converts benzene to pure 1,4-cyclohexadiene, see Brandsma, L.; van Soolingen, J.; Andringa, H. *Synth. Commun.* ***1990***, *20*, 2165. Also see, Weitz, I.S.; Rabinovitz, M. *J. Chem. Soc. Perkin Trans. 1*, ***1993***, 117.

[533] For a monograph, see Akhrem, A.A.; Reshotova, I.G.; Titov, Yu.A. *Birch Reduction of Aromatic Compounds*, Plenum, NY, ***1972***. For reviews, see Birch, A.J. *Pure Appl. Chem.* ***1996***, *68*, 553; Rabideau, P.W. *Tetrahedron* ***1989***, *45*, 1579; Birch, A.J.; Subba Rao, G. *Adv. Org. Chem.* ***1972***, *8*, 1; Kaiser, E.M. *Synthesis* ***1972***, 391; Harvey, R.G. *Synthesis* ***1970***, 161; House, H.O. *Modern Synthetic Reaction*, 2nd ed., W.A. Benjamin, NY, ***1972***, pp. 145–150, 173–209; Hückel, W. *Fortschr. Chem. Forsch.* ***1966***, *6*, 197; Smith, M., in Augustine, R.L. *Reduction Techniques and Applications in Organic Synthesis*, Marcel Dekker, NY, ***1968***, pp. 95–170.

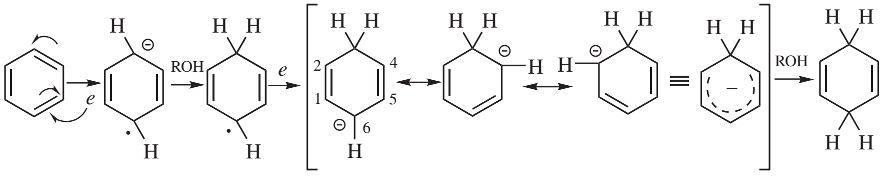
[534] Donohoe, T.J.; House, D. *J. Org. Chem.* ***2002***, *67*, 5015.

[535] Kinoshita, T.; Ichinari, D.; Sinya, J. *J. Heterocyclic Chem.* ***1996***, *33*, 1313.

[536] Donohoe, T.J.; McRiner, A.J.; Helliwell, M.; Sheldrake, P. *J. Chem. Soc., Perkin Trans. 1* ***2001***, 1435.

[537] Guo, Z.; Schultz, A.G. *J. Org. Chem.* ***2001***, *66*, 2154.

increase the reaction rate and are found on the reduced positions of the product.[538] The regioselectivity of the reaction has been examined.[539] The mechanism involves solvated electrons,[540] which are transferred from the metal to the solvent, and hence to the ring:[541]



110 **111**

The sodium becomes oxidized to Na^+ and creates a radical ion (**110**).[542] There is a great deal of evidence from ESR spectra for these species.[543] The radical ion accepts a proton from the alcohol to give a radical, which is reduced to a carbanion by another sodium atom. Finally, **111** 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 **110** are frequently obtained. There is evidence[544] at least with some substrates, for example, biphenyl, that the radical ion corresponding to **110** is converted to the carbanion corresponding to **111** by a different pathway, in which the order of the steps is reversed: first a second electron is gained to give a dianion,[542] which then acquires a proton, producing the intermediate corresponding to **111**.

Ordinary alkenes 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 alkenes, internal alkynes (**15-12**),[545] and conjugated alkenes (with C=C or C=O) are reduced under these conditions.

Note that **111** is a resonance hybrid; that is, we can write the two additional canonical forms shown. 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

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

[539] Zimmerman, H.E.; Wang, P.A. *J. Am. Chem. Soc.* ***1993***, *115*, 2205.

[540] For reviews of solvated electrons and related topics, see Dye, J.L. *Prog. Inorg. Chem.* ***1984***, *32*, 327–441; Alpatova, N.M.; Krishtalik, L.I.; Pleskov, Y.V. *Top. Curr. Chem.* ***1987***, *138*, 149–219.

[541] Birch, A.J.; Nasipuri, D. *Tetrahedron* ***1959***, *6*, 148.

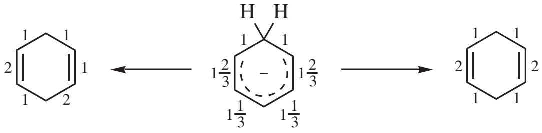
[542] For a review of radical ions and diions generated from aromatic compounds, see Holy, N.L. *Chem. Rev.* ***1974***, *74*, 243.

[543] For example, see Jones, M.T., in Kaiser, E.T.; Kevan, L. *Radical Ions*, Wiley, NY, ***1968***, pp. 245–274; Bowers, K.W. *Adv. Magn. Reson.*, ***1965***, *1*, 317; Carrington, A. *Q. Rev. Chem. Soc.* ***1963***, *17*, 67.

[544] Lindow, D.F.; Cortez, C.N.; Harvey, R.G. *J. Am. Chem. Soc.* ***1972***, *94*, 5406; Rabideau, P.W.; Peters, N.K.; Huser, D.L. *J. Org. Chem.* ***1981***, *46*, 1593.

[545] See Brandsma, L.; Nieuwenhuizen, W.F.; Zwikker, J.W. Mäeorg, U. *Eur. J. Org. Chem.* ***1999***, 775.

to give the 1,3-diene?[546] 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*.[547] According to this principle, "those elementary reactions will be favored that involve the least change in atomic position and electronic configuration."[547] The principle can be applied to the case at hand in the following manner (simplified): The valence-bond bond orders (p. 32) for the six carbon–carbon bonds (on the assumption that each of the three forms contributes equally) are (going around the ring) $1\frac{2}{3}$, 1, 1, $1\frac{2}{3}$, $1\frac{1}{3}$, 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 ^{13}C NMR spectrum of **111** 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.[548]

Reduction of aromatic rings with lithium[549] or calcium[550] in amines (instead of ammonia: called *Benkeser reduction*) 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.[551] Lithium triethylborohydride ($LiBEt_3H$) has also been used, to reduce pyridine derivatives to piperidine derivatives.[552]

Transition metals and metal compounds can reduce aromatic rings in the proper medium. Indium metal reduces the pyridine ring in quinoline in aqueous ethanol solution[553] as well as the C=C unit in the five-membered ring of indole

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[546] For a discussion of this question, see Rabideau, P.W.; Huser, D.L. *J. Org. Chem.* ***1983***, *48*, 4266.

[547] Hine, J. *J. Org. Chem.* ***1966***, *31*, 1236. For a review of this principle, see Hine, J. *Adv. Phys. Org. Chem.* ***1977***, *15*, 1. See also, Tee, O.S. *J. Am. Chem. Soc.* ***1969***, *91*, 7144; Jochum, C.; Gasteiger, J.; Ugi, I. *Angew. Chem. Int. Ed.* ***1980***, *19*, 495.

[548] Bates, R.B.; Brenner, S.; Cole, C.M.; Davidson, E.W.; Forsythe, G.D.; McCombs, D.A.; Roth, A.S. *J. Am. Chem. Soc.* ***1973***, *95*, 926.

[549] Reggel, L.; Friedel, R.A.; Wender, I. *J. Org. Chem.* ***1957***, *22*, 891; Benkeser, R.A.; Agnihotri, R.K.; Burrous, M.L.; Kaiser, E.M.; Mallan, J.M.; Ryan, P.W. *J. Org. Chem.* ***1964***, *29*, 1313; Kwart, H.; Conley, R.A. *J. Org. Chem.* ***1973***, *38*, 2011.

[550] Benkeser, R.A.; Belmonte, F.G.; Kang, J. *J. Org. Chem.* ***1983***, *48*, 2796. See also, Benkeser, R.A.; Laugal, J.A.; Rappa, A. *Tetrahedron Lett.* ***1984***, *25*, 2089.

[551] One, two, or all three double bonds of certain aromatic nitrogen heterocycles can be reduced with metallic hydrides, such as $NaBH_4$ or $LiAlH_4$. For a review, see Keay, J.G. *Adv. Heterocycl. Chem.* ***1986***, *39*, 1.

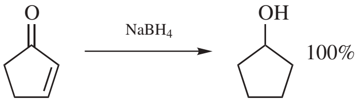
[552] Blough, B.E.; Carroll, F.I. *Tetrahedron Lett.* ***1993***, *34*, 7239.

[553] Moody, C.J.; Pitts, M.R. *Synlett* ***1998***, 1029.

derivatives.[554] Samarium iodide (SmI_2) reduces pyridine in aq. THF[555] and phenol in MeOH/KOH.[556] Ammonium formate and a Pd—C catalyst reduces pyridine *N*-oxide to piperidine in methanol.[557] The nitrogen-containing ring of quinolines is reduced with an iridium catalyst in isopropanol.[558]

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.

15-14 Reduction Of The Double or Triple Bonds Conjugated to Carbonyls, Cyano, and so on.



In certain cases,[559] metallic hydride reagents may also reduce double bonds in conjugation with C=O bonds, as well as reducing the C=O bonds, as in the conversion of cyclopentenone to cyclopentanol.[560] The reagent $NaBH_4$ has a greater tendency than $LiAlH_4$ to effect this double reduction, although even with $NaBH_4$ the product of single reduction (of the C=O bond) is usually formed in larger amount than the doubly reduced product. Lithium aluminium hydride gives significant double reduction only in cinnamyl systems, for example, with PhCH=CHCOOH.[561] Lithium aluminium hydride also reduces the double bonds of allylic alcohols[562] and $NaBH_4$ in MeOH—THF[563] or $NaCNBH_3$ on a zeolite[564] reduces α,β-unsaturated nitro compounds to nitroalkanes. The C=C unit proximal to the carbonyl in dienyl amides is selectively reduced with $NaBH_4/I_2$.[565] Mixed hydride reducing agents, such as $NaBH_4$—$BiCl_3$,[566] $NaBH_4$—$InCl_3$,[567] borohydride exchange resin (BER)—$CuSO_4$,[568] and Dibal—$Co(acac)_2$[569] have been

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[554] Pitts, M.R.; Harrison, J.R.; Moody, C.J. *J. Chem. Soc., Perkin Trans. 1*, **2001**, 955.

[555] Kamochi, Y.; Kudo, T. *Heterocycles* ***1993***, *36*, 2383.

[556] Kamochi, Y.; Kudo, T. *Tetrahedron Lett.* ***1994***, *35*, 4169.

[557] Zacharie, B.; Moreau, N.; Dockendorff, C. *J. Org. Chem.* ***2001***, *66*, 5264.

[558] Fujita, K.; Kitatsuji, C.; Furukawa, S.; Yamaguchi, R. *Tetrahedron Lett.* ***2004***, *45*, 3215.

[559] For discussion, see Meyer, G.R. *J. Chem. Educ.* ***1981***, *58*, 628.

[560] Brown, H.C.; Hess, H.M. *J. Org. Chem.* ***1969***, *34*, 2206. For other methods of reducing both double bonds, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, p. 1096.

[561] Nystrom, R.F.; Brown, W.G. *J. Am. Chem. Soc.* ***1947***, *69*, 2548; ***1948***, *70*, 3738; Gammill, R.B.; Gold, P.M.; Mizsak, S.A. *J. Am. Chem. Soc.* ***1980***, *102*, 3095.

[562] For discussions of the mechanism of this reaction, see Snyder, E.I. *J. Org. Chem.* ***1967***, *32*, 3531; Borden, W.T. *J. Am. Chem. Soc.* ***1968***, *90*, 2197; Blunt, J.W.; Hartshorn, M.P.; Soong, L.T.; Munro, M.H.G. *Aust. J. Chem.* ***1982***, *35*, 2519; Vincens, M.; Fadel, R.; Vidal, M. *Bull. Soc. Chim. Fr.* ***1987***, 462.

[563] Varma, R.S.; Kabalka, G.W. *Synth. Commun.* ***1985***, *15*, 151.

[564] Gupta, A.; Haque, A.; Vankar, Y.D. *Chem. Commun.* ***1996***, 1653.

[565] Das, B.; Kashinatham, A.; Madhusudhan, P. *Tetrahedron Lett.* ***1998***, *39*, 677.

[566] Ren, P.-D.; Pan, S.-F.; Dong, T.-W.; Wu, S.-H. *Synth. Commun.* ***1995***, *25*, 3395.

[567] Ranu, B.C.; Samanta, S. *Tetrahedron Lett.* ***2002***, *43*, 7405.

[568] Sim, T.B.; Yoon, N.M. *Synlett* ***1995***, 726.

[569] Ikeno, T.; Kimura, T.; Ohtsuka, Y.; Yamada, T. *Synlett* ***1999***, 96.

used. The $InCl_3$—$NaBH_4$ reagent was used to covert conjugated diene ketones (C=C—C=C—C=O) selectively to the nonconjugated alkenyl ketone (C=C—CH_2CH_2—C=O).[570]

Note that 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 $CoBr_2$.[571]

Reduction of only the C=C bond of conjugated C=C—C=O and C=C—C≡N systems[572] has been achieved by many reducing agents,[573] a few of which are H_2 and a Rh catalyst,[574] a Ru catalyst,[575] a Pd catalyst,[576] or an Ir catalyst,[577] and Raney nickel alone.[578] Reagents such as SmI_2,[579] and catecholborane[580] are effective. Conjugated ketones react with 2 equivalents of Cp_2TiCl in THF/MeOH to give the corresponding saturated ketone.[581] Indium metal in aqueous ethanol with ammonium chloride converts alkylidene dimalononitriles to the saturated dinitrile.[582] Zinc and acetic acid has been used for the conjugate reduction of dihydropyridin-4-ones.[583] Formic acid with a palladium catalysts reduced conjugated carboxylic acids.[584]

Silanes can be effective for the reduction of the C=C unit in conjugated systems in the presence of copper species.[585] $PhSiH_3$ and a nickel catalyst,[586] CuCl,[587] or a manganese catalyst.[588] In addition, PhR_2SiH with a copper catalyst,[589] and

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[570] Ranu, B.C.; Samanta, S. *J. Org. Chem.* ***2003***, *68*, 7130.

[571] See, for example, Ashby, E.C.; Lin, J.J. *J. Org. Chem.* ***1978***, *43*, 2567; Chung, S. *J. Org. Chem.* ***1979***, *44*, 1014. See also, Osby, J.O.; Heinzman, S.W.; Ganem, B. *J. Am. Chem. Soc.* ***1986***, *108*, 67.

[572] For a review of the reduction of α,β-unsaturated carbonyl compounds, see Keinan, E.; Greenspoon, N., in Patai, S.; Rappoport, Z. *The Chemistry of Enones*, pt. 2, Wiley, NY, ***1989***, pp. 923–1022. For a review of the stereochemistry of catalytic hydrogenation of α,β-unsaturated ketones, see Augustine, R.L. *Adv. Catal.* ***1976***, *25*, 56.

[573] For a long list of these, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 13–27.

[574] Djerassi, C.; Gutzwiller, J. *J. Am. Chem. Soc.* ***1966***, *88*, 4537; Cabello, J.A.; Campelo, J.M.; Garcia, A.; Luna, D.; Marinas, J.M. *J. Org. Chem.* ***1986***, *51*, 1786; Harmon, R.E.; Parsons, J.L.; Cooke, D.W.; Gupta, S.K.; Schoolenberg, J. *J. Org. Chem.* ***1969***, *34*, 3684.

[575] Chen, Y.-C.; Xue, D.; Deng, J.-G.; Cui, X.; Zhu, J.; Jiang, Y.-Z. *Tetrahedron Lett.* ***2004***, *45*, 1555.

[576] Sajiki, H.; Ikawa, T.; Hirota, K. *Tetrahedron Lett.* ***2003***, *44*, 8437; Nagano, H.; Yokota, M.; Iwazaki, Y. *Tetrahedron Lett.* ***2004***, *45*, 3035.

[577] Yue, T.-Y.; Nugent, W.A. *J. Am. Chem. Soc.* ***2002***, *124*, 13692.

[578] Barrero, A.F.; Alvarez-Manzaneda, E.J.; Chahboun, R.; Meneses, R. *Synlett* ***1999***, 1663. For an ultrasound-mediated reduction with Raney nickel, see Wang, H.; Lian, H.; Chen, J.; Pan, Y.; Shi, Y. *Synth. Commun.* ***1999***, *29*, 129.

[579] Cabrera, A.; Alper, H. *Tetrahedron Lett.* ***1992***, *33*, 5007. See also, Guo, H.; Zhang, Y. *Synth. Commun.* ***2000***, *30*, 1879.

[580] Evans, D.A.; Fu, G.C. *J. Org. Chem.* ***1990***, *55*, 5678.

[581] Moisan, L.; Hardouin, C.; Rousseau, B.; Doris, E. *Tetrahedron Lett.* ***2002***, *43*, 2013.

[582] Ranu, B.C.; Dutta, J.; Guchhait, S.K. *Org. Lett.* ***2001***, *3*, 2603.

[583] Comins, D.L.; Brooks, C.A.; Ingalls, C.L. *J. Org. Chem.* ***2001***, *66*, 2181.

[584] Arterburn, J.B.; Pannala, M.; Gonzlez, A.M.; Chamberlin, R.M. *Tetrahedron Lett.* ***2000***, *41*, 7847.

[585] Mori, A.; Fujita, A.; Nishihara, Y.; Hiyama, R. *Chem. Commun.* ***1997***, 2159.

[586] Boudjouk, P.; Choi, S.-B.; Hauck, B.J.; Rajkumar, A.B. *Tetrahedron Lett.* ***1998***, *39*, 3951.

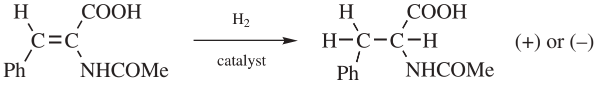
[587] Ito, H.; Ishizuka, T.; Arimoto, K.; Miura, K.; Hosomi, A. *Tetrahedron Lett.* ***1997***, *38*, 8887.

[588] Magnus, P.; Waring, M.J.; Scott, D.A. *Tetrahedron Lett.* ***2000***, *41*, 9731.

[589] Mori, A.; Fujita, A.; Kajiro, H.; Nishihara, Y.; Hiyama, T. *Tetrahedron* ***1999***, *55*, 4573.

$PhSiH_3$—$Mo(CO)_6$[590] have been used. Triphenylsilane was also used for the asymmetric reduction of nitro alkenes (C=C—NO_2).[591] Poly(methylhydrosiloxane) with a chiral copper catalyst gave conjugate reduction of conjugated esters to give the saturated derivative with high enantioselectivity.[592]

A β-bromo conjugated lactone was reduced to the β-bromolactone with modest enantioselectivity using an excess of Ph_3SiH and a CuCl catalyst with a chiral ligand.[593] A copper complex with a chiral ligand and poly(methylhydrosiloxane) gave reduction of the C=C unit in conjugated carbonyl systems with good enantioselectivity.[594] Tributyltin hydride, in the presence of $MgBr_2$•OEt_2 gave 1,4-reduction of conjugated esters.[595]



112 **113**

Optically active catalysts, primarily homogeneous, have been used to achieve enantioselective hydrogenations[596] of many prochiral conjugated substrates.[597] For example,[598] hydrogenation of **112** with a suitable catalyst gives (+) or (−)

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[590] Keinan, E.; Perez, D. *J. Org. Chem.* ***1987***, *52*, 2576.

[591] Czekelius, C.; Carreira, E.M. *Org. Lett.* ***2004***, *6*, 4575.

[592] Appella, D.H.; Moritani, Y.; Shintani, R.; Ferreira, E.M.; Buchwald, S.L. *J. Am. Chem. Soc.* ***1999***, *121*, 9473.

[593] Hughes, G.; Kimura, M.; Buchwald, S.L. *J. Am. Chem. Soc.* ***2003***, *125*, 11253.

[594] Jurkauskas, V.; Buchwald, S.L. *J. Am. Chem. Soc.* ***2002***, *124*, 2892; Lipshutz, B.H.; Servesko, J.M.; Taft, B.R. *J. Am. Chem. Soc.* ***2004***, *126*, 8352.

[595] Hirasawa, S.; Nagano, H.; Kameda, Y. *Tetrahedron Lett.* ***2004***, *45*, 2207.

[596] For a discussion of the mechanism of asymmetric hydrogenation of such systems using a ruthenium catalyst, see Kitamura, M.; Tsukamoto, M.; Bessho, Y.; Yoshimura, M.; Kobs, U.; Widhalm, M.; Noyori, R. *J. Am. Chem. Soc.* ***2002***, *124*, 6649. For a review of the mechanism of stereoselection in rhodium-catalyzed asymmetric hydrogenations, see Gridnev, I.D.; Imamoto, T. *Acc. Chem. Res.* ***2004***, *37*, 633.

[597] For reviews, see, in Morrison, J.D. *Asymmetric Synthesis*, Vol. 5, Academic Press, NY, ***1985***, the reviews by Halpern, J. pp. 41–69, Koenig, K.E. pp. 71–101, Harada, K. pp. 345–383; Ojima, I.; Clos, N.; Bastos, C. *Tetrahedron* ***1989***, *45*, 6901, 6902–6916; Jardine, F.H., in Hartley, F.R. *The Chemistry of the Metal–Carbon Bond*, Vol. 4, Wiley, NY, ***1987***, pp. 751–775; Nógrádi, M. *Stereoselective Synthesis*, VCH, NY, ***1986***, pp. 53–87; Knowles, W.S. *Acc. Chem. Res.* ***1983***, *16*, 106; Brunner, H. *Angew. Chem. Int. Ed.* ***1983***, *22*, 897; Klabunovskii, E.I. *Russ. Chem. Rev.* ***1982***, *51*, 630; Čaplar, V.; Comisso, G.;Šunjić, V. *Synthesis* ***1981***, 85; Morrison, J.D.; Masler, W.F.; Neuberg, M.K. *Adv. Catal.* ***1976***, *25*, 81; Kagan, H.B. *Pure Appl. Chem.* ***1975***, *43*, 401; Bogdanović, B. *Angew. Chem. Int. Ed.* ***1973***, *12*, 954. See also, Brewster, J.H. *Top. Stereochem.* ***1967***, *2*, 1, *J. Am. Chem. Soc.* ***1959***, *81*, 5475, 5483, 5493; Davis, D.D.; Jensen, F.R. *J. Org. Chem.* ***1970***, *35*, 3410; Jullien, F.R.; Requin, F.; Stahl-Larivière, H. *Nouv. J. Chim.* ***1979***, *3*, 91; Sathyanarayana, B.K.; Stevens, E.S. *J. Org. Chem.* ***1987***, *52*, 3170; Wroblewski, A.E.; Applequist, J.; Takaya, A.; Honzatko, R.; Kim, S.; Jacobson, R.A.; Reitsma, B.H.; Yeung, E.S.; Verkade, J.G. *J. Am. Chem. Soc.* ***1988***, *110*, 4144; Knowles, W.S. *Angew. Chem. Int. Ed.* ***2002***, *41*, 1999.

[598] For some other recent examples, see Hayashi, T.; Kawamura, N.; Ito, Y. *Tetrahedron Lett.* ***1988***, *29*, 5969; Muramatsu, H.; Kawano, H.; Ishii, Y.; Saburi, M.; Uchida, Y. *J. Chem. Soc., Chem. Commun.* ***1989***, 769; Amrani, Y.; Lecomte, L.; Sinou, D.; Bakos, J.; Toth, I.; Heil, B. *Organometallics* ***1989***, *8*, 542; Yamamoto, K.; Ikeda, K.; Lin, L.K. *J. Organomet. Chem.* ***1989***, *370*, 319; Waymouth, R.; Pino, P. *J. Am. Chem. Soc.* ***1990***, *112*, 4911; Ohta, T.; Takaya, H.; Noyori, R. *Tetrahedron Lett.* ***1990***, *31*, 7189; Ashby, M.T.; Halpern, J. *J. Am. Chem. Soc.* ***1991***, *113*, 589; Heiser, B.; Broger, E.A.; Crameri, Y. *Tetrahedron: Asymmetry* ***1991***, *2*, 51; Burk, M.J. *J. Am. Chem. Soc.* ***1991***, *113*, 8518.

113 (depending on which enantiomer of the catalyst is used) with an enantiomeric excess as high as 96%.[599] Prochiral substrates that give such high optical yields generally contain functional groups, such as a carbonyl group,[600] amide groups, cyano groups, or combinations of such groups as in **112**.[601] The catalyst in such cases[602] is usually a ruthenium[603] or rhodium complex with chiral phosphine ligands.[604] Iridium complexes have been used with excellent enantioselectivity.[605] Good asymmetric induction[606] has been achieved using chiral rhodium complexes with other chiral additives.[607] The role of solvent has been examined.[608] A pressure dependent enantioselective hydrogenation has been reported.[609] There are many examples for the reduction of alkylidene amino acids, amino esters or amido acids or esters that vary the catalyst and/or the chiral ligand.[610] Asymmetric catalytic hydrogenation has been reported for conjugated carboxylic acids[611] and conjugated ketones.[612] A ruthenium catalyst with a polymer supported chiral ligand has also

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[599] Koenig, K.E., in Morrison, J.D. *Asymmetric Synthesis*, Vol. 5, Academic Press, NY, ***1985***, p. 74.

[600] Reetz, M.T.; Mehler, G. *Angew. Chem. Int. Ed.* ***2000***, *39*, 3889.

[601] For tables of substrates that have been enantioselectively hydrogenated, see Koenig, K.E., in Morrison, J.D. *Asymmetric Synthesis* Vol. 5, Academic Press, NY, ***1985***, pp. 83–101.

[602] For a list of these, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 8–12. For reviews of optically active nickel catalysts, see Izumi, Y. *Adv. Catal.* ***1983***, *32*, 215; *Angew. Chem. Int. Ed.* ***1971***, *10*, 871. For a review of the synthesis of some of these phosphines, see Mortreux, A.; Petit, F.; Buono, G.; Peiffer, G. *Bull. Soc. Chim. Fr.* ***1987***, 631.

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[604] Lee, S.-g.; Zhang, Y.J. *Org. Lett.* ***2002***, *4*, 2429; Le, J.C.D.; Pagenkopf, B.L. *J. Org. Chem.* ***2004***, *69*, 4177; Fu, Y.; Guo, X.-X.; Zhu, S.-F.; Hu, A.-G.; Xie, J.-H.; Zhou, Q.-L. *J. Org. Chem.* ***2004***, *69*, 4648; Yi, B.; Fan, Q.-H.; Deng, G.-J.; Li, Y.-M.; Qiu, L.-Q.; Chan, A.S.C. *Org. Lett.* ***2004***, *6*, 1361.; Hoen, R.; van den Berg, M.; Bernsmann, H.; Minnaard, A.J.; de Vries, J.G.; Feringa, B.L. *Org. Lett.* ***2004***, *6*, 1433; Fu, Y.; Hou, G.-H.; Xie, J.-H.; Xing, L.; Wang, L.-X.; Zhou, Q.-L. *J. Org. Chem.* ***2004***, *69*, 8157; Peña, D.; Minnaard, A.J.; de Vries, J.G.; Feringa, B.L. *J. Am. Chem. Soc.* ***2002***, *124*, 14552; Evans, D.A.; Michael, F.E.; Tedrow, J.S.; Campos, K.R. *J. Am. Chem. Soc.* ***2003***, *125*, 3534; Hoge, G.; Wu, H.-P.; Kissel, W.S.; Pflum, D.A.; Greene, D.J.; Bao, J. *J. Am. Chem. Soc.* ***2004***, *126*, 5966; Ikeda, S.-i.; Sanuki, R.; Miyachi, H.; Miyashita, H.; Taniguchi, M.; Odashima, K. *J. Am. Chem. Soc.* ***2004***, *126*, 10331; Huang, H.; Liu, X.; Chen, S.; Chen, H.; Zheng, Z. *Tetrahedron Asymmetry* ***2004***, *15*, 2011.

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[606] Zhu, G.; Zhang, X. *J. Org. Chem.* ***1998***, *63*, 9590; Burk, M.J.; Casy, G.; Johnson, N.B. *J. Org. Chem.* ***1998***, *63*, 6084; Burk, M.J.; Allen, J.G.; Kiesman, W.F. *J. Am. Chem. Soc.* ***1998***, *120*, 657.

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[609] Heller, D.; Holz, J.; Drexler, H.-J.; Lang, J.; Drauz, K.; Krimmer, H.-P.; Börner, A. *J. Org. Chem.* ***2001***, *66*, 6816.

[610] Rhodium catalyst with a chiral bis(phosphine): Li. W.; Zhang, Z.; Xiao, D.; Zhang, X. *Tetrahedron Lett.* ***1999***, *40*, 6701. New chiral phosphines: Ohashi, A.; Imamoto, T. *Org. Lett.* ***2001***, *3*, 373.

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[612] Yamaguchi, M.; Nitta, A.; Reddy, R.S.; Hirama, M. *Synlett* ***1997***, 117.

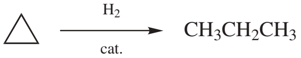
been used for conjugated acids.[613] Asymmetric hydrogenation of conjugated carboxylic acids in an ionic liquid is known using a chiral ruthenium complex[614] Enamino esters have been hydrogenated with high enantioselectivity using chiral rhodium catalysts.[615]

See **19-36** for methods of reducing C=O bonds in the presence of conjugated C=C bonds.

The C=C unit of conjugated aldehydes has been reduced using $AlMe_3$ with a catalytic amount of CuBr[616] and with ammonium formate/Pd–C.[617] Polymer-supported formate has been used for the 1,4-reduction of conjugated ketones[618] and conjugated acids using a rhodium catalyst and microwave irradiation.[619] Selective reduction of the C=C unit in conjugated ketones was accomplished with $Na_2S_2O_4$ in aqueous dioxane, and nonconjugated alkenes were not reduced.[620] Isopropanol and an iridium catalyst gives conjugate reduction of conjugated ketones.[621] Conjugate hydrostannation by an iodotin hydride ate complex, followed by hydrolysis converts unsaturated esters to saturated esters.[622] The reaction of conjugated ketones with aluminum chlorides, followed by treatment with water generates the saturated ketone.[623]

Baker's yeast reduces conjugated nitro compounds to nitroalkanes[624] and also the C=C unit of conjugated ketones.[625] Other enzymatic reductions are possible. A reductase from *Nicotiana tabacum* reduced a conjugated ketone to the saturated ketone, with excellent enantioselectivity.[626] Enzyme YNAR-I and NADP-H reduces conjugated nitro compounds to nitroalkanes.[627]

15-15 Reductive Cleavage of Cyclopropanes



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[613] Fan, Q.H.; Deng, G.-J.; Lin, C.-C.; Chan, A.S.C. *Tetrahedron Asymmetry* ***2001***, *12*, 1241.

[614] In bmim PF_6, 1-butyl-3-methylimidazolium hexafluorophosphate: Brown, R.A.; Pollet, P.; McKoon, E.; Eckert, C.A.; Liotta, C.L.; Jessop, P.G. *J. Am. Chem. Soc.* ***2001***, *123*, 1254.

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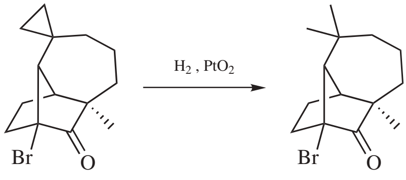
[626] Shimoda, K.; Kubota, N.; Hamada, H. *Tetrahedron Asymmetry* ***2004***, *15*, 2443; Hirata, T.; Shimoda, K.; Gondai, T. *Chem. Lett.* ***2000***, 850.

[627] Kawai, Y.; Inaba, Y.; Hayashi, M.; Tokitoh, N. *Tetrahedron Lett.* ***2001***, *42*, 3367.

Cyclopropanes can be cleaved by catalytic hydrogenolysis.[628] Among the catalysts used have been Ni, Pd, Rh,[629] and Pt. The reaction can often be run under mild conditions.[630] Certain cyclopropane rings, especially cyclopropyl ketones and aryl-substituted cyclopropanes,[631] can be reductively cleaved by an alkali metal (generally Na or Li) in liquid ammonia.[632] Similar reduction has been accomplished photochemically in the presence of $LiClO_4$.[633] This reaction is an excellent way to introduce a *gem*-dimethyl unit into a molecule. Hydrogenation of the cyclopropane ring in **114**, for example, gave the *gem*-dimethyl unit in **115** using PtO_2 (Adam's catalyst).[634]



114 **115**

F. A Metal on the Other Side

15-16 Hydroboration

$$3\;\; {>}\mathrm{C}{=}\mathrm{C}{<} \;+\; \mathrm{BH_3} \longrightarrow \left(\mathrm{H}-\overset{\diagdown}{\underset{/}{\mathrm{C}}}-\overset{|}{\underset{|}{\mathrm{C}}}\right)_3\mathrm{B}$$

When alkenes are treated with borane[635] in ether solvents, BH_3 adds across the double bond.[636] Borane cannot be prepared as a stable pure compound[637] (it dimerizes to diborane, B_2H_6), but it is commercially available in the form of

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[628] For reviews, see Charton, M., in Zabicky, J. *The Chemistry of Alkenes*, Vol. 2, Wiley, NY, ***1970***, pp. 588–592; Newham, J. *Chem. Rev.* ***1963***, *63*, 123; Rylander, P.N. *Catalytic Hydrogenation over Platinum Metals*, *Academic Press, NY*, ***1967***, pp. 469–474.

[629] Bart, S.C.; Chirik, P.J. *J. Am. Chem. Soc.* ***2003***, *125*, 886.

[630] See, for example, Woodworth, C.W.; Buss, V.; Schleyer, P.v.R. *Chem. Commun.* ***1968***, 569.

[631] See, for example, Walborsky, H.M.; Aronoff, M.S.; Schulman, M.F. *J. Org. Chem.* ***1970***, *36*, 1036.

[632] For a review, see Staley, S.W. *Sel. Org. Transform.* ***1972***, *2*, 309.

[633] Cossy, J.; Furet, N. *Tetrahedron Lett.* ***1993***, *34*, 8107.

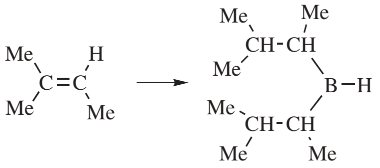
[634] Karimi, S.; Tavares, P. *J. Nat. Prod.* ***2003***, *66*, 520.

[635] For a review of this reagent, see Lane, C.F., in Pizey, J.S. *Synthetic Reagents*, Vol. 3, Wiley, NY, ***1977***, pp. 1–191.

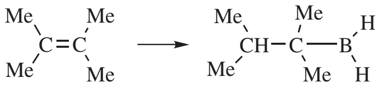
[636] For books on this reaction and its many applications, see Pelter, A.; Smith, K.; Brown, H.C. *Borane Reagents*, Academic Press, NY, ***1988***; Brown, H.C. *Boranes in Organic Chemistry*, Cornell University Press, Ithaca, NY, ***1972***, *Organic Syntheses Via Boranes, Wiley*, NY, ***1975***; Cragg, G.M.L. *Organoboranes in Organic Synthesis*, Marcel Dekker, NY, ***1973***. For reviews, see Matteson, D.S., in Hartley, F.R. *The Chemistry of the Metal-Carbon Bond*, Vol. 4, Wiley, NY, ***1987***, pp. 307–409, 315–337; Smith, K. *Chem. Ind. (London)* ***1987***, 603; Brown, H.C.; Vara Prasad, J.V.N. *Heterocycles* ***1987***, *25*, 641; Suzuki, A.; Dhillon, R.S. *Top. Curr. Chem.* ***1986***, *130*, 23.

[637] Fehlner, T.P. *J. Am. Chem. Soc.* ***1971***, *93*, 6366.

'ate' complexes with THF, Me_2S,[638] phosphines, or tertiary amines. The alkenes can be treated with a solution of one of these complexes (THF—BH_3 reacts at 0°C and is the most convenient to use; R_3N—BH_3 generally require temperatures of ~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 $NaBH_4$ and BF_3 etherate, which generates borane *in situ*.[639] With relatively unhindered alkenes, the process cannot be stopped with the addition of one molecule of BH_3 because the resulting RBH_2 adds to another molecule of alkene to give R_2BH, which in turn adds to a third alkene molecule, so that the isolated product is a trialkylborane R_3B. The reaction can be performed on alkenes with one to four substituents, including cyclic alkenes, but when the alkene is moderately hindered, the product *is* the dialkylborane R_2BH or even the monalkylborane RBH_2.[640] For example, **116** (*disiamylborane*) and **117** (*thexylborane*)[641] have been prepared in this manner. Monoalkylboranes RBH_2 (which can be prepared from hindered alkenes, as above) and dialkylboranes R_2BH also add to alkenes, to give the mixed trialkylboranes RR'_2 B and $R_2R'B$, respectively. Surprisingly, when methylborane $MeBH_2$,[642] which is not a bulky molecule, adds to alkenes in the solvent THF, the reaction can be stopped with one addition to give the dialkylboranes RMeBH.[643] Reaction of this with a second alkene produces the trialkylborane RR′MeB.[644] Other monoalkylboranes, *i*$PrBH_2$, *n*-$BuBH_2$, *s*-$BuBH_2$, and *t*-$BuBH_2$, behave similarly with internal alkenes, but not with alkenes of the type $RCH{=}CH_2$.[645]



Disiamylborane, **116**



Thexylborane, **117**

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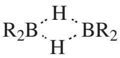
[638] For a review of BH_3•SMe_2, see Hutchins, R.O.; Cistone, F. *Org. Prep. Proced. Int.* ***1981***, *13*, 225. See Cadot, C.; Dalko, P.I.; Cossy, J. *Tetrahedron Lett.* ***2001***, *42*, 1661.

[639] For a list of hydroborating reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 1005–1009.

[640] Unless coordinated with a strong Lewis base such as a tertiary amine, mono and dialkylboranes actually exist as dimers, for example,  $R_2B\overset{H}{\underset{H}{\rangle\langle}}BR_2$ Brown, H.C.; Klender, G.J. *Inorg. Chem.* ***1962***, *1*, 204.

[641] For a review of the chemistry of thexylborane, see Negishi, E.; Brown, H.C. *Synthesis* ***1974***, 77.

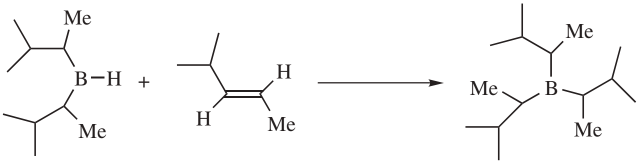
[642] Prepared from lithium methylborohydride and HCl: Brown, H.C.; Cole, T.E.; Srebnik, M.; Kim, K. *J. Org. Chem.* ***1986***, *51*, 4925.

[643] Srebnik, M.; Cole, T.E.; Brown, H.C. *J. Org. Chem.* ***1990***, *55*, 5051.

[644] For a method of synthesis of RR^1R^2B, see Kulkarni, S.U.; Basavaiah, D.; Zaidlewicz, M.; Brown, H.C. *Organometallics* ***1982***, *1*, 212.

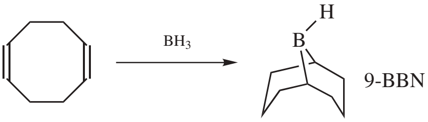
[645] Srebnik, M.; Cole, T.E.; Ramachandran, P.V.; Brown, H.C. *J. Org. Chem.* ***1989***, *54*, 6085.

In all cases, the boron goes to the side of the double bond that has more hydrogens, whether the substituents are aryl or alkyl.[646] This actually follows Markovnikov's rule, since boron is more positive than hydrogen. However, the regioselectivity is caused mostly by steric factors, although 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 reaction with boron and the alkene has electrophilic character.[647] When both sides of the double bond are 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 borane molecule. For example, treatment of *i*PrCH=CHMe with borane gave 57% of product with boron on the methyl-bearing carbon and 43% of the other, while treatment with **116** gave 95% **118** and only 5% of the other isomer.[648]



116 **118**

Another reagent with high regioselectivity is 9-borabicyclo[3.3.1]nonane (9-BBN), which is prepared by hydroboration of 1,5-cyclooctadiene,[649] and 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 alkene in the presence of a less reactive alkene.[650] For example, 1-pentene can be removed from a mixture of 1- and 2-pentenes, and a cis alkene can be selectively hydroborated in a mixture of the cis and trans isomers.



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[646] For a thorough discussion of the regioselectivity with various types of substrate and hydroborating agents, see Cragg, G.M.L.*Organoboranes in Organic Synthesis* Marcel Dekker, NY, ***1973***, pp.63–84, 137–197. See also, Brown, H.C.; Vara Prasad, J.V.N.; Zee, S. *J. Org. Chem.* ***1986***, *51*, 439.

[647] Brown, H.C.; Sharp, R.L. *J. Am. Chem. Soc.* ***1966***, *88*, 5851; Klein, J.; Dunkelblum, E.; Wolff, M.A. *J. Organomet. Chem.* ***1967***, *7*, 377. See also, Marshall, P.A.; Prager, R.H. *Aust. J. Chem.* ***1979***, *32*, 1251. For a study of hyperconjugation effects in substituted methylboranes, see Mo, Y.; Jiao, H. Schleyer, P.v.R. *J. Org. Chem.* ***2004***, *69*, 3493.

[648] Brown, H.C.; Zweifel, G. *J. Am. Chem. Soc.* ***1961***, *83*, 1241.

[649] See Knights, E.F.; Brown, H.C. *J. Am. Chem. Soc.* ***1968***, *90*, 5280, 5281; Brown, H.C.; Chen, J.C. *J. Org. Chem.* ***1981***, *46*, 3978; Soderquist, J.A.; Brown, H.C. *J. Org. Chem.* ***1981***, *46*, 4599.

[650] Brown, H.C.; Moerikofer, A.W. *J. Am. Chem. Soc.* ***1963***, *85*, 2063; Zweifel, G.; Brown, H.C. *J. Am. Chem. Soc.* ***1963***, *85*, 2066; Zweifel, G.; Ayyangar, N.R.; Brown, H.C. *J. Am. Chem. Soc.* ***1963***, *85*, 2072; Brown, H.C.; Sharp, R.L. *J. Am. Chem. Soc.* ***1966***, *88*, 5851; Klein, J.; Dunkelblum, E.; Wolff, M.A. *J. Organomet. Chem.* ***1967***, *7*, 377.

For most substrates, the addition in hydroboration is stereospecific and syn, with attack taking place from the less-hindered side.[651] Note that organoboranes can be analyzed using ^{11}B nmr.[652] The mechanism[653] may be a cyclic four-center one:[654]

When the substrate is an allylic alcohol or amine, the addition is generally anti,[655] although the stereoselectivity can be changed to syn by the use of catecholborane and the rhodium complexes mentioned above.[656] Because the mechanism is different, use of this procedure can result in a change in regioselectivity as well, for example, styrene $PhCH{=}CH_2$ gave $PhCH(OH)CH_3$.[657]

Monochloroborane[658] BH_2Cl coordinated with dimethyl sulfide shows greater regioselectivity than BH_3 for terminal alkenes or those of the form $R_2C{=}CHR$, and the hydroboration product is a dialkylchloroborane R_2BCl).[659] For example, 1-hexene gave 94% of the anti-Markovnikov product (the boron is on the less substituted carbon) with BH_3—THF, but 99.2% with BH_2Cl—SMe_2. Treatment of alkenes with dichloroboranedimethyl sulfide $BHCl_2$—SMe_2 in the presence of BF_3[660] or with BCl_3 and Me_3SiH[661] gives alkyldichloroboranes $RBCl_2$. Extensions of this basic approach are possible with dihalo alkylboranes. The reaction of an alkene with allyl dibromoborane, incorporated an allyl group and the born on adjacent carbons.[662]

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[651] Brown, H.C.; Zweifel, G. *J. Am. Chem. Soc.* ***1961***, *83*, 2544; Bergbreiter, D.E.; Rainville, D.P. *J. Org. Chem.* ***1976***, *41*, 3031; Kabalka, G.W.; Newton, Jr., R.J.; Jacobus, J. *J. Org. Chem.* ***1978***, *43*, 1567.

[652] Medina, J.R.; Cruz, G.; Cabrera, C.R.; Soderquist, J.A. *J. Org. Chem.* ***2003***, *68*, 4631.

[653] For kinetic studies, see Vishwakarma. L.C.; Fry, A. *J. Org. Chem.* ***1980***, *45*, 5306; Brown, H.C.; Chandrasekharan, J.; Wang, K.K. *J. Org. Chem.* ***1983***, *48*, 2901; *Pure Appl. Chem.* ***1983***, *55*, 1387–1414; Nelson, D.J.; Cooper, P.J. *Tetrahedron Lett.* ***1986***, *27*, 4693; Brown, H.C.; Chandrasekharan, J. *J. Org. Chem.* ***1988***, *53*, 4811.

[654] Brown, H.C.; Zweifel, G. *J. Am. Chem. Soc.* ***1959***, *81*, 247; Pasto, D.J.; Lepeska, B.; Balasubramaniyan, V. *J. Am. Chem. Soc.* ***1972***, *94*, 6090; Pasto, D.J.; Lepeska, B.; Cheng, T. *J. Am. Chem. Soc.* ***1972***, *94*, 6083; Narayana, C.; Periasamy, M. *J. Chem. Soc., Chem. Commun.* ***1987***, 1857. See, however, Jones, P.R. *J. Org. Chem.* ***1972***, *37*, 1886.

[655] See Still, W.C.; Barrish, J.C. *J. Am. Chem. Soc.* ***1983***, *105*, 2487.

[656] See Evans, D.A.; Fu, G.C.; Hoveyda, A.H. *J. Am. Chem. Soc.* ***1988***, *110*, 6917; Burgess, K.; Cassidy, J.; Ohlmeyer, M.J. *J. Org. Chem.* ***1991***, *56*, 1020; Burgess, K.; Ohlmeyer, M.J. *J. Org. Chem.* ***1991***, *56*, 1027.

[657] Hayashi, T.; Matsumoto, Y.; Ito, Y. *J. Am. Chem. Soc.* ***1989***, *111*, 3426; Zhang, J.; Lou, B.; Guo, G.; Dai, L. *J. Org. Chem.* ***1991***, *56*, 1670.

[658] For a review of haloboranes, see Brown, H.C.; Kulkarni, S.U. *J. Organomet. Chem.* ***1982***, *239*, 23.

[659] Brown, H.C.; Ravindran, N.; Kulkarni, S.U. *J. Org. Chem.* ***1979***, *44*, 2417.

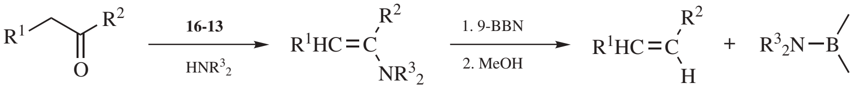
[660] Brown, H.C.; Racherla, U.S. *J. Org. Chem.* ***1986***, *51*, 895.

[661] Soundararajan, R.; Matteson, D.S. *J. Org. Chem.* ***1990***, *55*, 2274.

[662] Frantz, D.E.; Singleton, D.A. *Org. Lett.* ***1999***, *1*, 485.

An important use of the hydroboration reaction is oxidation of an organoborane to alcohols with hydrogen peroxide and NaOH (**12-27**). Organoboranes have been oxidized with Oxone®[663] and methanol/triethylamine/molecular oxygen.[664] The synthetic result is 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 (**10-73**), with α,β-unsaturated carbonyl compounds to give Michael-type addition of R and H (**15-27**), with CO to give alcohols and ketones (**18-23–18-24**); they can be reduced with carboxylic acids, providing an indirect method for reduction of double bonds (**15-11**), or they can be oxidized with chromic acid or pyridinium chlorochromate to give ketones[665] or aldehydes (from terminal alkenes),[666] dimerized with silver nitrate and NaOH (**14-26**), isomerized (**18-11**), or converted to amines (**12-32**), halides (**12-31**), or carboxylic acids.[667] They are thus useful intermediates for the preparation of a wide variety of compounds. Intramolecular hydroboration reaction are possible.[668]

Such functional groups as OR, OH, NH_2, SMe, halogen, and COOR may be present in the molecule,[669] 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.[670]



Enamines can also be converted to amino alcohols via hydroboration.[671] Allene–boranes react with aldehydes to give alkyne–alcohols.[672]

Use of the reagent diisopinocampheylborane **119** (prepared by treating optically active α-pinene with BH_3) results in enantioselective hydroboration–oxidation.[673] Since both (+) and (−) α-pinene are readily available, both enantiomers

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[663] Ripin, D.H.B.; Cai, W.; Brenek, S.J. *Tetrahedron Lett.* ***2000***, *41*, 5817.

[664] Cadot, C.; Dalko, P.I.; Cossy, J.; Ollivier, C.; Chuard, R.; Renaud, P. *J. Org. Chem.* ***2002***, *67*, 7193.

[665] Brown, H.C.; Garg, C.P. *J. Am. Chem. Soc.* ***1961***, *83*, 2951; *Tetrahedron* ***1986***, *42*, 5511; Rao, V.V.R.; Devaprabhakara, D.; Chandrasekaran, S. *J. Organomet. Chem.* ***1978***, 162, C9; Parish, E.J.; Parish, S.; Honda, H. *Synth. Commun.* ***1990***, *20*, 3265.

[666] Brown, H.C.; Kulkarni, S.U.; Rao, C.G.; Patil, V.D. *Tetrahedron* ***1986***, *42*, 5515.

[667] Soderquist, J.A.; Martinez, J.; Oyola, Y.; Kock, I. *Tetrahedron Lett.* ***2004***, *45*, 5541.

[668] See Shapland, P.; Vedejs, E. *J. Org. Chem.* ***2004***, *69*, 4094.

[669] See, for example, Brown, H.C.; Unni, M.K. *J. Am. Chem. Soc.* ***1968***, *90*, 2902; Brown, H.C.; Gallivan, Jr., R.M. *J. Am. Chem. Soc.* ***1968***, *90*, 2906; Brown, H.C.; Sharp, R.L. *J. Am. Chem. Soc.* ***1968***, *90*, 2915.

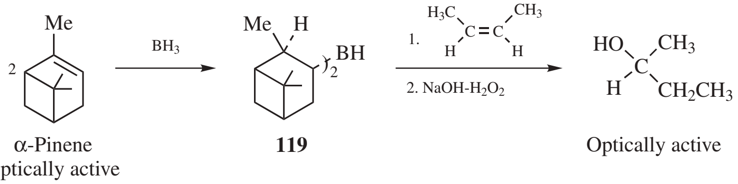
[670] Singaram, B.; Rangaishenvi, M.V.; Brown, H.C.; Goralski, C.T.; Hasha, D.L. *J. Org. Chem.* ***1991***, *56*, 1543.

[671] Goralski, C.T.; Hasha, D.L.; Nicholson, L.W.; Singaram, B. *Tetrahedron Lett.* ***1994***, *35*, 5165.

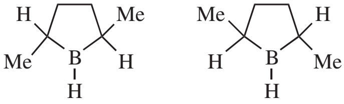
[672] Brown, H.C.; Khire, U.R.; Racherla, U.S. *Tetrahedron Lett.* ***1993***, *34*, 15.

[673] Brown, H.C.; Vara Prasad, J.V.N. *J. Am. Chem. Soc.* ***1986***, *108*, 2049.

can be prepared. Alcohols with moderate-to-excellent enantioselectivities have been obtained in this way.[674] However, **119** does not give good results with even moderately hindered alkenes; a better reagent for these compounds is isopinocampheylborane[675] although optical yields are lower. Limonylborane,[676] 2- and 4-dicaranylboranes,[677] a myrtanylborane,[678] and dilongifolylborane[679] have also been used. Other new asymmetric boranes have also been developed. The chiral cyclic boranes *trans*-2,15-dimethylborolanes (**51** and **52**) also add enantioselectively to alkenes (except alkenes of the form $RR'C{=}CH_2$) to give boranes of high optical purity.[680] When chiral boranes are added to trisubstituted alkenes of the form $RR'C{=}CHR''$, two new chiral centers are created, and, with **120** or **121**, only one of the four possible diastereomers is predominantly produced, in yields > 90%.[680] This has been called *double-asymmetric synthesis*.[681] An alternative asymmetric synthesis of alcohols involves the reaction of catechol borane with an alkene in the presence



α-Pinene Optically active **119** Optically active



(*R*, *R*) **120** **121** (*S*, *S*)

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[674] For reviews of enantioselective syntheses with organoboranes, see Brown, H.C.; Singaram, B. *Acc. Chem. Res.* ***1988***, *21*, 287; Srebnik, M.; Ramachandran, P.V. *Aldrichimica Acta* ***1987***, *20*, 9; Brown, H.C.; Jadhav, P.K.; Singaram, B. *Mod. Synth. Methods*, ***1986***, *4*, 307; Matteson, D.S. *Synthesis* ***1986***, 973; Brown, H.C.; Jadhav, P.K., in Morrison, J.D. *Asymmetric Synthesis* Vol. 2, Academic Press, NY, ***1983***, pp. 1–43. For a study of electronic effects, see Garner, C.M.; Chiang, S.; Nething, M.; Monestel, R. *Tetrahedron Lett.* ***2002***, *43*, 8339.

[675] Brown, H.C.; Jadhav, P.K.; Mandal, A.K. *J. Org. Chem.* ***1982***, *47*, 5074. See also, Brown, H.C.; Weissman, S.A.; Perumal, P.T.; Dhokte, U.P. *J. Org. Chem.* ***1990***, *55*, 1217. For an improved method, see Brown, H.C.; Singaram, B. *J. Am. Chem. Soc.* ***1984***, *106*, 1797; Brown, H.C.; Gupta, A.K.; Vara Prasad, J.V.N. *Bull. Chem. Soc. Jpn.* ***1988***, *61*, 93. For the crystal structure of this adduct, see Soderquist, J.A.; Hwang-Lee, S.; Barnes, C.L. *Tetrahedron Lett.* ***1988***, *29*, 3385.

[676] Jadhav, P.K.; Kulkarni, S.U. *Heterocycles* ***1982***, *18*, 169.

[677] Brown, H.C.; Vara Prasad, J.V.N.; Zaidlewicz, M. *J. Org. Chem.* ***1988***, *53*, 2911.

[678] Kiesgen de Richter, R.; Bonato, M.; Follet, M.; Kamenka, J. *J. Org. Chem.* ***1990***, *55*, 2855.

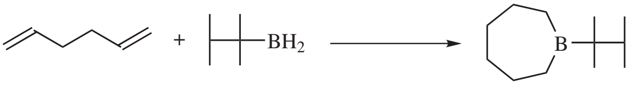
[679] Jadhav, P.K.; Brown, H.C. *J. Org. Chem.* ***1981***, *46*, 2988.

[680] Masamune, S.; Kim, B.M.; Petersen, J.S.; Sato, T.; Veenstra, J.S.; Imai, T. *J. Am. Chem. Soc.* ***1985***, *107*, 4549.

[681] For another enantioselective hydroboration method, see p. 1082.

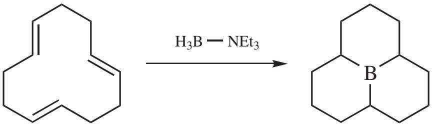
of a chiral rhodium catalyst, giving the alcohol enantioselectivity after the usual oxidation.[682]

The double bonds in a conjugated diene are hydroborated separately, that is, 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. Thexylborane[641] (**117**) is particularly useful for achieving the cyclic hydroboration of dienes, conjugated or nonconjugated, as in the formation of **122**.[683]



48 **122**

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.[684] One example is the formation of 9-BBN, shown above. Another is conversion of 1,5,9-cyclododecatriene to perhydro-9*b*-boraphenalene, **123**.[685] If a diene is treated with a diaminoborane and a samarium catalyst, oxidation leads to a carbocyclic ring with a pendant hydroxymethyl group.[686]



123

Triple bonds[687] 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 **15-4**. However, terminal alkynes give vinylic boranes[688] (and hence aldehydes) only when treated with a hindered borane, such as **116**, **117**, or catecholborane (p. 820),[689] or with $BHBr_2—SMe_2$.[690] The reaction between terminal alkynes and BH_3 produces

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[682] Demay, S.; Volant, F.; Knochel, P. *Angew. Chem. Int. Ed.* ***2001***, *40*, 1235.

[683] Brown, H.C.; Negishi, E. *J. Am. Chem. Soc.* ***1972***, *94*, 3567.

[684] For a review of cyclic hydroboration, see Brown, H.C.; Negishi, E. *Tetrahedron* ***1977***, *33*, 2331. See also, Brown, H.C.; Pai, G.G.; Naik, R.G. *J. Org. Chem.* ***1984***, *49*, 1072.

[685] Rotermund, G.W.; Köster, R. *Liebigs Ann. Chem.* ***1965***, *686*, 153; Brown, H.C.; Negishi, E.; Dickason, W.C. *J. Org. Chem.* ***1985***, *50*, 520.

[686] Molander, G.A; Pfeiffer, D. *Org. Lett.* ***2001***, *3*, 361.

[687] For a review of hydroboration of triple bonds, see Hudrlik, P.F.; Hudrlik, A.M., in Patai, S. *The Chemistry of the Carbn–Carbon Triple Bond*, pt. 1, Wiley, NY, ***1978***, pp. 203–219.

[688] For a review of the preparation and reactions of vinylic boranes, see Brown, H.C.; Campbell, Jr., J.B. *Aldrichimica Acta* ***1981***, *14*, 1.

[689] Brown, H.C.; Gupta, S.K. *J. Am. Chem. Soc.* ***1975***, *97*, 5249. For a review of catecholborane, see Lane, C.F.; Kabalka, G.W. *Tetrahedron* ***1976***, *32*, 981; Garrett, C.E.; Fu, G.C. *J. Org. Chem.* ***1996***, *61*, 3224.

[690] Brown, H.C.; Campbell Jr., J.B. *J. Org. Chem.* ***1980***, *45*, 389.

1,1-dibora compounds, which can be oxidized either to primary alcohols (with NaOH—H_2O_2) or to carboxylic acids (with *m*-chloroperoxybenzoic acid).[691] Double bonds can be hydroborated in the presence of triple bonds if the reagent is 9-BBN.[692] On the other hand, dimesitylborane selectively hydroborates triple bonds in the presence of double bonds.[693] Furthermore, it is often possible to hydroborate selectively one particular double bond of a nonconjugated diene.[694] A triple bond can be hydroborated in the presence of a ketone, and treatment with acetic acid reduces the C≡C unit to a cis- alkene (see **15-12**).[695] When the reagent is catecholborane, hydroboration is catalyzed by rhodium complexes,[696] such as Wilkinson's catalyst,[697] by SmI_2,[698] or lanthanide reagents.[699] Enantioselective hydroboration–oxidation has been achieved by the use of optically active rhodium complexes.[700]

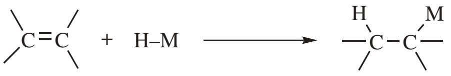
A chain extension variation involved the reaction of styrene with catecholborane and then Me_3SiCHN_2.[701] Subsequent oxidation with NaOH/H_2O_2 and the reaction with Bu_4NF gave 3-phenyl-1-propanol.

An unusual extension of hydroboration involves remote C—H activation. Aryl alkenes are treated with borane and then oxidized in the usual manner. The product is a phenol and a hydroxymethyl group (Ph—C=C—CH_3 → *o*-Ph—CH—CH—CH_2OH.[702]

OS **VI**, 719, 852, 919, 943; **VII**, 164, 339, 402, 427; **VIII**, 532.

15-17 Other Hydrometalation

Hydro-metallo-addition



Metal hydrides of Groups 13 (III A) and 14 (IV B) of the periodic table (e.g., AlH_3, GaH_3) as well as many of their alkyl and aryl derivatives (e.g., R_2AlH,

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[691] Zweifel, G.; Arzoumanian, H. *J. Am. Chem. Soc.* ***1967***, *89*, 291.

[692] Brown, H.C.; Coleman, R.A. *J. Org. Chem.* ***1979***, *44*, 2328.

[693] Pelter, A.; Singaram, S.; Brown, H.C. *Tetrahedron Lett.* ***1983***, *24*, 1433.

[694] For a list of references, see Gautam, V.K.; Singh, J.; Dhillon, R.S. *J. Org. Chem.* ***1988***, *53*, 187. See also, Suzuki, A.; Dhillon, R.S. *Top. Curr. Chem.* ***1986***, *130*, 23.

[695] Kabalka, G.W.; Yu, S.; Li, N.-S. *Tetrahedron Lett.* ***1997***, *38*, 7681.

[696] Burgess, K.; van der Donk, W.A.; Westcott, S.A.; Marder, T.B.; Baker, R.T. ; Calabrese, J.C. *J. Am. Chem. Soc.* ***1992***, *114*, 9350; Wescott, S.A.; Blom, H.P.; Marder, T.B.; Baker, R.T. *J. Am. Chem. Soc.* ***1992***, *114*, 8863; Evans, D.A.; Fu, G.C.; Hoveyda, A.H. *J. Am. Chem. Soc.* ***1992***, *114*, 6671.

[697] Männig, D.; Nöth, H. *Angew. Chem. Int. Ed.* ***1985***, *24*, 878. For a review, see Burgess, K.; Ohlmeyer, M.J. *Chem. Rev.* ***1991***, *91*, 1179.

[698] Evans, D.A.; Muci, A.R.; Stürmer, R. *J. Org. Chem.* ***1993***, *58*, 5307.

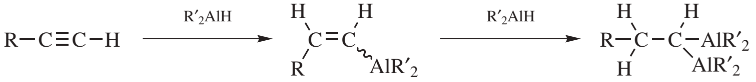
[699] Harrison, K.N.; Marks, T.J. *J. Am. Chem. Soc.* ***1992***, *114*, 9220.

[700] Burgess, K.; Ohlmeyer, M.J. *J. Org. Chem.* ***1988***, *53*, 5178; Hayashi, T.; Matsumoto, Y.; Ito, Y. *J. Am. Chem. Soc.* ***1989***, *111*, 3426; Sato, M.; Miyaura, N.; Suzuki, A. *Tetrahedron Lett.* ***1990***, *31*, 231; Brown, J.M.; Lloyd-Jones, G.C. *Tetrahedron: Asymmetry* ***1990***, *1*, 869.

[701] Goddard, J.-P.; LeGall, T.; Mioskowski, C. *Org. Lett.* ***2000***, *2*, 1455.

[702] Varela, J.A.; Peña, D.; Goldfuss, B.; Polborn, K.; Knochel, P. *Org. Lett.* ***2001***, *3*, 2395.

Ar_3SnH) add to double bonds to give organometallic compounds.[703] The hydroboration reaction (**15-16**) is the most important example, but other important metals in this reaction are aluminum,[704] tin,[705] and zirconium[706] [a Group 4 (IV B) metal]. Some of these reactions are uncatalyzed, but in other cases various types of catalyst have been used.[707] Hydrozirconation is most commonly carried out with Cp_2ZrHCl (Cp = cyclopentadienyl),[708] known as *Schwartz's reagent*. The mechanism with Group 13 (III A) hydrides seems to be electrophilic (or four-centered pericyclic with some electrophilic characteristics) while with Group 14 (IV A) hydrides a mechanism involving free radicals seems more likely. Dialkylmagnesium reagents have been obtained by adding MgH_2 to double bonds.[709] With Grignard reagents such as RMgX, the Grignard reagent can be added to an alkene $R'CH{=}CH_2$ to give $R'CH_2CH_2MgX$, with $TiCl_4$ as a catalyst.[710] With some reagents triple bonds[711] can add 1 or 2 equivalents, to give **124** or **125**.[712]



124 **125**

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[703] Negishi, E. *Adv. Met.-Org. Chem.* ***1989***, *1*, 177; Eisch, J.J. *The Chemistry of Organometallic Compounds*; Macmillan, NY, ***1967***, pp. 107–111. See also, Eisch, J.J.; Fichter, K.C. *J. Organomet. Chem.* ***1983***, *250*, 63.

[704] For reviews of organoaluminums in organic synthesis, see Dzhemilev, U.M.; Vostrikova, O.S.; Tolstikov, G.A. *Russ. Chem. Rev.* ***1990***, *59*, 1157; Maruoka, K.; Yamamoto, H. *Tetrahedron* ***1988***, *44*, 5001.

[705] For a review with respect to Al, Si, and Sn, see Negishi, E. *Organometallics in Organic Synthesis*, Vol. 1, Wiley, NY, ***1980***, pp. 45–48, 357–363, 406–412. For reviews of hydrosilylation, see Ojima, I. in Patai, S.; Rappoport, Z. *The Chemistry of Organic Silicon Compounds*, pt. 2, Wiley, NY, ***1989***, pp. 1479–1526; Alberti, A.; Pedulli, G.F. *Rev. Chem. Intermed.* ***1987***, *8*, 207; Speier, J.L. *Adv. Organomet. Chem.* ***1979***, *17*, 407; Andrianov, K.A.; Souč ek, J.; Khananashvili, L.M. *Russ. Chem. Rev.* ***1979***, *48*, 657.

[706] For reviews of hydrozirconation, and the uses of organozirconium compounds, see Negishi, E.; Takahashi, T. *Synthesis* ***1988***, 1; Dzhemilev, U.M.; Vostrikova, O.S.; Tolstikov, G.A. *J. Organomet. Chem.* ***1986***, *304*, 17; Schwartz, J.; Labinger, J.A. *Angew. Chem. Int. Ed.* ***1976***, *15*, 333. Also see Hoveyda, A.H.; Morken, J.P. *J. Org. Chem.* ***1993***, *58*, 4237.

[707] See, for example, Oertle, K.; Wetter, H. *Tetrahedron Lett.* ***1985***, *26*, 5511; Randolph, C.L.; Wrighton, M.S. *J. Am. Chem. Soc.* ***1986***, *108*, 3366; Maruoka, K.; Sano, H.; Shinoda, K.; Nakai, S.; Yamamoto, H. *J. Am. Chem. Soc.* ***1986***, *108*, 6036; Miyake, H.; Yamamura, H. *Chem. Lett.* ***1989***, 981; Doyle, M.P.; High, K.G.; Nesloney, C.L.; Clayton, Jr., T.W.; Lin, J. *Organometallics* ***1991***, *10*, 1225.

[708] For a method of preparing this reagent (which is also available commercially), see Buchwald, S.L.; LaMaire, S.J.; Nielsen, R.B.; Watson, B.T.; King, S.M. *Tetrahedron Lett.* ***1987***, *28*, 3895. It can also be generated *in situ*: Lipshutz, B.H.; Keil, R.; Ellsworth, E.L. *Tetrahedron Lett.* ***1990***, *31*, 7257.

[709] For a review, see Bogdanović, B. *Angew. Chem. Int. Ed.* ***1985***, *24*, 262.

[710] For a review, see Sato, F. *J. Organomet. Chem.* ***1985***, *285*, 53–64. For another catalyst, see Hoveyda, A.H.; Xu, Z. *J. Am. Chem. Soc.* ***1991***, *113*, 5079.

[711] For a review of the hydrometalation of triple bonds, see Hudrlik, P.F.; Hudrlik, A.M., in Patai, S. *The Chemistry of the Carbon-Carbon Triple Bond*, pt. 1, Wiley, NY, ***1978***, pp. 219–232.

[712] Wilke, G.; Müller, H. *Liebigs Ann. Chem.* ***1960***, *629*, 222; Eisch, J.J.; Kaska, W.C. *J. Am. Chem. Soc.* ***1966***, *88*, 2213; Eisch, J.J.; Rhee, S. *Liebigs Ann. Chem.* ***1975***, 565.

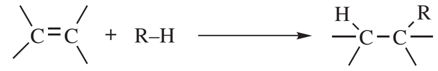
When 2 equivalents are added, electrophilic addition generally gives 1,1-dimetallic products **125** (as with hydroboration), while free-radical addition usually gives the 1,2-dimetallic products.

OS **VII**, 456; **VIII**, 268, 295, 507; **80**, 104. See also, OS **VIII**, 277, 381.

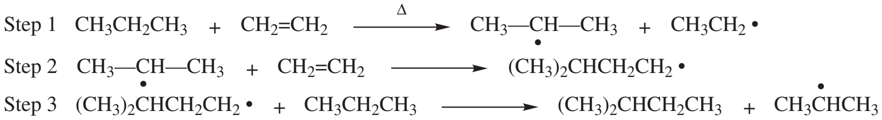
G. Carbon or Silicon on the Other Side

15-18 Addition of Alkanes

Hydro-alkyl-addition



There are two important ways of adding alkanes to alkenes: the thermal and the acid-catalysis method.[713] 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 (~500°C) at high pressures (150–300 atm) without a catalyst. As an example, propane and ethylene gave 55.5% isopentane, 7.3% hexanes, 10.1% heptanes, and 7.4% alkenes.[714] The mechanism is undoubtedly of a free-radical type and can be illustrated by one possible sequence in the reaction between propane and ethylene:



$$\text{Step 1}\quad CH_3CH_2CH_3 + CH_2{=}CH_2 \xrightarrow{\Delta} CH_3\text{—}\underset{\bullet}{C}H\text{—}CH_3 + CH_3CH_2\bullet$$

$$\text{Step 2}\quad CH_3\text{—}\underset{\bullet}{C}H\text{—}CH_3 + CH_2{=}CH_2 \longrightarrow (CH_3)_2CHCH_2CH_2\bullet$$

$$\text{Step 3}\quad (CH_3)_2CHCH_2CH_2\bullet + CH_3CH_2CH_3 \longrightarrow (CH_3)_2CHCH_2CH_3 + CH_3\overset{\bullet}{C}HCH_3$$

There is kinetic evidence that the initiation takes place primarily by steps like 1, which are called *symproportionation* steps[715] (the opposite of disproportionation, p. 280).

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 mechanism[716] (illustrated for a proton

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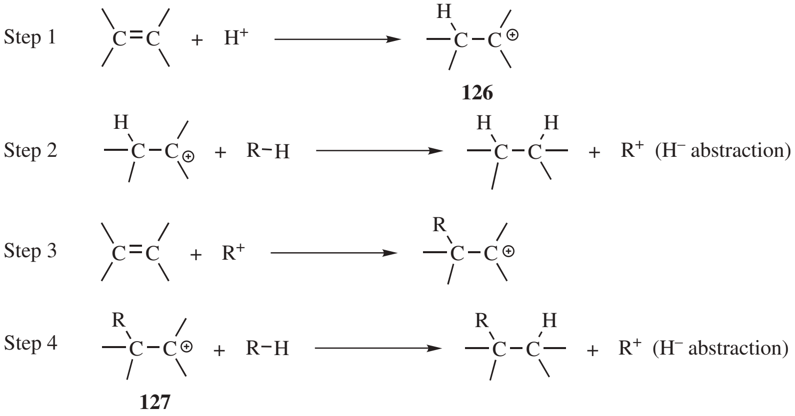
[713] For reviews, see Shuikin, N.I.; Lebedev, B.L. *Russ. Chem. Rev.* ***1966***, *35*, 448; Schmerling, L., in Olah, G.A. *Friedel–Crafts and Related Reactions*, Vol. 2, Wiley, NY, ***1964***, pp. 1075–1111, 1121–1122.

[714] Frey, E.J.; Hepp, H.J. *Ind. Eng. Chem.* ***1936***, *28*, 1439.

[715] Metzger, J.O. *Angew. Chem. Int. Ed.* ***1983***, *22*, 889; Hartmanns, J.; Klenke, K.; Metzger, J.O. *Chem. Ber.* ***1986***, *119*, 488.

[716] For a review, see Mayr, H. *Angew. Chem. Int. Ed.* ***1990***, *29*, 1371.

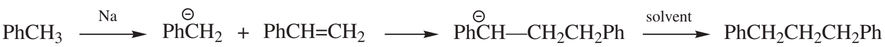
acid catalyst):



Carbocation **127** often rearranges before it abstracts a hydride, explaining, for example, why the principal product from the reaction between isobutane and ethylene is 2,3-dimethylbutane. It is also possible for **126** (or **127**) instead of abstracting a hydride, to add to another mole of alkene, so that not only rearrangement products but also dimeric and polymeric products are frequent. If the tri- or tetrasubstituted alkenes 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.[717] (For a free-radical hydromethyl-addition, see **15-28**.) Addition a cation to a vinyl bromide, generated from an α-ethoxy-lactam with trifluoroacetic acid, generated a ketone.[718] An intramolecular cyclization of 1-dodecene to cyclododecane was reported using aluminum chloride in an ionic liquid.[719]

Alkanes add to alkynes under photolysis conditions to give an alkene.[720] Tetrahydrofuran adds to alkynes to give the alkene with microwave irradiation.[721]

The reaction can also be base catalyzed, in which case there is nucleophilic addition and a carbanion mechanism.[722] 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:[723]



$$PhCH_3 \xrightarrow{Na} Ph\overset{\ominus}{C}H_2 + PhCH{=}CH_2 \longrightarrow Ph\overset{\ominus}{C}H\text{—}CH_2CH_2Ph \xrightarrow{solvent} PhCH_2CH_2CH_2Ph$$

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[717] Bolestova, G.I.; Parnes, Z.N.; Kursanov, D.N. *J. Org. Chem. USSR* ***1983***, *19*, 2175.

[718] Gesson, J.-P.; Jacquesy, J.-C.; Rambaud, D. *Tetrahedron* ***1993***, *49*, 2239.

[719] In bmim Cl, 1-butyl-3-methylimidazolium chloride: Qiao, K.; Deng, Y. *Tetrahedron Lett.* ***2003***, *44*, 2191.

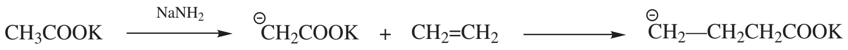
[720] Geraghty, N.W.A.; Hannan, J.J. *Tetrahedron Lett.* ***2001***, *42*, 3211.

[721] Zhang, Y.; Li, C.-J. *Tetrahedron Lett.* ***2004***, *45*, 7581.

[722] For reviews, see Pines, H.; Stalick, W.M. *Base-Catalyzed Reactions of Hydrocarbons and Related Compounds*, Academic Press, NY, ***1977***, pp. 240–422; Pines, H. *Acc. Chem. Res.* ***1974***, *7*, 155; Pines, H.; Schaap, L.A. *Adv. Catal.* ***1960***, *12*, 117, pp. 126.

[723] Pines, H.; Wunderlich, D. *J. Am. Chem. Soc.* ***1958***, *80*, 6001.

Conjugated dienes give 1,4-addition.[724] This reaction has also been performed with salts of carboxylic acids in what amounts to a method of alkylation of carboxylic acids[725] (see also, **10-59**).



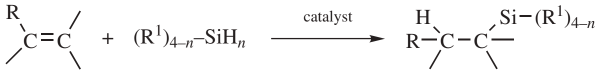
$$CH_3COOK \xrightarrow{NaNH_2} \overset{\ominus}{C}H_2COOK + CH_2{=}CH_2 \longrightarrow \overset{\ominus}{C}H_2{-}CH_2CH_2COOK$$

There are transition-metal catalyzed addition reaction of alkyl units to alkenes,[726] often proceeding with metal hydride elimination to form an alkene. An intramolecular cyclization reaction of an *N*-pyrrolidino amide alkene was reported using an iridium catalyst for addition of the carbon α to nitrogen to the alkene unit.[727]

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

15-19 Addition of Silanes

Silyl-hydro-addition



Although silanes bearing at least one Si—H unit do not generally react with alkenes or alkynes, in the presence of certain catalyst addition occurs to give the corresponding alkyl or vinyl silane. The reaction of an alkene with an yttrium,[728] ruthenium,[729] rhodium,[730] palladium,[731] lanthanum,[732] platinum[733], or samarium[734] catalyst addition occurs with high anti-Markovnikov selectivity. Silanes add to dienes with a palladium catalyst, and asymmetric induction is achieved by using a binapthyl additive.[735] Alkenes react with Li-(0) and *t*-Bu_2SiCl_2 to give a three-membered ring silane.[736] In the presence of BEt_3, silanes add to alkynes to give the corresponding vinyl silane[737] or to alkenes to give the alkylsilane, with

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[724] Eberhardt, G.G.; Peterson, H.J. *J. Org. Chem.* ***1965***, *30*, 82; Pines, H.; Stalick, W.M. *Tetrahedron Lett.* ***1968***, 3723.

[725] Schmerling, L.; Toekelt, W.G. *J. Am. Chem. Soc.* ***1962***, *84*, 3694.

[726] Kakiuchi, F.; Murai, S. *Acc. Chem. Res.* ***2002***, *35*, 826.

[727] DeBoef, B.; Pastine, S.J.; Sames, D. *J. Am. Chem. Soc.* ***2004***, *126*, 6556.

[728] Molander, G.A.; Julius, M. *J. Org. Chem.* ***1992***, *57*, 6347.

[729] Glaser, P.B.; Tilley, T.D. *J. Am. Chem.Soc.* ***2003***, *125*, 13640.

[730] Itami, K.; Mitsudo, K.; Nishino, A.; Yoshida, J.-i. *J. Org. Chem.* ***2002***, *67*, 2645; Tsuchiya, Y.; Uchimura, H.; Kobayashi, K.; Nishiyama, H. *Synlett* ***2004***, 2099.

[731] Motoda, D.; Shinokubo, H.; Oshima, K. *Synlett* ***2002***, 1529.

[732] Takaki, K.; Sonoda, K.; Kousaka, T.; Koshoji, G.; Shishido, T.; Takehira, K. *Tetrahedron Lett.* ***2001***, *42*, 9211.

[733] Perales, J.B.; van Vranken, D.L. *J. Org. Chem.* ***2001***, *66*, 7270; Sabourault, N.; Mignani, G.; Wagner, A.; Mioskowski, C. *Org. Lett.* ***2002***, *4*, 2117.

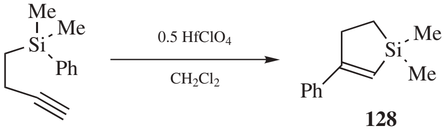
[734] Hou, Z.; Zhang, Y.; Tardif, O.; Wakatsuki, Y. *J. Am. Chem. Soc.* ***2001***, *123*, 9216.

[735] Hatanaka, Y.; Goda, K.; Yamashita, F.; Hiyama, T. *Tetrahedron Lett.* ***1994***, *35*, 7981.

[736] Driver, T.G.; Franz, A.K.; Woerpel, K.A. *J. Am. Chem. Soc.* ***2002***, *124*, 6524.

[737] Miura, K.; Oshima, K.; Utimoto, K. *Bull. Chem. Soc. Jpn.* ***1993***, *66*, 2356.

anti-Markovnikov selectivity.[738] Similar selectivity was observed when a silylated zinc reagent was added to a terminal alkyne.[739] Silanes add to alkynes to give a vinyl silane using Cp_2TiCl_2–*n*-butyllithium.[740] Siloxanes such as $(RO)_3SiH$ add to alkynes with a ruthenium catalyst to give the corresponding vinyl silane.[741] The reaction of Cl_2MeSiH and terminal alkynes, in ethanol–triethylamine with a ruthenium catalyst, to give primarily the Markovnikov vinyl silane.[742] However, Et_3SiH adds to terminal alkynes with a rhodium[743] or a platinum[744] catalyst to give the anti-Markovnikov vinyl silane. Using 0.5 equivalent of $HfClO_4$ with alkynes bearing a dimethylphenylsilyl unit gave a cyclic vinyl silane with transfer of the phenyl group to carbon (see **128**).[745] Dienes react with zirconium compounds and silanes to produce cyclic compounds in which the silyl group has also added to one C=C unit.[746] With an yttrium catalyst, $PhSiH_3$ reacts with nonconjugated dienes to give cyclic alkenes with a pendant CH_2SiH_2Ph group.[747] Rhodium compounds allow silanes to add to enamides to give the α-silylamide.[748] Allylsilanes add to certain allylic alcohols in the presence of Me_3SiOTf, via a S_N2'-like reaction, to give dienes.[749] Note that silanes open cyclopropane rings in the presence of 20% $AlCl_3$ to give the alkylsilane.[750] Formation of silanes via reaction with alkenes can be followed by reaction with fluoride ion and then oxidation to give an alcohol[751] (see **10-16**).



128

Silanes also add to alkenes under radical conditions (using AIBN) with high anti-Markovnikov selectivity.[752] An alternative route to alkylsilanes reacted an alkene with lithium metal in the presence of 3 equivalents of chlorotrimethylsilane, giving bis-1,2-trimethylsilyl compounds after treatment with water.[753] Silanes also

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[738] Rubin, M.; Schwier, T.; Gevorgyan, V. *J. Org. Chem.* ***2002***, *67*, 1936.

[739] Nakamura, S.; Uchiyama, M.; Ohwada, T. *J. Am. Chem. Soc.* ***2004***, *126*, 11146.

[740] Takahashi, T.; Bao, F.; Gao, G.; Ogasawara, M. *Org. Lett.* ***2003***, *5*, 3479.

[741] Trost, B.M.; Ball, Z.T. *J. Am. Chem. Soc.* ***2001***, *123*, 12726.

[742] Kawanami, Y.; Sonoda, Y.; Mori, T.; Yamamoto, K. *Org. Lett.* ***2002***, *4*, 2825.

[743] Sato, A.; Kinoshita, H.; Shinokubo, H.; Oshima, K. *Org. Lett.* ***2004***, *6*, 2217.

[744] Wu, W.; Li, C.-J. *Chem. Commun.* ***2003***, 1668.

[745] Asao, N.; Shimada, T.; Shimada, T.; Yamamoto, Y. *J. Am. Chem. Soc.* ***2001***, *123*, 10899. See also, Sudo, T.; Asao, N.; Yamamoto, Y. *J. Org. Chem.* ***2000***, *65*, 8919.

[746] Molander, G.A.; Corrette, C.P. *Tetrahedron Lett.* ***1998***, *39*, 5011.

[747] Muci, A.R.; Bercaw, J.E. *Tetrahedron Lett.* ***2000***, *41*, 7609.

[748] Murai, T.; Oda, T.; Kimura, F.; Onishi, H.; Kanda, T.; Kato, S. *J. Chem. Soc., Chem. Commun.* ***1994***, 2143.

[749] Toshima, K.; Ishizuka, T.; Matsuo, G.; Nakata, M. *Tetrahedron Lett.* ***1994***, *35*, 5673.

[750] Nagahara, S.; Yamakawa, T.; Yamamoto, H. *Tetrahedron Lett.* ***2001***, *42*, 5057.

[751] Jensen, J.F.; Svendsen, B.H.; la Cour, T.V.; Pedersen, H.L.; Johannsen, M. *J. Am. Chem. Soc.* ***2002***, *124*, 4558.

[752] Kopping, B.; Chatgilialoglu, C.; Zehnder, M.; Giese, B. *J. Org. Chem.* ***1992***, *57*, 3994.

[753] Yus, M.; Martínez, P.; Guijarro, D. *Tetrahedron* ***2001***, *57*, 10119.

add to alkenes to form anti-Markovnikov alkylsilane ($R_3Si—C—C—R'$) in the presence of a hyponitrite.[754]

Vinyl silanes add to conjugated carbonyl compounds in the presence of a ruthenium catalyst,[755] or to acrylonitriles with a cobalt catalyst.[756] Silyl phosphines react with conjugated ynones directly to give an enone with an α-trimethylsilyl and a β-phosphine group.[757] Siloxanes of the type $(RO)_3SiH$ add to the α-carbon of enamines in the presence of a dirhodium catalyst.[758] The uncatalyzed reaction of trimethylsilyl cyanide and ynamines, however, gave an enamine with a β-trimethylsilyl and an α-cyano group.[759]

15-20 Addition of Alkenes and/or Alkynes to Alkenes and/or Alkynes

Hydro-alkenyl-addition

$$CH_2{=}CH_2 \;+\; CH_2{=}CH_2 \xrightarrow{H^+} CH_2{=}CHCH_2CH_3$$

With certain substrates, alkenes can be dimerized by acid catalysts, so that the product is a dimer that contains one double bond.[760] A combination of zinc and a $CoCl_2$ catalyst accomplished the same type of coupling.[761] One alkene adds to another in the presence of a nickel catalyst.[762] Coupling conjugated alkenes with vinyl esters to give a functionalized conjugated diene is known, using a complex palladium–vanadium catalyst in an oxygen atmosphere.[763] This reaction is more often carried out internally, as in the formation of cyclohexene **129**. A palladium catalyzed cyclization is known, in which dienes are converted to cyclopentene derivatives such as **130**.[764] Ring-forming reactions with heterocyclic compounds such as indoles are known using $PtCl_2$.[765] A ruthenium catalyzed version of this reaction gave the five-membered ring with an exocyclic double bond.[766] Carbocyclization of an alkene unit to another alkene unit was reported

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[754] Dang, H.-S.; Roberts, B.P. *Tetrahedron Lett.* ***1995***, *36*, 2875.

[755] Kakiuchi, F.; Tanaka, Y.; Sato, T.; Chatani, N.; Murai, S. *Chem. Lett.* ***1995***, 679; Trost, B.M.; Imi, K.; Davies, I.W. *J. Am. Chem. Soc.* ***1995***, *117*, 5371.

[756] Tayama, O.; Iwahama, T.; Sakaguchi, S.; Ishii, Y. *Eur. J. Org. Chem.* ***2003***, 2286.

[757] Reisser, M.; Maier, A.; Maas, G. *Synlett* ***2002***, 1459.

[758] Hewitt, G.W.; Somers, J.J.; Sieburth, S.Mc.N. *Tetrahedron Lett.* ***2000***, *41*, 10175.

[759] Lukashev, N.V.; Kazantsev, A.V.; Borisenko, A.A.; Beletskaya, I.P. *Tetrahedron* ***2001***, *57*, 10309.

[760] For a review, see Onsager, O.; Johansen, J.E., in Hartley, F.R.; Patai, S. *The Chemistry of the Metal-Carbon Bond*, Vol. 3, Wiley, NY, ***1985***, pp. 205–257.

[761] Wang, C.-C.; Lin, P.-S.; Cheng, C.-H. *Tetrahedron Lett.* ***2004***, *45*, 6203.

[762] RajanBabu, T.V.; Nomura, N.; Jin, J.; Nandi, M.; Park, H.; Sun, X. *J. Org. Chem.* ***2003***, *68*, 8431.

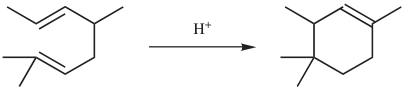
[763] Hatamoto, Y.; Sakaguchi, S.; Ishii, Y. *Org. Lett.* ***2004***, *6*, 4623.

[764] Kisanga, P.; Goj, L.A.; Widenhoefer, R.A. *J. Org. Chem.* ***2001***, *66*, 635.

[765] Liu, C.; Han, X.; Wang, X.; Widenhoefer, R.A. *J. Am. Chem. Soc.* ***2004***, *126*, 3700.

[766] Yamamoto, Y.; Nakagai, Y.-i.; Ohkoshi, N.; Itoh, K. *J. Am. Chem. Soc.* ***2001***, *123*, 6372; Mori, M.; Saito, N.; Tanaka, D.; Takimoto, M.; Sato, Y. *J. Am. Chem. Soc.* ***2003***, *125*, 5606; Michaut, M.; Santelli, M.; Parrain, J.-L. *Tetrahedron Lett.* ***2003***, *44*, 2157.

using an yttrium catalyst,[767] or a titanium catalyst.[768] In some cases, internal coupling of two alkenes can form larger rings.[769] Variations include treatment of similar dienes with $HSiMe_2OSiMe_3$ and KF-acetic acid to give a cyclopentane with a pendant trimethylsilylmethyl group trans to a methyl.[770] Exo-dig carbocyclization was reported using $HfCl_4$[771] palladium,[772] or titanium,[773] catalysts. Alkynes also add to alkenes for form rings in the presence of a palladium,[774] rhodium,[775] ruthenium,[776] iridium,[777] or a zirconium catalyst.[778] Alkene allene substrates were cyclized to form cyclic products with an exocyclic double bond using a palladium catalyst.[779] An interesting variation adds a silyl enol ether to an alkyne using $GaCl_3$ to give an unconjugated ketone (O=C–C–C=C).[780] Alkenes and alkynes can also add to each other to give cyclic products in other ways (see **15-63** and **15-65**).



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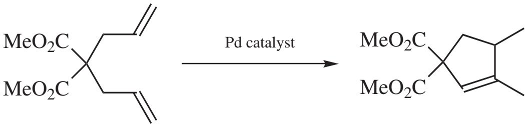

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Processes of this kind are important in the biosynthesis of steroids and tetra- and pentacyclic terpenes. For example, squalene 2,3-oxide is converted by enzymatic

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[767] Molander, G.A.; Dowdy, E.D.; Schumann, H. *J. Org. Chem.* ***1998***, *63*, 3386.

[768] Okamoto, S.; Livinghouse, T. *J. Am. Chem. Soc.* ***2000***, *122*, 1223. See Hart, D.J.; Bennett, C.E. *Org. Lett.* ***2003***, *5*, 1499.

[769] Toyota, M.; Majo, V.J.; Ihara, M. *Tetrahedron Lett.* ***2001***, *42*, 1555.

[770] Pei, T.; Widenhoefer, R.A. *J. Org. Chem.* ***2001***, *66*, 7639.

[771] Imamura, K.-i.; Yoshikawa, E.; Gevorgyan, V.; Yamamoto, Y. *J. Am. Chem. Soc.* ***1998***, *120*, 5339.

[772] Xie, X.; Lu, X. *Synlett* ***2000***, 707.

[773] Berk, S.C.; Grossman, R.B.; Buchwald, S.L. *J. Am. Chem. Soc.* ***1994***, *116*, 8593; *J. Am. Chem. Soc.* ***1993***, *115*, 4912.

[774] Galland, J.-C.; Savignac, M.; Genêt, J.-P. *Tetrahedron Lett.* ***1997***, *38*, 8695; Widenhoefer, R.A.; Perch, N.S. *Org. Lett.* ***1999***, *1*, 1103.

[775] Wender, P.A.; Dyckman, A.J. *Org. Lett.* ***1999***, *1*, 2089; Cao, P.; Wang, B.; Zhang, X. *J. Am. Chem. Soc.* ***2000***, *122*, 6490; Cao, P.; Zhang, X. *Angew. Chem. Int. Ed.* ***2000***, *39*, 4104.

[776] Fernández-Rivas, C.; Méndez, M.; Echavarren, A.M. *J. Am. Chem. Soc.* ***2000***, *122*, 1221; Fürstner, A.; Ackermann, L. *Chem. Commun.* ***1999***, 95.

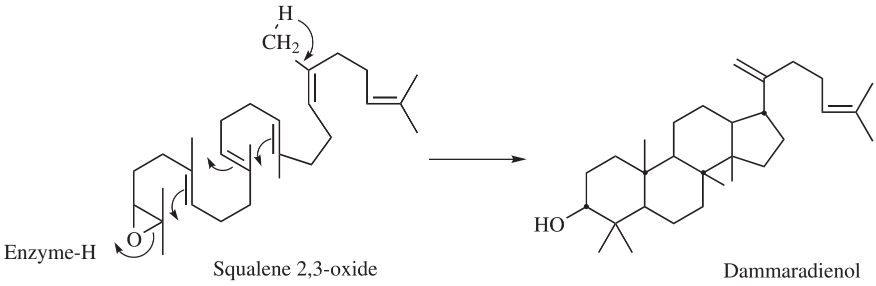
[777] Chatani, N.; Inoue, H.; Morimoto, T.; Muto, T.; Murai, S. *J. Org. Chem.* ***2001***, *66*, 4433.

[778] Miura, K.; Funatsu, M.; Saito, H.; Ito, H.; Hosomi, A. *Tetrahedron Lett.* ***1996***, *37*, 9059; Kemp, M.I.; Whitby, R.J.; Coote, S.J. *Synlett* ***1994***, 451; Wischmeyer, U.; Knight, K.S.; Waymouth, R.M. *Tetrahedron Lett.* ***1992***, *33*, 7735. Also see Maye, J.P.; Negishi, E. *Tetrahedron Lett.* ***1993***, *34*, 3359.

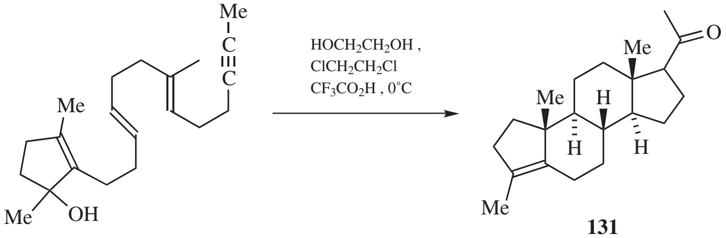
[779] Iodobenzene was added and a phenyl substituent was incorporated in the product. See Ohno, H.; Takeoka, Y.; Kadoh, Y.; Miyamura, K.; Tanaka, T. *J. Org. Chem.* ***2004***, *69*, 4541.

[780] Yamaguchi, M.; Tsukagoshi, T.; Arisawa, M. *J. Am. Chem. Soc.* ***1999***, *121*, 4074.

catalysis to dammaradienol.



The squalene → 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*.[781] Such reactions can also be carried out in the laboratory, without enzymes.[782] 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.[783] An example is formation of **131**,[784] also known as the *Johnson polyene cyclization*.[785]



131

Lewis acids can be used to initiate this cyclization,[786] including $EtAlCl_2$ used for the coupling of an alkyne and an alkene.[787] Cyclization to a tricyclic systems that included formation of a dihydropyran ring was reported using mercuric

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[781] Stork, G.; Burgstahler, A.W. *J. Am. Chem. Soc.* ***1955***, *77*, 5068; Eschenmoser, A.; Ruzicka, L.; Jeger, O.; Arigoni, D. *Helv. Chim. Acta* ***1955***, *38*, 1890.

[782] For reviews, see Gnonlonfoun, N. *Bull. Soc. Chim. Fr.* ***1988***, 862; Sutherland, J.K. *Chem. Soc. Rev.* ***1980***, *9*, 265; Johnson, W.S. *Angew. Chem. Int. Ed.* ***1976***, *15*, 9; *Bioorg. Chem.* ***1976***, *5*, 51; *Acc. Chem. Res.* ***1968***, *1*, 1; van Tamelen, E.E. *Acc. Chem. Res.* ***1975***, *8*, 152. For a review of the stereochemical aspects, see Bartlett, P.A., in Morrison, J.D. *Asymmetric Synthesis* Vol. 3, Academic Press, NY, ***1985***, pp. 341–409.

[783] Guay, D.; Johnson, W.S.; Schubert, U. *J. Org. Chem.* ***1989***, *54*, 4731 and references cited therein.

[784] Johnson, W.S.; Gravestock, M.B.; McCarry, B.E. *J. Am. Chem. Soc.* ***1971***, *93*, 4332.

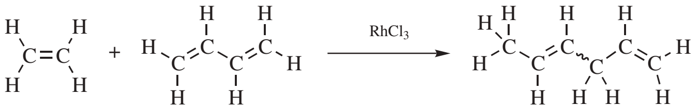
[785] Johnson, W.S. *Acc. Chem. Res.* ***1968***, *1*, 1; Hendrickson, J.B. *The Molecules of Nature*, W.A. Benjamin, NY, ***1965***, pp. 12–57; Kametani T.; Fukumoto, K. *Synthesis* ***1972***, 657.

[786] Sen, S.E.; Roach, S.L.; Smith, S.M.; Zhang, Y.Z. *Tetrahedron Lett.* ***1998***, *39*, 3969. For an asymmetric version using $SnCl_4$, see Ishihara, K.; Nakamura, S.; Yamamoto, H. *J. Am. Chem. Soc.* ***1999***, *121*, 4906.

[787] Asao, N.; Shimada, T.; Yamamoto, Y. *J. Am. Chem. Soc.* ***1999***, *121*, 3797.

bis(trifluorosulfonate) as an initiator.[788] A radical cyclization approach (**15-30**) to polyene cyclization using a seleno-ester anchor gave a tetracyclic system.[789]

The addition of alkenes to alkenes[790] can also be accomplished by bases.[791] Coupling reactions can occur using catalyst systems[792] consisting of nickel complexes and alkylaluminum compounds (known as *Ziegler catalysts*),[793] rhodium catalysts,[794] and other transition-metal catalysts, including iron.[795] The 1,4-addition of alkenes to conjugated dienes to give nonconjugated dienes[796] occurs with various transition-metal catalysts.



and the dimerization of 1,3-butadienes to octatrienes.[797] Ethylene adds to alkenes to form a new alkene in the presence of a nickel catalyst[798] or a zirconium catalyst,[799] to alkynes in the presence of a ruthenium catalyst[800] to form a diene, and allenes add to alkynes to give a diene with a titanium catalyst.[801]

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

$$\mathrm{HC{\equiv}CH} + \mathrm{HC{\equiv}CH} \xrightarrow[\mathrm{NH_4Cl}]{\mathrm{CuCl}} \mathrm{HC{\equiv}C{-}CH{=}CH_2}$$

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[788] Gopalan, A.S.; Prieto, R.; Mueller, B.; Peters, D. *Tetrahedron Lett.* ***1992***, *33*, 1679.

[789] Chen, L.; Gill, G.B.; Pattenden, G. *Tetrahedron Lett.* ***1994***, *35*, 2593.

[790] For a review of alkene dimerization and oligomerization with all catalysts, see Fel'dblyum, V.Sh.; Obeshchalova, N.V. *Russ. Chem. Rev.* ***1968***, *37*, 789.

[791] For a review, see Pines, H. *Synthesis* ***1974***, 309.

[792] For reviews, see Pillai, S.M.; Ravindranathan, M.; Sivaram, S. *Chem. Rev.* ***1986***, *86*, 353; Jira, R.; Freiesleben, W. *Organomet. React.* ***1972***, *3*, 1, 117; Heck, R.F. *Organotransition Metal Chemistry*, Academic Press, NY, ***1974***, pp. 84–94, 150–157; Khan, M.M.T.; Martell, A.E. *Homogeneous Catalysis by Metal Complexes*, Vol. 2, Academic Press, NY, ***1974***, pp. 135–15; Rylander, P.N. *Organic Syntheses with Noble Metal Catalysts*, Academic Press, NY, ***1973***, pp. 175–196; Tsuji, J. *Adv. Org. Chem.* ***1969***, *6*, 109, pp. 213. Also see, Kaur, G.; Manju, K.; Trehan, S. *Chem. Commun.* ***1996***, 581.

[793] See, for example, Onsager, O.; Wang, H.; Blindheim, U. *Helv. Chim. Acta* ***1969***, *52*, 187, 230; Fischer, K.; Jonas, K.; Misbach, P.; Stabba, R.; Wilke, G. *Angew. Chem. Int. Ed.* ***1973***, *12*, 943.

[794] Cramer, R. *J. Am. Chem. Soc.* ***1965***, *87*, 4717; *Acc. Chem. Res.* ***1968***, *1*, 186; Kobayashi, Y.; Taira, S. *Tetrahedron* ***1968***, *24*, 5763; Takahashi, N.; Okura, I.; Keii, T. *J. Am. Chem. Soc. 1975, 97*, 7489.

[795] Takacs, J.M.; Myoung, Y.C. *Tetrahedron Lett.* ***1992***, *33*, 317.

[796] Alderson, T.; Jenner, E.L.; Lindsey, Jr., R.V. *J. Am. Chem. Soc.* ***1965***, *87*, 5638; Hilt, G.; du Mesnil, F.-X.; Lüers, S. *Angew. Chem. Int. Ed.* ***2001***, *40*, 387. For a review see Su, A.C.L. *Adv. Organomet. Chem.* ***1979***, *17*, 269.

[797] See, for example, Denis, P.; Jean, A.; Croizy, J.F.; Mortreux, A.; Petit, F. *J. Am. Chem. Soc.* ***1990***, *112*, 1292.

[798] Nomura, N.; Jin, J.; Park, H.; RajanBabu, T.V. *J. Am. Chem. Soc.* ***1998***, *120*, 459; Monteiro, A.L.; Seferin, M.; Dupont, J.; de Souza, R.F. *Tetrahedron Lett.* ***1996***, *37*, 1157.

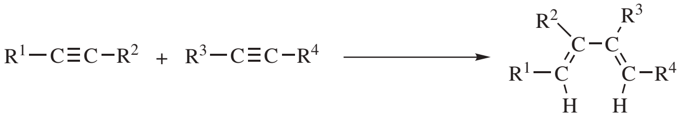
[799] Takahashi, T.; Xi, Z.; Fischer, R.; Huo, S.; Xi, C.; Nakajima, K. *J. Am. Chem. Soc.* ***1997***, *119*, 4561; Takahashi, T.; Xi, Z.; Rousset, C.J.; Suzuki, N. *Chem. Lett.* ***1993***, 1001.

[800] Kinoshita, A.; Sakakibara, N.; Mori, M. *J. Am. Chem. Soc.* ***1997***, *119*, 12388; Trost, B.M.; Indolese, A. *J. Am. Chem. Soc.* ***1993***, *115*, 4361.

[801] Urabe, H.; Takeda, T.; Hideura, D.; Sato, F. *J. Am. Chem. Soc.* ***1997***, *119*, 11295.

This type of alkyne dimerization is also catalyzed by nickel,[802] palladium,[803] lutetium,[804] and ruthenium catalysts.[805] Similar products are obtained by the cross-coupling an terminal alkynes with allene, using a combination of palladium and CuI catalysts.[806] The reaction has been carried out internally to convert diynes to large-ring cycloalkynes with an exocyclic double bond.[807] Diynes have also been cyclized to form cyclic enynes (an endocyclic double bond) using a diruthenium catalyst with ammonium tetrafluoroborate in methanol.[808] Enynes are similarly cyclized to cyclic alkenes with an endocyclic C=C unit, analogous to formation of **200** above, using a dicobalt catalyst.[809] A molecule containing two distal conjugated diene units was cyclized to give a bicyclic molecule with an exocyclic double bond using a palladium catalyst.[810] A nickel catalyst converted a similar system to a saturated five-membered ring containing an allylic group and a vinyl group.[811]

In another type of alkyne dimerization is the reductive coupling in which two molecules of alkyne, the same or different, give a 1,3-diene.[812]



In this method, one alkyne is treated with Schwartz's reagent (see **15-17**) 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 I_2 instead of aqueous acid, the 1,4-diiodo-1,3-diene is obtained instead, in comparable yield and isomeric purity. The reaction of alkynes with two equivalents of trimethylsilyldiazomethane and a ruthenium catalyst gave a conjugated diene with trimethylsilyl groups at C-1 and C-4.[813] Alkynes can also be coupled to allylic silyl ethers with a ruthenium catalysts to give dienes.[814] Other alkyne–allylic coupling reactions are known to give dienes.[815]

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[802] Ogoshi, S.; Ueta, M.; Oka, M.-A.; Kurosawa, H. *Chem. Commun.* ***2004***, 2732.

[803] Rubina, M.; Gevergyan, V. *J. Am. Chem. Soc.* ***2001***, *123*, 11107; Yang, C.; Nolan, S.P. *J. Org. Chem.* ***2002***, *67*, 591.

[804] Nishiura, M.; Hou, Z.; Wakatsuki, Y.; Yamaki, T.; Miyamoto, T. *J. Am. Chem. Soc.* ***2003***, *125*, 1184.

[805] Smulik, J.A.; Diver, S.T. *J. Org. Chem.* ***2000***, *65*, 1788.

[806] Bruyere, D.; Grigg, R.; Hinsley, J.; Hussain, R.K.; Korn, S.; Del Cierva, C.O.; Sridharan, V.; Wang, J. *Tetrahedron Lett.* ***2003***, *44*, 8669.

[807] Trost, B.M.; Matusbara, S.; Carninji, J.J. *J. Am. Chem. Soc.* ***1989***, *111*, 8745.

[808] Nishibayashi, Y.; Yamanashi, M.; Wakiji, I.; Hidai, M. *Angew. Chem. Int. Ed.* ***2000***, *39*, 2909.

[809] Ajamian, A.; Gleason, J.L. *Org. Lett.* ***2003***, *5*, 2409.

[810] Takacs, J.M.; Leonov, A.P. *Org. Lett.* ***2003***, *5*, 4317.

[811] Takimoto, M.; Mori, M. *J. Am. Chem. Soc.* ***2002***, *124*, 10008; Takimoto, M.; Nakamura, Y.; Kimura, K.; Mori, M. *J. Am. Chem. Soc.* ***2004***, *126*, 5956.

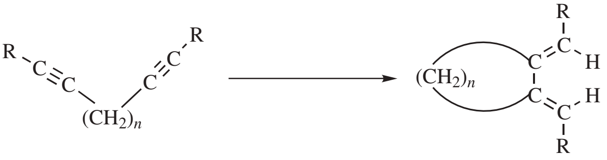
[812] Buchwald, S.L.; Nielsen, R.B. *J. Am. Chem. Soc.* ***1989***, *111*, 2870.

[813] Le Paih, J.; Dérien, S.; Özdemir, I.; Dixneuf, P.H. *J. Am. Chem. Soc.* ***2000***, *122*, 7400.

[814] Trost, B.M.; Surivet, J.-P.; Toste, F.D. *J. Am. Chem. Soc.* ***2001***, *123*, 2897.

[815] Trost, B.M.; Pinkerton, A.B.; Toste, F.D.; Sperrle, M. *J. Am. Chem. Soc.* ***2001***, *123*, 12504; Giessert, A.J.; Snyder, L.; Markham, J.; Diver, S.T. *Org. Lett.* ***2003***, *5*, 1793.

This reaction can also be done intramolecularly, as in the cyclization of diyne **132** to (*E*,*E*)-exocyclic dienes **133** by treatment with a zirconium,[816] rhodium,[817] or platinum complex.[818] A similar reaction was reported using a titanium catalyst from a diyne amide.[819]



132 **133**

Rings of four, five, and six members were obtained in high yield; seven-membered rings in lower yield. When the reaction is applied to enynes, compounds similar to **133** are formed using various catalysts, but with only one double bond[820] Internal coupling of alkene–allenes and a rhodium catalyst give similar products bearing a pendant vinyl group.[821] With a $PtCl_2$ catalyst, ring closure leads to a diene in some cases.[822] Larger rings can be formed from the appropriate enyne, including forming cyclohexadiene compounds.[823] Spirocyclic compounds can be prepared from enynes in this manner using formic acid and a palladium catalyst.[824] Enynes can also be converted to bicyclo[3.1.0]hexenes[825] or nonconjugated cyclohexadienes[826] using a gold catalyst. Internal coupling of an alkyne and a vinylidene cyclopropane unit with a palladium catalyst leads to a cyclopentene derivative with an exocyclic double bond.[827] Enynes having a conjugated alkene unit also undergo this reaction

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[816] Nugent, W.A.; Thorn, D.L.; Harlow, R.L. *J. Am. Chem. Soc.* ***1987***, *109*, 2788. See also, Trost, B.M.; Lee, D.C. *J. Am. Chem. Soc.* ***1988***, *110*, 7255; Tamao, K.; Kobayashi, K.; Ito, Y. *J. Am. Chem. Soc.* ***1989***, *111*, 6478.

[817] Jang, H.-Y.; Krische, M.J. *J. Am. Chem. Soc.* ***2004***, *126*, 7875.

[818] Madine, J.W.; Wang, X.; Widenhoefer, R.A. *Org. Lett.* ***2001***, *3*, 385; Méndez, M.; Muñoz, M.P. ; Nevado, C.; Cárdenas, D.J.; Echavarren, A.M. *J. Am. Chem. Soc.* ***2001***, *123*, 10511; Wang, X.; Chakrapani, H.; Madine, J.W.; Keyerleber, M.A.; Widenhoefer, R.A. *J. Org. Chem.* ***2002***, *67*, 2778. See also, Fürstner, A.; Stelzer, F.; Szillat, H. *J. Am. Chem. Soc.* ***2001***, *123*, 11863.

[819] Urabe, H.; Nakajima, R.; Sato, F. *Org. Lett.* ***2000***, *2*, 3481.

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[821] Makino, T.; Itoh, K. *Tetrahedron Lett.* ***2003***, *44*, 6335; Lei, A.; He, M.; Wu, S.; Zhang, X. *Angew. Chem. Int. Ed.* ***2002***, *41*, 3457.

[822] Harrison, T.J.; Dake, G.R. *Org. Lett.* ***2004***, *6*, 5023. See also, Ikeda, S.-i.; Sanuki, R.; Miyachi, H.; Miyashia, H.; Taniguchi, M.; Odashima, K. *J. Am. Chem. Soc.* ***2004***, *126*, 10331.

[823] Yamamoto, Y.; Kuwabara, S.; Ando, Y.; Nagata, H.; Nishiyama, H.; Itoh, K. *J. Org. Chem.* ***2004***, *69*, 6697.

[824] Hatano, M.; Mikami, K. *J. Am. Chem. Soc.* ***2003***, *125*, 4704.

[825] Luzung, M.R.; Markham, J.P.; Toste, F.D. *J. Am. Chem. Soc.* ***2004***, *126*, 10858.

[826] Zhang, L.; Kozmin, S.A. *J. Am. Chem. Soc.* ***2004***, *126*, 11806.

[827] Delgado, A.; Rodríguez, J.R.; Castedo, L.; Mascareñas, J.L. *J. Am. Chem. Soc.* ***2003***, *125*, 9282.

in the presence of $ZnBr_2$.[828] Using mercury (II) triflate in water, cyclization leads to five-membered rings having an exocyclic double bond, and a pendant alcohol group.[829] Enynes give cyclic compounds with an endocyclic double bond conjugated to another alkene unit (a conjugated diene) when treated with $GaCl_3$[830] or a platinum catalyst in an ionic liquid.[831] Allene–alkenes give a similar product with a palladium catalyst[832] or a ruthenium catalyst,[833] as do alkyne–allenes with a dirhodium catalyst.[834] Ethers having an enyne unit (propargylic and allylic) give dihydrofurans upon treatment with $Co_2(CO)_8$.[835] Amines and sulfonamides bearing two propargyl groups cyclize with a ruthenium catalyst to give the corresponding dihydropyrrole.[836]

There are many useful variations. Internal coupling of an alkyne with a vinyl halide, using triethylsilane and a palladium catalyst, gave the saturated cyclic compound with two adjacent exocyclic double bonds (a 2,3-disubstituted diene.[837] Alkynes can added to propargyl acetates using palladium catalyst to give an alkyne allene.[838] Two-Substituted malonate esters having a distal alkyne unit generated vinylidene cycloalkanes when treated with a catalytic amount of *n*-butyllithium.[839] Intramolecular coupling of alkenes and allylic sulfides using *tert*-butoxide/*n*-butyllithium, and then LiBr leads to a bicyclic compound containing a fused cyclopropane ring.[840] The reaction of an alkyne with a vinyl iodide and silver carbonate, with a palladium catalyst, gave a fulvene.[841] The reaction of a terminal alkyne and a vinyl cyclopropane, with a dirhodium catalyst, gives a cycloheptadiene.[842] Alkyne–alkenes were formed by coupling terminal alkynes and allenes in the presence of a palladium catalyst.[843] An alkyne was coupled internally to an allene using a palladium catalyst, with an exocyclic methylene

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[828] Yamazaki, S.; Yamada, K.; Yamabe, S.; Yamamoto, K. *J. Org. Chem.* ***2002***, *67*, 2889.

[829] Nishizawa, M.; Yadav, V.K.; Skwarczynski, M.; Takao, H.; Imagawa, H.; Sugihara, T. *Org. Lett.* ***2003***, *5*, 1609.

[830] Chatani, N.; Inoue, H.; Kotsuma, T.; Morai, S. *J. Am. Chem. Soc.* ***2002***, *124*, 10294.

[831] In bmim PF_6, 1-butyl-3-methylimidazolium hexafluorophosphate: Miyanohana, Y.; Inoue, H.; Chatani, N. *J. Org. Chem.* ***2004***, *69*, 8541.

[832] Frazén, J.; Löfstedt, J.; Dorange, I.; Bäckvall, J.-E. *J. Am. Chem. Soc.* ***2002***, *124*, 11246.

[833] Kang, S.-K.; Ko, B.-S.; Lee, D.-M. *Tetrahedron Lett.* ***2002***, *43*, 6693.

[834] Brummond, K.M.; Chen, H.; Sill, P.; You, L. *J. Am. Chem. Soc.* ***2002***, *124*, 15186. See also, Candran, N.; Cariou, K.; Hervé, G.; Aubert, C.; Fensterbank, L.; Malacria, M.; Marco-Contelles, J. *J. Am. Chem. Soc.* ***2004***, *126*, 3408.

[835] Ajamian, A.; Gleason, J.L. *Org. Lett.* ***2001***, *3*, 4161; Oh, C.H.; Han, J.W.; Kim, J.S.; Um, S.Y.; Jung, H.H.; Jang, W.H.; Won, H.S. *Tetrahedron Lett.* ***2000***, *41*, 8365; Ackermann, L.; Bruneau, C.; Dixneuf, P.H. *Synlett* ***2001***, 397.

[836] Trost, B.M.; Rudd, M.T. *Org. Lett.* ***2003***, *5*, 1467.

[837] Oh, C.H.; Park, S.J. *Tetrahedron Lett.* ***2003***, *44*, 3785.

[838] Condon-Gueugnot, S.; Linstrumelle, G. *Tetrahedron* ***2000***, *56*, 1851.

[839] Kitagawa, O.; Suzuki, T.; Fujiwra, H.; Fujita, M.; Taguchi, T. *Tetrahedron Lett.* ***1999***, *40*, 4585.

[840] Cheng, D.; Knox, K.R.; Cohen, T. *J. Am. Chem. Soc.* ***2000***, *122*, 412.

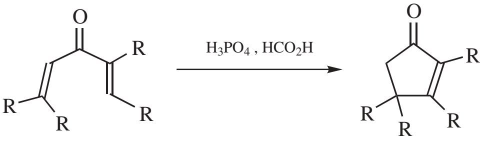
[841] Kotora, M.; Matsumura, H.; Gao, G.; Takahashi, T. *Org. Lett.* ***2001***, *3*, 3467.

[842] Wender, P.A.; Barzilay, C.M.; Dyckman, A.J. *J. Am. Chem. Soc.* ***2001***, *123*, 179.

[843] Rubin, M.; Markov, J.; Chuprakov, S.; Wink, D.J.; Gevorgyan, V. *J. Org. Chem.* ***2003***, *68*, 6251.

group trapped and a vinyltin derivative.[844] A similar process occurred with a rhodium catalyst, $RhCl(PPh_3)_3$, to incorporate a vinyl chloride.[845] Allene–allylic halide systems reacted with phenylboronic acid and a palladium catalyst to give cyclopentane rings with two pendant vinyl groups, one of which contained a phenyl group.[846]

In another reductive coupling, substituted alkenes ($CH_2{=}CH{-}Y$; Y = R, COOMe, OAc, CN, etc.) can be dimerized to substituted alkanes $CH_3CHY\text{-}CHYCH_3$ by photolysis in an H_2 atmosphere, using Hg as a photosensitizer.[847] Still another procedure involves palladium-catalyzed addition of vinylic halides to triple bonds to give 1,3-dienes.[848]



134 **135**

An important cyclization procedure involves acid-catalyzed addition of diene-ketones, such as **134**, where one conjugated alkene adds to the other conjugated alkene to form cyclopentenones (**135**). This is called the *Nazarov cyclization*.[849] Structural variations are possible that prepare a variety of cyclopentenones. When one of the C=C units is a vinyl ether, a cyclopentenone is formed with an oxygen attached to the alkenyl carbon.[850] Substituents on the C=C units, including $-CO_2Et$, lead to cyclopentenones that bear those substituents. The use of such a substrate with $AgSbF_6$, $CuBr_2$ and a chiral ligand gave the cyclopentenone with modest enantioselectivity.[851] Cyclization can also give the nonconjugated five-membered ring.[852] A reductive Nazarov cyclization was reported using $BF_3{\bullet}OEt_2$ and Et_3SiH, giving a cyclopentanone rather than a cyclopentenone.[853] A palladium catalyzed reaction that is related to the Nazarov cyclization converts terminal

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[844] Shin, S.; RajanBabu, T.V. *J. Am. Chem. Soc.* ***2001***, *123*, 8416.

[845] Tong, X.; Zhang, Z.; Zhang, X. *J. Am. Chem. Soc.* ***2003***, *125*, 6370.

[846] Zhu, G.; Zhang, Z. *Org. Lett.* ***2004***, *6*, 4041.

[847] Muedas, C.A.; Ferguson, R.R.; Crabtree, R.H. *Tetrahedron Lett.* ***1989***, *30*, 3389.

[848] Arcadi, A.; Bernocchi, E.; Burini, A.; Cacchi, S.; Marinelli, F.; Pietroni, B. *Tetrahedron Lett.* ***1989***, *30*, 3465.

[849] Nazarov, I.N.; Torgov, I.B.; Terekhova, L.N. *Izv. Akad. Nauk. SSSR otd. Khim. Nauk*, ***1942***, 200; Braude, E.A.; Forbes, W.F. *J. Chem. Soc.* ***1953***, 2208. Also see, Motoyoshiya, J.; Mizuno, K.; Tsuda, T.; Hayashi, S. *Synlett* ***1993***, 237; Oda, M.; Yamazaki, T.; Kajioka, T.; Miyatake, R.; Kuroda, S. *Liebigs Ann. Chem.* ***1997***, 2563. See Smith, D.A.; Ulmer II, C.W. *J. Org. Chem.* ***1993***, *58*, 4118 for a discussion of torquoselectivity and hyperconjugation in this reaction.

[850] Using $AlCl_3$, see Liang, G.; Gradl, S.N.; Trauner, D. *Org. Lett.* ***2003***, *5*, 4931. Using a $Cu(OTf)_2$ catalyst, see He, W.; Sun, X.; Frontier, A.J. *J. Am. Chem. Soc.* ***2003***, *125*, 14278. Using a scandium catalyst, see Liang, G.; Trauner, D. *J. Am. Chem. Soc.* ***2004***, *126*, 9544.

[851] Aggarwal, V.K.; Belfield, A.J. *Org. Lett.* ***2003***, *5*, 5075.

[852] Giese, S.; West, F.G. *Tetrahedron Lett.* ***1998***, *39*, 8393.

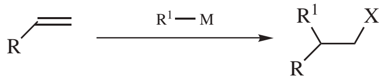
[853] Giese, S.; West, F.G. *Tetrahedron* ***2000***, *56*, 10221.

alkynes to fulvenes.[854] Note that a *retro*-Nazarov is possible with α-bromocyclopentanones.[855] In one variation using a aluminum complex, a cyclohexenone was formed.[856]

OS **VIII**, 190, 381, 505; **IX**, 310.

15-21 Addition of Organometallics to Double and Triple Bonds Not Conjugated to Carbonyls

Hydro-alkyl-addition



Neither Grignard reagents nor lithium dialkylcopper reagents generally add to ordinary C=C double bonds.[857] An exception is the reaction of $(PhMe_2Si)_2Cu(CN)Li$ to 8-oxabicyclo[3.2.1]oct-2-ene derivatives.[858] Grignard reagents usually add only to double bonds susceptible to nucleophilic attack, (e.g., fluoroalkenes and tetracyanoethylene).[859] However, active Grignard reagents (benzylic, allylic) also add to the double bonds of allylic amines,[860] and of allylic and homoallylic alcohols,[861] as well as to the triple bonds of propargyl alcohols and certain other alkynols.[862] Grignard reagents also add to alkynes in the presence of $MnCl_2$ at 100°C[863] and to alkenes in the presence of zirconium[864] or nickel[865] catalysts. It is likely that cyclic intermediates are involved in these cases, in which the magnesium coordinates with the heteroatom. Allylic, benzylic, and tertiary alkyl Grignard reagents also add to 1-alkenes and strained internal alkenes (e.g., norbornene), if the reaction is carried

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[854] Radhakrishnan, U.; Gevorgyan, V.; Yamamoto, Y. *Tetrahedron Lett.* ***2000***, *41*, 1971.

[855] Harmata, M.; Lee, D.R. *J. Am. Chem. Soc.* ***2002***, *124*, 14328. For a discussion of the scope and mechanism of the retro-Nazarov reaction, see Harmata, M.; Schreiner, P.R.; Lee, D.R.; Kirchhoefer, P.L. *J. Am. Chem. Soc.* ***2004***, *126*, 10954.

[856] Magomedev, N.A.; Ruggiero, P.L.; Tang, Y. *Org. Lett.* ***2004***, *6*, 3373.

[857] For reviews of the addition of RM to isolated double bonds, see Wardell, J.L.; Paterson, E.S., in Hartley, F.R.; Patai, S. *The Chemistry of the Metal–Carbon Bond*, Vol. 2, Wiley, NY, ***1985***, 219–338, pp. 268–296; Vara Prasad, J.V.N.; Pillai, C.N. *J. Organomet. Chem.* ***1983***, *259*, 1.

[858] Lautens, M.; Belter, R.K.; Lough, A.J. *J. Org. Chem.* ***1992***, *57*, 422.

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out in a hydrocarbon solvent, such as pentane rather than ether, or in the alkene itself as solvent, heated, under pressure if necessary, to 60–130°C.[866] Yields are variable. *Intramolecular* addition of RMgX to completely unactivated double and triple bonds has been demonstrated.[867] The reaction of tosylates bearing a remote alkene unit and a Grignard reagent leads to cyclization when a zirconium catalyst is used.[868] The intramolecular addition of a CH_2Br unit to the C=C unit of an allylic ether was accomplished using PhMgBr and a cobalt catalyst, give a functionalized tetrahydrofuran and incorporation of the phenyl group on the C=C unit as well.[869] Grignard reagents add to the C=C unit of $(MeO)_2CRCH{=}CH{-}R$ moieties to give a 3-alkyl substituted ketone with good enantioselectivity using a nickel catalyst and a chiral additive.[870] In a useful variation, vinyl epoxides react with Grignard reagents and CuBr to give an allylic alcohol via reaction at the C=C unit and concomitant opening of the epoxide.[871] Conjugated dienes react with arylmagnesium halides, Ph_3SiCl and a palladium catalyst to give a coupling product involving the reaction of two equivalents of the diene and incorporation of two $SiPh_3$ units.[872]

Organolithium reagents (primary, secondary, and tertiary alkyl and in some cases aryl) also add to the double and triple bonds of allylic and propargylic alcohols[873] (in this case tetramethylethylenediamine is a catalyst) and to certain other alkenes containing hetero groups, such as OR, NR_2, or SR. Addition of butyllithium to alkenes has been observed with good enantioselectivity when sparteine was added.[874] Mixing an organolithium reagent with transition metal compounds, such as $CeCl_3$[875] or $Fe(acac)_3$[876] leads to addition of the alkyl group. The intramolecular addition of RLi and R_2CuLi has been reported.[877] Organolithium reagents

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containing an alkene[377,878] or alkyne[879] unit cyclize[880] at low temperatures and quenching with methanol replaces the new C—Li bond with C—H. Cyclopropane derivatives have been formed in this manner.[881] Alkyllithium and alkenyllithium derivatives containing an ester moiety can be cyclized.[882] Tandem cyclization are possible with dienes and enynes to form more than one ring,[883] including bicyclic compounds.[884] Tandem cyclization is possible with alkyne iodides[885] or alkynes with a homoallylic CH_2Li unit.[886] The organolithium reagents can contain heteroatoms, such as nitrogen elsewhere in the molecule, and the organolithium species can be generated from an intermediate organotin derivative.[887] Organolithium reagents add to the less substituted C=C unit of conjugated dienes.[888] The organolithium compound can be generated *in situ* by reaction of an organotin compound with butyllithium, allowing cyclization of occur upon treatment with an excess of LiCl.[889]

Ketones with an α-hydrogen add to alkenes, intramolecular, when heated in a sealed tube with $CuCl_2$ and a palladium catalyst.[890] A similar reaction was reported using $Yb(OTf)_3$ and a palladium catalyst.[891] Keto esters add to alkynes using 10% benzoic acid and a palladium catalyst,[892] or an indium catalyst.[893] 1,3-Diketones add to dienes (1,4-addition) using a palladium catalyst,[894] a $AuCl_3$/AgOTf catalyst,[895] and this addition has been done intramolecularly using 2.4 equivalents of $CuCl_2$ and a palladium catalyst.[896] A related cyclization reaction was reported for diesters having a remote terminal alkyne unit in the molecule, with a palladium

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catalyst.[897] The intermolecular addition of diesters, such as malonates, to alkynes was accomplished in acetic acid and a palladium catalyst under microwave irradiation.[898] Enolate anions can add to allylic sulfides, forming β-lactams in some cases.[899] α-Potassio amines (from an *N*-Boc amine and KHMDS) undergoes intramolecular cyclization with an alkene unit to form a dihydropyrrole.[900] The enolate anion derived from the reaction of a nitrile with potassium *tert*-butoxide added to the less substituted carbon of the C=C unit of styrene in DMSO.[901] Similarly, the intramolecular addition of a nitrile enolate (from treatment with CsOH in *N*-methylpyrrolidinone) to an alkyne gave a cyclized product with an exocyclic methylene unit.[902] Silyl enol ethers add to alkynes using a tungsten catalyst.[903] Malonate derivatives add to alkenes in the presence of an $Al(OR)_3$ catalyst.[904]

Unactivated alkenes or alkynes[905] can react with other organometallic compounds under certain conditions. Trimethylaluminum reacts with 4-methyl-1-pentene, in the presence of Cl_2ZrCp_2, for example, and subsequent reaction with molecular oxygen leads to (2*R*),4-dimethyl-1-pentanol in good yield and 74% ee.[906] These reagents also add to alkynes.[907] Aluminum chloride mediated cyclization of α-iodo ketones to a pendant alkyne unit, in the presence of ICl, gave the spirocyclic ketone with an exocyclic C=CHI unit.[908] Isopropylchloroformate (iPrO$_2$CCl) reacts with an alkene, in conjunction with $Et_3Al_2Cl_3$, to add an isopropyl group.[909] Ruthenium catalysts have been used to add allylic alcohols to alkynes.[910] Samarium iodide (SmI_2) induces cyclization of a halide moiety to an alkyne unit[911] or an alkene unit[912] to form cyclized products. Copper complexes can catalyze similar cyclization to alkenes, even when an ester unit is present in the molecule.[913] The reaction of a dithioketal containing a remote alkene moiety, with a titanium complex, leads to cyclization and incorporation of an endocyclic C=C unit in the final product.[914] Allyl manganese compounds add to allenes to give nonconjugated dienes.[915]

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Vinyl halides add to allylic amines in the presence of Ni(cod)$_2$ where cod = 1, 5-cyclooctodine, followed by reduction with sodium borohydride.[916] Aryl iodides add to alkynes using a platinum complex in conjunction with a palladium catalyst.[917] A palladium catalyst has been used alone for the same purpose,[918] and the intramolecular addition of a arene to an alkene was accomplished with a palladium[919] or a GaCl$_3$ catalyst,[920] Alkyl iodides add intramolecularly to alkenes with a titanium catalyst,[921] or to alkynes using indium metal and additives.[922] The latter cyclization of aryl iodides to alkenes was accomplished with indium and iodine[923] or with SmI$_2$.[924]

Aromatic hydrocarbons, such as benzene add to alkenes using a ruthenium catalyst[925] a catalytic mixture of AuCl$_3$/AgSbF$_6$,[926] or a rhodium catalyst,[927] and ruthenium complexes catalyze the addition of heteroaromatic compounds, such as pyridine, to alkynes.[928] Such alkylation reactions are clearly reminiscent of the Friedel–Crafts reaction (**11-11**). Palladium catalysts can also be used to for the addition of aromatic compounds to alkynes,[929] and rhodium catalysts for addition to alkenes (with microwave irradiation).[930] Note that vinylidene cyclopropanes react with furans and a palladium catalyst to give allylically substituted furans.[931]

Arylboronic acids (p. 905) add to alkynes to give the substituted alkene using a rhodium catalyst.[932] Allenes react with phenylboronic acid and an aryl iodide, in the presence of a palladium catalyst, to give a substituted alkene.[933] 2-Bromo-1,6-dienes react with phenylboronic acid with a palladium catalyst to give a cyclopentane with an exocyclic double bond and a benzyl substituent.[934]

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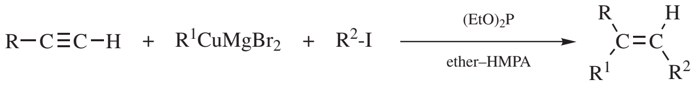
Organomanganese reagents add to alkenes.[935] Manganese triacetate [$Mn(OAc)_3$], in the presence of cupric acetate, facilitates intramolecular cyclization of a halide unit to an alkene.[936] A combination of $Mn(OAc)_2$ and $Co(OAc)_2$ catalysts, and an oxygen atmosphere in acetic acid, leads to addition of ketones to simple alkenes, give the 2-alkyl ketone.[937] Alkynes react with indium reagents, such as $(allyl)_3In_2I_3$, to form dienes (allyl substituted alkenes from the alkyne).[938] Allylic halides add to propargyl alcohols using indium metal to form the aryl organometallic *in situ*.[939] Allyltin reagents add to alkynes in a similar manner in the presence of $ZrCl_4$.[940] Alkylzinc reagents add to alkynes to give substituted alkenes in the presence of a palladium catalyst.[941] Allylzinc reagents add to alkynes in the presence of a cobalt catalyst.[942] A variation reacts dialkylzinc compounds with a 7-oxabicyclo[2.2.1]hept-2-ene system to give incorporation of the alkyl group and opening of the ring to give a cyclohexenol derivative.[943] Vinyltellurium add to alkynes in the presence of $CuI/PdCl_2$.[944]

An indirect addition converts alkynes to an organozinc compound using a palladium catalyst, which then reacts with allylic halides.[945] Similarly, the reaction of an alkyne with $Ti(O\textit{i}Pr)_4/2\ \textit{i}PrMgCl$ followed by addition of an alkyne leads to a conjugated diene.[946]

OS 81, 121.

15-22 The Addition of Two Alkyl Groups to an Alkyne

Dialkyl-addition



$$R{-}C{\equiv}C{-}H \;+\; R^1CuMgBr_2 \;+\; R^2\text{-}I \xrightarrow[\text{ether–HMPA}]{(EtO)_2P} \overset{R}{\underset{R^1}{}}C{=}C\overset{H}{\underset{R^2}{}}$$

Two different alkyl groups can be added to a terminal alkyne[947] in one laboratory step by treatment with an alkylcopper-magnesium bromide reagent (called *Normant*

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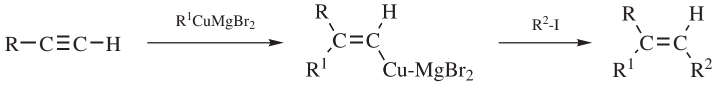
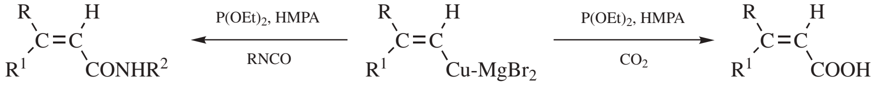
reagents)[948] and an alkyl iodide in ether–HMPA containing triethyl phosphite.[949] The groups add stereoselectively syn. The reaction, which has been applied to primary[950] R′ and to primary, allylic, benzylic, vinylic, and α-alkoxyalkyl R′, involves initial addition of the alkylcopper reagent,[951] followed by a coupling reaction (**10-57**):



136

Acetylene itself (R =H) undergoes the reaction with R_2CuLi instead of the Normant reagent.[952] The use of R′ containing functional groups has been reported.[953] If the alkyl iodide is omitted, the vinylic copper intermediate



136 can be converted to a carboxylic acid by the addition of CO_2 (see **16-30**) or to an amide by the addition of an isocyanate, in either case in the presence of HMPA and a catalytic amount of triethyl phosphite.[954] The use of I_2 results in a vinylic iodide.[955]

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.[956] Allyl ethers and iodobenzene have also been added using a

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[948] For the composition of these reagents see Ashby, E.C.; Smith, R.S.; Goel, A.B. *J. Org. Chem.* ***1981***, *46*, 5133; Ashby, E.C.; Goel, A.B. *J. Org. Chem.* ***1983***, *48*, 2125.

[949] Gardette, M.; Alexakis, A.; Normant, J.F. *Tetrahedron* ***1985***, *41*, 5887, and references cited therein. For an extensive list of references, see Marfat, A.; McGuirk, P.R.; Helquist, P. *J. Org. Chem.* ***1979***, *44*, 3888.

[950] For a method of using secondary and tertiary R, see Rao, S.A.; Periasamy, M. *Tetrahedron Lett.* ***1988***, *29*, 4313.

[951] The initial product, **136**, can be hydrolyzed with acid to give RR′C=CH$_2$. See Westmijze, H.; Kleijn, H.; Meijer, J.; Vermeer, P. *Recl. Trav. Chim. Pays-Bas* ***1981***, *100*, 98, and references cited therein.

[952] Alexakis, A.; Cahiez, G.; Normant, J.F. *Synthesis* ***1979***, 826; *Tetrahedron* ***1980***, *36*, 1961; Furber, M.; Taylor, R.J.K.; Burford, S.C. *J. Chem. Soc. Perkin Trans. 1*, ***1986***, 1809.

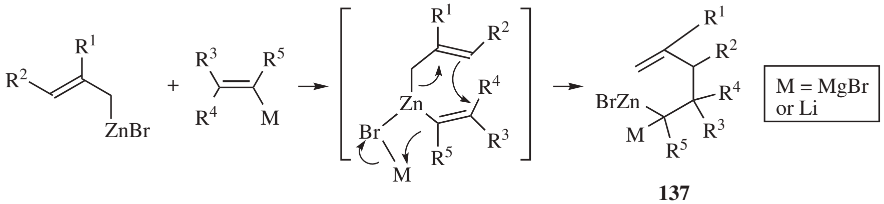
[953] Rao, S.A.; Knochel, P. *J. Am. Chem. Soc.* ***1991***, *113*, 5735.

[954] Normant, J.F.; Cahiez, G.; Chuit, C.; Villieras, J. *J. Organomet. Chem.* ***1973***, *54*, C53.

[955] Alexakis, A.; Cahiez, G.; Normant, J.F. *Org. Synth.* ***VII***, 290.

[956] Negishi, E.; Van Horn, D.E.; Yoshida, T. *J. Am. Chem. Soc.* ***1985***, *107*, 6639. For reviews, see Negishi, E. *Acc. Chem. Res.* ***1987***, *20*, 65; *Pure Appl. Chem.* ***1981***, *53*, 2333; Negishi, E.; Takahashi, T. *Aldrichimica Acta* ***1985***, *18*, 31.

zirconium complex.[957] Similarly, allyl ethers and allyl chlorides have been added.[958]



137

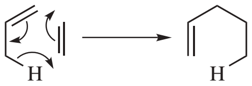
Allylic zinc bromides add to vinylic Grignard and lithium reagents to give the gem-dimetallo compounds **137**. The two metallo groups can be separately reacted with various nucleophiles.[959]

Arylboronic acids (p. 905) react with alkynes and 1 equivalent of an aryl iodide, with a palladium catalyst, to add two aryl groups across the triple bond.[960]

OS **VII**, 236, 245, 290.

15-23 The Ene Reaction

Hydro-allyl-addition



Alkenes can add to double bonds in a reaction different from those discussed in **15-20**, which, however, is still formally the addition of RH to a double bond. This is called the *ene reaction* or the *ene synthesis.*[961] For the reaction to proceed without a catalyst, one of the components must be a reactive dienophile (see **15-60** 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. Rather high reaction temperatures (250–450°C) are common unless the substrates are very

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[957] Hara, R.; Nishihara, Y.; Landré, P.D.; Takahashi, T. *Tetrahedron Lett.* ***1997***, *38*, 447.

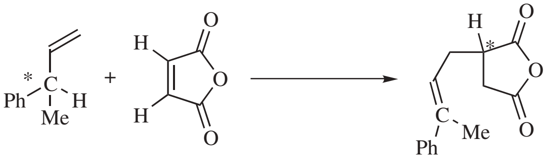
[958] Takahashi, T.; Kotora, M.; Kasai, K.; Suzuki, N. *Tetrahedron Lett.* ***1994***, *35*, 5685.

[959] Knochel, P.; Normant, J.F. *Tetrahedron Lett.* ***1986***, *27*, 1039, 1043, 4427, 4431, 5727.

[960] Zhou, C.; Emrich, D.E.; Larock, R.C. *Org. Lett.* ***2003***, *5*, 1579.

[961] Alder, K.; von Brachel, H. *Liebigs Ann. Chem.* ***1962***, *651*, 141. For a monograph, see Carruthers, W. *Cycloaddition Reactions in Organic Synthesis*, Pergamon, Elmsford, NY, ***1990***. For reviews, see Boyd, G.V., in Patai, S. *Supplement A: The Chemistry of Double-Bonded Functional Groups*, Vol. 2, pt. 1, Wiley, NY, ***1989***, pp. 477–525; Keung, E.C.; Alper, H. *J. Chem. Educ.* ***1972***, *49*, 97–100; Hoffmann, H.M.R. *Angew. Chem. Int. Ed.* ***1969***, *8*, 556. For reviews of intramolecular ene reactions see, Taber, D.F. *Intramolecular Diels–Alder and Alder Ene Reactions*, Springer, NY, ***1984***; pp. 61–94; Oppolzer, W.; Snieckus, V. *Angew. Chem. Int. Ed.* ***1978***, *17*, 476–486; Conia, J.M.; Le Perchec, P. *Synthesis* ***1975***, 1. See Desimoni, G.; Faita, G.; Righetti, P.P.; Sfulcini, A.; Tsyganov, D. *Tetrahedron* ***1994***, *50*, 1821 for solvent effects in the ene reaction.

activated. Note that steric acceleration of the uncatalyzed ene reaction is known.[962] Cyclopropene has also been used.[963] The reaction is compatible with a variety of functional groups that can be appended to the ene and dienophile.[964] *N,N*-Diallyl amides give an ene cyclization, for example.[965] The ene reaction is known with fullerene (see p. 94) derivatives.[966] 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 mechanism of the ene reaction of singlet ($^1\Delta_g$) oxygen with simple alkenes was found to involve two steps, with no intermediate.[967] A retro-ene reaction is known with allylic dithiocarbonate.[968] The reaction between maleic anhydride and optically active PhCHMeCH=CH$_2$ gave an optically active product (**138**),[969] which is strong evidence for a concerted rather than a stepwise mechanism.[970] The reaction can be highly stereoselective.[971]



138

The reaction can be extended to less-reactive enophiles by the use of Lewis acid catalysts, especially alkylaluminum halides.[972] Titanium catalysts,[973] Sc(OTf)$_3$,[974]

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[962] Choony, N.; Kuhnert, N.; Sammes, P.G.; Smith, G.; Ward, R.W. *J. Chem. Soc., Perkin Trans. 1* ***2002***, 1999.

[963] Deng, Q.; Thomas IV, B.E.; Houk, K.N.; Dowd, P. *J. Am. Chem. Soc.* ***1997***, *119*, 6902.

[964] For a review of ene reactions in which one of the reactants bears a Si or Ge atom, see Dubac, J.; Laporterie, A. *Chem. Rev.* ***1987***, *87*, 319.

[965] Cossy, J.; Bouzide, A. *Tetrahedron* ***1997***, *53*, 5775; Oppolzer, W.; Fürstner, A. *Helv. Chim. Acta* ***1993***, *76*, 2329; Oppolzer, W.; Schröder, F. *Tetrahedron Lett.* ***1994***, *35*, 7939.

[966] Wu, S.; Shu, L.; Fan, K. *Tetrahedron Lett.* ***1994***, *35*, 919.

[967] Singleton, D. A.; Hang, C.; Szymanski, M. J.; Meyer, M. P.; Leach, A. G.; Kuwata, K. T.; Chen, J. S.; Greer, A.; Foote, C. S.; Houk, K. N. *J. Am. Chem. Soc.* ***2003***, *125*, 1319.

[968] Eto, M.; Nishimoto, M.; Kubota, S.; Matsuoka, T.; Harano, K. *Tetrahedron Lett.* ***1996***, *37*, 2445.

[969] Hill, R.K.; Rabinovitz, M. *J. Am. Chem. Soc.* ***1964***, *86*, 965. See also, Garsky, V.; Koster, D.F.; Arnold, R.T. *J. Am. Chem. Soc.* ***1974***, *96*, 4207; Stephenson, L.M.; Mattern, D.L. *J. Org. Chem.* ***1976***, *41*, 3614; Nahm, S.H.; Cheng, H.N. *J. Org. Chem.* ***1986***, *51*, 5093.

[970] For other evidence for a concerted mechanism see Benn, F.R.; Dwyer, J.; Chappell, I. *J. Chem. Soc. Perkin Trans. 2*, ***1977***, 533; Jenner, G.; Salem, R.B.; El'yanov, B.; Gonikberg, E.M. *J. Chem. Soc. Perkin Trans. 2*, ***1989***, 1671. See Thomas IV, B.E.; Loncharich, R.J.; Houk, K.N. *J. Org. Chem.* ***1992***, *57*, 1354 for transition-state structures of the intramolecular ene reaction.

[971] Cossy, J.; Bouzide, A.; Pfau, M. *Tetrahedron Lett.* ***1992***, *33*, 4883; Ooi, T.; Maruoka, K.; Yamamoto, H. *Tetrahedron* ***1994***, *50*, 6505; Thomas IV, B.E.; Houk, K.N. *J. Am. Chem. Soc.* ***1993***, *115*, 790; Also see Masaya, K.; Tanino, K.; Kuwajima, I. *Tetrahedron Lett.* ***1994***, *35*, 7965.

[972] For reviews, see Chaloner, P.A., in Hartley, F.R. *The Chemistry of the Metal–Carbon Bond*, Vol. 4, Wiley, NY, ***1987***, pp. 456–460; Snider, B.B. *Acc. Chem. Res.* ***1980***, *13*, 426.

[973] Waratuke, S.A.; Johnson, E.S.; Thorn, M.G.; Fanwick, P.E.; Rothwell, I.P. *Chem. Commun.* ***1996***, 2617; Sturla, S.J.; Kablaoui, N.M.; Buchwald, S.L. *J. Am. Chem. Soc.* ***1999***, *121*, 1976.

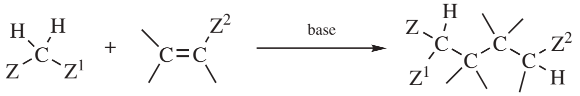
[974] Aggarwal, V.K.; Vennall, G.P.; Davey, P.N.; Newman, C. *Tetrahedron Lett.* ***1998***, *39*, 1997.

$LiClO_4$[975] yttrium,[976] nickel catalysts,[977] as well as a combination of silver and gold catalysts[978] have also been used. A magnesium-ene cyclization stereochemically directed by an allylic oxyanionic group has been reported.[979] The Lewis acid catalyzed reaction probably has a stepwise mechanism.[980] The ene reaction has also been mediated on certain resins,[981] and using formaldehyde that was encapsulated in zeolite.[982] An iridium catalyzed ene reaction has been done in an ionic liquid.[983] The carbonyl-ene reaction is also very useful, and often gives synthetically useful yields of products when catalyzed by Lewis acids,[984] including asymmetric catalysts.[985] Among the useful Lewis acids are scandium triflate[986] and chromium complexes.[987] Carbonyl ene cyclization has been reported on silica gel at high pressure (15 kbar).[988] Ene reactions with imines,[989] nitrile oxides,[990] as well as nitroso ene reactions are known.[991]

OS **IV**, 766; **V**, 459. See also, OS **VIII**, 427.

15-24 The Michael Reaction

Hydro-bis(ethoxycarbonyl)methyl-addition, and so on



Compounds containing electron-withdrawing groups (Z is defined on p. 1007) add, in the presence of bases, to alkenes of the form C=C–Z (including quinones).

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[975] Davies, A.G.; Kinart, W.J. *J. Chem. Soc. Perkin Trans. 2*, ***1993***, 2281.

[976] Molander, G.A.; Corrette, C.P. *J. Org. Chem.* ***1999***, *64*, 9697.

[977] Michelet, V.; Galland, J.-C.; Charruault, L.; Savignac, M.; Genêt, J.-P. *Org. Lett.* ***2001***, *3*, 2065.

[978] Kennedy-Smith, J.J.; Staben, S.T.; Toste, F.D. *J. Am. Chem. Soc.* ***2004***, *126*, 4526.

[979] Cheng, D.; Zhu, S.; Yu, Z.; Cohen, T. *J. Am. Chem. Soc.* ***2001***, *123*, 30.

[980] See Snider, B.B.; Ron E. *J. Am. Chem. Soc.* ***1985***, *107*, 8160.

[981] Cunningham, I.D.; Brownhill, A.; Hamereton, I.; Howlin, B.J. *Tetrahedron* ***1997***, *53*, 13473.

[982] Okachi, T.; Onaka, M. *J. Am. Chem. Soc.* ***2004***, *126*, 2306.

[983] Shibata, T.; Yamasaki, M.; Kadowaki, S.; Takagi, K. *Synlett* ***2004***, 2812.

[984] See Achmatowicz, O.; Bialeck-Florjańczyk, E. *Tetrahedron* ***1996***, *52*, 8827; Marshall, J.A.; Andersen, M.W. *J. Org. Chem.* ***1992***, *57*, 5851 for mechanistic discussions of this reaction.

[985] Mikami, K.; Terada, M.; Narisawa, S.; Nakai, T. *Synlett* ***1992***, 255; Wu, X.-M.; Funakoshi, K.; Sakai, K. *Tetrahedron Lett.* ***1993***, *34*, 5927. For a discussion of the mechanism of the chiral copper complex-catalyzed carbonyl ene reaction, see Morao, I.; McNamara, J.P.; Hillier, I.H. *J. Am. Chem. Soc.* ***2003***, *125*, 628.

[986] See Aggarwal, V.K.; Vennall, G.P.; Davey, P.N.; Newman, C. *Tetrahedron Lett.* ***1998***, *39*, 1997.

[987] Ruck, R.T.; Jacobsen, E.N. *J. Am. Chem. Soc.* ***2002***, *124*, 2882.

[988] Dauben, W.G.; Hendricks, R.T. *Tetrahedron Lett.* ***1992***, *33*, 603.

[989] Tohyama, Y.; Tanino, K.; Kuwajima, I. *J. Org. Chem.* ***1994***, *59*, 518; Yamanaka, M.; Nishida, A.; Nakagawa, M.; *Org. Lett.* ***2000***, *2*, 159.

[990] For a discussion of the mechanism of the intramolecular reaction, see Yu, Z.-X.; Houk, K.N. *J. Am. Chem. Soc.* ***2003***, *125*, 13825.

[991] Lu, X. *Org. Lett.* ***2004***, *6*, 2813. See also, Leach, A.G.; Houk, K.N. *J. Am. Chem. Soc.* ***2002***, *124*, 14820. For a review, see Adam, W.; Krebs, O. *Chem. Rev.* ***2003***, *103*, 4131.

This is called the *Michael reaction* and involves conjugate addition.[992] The compound RCH_2Z or $RCHZZ'$ can include aldehydes,[993] ketones,[994] esters[995] and diesters,[996] diketones,[997] keto-esters,[998] carboxylic acids and dicarboxylic acids,[999] nitriles,[1000] and nitro compounds,[1001] often with chiral catalysts or additives that give asymmetric induction. Enamines can also be used as the nucleophilic partner in Michael additions.[1002] In the most common examples, a base removes the acidic proton and then the mechanism is as outlined on p. 1008. The reaction has been carried out with conjugated substrates that include malonates, cyanoacetates, acetoacetates, other β-keto esters, and compounds of the form ZCH_3, ZCH_2R, $ZCHR_2$, and $ZCHRZ'$, including carboxylic esters, amides,[1003] ketones, aldehydes, nitriles, nitro compounds,[1004]

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[992] For reviews, see Yanovskaya, L.A.; Kryshtal, G.V.; Kulganek, V.V. *Russ. Chem. Rev.* ***1984***, *53*, 744; Bergmann, E.D.; Ginsburg, D.; Pappo, R. *Org. React.* ***1959***, *10*, 179; House, H.O. *Modern Synthetic Reaction*, 2nd ed., W.A. Benjamin, NY, ***1972***, pp. 595–623. The subject is also discussed at many places, in Stowell, J.C. *Carbanions in Organic Synthesis*, Wiley, NY, ***1979***.

[993] Hagiwara, H.; Okabe, T.; Hakoda, K.; Hoshi, T.; Ono, H.; Kamat, V.P.; Suzuki, T.; Ando, M. *Tetrahedron Lett.* ***2001***, *42*, 2705; Melchiorre, P.; Jørgensen, K.A. *J. Org. Chem.* ***2003***, *68*, 4151; Shimizu, K.; Suzuki, H.; Hayashi, E.; Kodama, T.; Tsuchiya, Y.; Hagiwara, H.; Kityama, Y. *Chem. Commun.* ***2002***, 1068; Willis, M.C.; McNally, S.J.; Beswick, P.J. *Angew. Chem. Int. Ed.* ***2004***, *43*, 340. For an intramolecular example, see Fonseca, M.T.H.; List, B. *Angew. Chem. Int. Ed.* ***2004***, *43*, 3958.

[994] Betancort, J.M.; Sakthivel, K.; Thayumanavan, R.; Barbas III, C.F. *Tetahedron Lett.* ***2001***, *42*, 4441; Enders, D.; Seki, A. *Synlett* ***2002***, 26. For an example using an α-hydroxy ketone, see Andrey, O.; Alexakis, A.; Bernardinelli, G. *Org. Lett.* ***2003***, *5*, 2559; Harada, S.; Kumagai, N.; Kinoshita, T.; Matsunaga, S.; Shibasaki, M. *J. Am. Chem. Soc.* ***2003***, *125*, 2582.

[995] Kim, S.-G.; Ahn, K.H. *Tetrahedron Lett.* ***2001***, *42*, 4175.

[996] Halland, N.; Aburel, P.S.; Jørgensen, K.A. *Angew. Chem. Int. Ed.* ***2003***, *42*, 661.

[997] da silva, F.M.; Gomes, A.K.; Jones Jr., J. *Can. J. Chem.* ***1999***, *77*, 624.

[998] Suzuki, T.; Torii, T. *Tetrahedron Asymmetry* ***2001***, *12*, 1077; García-Gómez, G.; Moretó, J.M. *Eur. J. Org. Chem.* ***2001***, 1359; Kobayashi, S.; Kakumoto, K.; Mori, Y.; Manabe, K. *Isr. J. Chem.* ***2001***, *41*, 247.

[999] Méou, A.; Lamarque, L.; Brun, P. *Tetrahedron Lett.* ***2002***, *43*, 5301.

[1000] Kraus, G.A.; Dneprovskaia, E. *Tetrahedron Lett.* ***2000***, *41*, 21. For an example using an α-cyano amide, see Wolckenhauer, S.A.; Rychnovsky, S.D. *Org. Lett.* ***2004***, *6*, 2745. For a review of conjugate addition to this relatively unreactive class of compounds, see Fleming, F.F.; Wang, Q. *Chem. Rev.* ***2003***, *103*, 2035.

[1001] Sebti, S.; Boukhal, H.; Hanafi, N.; Boulaajaj, S. *Tetrahedron Lett.* ***1999***, *40*, 6207; Novák, T.; Tatai, J.; Bakó, P.; Czugler, M.; Keglevich, G. Töke, L. *Synlett* ***2001***, 424; Halland, N.; Hazell, R.G.; Jørgensen, K.A. *J. Org. Chem.* ***2002***, *67*, 8331; Ooi, T.; Fujioka, S.; Maruoka, K. *J. Am. Chem. Soc.* ***2004***, *126*, 11790. For a reaction using nitromethane and a Mg–Al hydrotalcite catalyst, see Choudary, B.M.; Kantam, M.L.; Kavita, B.; Reddy, Ch.V.; Figueras, F. *Tetrahedron* ***2000***, *56*, 9357. For the importance of the aggregation state, see Strzalko, T.; Seyden-Penne, J.; Wartski, L.; Froment, F.; Corset, J. *Tetrahedron Lett.* ***1994***, *35*, 3935.

[1002] Sharma, U.; Bora, U.; Boruah, R.C.; Sandhu, J.S. *Tetrahedron Lett.* ***2002***, *43*, 143.

[1003] Taylor, M.S.; Jacobsen, E.N. *J. Am. Chem. Soc.* ***2003***, *125*, 11204.

[1004] For reviews of Michael reactions, where Z or Z′ is nitro, see Yoshikoshi, A.; Miyashita, M. *Acc. Chem. Res.* ***1985***, *18*, 284; Baer, H.H.; UrBas L., in Feuer, H. *The Chemistry of the Nitro and Nitroso Groups*, pt. 2, Wiley, NY, ***1970***, pp. 130–148. See Kumar, H.M.S.; Reddy, B.V.S.; Reddy, P.T.; Yadav, J.S. *Tetrahedron Lett.* ***1999***, *40*, 5387; Ji, J.; Barnes, D.M.; Zhang, J.; King, S.A.; Wittenberger, S.J.; Morton, H.E. *J. Am. Chem. Soc.* ***1999***, *121*, 10215; List, B.; Pojarliev, P.; Martin, H.J. *Org. Lett.* ***2001***, *3*, 2423; Alexakis, A.; Andrey, O. *Org. Lett.* ***2002***, *4*, 3611; Mase, N.; Thayumanavan, R.; Tanaka, F.; Barbas III, C.F. *Org. Lett.* ***2004***, *6*, 2527; Okino, T.; Hoashi, Y.; Takemoto, Y. *J. Am. Chem. Soc.* ***2003***, *125*, 12672; Ishii, T.; Fujioka, S.; Sekiguchi, Y.; Kotsuki, H. *J. Am. Chem. Soc.* ***2004***, *126*, 9558; Li, H.; Wang, Y.; Tang, L.; Deng, L. *J. Am. Chem. Soc.* ***2004***, *126*, 9906; Watanabe, M.; Ikagawa, A.; Wang, H.; Murata, K.; Ikariya, T. *J. Am. Chem. Soc.* ***2004***, *126*, 11148.

and sulfones, as well as other compounds with relatively acidic hydrogens, such as indenes and fluorenes. Vinylogous Michael reaction are well known, using a variety of nucleophilic species.[1005] Michael addition of methyl 2,2-dichloroacetate/ $LiN(TMS)_2$ where TMS = trinethysilyl, leads to formation of a cyclopropane ring.[1006] Similarly, the intramolecular Michael addition of an α-chloro ketone enolate anion, formed *in situ* using DABCO, leads to formation of a bicyclo[4.1.0] diketone.[1007] It is noted that activated aryl compounds undergo Michael addition in the presence of an imidazolidinone catalyst.[1008] Conjugate addition of nitrones using SmI_2 has been reported.[1009]

These reagents do not add to ordinary double bonds, except in the presence of free-radical initiators (**15-33**). 1,2 Addition (to the C=O or C≡N group) often competes and sometimes predominates (**16-38**).[1010] In particular, α,β-unsaturated *aldehydes* seldom give 1,4 addition.[1011] The Michael reaction has traditionally been performed in protic solvents, with catalytic amounts of base,[1012] 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.[1013] Silyl enol ethers can also be used, and in conjunction with chiral additives.[1014] Phase-transfer catalysts have been used,[1015] and ionic liquids have been used in conjunction with phase-transfer catalysis.[1016] Michael addition has been done in ionic liquids, adding aldehydes to conjugated nitro compounds using proline as a catalyst.[1017] Transition-metal compounds, such as $CeCl_3$,[1018] $Yb(OTf)_3$,[1019] $Bi(OTf)_3$,[1020] ferric chloride hexahydrate,[1021]

[1005] Ballini, R.; Bosica, G.; Fiorini, D. *Tetrahedron Lett.* ***2001***, *42*, 8471.

[1006] Escribano, A.; Pedregal, C.; González, R.; Fernádez, A.; Burton, K.; Stephenson, G.A. *Tetrahedron* ***2001***, *57*, 9423.

[1007] Bremeyer, N.; Smith, S.C.; Ley, S.V.; Gaunt, M.J. *Angew. Chem. Int. Ed.* ***2004***, *43*, 2681.

[1008] Paras, N.A.; MacMillan, D.W.C. *J. Am. Chem. Soc.* ***2002***, *124*, 7894.

[1009] Masson, G.; Cividino, P.; Py, S.; Vallée, Y. *Angew. Chem. Int. Ed.* ***2003***, *42*, 2265.

[1010] For a discussion of 1,2 versus 1,4-addition, see, Oare, D.A.; Heathcock, C.H. *Top. Stereochem.* ***1989***, *19*, 227, pp. 232–236.

[1011] For reports of successful 1,4-additions to α,β-unsaturated aldehydes, see Kryshtal, G.V.; Kulganek, V.V.; Kucherov, V.F.; Yanovskaya, L.A. *Synthesis* ***1979***, 107; Yamaguchi, M.; Yokota, N.; Minami, T. *J. Chem. Soc., Chem. Commun.* ***1991***, 1088.

[1012] See Macquarrie, D.J. *Tetrahedron Lett.* ***1998***, *39*, 4125 for the use of supported phenolates as catalysts.

[1013] For reviews of stereoselective Michael additions, see Oare, D.A.; Heathcock, C.H. *Top. Stereochem.* ***1991***, *20*, 87; ***1989***, *19*, 227.

[1014] Harada, T.; Adachi, S.; Wang, X. *Org. Lett.* ***2004***, *6*, 4877.

[1015] Kim, D.Y.; Huh, S.C. *Tetrahedron* ***2001***, *57*, 8933.

[1016] Dere, R.T.; Pal, R.R.; Patil, P.S.; Salunkhe, M.M. *Tetrahedron Lett.* ***2003***, *44*, 5351.

[1017] In bmim PF_6, 3-butyl-1-methylimidazolium hexafluorophosphate: Kotrusz, P.; Toma, S.; Schamlz, H.-G.; Adler, A. *Eur. J. Org. Chem.* ***2004***, 1577.

[1018] Boruah, A.; Baruah, M.; Prajapati, D.; Sandhu, J.S. *Synth. Commun.* ***1998***, *28*, 653; Bartoli, G.; Bosco, M.; Bellucci, M.C.; Marcantoni, E.; Sambri, L.; Torregiani, E. *Eur. J. Org. Chem.* ***1999***, 617.

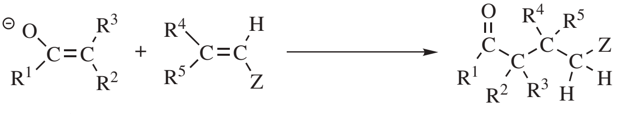
[1019] Keller, E.; Feringa, B.L. *Tetrahedron Lett.* ***1996***, *37*, 1879; Kotsuki, H.; Arimura, K. *Tetrahedron Lett.* ***1997***, *38*, 7583.

[1020] Varala, R.; Alam, M.M.; Adapa, S.R. *Synlett* ***2003***, 720.

[1021] For a review, see Christoffers, J. *Synlett* ***2001***, 723.

copper compounds,[1022] lanthanum complexes,[1023] ruthenium complexes,[1024] or scandium complexes[1025] also induce the reaction. In many cases, such compounds lead to catalytic enantioselective Michael additions.[1026] Conjugate addition has also been promoted by Y-zeolite,[1027] and water-promoted Michael additions have also been reported.[1028] Other catalysts have also been used.[1029] Vinylzinc complexes add to conjguated keotnes in the presence of a CuBr catlayst.[1030]

In a Michael reaction with suitably different R groups, two new stereogenic centers are created (see **139**).



139

In a diastereoselective process, one of the two pairs is formed exclusively or predominantly, as a racemic mixture.[1031] Many such examples have been reported.[672] In many of these cases, both the enolate anion and substrate can exist as (*Z*) or (*E*) isomers. With enolates derived from ketones or carboxylic esters, The (*E*) enolates gave the syn pair of enantiomers (p. 166), while (*Z*) enolates gave the anti pair.[1032] Nitro compounds add to conjugated ketones in the presence of a dipeptide and a piperazine.[1033] Malonate derivatives also add to conjugated ketones,[1034] and keto esters add to conjugated esters.[1035] Addition of chiral additives to the reaction, such as metal–salen complexes,[1036] proline derivatives,[1037] or (−)-sparteine,[1038]

[1022] Iguchi, Y.; Itooka, R.; Miyaura, N. *Synlett* ***2003***, 1040; Meyer, O.; Becht, J.-M.; Helmchen, G. *Synlett* ***2003***, 1539. For a discussion of the mechanism, see Comelles, J.; Moreno-Mañas, M.; Pérez, E.; Roglans, A.; Sebastián, R.M.; Vallribera, A. *J. Org. Chem.* ***2004***, *69*, 6834.

[1023] Kim, Y.S.; Matsunaga, S.; Das, J.; Sekine, A.; Ohshima, T.; Shibasaki, M. *J. Am. Chem. Soc.* ***2000***, *122*, 6506.

[1024] Watanabe, M.; Murata, K.; Ikariya, T. *J. Am. Chem. Soc.* ***2003***, *125*, 7508; Wadsworth, K.J.; Wood, F.K.; Chapman, C.J.; Frost, C.G. *Synlett* ***2004***, 2022. For a review, see Hayashi, T.; Yamasaki, K. *Chem. Rev.* ***2003***, *103*, 2829.

[1025] Mori, Y.; Kakumoto, K.; Manabe, K.; Kobayashi, S. *Tetahedron Lett.* ***2000***, *41*, 3107.

[1026] For a review, see Krause, N.; Hoffmann-Röder, A. *Synthesis* ***2001***, 171.

[1027] Sreekumar, R.; Rugmini, P.; Padmakumar, R. *Tetrahedron Lett.* ***1997***, *38*, 6557.

[1028] Lubineau, A.; Augé, J. *Tetrahedron Lett.* ***1992***, *33*, 8073.

[1029] Phosphoramidites: Grossman, R.B.; Comesse, S.; Rasne, R.M.; Hattori, K.; Delong, M.N. *J. Org. Chem.* ***2003***, *68*, 871. Fluorapatite: Zahouily, M.; Abrouki, Y.; Rayadh, A.; Sebti, S.; Dhimane, H.; David, M. *Tetrahedron Lett.* ***2003***, *44*, 2463.

[1030] Huang, X.; Pi, J. *Synlett* ***2003***, 481.

[1031] For a more extended analysis, see Oare, D.A.; Heathcock, C.H. *Top. Stereochem.* ***1989***, *19*, p. 237.

[1032] For example, see Oare, D.A.; Heathcock, C.H. *J. Org. Chem.* ***1990***, *55*, 157.

[1033] Tsogoeva, S.B.; Jagtap, S.B. *Synlett* ***2004***, 2624; Ballini, R.; Barboni, L.; Bosica, G.; Fiorini, D. *Synthesis* ***2002***, 2725.

[1034] Zhang, Z.; Dong, Y.-W.; Wang, G.-W.; Komatsu, K. *Synlett* ***2004***, 61.

[1035] Yadav, J.S.; Geetha, V.; Reddy, B.V.S. *Synth. Commun.* ***2002***, *32*, 3519.

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[1037] Yamaguchi, M.; Shiraishi, T.; Hirama, M. *J. Org. Chem.* ***1996***, *61*, 3520.

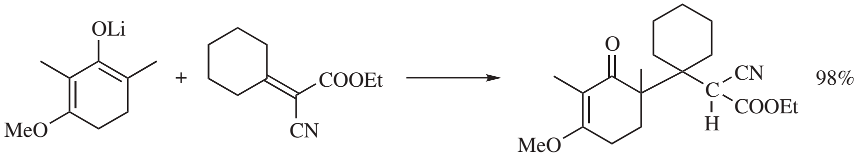
[1038] Xu, F.; Tillyer, R.D.; Tschaen, D.M.; Grabowski, E.J.J.; Reider, P.J. *Tetrahedron Assymetry* ***1998***, *9*, 1651.

lead to product formation with good-to-excellent asymmetric induction. Ultrasound has also been used to promote asymmetric Michael reactions.[1039] Intramolecular versions of Michael addition are known.[1040] A double Michael process is possible, where conjugate addition to an alkynyl ketone is followed by an intramolecular Michael to form a functionalized ring.[1041]

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).[1042] Enantioselective addition has also been achieved by the use of a chiral catalyst[1043] and by using optically active enamines instead of enolates.[1044] Chiral imines have also been used.[1045]

Mannich bases (see **16-19**) and β-halo carbonyl compounds can also be used as substrates; these are converted to the C=C–Z compounds *in situ* by the base (**16-19**, **17-13**).[1046] Substrates of this kind are especially useful in cases where the C=C–Z compound is unstable. The reaction of C=C–Z compounds with enamines (**10-69**) can also be considered a Michael reaction. Michael reactions are reversible.

When the substrate contains *gem*-Z groups (e.g., **141**), bulky groups can be added, if the reaction is carried out under aprotic conditions. For example, addition of enolate **140** to **141** gave **142** in which two adjacent quaternary centers have been formed.[1047]



140 **141** **142**

[1039] Mirza-Aghayan, M.; Etemad-Moghadam, G.; Zaparucha, A.; Berlan, J.; Loupy, A.; Koenig, M. *Tetrahedron Asymmetry* ***1995***, *6*, 2643.

[1040] Christoffers, J. *Tetrahedron Lett.* ***1998***, *39*, 7083.

[1041] Holeman, D.S.; Rasne, R.M.; Grossman, R.B. *J. Org. Chem.* ***2002***, *67*, 3149.

[1042] See, for example, Töke, L.; Fenichel, L.; Albert, M. *Tetrahedron Lett.* ***1995***, *36*, 5951; Corey, E.J.; Peterson, R.T. *Tetrahedron Lett.* ***1985***, *26*, 5025; Calderari, G.; Seebach, D. *Helv. Chim. Acta* ***1985***, *68*, 1592; Tomioka, K.; Ando, K.; Yasuda, K.; Koga, K. *Tetrahedron Lett.* ***1986***, *27*, 715; Posner, G.H.; Switzer, C. *J. Am. Chem. Soc.* ***1986***, *108*, 1239; Enders, D.; Demir, A.S.; Rendenbach, B.E.M. *Chem. Ber.* ***1987***, *120*, 1731. Also see, Hawkins, J.M.; Lewis, T.A. *J. Org. Chem.* ***1992***, *57*, 2114.

[1043] Yura, T.; Iwasawa, N.; Mukaiyama, T. *Chem. Lett.* ***1988***, 1021; Yura, T.; Iwasawa, N.; Narasaka, K.; Mukaiyama, T. *Chem. Lett.* ***1988***, 1025; Desimoni, G.; Quadrelli, P.; Righetti, P.P. *Tetrahedron* ***1990***, *46*, 2927.

[1044] See d'Angelo, J.; Revial, G.; Volpe, T.; Pfau, M. *Tetrahedron Lett.* ***1988***, *29*, 4427.

[1045] d'Angelo, J.; Desmaële, D.; Dumas, F.; Guingant, A. *Tetrahedron Asymmetry* ***1992***, *3*, 459.

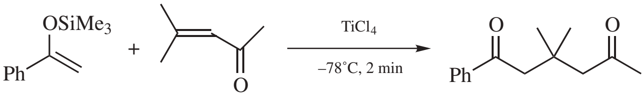
[1046] Mannich bases react with ketones *without* basic catalysts to give 1,5-diketones, but this process, known as the *thermal-Michael reaction*, has a different mechanism: Brown, H.L.; Buchanan, G.L.; Curran, A.C.W.; McLay, G.W. *Tetrahedron* ***1968***, *24*, 4565; Gill, N.S.; James, K.B.; Lions, F.; Potts, K.T. *J. Am. Chem. Soc.* ***1952***, *74*, 4923.

[1047] Holton, R.A.; Williams, A.D.; Kennedy, R.M. *J. Org. Chem.* ***1986***, *51*, 5480.

In certain cases, Michael reactions can take place under acidic conditions.[1048] Michael-type addition of radicals to conjugated carbonyl compounds is also known.[1049] Radical addition can be catalyzed by $Yb(OTf)_3$,[1050] but radicals add under standard conditions as well, even intramolecularly.[1051] Electrochemical-initiated Michael additions are known.

Michael reactions are sometimes applied to substrates of the type C≡C–Z, where the coproducts are conjugated systems of the type C=C–Z.[1052] 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.[1053]

In a closely related reaction, silyl enol ethers add to α,β-unsaturated ketones and esters when catalyzed[1054] by $TiCl_4$, for example,[1055]



$InCl_3$ also catalyzes this reaction.[1056] Aluminum compounds also catalyze this reaction[1057] and the reaction has been done in neat tri-*n*-propylaluminum.[1058] A solid-state version of the reaction used alumina•$ZnCl_2$.[1059] This reaction, also, has been performed diastereoselectively.[1060] Tin enolates have been used.[1061]

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; **VIII**, 87, 210, 219, 444, 467; **IX**, 526. See also, OS **VIII**, 148.

[1048] See Hajos, Z.G.; Parrish, D.R. *J. Org. Chem.* ***1974***, *39*, 1612; *Org. Synth.* ***VII***, 363.

[1049] Undheim, K.; Williams, K. *J. Chem. Soc., Chem. Commun.* ***1994***, 883; Bertrand, S.; Glapski, C.; Hoffmann, N.; Pete, J.-P. *Tetrahedron Lett.* ***1999***, *40*, 3169.

[1050] Sibi, M.P.; Jasperse, C.P.; Ji, J. *J. Am. Chem. Soc.* ***1995***, *117*, 10779. See Wu, J.H.; Radinov, R.; Porter, N.A. *J. Am. Chem. Soc.* ***1995***, *117*, 11029 for a related reaction involving $Zn(OTf)_2$.

[1051] Enholm, E.J.; Kinter, K.S. *J. Org. Chem.* ***1995***, *60*, 4850.

[1052] Rudorf, W.-D.; Schwarz, R. *Synlett* ***1993***, 369.

[1053] See, for example, Makosza, M. *Tetrahedron Lett.* ***1966***, 5489.

[1054] Other catalysts have also been used. For a list of catalysts, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 1576–1582. See also, Mukaiyama, T.; Kobayashi, S.; Tamura, M.; Sagawa, Y. *Chem. Lett.* ***1987***, 491; Mukaiyama, T.; Kobayashi, S. *J. Organomet. Chem.* ***1990***, *382*, 39.

[1055] Narasaka, K.; Soai, K.; Aikawa, Y.; Mukaiyama, T. *Bull. Chem. Soc. Jpn.* ***1976***, *49*, 779; Saigo, K.; Osaki, M.; Mukaiyama, T. *Chem. Lett.* ***1976***, 163; Matsuda, I. *J. Organomet. Chem.* ***1987***, *321*, 307; Narasaka, K. *Org. Synth,. 65*, 12. See also, Yoshikoshi, A.; Miyashita, M. *Acc. Chem. Res.* ***1985***, *18*, 284.

[1056] Loh, T.-P.; Wei, L.-L. *Tetrahedron* ***1998***, *54*, 7615.

[1057] Tucker, J.A.; Clayton, T.L.; Mordas, D.M. *J. Org. Chem.* ***1997***, *62*, 4370.

[1058] Kabbara, J.; Flemming, S.; Nickisch, K.; Neh, H.; Westermann, J. *Tetrahedron* ***1995***, *51*, 743.

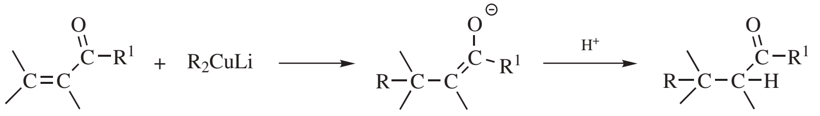
[1059] Ranu, B.C.; Saha, M.; Bhar, S. *Tetrahedron Lett.* ***1993***, *34*, 1989.

[1060] See Heathcock, C.H.; Uehling, D.E. *J. Org. Chem.* ***1986***, *51*, 279; Mukaiyama, T.; Tamura, M.; Kobayashi, S. *Chem. Lett.* ***1986***, 1017, 1817, 1821; ***1987***, 743.

[1061] Yasuda, M.; Ohigashi, N.; Shibata, I.; Baba, A. *J. Org. Chem.* ***1999***, *64*, 2180; Yasuda, M.; Chiba, K.; Ohigashi, N.; Katoh, Y.; Baba, A. *J. Am. Chem. Soc.* ***2003***, *125*, 7291.

15-25 1,4 Addition of Organometallic Compounds to Activated Double Bonds

Hydro-alkyl-addition



143

Lithium dialkylcopper reagents (see **10-57**) add to α,β-unsaturated aldehydes[1062] and ketones (R′ =H, R, Ar) to give conjugate addition products[1063] in a reaction closely related to the Michael reaction. α,β-Unsaturated esters are less reactive,[1064] and the corresponding acids do not react at all. R can be primary alkyl, vinylic,[1065] 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 **143** (see **12-17**).[1066] The use of Me_3SiCl also permits good yields with allylic R groups.[1067] Conjugated alkynyl-ketones also react via 1,4-addition to give substituted alkenyl-ketones.[1068]

Various functional groups, such as OH and unconjugated C=O groups, may be present in the substrate.[1069] Conjugated sulfones are also good substrates.[1070] An excess of the cuprate reagent relative to the conjugated substrate is often required. In general, 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 **12-36**) is expensive or available in limited amounts, particularly if an excess of the reagent

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[1062] For reviews, see Alexakis, A.; Chuit, C.; Commerçon-Bourgain, M.; Foulon, J.P.; Jabri, N.; Mangeney, P.; Normant, J.F. *Pure Appl. Chem.* ***1984***, *56*, 91.

[1063] House, H.O.; Respess, W.L.; Whitesides, G.M. *J. Org. Chem.* ***1966***, *31*, 3128. For reviews, see Posner, G.H. *Org. React.* ***1972***, *19*, 1; House, H.O. *Acc. Chem. Res.* ***1976***, *9*, 59. For a discussion of the mechanism and regioselectivity, see Yamanaka, M.; Kato, S.; Nakamura, E. *J. Am. Chem. Soc.* ***2004***, *126*, 6287. For examples of the use of this reaction in the synthesis of natural products, see Posner, G.H. *An Introduction to Synthesis Using Organocopper Reagents*, Wiley, NY, ***1980***, pp. 10–67. For a list of organocopper reagents that give this reaction, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 1599–1613, 1814–1824.

[1064] R_2CuLi also add to *N*-tosylated α,β-unsaturated amides: Nagashima, H.; Ozaki, N.; Washiyama, M.; Itoh, K. *Tetrahedron Lett.* ***1985***, *26*, 657.

[1065] Bennabi, S.; Narkunan, K.; Rousset, L.; Bouchu, D.; Ciufolini, M.A. *Tetrahedron Lett.* ***2000***, *41*, 8873.

[1066] Corey, E.J.; Boaz, N.W. *Tetrahedron Lett.* ***1985***, *26*, 6019; Alexakis, A.; Berlan, J.; Besace,Y. *Tetrahedron Lett.* ***1986***, *27*, 1047; Matsuza, S.; Horiguchi, Y.; Nakamura, E.; Kuwajima, I. *Tetrahedron* ***1989***, *45*, 349; Horiguchi, Y.; Komatsu, M.; Kuwajima, I. *Tetrahedron Lett.* ***1989***, *30*, 7087; Linderman, R.J.; McKenzie, J.R. *J. Organomet. Chem.* ***1989***, *361*, 31; Bertz, S.H.; Smith, R.A.J. *Tetrahedron* ***1990***, *46*, 4091. For a list of references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 1491–1492.

[1067] Lipshutz, B.H.; Ellsworth, E.L.; Dimock, S.H.; Smith, R.A.J. *J. Am. Chem. Soc.* ***1990***, *112*, 4404; Lipshutz, B.H.; James, B. *Tetrahedron Lett.* ***1993***, *34*, 6689.

[1068] Degl'Innocenti, A.; Stucchi, E.; Capperucci, A.; Mordini, A.; Reginato, G.; Ricci, A. *Synlett* ***1992***, *329*, 332.

[1069] For the use of enol tosylates of 1,2-diketones as substrates, see Charonnat, J.A.; Mitchell, A.L.; Keogh, B.P. *Tetrahedron Lett.* ***1990***, *31*, 315.

[1070] Domínguez, E.; Carretero, J.C. *Tetrahedron Lett.* ***1993***, *34*, 5803.

is required. The difficulty of group transfer can be overcome by using one of the mixed reagents $R(R'C{\equiv}C)CuLi$,[1071] $R(O{-}t{-}Bu)CuLi$,[1072] $R(PhS)CuLi$,[1073] each of which transfers only the R group. Mixed 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 $R(CN)CuLi$[1074] (prepared from RLi and CuCN) and $R_2Cu(CN)Li_2$[1075] also selectively transfer the R group.[1076] Other mixed reagents incorporate a ligand that is not easily transferred, such as $R(R'Se)Cu(CN)Li_2$, leading to selective transfer of the R group.[1077] The reaction has also been carried out[1078] with α,β-acetylenic ketones,[1079] esters, and nitriles.

Both Grignard and R_2CuLi reagents[1080] have also been added to systems of the form $C{\equiv}C{-}C{=}O$.[1081] 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 $RCu{\bullet}BF_3$ (R = primary).[1082] 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.[1083] Amine units have been transferred in this manner using α-lithio amides, CuCN, and additives ranging from LiCl to $Me_2NCH_2SnBu_3$, which gave conjugate addition of an amidomethyl unit, $-CH_2N(Me)Boc$.[1084] Other amino-cuprates are known to give conjugate addition reactions.[1085]

[1071] House, H.O.; Umen, M.J. *J. Org. Chem.* ***1973***, *38*, 3893; Corey, E.J.; Floyd, D.; Lipshutz, B.H. *J. Org. Chem.* ***1978***, *43*, 3419.

[1072] Posner, G.H.; Whitten, C.E. *Tetrahedron Lett.* ***1973***, 1815.

[1073] Posner, G.H.; Whitten, C.E.; Sterling, J.J. *J. Am. Chem. Soc.* ***1973***, *95*, 7788.

[1074] Gorlier, J.; Hamon, L.; Levisalles, J.; Wagnon, J. *J. Chem. Soc., Chem. Commun.* ***1973***, 88. For another useful mixed reagent, see Ledlie, D.B.; Miller, G. *J. Org. Chem.* ***1979***, *44*, 1006.

[1075] Lipshutz, B.H.; Wilhelm, R.S.; Kozlowski, J. *Tetrahedron Lett.* ***1982***, *23*, 3755; Lipshutz, B.H. *Tetrahedron Lett.* ***1983***, *24*, 127.

[1076] When the two R groups of $R_2Cu(CN)Li_2$ are different, one can be selectively transferred: Lipshutz, B.H.; Wilhelm, R.S.; Kozlowski, J.A. *J. Org. Chem.* ***1984***, *49*, 3938.

[1077] Zinn, F.K.; Ramos, E.C.; Comasseto, J.V. *Tetahedron Lett.* ***2001***, *42*, 2415.

[1078] For a list of references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 456–457.

[1079] Lee, P.H.; Park, J.; Lee, K.; Kim, H.-C. *Tetrahedron Lett.* ***1999***, *40*, 7109.

[1080] For example, see Corey, E.J.; Kim, C.U.; Chen, H.K.; Takeda, M. *J. Am. Chem. Soc.* ***1972***, *94*, 4395; Anderson, R.J.; Corbin, V.L.; Cotterrell, G.; Cox, G.R.; Henrick, C.A.; Schaub, F.; Siddall, J.B. *J. Am. Chem. Soc.* ***1975***, *97*, 1197.

[1081] For a review of the addition of organometallic reagents to conjugated enynes see Miginiac, L. *J. Organomet. Chem.* ***1982***, *238*, 235.

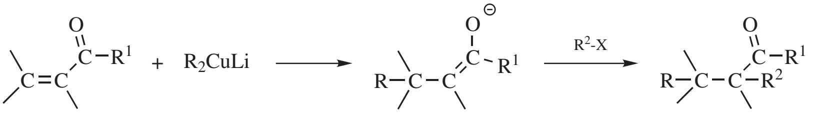
[1082] For a review, see Yamamoto, Y. *Angew. Chem. Int. Ed.* ***1986***, *25*, 947. For a discussion of the role of the BF_3, see Lipshutz, B.H.; Ellsworth, E.L.; Siahaan, T.J. *J. Am. Chem. Soc.* ***1988***, *110*, 4834; ***1989***, *111*, 1351.

[1083] Johnson, C.R.; Marren, T.J. *Tetrahedron Lett.* ***1987***, *28*, 27.

[1084] Dieter, R.K.; Velu, S.E. *J. Org. Chem.* ***1997***, *62*, 3798; Dieter, R.K.; Alexander, C.W. *Synlett* ***1993***, 407; Dieter, R.K.; Alexander, C.W.; Nice, L.E. *Tetrahedron* ***2000***, *56*, 2767; Dieter, R.K.;Lu, K.; Velu, S.E. *J. Org. Chem.* ***2000***, *65*, 8715. See Dieter, R.K.; Topping, C.M.; Nice, L.E. *J. Org. Chem.* ***2001***, *66*, 2302.

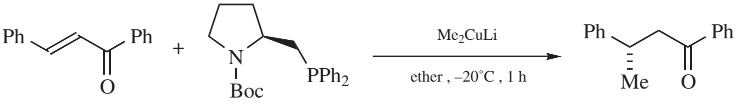
[1085] Yamamoto, Y.; Asao, N.; Uyehara, T. *J. Am. Chem. Soc.* ***1992***, *114*, 5427.

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.[1086] R_2CuLi also add to α,β-unsaturated sulfones[1087] but not to simple α,β-unsaturated nitriles.[1088] Organocopper reagents (RCu), as well as certain R_2CuLi add to α,β-unsaturated and acetylenic sulfoxides.[1089]



143

Conjugate addition of the cuprate to the α,β-unsaturated ketone leads to an enolate ion, **143**. It is possible to have this enolate anion reacts with an electrophilic species (*tandem vicinal difunctionalization*), in some cases at the O and in other cases at the C.[1090] For example, if an alkyl halide R^2X is present (R^2 = primary alkyl or allylic), the enolate **143** can be alkylated directly.[1091] Thus, by this method, both the α and β positions of a ketone are alkylated in one synthetic operation (see also, **15-22**).



144

79% (84% ee , S)

As with the Michael reaction (**15-24**) the 1,4-addition of organometallic compounds has been performed diastereoselectively[1092] and enantioselectively.[1093]

[1086] House, H.O.; Fischer, Jr., W.F. *J. Org. Chem.* ***1969***, *34*, 3615. See also, Daviaud, G.; Miginiac, P. *Tetrahedron Lett.* ***1973***, 3345.

[1087] Posner, G.H.; Brunelle, D.J. *Tetrahedron Lett.* ***1973***, 935.

[1088] House, H.O.; Umen, M.J. *J. Org. Chem.* ***1973***, *38*, 3893.

[1089] Truce, W.E.; Lusch, M.J. *J. Org. Chem.* ***1974***, *39*, 3174; ***1978***, *43*, 2252.

[1090] For reviews of such reactions, see Chapdelaine, M.J.; Hulce, M. *Org. React.* ***1990***, *38*, 225; Taylor, R.J.K. *Synthesis* ***1985***, 364. For a list of references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 1609–1612, 1826.

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The influence of solvent and additives on yield and selectivity has been examined.[1094] The conjugate addition of dimethyl cuprate in the presence of a chiral ligand, such as **144**, is an example.[1095] The use of chiral ligands with MgI_2/I_2 and Bu_3SnI gave conjugate addition products with α,β-unsaturated amides with good % ee.[1096] Chiral bis(oxazoline) copper catalysts have been used for the conjugate addition of indoles to α,β-unsaturated esters.[1097] Chiral templates have also been used with Grignard reagents, directly[1098] and in the presence of $AlMe_2Cl$.[1099] Many of the examples cited below involve the use of chiral additives, chiral catalysts, or chiral templates.

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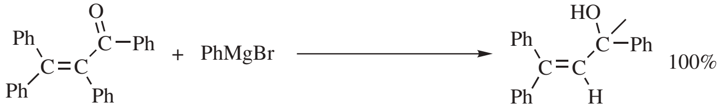

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Grignard reagents also add to conjugated substrates such as α,β-unsaturated ketones, cyano-ketones,[1100] esters, and nitriles,[1101] but 1,2-addition may seriously compete:[1102] The product is often controlled by steric factors. Thus **145** with phenylmagnesium bromide gives 100% 1,4-addition, while **146** 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, for example, CuCl, $Cu(OAc)_2$.[1103] A dialkyl copper–magnesium iodide complex ($R_2Cu{\bullet}MgI$) has been used for conjugate addition to chiral α,β-unsaturated amides.[1104] Grignard reagents mixed with $CeCl_3$ generates a reactive species that gives primarily 1,4-addition.[1105] It is likely that alkylcopper reagents, formed from RMgX and

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Cu^+ (cupric acetate is reduced to cuprous ion by excess RMgX), are the actual attacking species in these cases.[1063] Alkylidene malonic ester derivatives, $C{=}C(CO_2R)$, increase the facility of 1,4-addition with the two electron withdrawing groups.[1106] Alkylidene amido esters, $C{=}C(CO_2R)NHCOAr$, react with $EtI/Mg(ClO_4)_2$ and Bu_3SnH, in the presence of BEt_3/O_2 and a chiral ligand, to give the ethylated product $EtCHCH(CO_2R)NHCOAr$.[1107] This is probably a radical process (see **15-35**).

Organolithium reagents[1108] generally react with conjugated aldehydes, ketones and esters by 1,2-addition,[1109] but 1,4-addition was achieved with esters of the form C=C–COOAr, where Ar was a bulky group such as 2,6-di-*tert*-butyl-4-methoxyphenyl.[1110] Alkyllithium reagents can be made to give 1,4-addition with α,β-unsaturated ketones[1111] and aldehydes[1112] if the reactions are conducted in the presence of HMPA.[1113] Among organolithium reagents that have been found to add 1,4 in this manner are 2-lithio-1,3-dithianes (see **10-71**),[1114] vinyllithium reagents,[1115] and α-lithio allylic amides.[1116] Lithium–halogen exchange (**12-22**) generates an organolithium species that adds intramolecularly to conjugated esters to give cyclic and bicyclic products.[1117] 1,4-Addition of alkyllithium reagents to α,β-unsaturated aldehydes can also be achieved by converting the aldehyde to a benzothiazole derivative (masking the aldehyde function),[1118] from which the aldehyde group can be regenerated. When some conjugated acids are added to organolithium reagents, the conjugate addition product was isolated in good yield.[1119] α,β-Unsaturated nitro compounds undergo conjugate addition with aryllithium reagents, and subsequent treatment with acetic acid gives the α-aryl ketone.[1120]

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[1116] For an example using sparteine as a chiral additive, see Curtis, M.D.; Beak, P. *J. Org. Chem.* ***1999***, *64*, 2996.

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If the organolithium reagent is modified, 1,4-addition is more successful. The reaction of an aryllithium reagent with $B(OMe)_3$, for example, led to a rhodium-catalyzed conjugate addition with excellent enantioselectivity in when a chiral ligand was employed.[1121] Allylic tellurium reagents that are treated with lithium diisopropyl amide, and then conjugated esters give the 1,4-addition product, which cyclizes to form the corresponding cyclopropane derivative.[1122]

Boron reagents add to conjugated carbonyl compounds.[1123] Alkynyl borate esters (p. 815) give conjugate addition in the presence of boron trifluoride etherate,[1124] as do arylboronic acids (p. 815) with a rhodium,[1125] palladium,[1126] or a bismuth catalyst.[1127] Diethylzinc has also been used.[1128] Aryl boronic acids add to the double bond of vinyl sulfones in the presence of a rhodium catalyst.[1129] Similarly, $LiBPh(OMe)_3$ and a rhodium catalyst gave conjugate addition of the phenyl group to α,β-unsaturated esters.[1130] Potassium vinyltrifluoroborates (see p. 607) give 1,4-addition with a rhodium catalyst,[1131] as do aryltrifluoroborates.[1132]

Organozinc compounds add to conjugated systems. The use of chiral ligands is effective for conjugate addition of dialkylzinc compounds to α,β-unsaturated ketones, esters, and so on,[1133] including conjugated lactones.[1134] Many dialkylzinc compounds can be used, including vinylzinc compounds.[1135] Dialkylzinc

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[1135] For an example using a nickel catalyst with a chiral ligand, see Ikeda, S.-i.; Cui, D.-M.; Sato, Y. *J. Am. Chem. Soc.* ***1999***, *121*, 4712.

compounds and a chiral complex leads to enantioselective conjugate addition in conjunction with $Cu(OTf)_2$[1136] or other copper compounds.[1137] Diethylzinc adds to conjugated nitro compounds in the presence of a catalytic amount of $Cu(OTf)_2$ to give the conjugate addition product.[1138] Other transition-metal compounds can be used in conjunction with dialkylzinc compounds[1139] or with arylzinc halides (ArZnCl).[1140] Reaction of alkyl iodides with Zn/CuI with ultrasound generates an organometallic that adds to conjugated esters.[1141] 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.[1142] Mixed alkylzinc compounds also add to conjugated systems.[1143] Functionalized allylic groups can be added to terminal alkynes with allylic halides, zinc, and ultrasound, to give 1,4-dienes.[1144] Internal alkynes undergo 1,4-addition to conjugated esters using a combination of zinc metal and a cobalt complex as catalysts.[1145]

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Trialkylalanes R_3Al add 1,4 to α,β-unsaturated carbonyl compounds in the presence of nickel acetylacetonate[1146] or $Cu(OTf)_2$.[1147] In the presence of aluminum chloride, benzene reacts with conjugated amides to add a phenyl group to C-4.[1148] Alkyl halides react via conjugate addition using BEt_3 or $AlEt_3$.[1149] An alkynyl group can be added to the double bond of an α,β-unsaturated ketone by use of the diethylalkynylalane reagents $Et_2AlC{\equiv}CR$.[1150] In a similar manner, the alkenyl reagents $R_2AlCH{=}CR$ transfer an alkenyl group.[1151]

Terminal alkynes add to conjugated systems when using a ruthenium,[1152] palladium,[1153] or a rhodium catalyst.[1154] Triphenylbismuth (Ph_3Bi) and a rhodium catalyst gives conjugate addition of the phenyl group upon exposure to air.[1155] Similar reactivity is observed with a palladium catalyst in aqueous media.[1156] Lithium tetraalkylgallium reagents give 1,4-addition.[1157] Trimethyl(phenyl)tin and a rhodium catalyst gives conjugate addition of a methyl group[1158] and tetraphenyltin and a palladium catalyst adds a phenyl group.[1159] Allyltin compounds add an allyl group in the presence of a scandium catalyst.[1160] Benzylic bromides add to conjugated nitriles using a 2:1 mixture of $CrCl_3$ and manganese metal.[1161] Electrochemical conjugate addition to α,β-unsaturated ketones was reported using aryl halides and a cobalt catalyst.[1162] Aryl halides add in the presence of $NiBr_2$.[1163] Vinyl zirconium complexes undergo conjugate addition when using a rhodium catalyst.[1164] Pyrrole adds to conjugated alkynyl esters in the presence

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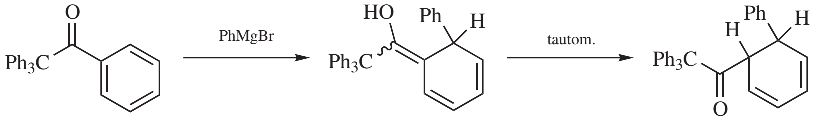
[1163] Condon, S.; Dupré, D.; Falgayrac, G.; Nédélec, J.-Y. *Eur. J. Org. Chem.* ***2002***, 105.

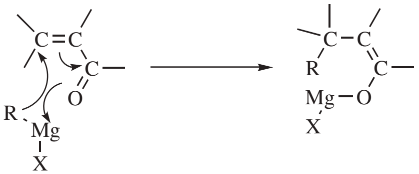
[1164] Kakuuchi, A.; Taguchi, T.; Hanzawa, Y. *Tetrahedron* ***2004***, *60*, 1293.

of palladium acetate, to give the 2-alkenyl pyrrole.[1165]



147

In certain cases, Grignard reagents add 1,4 to *aromatic* systems to give **147** after tautomerization (p. $$$) of the initial formed enol.[1166] 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 where 1,3,5-trinitrobenzene reacts with excess methylmagnesium halide to give 2,4,6-trinitro-1,3,5-trimethylcyclohexane.[1167]



The mechanisms of most of these reactions are not well known. The 1,4 uncatalyzed Grignard reaction has been postulated to proceed by the cyclic mechanism shown, but there is evidence against it.[1168] The R_2CuLi[1169] and copper-catalyzed Grignard additions may involve a number of mechanisms, since the actual attacking species and substrates are so diverse.[1170] A free-radical mechanism of some type

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[1165] Lu, W.; Jia, C.; Kitamura, T.; Fujiwara, Y. *Org. Lett.* ***2000***, *2*, 2927.

[1166] This example is from Schmidlin, J.; Wohl, J. *Ber.* ***1910***, *43*, 1145; Mosher, W.A.; Huber, M.B. *J. Am. Chem. Soc.* ***1953***, *75*, 4604. For a review of such reactions see Fuson, R.C. *Adv. Organomet. Chem.* ***1964***, *1*, 221.

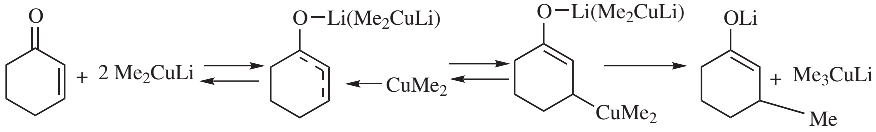
[1167] Severin, T.; Schmitz, R. *Chem. Ber.* ***1963***, *96*, 3081. See also, Bartoli, G. *Acc. Chem. Res.* ***1984***, *17*, 109; Bartoli, G.; Dalpozzo, R.; Grossi, L. *J. Chem. Soc. Perkin Trans. 2*, ***1989***, 573. For a study of the mechanism, see Bartoli, G.; Bosco, M.; Cantagalli, G.; Dalpozzo, R.; Ciminale, F. *J. Chem. Soc. Perkin Trans. 2*, ***1985***, 773.

[1168] House, H.O.; Thompson, H.W. *J. Org. Chem.* ***1963***, *28*, 360; Klein, J. *Tetrahedron* ***1964***, *20*, 465. See, however, Marets, J.; Rivière, H. *Bull. Soc. Chim. Fr.* ***1970***, 4320.

[1169] See Kingsbury, C.L.; Smith, R.A.J. *J. Org. Chem.* ***1997***, *62*, 4629. Also see, Bertz, S.H.; Miao, G.; Rossiter, B.E.; Snyder, J.P. *J. Am. Chem. Soc.* ***1995***, *117*, 11023; Snyder, J.P. *J. Am. Chem. Soc.* ***1995***, *117*, 11025; Vellekoop, A.S.; Smith, R.A.J. *J. Am. Chem. Soc.* ***1994***, *116*, 2902.

[1170] For some mechanistic investigations, see Berlan, J.; Battioni, J.; Koosha, K. *J. Organomet. Chem.* ***1978***, *152*, 359; *Bull. Soc. Chim. Fr.* ***1979***, II-183; Four, P.; Riviere, H.; Tang, P.W. *Tetrahedron Lett.* ***1977***, 3879; Casey, C.P.; Cesa, M.C. *J. Am. Chem. Soc.* ***1979***, *101*, 4236; Krauss, S.R.; Smith, S.G. *J. Am. Chem. Soc.* ***1981***, *103*, 141; Bartoli, G.; Bosco, M.; Dal Pozzo, R.; Ciminale, F. *J. Org. Chem.* ***1982***, *47*, 5227; Corey, E.J.; Boaz, N.W. *Tetrahedron Lett.* ***1985***, *26*, 6015; Yamamoto, Y.; Yamada, J.; Uyehara, T. *J. Am. Chem. Soc.* ***1987***, *109*, 5820; Ullenius, C.; Christenson, B. *Pure Appl. Chem.* ***1988***, *60*, 57; Christenson, B.; Olsson, T.; Ullenius, C. *Tetrahedron* ***1989***, *45*, 523; Krause, N. *Tetrahedron Lett.* ***1989***, *30*, 5219.

(perhaps SET) has been suggested[1171] although the fact that retention of configuration at R has been demonstrated in several cases rules out a completely free R• radical.[1172] For simple α,β-unsaturated ketones, such as 2-cyclohexenone, and Me_2CuLi, there is evidence[1173] for this mechanism:



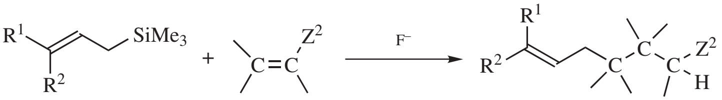
148

148 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.[1173] The ^{13}C NMR spectrum of an intermediate similar to **148** has been reported.[1174]

For the addition of organocopper reagents to alkynes and conjugated dienes, see **15-22**.

OS **IV**, 93; **V**, 762; **VI**, 442, 666, 762, 786; **VIII**, 112, 257, 277, 479; **IX**, 328, 350, 640.

15-26 The Sakurai Reaction



Allylic silanes $R_2C{=}CHCH_2SiMe_3$ can be used instead of silyl enol ethers (the *Sakurai reaction*).[1175] An allyl group can be added, to α,β-unsaturated carboxylic esters, amides and nitriles, with $CH_2{=}CHCH_2SiMe_3$ and F^- ion (see **15-47**).[1176] This reagent gave better results than lithium diallylcuprate (**15-25**). Catalytic Sakurai reactions are known.[1177] The palladium catalyzed reaction of conjugated ketones with $PhSi(OEt)_3$ with $SbCl_3$ and Bu_4NF in acetic acid gave the 1,4-addition product.[1178] A similar reaction was reported using $PhSi(OMe)_3$

[1171] See, for example, Ruden, R.A.; Litterer, W.E. *Tetrahedron Lett.* ***1975***, 2043; House, H.O.; Snoble, K.A.J. *J. Org. Chem.* ***1976***, *41*, 3076; Wigal, C.T.; Grunwell, J.R.; Hershberger, J. *J. Org. Chem.* ***1991***, *56*, 3759.

[1172] Näf, F.; Degen, P. *Helv. Chim. Acta* ***1971***, *54*, 1939; Whitesides, G.M.; Kendall, P.E. *J. Org. Chem.* ***1972***, *37*, 3718. See also, Ref. 1063.

[1173] Corey, E.J.; Hannon, F.J.; Boaz, N.W. *Tetrahedron* ***1989***, *45*, 545.

[1174] Bertz, S.H.; Smith, R.A.J. *J. Am. Chem. Soc.* ***1989***, *111*, 8276.

[1175] Hosomi, A.; Sakurai, H. *J. Am. Chem. Soc.* ***1977***, *99*, 1673; Jellal, A.; Santelli, M. *Tetrahedron Lett.* ***1980***, *21*, 4487; Sakurai, H.; Hosomi, A.; Hayashi, J. *Org. Synth.* ***VII***, 443; Kuhnert, N.; Peverley, J.; Robertson, J. *Tetrahedron Lett.* ***1998***, *39*, 3215. For a review, see Fleming, I.; Dunoguès, J.; Smithers, R. *Org. React.* ***1989***, *37*, 57, see pp. 127, 335–370. For a review of intramolecular additions, see Schinzer, D. *Synthesis* ***1988***, 263.

[1176] Majetich, G.; Casares, A.; Chapman, D.; Behnke, M. *J. Org. Chem.* ***1986***, *51*, 1745.

[1177] $InCl_3$: Lee, P.H.; Lee, K.; Sung, S.-y.; Chang, S. *J. Org. Chem.* ***2001***, *66*, 8646.

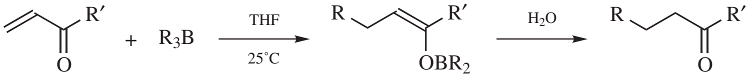
[1178] Denmark, S.E.; Amishiro, N. *J. Org. Chem.* ***2003***, *68*, 6997.

with a rhodium catalyst.[1179] In a related reaction, Ph_2SiCl_2, NaF and a rhodium catalyst gives conjugate addition of a phenyl group to α,β-unsaturated ketones.[1180] An interesting rhodium-catalyzed, conjugate addition of a phenyl group was reported using a siloxane polymer bearing Si—Ph units.[1181]

Silyl ketene acetals, RCH=C(OMe)$OSiMe_3$, add to conjugated ketones to give δ-keto esters, in $MeNO_2$ as solvent.[1182]

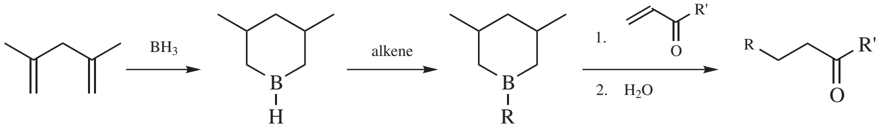
15-27 Conjugate Addition of Boranes to Activated Double Bonds

Hydro-alkyl-addition (overall transformation)



R′ = H, Me

Just as trialkylboranes add to simple alkenes (**15-16**), they 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 (also see, p. 631), which can be hydrolyzed to aldehydes or ketones.[1183] If water is present in the reaction medium from the beginning, the reaction can be run in one laboratory step. Since the boranes can be prepared from alkenes (**15-16**), 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 (CH_3CH=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.[1184] A disadvantage is



149

[1179] Oi, S.; Honma, Y.; Inoue, Y. *Org. Lett.* ***2002***, *4*, 667; Oi, S.; Taira, A.; Honma, Y.; Inoue, Y. *Org. Lett.* ***2003***, *5*, 97.

[1180] Huang, T.-S.; Li, C.-J. *Chem. Commun.* ***2001***, 2348.

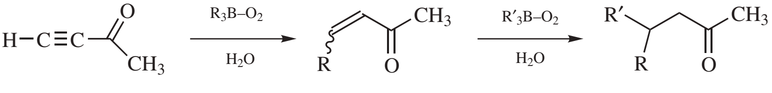
[1181] Koike, T.; Du, X.; Mori, A.; Osakada, K. *Synlett* ***2002***, 301.

[1182] RajanBabu, T.V. *J. Org. Chem.* ***1984***, *49*, 2083.

[1183] Suzuki, A.; Arase, A.; Matsumoto, H.; Itoh, M.; Brown, H.C.; Rogić, M.M.; Rathke, M.W. *J. Am. Chem. Soc.* ***1967***, *89*, 5708; Köster, R.; Zimmermann, H.; Fenzl, W. *Liebigs Ann. Chem.* ***1976***, 1116. For reviews, see Pelter, A.; Smith, K.; Brown, H.C. *Borane Reagents*, Academic Press, NY, ***1988***, pp. 301–305, 318–323; Brown, H.C.; Midland, M.M. *Angew. Chem. Int. Ed.* ***1972***, *11*, 692, sse pp. 694–698; Kabalka, G.W. *Intra-Sci. Chem. Rep.* ***1973***, *7(1)*, 57; Brown, H.C. *Boranes in Organic Chemistry*, Cornell University Press, Ithica, NY, ***1972***, pp. 413–433.

[1184] Brown, H.C.; Kabalka, G.W. *J. Am. Chem. Soc.* ***1970***, *92*, 712, 714. See also, Utimoto, K.; Tanaka, T.; Furubayashi, T.; Nozaki, H. *Tetrahedron Lett.* ***1973***, 787; Miyaura, N.; Kashiwagi, M.; Itoh, M.; Suzuki, A. *Chem. Lett.* ***1974***, 395.

that only one of the 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 β-alkyl borinate, such as **149**,[1185] which can be prepared as shown. **149** (R = *tert*-butyl) can be made by treatment of **149** (R = OMe) with *t*-BuLi. The use of this reagent permits *tert*-butyl groups to be added. β-1-Alkenyl-9-BBN compounds β-RCH = CR′-9-BBN (prepared by treatment of alkynes with 9-BBN or of RCH=CR′Li with β-methoxy-9-BBN[1186]) add to methyl vinyl ketones to give, after hydrolysis, γ,δ-unsaturated ketones,[1187] although β-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.[1184] The corresponding β-1-alkynyl-9-BBN compounds also give the reaction.[1188] Like the three substrates mentioned above, 3-butyn-2-one fails to react in the absence of air, but undergoes the reaction when exposed to a slow stream of air:[1189] Since the product, **150**, 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 **151**.



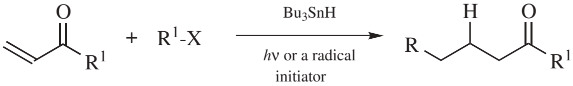
150 **151**

Vinyl boranes add to conjugated ketones in the presence of a rhodium catalyst (with high asymmetric induction in the presence of BINAP).[1190] Alkynyl-boranes also add to conjugated ketones, in the presence of BF_3.[1191]

The fact that these reactions are catalyzed by free-radical initiators and inhibited by galvinoxyl[1192] (a free-radical inhibitor) indicates that free-radical mechanisms are involved.

15-28 Radical Addition to Activated Double Bonds

Hydro-alkyl-addition



[1185] Brown, H.C.; Negishi, E. *J. Am. Chem. Soc.* ***1971***, *93*, 3777.

[1186] Brown, H.C.; Bhat, N.G.; Rajagopalan, S. *Organometallics* ***1986***, *5*, 816.

[1187] Jacob III, P.; Brown, H.C. *J. Am. Chem. Soc.* ***1976***, *98*, 7832; Satoh, Y.; Serizawa, H.; Hara, S.; Suzuki, A. *J. Am. Chem. Soc.* ***1985***, *107*, 5225. See also, Molander, G.A.; Singaram, B.; Brown, H.C. *J. Org. Chem.* ***1984***, *49*, 5024. Alkenyldialkoxyboranes, together with BF_3–etherate, also transfer vinylic groups: Hara, S.; Hyuga, S.; Aoyama, M.; Sato, M.; Suzuki, A. *Tetrahedron Lett.* ***1990***, *31*, 247.

[1188] Sinclair, J.A.; Molander, G.A.; Brown, H.C. *J. Am. Chem. Soc.* ***1977***, *99*, 954. See also, Molander, G.A.; Brown, H.C. *J. Org. Chem.* ***1977***, *42*, 3106.

[1189] Suzuki, A.; Nozawa, S.; Itoh, M.; Brown, H.C.; Kabalka, G.W.; Holland, G.W. *J. Am. Chem. Soc.* ***1970***, *92*, 3503.

[1190] Takaya, Y.; Ogasawara, M.; Hayashi, T. *Tetrahedron Lett.* ***1998***, *39*, 8479.

[1191] Fujishima, H.; Takada, E.; Hara, S.; Suzuki, A. *Chem. Lett.* ***1992***, 695.

[1192] Kabalka, G.W.; Brown, H.C.; Suzuki, A.; Honma, S.; Arase, A.; Itoh, M. *J. Am. Chem. Soc.* ***1970***, *92*, 710. See also, Arase, A.; Masuda, Y.; Suzuki, A. *Bull. Chem. Soc. Jpn.* ***1976***, *49*, 2275.

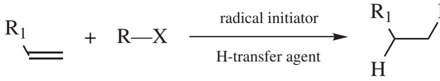
In a reaction similar to **15-25**, alkyl groups can be added to alkenes activated by, such groups as COR′, COOR′, CN, and even Ph.[1193] In the method illustrated above, the R group comes from an alkyl halide (R = primary, secondary, or tertiary alkyl; X = Br or I) and the hydrogen from the tin hydride. The reaction of *tert*-butyl bromide, Bu_3SnH and AIBN (p. 935), for example, adds a *tert*-butyl group to a conjugated ester via 1,4-addition.[1194] An alkene is converted to an alkylborane with catecholborane (p. 817) and when treated with a conjugated ketone and O_2, radical conjugate addtion leads to the β-substituted ketone.[1195] Organomercury hydrides (RHgH) generated *in situ* from RHgX and $NaBH_4$, can also be used.[1196] 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 $CH_2{=}CCl_2$), but the mercury method uses milder reaction conditions. Like **15-27**, these additions have free-radical mechanisms. The reaction has been used for free-radical cyclizations of the type discussed on p. 1125.[1197] Such cyclizations normally give predominant formation of 15-membered rings, but large rings (11–20 members) have also been synthesized by this reaction.[1198]

Free-radical addition of an aryl group and a hydrogen has been achieved by treatment of activated alkenes with a diazonium salt and $TiCl_3$.[1199] The addition of R_3Al takes place by a free-radical mechanism.[1146]

OS **VII**, 105.

15-29 Radical Addition to Unactivated Double Bonds[1200]

Alkyl-hydro-addition



[1193] For reviews, see Giese, B. *Radicals in Organic Synthesis: Formation of Carbon–Carbon Bonds*, Pergamon, Elmsford, NY, ***1986***, pp. 36–68; Giese, B. *Angew. Chem. Int. Ed.* ***1985***, *24*, 553; Larock, R.C. *Organomercury Compounds in Organic Synthesis*, Springer, NY, ***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 Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 1809–1813.

[1194] Hayen, A.; Koch, R.; Metzger, J.O. *Angew. Chem. Int. Ed.* ***2000***, *39*, 2758.

[1195] Ollivier, C.; Renaud, P. *Chem. Eur. J.* ***1999***, *5*, 1468.

[1196] For the use of tris(trimethylsilyl)silane, see Giese, B.; Kopping, B.; Chatgilialoglu, C. *Tetrahedron Lett.* ***1989***, *30*, 681.

[1197] For reviews, see Jasperse, C.P.; Curran, D.P.; Fevig, T.L. *Chem. Rev.* ***1991***, *91*, 1237; Curran, D.P. *Adv. Free Radical Chem. (Greenwich, Conn.)* ***1990***, *1*, 121; Giese, B. *Radicals in Organic Synthesis: Formation of Carbon-Carbon Bonds*, Pergamon, Elmsford, NY, ***1986***, pp. 151–169. For a list of references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 413–418.

[1198] See Porter, N.A.; Chang, V.H. *J. Am. Chem. Soc.* ***1987***, *109*, 4976.

[1199] Citterio, A.; Vismara, E. *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, S.; Palmieri, G. *Synthesis* ***1984***, 575; Lebedev, S.A.; Lopatina, V.S.; Berestova, S.S.; Petrov, E.S.; Beletskaya, I.P. *J. Org. Chem. USSR* ***1986***, *22*, 1238; Luche, J.L.; Allavena, C. *Tetrahedron Lett.* ***1988***, *29*, 5369; Varea, T.; González-Núñez, M.E.; Rodrigo-Chiner, J.; Asensio, G. *Tetrahedron Lett.* ***1989***, *30*, 4709; Barton, D.H.R.; Sarma, J.C. *Tetrahedron Lett.* ***1990***, *31*, 1965.

[1200] See Smith, M.B. *Organic Synthesis,* 2nd ed., McGraw-Hill, NY ***2001***, pp. 1167–1172

Radical addition to alkenes is usually difficult, except when addition occurs to conjugated carbonyl compounds (**15-24**). An important exception involves radicals bearing a heteroatom α to the carbon bearing the radical center. These radical are much more stable and can add to alkenes, usually with anti-Markovnikov orientation, as in the radical induced addition of HBr to alkenes (**15-2**).[1201] Examples of this type of reaction include the use of alcohol-, ester-,[1202] amino-, and aldehyde-stabilized radicals.[455] Carbon tetrachloride can be cleaved homolytically to generate Cl• and Cl_3C•, which can add to alkenes. The alkyl group of alkyl iodides adds to alkenes with BEt_3/O_2 as the initiator and in the presence of a tetraalkylammonium hypophosphite.[1203] When chloroform was treated with a ruthenium carbene complex, Cl_2CH add to the less substituted carbon of an alkene, and Cl to the more substituted carbon.[1204] The radical generated from $(EtO)_2POCH_2Br$ adds to alkenes to generate a new phosphonate ester.[1205] α-Bromo esters add to alkenes in the presence of BEt_3/air to give a γ-bromo ester.[1206] α-Bromo amides add the Br and the acyl carbon to an alkene using $Yb(OTf)_3$ with BEt_3/O_2 as the radical initiator.[1207] α-Iodo amides add to alkenes using a water soluble azobis initiator to give the iodo ester, which cyclizes under the reaction conditions to give a lactone.[1208] β-Keto dithiocarbonates, RC(=O)–C–SC(=S)OEt, generate the radical in the presence of a peroxide and add to alkenes.[1209] Malonate derivatives add to alkenes in the presence of a mixture of Mn/Co catalyst, in oxygenated acetic acid.[1210]

Other radicals can add to alkenes, and the rate constant for the addition of methyl radicals to alkenes has been studied,[1211] and the rate of radical additions to alkenes in general has also been studied.[1212] The kinetic and thermodynamic control of a radical addition regiochemistry has also been studied.[1213] Alkynes are generally less reactive than alkenes in radical coupling reactions.[1214] Nonradical nucleophiles usually react faster with alkynes than with alkenes, however.[1215]

[1201] See Curran, D.P. *Synthesis* ***1988***, 489 (see pp. 497–498).

[1202] Deng, L.X.; Kutateladze, A.G. *Tetrahedron Lett.* ***1997***, *38*, 7829.

[1203] Jang, D.O.; Cho, D.H.; Chung, C.-M. *Synlett* ***2001***, 1923.

[1204] Tallarico, J.A.; Malnick, L.M.; Snapper, M.L. *J. Org. Chem.* ***1999***, *64*, 344.

[1205] Baczewski, P.; Mikoajczyk, M. *Synthesis* ***1995***, 392.

[1206] Yorimitsu, H.; Shinokubo, H.; Matsubara, S.; Oshima, K.; Omoto, K.; Fujimoto, H. *J. Org. Chem.* ***2001***, *66*, 7776.

[1207] Mero, C.L.; Porter, N.A. *J. Am. Chem. Soc.* ***1999***, *121*, 5155.

[1208] Yorimitsu, H.; Wakabayashi, K.; Shinokubo, H.; Oshima, K. *Bull. Chem. Soc. Jpn.* ***2001***, *74*, 1963.

[1209] Ouvry, G.; Zard, S.Z. *Chem. Commun.* ***2003***, 778.

[1210] Hirase, K.; Iwahama, T.; Sakaguchi, S.; Ishii, Y. *J. Org. Chem.* ***2002***, *67*, 970.

[1211] Zytowski, T.; Fischer, H. *J. Am. Chem. Soc.* ***1996*** *118*, 437.

[1212] Avila, D.V.; Ingold, K.U.; Lusztyk, J.; Dolbier Jr., W.R.; Pan, H.-Q. *J. Org. Chem.* ***1996***, *61*, 2027.

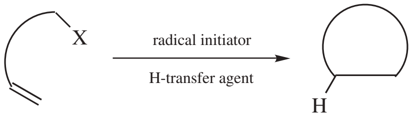
[1213] Leach, A.G.; Wang, R.; Wohlhieter, G.E.; Khan, S.I.; Jung, M.E.; Houk, K.N. *J. Am. Chem. Soc.* ***2003***, *125*, 4271.

[1214] Giese, B.; Lachhein, S. *Angew. Chem. Int. Ed.* ***1982***, *21*, 768; Giese, B.; Meixner, J. *Angew. Chem. Int. Ed.* ***1979*** *18* 154.

[1215] Dickstein, J.I.; Miller, G.I., in *The Chemistry of Carbon Carbon Triple Bonds*, Vol. 2, Patai, S., Ed., Wiley, NY ***1978***.

15-30 Radical Cyclization[1216]

Alkyl-hydro-addition



ω-Haloalkenes generate radicals upon treatment with reagents, such as AIBN or under photolysis conditions,[1217] and the radical carbon adds to the alkene to form cyclic compounds.[1218] This intramolecular addition of a radical to an alkene is called radical cyclization. In a typical example, haloalkene **154** reacts with the radical produced by AIBN to give radical **153**. The radical can add to the more substituted carbon to give **155** via a 5-exo–trig reaction (p. 305).[1219] If the radical adds to the less substituted carbon, **156** is formed via a 6-endo–trig reaction.[1220] In both cases, the product is another radical, which must be converted to an unreactive product. This is generally accomplished by adding a hydrogen transfer agent,[1221] such as tributyltin hydride (Bu_3SnH), which reacts with **155** to form methylcyclopentane and Bu_3Sn•, or with **156** to give cyclohexane. The Bu_3Sn• formed in both cases usually dimerizes to form $Bu_3SnSnBu_3$. Cyclization can compete with hydrogen transfer[1222] of Bu_3SnH to **153** to give **152**, the reduction product. In general, formation of the five-membered ring dominates the cyclization, but if addition to the C=C unit is relatively slow, the reduction product is formed preferentially. Radical rearrangements can also diminish the yield of the desired product.[1223] Given a choice between a larger and a smaller ring, radical cyclization generally gives the smaller ring,[1224] but not

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[1216] See Smith, M.B. *Organic Synthesis*, 2nd ed., McGraw-Hill, NY ***2001***, pp. 1172–1181. For a review of radical-mediated annulation reactions, see Rheault, T.R.; Sibi, M.P. *Synthesis* ***2003***, 803.

[1217] For example, see Pandey, G.; Reddy, G.D.; Chakrabarti, D. *J. Chem. Soc., Perkin Trans. 1* ***1996***, 219; Abe, M.; Hayashi, T.; Kurata, T. *Chem. Lett.* ***1994*** 1789; Pandey, G.; Hajra, S.; Ghorai, M.K. *Tetrahedron Lett.* ***1994***, *35*, 7837; Pandey, G.; Reddy, G.D. *Tetrahedron Lett.* ***1992***, *33*, 6533.

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[1219] For a discussion of whether 5-endo–trig radical cyclizations are favored or disfavored, see Chatgilialoglu, C.; Ferreri, C.; Guerra, M.; Timokhin, V.; Froudakis, G.; Gimisis, Z.T. *J. Am. Chem. Soc.* ***2002***, *124*, 10765.

[1220] For a review of 5-endo–trig radical cyclizations, see Ishibashi, H.; Sato, T.; Ikeda, M. *Synthesis* ***2002***, 695.

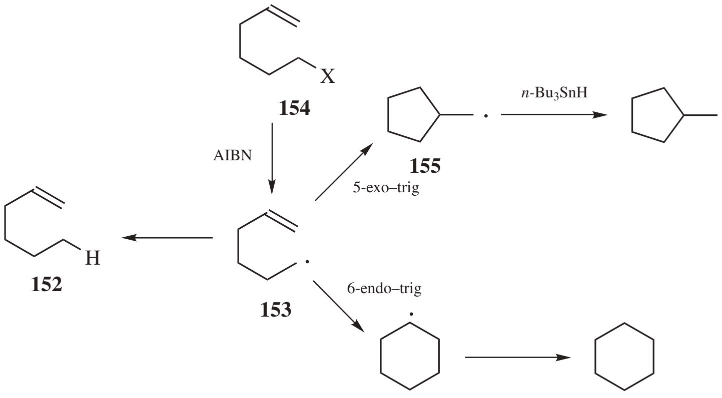
[1221] See Ha, C.; Horner, J.H.; Newcomb, M.; Varick, T.R.; Arnold, B.R.; Lusztyk, J. *J. Org. Chem.* ***1993***, *58* 1194.

[1222] For a discussion of the kinetics of radical cyclization, see Furxhi, E.; Horner, J.H.; Newcomb, M. *J. Org. Chem.* ***1999***, *64*, 4064. Rate constants have been determined for selected reactions: Tauh, P.; Fallis, A.G. *J. Org. Chem.* ***1999***, *64*, 6960.

[1223] Mueller, A.M.; Chen, P. *J. Org. Chem.* ***1998***, *63*, 4581.

[1224] Bogen, S; Malacria, M. *J. Am. Chem. Soc.* ***1996*** *118*, 3992.; Beckwith, A.L.J.; Ingold, K.U., in Vol 1 of *Rearrangements in Ground States and Excited States*, de Mayo, P., Ed., Academic Press, NY ***1980***, pp. 162–283. For a discussion of six- versus five-membered rings, see Gómez, A.M.; Company, M.D.; Uriel, C.; Valverde, S.; López, J.C. *Tetrahedron Lett.* ***2002***, *43*, 4997.

always.[1225] The mechanism of this reaction has been discussed.[1226] Formation of other size rings is possible of course. A 4-exo–trig radical cyclization has been studied,[1227] selectivity in a 7-endo versus 6-exo cyclization,[1228] and also an 8-endo-trig reaction.[1229] In radical cyclization to form large rings, 1,5- and 1,9-hydrogen atom abstractions can pose a problem[1230]



In cases where hydrogen atom transfer gives primarily reduced products, $Bu_3Sn—SnBu_3$ under photochemical generates the radical which can cyclize (see **15-46**),[1231] but a halogen atom transfer agent, such as iodoethane, is used rather than a hydrogen-transfer agent, so the final product is an alkyl iodide.

A mixture of a Grignard reagent and $CoCl_2$ has also been used to initiate aryl radical cyclizations.[1232] Titanium(III)-mediated radical cyclizations are known,[1233] and SmI_2-mediate reactions are possible in the presence of a nickel catalyst.[1234] Organoborane-mediated radical cyclizations are known.[1235] Electrochemically generated radicals also cyclize.[1236] The influence of the halogen atom on radical cyclization has been studied.[1237] Both phenylthio[1238] and phenylseleno

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[1225] Mayon, P.; Chapleur, Y. *Tetrahedron Lett.* ***1994***, *35*, 3703; Marco-Contelles, J.; Sánchez, B. *J. Org. Chem.* ***1993***, *58*, 4293.

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[1238] See, for example, Ikeda, M.; Shikaura, J.; Maekawa, N.; Daibuzono, K.; Teranishi, H.; Teraoka, Y.; Oda, N.; Ishibashi, H. *Heterocycles* ***1999***, *50*, 31.

groups[1239] can be used as 'leaving groups' for radical cyclization, where sulfur or selenium atom transfer leads to formation of the radical. A seleno ester, $R_2N{-}CH_2C({-}O)SeMe$, has also been used with $(Me_3Si)_3SiH$ (tristrimethylsilylsilane, TTMSS) and AIBN to generate $R_2NCH_2\bullet$.[1240] *O*-Phosphonate esters have also served as the leaving group.[1241] *N*-(2-bromophenylbenzyl)methylamino groups have been used as leaving groups for formation of a radical.[1242] Alkenes also serve as radical precursors, adding to another alkene,[1243] including conjugated systems.[1244]

Radical cyclization reaction often proceeds with high diastereoselectivity[1245] and high asymmetric induction when chiral precursors are used. Internal alkynes are good substrates for radical cyclization,[1246] but terminal alkynes tend to give mixtures of *exo/endo–dig* products (p. 305).[1247] *N*-Alkenyl pyridinium salts, with ortho-halogen substituents generate the aryl radical with Bu_3SnH/AIBN, which cyclizes on the pendant alkene unit.[1248] Cyclization of vinyl radicals[1249] and allenyl radicals[1250] are also well known. Ring expansion during radical cyclization is possible when the terminal intermediate is a cyclobutylcarbinyl radical.[1251]

Aryl radicals participate in radical cyclization reactions when the aromatic ring has an alkene or alkyne substituent. *o*-Iodo aryl allyl ethers cyclize to benzofuran derivatives, for example, when treated with AIBN, aqueous H_3PO_2 and $NaHCO_3$ in ethanol.[1252] Cyclization of an *o*-bromo-*N*-acyl aniline (a methacrylic acid derivative) with AIBN/Bu_3SnH gave an indolone under the typical conditions used for cyclization of alkenes.[1253]

Radical cyclization is compatible with the presence of other functional groups. Treatment of $XCH_2CON(R){-}C(R^1){=}CH_2$ derivatives ($X = Cl, Br, I$) with Ph_3SnH

[1239] See, for example, Ericsson, C.; Engman, L. *Org. Lett.* ***2001***, *3*, 3459.

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[1245] For a discussion of stereocontrol in radical processes, see Bouvier, J.-P.; Jung, G.; Liu, Z.; Guérin, B.; Guindon, Y. *Org. Lett.* ***2001***, *3*, 1391. See Bailey, W.F.; Longstaff, S.C. *Org. Lett.* ***2001***, *3*, 2217; Stalinski, K.; Curran, D.P. *J. Org. Chem.* ***2002***, *67*, 2982.

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and AIBN led to formation of a lactam via radical cyclization.[1254] Cyclization of *N*-iodoethyl-5-vinyl-2-pyrrolidinone led to the corresponding bicyclic lactam,[1255] and there are other examples of radical cyclization with molecules containing a lactam unit[1256] or an amide unit.[1257] β-Lactams can be produced by radical cyclization, using $Mn(OAc)_3$.[1258] Radical cyclization occurs with enamines as well.[1259] Photochemical irradiation of *N,N*-diallyl acrylamide leads to formation of a lactam ring, and in this case thiophenol was added to generate the phenylthio derivative.[1260] Phenylseleno *N*-allylamines lead to cyclic amines.[1261] ω-Iodo acrylate esters cyclize to form lactones,[1262] and allylic acetoxy compounds of the type $C{=}C{-}C{-}O_2C{-}CH_2I$ cyclize in a similar manner to give lactones.[1263] Iodolactonization (p. 1154) occurs under standard radical cyclization conditions using allylic acetoxy compounds[1264] and $HGaCl_2/BEt_3$ has been used to initiate the radical process.[1265] α-Bromo mixed acetals give α-alkoxy tetrahydrofuran derivatives[1266] and α-iodoacetals cyclize to give similar products.[1267] The reaction of an ortho-alkynyl aryl isonitrile with AIBN and 2.2 equivalents of Bu_3SnH gave an indole via 5-exo–digcyclization.[1268] Indole derivatives have also been prepared from ortho-iodo aniline derivatives, using AIBN and tristrimethylsilylsilane (TTMSS).[1269]

Acyl radicals can be generated and they cyclize in the usual manner.[1270]A polyene-cyclization reaction generated four rings, initiating the sequence by treatment

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of a phenylseleno ester with Bu_3SnH/AIBN to form the acyl radical, which added to the first alkene unit.[1271] The newly formed carbon radical added to the next alkene, and so on. Acyl radicals generated from Ts(R)NCOSePh derivatives cyclize to form lactams.[1272]

Radical cyclization of iodo aldehydes or ketones, at the carbon of the carbonyl, is effectively an acyl addition reaction (**16-24**, **16-25**). This cyclization is often reversible, and there are many fewer examples can addition to an alkene or alkyne. In one example, a δ-iodo aldehyde was treated with BEt_3/O_2 to initiate formation of the radical, and in the presence of Bu_3SnH cyclization gave a cyclopentanol.[1273] The reaction of an aldehyde-alkene with AIBN, 0.5 $PhSiH_3$ and 0.1 Bu_3SnH generated a radical from the alkene, which cyclized at the aldehyde to give cyclopentanol derivatives.[1274] An aldehyde-*O*-methyloxime generated a radical adjacent to nitrogen under standard conditions, which cyclized at the carbonyl to give a cyclic α-hydroxy *N*-methoxyamine.[1275] Alternatively an α-bromoacetal-*O*-methyl oxime cyclized at the C=NOMe unit under electrolytic conditions in the presence of cobaloxime.[1276]

The attacking radical in radical cyclization reactions is not limited to a carbon, and a number of heterocycles can be prepared.[1277] Amidyl radical are known and give cyclization reactions.[1278] Aminyl radical cyclizations have been reported.[1279] *N*-Chloroamine-alkenes give an aminyl radical when treated with $TiCl_3{\bullet}BF_3$, and cyclization give a pyrrolidine derivative with a pendant chloromethyl group.[1280] *N*-(S-substituted) amines give similar results using AIBN/Bu_3SnH.[1281] Oxime–alkenes cyclize to imines when treated with PhSSPh and TEMPO (p. 274).[1282] An oxygen radical can be generated under photochemical conditions, and they add to alkenes in a normal manner.[1283] Note that radical substitution occurs, and reaction of Ph_3SnH/AIBN and an *O*-amidyl compound having a phosphonate ester elsewhere in the molecule gave cyclization to a tetrahydrofuran derivative.[1284]

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15-31 Conjugate Addition With Heteroatom Nucleophiles

Other nucleophiles add to conjugated systems to give Michael-type products. Aniline derivatives add to conjugated aldehydes in the presence of a catalytic amount of DBU (p. 1132).[1285] Amines add to conjugated esters in the presence of $InCl_3$,[1286] $Bi(NO)_3$,[1287] $Cu(OTf)_2$,[1288] $CeCl_3/NaI/SiO_2$,[1289] $La(OTf)_3$,[1290] or $Yb(OTf)_3$ at 3 kbar,[1291] for example, to give β-amino esters. Palladium catalysts have been used as well.[1292] Conjugate addition of amines has also been promoted by lithium perchlorate,[1293] and by clay.[1294] This reaction can be initiated photochemically[1295] or with microwave irradiation.[1296] Lithium amides add to conjugated esters to give the β-amino ester.[1297] An intramolecular addition of an amine unit to a conjugated ketone in the presence of a palladium catalyst, or photochemically, led to cyclic amines.[1298] Amines add to conjugated thio-lactams.[1299] Chiral catalysts lead to enantioselective reactions.[1300] Chiral imines add in a highly stereoselective manner.[1301] Chiral additives, such as chiral Cinchona alkaloids[1302] or chiral naphthol derivatives,[1303] have also been used. The nitrogen of carbamates add to conjugated ketones with a platinum,[1304] palladium,[1305] copper,[1306] or with a bis-(triflamide) catalyst.[1307] The amine moiety of a carbamate adds to conjugated

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[1306] Wabnitz, T.C.; Spencer, J.B. *Tetrahedron Lett.* ***2002***, *43, 3*891.

[1307] Wabnitz, T.C.; Spencer, J.B. *Org. Lett.* ***2003***, *5*, 2141.

ketones with a polymer-supported acid catalyst,[1308] or with $BF_3{\bullet}OEt_2$.[1309] Chiral catalysts have been used for the conjugated addition of carbamates.[1310] The reaction of ammonium formate with 1,4-diphenylbut-2-en-1,4-dione, in PEG-200 and a palladium catalyst under microwave irradiation, gave 2,5-diphenylpyrrole.[1311]

Lactams have been shown to add to conjugated esters in the presence of $Si(OEt)_4$ and CsF.[1312] Phthalimide adds to alkylidene malononitriles via 1,4-addition with a palladium catalyst, and the resulting anion can be alkylated with an added allylic halide.[1313] Alkylidene amido amides, C=C(NHAc)CONHR, react with secondary amines in water to give the β-amino amido amide.[1314] Amines also add in a conjugate manner to alkynyl phosphonate esters, $C{\equiv}C{-}PO(OEt)_2$, using a CuI catalyst.[1315] Hydroxylamines add to conjugated nitro compounds to give 2-nitro hydroxylamines.[1316] *N,O*-Trimethylsilyl hydroxylamines add to conjugated esters, via nitrogen, using a copper catalyst.[1317] Trimethylsilyl azide with acetic acid reacts with conjugated ketones to give the β-azido ketone.[1318] Sodium azide adds to conjugated ketones in aqueous acetic acid and 20% PBu_3.[1319]

Phosphines react similarly to amines under certain conditions. Conjugate addition of R_2PH and a nickel catalyst give conjugate addition to α,β-unsaturated nitriles.[1320]

Alcohols add to conjugated ketones with a PMe_3 catalyst to give the β-alkoxy ketone.[1321] The conjugate addition of peroxide anions (HOO^- and ROO^-) to α,β-unsaturated carbonyl compounds is discussed in **15-48**.

bis(Silanes) add to alkylidene malonate derivatives in the presence of a copper catalyst to give β-silyl malonates, $RCH(SiR_3)CH(CO_2Me)_2$.[1322] Alkylsilane units add using bis(trialkylsilyl)zinc reagents with a CuCN catalyst.[1323]

Thiophenol and butyllithium (lithium phenylthiolate) adds to conjugated esters.[1324] Similar addition is observed with selenium compounds RSeLi.[1325]

[1308] Wabnitz, T.C.; Yu, J.-Q.; Spencer, J.B. *Synlett* ***2003***, 1070.

[1309] Xu, L.-W.; Li, L.; Xia, C.-G.; Zhou, S.-L.; Li, J.-W.; Hu, X.-X. *Synlett* ***2003***, 2337.

[1310] Palomo, C.; Oiarbide, M.; Halder, R.; Kelso, M.; Gómez-Bengoa, E.; García, J.M. *J. Am. Chem. Soc.* ***2004***, *126*, 9188.

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[1322] Clark, C.T.; Lake, J.F.; Scheidt, K.A. *J. Am. Chem. Soc.* ***2004***, *126*, 84.

[1323] Oestreich, M.; Weiner, B. *Synlett* ***2004***, 2139.

[1324] Kamimura, A.; Kawahara, F.; Omata, Y.; Murakami, N.; Morita, R.; Otake, H.; Mitsudera, H.; Shirai, M.; Kakehi, A. *Tetrahedron Lett.* ***2001***, *42*, 8497.

[1325] Zeni, G.; Stracke, M.P.; Nogueira, C.W.; Braga, A.L.; Menezes, P.H.; Stefani, H.A. *Org. Lett.* ***2004***, *6*, 1135.

Thiols react with conjugated amides via 1,4-addition with the addition of 10% $Hf(OTf)_4$ or other lanthanide triflates[1326] or to conjugated ketones in ionic solvents.[1327] Thiophenol adds in a similar manner in the presence of $Na_2CaP_2O_7$[1328] or LiAl–poly2a.[1329] Thioaryl moieties can be added in the presence of Yb[1330] or a catalytic amount of $(DHQD)_2PYR$ (a dihydroquinidine, see **15-48**).[1331] Thioalkyl units, such as BuS—, add to conjugated ketones using BuS—SnBu and In—I.[1332] Addition of conjugated lactones is possible to produce β-arylthiolated lactones.[1333]

α,β-Unsaturated sulfones undergo conjugate addition of a cyano group using Et_2AlCN.[1334] Trimethylsilyl cyanide (Me_3SiCN) adds a cyano group to α,β-unsaturated amines with a specialized aluminum salen-ytterbium catalyst.[1335]

15-32 Acylation of Activated Double Bonds and of Triple Bonds

Hydro-acyl-addition

Under some conditions, acid derivatives add directly to activated double bonds. Acetic anhydride, magnesium metal, and Me_3SiCl reacts with conjugated esters to give a γ-keto ester.[1336] Similar reaction with vinyl phosphonate esters leads to a γ-keto phosphonate ester.[1337] Thioesters undergo conjugate addition to α,β-unsaturated ketones in the presence of SmI_2.[1338] Using DBU (1,8-diazabicyclo [5.4.0] undec-7-ene) (p. 1132) and a thioimidazolium salt, acyl silanes, $Ar(C{=}O)SiMe_3$, add in a similar manner.[1339] Under microwave irradiation, aldehydes add to conjugated ketones using DBU/Al_2O_3 and a thiazolium salt.[1340] The conjugate addition

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[1326] Kobayashi, S.;Ogawa, C.; Kawamura, M.; Sugiura, M. *Synlett* ***2001***, 983.

[1327] In bmim PF_6, 1-butyl-3-methylimidazolium hexafluorophosphate: Yadav, J.S.; Reddy, B.V.S.; Baishya, G. *J. Org. Chem.* ***2003***, *68*, 7098.

[1328] Zahouily, M.; Abrouki, Y.; Rayadh, A. *Tetrahedron Lett.* ***2002***, *43*, 7729.

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[1330] Taniguchi, Y.; Maruo, M.; Takaki, K.; Fujiwara, Y. *Tetrahedron Lett.* ***1994***, *35*, 7789.

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[1332] Ranu, B.C.; Mandal, T. *Synlett* ***2004***, 1239.

[1333] Nishimura, K.; Tomioka, K. *J. Org. Chem.* ***2002***, *67*, 431.

[1334] Ruano, J.L.G.; García, M.C.; Laso, N.M.; Castro, A.M.M.; Ramos, J.H.R. *Angew. Chem. Int. Ed.* ***2001***, *40*, 2507.

[1335] With high enantioselectivity, see Sammis, G.M.; Danjo, H.; Jacobsen, E.N. *J. Am. Chem. Soc.* ***2004***, *126*, 9928.

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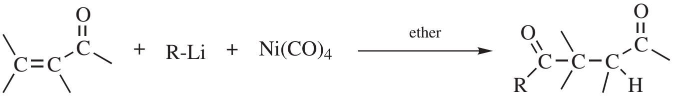
[1338] Blakskjær, P.; Høj, B.; Riber, D.; Skrydstrup, T. *J. Am. Chem. Soc.* ***2003***, *125*, 4030.

[1339] Mattson, A.E.; Bharadwaj, A.R.; Scheidt, K.A. *J. Am. Chem. Soc.* ***2004***, *126*, 2314.

[1340] Yadav, J.S.; Anuradha, K.; Reddy, B.V.S.; Eeshwaraiah, B. *Tetrahedron Lett.* ***2003***, *44*, 8959.

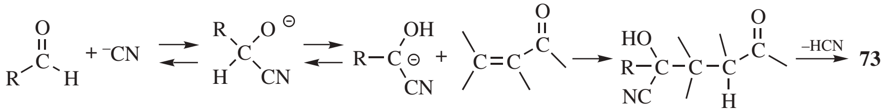
of acyl zirconium complexes in the presence of BF3•OEt_2 is catalyzed by palladium acetate.[1341]



157

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.[1342] The product is a 1,4-diketone, **157**. The R group may be aryl or primary alkyl. The reaction can also be applied to alkynes (which need not be activated), in which case 2 mol add and the product is also a 1,4-diketone (e.g., $R'C{\equiv}CH \rightarrow RCOCHR'CH_2COR$).[1343] In a different procedure, α,β-unsaturated ketones and aldehydes are acylated by treatment at −110°C with $R_2(CN)CuLi_2$ and CO. This method is successful for R = primary, secondary, and tertiary alkyl.[1344] For secondary and tertiary groups, R(CN)CuLi (which does not waste an R group) can be used instead.[1345]

Another method involves treatment with an aldehyde and cyanide ion (see **16-52**) in a polar aprotic solvent (e.g., DMF or DMSO).[1346]



158

This method has been applied to α,β-unsaturated ketones, esters, and nitriles to give the corresponding 1,4-diketones, γ-keto esters, and γ-keto nitriles, respectively (see also, **16-55**). The ion **158** is a synthon for the unavailable $R^{\ominus}$ C=O anion (see also, p. 634); it is a masked $R^{\ominus}$ C=O anion. Other masked carbanions that have been used in this reaction are the $RC^{\ominus}(CN)$ NR ion,[1347] the $EtSC^{\ominus}$ RSOEt ion[1348] (see p. 634), the $CH_2{=}C^{\ominus}$ OEt ion,[1349] $CH_2{=}C(OEt)Cu_2Li$,[1350] $CH_2{=}CMe(SiMe_3)$,[750]

[1341] Hanzawa, Y.; Tabuchi, N.; Narita, K.; Kakuuchi, A.; Yabe, M.; Taguchi, T. *Tetrahedron* ***2002***, *58*, 7559.

[1342] Corey, E.J.; Hegedus, L.S. *J. Am. Chem. Soc.* ***1969***, *91*, 4926.

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[1344] Seyferth, D.; Hui, R.C. *J. Am. Chem. Soc.* ***1985***, *107*, 4551. See also, Lipshutz, B.H.; Elworthy, T.R. *Tetrahedron Lett.* ***1990***, *31*, 477.

[1345] Seyferth, D.; Hui, R.C. *Tetrahedron Lett.* ***1986***, *27*, 1473.

[1346] For reviews, see Stetter, H.; Kuhlmann, H. *Org. React.* ***1991***, *40*, 407–496; Stetter, H. *Angew. Chem. Int. Ed.* ***1976***, *15*, 639. For a similar method involving thiazolium salts, see Stetter, H.; Skobel, H. *Chem. Ber.* ***1987***, *120*, 643; Stetter, H.; Kuhlmann, H.; Haese, W. *Org. Synth., 65*, 26.

[1347] Enders, D.; Gerdes, P.; Kipphardt, H. *Angew. Chem. Int. Ed.* ***1990***, *29*, 179.

[1348] Herrmann, J.L.; Richman, J.E.; Schlessinger, R.H. *Tetrahedron Lett.* ***1973***, 3271, 3275.

[1349] Beockman Jr., R.K.; Bruza, K.J.; Baldwin, J.E.; Lever Jr., O.W. *J. Chem. Soc., Chem. Commun.* ***1975***, 519.

[1350] Boeckman Jr., R.K ; Bruza, K.J. *J. Org. Chem.* ***1979***, *44*, 4781.

and the $RC^{\ominus}(OCHMeOEt)\ CN$ ion[1351] (see p. 640). In the last case, best results are obtained when R is a vinylic group. Anions of 1,3-dithianes (**10-71**) do not give 1,4-addition to these substrates (except in the presence of HMPA, see **15-25**), but add 1,2 to the C=O group instead (**16-38**).

In another procedure, acyl radicals derived from phenyl selenoesters ArCOSePh (by treatment of them with Bu_3SnH) add to α,β-unsaturated esters and nitriles to give γ-keto esters and γ-keto nitriles, respectively.[1352]

OS **VI**, 866; **VIII**, 620.

15-33 Addition of Alcohols, Amines, Carboxylic Esters, Aldehydes, and so on.

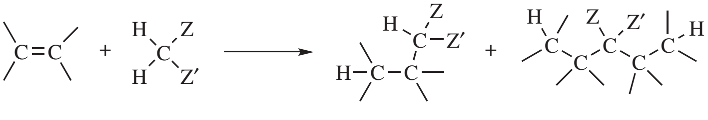
Hydro-acyl-addition, and so on.

Formates, primary, and secondary alcohols, amines, ethers, alkyl halides, compounds of the type $Z—CH_2— Z'$, and a few other compounds add to double bonds in the presence of free-radical initiators.[1353] 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. 1007). Formates and formamides[1354] add similarly:

W = OR, NH_2

Alcohols, ethers, amines, and alkyl halides add as follows (shown for alcohols):

ZCH_2Z' compounds react at the carbon bearing the active hydrogen:[1355]



[1351] Stork, G.; Maldonado, L. *J. Am. Chem. Soc.* ***1974***, *96*, 5272.

[1352] Boger, D.L.; Mathvink, R.J. *J. Org. Chem.* ***1989***, *54*, 1777.

[1353] For reviews, see Giese, B. *Radicals in Organic Synthesis: Formation of Carbon-Carbon Bonds*, Pergamon, Elmsford, NY, ***1986***, pp. 69–77; Vogel, H. *Synthesis* ***1970***, 99; Huyser, E.S. *Free-Radical Chain Reactions*, Wiley, NY, ***1970***, pp. 152–159; Elad, D. *Fortschr. Chem. Forsch.* ***1967***, *7*, 528. Hyponitrites have been used to initiate this reaction; see Dang, H.-S.; Roberts, B.P. *Chem. Commun.* ***1996***, 2201.

[1354] Elad, D. *Fortschr. Chem. Forsch.* ***1967***, *7*, 528, see pp. 530–543.

[1355] For example, see Cadogan, J.I.G.; Hey, D.H.; Sharp, J.T. *J. Chem. Soc. C* ***1966***, 1743; *J. Chem. Soc. B* ***1967***, 803; Hájek, M.; Málek, J. *Coll. Czech. Chem. Commun.* ***1979***, *44*, 3695.

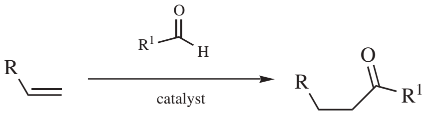
Similar additions have been successfully carried out with carboxylic acids, anhydrides,[1356] acyl halides, carboxylic esters, nitriles, and other types of compounds.[1357]

Similar reactions have been carried out on acetylene.[1358] In an interesting variation, thiocarbonates add to alkynes in the presence of a palladium catalyst to give a β-phenylthio α,β-unsaturated ester.[1359] Aldehydes add to alkynes in the presence of a rhodium catalyst to give conjugated ketones.[1360] In a cyclic version of the addition of aldehydes, 4-pentenal was converted to cyclopentanone with a rhodium–complex catalyst.[1361] An intramolecular acyl addition to an alkyne was reported using silyl ketones, acetic aid and a rhodium catalyst.[1362] In the presence of a palladium catalyst, a tosylamide group added to an alkene unit to generate *N*-tosylpyrrolidine derivatives.[1363]

OS **IV**, 430; **V**, 93; **VI**, 587, 615.

15-34 Addition of Aldehydes

Alkyl-carbonyl-addition



In the presence of metal catalysts, such as rhodium compounds[1364] or $Yb(OTf)_3$,[1365] aldehydes can add directly to alkenes to form ketones. The reaction of ω-alkenyl aldehydes with rhodium catalyst leads to cyclic ketones,[1366] with high enantioselectivity if chiral ligands are employed. Aldehydes also add to vinyl esters in the presence of hyponitrites and thioglycolates.[1367] The addition of aldehydes to activated double bonds, mediated by a catalytic amount of thiazolium salt in the presence of a

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[1356] de Klein, W.J. *Recl. Trav. Chim. Pays-Bas* ***1975***, *94*, 48.

[1357] Allen, J.C.; Cadogan, J.I.G.; Hey, D.H. *J. Chem. Soc.* ***1965***, 1918; Cadogan, J.I.G. *Pure Appl. Chem.* ***1967***, *15*, 153, pp. 153–158. See also, Giese, B.; Zwick, W. *Chem. Ber.* ***1982***, *115*, 2526; Giese, B.; Erfort, U. *Chem. Ber.* ***1983***, *116*, 1240.

[1358] For example, see Cywinski, N.F.; Hepp, H.J. *J. Org. Chem.* ***1965***, *31*, 3814; DiPietro, J.; Roberts, W.J. *Angew. Chem. Int. Ed.* ***1966***, *5*, 415.

[1359] Hua, R.; Takeda, H.; Onozawa, S.-y.; Abe, Y.; Tanaka, M. *J. Am. Chem. Soc.* ***2001***, *123*, 2899.

[1360] Kokubo, K.; Matsumasa, K.; Miura, M.; Nomura, M. *J. Org. Chem.* ***1997***, *62*, 4564.

[1361] Fairlie, D.P.; Bosnich, B. *Organometallics* ***1988***, *7*, 936, 946. Also see, Barnhart, R.W.; Wang, X.; Noheda, P.; Bergens, S.H.; Whelan, J.; Bosnich, B. *J. Am. Chem. Soc.* ***1994***, *116*, 1821 for an enantioselective version of this cyclization.

[1362] Yamane, M.; Amemiya, T.; Narasaka, K. *Chem. Lett.* ***2001***, 1210.

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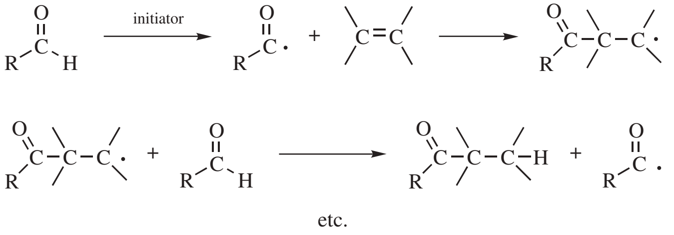
[1365] Curini, M.; Epifano, F.; Maltese, F.; Rosati, O. *Synlett* ***2003***, 552.

[1366] Barnhart, R.W.; McMorran, D.A.; Bosnich, B. *Chem. Commun.* ***1997***, 589.

[1367] Dang, H.-S.; Roberts, B.P. *J. Chem. Soc, Perkin Trans. 1*, ***1998***, 67.

weak base, is called the *Stetter reaction*,[1368] An internal addition of an alkynyl aldehyde, catalyzed by a rhodium complex, led to a cyclopentenone derivative.[1369] A similar carbonyl addition with benzaldehyde derivatives having an ortho-allylic ether led to a benzopyranone when treated with potassium hexamethyldisilazide.[1370]

These reactions are not successful when the alkene contains electron-withdrawing groups, such as halo or carbonyl groups. A free-radical initiator is required,[1371] usually peroxides or *UV* light. The mechanism is illustrated for aldehydes but is similar for the other compounds:

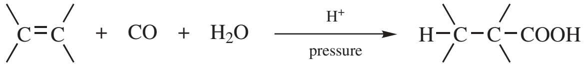


Polymers are often side products. Photochemical addition of aldehyde to conjugated C=C units can be efficient when a triplet sensitizer (p. 340), such as benzophenone is used.[1372]

A variation that is more of an acyl addition (**16-25**) involves the reaction of an allylic alcohol with benzaldehyde. With a ruthenium catalyst and in an ionic liquid, the C=C unit reacts with the aldehyde, with concomitant oxidation of the allylic alcohol unit, to give a β-hydroxy ketone, PhCHO +C=C–CH(OH)R → PhCH(OH)–CH(Me)COR.[1373] In another variation, formate esters add to alkenes using a ruthenium catalyst to give an alkyl ester via a formylation process.[1374]

15-35 Hydrocarboxylation

Hydro-carboxy-addition



[1368] Stetter, H.; Schreckenberg, M. *Angew. Chem., Int. Ed* ***1973***, *12*, 81; Stetter, H.; Kuhlmann, H. *Angew. Chem., Int. Ed.* ***1974***, *13*, 539; Stetter, H. *Angew. Chem., Int. Ed.* ***1976***, *15*, 639; Stetter, H.; Haese, W. *Chem. Ber.* ***1984***, *117*, 682; Stetter, H.; Kuhlmann, H. *Org. React.* ***1991***, *40*, 407; Enders, D.; Breuer, K.; Runsink, J.; Teles, J.H. *Helv. Chim. Acta* ***1996***, *79*, 1899; Kerr, M.S.; Rovis, T. *Synlett* ***2003***, 1934; Kerr, M.S.; Rovis, T. *J. Am. Chem. Soc.* ***2004***, *126*, 8876; Pesch, J.; Harms, K.; Bach, T. *Eur. J. Org. Chem.* ***2004***, 2025; Mennen, S.; Blank, J.; Tran-Dube, M.B.; Imbriglio, J.E.; Miller, S.J. *Chem. Commun.* ***2005***, 195. For examples of the Stetter reaction with acyl silanes, see Mattson, A.E.; Bharadwaj, A.R.; Scheidt, K.A. *J. Am. Chem. Soc.* ***2004***, *126*, 2314.

[1369] Tanaka, K.; Fu, G.C. *J. Am. Chem. Soc.* ***2002***, *124*, 10296.

[1370] Kerr, M.S.; de Alaniz, J.R.; Rovis, T. *J. Am. Chem. Soc.* ***2002***, *124*, 10298.

[1371] See Lee, E.; Tae, J.S.; Chong, Y.H.; Park, Y.C.; Yun, M.; Kim, S. *Tetrahedron Lett.* ***1994***, *35*, 129 for an example.

[1372] Kraus, G.A.; Liu, P. *Tetrahedron Lett.* ***1994***, *35*, 7723.

[1373] In bmim PF_6, 3-butyl-1-methylimidazolium hexafluorophosphate: Yang, X.-F.; Wang, M.; Varma, R.S.; Li, C.-J. *Org. Lett.* ***2003***, *5*, 657.

[1374] Na, Y.; Ko, S.; Hwang, L.K.; Chang, S. *Tetrahedron Lett.* ***2003***, *44*, 4475.

The acid-catalyzed hydrocarboxylation of alkenes (the *Koch reaction*) can be performed in a number of ways.[1375] In one method, the alkene is treated with carbon monoxide and water at 100–350°C and 500–1000-atm pressure with a mineral acid catalyst. However, the reaction can also be performed under milder conditions. If the alkene is first treated with CO and catalyst and then water added, the reaction can be accomplished at 0–50°C and 1–100 atm. If formic acid is used as the source of both the CO and the water, the reaction can be carried out at room temperature and atmospheric pressure.[1376] The formic acid procedure is called the *Koch–Haaf reaction* (the Koch–Haaf reaction can also be applied to alcohols, see **10-77**). Nearly all alkenes can be hydrocarboxylated by one or more of these procedures. However, conjugated dienes are polymerized instead. Hydrocarboxylation can also be accomplished under mild conditions (160°C and 50 atm) by the use of nickel carbonyl as catalyst. Acid catalysts are used along with the nickel carbonyl, but basic catalysts can also be employed.[1377] Other metallic salts and complexes can be used, sometimes with variations in the reaction procedure, including palladium,[1378] platinum,[1379] and rhodium[1380] catalysts. The $Ni(CO)_4$-catalyzed oxidative carbonylation with CO and water as a nucleophile is often called *Reppe carbonylation*.[1381] The toxic nature of nickel

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[1375] For reviews of hydrocarboxylation of double and triple bonds catalyzed by acids or metallic compounds, see Lapidus, A.L.; Pirozhkov, S.D. *Russ. Chem. Rev.* ***1989***, *58*, 117; Anderson, G.K.; Davies, J.A., in Hartley, F.R.; Patai, S. *The Chemistry of the Metal-Carbon Bond*, Vol. 3, Wiley, NY, ***1985***, pp. 335–359, 335–348; in Falbe, J. *New Syntheses with Carbon Monoxide*, Springer, NY, ***1980***, the articles by Mullen, A. pp. 243–308; and Bahrmann, H. pp. 372–413; in Wender, I.; Pino, P. *Organic Syntheses via Metal Carbonyls*, Vol. 2, Wiley, NY, ***1977***, the articles by Pino, P.; Piacenti, F.; Bianchi, M. pp. 233–296; and Pino, P.; Braca, G. pp. 419–516; Eidus, Ya.T.; Lapidus, A.L.; Puzitskii, K.V.; Nefedov, B.K. *Russ. Chem. Rev.* ***1973***, *42*, 199; *Russ. Chem. Rev.* ***1971***, *40*, 429; Falbe, J. *Carbon Monoxide in Organic Synthesis*, Springer, Berlin, ***1970***, pp. 78–174.

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[1378] For reviews, see Heck, R.F. *Palladium Reagents in Organic Synthesis*, Academic Press, NY, ***1985***, pp. 381–395; Bittler, K.; Kutepow, N.V.; Neubauer, D.; Reis, H. *Angew. Chem. Int. Ed.* ***1968***, *7*, 329. For a review with respect to fluoroalkenes, see Ojima, I. *Chem. Rev.* ***1988***, *88*, 1011, p. 1016. Seayad, A.; Jayasree, S.; Chaudhari, R.V. *Org. Lett.* ***1999***, *1*, 459; Mukhopadhyay, K.; Sarkar, B.R.; Chaudhari, R.V. *J. Am. Chem. Soc.* ***2002***, *124*, 9692. See also, the references cited in these latter articles.

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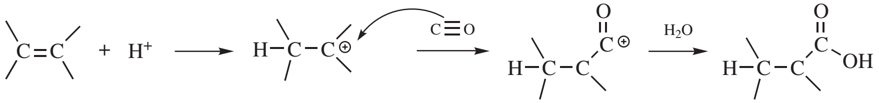
tetracarbonyl has led to development of other catalysts, including Co, Rh, Ir, Pd, and Pt, and Mo compounds.[1382] This reaction converts alkenes, alkynes and dienes and is tolerant of a wide variety of functional groups. When the additive is alcohol or acid, saturated or unsaturated acids, esters, or anhydrides are produced (see **15-36**). The transition-metal-catalyzed carbonylation has been done enantioselectively, with moderate-to-high optical yields, by the use of an optically active palladium complex catalyst.[1383] Dienes react with Cp_2TiCl_2/RMgCl and then with Me_2NCOCl to give amides.[1384] In the presence of formic acid, CO, and palladium acids can similarly be formed.[1385] Alkenes also react with $Fe(CO)_5$ and CO to give carboxylic acids.[1386] Electrochemical carboxylation procedures have been developed, including the conversion of alkenes to 1,4-butanedicarboxylic acids.[1387]

When applied to triple bonds, hydrocarboxylation gives α,β-unsaturated acids under very mild conditions. Triple bonds give unsaturated acids and saturated dicarboxylic acids when treated with carbon dioxide and an electrically reduced nickel complex catalyst.[1388] Alkynes also react with $NaHFe(CO)_4$, followed by $CuCl_2•2\ H_2O$, to give alkenyl acid derivatives.[1389] A related reaction with CO and palladium catalysts in the presence of $SnCl_2$ also leads to conjugated acid derivatives.[1390] Terminal alkynes react with CO_2 and $Ni(cod)_2$, and subsequent treatment with DBU (p. 1132) gives the α,β-unsaturated carboxylic acid.[1391]

When acid catalysts are employed, in the absence of nickel carbonyl, the mechanism[1392] involves initial attack by a proton, followed by attack of the resulting carbocation on carbon monoxide to give an acyl cation, which, with water, gives the product, **159**. Markovnikov's rule is followed, and carbon skeleton rearrangements and double-bond isomerizations (prior to attack by CO) are frequent.



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[1382] For a review, see Kiss, G. *Chem. Rev.* ***2001***, *101*, 3435.

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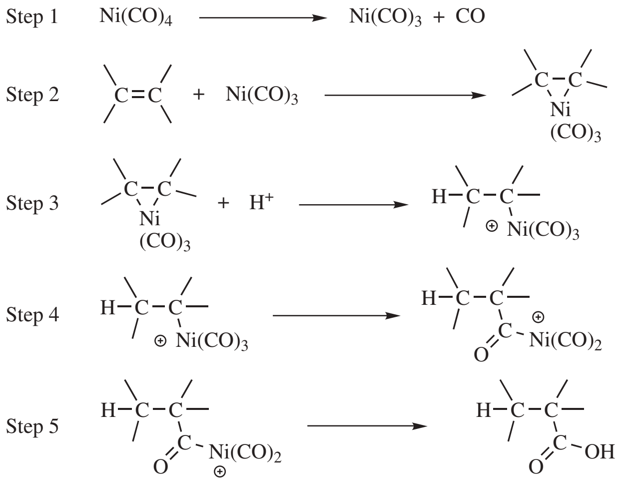
For the transition metal catalyzed reactions, the nickel carbonyl reaction has been well studied and the addition is syn for both alkenes and alkynes.[1393] The following is the accepted mechanism:[785]

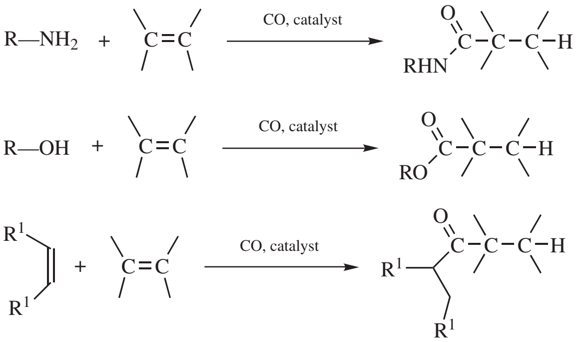


Step 3 is an electrophilic substitution. The principal step of the mechanism, step 4, is a rearrangement.

An indirect method for hydrocarboxylation involves the reaction of an alkene with a borate, $(RO)_2BH$ and a rhodium catalysts. Subsequent reaction with $LiCHCl_2$ and then $NaClO_2$ gives the Markovnikov carboxylic acid ($RC{=}C \rightarrow RC(COOH)CH_3$.[1394] When a chiral ligand is used, the reaction proceeds with good enantioselectivity.

15-36 Carbonylation, Alkoxycarbonylation and Aminocarbonylation of Double and Triple Bonds

Alkyl, Alkoxy or Amino-carbonyl-addition



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In the presence of certain metal catalysts, alkenes and alkynes can be carbonylated or converted to amides or esters.[1395] There are several variations. The reaction of an alkyl iodide and a conjugated ester with CO, $(Me_3Si)_3SiH$ and AIBN (p. 935) in supercritical CO_2 (p. 414) gave a γ-keto ester.[1396] Terminal alkynes react with CO and methanol, and in the presence of $CuCl_2$ and $PdCl_2$ the product is a β-chloro-α-β-unsaturated methyl ester.[1397] Conjugated dienes react with thiophenol, CO and palladium(II) acetate to give the β,γ-unsaturated thioester.[1398] Allene reacts with CO, methanol and a ruthenium catalyst go give methacrylic acid.[1399] 5-Iodo-1-pentene reacted with 40 atm of CO in butanol to give a cyclopentanone with a pendant ester ($-CH_2CO_2Bu$).[1400] Alkynes react with thiophenol and CO with a palladium[1401] or platinum[1402] catalyst to give a conjugated thioester. Terminal alkynes react with CO and methanol, using a combination of a palladium (II) halide and a copper (II) halide, to give a conjugated diester, $MeO_2C{-}C{=}C{-}CO_2Me$.[1403] A similar reaction with alkenes using a combination of a palladium and a molybdenum catalyst led to a saturated diester, $MeO_2C{-}C{-}C{-}CO_2Me$.[1404] Alkenes were converted to the dimethyl ester of 1,4-butanedioic acid derivatives with CO/O_2 and a combination of $PdCl_2$ and CuCl catalysts.[1405] Note that alkenes are converted to primarily the anti-Markovnikov ester upon treatment with arylmethyl formate esters ($ArCH_2OCHO$) and a ruthenium catalyst.[1406]

A bicyclic ketone was generated when 1,2-diphenylethyne was heated with CO, methanol and a dirhodium catalyst.[1407] 2-Iodostyrene reacted at 100°C with CO and a palladium catalyst to give the bicyclic ketone 1-indanone.[1408] Another variation reacted a conjugated allene–alkene with 5 atm of CO and a rhodium catalyst to give a bicyclic ketone.[1409] An intermolecular version of this reaction is known

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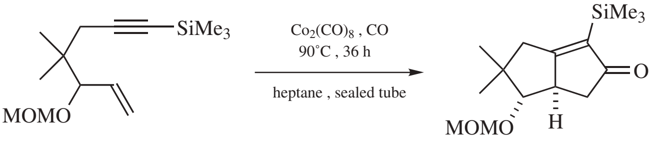
using a cobalt catalyst, giving a cyclopentenone[1410] in a reaction related to the Pauson–Khand reaction (see below). The reaction of a conjugated diene having a distal alkene unit and CO with a rhodium catalyst led to a bicyclic conjugated ketone.[1411] When a Stille coupling (**12-15**) is done in a CO atmosphere, conjugated ketones of the type C=C–CO–C=C are formed,[1412] suitable for a Nazarov cyclization (**15-20**). Alkynes were converted to cyclobutenones using $Fe_3(CO)_{12}$ to form the initial complex, followed by reaction with copper(II) chloride.[1413] An interesting variation treated cyclohexene with 5 equivalents of Oxone® and a $RuCl_3$ catalyst to give 2-hydroxycyclohexanone.[1414]

The reaction of dienes, diynes, or en-ynes with transition metals[1415] (usually cobalt)[1416] forms organometallic coordination complexes. In the presence of carbon monoxide, the metal complexes derived primarily from enynes (alkene–alkynes) form cyclopentenone derivatives in what is known as the *Pauson–Khand reaction*.[1417] The reaction involves (*1*) formation of a hexacarbonyldicobalt–alkyne complex and (*2*) decomposition of the complex in the presence of an alkene.[1418] A typical example is formation of **160**.[1419] Cyclopentenones can be prepared by an intermolecular reaction of a vinyl silane and an alkyne using CO and a ruthenium catalyst.[1420] Carbonylation of an alkene–diene using a rhodium catalyst leads to cyclization to an α-vinyl cyclopentanone.[1421] An yne–diene can also be used for the Pauson–Khand reaction.[1422]



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Rhodium,[1423] titanium,[1424] and tungsten[1425] complexes have also been used for this reaction. The reaction can be promoted photochemically[1426] and the rate is enhanced by the presence of primary amines.[1427] Coordinating ligands also accelerate the reaction,[1428] polymer-supported promoters have been developed[1429] and there are many possible variations in reaction conditions.[1430] The Pauson–Khand reaction has been done under heterogeneous reaction conditions,[1431] and with cobalt nanoparticles.[1432] A dendritic cobalt catalyst has been used.[1433] Ultrasound promoted[1434] and microwave promoted[1435] reactions have been developed. Polycyclic compounds (tricyclic and higher) are prepared in a relatively straightforward manner using this reaction.[1436] Asymmetric Pauson–Khand reactions are known.[1437]

The Pauson–Khand reaction is compatible with other groups or heteroatoms elsewhere in the molecule. These include ethers and aryl halides,[1438] esters,[1439]

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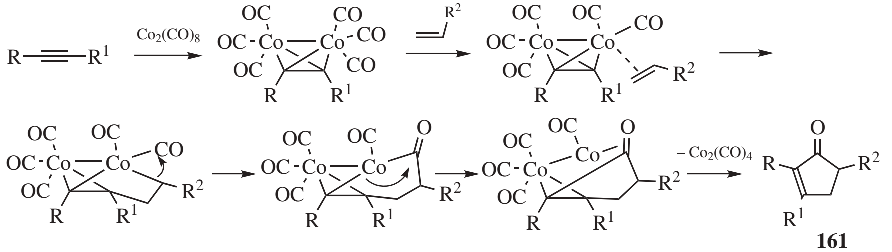
amides,[1440] alcohols,[1441] diols,[1442] and an indole unit.[1443] A silicon-tethered Pauson–Khand reaction is known.[1444] Allenes are reaction partners in the Pauson–Khand reaction.[1445] This type of reaction can be extended to form six-membered rings using a ruthenium catalyst.[1446] A double-Pauson–Khand process was reported.[1447] In some cases, an aldehyde can serve as the source of the carbonyl for carbonylation.[1448]

The accepted mechanism was proposed by Magnus,[1449] shown for the formation of **161**,[1450] and supported by Krafft's work.[1451] It has been shown that CO is lost from the Pauson–Khand complex prior to alkene coordination and insertion.[1452] Calculations concluded that the LUMO of the coordinated alkene plays a crucial role in alkene reactivity by determining the degree of back-donation in the complex.[1453]



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Other carbonylation methods are available. Carbonylation occurs with conjugated ketones to give 1.4-diketones, using phenylboronic acid (**13-12**), CO and a rhodium catalyst.[1454] A non-carbonylation route treated a conjugated diene with an

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excess of *tert*-butyllithium and quenching with carbon dioxide led to a cyclopentadienone.[1455] When quenched with CO rather than CO_2, a nonconjugated cyclopentenone was formed.[1456] It is noted that a carbonylation reaction with CO, a diyne and an iridium catalyst[1457] or a cobalt catalyst[1458] provided similar molecules.

The reaction of a secondary amine, CO, a terminal alkyne and *t*-$BuMe_2SiH$ with a rhodium catalyst led to a conjugated amide bearing the silyl group of the C=C unit.[1459] Reaction of a molecule containing an amine and an alkene unit was carboxylated with CO in the presence of a palladium catalyst to give a lactam.[1460] A similar reaction with a molecule containing an amine and an alkyne also generated a lactam, in the presence of CO and a rhodium catalyst.[1461] An intramolecular carbonylation reaction of a conjugated imine, with CO, ethylene and a ruthenium catalyst, led to a highly substituted β,γ-unsaturated lactam.[1462]

With any method, if the alkene contains a functional group, such as OH, NH_2, or $CONH_2$, the corresponding lactone (**16-63**),[1463] lactam (**16-74**), or cyclic imide may be the product.[1464] Titanium,[1465] palladium,[1466] ruthenium,[1467] and rhodium[1468] catalysts have been used to generate lactones. Allenic alcohols are converted to butenolides with 10 atm of CO and a ruthenium catalyst.[1469] Larger ring conjugated lactones can also be formed by this route using the appropriate allenic alcohol.[1470] Propargylic alcohols lead to β-lactones.[1471] Allenic tosyl-amides are converted to *N*-tosyl α,β-unsaturated pyrrolidinones using 20 atm of CO and a ruthenium catalyst.[1472] Conjugated imines are converted to similar products with CO, ethylene and a ruthenium catalyst.[1473] Propargyl alcohols are converted to

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[1456] Song, Q.; Chen, J.; Jin, X.; Xi, Z. *J. Am. Chem. Soc.* ***2001***, *123*, 10419; Song, Q.; Li, Z.; Chen, J.; Wang, C.; Xi, Z. *Org. Lett.* ***2002***, *4*, 4627.

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[1460] Okuro, K.; Kai, H.; Alper, H. *Tetrahedron Asymmetry* ***1997***, *8*, 2307.

[1461] Hirao, K.; Morii, N.; Joh, T.; Takahashi, S. *Tetrahedron Lett.* ***1995***, *36*, 6243; Shiba, T.; Zhou, D.-Y.; Onitsuka, K.; Takahashi, S. *Tetrahedron Lett.* ***2004***, *45*, 3211.

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[1463] Dong, C.; Alper, H. *J. Org. Chem.* ***2004***, *69*, 5011.

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[1471] Ma, S.; Wu, B.; Zhao, S. *Org. Lett.* ***2003***, *5*, 4429.

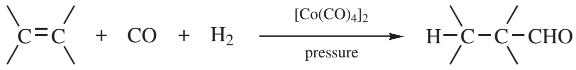
[1472] Kang, S.-K.; Kim, K.-J.; Yu, C.-M.; Hwang, J.-W.; Do, Y.-K. *Org. Lett.* ***2001***, *3*, 2851.

[1473] Chatani, N.; Kamitani, A.; Murai, S. *J. Org. Chem.* ***2002***, *67*, 7014.

butenolides with CO/H_2O and a rhodium catalyst.[1474] Propargyl alcohols generate lactones when treated with a chromium pentacarbonyl carbene complex.[1475] Amines add to allenes, in the presence of CO and a palladium catalyst, to form conjugated amides.[1476]

15-37 Hydroformylation

Hydro-formyl-addition



Alkenes can be hydroformylated[1477] by treatment with carbon monoxide and hydrogen over a catalyst. The most common catalysts are cobalt carbonyls (see below for a description of the mechanism) and rhodium complexes,[1478] but other transition metal compounds have also been used. Cobalt catalysts are less active than the rhodium type, and catalysts of other metals are generally less active.[1479] 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 alkenes > straight-chain internal alkenes > branched-chain alkenes. With terminal alkenes, for example, the aldehyde unit is formed on both the primary and secondary carbon, but proper choice of catalyst and additive leads to selectivity for the secondary product[1480] or primary

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[1475] Good, G.M.; Kemp, M.I.; Kerr, W.J. *Tetahedron Lett.* ***2000***, *41*, 9323.

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[1478] For example, see Brown, J.M.; Kent, A.G. *J. Chem. Soc. Perkin Trans. 1*, ***1987***, 1597; Hanson, B.E.; Davis, M.E. *J. Chem. Ed.*, ***1987***, *64*, 928; Jackson, W.R.; Perlmutter, P.; Suh, G. *J. Chem. Soc., Chem. Commun.* ***1987***, 724; Amer, I.; Alper, H. *J. Am. Chem. Soc.* ***1990***, *112*, 3674. See the references cited in these papers. For a review of the rhodium-catalyzed process, see Jardine, F.H., in Hartley, F.R. *The Chemistry of the Metal–Carbon Bond*, Vol. 4, Wiley, NY, ***1987***, pp. 733–818, pp. 778–784.

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product.[1481] Good yields for hydroformylation have been reported using rhodium catalysts in the presence of certain other additives.[1482] Among the side reactions are the aldol reaction (**16-34**), acetal formation, the Tishchenko reaction (**19-82**), and polymerization. In one case using a rhodium catalyst, 2-octene gave nonanal, presumably via a η^3-allyl complex (p. 116).[1483] Conjugated dienes give dialdehydes when rhodium catalysts are used[1484] but saturated mono-aldehydes (the second double bond is reduced) with cobalt carbonyls. Both 1,4- and 1,5-dienes may give cyclic ketones.[1485] Hydroformylation of triple bonds proceeds very slowly, and few examples have been reported.[1486] However, in the presence of a rhodium catalyst, the triple bond of a conjugated enyne is formylated.[1487] Many functional groups such as OH, CHO, COOR,[1488] CN, can be present in the molecule, although halogens usually interfere. Stereoselective syn addition has been reported,[1489] and also stereoselective anti addition.[1490] Asymmetric hydroformylation has been accomplished with a chiral catalyst,[1491] and in the presence of chiral additives.[1492] Cyclization to prolinal derivatives has been reported with allylic amines.[1493]

When dicobalt octacarbonyl, $[Co(CO)_4]_2$, is the catalyst, the species that actually adds to the double bond is tricarbonylhydrocobalt, $HCo(CO)_3$.[1494] Carbonylation $RCo(CO)_3 + CO \rightarrow RCo(CO)_4$ takes place, followed by a rearrangement and a

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[1485] For a review of ring closure reactions with CO, see Mullen, A., in Falbe, J. *New Syntheses with Carbon Monoxide*, Springer, NY, ***1980***, pp. 414–439. See also, Eilbracht, P.; Hüttmann, G.; Deussen, R. *Chem. Ber.* ***1990***, *123*, 1063, and other papers in this series.

[1486] For examples with rhodium catalysts, see Fell, B.; Beutler, M. *Tetrahedron Lett.* ***1972***, 3455; Botteghi, C.; Salomon, C. *Tetrahedron Lett.* ***1974***, 4285. For an indirect method, see Campi, E.; Fitzmaurice, N.J.; Jackson, W.R.; Perlmutter, P.; Smallridge, A.J. *Synthesis* ***1987***, 1032.

[1487] van den Hoven, B.G.; Alper, H. *J. Org. Chem.* ***1999***, *64*, 3964.

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reduction of the C—Co bond, similar to steps 4 and 5 of the nickel carbonyl mechanism shown in **15-35**. The reducing agent in the reduction step is tetracarbonylhydrocobalt, $HCo(CO)_4$,[1495] or, under some conditions, H_2.[1496] When $HCo(CO)_4$ was the agent used to hydroformylate styrene, the observation of CIDNP indicated that the mechanism is different, and involves free radicals.[1497] Alcohols can be obtained by allowing the reduction to continue after all the carbon monoxide is used up. It has been shown[1498] that the formation of alcohols is a second step, occurring after the formation of aldehydes, and that $HCo(CO)_3$ is the reducing agent.

OS **VI**, 338.

15-38 Addition of HCN

Hydro-cyano-addition

Ordinary alkenes do not react with HCN, but polyhalo alkenes and alkenes of the form C=C—Z add HCN to give nitriles.[1499] The reaction is therefore a nucleophilic addition and is base catalyzed. When Z is COR or, more especially, CHO, 1,2-addition (**16-53**) is an important competing reaction and may be the only reaction. Triple bonds react very well when catalyzed by an aqueous solution of CuCl, NH_4Cl, and HCl or by Ni or Pd compounds.[1500] The HCN can be generated *in situ* from acetone cyanohydrin (see **16-52**), avoiding the use of the poisonous HCN.[1501] One or 2 equivalents 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, for example, Et_2AlCN, or mixtures of HCN and trialkylalanes R_3Al are especially good reagents for conjugate addition of HCN[1502] to α,β-unsaturated ketones and α,β-unsaturated acyl halides. Hydrogen cyanide can be added to ordinary alkenes in the presence of dicobalt octacarbonyl[1503] or certain other

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[1495] Alemdaroǧ lu, N.H.; Penninger, J.L.M.; Oltay, E. *Monatsh. Chem.* ***1976***, *107*, 1153; Ungváry, F.; Markó, L. *Organometallics* ***1982***, *1*, 1120.

[1496] See Kovács, I.; Ungváry, F.; Markó, L. *Organometallics* ***1986***, *5*, 209.

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[1498] Aldridge, C.L.; Jonassen, H.B. *J. Am. Chem. Soc.* ***1963***, *85*, 886.

[1499] For reviews see Friedrich, K., in Patai, S.; Rappoport, Z. *The Chemistry of Functional Groups, Supplement C*, pt. 2, Wiley, NY, ***1983***, pp. 1345–1390; Nagata, W.; Yoshioka, M. *Org. React.* ***1977***, *25*, 255; Brown, E.S., in Wender, I.; Pino, P. *Organic Syntheses via Metal Carbonyls*, Vol. 2, Wiley, NY, ***1977***, pp. 655–672; Friedrich, K.; Wallenfels, K., in Rappoport, Z. *The Chemistry of the Cyano Group*, Wiley, NY, ***1970***, pp. 68–72.

[1500] Jackson, W.R.; Lovel, C.G. *Aust. J. Chem.* ***1983***, *36*, 1975.

[1501] Jackson, W.R.; Perlmutter, P. *Chem. Br.* ***1986***, 338.

[1502] For a review, see Nagata, W.; Yoshioka, M. *Org. React.* ***1977***, *25*, 255.

[1503] Arthur, Jr., P.; England, D.C.; Pratt, B.C.; Whitman, G.M. *J. Am. Chem. Soc.* ***1954***, *76*, 5364.

transition-metal compounds.[1504] An indirect method for the addition of HCN to ordinary alkenes uses an isocyanide (RNC) and Schwartz's reagent (see **15-17**); this method gives anti-Markovnikov addition.[1505] *tert*-Butyl isocyanide and $TiCl_4$ have been used to add HCN to C=C–Z alkenes.[1506] Pretreatment with NaI/Me_3SiCl followed by CuCN converts alkynes to vinyl nitriles.[1507]

When an alkene is treated with Me_3SiCN and $AgClO_4$, followed by aq. $NaHCO_3$, the product is the isonitrile (RNC) formed with Markovnikov selectivity.[1508] An alternative reagent is the cyanohydrin of acetone, which adds to alkenes to give a nitrile in the presence of a nickel complex.[1509]

OS **I**, 451; **II**, 498; **III**, 615; **IV**, 392, 393, 804; **V**, 239, 572; **VI**, 14.
For addition of ArH, see **11-12** (Friedel–Crafts alkylation).

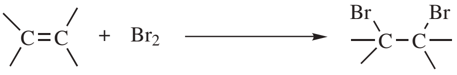
REACTIONS IN WHICH HYDROGEN ADDS TO NEITHER SIDE

Some of these reactions are *cycloadditions* (reactions **15-50**, **15-62**, **15-54**, and **15-57–15-66**). In such cases, addition to the multiple bond closes a ring:

A. Halogen on One or Both Sides

15-39 Halogenation of Double and Triple Bonds (Addition of Halogen, Halogen)

Dihalo-Addition



[1504] For a review, see Brown, E.S., in Wender, P.; Pino, P. *Organic Syntheses via Metal Carbonyls*, Vol. 2, Wiley, NY, ***1977***, pp. 658–667. For a review of the nickel-catalyzed process, see Tolman, C.A.; McKinney, R.J.; Seidel, W.C.; Druliner, J.D.; Stevens, W.R. *Adv. Catal.* ***1985***, *33*, 1. For studies of the mechanism see Tolman, C.A.; Seidel, W.C.; Druliner, J.D.; Domaille, P.J. *Organometallics* ***1984***, *3*, 33; Druliner, J.D. *Organometallics* ***1984***, *3*, 205; Bäckvall, J.E.; Andell, O.S. *Organometallics* ***1986***, *5*, 2350; McKinney, R.J.; Roe, D.C. *J. Am. Chem. Soc.* ***1986***, *108*, 5167; Funabiki, T.; Tatsami, K.; Yoshida, S. *J. Organomet. Chem.* ***1990***, *384*, 199. See also, Jackson, W.R.; Lovel, C.G.; Perlmutter, P.; Smallridge, A.J. *Aust. J. Chem.* ***1988***, *41*, 1099.

[1505] Buchwald, S.L.; LeMaire, S.J. *Tetrahedron Lett.* ***1987***, *28*, 295.

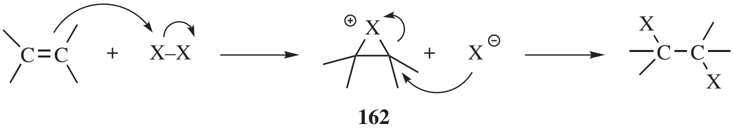
[1506] Ito, Y.; Kato, H.; Imai, H.; Saegusa, T. *J. Am. Chem. Soc.* ***1982***, *104*, 6449.

[1507] Luo, F.-T.; Ko, S.-L.; Chao, D.-Y. *Tetrahedron Lett.* ***1997***, *38*, 8061.

[1508] Kitano, Y.; Chiba, K.; Tada, M. *Synlett* ***1999***, 288.

[1509] Yan, M.; Xu, Q.-Y.; Chan, A.S.C. *Tetrahedron Asymmetry* ***2000***, *11*, 845.

Most double bonds are easily halogenated[1510] with bromine, chlorine, or inter-halogen compounds.[1511] Substitution can compete with addition in some cases.[1512] Iodination has also been accomplished, but the reaction is slower.[1513] Under free-radical conditions, iodination proceeds more easily.[1514] However, *vic*-diiodides are generally unstable and tend to revert to iodine and the alkene.



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The mechanism is usually electrophilic (see p. 1002), involving formation of an halonium ion (**162**),[1515] followed by nucleophilic opening to give the *vic*-dihalide. Nucleophilic attack is occurs with selectivity for the less substituted carbon with unsymmetrical alkenes. When free-radical initiators (or UV light) are present, addition can occur by a free-radical mechanism.[1516] Once Br• or Cl• radicals are formed, however, substitution may compete (**14-1** and **14-3**). This is especially important when the alkene 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. 187).[1517]

Under ordinary conditions fluorine itself is too reactive to give simple addition; it attacks other bonds and mixtures are obtained.[1518] 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.[1519] Addition of fluorine has also been accomplished with other reagents (e.g., *p*-Tol—$IF_2/Et_3N{\bullet}5\ HF$),[1520] and a mixture of PbO_2 and SF_4.[1521]

[1510] For a list of reagents that have been used for di-halo-addition, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 629–632.

[1511] For a monograph, see de la Mare, P.B.D. *Electrophilic Halogenation*, Cambridge University Press, Cambridge, ***1976***. For a review, see House, H.O. *Modern Synthetic Reaction*, 2nd ed., W.A. Benjamin, NY, ***1972***, pp. 422–431.

[1512] McMillen, D.W.; Grutzner, J.B. *J. Org. Chem.* ***1994***, *59*, 4516.

[1513] Sumrell, G.; Wyman, B.M.; Howell, R.G.; Harvey, M.C. *Can. J. Chem.* ***1964***, *42*, 2710; Zanger, M.; Rabinowitz, J.L. *J. Org. Chem.* ***1975***, *40*, 248.

[1514] Skell, P.S.; Pavlis, R.R. *J. Am. Chem. Soc.* ***1964***, *86*, 2956; Ayres, R.L.; Michejda, C.J.; Rack, E.P. *J. Am. Chem. Soc.* ***1971***, *93*, 1389.

[1515] See Lenoir, D.; Chiappe, C. *Chem. Eur. J.* ***2003***, *9*, 1037.

[1516] For example, see Poutsma, M.L. *J. Am. Chem. Soc.* ***1965***, *87*, 2161, 2172; *J. Org. Chem.* ***1966***, *31*, 4167; Dessau, R.M. *J. Am. Chem. Soc.* ***1979***, *101*, 1344.

[1517] For a review, see Cais, M., in Patai, S. *The Chemistry of Alkenes*, Vol. 1, Wiley, NY, ***1964***, p. 993.

[1518] See, for example, Fuller, G.; Stacey, F.W.; Tatlow, J.C.; Thomas, C.R. *Tetrahedron* ***1962***, *18*, 123.

[1519] Merritt, R.F. *J. Am. Chem. Soc.* ***1967***, *89*, 609; Barton, D.H.R.; Lister-James, J.; Hesse, R.H.; Pechet, M.M.; Rozen, S. *J. Chem. Soc. Perkin Trans. 1* ***1982***, 1105; Rozen, S.; Brand, M. *J. Org. Chem.* ***1986***, *51*, 3607.

[1520] Hara, S.; Nakahigashi, J.; Ishi-i, K.; Sawaguchi, M.; Sakai, H.; Fukuhara, T.; Yoneda, N. *Synlett* ***1998***, 495.

[1521] Bissell, E.R.; Fields, D.B. *J. Org. Chem.* ***1964***, *29*, 1591.

The reaction with bromine is very rapid and is easily carried out at room temperature,[1522] although the reaction is reversible under some conditions.[1523] In the case of bromine, an alkene•Br_2 complex has been detected in at least one case.[1524] Bromine is often used as a test, qualitative or quantitative, for unsaturation.[1525] The vast majority of double bonds can be successfully brominated. Even when aldehyde, ketone, amine, and so on functions are present in the molecule, they do not interfere, since the reaction with double bonds is faster. Bromination has been carried out in an ionic liquid.[1526]

Several other reagents add Cl_2 to double bonds, among them Me_3SiCl^- MnO_2,[1527] $NaClO_2/Mn(acac)_2$/moist Al_2O_3,[1528] $BnNEt_3MnO_4/Me_3SiCl$,[1529] and $KMnO_4$-oxalyl chloride.[1530] A convenient reagent for the addition of Br_2 to a double bond on a small scale is the commercially available pyridinium bromide perbromide $C_5H_5NH^+Br_3^-$.[1531] Potassium bromide with ceric ammonium nitrate, in water/dichloromethane, gives the dibromide.[1532] A combination of KBr and Selectfluor also give the dibromide.[1533] A combination of $CuBr_2$ in aq. THF and a chiral ligand led to the dibromide with good enantioselectivity.[1534] A mixture of (decyl)Me_3 $NMnO_4$ and Me_3SiBr is also an effective reagent.[1535] Either Br_2 or Cl_2 can also be added with $CuBr_2$ or $CuCl_2$ in the presence of a compound, such as acetonitrile, methanol, or triphenylphosphine.[1536]

[1522] See Bellucci, G.; Chiappe, C. *J. Org. Chem.* ***1993***, *58*, 7120 for a study of the rate and kinetics of alkene bromination.

[1523] Zheng, C.Y.; Slebocka-Tilk, H.; Nagorski, R.W.; Alvarado, L.; Brown, R.S. *J. Org. Chem.* ***1993***, *58*, 2122.

[1524] Bellucci, G.; Chiappe, C.; Bianchini, R.; Lenoir, D.; Herges, R. *J. Am. Chem. Soc.* ***1995***, *117*, 12001.

[1525] For a review of this, see Kuchar, E.J., in Patai, S. *The Chemistry of Alkenes*, Vol. 1, Wiley, NY, ***1964***, pp. 273–280.

[1526] In bmim Br, 1-butyl-3-methylimidazolium bromide: Chiappe, C.; Capraro, D.; Conte, V.; Picraccini, D. *Org. Lett.* ***2001***, *3*, 1061.

[1527] Bellesia, F.; Ghelfi, F.; Pagnoni, U.M.; Pinetti, A. *J. Chem. Res. (S)* ***1989***, *108*, 360.

[1528] Yakabe, S.; Hirano, M.; Morimoto, T. *Synth. Comun.* ***1998***, *28*, 1871.

[1529] Markó, I.E.; Richardson, P.R.; Bailey, M.; Maguire, A.R.; Coughlan, N. *Tetrahedron Lett.* ***1997***, *38*, 2339.

[1530] Markó, I.E.; Richardson, P.F. *Tetrahedron Lett.* ***1991***, *32*, 1831.

[1531] Fieser, L.F.; Fieser, M. *Reagents for Organic Synthesis*, Vol. 1, Wiley, NY, ***1967***, pp. 967–970. For a discussion of the mechanism with Br_3^-, see Bellucci, G.; Bianchini, R.; Vecchiani, S. *J. Org. Chem.* ***1986***, *51*, 4224.

[1532] Nair, V.; Panicker, S.B.; Augstine, A.; George, T.G.; Thomas, S.; Vairamani, M. *Tetrahedron* ***2001***, *57*, 7417.

[1533] Ye, C.; Shreeve, J.M. *J. Org. Chem.* ***2004***, *69*, 8561.

[1534] El-Quisairi, A.K.; Qaseer, H.A.; Katsigras, G.; Lorenzi, P.; Tribedi, U.; Tracz, S.; Hartman, A.; Miller, J.A.; Henry, P.M. *Org. Lett.* ***2003***, *5*, 439.

[1535] Hazra, B.G.; Chordia, M.D.; Bahule, B.B.; Pore, V.S.; Basu, S. *J. Chem. Soc. Perkin Trans. 1* ***1994***, 1667.

[1536] Koyano, T. *Bull. Chem. Soc. Jpn.* ***1970***, *43*, 1439, 3501; Uemura, S.; Tabata, A.; Kimura, Y.; Ichikawa, K. *Bull. Chem. Soc. Jpn.* ***1971***, *44*, 1973; Or, A.; Levy, M.; Asscher, M.; Vofsi, D. *J. Chem. Soc. Perkin Trans. 2* ***1974***, 857; Uemura, S.; Okazaki, H.; Onoe, A.; Okano, M. *J. Chem. Soc. Perkin Trans. 1* ***1977***, 676; Baird, Jr., W.C.; Surridge, J.H.; Buza, M. *J. Org. Chem.* ***191***, *36*, 2088, 3324.

Mixed halogenations have also been achieved, and the order of activity for some of the reagents is BrCl > ICl[1537] > Br_2 > IBr > I_2.[1538] Mixtures of Br_2 and Cl_2 have been used to give bromochlorination,[1539] as has tetrabutylammonium dichlorobromate, Bu_4NBrCl_2;[1540] iodochlorination has been achieved with $KICl_2$,[1541] $CuCl_2$, and either I_2, HI, or CdI_2; iodofluorination[1542] with mixtures of AgF and I_2;[1543] and mixtures of *N*-bromo amides in anhydrous HF give bromofluorination.[1544] 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;[1545] while addition of I along with Br, Cl, or F has been accomplished with the reagent bis(pyridine)iodo(I) tetrafluoroborate $I(Py)_2BF_4$ and Br^-, Cl^-, or F^-, respectively.[1546] This reaction (which is also successful for triple bonds[1547]) can be extended to addition of I and other nucleophiles (e.g., NCO, OH, OAc, and NO_2).[1547] Cyclohexene is converted to *trans*-2-fluoroiodocyclohexane under electrolytic conditions using $Et_4NI—Et_3N{\bullet}HF$ in the reaction medium.[1548]

Conjugated systems give both 1,2- and 1,4-addition.[1518] Triple bonds add bromine, although generally more slowly than double bonds (see p. 1015). Molecules that contain both double and triple bonds are preferentially attacked at the double bond. Addition of 2 equivalents of bromine to triple bonds gives 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.[1549] Molecular diiodine on Al_2O_3 adds to triple bonds to give good yields of 1,2-diiodoalkenes.[1550] Interestingly, 1,1-diiodo alkenes are prepared from an alkynyltin compound, via initial treatment with $Cp_2Zr(H)Cl$, and then 2.15 equivalents of iodine.[1551] A mixture of

[1537] For a review of ICl, see McCleland, C.W., in Pizey, J.S. *Synthetic Reagents*, Vol. 5, Wiley, NY, ***1983***, pp. 85–164.

[1538] White, E.P.; Robertson, P.W. *J. Chem. Soc.* ***1939***, 1509.

[1539] Buckles, R.E.; Forrester, J.L.; Burham, R.L.; McGee, T.W. *J. Org. Chem.* ***1960***, *25*, 24.

[1540] Negoro, T.; Ikeda, Y. *Bull. Chem. Soc. Jpn.* ***1986***, *59*, 3519.

[1541] Zefirov, N.S.; Sereda, G.A.; Sosounk, S.E.; Zyk, N.V.; Likhomanova, T.I. *Synthesis* ***1995***, 1359.

[1542] For a review of mixed halogenations where one side is fluorine, see Sharts, C.M.; Sheppard, W.A. *Org. React.* ***1974***, *21*, 125, see pp. 137–157. For a review of halogen fluorides in organic synthesis, see Boguslavskaya, L.S. *Russ. Chem. Rev.* ***1984***, *53*, 1178.

[1543] Evans, R.D.; Schauble, J.H. *Synthesis* ***1987***, 551; Kuroboshi, M.; Hiyama, T. *Synlett* ***1991***, 185.

[1544] Pattison, F.L.M.; Peters, D.A.V.; Dean, F.H. *Can. J. Chem.* ***1965***, *43*, 1689. For other methods, see Boguslavskaya, L.S.; Chuvatkin, N.N.; Kartashov, A.V.; Ternovskoi, L.A. *J. Org. Chem. USSR* ***1987***, *23*, 230; Shimizu, M.; Nakahara, Y.; Yoshioka, H. *J. Chem. Soc., Chem. Commun.* ***1989***, 1881.

[1545] Olah, G.A.; Nojima, M.; Kerekes, I. *Synthesis* ***1973***, 780; Olah, G.A.; Welch, J.T.; Vankar, Y.D.; Nojima, M.; Kerekes, I.; Olah, J.A. *J. Org. Chem.* ***1979***, *44*, 3872. For other halofluorination methods, see Rozen, S.; Brand, M. *J. Org. Chem.* ***1985***, *50*, 3342; ***1986***, *51*, 222; Alvernhe, G.; Laurent, A.; Haufe, G. *Synthesis* ***1987***, 562; Camps, F.; Chamorro, E.; Gasol, V.; Guerrero, A. *J. Org. Chem.* ***1989***, *54*, 4294; Ichihara, J.; Funabiki, K.; Hanafusa, T. *Tetrahedron Lett.* ***1990***, *31*, 3167.

[1546] Barluenga, J.; González, J.M.; Campos, P.J.; Asensio, G. *Angew. Chem. Int. Ed.* ***1985***, *24*, 319.

[1547] Barluenga, J.; Rodríguez, M.A.; González, J.M.; Campos, P.J.; Asensio, G. *Tetrahedron Lett.* ***1986***, *27*, 3303.

[1548] Kobayashi, S.; Sawaguchi, M.; Ayuba, S.; Fukuhara, T.; Hara, S. *Synlett* ***2001***, 1938.

[1549] Sinn, H.; Hopperdietzel, S.; Sauermann, D. *Monatsh. Chem.* ***1965***, *96*, 1036.

[1550] Hondrogiannis, G.; Lee, L.C.; Kabalka, G.W.; Pagni, R.M. *Tetrahedron Lett.* ***1989***, *30*, 2069.

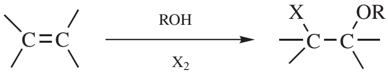
[1551] Dabdoub, M.J.; Dabdoub, V.B.; Baroni, A.C.M. *J. Am. Chem. Soc.* ***2001***, *123*, 9694.

$NaBO_3$ and NaBr adds two bromine atoms across a triple bond.[1552] With allenes it is easy to stop the reaction after only 1 equivalent has added, to give X—C—CX=C.[1553] 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; **IX**, 117; **76**, 159.

15-40 Addition of Hypohalous Acids and Hypohalites (Addition of Halogen, Oxygen)

Hydroxy-chloro-addition, and so on.[1554]
Alkoxy-chloro-addition, and so on.



Hypohalous acids (HOCl, HOBr, and HOI) can be added to alkenes[1555] to produce halohydrins.[1556] Both HOBr and HOCl are often generated *in situ* by the reaction between water and Br_2 or Cl_2, respectively. HOI, generated from I_2 and H_2O, also adds to double bonds, if the reaction is carried out in tetramethylene sulfone-$CHCl_3$[1557] or if an oxidizing agent, such as HIO_3 is present.[1558] Iodine and cerium sulfate in aqueous acetonitrile generates iodohydrins,[1559] as does iodine and ammonium acetate in acetic acid,[1560] or $NaIO_4$ with sodium bisulfite.[1561] The HOBr can also be conveniently added by the use of a reagent consisting of an *N*-bromo amide

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[1552] Kabalka, G.W.; Yang, K. *Synth. Commun.* ***1998***, *28*, 3807; Kabalka, G.W.; Yang, K.; Reddy, N.K.; Narayana, A. *Synth. Commun.* ***1998***, *28*, 925.

[1553] For a review of additions of halogens to allenes, see Jacobs, T.L., in Landor, S.R. *The Chemistry of Allenes*, Vol. 2, Academic Press, NY, ***1982***, pp. 466–483.

[1554] Addends are listed in order of priority in the Cahn–Ingold–Prelog system (p. 155).

[1555] For a list of reagents used to accomplish these additions, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 638–642.

[1556] For a review, see Boguslavskaya, L.S. *Russ. Chem. Rev.* ***1972***, *41*, 740.

[1557] Cambie, R.C.; Noall, W.I.; Potter, G.J.; Rutledge, P.S.; Woodgate, P.D. *J. Chem. Soc. Perkin Trans. 1* ***1977***, 266.

[1558] See, for example, Cornforth, J.W.; Green, D.T. *J. Chem. Soc. C* ***1970***, 846; Furrow, S.D. *Int. J. Chem. Kinet.* ***1982***, *14*, 927; Antonioletti, R.; D'Auria, M.; De Mico, A.; Piancatelli, G.; Scettri, A. *Tetrahedron* ***1983***, *39*, 1765.

[1559] Horiuchi, C.A.; Ikeda, A.; Kanamori, M.; Hosokawa, H.; Sugiyama, T.; Takahashi, T.T. *J. Chem. Res. (S)* ***1997***, 60.

[1560] Myint, Y.Y.; Pasha, M.A. *Synth. Commun.* ***2004***, *34*, 4477.

[1561] Masuda, H.; Takase, K.; Nishio, M.; Hasegawa, A.; Nishiyama, Y.; Ishii, Y. *J. Org. Chem.* ***1994***, *59*, 5550.

(e.g., NBS or *N*-bromoacetamide) and a small amount of water in a solvent, such as DMSO or dioxane.[1562] *N*-Iodosuccinimide (NIS) in aqueous dimethoxyethane leads to the iodohydrin.[1563] An especially powerful reagent for HOCl addition is *tert*-butyl hydroperoxide (or di-*tert*-butyl peroxide) along with $TiCl_4$. This reaction is generally complete within 15 min at −78°C.[1564] Chlorohydrins can be conveniently prepared by treatment of the alkene with Chloramine T ($TsNCl^-$ Na^+)[1565] in acetone–water.[1566] The compound HOI can be added by treatment of alkenes with periodic acid and $NaHSO_3$.[1567] The reaction of an alkene with polymeric $(SnO)_n$, and then HCl with $Me_3SiOOSiMe_3$ leads to the chlorohydrin.[1568] Hypervalent iodine compounds react with an alkene and iodine in aqueous media to give the iodohydrin.[1569]

The compound HOF has also been added, but this reagent is difficult to prepare in a pure state and *explosions have occurred.*[1570]

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 (forming a more stable carbocation). This carbocation (or bromonium or iodonium ion in the absence of an aqueous solvent) reacts with ^-OH or H_2O to give the product. If the substrate is treated with Br_2 or Cl_2 (or another source of positive halogen such as NBS) in an alcohol or a carboxylic acid solvent, it is possible to obtain, directly $X{-}\overset{|}{\underset{|}{C}}{-}\overset{|}{\underset{|}{C}}{-}OR$ or $X{-}\overset{|}{\underset{|}{C}}{-}\overset{|}{\underset{|}{C}}{-}OCOR$, respectively (see also, **15-48**).[1571] Even the weak nucleophile $CF_3SO_2O^-$ can participate in the second step: The addition of Cl_2 or Br_2 to alkenes in the presence of this ion resulted in the formation of some β-haloalkyl triflates.[1572] There is evidence that the mechanism with Cl_2 and H_2O is different from that with HOCl.[1573] HOCl and HOBr can be added to triple bonds to give dihalo carbonyl compounds $—CX_2—CO—$.

[1562] For examples, see Dalton, D.R.; Hendrickson, J.B.; Jones, D. *Chem. Commun.* ***1966***, 591; Dalton, D.R.; Dutta, V.P. *J. Chem. Soc. B* ***1971***, 85; Sisti, A.J. *J. Org. Chem.* ***1970***, *35*, 2670.

[1563] Smietana, M.; Gouverneur, V.; Mioskowski, C. *Tetahedron Lett.* ***2000***, *41*, 193.

[1564] Klunder, J.M.; Caron M.; Uchiyama, M.; Sharpless, K.B. *J. Org. Chem.* ***1985***, *50*, 912.

[1565] For reviews of this reagent, see Bremner, D.H., in Pizey, J.S. *Synthetic Reagents*, Vol. 6, Wiley, NY, ***1985***, pp. 9–59; Campbell, M.M.; Johnson, G. *Chem. Rev.* ***1978***, *78*, 65.

[1566] Damin, B.; Garapon, J.; Sillion, B. *Synthesis* ***1981***, 362.

[1567] Ohta, M.; Sakata, Y.; Takeuchi, T.; Ishii, Y. *Chem. Lett.* ***1990***, 733.

[1568] Sakurada, I.; Yamasaki, S.; Göttlich, R.; Iida, T.; Kanai, M.; Shibasaki, M. *J. Am. Chem. Soc.* ***2000***, *122*, 1245.

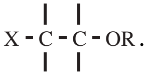
[1569] DeCorso, A.R.; Panunzi, B.; Tingoli, M. *Tetrahedron Lett.* ***2001***, *42*, 7245.

[1570] Migliorese, K.G.; Appelman, E.H.; Tsangaris, M.N. *J. Org. Chem.* ***1979***, *44*, 1711.

[1571] For a list of reagents that accomplish alkoxy-halo-addition, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 642–643.

[1572] Zefirov, N.S.; Koz'min, A.S.; Sorokin, V.D.; Zhdankin, V.V. *J. Org. Chem. USSR* ***1982***, *18*, 1546. For reviews of this and related reactions, see Zefirov, N.S.; Koz'min, A.S. *Acc. Chem. Res.* ***1985***, *18*, 154; *Sov. Sci. Rev. Sect. B* ***1985***, *7*, 297.

[1573] Buss, E.; Rockstuhl, A.; Schnurpfeil, D. *J. Prakt. Chem.* ***1982***, *324*, 197.

Alcohols and halogens react with alkenes to form halo ethers. When a homoallylic alcohol is treated with bromine, cyclization occurs to give a 3-bromotetrahydrofuran derivative.[1574] *tert*-Butyl hypochlorite (Me_3COCl), hypobromite, and hypoiodite[1575] add to double bonds to give halogenated *tert*-butyl ethers, X—C—C—$OCMe_3$. This is a convenient method for the preparation of tertiary ethers. Iodine and ethanol convert some alkenes to iodo-ethers.[1576] Iodine, alcohol and a $Ce(OTf)_2$ catalyst also generates the iodo-ether.[1577] When Me_3COCl or Me_3COBr is added to alkenes in the presence of excess ROH, the ether produced is  $\mathrm{X-\overset{|}{\underset{|}{C}}-\overset{|}{\underset{|}{C}}-OR}$.[1578] Vinylic ethers give β-halo acetals.[1579] A mixture of Cl_2 and SO_3 at −78°C converts alkenes to 2-chloro chlorosulfates $ClCHRCHROSO_2Cl$, which are stable compounds.[1580] Chlorine acetate [solutions of which are prepared by treating Cl_2 with $Hg(OAc)_2$ in an appropriate solvent] adds to alkenes to give acetoxy chlorides.[1581] Acetoxy fluorides have been obtained by treatment of alkenes with CH_3COOF.[1582]

For a method of iodoacetyl addition, see **15-48**.

An oxidative variation of this reaction treats a vinyl chloride with NaOCl and acetic acid, generating an α-chloro ketone.[1583]

OS **I**, 158; **IV**, 130, 157; **VI**, 184, 361, 560; **VII**, 164; **VIII**, 5, 9.

15-41 Halolactonization and Halolactamization

Halo-alkoxylation

Halo esters can be formed by addition of halogen atoms and ester groups to an alkene. Alkene carboxylic acids give a tandem reaction of formation of a halonium ion followed by intramolecular displacement of the carboxylic group to give a halo lactone. This tandem addition of X and OCOR is called

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[1574] Chirskaya, M.V.; Vasil'ev, A.A.; Sergovskaya, N.L.; Shovshinev, S.V.; Sviridov, S.I. *Tetrahedron Lett.* ***2004***, *45*, 8811.

[1575] Glover, S.A.; Goosen, A. *Tetrahedron Lett.* ***1980***, *21*, 2005.

[1576] Sanseverino, A.M.; de Mattos, M.C.S. *Synthesis* ***1998***, 1584. See Horiuchi, C.A.; Hosokawa, H.; Kanamori, M.; Muramatsu, Y.; Ochiai, K.; Takahashi, E. *Chem. Lett.* ***1995***, 13 for an example using I_2/MeOH/ceric ammonium nitrate.

[1577] Iranpoor, N.; Shekarriz, M. *Tetahedron* ***2000***, *56*, 5209.

[1578] Bresson, A.; Dauphin, G.; Geneste, J.; Kergomard, A.; Lacourt, A. *Bull. Soc. Chim. Fr.* ***1970***, 2432; ***1971***, 1080.

[1579] Weissermel, K.; Lederer, M. *Chem. Ber.* ***1963***, *96*, 77.

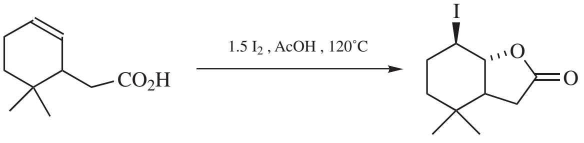
[1580] Zefirov, N.S.; Koz'min, A.S.; Sorokin, V.D. *J. Org. Chem.* ***1984***, *49*, 4086.

[1581] de la Mare, P.B.D.; O'Connor, C.J.; Wilson, M.A. *J. Chem. Soc. Perkin Trans. 2*, ***1975***, 1150. For the addition of bromine acetate, see Wilson, M.A.; Woodgate, P.D. *J. Chem. Soc. Perkin Trans. 2*, ***1976***, 141. For a list of reagents that accomplish acyloxy-halo-addition, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 643–644.

[1582] Rozen, S.; Lerman, O.; Kol, M.; Hebel, D. *J. Org. Chem.* ***1985***, *50*, 4753.

[1583] Van Brunt, M.P.; Ambenge, R.O.; Weinreb, S.M. *J. Org. Chem.* ***2003***, *68*, 3323.

halolactonization.[1584]

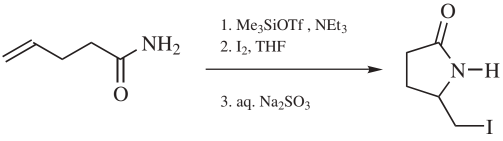


163 **164**

The most common version of this reaction is known as *iodolactonization*,[1585] and a typical example is the conversion of **163** to **164**.[1586] Bromo lactones and, to a lesser extent, chloro lactones have also been prepared. In general, addition of the halogen to an alkenyl acid, as shown, leads to the halo-lactone. Other reagents include $I^+(\text{collidine})_2PF_6^-$,[1587] KI/sodium persulfate.[1588] Thallium reagents, along with the halogen, have also been used.[1589] When done in the presence of a chiral titanium reagent, I_2, and CuO, lactones are formed with good enantioselectivity.[1590] ICl has been used, with formation of a quaternary center at the oxygen-bearing carbon of the lactone.[1591]

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. There is a gem-dimethyl effect that favors formation of 7–11-membered ring lactones by this procedure.[1592]

Formation of halo-lactams (**15-43**) by a similar procedure is difficult, but the problems have been overcome. Formation of a triflate followed by treatment with iodine leads to the iodo-lactam, **165**.[1593]



165

[1584] For reviews, see Cardillo, G.; Orena, M. *Tetrahedron* ***1990***, *46*, 3321; Dowle, M.D.; Davies, D.I. *Chem. Soc. Rev.* ***1979***, *8*, 171. For a list of reagents that accomplish this, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 1870–1876. For a review with respect to the stereochemistry of the reaction, see Bartlett, P.A., in Morrison, J.D. *Organic Synthesis*, Vol. 3, Wiley, NY, ***1984***, pp. 411–454, 416–425.

[1585] Klein, J. *J. Am. Chem. Soc.* ***1959***, *81*, 3611; van Tamelen, E.E.; Shamma, M. *J. Am. Chem. Soc.* ***1954***, *76*, 2315; House, H.O.; Carlson, R.G.; Babad, H. *J. Org. Chem.* ***1963***, *28*, 3359; Corey, E.J.; Albonico, S.M.; Koelliker, V.; Schaaf, T.K.; Varma, R.K. *J. Am. Chem. Soc.* ***1971***, *93*, 1491.

[1586] Yaguchi, Y.; Akiba, M.; Harada, M.; Kato, T. *Heterocycles* ***1996***, *43*, 601.

[1587] Homsi, F.; Rousseau, G. *J. Org. Chem.* ***1998***, *63*, 5255; Simonet, B.; Rousseau, G. *J. Org. Chem.* ***1993***, *58*, 4.

[1588] Royer, A.C.; Mebane, R.C.; Swafford, A.M. *Synlett* ***1993***, 899.

[1589] See Cambie, R.C.; Rutledge, P.S.; Somerville, R.F.; Woodgate, P.D. *Synthesis* ***1988***, 1009, and references cited therein.

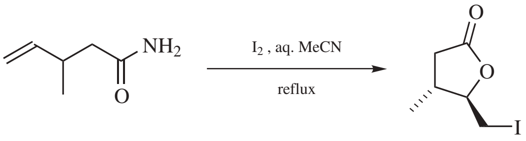
[1590] Inoue, T.; Kitagawa, O.; Kurumizawa, S.; Ochiai, O.; Taguchi, T. *Tetrahedron Lett.* ***1995***, *36*, 1479.

[1591] Haas, J.; Piguel, S.; Wirth, T. *Org. Lett.* ***2002***, *4*, 297.

[1592] Simonot, B.; Rousseau, G. *Tetrahedron Lett.* ***1993***, *34*, 4527.

[1593] Knapp, S.; Rodriques, K.E. *Tetrahedron Lett.* ***1985***, *26*, 1803.

A related cyclization of *N*-sulfonyl-amino-alkenes and NBS gave the bromo-lactam,[1594] and a dichloro-*N,N*-bis(allylamide) was converted to a dichloro-lactam with $FeCl_2$.[1595] It is noted that lactone formation is possible from unsaturated amides. The reaction of 3-methyl *N,N*-dimethylpent-4-ene amide with iodine in aqueous acetonitrile, for example, gave iodolactone **166**.[1596]

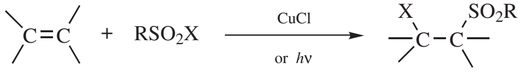


166

OS IX, 516.

15-42 Addition of Sulfur Compounds (Addition of Halogen, Sulfur)

Alkylsulfonyl-chloro-addition, and so on.[1597]



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.[1598] A combination of the anion $ArSO_2Na$, NaI, and ceric ammonium nitrate converts alkenes to vinyl sulfones.[1599] Triple bonds behave similarly, to give β-halo-α,β-unsaturated sulfones.[1600] In a similar reaction, sulfenyl chlorides, RSCl, give β-halo thioethers.[1601] 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 alkene with Me_3SiCl and Me_2SO.[1602] The use of Me_3SiBr and Me_2SO does not give this result; dibromides (**15-39**) are formed instead. β-Iodo

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[1594] Tamaru, Y.; Kawamura, S.; Tanaka, K.; Yoshida, Z. *Tetrahedron Lett.* ***1984***, *25*, 1063.

[1595] Tseng, C.K.; Teach, E.G.; Simons, R.W. *Synth. Commun.* ***1984***, *14*, 1027.

[1596] Ha, H.-J.; Lee, S.-Y.; Park, Y.-S. *Synth. Commun.* ***2000***, *30*, 3645.

[1597] When a general group (e.g., halo) is used, its priority is that of the lowest member of its group (see Ref. 1555). Thus the general name for this transformation is halo-alkylsulfonyl-addition because "halo" has the same priority as "fluoro," its lowest member.

[1598] Asscher, M.; Vofsi, D. *J. Chem. Soc.* ***1964***, 4962; Truce, W.E.; Goralski, C.T.; Christensen, L.W.; Bavry, R.H. *J. Org. Chem.* ***1970***, *35*, 4217; Sinnreich, J.; Asscher, M. *J. Chem. Soc. Perkin Trans. 1*, ***1972***, 1543.

[1599] Nair, V.; Augustine, A.; George, T.G.; Nair, L.G. *Tetrahedron Lett.* ***2001***, *42*, 6763.

[1600] Truce, W.E.; Wolf, G.C. *J. Org. Chem.* ***1971***, *36*, 1727; Amiel, Y. *J. Org. Chem.* ***1974***, *39*, 3867; Zakharkin, L.I.; Zhigareva, G.G. *J. Org. Chem. USSR* ***1973***, *9*, 918; Okuyama, T.; Izawa, K.; Fueno, T. *J. Org. Chem.* ***1974***, *39*, 351.

[1601] For reviews, see Rasteikiene, L.; Greiciute, D.; Lin'kova, M.G.; Knunyants, I.L. *Russ. Chem. Rev.* ***1977***, *46*, 548; Kühle, E. *Synthesis* ***1971***, 563.

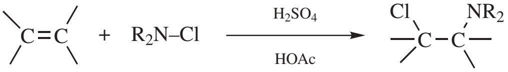
[1602] Bellesia, F.; Ghelfi, F.; Pagnoni, U.M.; Pinetti, A. *J. Chem. Res. (S)* ***1987***, 238. See also, Liu, H.; Nyangulu, J.M. *Tetrahedron Lett.* ***1988***, *29*, 5467.

thiocyanates can be prepared from alkenes by treatment with I_2 and isothiocyanatotributylstannane Bu_3SnNCS.[1603] Bromothiocyanation can be accomplished with Br_2 and thallium(I) thiocyanate.[1604] Lead (II) thiocyanate reacts with terminal alkynes in the presence of $PhICl_2$ to give the bis(thiocyanato) alkene, ArC(SCN)—CHSCN.[1605] Such compounds were also prepared from alkenes using KSCN and $FeCl_3$.[1606] β-Halo disulfides, formed by addition of arenethiosulfenyl chlorides to double-bond compounds, are easily converted to thiiranes by treatment with sodium amide or sodium sulfide.[1607]

OS **VIII**, 212. See also OS **VII**, 251.

15-43 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 alkenes, allenes, conjugated dienes, and alkynes, by treatment with dialkyl-*N*-chloroamines and acids.[1608] The reaction of $TsNCl_2$ and a $ZnCl_2$ catalyst gave the chloro tosylamine.[1609] These are free-radical additions, with initial attack by the $R_2NH^{\bullet+}$ radical ion.[1610] *N*-Halo amides RCONHX add RCONH and X to double bonds under the influence of uv light or chromous chloride.[1611] Amines add to allenes in the presence of a palladium catalyst.[1612] A mixture of *N*-(2-nosyl)NCl_2 and sodium *N*-(2-nosyl)NH^- with a CuOTf catalyst reacted with conjugated esters to give the *vicinal* (*E*)-3-chloro-2-amino ester.[1613] A variation of this latter reaction was done in an ionic liquid.[1614]

[1603] Woodgate, P.D.; Janssen, S.J.; Rutledge, P.S.; Woodgate, S.D.; Cambie, R.C. *Synthesis* ***1984***, 1017, and references cited therein. See also, Watanabe, N.; Uemura, S.; Okano, M. *Bull. Chem. Soc. Jpn.* ***1983***, *56*, 2458.

[1604] Cambie, R.C.; Larsen, D.S.; Rutledge, P.S.; Woodgate, P.D. *J. Chem. Soc. Perkin Trans. 1*, ***1981***, 58.

[1605] Prakash, O.; Sharma, V.; Batra, H.; Moriarty, R.M. *Tetrahedron Lett.* ***2001***, *42*, 553.

[1606] Yadav, J.S.; Reddy, B.V.S.; Gupta, M.K. *Synthesis* ***2004***, 1983.

[1607] Fujisawa, T.; Kobori, T. *Chem. Lett.* ***1972***, 935. For another method of alkene-thiirane conversion, see Capozzi, F.; Capozzi, G.; Menichetti, S. *Tetrahedron Lett.* ***1988***, *29*, 4177.

[1608] For reviews see Mirskova, A.N.; Drozdova, T.I.; Levkovskaya, G.G.; Voronkov, M.G. *Russ. Chem. Rev.* ***1989***, *58*, 250; Neale, R.S. *Synthesis* ***1971***, 1; Sosnovsky, G.; Rawlinson, D.J. *Adv. Free-Radical Chem.* ***1972***, *4*, 203, see pp. 238–249.

[1609] Li, G.; Wei, H.-X.; Kim, S.H.; Neighbors, M. *Org. Lett.* ***1999***, *1*, 395; Wei, H.-X.; Ki, S.H.; Li, G. *Tetrahedron* ***2001***, *57*, 3869.

[1610] For a review of these species, see Chow, Y.L.; Danen, W.C.; Nelson, S.F.; Rosenblatt, D.H. *Chem. Rev.* ***1978***, *78*, 243.

[1611] Tuaillon, J.; Couture, Y.; Lessard, J. *Can. J. Chem.* ***1987***, *65*, 2194, and other papers in this series. For a review, see Labeish, N.N.; Petrov, A.A. *Russ. Chem. Rev.* ***1989***, *58*, 1048.

[1612] Besson, L.; Goré, J.; Cazes, B. *Tetrahedron Lett.* ***1995***, *36*, 3857.

[1613] Li, G.; Wei, H.-X.; Kim, S.H. *Org. Lett.* ***2000***, *2*, 2249; Li, G.; Wei, H.-X.; Kim, S.H. *Tetrahedron* ***2001***, *57*, 8407.

[1614] In bmim BF_4, 1-butyl-3-methylimidazolium tetrafluoroborate: Xu, X.; Kotti, S.R.S.S.; Liu, J.; Cannon, J.F.; Headley, A.D.; Li, G. *Org. Lett.* ***2004***, *6*, 4881.

15-44 Addition of NOX and NO_2X (Addition of Halogen, Nitrogen)

Nitroso-chloro-addition

There are three possible products when NOCl is added to alkenes, a β-halo nitroso compound, an oxime, or a β-halo nitro compound.[1615] The initial product is always the β-halo nitroso compound,[1616] but these are stable only if the carbon bearing the nitrogen has no hydrogen. If it has, the nitroso compound tautomerizes to the oxime, H—C–N=O → C=N–OH. With some alkenes, the initial β-halo nitroso compound is oxidized by the NOCl to a β-halo nitro compound.[1617] 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, although syn addition has been reported in some cases.[1618] Markovnikov's rule is followed, the positive NO going to the carbon that has more hydrogens.

Nitryl chloride NO_2Cl also adds to alkenes, to give β-halo nitro compounds, but this is a free-radical process. The NO_2 goes to the less-substituted carbon.[1619] Nitryl chloride also adds to triple bonds to give the expected 1-nitro-2-chloro alkenes.[1620] The compound FNO_2 can be added to alkenes[1621] by treatment with HF in HNO_3[1622] or by addition of the alkene to a solution of nitronium tetrafluoroborate (NO_2^+ BF_4^-) (see **11-2**) in 70% polyhydrogen fluoride–pyridine solution[1623] (see also **15-37**).

OS **IV**, 711; **V**, 266, 863.

15-45 Addition of XN_3 (Addition of Halogen, Nitrogen)

Azido-iodo-addition

[1615] For a review, see Kadzyauskas, P.P.; Zefirov, N.S. *Russ. Chem. Rev.* ***1968***, *37*, 543.

[1616] For a review of preparations of *C*-nitroso compounds, see Gowenlock, B.G.; Richter-Addo, G.B. *Chem. Rev.* ***2004***, *104*, 3315.

[1617] For a review of the preparation of halo nitro compounds, see Shvekhgeimer, G.A.; Smirnyagin, V.A.; Sadykov, R.A.; Novikov, S.S. *Russ. Chem. Rev.* ***1968***, *37*, 351.

[1618] For example, see Meinwald, J.; Meinwald, Y.C.; Baker III, T.N. *J. Am. Chem. Soc.* ***1964***, *86*, 4074.

[1619] Shechter, H. *Rec. Chem. Prog.* ***1964***, *25*, 55–76.

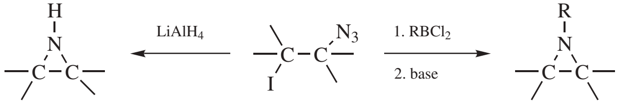
[1620] Schlubach, H.H.; Braun, A. *Liebigs Ann. Chem.* ***1959***, *627*, 28.

[1621] For a review, see Sharts, C.M.; Sheppard, W.A. *Org. React.* ***1974***, *21*, 125–406, see pp. 236–243.

[1622] Knunyants, I.L.; German, L.S.; Rozhkov, I.N. *Bull Acad. Sci. USSR Div. Chem. Sci.* ***1963***, 1794.

[1623] Olah, G.A.; Nojima, M. *Synthesis* ***1973***, 785.

The addition of iodine azide to double bonds gives β-iodo azides.[1624] The reagent can be prepared *in situ* from KI—NaN_3 in the presence of Oxone®-wet alumina.[1625] The addition is stereospecific and anti, suggesting that the mechanism involves a cyclic iodonium ion intermediate.[1626] The reaction has been performed on many double-bond compounds, including allenes[1627] and α,β-unsaturated ketones. Similar reactions can be performed with BrN_3[1628] and ClN_3. 1,4-Addition has been found with acyclic conjugated dienes.[1629] In the case of BrN_3, both electrophilic and free-radical mechanisms are important,[1630] while with ClN_3 the additions are chiefly free radical.[1631] The compound IN_3 also adds to triple bonds to give β-iodo-α,β-unsaturated azides.[1632]



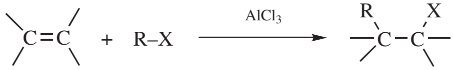
167 **168**

β-Iodo azides can be reduced to aziridines (**167**) with $LiAlH_4$[1633] or converted to *N*-alkyl- or *N*-arylaziridines (**168**) by treatment with an alkyl- or aryldichloroborane followed by a base.[1634] In both cases, the azide is first reduced to the corresponding amine (primary or secondary, respectively) and ring closure (**10-31**) follows. With Chloramine T ($TsNCl^-\ Na^+$) and 10% of pyridinium bromide perbromide, however, the reaction with alkenes give an *N*-tosyl aziridine directly.[1635]

OS **VI**, 893.

15-46 Addition of Alkyl Halides (Addition of Halogen, Carbon)

Alkyl-halo-addition[1062]



[1624] For reviews, see Dehnicke, K. *Angew. Chem. Int. Ed.* ***1979***, *18*, 507; Hassner, A. *Acc. Chem. Res.* ***1971***, *4*, 9; Biffin, M.E.C.; Miller, J.; Paul, D.B., in Patai, S. *The Chemistry of the Azido Group*, Wiley, NY, ***1971***, pp. 136–147. See Nair, V.; George, T.G.; Sheeba, V.; Augustine, A.; Balagopal, L.; Nair, L.G. *Synlett* ***2000***, 1597.

[1625] Curini, M.; Epifano, F.; Marcotullio, M.C.; Rosati, O. *Tetrahedron Lett.* ***2002***, *43*, 1201.

[1626] See, however, Cambie, R.C.; Hayward, R.C.; Rutledge, P.S.; Smith-Palmer, T.; Swedlund, B.E.; Woodgate, P.D. *J. Chem. Soc. Perkin Trans. 1*, ***1979***, 180.

[1627] Hassner, A.; Keogh, J. *J. Org. Chem.* ***1986***, *51*, 2767.

[1628] Azido-bromo-addition has also been done with another reagent: Olah, G.A.; Wang, Q.; Li, X.; Prakash, G.K.S. *Synlett* ***1990***, 487.

[1629] Hassner, A.; Keogh, J. *Tetrahedron Lett.* ***1975***, 1575.

[1630] Hassner, A.; Teeter, J.S. *J. Org. Chem.* ***1971***, *36*, 2176.

[1631] Even IN_3 can be induced to add by a free-radical mechanism [see, e.g., Cambie, R.C.; Jurlina, J.L.; Rutledge, P.S.; Swedlund, B.E.; Woodgate, P.D. *J. Chem. Soc. Perkin Trans. 1*, ***1982***, 327]. For a review of free-radical additions of XN_3, see Hassner, A. *Intra-Sci. Chem. Rep.* ***1970***, *4*, 109.

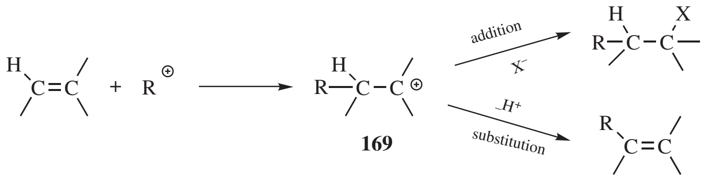
[1632] Hassner, A.; Isbister, R.J.; Friederang, A. *Tetrahedron Lett.* ***1969***, 2939.

[1633] Hassner, A.; Matthews, G.J.; Fowler, F.W. *J. Am. Chem. Soc.* ***1969***, *91*, 5046.

[1634] Levy, A.B.; Brown, H.C. *J. Am. Chem. Soc.* ***1973***, *95*, 4067.

[1635] Ali, S.I.; Nikalje, M.D.; Sudalai, A. *Org. Lett.* ***1999***, *1*, 705.

Alkyl halides can be added to alkenes in the presence of a Friedel–Crafts catalyst, most often $AlCl_3$.[1636] The yields are best for tertiary R. Secondary R can also be used, but primary R give rearrangement products (as with **11-11**). Methyl and ethyl halides, which cannot rearrange to a more stable secondary or tertiary carbocation, give no reaction at all. The attacking species is the carbocation formed from the alkyl halide and the catalyst (see **11-11**).[1637] 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 an additional molecule of alkene attacks the initially formed carbocation (**169**). Conjugated dienes can add 1,4.[1638] Triple bonds also undergo the reaction, to give vinylic halides.[1639]



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Simple polyhalo alkanes, such as CCl_4, $BrCCl_3$, ICF_3 and related molecules, add to alkenes in good yield.[1640] These are free-radical additions and require initiation, for example,[1641] by peroxides, metal halides (e.g., $FeCl_2$, CuCl),[1642] ruthenium catalysts,[1643] 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:

$$RHC{-}CH_2 + \bullet CX_3 \longrightarrow RH\dot{C}{-}CH_2CX_3 \xrightarrow{CX_4} RH\overset{X}{\overset{|}{C}}{-}CH_2CX_3 + \bullet CX_3$$

[1636] For a review, see Schmerling, L., in Olah, G.A. *Friedel–Crafts and Related Reactions*, Vol. 2, Wiley, NY, ***1964***, pp. 1133–1174. See also, Mayr, H.; Schade, C.; Rubow, M.; Schneider, R. *Angew. Chem. Int. Ed.* ***1987***, *26*, 1029.

[1637] For a discussion of the mechanism, see Pock, R.; Mayr, H.; Rubow, M.; Wilhelm, E. *J. Am. Chem. Soc.* ***1986***, *108*, 7767.

[1638] Kolyaskina, Z.N.; Petrov, A.A. *J. Gen. Chem. USSR* ***1962***, *32*, 1067.

[1639] See, for example, Maroni, R.; Melloni, G.; Modena, G. *J. Chem. Soc. Perkin Trans. 1*, ***1973***, 2491; ***1974***, 353.

[1640] For reviews, see Freidlina, R.Kh.; Velichko, F.K. *Synthesis* ***1977***, 145; Freidlina, R.Kh.; Chukovskaya, E.C. *Synthesis* ***1974***, 477.

[1641] For other initiators, see Matsumoto, H.; Nakano, T.; Takasu, K.; Nagai, Y. *J. Org. Chem.* ***1978***, *43*, 1734; Tsuji, J.; Sato, K.; Nagashima, H. *Tetrahedron* ***1985***, *41*, 393; Bland, W.J.; Davis, R.; Durrant, J.L.A. *J. Organomet. Chem.* ***1985***, *280*, 397; Phelps, J.C.; Bergbreiter, D.E.; Lee, G.M.; Villani, R.; Weinreb, S.M. *Tetrahedron Lett.* ***1989***, *30*, 3915.

[1642] For example, see Asscher, M.; Vofsi, D. *J. Chem. Soc.* ***1963***, 1887, 3921; *J. Chem. Soc. B* ***1968***, 947; Murai, S.; Tsutsumi, S. *J. Org. Chem.* ***1966***, *31*, 3000; Martin, P.; Steiner, E.; Streith, J.; Winkler, T.; Bellus, D. *Tetrahedron* ***1985***, *41*, 4057. For the addition of CH_2Cl_2 and PhBr, see Mitani, M.; Nakayama, M.; Koyama, K. *Tetrahedron Lett.* ***1980***, *21*, 4457.

[1643] Simal, F.; Wlodarczak, L.; Demonceau, A.; Noels, A.F. *Eur. J. Org. Chem.* ***2001***, 2689.

This type of polyhalo alkane adds to halogenated alkenes 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, **16-54**).[1644]

α-Iodolactones add to alkenes in the presence of BEt_3/O_2 to give the addition product.[1645] Other α-iodoesters add under similar conditions to give the lactone.[1646] Iodoesters also add to alkenes in the presence of BEt_3 to give iodo-esters that have not cyclized.[1647]

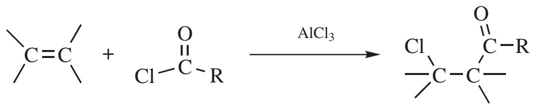
A variant of the free-radical addition method has been used for ring closure (see **15-30**).

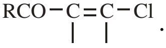
For another method of adding R and I to a triple bond (see **15-23**).

OS **II**, 312; **IV**, 727; **V**, 1076; **VI**, 21; **VII**, 290.

15-47 Addition of Acyl Halides (Addition of Halogen, Carbon)

Acyl-halo-addition



Acyl halides have been added to many alkenes, in the presence of Friedel–Crafts catalysts, although polymerization is a problem. The reaction has been applied to straight-chain, branched, and cyclic alkenes, but to very few containing functional groups, other than halogen.[1648] The mechanism is similar to that of **15-46**, and, as in that case, substitution competes (**12-16**). Increasing temperature favors substitution,[1649] 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.[1650] Iodo acetates have been formed from alkenes using iodine, $Pb(OAc)_2$ in acetic acid.[1651] The reaction can be performed on triple-bond compounds, producing compounds of the form  $RCO-\underset{|}{C}=\underset{|}{C}-Cl$.[1652] A *formyl* group and a halogen can be added to triple bonds by treatment with *N,N*-disubstituted formamides

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[1644] For a review with respect to fluoroalkenes, see Paleta, O. *Fluorine Chem. Rev.* ***1977***, *8*, 39.

[1645] Nakamura, T.; Yorimitsu, H.; Shinokubo, H.; Oshima, K. *Synlett* ***1998***, 1351.

[1646] Yorimitsu, H.; Nakamura, T.; Shinokubo, H.; Oshima, K. *J. Org. Chem.* ***1998***, *63*, 8604.

[1647] Baciocchi, E.; Muraglia, E. *Tetrahedron Lett.* ***1994***, *35*, 2763.

[1648] For reviews, see Groves, J.K. *Chem. Soc. Rev.* ***1972***, *1*, 73; House, H.O. *Modern Synthetic Reaction*, 2nd ed., W.A. Benjamin, NY, ***1972***, pp. 786–797; Nenitzescu, C.D.; Balaban, A.T., in Olah, G.A. *Friedel–Crafts and Related Reactions*, Vol. 3, Wiley, NY, ***1964***, pp. 1033–1152.

[1649] Jones, N.; Taylor, H.T.; Rudd, E. *J. Chem. Soc.* ***1961***, 1342.

[1650] For examples of 1,4-addition at low temperatures, see Melikyan, G.G.; Babayan, E.V.; Atanesyan, K.A.; Badanyan, Sh.O. *J. Org. Chem. USSR* ***1984***, *20*, 1884.

[1651] Bedekar, A.V.; Nair, K.B.; Soman, R. *Synth. Commun.* ***1994***, *24*, 2299.

[1652] For example, see Nifant'ev, E.Ye.; Grachev, M.A.; Bakinovskii, L.V.; Kara-Murza, C.G.; Kochetkov, N.K. *J. Appl. Chem. USSR* ***1963***, *36*, 646; Savenkov, N.F.; Khokhlov, P.S.; Nazarova, T.A.; Mochalkin, A.I. *J. Org. Chem. USSR* ***1973***, *9*, 914; Martens, H.; Janssens, F.; Hoornaert, G. *Tetrahedron* ***1975***, *31*, 177; Brownstein, S.; Morrison, A.; Tan, L.K. *J. Org. Chem.* ***1985***, *50*, 2796.

and $POCl_3$ (Vilsmeier conditions, see **11-18**).[1653] Chloroformates add to allenes in the presence of a rhodium catalyst go give a β-chloro, β,γ-unsaturated ester.[1654]

OS **IV**, 186; **VI**, 883; **VIII**, 254.

B. Oxygen, Nitrogen, or Sulfur on One or Both Sides

15-48 Hydroxylation (Addition of Oxygen, Oxygen)

Dihydroxy-addition

There are many reagents that add two OH groups to a double bond.[1655] The most common are OsO_4[1656] and alkaline $KMnO_4$,[1657] which give syn addition from the less-hindered side of the double bond. Less substituted double bonds are oxidized more rapidly than more substituted alkenes.[1658] Permanganate adds to alkenes to form an intermediate manganate ester (**171**), which is decomposed under alkaline conditions. Bases catalyze the decomposition of **171** by coordinating with the ester. Osmium tetroxide adds rather slowly but almost quantitatively to form a cyclic ester, such as **170**, as an intermediate, which can be isolated,[1659] but is usually decomposed solution, with sodium sulfite in ethanol or other reagents. The chief drawback to the use of OsO_4 is expensive and highly toxic, but the reaction is made catalytic in OsO_4 by using *N*-methylmorpholine-*N*-oxide (NMO),[1660] *tert*-butyl hydroperoxide in alkaline solution,[1661] H_2O_2,[1662] peroxyacid,[1663] flavin and

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[1653] Yen, V.Q. *Ann. Chim. (Paris)* ***1962***, *[13] 7*, 785.

[1654] Hua, R.; Tanaka, M. *Tetrahedron Lett.* ***2004***, *45*, 2367.

[1655] For reviews, see Hudlický, M. *Oxidations in Organic Chemistry*, American Chemical Society, Washington, ***1990***, pp. 67–73; Haines, A.H. *Methods for the Oxidation of Organic Compounds*, Academic Press, NY, ***1985***, pp. 73–98, 278–294; Sheldon, R.A.; Kochi, J.K. *Metal-Catalyzed Oxidations of Organic Compounds*, Academic Press, NY, ***1981***, pp. 162–171, 294–296. For a list of reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 996–1003.

[1656] For a review, see Schröder, M. *Chem. Rev.* ***1980***, *80*, 187. OsO_4 was first used for this purpose by Criegee, R. *Liebigs Ann. Chem.* ***1936***, *522*, 75. Also see, Norrby, P.-O.; Gable, K.P. *J. Chem. Soc. Perkin Trans. 2*, ***1996***, 171; Lohray, B.B.; Bhushan, V. *Tetrahedron Lett.* ***1992***, *33*, 5113.

[1657] For a review, see Fatiadi, A.J. *Synthesis* ***1987***, 85, 86. See Nelson, D.J.; Henley, R.L. *Tetrahedron Lett.* ***1995***, *36*, 6375 for rate of oxidation of alkenes.

[1658] Crispino, G.A.; Jeong, K.-S.; Kolb, H.C.; Wang, Z.-M.; Xu, D.; Sharpless, K.B. *J. Org. Chem.* ***1993***, *58*, 3785.

[1659] For a molecular-orbital study of the formation of **170**, see Jørgensen, K.A.; Hoffmann, R. *J. Am. Chem. Soc.* ***1986***, *108*, 1867.

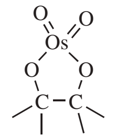
[1660] VanRheenen, V.; Kelly, R.C.; Cha, D.Y. *Tetrahedron Lett.* ***1976***, 1973; Iwasawa, N.; Kato, T.; Narasaka, K. *Chem. Lett.* ***1988***, 1721. See also, Ray, R.; Matteson, D.S. *Tetrahedron Lett.* ***1980***, 449.

[1661] Akashi, K.; Palermo, R.E.; Sharpless, K.B. *J. Org. Chem.* ***1978***, *43*, 2063.

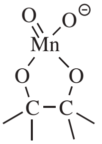
[1662] For a review, see Rylander, P.N. *Organic Syntheses withy Noble Metal Catalysts*, Academic Press, NY, ***1973***, pp. 121–133. See Venturello, C.; Gambaro, M. *Synthesis* ***1989***, 295; Usui, Y.; Sato, K.; Tanaka, M. *Angew. Chem. Int. Ed.* ***2003***, *42*, 5623.

[1663] Bergstad, K.; Piet, J.J.N.; Bäckvall, J.-E. *J. Org. Chem.* ***1999***, *64*, 2545.

TEAA,[1664] $K_3Fe(CN)_6$[1665] and non-heme iron catalysts.[1666] Polymer-bound OsO_4,[1667] and encapsulated OsO_4 have been shown to give the diol in the presence of NMO,[1668] as well as OsO_4^{-2} on an ion exchange resin.[1669] Dihydroxylation has also been reported in ionic liquids,[1670] and with fluorous osmium tetroxide.[1671] A catalytic amount of K_2OsO_4 with a Cinchona alkaloid on a ordered inorganic support, in the presence of $K_3Fe(CN)_6$, gives the cis-diol.[1672] Oxidation of pent-4-en-1-ol to valerolactone was accomplished with Oxone® and a catalytic amount of OsO_4 in DMF.[1673]



170



171

The end-product of the reaction of either potassium permanganate or osmium tetroxide under the conditions described above is a 1,2-diol. Potassium permanganate is a strong oxidizing agent and can oxidize the glycol product[1674] (see **19-7** and **19-10**). In acid and neutral solution it always does so; hence glycols must be prepared with alkaline[1675] permanganate, but the conditions must be mild. Even so, yields are seldom >50%, although they can be improved with phase-transfer catalysis[1676] or increased stirring.[1677] The use of ultrasound with permanganate

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[1664] Jonsson, S.Y.; Färnegårdh, K.; Bäckvall, J.-E. *J. Am. Chem. Soc.* ***2001***, *123*, 1365.

[1665] Minato, M.; Yamamoto, K.; Tsuji, J. *J. Org. Chem.* ***1990***, *55*, 766; Torii, S.; Liu, P.; Tanaka, H. *Chem. Lett.* ***1995***, 319; Soderquist, J.A.; Rane, A.M.; López, C.J. *Tetrahedron Lett.* ***1993***, *34*, 1893. See Corey, E.J.; Noe, M.C.; Grogan, M.J. *Tetrahedron Lett.* ***1994***, *35*, 6427; Imada, Y.; Saito, T.; Kawakami, T.; Murahashi, S.-I. *Tetrahedron Lett.* ***1992***, *33*, 5081 for oxidation using an asymmetric ligand.

[1666] Chen, K.; Costas, M.; Kim, J.; Tipton, A.K.; Que, Jr., L. *J. Am. Chem. Soc.* ***2002***, *124*, 3026.

[1667] Cainelli, G.; Contento, M.; Manescalchi, F.; Plessi, L. *Synthesis* ***1989***, 45; Ley, S.V.; Ramarao, C.; Lee, A.-L.; Østergaard, N.; Smith, S.C.; Shirley, I.M. *Org. Lett.* ***2003***, *5*, 185.

[1668] Nagayama, S.; Endo, M.; Kobayashi, S. *J. Org. Chem.* ***1998***, *63*, 6094.

[1669] Choudary, B.M.; Chowdari, N.S.; Jyothi, K.; Kantam, M.L. *J. Am. Chem. Soc.* ***2002***, *124*, 5341.

[1670] In bmim PF_6, 1-butyl-3-methylimidazolium hexafluorophosphate: Yao, Q. *Org. Lett.* ***2002***, *4*, 2197; Closson, A.; Johansson, M.; Bäckvall, J.-E. *Chem. Commun.* ***2004***, 1494. In emim BF_4, 1-ethyl-3-methylimidazolium tetrafluoroborate: Yanada, R.; Takemoto, Y. *Tetrahedron Lett.* ***2002***, *43*, 6849.

[1671] Huang, Y.; Meng, W.-D.; Qing, F.L. *Tetrahedron Lett.* ***2004***, *45*, 1965.

[1672] Motorina, I.; Crudden, C.M. *Org. Lett.* ***2001***, *3*, 2325.

[1673] Schomaker, J.M.; Travis, B.R.; Borhan, B. *Org. Lett.* ***2003***, *5*, 3089.

[1674] Or give more highly oxidized products, such as α-hydroxy ketones without going through the glycols. See, for example, Wolfe, S.; Ingold, C.F.; Lemieux, R.U. *J. Am. Chem. Soc.* ***1981***, *103*, 938; Wolfe, S.; Ingold, C.F. *J. Am. Chem. Soc.* ***1981***, *103*, 940. Also see, Lohray, B.B.; Bhushan, V.; Kumar, R.K. *J. Org. Chem.* ***1994***, *59*, 1375.

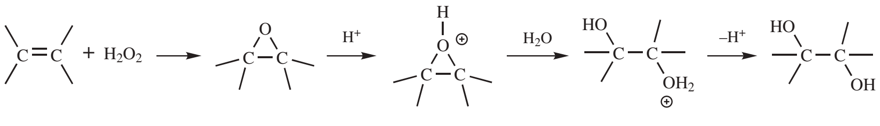
[1675] The role of the base seems merely to be to inhibit acid-promoted oxidations. The base does not appear to play any part in the mechanism: Taylor, J.E.; Green, R. *Can. J. Chem.* ***1985***, *63*, 2777.

[1676] See, for example, Weber, W.P.; Shepherd, J.P. *Tetrahedron Lett.* ***1972***, 4907; Ogino, T.; Mochizuki, K. *Chem. Lett.* ***1979***, 443.

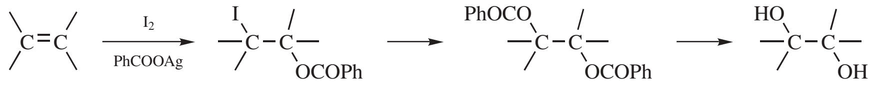
[1677] Taylor, J.E.; Williams, D.; Edwards, K.; Otonnaa, D.; Samanich, D. *Can. J. Chem.* ***1984***, *62*, 11; Taylor, J.E. *Can. J. Chem.* ***1984***, *62*, 2641.

dihydroxylation has resulted in good yields of the diol.[1678] There is evidence that cyclic esters (**171**) are intermediates for OsO_4 dihydroxylation.[1679] This reaction is the basis of the *Baeyer test* for the presence of double bonds. The oxidation is compatible with a number of functional groups, including trichloroacetamides.[1680]

Anti hydroxylation can be achieved by treatment with H_2O_2 and formic acid. In this case, epoxidation (**15-50**) occurs first, followed by an S_N2 reaction, which results in overall anti addition:



The same result can be achieved in one step with *m*-chloroperoxybenzoic acid and water.[1681] Overall anti addition can also be achieved by the method of Prévost (the *Prévost reaction*). In this method, the alkene is treated with iodine and silver benzoate in a 1:2 molar ratio. The initial addition is anti and results in a β-halo benzoate (**172**). These can be isolated, and this represents a method of addition of IOCOPh. However, under the normal reaction conditions, the iodine is replaced by a second PhCOO group. This is a nucleophilic substitution reaction, and it operates by the neighboring-group mechanism (p. 446), so the groups are still anti:



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Hydrolysis of the ester does not change the configuration. The *Woodward modification* of the Prévost reaction is similar, but results in overall syn hydroxylation.[1682] The alkene is treated with iodine and silver acetate in a 1:1 molar ratio in acetic acid containing water. Here again, the initial product is a β-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,[1683]

[1678] Varma, R.S.; Naicker, K.P. *Tetrahedron Lett.* ***1998***, *39*, 7463.

[1679] For some recent evidence, see Lee, D.G.; Chen, T. *J. Am. Chem. Soc.* ***1989***, *111*, 7534; Ogino, T.; Hasegawa, K.; Hoshino, E. *J. Org. Chem.* ***1990***, *55*, 2653. See, however, Freeman, F.; Chang, L.Y.; Kappos, J.C.; Sumarta, L. *J. Org. Chem.* ***1987***, *52*, 1461; Freeman, F.; Kappos, J.C. *J. Org. Chem.* ***1989***, *54*, 2730, and other papers in this series; Perez-Benito, J.F.; Lee, D.G. *Can. J. Chem.* ***1985***, *63*, 3545.

[1680] Donohoe, T.J.; Blades, K.; Moore, P.R.; Waring, M.J.; Winter, J.J.G.; Helliwell, M.; Newcombe, N.J.; Stemp, G. *J. Org. Chem.* ***2002***, *67*, 7946.

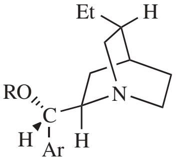
[1681] Fringuelli, F.; Germani, R.; Pizzo, F.; Savelli, G. *Synth. Commun.* ***1989***, *19*, 1939.

[1682] See Brimble, M.A.; Nairn, M.R. *J. Org. Chem.* ***1996***, *61*, 4801.

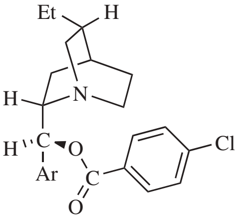
[1683] For another possible mechanism that accounts for the stereochemical result of the Woodward method, see Woodward, R.B.; Brutcher, Jr., F.V. *J. Am. Chem. Soc.* ***1958***, *80*, 209.

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 alkene.[1684] Both the Prévost and the Woodward methods[1685] have also been carried out in high yields with thallium(I) acetate and thallium(I) benzoate instead of the silver carboxylates.[1686] Note that cyclic sulfates can be prepared from alkenes by reaction with PhIO and SO_3•DMF.[1687]

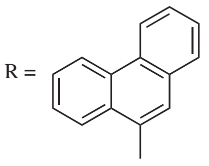
With suitable substrates, addition of two OH groups creates one new stereogenic center from a terminal alkene and two new stereogenic centers from internal alkenes. Addition to alkenes of the form $RCH{=}CH_2$ has been made enantioselective, and addition to $RCH{=}CHR'$ both diastereoselective[1688] and enantioselective,[1689] by using chiral additives or chiral catalysts,[1690] such as **173**, **174** (derivatives of the

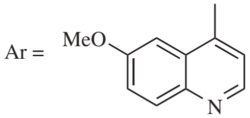


173
9′-Phenanthryl ether of
dihydroquinidine



174
Dihydroquinine
p-chlorobenzoate





[1684] For another method of syn hydroxylation, which can be applied to either face, see Corey, E.J.; Das, J. *Tetrahedron Lett.* ***1982***, *23*, 4217.

[1685] For some related methods, see Jasserand, D.; Girard, J.P.; Rossi, J.C.; Granger, R. *Tetrahedron Lett.* ***1976***, 1581; Ogata, Y.; Aoki, K. *J. Org. Chem.* ***1966***, *31*, 1625; Mangoni, L.; Adinolfi, M.; Barone, G.; Parrilli, M. *Tetrahedron Lett.* ***1973***, 4485; *Gazz. Chim. Ital.* ***1975***, *105*, 377; Horiuchi, C.A.; Satoh, J.Y. *Chem. Lett.* ***1988***, 1209; Campi, E.M.; Deacon, G.B.; Edwards, G.L.; Fitzroy, M.D.; Giunta, N.; Jackson, W.R.; Trainor, R. *J. Chem. Soc., Chem. Commun.* ***1989***, 407.

[1686] Cambie, R.C.; Hayward, R.C.; Roberts, J.L.; Rutledge, P.S. *J. Chem. Soc. Perkin Trans. 1*, ***1974***, 1858, 1864; Cambie, R.C.; Rutledge, P.S. *Org. Synth.* ***VI***, 348.

[1687] Robinson, R.I.; Woodward, S. *Tetrahedron Lett.* ***2003***, *44*, 1655.

[1688] For diastereoselective, but not enantioselective, addition of OsO_4, see Cha, J.K.; Christ, W.J.; Kishi, Y. *Tetrahedron* ***1984***, *40*, 2247; Stork, G.; Kahn, M. *Tetrahedron Lett.* ***1983***, *24*, 3951; Vedejs, E.; McClure, C.K. *J. Am. Chem. Soc.* ***1986***, *108*, 1094; Evans, D.A.; Kaldor, S.W. *J. Org. Chem.* ***1990***, *55*, 1698.

[1689] Lohray, B.B. *Tetrahedron Asymmetry* ***1992***, *3*, 1317.

[1690] For a review of enantioselective oxidation methodologies, see Bonini, C.; Righi, G. *Tetrahedron* ***2002***, *58*, 4981. For a study using triazines as a new class of ligand, see McNamara, C.A.; King, F.; Bradley, M. *Tetrahedron Lett.* ***2004***, *45*, 8527. See also, Kuang, Y.-Q.; Zhang, S.-Y.; Jiang, R.; Wei, L.-L. *Tetrahedron Lett.* ***2002***, *43*, 3669; Jiang, R.; Kuang, Y.; Sun, X.; Zhang, S. *Tetrahedron Asymmetry* ***2004***, *15*, 743.

naturally occurring quinine and quinuclidine),[1691] along with OsO_4, in what is called *Sharpless asymmetric dihydroxylation*.[1692] Other chiral ligands[1693] have also been used, as well as polymer[1694] and silica-bound[1695] *Cinchona* alkaloids. These amines bind to the OsO_4 *in situ* as chiral ligands, causing it to add asymmetrically.[1696] This has been done both with the stoichiometric and with the catalytic method.[1697] The catalytic method has been extended to conjugated dienes, which give tetrahydroxy products diastereoselectively,[1698] and to conjugated ketones.[1699] Asymmetric dihydroxylation has also been reported with chiral alkenes.[1700] Ligands **173** and **174** not only cause enantioselective addition, but also accelerate the reaction, so that they may be useful even where enantioselective addition is not required.[1701] Although **173** and **174** are not enantiomers, they give enantioselective addition to a given alkene in the opposite sense; for example, styrene predominantly gave the (*R*)-diol with **173**, and the

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[1691] Wai, J.S.M.; Marko, I.; Svendsen, J.S.; Finn, M.G.; Jacobsen, E.N.; Sharpless, K.B. *J. Am. Chem. Soc.* ***1989***, *111*, 1123; Kwong, H.; Sorato, C.; Ogina, Y.; Chen, H.; Sharpless, K.B. *Tetrahedron Lett.* ***1990***, *31*, 2999; Shibata, T.; Gilheany, D.C.; Blackburn, B.K.; Sharpless, K.B. *Tetrahedron Lett.* ***1990***, *31*, 3817; Sharpless, K.B.; Amberg, W.; Beller, M.; Chens, H.; Hartung, J.; Kawanami, Y.; Lübben, D.; Manoury, E.; Ogino, Y.; Shibata, T.; Ukita, T. *J. Org. Chem.* ***1991***, *56*, 4585.

[1692] Kolb, H.C.; Van Nieuwenhze, M.S.; Sharpless, K.B. *Chem. Rev.* ***1994***, *94*, 2483. Also see, Smith, M.B. *Organic Synthesis*, 2nd ed., McGraw-Hill, NY, ***2001***, pp. 248–254.

[1693] Wang, L.; Sharpless, K.B. *J. Am. Chem. Soc.* ***1992***, *114*, 7568; Xu, D.; Crispino, G.A.; Sharpless, K.B. *J. Am. Chem. Soc.* ***1992***, *114*, 7570; Corey, E.J.; Jardine, P.D.; Virgil, S.; Yuen, P.; Connell, R.D. *J. Am. Chem. Soc.* ***1989***, *111*, 9243; Corey, E.J.; Lotto, G.I. *Tetrahedron Lett.* ***1990***, *31*, 2665; Tomioka, K.; Nakajima, M.; Koga, K. *J. Am. Chem. Soc.* ***1987***, *109*, 6213; *Tetrahedron Lett.* ***1990***, *31*, 1741; Rosini, C.; Tanturli, R.; Pertici, P.; Salvadori, P. *Tetrahedron Asymmetry* ***1996***, *7*, 2971; Sharpless, K.B.; Amberg, W.; Bennani, Y.L.; Crispino, G.A.; Hartung, J.; Jeong, K.-S.; Kwong, H.-L.; Morikawa, K.; Wang, Z.-M.; Xu, D.; Zhang, X.-L. *J. Org. Chem.* ***1992***, *57*, 2768.

[1694] Bolm, C.; Gerlach, A. *Eur. J. Org. Chem.* ***1998***, 21; Lohray, B.B.; Nandanan, E.; Bhushan, V. *Tetrahedron Asymmetry* ***1996***, *7*, 2805; Lohray, B.B.; Thomas, A.; Chittari, P.; Ahuja, J.; Dhal, P.K. *Tetrahedron Lett.* ***1992***, *33*, 5453. For a review, see Karjalainen, J.K.; Hormi, O.E.O.; Sherrington, D.C. *Tetrahedron Asymmetry* ***1998***, *9*, 1563.

[1695] Song, C.E.; Yang, J.W.; Ha, H.-J. *Tetrahedron Asymmetry* ***1997***, *8*, 841.

[1696] For discussions of the mechanism of the enantioselectivity, see Corey, E.J.; Noe, M.C. *J. Am. Chem. Soc.* ***1996***, *118*, 319; Norrby, P.-O.; Kolb, H.C.; Sharpless, K.B. *J. Am. Chem. Soc.* ***1994***, *116*, 8470; Veldkamp, A.; Frenking, G. *J. Am. Chem. Soc.* ***1994***, *116*, 4937; Wu, Y.-D.; Wang, Y.; Houk, K.N. *J. Org. Chem.* ***1992***, *57*, 1362; Jørgensen, K.A. *Tetrahedron Lett.* ***1990***, *31*, 6417. See Nelson, D.W.; Gypser, A.; Ho, P.T.; Kolb, H.C.; Kondo, T.; Kwong, H.-L.; McGrath, D.V.; Rubin, A.E.; Norrby, P.-O.; Gable, K.P.; Sharpless, K.B. *J. Am. Chem. Soc.* ***1997***, *119*, 1840 for a discussion of electronic effects and Kolb, H.C.; Andersson, P.G.; Sharpless, K.B. *J. Am. Chem. Soc.* ***1994***, *116*, 1278 for a kinetic study.

[1697] For other examples of asymmetric dihydroxylation, see Yamada, T.; Narasaka, K. *Chem. Lett.* ***1986***, 131; Tokles, M.; Snyder, J.K. *Tetrahedron Lett.* ***1986***, *27*, 3951; Annunziata, R.; Cinquini, M.; Cozzi, F.; Raimondi, L.; Stefanelli, S. *Tetrahedron Lett.* ***1987***, *28*, 3139; Hirama, M.; Oishi, T.; Itô, S. *J. Chem. Soc., Chem. Commun.* ***1989***, 665.

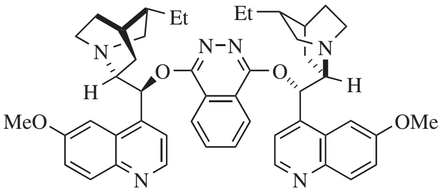
[1698] Park, C.Y.; Kim, B.M.; Sharpless, K.B. *Tetrahedron Lett.* ***1991***, *32*, 1003.

[1699] Walsh, P.J.; Sharpless, K.B. *Synlett* ***1993***, 605.

[1700] Oishi, T.; Iida, K.; Hirama, M. *Tetrahedron Lett.* ***1993***, *34*, 3573.

[1701] See Jacobsen, E.N.; Marko, I.; France, M.B.; Svendsen, J.S.; Sharpless, K.B. *J. Am. Chem. Soc.* ***1989***, *111*, 737.

(*S*)-diol with **174**.[1702] Note that ionic liquids have been used in asymmetric dihydroxylation.[1703]



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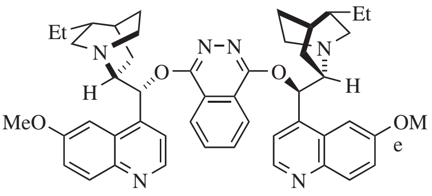

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Two phthalazine derivatives,[1704] (DHQD)$_2$PHAL (**175**) and (DHQ)$_2$PHAL (**176**) used in conjunction with an osmium reagent improve the efficiency and ease of use, and are commercial available as AD-mix-β™ (using **175**) and AD-mix-α™ (using **176**). Catalyst **175** is prepared from dihydroquinidine (DHQD) and 1,4-dichlorophthalazine (PHAL), and **176** is prepared from dihydroquinine (DHQ) and PHAL. The actual oxidation labeled AD-mix α- or β-uses **176** or **175**, respectively, mixed with potassium osmate [$K_2OsO_2(OH)_4$], powdered $K_3Fe(CN)_6$, and powdered K_2CO_3 in an aqueous solvent mixture.[1705] These additives have been used in conjunction with microencapsulated OsO_4,[1705] and polymer bound **175** has been used.[1706] A catalytic amount of flavin has been used.[1707] Both **175**[1708] and **176**[1709] have been used to generate diols with high enantioselectivity. Oxidation of a terminal alkene with AD-mix and then oxidation with TEMPO/NaOCl/$NaOCl_2$ leads to α-hydroxyl carboxylic acids with high enantioselectivity.[1710]

Enantioselective and diastereoselective addition have also been achieved by using preformed derivatives of OsO_4, already containing chiral ligands,[1711] and by the use of OsO_4 on alkenes that have a chiral group elsewhere in the molecule.[1712]

[1702] Jacobsen, E.N.; Marko, I.; Mungall, W.S.; Schröder, G.; Sharpless, K.B. *J. Am. Chem. Soc.* ***1988***, *110*, 1968.

[1703] See Branco, L.C.; Afonso, C.A.M. *J. Org. Chem.* ***2004***, *69*, 4381; Branco, L.C.; Afonso, C.A.M. *Chem. Commun.* ***2002***, 3036.

[1704] Sharpless, K.B.; Amberg, W.; Bennani, Y.L.; Crispino, G.A.; Hartung, J.; Jeong, K.-S.; Kwong, H.-L.; Morikawa, K.; Wang, Z.-M.; Xu, D.; Zhang, X.-L. *J. Org. Chem.* ***1992***, *57*, 2768.

[1705] Kobayashi, S.; Ishida, T.; Akiyama, R. *Org. Lett.* ***2001***, *3*, 2649.

[1706] Kuang, Y.-Q.; Zhang, S.-Y.; Wei, L.-L. *Tetrahedron Lett.* ***2001***, *42*, 5925.

[1707] Jonsson, S.Y.; Adolfsson, H.; Bäckvall, J.-E. *Org. Lett.* ***2001***, *3*, 3463.

[1708] Krief, A.; Colaux-Castillo, C. *Tetrahedron Lett.* ***1999***, *40*, 4189.

[1709] Junttila, M.H.; Hormi, O.E.O. *J. Org. Chem.* ***2004***, *69*, 4816.

[1710] Aladro, F.J.; Guerra, I.M.; Moreno-Dorado, F.J.; Bustamante, J.M.; Jorge, Z.D.; Massanet, G.M. *Tetrahedron Lett.* ***2000***, *41*, 3209.

[1711] Kokubo, T.; Sugimoto, T.; Uchida, T.; Tanimoto, S.; Okano, M. *J. Chem. Soc., Chem. Commun.* ***1983***, 769.

[1712] Hauser, F.M.; Ellenberger, S.R.; Clardy, J.C.; Bass, L.S. *J. Am. Chem. Soc.* ***1984***, *106*, 2458; Johnson, C.R.; Barbachyn, M.R. *J. Am. Chem. Soc.* ***1984***, *106*, 2459.

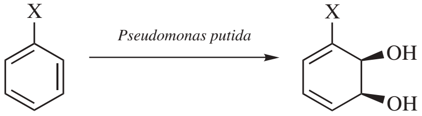
Alkenes can also be oxidized with metallic acetates such as lead tetraacetate[1713] or thallium(III) acetate[1714] to give bis(acetates) of glycols.[1715] Oxidizing agents, such as benzoquinone, MnO_2, or O_2, along with palladium acetate, have been used to convert conjugated dienes to 1,4-diacetoxy-2-alkenes (1,4-addition).[1716] Sodium periodate and sulfuric acid in aqueous media converts conjugated esters to dihydroxy esters.[1717] Diols are also produced by the reaction of a terminal alkyne with Bu_3SnH, followed by ozonolysis, followed by reduction with $BH_3{\bullet}SMe_2$.[1718] 1,2-Diols are also generated from terminal alkynes by two sequential reactions with a platinum catalyst, and then a palladium catalyst, both with $HSiCl_3$, and a final oxidation with H_2O_2—KF.[1719]

1,2-Dithiols can be prepared from alkenes.[1720]

OS **II**, 307; **III**, 217; **IV**, 317; **V**, 647; **VI**, 196, 342, 348; **IX**, 251, 383.

15-49 Dihydroxylation of Aromatic Rings

Dihydroxy-addition



One π-bond of an aromatic ring can be converted to a cyclohexadiene 1,2-diol by reaction with enzymes associated with *Pseudomonas putida*.[1721] A variety of substituted aromatic compounds can be oxidized, including bromobenzene, chlorobenzene,[1722] and toluene.[1723] In these latter cases, introduction of the hydroxyl

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[1713] For a review, see Moriarty, R.M. *Sel Org. Transform.* ***1972***, *2*, 183–237.

[1714] See, for example, Uemura, S.; Miyoshi, H.; Tabata, A.; Okano, M. *Tetrahedron* ***1981***, *37*, 291. For a review of the reactions of thallium (III) compounds with alkenes, see Uemura, S., in Hartley, F.R. *The Chemistry of the Metal–Carbon Bond*, Vol. 4, Wiley, NY, ***1987***, pp. 473–538, 497–513. For a review of thallium (III) acetate and trifluoroacetate, see Uemura, S., in Pizey, J.S. *Synthetic Reagents*, Vol. 5, Wiley, NY, ***1983***, pp. 165–187.

[1715] For another method, see Fristad, W.E.; Peterson, J.R. *Tetrahedron* ***1984***, *40*, 1469.

[1716] See Bäckvall, J.E.; Awasthi, A.K.; Renko, Z.D. *J. Am. Chem. Soc.* ***1987***, *109*, 4750, and references cited therein. For articles on this and related reactions, see Bäckvall, J.E. *Bull. Soc. Chim. Fr.* ***1987***, 665; *New. J. Chem.* ***1990***, *14*, 447. For another method, see Uemura, S.; Fukuzawa, S.; Patil, S.R.; Okano, M. *J. Chem. Soc. Perkin Trans. 1*, ***1985***, 499.

[1717] Plietker, B.; Niggemann, M. *Org. Lett.* ***2003***, *5*, 3353.

[1718] Gómez, A.M.; Company, M.D.; Valverde, S.; López, J.C. *Org. Lett.* ***2002***, *4*, 383.

[1719] Shimada, T.; Mukaide, K.; Shinohara, A.; Han, J.W.; Hayashi, T. *J. Am. Chem. Soc.* ***2004***, *124*, 1584.

[1720] Elgemeie, G.H.; Sayed, S.H. *Synthesis* ***2001***, 1747.

[1721] Gibson, D.T.; Koch, J.R.; Kallio, R.E. *Biochemistry* ***1968***, *7*, 2653; Brown, S.M., in Hudlicky, T. *Organic Synthesis: Theory and Practice*, JAI Press, Greenwich, CT., ***1993***, Vol. 2, p. 113; Carless, H.A.J. *Tetrahedron Asymmetry* ***1992***, *3*, 795; Widdowson, D.A.; Ribbons, D.A.; Thomas, S.D. *Janssenchimica Acta* ***1990***, *8*, 3.

[1722] Gibson, D.T.; Koch, J.R.; Schuld, C.L.; Kallio, R.E. *Biochemistry* ***1968***, *7*, 3795; Hudlicky, T.; Price, J.D. *Synlett.* ***1990***, 159.

[1723] Gibson, D.T.; Hensley, M.; Yoshioka, H.; Mabry, T.J. *Biochemsitry* ***1970***, *9*, 1626.

groups generates a chiral molecule that can be used as a template for asymmetric syntheses.[1724]

OS **X**, 217.

15-50 Epoxidation (Addition of Oxygen, Oxygen)

***epi*-Oxy-addition**

Alkenes can be epoxidized with many peroxyacids,[1725] of which *m*-chloroperoxybenzoic has been the most often used. The reaction, called the *Prilezhaev reaction*, has wide utility.[1726] Alkyl, aryl, hydroxyl, ester, and other groups may be present, although not amino groups, since these are affected by the reagent. Electron-donating groups increase the rate, and the reaction is particularly rapid with tetraalkyl alkenes. Conditions are mild and yields are high. Other peroxyacids, especially peroxyacetic and peroxybenzoic, are also used; trifluoroperoxyacetic acid[1727] and 3,5-dinitroperoxybenzoic acid[1728] are particularly reactive ones. Transition metal catalysts can facilitate epoxidation of alkenes at low temperatures or with alkenes that may otherwise react sluggishly.[1729] Magnesium monoperoxyphthalate (MMPP)[1730] is commercially available, and has been

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[1724] Hudlicky, T.; Gonzalez, D.; Gibson, D.T. *Aldrichimica Acta* ***1999***, *32*, 35; Hudlicky, T.; Luna, H.; Barbieri, G.; Kwart, L.D. *J. Am. Chem. Soc.* ***1988***, *110*, 4735; Hudlicky, T.; Seoane, G.; Pettus, T. *J. Org. Chem.* ***1989***, *54*, 4239; Ley, S.V.; Redgrave, A.J. *Synlett* ***1990***, 393; Ley, S.V.; Sternfeld, F.; Taylor, S. *Tetrahedron Lett.* ***1987***, *28*, 225; Hudlicky, T.; Olivo, H.F. *Tetrahedron Lett.* ***1991***, *32*, 6077; Hudlicky, T.; Luna, H.; Price, J.D.; Rulin, F. *J. Org. Chem.* ***1990***, *55*, 4683; Hudlicky, T.; Olivo, H.F. *J. Am. Chem. Soc.* ***1992***, *114*, 9694. Also see, Smith, M.B. *Organic Synthesis*, 2nd ed., McGraw-Hill, NY, ***2001***, pp. 256–258.

[1725] For a list of reagents, including peracids and others, used for epoxidation, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 915–927.

[1726] For reviews, see Hudlický, M. *Oxidations in Organic Chemistry*, American Chemical Society, Washington, DC, ***1990***, pp. 60–64; Haines, A.H. *Methods for the Oxidation of Organic Compunds*, Academic Press, NY, ***1985***, pp. 98–117, 295–303; Dryuk, V.G. *Russ. Chem. Rev.* ***1985***, *54*, 986; Plesničar, B., in Trahanovsky, W.S. *Oxidation in Organic Chemistry*, pt. C, Academic Press, NY, ***1978***, pp. 211–252; Swern, D., in Swern, D. *Organic Peroxides*, Vol. 2, Wiley, NY, ***1971***, pp. 355–533; Metelitsa, D.I. *Russ. Chem. Rev.* ***1972***, *41*, 807; Hiatt, R., in Augustine, R.L.; Trecker, D.J. *Oxidation*, Vol. 2, Marcel Dekker, NY, ***1971***; pp. 113–140; House, H.O. *Modern Synthetic Reaction*, 2nd ed., W.A. Benjamin, NY, ***1972***, pp. 292–321. For a review pertaining to the stereochemistry of the reaction, see Berti, G. *Top Stereochem.* ***1973***, *7*, 93, p. 95.

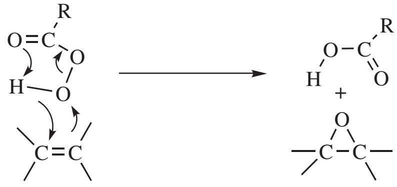
[1727] Emmons, W.D.; Pagano, A.S. *J. Am. Chem. Soc.* ***1955***, *77*, 89.

[1728] Rastetter, W.H.; Richard, T.J.; Lewis, M.D. *J. Org. Chem.* ***1978***, *43*, 3163.

[1729] Cu catalysts: Andrus, M.B.; Poehlein, B.W. *Tetrahedron Lett.* ***2000***, *41*, 1013. Fe catalysts: Dubois, G.; Murphy, A.; Stack, T.D.P. *Org. Lett.* ***2003***, *5*, 2469. Mn catalysts: Murphy, A.; Pace, A.; Stack, T.D.P. *Org. Lett.* ***2004***, *6*, 3119; Murphy, A.; Dubois, G.; Stack, T.D.P. *J. Am. Chem. Soc.* ***2003***, *125*, 5250.

[1730] Brougham, P.; Cooper, M.S.; Cummerson, D.A.; Heaney, H.; Thompson, N. *Synthesis* ***1987***, 1015; Querci, C.; Ricci, M. *J. Chem. Soc., Chem. Commun.* ***1989***, 889. For a reaction using moist MMPP, see Foti, C.J.; Fields, J.D.; Kropp, P.J. *Org. Lett.* ***1999***, *1*, 903.

shown to be a good substitute for *m*-chloroperoxybenzoic acid in a number of reactions.[1731]



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The one-step mechanism involving a transition state, such as **177**,[1731] was proposed by Bartlett:[1732] Evidence for this concerted mechanism is as follows:[1733] (*1*) The reaction is second order. If ionization were the rate-determining step, it would be first order in peroxyacid. (*2*) The reaction readily takes place in nonpolar solvents, where formation of ions is inhibited.[1734] (*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.[1735] (*4*) The addition is stereospecific (i.e., a trans-alkene gives a trans-epoxide and a cis-alkene a cis-epoxide) even in cases where electron-donating substituents would stabilize a hypothetical carbocation intermediate.[1736] 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.[1737]

[1731] For discussions of the mechanism, see Dryuk, V.G. *Tetrahedron* ***1976***, *32*, 2855; Finn, M.G.; Sharpless, K.B., in Morrison, J.D. *Asymmetric Synthesis*, Vol. 5, Wiley, NY, ***1985***, pp. 247–308; Bach, R.D.; Canepa, C.; Winter, J.E.; Blanchette, P.E. *J. Org. Chem.* ***1997***, *62*, 5191. For a review of polar mechanisms involving peroxides, see Plesnicar, B., in Patai, S. *The Chemistry of Peroxides*, Wiley, NY, ***1983***, pp. 521–584. See Freccero, M.; Gandolfi, R.; Sarzi-Amadè, M.; Rastelli, A. *J. Org. Chem.* ***2002***, *67*, 8519. For a discussion of arene–arene interactions as related to selectivity, see Kishikawa, K.; Naruse, M.; Kohmoto, S.; Yamamoto, M.; Yamaguchi, K. *J. Chem. Soc., Perkin Trans. 1* ***2001***, 462.

[1732] Bartlett, P.D. *Rec. Chem. Prog.* ***1957***, *18*, 111. For other proposed mechanisms, see Kwart, H.; Hoffman, D.M. *J. Org. Chem.* ***1966***, *31*, 419; Hanzlik, R.P.; Shearer, G.O. *J. Am. Chem. Soc.* ***1975***, *97*, 5231.

[1733] Ogata, Y.; Tabushi, I. *J. Am. Chem. Soc.* ***1961***, *83*, 3440; Freccero, M.; Gandolfi, R.; Sarzi-Amadè, M.; Rastelli, A. *J. Org. Chem.* ***2004***, *69*, 7479. See also, Woods, K.W.; Beak, P. *J. Am. Chem. Soc.* ***1991***, *113*, 6281. Also see, Vedejs, E.; Dent III, W.H.; Kendall, J.T.; Oliver, P.A. *J. Am. Chem. Soc.* ***1996***, *118*, 3556.

[1734] See Gisdakis, P.; Rösch, N. *Eur. J. Org. Chem.* ***2001***, 719.

[1735] Khalil, M.M.; Pritzkow, W. *J. Prakt. Chem.* ***1973***, *315*, 58; Schneider, H.; Becker, N.; Philippi, K. *Chem. Ber.* ***1981***, *114*, 1562; Batog, A.E.; Savenko, T.V.; Batrak, T.A.; Kucher, R.V. *J. Org. Chem. USSR* ***1981***, *17*, 1860.

[1736] For a computational study of facial selectivity, see Freccero, M.; Gandolfi, R.; Sarzi-Amadè, M.; Rastelli, A. *J. Org. Chem.* ***2000***, *65*, 8948.

[1737] See Berti, G. *Top. Stereochem.* ***1973***, *7*, 93, 130–162; Houk, K.N.; Liu, J.; DeMello, N.C.; Condroski, K.R. *J. Am. Chem. Soc.* ***1997***, *119*, 10147.

In general, peroxides (HOOH and ROOH) are poor regents for epoxidation of simple alkenes since OH and OR are poor leaving groups in the concerted mechanism shown above.[1738] Aqueous hydrogen peroxide epoxidizes alkenes in the presence of fluorous compounds, such as CF_3CH_2OH[1739] or hexafluoroacetone.[1740] Transition-metal catalysts[1741] have been used with alkyl hydroperoxides.[1742] In the presence of other reagents,[1743] peroxides give good yields of the epoxide. These coreagents include dicyclohexylcarbodiimide,[1744] magnesium aluminates,[1745] metalloporphyrins,[1746] hydrotalcite[1747] with microwave irradiation,[1748] fluorous aryl selenides,[1749] and arsines in fluorous solvents.[1750] The catalyst $MeReO_3$[1751] has been used for epoxidation with sodium percarbonate and pyrazole,[1752] with hydrogen peroxide,[1753] and with urea—H_2O_2.[1754] Epoxidation occurs with $FeSO_4$/silica,[1755] and with N_2O and a zinc catalyst.[1756] Epoxidation occurs when alkenes

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[1738] See Deubel, D.V.; Frenking, G.; Gisdakis, P.; Herrmann, W.A.; Rösch, N.; Sundermeyer, J. *Acc. Chem. Res.* ***2004***, *37*, 645.

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[1740] Shu, L.; Shi, Y. *J. Org. Chem.* ***2000***, *65*, 8807.

[1741] **V**: Sharpless, K.B.; Verhoeven, T.R. *Aldrichimica Acta* ***1979***, *12*, 63; Hoshino, Y.; Yamamoto, H. *J. Am. Chem. Soc.* ***2000***, *122*, 10452; Lattanzi, A.; Leadbeater, N.E. *Org. Lett.* ***2002***, *4*, 1519; Torres, G.; Torres, W.; Prieto, J.A. *Tetrahedron* ***2004***, *60*, 10245. **Mn**: Lane, B.S.; Vogt, M.; De Rose, V.T.; Burgess, K. *J. Am. Chem. Soc.* ***2002***, *124*, 11946. **Ti**: Della Sala, G.D.; Giordano, L.; Lattanzi, A.; Proto, A.; Screttri, A. *Tetrahedron* ***2000***, *56*, 3567; Lattanzi, A.; Iannece, P.; Screttri, A. *Tetrahedron Lett.* ***2002***, *43*, 5629. **Pd**: Yu, J.-Q.; Corey, E.J. *Org. Lett.* ***2002***, *4*, 2727. **Ru**: Adam, W.; Alsters, P.L.; Neumann, R.; Saha-Möller, C.; Sloboda-Rozner, D.; Zhang, R. *Synlett* ***2002***, 2011. **La**: Nemoto, T.; Ohshima, T.; Yamaguchi, K.; Shibasaki, M. *J. Am. Chem. Soc.* ***2001***, *123*, 2725; Chen, R.; Qian, C.; de Vries, J.G. *Tetrahedron* ***2001***, *57*, 9837; Nemoto, T.; Kakei, H.; Gnanadesikan, V.; Tosaki, S.-y.; Ohshima, T.; Shibasaki, M. *J. Am. Chem. Soc.* ***2002***, *124*, 14544.

[1742] For a table containing several common catalysts, see Hiatt, R., in Augustine, R.L.; Trecker, D.J. *Oxidation*, Vol. 2, Marcel Dekker, NY, ***1971***, p. 124.

[1743] For other methods of converting alkenes to epoxides, see Bruice, T.C. *Aldrichimica Acta* ***1988***, *21*, 87; Adam, W.; Curci, R.; Edwards, J.O. *Acc. Chem. Res.* ***1989***, *22*, 205.

[1744] Majetich, G.; Hicks, R.; Sun, G.-r.; McGill, P. *J. Org. Chem.* ***1998***, *63*, 2564; Murray, R.W.; Iyanar, K. *J. Org. Chem.* ***1998***, *63*, 1730.

[1745] Yamaguchi, K.; Ebitani, K.; Kaneda, K. *J. Org. Chem.* ***1999***, *64*, 2966.

[1746] Chan, W.-K.; Liu, P.; Yu, W.-Y.; Wong, M.-K.; Che, C.-M. *Org. Lett.* ***2004***, *6*, 1597.

[1747] For an example without microwave irradiation, see Pillai, U.R.; Sahle-Demessie, E.; Varma, R.S. *Synth. Commun.* ***2003***, *33*, 2017.

[1748] Pillai, U.R.; Sahle-Demessie, E.; Varma, R.S. *Tetrahedron Lett.* ***2002***, *43*, 2909.

[1749] Betzemeier, B.; Lhermitte, F.; Knochel, P. *Synlett* ***1999***, 489.

[1750] Van Vliet, M.C.A.; Arends, I.W.C.E.; Sheldon, R.A. *Tetrahedron Lett.* ***1999***, *40*, 5239.

[1751] For a polymer-supported $MeReO_3$ reagent, see Saladino, R.; Neri, V.; Pelliccia, A.R.; Caminiti, R.; Sadun, C. *J. Org. Chem.* ***2002***, *67*, 1323.

[1752] Vaino, A.R. *J. Org. Chem.* ***2000***, *65*, 4210.

[1753] van Vliet, M.C.A.; Arends, I.W.C.E.; Sheldon, R.A. *Chem. Commun.* ***1999***, 821; Adolfsson, H.; Copéret, C.; Chiang, J.P.; Yudin, A.K. *J. Org. Chem.* ***2000***, *65*, 8651; Iskra, J.; Bonnet-Delpon, D.; Bégué, J.-P. *Tetrahedron Lett.* ***2002***, *43*, 1001.

[1754] Owens, G.S.; Abu-Omar, M.M. *Chem. Commun.* ***2000***, 1165.

[1755] Monfared, H.H.; Ghorbani, M. *Monat. Chem.* ***2001***, *132*, 989.

[1756] Ben-Daniel, R.; Weiner, L.; Neumann, R. *J. Am. Chem. Soc.* ***2002***, *124*, 8788.

are treated with oxygen gas, *N*-hydroxyphthalimide, and a mixture of cobalt and molybdenum catalyst.[1757]

Other epoxidation methods are available. Enzymatic epoxidation[1758] and epoxidation with catalytic antibodies[1759] have been reported. Chromyl chloride (CrO_2Cl_2) reacts with alkenes, even at −78°C to give an epoxide and numerous side products including chlorohydrins and dichlorides.[1760] Several mechanisms have been proposed.[1761] Epoxidation has been done in ionic liquids using 10% H_2O_2 with $MnSO_4$[1762] or an iron catalyst.[1763] Hypervalent iodine compounds, such as $PhI(OAc)_2$, in conjunction with a ruthenium catalyst in aqueous media, converts alkenes to epoxides.[1764] This reagent has been used in an ionic liquid with a manganese catalyst.[1765]

Dioxiranes,[1766] such as dimethyl dioxirane (**178**),[1767] either isolated or generated *in situ*,[1768] are important epoxidation reagents. With dimethyloxirane, C—H insertion reactions can occur preferentially.[1769] The reaction with alkenes is rapid, mild, safe, and a variety methods have been developed using an oxidant as a coreagent. The most commonly used coreagent is probably potassium peroxomonosulfate ($KHSO_5$). Oxone® (2 $KHSO_5$•$KHSO_4$•K_2SO_4) is a common source of $KHSO_5$. Oxone® reacts with ketones[1770] and sodium bicarbonate to convert an alkene

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[1757] Iwahama, T.; Hatta, G.; Sakaguchi, S.; Ishii, Y. *Chem. Commun.* ***2000***, 163.

[1758] **Haloperoxidases**: Hu, S.; Hager, L.P. *Tetrahedron Lett.* ***1999***, *40*, 1641; Dembitsky, V.M. *Tetrahedron* ***2003***, *59*, 4701. ***E. coli JM109(pTAB19)***: Bernasconi, S.; Orsini, F.; Sello, G.; Colmegna, A.; Galli, E.; Bestetti, G. *Tetrahedron Lett.* ***2000***, *41*, 9157. **Cyclohexanone monooxygenase**: Colonna, S.; Gaggero, N.; Carrea, G.; Ottolina, G.; Pasta, P.; Zambianchi, F. *Tetrahedron Lett.* ***2002***, *43*, 1797.

[1759] Chen, Y.; Reymond, J.-L. *Synthesis* ***2001***, 934.

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[1761] For leading references, see Rappe, A.K.; Li, S. *J. Am. Chem. Soc.* ***2003***, *125*, 11188.

[1762] In bmim BF_4, 1-butyl-3-methylimidazolium tetrafluoroborate: Tong, K.-H.; Wong, K.-Y.; Chan, T.H. *Org. Lett.* ***2003***, *5*, 3423.

[1763] In bmim Br, 1-butyl-3-methylimidazolium bromide: Srinivas, K.A.; Kumar, A.; Chauhan, S.M.S. *Chem. Commun.* ***2002***, 2456.

[1764] Tse, M.K.; Bhor, S.; Klawonn, M.; Döbler, C.; Beller, M. *Tetrahedron Lett.* ***2003***, *44*, 7479.

[1765] In bmim PF_6, 1-butyl-3-methylimidazolium hexafluorophosphate: Li, Z.; Xia, C.-G. *Tetrahedron Lett.* ***2003***, *44*, 2069.

[1766] For general leading references, see Murray, R.W. *Chem. Rev.* ***1989***, *89*, 1187; Adam, W.; Curci, R.; Edwards, J.O. *Acc. Chem. Res.* ***1989***, *22*, 205; Curci, R.; Dinoi, A.; Rubino, M.E. *Pure Appl. Chem.* ***1995***, *67*, 811; Clennan, E.L. *Trends in Organic Chemistry,* ***1995***, *5*, 231; Adam, W.; Smerz, A.K. *Bull Soc. Chim. Belg.* ***1996***, *105*, 581; Denmark, S.E.; Wu, Z. *Synlett* ***1999***, 847.

[1767] Frohn, M.; Wang, Z.-X.; Shi, Y. *J. Org. Chem.* ***1998***, *63*, 6425. See Angelis, Y.; Zhang, X.; Organopoulos, M. *Tetrahedron Lett.* ***1996***, *37*, 5991 for a discussion of the mechanism of this oxidation.

[1768] See Curci, R.; Fiorentino, M.; Troisi, L.; Edwards, J.O.; Pater, R.H. *J. Org. Chem.* ***1980***, *45*, 4758; Gallopo, A.R.; Edwards, J.O. *J. Org. Chem.* ***1981***, *46*, 1684; Corey, P.E; Ward, F.E. *J. Org. Chem.* ***1986***, *51*, 1925; Adam, W.; Hadjiarapoglou, L.; Smerz, A. *Chem. Ber.* ***1991***, *124*, 227; Yang, D.; Wong, M.K.; Yip, Y.C. *J. Org. Chem.* ***1995***, *60*, 3887; Denmark, S.E.; Wu, Z. *J. Org. Chem.* ***1998***, *63*, 2810, and references cited therein; Frohn, M.; Wang, Z.-X.; Shi, Y. *J. Org. Chem.* ***1998***, *63*, 6425; Yang, D.; Yip, Y.-C.; Tang, M.-W.; Wong, M.-K.; Cheung, K.-K. *J. Org. Chem.* ***1998***, *63*, 9888, and references cited therein.

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to an epoxide. Oxone® also converts alkenes to epoxides in the presence of certain additives, such as *N,N*-dialkylalloxans.[1771] Oxone, usually with hydrogen peroxide or another similar oxidant, can be used with chiral ketones[1772] or aldehydes to convert alkenes to chiral, nonracemic epoxides.[1773] Chiral dioxiranes have reportedly given nonracemic epoxides.[1774] Hydrogen peroxide, in the presence of chiral ketones in acetonitrile (or other nitrile solvents), probably converts alkenes to epoxides with good enantioselectivity by *in situ* generation of dioxirane.[1775] Epoxidation does not occur in good yields with these reagents in most other solvents, and it is suggested that the active agent that generates dioxirane is peroxyimidic acid MeC(=NH)OOH.[1776] Note that benzaldehyde with Chloramine-M[1777] will convert alkenes to epoxides.[1778] Amines, including chiral amines can be similarly used with aldehydes with aqueous sodium bicarbonate.[1779]

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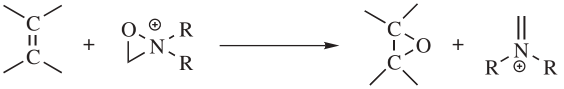
oxirene



179

Oxone® oxidizes iminium salts to an oxaziridinium intermediate **179**, which can transfer oxygen to an alkene to form an epoxide and regenerate the iminium salt.[1780]

[1771] Carnell, A.J.; Johnstone, R.A.W.; Parsy, C.C.; Sanderson, W.R. *Tetrahedron Lett.* ***1999***, *40*, 8029.

[1772] For reviews, see Shi, Y. *Acc. Chem. Res.* ***2004***, *37*, 488; Yang, D. *Acc. Chem. Res.* ***2004***, *37*, 497.

[1773] For leading references, see: Denmark, S.E.; Wu, Z.; Crudden, C.M.; Matsuhashi, H. *J. Org. Chem.* ***1997***, *62*, 8288; Yang, D.; Yip, Y.-C.; Chen, J.; Cheung, K.-K. *J. Am. Chem. Soc.* ***1998***, *120*, 7659; Daly, A.M.; Renehan, M.F.; Gilheany, D.G. *Org. Lett.* ***2001***, *3*, 663; Tian, H.; She, X.; Yu, H.; Shu, L.; Shi, Y. *J. Org. Chem.* ***2002***, *67*, 2435; Denmark, S.E.; Matsuhashi, H. *J. Org. Chem.* ***2002***, *67*, 3479; Arsmtrong, A.; Ahmed, G.; Dominguez-Fernandez, B.; Hayter, B.R.; Wailes, J.S. *J. Org. Chem.* ***2002***, *67*, 8610; Wu, X.-Y.; She, X.; Shi, Y. *J. Am. Chem. Soc.* ***2002***, *124*, 8792; Matsumoto, K.; Tomioka, K. *Tetrahedron Lett.* ***2002***, *43*, 631; Bez, G.; Zhao, C.-G. *Tetrahedron Lett.* ***2003***, *44*, 7403. For a carbonyl derivative bound to cyclodextrin, see Chan, W.-K.; Yu, W.-y.; Che, C.-M.; Wong, M.-K. *J. Org. Chem.* ***2003***, *68*, 6576.

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[1776] Payne, G.B.; Deming, P.H.; Williams, P.H. *J. Org. Chem.* ***1961***, *26*, 659; Payne, G.B. *Tetrahedron* ***1962***, *18*, 763; McIsaac, Jr., J.E.; Ball, R.E.; Behrman, E.J. *J. Org. Chem.* ***1971***, *36*, 3048; Bach, R.D.; Knight, J.W. *Org. Synth.* ***1981***, *60*, 63; Arias, L.A.; Adkins, S.; Nagel, C.J.; Bach, R.D. *J. Org. Chem.* ***1983***, *48*, 888.

[1777] For the preparation of Chloramine-M, see Rudolph, J.; Sennhenn, P.C.; Vlaar, C.P.; Sharpless, K.B. *Angew. Chem. Int. Ed.* ***1996***, *35*, 2810.

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[1779] Wong, M.-K.; Ho, L.-M.; Zheng, Y.-S.; Ho, C.-Y.; Yang, D. *Org. Lett.* ***2001***, *3*, 2587.

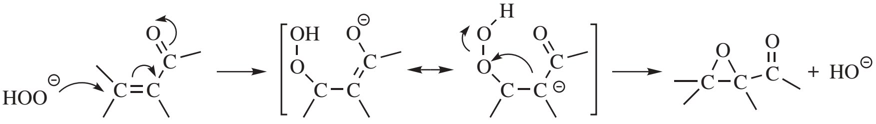
[1780] See Lusinchi, X.; Hanquet, G. *Tetrahedron* ***1997***, *53*, 13727; Hanquet, G.; Lusinchi, X.; Milliet, P. *Tetrahedron Lett.* ***1988***, *29*, 3941; Bohé, L.; Kammoun, M. *Tetrahedron Lett.* ***2002***, *43*, 803; Bohé, L.; Kammoun, M. *Tetrahedron Lett.* ***2004***, *45*, 747.

This variation has been applied to asymmetric[1781] epoxidations using chiral iminium salt precursors.[1782]

Although cis–trans isomerization of epoxides is not formally associated with this section, it is clearly a potential problem in the conversion of an alkene to an epoxide. There are several catalysts for this process.[1783]

It would be useful if triple bonds could be similarly epoxidized to give oxirenes, but they are not stable compounds.[1784] Two of them have been trapped in solid argon matrices at very low temperatures, but they decayed on warming to 35 K.[1785] Oxirenes probably form in the reaction,[1786] 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. 38).

Conjugated dienes can be epoxidized (1,2-addition), although the reaction is slower than for corresponding alkenes, but α,β-unsaturated ketones do not generally give epoxides when treated with peroxyacids.[1787] The epoxidation of α,β-unsaturated ketones with hydrogen peroxide under basic conditions is known as the *Waits–Scheffer epoxidation*, discovered in 1921.[1788] This fundamental reaction has been extended to α,β-unsaturated ketones (including quinones), aldehydes, and sulfones.[1789] This is a nucleophilic addition by a Michael-type mechanism, involving attack by HO_2^-:[1790] This reaction is another example of 1,4-addition of a heteroatom containing species as discussed in **15-31**.



[1781] For a discussion of the origins of selectivity in these reactions, see Washington, I.; Houk, K. N. *J. Am. Chem. Soc.* ***2000***, *122*, 2948.

[1782] See Jacobson, E.N., in Ojima, I. *Catalytic Asymmetric Synthesis*, VCH, NY, ***1993***, pp. 159–203; Armstrong, A.; Ahmed, G.; Garnett, I.; Goacolou, K.; Wailes, J.S. *Tetrahedron* ***1999***, *55*, 2341; Minakata, S.; Takemiya, A.; Nakamura, K.; Ryu, I.; Komatsu, M. *Synlett* ***2000***, 1810; Page, P.C.B.; Rassias, G.A.; Barros, D.; Ardakani, A.; Buckley, B.; Bethell, D.; Smith, T.A.D.; Slawin, A.M.Z. *J. Org. Chem.* ***2001***, *66*, 6926; Page, P.C.B.; Barros, D.; Buckley, B.R.; Ardakani, A.; Marples, B.A. *J. Org. Chem.* ***2004***, *69*, 3595; Page, P.C.B.; Buckley, B.R.; Blacker, A.J. *Org. Lett.* ***2004***, *6*, 1543; Page, P.C.B.; Rassias, G.A.; Barros, D.; Ardakani, A.; Bethell, D.; Merrifield, E. *Synlett* ***2002***, 580.

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[1785] Torres, M.; Bourdelande, J.L.; Clement, A.; Strausz, O.P. *J. Am. Chem. Soc.* ***1983***, *105*, 1698. See also, Laganis, E.D.; Janik, D.S.; Curphey, T.J.; Lemal, D.M. *J. Am. Chem. Soc.* ***1983***, *105*, 7457.

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[1789] For example, see Payne, G.B.; Williams, P.H. *J. Org. Chem.* ***1961***, *26*, 651; Zwanenburg, B.; ter Wiel, J. *Tetrahedron Lett.* ***1970***, 935.

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α,β-Unsaturated compounds can be epoxidized alkyl hydroperoxides and a base,[1791] or with H_2O_2 and a base or heteropoly acids.[1792] The reaction has been done in D_2O using sodium bicarbonate with hydrogen peroxide.[1793] The reaction has been done with LiOH and polymer-bound quaternary ammonium salts.[1794] Epoxides can also be prepared by treating alkenes with oxygen or with an alkyl peroxide[1795] catalyzed by a complex of a transition metal such as V, Mo, Ti, La,[1796] or Co.[1797] The reaction with oxygen, which can also be carried out without a catalyst, is probably a free-radical process.[1798] Conjugated ketones are oxidized to epoxy-ketones with $NaBO_3$ and tetrahexylammonium hydrogen sulfate,[1799] KF-Al_2O_3/*tert*-butyl hydroperoxide.[1800] α,β-Unsaturated esters react normally to give glycidic esters.[1801] When a carbonyl group is elsewhere in the molecule but not conjugated with the double bond, the Baeyer–Villiger reaction (**18-19**) may compete. Allenes[1802] are converted by peroxyacids to allene oxides[1803] or spiro dioxides, both of which species can in certain cases be isolated[1804] but more often are unstable under the reaction conditions and react further to give other products.[1805]

Asymmetric Weitz–Scheffer epoxidation is commonly used for the epoxidation of electron-poor alkenes. Cinchona-derived phase-transfer catalysts, initially used

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[1795] For example, see Gould, E.S.; Hiatt, R.R.; Irwin, K.C. *J. Am. Chem. Soc.* ***1968***, *90*, 4573; Sharpless, K.B.; Michaelson, R.C. *J. Am. Chem. Soc.* ***1973***, *95*, 6136; Kochi, J.K. *Organometallic Mechanisms and Catalysis*; Academic Press, NY, ***1978***, pp. 69–73; Ledon, H.J.; Durbut, P.; Varescon, F. *J. Am. Chem. Soc.* ***1981***, *103*, 3601; Mimoun, H.; Mignard, M.; Brechot, P.; Saussine, L. *J. Am. Chem. Soc.* ***1986***, *108*, 3711; Laszlo, P.; Levart, M.; Singh, G.P. *Tetrahedron Lett.* ***1991***, *32*, 3167.

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[1799] Straub, T.S. *Tetrahedron Lett.* ***1995***, *36*, 663.

[1800] Yadav, V.K.; Kapoor, K.K. *Tetrahedron Lett.* ***1994***, *35*, 9481.

[1801] MacPeek, D.L.; Starcher, P.S.; Phillips, B. *J. Am. Chem. Soc.* ***1959***, *81*, 680.

[1802] For a review of epoxidation of allenes, see Jacobs, T.L., in Landor, S.R. *The Chemistry of Allenes*, Vol. 2, Academic Press, NY, ***1982***, pp. 417–510, 483–491.

[1803] For a review of allene oxides, see Chan, T.H.; Ong, B.S. *Tetrahedron* ***1980***, *36*, 2269.

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by Wynberg, are now common.[1806] Enantioselectivities can be significantly improved by changes of the catalyst structure as well as the type of oxidant.[1807] A Yb-BINOL complex, with *t*-BuOOH led to epoxidation of conjugated ketones with high asymmetric induction,[1808] as did a mixture of NaOCl and a *Cinchona* alkaloid.[1809] Other enantioselective methods include treatment with diethylzinc, O_2, in the presence of a chiral amino-alcohol, to give the epoxy-ketone.[1810] Similarly, treatment with aqueous NaOCl[1811] or with an alkyl hydroperoxide[1812] and a chiral phase-transfer agent leads to chiral nonracemic epoxy-ketones.

Another important asymmetric epoxidation of a conjugated systems is the reaction of alkenes with polyleucine, DBU and urea—H_2O_2, giving an epoxy-carbonyl compound with good enantioselectivity.[1813] The hydroperoxide anion epoxidation of conjugated carbonyl compounds with a polyamino acid, such as poly-L-alanine or poly-L-leucine is known as the *Juliá–Colonna epoxidation.*[1814] Epoxidation of conjugated ketones to give nonracemic epoxy-ketones was done with aq. NaOCl and a Cinchona alkaloid derivative as catalyst.[1815] A triphasic phase-transfer catalysis protocol has also been developed.[1816] β-Peptides have been used as catalysts in this reaction.[1817]

Allylic alcohols can be converted to epoxy-alcohols with *tert*-butylhydroperoxide on molecular sieves,[1818] or with peroxy acids.[1819] The addition of an appropriate chiral ligand to the metal-catalyzed hydroperoxide epoxidation of allylic alcohols leads to high enantioselectivity. This important modification is

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[1808] Watanabe, S.; Arai, T.; Sasai, H.; Bougauchi, M.; Shibasaki, M. *J. Org. Chem.* ***1998***, *63*, 8090.

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known as the *Sharpless asymmetric epoxidation*,[1820] where allylic alcohols are converted to optically active epoxides with excellent enantioselectivity by treatment with *t*-BuOOH, titanium tetraisopropoxide and optically active diethyl tartrate.[1821] The $Ti(OCHMe_2)_4$ and diethyl tartrate can be present in catalytic amounts (15–10 mol%) if molecular sieves are present.[1822] Polymer-supported catalysts have also been reported.[1823] Both (+) and (−) diethyl tartrate are readily available, so either enantiomer of the product can be prepared. The method has been successful for a wide range of primary allylic alcohols, including substrates where the double bond is mono-, di-, tri-, and tetrasubstituted,[1824] and is highly useful in natural product synthesis. The mechanism of the Sharpless epoxidation is believed to involve attack on the substrate by a compound[1825] formed from the titanium alkoxide and the diethyl tartrate to produce a complex that also contains the substrate and the *t*-BuOOH.[1826]

Ordinary alkenes (without an allylic OH group) do not give optically active alcohols by the Sharpless protocol because binding to the catalyst is necessary for enantioselectivity. Simples alkenes can be epoxidized enantioselectively with sodium hypochlorite (NaOCl, commercial bleach) and an optically active manganese-complex catalyst.[1827] An important variation of this oxidation uses a manganese–salen complex[1828] with various oxidizing agents, in what is called

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[1826] For a review of the mechanism, see Finn, M.G.; Sharpless, K.B., in Morrison, J.D. *Asymmetric Synthesis*, Vol. 5, Academic Press, NY, ***1985***, p. 247. For other mechanistic studies, see Jørgensen, K.A.; Wheeler, R.A.; Hoffmann, R. *J. Am. Chem. Soc.* ***1987***, *109*, 3240; Carlier, P.R.; Sharpless, K.B. *J. Org. Chem.* ***1989***, *54*, 4016; Corey, E.J. *J. Org. Chem.* ***1990***, *55*, 1693; Woodard, S.S.; Finn, M.G.; Sharpless, K.B. *J. Am. Chem. Soc.* ***1991***, *113*, 106; Finn, M.G.; Sharpless, K.B. *J. Am. Chem. Soc.* ***1991***, *113*, 113; Takano, S.; Iwebuchi, Y.; Ogasawara, K. *J. Am. Chem. Soc.* ***1991***, *113*, 2786. See Cui, M.; Adam, W.; Shen, J.H.; Luo, X.M.; Tan, X.J.; Chen, K.X.; Ji, R.Y.; Jiang, H.L. *J. Org. Chem.* ***2002***, *67*, 1427.

[1827] Jacobsen, E.N.; Zhang, W.; Muci, A.R.; Ecker, J.R.; Deng, L. *J. Am. Chem. Soc.* ***1991***, *113*, 7063. See also, Irie, R.; Noda, K.; Ito, Y.; Katsuki, T. *Tetrahedron Lett.* ***1991***, *32*, 1055; Halterman, R.L.; Jan, S. *J. Org. Chem.* ***1991***, *56*, 5253.

[1828] These complexes have been characterized. See Adam, W.; Mock-Knoblauch, C.; Saha-Moller, C.R.; Herderich, M. *J. Am. Chem. Soc.* ***2000***, *122*, 9685.

the *Jacobsen–Katsuki reaction*.[1829] Apart from the commonly used NaOCl, urea—H_2O_2 has been used.[1830] With this reaction, simple alkenes can be epoxidized with high enantioselectivity.[1831] The mechanism of this reaction has been examined.[1832] Radical intermediates have been suggested for this reaction,[1833] A polymer-bound $Mn^{(III)}$–salen complex, in conjunction with NaOCl, has been used for asymmetric epoxidation.[1834] Chromium–salen complexes[1835] and ruthenium–salen complexes[1836] have been used for epoxidation. Manganese porphyrin complexes have also been used.[1837] Cobalt complexes give similar results.[1838] A related epoxidation reaction used an iron complex with molecular oxygen and isopropanal.[1839] Nonracemic epoxides can be prepared from racemic epoxides with salen–cobalt(II) catalysts following a modified procedure for kinetic resolution.[1840]

In a different type of reaction, alkenes are photooxygenated (with singlet O_2, see **14-7**) in the presence of a Ti, V, or Mo complex to give epoxy alcohols, such as **180**, formally derived from allylic hydroxylation followed by epoxidation.[1841] In other cases, modification of the procedure gives simple epoxidation.[1842] Alkenes react with aldehydes and oxygen, with palladium-on-silica[1843] or a ruthenium catalyst,[1844]

[1829] Hosoya, N.; Hatayama, A.; Irie, R.; Sasaki, H.; Katsuki, T. *Tetrahedron* ***1994***, *50*, 4311, and references cited therein; Brandes, B.D.; Jacobsen, E.N. *J. Org. Chem.* ***1994***, *59*, 4378; Sasaki, H.; Irie, R.; Hamada, T.; Suzuki, K.; Katsuki, T. *Tetrahedron* ***1994***, *50*, 11827; Brandes, B.D.; Jacobsen, E.N. *Tetrahedron Lett.* ***1995***, *36*, 5123; Nishikori, H.; Ohta, C.; Katsuki, T. *Synlett* ***2000***, 1557; Tangestaninejad, S.; Habibi, M.H.; Mirkhani, V.; Moghadam, M. *Synth. Commun.* ***2002***, *32*, 3331.

[1830] Kureshy, R.I.; Khan, N.H.; Abdi, S.H.R.; Patel, S.T.; Jasra, R.V. *Tetrahedron Asymmetry* ***2001***, *12*, 433.

[1831] For a discussion of stereocontrol factors, see Nishida, T.; Miyafuji, A.; Ito, Y.N.; Katsuki, T. *Tetrahedron Lett.* ***2000***, *41*, 7053.

[1832] See Linker, T. *Angew. Chem., Int. Ed.* ***1997***, *36*, 2060. See Adam, W.; Roschmann, K.J.; Saha-Möller, C.R. *Eur. J. Org. Chem.* ***2000***, 3519. For the importance of electronic effects, see Cavallo, L.; Jacobsen, H. *J. Org. Chem.* ***2003***, *68*, 6202.

[1833] Cavallo, L.; Jacobsen, H. *Angew. Chem. Int. Ed.* ***2000***, *39*, 589.

[1834] Song, C.E.; Roh, E.J.; Yu, B.M.; Chi, D.Y.; Kim, S.C.; Lee, K.J. *Chem. Commun.* ***2000***, 615; Ahn, K.-H.; Park, S.W.; Choi, S.; Kim, H.-J.; Moon, C.J. *Tetrahedron Lett.* ***2001***, *42*, 2485.

[1835] Daly, A.M.; Renehan, M.F.; Gilheany, D.G. *Org. Lett.* ***2001***, *3*, 663; O'Mahony, C.P.; McGarrigle, E.M.; Renehan, M.F.; Ryan, K.M.; Kerrigan, N.J.; Bousquet, C.; Gilheany, D.G. *Org. Lett.* ***2001***, *3*, 3435. See the references cited therein.

[1836] Nakata, K.; Takeda, T.; Mihara, J.; Hamada, T.; Irie, R.; Katsuki, T. *Chem. Eur. J.* ***2001***, *7*, 3776.

[1837] Konishi, K.; Oda, K.; Nishida, K.; Aida, T.; Inoue, S. *J. Am. Chem. Soc.* ***1992***, *114*, 1313.

[1838] Takai, T.; Hata, E.; Yorozu, K.; Mukaiyama, T. *Chem. Lett.* ***1992***, 2077.

[1839] Saalfrank, R.W.; Reihs, S.; Hug, M. *Tetrahedron Lett.* ***1993***, *34*, 6033.

[1840] Savle, P.S.; Lamoreaux, M.J.; Berry, J.F.; Gandour, R.D. *Tetrahedron Asymmetry* ***1998***, *9*, 1843.

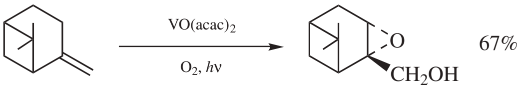
[1841] Adam, W.; Braun, M.; Griesbeck, A.; Lucchini, V.; Staab, E.; Will, B. *J. Am. Chem. Soc.* ***1989***, *111*, 203.

[1842] See Iwahama, T.; Hatta, G.; Sakaguchi, S.; Ishii, Y. *Chem. Commun.* ***2000***, 163.

[1843] Gao, H.; Angelici, R.J. *Synth. Commun.* ***2000***, *30*, 1239; Chen, W.; Yamada, J.; Matsumoto, K. *Synth. Commun.* ***2002***, *32*, 17; Ragagnin, G.; Knochel, P. *Synlett* ***2004***, 951.

[1844] Srikanth, A.; Nagendrappa, G.; Chandrasekaran, S. *Tetrahedron* ***2003***, *59*, 7761; Qi, J.Y.; Qiu, L.Q.; Lam, K.H.; Yip, C.W.; Zhou, Z.Y.; Chan, A.S.C. *Chem. Commun.* ***2003***, 1058.

to give the epoxide.



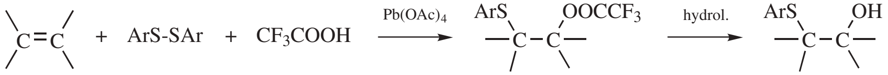
180

Thiiranes can be prepared directly from alkenes using specialized reagents.[1845] Thiourea with a tin catalyst gives the thiirane, for example.[1846] Interestingly, internal alkynes were converted to 1,2-dichorothiiranes by reaction with S_2Cl_2 (sulfur monochloride).[1847] It is noted that epoxides are converted to thiiranes with ammonium thiocyanate and a cerium complex.[1848] A trans-thiiration reaction occurs with a molybdenum catalyst, in which an alkene reacts with styrene thiirane to give the new thiirane.[1849]

OS **I**, 494; **IV**, 552, 860; **V**, 191, 414, 467, 1007; **VI**, 39, 320, 679, 862; **VII**, 121, 126, 461; **VIII**, 546; **IX**, 288; **X**, 29; **80**, 9.

15-51 Hydroxysulfenylation (Addition of Oxygen, Sulfur)

Hydroxy-arylthio-addition (overall transformation)



$$\mathrm{>C=C<} + \mathrm{ArS{-}SAr} + \mathrm{CF_3COOH} \xrightarrow{\mathrm{Pb(OAc)_4}} \overset{\mathrm{ArS}}{-\mathrm{C}}-\overset{\mathrm{OOCCF_3}}{\mathrm{C}-} \xrightarrow{\text{hydrol.}} \overset{\mathrm{ArS}}{-\mathrm{C}}-\overset{\mathrm{OH}}{\mathrm{C}-}$$

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.[1850] Manganese and copper acetates have been used instead of $Pb(OAc)_4$.[1851] Addition of the groups OH and RSO has been achieved by treatment of alkenes with O_2 and a thiol RSH.[1852] Two RS groups were added, to give *vic*-dithiols, by treatment of the alkene with a disulfide RSSR and BF_3-etherate.[1853] This reaction

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[1845] Capozzi, G.; Menichetti, S.; Neri, S.; Skowronska, A. *Synlett* ***1994***, 267; Adam, W.; Bargon, R.M. *Eur. J. Org. Chem.* ***2001***, 1959; Adam, W.; Bargon, R.M. *Chem. Commun.* ***2001***, 1910.

[1846] Tangestaninejad, S.; Mirkhani, V. *Synth. Commun.* ***1999***, *29*, 2079.

[1847] Nakayama, J.; Takahashi, K.; Watanabe, T.; Sugihara, Y.; Ishii, A. *Tetrahedron Lett.* ***2000***, *41*, 8349.

[1848] Iranpoor, N.; Tamami, B.; Shekarriz, M. *Synth. Commun.* ***1999***, *29*, 3313.

[1849] Adam, W.; Bargon, R.M.; Schenk, W.A. *J. Am. Chem. Soc.* ***2003***, *125*, 3871.

[1850] Trost, B.M.; Ochiai, M.; McDougal, P.G. *J. Am. Chem. Soc.* ***1978***, *100*, 7103. For a related reaction, see Zefirov, N.S.; Zyk, N.V.; Kutateladze, A.G.; Kolbasenko, S.I.; Lapin, Yu.A. *J. Org. Chem. USSR* ***1986***, *22*, 190.

[1851] Bewick, A.; Mellor, J.M.; Owton, W.M. *J. Chem. Soc. Perkin Trans. 1*, ***1985***, 1039; Bewick, A.; Mellor, J.M.; Milano, D.; Owton, W.M. *J. Chem. Soc. Perkin Trans. 1*, ***1985***, 1045; Samii, Z.K.M.A.E.; Ashmawy, M.I.A.; Mellor, J.M. *Tetrahedron Lett.* ***1986***, *27*, 5289.

[1852] Chung, M.; D'Souza, V.T.; Szmant, H.H. *J. Org. Chem.* ***1987***, *52*, 1741, and other papers in this series.

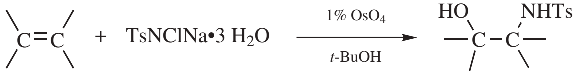
[1853] Caserio, M.C.; Fisher, C.L.; Kim, J.K. *J. Org. Chem.* ***1985***, *50*, 4390; Inoue, H.; Murata, S. *Heterocycles* ***1997***, *45*, 847.

has been carried out internally.[1854] In a similar manner, reaction of alkenes with ceric ammonium nitrate, diphenyl diselenide in methanol leads to vicinally substituted phenylselenyl methyl ethers.[1855] Dimethyl diselenide adds to alkenes to form vicinal bis-methylselenyl compounds, in the presence of tin tetrachloride.[1856]

Halo-ethers can be formed by the reaction of alkenyl alcohols with various reagents. Hept-6-en-1-ol reacts with (collidine)$_2$I$^+$PF$_6^-$, for example, to form 2-iodomethyl-1-oxacycloheptane.[1857]

15-52 Oxyamination (Addition of Oxygen, Nitrogen)

Tosylamino-hydroxy-addition



N-Tosylated β-hydroxy alkylamines (which can be easily hydrolyzed to β-hydroxyamines[1858]) can be prepared[1859] by treatment of alkenes with the trihydrate of Chloramine-T (*N*-chloro-*p*-toluenesulfonamide sodium salt)[1566] and a catalytic amount of OsO_4.[1860] In some cases, yields can be improved by the use of phase-transfer catalysis.[1861] The reaction has been carried out enantioselectively.[1862] Alkenes can be converted to amido alcohols enantioselectivity by modification of this basic scheme. The *Sharpless asymmetric aminohydroxylation* employs a catalyst consisting of *Cinchona* alkaloid derived ligands and an osmium species in combination with a stoichiometric nitrogen source that also functions as the oxidant.[1863] The reaction of a carbamate with (DHQ)$_2$PHAL (**176**) and the osmium compound, with NaOH and *tert*-butyl hypochlorite, leads to a diastereomeric mixture of amido alcohols **181** and **182**, each formed with high enantioselectivity.[1864] In general, the nitrogen adds to the less sterically hindered carbon of the alkene to give the major product. *N*-Bromoamides, in the presence of a catalytic amount of (DHQ)$_2$PHAL

[1854] Tuladhar, S.M.; Fallis, A.G. *Tetrahedron Lett.* ***1987***, *28*, 523. For a list of other examples, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 905–908.

[1855] Bosman, C.; D'Annibale, A.; Resta, S.; Trogolo, C. *Tetrahedron Lett.* ***1994***, *35*, 6525. See Ogawa, A.; Tanaka, H.; Yokoyama, H.; Obayashi, R.; Yokoyama, K.; Sonoda, N. *J. Org. Chem.* ***1992***, *57*, 111 for formation of mixed PhS—PhSe- compounds from alkenes.

[1856] Hermans, B.; Colard, N.; Hevesi, L. *Tetrahedron Lett.* ***1992***, *33*, 4629.

[1857] Brunel, Y.; Rousseau, G. *Synlett* ***1995***, 323.

[1858] For some reactions of the oxyamination products, see Bäckvall, J.E.; Oshima, K.; Palermo, R.E.; Sharpless, K.B. *J. Org. Chem.* ***1979***, *44*, 1953.

[1859] Sharpless, K.B.; Chong, A.O.; Oshima, K. *J. Org. Chem.* ***1976***, *41*, 177. See Rudolph, J.; Sennhenn, P.C.; Vlaar, C.P.; Sharpless, K.B. *Angew. Chem. Int. Ed.* ***1996***, *35*, 2810 for a discussion of the influence of substituents on nitrogen in this reaction.

[1860] See Fokin, V.V.; Sharpless, K.B. *Angew. Chem. Int. Ed.* ***2001***, *40*, 3455.

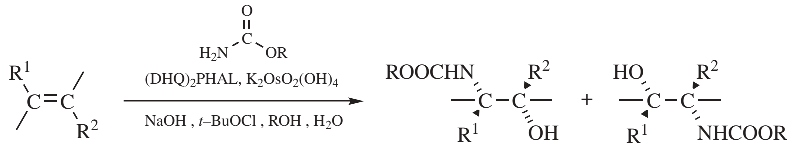
[1861] Herranz, E.; Sharpless, K.B. *J. Org. Chem.* ***1978***, *43*, 2544.

[1862] Hassine, B.B.; Gorsane, M.; Pecher, J.; Martin, R.H. *Bull. Soc. Chim. Belg.* ***1985***, *94*, 759.

[1863] For a review, see Bodkin, J.A.; McLeod, M.D. *J. Chem. Soc., Perkin Trans. 1* ***2002***, 2733.

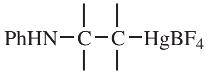
[1864] Li, G.; Chang, H.-T.; Sharpless, K.B. *Angew. Chem., Int. Ed.* ***1996***, *35*, 451.

and LiOH converts conjugated esters to β-amido-α-hydroxy esters with good enantioselectivity.[1865] In another procedure, certain β-hydroxy secondary alkylamines can be prepared by treatment of alkenes with the osmium compound *t*-Bu—N=OsO_3, followed by reductive cleavage with $LiAlH_4$ of the initially formed osmic esters.[1866] It is presumed that Ts—N=OsO_3 is an intermediate in the Chloramine-T reaction. Another oxyamination reaction involves treatment of a palladium complex of the alkene with a secondary or primary amine, followed by lead tetraacetate or another oxidant.[1867]



181 **182**

The organolanthanide-catalyzed alkene hydroamination has been reported.[1868] With this approach, amino alkenes (not enamines) can be cyclized to form cyclic amines,[1869] and amino alkynes lead to cyclic imine.[1870] The use of synthesized *C*-1[1871] and *C*-2 symmetric[1872] chiral organolanthanide complexes give the amino alcohol with good enantioselectivity.

β-Amino alcohols can be prepared by treatment of an alkene with a reagent prepared from HgO and HBF_4 along with aniline to give an aminomercurial compound  $PhHN-\overset{|}{\underset{|}{C}}-\overset{|}{\underset{|}{C}}-HgBF_4$ (aminomercuration; see **15-7**) which is hydrolyzed

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[1865] Demko, Z.P.; Bartsch, M.; Sharpless, K.B. *Org. Lett.* ***2000***, *2*, 2221.

[1866] Hentges, S.G.; Sharpless, K.B. *J. Org. Chem.* ***1980***, *45*, 2257. Also see, Rubinstein, H.; Svendsen, J.S. *Acta Chem. Scand. B* ***1994***, *48*, 439. For another method, in which the NH in the product is connected to an easily removable protecting group, see Herranz, E.; Sharpless, K.B. *J. Org. Chem.* ***1980***, *45*, 2710.

[1867] Bäckvall, J.E.; Björkman, E.E. *Acta Chem. Scand. Ser. B* ***1984***, *38*, 91; Bäckvall, J.E.; Bystrom, S.E. *J. Org. Chem.* ***1982***, *47*, 1126.

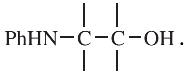
[1868] Ryu, J.-S.; Li, G.Y.; Marks, T.J. *J. Am. Chem. Soc.* ***2003***, *125*, 12584; Li, Y.; Marks, T.J. *Organometallics* ***1996***, *15*, 3770; Gagné, M.R.; Stern, C.L.; Marks, T.J. *J. Am Chem. Soc.* ***1992***, *114*, 275; Gagné, M.R.; Marks, T.J. *J. Am Chem. Soc.* ***1989***, *111*, 4108. For a review, see Hong, S.; Marks, T.J. *Acc. Chem. Res.* ***2004***, *37*, 673.

[1869] Gagné, M.R.; Stern, C.L.; Marks, T.J. *J. Am Chem. Soc.* ***1992***, *114*, 275; Gagné, M.R.; Marks, T.J. *J. Am Chem. Soc.* ***1989***, *111*, 4108.

[1870] Li, Y.; Marks, T.J. *J. Am. Chem. Soc.* ***1996***, *118*, 9295; Li, Y.; Fu, P.-F.; Marks, T.J. *Organometallics* ***1994***, *13*, 439; Li, Y.; Marks, T.J. *J. Am. Chem. Soc.* ***1998***, *120*, 1757; Li, Y.; Marks, T.J. *J. Am. Chem. Soc.* ***1996***, *118*, 707.

[1871] Douglass, M.R.; Ogasawara, M.; Hong, S.; Metz, M.V.; Marks, T.J. *Organometallics* ***2002***, *21*, 283; Giardello, M.A.; Conticello, V.P.; Brard, L.; Gagné, M.R.; Marks, T.J. *J. Am. Chem. Soc.* ***1994***, *116*, 10241; Giardello, M.A.; Conticello, V.P.; Brard, L.; Sabat, M.; Rheingold, A.L.; Stern, C.L.; Marks, T.J. *J. Am. Chem. Soc.* ***1994***, *116*, 10212; Gagné, M.R.; Brard, L.; Conticello, V.P.; Giardello, M.A.; Stern, C.L.; Marks, T.J. *Organometallics* ***1992***, *11*, 2003.

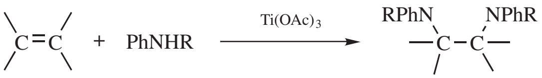
[1872] Hong, S.; Tian, S.; Metz, M.V.; Marks, T.J. *J. Am. Chem. Soc.* ***2003***, *125*, 14768.

to  $PhHN{-}C{-}C{-}OH$.[1873] The use of an alcohol instead of water gives the corresponding amino ether. β-Azido alcohols are prepared by the reaction of an alkene with $Me_3SiOOSiMe_3$, Me_3SiN_3, and 20% $(Cl_2SnO)_n$, followed by treatment with aqueous acetic acid.[1874]

OS **VII**, 223, 375.

15-53 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.[1875] The reaction is not successful for primary aliphatic amines. In another procedure, alkenes can be diaminated by treatment with the osmium compounds R_3NOsO (R = *t*-Bu) and R_2NOsO_2,[1876] analogous to the osmium compound mentioned at **15-52**.[1877] The palladium-promoted method of **15-52** has also been extended to diamination.[1878] Alkenes can also be diaminated[1879] indirectly by treatment of the aminomercurial compound mentioned in **15-52** with a primary or secondary aromatic amine.[1880] The reaction of an alkene with *N*-arylsulfonyl dichloroamines, $ArSO_2NCl_2$, followed by reaction with aqueous Na_2SO_3, gives the *anti*-*vic*-diacetamde.[1881]

Two azido groups can be added to double bonds by treatment with sodium azide and iodosobenzene in acetic acid, $C{=}C + NaN_3 + PhIO \rightarrow N_3{-}C{-}C{-}N_3$.[1882]

[1873] Barluenga, J.; Alonso-Cires, L.; Asensio, G. *Synthesis* ***1981***, 376.

[1874] Sakurada, I.; Yamasaki, S.; Kanai, M.; Shibasaki, M. *Tetrahedron Lett.* ***2000***, *41*, 2415.

[1875] Gómez Aranda, V.; Barluenga, J.; Aznar, F. *Synthesis* ***1974***, 504.

[1876] Chong, A.O.; Oshima, K.; Sharpless, K.B. *J. Am. Chem. Soc.* ***1977***, *99*, 3420. See also, Sharpless, K.B.; Singer, S.P. *J. Org. Chem.* ***1976***, *41*, 2504.

[1877] For a X-ray structure of the osmium intermediate, see Muñiz, K.; Iesato, A.; Nieger, M. *Chem. Eur. J.* ***2003***, *9*, 5581.

[1878] Bäckvall, J. *Tetrahedron Lett.* ***1978***, 163.

[1879] For other diamination methods, see Michejda, C.J.; Campbell, D.H. *J. Am. Chem. Soc.* ***1979***, *101*, 7687; Becker, P.N.; White, M.A.; Bergman, R.G. *J. Am. Chem. Soc.* ***1980***, *102*, 5676; Becker, P.N.; Bergman, R.G. *Organometallics* ***1983***, *2*, 787; Jung, S.; Kohn, H. *Tetrahedron Lett.* ***1984***, *25*, 399; *J. Am. Chem. Soc.* ***1985***, *107*, 2931; Osowska-Pacewicka, K.; Zwierzak, A. *Synthesis* ***1990***, 505.

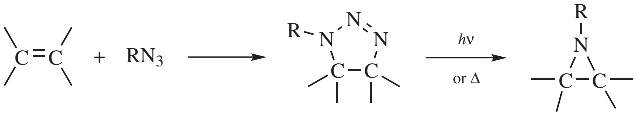
[1880] Barluenga, J.; Alonso-Cires, L.; Asensio, G. *Synthesis* ***1979***, 962.

[1881] Li, G.; Kim, S.H.; Wei, H.-X. *Tetrahedron Lett.* ***2000***, *41*, 8699.

[1882] Moriarty, R.M.; Khosrowshahi, J.S. *Tetrahedron Lett.* ***1986***, *27*, 2809. For other methods, see Minisci, F.; Galli, R. *Tetrahedron Lett.* ***1962***, 533; Fristad, W.E.; Brandvold, T.A.; Peterson, J.R.; Thompson, S.R. *J. Org. Chem.* ***1985***, *50*, 3647.

15-54 Formation of Aziridines (Addition of Nitrogen, Nitrogen)

***epi*-Arylimino-addition**, and so on.



Triazoline

Aziridines can be prepared directly from double-bond compounds by photolysis or thermolysis of a mixture of the substrate and an azide.[1883] The reaction has been carried out with R = aryl, cyano, EtOOC, and RSO_2, as well as other groups. The reaction can take place by at least two pathways.

In one pathway a 1,3-dipolar addition (**15-58**) takes place to give a triazoline (which can be isolated), followed thermal by extrusion of nitrogen (**17-34**). Evidence for the nitrene pathway is most compelling for R = acyl groups. In the other, the azide is converted to a nitrene, which adds to the double bond in a manner analogous to that of carbene addition (**15-64**). Sulfonyloxy amines, such as $ArSO_2ONHCO_2Et$, form an aziridine when treated with CaO in the presence of a conjugated carbonyl compound.[1884] In the presence of copper,[1885] cobalt,[1886] or rhodium complexes,[1887] ethyl diazoacetate adds to imines to give aziridines. Diazirines (p. 288) with *n*-butyllithium converted conjugated amides to the α,β-aziridino amide.[1888] Calcium oxide has also been used to generate the nitrene,[1889] including nitrene precursors that have an attached chiral ester.[1890] Other specialized reagents have also been used.[1891] As discussed on p. 293, singlet nitrenes add stereospecifically while triplet nitrenes do not. Diphenyl sulfimide (Ph_2SNH) converts

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[1883] For reviews, see Dermer, O.C.; Ham, G.E. *Ethylenimine and Other Aziridines*, Academic Press, NY, ***1969***, pp. 68–79; Muller, L.L.; Hamer, J. *1,2-Cycloaddition Reactions*, Wiley, NY, ***1967***.

[1884] Fioravanti, S.; Pellacani, L.; Tabanella, S.; Tardella, P.A. *Tetrahedron* ***1998***, *54*, 14105; Fioravanti, S.; Morreale, A.; Pellacani, L.; Tardella, P.A. *Synthesis* ***2001***, 1975. For an enantioselective version of this reaction using a chiral ester auxiliary, see Fioravanti, S.; Morreale, A.; Pellacani, L.; Tardella, P.A. *J. Org. Chem.* ***2002***, *67*, 4972.

[1885] Li, Z.; Zheng, Z.; Chen, H. *Tetrahedron Asymmetry* ***2000***, *11*, 1157; Wong, H.L.; Tian, Y.; Chan, K.S. *Tetrahedron Lett.* ***2000***, *41*, 7723; Sanders, C.J.; Gillespie, K.M.; Scott, P. *Tetrahedron Asymmetry* ***2001***, *12*, 1055; Ma, J.-A.; Wang, L.-X.; Zhang, W.; Zhou, W.; Zhou, Q.-L. *Tetrahedron Asymmetry* ***2001***, *12*, 2801.

[1886] Ikeno, T.; Nishizuka, A.; Sato, M.; Yamada, T. *Synlett* ***2001***, 406.

[1887] Mohan, J.M.; Uphade, T.S.S.; Choudhary, V.R.; Ravindranathan, T.; Sudalai, A. *Chem. Commun.* ***1997***, 1429; Moran, M.; Bernardinelli, G.; Müller, P. *Helv. Chim. Acta* ***1995***, *78*, 2048.

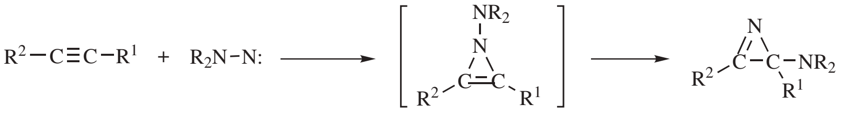
[1888] Hori, K.; Sugihara, H.; Ito, Y.N.; Katsuki, T. *Tetrahedron Lett.* ***1999***, *40*, 5207; Ishihara, H.; Ito, Y.N.; Katsuki, T. *Chem. Lett.* ***2001***, 984.

[1889] Carducci, M.; Fioravanti, S.; Loreta, M.A.; Pellacani, L.; Tardella, P.A. *Tetrahedron Lett.* ***1996***, *37*, 3777.

[1890] Fioravanti, S.; Morreale, A.; Pellacani, L.; Tardella, P.A. *Tetrahedron Lett.* ***2003***, *44*, 3031.

[1891] Aires-de-Sousa, J.; Labo, A.M.; Prabhakar, S. *Tetrahedron Lett.* ***1996***, *37*, 3183.

Michael-type substrates to the corresponding aziridines.[1892] Aminonitrenes (R_2NN:) have been shown to add to alkenes[1893] to give *N*-substituted aziridines and to triple bonds to give 1-azirines, which arise from rearrangement of the initially formed 2-azirines.[1894] Like oxirenes (see **15-50**), 2-azirines are unstable, probably because of anti-aromaticity. 1-Azirines can be reduced to give chiral aziridines.[1895]



2-Azirine 1-Azirine

An alternative preparation of aziridines reacts an alkene with iodine and chloramine-T, generating the corresponding *N*-tosyl aziridine.[1896] Chloramine T and NBS also gives the *N*-tosyl aziridine,[1897] and bromamine-T ($TsNBr^-Na^+$) has been used in a similar manner,[1898] and also TsNIK.[1899] Diazoalkanes react with imines to give aziridines.[1900] Another useful reagent is NsN=IPh, which reacts with alkenes in the presence of rhodium compounds[1901] or $Cu(OTf)_2$[1902] to give *N*-Ns aziridines. Other sulfonamide reagents can be used,[1903] including PhI=NTs.[1904] Enantioselective aziridination is possible using this reaction with

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[1892] Furukawa, N.; Yoshimura, T.; Ohtsu, M.; Akasaka, T.; Oae, S. *Tetrahedron* ***1980***, *36*, 73. For other methods, see Groves, J.T.; Takahashi, T. *J. Am. Chem. Soc.* ***1983***, *105*, 2073; Mahy, J.; Bedi, G.; Battioni, P.; Mansuy, D. *J. Chem. Soc. Perkin Trans. 2*, ***1988***, 1517; Atkinson, R.S.; Kelly, B.J. *J. Chem. Soc. Perkin Trans. 1*, ***1989***, 1515.

[1893] Siu, T.; Yudin, A.K. *J. Am. Chem. Soc.* ***2002***, *124*, 530.

[1894] Anderson, D.J.; Gilchrist, T.L.; Rees, C.W. *Chem. Commun.* ***1969***, 147.

[1895] Roth, P.; Andersson, P.G.; Somfai, P. *Chem. Commun.* ***2002***, 1752.

[1896] Ando, T.; Kano, D.; Minakata, S.; Ryu, I.; Komatsu, M. *Tetrahedron* ***1998***, *54*, 13485. For the use of $TsNCl_2$, see Chen, D.; Timmons, C.; Guo, L.; Xu, X.; Li, G. *Synthesis* ***2004***, 2479.

[1897] Thakur, V.V.; Sudalai, A. *Tetrahedron Lett.* ***2003***, *44*, 989.

[1898] Vyas, R.; Chanda, B.M.; Bedekar, A.V. *Tetrahedron Lett.* ***1998***, *39*, 4715; Hayer, M.F.; Hossain, M.M. *J. Org. Chem.* ***1998***, *63*, 6839. This reaction was catalyzed by $CuCl_2$ with microwave irradiation, see Chanda, B.M.; Vyas, R.; Bedekar, A.V. *J. Org. Chem.* ***2001***, *66*, 30. Iron catalysts have been used, see Vyas, R.; Gao, G.-Y.; Hardin, J.D.; Zhang, X.P. *Org. Lett.* ***2003***, *6*, 1907.

[1899] Jain, S.L.; Sain, B. *Tetrahedron Lett.* ***2003***, *44*, 575.

[1900] Casarrubios, L.; Pérez, J.A.; Brookhart, M.; Templeton, J.L. *J. Org. Chem.* ***1996***, *61*, 8358.

[1901] Müller, P.; Baud, C.; Jacquier, Y. *Tetrahedron* ***1996***, *52*, 1543. Also see, Södergren, M.J.; Alonso, D.A.; Bedekar, A.V.; Andersson, P.G. *Tetrahedron Lett.* ***1997***, *38*, 6897.

[1902] Knight, J.G.; Muldowney, M.P. *Synlett* ***1995***, 949. See also, Dauben, P.; Sanière, L.; Tarrade, A.; Dodd, R.H. *J. Am. Chem. Soc.* ***2001***, *123*, 7707; Shi, M.; Wang, C.-J.; Chan, A.S.C. *Tetrahedron Asymmetry* ***2001***, *12*, 3105.

[1903] $PhI{=}NSO_2CH_2CCl_3$: GuthiKonda, K.; Du Bois, J. *J. Am. Chem. Soc.* ***2002***, *124*, 13672. See also, Di Chenna, P.H.; Robert-Peillard, F.; Dauban, P.; Dodd, R.H. *Org. Lett.* ***2004***, *6*, 4503; Kwong, H.-L.; Liu, D.; Chan, K.-Y.; Lee, C.-S.; Huang, K.-H.; Che, C.-M. *Tetrahedron Lett.* ***2004***, *45*, 3965.

[1904] Vedernikov, A.N.; Caulton, K.G. *Org. Lett.* ***2003***, *5*, 2591; Cui, Y.; He, C. *J. Am. Chem. Soc.* ***2003***, *125*, 16202. $PhI{=}NSO_2CH_2CH_2SiMe_3$: Dauban, P.; Dodd, R.H. *J. Org. Chem.* ***1999***, *64*, 5304, and see Nishimura, M.; Minakata, S.; Takahashi, T.; Oderaotoshi, Y.; Komatsu, M. *J. Org. Chem.* ***2002***, *67*, 2101.

chiral ligands.[1905] This reagent has been used in ionic liquids with a copper catalyst.[1906] Such reactions are catalyzed by palladium[1907] and methyl trioxorhenium ($MeReO_3$) can be used in these reactions.[1908] Manganese–salen catalysts have also been used with this reagent.[1909] A nitrido manganese–salen complex was also used with ditosyl anhydride, converting a conjugated diene to an allylic *N*-tosylaziridine.[1910]

Nitrenes can also add to aromatic rings to give ring-expansion products analogous to those mentioned in **15-62**.[1911]

OS **VI**, 56.

15-55 Aminosulfenylation (Addition of Nitrogen, Sulfur)

Arylamino-arylthio-addition

An amino and an arylthio group can be added to a double bond by treatment with a sulfenanilide PhSNHAr in the presence of BF_3-etherate.[1912] The addition is anti, and the mechanism probably involves a thiiranium ion.[1913] In another aminosulfenylation procedure, the substrate is treated with dimethyl(methylthio)sulfonium fluoroborate ($MeSSMe_2\ BF_4^-$) and ammonia or an amine,[1914] the latter acting as a nucleophile. This reaction was extended to other nucleophiles:[1915] N_3^-,[1916]

[1905] See Gillespie, K.M.; Sanders, C.J.; O'Shaughnessy, P.; Westmoreland, I.; Thickitt, C.P.; Cott, P. *J. Org. Chem.* ***2002***, *67*, 3450.

[1906] In bmim BF_4, 1-butyl-3-methylimidazolium tetrafluoroborate: Kantam, M.L.; Neeraja, V.; Kavita, B.; Haritha, Y. *Synlett* ***2004***, 525.

[1907] Antunes, A.M.M.; Marto, S.J.L.; Branco, P.S.; Prabhakar, S.; Lobo, A.M. *Chem. Commun.* ***2001***, 405.

[1908] Jean, H.-J.; Nguyen, S.B.T. *Chem. Commun.* ***2001***, 235.

[1909] O'Connor, K.J.; Wey, S.-J.; Burrows, C.J. *Tetrahedron Lett.* ***1992***, *33*, 1001; Nishikori, H.; Katsuki, T. *Tetrahedron Lett.* ***1996***, *37*, 9245; Noda, K.; Hosoya, N.; Irie, R.; Ito, Y.; Katsuki, T. *Synlett* ***1993***, 469.

[1910] Nishimura, M.; Minakata, S.; Thonchant, S.; Ryu, I.; Komatsu, M. *Tetrahedron Lett.* ***2000***, *41*, 7089.

[1911] For example, see Hafner, K.; König, C. *Angew. Chem. Int. Ed.* ***1963***, *2*, 96; Lwowski, W.; Johnson, R.L. *Tetrahedron Lett.* ***1967***, 891.

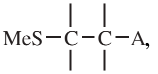
[1912] Benati, L.; Montavecchi, P.C.; Spagnolo, P. *Tetrahedron Lett.* ***1984***, *25*, 2039. See also, Brownbridge, P. *Tetrahedron Lett.* ***1984***, *25*, 3759.

[1913] See Ref. 21.

[1914] Trost, B.M.; Shibata, T. *J. Am. Chem. Soc.* ***1982***, *104*, 3225; Caserio, M.C.; Kim., J.K. *J. Am. Chem. Soc.* ***1982***, *104*, 3231.

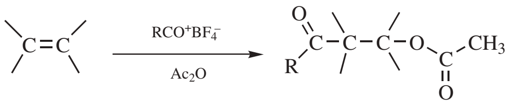
[1915] Trost, B.M.; Shibata, T.; Martin, S.J. *J. Am. Chem. Soc.* ***1982***, *104*, 3228; Trost, B.M.; Shibata, T. *J. Am. Chem. Soc.* ***1982***, *104*, 3225. For an extension that allows A to be C≡CR, see Trost, B.M.; Martin, S.J. *J. Am. Chem. Soc.* ***1984***, *106*, 4263.

[1916] Sreekumar, R.; Padmakumar, R.; Rugmini, P. *Chem. Commun.* ***1997***, 1133.

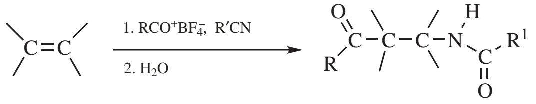
NO_2^- CN^-, ^-OH, and ^-OAc to give  $\mathrm{MeS{-}\overset{|}{\underset{|}{C}}{-}\overset{|}{\underset{|}{C}}{-}A}$, where A = N_3, NO_2, CN, OH, and OAc, respectively. An RS (R = alkyl or aryl) and an NHCOMe group have been added in an electrochemical procedure.[1917]

15-56 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.[1918] 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 to give **183**, if a nitrile is used in place of the anhydride. Similarly, halo acetoxylation is known.[1919] This reaction has also been carried out on triple bonds, to give the unsaturated analogs of **183** (syn addition).[1920]



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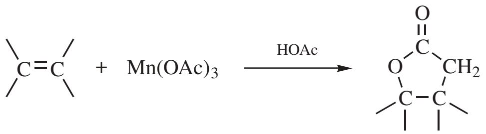
15-57 The Conversion of Alkenes to γ-Lactones (Addition of Oxygen, Carbon)



This reaction is clearly related to forming esters and lactones by reaction of carboxylic acids with alkenes (**15-6**), but the manganese reagent leads to

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[1917] Bewick, A.; Coe, D.E.; Mellor, J.M.; Owton, M.W. *J. Chem. Soc. Perkin Trans. 1*, ***1985***, 1033.

[1918] Shastin, A.V.; Balenkova, E.S. *J. Org. Chem. USSR* ***1984***, *20*, 870.

[1919] Hashem, Md.A.; Jung, A.; Ries, M.; Kirschning, A. *Synlett* ***1998***, 195.

[1920] Gridnev, I.D.; Balenkova, E.S. *J. Org. Chem. USSR* ***1988***, *24*, 1447.

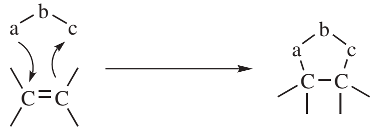
differences. Alkenes react with manganese(III) acetate to give γ-lactones.[1921] The mechanism is probably free radical, involving addition of •CH_2COOH to the double bond. Ultrasound improves the efficiency of the reaction.[1922] In a related reaction, cyclohexene reacted with $MeO_2CCH_2CO_2K$ and $Mn(OAc)_3$ to give an α-carbomethoxy bicyclic lactone.[1923] The use of dimethyl malonate and ultrasound in this reaction gave the same type of product.[1924] Lactone formation has also been accomplished by treatment of alkenes with α-bromo carboxylic acids in the presence of benzoyl peroxide as catalyst,[1925] and with alkylidene chromium pentacarbonyl complexes.[1926] Alkenes can also be converted to γ- lactones by indirect routes.[1927] Chromium–carbene complexes add to alkenes to give β-lactones using ultrasound.[1928]

An intramolecular variation of this reaction is known, involving amides, which generates a lactam.[1929]

OS **VII**, 400.

For addition of aldehydes and ketones, see the Prins reaction (**16-54**), and reactions **16-95** and **16-96**.

15-58 1,3-Dipolar Addition (Addition of Oxygen, Nitrogen, Carbon)



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There are a large group of reactions ([3 + 2]-cycloadditions) in which five-membered heterocyclic compounds are prepared by addition of 1,3-dipolar compounds to double bonds. This reaction is quite useful in the synthesis of alkaloids,[1930] including asymmetric syntheses.[1931] These dipolar compounds have a

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[1921] Bush Jr., J.B.; Finkbeiner, H. *J. Am. Chem. Soc.* ***1968***, *90*, 5903; Heiba, E.I.; Dessau, R.M.; Koehl, Jr., W.J. *J. Am. Chem. Soc.* ***1968***, *90*, 5905; Heiba, E.I.; Dessau, R.M.; Rodewald, P.G. *J. Am. Chem. Soc.* ***1974***, *96*, 7977; Midgley, G.; Thomas, C.B. *J. Chem. Soc. Perkin Trans. 2*, ***1984***, 1537; Ernst, A.B.; Fristad, W.E. *Tetrahedron Lett.* ***1985***, *26*, 3761; Shundo, R.; Nishiguchi, I.; Matsubara, Y.; Hirashima, T. *Tetrahedron* ***1991***, *47*, 831. See also, Corey, E.J.; Gross, A.W. *Tetrahedron Lett.* ***1985***, *26*, 4291.

[1922] D'Annibale, A.; Trogolo, C. *Tetrahdron Lett.* ***1994***, *35*, 2083.

[1923] Lamarque, L.; Méou, A.; Brun, P. *Tetrahedron* ***1998***, *54*, 6497.

[1924] Allegretti, M.; D'Annibale, A.; Trogolo, C. *Tetrahedron* ***1993***, *49*, 10705.

[1925] Nakano, T.; Kayama, M.; Nagai, Y. *Bull. Chem. Soc. Jpn.* ***1987***, *60*, 1049. See also, Kraus, G.A.; Landgrebe, K. *Tetrahedron Lett.* ***1984***, *25*, 3939.

[1926] Wang, S.L.B.; Su, J.; Wulff, W.D. *J. Am. Chem. Soc.* ***1992***, *114*, 10665.

[1927] See, for example, Boldt, P.; Thielecke, W.; Etzemüller, J. *Chem. Ber.* ***1969***, *102*, 4157; Das Gupta, T.K.; Felix, D.; Kempe, U.M.; Eschenmoser, A. *Helv. Chim. Acta* ***1972***, *55*, 2198; Bäuml, E.; Tscheschlok, K.; Pock, R.; Mayr, H. *Tetrahedron Lett.* ***1988***, *29*, 6925.

[1928] Caldwell, J.J.; Harrity, J.P.A.; Heron, N.M.; Kerr, W.J.; McKendry, S.; Middlemiss, D. *Tetrahedron Lett.* ***1999***, *40*, 3481; Caldwell, J.J.; Kerr, W.J.; McKendry, S. *Tetrahedron Lett.* ***1999***, *40*, 3485.

[1929] Davies, D.T.; Kapur, N.; Parsons, A.F. *Tetrahedron Lett.* ***1998***, *39*, 4397.

[1930] See Broggini, G.; Zecchi, G. *Synthesis* ***1999***, 905.

[1931] Karlsson, S.; Högberg, H.-E. *Org. Prep. Proceed. Int.* ***2001***, *33*, 103.

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 (see Table 15.3).[1932] The reaction can then be formulated as shown to generate **184**. Note that the initial reaction of potassium permanganate (**15-48**) occurs by [3 + 2]-cycloaddition to give a manganate ester (**171**).[1933] [3+2]-Cycloadditions occur with other metal oxides.[1934] Hydrazones have also been reported to give [3 + 2]-cycloadditions.[1935]

1,3-Dipoles of the type shown in Table 15.3 have an atom with six electrons in the outer shell, which is usually unstable, and such compounds will delocalize the change to alleviate this electronic arrangement (they are resonance stabilized). 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:

$$\overset{\ominus}{\text{a}}-\text{b}=\overset{\oplus}{\text{c}}- \quad \longleftrightarrow \quad \overset{\ominus}{\text{a}}-\text{b}\equiv\overset{\oplus}{\text{c}}-$$

[1932] For a treatise, see Padwa, A. *1,3-Dipolar Cycloaddition Chemistry* 2 vols., Wiley, NY, ***1984***. For general reviews, see Carruthers, W. *Cycloaddition reactins in Organic Synthesis*, Pergamon, Elmsford, NY, ***1990***; Drygina, O.V.; Garnovskii, A.D. *Russ. Chem. Rev.* ***1986***, *55*, 851; Samuilov, Ya.D.; Konovalov, A.I. *Russ. Chem. Rev.* ***1984***, *53*, 332; Beltrame, P., in Bamford, C.H.; Tipper, C.F.H. *Comprhensive Chemical Kinetics*, Vol. 9, Elsevier, NY, ***1973***, pp. 117–131; Huisgen, R.; Grashey, R.; Sauer, J., in Patai, S. *The Chemistry of Alkenes*, Vol. 1, Wiley, NY, ***1964***, pp. 806–878; Huisgen, R. *Helv. Chim. Acta* ***1967***, *50*, 2421; *Bull. Soc. Chim. Fr.* ***1965***, 3431; *Angew. Chem. Int. Ed.* ***1963***, *2*, 565, 633. For specific monographs and reviews, see Torssell, K.B.G. *Nitrile Oxides, Nitrones, and Nitronates in Organic Synthesis*; VCH, NY, ***1988***; Scriven, E.F.V. *Azides and Nitrenes*; Academic Press, NY, ***1984***; Stanovnik, B. *Tetrahedron* ***1991***, *47*, 2925 (diazoalkanes); Kanemasa, S.; Tsuge, O. *Heterocycles* ***1990***, *30*, 719 (nitrile oxides); Paton, R.M. *Chem. Soc. Rev.* ***1989***, *18*, 33 (nitrile sulfides); Terao, Y.; Aono, M.; Achiwa, K. *Heterocycles* ***1988***, *27*, 981 (azomethine ylids); Vedejs, E. *Adv. Cycloaddit.* ***1988***, *1*, 33 (azomethine ylids); DeShong, P.; Lander, Jr., S.W.; Leginus, J.M.; Dicken, C.M. *Adv. Cycloaddit.* ***1988***, *1*, 87 (nitrones); Balasubramanian, N. *Org. Prep. Proced. Int.* ***1985***, *17*, 23 (nitrones); Confalone, P.N.; Huie, E.M. *Org. React.* ***1988***, *36*, 1 (nitrones); Padwa, A., in Horspool, W.M. *Synthetic Organic Photochemistry*, Plenum, NY, ***1984***, pp. 313–374 (nitrile ylids); Bianchi, G.; Gandolfi, R.; Grünanger, P., in Patai, S.; Rappoport, Z. *The Chemistry of Functional Groups, Supplement C*, pt. 1, Wley, NY, ***1983***, pp. 752–784 (nitrile oxides); Black, D.S.; Crozier, R.F.; Davis, V.C. *Synthesis* ***1975***, 205 (nitrones); Stuckwisch, C.G. *Synthesis* ***1973***, 469 (azomethine ylids, azomethine imines). For reviews of intramolecular 1,3-dipolar additions, see Padwa, A., in Padwa, A. treatise cited above, Vol. 2, pp. 277–406; Padwa, A.; Schoffstall, A.M. *Adv. Cycloaddit.* ***1990***, *2*, 1; Tsuge, O.; Hatta, T.; Hisano, T., in Patai, S. *Supplement A: The Chemistry of Double-bonded Functional Groups*, Vol. 2, pt. 1, Wiley, NY, ***1989***, pp. 345–475; Padwa, A. *Angew. Chem. Int. Ed.* ***1976***, *15*, 123. For a review of azomethine ylids, see Tsuge, O.; Kanemasa, S. *Adv. Heterocycl. Chem.* ***1989***, *45*, 231. For reviews of 1,3-dipolar cycloreversions, see Bianchi, G.; Gandolfi, R. in Padwa, A. treatise cited above, Vol. 2, pp. 451–542; Bianchi, G.; De Micheli, C.; Gandolfi, R. *Angew. Chem. Int. Ed.* ***1979***, *18*, 721. For a related review, see Petrov, M.L.; Petrov, A.A. *Russ. Chem. Rev.* ***1987***, *56*, 152. For the use of this reaction to synthesize natural products, see papers in *Tetrahedron* ***1985***, *41*, 3447.

[1933] Houk, K.N.; Strassner, T. *J. Org. Chem.* ***1999***, *64*, 800.

[1934] See Gisdakis, P.; Rösch, N. *J. Am. Chem. Soc.* ***2001***, *123*, 697.

[1935] Kobayashi, S.; Hirabayashi, R.; Shimizu, H.; Ishitani, H.; Yamashita, Y. *Tetrahedron Lett.* ***2003***, *44*, 3351.

TABLE 15.3. Some Common 1,3-Dipolar Compounds

Type 1		
	Azide	$R-\overset{\ominus}{N}-N=\overset{\oplus}{N} \longleftrightarrow R-\overset{\ominus}{N}-\overset{\oplus}{N}\equiv N$
	Diazoalkane[1936]	$R_2\overset{\ominus}{C}-N=\overset{\oplus}{N} \longleftrightarrow R_2\overset{\ominus}{C}-\overset{\oplus}{N}\equiv N$
	Nitrous oxide	$\overset{\ominus}{O}-N=\overset{\oplus}{N} \longleftrightarrow \overset{\ominus}{O}-\overset{\oplus}{N}\equiv N$
	Nitrile imine[1937]	$R-\overset{\ominus}{N}-N=\overset{\oplus}{C}R' \longleftrightarrow R-\overset{\ominus}{N}-\overset{\oplus}{N}\equiv CR'$
	Nitrile ylid[1938]	$R_2\overset{\ominus}{C}-N=\overset{\oplus}{C}R' \longleftrightarrow R_2\overset{\ominus}{C}-\overset{\oplus}{N}\equiv CR'$
	Nitrile oxide[1939]	$\overset{\ominus}{O}-N=\overset{\oplus}{C}R \longleftrightarrow \overset{\ominus}{O}-\overset{\oplus}{N}\equiv CR$
Type 2		
	Azomethine imine	$R_2\overset{\ominus}{C}-\underset{\underset{R^2}{\vert}}{N}-\overset{\oplus}{N}R' \longleftrightarrow R_2\overset{\ominus}{C}-\underset{\underset{R^2}{\vert}}{\overset{\oplus}{N}}=NR'$
	Azoxy compound	$\overset{\ominus}{O}-\underset{\underset{R}{\vert}}{N}-\overset{\oplus}{N}R' \longleftrightarrow \overset{\ominus}{O}-\underset{\underset{R}{\vert}}{\overset{\oplus}{N}}=NR'$
	Azomethine ylid[1940]	$R_2\overset{\ominus}{C}-\underset{\underset{R^2}{\vert}}{N}-\overset{\oplus}{C}R'_2 \longleftrightarrow R_2\overset{\ominus}{C}-\underset{\underset{R^2}{\vert}}{\overset{\oplus}{N}}=CR'_2$
	Nitrone	$\overset{\ominus}{O}-\underset{\underset{R'}{\vert}}{N}-\overset{\oplus}{C}R_2 \longleftrightarrow \overset{\ominus}{O}-\underset{\underset{R'}{\vert}}{\overset{\oplus}{N}}=CR_2$
	Carbonyl oxide[1941]	$\overset{\ominus}{O}-O-\overset{\oplus}{C}R_2 \longleftrightarrow \overset{\ominus}{O}-\overset{\oplus}{O}=CR_2$
	Ozone	$\overset{\ominus}{O}-O-\overset{\oplus}{O} \longleftrightarrow \overset{\ominus}{O}-\overset{\oplus}{O}=O$

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

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[1936] See Baskaran, S.; Vasu, J.; Prasad, R.; Kodukulla, K.; Trivedi, G.K. *Tetrahedron* ***1996***, *52*, 4515.

[1937] Foti, F.; Grassi, G.; Risitano, F. *Tetrahedron Lett.* ***1999***, *40*, 2605.

[1938] Raposo, C.; Wilcox, C.S. *Tetrahedron Lett.* ***1999***, *40*, 1285.

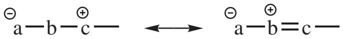
[1939] See Nishiwaki, N.; Uehara, T.; Asaka, N.; Tohda, Y.; Ariga, M.; Kanemasa, S. *Tetrahedron Lett.* ***1998***, *39*, 4851; Jung, M.E.; Vu, B.T. *Tetrahedron Lett.* ***1996***, *37*, 451; Weidner-Wells, M.A.; Fraga, S.A.; Demers, J.P. *Tetrahedron Lett.* ***1994***, *35*, 6473; Easton, C.J.; Hughes, C.M.; Tiekink, E.R.T.; Lubin, C.E.; Savage, G.P.; Simpson, G.W. *Tetrahedron Lett.* ***1994***, *35*, 3589; Brown, F.K.; Raimondi, L.; Wu, Y.-D.; Houk, K.N. *Tetrahedron Lett.* ***1992***, *33*, 4405; Raimondi, L.; Wu, Y.-D.; Brown, F.K.; Houk, K.N. *Tetrahedron Lett.* ***1992***, *33*, 4409. For a synthesis of nitrile oxides, see Muri, D.; Bode, J.W.; Carreira, E.M. *Org. Lett.* ***2000***, *2*, 539. Nitrolic acids are precursors, see Matt, C.; Gissot, A.; Wagner, A.; Mioskowski, C. *Tetrahedron Lett.* ***2000***, *41*, 1191.

[1940] For a review, see Pearson, W.H.; Stoy, P. *Synlett* ***2003***, 903. For chloroiminium salts as precursors, see Anderson, R.J.; Batsanov, A.S.; Belskaia, N.; Groundwater, P.W.; Meth-Cohn, O.; Zaytsev, A. *Tetrahedron Lett.* ***2004***, *45*, 943.

[1941] See Iesce, M.R.; Cermola, F.; Giordano, F.; Scarpati, R.; Graziano, M.L. *J. Chem. Soc. Perkin Trans. 1*, ***1994***, 3295; MuCullough, K.J.; Sugimoto, T.; Tanaka, S.; Kusabayashi, S.; Nojima, M. *J. Chem. Soc. Perkin Trans. 1*, ***1994***, 643.

nitrogen; hence there are six types. Among these are azides ($a = b = c = \mathrm{N}$) 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:



$$\overset{\ominus}{a}-b-\overset{\oplus}{c}- \longleftrightarrow \overset{\ominus}{a}-\overset{\oplus}{b}=c-$$

   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*,[1942] the reaction has been accomplished for at least 15, but not in all cases with a carbon–carbon double bond (the reaction also can be carried out with other double bonds[1943]). Not all alkenes undergo 1,3-dipolar addition equally well. The reaction is most successful for those that are good dienophiles in the Diels–Alder reaction (**15-60**). The addition is stereospecific and syn, and the mechanism is probably a one-step concerted process,[1944] as illustrated above,[1945] largely controlled by Frontier Molecular Orbital considerations.[1946] In-plane aromaticity has been invoked for these dipolar cycloadditions.[1947] As expected for this type of mechanism, the rates do not vary much with changes in solvent,[1948] although rate acceleration has been observed in ionic liquids.[1949] Nitrile oxide cycloadditions have also been done in supercritical carbon dioxide.[1950] There are no simple rules

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[1942] For a review of some aspects of this, see Grigg, R. *Chem. Soc. Rev.* ***1987***, *16*, 89.

[1943] For a review of 1,3-dipolar addition to other double bonds, see Bianchi, G.; De Micheli, C.; Gandolfi, R., in Patai, S. *Supplement A: The Chemistry of Double-Bonded Functional Groups*, pt. 1, Wiley, NY, ***1977***, pp. 369–532. For a review of such addition to the C=S bond, see Dunn, A.D.; Rudorf, W. *Carbon Disulfide in Organic Chemistry*, Wiley, NY, ***1989***, pp. 97–119.

[1944] Di Valentin, C.; Freccero, M.; Gandolfi, R.; Rastelli, A. *J. Org. Chem.* ***2000***, *65*, 6112. For a theoretical study of transition states, see Lu, X.; Xu, X.; Wang, N.; Zhang, Q. *J. Org. Chem.* ***2002***, *67*, 515. For a theoretical study of stepwise vs. concerted reactions, see DiValentin, C.; Freccero, M.; Gandolfi, R.; Rastelli, A. *J. Org. Chem.* ***2000***, *65*, 6112. For a discussion of loss of concertedness in reactions of azomethine ylids, see Vivanco, S.; Lecea, B.; Arrieta, A.; Prieto, P.; Morao, I.; Linden, A.; Cossío, F.P. *J. Am. Chem. Soc.* ***2000***, *122*, 6078.

[1945] For a review, see Huisgen, R. *Adv. Cycloaddit.* ***1988***, *1*, 1. For discussions, see Huisgen, R. *J. Org. Chem.* ***1976***, *41*, 403; Firestone, R.A. *Tetrahedron* ***1977***, *33*, 3009; Harcourt, R.D. *Tetrahedron* ***1978***, *34*, 3125; Haque, M.S. *J. Chem. Educ.* ***1984***, *61*, 490; Al-Sader, B.H.; Kadri, M. *Tetrahedron Lett.* ***1985***, *26*, 4661; Houk, K.N.; Firestone, R.A.; Munchausen, L.L.; Mueller, P.H.; Arison, B.H.; Garcia, L.A. *J. Am. Chem. Soc.* ***1985***, *107*, 7227; Majchrzak, M.W.; Warkentin, J. *J. Phys. Org. Chem.* ***1990***, *3*, 339.

[1946] Caramella, P.; Gandour, R.W.; Hall, J.A.; Deville, C.G.; Houk, K.N. *J. Am. Chem. Soc.* ***1977***, *99*, 385, and references cited therein.

[1947] Morao, I.; Lecea, B.; Cossío, F.P. *J. Org. Chem.* ***1997***, *62*, 7033; Cossío, F.P.; Marao, I.; Jiao, H.; Schleyer, P.v.R. *J. Am. Chem. Soc.* ***1999***, *121*, 6737.

[1948] For a review of the role of solvents in this reaction, see Kadaba, P.K. *Synthesis* ***1973***, 71.

[1949] Dubreuil, J.F.; Bazureau, J.P. *Tetrahedron Lett.* ***2000***, *41*, 7351.

[1950] Lee, C.K.Y; Holmes, A.B.; Al-Duri, B.; Leeke, G.A.; Santos, R.C.D.; Seville, J.P.K. *Chem. Commun.* ***2004***, 2622.

covering orientation in 1,3-dipolar additions. The regioselectivity has been explained by molecular-orbital treatments,[1951] where overlap of the largest orbital coefficients of the atoms forming the new bonds leads to the major regioisomer. When the 1,3-dipolar compound is a thiocarbonyl ylid ($R_2C{=}S^+{-}CH_2^-$) the addition has been shown to be nonstereospecific with certain substrates but stereospecific with others, indicating a nonsynchronous mechanism in these cases, and in fact, a diionic intermediate (see mechanism *c* on p. 1224) has been trapped in one such case.[1952] In a theoretical study of the 1,3-dipolar cycloadditions (diazomethane and ethene; fulminic acid [H—C≡N—O] and ethyne),[1953] calculations based on valence bond descriptions suggest that many concerted 1,3-dipolar cycloaddition reactions follow an electronic heterolytic mechanism where the movement of well-identifiable orbital pairs are retained along the entire reaction path from reactants to product.[1954]

An antibody-catalyzed [3 + 2]-cycloaddition has been reported.[1955] Metal assisted dipolar additions are also known.[1956]

Many of the cycloadducts formed from the dipoles in Table 15.3 are unstable, leading to other products. The reaction of alkyl azides with alkenes generates triazolines (**15-54**), which extrude nitrogen (N≡N) upon heating or photolysis to give an aziridine.

[3 + 2]-Cycloaddition reactions occur intramolecularly to generate bicyclic and polycyclic compounds.[1957] The intramolecular cycloaddition of azomethine imines give bicyclic pyrrazolidines for example.[1958] When diazoalkanes, including diazo acetates such as N_2CHCO_2Et react with an alkene and a chromium catalyst the initially formed product is a five-membered ring, a pyrazoline. Pyrazolines are generally unstable and extrusion of nitrogen leads to a cyclopropane.[1959]

There are many cases where the [3 + 2]-cycloaddition leads to cycloadducts with high enantioselectivity.[1960] Cycloaddition of diazo esters with a cobalt catalyst having a chiral ligand leads to cyclopropane derivatives with good enantioselectivity.[1961]

[1951] For a review, see Houk, K.N.; Yamaguchi, K., in Padwa, A. *1,3-Dipolar Cycloaddition Chemistry* Vol. 2, Wiley, NY, ***1984***, pp. 407–450. See also, Burdisso, M.; Gandolfi, R.; Quartieri, S.; Rastelli, A. *Tetrahedron* ***1987***, *43*, 159.

[1952] Huisgen, R.; Mloston, G.; Langhals, E. *J. Am. Chem. Soc.* ***1986***, *108*, 6401; *J. Org. Chem.* ***1986***, *51*, 4085; Mloston, G.; Langhals, E.; Huisgen, R. *Tetrahedron Lett.* ***1989***, *30*, 5373; Huisgen, R.; Mloston, G. *Tetrahedron Lett.* ***1989***, *30*, 7041.

[1953] Karadakov, P.B.; Cooper, D.L.; Gerratt, J. *Theor. Chem. Acc.* ***1998***, *100*, 222.

[1954] Blavins, J.J.; Karadakov, P.B.; Cooper, D.L. *J. Org. Chem.* ***2001***, *66*, 4285.

[1955] Toker, J.D.; Wentworth Jr., P.; Hu, Y.; Houk, K.N.; Janda, K.D. *J. Am. Chem. Soc.* ***2000***, *122*, 3244.

[1956] Kanemasa, S. *Synlett* ***2002***, 1371.

[1957] For reviews, see Padwa, A. *Angew. Chem. Int. Ed.* ***1976***, *15*, 123; Oppolzer, W. *Angew. Chem. Int. Ed.* ***1977***, *16*, 10 (see pp. 18–22).

[1958] Dolle, R.E.; Barden, M.C.; Brennan, P.E.; Ahmed, G.; Tran, V.; Ho, D.M. *Tetrahedron Lett.* ***1999***, *40*, 2907.

[1959] Jan, D.; Simal, F.; Demonceau, A.; Noels, A.F.; Rufanov, K.A.; Ustynyuk, N.A.; Gourevitch, D.N. *Tetrahedron Lett.* ***1999***, *40*, 5695.

[1960] Gothelf, K.V.; Jørgensen, K.A. *Chem. Rev.* ***1998***, *98*, 863.

[1961] Niimi, T.; Uchida, T.; Irie, R.; Katsuki, T. *Tetrahedron Lett.* ***2000***, *41*, 3647.

Cycloaddition of nitrones and pyrazolinones with a copper catalyst and a chiral ligand leads to pyrrolidine derivatives with good enantioselectivity.[1962]

Conjugated dienes generally give exclusive 1,2-addition, although 1,4 addition (a [3 + 4]-cycloaddition) has been reported.[1963] Carbon–carbon triple bonds can also undergo 1,3-dipolar addition.[1964] For example, azides react to give triazoles, **185**.

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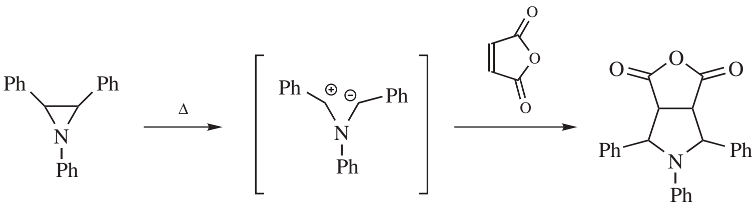
The 1,3-dipolar reagent can in some cases be generated by the *in situ* opening of a suitable three-membered ring system. For example, aziridines open to give a zwitterion, such as **186**, which can add to activated double bonds to give pyrrolidines.[1965]



186

Aziridines also add to C≡C triple bonds as well as to other unsaturated linkages, including C=O, C=N, and C≡N.[1966] In some of these reactions it is a C—N bond of the aziridine that opens rather than the C—C bond.

For other [3 + 2]-cycloadditions, see **15-59**.

OS **V**, 957, 1124; **VI**, 592, 670; **VIII**, 231. Also see, OS **IV**, 380.

C. Carbon on Both Sides

Reactions **15-58–15-64** are cycloaddition reactions.[1967]

[1962] Sibi, M.P.; Ma, Z.; Jasperse, C.P. *J. Am. Chem. Soc.* ***2004***, *126*, 718.

[1963] Baran, J.; Mayr, H. *J. Am. Chem. Soc.* ***1987***, *109*, 6519.

[1964] For reviews, see Bastide, J.; Hamelin, J.; Texier, F.; Quang, Y.V. *Bull. Soc. Chim. Fr.* ***1973***, 2555; 2871; Fuks, R.; Viehe, H.G., in Viehe, H.G. *Acetylenes*, Marcel Dekker, NY, ***1969***, pp. 460–477.

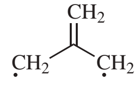
[1965] For a review, see Lown, J.W., in Padwa, A. *1,3-Dipolar Cycloaddition Chemistry*, Vol 1. Wiley, NY, ***1984***, pp. 683–732.

[1966] For reviews, see Lown, J.W. *Rec. Chem. Prog.* ***1971***, *32*, 51; Gladysheva, F.N.; Sineokov, A.P.; Etlis, V.S. *Russ. Chem. Rev.* ***1970***, *39*, 118.

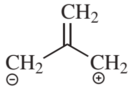
[1967] For a system of classification of cycloaddition reactions, see Huisgen, R. *Angew. Chem. Int. Ed.* ***1968***, *7*, 321. For a review of certain types of cycloadditions leading to 3- to 6-membered rings involving 2, 3, or 4 components, see Posner, G.H. *Chem. Rev.* ***1986***, *86*, 831. See also, the series *Advances in Cycloaddition*.

15-59 All-Carbon [3 + 2]-Cycloadditions[1968]

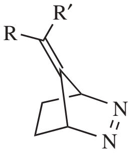
Several methods have been reported for the formation of cyclopentanes by [3 + 2]-cycloadditions.[1969] Heating a conjugated ketones wtih trialkylphosneines genrates an intermdiate that adds to conjugated alkynes.[1970] One type involves reagents that produce intermediates **187** or **188**.[1971] A synthetically useful example[1972] uses 2-[(trimethylsilyl)methyl]-2-propen-1-yl acetate (**191**) (which is commercially available) and a palladium or other transition-metal catalyst to generate **187** or **188**, which adds to double bonds, to give, in



187



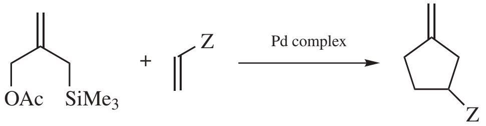
188



189

190

good yields, cyclopentanes with an exocyclic double bond. Note that **95** also reacts with *N*-tosyl aziridines, with 20% *n*-butyllithium and 10% of Pd(OAc)$_2$, to give a vinylidene piperidine derivative.[1973] Similar or identical intermediates generated from bicyclic azo compounds **189** (see **17-34**) or methylenecyclopropane **190**[1974] also add to activated double bonds. With suitable substrates the addition can be enantioselective.[1975]



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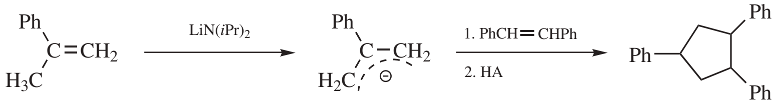
In a different type of procedure, [3 + 2]-cycloadditions are performed with allylic anions. Such reactions are called 1,3-anionic cycloadditions.[1976] For example, α-methylstyrene adds to stilbene on treatment with the strong base LDA.[1977]



[1968] See Smith, M.B. *Organic Synthesis, 2nd* ed., McGraw-Hill, NY, ***2001***, pp. 999–1010.

[1969] For a list of methods, with references, see Trost, B.M.; Seoane, P.; Mignani, S.; Acemoglu, M. *J. Am. Chem. Soc.* ***1989***, *111*, 7487.

[1970] Wang, J.-C.; Ng, S.-S.; Krische, M.J. *J. Am. Chem. Soc.* ***2003***, *125*, 3682.

[1971] For reviews, see Trost, B.M. *Pure Appl. Chem.* ***1988***, *60*, 1615; *Angew. Chem. Int. Ed.* ***1986***, *25*, 1.

[1972] See, for example, Trost, B.M.; Lynch, J.; Renaut,P.; Steinman, D.H. *J. Am. Chem. Soc.* ***1986***, *108*, 284.

[1973] Hedley, S.J.; Moran, W.J.; Price, D.A.; Harrity, J.P.A. *J. Org. Chem.* ***2003***, *68*, 4286.

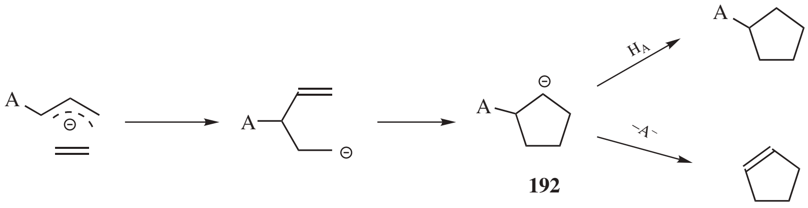
[1974] See Yamago, S.; Nakamura, E. *J. Am. Chem. Soc.* ***1989***, *111*, 7285.

[1975] See Binger, P.; Schäfer, B. *Tetrahedron Lett.* ***1988***, *29*, 529; Chaigne, F.; Gotteland, J.; Malacria, M. *Tetrahedron Lett.* ***1989***, *30*, 1803.

[1976] For reviews, see Kauffmann, T. *Top. Curr. Chem.* ***1980***, *92*, 109, pp. 111–116; *Angew. Chem. Int. Ed.* ***1974***, *13*, 627.

[1977] Eidenschink, R.; Kauffmann, T. *Angew. Chem. Int. Ed.* ***1972***, *11*, 292.

The mechanism can be outlined as



In the case above, **192** 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.[1978] In these cases the reagent is an allylic anion, but similar [3 + 2]-cycloadditions involving allylic cations have also been reported.[1979]

OS **VIII**,173, 347.

15-60 The Diels–Alder Reaction

(4 + 2)*cyclo*-Ethylene-1/4/addition or **(4 + 2)*cyclo*-[Bu*t*-2-ene-1,4-diyl]-1/2/ addition**, and so on.

In the prototype *Diels–Alder reaction* the double bond of an alkene adds 1,4 to a conjugated diene (a [4 + 2]-cycloaddition),[1980] so the product is always a cyclohexene. The cycloaddition is not limited to alkenes or to dienes (see **15-61**), but the substrate that reacts with the diene is called a *dienophile*. The reaction is of

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[1978] See, for example, Padwa, A.; Yeske, P.E. *J. Am. Chem. Soc.* ***1988***, *110*, 1617; Beak, P.; Burg, D.A. *J. Org. Chem.* ***1989***, *54*, 1647.

[1979] For example, see Hoffmann, H.M.R.; Vathke-Ernst, H. *Chem. Ber.* ***1981***, *114*, 2208, 2898; Klein, H.; Mayr, H. *Angew. Chem. Int. Ed.* ***1981***, *20*, 1027; Noyori, R.; Hayakawa, Y. *Tetrahedron* ***1985***, *41*, 5879.

[1980] For a monograph, see Wasserman, A. *Diels-Alder Reactions*, Elsevier, NY, ***1965***. For reviews, see Fleming, I. *Pericyclic Reactions*, Oxford University Press, Oxford, ***1999***, pp. 7–30; Roush, W.R. *Adv. Cycloaddit.* ***1990***, *2*, 91; Carruthers, W. *Cycloaddition Reactions in Organic Synthesis*, Pergamon, Elmsford, NY, ***1990***; Brieger, G.; Bennett, J.N. *Chem. Rev.* ***1980***, *80*, 63; Oppolzer, W. *Angew. Chem. Int. Ed.* ***1977***, *16*, 10; Beltrame, P., in Bamford, C.H.; Tipper, C.F.H *Comprehensive Chemical Kinetics*, Vol. 9, Elsevier, NY, ***1973***, pp. 94–117; Huisgen, R.; Grashey, R.; Sauer, J., in Patai, S. *The Chemistry of Alkenes*, Vol. 1, Wiley, NY, ***1964***, pp. 878–929; Carruthers, W. *Some Modern Methods of Organic Synthesis*, 3rd. ed., Cambridge University Press, Cambridge, ***1986***, pp. 183–244; Sauer, J. *Angew. Chem. Int. Ed.* ***1966***, *5*, 211; ***1967***, *6*, 16. For a monograph on intramolecular Diels–Alder reactions, see Taber, D.F. *Intramolecular Diels–Alder and Alder Ene Reactions*, Springer, NY, ***1984***. For reviews, see Deslongchamps, P. *Aldrichimica Acta* ***1991***, *24*, 43; Craig, D. *Chem. Soc. Rev.* ***1987***, *16*, 187; Salakhov, M.S.; Ismailov, S.A. *Russ. Chem. Rev.* ***1986***, *55*, 1145; Fallis, A.G. *Can. J. Chem.* ***1984***, *62*, 183. For a long list of references to various aspects of the Diels–Alder reaction, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 523–544.

very broad scope[1981] and reactivity of dienes and dienophiles can be predicted based on analysis of the HOMOs[1982] and LUMOs of these species (frontier molecular orbital theory).[1983] Ethylene and simple alkenes make poor dienophiles, unless high temperatures and/or pressures are used. Most dienophiles are of the form $-\underset{|}{C}=\underset{|}{C}-Z$ or $Z-\underset{|}{C}=\underset{|}{C}-Z'$, where Z and Z′ are electron-withdrawing groups,[1984] such as CHO, COR,[1985] COOH, COOR, COCl, COAr, CN,[1986] NO_2,[1987] Ar, CH_2OH, CH_2Cl, CH_2NH_2, CH_2CN, CH_2COOH, halogen, $PO(OEt)_2$,[1988] or C=C. In the last case, the dienophile is itself a diene.[1989] Particularly common dienophiles are maleic anhydride[1990] and quinones.[1991] Triple bond compounds (–C≡C–Z or Z–C≡C– Z′) may be dienophiles,[1992] generating nonconjugated cyclohexadienes (**193**), and this reaction can be catalyzed by transition-metal compounds.[1993] Allenes react as dienophiles, but without activating groups are very poor dienophiles.[1994]

193

[1981] For a review of reactivity in the Diels–Alder reaction, see Konovalov, A.I. *Russ. Chem. Rev.* ***1983***, *52*, 1064.

[1982] For a correlation of ionization potential and HOMO correlation with alkene reactions, see Nelson, D.J.; Li, R.; Brammer, C. *J. Org. Chem.* ***2001***, *66*, 2422.

[1983] For a discussion of Frontier Orbital interactions, see Spino, C.; Rezaei, H.; Dory, Y.L. *J. Org. Chem.* ***2004***, *69*, 757. For tables of experimentally determined HOMOs and LUMOs for dienes and dienophiles, see Smith, M.B. *Organic Synthesis*, 2nd ed., McGraw-Hill, NY, ***2001***, pp. 917–940.

[1984] For a density-Functional theory analysis see Domingo, L.R. *Eur. J. Org. Chem.* ***2004***, 4788.

[1985] For a review of Diels–Alder reactions with cyclic enones, see Fringuelli, F.; Taticchi, A.; Wenkert, E. *Org. Prep. Proced. Int.* ***1990***, *22*, 131.

[1986] For a review of the Diels–Alder reaction with acrylonitrile, see Butskus, P.F. *Russ. Chem. Rev.* ***1962***, *31*, 283. For a review of tetracyanoethylene as a dienophile, see Ciganek, E.; Linn, W.J.; Webster, O.W., in Rappoport, Z. *The Chemistry of the Cyano Group*, Wiley, NY, ***1970***, pp. 449–453.

[1987] For a review of the Diels–Alder reaction with nitro compounds, see Novikov, S.S.; Shuekhgeimer, G.A.; Dudinskaya, A.A. *Russ. Chem. Rev.* ***1960***, *29*, 79.

[1988] McClure, C.K.; Herzog, K.J.; Bruch, M.D. *Tetrahedron Lett.* ***1996***, *37*, 2153.

[1989] Johnstone, R.A.W.; Quan, P.M. *J. Chem. Soc.* ***1963***, 935.

[1990] For a review of Diels–Alder reactions with maleic anhydride see Kloetzel, M.C. *Org. React.* ***1948***, *4*, 1.

[1991] For reviews of Diels–Alder reactions with quinones, see Finley, K.T., in Patai, S *The Chemistry of the Quinoid Compounds*, Vol. 1, pt. 2, Wiley, NY, ***1988***, pp. 986–1018; Patai, S.; Rapaport, Z. Vol. 2, pt. 1 ***1988***, 537–717, 614–645. For a review of the synthesis of quinones using Diels–Alder reactions, see Naruta, Y.; Maruyama, K. in the same treatise, Vol. 2, pt. 1, pp. 241–402, 277–303.

[1992] For reviews of triple bonds in cycloaddition reactions, see Bastide, J.; Henri-Rousseau, O., in Patai, S. *The Chemistry of the Carbon-Carbon Triple Bond*, pt. 1, Wiley, NY, ***1978***, pp. 447–522, Fuks, R.; Viehe, H.G., in Viehe, H.G. *Acetylenes*, Marcel Dekker, NY, ***1969***, pp. 477–508.

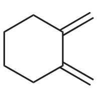
[1993] See Paik, S.-J.; Son, S.U.; Chung, Y.K. *Org. Lett.* ***1999***, *1*, 2045.

[1994] For a review of allenes as dienes or dienophiles, see Hopf, H., in Landor, S.R. *The Chemistry of Allenes*, Vol. 2, Academic Press, NY, ***1982***, pp. 563–577. See Nendel, M.; Tolbert, L.M.; Herring, L.E.; Islam, Md.N.; Houk, K.N. *J. Org. Chem.* ***1999***, *64*, 976.

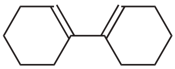
Ketenes, however, do not undergo Diels–Alder reactions.[1995] Benzynes, although not isolable, act as dienophiles and can be trapped with dienes,[1996] for example,

194

The low reactivity of simple alkenes can be overcome by incorporating an electron-withdrawing group to facilitate the cycloaddition, but a group that can be removed after the cycloaddition. An example is phenyl vinyl sulfone $PhSO_2CH{=}CH_2$.[1997] The $PhSO_2$ group can be easily removed with Na–Hg after the ring-closure reaction. Similarly, phenyl vinyl sulfoxide ($PhSOCH{=}CH_2$) can be used as a synthon for acetylene.[1998] In this case PhSOH is lost from the sulfoxide product (**17-12**).



195



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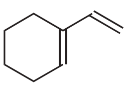

197

Electron-donating substituents in the diene accelerate the reaction; electron-withdrawing groups retard it.[1999] For the dienophile it is just the reverse: donating groups decrease the rate, and withdrawing groups increase it. The cisoid conformation is required for the cycloaddition,[2000] and acyclic dienes are conformationally mobile so the cisoid conformation will be available. 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.[2001] Dienes can be open-chain, inner-ring (e.g., **194**), outer-ring[2002] (e.g., **195**), across

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[1995] Ketenes react with conjugated dienes to give 1,2-addition (see **15–49**).

[1996] For a review of benzynes as dienophiles, see Hoffmann, R.W. *Dehydrobenzene and Cycloalkynes*; Academic Press, NY, ***1967***, pp. 200–239. For a review of the reactions of benzynes with heterocyclic compounds see Bryce, M.R.; Vernon, J.M. *Adv. Heterocycl. Chem.* ***1981***, *28*, 183–229.

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[1999] For a discussion of the electrophilicity power of dienes and dienophiles, see Domingo, L.R.; Aurell, M.J.; Pérez, P.; Contreras, R. *Tetrahedron* ***2002***, *58*, 4417.

[2000] For a discussion of ground state conformations, see Bur, S.K.; Lynch, S.M.; Padwa, A. *Org. Lett.* ***2002***, *4*, 473.

[2001] Sauer, J.; Lang, D.; Mielert, A. *Angew. Chem. Int. Ed.* ***1962***, *1*, 268; Sauer, J.; Wiest, H. *Angew. Chem. Int. Ed.* ***1962***, *1*, 269. See, however, Scharf, H.; Plum, H.; Fleischhauer, J.; Schleker, W. *Chem. Ber.* ***1979***, *112*, 862.

[2002] For reviews of Diels-Alder reactions of some of these compounds, see Charlton, J.L.; Alauddin, M.M. *Tetrahedron* ***1987***, *43*, 2873; Oppolzer, W. *Synthesis* ***1978***, 793.

rings (e.g., **196**), or inner-outer (e.g., **197**), except that they may not be frozen into a transoid conformation (see p. 1201). They need no special activating groups, and nearly all conjugated dienes undergo the reaction with suitable dienophiles.[2003]

In most Diels–Alder reactions, no catalyst is needed, but Lewis acids are effective catalysts in many cases,[2004] particularly 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,[2005] and, in the case of enantioselective reactions, the extent of enantioselectivity. It has been shown that $InCl_3$ is an effective catalyst for aqueous Diels–Alder reactions,[2006] which is suitable for ionic Diels–Alder reactions,[2007] and there are other Lewis acid catalysts that are effective in water.[2008] Brønsted acids have also been used to accelerate the rate of the Diels–Alder reaction.[2009] Lanthanum triflate [$La(OTf)_3$] has been reported as a reusable catalyst[2010] and Me_3SiNTf_2 has been used as a green Lewis acid catalyst.[2011] Cationic Diels–Alder catalysts have been developed, particularly oxazaborolidine catalysts.[2012] Some Diels–Alder reactions can also be catalyzed by the addition of a stable cation radical,[2013] for

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[2003] For a monograph on dienes, with tables showing > 800 types, see Fringuelli, F.; Taticchi, A. *Dienes in the Diels–Alder Reaction*, Wiley, NY, ***1990***. For a review of Diels–Alder reactions with 2-pyrones, see Shusherina, N.P. *Russ. Chem. Rev.* ***1974***, *43*, 851. For reviews of dienes with hetero substituents, see Danishefsky, S. *Chemtracts: Org. Chem.* ***1989***, *2*, 273; Petrzilka, M.; Grayson, J.I. *Synthesis* ***1981***, 753. For dienes containing a 1-$CONR_2$ group, see Smith, M.B. *Org. Prep. Proced. Int.* ***1990***, *22*, 315; Robiette, R.; Cheboub-Benchaba, K.; Peeters, D.; Marchand-Brynaert, J. *J. Org. Chem.* ***2003***, *68*, 9809. For dienes containing a 1-$NRCO_2R$ group, see Huang, Y.; Iwama, T.; Rawal, V.H. *J. Am. Chem. Soc.* ***2002***, *122*, 5950.

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[2011] Mathieu, B.; Ghosez, L. *Tetrahedron* ***2002***, *58*, 8219.

[2012] See Sprott, K.T.; Corey, E.J. *Org. Lett.* ***2003***, *5*, 2465; Corey, E.J.; Shibata, T.; Lee, T.W. *J. Am. Chem. Soc.* ***2002***, *124*, 3808; Ryu, D.H.; Lee, T.W.; Corey, E.J. *J. Am. Chem. Soc.* ***2002***, *124*, 9992.

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example, tris(4-bromophenyl)aminium hexachloroantimonate $Ar_3N^{\bullet +}$ $SbCl_6^-$.[2014] Carbazoles are dienophiles for cation radical Diels–Alder reactions.[2015] Zirconocene-catalyzed cationic Diels–Alder reactions are known.[2016] Certain antibodies have been developed that catalyze Diels–Alder reactions.[2017] Photochemically induced Diels–Alder reactions are also known.[2018] Cyclodextrins exhibit noncovalent catalysis of Diels–Alder reactions.[2019] There are cases of hydrogen-bonding acceleration.[2020]

A number of other methods have been reported for the acceleration of Diels–Alder reactions,[2021] including the use of microwave irradiation,[2022] ultrasound,[2023] absorption of the reactants on chromatographic absorbents,[2024] via encapsulation techniques,[2025] and the use of an ultracentrifuge[2026] (one of several ways to achieve reaction at high pressures).[2027] Solid-state Diels–Alder reactions are known.[2028] One of the most common methods is to use water as a solvent or a cosolvent (a hydrophobic effect).[2029] The influence of hydrophobicity of reactants

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[2014] For a review, see Bauld, N.L. *Tetrahedron* ***1989***, *45*, 5307.

[2015] Gao, D.; Bauld, N.L. *Tetrahedron Lett.* ***2000***, *41*, 5997.

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[2017] Meekel, A.A.P.; Resmini, M.; Pandit, U.K. *J. Chem. Soc., Chem. Commun.* ***1995***, 571; Zhang, X.; Deng, Q.; Yoo, S.H.; Houk, K.N. *J. Org. Chem.* ***2002***, *67*, 9043.

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[2020] Pearson, R.J.; Kassianidis, E.; Philip, D. *Tetrahedron Lett.* ***2004***, *45*, 4777.

[2021] See Smith, M.B. *Organic Synthesis, 2nd* ed., McGraw-Hill, NY, ***2001***, pp. 944–953.

[2022] Giguere, R.J.; Bray, T.L.; Duncan, S.M.; Majetich, G. *Tetrahedron Lett.* ***1986***, *27*, 4945; Berlan, J.; Giboreau, P.; Lefeuvre, S.; Marchand, C. *Tetrahedron Lett.* ***1991***, *32*, 2363; DaCunha, L.; Garrigues, B. *Bull. Soc. Chim. Belg.* ***1997***, *106*, 817; Jankowski, C.K.; LeClair, G.; Bélanger, J.M.R.; Paré, J.R.J.; Van Calsteren, M.-R. *Can. J. Chem.* ***2001***, *79*, 1906. For a review, see de la Hoz, A.; Díaz-Ortis, A.; Moreno, A.; Langa, F. *Eur. J. Org. Chem.* ***2000***, 3659. For the effect of pressure of microwave-enhanced Diels–Alder reactions, see Kaval, N.; Dehaen, W.; Kappe, C.O.; van der Eycken, E. *Org. Biomol. Chem.* ***2004***, *2*, 154.

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[2026] Dolata, D.P.; Bergman, R. *Tetrahedron Lett.* ***1987***, *28*, 707.

[2027] For reviews, see Isaacs, N.S.; George, A.V. *Chem. Br.* ***1987***, 47–54; Asano, T.; le Noble, W.J. *Chem. Rev.* ***1978***, *78*, 407. See also, Firestone, R.A.; Smith, G.M. *Chem. Ber.* ***1989***, *122*, 1089.

[2028] Kim, J.H.; Hubig, S.M.; Lindeman, S.V.; Kochi, J.K. *J. Am. Chem. Soc.* ***2001***, *123*, 87.

[2029] Rideout, D.C.; Breslow, R. *J. Am. Chem. Soc.* ***1980***, *102*, 7816. For a review, see Breslow, R. *Acc. Chem. Res.* ***1991***, *24*, 159; Furlani, T.R.; Gao, J. *J. Org. Chem.* ***1996***, *61*, 5492. See also, Grieco, P.A.; Garner, P.; He, Z. *Tetrahedron Lett.* ***1983***, 1897; Blokzijl, W.; Blandamer, M.J.; Engberts, J.B.F.N. *J. Am. Chem. Soc.* ***1991***, *113*, 4241; Breslow, R.; Rizzo, C.J. *J. Am. Chem. Soc.* ***1991***, *113*, 4340; Engberts, J.B.F.N. *Pure Appl. Chem.* ***1995***, *67*, 823; Pindur, U.; Lutz, G.; Otto, C. *Chem. Rev.* ***1993***, *93*, 741; Otto, S.; Blokzijl, W.; Engberts, J.B.F.N. *J. Org. Chem.* ***1994***, *59*, 5372; Otto, S.; Egberts, J.B.F.N. *Pure. Appl. Chem.* ***2000***, *72*, 1365.

on the reaction has been examined[2030] as has micellular effects.[2031] Another alternative reaction medium is the use of 5 *M* $LiClO_4$ in Et_2O as solvent,[2032] An alternative to lithium perchlorate in ether is lithium triflate in acetonitrile.[2033] The addition of HPO_4^-– to an aqueous ethanol solution has also been shown to give an small rate enhancement.[2034] This appears to be the only case where an anion is responsible for a rate enhancement. The *retro*-Diels–Alder reaction has also been done in water.[2035]

It is noted that the Diels–Alder reaction has been done with supercritical CO_2[2036] and with supercritical water[2037] as solvents. Diels–Alder reactions on solid supports have also been reported,[2038] and zeolites have been used in conjunction with catalytic agents.[2039] Alumina has been used to promote Diels–Alder reactions.[2040] Diels–Alder reactions can be done in ionic liquids,[2041] including asymmetric Diels–Alder reactions.[2042]

When an unsymmetrical diene adds to an unsymmetrical dienophile, regioisomeric products (not counting stereoisomers) are possible. Rearrangements have been encountered in some cases.[2043] In simple cases, 1-substituted dienes give cyclohexenes with a 1,2- and a 1,3- substitution pattern. 2-Substituted dienes

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[2030] Meijer, A.; Otto, S.; Engberts, J.B.F.N. *J. Org. Chem.* ***1998***, *63*, 8989; Rizzo, C.J. *J. Org. Chem.* ***1992***, *57*, 6382.

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[2032] Grieco, P.A.; Nunes, J.J.; Gaul, M.D. *J. Am. Chem. Soc.* ***1990***, *112*, 4595. See also, Braun, R.; Sauer, J. *Chem. Ber.* ***1986***, *119*, 1269; Grieco, P.A.; Handy, S.T.; Beck, J.P. *Tetrahedron Lett.* ***1994***, *35*, 2663. For the possibility of migration of terminal dienes prior to cycloaddition see Grieco, P.A.; Beck, J.P.; Handy, S.T.; Saito, N.; Daeuble, J.F. *Tetrahedron Lett.* ***1994***, *35*, 6783. An alternative to this catalyst is $LiNTf_2$ in ether, see Handy, S.T.; Grieco, P.A.; Mineur, C.; Ghosez, L. *Synlett* ***1995***, 565.

[2033] Augé, J.; Gil, R.; Kalsey, S.; Lubin-Germain, N. *Synlett* ***2000***, 877.

[2034] Pai, C.K.; Smith, M.B. *J. Org. Chem.* ***1995***, *60*, 3731; Smith, M.B.; Fay, J.N.; Son, Y.C. *Chem. Lett.* ***1992***, 2451.

[2035] Wijnen, J.W.; Engberts, J.B.F.N. *J. Org. Chem.* ***1997***, *62*, 2039.

[2036] Renslo, A.R.; Weinstein, R.D.; Tester, J.W.; Danheiser, R.L. *J. Org. Chem.* ***1997***, *62*, 4530; Oakes, R.S.; Heppenstall, T.J.; Shezad, N.; Clifford, A.A.; Rayner, C.M. *Chem. Commun.* ***1999***, 1459. For an asymmetric cycloaddition, see Fukuzawa, S.-i.; Metoki, K.; Esumi, S.-i. *Tetrahedron* ***2003***, *59*, 10445.

[2037] Harano, Y.; Sato, H.; Hirata, F. *J. Am. Chem. Soc.* ***2000***, *122*, 2289.

[2038] For a review, see Yli-Kauhaluoma, J. *Tetrahedron* ***2001***, *57*, 7053. For silica and alumina-modified Lewis acid catalysts, see Cativiela, C.; Figueras, F.; García, J.I.; Mayoral, J.A.; Pires, E.; Royo, A.J. *Tetrahedron Asymmetry* ***1993***, *4*, 621.

[2039] Eklund, L.; Axelsson, A.-K.; Nordahl, Å.; Carlson, R. *Acta Chem. Scand.* ***1993***, *47*, 581.

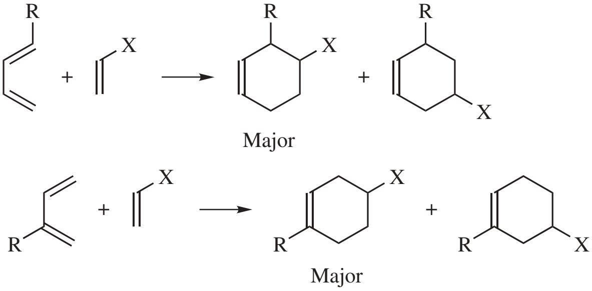
[2040] Pagni, R.M.; Kabalka, G.W.; Hondrogiannis, G.; Bains, S.; Anosike, P.; Kurt, R. *Tetrahedron* ***1993***, *49*, 6743.

[2041] In **bmim** BF_4 and ClO_4: 1-butyl-3-methylimidazolium tetrafluoroborate and perchlorate: Fischer, T.; Sethi, A.; Welton, T.; Woolf, J. *Tetrahedron Lett.* ***1999***, *40*, 793. In **chloroaluminates**: Lee, C.W. *Tetrahedron Lett.* ***1999***, *40*, 2461. In **phosphonium tosylates**: Ludley, P.; Karodia, N. *Tetrahedron Lett.* ***2001***, *42*, 2011. In **pyridinium salts**: Xiao, Y.; Malhotra, S.V. *Tetrahedron Lett.* ***2004***, *45*, 8339. In **HBuIm**, hydrogenbutylimidazolium tetrafluoroborate and **DiBuIm**, 1,3-dibutylimidazolium, tetrafluoroborate: Jaegar, D. A.; Tucker, C. E. *Tetrahedron Lett.* ***1989***, *30*, 1785.

[2042] Meracz, I.; Oh, T. *Tetrahedron Lett.* ***2003***, *44*, 6465.

[2043] Murali, R.; Scheeren, H.W. *Tetrahedron Lett.* ***1999***, *40*, 3029.

lead to 1,4- and 1,3-disubstituted products.



Although mixtures are often obtained, usually one predominates, the one indicated above, but selectivity depends on the nature of the substituents on both diene and alkene. This regioselectivity, in which the "ortho" or "para" product is favored over the "meta," has been explained by molecular-orbital considerations.[2044] When $X = NO_2$, regioselectivity to give the "ortho" or "para" product was very high at room temperature, and this method, combined with subsequent removal of the NO_2 (see **19-67**) has been used to perform regioselective Diels–Alder reactions.[2045]

The stereochemistry of the Diels–Alder reaction can be considered from several aspects:[2046]

1. With respect to the dienophile, the addition is stereospecifically syn, with very few exceptions.[2047] This means that groups that are cis in the alkene will be cis in the cyclohexene ring, (A—B and C—D) and groups that are trans in the alkene will be trans in the cyclohexene ring (A—D and C—B).

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. This

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[2044] Feuer, J.; Herndon, W.C.; Hall, L.H. *Tetrahedron* ***1968***, *24*, 2575; Inukai, T.; Sato, H.; Kojima, T. *Bull. Chem. Soc. Jpn.* ***1972***, *45*, 891; Epiotis, N.D. *J. Am. Chem. Soc.* ***1973***, *95*, 5624; Sustmann, R. *Pure Appl. Chem.* ***1974***, *40*, 569; Trost, B.M.; Vladuchick, W.C.; Bridges, A.J. *J. Am. Chem. Soc.* ***1980***, *102*, 3554; Alston, P.V.; Gordon, M.D.; Ottenbrite, R.M.; Cohen, T. *J. Org. Chem.* ***1983***, *48*, 5051; Kahn, S.D.; Pau, C.F.; Overman, L.E.; Hehre, W.J. *J. Am. Chem. Soc.* ***1986***, *108*, 7381.

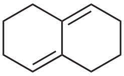
[2045] Danishefsky, S.; Hershenson, F.M. *J. Org. Chem.* ***1979***, *44*, 1180; Ono, N.; Miyake, H.; Kamimura, A.; Kaji, A. *J. Chem. Soc. Perkin Trans. 1*, ***1987***, 1929. For another method of controlling regioselectivity, see Kraus, G.A.; Liras, S. *Tetrahedron Lett.* ***1989***, *30*, 1907.

[2046] See Smith, M.B. *Organic Synthesis, 2nd* ed., McGraw-Hill, NY, ***2001***, pp. 933–940, 968–977; Bakalova, S.M.; Santos, A.G. *J. Org. Chem.* ***2004***, *69*, 8475.

[2047] For an exception, see Meier, H.; Eckes, H.; Niedermann, H.; Kolshorn, H. *Angew. Chem. Int. Ed.* ***1987***, *26*, 1046.

selectivity is predicted by disrotatory motion of the substituent in the transition state[2048] of the reaction (see **18-27**).

3. The diene must be in the cisoid conformation. If it is frozen into the transoid conformation, as in **198**, 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.



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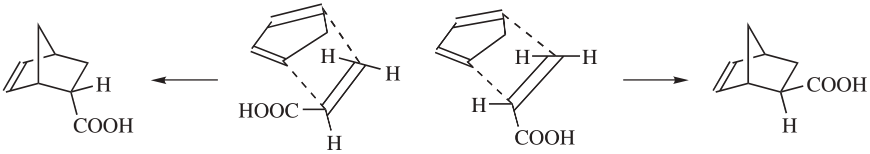
4. When the diene is cyclic, there are two possible ways in which addition can occur if the dienophile is not symmetrical. The larger side of the dienophile may be under the ring (*endo addition*), or it may be the smaller side (*exo addition*):



Endo addition Exo addition

Most of the time, the addition is predominantly endo; that is, the more bulky side of the alkene is under the ring, and this is probably true for open-chain dienes also.[2049] However, exceptions are known, and in many cases mixtures of exo and endo addition products are found.[2050] An imidazolidone catalyst was used to give a 1:1.3 mixture favoring the exo isomer in a reaction of conjugated aldehydes and cyclopentadiene.[2051] It has been argued that facial selectivity is not due to torsional angle decompression.[2052] Secondary orbital interactions.[2053] have been invoked, but this approach has been called into question.[2054] There has been a direct evaluation of such interactions, however.[2055] The endo/exo ratio can be influenced by the nature of the solvent.[2056]

[2048] Robiette, R.; Marchand-Brynaert, J.; Peeters, D. *J. Org. Chem.* ***2002***, *67*, 6823.

[2049] See, for example, Baldwin, J.E.; Reddy, V.P. *J. Org. Chem.* ***1989***, *54*, 5264. For a theoretical study for endo selectivity, see Imade, M.; Hirao, H.; Omoto, K.; Fujimoto, H. *J. Org. Chem.* ***1999***, *64*, 6697.

[2050] See, for example, Alder, K.; Günzl, W. *Chem. Ber.* ***1960***, *93*, 809; Stockmann, H. *J. Org. Chem.* ***1961***, *26*, 2025; Jones, D.W.; Wife, R.L. *J. Chem. Soc., Chem. Commun.* ***1973***, 421; Lindsay Smith, J.R.; Norman, R.O.C.; Stillings, M.R. *Tetrahedron* ***1978***, *34*, 1381; Mülle, P.; Bernardinelli, G.; Rodriguez, D.; Pfyffer, J.; Schaller, J. *Chimia* ***1987***, *41*, 244.

[2051] Ahrendt, K.A.; Borths, C.J.; MacMillan, D.W.C. *J. Am. Chem. Soc.* ***2000***, *122*, 4243.

[2052] Hickey, E.R.; Paquette, L.A. *Tetrahedron Lett.* ***1994***, *35*, 2309, 2313.

[2053] Hoffmann, R.; Woodward, R.B. *J. Am. Chem. Soc.* ***1965***, *87*, 4388, 4389.

[2054] García, J.I.; Mayoral, J.A.; Salvatella, L. *Acc. Chem. Res.* ***2000***, *33*, 658.

[2055] Arrieta, A.; Cossío, F.P.; Lecea, B. *J. Org. Chem.* ***2001***, *66*, 6178.

[2056] Cainelli, G.; Galletti, P.; Giacomini, D.; Quintavalla, A. *Tetrahedron Lett.* ***2003***, *44*, 93.

5. As we have seen, the Diels–Alder reaction can be both stereoselective and regioselective.[2057] In some cases, the Diels–Alder reaction can be made enantioselective[2058] Solvent effects are important in such reactions.[2059] The role of reactant polarity on the course of the reaction has been examined.[2060] Most enantioselective Diels–Alder reactions have used a chiral dienophile (e.g., **199**) and an achiral diene,[2061] along with a Lewis acid catalyst (see below). In such cases, addition of the diene to the two faces[2062] of **199** takes place at different rates, and **200** and **201** are formed in different amounts.[2063] An achiral compound A can be converted to a chiral compound by a chemical reaction with a compound B that is enantiopure. After the reaction, the resulting diastereomers can be separated, providing enantiopure compounds, each with a bond between molecule A and chiral compound B (a chiral auxiliary). Common chiral auxiliaries include chiral carboxylic acids, alcohols, or sultams. 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.[2064] Many chiral catalysts

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[2057] Domingo, L.R.; Picher, M.T.; Andrés, J.; Safont, V.S. *J. Org. Chem.* ***1997***, *62*, 1775. Also see, Smith, M.B. *Organic Synthesis*, 2nd ed., McGraw-Hill, NY, ***2001***, pp. 933–940, 968–977. See Ujaque, G.; Norton, J.E.; Houk, K.N. *J. Org. Chem.* **2002**, *67*, 7179.

[2058] See Corey, E.J.; Sarshar, S.; Lee, D.-H. *J. Am. Chem. Soc.* ***1994***, *116*, 12089. For reviews, see Taschner, M.J. *Org. Synth: Theory Appl.* ***1989***, *1*, 1; Helmchen, G.; Karge, R.; Weetman, J. *Mod. Synth. Methods* ***1986***, *4*, 261; Paquette, L.A. in Morrison, J.D. *Asymmetric Synthesis*, Vol. 3, Academic Press, NY, ***1983***, pp. 455–501; Oppolzer, W. *Angew. Chem. Int. Ed.* ***1984***, *23*, 876. See also, the list of references in Macaulay, J.B.; Fallis, A.G. *J. Am. Chem. Soc.* ***1990***, *112*, 1136.

[2059] Ruiz-López, M.F.; Assfeld, X.; García, J.I.; Mayoral, J.A.; Salvatella, L. *J. Am. Chem. Soc.* ***1993***, *115*, 8780.

[2060] Sustmann, R.; Sicking, W. *J. Am. Chem. Soc.* ***1996***, *118*, 12562.

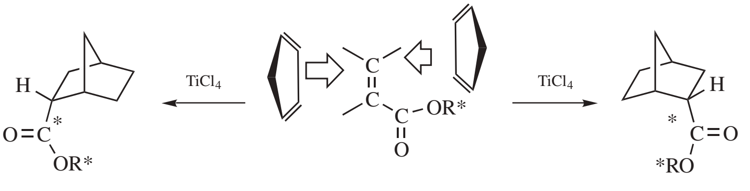
[2061] For the use of chiral dienes, see Fisher, M.J.; Hehre, W.J.; Kahn, S.D.; Overman, L.E. *J. Am. Chem. Soc.* ***1988***, *110*, 4625; Menezes, R.F.; Zezza, C.A.; Sheu, J.; Smith, M.B. *Tetrahedron Lett.* ***1989***, *30*, 3295; Charlton, J.L.; Plourde, G.L.; Penner, G.H. *Can. J. Chem.* ***1989***, *67*, 1010; Tripathy, R.; Carroll, P.J.; Thornton, E.R. *J. Am. Chem. Soc.* ***1990***, *112*, 6743; ***1991***, *113*, 7630; Rieger, R.; Breitmaier, E. *Synthesis* ***1990***, 697.

[2062] For a discussion of facial selectivity, see Xidos, J.D.; Poirier, R.A.; Pye, C.C.; Burnell, D.J. *J. Org. Chem.* ***1998***, *63*, 105.

[2063] Oppolzer, W.; Kurth, M.; Reichlin, D.; Moffatt, F.*Tetrahedron Lett.* ***1981***, *22*, 2545. See also, Walborsky, H.M.; Barash, L.; Davis, T.C. *Tetrahedron* ***1963***, *19*, 2333; Furuta, K.; Iwanaga, K.; Yamamoto, H. *Tetrahedron Lett.* ***1986***, *27*, 4507; Evans, D.A.; Chapman, K.T.; Bisaha, J. *J. Am. Chem. Soc.* ***1988***, *110*, 1238; Mattay, J.; Mertes, J.; Maas, G. *Chem. Ber.* ***1989***, *122*, 327; Alonso, I.; Carretero, J.C.; Garcia Ruano, J.L. *Tetrahedron Lett.* ***1989***, *30*, 3853; Tomioka, K.; Hamada, N.; Suenaga, T.; Koga, K. *J. Chem. Soc. Perkin Trans. 1*, ***1990***, 426; Cativiela, C.; López, P.; Mayoral, J.A. *Tetrahedron: Asymmetry* ***1990***, *1*, 61.

[2064] For a review, see Narasaka, K. *Synthesis* ***1991***, 1. For some recent examples, see Bir, G.; Kaufmann, D. *J. Organomet. Chem.* ***1990***, *390*, 1; Rebiere, F.; Riant, O.; Kagan, H.B. *Tetrahedron: Asymmetry* ***1990***, *1*, 199; Terada, M.; Mikami, K.; Nakai, T. *Tetrahedron Lett.* ***1991***, *32*, 935; Corey, E.J.; Imai, N.; Zhang, H. *J. Am. Chem. Soc.* ***1991***, *113*, 728; Narasaka, K.; Tanaka, H.; Kanai, F. *Bull. Chem. Soc. Jpn.* ***1991***, *64*, 387; Hawkins, J.M.; Loren, S. *J. Am. Chem. Soc.* ***1991***, *113*, 7794; Evans, D.A.; Barnes, D.M.; Johnson, J.S.; Lectka, T.; von Matt, P.; Miller, S.J.; Murry, J.A.; Norcross, R.D.; Shaughnessy, E.A.; Campos, K.R. *J. Am. Chem. Soc.* ***1999***, *121*, 7582.

have been developed.[2065] In many cases, asymmetric Lewis acids form a chiral complex with the dienophile.[2066]



200 **199** **201**

R = (+) or (–) phenylmenthyl

Many interesting compounds can be prepared by the Diels–Alder reaction,[2067] some of which would be hard to make in any other way. Azelines react with dienes to form cyclohexene derivatives fused to a four-membered ring amine (azetidine).[2068] The C_{60}-Fullerenes undergo Diels–Alder reactions,[2069] and the reaction is reversible.[2070] Bicyclic sultams can be prepared by an intramolecular Diels–Alder reaction.[2071] Polycyclic lactones can be prepared.[2072]Aromatic compounds can behave as dienes,[2073] but benzene is very unreactive toward dienophiles,[2074] and very few dienophiles (one of them is benzyne) have been reported to give Diels–Alder adducts with it.[2075] Naphthalene and phenanthrene are also quite resistant, although naphthalene has given Diels–Alder addition at high pressures.[2076] 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

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[2065] For a review, see Corey, E.J. *Angew. Chem. Int. Ed.* ***2002***, *41*, 1651. See also, Doyle, M.P.; Phillips, I.M.; Hu, W. *J. Am. Chem. Soc.* ***2001***, *123*, 5366; Owens, T.D.; Hollander, F.J.; Oliver A.G.; Ellman, J.A. *J. Am. Chem. Soc.* ***2001***, *123*, 1539; Faller, J.W.; Grimmond, B.J.; D'Alliessi, D.G. *J. Am. Chem. Soc.* ***2001***, *123*, 2525; Bolm, C.; Simić, O. *J. Am. Chem. Soc.* ***2001***, *123*, 3830; Fukuzawa, S.; Komuro, Y.; Nakano, N.; Obara, S. *Tetrahedron Lett.* ***2003***, *44*, 3671.

[2066] Hawkins, J.M.; Loren, S.; Nambu, M. *J. Am. Chem Soc.* ***1994***, *116*, 1657. See Sibi, M.P.; Venkatraman, L.; Liu, M.; Jaspersé, C.P. *J. Am. Chem. Soc.* ***2001***, *123*, 8444.

[2067] For a review of this reaction in synthesis, see Nicolaou, K.C.; Snyder, S.A.; Montagnon, T.; Vassilkogiannakis, G. *Angew. Chem. Int. Ed.* ***2002***, *41*, 1669.

[2068] Dave, P.R.; Duddu, R.; Surapaneni, R.; Gilardi, R. *Tetrahedron Lett.* ***1999***, *40*, 443.

[2069] Murata, Y.; Kato, N.; Fujiwara, K.; Komatsu, K. *J. Org. Chem.* ***1999***, *64*, 3483.

[2070] Wang, G.-W.; Saunders, M.; Cross, R.J. *J. Am. Chem. Soc.* ***2001***, *123*, 256.

[2071] Greig, I.R.; Tozer, M.J.; Wright, P.T. *Org. Lett.* ***2001***, *3*, 369.

[2072] Vlaar, M.J.M.; Lor, M.H.; Ehlers, A.W.; Schakel, M.; Lutz, M.; Spek, A.L.; Lammertsma, K. *J. Org. Chem.* ***2002***, *67*, 2485.

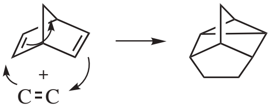
[2073] For a review, see Wagner-Jauregg, T. *Synthesis* ***1980***, 165, 769. See also, Balaban, A.T.; Biermann, D.; Schmidt, W. *Nouv. J. Chim.* ***1985***, *9*, 443.

[2074] However, see Chordia, M.D.; Smith, P.L.; Meiere, S.H.; Sabat, M.; Harman, W.D. *J. Am. Chem. Soc.* ***2001***, *123*, 10756.

[2075] Miller, R.G.; Stiles, M. *J. Am. Chem. Soc.* ***1963***, *85*, 1798; Meyerson, S.; Fields, E.K. *Chem. Ind. (London)* ***1966***, 1230; Ciganek, E. *Tetrahedron Lett.* ***1967***, 3321; Friedman, L. *J. Am. Chem. Soc.* ***1967***, *89*, 3071; Liu, R.S.H.; Krespan, C.G. *J. Org. Chem.* ***1969***, *34*, 1271.

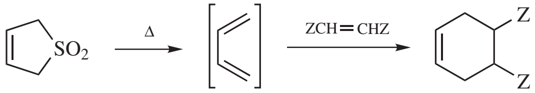
[2076] Plieninger, H.; Wild, D.; Westphal, J. *Tetrahedron* ***1969***, *25*, 5561.

reaction between benzyne and anthracene:[2077] 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, for example,[2078]



This last reaction is known as the *homo–Diels–Alder reaction*. A similar reaction has been reported with alkynes, using a mixture of a cobalt complex, ZnI_2 and tetrabutylammonium borohydride as catalysts.[2079]

Competing reactions are polymerization of the diene or dienophile, or both, and [1,2]-cycloaddition (**15-63**). Intramolecular versions of the Diels–Alder reaction are well-known, and this is a powerful method for the synthesis of mono- and polycyclic compounds.[2080] There are many examples and variations. Internal Diels–Alder reactions can be viewed as linking the diene and alkene by a tether, usually of carbon atoms. If the tether is replaced by functional groups that allow the selectivity inherent to the intramolecular cycloaddition, but can be cleaved afterward, a powerful modification is available. Indeed, such tethered cycloaddition reactions are increasingly common. After cycloaddition, the tether can be cleaved to give a functionalized cyclohexene derivative. Such tethered reactions allow enhancement of stereoselectivity[2081] and sometimes reactivity, relative to an untethered reaction, giving an indirect method for enhancing those parameters. Tethers or linkages include C—O—SiR_2—C[2082] or a C—O—SiR_2—O—C,[2083] or hydroxamides.[2084] Transient tethers can be used, as in the reaction of a diene having an allylic alcohol unit in a reaction is allyl alcohol, with $AlMe_3$, to give the cycloadduct with good selectivity.[2085]



3-Sulfolene

[2077] Wittig, G.; Niethammer, K. *Chem. Ber.* ***1960***, *93*, 944; Wittig, G.; Härle, H.; Knauss, E.; Niethammer, K. *Chem. Ber.* ***1960***, *93*, 951. For a review of triptycene, see Skvarchenko, V.R.; Shalaev, V.K.; Klabunovskii, E.I. *Russ. Chem. Rev.* ***1974***, *43*, 951.

[2078] See, for example, Fickes, G.N.; Metz, T.E. *J. Org. Chem.* ***1978***, *43*, 4057; Paquette, L.A.; Kesselmayer, M.A.; Künzer, H. *J. Org. Chem.* ***1988***, *53*, 5183.

[2079] Hilt, G.; du Mesnil, F.-X. *Tetrahedron Lett.* ***2000***, *41*, 6757.

[2080] Carlson, R.G. *Ann. Rep. Med. Chem.* ***1974***, *9*, 270; Oppolzer, W. *Angew. Chem. Int. Ed.* ***1977***, *16*, 10 (see pp. 10–18); Brieger, G.; Bennett, J.N. *Chem. Rev.* ***1980***, *80*, 63 (see p. 67); Fallis, A.G. *Can. J. Chem.* ***1984***, *62*, 183; Smith, M.B. *Org. Prep. Proceed. Int.* ***1990***, *22*, 315.

[2081] For a discussion of the origins of stereoselectivity in intramolecular tethered reactions, see Tantillo, D.J.; Houk, K.N.; Jung, M.E. *J. Org. Chem.* ***2001***, *66*, 1938.

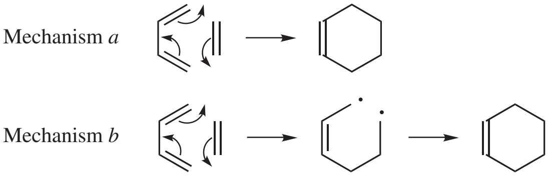
[2082] Stork, G.; Chan, T.Y.; Breault, G.A. *J. Am. Chem. Soc.* ***1992***, *114*, 7578.

[2083] Craig, D.; Reader, J.C. *Tetrahedron Lett.* ***1992***, *33*, 6165.

[2084] Ishikawa, T.; Senzaki, M.; Kadoya, R.; Morimoto, T.; Miyake, N.; Izawa, M.; Saito, S. Kobayashi, H. *J. Am. Chem. Soc.* ***2001***, *123*, 4607.

[2085] Bertozzi, F.; Olsson, R.; Frejd, T. *Org. Lett.* ***2000***, *2*, 1283.

The Diels–Alder reaction is usually reversible, although the retro reaction typically occurs at significantly higher temperatures than the forward reaction. However, the reversibility of the reaction and has been used to protect double bonds.[2086] 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.[2087] Butadiene is generated *in situ* by a reverse Diels–Alder reaction (see **17-20**).



There are, broadly speaking, three possible mechanisms that have been considered for the uncatalyzed Diels-Alder reaction.[2088] 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.[2089] A diradical formed in this manner must be a singlet; that is, the two unpaired electrons must have opposite spins, by an argument similar to that outlined on p. 277. 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*,[2090] although it is possible

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[2086] For reviews of the reverse Diels–Alder reaction, see Ichihara, A. *Synthesis* ***1987***, 207; Lasne, M.; Ripoll, J.L. *Synthesis* ***1985***, 121; Ripoll, J.L.; Rouessac, A.; Rouessac, F. *Tetrahedron* ***1978***, *34*, 19; Brown, R.F.C. *Pyrolytic Methods in Organic Chemistry*, Academic Press, NY, ***1980***, pp. 259–281; Kwart, H.; King, K. *Chem. Rev.* ***1968***, *68*, 415.

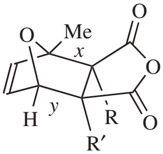
[2087] Sample Jr., T.E.; Hatch, L.F. *Org. Synth.* ***VI***, 454. For a review, see Chou, T.; Tso, H. *Org. Prep. Proced. Int.* ***1989***, *21*, 257.

[2088] For reviews, see Sauer, J.; Sustmann, R. *Angew. Chem. Int. Ed.* ***1980***, *19*, 779; Houk, K.N. *Top. Curr. Chem.* ***1979***, *79*, 1; Seltzer, S. *Adv. Alicyclic Chem.* ***1968***, *2*, 1; Ref. 1981. For a review of the application of quantum-chemical methods to the study of this reaction, see Babichev, S.S.; Kovtunenko, V.A.; Voitenko, Z.V.; Tyltin, A.K. *Russ. Chem. Rev.* ***1988***, *57*, 397. For a discussion of synchronous versus nonsynchronous mechanisms, see Beno, B.R.; Houk, K.N.; Singleton, D.A. *J. Am. Chem. Soc.* ***1996***, *118*, 9984; Singleton, D.A.; Schulmeier, B.E.; Hang, C.; Thomas, A.A.; Leung, S.-W.; Merrigan, S.R. *Tetrahedron* ***2001***, *57*, 5149. Also see, Li, Y.; Houk, K.N. *J. Am. Chem. Soc.* ***1993***, *115*, 7478 for the dimerization mechanism of 1,3-butadiene.

[2089] For a discussion of a diradical stepwise versus concerted mechanism for reactions with chalcogens, see Orlova, G.; Goddard, J.D. *J. Org. Chem.* ***2001***, *66*, 4026.

[2090] For a contrary view, see Dewar, M.J.S.; Olivella, S.; Stewart, J.J.P. *J. Am. Chem. Soc.* ***1986***, *108*, 5771. For arguments against this view, see Houk, K.N.; Lin, Y.; Brown, F.K. *J. Am. Chem. Soc.* ***1986***, *108*, 554; Hancock, R.A.; Wood, Jr., B.F. *J. Chem. Soc., Chem. Commun.* ***1988***, 351; Gajewski, J.J.; Peterson, K.B.; Kagel, J.R.; Huang, Y.C.J. *J. Am. Chem. Soc.* ***1989***, *111*, 9078.

that a diradical[2091] or even a diion[2092] mechanism may be taking place in some cases. Radical cation Diels–Alder reactions have been considered.[2093] 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 **202**, the isotope effect k_I/k_{II} was equal to 1.00 within experimental error.[2094] If bond *x* were to break before bond *y*, there



202

I: R = H, R′ = D

II: R = D, R′ = H

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 reaction[2095] and the result was the same. There is also other evidence for mechanism *a*.[2096] However, the fact that the mechanism is concerted does not necessarily mean that it is synchronous.[2097] 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;[2098] that is, it could have a transition state in which one

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[2091] See, for example, Bartlett, P.D.; Mallet, J.J. *J. Am. Chem. Soc.* ***1976***, *98*, 143; Jenner, G.; Rimmelin, J. *Tetrahedron Lett.* ***1980***, *21*, 3039; Van Mele, B.; Huybrechts, G. *Int. J. Chem. Kinet.* ***1987***, *19*, 363; ***1989***, *21*, 967.

[2092] For a reported example, see Gassman, P.G.; Gorman, D.B. *J. Am. Chem. Soc.* ***1990***, *112*, 8624.

[2093] Haberl, U.; Wiest, O.; Steckhan, E. *J. Am. Chem. Soc.* ***1999***, *121*, 6730.

[2094] Seltzer, S. *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, J.J. *Isot. Org. Chem.* ***1987***, *7*, 115–176.

[2095] Van Sickle, D.E.; Rodin, J.O. *J. Am. Chem. Soc.* ***1964***, *86*, 3091.

[2096] See, for example, Dewar, M.J.S.; Pyron R.S. *J. Am. Chem. Soc.* ***1970***, *92*, 3098; Brun, C.; Jenner, G. *Tetrahedron* ***1972***, *28*, 3113; Doering, W. von E.; Franck-Neumann, M.; Hasselmann, D.; Kaye, R.L. *J. Am. Chem. Soc.* ***1972***, *94*, 3833; McCabe, J.R.; Eckert, C.A. *Acc. Chem. Res.* ***1974***, *7*, 251; Berson, J.A.; Dervan, P.B.; Malherbe, R.; Jenkins, J.A. *J. Am. Chem. Soc.* ***1976***, *98*, 5937; Rücker, C.; Lang, D.; Sauer, J.; Friege, H.; Sustmann, R. *Chem. Ber.* ***1980***, *113*, 1663; Tolbert, L.M.; Ali, M.B. *J. Am. Chem. Soc.* ***1981***, *103*, 2104.

[2097] For an example of a study of a reaction that is concerted but asynchronous, see Avalos, M.; Babiano, R.; Clemente, F.R.; Cintas, P.; Gordillo, R.; Jiménez, J.L.; Palacios, J.C. *J. Org. Chem.* ***2000***, *65*, 8251

[2098] Woodward, R.B.; Katz, T.J. *Tetrahedron* ***1959***, *5*, 70; Liu, M.T.H.; Schmidt, C. *Tetrahedron* ***1971***, *27*, 5289; Dewar, M.J.S.; Pyron R.S. *J. Am. Chem. Soc.* ***1970***, *92*, 3098; Papadopoulos, M.; Jenner, G. *Tetrahedron Lett.* ***1982***, *23*, 1889; Houk, K.N.; Loncharich, R.J.; Blake, J.F.; Jorgensen, W.L. *J. Am. Chem. Soc.* ***1989***, *111*, 9172; Lehd, M.; Jensen, F. *J. Org. Chem.* ***1990***, *55*, 1034.

bond has been formed to a greater degree than the other.[2099] A biradical mechanism has been proposed for some Diels–Alder reactions.[2100]

In another aspect of the mechanism, the effects of electron-donating and electron-withdrawing substituents (p. 1196) 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, although the latter is normally the most reactive dienophile known. It is apparent, then, that this diene is the electrophile in its Diels–Alder reactions.[2101] Reactions of this type are said to proceed with *inverse electron demand*.[2102]

We have emphasized that the Diels–Alder reaction generally takes place rapidly and conveniently. In sharp contrast, the apparently similar dimerization of alkenes to cyclobutanes (**15-63**) gives very poor results in most cases, except when photochemically induced. Woodward and Hoffmann, and Fukui have shown that these contrasting results can be explained by the *principle of conservation of orbital symmetry*,[2103] which predicts that certain reactions are allowed and others forbidden. The orbital-symmetry rules (also called the Woodward–Hoffmann rules)[2104] apply *only to concerted reactions*, for example, 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

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[2099] For a theoretical investigation of the ionic Diels–Alder reaction, see dePascual-Teresa, B.; Houk, K.N. *Tetrahedron Lett.* ***1996***, *37*, 1759. For a discussion of the origin of synchronicity in the transition state of polar Diels–Alder reactions, see Domingo, L.R.; Aurell, M.J.; Pérez, P.; Contreras, R. *J. Org. Chem.* ***2003***, *68*, 3884.

[2100] de Echagüen, C.O.; Ortuño, R.M. *Tetrahedron Lett.* ***1995***, *36*, 749. See Li, Y.; Padias, A.B.; Hall Jr., H.K. *J. Org. Chem.* ***1993***, *58*, 7049 for a discussion of diradicals in concerted Diels–Alder reactions.

[2101] Sauer, J.; Wiest, H. *Angew. Chem. Int. Ed.* ***1962***, *1*, 269.

[2102] For a review, see Boger, D.L.; Patel, M. *Prog. Heterocycl. Chem.* ***1989***, *1*, 30. Also see, Pugnaud, S.; Masure, D.; Hallé, J.-C.; Chaquin, P. *J. Org. Chem,.* ***1997***, *62*, 8687; Wan, Z.-K.; Snyder, J.K. *Tetrahedron Lett.* ***1998***, *39*, 2487; Markó, I.E.; Evans, G.R. *Tetrahedron Lett.* ***1994***, *35*, 2767, 2771.

[2103] For monographs, see Fleming, I. *Pericyclic Reactions*, Oxford University Press, Oxford, ***1999***, pp. 31–56; Gilchrist, T.L.; Storr, R.C. *Organic Reactions and Orbital Symmetry*, 2nd ed., Cambridge University Press, Cambridge, ***1979***; Fleming, I. *Frontier Orbitals and Organic Chemical Reactions*, Wiley, NY, ***1976***; Woodward, R.B.; Hoffmann, R. *The Conservation of Orbital Symmetry*, Academic Press, NY, ***1970*** [the text of this book also appears in *Angew. Chem. Int. Ed.* ***1969***, *8*, 781; Lehr, R.E.; Marchand, A.P. *Orbital Symmetry*, Academic Press, NY, ***1972***. For reviews, see Pearson, R.G. *J. Chem. Educ.* ***1981***, *58*, 753; in Klopman, G. *Chemical Reactivity and Reaction Paths*, Wiley, NY, ***1974***, the articles by Fujimoto, H.; Fukui, K. pp. 23–54, Klopman, G. pp. 55–165, Herndon, W.C.; Feuer, J.; Giles, W.B.; Otteson, D.; Silber, E. pp. 275–299; Michl, J. pp. 301–338; Simonetta, M. *Top. Curr. Chem.* ***1973***, *42*, 1; Houk, K.N. *Surv. Prog. Chem.* ***1973***, *6*, 113; Vollmer, J.J.; Servis, K.L. *J. Chem. Educ.* ***1970***, *47*, 491; Gill, G.B. *Essays Chem.* ***1970***, *1*, 43; *Q. Rev. Chem. Soc.* ***1968***, *22*, 338; Seebach, D. *Fortschr. Chem. Forsch.* ***1969***, *11*, 177; Miller, S.I. *Adv. Phys. Org. Chem.* ***1968***, *6*, 185; Miller, S.I. *Bull. Soc. Chim. Fr.* ***1966***, 4031. For a review of applications to inorganic chemistry, see Pearson, R.G. *Top Curr. Chem.* ***1973***, *41*, 75.

[2104] Chattaraj, P.K.; Fuentealba, P.; Gómez, B.; Contreras, R. *J. Am. Chem. Soc.* ***2000***, *122*, 348.

of which are used more frequently than others.[2105] Of these three, we will discuss two: the frontier-orbital method and the Möbius–Hückel method. The third, called the correlation diagram method,[2106] is less convenient to apply than the other two.

The Frontier Orbital Method[2107]

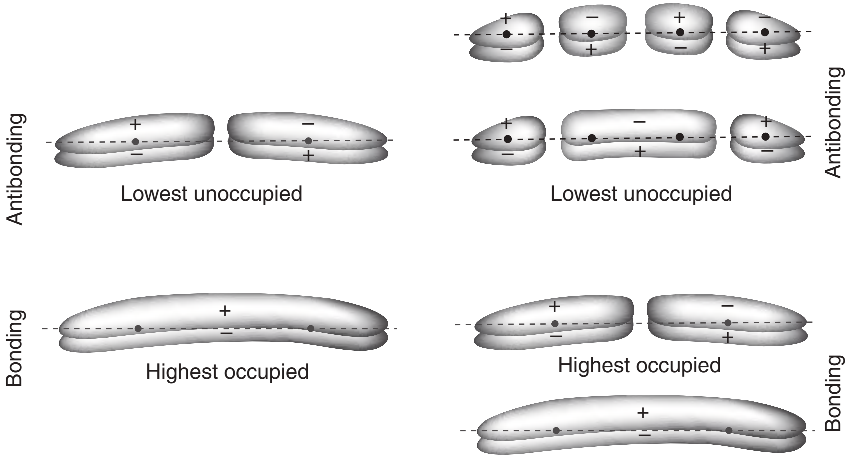
As applied to cycloaddition reactions the rule is that *reactions are allowed only when all overlaps between the highest occupied molecular orbital* (HOMO) *of one reactant and the lowest unoccupied molecular orbital* (LUMO) *of the other are such that a positive lobe overlaps only with another positive lobe and a negative lobe only with another negative lobe*. We may recall that monoalkenes have two π molecular orbitals (p. 10) and that conjugated dienes have four (p. 38), as shown in Fig. 15.2. A concerted cyclization of two monoalkenes (a [2 + 2]-reaction) is not allowed because it would require that a positive lobe overlap with a negative lobe (Fig. 15.3). On the other hand, the Diels–Alder reaction (a [4 + 2]-reaction) is allowed, whether considered from either direction (Fig. 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 (Fig. 15.5) and the [4 + 2]-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.

[2105] For other approaches, see Epiotis, N.D. *Theory of Organic Reactions*, Springer, NY, ***1978***; Epiotis, N.D.; Shaik, S. *J. Am. Chem. Soc.* ***1978***, *100*, 1, 9; Halevi, E.A. *Angew. Chem. Int. Ed.* ***1976***, *15*, 593; Shen, K. *J. Chem. Educ.* ***1973***, *50*, 238; Salem, L. *J. Am. Chem. Soc.* ***1968***, *90*, 543, 553; Trindle, C. *J. Am. Chem. Soc.* ***1970***, *92*, 3251, 3255; Mulder, J.J.C.; Oosterhoff, L.J. *Chem. Commun.* ***1970***, 305, 307; Goddard III, W.A. *J. Am. Chem. Soc.* ***1970***, *92*, 7520; ***1972***, *94*, 793; Herndon, W.C. *Chem. Rev.* ***1972***, *72*, 157; Perrin, C.L. *Chem. Br.* ***1972***, *8*, 163; Langlet, J.; Malrieu, J. *J. Am. Chem. Soc.* ***1972***, *94*, 7254; Pearson, R.G. *J. Am. Chem. Soc.* ***1972***, *94*, 8287; Mathieu, J. *Bull. Soc. Chim. Fr.* ***1973***, 807; Silver, D.M.; Karplus, M. *J. Am. Chem. Soc.* ***1975***, *97*, 2645; Day, A.C. *J. Am. Chem. Soc.* ***1975***, *97*, 2431; Mok, K.; Nye, M.J. *J. Chem. Soc. Perkin Trans. 2*, ***1975***, 1810; Ponec, R. *Collect. Czech. Chem. Commun.* ***1984***, *49*, 455; ***1985***, *50*, 1121; Hua-ming, Z.; De-xiang, W. *Tetrahedron* ***1986***, *42*, 515; Bernardi, F.; Olivucci, M.; Robb, M.A. *Res. Chem. Intermed.* ***1989***, *12*, 217; *Acc. Chem. Res.* ***1990***, *23*, 405.

[2106] For excellent discussions of this method, see Woodward, R.B.; Hoffmann, R. *The Conservation of Orbital Symmetry*, Academic Press, NY, ***1970***; *Angew. Chem. Int. Ed.* ***1969***, *8*, 781; Jones, R.A.Y. *Physical and Mechanistic Organic Chemistry* 2nd ed., Cambridge University Press, Cambridge, ***1984***, pp. 352–366; Klumpp, G.W. *Reactivity in Organic Chemistry*, Wiley, NY, ***1982***, pp. 378–389; Yates, K. *Hückel Molecular Orbital Theory*, Academic Press, NY, ***1978***, pp. 263–276.

[2107] Fukui, K.; Fujimoto, H. *Bull. Chem. Soc. Jpn.* ***1967***, *40*, 2018; ***1969***, *42*, 3399; Fukui, K. *Fortschr. Chem. Forsch.* ***1970***, *15*, 1; *Acc. Chem. Res.* ***1971***, *4*, 57; Houk, K.N. *Acc. Chem. Res.* ***1975***, *8*, 361. See also, Chu, S. *Tetrahedron* ***1978***, *34*, 645. For a monograph on Frontier Orbitals see Fleming, I. *Pericyclic Reactions*, Oxford University Press, Oxford, **1999**. For reviews, see Fukui, K. *Angew. Chem. Int. Ed.* ***1982***, *21*, 801; Houk, K.N., in Marchand, A.P.; Lehr, R.E. *Pericyclic Reactions*, Vol. 2; Academic Press, NY, ***1977***, pp. 181–271.



π orbitals of an isolated C = C bond.

π orbitals of a conjugated diene

Fig. 15.2. Schematic drawings of the π-orbitals of an isolated C=C bnd and a conjugated diene.

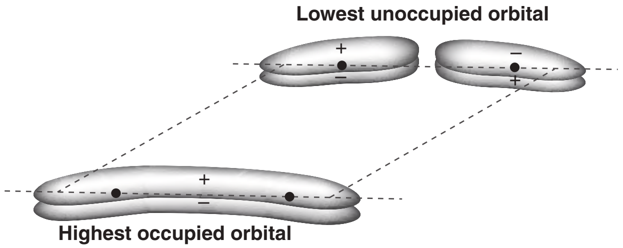


Fig. 15.3. Overlap of orbitals in a thermal [2 + 2]-cycloaddition.

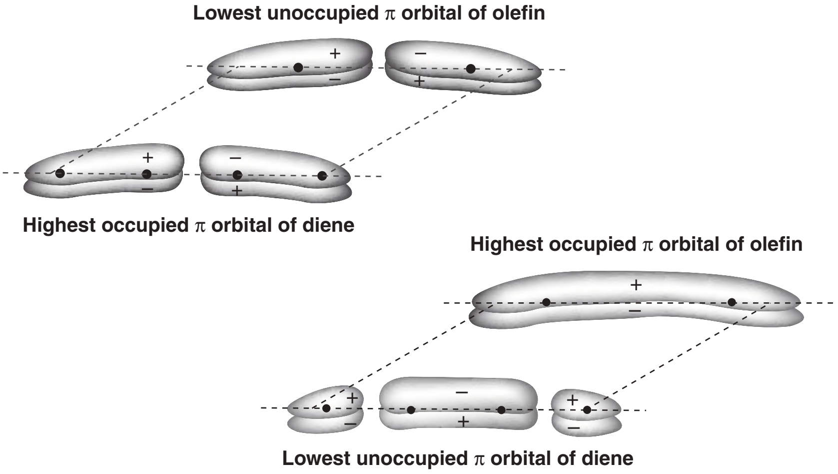


Fig. 15.4. Two ways for orbitals to overlap in a thermal [4 + 2]-cycloaddition.

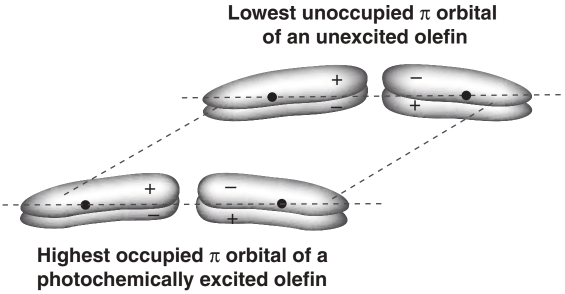


Fig. 15.5. Overlap of orbitals in a photochemical $[2+2]$-cycloaddition.

The Möbius–Hückel Method[2108]

In this method, the orbital symmetry rules are related to the Hückel aromaticity rule discussed in Chapter 2.[2109] 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 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* (Fig. 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 $[4+2]$ ring closures. What we look for are *sign inversions*. In Fig. 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

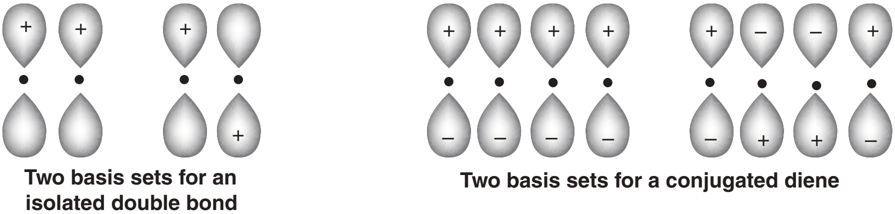


Fig. 15.6. Some basis sets.

[2108] Zimmerman, H.E., in Marchand, A.P.; Lehr, R.E. *Pericyclic Reactions*, Vol. 2, Academic Press, NY, ***1977***, pp. 53–107; *Acc. Chem. Res.* ***1971***, *4*, 272; *J. Am. Chem. Soc.* ***1966***, *88*, 1564, 1566; Dewar, M.J.S. *Angew. Chem. Int. Ed.* ***1971***, *10*, 761; Jefford, C.W.; Burger, U. *Chimia*, ***1971***, *25*, 297; Herndon, W.C. *J. Chem. Educ.* ***1981***, *58*, 371.

[2109] See Morao, I.; Cossío, F.P. *J. Org. Chem.* ***1999***, *64*, 1868.

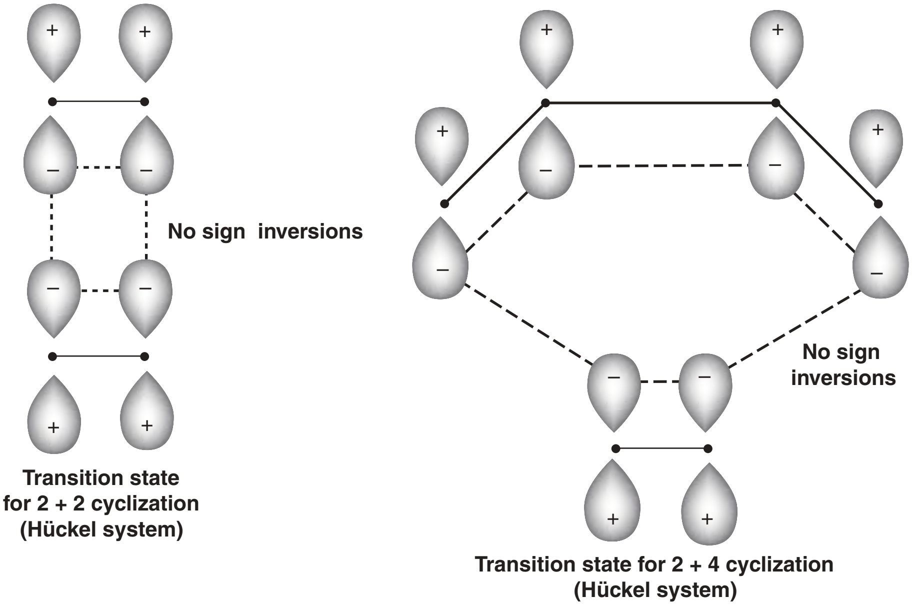


Fig. 15.7. Transition states illustrating Hückel–Möbius rules for cycloaddition reactions.

inversions are called *Möbius systems* (because of the similarity to the Möbius strip, which is a mathematical surface, shown in Fig. 15.8). Möbius systems do not enter into either of these reactions, but an example of such a system is shown on p. $$$.

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 [4 + 2]- and [2 + 2]-cycloadditions are Hückel systems, the Möbius–Hückel method predicts that the [4 + 2]-reaction, with 6 electrons, is thermally allowed,

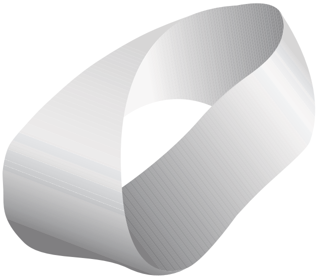


Fig. 15.8. A Möbius strip. Such a strip is easily constructed by twisting a thin strip of paper 180° and fastening the ends together.

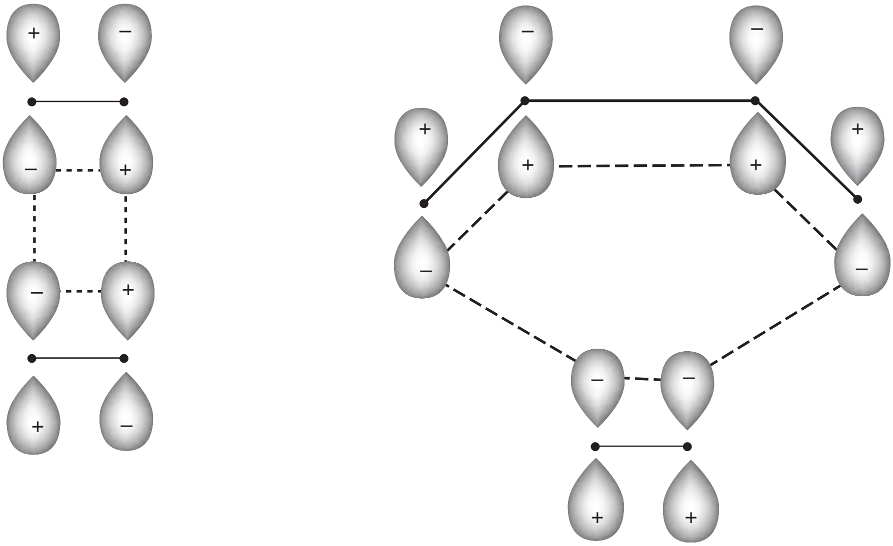


Fig. 15.9. Transition states of [2 + 2]- and [4 + 2]-cyclizations involing other basis sets.

but the [2 + 2]-reaction is not. One the other hand, the [2 + 2]-reaction is allowed photochemically, while the [4 + 2]-reaction is forbidden.

Note that both the [2 + 2] and [4 + 2] transition states are Hückel systems no matter what basis sets we chose. For example, Fig. 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 [4 + 2]-cycloadditions and photochemical [2 + 2]-cycloadditions (and the reverse ring openings) are allowed, while photochemical [4 + 2] 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 **15-53**). 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, that is, where two σ bonds are formed (or broken) at about the same time.[2110] 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

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[2110] For a discussion of concertedness in these reactions see Lehr, R.E.; Marchand, A.P., in Marchand, A.P.; Lehr, R.E. *Pericyclic Reactions*, Vol. 1, Academic Press, NY, ***1977***, pp. 1–51.

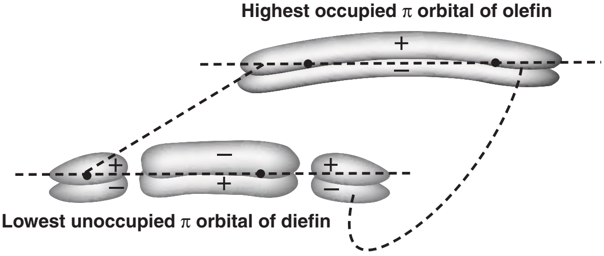

Fig. 15.10. Overlap of orbitals in an antarafacial thermal [4 + 2]-cycloaddition.

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 cannot[2111] take place by a cyclic mechanism because their activation energies would be too high (however, see below). As we will see (**15-62**), such reactions largely occur by two-step mechanisms. Similarly, [4 + 2]-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*).[2112]

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 $[_{\pi}2_s + {}_{\pi}4_s]$-cycloaddition (the subscript π indicates that π electrons are involved in the 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, that is, 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 alkene and the lowest unoccupied π orbital of the diene would have to occur as shown in Fig. 15.10, with a + lobe

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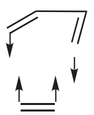
[2111] The possibility has been raised that some disallowed reactions may nevertheless proceed by concerted mechanisms: see Schmidt, W. *Helv. Chim. Acta* ***1971***, *54*, 862; *Tetrahedron Lett.* ***1972***, 581; Muszkat, K.A.; Schmidt, W. *Helv. Chim. Acta* ***1971***, *54*, 1195; Baldwin, J.E.; Andrist, A.H.; Pinschmidt Jr., R.K. *Acc. Chem. Res.* ***1972***, *5*, 402; Berson, J.A. *Acc. Chem. Res.* ***1972***, *5*, 406; Baldwin, J.E., in Marchand, A.P.; Lehr, R.E. *Pericyclic Reactions*, Vol. 2, Academic Press, NY, ***1977***, pp. 273–302.

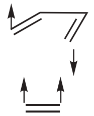
[2112] For example, see Sieber, W.; Heimgartner, H.; Hansen, H.; Schmid, H. *Helv. Chim. Acta* ***1972***, *55*, 3005. For discussions see Bartlett, P.D.; Helgeson, R.; Wersel, O.A. *Pure Appl. Chem.* ***1968***, *16*, 187; Seeley, D.A. *J. Am. Chem. Soc.* ***1972***, *94*, 4378; Kaupp, G. *Angew. Chem. Int. Ed.* ***1972***, *11*, 313, 718.

overlapping a – lobe. Since like signs are no longer overlapping, the thermal reaction is now forbidden. Similarly, thermal $[_{\pi}4_s + _{\pi}2_a]$- and



Normal Diels–Adler reaction

$[4_s + 2_s]$



Twisted Diels–Adler reaction

$[4_a + 2_s]$

$[_{\pi}2_a + _{\pi}2_a]$-cyclizations are forbidden, while thermal $[_{\pi}4_a + _{\pi}2_a]$- 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 [4 + 2]-cyclization,[2113] 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 **15-63**). 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 addition.[2114] In the case of [4 + 2] addition of butadiene to itself, the approach can be exo or endo. It can be seen (Fig. 15.11) that whether the HOMO of the diene overlaps with the LUMO of the alkene or vice versa, the endo orientation is stabilized by additional secondary overlap of orbitals[2115] 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.[2116] 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.[2117]

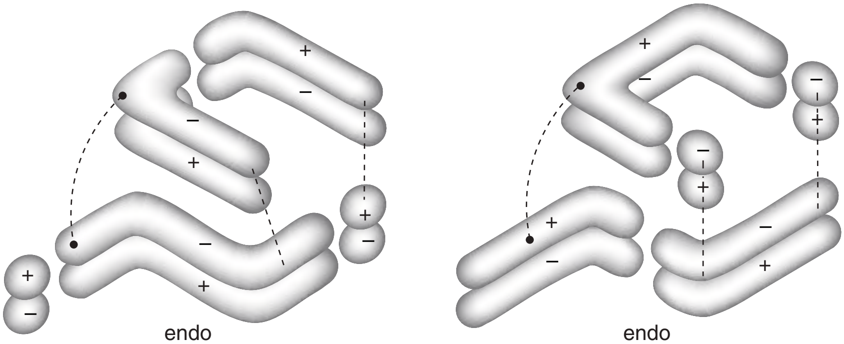
[2113] A possible photochemical $[_{\pi}2a + _{\pi}4_s]$-cycloaddition has been reported: Hart, H.; Miyashi, T.; Buchanan, D.N.; Sasson, S. *J. Am. Chem. Soc.* ***1974***, *96*, 4857.

[2114] Hoffmann, R.; Woodward, R.B. *J. Am. Chem. Soc.* ***1965***, *87*, 4388.

[2115] For reviews of secondary orbital interactions, see Ginsburg, D. *Tetrahedron* ***1983***, *39*, 2095; Gleiter, R.; Paquette, L.A. *Acc. Chem. Res.* ***1983***, *16*, 328. For a new secondary orbital interaction see Singleton, D.A. *J. Am. Chem. Soc.* ***1992***, *114*, 6563.

[2116] See, for example, Cookson, R.C.; Drake, B.V.; Hudec, J.; Morrison, A. *Chem. Commun.* ***1966***, 15; Itô, S.; Fujise, Y.; Okuda, T.; Inoue, Y. *Bull. Chem. Soc. Jpn.* ***1966***, *39*, 1351; Paquette, L.A.; Barrett, J.H.; Kuhla, D.E. *J. Am. Chem. Soc.* ***1969***, *91*, 3616; Houk, K.N.; Woodward, R.B. *J. Am. Chem. Soc.* ***1970***, *92*, 4143, 4145; Jones, D.W.; Kneen, G. *J. Chem. Soc., Chem. Commun.* ***1973***, 420. Also see Apeloig, Y.; Matzner, E. *J. Am. Chem. Soc.* ***1995***, *117*, 5375.

[2117] See, for example, Houk, K.N.; Luskus, L.J. *J. Am. Chem. Soc.* ***1971***, *93*, 4606; Kobuke, Y.; Sugimoto, T.; Furukawa, J.; Fueno, T. *J. Am. Chem. Soc.* ***1972***, *94*, 3633; Jacobson, B.M. *J. Am. Chem. Soc.* ***1973***, *95*, 2579; Mellor, J.M.; Webb, C.F. *J. Chem. Soc. Perkin Trans. 2*, ***1974***, 17, 26; Fox, M.A.; Cardona, R.; Kiwiet, N.J. *J. Org. Chem.* ***1987***, *52*, 1469.

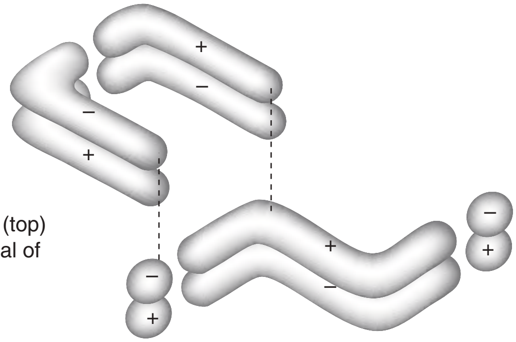


endo

Highest-occupied orbital of diene (top)
overlaps lowest-unoccupied orbital of
“orbital” (bottom)

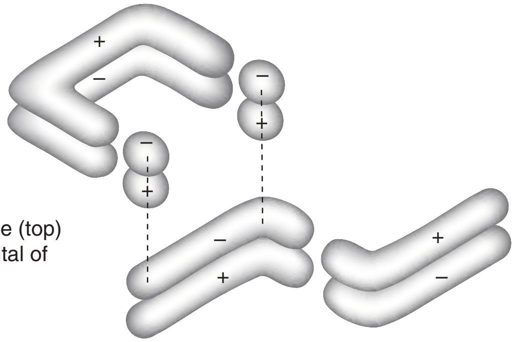
endo

Lowest-occupied orbital of diene (top)
overlaps highest-unoccupied orbital of
“olefin” (bottom)



exo

Highest-occupied orbital of diene (top)
overlaps lowest-unoccupied orbital of
“olefin” (bottom)



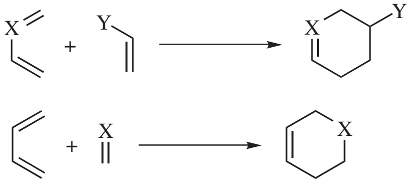
exo

Lowest unoccupied orbital of diene (top)
overlaps lowest-unoccupied orbital of
“olefin” (bottom)

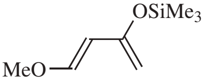
Fig. 15.11. Overlap of orbitals in [4 + 2]-cycloaddition of dienes.

OS **II**, 102; **III**, 310, 807; **IV**, 238, 738, 890, 964; **V**, 414, 424, 604, 985, 1037; **VI**, 82, 196, 422, 427, 445, 454; **VII**, 4, 312, 485; **VIII**, 31, 38, 298, 353, 444, 597; **IX**, 186, 722; **75**, 201; **81**, 171. For a reverse Diels–Alder reaction, see OS **VII**, 339.

15-61 Heteroatom Diels–Alder Reactions



Carbon–carbon multiple bonds are not the only units that can participate in Diels–Alder reactions. Other double- and triple-bond compounds can be dienophiles and they give rise to heterocyclic compounds.[2118] Among these are N≡C—, —N=C—,[2119] iminium salts,[2120] —N=N—, O=N—,[2121] and —C=O compounds[2122] and even molecular oxygen (**15-62**). It is noted that in the presence of a $YbCl_3$ catalyst, azirines reaction with dienes to give a 1-azabicyclo[4.1.0] heptene.[2123] Several catalysts can be used, depending on the nature of the heteroatoms incorporated into the alkene or diene.[2124] Intramolecular cycloaddition with a diene–imine substrate leads to pyrrolidines.[2125]



203

Aldehydes react with suitably functionalized dienes, such as **203**, known as *Danishefsky's diene*,[2126] and the reaction usually requires a Lewis acid catalyst

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[2118] For transition structures for selected hetero Diels–Alder reactions, see McCarrick, M.A.; Wu, Y.-D.; Houk, K.N. *J. Org. Chem.* ***1993***, *58*, 3330.

[2119] Nogue, D.; Paugam, R.; Wartski, L. *Tetrahedron Lett.* ***1992***, *33*, 1265; Collin, J.; Jaber, N.; Lannou, M.I. *Tetrahedron Lett.* ***2001***, *42*, 7405; Hedberg, C.; Pinho, P.; Roth, P.; Andersson, P.G. *J. Org. Chem.* ***2000***, *65*, 2810. For a review see Buonora, P.; Olsen, J.-C.; Oh, T. *Tetrahedron* ***2001***, *57*, 6099; Anniyappan, M.; Muralidharan, D.; Perumal, P.T. *Tetrahedron Lett.* ***2003***, *44*, 3653.

[2120] Domingo, L.R. *J. Org. Chem.* ***2001***, *66*, 3211; Chou, S.-S.P.; Hung, C.-C. *Synth. Commun.* ***2001***, *31*, 1097.

[2121] Martin, S.F.; Hartmann, M.; Josey, J.A. *Tetrahedron Lett.* ***1992***, *33*, 3583.

[2122] For monographs on dienes and dienophiles with heteroatoms, see Boger, D.L.; Weinreb, S.M. *Hetero Diels–Alder Methodology in Organic Synthesis*, Academic Press, NY, ***1987***; Hamer, J. *1,4-Cycloaddition Reactions*, Academic Press, NY, ***1967***. For reviews, see Weinreb, S.M.; Scola, P.M. *Chem. Rev.* ***1989***, *89*, 1525; Boger, D.L., in Lindberg, T. *Strategies and Tactics in Organic Synthesis*, Vol. 2, Academic Press, NY, ***1989***, pp. 1–56; Kametani, T.; Hibino, S. *Adv. Heterocycl. Chem.* ***1987***, *42*, 245; Boger, D.L. *Tetrahedron* ***1983***, *39*, 2869; Weinreb, S.M.; Staib, R.R. *Tetrahedron* ***1982***, *38*, 3087; Weinreb, S.M.; Levin, J.I. *Heterocycles* ***1979***, *12*, 949; Desimoni, G.; Tacconi, G. *Chem. Rev.* ***1975***, *75*, 651; Kresze, G.; Firl, J. *Fortschr. Chem. Forsch.* ***1969***, *11*, 245. See also, Katritzky, A.R.; Dennis, N. *Chem. Rev.* ***1989***, *89*, 827; Schmidt, R.R. *Acc. Chem. Res.* ***1986***, *19*, 250; Boger, D.L. *Chem. Rev.* ***1986***, *86*, 781.

[2123] Ray, C.A.; Risberg, E.; Somfai, P. *Tetrahedron Lett.* ***2001***, *42*, 9289.

[2124] See Molander, G.A.; Rzasa, R.M. *J. Org. Chem.* ***2000***, *65*, 1215.

[2125] Amos, D.T.; Renslo, A.R.; Danhesier, R.L. *J. Am. Chem. Soc.* ***2003***, *125*, 4970.

[2126] Danishefsky, S.; Kitahara, T.; Schuda, P.F.; Etheredge, S.J. *J. Am. Chem. Soc.* ***1976***, *98*, 3028; Danishefsky, S.; Kitahara, T.; McKee, R.; Schuda, P.F. *J. Am. Chem. Soc.* ***1976***, *98*, 6715; Danishefsky, S.; Schuda, P.F.; Kitahara, T. Etheredge, S.J. *J. Am. Chem. Soc.* ***1977***, *99*, 6066.

such as lanthanide compounds. Aldehydes react using a chiral titanium[2127] or a zirconium[2128] catalyst to give the dihydropyran with good enantioselectivity. Note that the reaction of Danishefsky's diene with an imine, formed *in situ* by reaction of an aryl aldehyde and an aniline derivative, proceeds without a Lewis acid.[2129] Such reactions of aldehydes can be catalyzed with Lewis acids and transition-metal catalysts. The Diels–Alder reaction of aldehydes with dienes can be catalyzed by many transition-metal compounds, including cobalt[2130] and indium[2131] catalyst. Ketones also react with suitably functionalized dienes.[2132]

Azadienes undergo Diels–Alder reactions to form pyridine, dihydro- and tetrahydropyridine derivatives.[2133] Aza-Diels–Alder reactions have been done in ionic liquids.[2134] Similarly, acyl iminium salts C=N(R)–C=O react with alkenes via cycloaddition.[2135] *N*-Vinyl lactim ethers undergo Diels–Alder reactions with a limited set of dienophiles.[2136] Thioketones react with dienes to give Diels–Alder cycloadducts.[2137] The carbonyl group of lactams have also been shown to be a dienophile.[2138] Certain heterocyclic aromatic rings (among them furans)[2139] 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.[1999] Nitroso compounds of the type *t*-BuO_2C–N=O react with dienes to give the corresponding 2-azadihydropyran.[2140]

Catalysts, such as $Fe(BuEtCHCO_2)_3$, have been developed that are effective for the heteroatom Diels–Alder reaction.[2141] Indium trichloride ($InCl_3$) is a good catalyst for imino-Diels–Alder reactions.[2142] Hetero-Diels–Alder reactions involving carbonyls have been done in water.[2143] Ultrasound has been used to promote the Diels–Alder reactions of 1-azadienes.[2144] Polymer-supported dienes have been used.[2145]

[2127] Wang, B.; Feng, X.; Huang, Y.; Liu, H.; Cui, X.; Jiang, Y. *J. Org. Chem.* ***2002***, *67*, 2175.

[2128] Yamashita, Y.; Saito, S.; Ishitani, H.; Kobayashi, S. *J. Am. Chem. Soc.* ***2003***, *125*, 3793.

[2129] Yuan, Y.; Li, X.; Ding, K. *Org. Lett.* ***2002***, *4*, 3309.

[2130] Kezuka, S.; Mita, T.; Ohtsuki, N.; Ikeno, T.; Yamada, T. *Bull. Chem. Soc. Jpn.* ***2001***, *74*, 1333.

[2131] Ali, T.; Chauhan, K.K.; Frost, C.G. *Tetrahedron Lett.* ***1999***, *40*, 5621.

[2132] Huang, Y.; Rawal, V.H.; *J. Am. Chem. Soc.* ***2002***, *124*, 9662; Jørgensen, K.A. *Eur. J. Org. Chem.* ***2004***, 2093.

[2133] Gilchrist, T.L.; Gonsalves, A.M. d'A.R.; Pinho e Melo, T.M.V.D. *Pure Appl. Chem.* ***1996***, *68*, 859; Jayakumar, S.; Ishar, M.P.S.; Mahajan, M.P. *Tetrahedron* ***2002***, *58*, 379.

[2134] Yadav, J.S.; Reddy, B.V.S.; Reddy, J.S.S.; Rao, R.S. *Tetrahedron* ***2003***, *59*, 1599.

[2135] Suga, S.; Nagaki, A.; Tsutsui, Y.; Yoshida, J.-i. *Org. Lett.* ***2003***, *5*, 945.

[2136] Sheu, J.; Smith, M.B.; Matsumoto, K. *Synth. Commun*, ***1993***, *23*, 253.

[2137] Schatz, J.; Sauer, J. *Tetrahedron Lett.* ***1994***, *35*, 4767.

[2138] Degnan, A.P.; Kim, C.S.; Stout, C.W.; Kalivretenos, A.G. *J. Org. Chem.* ***1995***, *60*, 7724.

[2139] For reviews, see Katritzky, A.R.; Dennis, N. *Chem. Rev.* ***1989***, *89*, 827; Schmidt, R.R. *Acc. Chem. Res.* ***1986***, *19*, 250; Boger, D.L. *Chem. Rev.* ***1986***, *86*, 781. See Hayashi, Y.; Nakamura, M.; Nakao, S.; Inoue, T.; Shoji, M. *Angew. Chem. Int. Ed.* ***2002***, *41*, 4079.

[2140] Bach, P.; Bols, M. *Tetrahedron Lett.* ***1999***, *40*, 3461.

[2141] Gorman, D.B.; Tomlinson, I.A. *Chem. Commun.* ***1998***, 25.

[2142] Babu, G.; Perumal, P.T. *Tetrahedron* ***1998***, *54*, 1627.

[2143] Lubineau, A.; Augé, J.; Grand, E.; Lubin, N. *Tetrahedron* ***1994***, *50*, 10265.

[2144] Villacampa, M.; Pérez, J.M.; Avendaño, C.; Menéndez, J.C. *Tetrahedron* ***1994***, *50*, 10047.

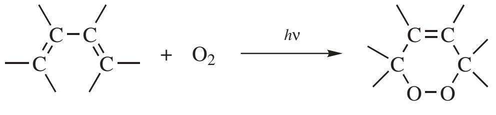
[2145] Pierres, C.; George, P.; van Hijfte, L.; Ducep, J.-B.; Hibert, M.; Mann, A. *Tetrahedron Lett.* ***2003***, *44*, 3645.

Hetero- Diels–Alder reactions that proceed with good to excellent asymmetric induction are well known.[2146] Chiral 1-aza-dienes have been developed as substrates, for example.[2147] Chiral catalysts have been developed.[2148] Conjugated aldehydes react with vinyl ethers, with a chiral chromium catalyst, in an inverse electron demand cycloaddition that give a dihydropyran with good enantioselectivity.[2149] Vinyl sulfilimines have been used in chiral Diels–Alder reactions.[2150]

OS **IV**, 311; **V**, 60, 96; **80**, 133. See also OS **VII**, 326.

15-62 Photooxidation of Dienes (Addition of Oxygen, Oxygen)

[4 + 2] *OC*,*OC*-*cyclo*-Peroxy-1/4/addition



204

Conjugated dienes react with oxygen under the influence of light to give cyclic peroxides **204**.[2151] The reaction has mostly[2152] been applied to cyclic dienes.[2153] Cycloaddition of furan has been reported using singlet oxygen.[2154] The scope extends to certain aromatic compounds such as phenanthrene.[2155] 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. 340).

[2146] Yao, S.; Johannsen, M.; Audrain, H.; Hazell, R.G.; Jørgensen, K.A. *J. Am. Chem. Soc.* ***1998***, *120*, 8599; Pouilhès, A.; Langlois, Y.; Nshimyumkiza, P.; Mbiya, K.; Ghosez, L. *Bull. Soc. Chim. Fr.* ***1993***, *130*, 304.

[2147] Beaudegnies, R.; Ghosez, L. *Tetrahedron Asymmetry* ***1994***, *5*, 557.

[2148] Du, H.; Long, J.; Hu, J.; Li, X.; Ding, K. *Org. Lett.* ***2002***, *4*, 4349; Du, H.; Ding, K. *Org. Lett.* ***2003***, *5*, 1091; Macheño, O.G.; Arrayás, R.G.; Carretero, J.C. *J. Am. Chem. Soc.* ***2004***, *126*, 456.

[2149] Gademann, K.; Chavez, D.E.; Jacobsen, E.N. *Angew. Chem. Int. Ed.* ***2002***, *41*, 3059.

[2150] Ruano, J.L.G.; Clemente, F.R.; Gutiérrez, L.G.; Gordillo, R.; Castro, A.M.M.; Ramos, J.H.R. *J. Org. Chem.* ***2002***, *67*, 2926.

[2151] For reviews, see Clennan, E.L. *Tetrahedron* ***1991***, *47*, 1343; *Adv. Oxygenated Processes* ***1988***, *1*, 85; Wasserman, H.H.; Ives, J.L. *Tetrahedron* ***1981***, *37*, 1825; Denny, R.W.; Nickon, A. *Org. React.* ***1973***, *20*, 133; Adams, W.R. in Augustine, R.L.; Trecker, D.J. *Oxidation*, Vol. 2, Marcel Dekker, NY, ***1971***, pp. 65–112; Gollnick, K. *Adv. Photochem.* ***1968***, *6*, 1; Schönberg, A. *Preparative Organic Photochemistry*, Springer, NY, ***1968***, pp. 382–397; Gollnick, K.; Schenck, G.O., in Hamer, T. *1,4-Cycloaddition Reactions*, Academic Press, NY, ***1967***, pp. 255–344; Arbuzov, Yu.A. *Russ. Chem. Rev.* ***1965***, *34*, 558.

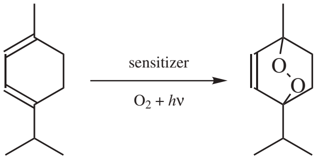
[2152] For many examples with acyclic dienes, see Matsumoto, M.; Dobashi, S.; Kuroda, K.; Kondo, K. *Tetrahedron* ***1985***, *41*, 2147.

[2153] For reviews of cyclic peroxides, see Saito, I.; Nittala, S.S., in Patai, S. *The Chemistry of Peroxides*, Wiley, NY, ***1983***, pp. 311–374; Balci, M. *Chem. Rev.* ***1981***, *81*, 91; Adam, W.; Bloodworth, A.J. *Top. Curr. Chem.* ***1981***, *97*, 121.

[2154] Onitsuka, S.; Nishino, H.; Kurosawa, K. *Tetrahedron* ***2001***, *57*, 6003.

[2155] For reviews, see in Wasserman, H.H.; Murray, R.W. *Singlet Oxygen*; Academic Press, NY, ***1979***, the articles by Wasserman, H.H.; Lipshutz, B.H. pp. 429–509; Saito, I.; Matsuura, T. pp. 511–574; Rigaudy, J. *Pure Appl. Chem.* ***1968***, *16*, 169.

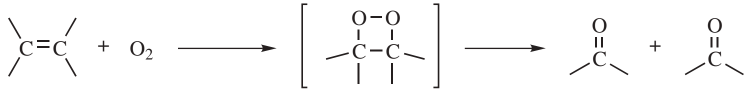
Among these is α-terpinene, which is converted to ascaridole:



As in **14-7**, it is not the ground-state oxygen (the triplet), that reacts, but the excited singlet state,[2156,2157] so the reaction is actually a Diels–Alder reaction (see **15-60**) with singlet oxygen as dienophile:[2158]

Like **15-60**, this reaction is reversible.

We have previously discussed the reaction of singlet oxygen with double-bond compounds to give



205

hydroperoxides (**14-7**), but singlet oxygen can also react with double bonds in another way to give a dioxetane intermediate[2159] (**205**), which usually cleaves to

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[2156] For books on singlet oxygen, see Frimer, A.A. *Singlet O_2*, 4 vols., CRC Press, Boca Raton, FL, ***1985***; Wasserman, H.H.; Murray, R.W. *Singlet Oxygen*, Academic Press, NY, ***1979***. For reviews, see Frimer, A.A. in Patai, S. *The Chemistry of Peroxides*, Wiley, NY, ***1983***, pp. 201–234; Gorman, A.A.; Rodgers, M.A.J. *Chem. Soc. Rev.* ***1981***, *10*, 205; Shinkarenko, N.V.; Aleskovskii, V.B. *Russ. Chem. Rev.* ***1981***, *50*, 220; Shlyapintokh, V.Ya.; Ivanov, V.B. *Russ. Chem. Rev.* ***1976***, *45*, 99; Ohloff, G. *Pure Appl. Chem.* ***1975***, *43*, 481; Kearns, D.R. *Chem. Rev.* ***1971***, *71*, 395; Wayne, R.P. *Adv. Photochem.* ***1969***, *7*, 311.

[2157] For reviews, see Turro, N.J.; Ramamurthy, V., in de Mayo, P. *Rearrangements in Ground and Excited States*, Vol. 3, Academic Press, NY, ***1980***, pp. 1–23; Murray, R.W., in Wasserman, H.H.; Murray, R.W. *Singlet Oxygen*, Academic Press, NY, ***1979***, pp. 59–114. For a general monograph, see Adam, W.; Cilento, G. *Chemical and Biological Generation of Excited States*, Academic Press, NY, ***1982***.

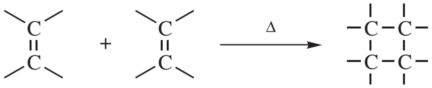
[2158] Corey, E.J.; Taylor, W.C. *J. Am. Chem. Soc.* ***1964***, *86*, 3881; Foote, C.S.; Wexler, S.; Ando, W. *Tetrahedron Lett.* ***1965***, 4111; Monroe, B.M. *J. Am. Chem. Soc.* ***1981***, *103*, 7253. See also, Hathaway, S.J.; Paquette, L.A. *Tetrahedron Lett.* ***1985***, *41*, 2037; O'Shea, K.E.; Foote, C.S. *J. Am. Chem. Soc.* ***1988***, *110*, 7167.

[2159] For reviews, see Adam, W.; Cilento, G. *Angew. Chem. Int. Ed.* ***1983***, *22*, 529; Schaap, A.; Zaklika, K.A. in Wasserman, H.H.; Murray, R.W. *Singlet Oxygen*, Academic Press, NY, ***1979***, pp. 173–242; Bartlett, P.D. *Chem. Soc. Rev.* ***1976***, *5*, 149. For discussions of the mechanisms see Frimer, A.A. *Chem. Rev.* ***1979***, *79*, 359; Clennan, E.L.; Nagraba, K. *J. Am. Chem. Soc.* ***1988***, *110*, 4312.

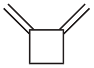
aldehydes or ketones,[2160] but has been isolated.[2161] Both the six-membered cyclic peroxides[2162] and the four-membered **205**[2163] have been formed from oxygenation reactions that do not involve singlet oxygen. If cyclic peroxides, such as **205**, are desired, better reagents[2164] are triphenyl phosphite ozonide $(PhO)_3PO_3$ and triethylsilyl hydrotrioxide ($Et_3SiOOOH$), but yields are not high.[2165]

15-63 [2 + 2]-Cycloadditions

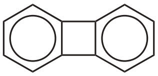
[2 + 2]*cyclo*-Ethylene-1/2/addition



The thermal reaction between two molecules of alkene to give cyclobutane derivatives (a [2 + 2]-cycloaddition) can be carried out where the alkenes are the same or different, but the reaction is not a general one for alkenes.[2166] The cycloaddition can be catalyzed by certain transition-metal complexes.[2167] Dimerization of like alkenes occurs with the following compounds: $F_2C{=}CX_2$ ($X = F$ or Cl) and certain other



206



Biphenylene

[2160] For discussions see Kearns, D.R. *Chem. Rev.* ***1971***, *71*, 395, 422–424; Foote, C.S. *Pure Appl. Chem.* ***1971***, *27*, 635.

[2161] For reviews of 1,2-dioxetanes see Adam, W., in Patai, S. *The Chemistry of Peroxides*, Wiley, NY, ***1983***, pp. 829–920; Bartlett, P.D.; Landis, M.E., in Wasserman, H.H.; Murray, R.W. *Singlet Oxygen*, Academic Press, NY, ***1979***, pp. 243–286; Adam, W. *Adv. Heterocycl. Chem.* ***1977***, *21*, 437. See also, Inoue, Y.; Hakushi, T.; Turro, N.J. *Kokagaku Toronkai Koen Yoshishu* ***1979***, 150 [*C.A. 92*, 214798q]; Adam, W.; Encarnación, L.A.A. *Chem. Ber.* ***1982***, *115*, 2592; Adam, W.; Baader, W.J. *Angew. Chem. Int. Ed.* ***1984***, *23*, 166.

[2162] See Nelson, S.F.; Teasley, M.F.; Kapp, D.L. *J. Am. Chem. Soc.* ***1986***, *108*, 5503.

[2163] For a review, see Nelson, S.F. *Acc. Chem. Res.* ***1987***, *20*, 269.

[2164] For another reagent, see Curci, R.; Lopez, L.; Troisi, L.; Rashid, S.M.K.; Schaap, A.P. *Tetrahedron Lett.* ***1987***, *28*, 5319.

[2165] Posner, G.H.; Weitzberg, M.; Nelson, W.M.; Murr, B.L.; Seliger, H.H. *J. Am. Chem. Soc.* ***1987***, *109*, 278.

[2166] For reviews, see Carruthers, W. *Cycloaddition Reactions in Organic Synthesis*, Pergamon, Elmsford, NY, ***1990***; Reinhoudt, D.N. *Adv. Heterocycl. Chem.* ***1977***, *21*, 253; Roberts, J.D.; Sharts, C.M. *Org. React.* ***1962***, *12*, 1; Gilchrist, T.L.; Storr, R.C. *Organic Reactions and Orbital Symmetry* 2nd ed., Cambridge University Press, Cambridge, ***1979***, pp. 173–212; Beltrame, P., in Bamford, C.H.; Tipper, C.F.H. Ref. 1, Vol. 9, pp. 131–152; Huisgen, R.; Grashey, R.; Sauer, J., in Patai, S. *The Chemistry of Alkenes*, Vol. 1, Wiley, NY, ***1964***, pp. 779–802. For a review of the use of [2 + 2]-cycloadditions in polymerization reactions, see Dilling, W.L. *Chem. Rev.* ***1983***, *83*, 1. For a list of references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 546–647, 1341–1344.

[2167] For an example using $EtAlCl_2$ see Takasu, K.; Ueno, M.; Inanaga, K.; Ihara, M. *J. Org. Chem.* ***2004***, *69*, 517.

fluorinated alkenes (although not $F_2C{=}CH_2$), allenes (to give derivatives of **206**),[2168] benzynes (to give biphenylene derivatives),[2169] activated alkenes (e.g., styrene, acrylonitrile, butadiene), and certain methylenecyclopropanes.[2170] Dimerization of allenes lead to bis(alkylidene) cyclobutanes.[2171] Substituted ketenes can dimerize to give cyclobutenone derivatives, although ketene itself dimerizes in a different manner, to give an unsaturated β-lactone (**16-95**).[2172] Alkenes react with activated alkynes, with a ruthenium catalyst, to give cyclobutenes.[2173]

Intramolecular [2 + 2]-cycloadditions are common in which a diene is converted to a bicyclic compound with a four-membered ring fused to another ring. Heating *N*-vinyl imines, where the vinyl moiety is a silyl enol, gives β-lactams.[2174] Apart from photochemical initiation of such reactions, intramolecular cycloaddition of two conjugated ketone units, in the presence of $PhMeSiH_2$ and catalyzed by cobalt compounds, leads to the bicyclic compound with two ketone substituents.[2175] In a variation of this reaction, a diyne was treated with Ti(O*i*Pr)$_4$/2 *i*-PrMgCl to generate a bicyclic cyclobutene with two vinylidene units.[2176]

Ketenes react with many alkenes to give cyclobutanone derivatives[2177] and intermolecular cycloadditions are well known.[2178] typical reaction is that of dimethylketene and ethene to give 2,2-dimethylcyclobutanone.[2179] Ketenes react with imines via [2 + 2]-cycloaddition to produce β-lactams.[2180] Cycloaddition of an imine with a conjugated ester in the presence of Et_2MeSiH and an iridium

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[2168] For a review, see Fischer, H., in Patai, S. *The Chemistry of Alkenes*, Vol. 1, Wiley, NY, ***1964***, pp. 1064–1067.

[2169] For cycloaddition with a pyridyne, see Mariet, N.; Ibrahim-Ouali, M.; Santelli, M. *Tetrahedron Lett.* ***2002***, *43*, 5789.

[2170] Dolbier, Jr., W.R.; Lomas, D.; Garza, T.; Harmon, C.; Tarrant, P. *Tetrahedron* ***1972***, *28*, 3185.

[2171] Saito, S.; Hirayama, K.; Kabuto, C.; Yamamoto, Y. *J. Am. Chem. Soc.* ***2000***, *122*, 10776.

[2172] Farnum, D.G.; Johnson, J.R.; Hess, R.E.; Marshall, T.B.; Webster, B. *J. Am. Chem. Soc.* ***1965***, *87*, 5191; Dehmlow, E.V.; Pickardt, J.; Slopianka, M.; Fastabend, U.; Drechsler, K.; Soufi, J. *Liebigs Ann. Chem.* ***1987***, 377.

[2173] Jordan, R.W.; Tam, W. *Org. Lett.* ***2000***, *2*, 3031.

[2174] Bandin, E.; Favi, G.; Martelli, G.; Panunzio, M.; Piersanti, G. *Org. Lett.* ***2000***, *2*, 1077.

[2175] Baik, T.-G.; Luis, A.L.; Wang, L.-C.; Krische, M.J. *J. Am. Chem. Soc.* ***2001***, *123*, 6716.

[2176] Delas, C.; Urabe, H.; Sato, F. *Tetrahedron Lett.* ***2001***, *42*, 4147.

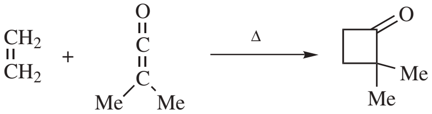
[2177] An example is de Faria, A.R.; Matos, C.R.; Correia, C.R.D. *Tetrahedron Lett.* ***1993***, *34*, 27.

[2178] Krepski, L.R.; Hassner, A. *J. Org. Chem.* ***1978***, *43*, 2879; Bak, D.A.; Brady, W.T. *J. Org. Chem.* ***1979***, *44*, 107; Martin, P.; Greuter, H.; Belluš, D. *Helv. Chim. Acta.*, ***1984***, *64*, 64; Brady, W.T. *Synthesis* ***1971***, 415.

[2179] Sustmann, R.; Ansmann, A.; Vahrenholt, F. *J. Am. Chem. Soc.* ***1972***, *94*, 8099; Desimoni, G.; Tacconi, G.; Barco, A.; Pollini, G.P. *Natural Product Synthesis Through Pericyclic Reactions*, American Chemical Society, Washington, DC, ***1983***, pp. 119–254, 39.

[2180] For reviews of the formation of β-lactams, see Brown, M.J. *Heterocycles* ***1989***, *29*, 2225; Isaacs, N.S. *Chem. Soc. Rev.* ***1976***, *5*, 181; Mukerjee, A.K.; Srivastava, R.C. *Synthesis* ***1973***, 327. For a review of cycloaddition reactions of imines, see Sandhu, J.S.; Sain, B. *Heterocycles* ***1987***, *26*, 777. For a new catalyst, see Wack, H.; France, S.; Hafez, A.M.; Drury, III, W.J.; Weatherwax, A.; Lectka, T. *J. Org. Chem.* ***2004***, *69*, 4531.

catalyst also gives a β-lactam.[2181]



Different alkenes combine as follows:

1. $F_2C{=}CX_2$ ($X = F$ or Cl), especially $F_2C{=}CF_2$, form cyclobutanes with many alkenes. Compounds of this type even react with conjugated dienes to give four-membered rings rather than undergoing normal Diels–Alder reactions.[2182]
2. Allenes[2183] and ketenes[2184] react with activated alkenes and alkynes. Ketenes give 1,2-addition, even with conjugated dienes.[2185] Ketenes also add to unactivated alkenes if sufficiently long reaction times are used.[2186] Allenes and ketenes also add to each other.[2187]
3. Enamines[2188] form four-membered rings with Michael-type alkenes[2189] and ketenes.[2190] In both cases, only enamines from aldehydes give stable

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[2181] Townes, J.A.; Evans, M.A.; Queffelec, J.; Taylor, S.J.; Morken, J.P. *Org. Lett.* ***2002***, *4*, 2537.

[2182] Bartlett, P.D.; Montgomery, L.K.; Seidel, B. *J. Am. Chem. Soc.* ***1964***, *86*, 616; De Cock, C.; Piettre. S.; Lahousse, F.; Janousek, Z.; Merényi, R.; Viehe, H.G. *Tetrahedron* ***1985***, *41*, 4183.

[2183] For reviews of [2 + 2]-cycloadditions of allenes, see Schuster, H.F.; Coppola, G.M. *Allenes in Organic Synthesis*, Wiley, NY, ***1984***, pp. 286–317; Hopf, H., in Landor, S.R.I. *The Chemistry of Allenes*, Vol. 2, Academic Press, NY, ***1982***, pp. 525–562; Ghosez, L.; O'Donnell, M.J., in Marchand, A.P.; Lehr, R.E. *Pericyclic Reactions*, Vol. 2, Academic Press, NY, ***1977***, pp. 79–140; Baldwin, J.E.; Fleming, R.H. *Fortschr. Chem. Forsch.* ***1970***, *15*, 281.

[2184] For reviews of cycloadditions of ketenes, see Ghosez, L.; O'Donnell, M.J. in Marchand, A.P.; Lehr, R.E. *Pericyclic Reactions*, Vol. 2, Academic Press, NY, ***1977***; Brady, W.T. *Synthesis* ***1971***, 415; Luknitskii, F.I.; Vovsi, B.A. *Russ. Chem. Rev.* ***1969***, *38*, 487; Ulrich, H. *Cycloaddition Reactions of Heterocumulenes*, Academic Press, NY, ***1967***, pp. 38–121; Holder, R.W. *J. Chem. Educ.* ***1976***, *53*, 81. For a review of intramolecular cycloadditions of ketenes to alkenes, see Snider, B.B. *Chem. Rev.* ***1988***, *88*, 793.

[2185] See, for example, Martin, J.C.; Gott, P.G.; Goodlett, V.W.; Hasek, R.H. *J. Org. Chem.* ***1965***, *30*, 4175; Brady, W.T.; O'Neal, H.R. *J. Org. Chem.* ***1967***, *32*, 2704; Huisgen, R.; Feiler, L.A.; Otto, P. *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, P.K.; Balls, D.M.; Brown, D.J. *J. Org. Chem.* ***1968***, *33*, 2211; Corey, E.J.; Ravindranathan, T.; Terashima, S. *J. Am. Chem. Soc.* ***1971***, *93*, 4326. For a review of ketene equivalents, see Ranganathan, S.; Ranganathan, D.; Mehrotra, A.K. *Synthesis* ***1977***, 289.

[2186] Huisgen, R.; Feiler, L.A. *Chem. Ber.* ***1969***, *102*, 3391; Bak, D.A.; Brady, W.T. *J. Org. Chem.* ***1979***, *44*, 107.

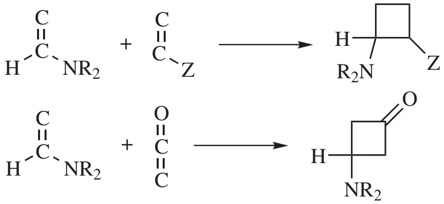
[2187] Bampfield, H.A.; Brook, P.R.; McDonald, W.S. *J. Chem. Soc., Chem. Commun.* ***1975***, 132; Gras, J.; Bertrand, M. *Nouv. J. Chim.* ***1981***, *5*, 521.

[2188] For a review of cycloaddition reactions of enamines, see Cook, A.G., in Cook, A.G. *Enamines*, 2nd ed.; Marcel Dekker, NY, ***1988***, pp. 347–440.

[2189] Brannock, K.C.; Bell, A.; Goodlett, V.W.; Thweatt, J.G. *J. Org. Chem.* ***1964***, *29*, 813.

[2190] Berchtold, G.A.; Harvey, G.R.; Wilson, G.E. *J. Org. Chem.* ***1961***, *26*, 4776; Opitz, G.; Kleeman, M. *Liebigs Ann. Chem.* ***1963***, *665*, 114; Hasek, R.H.; Gott, P.G.; Martin, J.C. *J. Org. Chem.* ***1966***, *31*, 1931.

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. Alkenes with electron-withdrawing groups may form cyclobutanes with alkenes containing electron-donating groups. The enamine reactions, mentioned above, are examples of this, but it has also been accomplished with tetracyanoethylene and similar molecules, which give substituted cyclobutanes when treated with alkenes of the form C=C—A, where A may be OR,[2191] SR (enol and thioenol ethers),[2192] cyclopropyl,[2193] or certain aryl groups.[2194]

Solvents are not necessary for [2 + 2]-cycloadditions. They are usually carried out at 100–225°C under pressure, although the reactions in Group 4 (IVB) occur under milder conditions.

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 transition-metal compounds.[2195] Photochemical[2196] $[_{\pi}2 + _{s}2]$-cycloadditions have also been reported. Among the catalysts used are Lewis acids[2197] and phosphine–nickel complexes.[2198] Certain of the reverse cyclobutane ring openings can also be catalytically induced (**18-38**). The role of the catalyst is not certain and may be different in each case. One possibility is that the

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[2191] For a review with ketene acetals $R_2C{=}C(OR')_2$, see Scheeren, J.W. *Recl. Trav. Chim. Pays-Bas* ***1986***, *105*, 71–84.

[2192] Williams, J.K., Wiley, D.W.; McKusick, B.C. *J. Am. Chem. Soc.* ***1962***, *84*, 2210.

[2193] Nishida, S.; Moritani, I.; Teraji, T. *J. Org. Chem.* ***1973***, *38*, 1878.

[2194] Nagata, J.; Shirota, Y.; Nogami, T.; Mikawa, H. *Chem. Lett.* ***1973***, 1087; Shirota, Y.; Yoshida, K.; Nogami, T.; Mikawa, H. *Chem. Lett.* ***1973***, 1271.

[2195] For reviews, see Dzhemilev, U.M.; Khusnutdinov, R.I.; Tolstikov, G.A. *Russ. Chem. Rev.* ***1987***, *56*, 36; Kricka, L.J.; Ledwith, A. *Synthesis* ***1974***, 539.

[2196] Freeman, P.K.; Balls, D.M. *J. Org. Chem.* ***1967***, *32*, 2354; Wiskott, E.; Schleyer, P.v.R. *Angew. Chem. Int. Ed.* ***1967***, *6*, 694; Prinzbach, H.; Eberbach, W. *Chem. Ber.* ***1968***, *101*, 4083; Prinzbach, H.; Sedelmeier, G.; Martin, H. *Angew. Chem. Int. Ed.* ***1977***, *16*, 103.

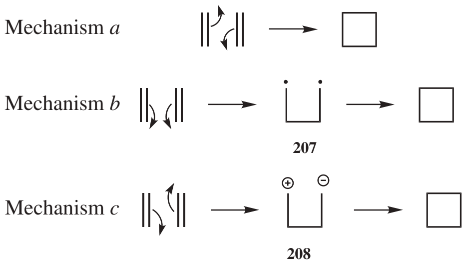
[2197] Yamazaki, S.; Fujitsuka, H.; Yamabe, S.; Tamura, H. *J. Org. Chem.* ***1992***, *57*, 5610. West, R.; Kwitowski, P.T. *J. Am. Chem. Soc.* ***1968***, *90*, 4697; Lukas, J.H.; Baardman, F.; Kouwenhoven, A.P. *Angew. Chem. Int. Ed.* ***1976***, *15*, 369.

[2198] See, for example, Hoover, F.W.; Lindsey Jr., R.V. *J. Org. Chem.* ***1969***, *34*, 3051; Noyori, R.; Ishigami, T.; Hayashi, N.; Takaya, H. *J. Am. Chem. Soc.* ***1973***, *95*, 1674; Yoshikawa, S.; Aoki, K.; Kiji, J.; Furukawa, J. *Tetrahedron* ***1974***, *30*, 405.

presence of the catalyst causes a forbidden reaction to become allowed, through coordination of the catalyst to the π or s bonds of the substrate.[2199] In such a case, the reaction would of course be a concerted $[2_s + 2_s]$-process. [2200] However, the available evidence is more consistent with nonconcerted mechanisms involving metal–carbon σ-bonded intermediates, at least in most cases.[2201] For example, such an intermediate was isolated in the dimerization of norbornadiene, catalyzed by iridium complexes.[2202]

Thermal cycloadditions leading to four-membered rings can also take place between a cyclopropane ring and an alkene or alkyne[2203] bearing electron-withdrawing groups.[2204] These reactions are $[{}_\pi 2 + {}_s 2]$-cycloadditions. Ordinary cyclopropanes do not undergo the reaction, but it has been accomplished with strained systems such as bicyclo[1.1.0]butanes[2205] and bicyclo[2.1.0]pentanes. For example, bicyclo[2.1.0]pentane reacts with maleonitrile (or fumaronitrile) to give all three isomers of 2,3-dicyanonorbornane, as well as four other products.[2206] The lack of stereospecificity and the negligible effect of solvent on the rate indicate a diradical mechanism.

The reaction is similar to the Diels–Alder (in action, not in scope), and if dienes are involved, the latter reaction may compete, although most alkenes react with a diene either entirely by 1,2 or entirely by 1,4 addition. Three mechanisms can be proposed[2207] analogous to those proposed for the Diels–Alder reaction. Mechanism *a* is a



[2199] For discussions, see Labunskaya, V.I.; Shebaldova, A.D.; Khidekel, M.L. *Russ. Chem. Rev.* ***1974***, *43*, 1; Mango, F.D. *Top. Curr. Chem.* ***1974***, *45*, 39; *Tetrahedron Lett.* ***1973***, 1509; *Intra-Sci. Chem. Rep.* ***1972***, *6 (3)*, 171; *CHEMTECH* ***1971***, *1*, 758; *Adv. Catal.* ***1969***, *20*, 291; Mango, F.D.; Schachtschneider, J.H. *J. Am. Chem. Soc.* ***1971***, *93*, 1123; ***1969***, *91*, 2484; van der Lugt, W.T.A.M. *Tetrahedron Lett.* ***1970***, 2281; Wristers, J.; Brener, L.; Pettit, R. *J. Am. Chem. Soc.* ***1970***, *92*, 7499.

[2200] See Bachrach, S.M.; Gilbert, J.C. *J. Org. Chem.* ***2004***, *69*, 6357; Ozkan, I.; Kinal, A. *J. Org. Chem.* ***2004***, *69*, 5390.

[2201] See, for example, Cassar, L.; Halpern, J. *Chem. Commun.* ***1970***, 1082; Doyle, M.J.; McMeeking, J.; Binger, P. *J. Chem. Soc., Chem. Commun.* ***1976***, 376; Grubbs, R.H.; Miyashita, A.; Liu, M.M.; Burk, P.L. *J. Am. Chem. Soc.* ***1977***, *99*, 3863.

[2202] Fraser, A.R.; Bird, P.H.; Bezman, S.A.; Shapley, J.R.; White, R.; Osborn, J.A. *J. Am. Chem. Soc.* ***1973***, *95*, 597.

[2203] Gassman, P.G.; Mansfield, K.T. *J. Am. Chem. Soc.* ***1968***, *90*, 1517, 1524.

[2204] For a review, see Gassman, P.G. *Acc. Chem. Res.* ***1971***, *4*, 128.

[2205] Cairncross, A.; Blanchard, E.P. *J. Am. Chem. Soc.* ***1966***, *88*, 496.

[2206] Gassman, P.G.; Mansfield, K.T.; Murphy, T.J. *J. Am. Chem. Soc.* ***1969***, *91*, 1684.

[2207] For a review, see Bartlett, P.D. *Q. Rev. Chem. Soc.* ***1970***, *24*, 473.

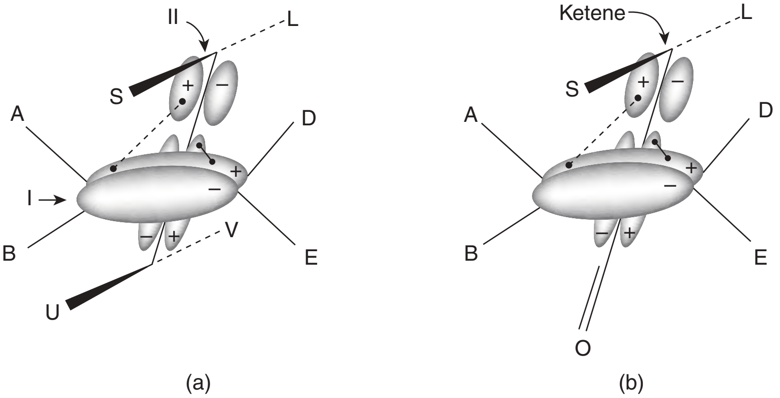


Fig. 15.12. Orbital overlap in $[_{\pi}2_s + {_{\pi}2_s}]$-cycloaddition between (*a*) two alkene molecules and (*b*) a ketene and an alkene. S and L stand for small and large

concerted pericyclic process, and mechanisms *b* and *c* are two-step reactions involving, respectively, a diradical (**207**) and a diion (**208**) intermediate. As in **15-60**, 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, although if the second step of these processes takes place very rapidly, before **207** or **208** 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 [4 + 2]-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. 1212), and there is much evidence that ketenes and certain other linear molecules[2208] 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 (Fig. 15.12*a*) that the + lobe of the HOMO of one molecule (I) overlaps with both + lobes of the LUMO of the other (II), even although 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 alkenes,[2209] but if

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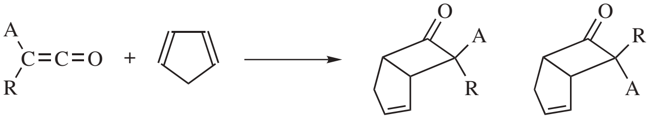
[2208] There is evidence that a cyclopentyne (generated *in situ*) also adds to a double bond by an antarafacial process: Gilbert, J.C.; Baze, M.E. *J. Am. Chem. Soc.* ***1984***, *106*, 1885.

[2209] See, for example, Padwa, A.; Koehn, W.; Masaracchia, J.; Osborn, C.L.; Trecker, D.J. *J. Am. Chem. Soc.* ***1971***, *93*, 3633; Bartlett, P.D.; Cohen, G.M.; Elliott, S.P.; Hummel, K.; Minns, R.A.; Sharts, C.M.; Fukunaga, J.Y. *J. Am. Chem. Soc.* ***1972***, *94*, 2899.

molecule II is a ketene (Fig. 15.12*b*), the group marked U is not present and the $[_{\pi}2_s + _{\pi}2_a]$-reaction can take place. Among the evidence[2210] for this mechanism[2211] is the following: (*1*) The reactions are stereospecific.[2212] (*2*) The isomer that forms is the *more-hindered one*. Thus methylketene plus cyclopentadiene gave only the endo product (**209**, A = H, R = CH_3).[2213] Even more remarkably, when



A = H or halogen

endo **209** endo **210**

haloalkyl ketenes RXC=C=O were treated with cyclopentadiene, the endo/exo ratio of the product (**209**, **210**, A = halogen) actually *increased* substantially when R was changed from Me to *i*-Pr to *t*-Bu![2214] One would expect preferential formation of the exo products (**210**) from $[_{\pi}2_s + _{\pi}2_s]$-cycloadditions where the molecules approach each other face-to-face, but a $[_{\pi}2_s + _{\pi}2_a]$ process leads to endo products because the ketene molecule (which for steric reasons would approach with its smaller group directed toward the alkene) must twist as shown in Fig. 15.13 (L = larger; S = smaller group) in order for the + lobes to interact and this swings the larger group into the endo position.[2215] 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

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[2210] For other evidence, see Baldwin, J.E.; Kapecki, J.A. *J. Am. Chem. Soc.* ***1970***, *92*, 4874; Brook, P.R.; Griffiths, J.G. *Chem. Commun.* ***1970***, 1344; Egger, K.W. *Int. J. Chem. Kinet.* ***1973***, *5*, 285; Moon, S.; Kolesar, T.F. *J. Org. Chem.* ***1974***, *39*, 995; Isaacs, N.S.; Hatcher, B.G. *J. Chem. Soc., Chem. Commun.* ***1974***, 593; Hassner, A.; Cory, R.M.; Sartoris, N. *J. Am. Chem. Soc.* ***1976***, *98*, 7698; Gheorghiu, M.D.; Pârvulescu, L.; Drâghici, C.; Elian, M. *Tetrahedron* ***1981***, *37 Suppl.*, 143. See, however, Holder, R.W.; Graf, N.A.; Duesler, E.; Moss, J.C. *J. Am. Chem. Soc.* ***1983***, *105*, 2929.

[2211] On the other hand, molecular-orbital calculations predict that the cycloaddition of ketenes to alkenes does not take place by a $[_{\pi}2_s + _{\pi}2_a]$ mechanism: Wang, X.; Houk, K.N. *J. Am. Chem. Soc.* ***1990***, *112*, 1754; Bernardi, F.; Bottoni, A.; Robb, M.A.; Venturini, A. *J. Am. Chem. Soc.* ***1990***, *112*, 2106; Valentí, E.; Pericàs, M.A.; Moyano, A. *J. Org. Chem.* ***1990***, *55*, 3582.

[2212] Huisgen, R.; Feiler, L.A.; Binsch, G. *Angew. Chem. Int. Ed.* ***1964***, *3*, 753; *Chem. Ber.* ***1969***, *102*, 3460; Martin, J.C.; Goodlett, V.W.; Burpitt, R.D. *J. Org. Chem.* ***1965***, *30*, 4309; Montaigne, R.; Ghosez, L. *Angew. Chem. Int. Ed.* ***1968***, *7*, 221 Bertrand, M.; Gras, J.L.; Goré, J. *Tetrahedron* ***1975***, *31*, 857; Marchand-Brynaert, J.; Ghosez, L. *J. Am. Chem. Soc.* ***1972***, *94*, 2870; Huisgen, R.; Mayr, H. *Tetrahedron Lett.* ***1975***, 2965, 2969.

[2213] Brady, W.T.; Hoff, E.F.; Roe, Jr., R.; Parry III, F.H. *J. Am. Chem. Soc.* ***1969***, *91*, 5679; Rey, M.; Roberts, S.; Dieffenbacher, A.; Dreiding, A.S. *Helv. Chim. Acta* ***1970***, *53*, 417. See also, Brady, W.T.; Parry III, F.H.; Stockton, J.D. *J. Org. Chem.* ***1971***, *36*, 1486; DoMinh, T.; Strausz, O.P. *J. Am. Chem. Soc.* ***1970***, *92*, 1766; Isaacs, N.S.; Stanbury, P. *Chem. Commun.* ***1970***, 1061; Brook, P.R.; Harrison, J.M.; Duke, A.J. *Chem. Commun.* ***1970***, 589; Dehmlow, E.V. *Tetrahedron Lett.* ***1973***, 2573; Rey, M.; Roberts, S.M.; Dreiding, A.S.; Roussel, A.; Vanlierde, H.; Toppet, S.; Ghosez, L. *Helv. Chim. Acta* ***1982***, *65*, 703.

[2214] Brady, W.T.; Roe Jr., R. *J. Am. Chem. Soc.* ***1970***, *92*, 4618.

[2215] Brook, P.R.; Harrison, J.M.; Duke, A.J. *Chem. Commun.* ***1970***, 589

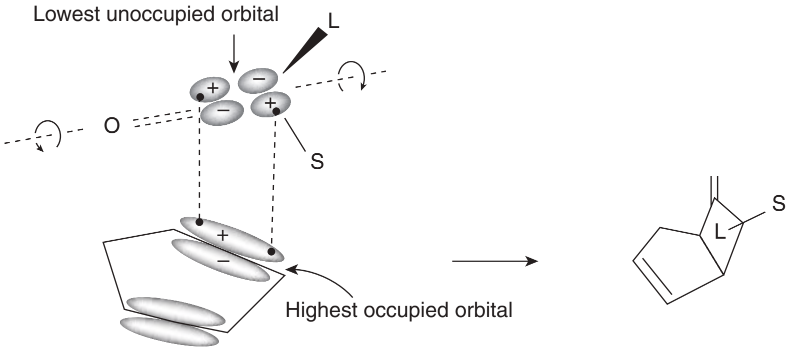

Fig. 15.13. Orbital overlap in the reaction of a ketene with cyclopentadiene. S and L stand for small and large.

considerations of steric hindrance (we may call them *masochistic steric effects*), but they are just what is predicted for a $[_{\pi}2_s + {}_{\pi}2_a]$-reaction. (*3*) There is only moderate polar solvent acceleration.[2216] (*4*) The rate of the reaction is not very sensitive to the presence of electron-withdrawing or electron-donating substituents.[2217] Because cycloadditions involving allenes are often stereospecific, it has been suggested that these also take place by the $[_{\pi}2_s + {}_{\pi}2_a]$ mechanism,[2218] but the evidence in these cases is more consistent with the diradical mechanism *b*.[2219]

The diradical mechanism *b* is most prominent in the reactions involving fluorinated alkenes.[2220] These reactions are generally not stereospecific[2221] 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 **211**, not **212**. If one pair of electrons moved before the other, the positive end of one molecule would be expected to attack the

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[2216] Brady, W.T.; O'Neal, H.R. *J. Org. Chem.* ***1967***, *32*, 612; Huisgen, R.; Feiler, L.A.; Otto, P. *Tetrahedron Lett.* ***1968***, 4485, *Chem. Ber.* ***1969***, *102*, 3444; Sterk, H. *Z. NaturForsch. Teil B* ***1972***, *27*, 143.

[2217] Baldwin, J.E.; Kapecki, J.A. *J. Am. Chem. Soc.* ***1970***, *92*, 4868; Isaacs, N.S.; Stanbury, P. *J. Chem. Soc. Perkin Trans. 2*, ***1973***, 166.

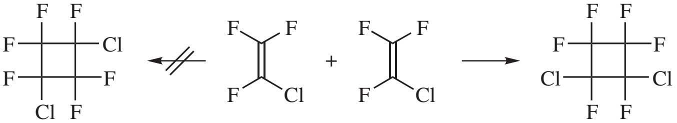
[2218] For example, see Kiefer, E.F.; Okamura, M.Y. *J. Am. Chem. Soc.* ***1968***, *90*, 4187; Baldwin, J.E.; Roy, U.V. *Chem. Commun.* ***1969***, 1225; Moore, W.R.; Bach, R.D.; Ozretich, T.M. *J. Am. Chem. Soc.* ***1969***, *91*, 5918.

[2219] Muscio Jr., O.J.; Jacobs, T.L. *Tetrahedron Lett.* ***1969***, 2867; Taylor, D.R.; Warburton, M.R.; Wright, D.B. *J. Chem. Soc. C* ***1971***, 385; Dai, S.; Dolbier Jr., W.R. *J. Am. Chem. Soc.* ***1972***, *94*, 3946; Duncan, W.G.; Weyler Jr., W.; Moore, H.W. *Tetrahedron Lett.* ***1973***, 4391; Grimme, W.; Rother, H. *Angew. Chem. Int. Ed.* ***1973***, *12*, 505; Levek, T.J.; Kiefer, E.F. *J. Am. Chem. Soc.* ***1976***, *98*, 1875; Pasto, D.J.; Yang, S.H. *J. Org. Chem.* ***1986***, *51*, 1676; Dolbier, D.W.; Seabury, M. *Tetrahedron Lett.* ***1987***, *28*, 1491; *J. Am. Chem. Soc.* ***1987***, *109*, 4393; Dolbier Jr., W.R.; Weaver, S.L. *J. Org. Chem.* ***1990***, *55*, 711; Becker, D.; Denekamp, C.; Haddad, N. *Tetrahedron Lett.* ***1992***, *33*, 827.

[2220] It has been argued that the mechanism here is not the diradical mechanism, but the $[_{\pi}2_s + {}_{\pi}2_a]$ mechanism: Roberts, D.W. *Tetrahedron* ***1985***, *41*, 5529.

[2221] Bartlett, P.D.; Hummel, K.; Elliott, S.P.; Minns, R.A. *J. Am. Chem. Soc.* ***1972***, *94*, 2898.

negative end of the other.[2222]



212 **211**

The diion mechanism[2223] *c* has been reported for at least some of the reactions[2224] in categories 3 and 4,[2225] as well as some ketene dimerizations.[2226] 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.[2227] Some of these reactions are nonstereospecific, but others are stereospecific.[2228] 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 alkene 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 **207** or **208** help to stabilize a diradical, while donors, such as oxygen and nitrogen, favor a diion (they stabilize the positively charged end).[2229] A table on p. 451 of Ref. 2230 shows which mechanism is more likely for [2 + 2]-cycloadditions of various pairs of alkenes.

Thermal cleavage of cyclobutanes[2230] to give two alkene molecules (*cycloreversion*,[2231] the reverse of [2 + 2]-cycloaddition) operates by the diradical mechanism,

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[2222] For additional evidence based on radical stabilities, see Silversmith, E.F.; Kitahara, Y.; Caserio, M.C.; Roberts, J.D. *J. Am. Chem. Soc.* ***1958***, *80*, 5840; Bartlett, P.D.; Montgomery, L.K.; Seidel, B. *J. Am. Chem. Soc.* ***1964***, *86*, 616; De Cock, C.; Piettre. S.; Lahousse, F.; Janousek, Z.; Merényi, R.; Viehe, H.G. *Tetrahedron* ***1985***, *41*, 4183; Doering, W. von E.; Guyton, C.A. *J. Am. Chem. Soc.* ***1978***, *100*, 3229.

[2223] For reviews of this mechanism, see Huisgen, R. *Acc. Chem. Res.* ***1977***, *10*, 117, 199; Huisgen, R.; Schug, R.; Steiner, G. *Bull. Soc. Chim. Fr.* ***1976***, 1813.

[2224] For a review of cycloadditions with polar intermediates, see Gompper, R. *Angew. Chem. Int. Ed.* ***1969***, *8*, 312.

[2225] The reactions of ketenes with enamines are apparently not concerted, but take place by the diionic mechanism: Otto, P.; Feiler, L.A.; Huisgen, R. *Angew. Chem. Int. Ed.* ***1968***, *7*, 737.

[2226] See Moore, H.W.; Wilbur, D.S. *J. Am. Chem. Soc.* ***1978***, *100*, 6523.

[2227] Proskow, S.; Simmons, H.E.; Cairns, T.L. *J. Am. Chem. Soc.* ***1966***, *88*, 5254. See also, Huisgen, R. *Pure Appl. Chem.* ***1980***, *52*, 2283.

[2228] Proskow, S.; Simmons, H.E.; Cairns, T.L. *J. Am. Chem. Soc.* ***1966***, *88*, 5254; Huisgen, R.; Steiner, G. *J. Am. Chem. Soc.* ***1973***, *95*, 5054, 5055.

[2229] Hall, Jr., H.K. *Angew. Chem. Int. Ed.* ***1983***, *22*, 440.

[2230] See Frey, H.M. *Adv. Phys. Org. Chem.* ***1966***, *4*, 147, see pp. 170–175, 180–183.

[2231] For reviews of [2 + 2]-cycloreversions, see Schaumann, E.; Ketcham, R. *Angew. Chem. Int. Ed.* ***1982***, *21*, 225; Brown, R.F.C. *Pyrolytic Methods in Organic Chemistry*, Academic Press, NY, **1980**, pp. 247–259. See also, Reddy, G.D.; Wiest, O.; Hudlický, T.; Schapiro, V.; Gonzalez, D. *J. Org. Chem.* ***1999***, *64*, 2860.

and the [$_{\sigma}2_{s} + _{\sigma}2_{a}$] pathway has not been found[2232] (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. 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 **15-65**)[2233] or in the presence of a suitable coordination compound, so that the cyclobutadiene is produced in the form of a complex (p. 76).[2234]

Although thermal [2 + 2]-cycloaddition reactions are essentially limited to the cases described above, many (although by no means all) double-bond compounds undergo such reactions *when photochemically excited* (either directly or by a photosensitizer, see p. 340), even if they are not in the above categories.[2235] Simple alkenes absorb in the far UV (p. 332), which is difficult to reach experimentally, although this problem can sometimes be overcome by the use of suitable photosensitizers. The reaction has been applied to simple alkenes[2236] (especially to strained compounds, such as cyclopropenes and cyclobutenes), but more often the double-bond compounds involved are conjugated dienes,[2237] α,β-unsaturated ketones,[2238]

[2232] See, for example, Cocks, A.T.; Frey, H.M.; Stevens, I.D.R. *Chem. Commun.* ***1969***, 458; Srinivasan, R.; Hsu, J.N.C. *J. Chem. Soc., Chem. Commun.* ***1972***, 1213; Paquette, L.A.; Carmody, M.J. *J. Am. Chem. Soc.* ***1976***, *98*, 8175. See however Cant, P.A.E.; Coxon, J.M.; Hartshorn, M.P. *Aust. J. Chem.* ***1975***, *28*, 391; Doering, W. von E.; Roth, W.R.; Breuckmann, R.; Figge, L.; Lennartz, H.; Fessner, W.; Prinzbach, H. *Chem. Ber.* ***1988***, *121*, 1.

[2233] For a review of these cases, and of cycloadditions of triple to double bonds, see Fuks, R.; Viehe, H.G., in Viehe, H.G. *Acetylenes*, Marcel Dekker, NY, ***1969***, pp. 435–442.

[2234] D'Angelo, J.; Ficini, J.; Martinon, S.; Riche, C.; Sevin, A. *J. Organomet. Chem.* ***1979***, *177*, 265. For a review, see Hogeveen, H.; Kok, D.M., in Patai, S.; Rappoport, Z. *The Chemistry of Functional Groups, Supplement C*, pt. 2, Wiley, NY, ***1983***, pp. 981–1013.

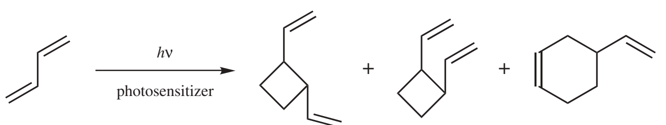
[2235] For reviews, see Demuth, M.; Mikhail, G. *Synthesis* ***1989***, 145; Ninomiya, I.; Naito, T. *Photochemical Synthesis*, Academic Press, NY, ***1989***, pp. 58–109; Ramamurthy, V.; Venkatesan, K. *Chem. Rev.* ***1987***, *87*, 433; Lewis, F.D. *Adv. Photochem.* ***1986***, *13*, 165; Wender, P.A., in Coyle, J.D. *Photochemistry in Organic Synthesis*, Royal Society of Chemistry, London, ***1986***, pp. 163–188; Schreiber, S.L. *Science*, ***1985***, *227*, 857; Neckers, D.C.; Tinnemans, A.H.A., in Horspool, W.M. *Synthetic Organic Photochemistry*, Plenum, NY, ***1984***, pp. 285–311; Baldwin, S.W. *Org. Photochem.* ***1981***, *5*, 123; Turro, N.J. *Modern Molecular Photochemistry*, W.A. Benjamin, NY, ***1978***, pp. 417–425, 458–465; Kricka, L.J.; Ledwith, A. *Synthesis* ***1974***, 539; Herndon, W.C. *Top. Curr. Chem.* ***1974***, *46*, 141; Sammes, P.G. *Q. Rev. Chem. Soc.* ***1970***, *24*, 37, 46–55; Crowley, K.J.; Mazzocchi, P.H., in Zabicky, J. *The Chemistry of Alkenes*, Vol. 2, Wiley, NY, ***1970***, 297–316; Turro, N.J.; Dalton, J.C.; Weiss, D.S. *Org. Photochem.* ***1969***, *2*, 1; Trecker, D.J. *Org. Photochem.* ***1969***, *2*, 63; Scharf, H. *Fortschr. Chem. Forsch.* ***1969***, *11*, 216; Steinmetz, R. *Fortschr. Chem. Forsch.* ***1967***, *7*, 445; Fonken, G.J. *Org. Photochem.* ***1967***, *1*, 197; Chapman, O.L.; Lenz, G. *Org. Photochem.* ***1967***, *1*, 283; Schönberg, A. *Preparative Organic Photochemistry*, Springer, NY, ***1968***, pp. 70–96, 109–117; Warrener, R.N.; Bremner, J.B. *Rev. Pure Appl. Chem.* ***1966***, *16*, 117, 122–128.

[2236] For examples of nonphotosensitized dimerization of simple alkenes, see Arnold, D.R.; Abraitys, V.Y. *Chem. Commun.* ***1967***, 1053; Yamazaki, H.; Cvetanović, R.J. *J. Am. Chem. Soc.* ***1969***, *91*, 520.

[2237] For a review, see Dilling, W.L. *Chem. Rev.* ***1969***, *69*, 845.

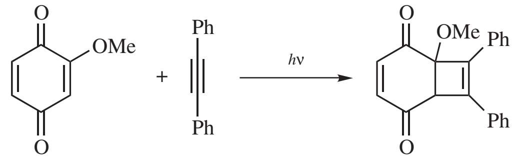
[2238] For reviews of various aspects of this subject, see Cossy, J.; Carrupt, P.; Vogel, P., in Patai, S. *Supplement A: The Chemistry of Double-Bonded Functional Groups*, Vol. 2, pt. 2, Wiley, NY, ***1989***, pp. 1369–1565; Kemernitskii, A.V.; Ignatov, V.N.; Levina, I.S. *Russ. Chem. Rev.* ***1988***, *57*, 270; Weedon, A.C., in Horspool, W.M. *Synthetic Organic Photochemistry*, Plenum, NY, ***1984***, pp. 61–143; Lenz, G.R. *Rev. Chem. Intermed.* ***1981***, *4*, 369; Margaretha, P. *Chimia*, ***1975***, *29*, 203; Bauslaugh, P.G. *Synthesis* ***1970***, 287; Eaton, P.E. *Acc. Chem. Res.* ***1968***, *1*, 50; Schuster, D.I.; Lem, G.; Kaprinidis, N.A. *Chem. Rev.* ***1993***, *93*, 3; Erickson, J.A.; Kahn, S.D. *Tetrahedron* ***1993***, *49*, 9699.

acids, or acid derivatives, or quinones, since these compounds, because they are conjugated, absorb at longer wavelengths (p. 332). Both dimerizations and mixed additions are common, some examples being (see also, the example on p. 347):



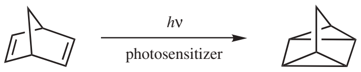
Diels–Alder product

Ref. [2239]



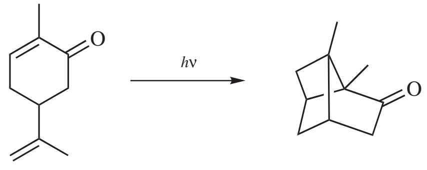
Ref. [2240]

Photochemical [2 + 2]-cycloadditions can also take place intramolecularly if a molecule has two double bonds that are properly oriented.[2241] The cyclization of the quinone dimer shown above is one example. Other examples are



Quadricyclane

Ref. [2242]



Carvone

Carvonecamphor

Ref. [2243]

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

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[2239] Liu, R.S.H.; Turro, N.J.; Hammond, G.S. *J. Am. Chem. Soc.* ***1965***, *87*, 3406; Cundall, R.B.; Griffiths, P.A. *Trans. Faraday Soc.* ***1965***, *61*, 1968; DeBoer, C.D.; Turro, N.J.; Hammond, G.S. *Org. Synth.* ***V***, 528.

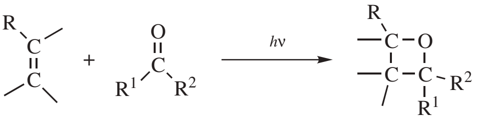
[2240] Pappas, S.P.; Pappas, B.C. *Tetrahedron Lett.* ***1967***, 1597.

[2241] For reviews, see Becker, D.; Haddad, N. *Org. Photochem.* ***1989***, *10*, 1–162; Crimmins, M.T. *Chem. Rev.* ***1988***, *88*, 1453; Oppolzer, W. *Acc. Chem. Res.* ***1982***, *15*, 135; Prinzbach, H. *Pure Appl. Chem.* ***1968***, *16*, 17; Dilling, W.L. *Chem. Rev.* ***1966***, *66*, 373.

[2242] Hammond, G.S.; Turro, N.J.; Fischer, A. *J. Am. Chem. Soc.* ***1961***, *83*, 4674; Dauben, W.G.; Cargill, R.L. *Tetrahedron* ***1961***, *15*, 197. See also, Cristol, S.J.; Snell, R.L. *J. Am. Chem. Soc.* ***1958***, *80*, 1950.

[2243] Ciamician, G.; Silber, P. *Ber.* ***1908***, *41*, 1928; Büchi, G.; Goldman, I.M. *J. Am. Chem. Soc.* ***1957***, *79*, 4741.

obtained instead of the desired product.



213

The photochemical cycloaddition of a carbonyl, generally from an aldehyde or ketone, and an alkene is called the *Paternò–Büchi reaction.*[2244] This $[2+2]$-cycloaddition gives an oxetane (**213**) and the reaction is believed to proceed via a diradical intermediate. Silyl enol ethers react with aldehydes under nonphotochemical conditions using $ZnCl_2$ at 25°C or $SnCl_4$ at $-78°C$.[2245]

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.[2246] The nonphotosensitized dimerizations of *cis*- and *trans*-2-butene are stereospecific,[2247] 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.[2248] In one intramolecular case, the intermediate diradical has been trapped.[2249] 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,[2250] the initially formed diradical must be a triplet; that is, 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

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[2244] Paternò, E.; Chieffi, C. *Gazz. Chim. Ital.* ***1909***, *39*, 341; Büchi, G.; Inman, C.G.; Lipinsky, E.S. *J. Am. Chem. Soc.* ***1954***, *76*, 4327. See García-Expósito, E.; Bearpark, M.J.; Ortuño, R.M.; Robb, M.A.; Branchadell, V. *J. Org. Chem.* ***2002***, *67*, 6070.

[2245] Wang, Y.; Zhao, C.; Romo, D. *Org. Lett.* ***1999***, *1*, 1197.

[2246] We have previously seen (p. $$$) that reactions between two excited molecules are extremely rare.

[2247] Yamazaki, H.; Cvetanović, R.J. *J. Am. Chem. Soc.* ***1969***, *91*, 520; Yamazaki, H.; Cvetanović, R.J.; Irwin, R.S. *J. Am. Chem. Soc.* ***1976***, *98*, 2198. For other likely examples, see Lewis, F.D.; Hoyle, C.E.; Johnson, D.E. *J. Am. Chem. Soc.* ***1975***, *97*, 3267; Lewis, F.D.; Kojima, M. *J. Am. Chem. Soc.* ***1988***, *110*, 8660.

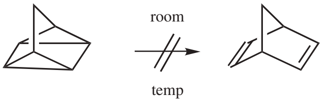
[2248] Maradyn, D.J.; Weedon, A.C. *Tetrahedron Lett.* ***1994***, *35*, 8107.

[2249] Becker, D.; Haddad, N.; Sahali, Y. *Tetrahedron Lett.* ***1989***, *30*, 2661.

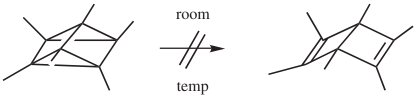
[2250] This is an example of the Wigner spin conservation rule (p. 340). Note that spin conservation is something entirely different from symmetry conservation.

place and the diradical to cyclize. We would therefore predict nonstereospecificity, and that is what is found.[2251] It has been believed that at least some [2 + 2]-photocycloadditions take place by way of exciplex intermediates[2252] [an *exciplex*[2253] is an excited EDA complex (p. 342) that 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.[2254]

In **15-60**, 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 although highly strained. For example, quadricyclane and hexamethylprismane[2255] are thermodynamically much less stable (because much more strained) than their corresponding isomeric dienes, norbornadiene and hexamethylbicyclo[2.2.0]hexadiene (**214**).[2256] 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 ${}_s2 + {}_s2$ 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.[2257] It is also possible to conceive of simple



Quadricyclane Norbornadiene



Hexamethylprismane

214
(A Dewar benzene)

[2251] See, for example, Liu, R.S.H.; Hammond, G.S. *J. Am. Chem. Soc.* ***1967***, *89*, 4936; Kramer, B.D.; Bartlett, P.D. *J. Am. Chem. Soc.* ***1972***, *94*, 3934.

[2252] See, for example, Farid, S.; Doty, J.C.; Williams, J.L.R. *J. Chem. Soc., Chem. Commun.* ***1972***, 711; Mizuno, K.; Pac, C.; Sakurai, H. *J. Am. Chem. Soc.* ***1974***, *96*, 2993; Caldwell, R.A.; Creed, D. *Acc. Chem. Res.* ***1980***, *13*, 45; Mattes, S.L.; Farid, S. *Acc. Chem. Res.* ***1982***, *15*, 80; Swapna, G.V.T.; Lakshmi, A.B.; Rao, J.M.; Kunwar, A.C. *Tetrahedron* ***1989***, *45*, 1777.

[2253] For a review of exciplexes, see Davidson, R.S. *Adv. Phys. Org. Chem.* ***1983***, *19*, 1–130.

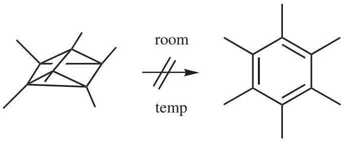
[2254] Schuster, D.I.; Heibel, G.E.; Brown, P.B.; Turro, N.J.; Kumar, C.V. *J. Am. Chem. Soc.* ***1988***, *110*, 8261.

[2255] This compound can be prepared by photolysis of **210**, another example of an intramolecular photochemical [2 + 2]-cycloaddition: Lemal, D.M.; Lokensgard, J.P. *J. Am. Chem. Soc.* ***1966***, *88*, 5934; Schäfer, W.; Criegee, R.; Askani, R.; Grüner, H. *Angew. Chem. Int. Ed.* ***1967***, *6*, 78.

[2256] For a review of this compound, see Schäfer, W.; Hellmann, H. *Angew. Chem. Int. Ed.* ***1967***, *6*, 518.

[2257] These conversions can also be carried out by the use of transition-metal catalysts: Hogeveen, H.; Volger, H.C. *Chem. Commun.* ***1967***, 1133; *J. Am. Chem. Soc.* ***1967***, *89*, 2486; Kaiser, K.L.; Childs, R.F.; Maitlis, P.M. *J. Am. Chem. Soc.* ***1971***, *93*, 1270; Landis, M.E.; Gremaud, D.; Patrick, T.B. *Tetrahedron Lett.* ***1982***, *23*, 375; Maruyama, K.; Tamiaki, H. *Chem. Lett.* ***1987***, 683.

bond rearrangements whereby hexamethylprismane is converted to hexamethylbenzene, which



of course is far more stable than either hexamethylprismane or **214**. It has been calculated that hexamethylbenzene is at least 90 kcal mol^{-1} (380 kJ mol^{-1}) more stable than hexamethylprismane. The fact that hexamethylprismane does not spontaneously undergo this reaction has prompted the observation[2258] that the prismane has "the aspect of an angry tiger unable to break out of a paper cage." However, a correlation diagram for this reaction[2259] 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.[2259]

Bicyclo[2.2.0]hexadienes and prismanes are *valence isomers* of benzenes.[2260] 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. 32, it was mentioned that Dewar formulas are canonical forms (although 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; **VIII**, 82, 116, 306, 377; **IX**, 28, 275; **80**, 160. For the reverse reaction, see OS **V**, 734.

15-64 The Addition of Carbenes and Carbenoids to Double and Triple Bonds

***epi*-Methylene-addition**

[2258] Woodward, R.B.; Hoffmann, R. *The Conservation of Orbital Symmetry* Acaademic Press, NY, ***1970***, pp. 107–112.

[2259] See, for example, Oth, J.F.M. *Recl. Trav. Chim. Pays-Bas* ***1968***, *87*, 1185.

[2260] For reviews of valence isomers of benzene, see Kobayashi, Y.; Kumadaki, I. *Adv. Heterocycl. Chem.* ***1982***, *31*, 169; *Acc. Chem. Res.* ***1981***, *14*, 76; van Tamelen, E.E. *Acc. Chem. Res.* ***1972***, *5*, 186; *Angew. Chem. Int. Ed.* ***1965***, *4*, 738; Bolesov, I.G. *Russ. Chem. Rev.* ***1968***, *37*, 666; Viehe, H.G. *Angew. Chem. Int. Ed.* ***1965***, *4*, 746; Schäfer, W.; Hellmann, H. *Angew. Chem. Int. Ed.* ***1967***, *6*, 518.

Carbenes and substituted carbenes add to double bonds to give cyclopropane derivatives by what can be considered as a formal [1 + 2]-cycloaddition.[2261] Many carbene derivatives, for example, PhCH, ROCH,[2262] $Me_2C{=}C$, $C(CN)_2$, have been added to double bonds, but the reaction is often performed with CH_2 itself, with halo and dihalocarbenes,[2263] and with carbalkoxycarbenes[2264] (generated from diazoacetic esters). Alkylcarbenes HCR have been added to alkenes,[2265] but more often these rearrange to give alkenes (p. 291). The carbene can be generated in any of the ways normally used (p. 287). However, most reactions in which a cyclopropane is formed by treatment of an alkene 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. 288) is actually involved.

Carbene itself ($:CH_2$) is extremely reactive and gives many side reactions, especially insertion reactions (**12-21**), which greatly reduce yields. This competition is also true with rhodium-catalyzed diazoalkane cyclopropanations[2266] (see below). When it is desired to add $:CH_2$ for preparative purposes, free carbene is not used, but the Simmons–Smith procedure (p. 1241) 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.[2267] The absolute rate constant for addition of selected alkoxychlorocarbene to butenes has been measured to range from 330 to $1 \times 10^4 \, M^{-1} \, s^{-1}$.[2268] A few of the many ways[2269] in which halocarbenes or carbenoids are generated for

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[2261] For reviews, see, in Rappoport, Z. *The Chemistry of the Cyclopropyl Group*, Wiley, NY, ***1987***, the reviews by Tsuji, T.; Nishida, S., pt. 1, pp. 307–373; Verhé, R.; De Kimpe, N. pt. 1, pp. 445–564; Marchand, A.P., in Patai, S. *Supplement A: The Chemistry of Double-Bonded Functional Groups*, pt. 1, Wiley, NY, ***1977***, pp. 534–607, 625–635; Bethell, D., in McManus, S.P. *Organic Reactive Intermediates*; Academic Press, NY, ***1973***, pp. 101–113; in Patai, S. *The Chemistry of Alkenes*, Vol. 1, Wiley, NY, ***1964***, the articles by Cadogan, J.I.G.; Perkins, M.J. pp. 633–671; Huisgen, R.; Grashey, R.; Sauer, J. pp. 755–776; Kirmse, W. *Carbene Chemistry* 2nd ed.; Academic Press, NY, ***1971***, pp. 85–122, 267–406. For a review of certain intramolecular additions, see Burke, S.D.; Grieco, P.A. *Org. React.* ***1979***, *26*, 361. For a list of reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 135–153.

[2262] For a review, see Schöllkopf, U. *Angew. Chem. Int. Ed.* ***1968***, *7*, 588.

[2263] For a review of the addition of halocarbenes, see Parham, W.E.; Schweizer, E.E. *Org. React.* ***1963***, *13*, 55.

[2264] For a review, see Dave, V.; Warnhoff, E.W. *Org. React.* ***1970***, *18*, 217.

[2265] For example see Frey, H.M. *J. Chem. Soc.* ***1962***, 2293.

[2266] Doyle, M.P.; Phillips, I.M. *Tetrahedron Lett.* ***2001***, *42*, 3155. For a review, see Merlic, C.A.; Zechman, A.L. *Synthesis* ***2003***, 1137.

[2267] For reviews of carbene selectivity in this reaction, see Moss, R.A. *Acc. Chem. Res.* ***1989***, *22*, 15; ***1980***, *13*, 58. For a review with respect to halocarbenes, see Kostikov, R.R.; Molchanov, A.P.; Khlebnikov, A.F. *Russ. Chem. Rev.* ***1989***, *58*, 654.

[2268] Moss, R.A.; Ge, C.-S.; Wostowska, J.; Jang, E.G.; Jefferson, E.A.; Fan, H. *Tetrahedron Lett.* ***1995***, *36*, 3083.

[2269] Much of the work in this field has been carried out by Seyferth, D. and co-workers; see, for example, Seyferth, D.; Haas, C.K. *J. Org. Chem.* ***1975***, *40*, 1620; Seyferth, D.; Haas, C.K.; Dagani, D. *J. Organomet. Chem.* ***1976***, *104*, 9.

this reaction are the following,[2270] most of which involve formal elimination (the first two steps of the S_N1cB mechanism, p. 521):

$$CH_2Cl_2 + RLi \xrightarrow{\quad} CHCl$$

$$N_2CHBr \xrightarrow{h\nu} CHBr$$

$$CHCl_3 + {}^{-}OH \xrightarrow{\quad} CCl_2$$

$$PhHgCCl_2Br \xrightarrow{\Delta} CCl_2 \quad \text{Ref.}^{2271}$$

$$Me_3SnCF_3 + NaI \xrightarrow{\quad} CF_2 \quad \text{Ref.}^{2272}$$

$$Me_2CBr_2 \xrightarrow{\text{electrolysis}} Me_2C\colon \quad \text{Ref.}^{2273}$$

The reaction between $CHCl_3$ and HO– is often carried out under phase transfer conditions.[2274] It has been shown that the reaction between $PhCHCl_2$ and *t*-BuOK produces a carbenoid, but when the reaction is run in the presence of a crown ether, the free Ph(Cl)C: is formed instead.[2275] The reaction of iodoform and $CrCl_2$ leads to iodocyclopropanes upon reaction with alkenes.[2276] Dihalocyclopropanes are very useful compounds[2277] that can be reduced to cyclopropanes, treated with magnesium or sodium to give allenes (**18-3**), or converted to a number of other products.

Alkenes of all types can be converted to cyclopropane derivatives by this reaction, but difficulty may be encountered with sterically hindered ones.[2278]

[2270] A much longer list, with references, is given, in Kirmse, W. *Carbene Chemistry Carbene Chemistry* 2nd ed., Academic Press, NY, ***1971***, pp. 313–319. See also, Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 135–143.

[2271] For a review of the use of phenyl(trihalomethyl)mercury compounds as dihalocarbene or dihalocarbenoid precursors, see Seyferth, D. *Acc. Chem. Res.* ***1972***, *5*, 65. For a review of the synthesis of cyclopropanes with the use of organomercury reagents, see Larock, R.C. *Organomercurcury Compounds in Organic Synthesis*, Springer, NY, ***1985***, pp. 341–380.

[2272] For reviews of flourinated carbenes, see Seyferth, D., in Moss, R.A.; Jones, Jr., M. *Carbenes*, Vol. 2, Wiley, NY, ***1975***, pp. 101–158; Sheppard, W.A.; Sharts, C.M. *Organic Fluorine Chemistry*, W. A. Benjamin, NY, ***1969***, pp. 237–270.

[2273] Léonel, E.; Paugam, J.P.; Condon-Gueugnot, S.; Nédélec, Y.-Y. *Tetrahedron* ***1998***, *54*, 3207.

[2274] For reviews of the use of phase-transfer catalysis in the addition of dihalocarbenes to C=C bonds, see Starks, C.M.; Liotta, C. *Phase Transfer Catalysis*, Academic Press, NY, ***1978***, pp. 224–268; Weber, W.P.; Gokel, G.W. *Phase Transfer Catalysis in Organic Synthesis*, Springer, NY, ***1977***, pp. 18–43, 58–62. For a discussion of the mechanism, see Gol'dberg, Yu.Sh.; Shimanskaya, M.V. *J. Org. Chem. USSR* ***1984***, *20*, 1212.

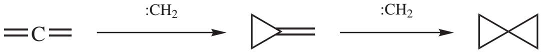
[2275] Moss, R.A.; Pilkiewicz, F.G. *J. Am. Chem. Soc.* ***1974***, *96*, 5632; Moss, R.A.; Lawrynowicz, W. *J. Org. Chem.* ***1984***, *49*, 3828.

[2276] Takai, K.; Toshikawa, S.; Inoue, A.; Kokumai, R. *J. Am. Chem. Soc.* ***2003***, *125*, 12990.

[2277] For reviews of dihalocyclopropanes, see Banwell, M.G.; Reum, M.E. *Adv. Strain Org. Chem.* ***1991***, *1*, 19–64; Kostikov, R.R.; Molchanov, A.P.; Hopf, H. *Top. Curr. Chem.* ***1990***, *155*, 41–80; Barlet, R.; Vo-Quang, Y. *Bull. Soc. Chim. Fr.* ***1969***, 3729–3760.

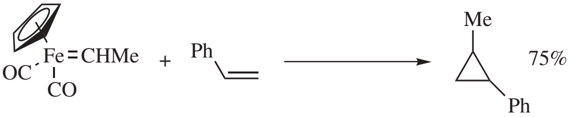
[2278] Dehmlow, E.V.; Eulenberger, A. *Liebigs Ann. Chem.* ***1979***, 1112.

Even tetracyanoethylene, which responds very poorly to electrophilic attack, gives cyclopropane derivatives with carbenes.[2279] Conjugated dienes give 1,2-addition to give a vinylcyclopropane.[2280] Addition of a second mole gives bicyclopropyl derivatives.[2281] 1,4-Addition is rare but has been reported in certain cases.[2282] Carbene adds to ketene to give cyclopropanone.[2283] Allenes react with carbenes to give cyclopropanes with exocyclic unsaturation:[2284]



A second equivalent gives spiropentanes. In fact, any size ring with an exocyclic double bond can be converted by a carbene to a spiro compound.[2285]

Free carbenes can also be avoided by using transition-metal–carbene complexes $L_nM{=}CRR'$ (L = a ligand, M = a metal),[2286] which add the group CRR′ to double bonds.[2287] An example is the reaction of iron carbene **215**.[2288]



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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

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[2279] Cairns, T.L.; McKusick, B.C. *Angew. Chem.* ***1961***, *73*, 520.

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[2283] Turro, N.J.; Hammond, W.B. *Tetrahedron* ***1968***, *24*, 6017; Rothgery, E.F.; Holt, R.J.; McGee, Jr., H.A. *J. Am. Chem. Soc.* ***1975***, *97*, 4971. For a review of cyclopropanones, see Wasserman, H.H.; Berdahl, D.R.; Lu, T., in Rappoport, Z. *The Chemistry of the Cyclopropyl Group*, Wiley, NY, ***1987***, pt. 2, pp. 1455–1532.

[2284] For reviews of the addition of carbenes and carbenoids to allenes, see Landor, S.R., in Landor, S.R. *The Chemistry of Allenes,* Vol. 2, Academic Press, NY, ***1982***, pp. 351–360; Bertrand, M. *Bull. Soc. Chim. Fr.* ***1968***, 3044–3054. For a review of the synthetic uses of methylenecyclopropanes and cyclopropenes, see Binger, P.; Büch, H.M. *Top. Curr. Chem.* ***1987***, *135*, 77.

[2285] For a review of the preparation of spiro compounds by this reaction, see Krapcho, A.P. *Synthesis* ***1978***, 77–126.

[2286] Doyle, M.P.; McKervey, M.A.; Ye, T. *Modern Catalytic Methods for Organic Synthesis with Diazo Compounds*, Wiley, NY, ***1998***.

[2287] For reviews, see Helquist, P. *Adv. Met.-Org. Chem.* ***1991***, *2*, 143; Brookhart, M.; Studabaker, W.B. *Chem. Rev.* ***1987***, *87*, 411; Syatkovskii, A.I.; Babitskii, B.D. *Russ. Chem. Rev.* ***1984***, *53*, 672.

[2288] Brookhart, M.; Tucker, J.R.; Husk, G.R. *J. Am. Chem. Soc.* ***1983***, *105*, 258.

most important. Chromium complexes have been used for the cyclopropanation of alkenes.[2289]

Polymer-supported benzenesulfonyl azides have been developed as a safe diazo-transfer reagent.[2290] These compounds, including CH_2N_2 and other diazoalkanes, react with metals or metal salts (copper, palladium,[2291] and rhodium are most commonly used) to give the carbene complexes that add: CRR′ to double bonds.[2292] Diazoketones and diazoesters with alkenes to give the cyclopropane derivative, usually with a transition-metal catalyst, such as a copper complex.[2293] The ruthenium catalyst reaction of diazoesters with an alkyne give a cyclopropene.[2294] An X-ray structure of an osmium catalyst intermediate has been determined.[2295] Electron-rich alkenes react faster than simple alkenes.[2296]

Optically active complexes have been used for enantioselective cyclopropane synthesis.[2297] Decomposition of diazoalkanes in the presence of chiral rhodium[2298] copper,[2299] or ruthenium[2300] complexes leads to optically active cyclopropanes.

[2289] Barluenga, J.; Aznar, F.; Gutiérrez, I.; García-Granda, S. Llorca-Baragaño, M.A. *Org. Lett.* ***2002***, *4*, 4233.

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[2292] For reviews, see Adams, J.; Spero, D.M. *Tetrahedron* ***1991***, *47*, 1765; Collman, J.P., Hegedus, L.S.; Norton, J.R.; Finke, R.G. *Principles and Applications of Organotransition Metal Chemistry* University Science Books, Mill Valley, CA ***1987***, pp. 800–806; Maas, G. *Top. Curr. Chem.* ***1987***, *137*, 75; Doyle, M.P. *Chem. Rev.* ***1986***, *86*, 919; *Acc. Chem. Res.* ***1986***, *19*, 348; Heck, R.F. *Palladium Reagents in Organic Synthesis*, Academic Press, NY, ***1985***, pp. 401–407; Wulfman, D.S.; Poling, B. *React. Intermed. (Plenum)* ***1980***, *1*, 321; Müller, E.; Kessler, H.; Zeeh, B. *Fortschr. Chem. Forsch.* ***1966***, *7*, 128.

[2293] Díaz-Requejo, M.M.; Belderraín, T.R.; Trofimenko, S.; Pérez, P.J. *J. Am. Chem. Soc.* ***2001***, *123*, 3167. For a discussion of the mechanism and selectivity, see Bühl, M.; Terstegen, F.; Löffler, F.; Meynhardt, B.; Kierse, S.; Müller, M.; Näther, C.; Lüning, U. *Eur. J. Org. Chem.* ***2001***, 2151.

[2294] Lou, Y.; Horikawa, M.; Kloster, R.A.; Hawryluk, N.A.; Corey, E.J. *J. Am. Chem. Soc.* ***2004***, *126*, 8916.

[2295] Li, Y.; Huang, J.-S.; Zhou, Z.-Y.; Che, C.-M. *J. Am. Chem. Soc.* ***2001***, *123*, 4843.

[2296] See Davies, H.M.L.; Xiang, B.; Kong, N.; Stafford, D.G. *J. Am. Chem. Soc.* ***2001***, *123*, 7461.

[2297] Brookhart, M.; Liu, Y.; Goldman, E.W.; Timmers, D.A.; Williams, G.D. *J. Am. Chem. Soc.* ***1991***, *113*, 927; Lowenthal, R.E.; Abiko, A.; Masamune, S. *Tetrahedron Lett.* ***1990***, *31*, 6005; Evans, D.A.; Woerpel, K.A.; Hinman, M.M.; Faul, M.M. *J. Am. Chem. Soc.* ***1991***, *113*, 726; Ito, K.; Katsuki, T. *Tetrahedron Lett.* ***1993***, *34*, 2661. For a review of enantioselective cyclopropanation using carbenoid chemistry see Singh, V.K.; DattaGupta, A.; Sekar, G. *Synthesis* ***1997***, 137. For the effect of diazoalkane structure of stereoselectivity, see Davies, H.M.L.; Bruzinski, P.R.; Fall, M.J. *Tetrahedron Lett.* ***1996***, *37*, 4133.

[2298] Davies, H.M.L.; Rusiniak, L. *Tetrahedron Lett.* ***1998***, *39*, 8811; Haddad, N.; Galili, N. *Tetrahedron Asymmetry* ***1997***, *8*, 3367; Ichiyanagi, T.; Shimizu, M.; Fujisawa, T. *Tetrahedron* ***1997***, *53*, 9599; Fukuda, T.; Katsuki, T. *Tetrahedron* ***1997***, *53*, 7201; Frauenkron M.; Berkessel, A. *Tetrahedron Lett.* ***1997***, *38*, 7175; Doyle, M.P.; Zhou, Q.-L.; Charnsangavej, C.; Longoria, M.A.; McKervey, M.A.; Garcia, C.F. *Tetrahedron Lett.* ***1996***, *37*, 4129.

[2299] Díaz-Requejo, M.M.; Caballero, A.; Belderraín, T.R.; Nicasio, M.C.; Trofimenko, S.; Pérez, P.J. *J. Am. Chem. Soc.* ***2002***, *124*, 978.

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The use of chiral additives with a rhodium complex also leads to cyclopropanes enantioselectively.[2301] An important chiral rhodium species is Rh_2(*S*-DOSP)$_4$,[2302] which leads to cyclopropanes with excellent enantioselectivity in carbene cyclopropanation reactions.[2303] Asymmetric, intramolecular cyclopropanation reactions have been reported.[2304] The copper catalyzed diazoester cyclopropanation was reported in an ionic liquid.[2305] It is noted that the reaction of a diazoester with a chiral dirhodium catalyst leads to β-lactones with modest enantioselectivity.[2306] Phosphonate esters have been incorporated into the diazo compound.[2307]

Triple-bond compounds[2308] react with carbenes to give cyclopropenes, except that in the case of acetylene itself, the cyclopropenes first formed cannot be isolated because they rearrange to allenes.[2309] Cyclopropenones (p. 73) are obtained by hydrolysis of dihalocyclopropenes.[2310]

Most carbenes are electrophilic, and, in accord with this, electron-donating substituents on the alkene increase the rate of the reaction, and electron-withdrawing groups decrease it,[2311] although the range of relative rates is not very great.[2312] As discussed on p. 284, carbenes in the singlet state (which is the most common state) react stereospecifically and syn,[2313] probably by a one-step mechanism,[2314] similar

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[2301] Aggarwal, V.K.; Smith, H.W.; Hynd, G. ; Jones, R.V.H.; Fieldhouse, R.; Spey, S.E. *J. Chem. Soc., Perkin Trans. 1* ***2000***, 3267; Yao, X.; Qiu, M.; Lü, W.; Chen, H.; Zheng, Z. *Tetrahedron Asymmetry* ***2001***, *12*, 197.

[2302] Doyle, M.P. *Pure Appl. Chem.* ***1998***, *70* 1123; Doyle, M.P.; Protopopova, M.N. *Tetrahedron* ***1998***, *54*, 7919; Martin, S.F.; Spaller, M.R.; Liras, L.; Hartman, B. *J. Am. Chem. Soc.* ***1994***, *116*, 4493; Davies, H.M.L.; Hansen, T.; Churchill, M.R. *J. Am. Chem. Soc.* ***2000***, *122*, 3063; Davies, H.M.L.; Hansen, T. *J. Am. Chem. Soc.* ***1997***, *119*, 9075. See also, Davies, H.M.L. *Aldrichimica Acta* ***1997***, *30*, 107. For related chiral ligands see Nagashima, T.; Davies, H.M.L. *Org. Lett.* ***2002***, *4*, 1989; Davies, H.M.L.; Lee, G.H. *Org. Lett.* ***2004***, *6*, 2117.

[2303] Davies, H.M.L.; Townsend, R.J. *J. Org. Chem.* ***2001***, *66*, 6595; Davies, H.M.; Boebel, T.A. *Tetrahedron Lett.* ***2000***, *41*, 8189.

[2304] Piqué, C.; Fähndrich, B.; Pfaltz, A. *Synlett* ***1995***, 491; Barberis, M.; Pérez-Prieto, J.; Stiriba, S.-E.; Lahuerta, P. *Org. Lett.* ***2001***, *3*, 3317; Saha, B.; Uchida, T.; Katsuki, T. *Synlett* ***2001***, 114; Honma, M.; Sawada, T.; Fujisawa, Y.; Utsugi, M.; Watanabe, H.; Umino, A.; Matsumura, T.; Hagihara, T.; Takano, M.; Nakada, M. *J. Am. Chem. Soc.* ***2003***, *125*, 2860.

[2305] In emim NTf_2, 1-ethyl-3-methylimidazolium triflimide: Fraile, J.M.; García, J.I.; Herrerías, C.I.; Mayoral, J.A.; Carrié, D.; Vaultier, M. *Tetrahedron Asymmetry* ***2001***, *12*, 1891.

[2306] Doyle, M.P.; May, E.J. *Synlett* ***2001***, 967.

[2307] Ferrand, Y.; Le Maux, P.; Simonneaux, G. *Org. Lett.* ***2004***, *6*, 3211.

[2308] For reviews, see Fuks, R.; Viehe, H.G., in Viehe, H.G. *Acetylenes*, Marcel Dekker, NY, ***1969***, pp. 427–434; Closs, G.L. *Adv. Alicyclic Chem.* ***1966***, *1*, 53–127, see pp. 58–65.

[2309] Frey, H.M. *Chem. Ind. (London)* ***1960***, 1266.

[2310] Vol'pin, M.E.; Koreshkov, Yu.D.; Kursanov, D.N. *Bull. Acad. Sci. USSR Div. Chem. Sci.* ***1959***, 535.

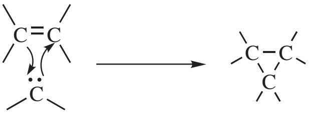
[2311] Skell, P.S.; Garner, A.Y. *J. Am. Chem. Soc.* ***1956***, *78*, 5430; Doering, W. von E.; Henderson, Jr., W.A. *J. Am. Chem. Soc.* ***1958***, *80*, 5274; Mitsch, R.A.; Rodgers, A.S. *Int. J. Chem. Kinet.* ***1969***, *1*, 439.

[2312] For a review of reactivity in this reaction, with many comprehensive tables of data, see Moss, R.A., in Jones, Jr. M.; Moss, R.A. *Carbenes*, Vol. 1, Wiley, NY, ***1973***, pp. 153–304. See also, Cox, D.P.; Gould, I.R.; Hacker, N.P.; Moss, R.A.; Turro, N.J. *Tetrahedron Lett.* ***1983***, *24*, 5313.

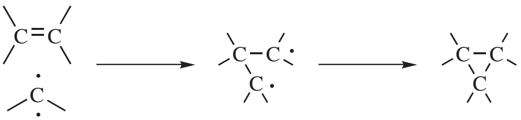
[2313] Woodworth, R.C.; Skell, P.S. *J. Am. Chem. Soc.* ***1959***, *81*, 3383; Jones Jr., M.; Ando, W.; Hendrick, M.E.; Kulczycki Jr., A.; Howley, P.M.; Hummel, K.F.; Malament, D.S. *J. Am. Chem. Soc.* ***1972***, *94*, 7469.

[2314] For evidence that at least some singlet carbenes add by a two-step mechanism, see Giese, B.; Lee, W.; Neumann, C. *Angew. Chem. Int. Ed.* ***1982***, *21*, 310.

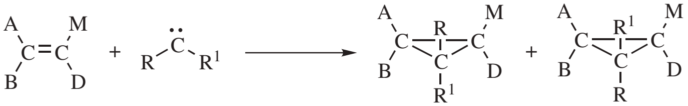
to mechanism *a* of **15-60** and **15-63**:



Infrared spectra of a carbene and the cyclopropane product have been observed in an argon matrix at 12–45 K.[2315] Carbenes in the triplet state react nonstereospecifically,[2316] probably by a diradical mechanism, similar to mechanism *b* of **15-49** and **15-63**:

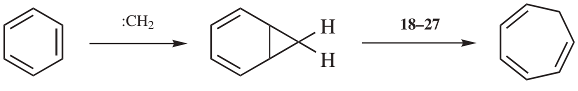


For carbenes or carbenoids of the type R—C—R′ there is another aspect of stereochemistry.[2317] When these species are added to all but symmetrical alkenes, two isomers are possible, even if the four groups originally on the double–bond carbons maintain their configurations:



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.[2318] The products are usually unstable and rearrange to give ring expansion. Carbene reacts with benzene to give cycloheptatriene (**216**),[2319]



Norcaradiene **216**

[2315] Nefedov, O.M.; Zuev, P.S.; Maltsev, A.K.; Tomilov, Y.V. *Tetrahedron Lett.* ***1989***, *30*, 763.

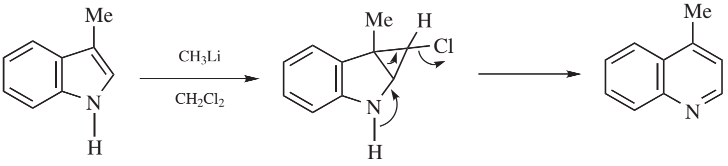
[2316] Skell, P.S.; Klebe, J. *J. Am. Chem. Soc.* ***1960***, *82*, 247. See also, Jones, Jr., M.; Tortorelli, V.J.; Gaspar, P.P.; Lambert, J.B. *Tetrahedron Lett.* ***1978***, 4257.

[2317] For reviews of the stereochemistry of carbene and carbenoid addition to double bonds, see Moss, R.A. *Sel. Org. Transform.*, ***1970***, *1*, 35–88; Closs, G.L. *Top Stereochem.* ***1968***, *3*, 193–235. For a discussion of enantioselectivity in this reaction, see Nakamura, A. *Pure Appl. Chem.* ***1978***, *50*, 37.

[2318] See Giese, C.M.; Hadad, C.M. *J. Org. Chem.* ***2002***, *67*, 2532.

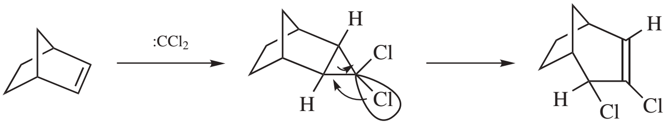
[2319] Doering, W. von E.; Knox, L.H. *J. Am. Chem. Soc.* ***1951***, *75*, 297.

but not all carbenes are reactive enough to add to benzene. The norcaradiene intermediate cannot be isolated in this case[2320] (it undergoes an electrocyclic rearrangement, **18-27**), although certain substituted norcaradienes, for example, the product of addition of: $C(CN)_2$ to benzene,[2321] have been isolated.[2322] 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 diazomethane (CH_2N_2) in the aromatic compound as solvent with CuCl or CuBr.[2323] By this method better yields of cycloheptatrienes are obtained without insertion side products. Picosecond optical grating calorimetry has been used to investigate the photochemical decomposition of diazomethane in benzene, and it appears that a transient is formed that is consistent with a weak complex between singlet methylene and benzene.[2324] Chlorocarbene, :CHCl, is active enough to add to benzene, but dihalocarbenes do not add to benzene or toluene, only to rings with greater electron density. Pyrroles and indoles can be expanded, respectively, to pyridines and quinolines by treatment with halocarbenes[2325] via the initially formed adduct **217** in the case of the indole.



217

In such cases, a side reaction that sometimes occurs is expansion of the *six-membered* ring. Ring expansion can occur even with non–aromatic compounds, when the driving force is supplied by relief of strain (see **218**).[2326]



218

[2320] It has been detected by uv spectroscopy: Rubin, M.B. *J. Am. Chem. Soc.* ***1981***, *103*, 7791.

[2321] Ciganek, E. *J. Am. Chem. Soc.* ***1967***, *89*, 1454.

[2322] See, for example, Mukai, T.; Kubota, H.; Toda, T. *Tetrahedron Lett.* ***1967***, 3581; Maier, G.; Heep, U. *Chem. Ber.* ***1968***, *101*, 1371; Ciganek, E. *J. Am. Chem. Soc.* ***1971***, *93*, 2207; Dürr, H.; Kober, H. *Tetrahedron Lett.* ***1972***, 1255, 1259; Vogel, E.; Wiedemann, W.; Roth, H.D.; Eimer, J.; Günther, H. *Liebigs Ann. Chem.* ***1972***, *759*, 1; Bannerman, C.G.F.; Cadogan, J.I.G.; Gosney, I.; Wilson, N.H. *J. Chem. Soc., Chem. Commun.* ***1975***, 618; Takeuchi, K.; Kitagawa, T.; Senzaki, Y.; Okamoto, K. *Chem. Lett.* ***1983***, 73; Kawase, T.; Iyoda, M.; Oda, M. *Angew. Chem. Int. Ed.* ***1987***, *26*, 559.

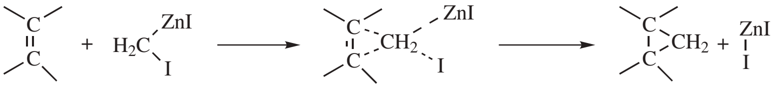
[2323] Wittig, G.; Schwarzenbach, K. *Liebigs Ann. Chem.* ***1961***, *650*, 1; Müller, E.; Fricke, H. *Liebigs Ann. Chem.* ***1963***, *661*, 38; Müller, E.; Kessler, H.; Fricke, H.; Kiedaisch, W. *Liebigs Ann. Chem.* ***1961***, *675*, 63.

[2324] Khan, M.I.; Goodman, J.L. *J. Am. Chem. Soc.* ***1995***, *117*, 6635.

[2325] For a review of the reactions of heterocyclic compounds with carbenes, see Rees, C.W.; Smithen, C.E. *Adv. Heterocycl. Chem.* ***1964***, *3*, 57–78.

[2326] Jefford, C.W.; Gunsher, J.; Hill, D.T.; Brun, P.; Le Gras, J.; Waegell, B. *Org. Synth.* ***VI***, 142. For a review of the addition of halocarbenes to bridged bicyclic alkenes see Jefford, C.W. *Chimia*, ***1970***, *24*, 357–363.

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.[2327] 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.[2328] The Zn–Cu couple can be prepared in several ways,[2329] of which heating Zn dust with CuCl in ether under nitrogen[2330] is particularly convenient. The reaction has also been done with unactivated zinc and ultrasound.[2331] When $TiCl_4$ is used along with Zn and CuCl, CH_2I_2 can be replaced by the cheaper CH_2Br_2.[2332] The actual attacking species is an organozinc intermediate, probably $(ICH_2)_2Zn{\bullet}ZnI_2$, which is stable enough for isolable solutions.[2333] An X-ray crystallographic investigation of the intermediate, complexed with a diether, has been reported.[2334] The addition is stereospecifically syn, and a concerted mechanism[2335] is likely, perhaps[2336]



Asymmetric induction is possible when chiral additives are used.[2337] With the Simmons–Smith procedure, as with free carbenes, conjugated dienes give 1,2-addition,[2338] and allenes give methylenecyclopropanes or spiropentanes.[2339]

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.[2340] This method can be adapted to the introduction of RCH and ArCH by the use of $RCHI_2$

[2327] For reviews, see Simmons, H.E.; Cairns, T.L.; Vladuchick, S.A.; Hoiness, C.M. *Org. React.* ***1973***, *20*, 1–131; Furukawa, J.; Kawabata, N. *Adv. Organomet. Chem.* ***1974***, *12*, 83–134, see pp. 84–103.

[2328] Simmons, H.E.; Smith, R.D. *J. Am. Chem. Soc.* ***1959***, *81*, 4256.

[2329] Shank, R.S.; Shechter, H. *J. Org. Chem.* ***1959***, *24*, 1525; LeGoff, E. *J. Org. Chem.* ***1964***, *29*, 2048. For the use of a Zn—Ag couple, see Denis, J.M.; Girard, C.; Conia, J.M. *Synthesis* ***1972***, 549.

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[2331] Repič; O.; Lee, P.G.; Giger, U. *Org. Prep. Proced. Int.* ***1984***, *16*, 25.

[2332] Friedrich, E.C.; Lunetta, S.E.; Lewis, E.J. *J. Org. Chem.* ***1989***, *54*, 2388.

[2333] Blanchard, E.P.; Simmons, H.E. *J. Am. Chem. Soc.* ***1964***, *86*, 1337. For an analysis of the reaction by density functional theory, see Fang, W.-H.; Phillips, D.L.; Wang, D.-q.; Li, Y.-L. *J. Org. Chem.* ***2002***, *67*, 154.

[2334] Denmark, S.E.; Edwards, J.P.; Wilson, S.R. *J. Am. Chem. Soc.* ***1991***, *113*, 723.

[2335] Dargel, T.K.; Koch, W. *J. Chem. Soc. Perkin Trans. 2*, ***1996***, 877.

[2336] Simmons, H.E.; Blanchard, E.P.; Smith, R.D. *J. Am. Chem. Soc.* ***1964***, *86*, 1347. For a discussion of the transition state and intermediate in this reaction, see Bernardi, F.; Bottoni, A.; Miscione, G.P. *J. Am. Chem. Soc.* ***1997***, *119*, 12300.

[2337] Charette, A.B.; Juteau, H.; Lebel, H.; Molinaro, C. *J. Am. Chem. Soc.* ***1998***, *120*, 11943; Kitajima, H.; Ito, K.; Aoki, Y.; Katsuki, T. *Bull. Chem. Soc. Jpn.* ***1997***, *70*, 207; Imai, N.; Sakamoto, K.; Maeda, M.; Kouge, K.; Yoshizane, K.; Nokami, J. *Tetrahedron Lett*, ***1997***, *38*, 1423; Denmark, S.E.; Edwards, J.P. *Synlett* ***1992***, 229; Balsells, J.; Walsh, P.J. *J. Org. Chem.* ***2000***, *65*, 5005.

[2338] Overberger, C.G.; Halek, G.W. *J. Org. Chem.* ***1963***, *28*, 867.

[2339] Charette, A.B.; Jolicoeur, E.; Bydlinski, G.A.S. *Org. Lett.* ***2001***, *3*, 3293.

[2340] See Charette, A.B.; Beauchemin, A.; Marcoux, J.-F. *Tetrahedron Lett.* ***1999***, *40*, 33; Zhao, C.; Wang, D.; Phillips, D.L. *J. Am. Chem. Soc.* ***2002***, *124*, 12903.

or $ArCHI_2$ instead of the dihalomethane.[2341] The reaction is compatible with other functionality in the carbenoid complex. The reaction of RCO_2CH_2I with diethyl zinc and an alkene under photolysis conditions give a cyclopropane.[2342] Chiral additives lead to enantioselectivity in the cyclopropanation reaction.[2343] In another method, CH_2I_2 or $MeCHI_2$ is used along with an alane R_3Al to transfer CH_2 or CHMe.[2344] Titanium complexes have been used similarly.[2345] Samarium and CH_2I_2 has been used for the cyclopropanation of conjugated amides.[2346] For the conversion of enolates to cyclopropanols, CH_2I_2 has been used along with SmI_2.[2347]

Other cyclopropanation techniques have been developed. Treatment of an alkene with $ArCH(SnBu_3)OCO_2Me$ and $BF_3{\bullet}OEt_2$ leads to the cyclopropane with high cis-selectivity.[2348] Diodomethane in the presence of isopropylmagnesium chloride has been used to cyclopropanate allyl alcohols.[2349]

The Simmons–Smith reaction is the basis of a method for the indirect α methylation of a ketone.[2350] The ketone (illustrated for cyclohexanone) is first converted to an enol ether, an enamine (**16-13**) or silyl enol ether[2351] (**12-17**) and cyclopropanation via the Simmons–Smith reaction is followed by hydrolysis to give the α methylated ketone. A related procedure using diethylzinc and diiodomethane allows ketones to be chain-extended by one carbon.[2352] In another variation, phenols can be ortho-methylated in one laboratory step, by treatment with Et_2Zn and CH_2I_2.[2353]

Diazoesters react with amines with a rhodium catalyst to give α-amino esters.[2354] Diazoesters also react with aldehydes and a rhodium catalyst, and the product is an α,β-epoxy ester.[2355] Diazoalkanes react similarly with aldehydes to give an alkene ($Me_3SiCH{=}N_2 + ArCHO \rightarrow ArCH{=}CHOSiMe_3$).[2356]

OS **V**, 306, 855, 859, 874; **VI**, 87, 142, 187, 327, 731, 913, 974; **VII**, 12, 200, 203; **VIII**, 124, 196, 321, 467; **IX**, 422; **76**, 86.

[2341] Nishimura, J.; Kawabata, N.; Furukawa, J. *Tetrahedron* ***1969***, *25*, 2647; Miyano, S.; Hashimoto, H. *Bull. Chem. Soc. Jpn.* ***1973***, *46*, 892; Friedrich, E.C.; Biresaw, G. *J. Org. Chem.* ***1982***, *47*, 1615.

[2342] Charette, A.B.; Beauchemin, A.; Fraancoeur, S. *J. Am. Chem. Soc.* ***2001***, *123*, 8139.

[2343] Long, J.; Yuan, Y.; Shi, Y. *J. Am. Chem. Soc.* ***2003***, *125*, 13632.

[2344] Maruoka, K.; Fukutani, Y.; Yamamoto, H. *J. Org. Chem.* ***1985***, *50*, 4412; *Org. Synth., 67*, 176.

[2345] Charette, A.B.; Molinaro, C.; Brochu, C. *J. Am. Chem. Soc.* ***2001***, *123*, 12168.

[2346] Concellón, J.M.; Rodríguez-Solla, H.; Gómez, C. *Angew. Chem. Int. Ed.* ***2002***, *41*, 1917.

[2347] Imamoto, T.; Takiyama, N. *Tetrahedron Lett.* ***1987***, *28*, 1307. See also, Molander, G.A.; Harring, L.S. *J. Org. Chem.* ***1989***, *54*, 3525.

[2348] Sugawara, M.; Yoshida, J. *J. Am. Chem. Soc.* ***1997***, *119*, 11986.

[2349] Bolm, C.; Pupowicz, D. *Tetrahedron Lett.* ***197***, *38*, 7349.

[2350] See Wenkert, E.; Mueller, R.A.; Reardon Jr., E.J.; Sathe, S.S.; Scharf, D.J.; Tosi, G. *J. Am. Chem. Soc.* ***1970***, *92*, 7428 for the enol ether procedure; Kuehne, M.E.; King, J.C. *J. Org. Chem.* ***1973***, *38*, 304 for the enamine procedure; Conia, J.M. *Pure Appl. Chem.* ***1975***, *43*, 317–326 for the silyl ether procedure.

[2351] In the case of silyl enol ethers, the inner bond can be cleaved with $FeCl_3$, giving a ring-enlarged β-chloro ketone: Ito, Y.; Fujii, S.; Saegusa, T. *J. Org. Chem.* ***1976***, *41*, 2073; *Org. Synth.* ***VI***, 327.

[2352] Brogan, J.B.; Zercher, C.K. *J. Org. Chem.* ***1997***, *62*, 6444.

[2353] Lehnert, E.K.; Sawyer, J.S.; Macdonald, T.L. *Tetrahedron Lett.* ***1989***, *30*, 5215.

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[2355] Doyle, M.P.; Hu, W.; Timmons, D.J. *Org. Lett.* ***2001***, *3*, 933.

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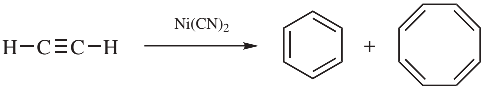
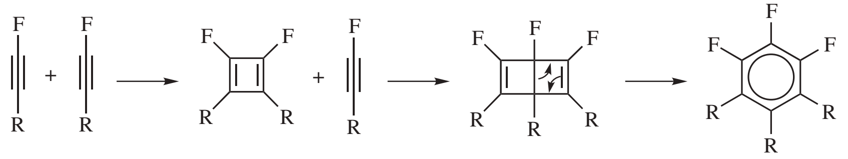
15-65 Trimerization and Tetramerization of Alkynes



Aromatic compounds can be prepared by cyclotrimerization of alkynes[2357] or triynes. Cyclotrimerization is possible by heating to 450–600°C with no catalyst.[2358] The *spontaneous* (no catalyst) trimerization of *t*-BuC≡CF gave 1,2,3-tri-*tert*-butyl-4,5,6-trifluorobenzene (**220**), the first time three adjacent *tert*-butyl groups had been put onto a benzene ring.[2359] The fact that this is a head-to-head joining allows formation of **220** from two alkynes. The fact that **219** (a Dewar benzene) was also isolated lends support to this scheme.[2360] Three equivalents of 3-hexyne trimerized to hexaethylbenzene at 200°C in the presence of Si_2Cl_6.[2361]



R = *tert*-butyl **219** **220**

When acetylene is heated with nickel cyanide, other Ni(II) or Ni(0) compounds, or similar catalysts, it gives benzene and cyclooctatetraene.[2362] It is possible to get more of either product by a proper choice of catalyst. Substituted acetylenes give substituted benzenes.[2363] This reaction has been used to prepare very crowded

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[2357] For a review, see Rubin, M.; Sromek, A.W.; Gevorgyan, V. *Synlett* ***2003***, 2265.

[2358] Kociolek, M.G.; Johnson, R.P. *Tetrahedron Lett.* ***1999***, *40*, 4141.

[2359] Viehe, H.G.; Merényi, R.; Oth, J.F.M.; Valange, P. *Angew. Chem. Int. Ed.* ***1964***, *3*, 746; Viehe, H.G.; Merényi, R.; Oth, J.F.M.; Senders, J.R.; Valange, P. *Angew. Chem. Int. Ed.* ***1964***, *3*, 755.

[2360] For other reactions between cyclobutadienes and triple bonds to give Dewar benzenes, see Wingert, H.; Regitz, M. *Chem. Ber.* ***1986***, *119*, 244.

[2361] Yang, J.; Verkade, J.G. *J. Am. Chem. Soc.* ***1998***, *120*, 6834.

[2362] For reviews, see Winter, M.J., in Hartley, F.R.; Patai, S. *The Chemistry of the Metal–Carbon Bond*, Vol. 3, Wiley, NY, ***1985***, pp. 259–294; Vollhardt, K.P.C. *Angew. Chem. Int. Ed.* ***1984***, *23*, 539; *Acc. Chem. Res.* ***1977***, *10*, 1; Maitlis, P.M. *J. Organomet. Chem.* ***1980***, *200*, 161; *Acc. Chem. Res.* ***1976***, *9*, 93; *Pure Appl. Chem.* ***1972***, *30*, 427; Yur'eva, L.P. *Russ. Chem. Rev.* ***1974***, *43*, 48; Khan, M.M.T.; Martell, A.E. *Homogeneous Catalysis by Metal Complexes*, Vol. 2, Academic Press, NY, **1974**, pp. 163–168; Reppe, W.; Kutepow, N.V.; Magin, A. *Angew. Chem. Int. Ed.* ***1969***, *8*, 727; Fuks, R.; Viehe, H.G. in Viehe, H.G. *Acetylenes*, Marcel Dekker, NY, ***1969***, pp. 450–460; Hoogzand, C.; Hübel, W., in Wender, I.; Pino, P. *Organic Syntheses Via Metal Carbonyls*, Vol. 1, Wiley, NY, ***1968***, pp. 343–371; Reikhsfel'd, V.O.; Makovetskii, K.L. *Russ. Chem. Rev.* ***1966***, *35*, 510. For a list of reagents, with references, see Larock, R.C. *Comprehensive Organic Transformations*, 2nd ed., Wiley-VCH, NY, ***1999***, pp. 198–201. For a review of metal-catalyzed cycloadditions of alkynes to give rings of all sizes, see Schore, N.E. *Chem. Rev.* ***1988***, *88*, 1081.

[2363] Sigman, M.S.; Fatland, A.W.; Eaton, B.E. *J. Am. Chem. Soc.* ***1998***, *120*, 5130; Gevorgyan, V.; Takeda, A.; Yamamoto, Y. *J. Am. Chem. Soc.* ***1997***, *119*, 11313; Takeda, A.; Ohno, A.; Kadota, I.; Gevorgyan, V.; Yamamoto, Y. *J. Am. Chem. Soc.* ***1997***, *119*, 4547; Larock, R.C.; Tian, Q. *J. Org. Chem.* ***1998***, *63*, 2002; Sato, Y.; Nishimata, T.; Mori, M. *J. Org. Chem.* ***1994***, *59*, 6133; Grissom, J.W.; Calkins, T.L. *Tetrahedron Lett.* ***1992***, *33*, 2315.

molecules. Diisopropylacetylene was trimerized over $CO_2(CO)_8$[2364] and over $Hg[Co(CO)_4]_2$ to hexaisopropylbenzene.[2365] The six isopropyl groups are not free to rotate but are lined up perpendicular to the plane of the benzene ring. Highly substituted benzene derivatives have also been prepared using a rhodium,[2366] nickel,[2367] titanium,[2368] molybdenum,[2369] ruthenium,[2370] cobalt,[2371] or a palladium[2372] catalyst. Alkynes react with allenes and a nickel catalyst go give highly substituted benzene derivatives.[2373] Conjugated ketones react with internal alkynes with Me_3Al and a nickel catalyst[2374] leads to an aromatic ring fused to a cyclic ketone after reaction with DBU and air.[2375] *N*-Aryl chloroimines react with alkynes and a rhodium catalyst to give quinolines,[2376] as do *N*-aryl alkynyl imines with a tungsten complex.[2377]

An intramolecular cyclotrimerization has been reported by condensation of a diyne[2378] with an alkyne in the presence of a palladium,[2379] molybdenum,[2380] nickel,[2381] rhodium,[2382] iridium,[2383] or ruthenium catalyst.[2384] Triynes have been

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[2364] See Yong, L.; Butenschön, H. *Chem. Commun.* ***2002***, 2852. For a modification that gives a phenol from 3,3-dimethyl-1-butyne, see Marchueta, I.; Olivella, S.; Solà, L.; Moyano, A.; Pericàs, M.A.; Riera, A. *Org. Lett.* ***2001***, *3*, 3197.

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[2372] Gevorgyan, V.; Takeda, A.; Homma, M.; Sadayori, N.; Radhakrishnan, U.; Yamamoto, Y. *J. Am. Chem. Soc.* ***1999***, *121*, 6391; Gevorgyan, V.; Quan, L.G.; Yamamoto, Y. *J. Org. Chem.* ***2000***, *65*, 568. For a reaction in conjunction with silver carbonate, see Kawasaki, S.; Satoh, T.; Miura, M.; Nomura, M. *J. Org. Chem.* ***2003***, *68*, 6836; In conjunction with $CuCl_2$, see Li, J.-H.; Xie, Y.-X. *Synth. Commun.* ***2004***, *34*, 1737.

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[2376] Amii, H.; Kishikawa, Y.; Uneyama, K. *Org. Lett.* ***2001***, *3*, 1109.

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[2378] See Kawathar, S.P.; Schreiner, P.R. *Org. Lett.* ***2002***, *4*, 3643.

[2379] Yamamoto, Y.; Nagata, A.; Itoh, K. *Tetrahedron Lett.* ***1999***, *40*, 5035; Gevorgyan, V.; Radhakrishnan, U.; Takeda, A.; Rubina, M.; Rubin, M.; Yamamoto, Y. *J. Org. Chem.* ***2001***, *66*, 2835. See also, Tsukada, N.; Sugawara, S.; Nakaoka, K.; Inoue, Y. *J. Org. Chem.* ***2003***, *68*, 5961.

[2380] Hara, R.; Guo, Q.; Takahashi, T. *Chem. Lett.* ***2000***, 140.

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[2384] Yamamoto, Y.; Ogawa, R.; Itoh, K. *Chem. Commun.* ***2000***, 549; Witulski, B.; Stengel, T.; Fernández-Hernandez, J.M. *Chem. Commun.* ***2000***, 1965.

similarly condensed with a rhodium catalyst.[2385] The internal cyclotrimerization of a triyne, utilizing a siloxy tether and a cobalt catalyst has been reported.[2386] Fused ring aromatic compounds are prepared by this method. Similar results were obtained from diynes and allenes with a nickel catalyst.[2387] bis(Enynes) are cyclized to bicyclic arenes using a palladium catalyst.[2388] Diynes with nitriles and a ruthenium catalyst lead to isoquinolines.[2389] Pyridines fused to carboxylic rings can be prepared by similar methodology using a cyanoamine and a cobalt catalyst.[2390] In the presence of $PhMe_2SiH$, CO and a rhodium catalyst, a nonconjugated triyne leads to a tricyclic compound in which a benzene ring is fused to two carbocyclic rings.[2391] Internal cyclotrimerization of an aryl alkynyl ketone where the aryl group has an *ortho* trimethylsiylalkyne substituent gives a tetracyclic naphthalene derivative with a fused cyclopentanone unit.[2392] An isocyanate (Ar—N=C=O) reacts with a diyne and a ruthenium catalyst to give a bicyclic pyridone.[2393] Benzene derivatives with ortho alkyne units can be converted to naphthalene derivatives in aqueous NaOH with hydrazine, Te, $NaBH_4$ and sonication.[2394] Benzene derivatives having ortho imine and alkyne substituents give an isoquinoline when treated with iodine[2395] or with a palladium catalyst.[2396] Imino and iodo substituents with a silyl alkyne and a palladium catalyst leads to an isoquinoline.[2397] Vinyl and alkyne substituents with a ruthenium catalyst lead to naphthalene derivatives.[2398] Ortho alkynyl and epoxy substituents leads to β-naphthols using a ruthenium catalyst.[2399] Cyclotrimerization occurs with alkynyl boronic esters.[2400]

In contrast to the spontaneous reaction, the catalyzed process seldom gives the 1,2,3-trisubstituted benzene isomer from an acetylene RC≡CH. The chief product is usually the 1,2,4-isomer,[2401] with lesser amounts of the 1,3,15-isomer also generally obtained, but little if any of the 1,2,3-isomer. The mechanism of

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[2385] Kinoshita, H.; Shinokubo, H.; Oshima, K. *J. Am. Chem. Soc.* ***2003***, *125*, 7784.

[2386] Chouraqui, G.; Petit, M.; Aubert, C.; Malacria, M. *Org. Lett.* ***2004***, *6*, 1519.

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[2393] Yamamoto, Y.; Takagishi, H.; Itoh, K. *Org. Lett.* ***2001***, *3*, 2117.

[2394] Landis, C.A.; Payne, M.M.; Eaton, D.L.; Anthony, J.E. *J. Am. Chem. Soc.* ***2004***, *126*, 1338.

[2395] Huang, Q.; Hunter, J.A.; Larock, R.C. *Org. Lett.* ***2001***, *3*, 2973.

[2396] Dai, G.; Larock, R.C. *Org. Lett.* ***2001***, *3*, 4035; Dai, G.; Larock, R.C. *J. Org. Chem.* ***2003***, *68*, 920; Dai, G.; Larock, R.C. *Org. Lett.* ***2002***, *4*, 193.

[2397] Roesch, K.R.; Larock, R.C. *J. Org. Chem.* ***2002***, *67*, 86.

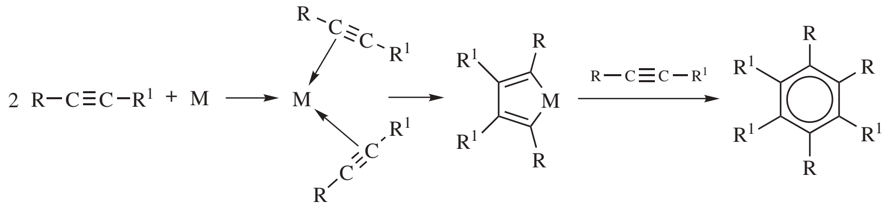
[2398] Klumpp, D.A.; Beauchamp, P.S.; Sanchez, Jr., G.V.; Aguirre, S.; de Leon, S. *Tetrahedron Lett.* ***2001***, *42*, 5821.

[2399] Madhusaw, R.J.; Lin, M.-Y.; Shoel, S.Md.A.; Liu, R.-S. *J. Am. Chem. Soc.* ***2004***, *126*, 6895.

[2400] Gandon, V.; Leca, D.; Aechtner, T.; Vollhardt, K.P.C.; Malacria, M.; Aubert, C. *Org. Lett.* ***2004***, *6*, 3405.

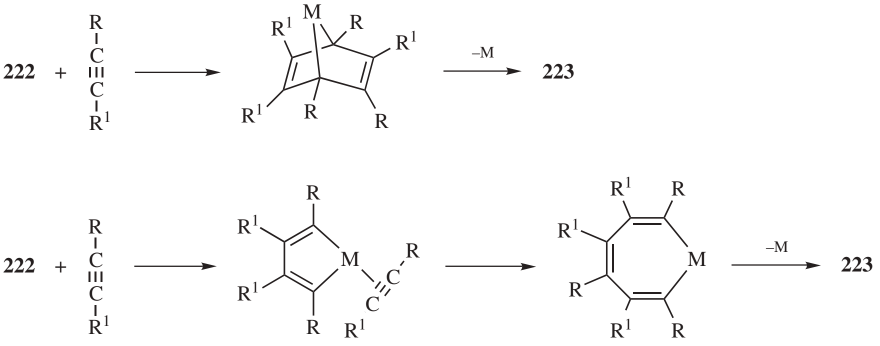
[2401] See Saito, S.; Kawasaki, T.; Tsuboya, N.; Yamamoto, Y. *J. Org. Chem.* ***2001***, *66*, 796.

the catalyzed



221 **222** **223**

reaction to form benzenes[2402] is believed to go through a species **221** in which two molecules of alkyne coordinate with the metal, and another species **222**, a five-membered heterocyclic intermediate.[2403] Such intermediates (where M = Rh, Ir, Zr,[2404] or Ni) have been isolated and shown to give benzenes (**223**) when treated with alkynes.[2405] 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:[2406]



[2402] For studies of the mechanism of the reaction that produces cyclooctatetraenes, see Diercks, R.; Stamp, L.; Kopf, J.; Tom Dieck, H. *Angew. Chem. Int. Ed.* ***1984***, *23*, 893; Colborn, R.E.; Vollhardt, K.P.C. *J. Am. Chem. Soc.* ***1986***, *108*, 5470; Lawrie, C.J.; Gable, K.P.; Carpenter, B.K. *Organometallics* ***1989***, *8*, 2274.

[2403] See, for example, Colborn, R.E.; Vollhardt, K.P.C. *J. Am. Chem. Soc.* ***1981***, *103*, 6259; Kochi, J.K. *Organometallic Mechanisms and Catalysis*, Academic Press, NY, ***1978***, pp. 428–432; Collman, J.P., Hegedus, L.S.; Norton, J.R.; Finke, R.G. *Principles and Applications of Organotransition Metal Chemistry*, University Science Books, Mill Valley, CA ***1987***, pp. 870–877; Eisch, J.J.; Sexsmith, S.R. *Res. Chem. Intermed.* ***1990***, *13*, 149–192.

[2404] Takahahsi, T.; Ishikawa, M.; Huo, S. *J. Am. Chem. Soc.* ***2002***, *124*, 388.

[2405] See, for example, Collman, J.P. *Acc. Chem. Res.* ***1968***, *1*, 136; Yamazaki, H.; Hagihara, N. *J. Organomet. Chem.* ***1967***, *7*, P22; Wakatsuki, Y.; Kuramitsu, T.; Yamazaki, H. *Tetrahedron Lett.* ***1974***, 4549; Moseley, K.; Maitlis, P.M. *J. Chem. Soc. Dalton Trans.* ***1974***, 169; Müller, E. *Synthesis* ***1974***, 761; Eisch, J.J.; Galle, J.E. *J. Organomet. Chem.* ***1975***, *96*, C23; McAlister, D.R.; Bercaw, J.E.; Bergman, R.G. *J. Am. Chem. Soc.* ***1977***, *99*, 1666.

[2406] There is evidence that the mechanism of the last step more likely resembles the Diels–Alder pathway than the ring expansion pathway: Bianchini, C.; Caulton, K.G.; Chardon, C.; Eisenstein, O.; Folting, K.; Johnson, T.J.; Meli, A.; Peruzzini, M.; Raucher, D.J.; Streib, W.E.; Vizza, F. *J. Am. Chem. Soc.* ***1991***, *113*, 5127.

In at least one case the mechanism is different, going through a cyclobutadiene–nickel complex (see p. 76), which has been isolated.[2407] Similar results were obtained with a titanium complex.[2408] Using a mixture of $PdCl_2$ and $CuCl_2$, however, aliphatic alkynes are converted to the 1,3,5-trialkyl benzene derivative.[2409]

Alkoxy chromium carbenes (Fischer carbene complexes) react with phenylalkynes to give naphthalene derivatives.[2410] These chromium carbenes react with alkynyl boronates, cerium(IV) compounds, and then PhBr and a palladium catalyst to give a naphthoquinone.[2411] Diynes react to give cyclotrimerization.[2412] It is noted that vinyl chromium carbenes react directly with alkynes to give spirocyclic compounds (spiro[4.4]nona-1,3,6-trienes).[2413] Benzofurans can be prepared using methoxy carbenes.[2414] Amino-substituted chromium carbenes react with alkynes and then silica to give substituted benzene derivatives that have an aminoalkyl ($-NR_2$) substituent.[2415] Imino-substituted chromium carbenes react with alkynes to give pyrrole derivatives.[2416] Fischer carbene complexes react with alkynes to give the *Dötz benzannulation*,[2417] giving *p*-alkoxylphenol derivatives. Modification of this basic technique can lead to eight-membered ring carbocycles (see **15-66**).[2418]

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.[2419]

In a related reaction, heating ketones in the presence of $TlCl_3OTf$ leads to 1,3,5-trisubstituted arenes.[2420] Heating acetophenone with $TiCl_4$ gives 1,3,5-triphenylbenzene.[2421] Nitriles react with 2 mol of acetylene, in the presence of a cobalt catalyst, to give 2-substituted pyridines.[2422] Propargyl amines react with cyclohexanone derivatives and a gold complex give tetrahydroquinolines.[2423] Treatment of alkynes with Cp_2ZrEt_2 followed by reaction with acetonitrile and then a second alkyne with a nickel catalyst gives a highly substituted pyridine.[2424] This reaction can be done intramolecularly using a photochemically induced reaction with a

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[2407] Mauret, P.; Alphonse, P. *J. Organomet. Chem.* ***1984***, *276*, 249. See also, Pepermans, H.; Willem, R.; Gielen, M.; Hoogzand, C. *Bull. Soc. Chim. Belg.* ***1988***, *97*, 115.

[2408] Suzuki, D.; Urabe, H.; Sato, F. *J. Am. Chem. Soc.* ***2001***, *123*, 7925.

[2409] Li, J.; Jiang, H.; Chen, M. *J. Org. Chem.* ***2001***, *66*, 3627.

[2410] Pulley, S.R.; Sen, S.; Vorogushin, A.; Swanson, E. *Org. Lett.* ***1999***, *1*, 1721; Jackson, T.J.; Herndon, J.W. *Tetrahedron* ***2001***, *57*, 3859.

[2411] Davies, M.W.; Johnson, C.N.; Harrity, J.P.A. *J. Org. Chem.* ***2001***, *66*, 3525.

[2412] Jiang, M.X.-W.; Rawat, M.; Wulff, W.D. *J. Am. Chem. Soc.* ***2004***, *126*, 5970.

[2413] Schirmer, H.; Flynn, B.L.; de Meijere, A. *Tetrahedron* ***2000***, *56*, 4977.

[2414] Herndon, J.W.; Zhang, Y.; Wang, H.; Wang, K. *Tetrahedron Lett.* ***2000***, *41*, 8687.

[2415] Barluenga, J.; López, L.A.; Martínez, S.; Tomás, M. *Tetrahedron* ***2000***, *56*, 4967.

[2416] Campos, P.J.; Sampedro, D.; Rodríquez, M.A. *J. Org. Chem.* ***2003***, *68*, 4674.

[2417] Dötz, K.H. *Angew. Chem. Int. Ed.* ***1975***, *14*, 644.

[2418] Barluenga, J.; Aznar, F.; Palomero, M.A. *Angew. Chem. Int. Ed.* ***2000***, *39*, 4346.

[2419] Parker, W.L.; Hexter, R.M.; Siedle, A.R. *J. Am. Chem. Soc.* ***1985***, *107*, 4584.

[2420] Iranpoor, N.; Zeynizaded, B. *Synlett* ***1998***, 1079.

[2421] Li, Z.; Sun, W.-H.; Jin, X.; Shao, C. *Synlett* ***2001***, 1947.

[2422] Heller, B.; Oehme, G. *J. Chem. Soc., Chem. Commun.* ***1995***, 179.

[2423] Abbiati, G.; Arcadi, A.; Bianchi, G.; Di Giuseppe, S.; Marinelli, F.; Rossi, E. *J. Org. Chem.* ***2003***, *68*, 6959.

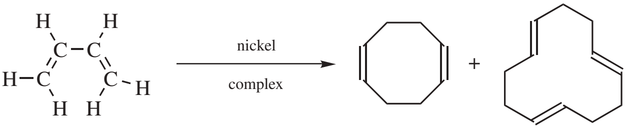
[2424] Takahashi, T.; Tsai, F.Y.; Kotora, M. *J. Am. Chem. Soc.* ***2000***, *122*, 4994.

cobalt catalyst and *p*-TolCN to give pyridines incorporated into macrocycles.[2425] Alkynyl esters react with enamino esters with a $ZnBr_2$ catalyst to give substituted pyridines.[2426] α-Halo oxime ethers react with alkynes and Grignard reagents, with a mixture of palladium and copper catalysts, to give pyrimidines.[2427] Triketones fix nitrogen gas in the presence of $TiCl_4$ and lithium metal to form bicyclic pyrrole derivatives.[2428]

OS **VII**, 256; **IX**, 1; **80**, 93.

15-66 Other Cycloaddition Reactions

***cyclo*-[But-2-en-1,4-diyl]-1/4/addition**, and so on



Cycloaddition reactions other than [4 + 2], [3 + 2], or [2 + 2] are possible, often providing synthetically useful routes to cyclic compounds. 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.[2429] Thus butadiene gives 1,5-cyclooctadiene and 1,5,9-cyclododecatriene.[2430] The relative amount of each product can be controlled by use of the proper catalyst. For example, $Ni{:}P(OC_6H_4\text{—}o\text{—}Ph)_3$ 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–alkene complexes.[2431] The rhodium catalyzed intramolecular cycloaddition of a furan with a conjugated diazoester gives a [3 + 4]-cycloadduct.[2432] The suprafacial thermal addition of an allylic cation to a diene (a [4 + 3]-cycloaddition) is allowed by the Woodward–Hoffmann rules (this reaction would

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[2425] Moretto, A.F.; Zhang, H.-C.; Maryanoff, B.E. *J. Am. Chem. Soc.* ***2001***, *123*, 3157.

[2426] Bagley, M.C.; Dale, J.W.; Hughes, D.D.; Ohnesorge, M.; Philips, N.G.; Bower, J. *Synlett* ***2001***, 1523.

[2427] Kikiya, H.; Yagi, K.; Shinokubo, H.; Oshima, K. *J. Am. Chem. Soc.* ***2002***, *124*, 9032.

[2428] Mori, M.; Hori, M.; Sato, Y. *J. Org. Chem.* ***1998***, *63*, 4832; Mori, M.; Hori, K.; Akashi, M.; Hori, M.; Sato, Y.; Nishida, M. *Angew. Chem. Int. Ed.* ***1998***, *37*, 636.

[2429] For reviews, see Wilke, G. *Angew. Chem. Int. Ed.* ***1988***, *27*, 186; Tolstikov, G.A.; Dzhemilev, U.M. *Sov. Sci. Rev. Sect. B* ***1985***, *7*, 237, 278–290; Heimbach, P.; Schenkluhn, H. *Top Curr. Chem.* ***1980***, *92*, 45; Baker, R. *Chem. Rev.* ***1973***, *73*, 487, see pp. 489–512; Semmelhack, M.F. *Org. React.* ***1972***, *19*, 115, pp. 128–143; Khan, M.M.T.; Martell, A.E. *Homogeneous Catalysis by Metal Complexes*, Vol. 2, Academic Press, NY, ***1974***, pp. 159–163; Heck, R.F. *Organotransition Metal Chemistry*, Academic Press, NY, ***1974***, pp. 157–164.

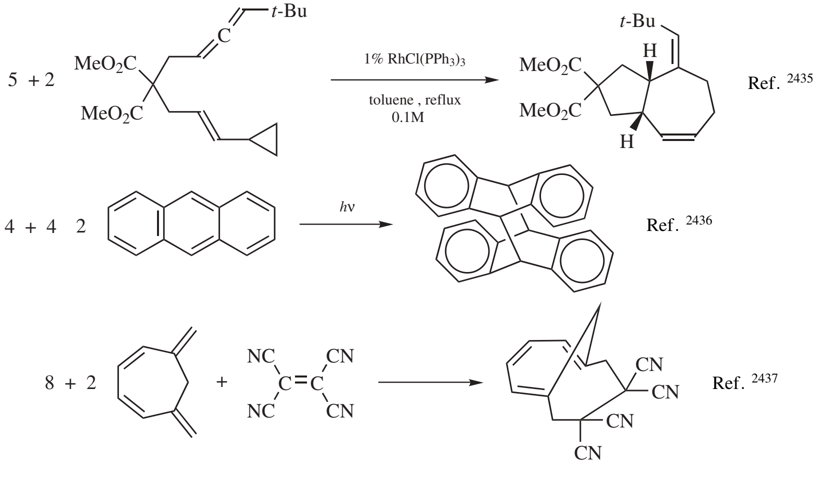
[2430] For a review of the 1,5,9-cyclododecatrienes (there are four stereoisomers, of which the *ttt* is shown above), see Rona, P. *Intra-Sci. Chem. Rep.* ***1971***, *5*, 105.

[2431] For example, see Heimbach, P.; Wilke, G. *Liebigs Ann. Chem.* ***1969***, *727*, 183; Barnett, B.; Büssemeier, B.; Heimbach, P.; Jolly, P.W.; Krüger, C.; Tkatchenko, I.; Wilke, G. *Tetrahedron Lett.* ***1972***, 1457; Barker, G.K.; Green, M.; Howard, J.A.K.; Spencer, J.L.; Stone, F.G.A. *J. Am. Chem. Soc.* ***1976***, *98*, 3373; Graham, G.R.; Stephenson, L.M. *J. Am. Chem. Soc.* ***1977***, *99*, 7098.

[2432] Davies, H.M.L.; Calvo, R.L.; Townsend, R.-J.; Ren, P.; Churchill, R.M. *J. Org. Chem.* ***2000***, *65*, 4261. For reviews of [3 + 4]-cycloadditions see Mann, J. *Tetrahedron* ***1986***, *42*, 4611; Hoffmann, H.M.R. *Angew. Chem. Int. Ed.* ***1984***, *23*, 1; ***1973***, *12*, 819; Noyori, R. *Acc. Chem. Res.* ***1979***, *12*, 61.

be expected to follow the same rules as the Diels–Alder reaction[2433]). Chiral cations have been used in [4 + 3]-cycloadditions.[2434]

As we saw in **15-60**, 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, although 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



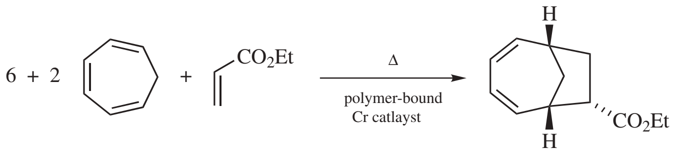
[2433] Garst, M.E.; Roberts, V.A.; Houk, K.N.; Rondan, N.G. *J. Am. Chem. Soc.* ***1984***, *106*, 3882.

[2434] Harmata, M; Jones, D.E.; Kahraman, M.; Sharma, U.; Barnes, C.L. *Tetrahedron Lett.* ***1999***, *40*, 1831.

[2435] Wender, P.A.; Glorius, F.; Husfeld, C.O.; Langkopf, E.; Love, J.A. *J. Am. Chem. Soc.* ***1999***, *121*, 5348. For another example, see Trost, B.M.; Toste, F.D.; Shen, H. *J. Am. Chem. Soc.* ***2000***, *122*, 2379. See also, Wender, P.A.; Gamber, G.G.; Scanio, M.J.C. *Angew. Chem. Int. Ed.* ***2001***, *40*, 3895; Wender, P.A.; Pedersen, T.M.; Scanio, M.J.C. *J. Am. Chem. Soc.* ***2002***, *124*, 15154; Wender, P.A.; Love, J.A.; Williams, T.J. *Synlett* ***2003***, 1295.

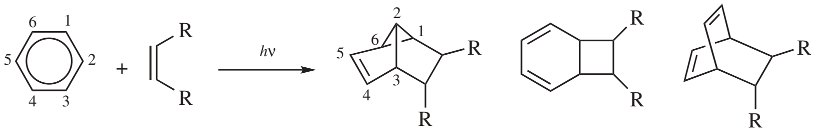
[2436] Shönberg, A. *Preparative Organic Photochemistry*, Springer, NY, ***1968***, pp. 97–99. For other examples see Sieburth, S.Mc.N.; McGee, Jr., K.F.; Al-Tel, T.H. *Tetrahedron Lett.* ***1999***, *40*, 4007; Sieburth, S.Mc.N.; Lin, C.H.; Rucando, D. *J. Org. Chem.* ***1999***, *64*, 950, 954; Zhu, M.; Qiu, Z.; Hiel, G.P.; Sieburth, S.Mc.N. *J. Org. Chem.* ***2002***, *67*, 3487.

[2437] Farrant, G.C.; Feldmann, R. *Tetrahedron Lett.* ***1970***, 4979.



Ref. [2438]

Benzene rings can undergo photochemical cycloaddition with alkenes.[2439] The major product is usually the 1,3-addition product **224** (in which a three-membered ring has also been formed), although some of the 1,2 product **225** (**15-63**) is sometimes formed as well. (**225** is usually the main product where the alkene bears electron-withdrawing groups and the aromatic compound electron-donating groups, or vice versa.) The 1,4 product **226** 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 alkenes bearing various groups.[2440]



224 **225** **226**

A [2 + 2 + 2]-cycloaddition reaction is also known, facilitated by Ni(cod)$_2$[2441] or a cobalt catalyst.[2442] [2 + 2 + 1]-Cycloaddition is known.[2443] A cobalt catalyst is used for a [4 + 2 + 2]-cycloaddition of 1,3-butadiene and bicyclo[2.2.2]octa-2,5-diene.[2444] Eight-membered rings are products by a rhodium catalyzed [4 + 2 + 2]-cycloaddition.[2445] Chromium catalysts are available for [6 + 4]-cycloadditions.[2446]

OS **VI**, 512; **VII**, 485; **X**, 1, 336.

[2438] Rigby, J.H.; Kondratenko, M.A.; Fiedler, C. *Org. Lett.* ***2000***, *2*, 3917; Rigby, J.H.; Mann, L.W.; Myers, B.J. *Tetrahedron Lett.* ***2001***, *42*, 8773. See Rigby, J.H.; Ateeq, H.S.; Charles, N.R.; Henshilwood, J.A.; Short, K.M.; Sugathapala, P.M. *Tetrahedron* ***1993***, *49*, 5495.

[2439] For reviews, see Wender, P.A.; Ternansky, R.; deLong, M.; Singh, S.; Olivero, A.; Rice, K. *Pure Appl. Chem.* ***1990***, *62*, 1597; Gilbert, A., in Horspool, W.M. *Synthetic Organic Photochemistry*, Plenum, NY, ***1984***, pp. 1–60. For a review of this and related reactions, see McCullough, J.J. *Chem. Rev.* ***1987***, *87*, 811.

[2440] See the table, in Wender, P.A.; Siggel, L.; Nuss, J.M. *Org. Photochem.* ***1989***, *10*, 357, pp. 384–415.

[2441] Lautens, M.; Edwards, L.G.; Tam, W.; Lough, A.J. *J. Am. Chem. Soc.* ***1995***, *117*, 10276; Louie, J.; Gibby, J.E.; Farnsworth, M.V.; Tekavec, T.N. *J. Am. Chem. Soc.* ***2002***, *124*, 15188.

[2442] Slowinski, F.; Aubert, C.; Malacria, M. *Tetrahedron Lett.* ***1999***, *40*, 5849.

[2443] Knölker, H.-J.; Braier, A.; Bröcher, D.J.; Jones, P.G.; Piotrowski, H. *Tetrahedron Lett.* ***1999***, *40*, 8075; Chatani, N.; Tobisu, M.; Asaumi, T.; Fukumoto, Y.; Murai, S. *J. Am. Chem. Soc.* ***1999***, *121*, 7160.

[2444] Kiattansakul, R.; Snyder, J.K. *Tetrahedron Lett.* ***1999***, *40*, 1079.

[2445] Gilbertson, S. R.; DeBoef, B.*J. Am. Chem. Soc.* ***2002***, *124*, 8784.

[2446] Kündig, E.P.; Robvieux, F.; Kondratenko, M. *Synthesis* ***2002***, 2053.